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Food Restriction and Body Image Distortion in Pregnant Mothers: Outcomes for Exposed Children

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FOOD RESTRICTION AND BODY IMAGE DISTORTION IN PREGNANT MOTHERS: OUTCOMES FOR EXPOSED CHILDREN

by

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This manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy

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ABSTRACT

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Background: Developmental trajectories in the growing child do not originate at birth. Rather, critical periods may exist in pregnancy, during which the determinants of malnutrition are especially vulnerable to the effects of stress and other complications. Prenatal malnutrition has been consistently associated with negative consequences for the growth, development, and overall physical and mental health of affected offspring in both human and animal models. While most available literature on human prenatal malnutrition comes from famine research, there is some evidence that restrictive eating disorders in pregnant women may be associated with similar outcomes.

Hypotheses: We hypothesize that prenatal exposure to maternal subclinical symptoms of restricted eating disorders, characterized in this study as food restriction and body image distortion (FRBID), are associated with adverse outcomes for children. Specifically, we hypothesize that *in utero* FRBID exposure will be associated with early indicators of psychopathology at 48, 60, and 72 months of age. We also hypothesize that *in utero* exposure to FRBID will be associated with decreased body measurements at birth (birthweight percentile and small for gestational age), and elevated Body Mass Index (BMI) percentiles in early childhood at 48, 60, and 72 months of age compared with non-exposed controls. Finally, we hypothesize that weight percentile change between birth and 48, 60 and 72 months mediate the relationship between FRBID and early indicators of psychopathology and BMI percentiles.

Methods: Data were obtained for 204 mother-child dyads. Thirty percent (n=63) of mothers reported some level of FRBID during pregnancy, whereas 69.6% (n=142) denied any FRBID.

These mother-child dyads were followed throughout pregnancy and have subsequently participated in yearly follow-up assessments at 48, 60, and 72 months. The predictor variables in this study include maternal food restriction during pregnancy and maternal body image distortion, assessed retrospectively with the Food Restriction Questionnaire (FRQ). Participants endorsing symptoms in the FRQ were divided into dichotomous groups of FRBID+ and FRBID-, such that FRBID+ participants endorsed at least one FRBID symptom during pregnancy. The primary outcome variables in this study include child's height/weight/ BMI percentile at birth and follow-up, as well as early indicators of child psychopathology (BASC-2) at 48, 60, and 72 months. A potential mediator in this study is weight percentile change, which was assessed by the change of weight percentile from birth to 72 months.

Results: FRBID-exposed children were found to be at a significantly greater risk for select internalizing and externalizing disorders as measured by dichotomous and continuous BASC-2 data at 48, 60, and 72 months when compared with controls. No significant differences were observed in child body measurements in adjusted or unadjusted analyses at any age. Similarly, there was no notable increase observed in the risk for "small for gestational age" at birth in unadjusted or adjusted models. No evidence was found to support the hypothesis that weight gain trajectories during early childhood mediate the relationship between FRBID and any clinical child behaviors.

DEDICATION

To my parents, Maureen and Larry, for your unconditional love and support. And to my fiancé, Matt, for cheering me on through every stage of this doctoral journey. Thank you.

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Introduction

Developmental trajectories in the growing child do not originate at birth. Rather, critical periods may exist in pregnancy, during which the determinants of malnutrition are especially vulnerable to the effects of stress and other complications (DiPietro, Hodgson, Costigan, & Hilton, 1996; Wadhwa, Buss, Entringer, & Swanson, 2001). During this critical period, a developing fetus must rely solely on the pregnant mother for nutrients, oxygen, and ultimately survival. Lack of nutrients and/or caloric deficits *in utero* have been consistently associated with negative consequences for the growth, development, and overall health of affected offspring in both human and animal models (McArdle, Andersen, Jones, & Gambling, 2006).

Animal Models

A wealth of animal research suggests that a fetus can be "programmed" *in utero* for subsequent development and health following a stressful event such as food restriction (Barker, 1992). These negative effects can be long-term and may be evident even in adulthood (McArdle et al., 2006). An advantage of animal models is experimental control over variables related to food restriction, including timing of exposure, percentage of calorie reduction, and the mother's physical environment. One way in which fetal programming has been evaluated in animal models is through diet manipulation whereby pregnant mothers were given a low-protein diet to simulate stressful periods in which food intake is diminished. A series of studies ; Langley-Evans et al., 1999; Bellinger, Lilley, & Langley-Evans, 2004) exploring the effects of low-protein diets in rats established critical time periods during which different effects of low-protein diets *in utero* were observed. Rats, which were fed a low-protein diet prior to conception, had pups that

grew more rapidly than controls from days 14-19, making them significantly larger than controls at this stage in development. Notably, these same pups grew more slowly than controls after day 19 and were significantly smaller than controls at birth. When the low-protein diet was given to mothers only after conception, however, the pups grew significantly faster than controls until day 14 but were significantly smaller than controls after day 19. These changes may be explained in part by earlier findings in rats by Winick and Noble (1966), who showed that mothers who were fed altered protein supplies while pregnant gave birth to offspring that showed changes in cell number in tissues such as the pancreas.

Animal models have also been used to evaluate the impact of diets low in iron (McArdle et al., 2006). Numerous studies have demonstrated that iron-deficient pregnant rodents have altered placental function, resulting in increased expression of placental cytokines that are associated with poor pregnancy outcomes, such as lower birth weight and premature birth (Gambling et al., 2002). Altered placental function due to iron deficiency can also affect the transfer of other nutrients, such as amino acids, which, in turn, can alter the expression of specific transporter genes such as *GLUT3*, *SNAT1*, *SNAT2* and *SNAT4*, (Belkacemi et al. 2011; Langley-Evans, 1997; Lesage et al. 2002; McArdle, Anderson, Jones, & Gambling, 2006). At birth, pups exposed to iron deficiency via mothers *in utero* were significantly smaller in overall size and had smaller kidneys, enlarged hearts, and higher blood pressure as compared to their unexposed counterparts. By six weeks, these differences were no longer significant in females, whereas males showed increased systolic blood pressure up to 38 weeks. In contrast, female pups initially showed a similar pattern of increased systolic blood pressure at 10 weeks, however this difference attenuated up to 16 weeks of age (McArdle et al., 2006).

Human Studies

While extensive evidence is available concerning the short-term implications of maternal malnutrition on the developing fetus (i.e., intrauterine growth restriction (IUGR), low birthweight) (Abu-Saad & Fraser, 2010), it was not until recent years that the long-lasting effects of malnutrition *in utero* have been studied in humans. Due to ethical constraints, variables cannot be manipulated in human studies as they are in animal models; as such, cohort studies of significant famines are leveraged as natural experiments to evaluate the downstream effects of food intake during pregnancy. In a large-scale study utilizing maternity records at the University of Amsterdam, researchers identified 3307 live-born singleton births in three Dutch cities exposed to the "Dutch Hunger Winter", a period of famine in the Netherlands during the second world war. They further selected a subsample of 2,417 live births of mothers who were exposed to famine during or immediately preceding their pregnancy (born February 21st, 1945, through March 1st, 1946) and a control group of 890 live births of mothers who were not exposed to famine during their pregnancies (born between 1943 and 1947) (Lumey et. Al., 2007). These researchers found that birthweights were lower for offspring exposed to prenatal famine. Researchers posit that this decreased birthweight was due to both shorter gestation and slowed fetal growth rate (Lumey, 1992). Stein et al. (2004) subsequently conducted a more detailed report on newborn body proportions following *in utero* famine exposure. They found that birthweight, crown-to-heel length, and head circumference were all significantly reduced following famine exposure in late gestation. However, no notable changes were observed for first trimester exposure.

Understanding the relationship between body measurements at birth and prenatal food restriction is vitally important in developmental and lifespan sciences, as birth size and weight

have significant implications for adult body composition later in life. Numerous studies have linked low birthweight with elevated weight, BMI, waist circumference, body fat composition, and/or obesity later in life (Ravelli et al., 1999; Eriksson et al., 2001; Pietilainen et al., 2001). In one study utilizing data from the Dutch Hunger Winter, a five-month period of acute starvation during the final months of World War II between 1944 and 1945, researchers have linked birthweight with significantly greater weight (SD score=9.6, $p<.05$) and BMI (SD score=2.7, $p<0.5$), at age 19 (Dutch POPS-19 Collaborative Study Group, 2005). While these elevated body measurements may seem counterintuitive, they may be explained by a pattern of "catch-up weight" in early infancy, during which low-birthweight infants gain weight at a more rapid rate than their normal-birthweight counterparts. The presence of this catch-up weight event in infancy may be the catalyst for elevated BMI and altered body composition in adulthood, which may in turn put individuals at greater risk for other adverse health outcomes.

Stettler et al. (2002) further explored this pattern of rapid weight gain in infants, particularly the first four months of life. Utilizing a sample of 27,899 participants born full term between 1959 and 1965, they found a significant association between rate of weight gain during the first four months and childhood overweight status at seven years, such that infants with the most rapid weight gain during this four-month period were more likely to be overweight at the age of seven (OR: 1.38; 95% CI). Of note, all participants in this sample were born at full term, addressing potential confounders in previous literature wherein premature births may have contributed to this trend. Infants who are born with low birthweights are at a higher risk of experiencing rapid weight gain during the first four months, which are a critical period for the development of potential obesity later in life, suggesting the importance of evaluating a combination of food restriction *in utero* and a catch-up weight in infancy. Furthermore, even for

those who were born with low birthweights and did not have higher than average BMI in adult life, there was still an increased risk for high overall body fat content in adolescence and adulthood despite normal or low BMI (McMillen, Adam, & Mühlhäusler, 2005). Notably, low-birthweight individuals are at higher risk for reduced muscle mass and greater abdominal distribution of adipose tissue later in life, even in individuals with lower BMI in adulthood.

Low birthweight is also associated with numerous other physical and mental health outcomes, and it is possible that this relationship between catch-up weight in infancy and subsequent body measurement abnormalities later in life may, at least in part, mediate the relationship between prenatal food restriction and health outcomes later in life. In other words, prenatal food restriction may set the stage for higher risk of low-birthweight infants, in turn putting these infants at higher risk for abnormally high rates of weight gain during the first four months of life; this catch-up weight may further set the child on a trajectory for abnormal body measurements and fat distribution, which could put them at greater risk for a range of health problems as their lives progress.

One major health concern for low body measurements at birth is an increased risk for coronary events as adults. Barker et al. (2005) studied coronary events in 2003 people born in Helsinki from 1934 to 1994. They found that low birthweight newborns who experience a period of rapid weight gain postnatally had BMIs that rose progressively faster than BMIs of non-exposed children, culminating in BMIs that reached or exceeded average BMIs at 11 years of age. These findings were stronger for girls than for boys but remained evident regardless of sex. Further, small birth size and high BMI at age 11 were associated with greater risk for coronary events in adulthood among both men and women. These findings are relevant to the current study, as coronary events in adulthood are linked to both prenatal and postnatal growth. Further,

Barker et al. (2005) controlled for socioeconomic status (SES) in adulthood and found that the effects of body size at birth and at 11 years on adult coronary events were independent of SES at adulthood. The development of insulin resistance is also associated with low birthweight and increased BMI at 11 years of age (Barker et al, 2005). Insulin resistance, which can be measured by raised fasting plasma insulin and proinsulin concentrations, is also a risk factor for coronary heart disease.

The pattern of rapid growth following low birthweight may be linked with the development of insulin resistance, which in turn is associated with an increased risk for coronary heart disease later in life. Therefore, it is worthwhile to evaluate the relationship between low birthweight/size initiated by fetal undernutrition, such that a lack of caloric intake and micronutrients *in utero* can start a cascade of adverse health events including coronary heart disease (Harding, 2001). It has been speculated that when a fetus is not receiving the nutrients it needs, it may develop "thrifty" metabolic settings to maximize on the nutrients available, and these alterations in metabolism may result in tissues that are resistant to insulin effects (Phillips, 1996). Furthermore, it is alarming to know that infants who are underweight or short at birth are more likely to have a deficiency in muscle tone because this problem will likely continue as the child ages, as most cell replication in muscle occurs prenatally (Barker et al, 2005). Rapid weight gain in these infants could lead to disproportionately high fat mass compared with muscle mass, potentially underlying the relationship between rapid growth in infancy and insulin resistance, which could in turn be a factor in the increased risk for coronary disease in adulthood.

Body measurements at birth, including weight, length, body proportions, and placental weight are not only risk factors for coronary disease, but have also been linked to hypertension, glucose intolerance, diabetes, and hyperlipidemia in adulthood (Harding, 2001). Similar to the

animal findings discussed earlier in this review, it is likely that fetal programming plays a significant role in this trajectory in humans. Critical periods occur during gestation and in infancy, during which adverse events (caloric deficiency during gestation and a catch-up weight in infancy) can result in long-term alterations of the individual.

Research indicates that restricted caloric intake during pregnancy is also responsible for a host of other negative physical health outcomes. One such adverse outcome is associated with lipid profiles in offspring of mothers consuming calorie-restricted diets during pregnancy Lumey et al. (2009) found that famine exposure during any trimester was linked to increased levels of total cholesterol and triglycerides in female offspring in adulthood. Further, prenatal food restriction has also been associated with increased ratios of low-density to high-density lipoproteins (LDL/HDL ratios) in adult offspring, such that LDL was higher, and HDL was lower at 50 years of age (Roseboom et al,, 2000). Relatedly, restricted caloric intake during pregnancy may also be associated with differences in blood pressure in adult offspring, though these findings are mixed. Famine researchers examining men and women exposed to prenatal famine found no significant relationship with blood pressure at age 50 (Roseboom et al., 1999).

The relationship between prenatal food restriction and cardiovascular outcomes is also unclear, as findings vary among available studies on this association. Painter et al., (2006) found that exposure to famine during early gestation was only marginally associated with increased risk of coronary artery disease by age 58. Stanner et al., (1997) also did not find a significant relationship. In contrast, Painter et al., (2007) found a significant relationship between prenatal famine exposure and intima media thickness of the carotid artery, a measure of coronary artery disease risk.

There is also a documented relationship between *in utero* exposure to food restriction and metabolic syndrome (Lumey, Stein, & Susser, 2011). Metabolic syndrome is a cluster of risk factors for diabetes mellitus (DM) and cardiovascular disease that often co-occur, such as large waist circumference, elevated blood pressure, high blood glucose levels, or abnormal blood lipids (Alberti et al, 2009). In famine research, however, these results have not been consistent, such that some researchers have found a significant relationship, while others find that criteria for metabolic syndrome is not fully met in affected offspring.

Importantly, it is not only the deficit in caloric intake that could lead to suboptimal development; the quality of nutrients in available food may also be an important factor. The number of micronutrients consumed may also need to be considered when understanding the relationship between food deficiency and adult cardiovascular problems, mediating through larger BMI and obesity in childhood. Prenatal zinc deficiency (defined as serum zinc concentration below 13 μmol/L), for example, is associated with increased risk for pregnancy complications, labor activities disorders, hypogalactia, and decreased zinc concentrations in breast milk (Scheplyagina, 2005). Further, decreased zinc concentrations in umbilical blood is associated with decreased body height and body mass of offspring; umbilical blood serum zinc concentrations below 13 μmol/L are associated with a reduced rate of liner growth and a delay in psycho-motor development in children in the first year of life. Most alarming, decreased umbilical blood serum zinc concentrations are significantly associated with child morbidity at birth and in the first year of life.

Chronic lung diseases, including emphysema, asthma, and chronic bronchitis have also been linked to prenatal famine exposure. Lopuhaa et al., (2000) found an increased risk of these chronic lung diseases was observed in adults at 50 years of age who were exposed to prenatal

famine during mid-gestation. In this sample, 18% of midgestation famine-exposed adults reported a chronic lung condition, which was significantly different from controls. However, no significant differences in clinical markers for allergic and respiratory function (i.e., IgE markers concentrations) or lung function tests were observed between affected participants and controls.

Research on overall mortality rates in those exposed to prenatal famine provides mixed results. Famine research in the Netherlands and in Finland has not yielded significant differences between life expectancies of prenatally famine-exposed adults and controls (Lumey, Stein, & Susser, 2011; Painter et al., 2005; Kannisto, Christensen, & Vaupel, 1997). However, famine research in Bangladesh and Gambia have yielded different results. Moore et al (2004) found that children exposed to prenatal famine in Bangladesh had a significantly increased risk of mortality at 1 year of age; this increased mortality risk ceased to be significant after 15 years of age. However, Moore et al. (1997) found that prenatal famine-exposed mortality rates continued to increase after 15 years of age in rural Gambia. It is possible that these differences between the Netherlands and Bangladesh and Gambia may be partly explained by access to high quality medical care or the duration of the famine that individuals endured.

Physical health issues are not the only adverse health outcomes associated with malnutrition *in utero*. Physical health and mental health problems often go hand-in-hand. Considering what we know about fetal programming and the potential for stressful events during pregnancy (e.g., malnutrition) to negatively affect human development and contribute to abnormalities in adulthood, it is reasonable to hypothesize that individuals exposed to prenatal malnutrition may be at elevated risk for mental health problems as well. Indeed, research suggests there is an elevated risk for psychiatric disorders, neurodevelopmental abnormalities, and cognitive deficits in exposed populations.

Psychiatric Disorders in Offspring

Various psychiatric disorders in adulthood have been associated with malnutrition *in utero*, including affective psychosis, unipolar depression, bipolar disorder, and neurotic depression (Brown, Susser, Lin, Neugebauer, & Gorman, 1995; Brown, van Os, Driessens, Hoek, & Susser, 2000). Affective psychosis, which was a diagnosis in the DSM III, is characterized by a severe disturbance of mood and at least one psychotic symptom (i.e., delusions) (APA 1980). Bipolar disorder is a mood disorder characterized by alternating periods of depressive and manic behaviors (APA, 2013). In contrast, unipolar depression only consists of depressive symptoms, without any manic episodes during the course of illness. Neurotic depression, which is an ICD-9 criterion (WHO, 1998), is characterized by depression linked to a disturbing experience that is a disproportionate response to the situation. In a study exploring affective disorders in adults exposed to the Dutch famine, second trimester exposure was associated with a significantly greater risk (broad: RR (95% confidence interval) = broad: 2.26 (1.43, 3.57), p=.07; restricted: 2.40 (1.49, 3.89), p=.03) (of developing affective psychosis in adulthood in males, but not females (Brown & Susser, 1995). The authors also explored the relationship between neurotic depression and *in utero* famine exposure but did not find a significant association.

In a subsequent study, third trimester exposure was found to significantly increase the risk (RR=1.50, 95% CI= 1.05-2.02, p=.02) of developing a major affective disorder requiring hospitalization in adulthood for both men and women (Brown et al., 2000). Second trimester exposure remained significant for men, although it was only marginally associated with this risk for women. For unipolar depression specifically, there was a significantly increased risk for both second (RR=1.54, 95% CI= 1.12-2.13, p=.01) and third trimester exposure (RR=1.45, 95%

CI=1.07=1.97, p=.02). Bipolar depression was only marginally associated with second trimester exposure (RR=1.39, 95% CI= 0.94-2.06, p=.08) for both men and women. In sum, the literature shows that the second trimester appears to be the most critical time for affective disorders, and that males may be more vulnerable to the harmful effects of maternal malnutrition during this period than females.

Psychotic disorders such as schizophrenia have also been examined in cohorts exposed to the famines. Schizophrenia is a psychotic disorder characterized by disorganized thoughts and behaviors, delusions, hallucinations, and negative symptoms (APA, 2013). Susser, Neugebauer, Hoek, Brown, Lin, Labovitz, and Gorman (1996) examined the frequency of hospitalized patients who met criteria for schizophrenia in adulthood in a cohort exposed to the Dutch famine. For those exposed during the first trimester of pregnancy (born October 15-December 31), there was a two-fold increased risk (RR = 2.0, 95% CI = 1.2-3.4, P<.01) (for developing schizophrenia in adulthood. This finding was significant for both men and women.

Risk for adult onset of schizophrenia was also assessed in cohorts exposed to the Chinese famine (St. Clair et al., 2005). However, the authors were not able to report specific trimester effects. In line with the previous Dutch famine study, there was a two-fold increased risk for developing schizophrenia for those born in 1960 (RR=2.30, 95% CI= 1.99-2.65, p<.001) and 1961 (RR=1.93, 95% CI= 1.68-2.23, p<.001) at the height of the Chinese famine.

Of note, a follow-up study on schizophrenia risk and the Chinese famine did find some important differences between the Dutch famine and the Chinese famine in terms of schizophrenia risk (Xu, Sun, Liu, Feng, Yu, Yang, & He, 2009). Patterns in rural settings of the Chinese 1960-1961 cohort were most similar to findings from the Dutch cohort, such that being conceived during the height of the famine increased the risk for schizophrenia when compared

with pre-and-post famine cohorts. In contrast, surprisingly, this pattern was not observed in urban settings: the post-famine cohort in rural settings (RR=2.25, 95% CI= 1.48-1.92, p<.001) had the highest risk of developing schizophrenia when compared with the pre-famine and famine cohort in urban settings (RR=1.12, 95% CI= 0.93-1.36, p=.239). Furthermore, there was no significant difference between the pre-famine and famine cohort in the risk for developing schizophrenia in rural settings. The authors hypothesized that the higher mortality rate in rural areas throughout the history (including pre, during and post-famine periods), compared to that in urban setting, may explain these results. Those findings suggest that the effect of population selection in the famine cohort may have led to the survival of only those least susceptible and most resilient to disease.

Schizophrenia spectrum personality disorders may also be associated with prenatal famine. Susser et al., (1996) found a twofold increased risk of developing a schizophrenia spectrum personality disorder among 18-year-old males exposed to -famine in utero, relative to unexposed counterparts (RR=2.7, 95% CI= 1.5-5.1, p=.009) Antisocial personality disorder (ASPD), a disorder characterized by a pattern of disregard for and violations of the rights of others, manifested through repeated illegal acts, dishonesty, aggressiveness, and a lack of remorse (APA, 2013), was also assessed as a potential risk following famine exposure (Neugebauer, Hoek, & Susser, 1999). Similar to the previous study, the study cohort was comprised of 18-year-old men born during the Dutch famine. Men who were exposed to peak famine during their first and/or second trimester had a significantly higher risk for developing ASPD by the age of 18 than controls who were exposed later in gestation (RR=2.5, 95% CI=1.5-4.2, p=.02). When comparing first trimester exposure, second trimester exposure, and a combination of first and second trimester exposure, there is no significant difference between

their increased risks of developing ASPD, providing consistent evidence that there was a trimester specific association with an increased risk for personality disorders. One can infer, then, that exposure during early and middle pregnancy may induce a magnified risk for the development of ASPD as compared to late pregnancy exposure.

Disordered Eating in Mothers: Effects on Offspring

It is reasonable to infer that food restriction during pregnancy in the absence of famine would be associated with similar adverse outcomes in offspring exposed to prenatal famine. One such scenario in which food restriction would persist despite highly available food resources is restricted-disordered eating, a pattern observed in Anorexia Nervosa. Anorexia Nervosa (AN) is an eating and feeding disorder characterized by caloric restriction resulting in low body weight, intense fear of gaining weight or becoming fat, disturbance in accurately assessing one's body weight/size, undue influence of body weight/shape on self-evaluation, and persistent lack of recognition of the seriousness of one's low body weight (American Psychiatric Association, 2013). AN during pregnancy could result in restricted caloric and micronutrient intake, likely setting up a trajectory for outcomes in their growing offspring similar to those observed in famine research. Indeed, a range of adverse outcomes for offspring of mothers with AN and related eating disorders have been observed. Pregnant mothers with AN are more likely to give birth to offspring prematurely (Solid et al, 2004). Even for full-term deliveries, there is a significantly increased risk of lower birthweight, smaller head circumference, microcephaly, and small for gestational age (SGA) at birth for offspring of AN mothers compared with women without AN (Kouba et al, 2005).

In addition to body measurement abnormalities at birth, other adverse health outcomes studied in famine research have also been observed in offspring of mothers with disordered eating. Popvic et al. (2018) found that offspring of mothers with eating disorders, including AN, were at an increased risk of developing wheezing symptoms during infancy; specifically, this increase in wheezing was observed between 6 and 18 months of age. The study controlled for comorbid depression and anxiety and found that this pattern was present independent of depression and anxiety in mothers. The authors state that these wheezing symptoms suggest that the children whose mothers had AN during pregnancy may develop long-term respiratory health problems as they age.

It is possible that the adverse health outcomes observed in offspring of AN mothers may be partly explained by abnormalities in offspring umbilical cord blood DNA methylation (Kazmi et al., 2017). Maternal nutrition during pregnancy can influence epigenetic modifications in humans. Specifically, restricted intake of micronutrients and protein during pregnancy is associated with lower global methylation levels and hypomethylation. Kazmi et al. (2017) found altered DNA methylation in loci relevant to metabolism in offspring. As umbilical cord blood methylation is a potential early biomarker for altered neurodevelopmental trajectory in offspring, it is possible that the abnormalities observed in umbilical cord blood DNA methylation in offspring of AN mothers may be biomarkers of disrupted metabolic pathways. The authors identified differences in differentially methylated CpGs between offspring of mothers with AN and without AN during pregnancy. Specifically, *DHCR24*, a gene associated with lipid synthesis and responsive to estrogen, was found to be abnormal in offspring of mothers with AN during pregnancy. The expression of *DHCR24* is associated with fetal programming, and hepatic transcription of this gene has been found to be differentially induced by maternal undernutrition

and low protein in rats (Ellis et al, 2014). In humans, the expression of *DHCR24* has been associated with more optimal fetal growth (Kazmi et al, 2017). These biological findings may help to explain the developmental effects of maternal AN during pregnancy on offspring, as well as the specific risk pathways associated with intergenerational risks of AN.

Mental Health Outcomes in Children

In addition to physical health outcomes, adverse neurobehavioral and cognitive outcomes have also been observed in children of mothers with AN (Kothari, Barona, Treasure,& Micali, 2015). Children of mothers with eating disorders, including AN, are more likely to have difficulties in social understanding, visuo-motor functioning, and some domains of executive functioning. Further, overall intelligence scores in children whose mothers had eating disorders are lower than non-exposed children. In a recent study, these neurobehavioral outcomes were studied in newborns and infants of mothers with and without eating disorder (Barona et al., 2017). The infants of mothers with eating disorders displayed poorer language and motor development than infants of mothers without it. Of note, comorbid maternal anxiety disorders explain some, but not all, of this effect.

There is limited available research on psychopathology outcomes in offspring of AN mothers. However, Micali et al., (2014) conducted a retrospective study on a cohort of children exposed to mothers with AN and bulimia nervosa (BN) during pregnancy, revealing valuable insights into the potential mental health trajectories in these children. They found that children of women with eating disorders were more likely to have psychological problems, particularly in emotional, conduct, and hyperactivity domains than children of women without the disorders at age 3.5. Strikingly, there was a twofold increase in risk for any psychological problem in

children born to mothers with AN (OR=1.8, 95% CI=1.8-2.5,p<.01). The study also found sex differences in outcomes, such that prenatal AN exposed girls had a two and a half-fold higher risk of having two or more comorbid psychological problems (OR = 2.6, 95% CI=1.2–4.6, p = .02).For boys, there was a twofold risk of emotional problems (OR=2.0, 95% CI=1.2-3.4, p<.01), but no significant differences in conduct or hyperactivity problems. These results should be interpreted with caution, however, as many of the AN mothers in this study also had comorbid mood and anxiety disorders and effects of those disorders were not controlled for. It should be noted that mothers with depression and anxiety during the third trimester of pregnancy are more likely to give birth to children with psychological problems, and maternal mood/anxiety disorders are associated with an additive effect with maternal eating disorders on the psychological effects in offspring (Micali, Simonoff, & Treasure, 2011). There was a significant direct effect of AN on psychological outcomes for emotional problems (OR=1.4, 95% CI=1.2-1.6, p<.005), conduct problems (OR=1.6, 95% CI= 1.4-1.9, p<.005) and hyperactivity (OR=1.4 95% CI=1.2-1.6, p<.005), however the effect sizes were notably smaller.

Conclusion

Understanding the pathways of risk associated with disorder eating in mothers and prenatal undernutrition on the overall health trajectory of exposed offspring is imperative for implementing evidence-based preventative measures in pregnant women and their offspring. Further, there is evidence of intergenerational effects of prenatal food restriction, suggesting that the cycle of adverse health outcomes does not end with the first generation of offspring, but rather continues on to subsequent generations. A wealth of famine literature suggests that malnutrition in one's grandparent may affect body measurements and growth patterns in the individual (Lumey et al.,

2011). For example, women exposed prenatally to the Dutch famine in the first or second trimester were more likely to have offspring of their own with low birthweight. Further, prenatal famine-exposed women in the Netherlands were more likely to give birth to children with reduced length. Findings in China were different however, such that offspring of famine-exposed women were more likely to be heavier at birth; this finding may be due to selective fertility of larger mothers during the time of famine, however (Huang et al., 2010). While famine itself is relatively rare in developed nations, as stated earlier, eating disorders have become increasingly common in recent decades and can mimic the starvation associated with famine (Guisinger, 2003). Women with a history of disordered eating or body image disturbances are particularly vulnerable to restricted calorie diets while pregnant, which may in turn have negative consequences for the fetus.

This trend in disordered eating in the modern society had one of the gravest implications among pregnant women. Pregnant women are recommended to gain weight during pregnancy in order to facilitate optimal growth and development of the fetus. The recommended weight gain varies depending on the BMI of the mother, typically ranging from 11 to 40 pounds over the course of pregnancy. Despite these recommendations, some women restrict their caloric intake while pregnant, which can lead to suboptimal weight gain of the mother. In one large scale study (n= 1643), 23% of women gained less weight than was recommended to them by health professionals (Cogswell, Scanlon, Fein, & Schieve, 1999). In recent years, increasing attention has been drawn to the dieting behaviors among pregnant mothers who are concerned about their body image or are fearful of weight gain. In some cultures, including Western culture, the “ideal” body size for women is smaller than it has been in the past, leading to additional pressure for women to control their weight gain during pregnancy. Furthermore, unrealistic expectations for remaining fit while pregnant and the pressure to quickly bounce back to pre-pregnancy weight

after birth have been perpetuated by popular culture. When mothers-to-be are asked about their fears, it is common for them to express concerns about no longer being attractive to their partners due to weight gain (Wiles, 1994). Negative body image is an increasingly salient concern for pregnant mothers, which may contribute to insufficient nutritional intake.

Not all mothers who restrict calories, have body image distortion, or have fears of gaining weight will meet criteria for an eating disorder. The limited research available on disordered eating behaviors in pregnant mothers focuses on diagnosed eating disorders, including AN. However, to our knowledge, no study has examined *subclinical* restrictive eating disorders in pregnant mothers and outcomes in offspring. It is important that this population be studied, as many pregnant women experience some AN symptoms, and might not be considered clinically when they do not meet criteria for the disorder. Given what we know about malnutrition during pregnancy and long-term outcomes for offspring, it is possible that subclinical disordered eating behaviors can have a lasting negative impact on offspring despite those behaviors not meeting DSM criteria for an eating disorder. The current study aims to investigate this potential risk in pregnant mothers who exhibit some eating disorders symptomology on suboptimal child behaviors and clinical symptoms.

Hypotheses

The following three hypotheses will be tested:

1) *In utero* exposure to food restriction and body image distortion (FRBID) will be associated with early indicators of psychopathology at 48, 60, and 72 months of age.
2) *In utero* exposure to FRBID will be associated with a) decreased body measurements (birthweight percentile and small for gestational age) at birth, and b) elevated BMI percentiles in early childhood at 48, 60, and 72 months of age compared with non-exposed controls.
3) Weight percentile change between birth and 48, 60, and 72 months of age will mediate the relationship between FRBID and early indicators of psychopathology and BMI percentiles.

Methods

Participants

Data were obtained for 204 females. Thirty percent (n=63) reported some level of food restriction and body image distortion (FRBID) during pregnancy, whereas 69.6% (n=142) denied any FRBID. Participants were recruited from the prenatal obstetrics and gynecological (OB/GYN) clinics at Mount Sinai Medical Center and New York-Presbyterian/Queens in New York City during their second trimester of pregnancy. These mother-child dyads were followed throughout pregnancy and have subsequently participated in yearly follow-up assessments. Exclusion criteria for participation included HIV infection, maternal psychosis, maternal age < 15 years, life-threatening maternal medical complications, and congenital or chromosomal abnormalities in the fetus. A detailed description of the study can be found elsewhere (Finik and Nomura, 2017). Demographic information, including maternal education, marital status, race, and age was reported by participants during the second trimester and updated during yearly visits. All participants gave written consent according to the protocol approved by the Institutional Review Boards at the City University of New York, New York-Presbyterian/Queens, and the Icahn School of Medicine at Mount Sinai.

Materials

Food Restriction Questionnaire

The Food Restriction Questionnaire (FRQ) is an 8-item measure created by the author to specifically assess AN symptoms during pregnancy. The measure primarily assesses restricted eating behaviors during pregnancy. The FRQ also assesses body image distortion and fear of

gaining weight during pregnancy. Sample questions include: “During your pregnancy, did you ever purposely restrict how much food you ate? For example, did you ever limit calories, go on a diet, or not eat when you felt hungry?”, “During your pregnancy, did you ever intensely fear gaining weight or becoming fat?”, “During your pregnancy, did your body weight or shape significantly influence how you felt about yourself?”, and “From the time of conception until the peak of your pregnancy (right before your baby was born) approximately how much weight did you gain?”. The FRQ is administered yearly for each participating mother by trained research assistants. Factor Analyses revealed that the FRQ has an overall reliability of .72 and contains 2 factors: Dieting Behaviors” (alpha=.88) and Body Image Distortion (alpha=.65). Of the 205 mothers in our sample, 63 (30.7%) endorsed at least one FRQ item.

Behavior Assessment System for Children–Second Edition (BASC-2): Parent Rating Scales–Preschool

The Behavior Assessment System for Children–Second Edition (BASC-2) is 4-point Likert-type rating scale comprised of 134 items assessing parental report of child psychosocial competence (Reynolds & Kamphaus, 2004). The measure consists of 5 composite scales: Adaptive Skills, Behavioral Symptoms Index, Externalizing Problems, Internalizing Problems, and School Problems. Internal consistency has been demonstrated to have coefficient alpha reliabilities in the .90s for the composite scales, and coefficient alpha reliabilities in the .80s for individual scales. The test-retest reliabilities were in the .80s for composite scores and in the .70s and .80s for individual scales. Median inter-rater reliabilities for composite scores and individual scales were in the .70s. To assess validity, the BASC-2 was compared to other child behavioral measures; overall, the BASC-2 correlated highly with these scales, ranging from .70 to .90. The

BASC-2 was administered to mothers yearly in a paper-and-pencil format. Individual items included behaviors such as “shares toys or possessions with other children”, “acts without thinking”, and “is sad”, with 4-point Likert-type response options (*Never, Sometimes, Often*, or *Almost Always*). It will produce 8 dimensions of behaviors, including hyperactivity, aggression, anxiety, depression, withdrawn behaviors, somatization, atypical behaviors, and attention problems. The scores were standardized with the score of 50 to be a norm with a standard deviation of 10. The scores greater than 60 were considered as “at-risk” and those greater than 70 as “clinically significant”. We used the cut-off point of 60 to create dichotomous measures of 8 clinical scores that were used as our secondary measures.

Height and Weight

The child’s height (cm) and weight (kg) are physically measured by a trained research assistant each year.

Procedure

The independent variables in this study include maternal food restriction during pregnancy and maternal body image distortion. Maternal food restriction and body image distortion during pregnancy were assessed retrospectively with the Food Restriction Questionnaire (FRQ) with mothers. Participants endorsing symptoms in the FRQ were divided into dichotomous groups of FRBID+ and FRBID-, such that FRBID+ participants endorsed at least one FRBID symptom. A potential mediate in this study is weight percentile change, which is assessed by the change of weight percentile from birth to 48 months, birth to 60 months, and birth to 72 months.

The dependent variables in this study include 1) child's height/weight/ BMI percentile at birth and follow-up, 2) early indicators of child psychopathology. As described earlier, child psychopathology will be assessed by the BASC at 48, 60, and 72 months; endorsement of symptoms on 8 individual subscales (hyperactivity, aggression, anxiety, depression, atypicality, withdrawal, somatization, attention problems), as well as 2 composite measures (externalizing problems, and internalizing problems) will be assessed in both dichotomous and continuous analyses.

Potential Confounders

Child's sex, maternal education, race, maternal psychosocial stress during pregnancy, and other psychopathology such as mood disorders, anxiety disorders, and psychotic disorders during pregnancy are potential confounders in this study. Mothers' Depression and anxiety are a priori determined as potential confounders as they are associated with both our predictors and outcomes.

Statistical Analyses

Data were entered and analyzed using SPSS version 26. Descriptive statistics included calculating percentages for categorical variables and means and standard deviations for continuous variables. Between-group differences were examined using Chi-squares and logistical regression for categorical variables and with general linear models for continuous variables. Mediation analyses were conducted using Model 4 from the PROCESS macro for SPSS (Hayes, 2017). The indirect effect (a*b) was tested using bootstrapping procedures. Unstandardized indirect effects were computed for 10,000 bootstrapped samples and 95% confidence interval were computed by determining the indirect effects at the 2.5th and 97.5th percentiles.

Results

Sociodemographic Characteristics

Data were obtained for 204 females. Thirty percent (n=63) reported some level of food restriction and body image distortion (FRBID) during pregnancy, whereas 69.6% (n=142) denied any FRBID. Overall, the sample was comprised mostly of individuals who were Hispanic (44.6%), between 22 and 30 years of age (54.9%) and married (50.5%). Table 1 provides further details about sample characteristics. Although a statistical trend (p=.063) was observed for differences in education level, no significant differences between women with and without a history of FRBID were observed in demographic characteristics between (Table 1).

FRBID Exposure and BASC Outcomes

To examine associations between in-utero exposure to subclinical AN (FRBID) and early indicators of psychopathology at 48, 60, and 72 months of age, child behavioral problems as measured by BASC-2 (Reynolds & Kamphaus, 2004) scores were examined using logistic regression and multivariate general linear modelling. The first approach used multivariate general linear modelling to examine BASC *T*-scores on a continuous basis. In both approaches, unadjusted and adjusted analyses controlling for demographic variables (i.e., maternal age, race, marital status, and education as well as child biological sex) were conducted. Separate models were performed for BASC *T*-scores at 48, 60, and 72 months. The second approach involved logistic regression with BASC scores dichotomized as either within normal limits (*T*-score between 40-60) or at-risk (*T*-score $\geq$ 60).

Child Behaviors

Dimensional child behavior outcomes were examined by the FRBID status. At 48 months (Table 5), FRBID youth had significantly higher BASC scores compared to non-FRBID youth for depression ($F(1,158)=3.76$, $p=.054$) and somatization ($F(1,158)=3.74$, $p=.055$). Similarly, youth with mothers with a history of FRBID had significantly higher scores for externalizing problems ($F(1,158)=4.88$, $p=.029$) and internalizing problems ($F(1,158)=5.65$, $p=.019$). Somewhat paradoxically, FRBID youth also had significantly higher scores on measures of adaptability ($F(1,158)=4.30$, $p=.040$).

At 60 months (Table 6), significant differences were also observed between FRBID and non-FRBID youth in mean scores on a number of BASC scales. After adjusting for demographics, FRBID youth had significantly higher scores on aggression ($F(1,192)=6.35$, $p=.029$), anxiety ($F(1,192)=4.80$, $p=.030$), and depression ($F(1,192)=9.655$, $p=.002$). In addition, these elevations resulted in significantly higher scores on the composite scales for externalizing problems ($F(1,192)=4.64$, $p=.032$) and internalizing problems ($F(1,192)=9.49$, $p=.002$). Significantly higher scores in somatization in unadjusted analyses ($p=.05$) were attenuated once demographic characteristics were controlled for, resulting in a statistical trend ($F(1,192)=3.50$, $p=.063$) for youth of mothers a history of FRBID having higher scores in somatization.

Finally, the same analyses examined differences in BASC scores at age 72 months. As can be seen in Table 7, no significant differences were observed in adjusted analyses. In unadjusted analyses, FRBID youth had significantly higher somatization scores, ($F(1,120)=3.76$, $p=.054$). However, once demographic variables were controlled for, the between-group differences were no longer statistically significant ($p=.14$).

Clinical Problems in Children Measured in Dichotomous BASC outcomes

As demonstrated in Table 2, in unadjusted analyses offspring of mothers with FRBID were three times more likely to score in the at-risk range at age 48 months for hyperactivity (OR=3.28, 95% CI=1.18-9.14) and twice as likely for somatization (OR=2.41, 95% CI=1.00-6.05). After adjusting for demographic characteristics, hyperactivity remained significant (OR=3.15, 95% CI=1.09-9.07). No other significant associations were observed after controlling for demographics between FRBID history and psychopathology at age 48 months, however weak statistical trends (p=.08) were observed for somatization and functional communication.

At age 60 months (Table 3), children with FRBID mothers were significantly more likely than non-FRBID children to be rated as at-risk for depression (OR=3.36, 95% CI=1.53-7.36) and internalizing problems (OR=2.71, 95% CI=1.26-5.85). No other significant associations were observed.

Table 4 shows results of logistic regression analyses at age 72 months. Results revealed FRBID-exposed offspring were significantly more likely to have clinically elevated scores for somatization (OR=2.89, 95% CI=1.01-8.24) and withdrawal (OR=3.87, 95% 1.14-13.19). In unadjusted analyses, FRBID youth were more likely to have at-risk scores for internalization problems (OR=2.52, 95% CI=1.04-6.13) and clinically significant deficits in adaptive skills (OR=0.21, 95% CI=0.05-0.98). However, adjusting for demographic characteristics attenuated these results, leading to statistical trends (p=.08) toward children of mothers with a history of FRBID being associated with lower adaptive skills and higher internalization problems.

FRBD Exposure and Body Measurement Outcomes

In-utero exposure to subclinical AN (FRBID) was not significantly associated with decreased body measurements at birth (i.e., birthweight percentile, classified as "small for gestational age") or elevated BMI percentiles in early childhood at 48, 60, and 72 months of age compared with non-exposed controls. As can be seen in Table 8, no differences were observed in body measurements in unadjusted analyses or after controlling for confounders. Similarly, there is no notable increase in the risk for gestational age at birth in unadjusted (OR=0.42, 95% CI=0.09-2.00, p=.26) or adjusted models (OR=1.90, 95% CI=0.38-9.43, p=.43).

Mediation Analysis

Building on the model that showed associations between FRBID on specific child behavior scores, we examined whether "weight percentile change" (i.e., defined as weight gain between birth and 48, 60 and 72 months) mediated the associations between FRBID and clinical child behavior (Figure 1).

No evidence was found to support that changes in weight mediated the relationship between FRBID and any clinical child behaviors. Specifically, at 48 months, no indirect effect was observed for depression (a*b= -0.03, 95% CI= -0.66, 0.52, adjusted a*b= -0.001, 95% CI = -0.73, 0.55, p=.701), somatization (a*b= 0.05, 95% CI= -0.47, 0.72, adjusted a*b= 0.005, 95% CI = -0.64, 0.52, p=.645), adaptability (a*b= -0.01, 95% CI= -0.52, 0.62, adjusted a*b= -0.006, 95% CI = -0.51, 0.74, p=.931), externalizing problems (a*b= 0.08, 95% CI= -0.60, 0.78, adjusted a*b= 0.02, 95% CI = -0.81, 0.59, p=.390), or internalizing problems (a*b= 0.06, 95% CI= -0.50, 0.77, adjusted a*b= 0.03, 95% CI = -0.84, 0.68, p=.549).

At 60 months no evidence of mediation was detected for aggression (a*b= 0.08, 95% CI= -0.37, 0.72, adjusted a*b= 0.08, 95% CI = -0.58, 0.78, p=.418), anxiety (a*b= 0.08, 95% CI= -0.57, 0.78, adjusted a*b= 0.02, 95% CI = -0.61, 0.87, p=.685), depression (a*b= 0.24, 95% CI= -0.36, 1.09, adjusted a*b= 0.15, 95% CI = -0.47, 0.88, p=.320), externalizing problems (a*b= 0.22, 95% CI= -0.30, 1.07, adjusted a*b= 0.10, 95% CI = -0.42, 0.79, p=.203)., or internalizing problems (a*b= 0.33, 95% CI= -0.43, 1.31, adjusted a*b= 0.23, 95% CI = -0.66, 1.18, p=.082). At 72 months, scores on somatization were not mediated by "catch-up weight," (a*b= -0.08, 95% CI= -0.77, 0.49, adjusted a*b= 0.01, 95% CI = -0.49, 0.57, p=.711).

Discussion

FRBID during pregnancy and clinical behaviors in children

This study examined the impact of food restriction and body image distortion (FRBID) in pregnant women on their offspring at birth, 48 months, 60 months, and 72 months. The first aim of determining whether FRBID-exposed children were more likely to be at risk for psychopathology yielded significant results. FRBID-exposed children were at an increased risk for a range of both internalized and externalized mental health symptoms at 48 months (depression, somatization, externalizing problems, internalizing problems) and 60 months (aggression, depression, anxiety, depression, externalizing problems, internalizing problems).

While no BASC scores were significant at 72 months for continuous BASC outcomes after controlling for confounders, unadjusted values were significant for somatization. Interestingly, FRBID-exposed children had higher adaptability T-scores than controls at 48 months. While this trend of greater adaptability T-scores for FRBID-exposed groups continued at 60 months and 72 months, it did not reach significance. BASC score findings differed slightly for analyses utilizing dichotomous at-risk BASC cut-offs, such that mental health symptoms were primarily externalized at 48 months (hyperactivity) and primarily internalized at 60 months (depression, internalizing problems) and 72 months (somatization, withdrawal). Dichotomous BASC outcomes also revealed poorer adaptive skills among FRBID-exposed groups compared with controls at 72 months, but this trend did not reach significance at 48 months or 60 months.

Upon further exploration, at 48 months T-score values for some internalized symptoms (depression, somatization, internalizing problems) were significantly more elevated for FRBID-exposed children but were at times just below the cut-off for the dichotomous “at-risk” value. A

similar phenomenon occurred at 60 months and 72 months, such that some externalized symptoms (aggression, externalizing problems) did not quite meet the "at-risk" cut-off for FRBID-exposed children but were still significantly elevated compared with controls.

These findings are largely consistent with previous literature on the relationship between restricted dietary intake during pregnancy and psychological outcomes for offspring. Importantly, Aim 1 of the current study draws numerous parallels to the Dutch and Chinese famines previously discussed in the introduction. For example, numerous studies utilizing Dutch famine data found a significant relationship between prenatal malnutrition and depression (Brown, Susser, Lin, Neugebauer, & Gorman, 1995; Brown, van Os, Driessens, Hoek, & Susser, 2000; Brown & Susser, 1995). Elevated BASC scores for internalized symptoms, including depression, may indicate early signs of clinical depression and other internalized disorders later in life (Catspi, Moffitt, Newman, & Silvia 1996; Rosellini, Liu, Anderson, Sbi, Tung, and Knyazhanskaya, 2020).

The current study's findings on externalizing symptoms including aggression, hyperactivity, and externalizing problems, may similarly draw parallels to Dutch Famine findings on the relationship between prenatal malnutrition and ASPD in adulthood (Neugebauer, Hoek, & Susser, 1999). Research suggests that aggression and hyperactivity in early childhood may predict conduct disorder is adolescence and ASPD in adulthood (Simonoff, Elander, Holmshaw, Pickles, Murray, & Rutter, 2004). Potential parallels to Dutch and Chinese famine study findings on the relationship between prenatal malnutrition and psychotic disorders are more difficult to link to the current study (Susser et al., 1996; St. Clair et. al, 2005; Xu et al., 2009). While early childhood symptoms can be difficult to link to adult-onset of psychotic disorders due to a broad range of potential prodromal symptoms, research suggests that

eccentric, odd, or atypical behaviors in childhood may play a role in predicting psychotic disorders later in life (Antshel, Shprintzen, Fremont, Higgins, Faraone, & Kates, 2010). While atypicality was marginally significant for higher BASC T-scores at 48 months, it was not significantly related to FRBID exposure at any other age group. Of note, there was a consistent but non-significant trend for all age groups in both continuous and dichotomous BASC outcomes that atypicality means were higher for FRBID-exposed groups. It is possible that the small sample size in this study paired with the relatively rare prevalence of atypicality in children compared with internalizing/externalizing disorders played a role in these non-significant findings.

The Aim 1 results of this study also replicate some of the findings of Micali et al., (2014), who found that children of women with eating disorders were more likely to have psychological problems in emotional, conduct, and hyperactivity domains. This connection between famine and disordered eating is an important one, as it highlights the similarity in risk that both can impose during pregnancy. While "emotional" and "conduct" domains specifically were not assessed in this study, some BASC variables provide similar symptom presentations. Depression and internalizing problems, both of which were significantly linked to prenatal FRBID exposure, draw parallels to the emotional domain. Similarly, our findings of increased aggression in FRBID-exposed children lends further support to the findings of Micalai et. al., (2014) that prenatal exposure to disordered eating during pregnancy increases the risk of developing conduct disorder symptoms later in life. Our study's findings on the increased risk of hyperactivity for FRBID-exposed children further replicate the findings of Micalai et. al., (2014).

FRBID during pregnancy and birthweight/ BMI percentiles for children

The second aim of determining whether birthweight and BMI percentiles were significantly impacted by FRBID exposure confirmed the null hypothesis. Neither birthweight nor BMI percentile at 48 months, 60 months, or 72 months were significantly related to FRBID exposure during pregnancy. Surprisingly, there was a consistent but non-significant trend of higher birthweight and higher BMI percentile for all age groups for FRBID-exposed groups compared with controls. The non-significant trend of higher BMI percentiles during childhood, however, are supported by famine literature. Ravelli, Meulen, Osmond,Barker, and Bleker (1999) found that women exposed to the Dutch Famine during early gestation had significantly higher BMIs than non-exposed women. Similarly, Dietz (1994) found that men exposed prenatally to the Dutch Famine during the first half of gestation were also more likely to be obese (body weight for height ≥120% according to an external standard) than non-exposed controls.

The findings on birthweight and birthweight percentile are not consistent with previous literature on prenatal famine exposure. Lumey (2002) and Stein et al. (2004) found that birthweights for prenatal famine-exposed infants were significantly lower than controls, which contrasts with the current study's results. However, famine literature researchers posited that shorter gestation periods for famine-exposed infants likely explained some of this effect. Of note, there were no significant differences in premature births between FRBID and non-FRBID exposed groups in the current study, which may account for some differences in results. Further, Stein et al. (2004) found that weight and body size differences were only observed in mothers with famine exposure during late gestation, rather than early or mid-gestation. The current study

did not account for timing of exposure to FRBID, and may have resulted in different findings if 3rd trimester FRBID exposure specifically was explored.

The current study's findings on body weight/size and prenatal FRBID exposure also differ from previous research on AN in pregnant mothers. Kouba et al. (2005) found that mothers who met criteria for AN were more likely to give birth to infants with lower birthweight, smaller body measurements, and small for gestational age (SGA). Crucially, the authors found that this effect remained even for full-term deliveries, and not just for pre-term infants. A key difference between the findings of Kouba et al. (2005) and the current study, however, is that no mothers in the FRBID+ group fully met DSM criteria for AN, and rather had subclinical symptoms. It is possible that the severity of AN symptoms necessary for an AN diagnosis may be a critical factor in whether or not infant birthweight and size is impacted.

Animal research on the relationship between body weight and size and food restriction during pregnancy also conflicts with this study's results. Numerous researchers have found that rodents exposed to caloric or micronutrient restriction *in utero* were born with lower body measurements (Langley-Evans, 1997; Langley-Evans et al., 1999; Bellinger, Lilley, Langley-Evans, 2004; Winick & Noble, 1996). These researchers also observed that rodent pups gained weight more rapidly than controls after birth. However, Winick and Noble (1966) found that rat pups exposed to food restriction had a period of rapid growth from birth to 14 days, and were significantly larger and heavier than controls between 14-19 days. The non-significant trend in the current study of higher BMI percentiles between 48 and 72 months at first may resemble a similar phenomenon, however, there is no evidence of more rapid growth between birth and 48 months for FRBID-exposed groups compared with controls suggesting a different mechanism in the current study than seen in animal models.

In post-hoc analyses, the author of the current study sought to explore whether there were differences in small for gestational age (SGA) infants (defined as the bottom 10th birthweight percentile) between FRBID- and FRBID+ groups, and no significant differences were found. Similar to other body measurement findings in the current study, however, a larger percentage of non-FRBID exposed infants met criteria for SGA (10.2%) than FRBID-exposed infants (4.6%), however, these differences were not significant.

Further analyses revealed that while FRBID overall was not significantly linked to birthweight, birthweight percentile, or SGA at birth. However, one factor of FRBID, being underweight during one's pregnancy, was significantly associated with all of these outcomes. Specifically, a subset of FRBID-exposed mothers who reported that their weight was lower than their doctor recommended during pregnancy gave birth to babies with significantly lower birthweights than controls ($p=.004$), more likely to give birth to babies with lower birthweight percentiles than controls ($p=.015$), and more likely to give birth to SGA babies ($p=.047$) than controls. These findings highlight a crucial difference between the FRBID group overall and previous experimental groups in famine research, AN research, and animal research. Many mothers in the current study who met criteria for the FRBID group were not considered underweight by their medical providers. That is, despite concerns about their body weight and shape and potential dieting behaviors, many women in the FRBID group met their doctors' expectations for weight gain. These findings suggest that fixation on body shape and diet alone may not necessarily impact birthweight and growth trajectories of offspring. Rather, the mothers' weight may need to be significantly lower than suggested by medical professionals in order to observe this effect.

Weight percentile change as a potential mediator between FRBID and BASC outcomes

The third aim of the current study was to determine whether weight percentile change from birth to childhood mediates the relationship between FRBID and BASC scores. Mediation analyses were conducted only for continuous BASC outcomes significantly associated with FRBID in previous analyses at 48, 60, and 72 months of age. None of the 11 mediation analyses showed a significant mediation effect of weight percentile change. Of note, a potential explanation for the lack of mediation effect for any of these 11 analyses may be due to missing data. 102 participants in our sample were not included in the mediation analyses because they were missing body measurement data at 48 months, 60 months, and/or 72 months. The impact that missing data may have had on our study will be further explored in the "Limitations" section of this discussion. We chose not to impute the missing values in the current study but it would be a consideration if we continue to evaluate the plausible mediating paths.

In order to further explore these insignificant results, analyses on the potential relationship between FRBID and the weight change variables as well as analyses on the potential relationship between the weight change variables and BASC outcomes were conducted. One-way ANOVAs did not reveal any significant relationships between FRBID and weight change variables or weight change variables and BASC. However, there was a consistent insignificant trend across age groups such that non-FRBID groups gained more weight than FRBID groups. At 72 months, these findings were marginally significant ($F(1,97)=2.00$, $p=.10$) such that FRBID groups BMI percentiles decreased by a mean of 8.39%ile from birth to 72 months, while non-FRBID groups BMI percentiles increased by a mean of 10.78 %ile from birth to 72 months. These findings, while inconsistent with famine literature, may shed light on the findings of AIM 2 in which there was a consistent but insignificant trend that birthweights and birthweight

percentiles were higher for FRBID groups. Perhaps these relatively higher birthweights and birthweight percentiles for FRBID groups contributed to their relatively lower rate of weight gain during childhood compared with non-FRBID controls.

Strengths and limitations

There are several strengths in this research. First, the current study is the prospective assessment of child neurobehavioral indices over time, such that participants were assessed during pregnancy, 48 months after birth, 60 months after birth, and 72 months after birth. Second, the sample utilized in this study is made up of an urban ethnic and financial minority population. This is in contrast with much of the previous literature on disordered eating during pregnancy for which participants were predominantly white women, many of whom were of higher socio-economic status (Cachelin, Rebeck, Veisel, & Striegel-Moore, 2001). Populations consisting of urban and ethnic minorities, particularly those who lower in SES, are at higher risk for both maternal and child psychological disorders. Cumulative exposure to discrimination, both in the mental health system and the broader society, likely drives much of this trend (Wallace, Nazroo, & Becares, 2016). Third, the study brought lights on detrimental effects of subclinical disordered eating on offspring by specifically targeting a subclinical population. To our knowledge, no other research on the impact of subclinical disordered eating on the mental health of offspring has been previously conducted. By focusing on women with symptoms of restrictive eating disorders who don't fully meet criteria for AN, we can prevent this population of women from "slipping through the cracks" in developmental research. Many women restrict their diets while pregnant, and it is important that they are represented in research on this topic. As presented in this research, even subclinical disordered eating in mothers during pregnancy can

have long-term consequences in their offspring in the early to middle childhood. This provides an important platform for clinicians to educate pregnant women on the impact their eating behaviors during pregnancy could have on their unborn children for years to come.

A limitation of the current study is the relatively small sample size. In contrast with some large-scale famine studies cited in this manuscript, the current study does not have access to nation-wide medical records and relies on local community members who are willing to participate in a research study with their young children. The COVID-19 pandemic further impacted the sample such that many scheduled follow-up visits were cancelled, and some participants moved away from the metro area or were otherwise "lost-to-follow". This led to missing data, which was a particular problem for the mediation analyses. Only cases that had data available for FRBID, body measurements at all four age groups, and BASC outcomes were included in the mediation analyses, which meant that 102 cases were excluded. In the mediation analyses, this missing data clearly impacted the outcomes as direct effects were no longer significant. It is possible that the outcomes of this study may have been more robust if this missing data were avoided.

Another limitation of the current study is the retrospective nature of the FRBID assessment. Mothers were asked a series of questions about their eating behaviors, body image, and weight gain during pregnancy, however, these questions were asked when the respective children were in early childhood via structured clinical interviews. Interviewers were trained to minimize the recall bias and provided key milestone events corresponding to the time of their pregnancy. Nevertheless, mothers needed to think back to the time of their pregnancy in order to complete the FRBID assessment. It is possible that errors or inaccuracies occurred due to this. Body measurements and BASC data for children, however, were obtained at the time of in-

person assessments at the current age of the child. While many covariates were consistently controlled for in the current study (race, age of mother at time of birth, education of mother, marital status of mother, sex of child), there were some variables that were not possible to control for. The mothers' birthweight, data about the father, and gene expression were not controlled for in the current study. Future research on this topic would benefit from investigating these potentially confounding factors.

Clinical Implications

Clinically, our findings can be of particular interest to medical professionals and pregnant women. There are a number of reasons why women may not be consuming an adequate number of calories during pregnancy, which could mimic the restricted caloric intake observed in famine research. Persistent nausea, dietary restrictions, and financial burden are some potential reasons for this. Body image disturbances related to pregnancy weight also contribute to dieting behaviors. Of note, among our participants, anxiety related to appearance and body change measured during pregnancy was a significant predictor for childhood problems. Eating disorders have become increasingly common in recent decades and can mimic the starvation associated with famine (Kueper, et al., 2015). Women with a history of disordered eating or body image disturbance may be particularly vulnerable to restricted calorie diets while pregnant, which may in turn have negative consequences for the fetus. Women should be screened for these risk factors and identified by OBGYNs and other medical professionals. It is important that women who are at risk for calorie restriction during pregnancy be educated about the potential consequences for their child. If necessary, both nutritional counseling and group psychotherapy should be made available to mothers so that adequate nutrition is obtained. In addition to

screening pregnant women, children of mothers with disordered eating and distorted body image could also be screened for early indicators of psychopathology. Specifically, symptoms of internalizing and externalizing symptoms in young children should be addressed, as famine research suggests that these problems may persist into adulthood.

Future Directions

Future research should take advantage of the strengths of both animal and human models. It will be extremely fruitful if translational research is conducted with a focus on animal models so that underlying mechanisms for increased risk of distinct mental disorders related to the distinct timing of exposure can be better understood through greater experimental control and manipulation. As previously discussed, ethical constraints do not allow us to conduct controlled experiments with food restriction in pregnant humans. By working with animals such as mice and rats, researchers can precisely control caloric and micronutrient intake. Furthermore, potentially confounding factors such as health problems in pregnant animals, ingestion of non-food substitutes, genetic predisposition for certain behaviors, and postnatal environmental factors can be controlled for. Moreover, animal research with rodents would allow us to observe potential effects across multiple generations, as the lifespan is much shorter for these animals (Li et al, 2016). It would be illuminating to learn what, if any, permanent genetic alterations are caused by prenatal malnutrition and passed on to subsequent generations.

Future human research on food restriction and body image distortion in pregnant women would benefit greatly from a larger sample size, which may shed light on the non-significant trend in the current study of higher birthweight and lower change in weight percentile in FRBID-exposed children. It would be helpful to have a routine assessments of diet related problems

among pregnant mothers while they were pregnant, which will lead to an ultimate prevention of neurobehavioral impairment in children. Further analyses of the different factors of FRBID would also be beneficial for understanding more specific risk factors for adverse behavioral outcomes in children. Perhaps certain elements of FRBID are impacting child development more than others. Understanding this more precisely would help clinicians and pregnant women assess the risk of adverse feeding behaviors and body image.

Conclusion

The current study sought to determine the impact of food restriction and body image distortion (FRBID) in pregnant mothers on the development of the growing child. Our sample consisted of 204 mothers, 63 of whom met the criteria for FRBID. At 48 months, 60 months, and 72 months of age, children with FRBID+ mothers were significantly more likely to develop symptoms of internalizing and externalizing disorders. The current study did not find evidence of significant differences in birthweight, birthweight percentile, or BMI percentile at 48 months, 60 months, or 72 months between FRBID+ and FRBID- groups. There is also no evidence of a mediation effect of weight percentile changes between FRBID exposure and significant BASC outcomes.

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Table 1
Sociodemographic characteristics

Characteristic	Total Sample (N=205) *n* (%)	FRBID No (N=142) *n* (%)	FRBID Yes (N=63) *n* (%)	Statistic(df)	*P value*
Race				$X^2(4)=8.05$	.090
White	44 (21.6%)	27 (19.0%)	17 (24.4%)		
Black	35 (17.2%)	31 (21.8%)	4 (6.5%)		
Hispanic	91 (44.6%)	62 (43.7%)	29 (46.8%)		
Asian-American	21 (10.3%)	13 (9.2%)	8 (12.9%)		
Other	13 (6.4%)	9 (6.3%)	4 (6.5%)		
Age, years				$X^2(4)=8.05$	.090
Under 18	8 (3.9%)	7 (4.9%)	1 (1.6%)		
18-21	34 (16.7%)	26 (18.3%)	8 (12.9%)		
22-30	112 (54.9%)	79 (55.6%)	33 (53.2%)		
31-40	37 (18.1%)	25 (17.6%)	12 (19.4%)		
41-50	13 (6.4%)	5 (3.5%)	8 (12.9%)		
Education				$X^2(6)=11.96$	.063
Primary	6 (2.9%)	4 (2.8%)	2 (3.2%)		
Some H.S.	19 (9.3%)	16 (11.3%)	3 (4.8%)		
High school or GED	38 (18.6%)	31 (21.8%)	7 (11.3%)		
Some College	49 (24.0%)	27 (19.0%)	22 (35.5%)		
Associates	18 (8.8%)	12 (8.5%)	6 (9.7%)		
Bachelors	40 (19.6%)	25 (17.6%)	15 (24.2%)		
Graduate	34 (16.7%)	27 (19.0%)	7 (11.3%)		
Marital Status				$X^2(3)=4.39$	.222
Married	103 (50.5%)	69 (48.6%)	34 (54.8%)		
Common Law	9 (4.4%)	5 (3.5%)	4 (6.5%)		
Single	89 (43.6%)	67 (47.2%)	22 (35.5%)		
Divorced/Sep.	3 (1.5%)	1 (0.7%)	2 (3.2%)		
Child Sex				$X^2(1)=0.53$	.466
Male	100 (49.0%)	72 (50.7%)	28 (45.2%)		
Female	104 (51.0%)	70 (49.3%)	34 (54.8%)		

Table 1a
Principal component analysis and internal consistency of Food Restriction and Body Image Distortion (FRBID)

	Component			
FRBID item	1	2	3	Total
Dieting Behaviors				
Food restriction	**0.92**	-0.19	0.17	
Frequency of food restriction	**0.81**	-0.28	0.25	
Restricted weight gain by a MD's recommendation	**0.84**	-0.18	0.11	
Food restriction related to concerns about gaining weight	**0.71**	0.30	-0.34	
Restricting food led to a positive consequence	**0.78**	-0.10	0.09	
Body Image Distortion				
Intense fear of gaining weight	0.15	**0.65**	-0.21	
Felt the body shape too big or too fat	0.02	**0.77**	0.42	
Body weight influenced how participant felt	0.15	**0.74**	0.40	
Dieting Because of Negative Body Image				
Negative body image related to food restriction	0.49	0.38	**-0.65**	
Cronbach's coefficient alpha	0.88	0.65	NA	0.73

NA= not applicable due to a single item forming the third factor.

Table 2
Odds of at-risk BASC scores at age 48 months

BASC scales	FRBID No (N=142) n (%)	FRBID Yes (N=63) n (%)	Odds Ratio (95% CI) Unadjusted	*P value*	Adjusted	*P value*
Hyperactivity	8 (7.1%)	9 (20.0%)	3.28 (1.18-9.14)	**.02**	3.15 (1.09-9.07)	**.03**
Aggression	8 (7.1%)	4 (8.9%)	1.28 (0.37-4.49)	.70	1.20 (0.33-4.40)	.78
Anxiety	22 (19.5%)	12 (26.7%)	1.50 (0.67-3.38)	.32	1.50 (0.65-3.47)	.35
Depression	12 (10.6%	9 (20.0%)	2.10 (0.89-5.41)	.12	2.1 (0.79-5.57)	.14
Somatization	12 (10.6%)	10 (22.2%)	2.41 (1.00-6.05)	.**05**	2.27 (0.87-5.90)	**.**08
Atypicality	26 (23.0%)	11 (24.4%)	1.08 (0.48-2.43)	.85	1.15 (0.60-2.65)	.74
Withdrawal	12 (12.4%)	6 (13.3%)	1.09 (0.39-3.03)	.87	1.12 (0.38-3.27)	.84
Attention Problems	20 (17.7%)	9 (20.0%)	1.16 (0.48-2.79)	.74	1.28 (0.51-3.20)	.59
Adaptability	42 (37.5%)	11 (24.4%)	0.54 (0.25-1.18)	.12	0.55 (0.25-1.23)	.15
Social Skills	13 (11.5%)	4 (8.9%)	0.75 (0.23-2.44)	.63	0.90 (0.27-3.01)	.86
Activities of Daily Living	12 (15.9%)	7 (15.6%)	0.97 (0.38-2.52)	.95	1.00 (0.37-2.68)	.99
Functional Communication	13 (11.5%)	9 (20.0%)	1.92 (0.76-4.88)	.16	2.41 (0.90-6.51)	.08
Externalizing Problems	9 (8.0%)	8 (17.8%)	2.47 (0.89-6.89)	.07	2.52 (0.87-7.31)	.09
Internalizing Problems	14 (12.5%)	11 (24.4%)	2.27 (0.94-5.46)	.06	2.17 (0.88-5.34)	.09
Adaptive Skills	22 (19.6%)	6 (13.3%)	0.63 (0.27-1.67)	.63	0.72 (0.27-2.04)	.57

Symptom scores were dichotomized at 60 or greater for clinical behaviors and 40 or less for adaptive behaviors, which are considered to be “at-risk” according to the BASC manual.

Table 3
Odds of at-risk BASC scores at age 60 months

BASC scales	FRBID No (N=142) n (%)	FRBID Yes (N=63) n (%)	Odds Ratio (95% CI) Unadjusted	*P value*	Adjusted *	*P value*
Hyperactivity	15 (11.0)	9 (15.8)	1.51 (0.62-3.69)	.36	1.62 (0.65-4.09)	.30
Aggression	10 (7.2)	8 (13.6)	2.01 (0.75-5.38)	.16	1.88 (0.67-5.29)	.22
Anxiety	29 (21)	17 (28.8)	1.52 (0.76-3.05)	24	1.53 (0.73-3.15)	.25.
Depression	16 (11.6)	18 (30.5)	3.35 (1.56-7.16)	**<.001**	3.36 (1.53-7.36)	**<.001**
Somatization	16 (11.6)	12 (20.3)	1.95 (0.86-4.42)	.11	1.94 (0.82-4.57)	.13
Atypicality	29 (21.0)	14 (23.7)	1.17 (0.57-2.42)	.67	1.28 (0.60-2.74)	.52
Withdrawal	21 (15.2)	6 (10.2)	0.63 (0.24-1.7)	.35	0.55 (0.20-1.49)	.24
Attention Problems	27 (19.6)	15 (25.4)	1.40 (0.68-2.88)	.36	1.60 (0.76-3.40)	.22
Adaptability	42 (30.4)	14 (23.7)	0.77 (0.35-1.43)	.34	0.75 (0.37-1.54)	.44
Social Skills	16 (11.6)	7 (11.9)	1.02(0.40-2.64)	.96	1.16 (0.44-3.02)	.76
Activities of Daily Living	21 (15.2)	9 (15.3)	1.00 (0.43-2.34)	.99	0.87 (0.36-2.14)	.76
Functional	17 (12.3)	6 (10.2)	0.81 (0.30-2.16)	.67	0.90 (0.33-2.49)	.84
Externalizing Problems	13 (9.4)	9 (15.3)	1.73 (0.69-4.30)	.23	1.69 (0.65-4.38)	.28
Internalizing	19 (13.8)	18 (30.5)	2.75 (1.13-5.74)	**.01**	2.71 (1.26-5.85)	**.01**
Adaptive Skills	25 (18.1)	9 (15.3)	0.81 (.35-1.87)	.62	0.86 (0.37-2.05)	.74

Table 4
Odds of at-risk BASC scores at age 72 months

	FRBID		Odds Ratio (95% CI)			
BASC scales	No (N=142) n (%)	Yes (N=63) n (%)	Unadjusted	*P value*	Adjusted *	*P value*
Hyperactivity	12 (14.8)	4 (10.0)	0.64 (0.19-2.12)	.46	0.71 (0.20-2.49)	.59
Aggression	9 (11.1)	6 (15.0)	1.41 (0.47-4.27	.54	1.80 (0.54-5.98)	.34
Anxiety	16 (19.8)	11 (27.5)	1.54 (0.64-3.73)	.34	1.40 (0.54-3.67)	.49
Depression	12 (14.8)	9 (22.5)	1.67 (0.64-4.37)	.29	1.81 (0.66-4.97)	.25
Somatization	10 (12.3)	11 (27.5)	2.69 (1.03-7.02)	**.04**	2.89 (1.01-8.24)	**.05**
Atypicality	15 (18.5)	7 (17.5)	0.99 (0.35-2.51	.89	1.07 (.36-3.15)	.90
Withdrawal	5 (6.2)	8 (20.0)	3.80 (1.16-12.51)	**.02**	3.87 (1.14-13.19)	**.03**
Attention Problems	18 (22.2)	9 (22.5)	1.02 (0.41-2.52)	.97	1.04 (0.41-2.65)	.93
Adaptability	21 (25.9)	6 (15.0)	0.51 (0.19-1.37)	.17	0.60 (0.21-1.75)	.90
Social Skills	11 (13.6)	4 (10.0)	0.71 (0.21-2.38)	.57	0.82 (0.24-2.84)	.75
Activities of Daily	6 (7.4)	2 (5.0)	0.66 (0.13-3.42)	.62	0.63 (0.12-3.44)	.60
Functional	10 (12.3)	3 (7.5)	0.57 (.15-2.22)	.42	0.66 (.16-2.66)	.56
Externalizing Problems	11 (13.6)	3 (7.5)	0.52 (.14-1.97)	.32	0.64 (.16-2.60)	.54
Internalizing Problems	13 (16.0)	13 (32.5)	2.52 (1.04-6.13)	**.04**	2.30 (.86-5.93)	.08
Adaptive Skills	16 (19.8)	2 (5.0)	0.21 (0.05-0.98)	**.03**	0.25 (.05-1.13)	.08

Table 5
Average BASC *T*-scores at 48 months

BASC Scales	FRBID: No (N=142) *M (SD)*		FRBID: Yes (N=63) *M (SD)*		Unadjusted p-value	Adjusted p-value
Hyperactivity	48.83	(9.27)	51.38	(9.13)	.12	.11
Aggression	46.96	(8.19)	49.96	(11.37)	.06	.08
Anxiety	49.80	(10.16)	52.33	(11.56)	.17	.21
Depression	47.26	(9.80)	50.78	(10.94)	**.05**	**.05**
Somatization	48.73	(8.76)	52.22	(11.07)	**.03**	**.05**
Atypicality	50.28	(9.84)	53.16	(11.85)	.12	.10
Withdrawal	49.88	(8.62)	49.91	(8.83)	.98	.97
Attention Problems	51.03	(9.89)	50.67	(11.92)	.84	.96
Adaptability	45.60	(10.29)	49.58	(9.54)	**.02**	**.04**
Social Skills	51.97	(10.47)	55.16	(9.94)	.08	.16
Activities of Daily Living	50.14	(11.23)	48.42	(8.67)	.35	.32
Functional Communication	49.21	(8.35)	49.36	(8.24)	.92	.85
Externalizing Problems	48.15	(8.85)	51.91	(12.08)	**.03**	**.02**
Internalizing Problems	48.76	(9.42)	53.47	(12.64)	**.01**	**.01**
Adaptive Skills	48.91	(9.32)	50.73	(8.81)	.28	.41

Table 6
Average BASC *T*-scores at 60 months

BASC Scales	FRBID No (N=142) *M (SD)*		FRBID Yes (N=63) *M (SD)*		Unadjusted p-value	Adjusted p-value
Hyperactivity	48.69	(10.09)	51.11	(9.31)	.12	.09
Aggression	46.64	(8.20)	50.56	(11.32	**<.0001**	**.01**
Anxiety	51.45	(10.78)	55.26	(10.43)	**.02**	**.03**
Depression	47.90	(9.92)	53.09	(10.04)	**.001**	**.002**
Somatization	48.74	(9.54)	51.75	(11.05)	**.05**	.06
Atypicality	49.93	(10.38)	51.82	(10.70)	.25	.16
Withdrawal	49.89	(9.27)	49.60	(8.57)	.83	.76
Attention Problems	50.22	(9.75)	50.00	(10.21)	.88	.81
Adaptability	46.88	(10.23)	48.75	(10.15)	.24	.37
Social Skills	52.67	(10.65)	53.92	(10.91)	.45	.60
Activities of Daily Living	50.35	(10.95)	49.34	(9.11)	.53	.52
Functional Communication	49.25	(8.37)	50.41	(8.47)	.37	.51
Externalizing Problems	47.69	(8.62)	50.90	(10.04)	**.02**	**.03**
Internalizing Problems	49.04	(10.25)	54.54	(11.90)	**<.0001**	**.002**
Adaptive Skills	49.77	(9.43)	50.78	(9.92)	.50	.64

Table 7
Average BASC *T*-scores at 72 months

BASC Scales	FRBID: No (N=142) *M (SD)*		FRBID: Yes (N=63) *M (SD)*		Unadjusted p-value	Adjusted p-value
Hyperactivity	47.62	(9.92)	48.56	(9.72)	.50	.62
Aggression	46.44	(9.14)	47.07	(8.26)	.71	.75
Anxiety	52.41	(9.50)	54.30	(9.71)	.17	.26
Depression	48.70	(11.73)	50.00	(10.51)	.51	.42
Somatization	48.70	(9.83)	52.00	(11.65)	**.05**	.14
Atypicality	49.23	(10.99)	49.38	(10.09)	.90	.64
Withdrawal	48.62	(7.51)	48.53	(10.02)	.99	.82
Attention Problems	50.14	(9.70)	49.92	(9.73)	.89	.86
Adaptability	47.44	(11.40)	50.92	(10.91)	.11	.15
Social Skills	53.02	(11.08)	55.00	(8.87)	.29	.38
Activities of Daily Living	52.40	(10.39)	54.10	(9.07)	.28	.29
Functional Communication	50.83	(9.02)	52.92	(8.36)	.21	.32
Externalizing Problems	46.82	(9.53)	47.64	(8.94)	.58	.66
Internalizing Problems	49.95	(10.47)	52.71	(10.79)	.10	.15
Adaptive Skills	51.18	(10.28)	54.23	(9.33)	.10	.14

Table 8
Average Birthweight and Body Mass Index (BMI) at 48, 60, and 72 Months

Body Measurement	FRBID: No (N=142) *M (SD)*		FRBID: Yes (N=63) *M (SD)*		Unadjusted p-value	Adjusted p-value
Birthweight						
Grams	3202.29	(535.62)	3263.07	(663.36)	.55	.59
Percentile	60.10	(30.21)	63.90	(29.91)	.49	.80
BMI percentile						
48 months	64.60	(32.39)	68.21	(28.80)	.51	.52
60 months	66.56	(30.70)	70.00	(26.04)	.48	.47
72 months	65.35	(31.00)	68.71	(29.67)	.52	.57

Figure 1
Associations between FRBID and BASC depression score at 48 months as mediated by weight change since birth

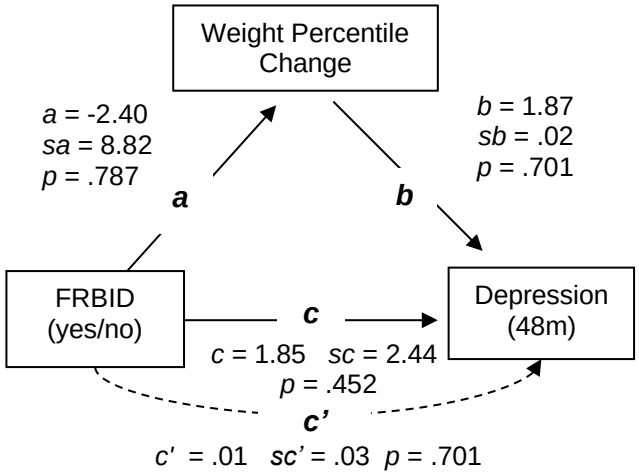

Figure 2
Associations between FRBID and BASC somatization score at 48 months as mediated by weight change since birth

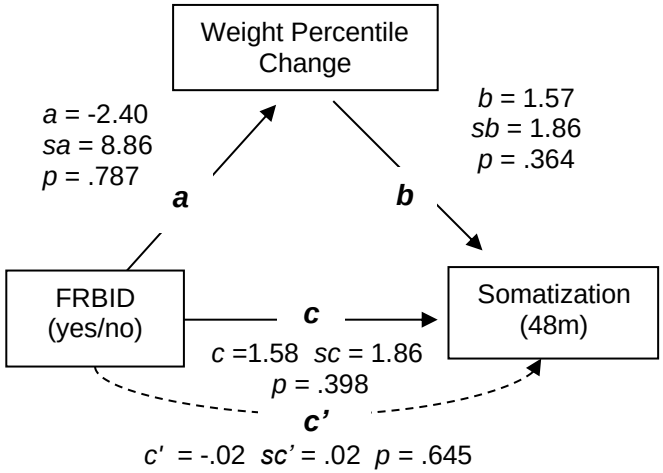

Figure 3
Associations between FRBID and BASC adaptability score at 48 months as mediated by weight change since birth

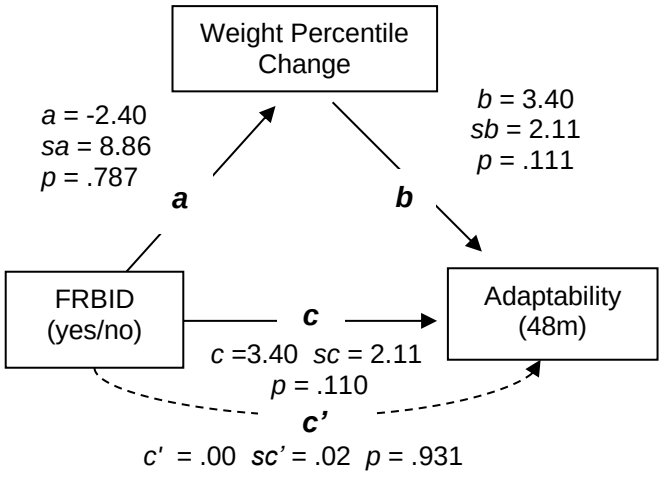

Figure 4
Associations between FRBID and BASC externalizing problems score at 48 months as mediated by weight change since birth

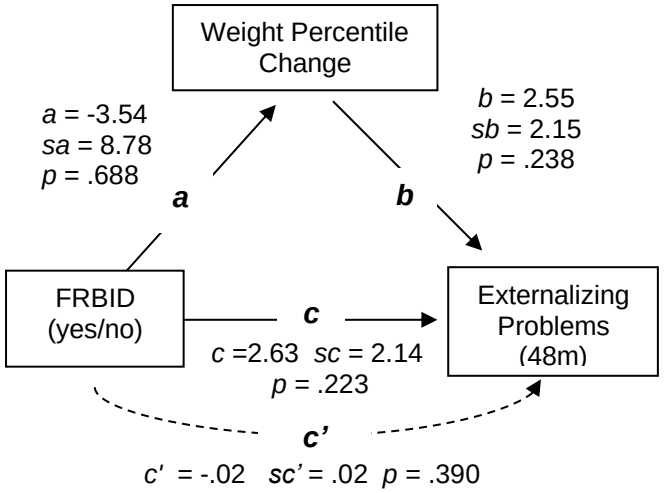

Figure 5
Associations between FRBID and BASC internalizing problems score at 48 months as mediated by weight change since birth

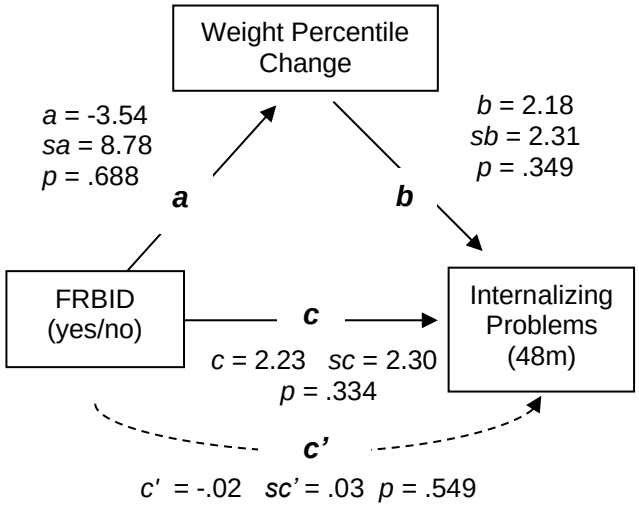

Figure 6
Associations between FRBID and BASC aggression score at 60 months as mediated by weight change since birth

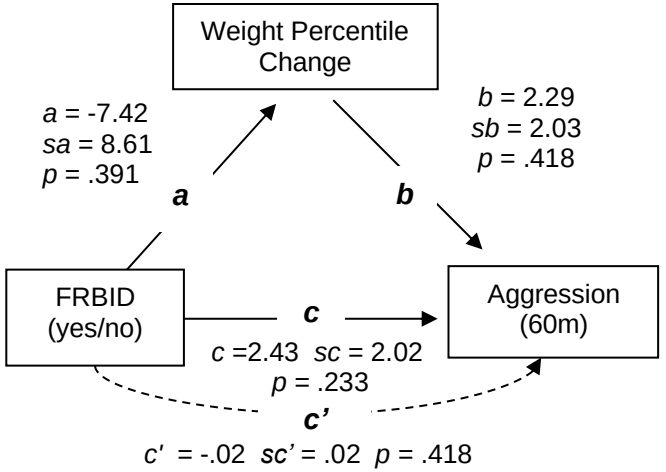

Figure 7
Associations between FRBID and BASC anxiety score at 60 months as mediated by weight change since birth

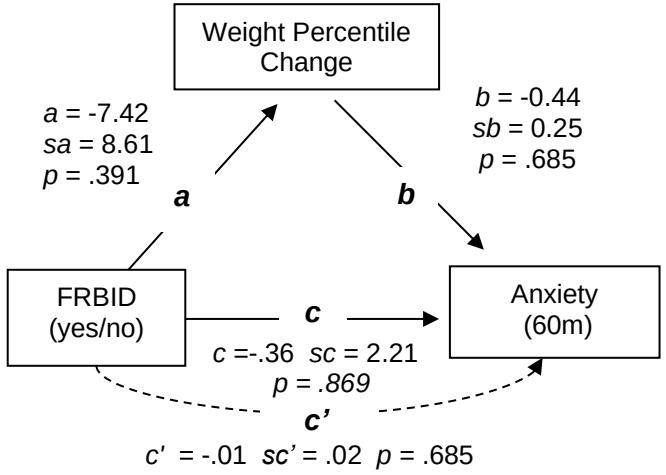

Figure 8
Associations between FRBID and BASC depression score at 60 months as mediated by weight change since birth

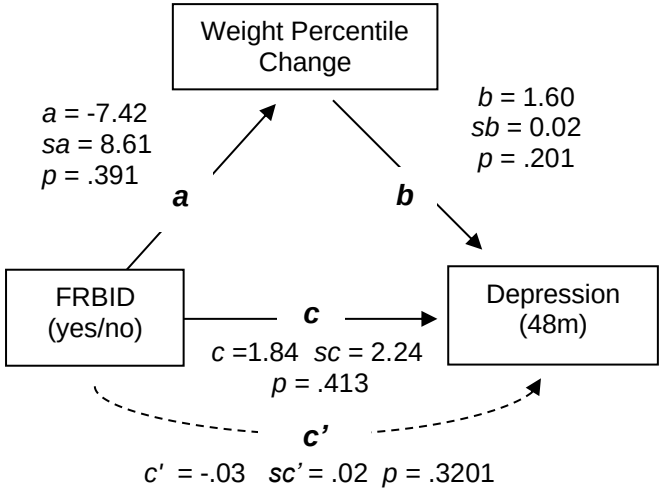

Figure 9
Associations between FRBID and BASC externalizing problems score at 60 months as mediated by weight change since birth

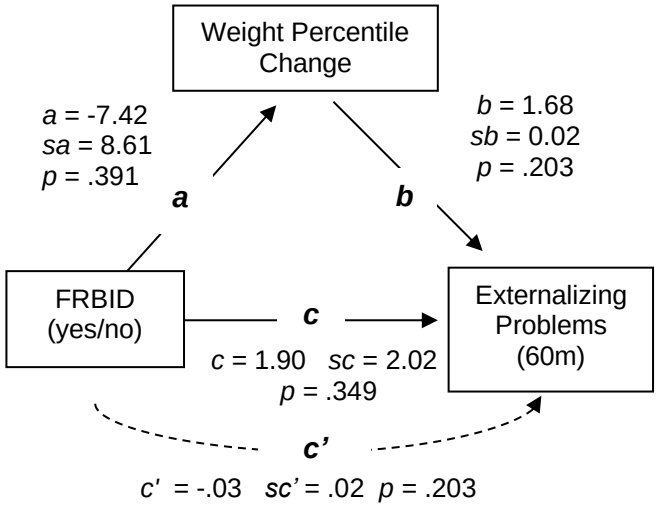

Figure 10
Associations between FRBID and BASC internalizing problems score at 60 months as mediated by weight change since birth

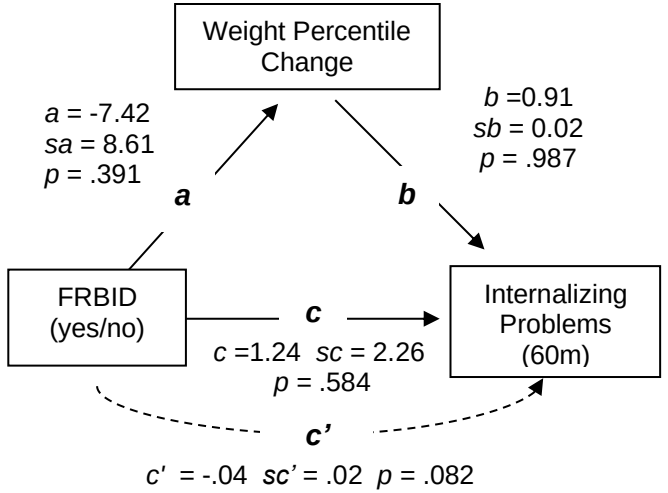

Figure 11
Associations between FRBID and BASC somatization score at 72 months as mediated by weight change since birth