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Lifetime Socioeconomic Status, Historical Context, and Genetic Inheritance in Shaping Body Mass in Middle and Late Adulthood

Hexuan Liu^{1,3} and Guang Guo^{1,2,3}

¹Department of Sociology, the University of North Carolina at Chapel Hill

²Carolina Center for Genome Sciences, the University of North Carolina at Chapel Hill

³Carolina Population Center, the University of North Carolina at Chapel Hill

Abstract

This study demonstrates body mass in middle and late adulthood as a consequence of the complex interplay among individuals' genes, lifetime socioeconomic experiences, and the historical context in which they live. Drawing on approximately 9,000 genetic samples from the Health and Retirement Study, we first investigate how socioeconomic status (SES) over the life course moderates the impact of 32 established obesity-related genetic variants on body mass index (BMI) in middle and late adulthood. Further, we consider differences across birth cohorts in the genetic influence on BMI and cohort variations in the moderating effects of life-course SES on the genetic influence. Our analyses suggest that persistently low SES over the life course or downward mobility (e.g., high SES in childhood but low SES in adulthood) amplified the genetic influence on BMI, while persistently high SES or upward mobility (e.g., low SES in childhood but high SES in adulthood) compensated for such influence. For more recent birth cohorts, while the genetic influence on BMI became stronger, the moderating effects of lifetime SES on the genetic influence were weaker compared to earlier cohorts. We discuss these findings in light of social changes during the obesity epidemic in the United States.

Keywords

obesity; lifetime socioeconomic status; cohort; gene-environment interaction

INTRODUCTION

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, asthma, and high blood pressure (Mokdad *et al.* 2003). Obesity is a complex trait affected by genetic factors, socioeconomic status (SES), and historical context. In recent years, one important breakthrough in genomics is the discovery of specific 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;

Wen *et al.* 2012). These genetic variants, involved in various biological pathways such as energy balance and metabolism, play important roles in the development of obesity. At the societal level, socioeconomic factors have long been attributed as “fundamental causes” 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). In developed countries such as the United States, low SES is well documented to be associated with overweight and obesity (McLaren 2007; Sobal and Stunkard 1989). Moreover, recent decades have witnessed advances in food manufacturing and marketing practices, and growing cultural and technological adaptation. These changes also contribute to increasing obesity in the United States (Keith *et al.* 2006; Reither *et al.* 2009).

This study seeks to tie up the three lines of inquiry, namely, genetic inheritance, SES, and socio-historical contexts, to advance our understanding of obesity. As shown by gene-environment interaction (G × E) studies (Boardman *et al.* 2014; Demerath *et al.* 2013; Rokholm *et al.* 2011), genetic, socioeconomic, and historical factors do not act independently, but interactively, to affect obesity-related traits. Extant G×E studies, however, have typically focused on socioeconomic factors measured at one time point, and paid less attention to transitions and trajectories of one’s socioeconomic status (SES) and changes in the historical context in which one lives. These life-course dynamics, which often provide opportunities for behavioral change (Elder 1985; Elder *et al.* 2003; Ryder 1965), can be critical in shaping the relationship between genotypes and phenotypes. This calls for an integration of genetic research and life-course sociology in the investigation of obesity.

There are three specific aims of this study. First, we examine how SES over the life course moderates the genetic influence on body mass index (BMI) in middle and late adulthood. Second, we consider differences across birth cohorts in the genetic influence based on the proposition that cohort differences reflect changes in the socio-historical context in which individual lives unfold. Third, we investigate cohort variations in the moderating effects of life-course SES on the genetic influence. To achieve these aims, we take advantage of the accelerated multi-cohort longitudinal design of the Health and Retirement Study (HRS), the large-scale genetic sample in HRS (N = 8816), and the recently established 32 obesity-related genetic variants in genomic studies.

CONCEPTUAL FRAMEWORK AND RESEARCH HYPOTHESES

Gene-Environment Interaction Models

Genetic factors are influential in determining obesity-related traits, but their impact is, to a great extent, conditioned by an individual’s health behavior and the social context. Within the G×E paradigm, three different conceptual models have provided important explanations of how behavioral and contextual factors moderate genetic effects: *social trigger/compensation*, *social push*, and *differential susceptibility*.

The *social trigger/compensation* model includes two components and is graphically illustrated in Panel (a) of Figure 1. First, the *social trigger* component, also referred to as the *diathesis stress* model, emphasizes the harmful influences of adverse conditions (Ellis *et al.*

2011). Accordingly, unhealthy behaviors or environments may trigger or magnify effects of the risk alleles (Ravussin and Bouchard 2000). An example can be found in the study of Sonestedt *et al.* (2009), where the relationship between fat mass and the *FTO* (i.e., fat mass and obesity-associated protein) gene was observed to be stronger among those who reported a high-fat diet than those who reported a low-fat diet. Second, the *compensation* component underscores the protection of favorable conditions against genetic risk. As demonstrated by Kilpeläinen *et al.* (2011), higher degrees of physical activity were linked to a significant reduction in genetic risk of obesity. The *compensation* could be stronger such that genetic effects expressing under “normal” conditions do not manifest themselves under enriched behavioral or environmental conditions (i.e., *strong compensation*) (Shanahan and Boardman 2009). Rampersaud *et al.* (2008) found risk alleles of two polymorphisms on the *FTO* gene were strongly associated with increased BMI. Such associations were, nonetheless, completely attenuated among physically active individuals.

In contrast to the *social trigger/compensation* model, the *social push* model does not emphasize direct environmental effects on the genetic contribution. Rather, this model proposes that the genetic contribution can be camouflaged under strong environmental influences (Raine 2002). For example, individuals who keep a healthy diet and do regular physical exercises are less likely to become obese in spite of their genetic propensities. Also, if people live in an obesogenic environment and often eat unhealthy foods such as fatty fast foods or sugary desserts, they may gain weight regardless of whether they possess obesity-related genotypes or not. Under both circumstances, the environmental influences are the dominant causes and there is little room for genes to act. The genetic influences, therefore, are expected to be most salient among individuals exposed to medium levels of environmental risk. In a G×E study using twin data, the heritability of BMI was shown to be the highest for students attending schools with moderate body-size norms, whereas the genetic contribution is markedly less prominent for those in schools with stronger or weaker body-size norms (Boardman *et al.* 2012).

The *differential susceptibility* model has increasingly drawn attention in recent years (Belsky *et al.* 2007; Belsky and Pluess 2009). Accordingly, individuals with certain genotypes are more sensitive to environmental conditions. Compared to others, genetically sensitive individuals may find it easier to gain weight in obesogenic environments, whereas the same individuals are more likely to lose weight if they stay on a diet and keep physically active. As shown in Panel (c) of Figure 1, the direction of the genetic influence varies under differential conditions. Consequently, a genetic association with the outcome may be undetectable if environmental variations are ignored. There is empirical evidence for this differential susceptibility model that variants in the dopamine D4 receptor (*DRD4*) and the serotonin transporter gene (*5HTTLPR*) played protective roles under least-risky conditions, while the same variants produced genetic risks under most adverse social conditions (Daw *et al.* 2013; Simons *et al.* 2011; Mitchell *et al.* 2011).

Socioeconomic Status, Genes, and Obesity

In the present study, we use SES as our indicator of social environment. In contrast to previous G×E studies that mainly focused on socioeconomic factors measured at one time

point (Boardman *et al.* 2014; Boardman *et al.* 2012; Guo *et al.* 2007), we consider the dynamics of individuals' socioeconomic experiences over the life course. In the following we describe three distinct, but related, life-course perspectives: *sensitive period*, *social accumulation*, and *social mobility*. We then link the three perspectives and the G×E models to develop hypotheses on how timing, accumulation (i.e., duration), and stability of socioeconomic exposures moderate the genetic influence on obesity-related traits in middle and late adulthood.

The *sensitive period* perspective predicts that certain periods over the life course have stronger effects 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. Also, because these 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 of 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 degrees 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 of obesity in later life (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 a desire to lose weight, which starts in adolescence or even earlier, is more common among women with high SES than those with low SES (Dornbusch *et al.* 2001; Jeffery and French 1996; Jeffery *et al.* 1991).

In contrast to the *sensitive period* perspective that stresses the importance of the timing of exposure, the *social accumulation* perspective emphasizes the overall amount or duration of SES-related exposures. It states that socioeconomic (dis)advantages over the life course accumulate to affect health outcomes. There is growing research considering cumulative (dis)advantage (i.e., duration) as a mechanism that produces health problems in adulthood. Based on multiple indicators of SES in 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 in a study of adults from Alameda County in the United States (Lynch *et al.* 1997). Padyab and Norberg (2014) examined SES disadvantage in three phases of life. They showed that higher levels of

cumulative SES disadvantage were associated with higher BMI among women in late adulthood.

The *social mobility* perspective proposes that the direction of SES mobility over the life course has important implications for health outcomes at later stages. Upward mobility, an increase in SES after childhood, may lead to better health in later life (Cohen *et al.* 2010). In other words, the adverse effects of low SES earlier in life could be partially or fully remedied by higher SES at a later time. In contrast, downward mobility, a decline from higher to lower SES, may lead to poorer health, even for people with high SES in childhood. Heraclides and Brunner (2010) observed that participants experiencing downward mobility had a higher risk 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 those experiencing low SES throughout the life course (Malhotra *et al.* 2013).

Given the relationship between SES and various proximate factors (e.g., diet, physical activity, etc.) that modify the genetic contribution to obesity, we expect that *genetic influences on obesity-related traits are socioeconomically moderated* (H_1). According to the *social trigger/compensation* perspective, genetic risk is likely to be triggered by exposure to low SES, but to be compensated for by exposure to high SES. The genetic influence on body mass in middle and late adulthood therefore is hypothesized to be greater for individuals who experienced lower levels of childhood SES, less cumulative socioeconomic advantage, or downward mobility over the life course than for those who experienced higher levels of childhood SES, more cumulative socioeconomic advantage, or upward mobility. From the *social push* perspective, the genetic contribution may be masked by environmental influences among most socioeconomically (dis)advantaged individuals. Accordingly, the genetic influence on body mass in middle and late adulthood is predicted to be more salient among individuals experiencing medium levels of childhood SES, cumulative socioeconomic (dis)advantage, or SES mobility than those experiencing highest/lowest levels of childhood SES, most/least cumulative socioeconomic advantage, or persistently high/low SES over the life course. Finally, from the *differential susceptibility* perspective, some individuals are genetically more sensitive than others to either high or low SES. These genetically sensitive individuals might have higher levels of body mass (i.e., higher risk of overweight or obesity) in middle or late adulthood than others if they experienced low SES over the life course, whereas such individuals are likely to have lower levels of body mass (i.e., lower risk of overweight or obesity) if they experienced high SES over the life course.

Cohort Effects as an Indicator of Historical Change

In this study, we use cohort effects as an indicator of historical change to examine whether the genetic influence on body mass in middle and late adulthood and the moderating effects of SES on the genetic influence are contingent upon historical context. A cohort is a group of individuals who experience same historical and social events at the same ages (Ryder 1965). Different cohorts may have diverse life experiences inasmuch as they encounter historical and social changes at various stages of their lives. In his classic work on the children of the Great Depression, Elder ([1974] 1999) demonstrated that the impact of early-

life socioeconomic hardship on physical and emotional health varied by social class for the Oakland cohort (born in the early 1920s), namely that the most disadvantaged suffered the most adverse health consequences during adulthood. Importantly, when compared with a younger cohort (born in the late 1920s) who were more afflicted by the Great Depression, the Oakland males were better off in later life, possibly due to benefits of earlier entry into military service (Elder 1986). There is a growing interest in cohort effects on the genetic contribution to health outcomes. The genetic influence on smoking, for example, has been found to differ before and after the implementation of legislation on smoking behaviors (Boardman *et al.* 2010; Boardman *et al.* 2011; Kendler *et al.* 2000).

The cohort consideration has been extended to the study of obesity-related traits. Using cross-sectional data from southwestern Ohio, Demerath *et al.* (2013) examined birth-year variation in the associations between a genetic risk score based on obesity-related genetic variants and phenotypes such as BMI, waist circumference and skinfold thickness. They showed that the genetic association with BMI for males born in 1970, compared to those born in 1930, was three times as great. Such an increase in the genetic influence on BMI was attributed to the obesity epidemic. According to national surveys, the prevalence of obesity in the United States has risen 2.5-fold since the late 1970s (Flegal *et al.* 2012; Flegal *et al.* 1998; Flegal *et al.* 2010). Various factors have been claimed to be responsible for this obesity epidemic, such as advances in specific food manufacturing and marketing practices (e.g., the increasing availability of fast food and vending machines in public places), increased cultural and technological adaptation, reduced physical activity, etc. (Keith *et al.* 2006). In this study, we use a nationally representative, longitudinal sample to revisit the cohort-effect hypothesis, namely that *the genetic influence on body mass is greater among recent cohorts than earlier ones* (H₂).

Whereas the prevalence of obesity has increased in all SES groups since the 1970s, SES disparities of obesity have decreased for both male and female adults in the United States (Wang and Beydoun 2007). Specifically, the low-to-high SES ratio (i.e., prevalence in low SES group/prevalence in high-SES group) has reduced from 1.6 in the early 1970s to 1.1 in late 1990s for males, and from 3.4 to 1.3 for females. The high-SES group experienced the highest rate of increase in the prevalence of obesity (Zhang and Wang 2004). Therefore, we hypothesize that *the cohort differences in the genetic influence on body mass are greater for more socioeconomically advantaged groups*. In other words, *the moderating effects of SES on the genetic influence are weaker in more recent cohorts than in earlier cohorts* (H₃). We test this hypothesis from each of the three life-course perspectives (i.e., *sensitive period*, *social accumulation* and *social mobility*).

It should be noted that the relationships among genes, SES, and body mass can be complicated by race or ethnicity. Importantly, the 32 obesity-related genetic variants used in this study were discovered in genome-wide association studies (GWAS) using white samples (Speliotes *et al.* 2010). It is uncertain whether these discoveries are replicable in other racial/ethnic groups (Belsky *et al.* 2013; Domingue *et al.* 2014). We did sensitivity analysis by combining the white and black samples. The main results are similar to those based on only white samples. This is likely due to the fact that whites comprise the majority of the sample. The small size of minority samples does not afford sufficient statistical power for separate

G×E analysis. Moreover, our preliminary analysis shows higher SES at different life stages is associated with lower BMI among whites, whereas such a pattern does not exist among blacks. This is consistent with findings in previous studies of SES disparities in obesity-related traits (Braveman *et al.* 2010; Wang and Beydoun 2007; Zhang and Wang 2004). For these reasons, we focus on non-Hispanic whites in this study.

DATA AND MEASUREMENT

Data

Data for this study come from the 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. DNA samples were collected in 2006 and 2008. Of the collected samples, 13,129 were put into genotyping production using the Illumina Human Omni-2.5 Quad beadchip, and 12,507 passed the University of Washington Genetics Coordinating Center's (GCC) standardized quality control processes. Among these samples, 8,816 are non-Hispanic whites and they compose our analytic sample.

Variable Measurement

Outcome Variable—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.

Cohort Measure—Cohort is based on respondents' birth year. 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 Baby Boomers (EBB) cohort (born 1948–1953) surveyed in 2004–2012; and Mid Baby Boomers (MBB) cohort (born 1954–60) surveyed in 2010 and 2012. When the present study is conducted, genetic data are available for AHEAD, CODA, HRS, WB, and EBB cohorts. Importantly, unlike a cross-sectional study in which all measurements are taken at the same time, respondents of each cohort in HRS were repeatedly examined at different ages, allowing for cohort and age effects to be disentangled.

SES Measures—SES is multidimensional (i.e., it can be measured by educational attainment, occupational status, income, wealth, etc.), and the roles of different dimensions of SES vary over the life course. Specifically, one's SES in childhood primarily depends on his/her parents' SES. The transition from parental SES to one's own SES is mainly achieved through education. In middle/late adulthood, the role of wealth becomes increasingly important. Accordingly, we used three life-course SES measures respectively for SES in childhood, young adulthood, and middle/late adulthood. Childhood SES is measured by father's occupation ("What was your father's occupation when you were 16?"). Young-adulthood SES is based on years of education ("What is the highest grade of school or year

of college you completed?”). Middle/late-adulthood SES is based on household wealth (sum of all types of assets, pensions, etc.).¹ 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).

The same SES measure may have somewhat different meaning for different cohorts. 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.² This issue was addressed by within-cohort standardization. Specifically, we recoded the SES measures into relative indicators based on a baseline sample. The baseline sample includes onset measures for all respondents (either provided DNA or did not).³ These measures were taken in 1992 for HRS, 1993 for AHEAD, 1998 for CODA and WB, and 2004 for EBB. 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 measures⁴ within each birth cohort in the baseline sample.

To test the moderating effects of cumulative socioeconomic (dis)advantage on the genetic influence on BMI, we constructed a cumulative socioeconomic advantage score (CAS) (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 the moderating effects of SES trajectories on the genetic influence, we defined eight mutually exclusive and exhaustive SES mobility trajectories based on respondents’ SES at three time points (childhood to early adulthood to middle/late adulthood): (1) low/medium childhood SES, low/medium young-adulthood SES, and low/medium middle/late -adulthood SES (LLL); (2) low/medium childhood SES, low/medium young-adulthood SES, and high middle/late-adulthood SES (LLH); (3) low/medium childhood SES, high young-adulthood SES, and low/medium middle/late-adulthood SES (LHL); (4) low/medium childhood SES, high young-adulthood SES, and high middle/late-adulthood SES (LHH); (5) high childhood SES, low/medium young-adulthood SES, and low/medium middle/late-adulthood SES (HLL); (6) high childhood SES, low/medium young-adulthood SES, and high middle/late-adulthood SES (HLH); (7) high childhood SES, high young-adulthood SES, and low/medium middle/late-adulthood SES (HHL); (8) high childhood SES, high young-adulthood SES, and high middle/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. The results are not sensitive to the specification of young adulthood SES. To simplify the interpretation, we combined LLL and

¹To minimize reverse causality, we chose wealth measured at each respondent’s entry into the study.

²We 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.

³When constructing the SES indicators, we used the baseline sample instead of the analytic sample to minimize potential biases due to sample selection.

⁴Father’s occupation is transformed into occupation prestige score (NORC scale) before being recoded into a relative childhood SES indicator. Years of education was trichotomized for males and females separately.

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—In this study, we focused on 32 BMI-related single-nucleotide polymorphisms (SNPs). The association between each of the SNPs and BMI has been repeatedly validated using independent samples of European ancestry (Speliotes *et al.* 2010). Sixteen of the 32 SNPs were not included on the HRS-used Illumina Human Omni-2.5 Quad beadchip, and so we instead used genotypes imputed utilizing the phase 1 reference panel from the 1000 Gnomes Project (Howie *et al.* 2011; Li *et al.* 2009). Genotype imputation was conducted using the IMPUTE2 software (Howie *et al.* 2009). The imputation quality R^2 values range from .99 to 1.0 (see Appendix A for more details).

Control Variables—The relationship between SES and health is complicated and could be bidirectional (Case *et al.* 2005; Conley and Bennett 2000; Smith 2009). Individuals in poor health may be trapped in low SES. To address reverse causality, we used a baseline health measure based on a survey question “Consider your health while you were growing up, from birth to age 16. Would you say that your health during that time was excellent, very good, good, fair, or poor?” In our preliminary analysis, poor health in childhood significantly predicted low SES in young and middle/late adulthood. We controlled childhood health as a covariate in all regression models including SES as a predictor of BMI. We also conducted a sensitivity analysis by removing individuals who reported that they were in poor health in early life. This is consistent with previous studies in which researchers restricted their sample to individuals who were not in poor health at the baseline (Qi *et al.* 2012; Willson *et al.* 2007). The alternative approach produced very similar results.

Age is measured at the time of each survey. In our analytical models, we centered age at the grand median to obtain more interpretable results. Other control variables include 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 the risk of overweight or obesity, but smoking is an exception. Research has shown that lower SES is linked to a greater prevalence of smoking (Hiscock *et al.* 2012), which is known to be associated with lower BMI. Also, our preliminary analysis suggests that low-SES respondents were less likely to drink alcoholic beverages, and a lower frequency of drinking was associated with lower BMI. Therefore, we controlled for smoking (smoker or not), and drinking (ever drank alcoholic beverages or not) as two suppressors when assessing the relationship between SES and BMI. In addition, although we focused on non-Hispanic whites, population stratification within racial groups may confound the G×E results. To account for population stratification, we controlled for largest 10 principle components (PCs) in our G×E analysis (Price *et al.* 2006). These PCs were constructed on the basis of genome-wide SNPs with pair-wise squared correlation (R^2) smaller than 0.2.

ANALYTIC STRATEGY

Genetic Predisposition Score

We first constructed a genetic predisposition score (GPS) by summing up the number of risk alleles across the 32 obesity-related SNPs (Belsky *et al.* 2013; Domingue *et al.* 2014). Before summation, each SNP was weighted according to its relative effect size (β coefficient) on BMI. To have a more precise effect size of the SNPs, β coefficients were obtained from a meta-analysis of GWAS involving about 250,000 individuals that provides robust replication for the 32 SNPs (Speliotes *et al.* 2010).

Multivariate Analysis

We examined the interaction effects of obesity genes, SES, and cohort on BMI using multilevel models. Our sample consists of spousal pairs measured repeatedly over HRS waves. These measures are not independent from each other. Multilevel models have been developed to address the correlation structure among observations (Raudenbush and Bryk 2002). The following equations describe our model:

Level 1:

$$\begin{aligned} \text{BMI}_{jit} = & \beta_{0j} + \beta_1 \text{GPS}_{ji} + \beta_2 \text{SES}_{ji} + \beta_3 \text{Cohort}_{ji} \\ & + \beta_4 (\text{GPS}_{ji} \times \text{SES}_{ji}) + \beta_5 (\text{GPS}_{ji} \times \text{Cohort}_{ji}) + \beta_6 (\text{SES}_{ji} \times \text{Cohort}_{ji}) \\ & + \beta_7 (\text{GPS}_{ji} \times \text{SES}_{ji} \times \text{Cohort}_{ji}) \\ & + \sum_p \gamma_p C_{pji} + \sum_q \gamma_q C_{qjit} + \varepsilon_{jit}, \end{aligned}$$

Level 2:

$$\text{cov}(\text{BMI}_{jit_1}, \text{BMI}_{jit_2}) = \sigma^2 \rho^{|t_2 - t_1|},$$

Level 3:

$$\beta_{0j} = \beta_0 + u_j$$

where BMI_{jit} is the BMI measure for respondent i in household j at time t , for $i = 1, \dots, I$, $j = 1, \dots, J$, and $t = 1, \dots, T_j$; T_j is the number of measurements ranging from 1 to 11; GPS_{ji} , SES_{ji} , and Cohort_{ji} respectively represent grand-median-centered GPS⁵, SES (i.e., childhood SES, cumulative advantage score, or SES mobility trajectory) and birth cohort for respondent i in household j ; C_{pji} represents time-invariant covariates such as region, rural, PCs, and childhood health status for $p = 1, \dots, P$, with P being the maximum number of such covariates; C_{qjit} represents time-varying covariates such as age, age squared, smoking, and drinking, for $q = 1, \dots, Q$, with Q being the maximum number of such covariates; ε_{jit} is the level 1 residual term with $\varepsilon_{jit} \sim N(0, \sigma^2)$, and u_j is the level 3 random effect at the household level with $u_j \sim N(0, \sigma_u^2)$. The correlation between

⁵Grand-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.

repeated measures (i.e., the level 2 random effect) is modeled using the SP(POW) structure in SAS 9.3 which provides a generalization of the autoregressive 1 structure (see Appendix B for more details).

To examine average GPS \times SES interaction effects on BMI over birth cohorts (H_1), we first estimated reduced models without GPS \times Cohort, SES \times Cohort, and GPS \times SES \times Cohort interactions (Models 1a–c). We then estimated an average GPS \times Cohort interaction effect over SES groups (H_2) by fitting a reduced model without SES, GPS \times SES, SES \times Cohort, and GPS \times SES \times Cohort terms (Model 2). Finally, to assess cohort differences in the moderating effects of SES on the genetic association with BMI (H_3), we estimated the full model with all two- and three-way interaction terms among GPS, SES, and cohort (Models 3a–c). We compared models in which cohort is coded as a set of dummy variables with models where it is treated as a continuous variable with greater values indicating more recent cohorts (i.e., AHEAD = 1; CODA = 2; HRS = 3; WB = 4; EBB = 5). Results suggested linear cohort patterns, thus we report multivariate results based on the continuous cohort measure. As such, positive GPS \times Cohort interaction indicates increased genetic association with BMI in more recent cohorts, and negative GPS \times SES \times Cohort interaction indicates decreased moderating effects of SES on the genetic association with BMI in more recent cohorts.

Cohort Analysis Adjusting for Age

Although the accelerated multi-cohort longitudinal design of HRS allows us to disentangle age and cohort effects, it also has a limitation, namely that some ages were not observed for all cohorts. The AHEAD cohort was not observed before 70 years of age and the WB and EBB cohorts had not reached 70 when the most recent wave (2012) of data was collected. The differential age distribution by cohort may affect the accuracy of the cohort-difference estimates (Yang and Land 2013). Particularly, studies have shown age-related decline in lean body mass (Han *et al.* 2011; Villareal *et al.* 2005; Zamboni *et al.* 2005). Consequently cohort differences in genetic association with BMI might be driven by weight loss as the older cohorts are more likely to experience weight loss than the younger ones. To address this potential issue, we formed an age-comparable sample from overlapping age groups in AHEAD, CODA, and HRS cohorts. WB and EBB were not included because of their limited age overlap with other cohorts. For each cohort in the selected subsample, age ranges from 70 to 81 with a mean age of 73.4. Using the age-comparable sample, we replicated the cohort analysis and compared the results with those from the entire analytic sample.

RESULTS

Bivariate Relationships between Key Variables

Before testing the hypotheses, we examined bivariate associations of GPS, SES, and Cohort with BMI. In HRS, GPS values range from 16 to 43 (i.e., number of risk alleles), with higher scores indicating greater genetic propensities to obesity. GPS is positively associated with BMI (see Figure 2). An increment of 10 risk alleles is associated with a 1.3 kg/m² increase in BMI (i.e., about 10 lbs. for a 6-foot person). The first row in Table 2a shows the bivariate

correlation between GPS and BMI for each of the five cohorts. As can be seen, the GPS-BMI correlation is stronger for more recent cohorts than earlier ones.

Socioeconomic gaps in BMI (before age adjustment) are illustrated by the differences between rows in Table 2a, and inter-cohort variations by the differences between columns. In all five cohorts, BMI is typically higher among respondents with lower SES at each of the three life stages (two exceptions are young-adulthood-SES-BMI associations in AHEAD and HRS). 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. In almost all SES categories, BMI is higher in more recent cohorts than earlier ones.

The cohort patterns in BMI are likely to be confounded by differential age distribution across cohorts. Nevertheless, as demonstrated by Table 2b, such patterns still largely hold in the age-comparable sample where age is comparable across AHEAD, CODA, and HRS cohorts. This implies that the cohort patterns are not due to different age distributions across cohorts.

Moderating Effects of SES on the Genetic Association with BMI (H_1)

Table 3 displays the results of Models 1a–c testing for interactions of SES and GPS on BMI. As shown in the first column in Table 3, the interaction term in Model 1a (i.e., GPS \times childhood SES) is not significant at the .05 level, suggesting that there is no difference in the genetic association with BMI among individuals with different levels of childhood SES.

Results from Model 1b are consistent with the prediction of the *social trigger/compensation* model: that is, the genetic influence on BMI is greater for individuals who experienced less socioeconomic advantage than for those who experienced more socioeconomic advantage over the life course. Panel (1) of Figure 3 shows the genetic association with BMI for respondents with different CAS. Specifically, for respondents who experienced high SES at all three phases (i.e., CAS = 3), an increment of 10 risk alleles is associated with .7 increases in BMI ($P = .07$). The genetic association with BMI increased to 1.0, 1.4, and 1.7, respectively for those who experienced high SES at two, one and zero phases ($P < .05$ for interaction). Viewed differently, the socioeconomic differences in BMI may depend on genetic propensity. As can be seen, cumulative socioeconomic advantage significantly decreases an individual's BMI when his/her GPS 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.

Results from Model 1c support the *social trigger/compensation* model, which predicts that the genetic influence on BMI is greater among individuals who experienced stable and low SES or downward mobility, compared to those who experienced stable and high SES or upward mobility. As Panel (2) of Figure 3 displays, the increases in BMI per increment of 10 risk alleles are .7 for stable and high, .8 for upwardly mobile, 1.8 for downwardly mobile, and 1.6 for stable and low ($P < .01$ for interaction). Again, these results also suggest that the

socioeconomic gaps in BMI are conditioned on genetic propensity. BMI in the downward mobility trajectory is significantly higher than that in the stable and high trajectory only for respondents with a GPS greater than 28.

Cohort Differences in the Genetic Association with BMI (H₂)

The first two columns in Table 4 demonstrate results of testing cohort differences in the genetic association with BMI based on the whole analytic sample and the age-comparable sample. In line with H₂, Model 2 shows positive GPS × Cohort interactions, net of age, gender, and other covariates, suggesting increased genetic influence on BMI in more recent cohorts. On average, the genetic association with BMI increased by .03 in one cohort over a prior cohort (P<.01 for interaction).

Cohort Differences in the Moderating Effects of SES (H₃)

Columns 3–8 in Table 4 show cohort differences in the moderating effects of SES on the genetic influence. Models 3b and 3c show negative three-way GPS × cumulative advantage/mobility × Cohort interactions (P<.05 for interaction). Figures 4 and 5 show that the GPS × cumulative advantage/mobility interactions for BMI are weaker in more recent cohorts. Consistent with H₃, cohort differences in the genetic association with BMI are greater in socioeconomically advantaged groups than in disadvantaged groups. Whereas in AHEAD, CODA, and HRS the genetic association is much weaker among respondents experiencing upward mobility or stable and high SES than those experiencing downward mobility or stable and low SES, in WB and EBB there is no significant difference in the genetic association across SES groups.

In spite of reduced statistical power, the direction and magnitude of two- and three-way interactions estimated from the age-comparable sample are mostly consistent with that based on the whole sample. Again, this suggests that our cohort-difference results are robust to differences in the age distribution across cohorts.

Assessing the Effect of Selection Bias

While our analysis shows significant interactions of SES, obesity-related genes, and birth cohort on BMI in middle and late adulthood, the story is, in fact, more complicated. Selection processes could have played a role. The final step of our analysis is to assess the effect of selection bias.

Two types of selection can confound our results. First, one's exposure to SES-related environments may depend upon his or her genotype (rGE). Individuals with certain genotypes might be more likely to develop obesity-related health problems, and these problems in childhood may adversely affect their socioeconomic opportunities in later life (Haas 2006; Palloni *et al.* 2009). The existence of such rGE can bias our GPS × SES analysis (Jaffee and Price 2007; Wagner *et al.* 2013). To detect rGE, we examined correlations between GPS and SES measures. Differential distribution of the GPS by SES would indicate the existence of rGE. Figure 6 demonstrates that the mean and variance of the GPS are similar across different SES categories in childhood, young adulthood, and middle/late adulthood. Table 5 shows the comparison of the mean GPS across different SES

categories within each cohort. Overall, there are no clear SES patterns in the distribution of GPS.

Second, DNA samples were taken in 2006 and 2008, when ages of AHEAD range from 83–101, CODA from 76–82, HRS from 65–75, WB from 65–70, and EBB from 53–60. The retention of healthier, more affluent respondents in older cohorts can lead to confounded cohort-difference results that reflect differential characteristics between robust survivors and others in the population, rather than “real” effects of socio-historical changes. Specifically, AHEAD and CODA have a higher proportion of robust survivors, who may be less genetically predisposed to obesity than participants in other cohorts. Yet results in Table 5 show that the distribution of GPS does not significantly differ across birth cohorts in most SES groups. Furthermore, we replicated the cohort-difference analyses using a more homogeneous subsample that includes all “survival elites,” who were observed at age 80 or older. As Table 6 demonstrates, despite reduced statistical power, results estimated using the Survival Elites subsample are consistent with those based on the whole sample, indicating that our cohort-difference findings are robust against potential confounding from differential surviving across cohorts.

DISCUSSION AND CONCLUSIONS

This study makes important contributions to the G×E literature and the life-course paradigm. First of all, one of the biggest challenges in G×E research is to provide convincing evidence that social context interacts with genetic makeup to influence health outcomes. Over the decades, sociologists have developed a sophisticated understanding of social context, which is “multilevel, multidomain, longitudinal.” (Boardman *et al.* 2013: S64) Yet incorporating all these complexities in social context has been proved difficult and most empirical studies have considered only one environmental factor at a time (Boardman *et al.* 2014; Guo *et al.* 2008; Pescosolido *et al.* 2008; Shanahan *et al.* 2008; Simons *et al.* 2011). In this paper, we take on the challenge to examine how socioeconomic experiences over the life course and historical context moderate the genetic influence on BMI in middle and late adulthood. We developed hypotheses combining distinct G×E conceptual models (i.e., *social trigger/compensation*, *social push*, and *differential susceptibility*) and life-course perspectives addressing the SES-obesity relationship (i.e., *sensitive period*, *social accumulation*, and *social mobility*). Our empirical findings based on the HRS genetic sample support the *social trigger/compensation* model, which predicts that stable and low SES or downward mobility amplify the genetic influence on BMI, whereas stable and high SES or upward mobility compensate for such influence. However, there is no evidence that the genetic influence on BMI differs by levels of SES at a single life stage (e.g., childhood). This highlights the importance of considering timing, duration, and stability of socio-environmental exposures in the investigation of G×E interactions.

Secondly, viewed from a different perspective, our G×E findings also suggest that socioeconomic influences may depend on individuals’ genetic make-up. In our sample, higher SES was associated with lower BMI, but mainly among respondents with relatively high GPS. Without genetic information, the socioeconomic gaps in BMI would be

unobservable. This underscores the significance of incorporating genetic factors into empirical models and theoretical discussions regarding social inequality in health outcomes.

Thirdly, we provided evidence for the increased genetic influence on BMI in more recent birth cohorts. This finding is consistent with previous research based on regional data (Demerath *et al.* 2013). Importantly, we assessed the cohort differences using nationally representative data. Also, the accelerated multi-cohort longitudinal design of HRS offers us opportunity to disentangle cohort effects and age effects. We demonstrated that the cohort-difference results were, for the most part, maintained when using a subsample with an equal age distribution across birth cohorts. These results provide additional evidence that the cohort-difference findings may be somewhat affected, but not predominantly driven by age effects (e.g., age-related weight loss).

Fourthly, we found that the cohort differences in the genetic association with BMI was primarily among the most affluent individuals (see Figure 7). This might be attributable to social changes during the obesity epidemic such as increased cultural and technological adaptation (Ryder 1965). It is likely that affluent individuals in more recent cohorts had longer “screen time” (e.g., time spent in front of a computer) and engaged less in physical activity compared to their counterparts in earlier cohorts. Such social changes might lead to epigenetic modifications that regulate gene expression, thereby exacerbating genetic risk of obesity. Currently large-scale human studies of epigenetic mechanisms are still rare, and the relationship between obesity-related traits and epigenetic modifications is not well understood. Extant studies have shown an association of *FTO* gene variants and methylation variation (Almén *et al.* 2012; Bell *et al.* 2010). These studies, however, are typically small and lack statistical power to assess complex interactions among the environment, genotype, and epigenetic modifications. We hope advances in epigenetic technology in conjunction with increasingly available large-scale data will facilitate our understanding of specific mechanisms through which changes in social context shape the genetic influences on obesity-related traits in the future.

Finally, we conducted G×E analysis using a genetic predisposition score based on 32 established genetic variants related to BMI. This polygenic score approach helps to minimize the multiple testing problem in single-variant analysis and maximize statistical power. Identified in GWAS using stringent criteria (e.g., each variant-BMI association with $p\text{-value} < 5 \times 10^{-8}$) and replicated in independent samples (Speliotes *et al.* 2010), the 32 SNPs provide credibility for assessment of genetic association with BMI.

It is important to mention that although our empirical findings are consistent with the *social trigger/compensation* model, they do not necessarily disprove the other G×E models. The *social push* model predicts that genetic influences are most significant in benign environments, but may be masked under extreme environments. A critical challenge in assessing this model is that some extreme environmental conditions may not be captured in the survey data. For instance, individuals suffering from prolonged starvation during a famine were unlikely to become obese in spite of their genetic makeup. Such individuals, however, might not be included in the sample. Moreover, as previously mentioned, the 32 genetic variants used to construct the GPS are based on GWAS meta-analysis assuming

homogenous effects of risk alleles across samples. This assumption is, to some extent, at odds with the *differential susceptibility* model, which predicts that genetic effects may have opposite directions under differential environmental conditions (e.g., positive effects under adverse conditions but negative effects under favorable conditions). Such genetic variants might exist, but they do not stand out when their average effects on the whole population are assessed ignoring environmental variations. In other words, the current GWAS methods select against genetic variants that satisfy the *differential susceptibility* model. Discovery of such genetic variants may require a genome-wide gene-environment interaction (GWGEI) approach that allows heterogeneous genetic effects under differential environmental conditions (Boardman *et al.* 2014).

We acknowledge some limitations in the current study. We used three different indicators in assessing SES at childhood, young adulthood, and middle/late adulthood. Shifts in these indicators may affect the interpretability of the SES effects. A more refined lifetime SES indicator might be a composite measure with varying weights on different dimensions of SES (e.g., parental SES has more weight in measuring childhood SES, educational attainment has more weight in measuring young adulthood SES, and household wealth has more weight in measuring middle/late adulthood SES). In HRS, however, income and wealth information is only available after age 50, and educational attainment is the only indicator of young adulthood SES. Moreover, we did not include minority samples in our analysis. Although genetic information is available for some minorities (e.g., blacks and Asians), their sample size is insufficient to achieve adequate statistical power for separate G×E analysis. Future research can use more refined measures and extend the analysis in this study to other racial populations when data become available.

Despite these limitations, this study demonstrates body mass in middle and late adulthood as a consequence of the complex interplay among individuals' genes, dynamic socioeconomic experiences, and historical context in which they live. Nowadays molecular genetic data are increasingly available in large-scale datasets (e.g., the Fragile Families Study, the Framingham Heart Study, the National Longitudinal Study of Adolescent to Adult Health, the Wisconsin Longitudinal Study), thereby providing researchers unprecedented opportunities to study interactive influences of socio-environmental factors and genetic factors on health and social behaviors. The theoretical framework and methods in this paper could be expanded to study other complex traits of interest to social scientists.

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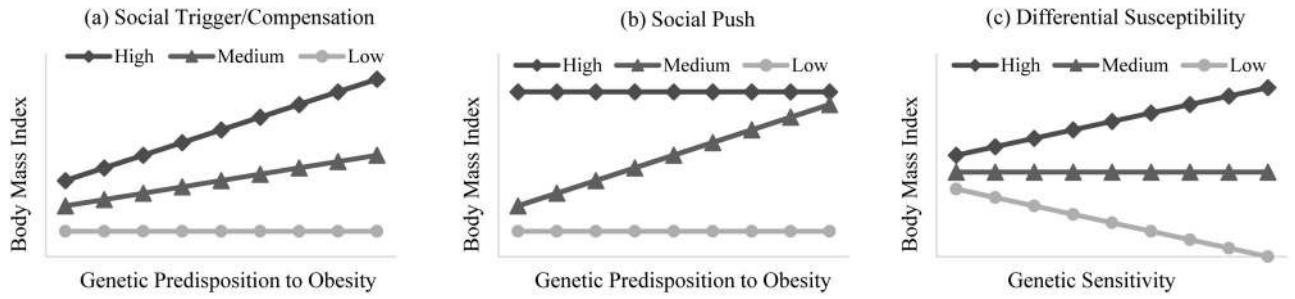


Figure 1.
 Conceptual Gene-Environment Interaction Models

Note: Lines with circles represent genetic association with BMI in lowest level of environmental risk compared to medium (triangles) and high (diamonds) risk. The magnitude of the genetic association is indicated by the slope. A steeper slope means greater genetic association.

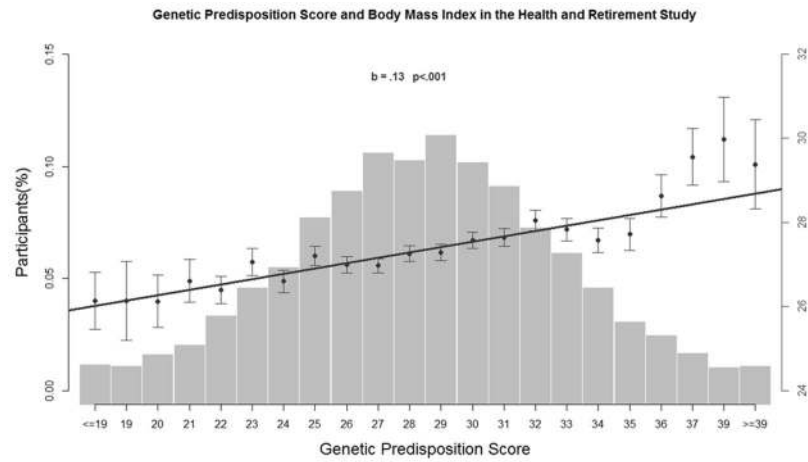


Figure 2. Genetic Predisposition Score and Body Mass Index in the Health and Retirement Study
Note: GPS is calculated as the number of weighted risk alleles (ranging from 16 to 43) for each participant. The X axis represents GPS and the Y axis on right represents mean BMI (\pm S.E.) of participants in 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.

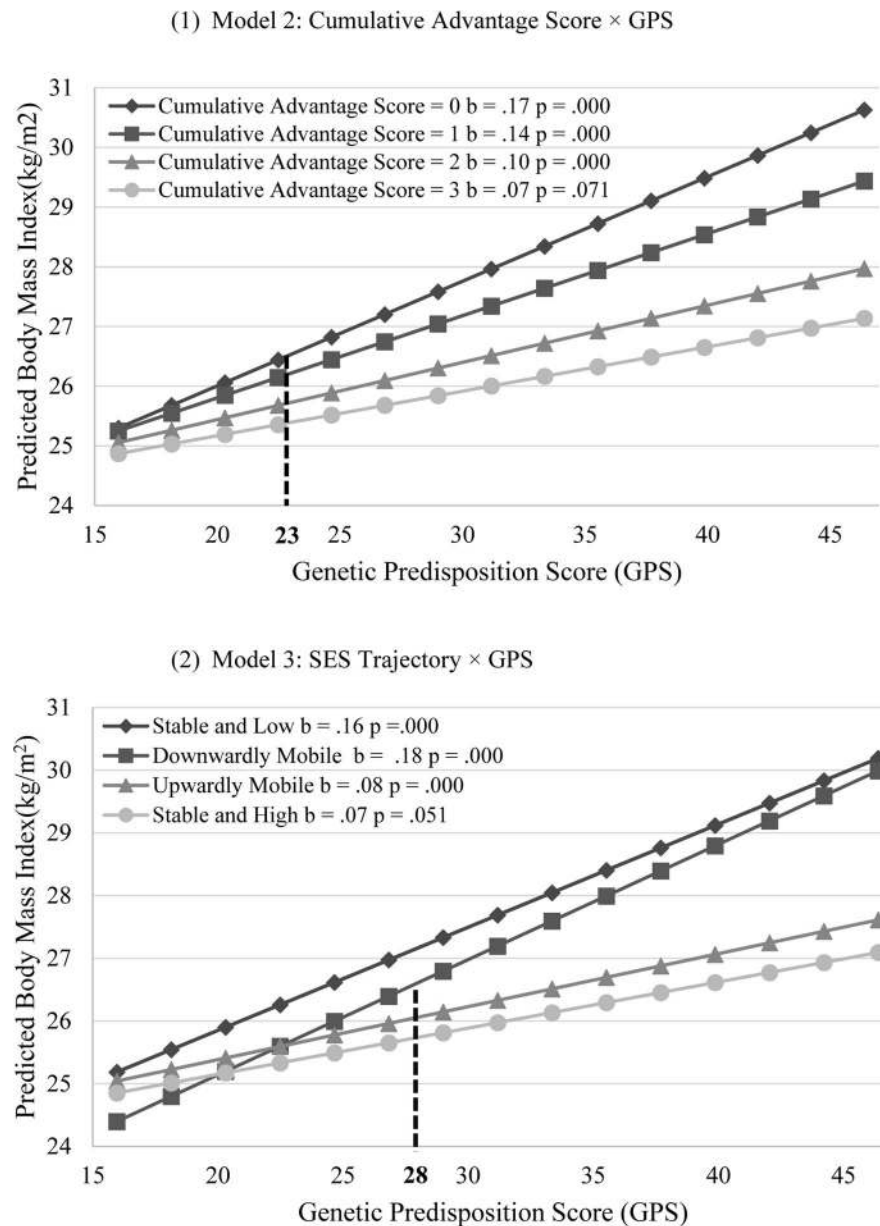


Figure 3.

Genetic Association with BMI for Individuals with Differential Life-Course SES

Notes: (1) Genetic association with BMI is weaker for individuals experiencing more socioeconomic advantage than those experiencing less socioeconomic advantage over the life course. (2) Genetic association with BMI is weaker for those experiencing stable and high SES or upward mobility than those experiencing stable and low SES or downward mobility. (3) Cumulative socioeconomic advantage significantly decreases an individual's BMI only when his/her GPS is greater than 23 (i.e., possessing more than 23 risk alleles). (4) The average BMI in the stable and high trajectory is significantly lower than that in the downward mobile trajectory only for those with a GPS greater than 28.

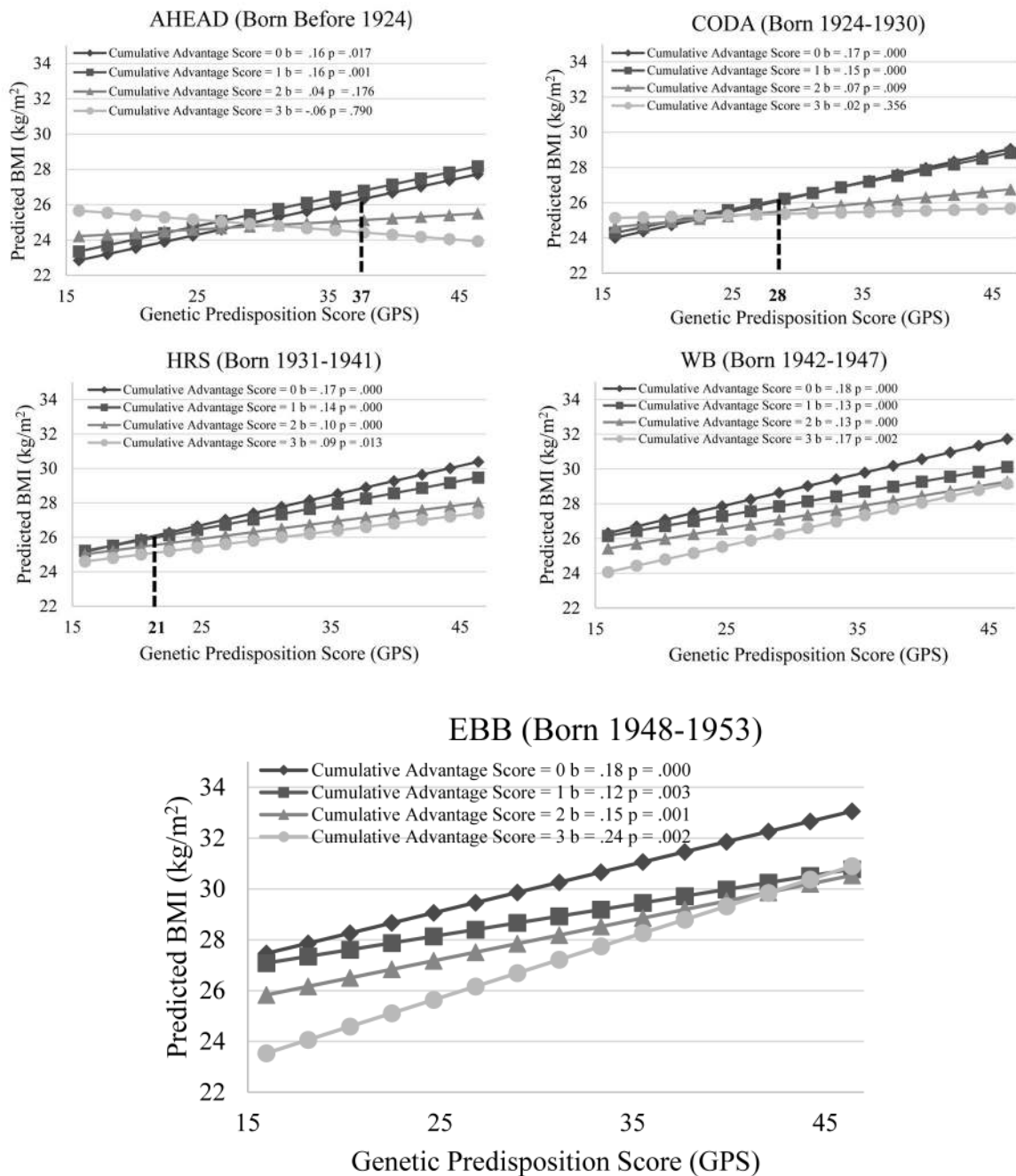


Figure 4. Genetic Association with BMI for Individuals with Different Levels of Cumulative Socioeconomic Advantages by Birth Cohort Net of Age and Other Covariates (Estimated Using the Whole Analytic Sample)
Note: (1) In AHEAD, CODA, and HRS cohorts, the genetic association with BMI is much weaker among those experiencing high SES in at least two of the three life stages (i.e., CAS = 2 or 3) than others (i.e., CAS = 0, 1). In WB and EBB, however, there is no significant difference in the genetic association with BMI across SES groups. (2) The mean BMI of individuals with CAS = 3 is significantly lower than that of those with CAS = 0 when the GPS is

greater than 37 in AHEAD, 28 in CODA, 21 in HRS. Such interaction patterns are less obvious or nonexistent in WB and EBB.

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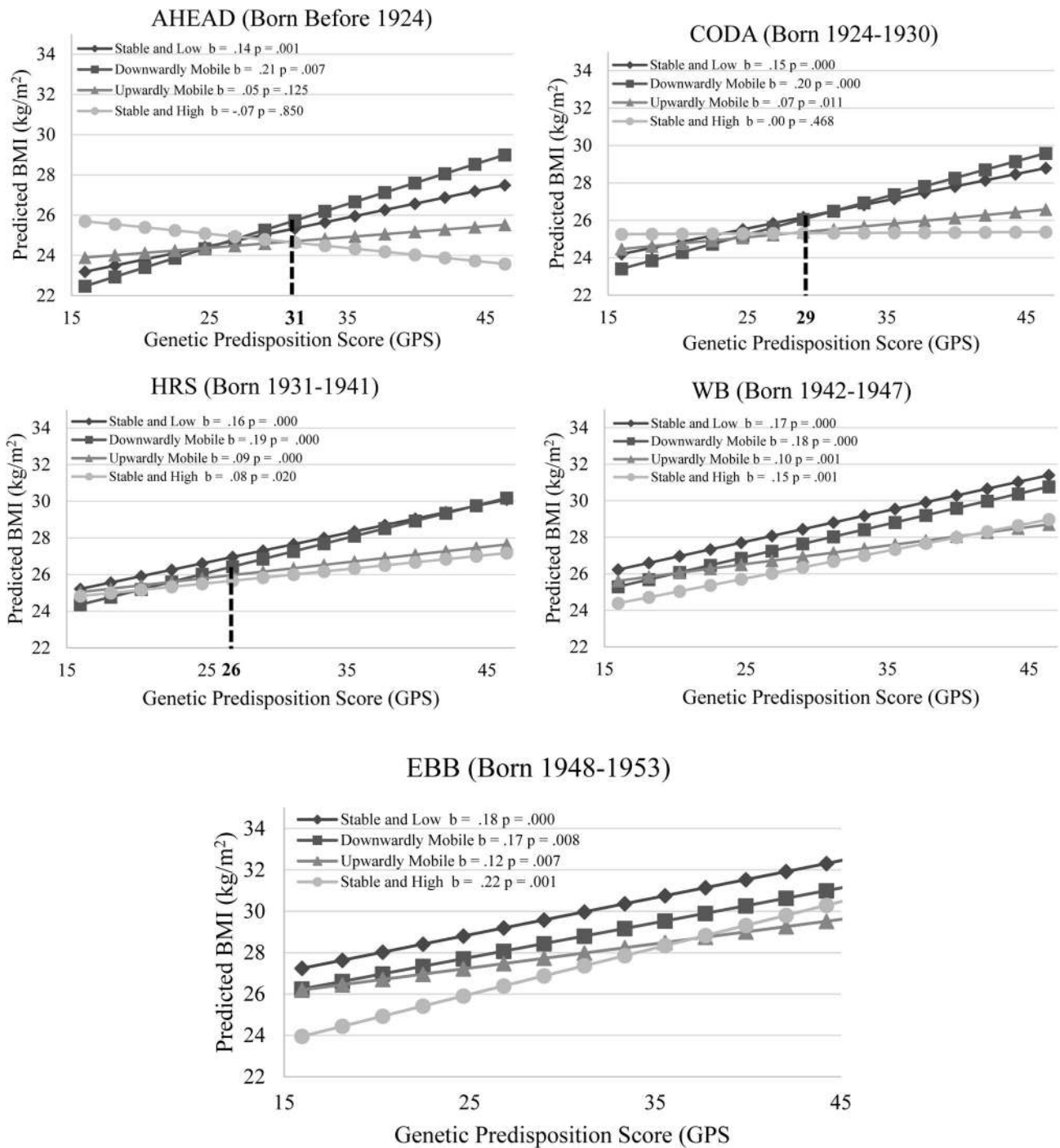


Figure 5. Genetic Association with BMI for Individuals in Different SES Mobility Trajectories by Birth Cohort Net of Age and Other Covariates (Estimated Using the Whole Analytic Sample)

Note: (1) In AHEAD, CODA, and HRS cohorts, the genetic association with BMI is much weaker among those experiencing stable and high SES or upward mobility than those

experiencing stable and low SES or downward mobility. In WB and EBB, however, there are no significant differences in the genetic association with BMI across SES groups. (2) The mean BMI in the stable and high trajectory is significantly lower than that in the downward mobile trajectory when the GPS is greater than 31 in AHEAD, 29 in CODA, 26 in HRS. Such interaction patterns are less obvious or nonexistent in WB and EBB.

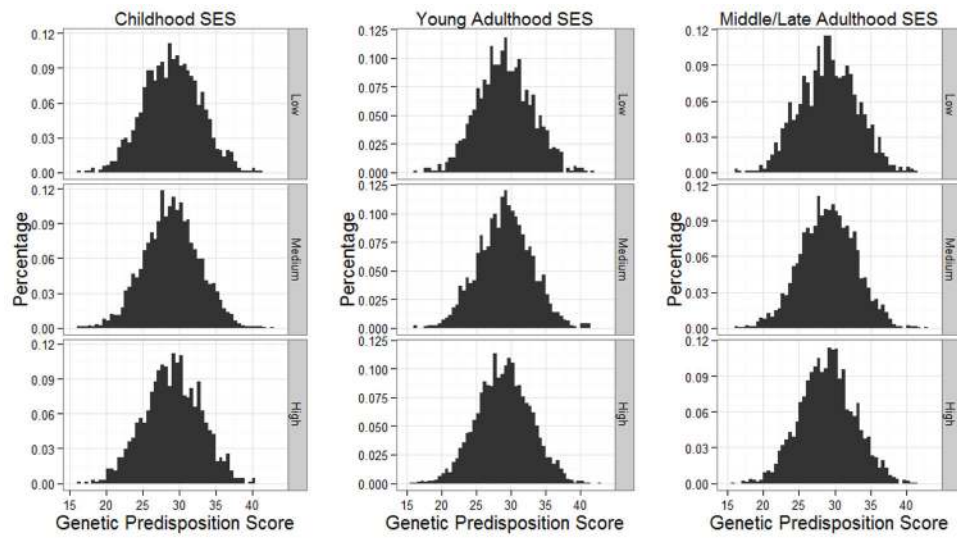


Figure 6.

Distribution of the Genetic Predisposition Score by SES

Note: The distribution of the genetic predisposition score is similar across levels of SES in childhood, young adulthood, and Middle/late adulthood.

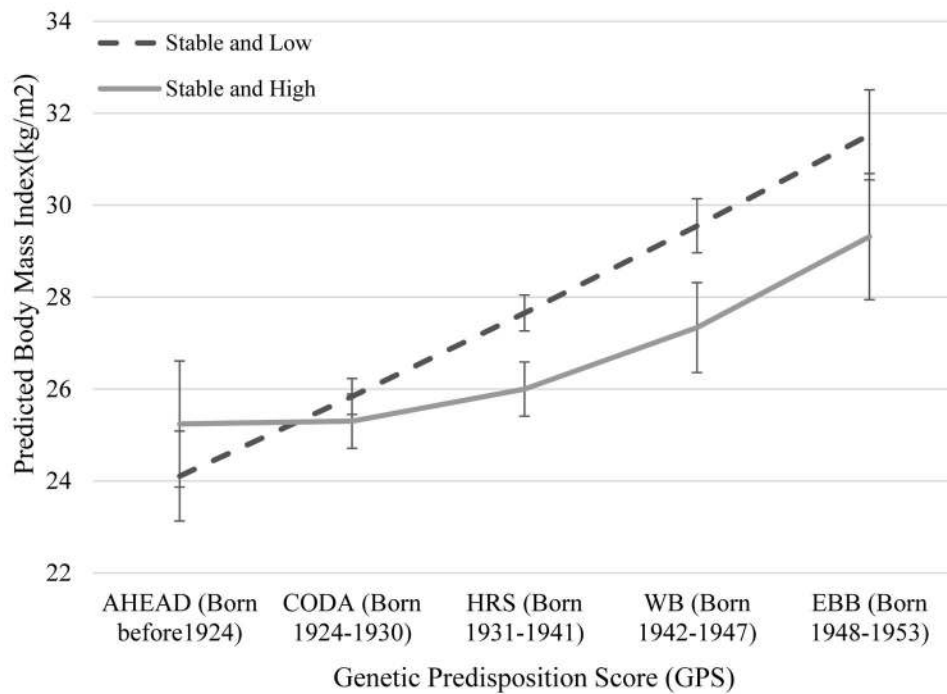


Figure 7. Genetic Association with BMI for Individuals in Stable and Low and Stable and High Trajectories by Birth Cohort

Note: Cohort differences in the genetic association with BMI are indicated by changes in the slope. I bars indicate 95% confidence intervals. The Slope becomes steeper in more recent cohorts for the stable and high group but not for the stable and low group, suggesting that the genetic association with BMI is greater in more recent cohorts for individuals experiencing stable and high SES, while there is little cohort difference in the genetic association with BMI for those experiencing stable and low SES.

Table 1

Analytic Sample Summary Statistics by Cohort: Health and Retirement Study

Dependent Variable	AHE/AD (Born before 1924)	CODA (Born 1924–1930)	HRS (Born 1931–1941)	WB (Born 1942–1947)	EBB (Born 1948–1953)
	Mean/% (SE)	Mean/% (SE)	Mean/% (SE)	Mean/% (SE)	Mean/% (SE)
Independent Variables					
BMI ^a	25.66(.13)	26.71(.12)	26.69(.08)	27.28(.14)	28.07(.15)
Genetic Predisposition Score (GPS)	28.71(.13)	29.07(.10)	29.07(.07)	29.01(.10)	29.21(.10)
Childhood SES (Father's Occupation)					
Low	.18	.18	.21	.24	.18
Medium	.38	.56	.51	.45	.44
High	.33	.14	.16	.18	.26
Missing	.11	.12	.12	.13	.12
Young Adulthood SES (Years of Education)					
Low	.10	.19	.17	.12	.07
Medium	.12	.15	.18	.44	.45
High	.78	.66	.65	.44	.48
Middle/Late Adulthood SES (Wealth)					
Low	.12	.18	.20	.23	.22
Medium	.33	.35	.36	.36	.37
High	.55	.47	.44	.41	.41
Cumulative Advantage in SES (CAS)					
CAS(=0)	.09	.18	.19	.29	.27
CAS(=1)	.27	.33	.33	.29	.27
CAS(=2)	.35	.31	.28	.21	.23
CAS(=3)	.18	.06	.08	.07	.10
CAS Missing	.11	.12	.13	.14	.13
SES Trajectory					
Stable and Low	.27	.39	.41	.42	.39
Downwardly Mobile	.13	.06	.06	.08	.13
Upwardly Mobile	.29	.35	.31	.27	.23

	AHEAD (Born before 1924)	CODA (Born 1924–1930)	HRS (Born 1931–1941)	WB (Born 1942–1947)	EBB (Born 1948–1953)
	Mean/% (SE)	Mean/% (SE)	Mean/% (SE)	Mean/% (SE)	Mean/% (SE)
Stable and High	.20	.08	.09	.09	.13
SES Trajectory Missing	.11	.12	.13	.14	.12
Covariates					
Age	73.98(.12)	69.12(.09)	56.09(.06)	52.43(.06)	52.70(.05)
Female	.62	.56	.54	.61	.56
Region					
Midwest	.31	.35	.34	.31	.38
Northeast	.19	.23	.22	.22	.20
South	.30	.24	.30	.28	.21
West	.19	.10	.10	.10	.13
Other	.00	.01	.04	.02	.00
Region Missing	.01	.07	.00	.07	.08
Rural					
Rural	.35	.44	.48	.47	.42
Urban	.52	.53	.49	.51	.57
Rural Missing	.13	.03	.03	.02	.01
Smoking ^a					
Smoker	.05	.09	.21	.24	.21
Nonsmoker	.95	.91	.79	.76	.79
Drinking ^a					
Ever Drank	.62	.62	.66	.66	.71
Never Drank	.38	.38	.34	.34	.29
N	909	1480	3483	1521	1423

Note:

^aFor time-varying variables, summary statistics are based on the onset measure in the analytic sample.

Table 2a
Genetic and Socioeconomic Associations with BMI (Standard Error) in Five Cohorts

	AHEAD (Born before 1924) Mean Age = 74.0	CODA (Born 1924–1930) Mean Age = 69.1	HRS (Born 1931–1941) Mean Age = 56.1	WB (Born 1942–1947) Mean Age = 52.4	EBB (Born 1948–1953) Mean Age = 52.7	Overall Mean Age = 58.9
	(1)	(2)	(3)	(4)	(5)	(6)
Genetic Association^a	.01(.03)	.12(.03)***	.13(.02)***	.17(.03)***	.16(.04)***	.13(.01)***
	(N = 909)	(N = 1480)	(N = 3483)	(N = 1521)	(N = 1423)	(N = 8816)
Childhood SES						
Low	26.48(.32)*	26.84(.29)	27.12(.18)***	27.82(.28)*	28.48(.34)**	27.36(.12)***
	(N = 163)	(N = 268)	(N = 727)	(N = 361)	(N = 254)	(N = 1773)
Medium	25.58(.21)*	26.64(.15)	26.71(.11)***	27.24(.22)*	28.41(.24)**	26.94(.08)***
	(N = 344)	(N = 833)	(N = 1775)	(N = 685)	(N = 629)	(N = 4266)
High	25.51(.22)*	26.68(.32)	26.17(.19)***	26.77(.30)*	27.11(.27)**	26.41(.11)***
	(N = 302)	(N = 196)	(N = 540)	(N = 269)	(N = 363)	(N = 1670)
Young Adulthood SES						
Low	26.22(.42)**	27.44(.26)***	27.11(.20)***	28.03(.42)**	30.00(.78)***	27.47(.15)***
	(N = 94)	(N = 275)	(N = 583)	(N = 182)	(N = 94)	(N = 1228)
Medium	26.54(.43)**	27.35(.26)***	27.51(.16)***	27.50(.22)**	28.68(.23)***	27.77(.11)***
	(N = 109)	(N = 229)	(N = 640)	(N = 668)	(N = 637)	(N = 2283)
High	25.45(.14)**	26.35(.15)***	26.36(.10)***	26.88(.20)**	27.20(.21)***	26.41(.06)***
	(N = 705)	(N = 975)	(N = 2255)	(N = 663)	(N = 677)	(N = 5275)
Middle/Late Adulthood SES						
Low	26.38(.47)*	27.61(.34)***	27.30(.21)***	28.37(.32)***	29.46(.40)***	27.91(.14)***
	(N = 107)	(N = 270)	(N = 683)	(N = 356)	(N = 315)	(N = 1731)
Medium	25.67(.23)*	27.08(.19)***	27.01(.13)***	27.44(.24)***	28.63(.26)***	27.24(.09)***
	(N = 303)	(N = 509)	(N = 1258)	(N = 546)	(N = 525)	(N = 3141)
High	25.50(.17)*	26.09(.15)***	26.16(.11)***	26.51(.20)***	26.82(.20)***	26.21(.07)***
	(N = 499)	(N = 701)	(N = 1542)	(N = 619)	(N = 583)	(N = 3944)
Cumulative Advantage in SES (CAS)						
CAS(=0)	26.59(.50)**	27.56(.25)***	27.53(.18)***	28.25(.30)***	29.58(.33)***	28.09(.13)***

	AHEAD (Born before 1924) Mean Age = 74.0	CODA (Born 1924–1930) Mean Age = 69.1	HRS (Born 1931–1941) Mean Age = 56.1	WB (Born 1942–1947) Mean Age = 52.4	EBB (Born 1948–1953) Mean Age = 52.7	Overall Mean Age = 58.9
	(1)	(2)	(3)	(4)	(5)	(6)
CAS(=1)	(N = 85) 25.99(.26)**	(N = 261) 26.84(.21)**	(N = 649) 27.08(.14)**	(N = 441) 27.04(.25)**	(N = 378) 27.95(.27)**	(N = 1814) 27.05(.09)**
CAS(=2)	(N = 241) 25.54(.22)**	(N = 481) 26.17(.19)**	(N = 1138) 26.11(.14)**	(N = 443) 26.65(.27)**	(N = 380) 27.20(.29)**	(N = 2683) 26.27(.09)**
CAS(=3)	(N = 316) 25.30(.28)**	(N = 460) 25.96(.46)**	(N = 982) 25.46(.24)**	(N = 322) 26.46(.48)**	(N = 330) 26.06(.36)**	(N = 2410) 25.73(.15)**
(N = 166)	(N = 94)	(N = 94)	(N = 268)	(N = 104)	(N = 144)	(N = 776)
SES Trajectory						
Stable and Low	(N = 245) 26.09(.27)*	(N = 586) 27.17(.19)**	(N = 1429) 27.24(.13)**	(N = 644) 27.98(.24)**	(N = 554) 29.12(.26)**	(N = 3458) 27.59(.09)**
Downwardly Mobile	(N = 120) 25.69(.37)*	(N = 87) 27.52(.48)**	(N = 228) 26.76(.31)**	(N = 128) 27.05(.44)**	(N = 171) 28.07(.45)**	(N = 734) 27.03(.18)**
Upwardly Mobile	(N = 262) 25.66(.24)*	(N = 515) 26.14(.17)**	(N = 1073) 26.28(.13)**	(N = 402) 26.59(.25)**	(N = 329) 27.27(.28)**	(N = 2581) 26.36(.09)**
Stable and High	(N = 182) 25.39(.27)*	(N = 109) 26.02(.41)**	(N = 312) 25.73(.23)**	(N = 141) 26.51(.40)**	(N = 192) 26.26(.30)**	(N = 936) 25.93(.14)**

Note: The first row includes estimated genetic association with BMI (β) for each cohort and analyses use t-test to test whether β equals to 0. Values in other rows are means of BMI calculated using onset measures in the analytic sample. In columns (1), (2), (3), (4), and (5), analyses use ANOVA to test for mean socioeconomic differences in BMI. In column (6), analyses use ANOVA to test for mean cohort differences in BMI.

* p < .05;

** p < .01;

*** p < .001.

Table 2b

Genetic and Socioeconomic Associations with BMI (Standard Error) in the Age-comparable Sample

	AHEAD (Born before 1924)		CODA (Born 1924–1930)		HRS (Born 1931–1941)		Overall	
	Mean Age =73.4	Mean Age =73.4	Mean Age =73.4	Mean Age =73.4	Mean Age =73.4	Mean Age =73.4	Mean Age =73.4	Mean Age =73.4
	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Genetic Association^a	.02(.04)	.12(.03)***	.13(.02)***	.12(.02)***	.13(.02)***	.12(.02)***	.12(.02)***	.12(.02)***
	(N = 844)	(N = 1449)	(N = 3302)	(N = 3302)	(N = 3302)	(N = 5595)	(N = 5595)	(N = 5595)
Childhood SES								
Low	26.58(.33)**	27.03(.29)	28.04(.21)**	27.59(.15)***	28.04(.21)**	27.59(.15)***	27.59(.15)***	27.59(.15)***
	(N = 155)	(N = 263)	(N = 683)	(N = 1101)	(N = 683)	(N = 1101)	(N = 1101)	(N = 1101)
Medium	25.66(.22)**	26.71(.16)	27.56(.13)**	27.10(.09)***	27.56(.13)**	27.10(.09)***	27.10(.09)***	27.10(.09)***
	(N = 325)	(N = 816)	(N = 1690)	(N = 2831)	(N = 1690)	(N = 2831)	(N = 2831)	(N = 2831)
High	25.47(.23)**	26.96(.32)	27.06(.22)**	26.59(.15)***	27.06(.22)**	26.59(.15)***	26.59(.15)***	26.59(.15)***
	(N = 276)	(N = 192)	(N = 510)	(N = 978)	(N = 510)	(N = 978)	(N = 978)	(N = 978)
Young Adulthood SES								
Low	26.17(.44)*	27.50(.29)***	27.99(.24)***	27.67(.18)**	27.99(.24)***	27.67(.18)**	27.67(.18)**	27.67(.18)**
	(N = 88)	(N = 265)	(N = 537)	(N = 890)	(N = 537)	(N = 890)	(N = 890)	(N = 890)
Medium	26.80(.46)*	27.44(.29)***	28.34(.19)***	27.95(.15)***	28.34(.19)***	27.95(.15)***	27.95(.15)***	27.95(.15)***
	(N = 99)	(N = 227)	(N = 616)	(N = 942)	(N = 616)	(N = 942)	(N = 942)	(N = 942)
High	25.48(.15)*	26.52(.15)***	27.31(.11)***	26.79(.08)***	27.31(.11)***	26.79(.08)***	26.79(.08)***	26.79(.08)***
	(N = 656)	(N = 956)	(N = 2146)	(N = 3758)	(N = 2146)	(N = 3758)	(N = 3758)	(N = 3758)
Middle/Late Adulthood SES								
Low	26.47(.49)*	27.82(.38)***	28.45(.25)***	28.08(.20)***	28.45(.25)***	28.08(.20)***	28.08(.20)***	28.08(.20)***
	(N = 98)	(N = 263)	(N = 626)	(N = 987)	(N = 626)	(N = 987)	(N = 987)	(N = 987)
Medium	25.79(.24)*	27.24(.19)***	27.82(.15)***	27.39(.11)***	27.82(.15)***	27.39(.11)***	27.39(.11)***	27.39(.11)***
	(N = 279)	(N = 499)	(N = 1192)	(N = 1970)	(N = 1192)	(N = 1970)	(N = 1970)	(N = 1970)
High	25.49(.17)*	26.19(.15)***	27.08(.12)***	26.57(.09)***	27.08(.12)***	26.57(.09)***	26.57(.09)***	26.57(.09)***
	(N = 467)	(N = 687)	(N = 1484)	(N = 2638)	(N = 1484)	(N = 2638)	(N = 2638)	(N = 2638)
Cumulative Advantage in SES (CAS)								
CAS(=0)	26.76(.54)**	27.55(.30)***	28.22(.22)***	27.92(.17)***	28.22(.22)***	27.92(.17)***	27.92(.17)***	27.92(.17)***

	AHEAD (Born before 1924) Mean Age =73.4	CODA (Born 1924–1930) Mean Age =73.4	HRS (Born 1931–1941) Mean Age =73.4	Overall Mean Age =73.4
	(1)	(2)	(3)	(4)
CAS(=1)	(N = 77) 26.13(.27) **	(N = 251) 27.10(.22) ***	(N = 609) 28.08(.17) ***	(N = 937) 27.57(.12) ***
CAS(=2)	(N = 229) 25.56(.23) **	(N = 475) 26.22(.19) ***	(N = 1077) 26.87(.16) ***	(N = 1781) 26.47(.11) ***
CAS(=3)	(N = 294) 25.20(.29) **	(N = 453) 26.24(.47) ***	(N = 937) 26.64(.29) ***	(N = 1684) 26.12(.11) ***
SES Trajectory				
Stable and Low	(N = 155) 26.23(.28) *	(N = 91) 27.32(.21) ***	(N = 257) 28.11(.16) ***	(N = 503) 27.70(.12) ***
Downwardly Mobile	(N = 230) 25.75(.40) *	(N = 572) 27.81(.48) ***	(N = 1345) 27.47(.35) ***	(N = 2147) 27.09(.24) **
Upwardly Mobile	(N = 107) 25.71(.25) *	(N = 86) 26.19(.18) ***	(N = 210) 27.16(.15) ***	(N = 403) 26.68(.11) ***
Stable and High	(N = 250) 25.30(.28) *	(N = 507) 26.28(.41) ***	(N = 1028) 26.78(.27) ***	(N = 1785) 26.25(.18) ***
	(N = 169)	(N = 106)	(N = 300)	(N = 575)

Note: The first row includes estimated genetic association with BMI (β) for each cohort and analyses use t-test to test whether β equals to 0. Values in other rows are means of BMI calculated using onset measures in the analytic sample. In columns (1), (2), and (3), analyses use ANOVA to test for mean socioeconomic differences in BMI. In column (4), analyses use ANOVA to test for mean cohort differences in BMI.

* p < .05;
 ** p < .01;
 *** p < .001.

Table 3

Coefficients (Standard Error) of Multilevel Models Assessing Moderating Effects of SES on the Genetic Association with BMI (H_1)

	<u>Sensitive Period (Model 1a)</u>	<u>Social Accumulation (Model 1b)</u>	<u>Social Mobility (Model 1c)</u>
Genetic Predisposition Score (GPS)^a	.12(.03) ***	.07(.04) †	.07(.04) †
Childhood SES			
Low	.57(.16) ***		
Medium	.31(.13) *		
High			
Cumulative Advantage in SES (CAS)			
CAS(=0)		1.74(.20) ***	
CAS(=1)		1.20(.19) ***	
CAS(=2)		.46(.18) *	
CAS(=3)			
SES Trajectory			
Stable and Low			1.53(.17) ***
Downwardly Mobile			1.01(.23) ***
Upwardly Mobile			.32(.17) †
Stable and High			
GPS × Childhood SES			
GPS × Low SES	.04(.04)		
GPS × Medium SES	-.00(.03)		
GPS × High SES			
GPS × Cumulative Advantage in SES (CAS)			
GPS × CAS(=0)		.10(.05) *	
GPS × CAS(=1)		.07(.05)	
GPS × CAS(=2)		.03(.05)	
GPS × CAS(=3)			
GPS × SES Trajectory			
GPS × Stable and Low			.09(.04) *
GPS × Downwardly Mobile			.11(.06) *
GPS × Upwardly Mobile			.01(.04)
GPS × Stable and High			
Covariates			
Age ^b	.16(.01) ***	.16(.01) ***	.16(.01) ***
Age ²	-.01(.00) ***	-.01(.00) ***	-.01(.00) ***
Cohort	.87(.07) ***	.86(.07) ***	.91(.07) ***
Age × Cohort	-.01(.00) **	-.01(.00) **	-.01(.00) **
Female	-.82(.10) ***	-.74(.09) ***	-.90(.09) ***

	<u>Sensitive Period (Model 1a)</u>	<u>Social Accumulation (Model 1b)</u>	<u>Social Mobility (Model 1c)</u>
Male			
Childhood Health	-.02(.06)	-.01(.06)	-.00(.06)
Smoking (Yes)	-.67(.05)***	-.66(.05)***	-.66(.05)***
Smoking (No)			
Drinking (Yes)	.09(.02)***	.09(.02)***	.09(.02)***
Drinking (No)			
Midwest	.48(.19)**	.47(.19)*	.48(.19)**
Northeast	.13(.20)	.17(.20)	.15(.20)
South	-.02(.19)	-.01(.19)	-.01(.19)
Other	-.10(.38)	-.13(.38)	-.11(.38)
West			
Rural	.20(.11)	.14(.11)	.21(.11)*
Urban			
Random-Effect Variance			
σ^2	15.22(.35)***	15.29(.35)***	15.11(.34)***
ρ	.94(.00)***	.94(.00)***	.94(.00)***
σ_u^2	10.04(.46)***	10.04(.46)***	10.23(.45)***
Sample Size	7,670	7,670	7,695

Note: All models control for the largest 10 principal components for adjusting population stratification. Model 1 also controls for young adulthood and middle/late adulthood SES;

^aGPS is grand median centered;

^bAge is grand median centered.

[†] p < .05;

^{††} p < .01;

^{†††} p < .001 (one-tailed tests)

* p < .05;

** p < .01;

*** p < .001 (two-tailed tests).

Table 4

Coefficients (Standard Error) of Multilevel Models Assessing Cohort Differences in the Genetic Association with BMI (H₂) and Cohort Differences in the Moderating Effects of SES Based on the Age-comparable Sample and the Whole Analytic Sample (H₃)

	Cohort Difference (Model 2)		Sensitive Period (Model 3a)		Social Accumulation (Model 3b)		Social Mobility (Model 3c)	
	Whole Sample	Age-comparable Sample	Whole Sample	Age-comparable Sample	Whole Sample	Age-comparable Sample	Whole Sample	Age-comparable Sample
Genetic Predisposition Score (GPS) × Cohort	.03(.01)**	.05(.02)*	.04(.02)†	.09(.05)†	.08(.03)**	.11(.06)†	.08(.03)**	.12(.06)*
GPS × Childhood SES								
GPS × Low SES			.11(.08)	.20(.12)†				
GPS × Medium SES			.02(.07)	.04(.09)				
GPS × High SES								
GPS × Cumulative Advantage in SES (CAS)								
GPS × CAS(=0)					.22(.10)*	.30(.18)†		
GPS × CAS(=1)					.22(.09)*	.19(.12)		
GPS × CAS(=2)					.11(.08)	.23(.11)*		
GPS × CAS(=3)								
GPS × SES Trajectory								
GPS × Stable and Low							.22(.08)**	.24(.12)*
GPS × Downwardly Mobile							.31(.11)**	.37(.15)*
GPS × Upwardly Mobile							.13(.08)†	.20(.11)†
GPS × Stable and High								
GPS × Childhood SES × Cohort								
GPS × Low × Cohort			-.04(.03)	-.11(.07)				
GPS × Medium × Cohort			-.01(.03)	-.02(.06)				

	Cohort Difference (Model 2)		Sensitive Period (Model 3a)		Social Accumulation (Model 3b)		Social Mobility (Model 3c)	
	Whole Sample	Age-comparable Sample	Whole Sample	Age-comparable Sample	Whole Sample	Age-comparable Sample	Whole Sample	Age-comparable Sample
GPS × High × Cohort								
GPS × Cumulative Advantage in SES (CAS) × Cohort								
GPS × CAS(=0) × Cohort					-0.07(.04) [‡]			
GPS × CAS(=1) × Cohort					-0.09(.04) [*]	-0.11(.11)		
GPS × CAS(=2) × Cohort					-0.05(.04)	-0.04(.08)		
GPS × CAS(=3) × Cohort						-0.11(.07)		
GPS × SES Trajectory × Cohort								
GPS × Stable and Low × Cohort								
GPS × Downwardly Mobile × Cohort								
GPS × Upwardly Mobile × Cohort								
GPS × Stable and High × Cohort								
Sample Size	7,670	4,562	7,670	4,562	7,670	4,562	7,695	4,567

Note: The age-comparable sample is selected from overlapping age groups in AHEAD, CODA, and HRS cohorts. For each cohort in the age-comparable sample, age ranges from 70 to 81 with a mean age of 73.4. All models control for grand-median-centered age, age squared, sex, childhood health, region, rural, smoking, drinking, and the largest 10 principal components for adjusting population stratification. Sensitive-period models also control for young adulthood and middle/late adulthood SES.

[‡] p < .05;

^{††} p < .01;

^{†††} p < .001 (one-tailed tests)

* p < .05;

** p < .01;

p < .001 (two-tailed tests).

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Table 5
Mean Genetic Predisposition Score (Standard Error) by SES in Five Birth Cohorts

	(1)	(2)	(3)	(4)	(5)	(6)
	AHEAD (Born before 1924)					
	CODA (Born 1924–1930)		HRS (Born 1931–1941)		WB (Born 1942–1947)	
	EBB (Born 1948–1953)		Overall			
Childhood SES						
Low	29.10(.29)	28.96(.22)	29.10(.14)	28.89(.21)	29.04(.25)	29.02(.09)
Medium	28.74(.20)	29.11(.13)	29.06(.09)	28.82(.15)	29.38(.15)	29.05(.06)
High	28.67(.22)	28.99(.25)	29.13(.17)	29.35(.24)	29.10(.20)	29.06(.09)
Young Adulthood SES						
Low	28.42(.43)	29.06(.23)	29.16(.16)	29.08(.31)	29.65(.42)	29.11(.11)
Medium	29.40(.32)	29.14(.24)	29.28(.15)	28.97(.16)	29.22(.15)	29.16(.08)
High	28.66(.14)	29.05(.12)	28.99(.08)	29.04(.15)	29.13(.15)	28.98(.05)
Middle/Late Adulthood SES						
Low	28.40(.39)	28.70(.23)	29.27(.15)	29.38(.21)*	29.42(.23)	29.18(.10)**
Medium	28.77(.20)	29.22(.17)	29.02(.11)	29.08(.17)*	29.26(.17)	29.08(.07)
High	28.75(.17)	29.10(.14)	29.03(.10)	28.73(.15)*	29.04(.15)	28.96(.06)
Cumulative Advantage in SES (CAS)						
CAS(=0)	29.78(.40)	28.96(.22)	29.44(.15)	28.81(.20)	29.43(.20)	29.23(.09)
CAS(=1)	28.45(.23)	29.31(.17)	29.01(.11)	29.26(.18)	29.38(.21)	29.11(.07)*
CAS(=2)	28.72(.22)	28.80(.17)	28.81(.12)	28.61(.20)	28.98(.22)	28.79(.08)
CAS(=3)	28.92(.31)	29.36(.37)	29.54(.23)	29.30(.40)	28.91(.27)	29.23(.13)
SES Trajectory						
Stable and Low	28.94(.23)	29.12(.15)	29.17(.10)	29.01(.16)	29.33(.17)	29.14(.07)
Downwardly Mobile	28.46(.35)	28.55(.38)	28.83(.28)	29.43(.33)	29.44(.33)	28.98(.15)*
Upwardly Mobile	28.77(.24)	29.02(.16)	28.95(.11)	28.58(.19)	29.18(.21)	28.92(.07)
Stable and High	28.81(.29)	29.34(.34)	29.35(.22)	29.28(.34)	28.79(.25)	29.12(.12)

Note: In columns (1), (2), (3), (4), and (5), analyses use ANOVA to test for mean SES differences in GPS. In column (6), analyses use ANOVA to test for mean cohort differences in GPS.

* p < .05;

** p < .01;

100>.d

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Table 6

Assessing Selection Bias: Coefficients (Standard Error) of Multilevel Models Based on the Survival Elites Subsample and the Whole Analytic Sample

	Social Accumulation			Social Mobility		
	Whole Sample	Survival Elites Subsample	Whole Sample	Survival Elites Subsample	Whole Sample	Survival Elites Subsample
Genetic Predisposition Score (GPS) × Cohort	.03(.01)**	.04(.03)	.08(.03)**	.12(.08)	.08(.03)**	.16(.08)*
GPS × Cumulative Advantage in SES (CAS)						
GPS × CAS(=0)			.22(.10)*	.29(.19)		
GPS × CAS(=1)			.22(.09)*	.26(.11)*		
GPS × CAS(=2)			.11(.08)	.23(.10)*		
GPS × CAS(=3)						
GPS × SES Trajectories						
GPS × Stable and Low					.22(.08)**	.24(.11)*
GPS × Downwardly Mobile					.31(.11)**	.41(.14)**
GPS × Upwardly Mobile					.13(.08) [†]	.24(.10)*
GPS × Stable and High						
GPS × Cumulative Advantage in SES (CAS) × Cohort						
GPS × CAS(=0) × Cohort			-.07(.04)	-.10(.15)		
GPS × CAS(=1) × Cohort			-.09(.04)*	-.13(.11)		
GPS × CAS(=2) × Cohort			-.05(.04)	-.11(.10)		
GPS × CAS(=3) × Cohort						
GPS × SES Trajectory × Cohort						
GPS × Stable and Low × Cohort					-.06(.03)*	-.11(.10)
GPS × Downwardly Mobile × Cohort					-.09(.04)*	-.31(.15)*
GPS × Upwardly Mobile × Cohort					-.06(.04) [†]	-.21(.10)*
GPS × Stable and High × Cohort						
Sample Size	7,670	2,066	7,670	2,066	7,695	2,068

Note: The Survival Elites subsample includes respondents who lived to at least age 80. All models control for grand-median-centered age, age squared, sex, childhood health, region, rural, smoking, drinking, and the largest 10 principal components for adjusting population stratification.

[†] p < .05;

```
***  
;10' > d  
**  
;50' > d  
*  
(one-tailed tests)  
;10' > d  
**  
;50' > d  
*  
(two-tailed tests)
```

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Appendix A

Detailed Information about 32 Established SNPs for BMI

Chromosome	Nearest Gene	GWAS SNP ^a	HRS SNP	Imputation Quality	R ²	R ² with GWAS SNP	Allele		GWAS Beta ^c	HRS Beta	Effect Allele Frequency ^d
							Effect ^c	Other			
1	SEC16B	rs543874	rs543874	1.00	1.00	1.00	G	A	.22	.08	.20
1	TNNI3K	rs1514175	rs1514175	1.00	1.00	1.00	A	G	.07	.09	.47
1	PTBP2	rs1555543	rs10489741 ^b	1.00	1.00	1.00	C	A	.06	.09	.57
1	NEGR1	rs2815752	rs2815752	1.00	1.00	1.00	A	G	.13	.09	.62
2	LRP1B	rs2890652	rs2890652 ^b	1.00	1.00	1.00	C	T	.09	.05	.19
2	FANCL	rs887912	rs887912 ^b	1.00	1.00	1.00	T	C	.10	.06	.24
2	RBJ	rs713586	rs713586 ^b	1.00	1.00	1.00	C	T	.14	.20	.52
2	TMEM18	rs2867125	rs2867125	1.00	1.00	1.00	C	T	.31	.27	.84
3	CADM2	rs13078807	rs13078807	1.00	1.00	1.00	G	A	.10	-.04	.17
3	ETV5	rs9816226	rs9816226 ^b	.99	1.00	1.00	T	A	.14	.21	.82
4	SLC39A8	rs13107325	rs13107325	1.00	1.00	1.00	T	C	.19	.36	.06
4	GNPDA2	rs10938397	rs10938397	1.00	1.00	1.00	G	A	.18	.10	.40
5	ZNF608	rs4836133	rs4836133 ^b	1.00	1.00	1.00	A	C	.07	.12	.58
5	FLJ35779	rs2112347	rs2112347 ^b	1.00	1.00	1.00	T	G	.10	.16	.62
6	TFAP2B	rs987237	rs987237	1.00	1.00	1.00	G	A	.13	.04	.18
6	NUDT3	rs206936	rs206936	1.00	1.00	1.00	G	A	.06	.03	.27
9	LRRN6C	rs10968576	rs10968576	1.00	1.00	1.00	G	A	.11	.26	.28
11	MTCH2	rs3817334	rs3817334 ^b	1.00	1.00	1.00	T	C	.06	.05	.39
11	RPL27A	rs4929949	rs4929949 ^b	1.00	1.00	1.00	C	T	.06	-.03	.49
11	BDNF	rs10767664	rs10767664 ^b	1.00	1.00	1.00	A	T	.19	.15	.80
12	FAIM2	rs7138803	rs7138803	1.00	1.00	1.00	A	G	.12	.14	.34
13	MTIF3	rs4771122	rs9512699 ^b	1.00	1.00	.87	G	A	.09	.22	.18
14	PRKD1	rs11847697	rs10134820 ^b	1.00	1.00	.74	T	C	.17	-.03	.06
14	NRXN3	rs10150332	rs10150332 ^b	1.00	1.00	1.00	C	T	.13	.03	.23
15	MAP2K5	rs2241423	rs2241423	1.00	1.00	1.00	G	A	.13	.21	.72

Chromosome	Nearest Gene	GWAS SNP ^a	HRS SNP	Imputation Quality	R ² with GWAS SNP	Allele		GWAS Beta ^c	HRS Beta	Effect Allele Frequency ^d
						Effect ^b	Other			
16	SH2B1	rs7359397	rs7359397 ^b	1.00	1.00	T	C	.15	.18	.35
16	FTO	rs1558902	rs1558902 ^b	1.00	1.00	A	T	.39	.30	.35
16	GPRCSB	rs12444979	rs12444979	1.00	1.00	C	T	.17	.25	.87
18	MC4R	rs571312	rs571312	1.00	1.00	A	C	.23	.29	.24
19	KCTD15	rs29941	rs29941 ^b	1.00	1.00	G	A	.06	.09	.70
19	TMEM160	rs3810291	rs3810291	1.00	1.00	A	G	.09	.13	.59
19	QPCTL	rs2287019	rs2287019	1.00	1.00	C	T	.15	.22	.89

Note:

^a rs ids of BMI-related SNPs in Speliotes *et al.* (2010).

^b Imputed SNPs

^c Effect size in kg/m² of BMI obtained from Speliotes *et al.* (2010).

^d Effect allele frequency in HRS.

Appendix B

To illustrate, suppose there are three respondents: A, B, and C. A and B were from household 1, and C was from household 2. A was measured in 1992 and 1994, B only in 1992, and C in 1993 and 1998. Then the covariance matrix for the 5 BMI measures will be:

$$\begin{aligned}
 & \begin{pmatrix} BMI_{1A}(1992) \\ BMI_{1A}(1994) \\ BMI_{1B}(1992) \\ BMI_{2C}(1993) \\ BMI_{2C}(1998) \end{pmatrix} \\
 & Cov = \begin{pmatrix} \sigma_u^2 & \sigma_u^2 & 0 & 0 \\ \sigma_u^2 & \sigma_u^2 & \rho & 0 \\ \sigma_u^2 & \rho & \sigma_u^2 & 0 \\ \sigma_u^2 & 0 & 0 & \sigma_u^2 \\ \sigma_u^2 & 0 & 0 & \sigma_u^2 \end{pmatrix} \\
 & = \begin{pmatrix} \sigma_u^2 & \sigma_u^2 & 0 & 0 & 0 \\ \sigma_u^2 & \sigma_u^2 & \rho & 0 & 0 \\ \sigma_u^2 & \rho & \sigma_u^2 & 0 & 0 \\ \sigma_u^2 & 0 & 0 & \sigma_u^2 & 0 \\ \sigma_u^2 & 0 & 0 & 0 & \sigma_u^2 \end{pmatrix} \\
 & = \begin{pmatrix} \sigma_u^2 & \sigma_u^2 & 0 & 0 & 0 \\ \sigma_u^2 & \sigma_u^2 + \rho^2 & \rho & 0 & 0 \\ \sigma_u^2 & \rho & \sigma_u^2 + \rho^2 & 0 & 0 \\ \sigma_u^2 & 0 & 0 & \sigma_u^2 + \rho^2 & 0 \\ \sigma_u^2 & 0 & 0 & 0 & \sigma_u^2 + \rho^2 \end{pmatrix}
 \end{aligned}$$

Appendix C

Coefficients (Standard Error) of Multilevel Models Assessing Moderating Effects of SES on the Genetic Association with BMI for Females and Males in HRS

	Sensitive Period		Social Accumulation		Social Mobility	
	Female	Male	Female	Male	Female	Male
Genetic Predisposition Score (GPS)^a	.13(.05)**	.15(.04)***	.06(.07)	.07(.06)	.06(.07)	.09(.05) [†]
GPS × Childhood SES						
GPS × Low SES	.02(.06)	.01(.06)				
GPS × Medium SES	-.02(.05)	-.01(.05)				
GPS × High SES						
GPS × Cumulative Advantage in SES (CAS)						
GPS × CAS(=0)			.08(.08)	.09(.07)		.09(.07)
GPS × CAS(=1)			.08(.08)	.09(.07)		.15(.08) [†]
GPS × CAS(=2)			.05(.08)	.08(.07)		.04(.06)
GPS × CAS(=3)						
GPS × SES Trajectory						
GPS × Stable and Low						.08(.06)
GPS × Downwardly Mobile						.13(.09)
GPS × Upwardly Mobile						.00(.07)
GPS × Stable and High						
Sample Size	4,325	3,345	4,325	3,345	4,340	3,355

Note: To test if the main findings differ substantially between genders, we estimated GxE models separately for males and females. Results show similar patterns in the major associations of interest between males and females. All models control for grand-median-centered age, age squared, sex, childhood health, region, rural, smoking, drinking, and the largest 10 principal components for adjusting population stratification. Sensitive-period models also control for young adulthood and middle/late adulthood SES.

^aGPS is grand median centered;

[†] p < .05;

^{††} p < .01;

^{†††} p < .001 (one-tailed tests)

* p < .05;

.0001 (two-tailed tests).

;10' > d
**

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Appendix D

Bivariate Genome-wide Covariance Estimates For BMI and SES Measures

	Childhood SES	Young Adulthood SES	Late Adulthood SES	Cumulative Advantage in SES	SES Trajectory
Genetic variance					
BMI	5.49(1.86)	5.80(1.84)	5.89(1.84)	5.86(1.84)	5.92(1.84)
SES	.08(.03)	.19(.04)	.20(.04)	.34(.08)	.32(.11)
Cov(BMI, SES)	-.26(.18)	-.31(.19)	-.08(.21)	-.32(.27)	-.22(.32)
Residual variance					
BMI	20.54(1.32)	20.33(1.31)	20.27(1.31)	20.29(1.30)	20.25(1.30)
SES	.39(.02)	.39(.03)	.44(.03)	.64(.05)	1.03(.08)
Cov(BMI, SES)	-.03(.13)	-.16(.14)	-.44(.14)	-.51(.19)	-.57(.23)
Phenotypic variance					
BMI	26.03(.71)	26.13(.71)	26.16(.71)	26.15(.71)	26.17(.71)
SES	.47(.01)	.58(.02)	.64(.02)	.98(.03)	1.35(.04)
Heritability					
BMI	.21(.07)	.22(.07)	.23(.07)	.22(.07)	.23(.07)
SES	.17(.07)	.32(.06)	.32(.06)	.35(.07)	.23(.08)
rGE Test					
rG	-.39(.30)	-.30(.18)	-.07(.18)	-.22(.19)	-.16(.23)
df	1	1	1	1	1
p-value	.14	.10	.70	.22	.50

Note: To detect potential correlation between SES variables and genetic variants other than the 32 GWAS SNPs used to construct the GPS, we employed bivariate genome-wide-complex-trait-analysis (GCTA) model to assess rGE based on the whole genome (Lee *et al.* 2012). As a result, there is no significant evidence that SES and BMI are influenced by common variants from the whole genome.