Socioeconomic Status over the Life Course and Polygenic Risks for Obesity in the U.S. Elderly Population

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INTRODUCTION

Studies of gene-environment interaction (GxE) have largely contributed to our understanding on how the social context and genetic factors interdependently influence health and social outcomes (Boardman *et al.* 2014; Guo *et al.* 2008; Pescosolido *et al.* 2008; Simons *et al.* 2011). Yet, extant GxE studies have typically focused on environmental factors measured at one time point and ignored dynamics in one's social experiences, which can play a crucial role in shaping subsequent behaviors. Moreover, traits of interest to social scientists such as cognition, educational attainment, and health behaviors, haven been found to be associated with many genetic variants by genome-wide association studies (GWAS) (Davies *et al.* 2014; Rietveld *et al.* 2013; Ripke *et al.* 2013; Sklar *et al.* 2011; Speliotes *et al.* 2010). However, very few social scientists have taken advantage of these recent advances in genomic studies in the investigation of GxE.

The aim of this study is to combine the life-course paradigm and recent findings of GWAS to assess how socioeconomic status (SES) over the life course and genetic factors interactively influence body mass index (BMI) in late adulthood. Specifically, we are interested in whether the joint effect of a collection of obesity-related genetic polymorphisms on BMI in old age depends on SES trajectories.

Currently in the United States, more than two-thirds of adults are overweight or obese (Flegal *et al.* 2012). This figure is alarming given that obesity is associated with numerous health

problems such as diabetes, high blood pressure, high cholesterol, asthma, and arthritis (Mokdad *et al.* 2003). Research has consistently shown that SES is strongly related to obesity (McLaren 2007; Monteiro *et al.* 2004; Pollitt *et al.* 2005; Senese *et al.* 2009). Most studies on the relationship between SES and obesity have focused on a single measure of SES. However, there is growing awareness that instability of SES might have important implications for health during adulthood (Braveman *et al.* 2005; Galobardes *et al.* 2006a; Galobardes *et al.* 2006b). Childhood SES may influence adult health outcomes independently of, or in relation to, adult SES. This has led to an interest in the influence of SES during particular stages of life, and changes in SES over the life course on later life health. Three perspectives have been postulated in terms of the association between life-course SES and health outcomes: *sensitive period*, *accumulation of (dis)advantage,* and *social mobility* (Berkman 2009; Cohen *et al.* 2010; Kuh *et al.* 2003; Loucks *et al.* 2010; Pollitt *et al.* 2005; Shanahan and Hofer 2011; Shavers 2007). The *sensitive period* perspective hypothesizes that certain stages of life have a stronger impact on later health outcomes than others. The *accumulation of (dis)advantage* perspective posits that the accumulated SES (dis)advantage over the life course is associated with adult health outcomes. Finally, the *social mobility* model suggests that stability or mobility across SES levels over the life course also has an impact on health outcomes.

This study is among the first efforts to integrate GWAS findings into the models addressing the relationship between SES and health behavior. Using indicators of SES at different life stages and genome-wide data in the Health and Retirement Study (HRS), we find that stable and high SES over the life course compensates for genetic risks of overweight or obesity in late adulthood.

GENE-ENVIRONMENT INTERACTION MODELS

Many traits of interest to social scientists are consequence of genetic and environmental factors, as well as interactions among them. Shanahan and Hofer (2005) develop several typologies to understand GxE mechanisms. At least two of them may shed light on GxE for obesity-related traits: *contextual triggering* and *social compensation*.

Central to the *contextual triggering* mechanism is the coaction of risky environments and risky genes. Contextual triggering can be weak or strong. In its weak form, unhealthy environments may increase genetic effects by triggering the expression of the risky alleles. An example is Sonestedt *et al.* (2009) study, where the relationship between fat mass and *FTO* (i.e., fat mass and obesity-associated protein) gene was found to be stronger among those who reported a high-fat diet than those who reported a low-fat diet. In a more recent study, based on a polygenic predisposition score, Qi *et al.* (2012) found that the genetic association with BMI was greater among individuals with a higher intake of sugar-sweetened beverages than those with a lower intake. The strong *triggering*, as illustrated in Panel (b) of Figure 1, refers to circumstances in which genetic risks merely manifest themselves under adverse conditions but not under "normal" conditions. Compared to *weak triggering*, this *strong triggering* mechanism has received less attention in explanations of GxE for obesity-related traits. A famous example on other phenotypes is the study of Caspi *et al.* (2002) on antisocial behaviors. In this study, the authors identified an association between the *MAOA* (the monoamine oxidase A) gene and antisocial behaviors, but mainly among test subjects who experienced childhood maltreatment.

In contrast to the *contextual triggering* model which stresses the harmful influence of adverse conditions, the *social compensation* model underscores the protective influence of favorable conditions. According to Shanahan and Boardman (2009), in some cases, *compensation* and *triggering* can be two ends of a continuum, where the former represents an

absence of stressors that trigger the expression of risky genes (i.e., *weak compensation*). As shown by Andreasen *et al.* (2008) and Li *et al.* (2010), higher levels of physical activity were linked to a significant reduction in the genetic risk for obesity. Furthermore, the compensation could be stronger such that genetic effects that express under "normal" conditions do not manifest themselves under enriched social or environmental conditions (i.e., *strong compensation*). This perspective is shown graphically in Panel (c) of Figure 1. Like *strong triggering*, this *strong compensation* mechanism is largely understudied in obesity-related research, but it is supported by findings on other phenotypes. Shanahan *et al.* (2007) found that dopamine receptor type 2 (DRD2 TaqlA) was associated with a decreased likelihood of school continuation for both white and black males, however, this association was completely attenuated among respondents who reported a teacher as their mentor (i.e., an adult who made an important positive difference early in their lives).

[Figure 1 about here]

In summary, three conceptual GxE models can be formed on the basis of *contextual triggering* and *social compensation* typologies: *weak trigger/compensation*, *strong triggering*, and *strong compensation*. It should be noted these models do not necessarily suggest mutually exclusive relationships among the environment, genes, and the phenotype. Instead, they indicate the complexity of these relationships. Using SES as an indicator of the social environment, we investigate the complex relationships among SES, genes, and obesity, as explained in the following section.

LITERATURE REVIEW AND RESEARCH HYPOTHESES

Socioeconomic Status, Genes, and Obesity

SES has been attributed as a fundamental cause of health and mortality (Link and Phelan 1995). Research has consistently shown a relationship between low SES and poor health outcomes (Braveman *et al.* 2010; Kanjilal *et al.* 2006; Kennedy *et al.* 1998; Minkler *et al.* 2006; Thurston *et al.* 2005). It is particularly well-documented that low SES is associated with overweight and obesity in developed countries (McLaren 2007; Monteiro *et al.* 2004; Senese *et al.* 2009; Wang and Beydoun 2007). There are various explanations of the relationship between low SES and obesity. It has been suggested that, compared to high-SES individuals, those with low SES typically lack access to resources and knowledge of nutrition and health, have greater exposure to obesogenic environments, and are less physically active because of deprived or unsafe residential environments (Boslaugh *et al.* 2004; Burdette and Whitaker 2005; Ellaway *et al.* 1997; Lynch *et al.* 1997; Martikainen *et al.* 2003). All of these factors might result in unbalanced energy intake and energy expenditure, thereby contributing to obesity.

While most research on the relationship between SES and obesity focuses on a single measure of SES (McLaren 2007; Monteiro *et al.* 2004), this research recognizes the importance of SES over the life course and examines three distinct, but related, perspectives: *sensitive period*, *social accumulation*, and *social mobility*.

Sensitive period

The *sensitive period* perspective posits that certain periods over the life-course have a stronger influence on later outcomes than other periods. A large number of studies have shown that one's SES during childhood and adolescence is associated with obesity-related traits in adulthood (Pollitt *et al.* 2005; Senese *et al.* 2009). There are three major explanations for such an association. The first explanation focuses on affordability and availability of resources. Compared to energy-dense, less nutritious foods, healthy and nutrient-dense foods (e.g., fruits

and vegetables) are typically more expensive, thus less affordable for low-SES families (Darmon and Drewnowski 2008; Neumark-Sztainer *et al.* 2003). Moreover, low-SES families are more likely than high-SES families to be located in poor communities with limited access to public exercise facilities, and because such communities are often viewed as unsafe, children's physical activities outdoors are restricted by their parents (Lumeng *et al.* 2006). Lack of nutritious food and physical activity during early life stages could put individuals at higher risk for overweight or obesity throughout the life course. Secondly, children from low-SES families typically suffer more from family risks (e.g., marital instability and conflict), and consequently have greater difficulties with emotion regulation and social competence (Repetti *et al.* 2002; Troxel and Matthews 2004). Poor emotion regulation during childhood may result in higher levels of anxiety, depression, eating disorders, and an inability to form and maintain strong relationships and to secure social support—all of which could raise the risk for obesity at later life stages (Alvarez *et al.* 2007; Anderson *et al.* 2006; Herzer *et al.* 2011). Thirdly, the relationship between childhood SES and adult obesity is also influenced by social norms on body weight and attitudes toward obesity (Power and Parsons 2000). Researchers have found that dieting is more common among high-SES women (Jeffery and French 1996; Jeffery *et al.* 1991), and there is evidence that girls' desire to be thin starts in adolescence or even earlier (Dornbusch *et al.* 1984).

Given the association between childhood SES and various proximate factors (e.g., diet, physical activity etc.) that have been found to modify the expression of genes related to overweight or obesity, we expect that the *genetic risks for overweight or obesity differ among people with different levels of childhood SES* (H_1). Combining the *sensitive period* perspective and three GxE models, we develop three hypotheses:

H_{1a} (weak triggering/compensation): The genetic risks for overweight or obesity are greater among individuals with lower levels of childhood SES than those with higher levels of childhood SES.

H_{1b} (strong triggering): The genetic risks for overweight or obesity manifest only among individuals with low childhood SES, but not among those with high or medium childhood SES.

H_{1c} (strong compensation): The genetic risks for overweight or obesity manifest among individuals with low or medium childhood SES, but not among those with high childhood SES.

Social Accumulation

In contrast to the *sensitive period* perspective, the *social accumulation* perspective does not emphasize the SES-related exposures that occur at certain stages of the life course. Rather, it hypothesizes that socioeconomic (dis)advantages over the life course accumulate to influence health outcomes. There is growing research considering cumulative (dis)advantage as a mechanism producing mortality and health problems in adulthood (Heraclides and Brunner 2010; Kuh *et al.* 2002; Lynch *et al.* 1997; Malhotra *et al.* 2013). Based on multiple indicators of SES at childhood and early adulthood, a study of a British postwar cohort reports that the mortality for individuals with persistently low SES from childhood to early adulthood was three to five times higher than for those with persistently high SES (Kuh *et al.* 2002). Similar cumulative effects of low SES are found based on a study of adults from Alameda County in the United States (Lynch *et al.* 1997). One example of obesity-related traits is the research of Heraclides and Brunner (2010). Using cross-sectional data from the Whitehall II study, the authors found that the odds of overweight or obesity were 61% higher for women who experienced disadvantage in one life phase, 66% higher for those who experienced disadvantage

in two phases, and 160% higher for those disadvantaged in all phases, relative to those who experienced no disadvantage in all phases.

As to our knowledge, no one has considered cumulative (dis)advantage as an environmental indicator in the investigation of GxE. To address this gap, we examine how cumulative (dis)advantage interacts with obesity genes in influencing obesity in late adulthood. We expect *the genetic risks for overweight or obesity are moderated by cumulative (dis)advantage in SES over the life course* (H_2). Specifically, we hypothesize:

H_{2a} (weak triggering/compensation): The genetic risks for overweight or obesity are greater for individuals experiencing less socioeconomic advantage than those experiencing more socioeconomic advantage over the life course.

H_{2b} (strong triggering): The genetic risks for overweight or obesity manifest only among individuals experiencing the most socioeconomic disadvantage over the life course, but not among others.

H_{2c} (strong compensation): The genetic risks for overweight or obesity manifest among all individuals except those experiencing the most socioeconomic advantage over the life course.

Social Mobility

Like the *social accumulation* perspective, the *social mobility* perspective also emphasizes the joint effects of SES-related exposures. What is more, the latter suggests that the direction of SES mobility over the life course has important implications for health outcomes at later stages. According to Cohen *et al.* (2010), upward mobility, an increase in SES after childhood, leads to better health in later life. In other words, adverse effects of low SES at earlier life stages could be partially or fully remedied by higher SES at a later time. In contrast, downward mobility, a

decline from higher levels to lower levels of SES, leads to poorer health, even for people with high SES in childhood. Empirical studies, however, have found mixed findings with regard to the influence of social mobility in SES on obesity-related traits. Heraclides and Brunner (2010) found participants experiencing upward mobility did not have a lower prevalence of overweight and obesity than those with stable and low SES, whereas downwardly mobile participants had a higher prevalence of overweight and obesity than those with stable and high SES throughout the life course. A later study based on a sample of Southeast Asians provided evidence that women experiencing upward social mobility had lower odds of obesity relative to both those experiencing stable low SES and high SES throughout the life course (Malhotra *et al.* 2013).

In the present study, we consider mobility in one's SES-related experiences as an environmental indicator and examine how SES mobility trajectories moderate influences of obesity genes on obesity in late adulthood. We expect that *genetic risks for overweight or obesity vary across SES trajectories* (H_3). Specifically, we hypothesize:

H_{3a} (weak triggering/compensation): The genetic risks for overweight or obesity are greater among individuals experiencing stable and low SES or downward mobility, compared to those experiencing stable and high SES or upward mobility.

H_{3b} (strong triggering): The genetic risks for overweight or obesity manifest only among individuals with stable and low SES over the life course, but not among those in other SES trajectories.

H_{3c} (strong compensation): The genetic risks for overweight or obesity manifest among all individuals except those with stable and high SES over the life course.

DATA AND METHOD

Data for this study come from Health and Retirement Study (HRS). HRS is a longitudinal study of Americans over age 50 conducted every two years from 1992 to 2012; it collects information on economic, health, social, and other factors relevant to aging and retirement. HRS includes six birth cohorts with different entry years: the Study of Assets and Health Dynamics Among the Oldest Old (AHEAD) cohort (born before 1924) surveyed in 1993, 1995, and 1998-2012; Children of Depression (CODA) cohort (born 1924-1930) surveyed in 1998-2012; HRS cohort (born 1931-1941) surveyed from 1992-2012; War Baby (WB) cohort (born 1942-1947) surveyed in 1998-2012; Early Boomers (EB) cohort (born 1948-1953) surveyed in 2004-2012; and Mid Boomers (MB) cohort (born 1954-60) surveyed in 2010 and 2012.

DNA samples were collected in 2006 and 2008. Of the collected samples, 13,129 were put into genotyping production and 12,507 passed the University of Washington Genetics Coordinating Center's (GCC) standardized quality control processes. Before imputation, 53 samples had a missing call rate (MCR) greater than 2% and were excluded. Thus, imputed data are available for 12,454 individuals. We focused on non-Hispanic whites 65 years or older in this study. EB and MB cohorts were not included because respondents in these two cohorts had not reached 65 years old when the most recent wave (2012) was collected. To minimize potential reverse causality in the relationship between obesity and SES, we excluded participants who reported that they were in poor health from birth to age 16. All the restrictions resulted in our analytical sample of 7193 respondents.

Outcome Variable: BMI

The outcome variable in this study is BMI (weight[kg]/height[m]^2). Respondents were asked to report their height at least one time (e.g., at entry into the study) and to report their

weight at each wave. Based on height and weight information, we calculated BMI for all respondents at each wave assuming no change in their height.

SES Measures

We used three life-course SES measures respectively for SES in childhood, young adulthood, and late adulthood. Childhood SES is measured by father's occupation ("What was your father's occupation when you were 16?").[1] Young-adulthood SES is based on years of education ("What is the highest grade of school or year of college you completed?"). Late-adulthood SES is based on post-retirement wealth (sum of all types of assets, pensions etc.).[2] Imputed income and wealth are both available in HRS. Wealth was chosen over income as research shows the former is a more accurate measure of SES among older adults (Allin *et al.* 2009).

Absolute SES measures might be sensitive to cohort differences. For example, it is likely that a high school degree indicated high SES for individuals in earlier cohorts, but medium/low SES for those in later cohorts.[3] To address this, we recoded the SES measures into relative indicators based on a baseline sample. The baseline sample includes earliest measures of all respondents (either provided DNA or did not). These measures were taken in 1992 for HRS, 1993 for AHEAD, 1998 for CODA and WB. We trichotomized respondents into low, medium, and high SES categories on the basis of the first and second tertiles of each of the three SES measures[4] within each birth cohort in the baseline sample.

[1] Father's occupation is the most commonly used indicator of childhood SES (Senese et al. 2009).
[2] To minimize reverse causality, we chose wealth measured at each respondent's entry into the study.
[3] We conducted sensitivity analyses based on absolute SES measures (e.g., below high school, high school, above high school). The major findings remain, suggesting our findings are robust to different coding strategies.
[4] Father's occupation is transformed into occupation prestige score (Norc Scores) before being recoded into relative childhood SES indicator. Years of education was trichotomized for males and females separately.

To test H_2, we constructed a cumulative socioeconomic advantage score (CAS)[5] (Hallqvist *et al.* 2004; Heraclides and Brunner 2010; Loucks *et al.* 2009; Loucks *et al.* 2010; Luo and Waite 2005; Otero-Rodríguez *et al.* 2011). Each of the three life-course SES indicators was assigned a value of "1" for high SES and "0" for medium or low SES and then summed to form a total score, with possible values of 0, 1, 2, and 3. A higher value on this score indicates greater cumulative socioeconomic advantage.

To test H_3, we defined eight mutually exclusive and exhaustive SES mobility trajectories based on respondents' SES at three time points (childhood to early adulthood to late adulthood): (1) low/medium childhood SES, low/medium young-adulthood SES, and low/medium late-adulthood SES (LLL); (2) low/medium childhood SES, low/medium young-adulthood SES, and high late-adulthood SES (LLH); (3) low/medium childhood SES, high young-adulthood SES, and low/medium late-adulthood SES (LHL); (4) low/medium childhood SES, high young-adulthood SES, and high late-adulthood SES (LHH); (5) high childhood SES, low/medium young-adulthood SES, and low/medium late-adulthood SES (HLL); (6) high childhood SES, low/medium young-adulthood SES, and high late-adulthood SES (HLH); (7) high childhood SES, high young-adulthood SES, and low/medium late-adulthood SES(HHL); (8) high childhood SES, high young-adulthood SES, and high late-adulthood SES(HHH) (Beckett 2000; Hallqvist *et al.* 2004; Heraclides and Brunner 2010; James *et al.* 2006; Loucks *et al.* 2010; Luo and Waite 2005; Otero-Rodríguez *et al.* 2011). In preliminary analyses, we tested for different specifications of the SES trajectories and conducted sensitivity tests. We found the results are not sensitive to the specification of young adulthood SES. To simplify the interpretation, we

[5] We used a cumulative SES advantage score instead of a cumulative SES disadvantage score as we found the major difference is between high SES and medium/low SES in terms of the SES-BMI relationship.

combined LLL and LHL into "stable and low", HHH and HLH into "stable and high," LLH and LHH into "upwardly mobile," and HLL and HHL into "downwardly mobile."

Genetic Measures

Genetic factors play an important role in determining body weight. Family and twin studies show that genetic factors account for 40%-70% of the variation in body mass (Herrera and Lindgren 2010; Maes *et al.* 1997; Stunkard *et al.* 1986). Genome-wide association studies (GWAS) have discovered many genetic variants associated with obesity-related traits (Frayling *et al.* 2007; Loos *et al.* 2008; Meyre *et al.* 2009; Monda *et al.* 2013; Okada *et al.* 2012; Speliotes *et al.* 2010; Thorleifsson *et al.* 2009; Uppsala *et al.* 2010; Wen *et al.* 2012; Willer *et al.* 2009). It is challenging to conduct GxE analysis for complex traits that are affected by multi-genetic factors (Shanahan and Hofer 2011). One approach is to extend the current GWAS approach, namely testing for the interaction between each genetic variant in the genome and the environmental factor and using a stringent p-value threshold (e.g., 5×10^{-8}) to control for false positives. However, this approach can hardly provide consistent evidence for GxE for complex human traits such as BMI because any single genetic polymorphism provides inadequate information about individual differences (Boardman *et al.* 2014).

In recent years, polygenic scores have been developed to measure the collective contribution of multiple genetic variants (Belsky *et al.* 2012; Li *et al.* 2010; Qi *et al.* 2012). In this study, we constructed a genetic predisposition score (GPS) on the basis of 32 single-nucleotide polymorphisms (SNPs) found to be associated with BMI in individuals of European ancestry (see Table A1 for more details about the 32 SNPs). When calculating the GPS, each SNP was weighted according to its relative effect size (β coefficient) on BMI. To obtain a more precise effect size of the SNPs, β coefficients from one recent meta-analysis were used (Speliotes

et al. 2010). To make the GPS more interpretable, we rescaled it to let each unit of the score correspond to one risk allele (Qi *et al.* 2012). Possible GPS values range from 0 to 64, with higher scores indicating greater genetic propensities to overweight or obesity. Figure A1 displays a positive association between GPS and BMI (P<.001). The slope is estimated to be .13, meaning that an increment of 10 risk alleles is associated with 1.3 kg/m^2 increase in BMI (i.e., about 10 lbs for a 6-foot person).

Control Variables

The control variables include age, birth cohort, gender, region (i.e., in which census area the respondent was born), and rural (i.e., whether the respondent lived in a rural area at about age 10). As we previously mentioned, low SES is typically associated with unhealthy behaviors (e.g., eating an unhealthy diet, less physical exercise, etc.) that raise risks for overweight or obesity, but smoking is an exception. Research has shown that lower SES is linked to greater prevalence of smoking (Hiscock *et al.* 2012), which is known to be associated with lower BMI. Also, in our preliminary analysis we found that low-SES respondents were less likely to drink alcoholic beverages, and a lower frequency of drinking was associated with lower BMI. Therefore, in our analyses we controlled for smoking (smoker or not), and drinking (ever drank alcoholic beverages or not) as two suppressors of the relationship between SES and BMI.

[Table 1 about here]

ANALYTIC STRATEGY

Mixed-effects models are used to assess the associations among SES, GPS, and BMI. These models enable us to effectively utilize the multi-wave data on BMI. The following equation describes the structure of our models:

$$BMI_{it} = \beta_0 + \beta_1 SES_i + \beta_2 GPS_i + \beta_3 SES_i x\ GPS_i + \sum_p \gamma_p C_{pi} + \sum_q \gamma_q C_{qit} + \varepsilon_{it},$$

where BMI_{it} is the BMI measure for respondent i at time t, for I = 1, …n and t = 1, …, T_i; T_i is the number of measurements and ranges from 1 to 11; SES_i and GPS_i represent SES (i.e., childhood SES, CAS, or SES mobility trajectories) and grand-median-centered GPS[6] for individual i; the interaction term, $SES_i x\ GPS_i$, is used to assess the moderating effect of SES on the genetic association with BMI (i.e., testing for H_1- H_3); C_{pi} represents time-invariant covariates such as birth cohort, gender, region, and rural, for p = 1, …P, where P is the maximum number of such covariates; C_{qit} represents time-varying covariates such as age[7], smoking, and drinking, for q = 1, …Q, where Q is the maximum number of such covariates, and ε_{it} is the residual term with $\varepsilon_{it} \sim N(0, \sigma^2)$. To address the correlation between repeated measures, we used the SP(POW) structure in SAS 9.3 which provides a generalization of the AR(1) structure. SP(POW) models the covariance between two measurements at times t_1 and t_2 as $cov(BMI_{it_1}, BMI_{it_2}) = \sigma^2 \rho^{|t_2 - t_1|}$.[8]

RESULTS

Main Effects

Before testing the hypotheses, we examined socioeconomic gaps in BMI. Socioeconomic gaps are illustrated by the differences between rows in Table 2. As can be seen, in each of the four cohorts, BMI is higher for lower levels of SES at each of the three life stages (i.e.,

[6] Grand-median-centered GPS allows us to interpret the intercept as the average level of BMI for individuals with medium genetic propensities to overweight or obesity.

[7] In all the analyses, we used cohort-median-centered age to minimize the correlation between age and cohort, and by doing so we can interpret the intercept as the average level of BMI for individuals at the median age of the cohort (Chen et al. 2010; Miyazaki and Raudenbush 2000; Yang and Land 2013).

[8] We also fit random intercept and random coefficient models to the data. The generalized AR(1) models are chosen because they provide best model fits.

childhood, young adulthood, or late adulthood). Considering the cumulative socioeconomic advantage, BMI is higher for those who experienced SES advantages at fewer phases over the life course. With regard to the four SES mobility trajectories, BMI is lowest for individuals who experienced stable and high SES, higher for those who were upwardly mobile, higher for those who were downwardly mobile, and highest for those with stable and low SES throughout the life course.

[Table 2 about here]

[Table 3 about here]

Socioeconomic Status, Genes, and BMI

Table 3 displays the results of Models 1-3 testing for H_1-H_3. None of H_{1a}, $H_{1b,}$ or H_{1c} is supported by the results of Model 1. As shown in the first column in Table 3, the interaction term is not significant at the .05 level, suggesting that there is no difference in the genetic association among individuals with different levels of childhood SES.

Model 2 tests for $H_{2.}$ The results offer support for H_{2c}: that is, the genetic risks for overweight or obesity are expressed among all individuals except those who enjoyed most socioeconomic disadvantage over the life course. Model 2 reports that the genetic association with BMI is significantly greater than 0 for all respondents except those experiencing high SES at all three phases (i.e., CAS = 3, the reference category). To be specific, an increment of 10 risk alleles is associated with 1.2 [10 x (.04 + .08)] increase in BMI for those who experienced high SES at two phases (i.e., CAS = 2; P>.05 for interaction), and 1.5 [10 x (.04 + .11)] increase in BMI for those who did not experience high SES or experienced high SES at one phase (i.e., CAS = 0 or 1; P<.05 for interaction). Comparing results from Model 1 and Model 2, we argue that

instabilities in SES have important implications for genetic risks of overweight or obesity. Particularly, a decline from higher levels to lower levels of SES (i.e., downward mobility) might result in increased genetic risks for overweight or obesity. Panel (1) of Figure 2 shows the genetic association with BMI for respondents with different CAS. Viewed differently, the socioeconomic differences in BMI may depend on the genetic propensity. We used the John-Neyman (J-N) technique (Preacher 2006) to identify turning points and confidence bands. As can be seen, stable and high SES significantly decreased an individual's BMI when his/her genetic predisposition score is greater than 23. This implies that the socioeconomic gap in BMI manifests only for individuals with higher genetic propensities to overweight or obesity, but not for those with lower genetic propensities.

[Figure 2 about here]

Results from Model 3 provide evidence for H_{3c}. The genetic association with BMI is significantly greater than 0 for respondents in all SES trajectories except those with stable and high SES over the life course. The increases in BMI per increment of 10 risk alleles are .8 [10 x (.04 + .04)] for upwardly mobile respondents (P>.05 for interaction), 2.4 [10 x (.04 + .20)] for downwardly mobile respondents (P<.01 for interaction), and 1.5 [10 x (.04 + .11)] for those with stable and low SES (P<.05 for interaction). Again, these results also support that the idea that the socioeconomic gap in BMI is conditioned on the genetic propensity. As Panel (2) of Figure 2 displays, BMI in the downward mobility trajectory is significantly higher than that in the stable and high trajectory only for respondents with higher genetic propensities (i.e., a GPS greater than 28).

DISCUSSSION AND CONCLUSIONS

This study demonstrates how the life-course paradigm can benefit from and contribute to genomic research in studies of health disparities. We consider the joint influences of SES and genetic factors on BMI in the context of aging and the life course. We show how SES trajectories over the life course moderate genetic risks for obesity in late adulthood. Our findings provide support for the "strong compensation" hypothesis, which predicts that stable and high SES compensates for genetic risks of overweight or obesity in late adulthood.

Our study highlights the importance to combine knowledge from social sciences and genomic studies to understanding health disparities. First, studies have shown that environmental and genetic factors interactively influence obesity-related traits (Andreasen *et al.* 2008; Boardman *et al.* 2014; Graff *et al.* 2013; Graff *et al.* 2012; Karnehed *et al.* 2006; Li *et al.* 2010; Qi *et al.* 2012; Rampersaud *et al.* 2008; Sonestedt *et al.* 2009; Vimaleswaran *et al.* 2009a; Vimaleswaran *et al.* 2009b). However, extant GxE studies typically focus on varying genetic effects at different levels of one environmental factor (e.g., healthy diet versus unhealthy diet) but ignore changes in the environment over time. In the present study, we examine the interaction between genetic factors and SES at different life stages as well as SES mobility. We find that the genetic association with BMI is significantly weaker for respondents with stable and high SES over the life course as compared to those in some other SES trajectories, but there is no evidence that any one of the three SES indicators, individually, moderates the genetic association.[9] In other words, some significant SES x gene findings would be undetectable without taking into account changes in SES over the life course.

Secondly, we offer evidence that the SES-BMI association depends on individuals' genetic propensities to overweight or obesity. We find higher SES is associated with lower BMI,

[9] Additional results (not shown) also suggest the genetic association with BMI does not differ across levels of young and later adulthood SES.

but merely among respondents with high genetic propensities to overweight or obesity. Without genetic information, the SES gap in BMI would not be observed. This finding underscores the significance of incorporating genetic information into research of social inequality in health outcomes.

Our study is not without shortcomings. First, we focused on non-Hispanic whites but did not include minority samples in our analysis. Although genetic information is also available for some minority samples (e.g., blacks and Asians), their small sample size does not afford sufficient statistical power for separate GxE analyses. Future research can extend the analysis in this study to other racial populations when data are available. Secondly, although the SES measures in this research cover the three importance life stages, more subtle changes over the life course are undetectable. Thirdly, we adopted the propensity score approach to minimize the potential selection bias. However, this approach is based on an assumption that the selection mechanisms are observable. Bias due to unobservable mechanisms may still remain even after controlling for the propensity score in models.

Despite these limitations, this study offers a roadmap for the integration of genomic findings into research of social inequality in health outcomes. Nowadays molecular genetic data are increasing available in large-scale datasets (e.g., the Fragile Families Study, the Framingham Heart Study, the National Longitudinal Study of Adolescent Health, the Wisconsin Longitudinal Study etc.), thereby providing researchers unprecedented opportunities to study how socioenvironmental factors and genetic factors interactively influence health behavior. The theoretical framework and methods in this paper could be expanded to study other outcomes that are consequences of the complex interplay of environmental factors and individual propensities.

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Table 1. Sample Summary Statistics by Cohort: Health and Retirement Study, 1992 – 2012

	AHEAD (Born before 1924)	CODA (Born 1924-1930)	HRS (Born 1931-1941)	WB (Born 1942-1947)
	Mean/% (SE)	Mean/% (SE)	Mean/% (SE)	Mean/% (SE)
Dependent Variable				
BMI[a]	25.66(.13)	26.75(.12)	27.64(.09)	28.72(.18)
Independent Variables				
Genetic Predisposition Score (GPS)	28.71(.13)	29.09(.10)	29.08(.07)	29.03(.11)
Childhood SES				
Low	.18	.18	.21	.24
Medium	.38	.56	.51	.45
High	.33	.13	.16	.18
Missing	.11	.12	.13	.14
Young Adulthood SES				
Low	.10	.18	.16	.12
Medium	.12	.16	.18	.44
High	.78	.66	.65	.44
Late Adulthood SES				
Low	.12	.18	.20	.22
Medium	.33	.34	.36	.36
High	.55	.47	.44	.41
Cumulative Advantage in SES (CAS)				
0	.09	.17	.19	.29
1	.27	.33	.33	.29
2	.35	.31	.28	.21
3	.18	.06	.08	.07
CDS missing	.11	.13	.13	.14
SES trajectories				
Stable and low/medium	.27	.39	.41	.42
Downwardly mobile	.13	.06	.06	.08
Upwardly mobile	.29	.35	.31	.26
Stable and high	.20	.07	.09	.09
SES trajectories missing	.11	.12	.13	.14
Covariates				
Age	74.06(.13)	69.71(.09)	65.72(.02)	65.57(.02)
Female	.63	.56	.54	.60
Region				
Midwest	.31	.35	.34	.32
Northeast	.19	.22	.22	.22
South	.30	.23	.30	.27
West	.19	.10	.09	.10
Other	.00	.01	.04	.02
Region missing	.01	.08	.00	.07
Rural				
Rural	.35	.44	.48	.48
Urban	.52	.53	.50	.51
Rural missing	.13	.02	.02	.01
Smoking[a]				
Smoker	.05	.09	.15	.15
Nonsmoker	.95	.91	.85	.84
Smoking missing	.00	.00	.01	.01

Drinking[a]				
Ever drank	.62	.60	.56	.58
Never drank	.38	.40	.44	.42
N	897	1457	3424	1415

Note: [a] For time-varying variables, summary statistics are based on the earliest measure in the analytic sample.

Table 2. Mean Body Mass Index (Standard Error) by levels of Life-course SES in Four Birth Cohorts

	AHEAD (1)	CODA (2)	HRS (3)	WB (4)	Overall (5)
Childhood SES					
Low	26.54(.33)**	26.89(.30)	28.10(.20)***	29.32(.33)**	27.99(.14)***
Medium	25.62(.22)**	26.66(.15)	27.66(.12)***	28.77(.25)**	27.43(.09)***
High	25.46(.22)**	26.78(.32)	26.88(.20)***	27.82(.34)**	26.72(.13)***
Young Adulthood SES					
Low	26.22(.43)**	27.45(.27)***	27.96(.22)***	29.47(.51)***	27.91(.16)***
Medium	26.61(.44)**	27.35(.26)***	28.37(.18)***	29.16(.25)***	28.42(.13)***
High	25.44(.15)**	26.41(.15)***	27.35(.11)***	28.09(.23)***	26.96(.07)***
Late Adulthood SES					
Low	26.41(.47)*	27.66(.35)***	28.40(.23)***	30.01(.40)***	28.48(.17)***
Medium	25.67(.23)*	27.14(.19)***	28.03(.14)***	29.00(.26)***	27.78(.10)***
High	25.49(.17)*	26.11(.15)***	26.98(.22)***	27.75(.22)***	26.71(.08)***
Cumulative Advantage in SES					
0	26.69(.51)**	27.56(.27)***	28.37(.21)***	29.97(.33)***	28.59(.15)***
1	26.04(.26)**	26.96(.21)***	28.18(.16)***	28.48(.29)***	27.75(.11)***
2	25.52(.22)**	26.14(.19)***	26.86(.15)***	27.89(.31)***	26.65(.10)***
3	25.26(.28)**	26.10(.48)***	26.33(.27)***	27.22(.55)***	26.16(.18)***
SES Trajectories					
Stable and Low	26.18(.27)*	27.24(.20)***	28.29(.15)***	29.56(.26)***	28.17(.10)***
Downwardly Mobile	25.64(.37)*	27.56(.49)***	27.40(.32)***	28.42(.52)***	27.26(.21)***
Upwardly Mobile	25.67(.24)*	26.13(.17)***	27.11(.14)***	28.01(.29)***	26.87(.10)***
Stable and High	25.35(.27)*	26.15(.42)***	26.50(.25)***	27.29(.45)***	26.31(.16)***

Note: Means of BMI are based on respondents' earliest BMI measures in the study (i.e., BMI measured in 1992 for HRS, 1993 for the AHEAD, 1998 for CODA and WB). In columns (1), (2), (3), and (4), analyses use ANOVA to test for mean socioeconomic differences in BMI. In column (5), analyses use ANOVA to test for mean cohort differences in BMI.
*p≤ .05; ** p≤ .01; *** p≤ .001.

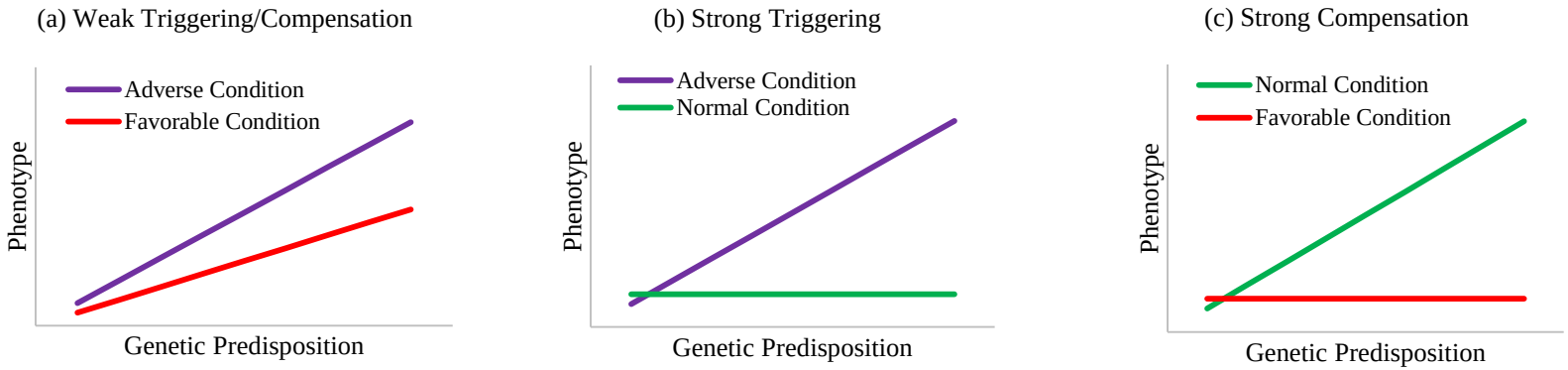
Table 3. Interaction of SES and Genetic Factors on BMI

	Sensitive Period	Accumulation of (dis)advantage	Social Mobility
	Model 1 (H_{1a}- H_{1c})	Model 2 (H_{2a}- H_{2c})	Model 3 (H_{3a}- H_{3c})
Genetic Predisposition Score (GPS)[a]	.13(.03)***	.04(.05)	.04(.04)
Childhood SES			
Low	.57(.19)**		
Medium	.34(.16)*		
High	.		
Cumulative Advantage in SES (CAS)			
0		1.81(.24)***	
1		1.22(.22)***	
2		.32(.21)	
3		.	
SES Trajectories			
Stable and Low (SL)			1.47(.20)***
Downwardly Mobile (DM)			.82(.27)**
Upwardly Mobile (UM)			.32(.20)
Stable and High (SH)			.
GPS x Childhood SES			
GPS x Low SES	- .00(.05)		
GPS x Medium SES	- .01(.04)	.	
GPS x High SES	.		
GPS x CAS			
GPS x CAS(=0)		.11(.05)*	
GPS x CAS(=1)		.11(.05)*	
GPS x CAS(=2)		.08(.06)	
GPS x CAS(=3)		.	
GPS x SES Trajectories			
GPS x SL			.11(.05)*
GPS x DM			.20(.07)**
GPS x UM			.04(.05)
GPS x SH			.
Covariates			
Age[b]	- .10(.01)***	- .10(.01)***	- .10(.01)***
Cohort	.72(.09)***	.70(.09)***	.74(.09)***
Age x Cohort	.04(.01)***	.04(.01)***	.04(.01)***
Female	- .59(.13)***	- .53(.12)***	- .73(.12)***
Male	.	.	.
Smoking (Yes)	-. 78(.07)***	-. 77(.07)***	-. 76(.07)***
Smoking (No)	.	.	.
Drinking (Yes)	.12(.03)***	.11(.03)***	.11(.03)***
Drinking (No)	.	.	.
Midwest	.49(.21)*	.49(.21)*	.51(.21)*
Northeast	.33(.22)	.37(.22)	.36(.22)
South	- .11(.21)	- .10(.21)	- .07(.21)
Other	- .29(.41)	- .30(.41)	- .23(.41)
West	.	.	.
Rural	.08(.13)	.02(.12)	.11(.12)
Urban	.	.	.
Propensity Score	-8.01(2.86)**	-9.39(2.82)***	-11.43(2.83)***
Random-Effect Variance			
σ^2	24.39(.40)***	24.44(.40)***	24.44.40)***
SP(POW)	.96(.00)***	.96(.00)***	.96(.00)***

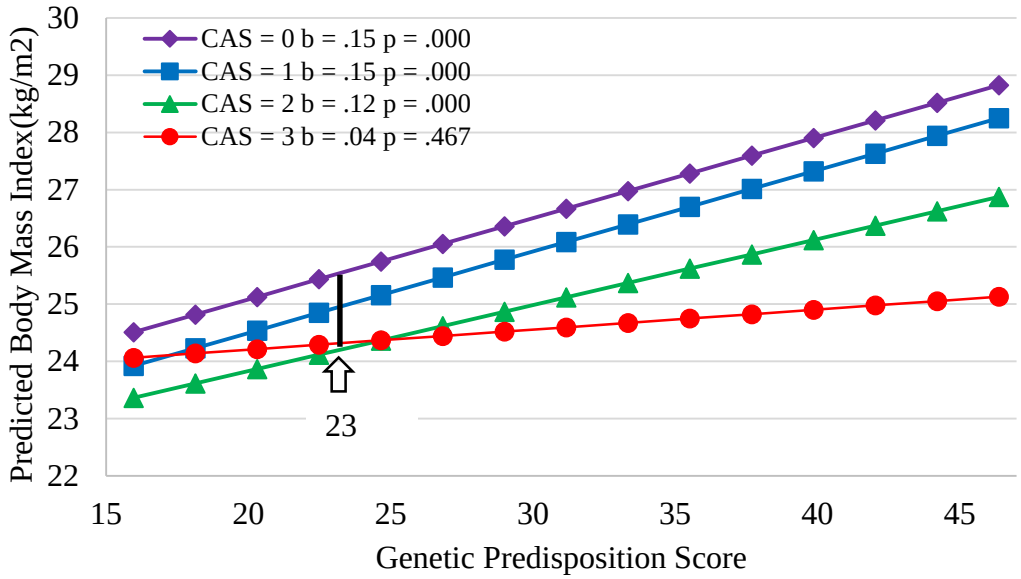
Goodness-of-fit			
BIC (smaller is better)	147,972.8	147,971.1	148,146.6
Sample Size			
N of persons	5,824	5,824	5,833
N of measures	33,727	33,727	33,770

Note: Model 1 also controls for young adulthood and late adulthood SES.
[a] GPS is grand median centered.
[b] Age is cohort median centered.
¶p≤ .05 (one-tailed tests)
*p≤ .05; ** p≤ .01; *** p≤ .001 (two-tailed tests).

Figure 1. Conceptual Gene-environment Interaction Models



(1) Model 2: CAS x GPS



(2) Model 3: SES Trajectory x GPS

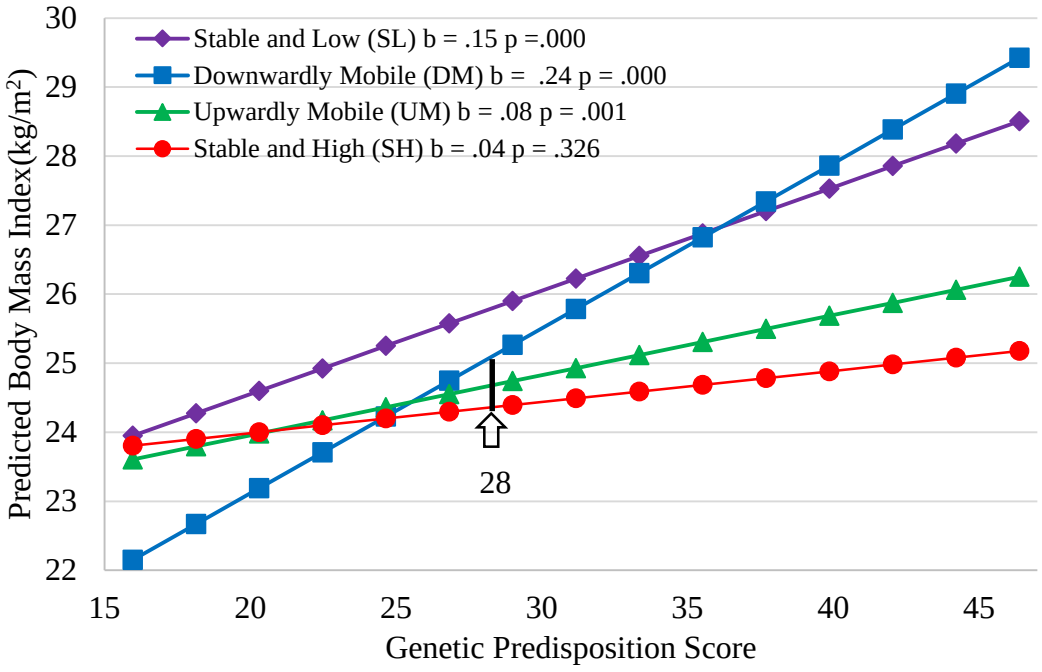


Figure 2: Genetic Association with BMI for Elderly with Differential Life-Course SES.
Note: Analysis is based on Johnson-Neyman 95% confidence bands.

Appendix

Table A1. Detailed Information about 32 Established SNPs for BMI

SNP	Nearest Gene		Allele			HRS	
		Chromosome	Effect[a]	Other	Beta	EAF[b]	r[2c]
rs543874	SEC16B	1	G	A	.22	.20	1
rs1514175	TNNI3K	1	A	G	.07	.47	1
rs1555543[d]	PTBP2	1	C	A	.06	.57	1
rs2815752	NEGR1	1	A	G	.13	.62	1
rs2890652	LRP1B	2	C	T	.09	.19	1
rs887912	FANCL	2	T	C	.10	.24	1
rs713586	RBJ	2	C	T	.14	.52	1
rs2867125	TMEM18	2	C	T	.31	.84	1
rs13078807	CADM2	3	G	A	.10	.17	1
rs9816226	ETV5	3	T	A	.14	.82	.99
rs13107325	SLC39A8	4	T	C	.19	.06	1
rs10938397	GNPDA2	4	G	A	.18	.40	1
rs4836133	ZNF608	5	A	C	.07	.58	1
rs2112347	FLJ35779	5	T	G	.10	.62	1
rs987237	TFAP2B	6	G	A	.13	.18	1
rs206936	NUDT3	6	G	A	.06	.27	1
rs10968576	LRRN6C	9	G	A	.11	.28	1
rs3817334	MTCH2	11	T	C	.06	.39	1
rs4929949	RPL27A	11	C	T	.06	.49	1
rs10767664	BDNF	11	A	T	.19	.80	1
rs7138803	FAIM2	12	A	G	.12	.34	1
rs4771122[d]	MTIF3	13	G	A	.09	.18	1
rs11847697[d]	PRKD1	14	T	C	.17	.06	1
rs10150332	NRXN3	14	C	T	.13	.23	1
rs2241423	MAP2K5	15	G	A	.13	.72	1
rs7359397	SH2B1	16	T	C	.15	.35	1
rs1558902	FTO	16	A	T	.39	.35	1
rs12444979	GPRC5B	16	C	T	.17	.87	1
rs571312	MC4R	18	A	C	.23	.24	1
rs29941	KCTD15	19	G	A	.06	.70	1
rs3810291	TMEM160	19	A	G	.09	.59	1
rs2287019	QPCTL	19	C	T	.15	.89	1

Note:

[a] Effect size in kg/m^2 of BMI obtained from Speliotes *et al.* (2010).

[b] Effect allele frequency in HRS.

[c] r^2 refers to the measurement of SNP imputation quality in HRS.

[d] Three SNPs are not included in the HRS imputed genotype data. SNPs with high levels of linkage disequilibrium were selected as alternatives. Specifically, rs1555543 is replaced by rs10489741 ($r^2 = 1$), rs4771122 by rs9512699 ($r^2 = .87$), and rs11847697 by rs10134820 ($r^2 = .74$).

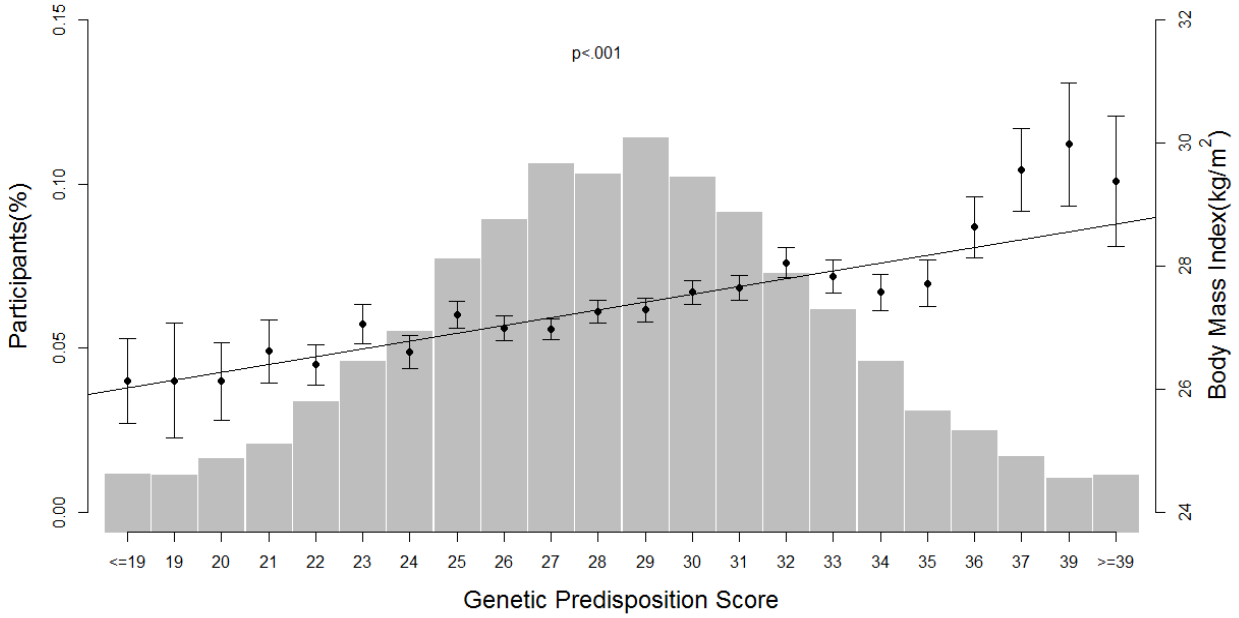


Figure A1. Genetic Predisposition Score (GPS) and Body Mass Index for HRS. GPS is calculated as the summation of weighted risk alleles (ranging from 16 to 43) for each participant. The X axis represents GPS and the Y axis on right represents mean BMI (± S.E.) of participants in corresponding GPS category, with the line showing the regression of the mean BMI values on GPS. The histogram (Y axis on left) shows the percentage of participants in each GPS category.