Are Genes Destiny? Exploring the Role of Intrauterine Environment in Moderating Genetic Influences on Body Weight

Jinho Kim

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ABSTRACT

By incorporating molecular genetic variants and the fetal origins of obesity hypothesis into a gene-environment interaction framework, this study investigates the potential interactive effects of variation in the obesity-associated gene (FTO) and intrauterine environment on body mass index (BMI) in adulthood. This study draws on data from the Wisconsin Longitudinal Study, and uses sibling comparisons that allow for quasi-experimental variations in both genetic and environmental factors. Findings demonstrated that even after controlling for unobserved family background, the FTO variants and birth weight are generally associated with adult BMI. Moreover, this study found that the effects of having a risk allele of the FTO gene are largely concentrated on those who were heavier at birth, providing evidence for a gene-environment interaction on BMI and the development of obesity. Results of this study suggest that genes are not destiny and environmental factors may offset the effects of obesity-promoting genes. In particular, efforts to counteract genetic effects on obesity may begin as early as in utero. Interventions to prevent higher birth weight may help reduce the risk of obesity later in life, by directly addressing the programming effects of the in utero environment and also indirectly moderating the obesity-promoting genetic effects.

Keywords: Gene-Environment Interaction; BMI; Obesity; FTO; Birth Weight

Jinho Kim¹

Department of Sociology

University of Wisconsin–Madison

1180 Observatory Drive

Madison, WI 53706

jinhokim@ssc.wisc.edu

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Introduction

In the United States, obesity has been increasingly viewed as a major health concern and is the focus of many public health efforts. In 2011-2012, more than one-third (34.9 percent or 78.6 million) of adults and 17 percent of adolescents were obese (Ogden et al. 2014). The prevalence of obesity in the general population is especially alarming since obesity leads to enormous health burdens and increased costs of medical care. It is well-known that obesity is associated with medical comorbidities such as diabetes, cardiovascular disease, cancer, depression, and overall mortality (Borrell and Samuel 2014). The estimated annual medical cost of obesity for the full non-institutionalized population of adults aged 18 and older was \$190 billion in 2005 U.S. dollars (approximately 5-10 percent of health care spending); the annual medical expenditures per person with obesity were \$2,741 (Cawley and Meyerhoefer 2012). In addition to these health-related and budgetary consequences, several studies have shown a negative relationship between obesity and labor market outcomes such as wages and employment status (Cawley 2004).

Discovering critical determinants of obesity has thus been a major focus for researchers across social science and public health/medical fields. Despite considerable scholarly attention to the topic, a major challenge to understanding the causes of obesity is that obesity has a complex etiology. In fact, obesity is a multifactorial abnormality caused by both genetic and environmental factors: a large body of research has long documented that obesity is determined by a number of factors, including genes (Locke 2015), prenatal and post-natal experiences (Oken, Levitan, and Gillman 2008), unhealthy diets and eating habits (Mozaffarian and Hao 2011), personality traits (Kim 2016), smoking (Chiolero and Faeh 2008), physical inactivity (Pietiläinen et al. 2008), and neighborhood factors (Papas et al. 2007).

More recent literature has argued that obesity has much deeper and more complex roots that may be regulated by both maternal and fetal factors. A large body of extant literature has documented the genetic underpinnings of common-form obesity, suggesting that individuals have some genetic predisposition to obesity. Despite some variability in the heritability estimates, a heritable component of body mass index (BMI) and fat mass is known to be generally large (40-60 percent) (Maes, Neale, and Eaves 1997). Emerging findings from recent molecular genetic studies have also begun to indicate the role that genes play in predisposing a person to obesity, though more research is required (Locke 2015). Then, the remaining question is whether “obesity genes” are destiny: can the genetic effects on obesity be moderated?

Although genetic variants are determined at conception and do not change except through epigenetic modifications and DNA mutations, a gene-environment interaction framework suggests that their effects may not be deterministic because their phenotypic manifestations are often subject to environmental influences throughout the life course (e.g., Guo, Roettger, and Cai 2008; Cook and Fletcher 2015a). A few studies have suggested that the effects of so-called “obesity genes” on the development of obesity may be moderated by environmental factors. Focusing on lifestyle (e.g., physical inactivity) and diet (e.g., fat, carbohydrates, protein, and minerals) as potential moderators, these studies argue that genes are not destiny. Rather, an individual’s health efforts to combat obesity counteract the genetic effects on obesity (Andreasen et al. 2008; Kilpelainen et al. 2011; Rampersaud et al. 2008; Ruiz 2010).

Despite existing evidence, two major gaps in the literature need to be addressed. First, several methodological issues plague past studies on this topic. A few examples include the possibility of a gene-environment correlation (rGE) (or gene-gene interaction) as well as the difficulty in obtaining exogenous environmental variation (Conley and Fletcher 2017; Fletcher

and Conley 2013). Second, and more substantively, previous studies focus exclusively on the association between obesity and behavioral traits, considered environmental factors. To the author's knowledge, no study has ever extended the focus to other environmental factors beyond lifestyle and diet (i.e., proximate determinants of BMI and obesity risk).

In order to address these critical research gaps, this study examines potential joint influences of genetic and early life environment on later BMI. In particular, this study focuses on environmental exposures dating as far back as intrauterine environment. Although relatively new, a number of epidemiological studies have found that higher birth weight, an indicator of intrauterine growth, is associated with an increase in the risk of obesity, suggesting that prenatal and early life influences may shape the trajectory of weight gain and body fat throughout the life course (i.e., fetal origins of obesity) (Oken and Gillman 2003). While higher birth weight is generally considered a more favorable intrauterine environment, increased risk of obesity is known to be one of a few exceptions to the beneficial effects of higher birth weight (Gaudet et al. 2014). Considering that in utero environment has a life-long impact on the development of obesity, knowledge about the interplay between genetic and intrauterine environment in determining risk of obesity will offer important new insights about the seemingly complex underpinning of obesity.

Using data from the Wisconsin Longitudinal Study (WLS), this study extends existing literature by examining how in utero environment could potentially alter or moderate the relationship between genetic effects and BMI in adulthood. More specifically, utilizing a conventional gene-environment interaction framework, this study examines whether the effects of variations in the FTO gene, the first locus known to be unequivocally associated with human body mass (Fawcett and Barroso 2010), on adult BMI (and obesity risk) differ based on whether

a person was exposed to certain intrauterine environments (i.e., higher birth weight). This analysis contributes to a better understanding of the development of obesity by incorporating molecular genetic variants into the conceptual framework for the fetal origins of obesity (e.g., Emily Oken and Gillman 2003). Another novel contribution of this study is the use of sibling comparisons that allow us to control for shared family-level characteristics that may confound the relationship between intrauterine conditions and future body weight, and to leverage a random component of within-sibling genomes (Fletcher and Lehrer 2011).

Background

Genes associated with fat mass and obesity

“Heritability” refers to the extent to which variation in a phenotypic trait in a population is determined by genetic variations within that population. Heritability of BMI or obesity is often estimated from twin and adoption studies that compare BMI between groups of individuals with variation in genetic relatedness. A comprehensive review of literature on heritability of BMI conducted by Maes and colleagues (1997) summarized that heritability estimates fall in the range of 40 to 60 percent. Despite some variability in heritability estimates, the heritable component of BMI and fat mass is known to be quite large.

Recent genome-wide association studies (GWAS) have genotyped a large amount of stretch of DNA to identify single nucleotide polymorphisms (SNPs) that explain genetic variability in BMI at the molecular level (e.g., Speliotes et al. 2010; Hägg et al. 2015; Locke 2015). Locke and colleagues (2015) suggest that the meta-analysis of nearly 340,000 individuals identified about 97 loci that are associated with BMI, and these loci explain approximately 3 percent of the variation in BMI (See, Conley and Fletcher, 2017, for more discussion about "missing heritability" mystery). Among individuals of European ancestry, the FTO gene, the first

fat mass and obesity associated gene, has the greatest effect on BMI as well as risk of obesity and explains the largest part of variance. And the FTO gene is the first and the only obesity-related gene that has been consistently replicated with a variety of obesity traits across multiple populations (Fawcett and Barroso 2010; Loos and Yeo 2014). Each additional minor risk allele in the FTO gene is associated with a 0.4 higher BMI, and about a 20 to 30 percent higher risk of obesity (Dina et al. 2007; Liu, Mou, and Cai 2013; Speliotes et al. 2010)

A SNP located in the first intron of the FTO gene on chromosome 16, rs1421085, is known to show the most association with obesity in the original work of Dina and colleagues (2007). Within the FTO gene, this SNP is likely to be co-inherited with the rs9930506 and rs17817449 SNP, and therefore, these three FTO SNPs are in strong linkage disequilibrium (Dina et al. 2007). However, Claussnitzer and colleagues (2015) suggest that rs1421085 SNP may be the causal variant. In their study, the authors identified which of the 89 variants in linkage disequilibrium across the FTO locus is the most likely “causal allele,” and concluded that the most likely risk variant is rs1421085. Moreover, the authors demonstrated that the rs1421085 T-to-C single-nucleotide alteration underlies the association between the FTO and obesity by disrupting ARID5B-mediated repression of IRX3 and IRX5.

A number of studies examining potential mechanisms that link variations in the FTO gene to obesity have focused largely on two major determinants of body weight regulation: food intake and physical activity (Andreasen et al. 2008; Fawcett and Barroso 2010; Loos and Yeo 2014; Scuteri et al. 2007; Speliotes et al. 2010). Although far from definitive, empirical evidence thus far provides more support for the role of the FTO gene in regulating food intake than influencing levels of physical activity. For example, there is increasing evidence that FTO variants are associated with a number of factors related to dietary traits, including increased

energy, dietary fat or protein intake, increased appetite and reduced satiety, poor food choices and eating habits, and loss of control over eating (Brunkwall et al. 2013; Tanofsky-Kraff et al. 2009; Wardle et al. 2008). In contrast, a number of studies, including a recent large-scale meta-analysis (Kilpelainen et al. 2011), suggest that SNPs in the FTO gene are not associated with levels of physical activity. These findings appear to indicate that the FTO variants may contribute to the risk of obesity, by influencing appetite and satiety signaling systems as well as pathways involved in energy expenditure.

Gene-environment interactions in obesity

In the past few decades, a growing literature in different disciplines has documented gene-environment interactions that refers differential responses to the effects of a genotype based on environmental conditions or vice versa (e.g., Guo, Roettger, and Cai 2008; Cook and Fletcher 2015a; Caspi and Moffitt 2006). These studies have suggested that although genetic variants are determined at conception and rarely change over the life course, their effects may not be deterministic because their phenotypic manifestations are often subject to environmental influences. In the human obesity literature, however, since the literature about genetic and environmental influences on obesity have been developed rather independently, conceptual frameworks and empirical evidence on gene-environment interactions are still in their infancy (Hernandez and Blazer 2006).

A few recent studies have begun to collect evidence that lends support for environmental factors offsetting the genetic predisposition to obesity. Most of the evidence so far has argued that the effects of so-called “obesity genes” may differ by environmental factors such as dietary and lifestyle factors that can directly or indirectly influence the balance of energy input and output. For example, studies found that individuals with the obesity-promoting FTO gene variant

tend to have a higher risk of obesity than their counterparts without the gene variant, but that being physically active lowers the risk (Andreasen et al. 2008; Kilpelainen et al. 2011; Rampersaud et al. 2008; Ruiz 2010). However, in contrast, other studies found no evidence of such gene-environment interactions (Leońska-duniec et al. 2016), suggesting that additional research may be needed.

While the majority of previous studies on gene-environment interactions in BMI has focused exclusively on behavioral traits as environmental factors, to the author's knowledge, no study has ever examined whether other environmental factors, besides diet and lifestyle in adulthood, may moderate the effects of genetic variants on BMI and the development of obesity. Especially, prenatal and early life influences may be an important environmental factors that might interact with a genetic factor to influence BMI since they are determined as early as genetic dispositions are, and have a life-long impact on BMI.

There has been growing recognition in recent years that in utero environment influences lifelong health and diseases (e.g., Barker et al. 2005). For example, numerous studies have demonstrated that fetal experiences are associated with later health risks such as cardiovascular disease, cancer, diabetes, respiratory diseases, and so on (Harding 2001). While research on the fetal origins of *obesity* has emerged relatively slowly (Oken and Gillman 2003), recent studies have found that birth weight is positively associated with BMI as well as obesity risk at both childhood and adulthood, suggesting that prenatal developmental conditions may contribute to a trajectory of weight gain and the development of obesity throughout the life course (e.g., Yu et al. 2011; Cnattingius et al. 2012; Schellong et al. 2012). These findings indicate that as a critical determinant of future obesity, higher birth weight may be understood as an adverse intrauterine environment, though higher birth weight is generally an indication of a more favorable in utero

environment (Gaudet et al. 2014). Although some studies have shown that lower birth weight is associated with higher BMI (lower lean body mass and greater central obesity), indicating a J-shaped, or even U-shaped, relationship between birth weight and BMI (Parsons, Power, and Manor 2001; Singhal et al. 2003), evidence of this association remains controversial and is yet to be firmly established (Oken and Gillman 2003; Yu et al. 2011).

Research on the fetal origins of health and diseases often argues that the effects of early life influences occur through biological programming, a process in which the trajectory of cellular or organ growth continues to be altered to compensate for an explicit insult occurring at a critical period of development. Similarly, scholars have suggested that in utero environment may be linked to the development of obesity, largely by influencing intrauterine developmental programming (Harding 2001; Oken and Gillman 2003; Singhal et al. 2003). Although specific mechanisms are not yet known, scholars argue that maternal over-nutrition, obesity, and/or diabetes result in fetal hyperglycemia and fetal hyperinsulinemia, which may in turn facilitate excessive fat deposition during the third trimester (e.g., Schellong et al. 2012). Increased adiposity in fetal life and subsequent high birth weight heighten levels of growth factors in utero, such as insulin and the insulin-like growth factors I and II (IGF-I and II) (Wheatcroft et al. 2007; Yu et al. 2011). Consequently, those who were heavier at birth may suffer a higher risk for developing obesity in adulthood by having higher proportions of total body fat relative to lean body mass in early life, which is likely to persist into adulthood (Catalano et al. 1992). These findings suggest that prenatal developmental conditions, particularly related to nutrient excess and insulin exposure, may have long-term effects on body weight regulation, though more research is required to investigate other possible biological mechanisms such as dysregulation of appetite/satiety and permanent changes in fat-mass ratio (Oken and Gillman 2003).

Reconciling molecular genetic studies of human obesity and the fetal origins of obesity framework (e.g., Emily Oken and Gillman 2003), it seems plausible to speculate that the effects of the FTO genetic variants on the development of obesity may be greater among those who have “adverse” intrauterine environment (i.e., higher birth weight). In other words, compared to those with normal birth weight, individuals with higher birth weight who were programmed in utero with an increased appetite and a predisposition to storing calories as fat may be more sensitive to the effects of FTO variants, also known to involve dysregulation of appetite/satiety.

The present study

Incorporating molecular genetic variants and the fetal origins of obesity hypothesis into a conventional gene-environment interaction framework, this study examines whether the effects of the genetic variants in the FTO gene on adult BMI (and obesity risk) differ based on whether a person was exposed to a certain intrauterine environment (i.e., higher birth weight). This study uses data from Wisconsin Longitudinal Study (WLS), a random sample of about one third of 1957 high school graduates in Wisconsin. The WLS data are appropriate for this study because they are one of the few datasets that contain both genetic and birth weight data for an adequate number of samples (See Herd et al., 2014).

There are several challenges in examining gene-environmental interaction research, which should be carefully addressed to facilitate causal inference (Fletcher and Conley 2013). First, in a non-experimental setting (i.e., without random assignment), it is often difficult to obtain exogenous environmental variation. As shown in the earlier section, past studies on obesity-related gene-environment interaction are also limited in that those studies rely heavily on endogenous environmental factors such as physical activity and dietary habits. This concern is also a critical issue to address in this study since the observed positive association between birth

weight and obesity may be spurious owing to the existence of a third factor that may affect both birth weight and obesity in adulthood (The, Adair, and Gordon-Larsen 2010).

Among others, measured and unmeasured family-level characteristics appear to be the strongest confounder to deal with in this study (Oken and Gillman 2003). For example, maternal smoking not only results in lower birth weight, but is highly correlated with a child's smoking, and consequently, lower child BMI. Similarly, eating habits and physical activity shared by family members as well as family-level socioeconomic status may serve as potential confounders. Moreover, the association between birth weight and adult BMI may be explained by genes shared by parents and child that influence both birth weight and later BMI. Failure to account for these potential confounders may lead to a spurious association between birth weight and body composition, which would make the present gene-environment interaction analysis invalid.

Leveraging exogenous environmental variation is also important. Specifically, when genotypes affect the environments (rGE), statistical interactions between genes and environment may be a spurious result of differential risk of exposure, rather than of environmental moderation of genetic effects. Relatedly, if environmental exposure is nothing but a proxy for the effect of unmeasured genes, gene-environment interaction cannot be identified (gene-gene interaction). Therefore, in order to ensure the validity of the present gene-environment interaction study, it is crucial to address potential unobserved family-level heterogeneity that may confound the relationship between birth weight and adult BMI (Loos et al. 2001, 2002; The et al. 2010), as well as reduce the possibility of a latent gene-gene interaction (Fletcher and Conley 2013).

In order to address these key challenges, this study adopts a between-sibling design that allows for quasi-experimental variation in both genotype and birth weight (e.g., Cook and Fletcher 2015b; Cook and Fletcher 2014; Cook and Fletcher 2015a). The major aims of this

sibling comparison model (or family fixed effects model) are to (1) separate unobserved family-level confounders from environmental effects and (2) control for potential unobserved genetic influences to uncover a gene-environment interaction, not a gene-gene interaction.

Methods

Data

Data were drawn from the Wisconsin Longitudinal Study (WLS), which is comprised of a random sample of one-third of the 1957 high school graduates in Wisconsin. One of the most important feature of the WLS data is that subsequent waves collected data on a singular selected sibling of the originally sampled graduate. For graduates, data were collected for 10,317 individuals, while for selected siblings, data were collected for 6,619 individuals. Data are a life-long panel (1957, 1964, 1975, 1992, 2003, and 2011 Waves), for which genetic data were collected in the 2003 Wave (2004 Wave for siblings).

The WLS contains data on BMI, the primary dependent variable of interest, for roughly 10,700 individuals: 6,700 graduates and 4,000 selected siblings. Genetic data for the WLS were collected in the 2003 (graduates) and 2004 (siblings) Waves, a time when the graduates and siblings were roughly 60 years of age. The sample of individuals who reported both birth weight and DNA data (including the SNP of FTO) is about 36 percent of the 10,700 sample: the sample sums up to roughly 3,800 individuals: 2,500 graduates and 1,300 siblings. Furthermore, data for complete sibling pairs reduce the sample of individuals with DNA and birth weight data from 3,800 to 876. Therefore, the ultimate analytic sample comprises of 876 respondents (or 438 sibling pairs) with complete data on DNA, birth weight, BMI, and other covariates used in estimation. In order to check if sample selection is a concern, robustness tests were conducted to estimate ordinary least squares (OLS) regression weighted with the inverse of the probability of

being in the sibling sample (based on BMI, birth year, gender, and family socioeconomic status measures).

Measures

The main dependent variable is BMI measured in 1992-1993, a time when the graduates and siblings were approximately in their early 50s. A BMI was calculated first by dividing weight in kilograms (kg) by height in meters (m) squared. In addition to a BMI, obesity status was also used as an outcome. Obesity status is a dichotomous indicator for those with a BMI of 30 or greater.

In this study, self-reported birth weight was used as a proxy for intrauterine environment. Birth weight was reported by respondents in the 2003 Wave for graduates and the 2004 Wave for the selected siblings. In the analyses of this study, birth weight was standardized to have the mean of zero and the standard deviation of one. As described in the earlier section, in terms of the genetic factor, this study focused on the FTO genetic variants. The functional variation is the result of variants in rs1421085 SNP. This SNP contains two alleles, or genetic variants: a “C” is a risk allele and a “T” is a non-risk allele. A person thus can have either one of the following possible combinations: (1) homozygotes for a C variant (C;C); (2) heterozygotes (C;T); and (3) homozygotes for a T variant (T;T). In the analysis, the measure of genetic variants was created based on a genotype model (comparing the three genotype groups separately) as well as a dominant model (homozygous non-risk genotype vs. risk allele carriers). Alternatively, for a robustness check, an additive allelic model (counted as zero, one and two risk alleles) and a recessive model (non-risk allele carriers vs. homozygous risk genotype) were also used.

Analytic strategy

The main empirical strategy considered the interaction between the FTO genetic variant and intrauterine environment (or prenatal developmental condition), for which birth weight was used as a proxy. As a baseline empirical specification, this study estimated variations of the following OLS regression model:

$$Y_{ij} = \beta_0 + \beta_1 FTO_SNP_{ij} + \beta_2 Std(BW)_{ij} + X_{ij}\beta_3 + Z_j\beta_4 + \varepsilon_{ij} \dots (1)$$

where i individuals within j families were considered. The main outcomes of interest were respondents' BMI and obesity status measured in their early 50s. In this analysis, for a binary outcome of obesity status, linear probability models were estimated because the sign and significance of the estimated coefficients of interaction terms in nonlinear models are known to be an inappropriate source of inferences about the true sign and significance of the interaction effect (Ai and Norton 2003; Greene 2010). Nonetheless, it was confirmed that results from nonlinear regressions (i.e., logistic regression analysis) were considerably consistent with the findings shown in this study (results not shown but available upon request). In Eq. (1), β_1 and β_2 present evidence of whether adult BMI was associated with the FTO variants and birth weight, respectively. X_{ij} is a vector of individual-level controls including gender, age (birth year), a sibling indicator, and birth order. Z_j is a vector of family-level controls including mother's education, father's education, and family income.

One of the most critical limitations of Eq. (1) is that there might be potential family-level confounders that affect both birth weight and later BMI. While some confounders such as family socioeconomic status and education, maternal smoking, gestational diabetes, mother's nutritional status, and so on are easily measured and available in some datasets, there could also be

unobserved confounding factors at the family level. In order to address this issue, as shown in Eq. (2), family fixed effects were controlled for.

$$Y_{ij} = \gamma_0 + \gamma_1 FTO_SNP_{ij} + \gamma_2 Std(BW)_{ij} + \gamma_3 FTO_SNP_{ij} \times Std(BW)_{ij} + X_{ij} \gamma_4 + \delta_j + \varepsilon_{ij} \cdots (2)$$

where δ_j is a set of family dummies. In this family fixed effects model, a vector of family-level characteristics in Eq. (1), Z_j , was omitted because siblings share family characteristics. In Eq. (2), the major coefficient of interest in this study was γ_3 , which captures the interaction effects of the FTO variants and birth weight. In all models, robust standard errors were clustered at the family-level.

The inclusion of family fixed effects also controls for unobserved genetic influences, which may lead to biased estimates of gene-environment interaction. Since siblings share about 50 percent of unique genetic variation, this sibling comparison model can partially control for potential unobserved genetic influences by accounting for a latent gene-gene interaction. Genetic variation leveraged by this study may thus be considered as quasi-exogenous because the variation in genotype of siblings is believed to come from the “genetic lottery” (Fletcher 2011; Fletcher and Lehrer 2011). In addition, sibling comparison models should eliminate bias from population stratification, a phenomenon wherein a certain population is composed of subgroups of individuals with distinct ancestry and varying allele frequencies at many loci (Fletcher and Conley 2013).

Results

Table 1 presents summary statistics. The average BMI was 26.5, and exactly 20% of respondents were categorized having obesity. For the analytic sample of this study, the distribution of the

FTO variants was about 14% for homozygotes for a C variant, 49% for heterozygotes, and 37% for homozygotes for a T variant. The mean birth weight was about 3,400 grams, which is considerably consistent with a recent trend analysis in birth weight in the United States (Donahue et al. 2010). In order to examine whether ex-ante differences in sample characteristics exist across genetic variants, summary statistics by genetic variants were reported. Except for the outcome of interest, there was only one characteristic, i.e., birth year, showing a statistical difference between homozygotes for T and homozygotes for C at 10% level.

As described earlier, in order for this gene-environment interaction study to be valid, the FTO variants should not predict birth weight (i.e., no gene-environment correlation). So, prior to examining gene-environment interaction, some evidence to support this claim was presented. First, existing genome-wide association studies found no significant association between the FTO variants and birth weight (Horikoshi et al. 2012, 2016), reducing concerns about the possibility of gene-environment correlation. Additionally, an empirical test was conducted to examine whether the FTO variants were associated with birth weight in the analytic sample of the study. Table 2 presents results of the models where birth weight was regressed on the FTO variants in the genotype (Columns 1-2) and dominant model (Columns 3-4). In Table 2, both OLS and fixed effects estimates show that variation in the FTO gene was not associated with birth weight, establishing the independence of genes and environment. Therefore, combining these results, it was argued that statistical interaction between genes and environments found in this study is the least likely to be spurious as a result of gene-environment correlation.

Table 3 examined whether the FTO variants and birth weight were associated with BMI in adulthood (Columns 1 and 4), and whether birth weight moderated the effects of the FTO gene on BMI (Column 5). Table 3 presents results for the genotype (Panel A) and dominant model

(Panel B). Supplementary analyses showed that results for additive allelic and recessive models were also substantially similar (results not shown but available upon request). All models presented in Table 3 except family fixed effects models included all individual- and family-level controls, whereas family fixed effects models omitted family-level controls shared by siblings. Robust standard errors clustered at the family level were presented in parentheses.

In Panel A, the OLS estimates from Column 1 demonstrated that the FTO variants, especially homozygotes for a C variant, were associated with adult BMI. Column 2 also show that the association between birth weight and adult BMI was statistically significant. As shown in Column 3, the inclusion of both genetic and environmental factors in the same model did not alter the associations found in Columns 1 and 2, though the coefficients were slightly reduced.

In order to remove unobserved family characteristics that might affect both birth weight and adult BMI and leverage within-family genetic variations, family fixed effects were added (Column 4). Results suggest that controlling for family fixed effects did not change the coefficient of the effect of homozygotes for a C variant (from 0.981 to 0.980), though the coefficient was less precisely estimated in the family fixed effects model due to large standard errors (Column 4). It is important to note that imprecise within-sibling estimates were common because within-sibling analysis relies on substantially reduced variation. Results of Column 4 show that those with homozygotes for a C variant in the FTO gene had approximately one-unit greater BMI than those with homozygotes for a T variant in the FTO gene. Moreover, the association between birth weight and adult BMI also remained robust to controls for unobserved family-level heterogeneity. A one standard deviation increase in birth weight was associated with an increase in BMI by about 0.6 (Column 4, Panel A).

Column 5 of Panel A shows whether there were gene-environment interactions on adult BMI. Results suggest that the effects of the FTO genetic variants were moderated by birth weight. Positive and statistically significant interaction terms indicate that the adverse effects of having a risk allele (i.e., C variant) on adult BMI were more pronounced among those who were heavier at birth. While the interaction effect appeared to be greater for homozygotes for a C variant ($b = 0.85$) than heterozygote carriers ($b = 1.21$), no statistically significant differences were found. In sum, these findings provide evidence that intrauterine environment moderates the effects of the FTO variants on BMI in adulthood.

Findings from the dominant model of Panel B were considerably similar with the ones in the genotype model (Panel A). Results show that the association between non-homozygotes for a T variant and adult BMI was somewhat robust to controls for family fixed effects, though the standard errors were too large to find the statistically significant results (Column 4). Those with heterozygotes or homozygotes for a C variant were more likely to have a greater BMI in adulthood, though again fixed effects estimates were imprecisely estimated with large standard errors. Similar to Panel A, Column 5 of Panel B suggests that the adverse effects of having a C variant (i.e., risk allele) in the FTO gene were greater among those with higher birth weight. Fig 1 plotted this interaction effect.

Table 4 presents results for the outcome of obesity status. In Table 4, similar patterns of gene-environment interaction were evident for the obesity outcome, though the main effects of the FTO variants and birth weight seemed less clear. In the genotype model (Panel A, Table 4), fixed effects estimates (which are preferred to the OLS estimates) suggest that those with homozygotes for a C variant were about 11 percentage points more likely to be obese than those with homozygotes of a T variant (Column 4). While the association between birth weight and

obesity risk was positive ($b = 0.02$), it was statistically insignificant. In examining a gene-environment interaction in obesity, similar to BMI, results indicate that the genetic effects of the FTO on the risk of obesity were greater for those who were heavier at birth (Column 5). The dominant model in Panel B of Table 4 yielded similar results for this interaction effect, though the main effects of having homozygotes of a C variant appeared to be less clear (Column 4). Results for the gene-environment interaction on obesity in the dominant model (shown in Column 5) were plotted in Fig 2. Fig 2 shows that those with a risk allele of the FTO gene who had higher birth weight were at highest risk for developing obesity in adulthood.

A supplementary analysis used different markers for birth weight, quantiles of birth weight, and low birth weight ($> 2,500$ grams), to assess whether these particular thresholds of birth weight matter. Results showed no evidence of nonlinear patterns in the interaction effects on both BMI and obesity (results not shown but available upon request). In addition, it was confirmed that using nonlinear regression (i.e., logistic regression analysis) did not alter the results of this study (results not shown but available upon request).

Discussion

Obesity, a major and global public health concern, is a complex, multifactorial disease with a genetic and environmental etiology. While lines of research on genetic and environmental determinants of obesity have been independently developed in the past few decades, relatively little is known about whether these factors interact to influence the development of obesity (Hernandez and Blazer 2006). This study investigated whether early life influences moderate the genetic effects on body weight in adulthood. More specifically, using the WLS data and family fixed effects model, this study explored the potential interaction effects between the obesity-

promoting gene (i.e., FTO gene) and in utero environment (i.e., birth weight) on adult BMI and obesity risk.

Consistent with prior research, the FTO variants and birth weight are shown to be associated with adult BMI. Results from fixed effects models also showed that these associations were quite robust to controls for family fixed effects, suggesting that they were not spuriously driven by unobserved family-level characteristics. This study also found robust evidence of a gene-environment interaction on BMI as well as the development of obesity in adulthood. Results suggest that the effects of having a risk allele (i.e., C variant) of the FTO gene are largely concentrated on those who were heavier at birth. These findings were considerably robust to using different measures of genetic variants, except recessive models (i.e., homozygotes for a C variant vs. heterozygotes and homozygotes for a T variant).

This study makes several contributions to existing literature. First, this research enhances our understanding of the development of obesity, by bridging biological sciences with social sciences to provide new and different forms of evidence, including a focus on the joint effect of genes and environment. To the author's knowledge, this study is the first to incorporate a new environmental factor (i.e., early life influences) other than lifestyle and diet into gene-environment interaction research. Second, this study adds to the growing literature on fetal origins of obesity by providing evidence on the role of early childhood environment in counteracting genetic effects. Early environmental influences such as exposure to favorable intrauterine environments (e.g., adequate birth weight) may suppress the adverse effects of genes on obesity, and the basis of this resiliency may stem from biology of the developmental process. Last but not least, the use of family fixed effects models allows for more rigorous empirical investigations on gene-environment interactions by (1) separating unobserved family-level

confounders from environmental effects, (2) uncovering gene-environment interaction, rather than gene-gene interaction, and (3) eliminating the likelihood of population stratification (Fletcher and Conley 2013).

Several limitations of this study should be noted. First, one issue with the WLS data is the ethnic homogeneity of the sample: the vast majority of the sample of the study (more than 99 percent) consists of individuals of European decent. Therefore, external validity of the findings of the current study should be limited accordingly. However, the lack of ethnic diversity is rather beneficial in examining the effects of genes and environments because the use of ethnically homogenous sample reduces biases arising from genetic or environmental clustering across ethnicities (Cook and Fletcher 2015a). Second, another concern is that birth weight was collected retrospectively in 2003, when the participants were in their mid-60s. Several studies have found that birth weights recorded in official records and self-reported birth weights correlate reasonably well and that the amount of error in retrospective reports of birth weight is generally small (Jaworowicz et al. 2010; Sanderson et al. 1998; Tehranifar et al. 2009). Despite such evidence, other studies have reported a poor degree of correspondence between these two sources (Andersson et al. 2000). Therefore, the results of the current study may be interpreted with some caution. Third, due to the birth weight and DNA data being collected at such a late period, sample selection may be a concern. For example, several factors that make respondents remain in the survey until the 2003 (graduates) and 2004 (siblings) Waves may be correlated with BMI and other economic and health measures. In order to examine the possibility of sample selection, a robustness test used the OLS models weighted with the inverse of the probability of being in the sibling sample (based on BMI, birth year, gender, and family SES measures) to confirm that results are considerably consistent. Lastly, the reliance on candidate gene approaches to measure

a genetic factor may be another limitation of this study. Although using polygenic scores (i.e., combining all the genetic variants that predict BMI or obesity) may be an alternative approach, unfortunately, other obesity-related SNPs are not available in the WLS. Moreover, the application of polygenic scores to gene-environment interaction is not without limitations, and is still an area of active research (See Conley and Fletcher, 2017 for more discussion).

The findings of this study may be relevant to policy. One of the major findings of this study is that genes are not destiny, and environmental factors may offset the effects of obesity-promoting genes. In particular, this study suggests that efforts to counteract the genetic effects on obesity can begin as early as in utero. Considering the roles of birth weight (i.e., intrauterine nutrition conditions) in moderating genetic effects, it seems to be critical to monitor trends in fetal growth and prevent high birth weight. This effort will help reduce the risk of obesity later in life (Schack-Nielsen et al. 2010) by directly addressing the programming effects of the in utero environment and indirectly moderating the obesity-promoting genetic effects. More specifically, since maternal obesity or over-nutrition during pregnancy is known to play a significant role in the development of fetal overgrowth (Gaudet et al. 2014), public health initiatives to reduce pregnancy weight and monitor and optimize gestational weight gain may be required.

Tables

Table 1. Summary statistics by genetic variants, Wisconsin Longitudinal Survey

	Full sample (N = 876)				Homozygotes for T (T;T) (N = 322)		Heterozygotes (C;T) (N = 428)		Homozygotes for C (C;C) (N = 126)	
	Mean	SD	Min	Max	Mean	SD	Mean	SD	Mean	SD
Dependent variables										
BMI	26.50	4.82	15.00	69.00	26.14†	4.32	26.57	5.07	27.21	5.10
Obesity	0.20	0.40	0.00	1.00	0.18	0.39	0.20	0.40	0.25	0.44
FTO variants										
Homozygotes for T (T;T)	0.37	0.48	0.00	1.00						
Heterozygotes (C;T)	0.49	0.50	0.00	1.00						
Homozygotes for C (C;C)	0.14	0.35	0.00	1.00						
Intrauterine environment										
Birth weight	3390.35	596.96	1133.98	5443.10	3351.67	615.56	3410.55	582.80	3420.61	595.86
Control variables										
Female	0.55	0.50	0.00	1.00	0.54	0.50	0.57	0.50	0.54	0.50
Birth year	39.86	4.76	24.00	61.00	40.16‡	4.98	39.83	4.60	39.19	4.67
Sibling indicator	0.50	0.50	0.00	1.00	0.50	0.50	0.49	0.50	0.52	0.50
Birth order	2.12	1.33	1.00	14.00	2.08	1.23	2.14	1.47	2.13	1.04
Father's education	10.21	3.39	2.00	21.00	10.28	3.38	10.21	3.43	10.00	3.29
Mother's education	10.89	2.78	2.00	18.00	10.85	2.77	10.96	2.74	10.70	2.93
Family income	63.17	34.75	4.00	150.00	63.10	35.29	62.92	34.62	64.18	34.02

Note. Statistical differences in levels of variables between genetic variants were assessed using chi-square tests for categorical variables and t-tests for continuous variables. † indicates statistical difference between Homozygotes for T and Homozygotes for C (C;C) at 5% level. ‡ indicates statistical difference between Homozygotes for T and Homozygotes for C (C;C) at 10% level.

Table 2. Regression models of FTO variants on birth weight

Dependent variable	(1) Std BW	(2) Std BW	(3) Std BW	(4) Std BW
Genotype model				
Heterozygotes (C;T)	0.113 (0.075)	0.133 (0.104)		
Homozygotes for C (C;C)	0.133 (0.112)	0.082 (0.159)		
Dominant model				
Heterozygotes (C;T) and Homozygotes for C (C;C)			0.117 (0.072)	0.127 (0.103)
Control variables ^a	Yes	Yes ^b	Yes	Yes ^b
Family fixed effects	No	Yes	No	Yes
N	876	876	876	876
R-squared	0.05	0.66	0.05	0.66

Note. Std BW = Standardized Birth Weight. a. Demographic and family controls include gender, age, a sibling indicator, birth order, father's education, mother's education, and family income. b. Family controls are omitted because siblings share family-level characteristics. In all models, robust standard errors were clustered at the family-level. In all models, homozygotes for T (T;T) were used as a reference category.

* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Table 3. Regression models of FTO variants and birth weight on BMI in adulthood, Genotype and dominant models

Dependent variable	(1) BMI	(2) BMI	(3) BMI	(4) BMI	(5) BMI
Panel A. Genotype model					
Gene (G)					
Heterozygotes (C;T)	0.476 (0.358)		0.432 (0.352)	0.331 (0.554)	0.410 (0.552)
Homozygotes for C (C;C)	1.007* (0.538)		0.955* (0.535)	1.082 (0.753)	1.307* (0.776)
Environment (E)					
Std BW		0.407** (0.174)	0.390** (0.172)	0.567** (0.236)	0.067 (0.316)
G × E					
Heterozygotes (C;T) × E					0.848** (0.422)
Homozygotes for C (C;C) × E					1.214** (0.592)
Control variables ^a	Yes	Yes	Yes	Yes ^b	Yes ^b
Family fixed effects	No	No	No	Yes	Yes
N	876	876	876	876	876
R-squared	0.05	0.05	0.05	0.67	0.68
Panel B. Dominant model					
Gene (G)					
Heterozygotes (C;T) and Homozygotes for C (C;C)	0.596* (0.339)		0.550* (0.333)	0.416 (0.552)	0.510 (0.551)
Environment (E)					
Std BW		0.407** (0.174)	0.391** (0.172)	0.562** (0.236)	0.079 (0.316)
G × E					
Heterozygotes (C;T) and Homozygotes for C (C;C) × E					0.904** (0.397)

Control variables ^a	Yes	Yes	Yes	Yes ^b	Yes ^b
Family fixed effects	No	No	No	Yes	Yes
N	876	876	876	876	876
R-squared	0.05	0.05	0.05	0.67	0.68

Note. BMI = Body Mass Index; Std BW = Standardized Birth Weight. a. Demographic and family controls include gender, age, a sibling indicator, birth order, father's education, mother's education, and family income. b. Family controls are omitted because siblings share family-level characteristics. In all models, robust standard errors were clustered at the family-level. In all models, homozygotes for T (T;T) were used as a reference category.

* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Table 4. Regression models of FTO variants and birth weight on obesity in adulthood, Genotype and dominant models

Dependent variable	(1) Obesity	(2) Obesity	(3) Obesity	(4) Obesity	(5) Obesity
Panel A. Genotype model					
Gene (G)					
Heterozygotes (C;T)	0.016 (0.029)		0.015 (0.029)	-0.010 (0.048)	-0.002 (0.049)
Homozygotes for C (C;C)	0.068 (0.046)		0.067 (0.046)	0.110* (0.064)	0.124* (0.066)
Environment (E)					
Std BW		0.008 (0.014)	0.007 (0.014)	0.019 (0.021)	-0.027 (0.031)
G × E					
Heterozygotes (C;T) × E					0.085** (0.038)
Homozygotes for C (C;C) × E					0.084 (0.055)
Control variables ^a	Yes	Yes	Yes	Yes ^b	Yes ^b
Family fixed effects	No	No	No	Yes	Yes
N	876	876	876	876	876
R-squared	0.02	0.02	0.02	0.63	0.64
Panel B. Dominant model					
Gene (G)					
Heterozygotes (C;T) and Homozygotes for C (C;C)	0.028 (0.029)		0.027 (0.028)	0.003 (0.047)	0.012 (0.048)
Environment (E)					
Std BW		0.008 (0.014)	0.007 (0.014)	0.018 (0.021)	-0.026 (0.031)
G × E					
Heterozygotes (C;T) and Homozygotes for C (C;C) × E					0.082** (0.037)

Control variables ^a	Yes	Yes	Yes	Yes ^b	Yes ^b
Family fixed effects	No	No	No	Yes	Yes
N	876	876	876	876	876
R-squared	0.02	0.02	0.02	0.63	0.63

Note. Std BW = Standardized Birth Weight. a. Demographic and family controls include gender, age, a sibling indicator, birth order, father's education, mother's education, and family income. b. Family controls are omitted because siblings share family-level characteristics. In all models, robust standard errors were clustered at the family-level. In all models, homozygotes for T (T;T) were used as a reference category.

* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$

Figures

Fig 1. Differential effects of FTO variants for birth weight on BMI in adulthood

Fig 2. Differential effects of FTO variants for birth weight on obesity in adulthood

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