

Gene-Environment interactions and the case of BMI and obesity: how much do they matter?

Yiyue Huangfu¹

Alberto Palloni^{1,2}

Hiram Beltrán-Sánchez³

Mary McEniry¹

1 Center for Demography and Ecology, Center for Demography and health of Aging, University of Wisconsin-Madison

2 Consejo Superior de Investigaciones Científicas (CSIC), Spain.

3 California Center for Population Research, University of California, Los Angeles

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Abstract

We investigate the demographic and population health implications of gene-environment interactions (GxE) in the case of BMI and obesity. We seek to answer three questions: (a) what is the first order impact of GxE effects on BMI and obesity, e.g. the direct effect of G in different E? (b) how large is the impact of GxE effects on second-order health outcomes associated with BMI and obesity, such as Type 2 Diabetes (T2D), disability, and mortality ? (c) is the range of available empirical estimates of GxE effects large enough to influence future trajectories of BMI, obesity, T2D, disability, and mortality? To limit the scope of the paper we focus on environments defined by birth cohorts. However, extensions to other environments, including but not limited to education, SES, early conditions, physical settings, are quite straightforward.

I. Introduction

Increasing rates of obesity prevalence in the 20th century appear simultaneously in high-income countries around 1970-80¹ and spread rapidly to low- and middle-income countries. Since 1975, the worldwide prevalence of obesity has trebled but varies widely across geographic regions (WHO 2021). Between 2000 and 2018 the US population obesity prevalence grew from 30.5% to 42.5% continuing a trend that began in the middle-sixties from a level of about 13%, clocking a doubling time of about 31 years (Fryar et al. 2020; Flegal et al. 1998).

More ominous is the rapid increase of obesity among children and adolescents. In the forty-year period between 1965-1969 to 2008, obesity prevalence among children and adolescents spiked from 5% to a level about twice as high while it trebled during the same period among those aged 6-19. Since then, prevalence rates increased to 15% and 20% in each age group respectively (CDC, 2022). Of relevance is the fact that, by virtue of the association between child and parental obesity (Lake et al. 1997), on one hand, and individuals' early childhood and adult obesity (Whitaker et al. 1997), on the other, these trends might lead to intergenerational 'transmission' of the phenotype.

Sizeable increases in human girth are not by themselves the cause of immediate concern.² What preoccupies scientists and health policy-makers alike is the evolution of phenotypes related to obesity. It is well established that obesity is associated with metabolic syndrome (Després and Lemieux 2006), elevated risks of chronic conditions such as T2D, CAD, cancer, stroke, midlife cognitive performance, late life cognitive decline, and increases fragility and disability (Field et al. 2001; Eckel et al. 2004). Although the direct impact of obesity on mortality is controversial, its indirect effects through chronic conditions and illnesses is undisputable (Mehta and Chang 2009, 2011; Stewart et al. 2009).

These relations between obesity, chronic illnesses and disability are hugely consequential. It has been estimated, for example, that in 2010-2012, the US medical costs of obesity hovered around a staggering 150 billion per year (2014 US dollars) (Kim and Basu 2016)

¹ Throughout we use the WHO definition of obesity and use the term to refer to individuals with body-mass index, BMI, exceeding 30 (<https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight>). As long as there is no equivocation, we use the expression 'effects on obesity' to mean increased risk of obesity as well as 'effects on BMI' (and vice-versa). The same applies to expressions such as 'obesity-related GxE interaction effects' which we will use as equivalent to 'BMI-related GxE interaction effects'. At times, and mercifully only when needed, we will refer to BMI and obesity as equivalent phenotypes by using the awkward 'BMI-obesity' expression.

² We do not belittle the personal consequences of obesity. In societies where the phenotype is stigmatized, it causes discrimination, maltreatment, isolation, and mental illness, and imposes an incalculable psychological cost to individuals. Furthermore, an important fraction of the economic burden associated with obesity is borne by the individuals themselves.

and could have been as large as 210 billion. Most of this spending is associated with treatment of T2D and other closely associated chronic conditions and disability (Finkelstein et al. 2009).

There is widespread consensus, supported by a large body of empirical research, that the root of the post-1950 increase of obesity is environmental and associated with wholesale changes in diet, physical activity, sleeping patterns, and stress (Swinburn et al. 2019). Over the last 50 or so years, global and local forces combined to generate so-called obesogenic environments or social and physical settings that expose individuals to preferences, behaviors, and material conditions that facilitate the emergence and persistence of the phenotype. These environments are well-entrenched and are unlikely to be dismantled any time soon (Popkin and Reardon 2018; Popkin et al. 2020). Thus, in the absence of massive behavioral and context-specific changes, it is likely that the obesity epidemic is here to stay and, with it, the associated burden of chronic conditions and disability.

Obesogenic environments, however, are not the only game in town.

Other determinants may either reinforce (or weaken) future trends of obesity and associated chronic conditions, even if obesogenic environments are unchanged. One of these is the genetic make-up of a population. Family and kin-based studies estimate that additive genetic effects contribute to a heritability estimated to be in the range between .40 and .70 (Farooqi 2000; Willyard 2014). More recently, GWAS studies confirm that body mass index (BMI) and other obesity markers such as waist-hip-ratio (WHR) and waist circumference, WC (Cheng et al. 2018; Wang et al. 2011) are polygenic traits that correlate with multiple allelic variants (Drong et al. 2012; Goodarzi 2018). Estimates of heritability from these studies are within a much lower but still non-negligible range, between 5 to 15 percent. However, even if the additive genetic effects were as large as suggested by twin and sibling studies, it is unlikely that by themselves they could play an important role in future trends. This is because, barring shifts in assortative mating and sharp differentials in net reproduction rates by body size, it is improbable that the existing gene pool will evolve to favor one human physical size over others. Consequently, additive allelic effects are not by themselves sufficient to power significant shifts in future trends of BMI, obesity, or associated health outcomes.³

³ While it is unlikely that vertical genetic transmission alone may become a driving force of the phenotype's trajectory, it is possible that it, in combination with cultural transmission, can have non-negligible impacts (Daza, S. and Palloni, A 2022). In the last section of the paper we explore the role of cultural transmission.

Enter gene-environment interactions, GxE, and we may have a different story⁴. In fact, GxE effects on BMI or obesity may also have indirect, second order, impacts on chronic illnesses, disability, and mortality. The main object of this paper is to examine jointly first and second order effects of GxE.

We seek to answer three questions: (a) what is the first order impact of GxE effects on BMI and obesity, e.g. the direct effect of G in different E? (b) how large is the second order impact of GxE effects, e.g. the impact on health outcomes associated with BMI and obesity? (c) is the range of available empirical estimates of GxE effects large enough to influence future trajectories of the BMI, obesity, and associated health outcomes? Because they have attracted a great deal of recent attention, we focus on environments defined by birth cohorts. However, extensions of arguments made here to other environments (education, SES, early conditions, physical settings) are quite straightforward⁵.

The paper is organized as follows: Section II briefly reviews interpretation and estimation problems and identifies levels of analyses. Section III describes models, empirical estimation, and results. Section IV evaluates GxE implications for future generations. Section V concludes.

II. GxE interaction effects: how large are they?

In the last ten to fifteen years, large GWAS studies have made possible the rapid growth of empirical studies that seek to identify the association between thousands of allelic variants and a growing array of phenotypes. An increasing fraction of these studies use polygenic risk scores (PRS) to estimate the additive effect of multiple allelic variants on a phenotype. Although in most cases the fraction of explained variance by PRS is quite small, these empirical findings support the idea that knowledge about many phenotypes of interest to social scientists could be much improved if, alongside other standard determinants, researchers consider the impact of genetic factors (Belsky et al. 2009; Belsky and Beaver 2011; Belsky and Pluess 2009; Boardman et al. 2013, 2014; Burt 2011; Harden 2021).

⁴ A further terminological precis: rather than using the expression 'GxE interaction', we will use the short-hand GxE and instead of using 'GxE interaction effects' (to refer to magnitude of effects), we will use 'GxE effects'

⁵ Birth cohort is one among many 'environments', E, highlighted in recent social research on GxE (Conley et al. 2016; Domingue et al. 2016; Guo et al. 2015; Walter et al. 2016). In the case of BMI and obesity, at least, birth cohort is a surrogate for 'timing of onset of widespread exposure to obesogenic environments'. The magnitude of GxE effects estimated with birth cohort as 'environment' are among the largest involving obesity and BMI.

An important part of this new research program focuses on gene-environment interactions, GxE, that is, variation of phenotypic response of a single genotype to changes in environments or, alternatively, variation of the phenotypic response of different genotypes in a fixed environment (Lewontin, 2006). In behavioral sciences, GxE refer to situations in which the *additive causal genetic effect* on a trait or behavior is significantly different amongst individuals belonging to well-characterized subgroups (defined by gender, age, education, SES) or within well-defined social settings (normative vs non-normative, exposed vs non-exposed to risks, part of a treatment or control group)⁶. GxE effects are also of interest in evolutionary biology and population genetics for, under assortative mating at least, they could influence the allelic composition of the population and can, in some cases, drive the evolution of these phenotypes under selection pressure (Coop 2019; Fox et al. 2019; Harpak and Przeworski 2021; Saltz et al. 2018)⁷.

GxE have been at the root of heated debates regarding the relevance of heritability of phenotypes, including the relative importance of genes and environments in the production of social and economic inequalities (Feldman and Lewontin 1975; Harden 2021; Lewontin 2006; Manski 2011). Empirical evidence from GWAS-based studies that identify GxE in multiple phenotypes, including education, IQ, non-cognitive traits, depression, onset of sexual activity, among the others, has recently been invoked to support the formulation of policy interventions that are better informed about the role of individuals' genotypes (Harden 2021). A common inference in these studies is that identification of GxE effects is not only relevant for theory-building but might also benefit the design of interventions for they can guide identification of subgroups that, by virtue of their genetic make-up, are at higher risks of deleterious outcomes in some environments (Belsky and Pluess 2009; Boardman et al. 2014; Caspi et al. 2002; Tuvblad et al. 2006; Boardman et al. 2013). Although this may be the correct inference, it is not altogether clear what the actual implications of GxE are, e.g. the “so what” question: how large are these effects? How do they stack up against other determinants that we could identify with similar or higher precision? If, for example, some phenotypes' sensitivity to genetic risks has

⁶ The literature distinguishes three main types of GxE, depending on the functional form of the relationship between genotype, environment, and outcomes. These are diathesis stress, differential susceptibility, and social push models (J Belsky et al. 2009; Boardman et al. 2014)

⁷ Throughout, we will focus on the causal effects of gene variants, namely the slopes of phenotypes relative to variables measuring genetic variation. In standard linear models these are not to be equated with heritability (h^2). The two metrics are indistinguishable only in classic path analysis, e.g. when all variables are standardized. When variables are their natural scales, h^2 and slopes, though related, can behave differently (Daza and Palloni 2022)

indeed increased across US birth cohorts (Conley et al. 2016), what does this mean for subpopulations that express them? In particular, how consequential are GxE effects involving obesity and a very large set of relevant environments, including educational attainment, SES, birth cohort, early conditions, residential location, among the others? And what do they imply for future trends of the phenotype and of those tightly linked to it?

Inferences about GxE effects are usually made at three different analytic levels. The first level demands quantification of the impact of GxE effects on shifts of the average phenotype across generations. This is the breeders' concern and is the target of researchers interested in selection pressures under which a phenotype may be evolving.

The second level consists of identification of either environments that modify the contribution of individual genetic risks or of groups of individuals whose genetic profiles make them more (less) vulnerable to express a phenotype under well-defined environments. In studies of individual depression, for example, the phenotype under study is the target of interest. In these cases, GxE effects may matter a great deal because they could shed light on modifiable environmental conditions that exacerbate (attenuate) the role of genetic propensities.

These first two levels are all about first order effects. The third analytic level is about second order effects, that is, those associated not with the phenotype under examination, but with one that is further down a causal pathway in which the phenotype under study is either an initial condition or a mediator. For example, a researcher may investigate the genetic determinants of age at first birth (Mills et al. 2021) or age at first sexual intercourse (Harden et al. 2008) not because these phenotypes are of intrinsic interest (though they might be) but because they are suspected to generate consequential outcomes such as higher fertility, lower labor force participation, early high school drop-out, onset of criminal activity or alcohol use (Harden 2014)⁸. The pressing concern could be to understand the mechanisms that produce these second-order outcomes as a response to changes in the phenotype under study. If age at first birth has a causal effect on females' subsequent labor force participation, a GxE associated with age at first birth could have important repercussions for aggregate female labor supply. For economists, the target quantity is not the variance in age at first birth or age at first sexual encounter that is explained by G or GxE but the magnitude of shifts in female labor supply that expected under fixed genetic profiles situated in different environments.

⁸ Second order phenotypes could be under the influence of additive allelic effects that may or may not affect the phenotype under immediate study.

A good illustration is the case of BMI and obesity. We know that increases in body size are just the beginning of a chain of physiological changes that lead to metabolic syndrome, prediabetes, T2D, circulatory dysfunctions, fragility, disability, and death. If risks of increased BMI (or probability of obesity) for individuals of a given genetic propensity are higher among those in the lowest educated groups (Tommerup et al. 2021) or in younger birth cohorts (Walter et al. 2016), a relevant issue for population health scientists is the *impact of these environmentally enhanced genetic risks on second order outcomes*⁹

III. GxE, BMI, obesity, and birth cohorts: impacts on health outcomes

To address the question about second-order GxE in the case of BMI and obesity, we use HRS data and estimate the magnitude of GxE effects in models predicting BMI and the probability of obesity as a function of birth cohort, BMI's PRS, and controls. We then evaluate the impact of changes in BMI (probability of obesity) induced by GxE effects on (i) probabilities of T2D, a chronic condition strongly associated with obesity and (ii) probabilities of disability, a key secondary consequence of both obesity and T2D.

a. Estimation of GxE first order effects on BMI and obesity

We use empirical estimates of GxE effects on BMI and convert them into predicted BMI changes, ΔBMI_{GxE} . First, we estimate a growth curve model (GCM) for BMI:

$$BMI_{it} = \alpha_0 + \alpha_1 cohort_i + \alpha_2 PGR_i + \alpha_3 cohort_i * PGR_i + \beta_{4i} age_{it} + \beta_{5i} age_{it}^2 + \beta'_6 \mathbf{X}_i + \mu_i + \varepsilon_{it}$$

where BMI_{it} is an individual's BMI in year t, $cohort_i$ is a series of 0/1 dummy variables for the cohort born before 1924, between 1925 and 1934, between 1935 and 1944, and between 1945 and 1960. PGR_i is the z-score of BMI' polygenic risk score, age_{it} is median-centered age at year t. \mathbf{X}_i is a vector of control variables including education, gender, principal components, and an indicator of adverse early conditions. The coefficients of age_{ij} and age_{it}^2 vary across individuals and μ_i is the random intercept for each respondent and ε_{it} is the error term. The quantity of interest, ΔBMI_{GxE} , is estimated as the product $\alpha_3 * PGR_i$ and represents the excess

⁹ Estimates first order GxE effects will, of course, always be relevant for those interested in the biology of obesity even if no effects are expected on second order phenotypes

BMI among those born between 1945-1959 with a PRS z-score equal to PRS_i relative to those born before 1945 and with identical PRS's

Because obesity is a dichotomous variable, we use a slightly different approach to that used for BMI. We first estimate a random effects model for the linear probability of obesity and then compute predicted values of the probability of obesity for each decile. The disadvantage of this strategy is that, although the definition of obesity depends only on BMI, there is no linkage between the GCM for BMI and the linear probability model for obesity. To circumvent this problem, we employ a second strategy in which the estimates of GxE effects for obesity are fully linked to the estimates from the GCM for BMI. (Supplemental Materials, Section I)

In addition to the HRS based estimates, we performed a search of recent empirical studies and identified a small set of estimates comparable to ours (Supplemental Materials, Section III). We use these alternative estimates to generate a range of potential impacts of first and second order impacts of GxE effects associated with BMI and obesity.

b. Estimation of second order effects on T2D and disability.

To assess impacts of GxE effects on the probabilities of T2D and disability, we use the HRS sample and estimate separate hazard models for each outcome¹⁰. We estimate two versions of these models, one including BMI as predictor and a second one including the logit of the probability of obesity. These models are of the following form:

$$\mu_{ik}(t; BMI_{it}, Z_i) = \mu_{ok}(t) \exp(\gamma BMI_{it} + \tau Z_i)$$

and

$$\mu_{ik}(t; LO_{it}, Z_i) = \mu_{ok}(t) \exp(\kappa LO_{it} + \tau Z_i)$$

where $\mu_{ik}(t; BMI_{it}, Z_i)$ and $\mu_{ik}(t; LO_{it}, Z_i)$ are hazards for outcome $k = 1$ (T2D) and $k = 2$ (disability) for the i th individual as functions of BMI_{it} or of the logit of the probability of obesity, LO_{it} . \mathbf{Z} is a vector of controls including age at baseline, t is duration of follow-up, and μ_{ok} is a baseline hazard (Gompertz for $k=2$ and log-logistic for $k=1$).¹¹

¹⁰ Richer estimates can be computed from multistate hazard models. However, the final inferences are no different from those we draw with the two-state models.

¹¹ Estimates of parameters of the hazard models are in Tables in Supplemental Materials, Section II

c. Results I: first order effects on BMI and obesity

To streamline presentation of results we proceed as follows. We divide the HRS sample distribution in deciles, $Z_{PGR}(d)$. The predicted change in the outcomes (ΔBMI_{GxE} or ΔLO_{GxE}) affecting the youngest cohort at decile d of the PRS is $\rho_d = Z_{PGR}(d) * \lambda$, where λ is the regression coefficient of the interaction term (dummy for youngest cohort and PRS), namely, α_3 in the case of BMI and analogous coefficient, α'_3 in the case of obesity.

The increase (decrease) in BMI (ΔBMI_{GxE}) or logit of probability of obesity (ΔLO_{GxE}) implied by a shift from decile d to decile $d+1$ is the product $\Delta \rho_d = Q_d * \lambda$ where $Q_d = Z_{PGR}(d+1) - Z_{PGR}(d)$. This is a local (decile specific) measure of the impact of GxE effects on the phenotype of the youngest birth cohort in HRS.

Figures 1a and 1b display $\Delta \rho_d$'s for BMI and the probabilities of obesity, respectively. To minimize cluttering, we only plot results associated with the highest and lowest estimates of GxE effects found in the literature as well as our own from HRS. The alternative GxE effects are in Supplementary Table 6. Not surprisingly, the $\Delta \rho_d$ values for BMI are largest at the extreme of the PRS distribution. The average $\Delta \rho_d$ across alternative estimates of GxE effects, however, ranges between .023 and .47 BMI units (approximately equivalent to between .07 to 1.4 kgs). These are relatively small shifts that pale in comparison to the additive effects of birth cohort (four times as high) or the direct effects of PRS (twice as high) (See estimates in Supplemental Materials, section I).

The GxE impact on the probabilities of obesity in Figure 1b first descends and then increases steadily with decile. The shift from the 9th to the 10th PRS decile translates into an increase of the probability of obesity of about .05, the largest observed.

Thus, first order impacts of GxE effect on BMI and obesity are quite modest and, as in many cases involving GxE, largest at the extremes of genetic risk scores distribution. The question we pose next is about the magnitude of second order effects on T2D and disability. To assess this we concentrate on impacts via obesity since the bulk of literature on the subject uses obesity as the main predictor.

d. Results II: second order effects

We use estimates of the hazard models to compute predicted hazards for ages 50-99 including (excluding) the contribution of either ΔBMI_{GxE} (in the case of BMI) or ΔLO_{GxE} (in the case of

obesity). We use these predicted hazards to construct T2D and disability single decrement tables and compute probabilities of surviving to ages $x > 50$ without experiencing the event and expected residual lifetimes at age 50. Because most empirical research in the area focuses preferentially on the association between obesity (not BMI) and T2D and disability, we only summarize results when obesity is the predictor.

Figures 2a and 2b display probabilities of surviving from age 50 to age 75 with no T2D and with no disability, respectively, predicted at each decile of the PRS distribution. As before, in each figure there are three plots, one for each of three alternative estimates of GxE effects. In addition, and as a reference, we include a straight line for estimated effects with no interaction term. Figure 2a for T2D shows that even at the extremes of the PRS distribution, differences in the single decrement survival probabilities between a scenario with large (green) and small (maroon) GxE effect are minuscule, less than .04. Further, within each plot, the difference in predicted values between the two extreme deciles is less than .06 when the effects attain a maximum and less than .02 when the effects attain their smallest value. Estimated values for HRS are less than .03. In the case of disability, the impacts are even smaller. For the largest GxE effect, the differences between the two extreme deciles in the probability of surviving with no disability is less than .01. If the effects were as large as in HRS, the differences would be less than .005.

For a more global assessment we turn to effects on the expected number of years to live (from age 50) without T2D or disability. Figures 3a and 3b display these values. In Figure 3a for T2D the maximum difference across the two extreme deciles of the PRS distribution is of the order 2.5 years (green line associated with the largest estimates of GxE effects). The estimate from HRS (blue line) leads to a maximum difference of about 1.0 years. However, the average of the estimated impact on years of life without T2D ranges between .005 and .05. A similar pattern emerges from Figure 3b for estimates of the number of years lived after age 50 with no disability. In this case the changes induced by GxE impacts are an order of magnitude smaller than those associated with T2D. For example, if the GxE effects were as strong as in HRS, the reduction in the expected number of years lived with no disability implied by a shift from the lowest to the highest PRS decile is about .60 years.

Finally, we estimate the expected years to be lived after age 50 *with either T2D or disability*. These are the most relevant parameters for estimation of individual and social health

costs of increased obesity prevalence. To compute these quantities, we construct multiple decrement tables accounting for the joint incidence of T2D and disability, on one hand, and mortality risks associated with them, on the other. We estimate hazard models for mortality in the same HRS sample and include T2D and disability as predictors (plus controls)¹². We then combine the predicted hazards with the single decrement tables for T2D and disability estimated before and, finally, compute expected duration of life with T2D or with disability (see Supplement Material Section II). Figures 4a and 4b display the average number of years of life after reaching the 50th birthday to be lived with T2D or disability. In both cases, and no matter how extreme a PRS decile is, the differences are trivial, generally smaller than .5 years.

IV. Impact on future trends: intergenerational transmission of BMI and obesity

We now address the third question posed at the outset: could GxE effects influence the phenotype in successive generations?

An intergenerational correlation of BMI and obesity has three sources. First, macro-environments that promote increases in body size are at least mildly correlated across generations. Second, obesity and BMI are phenotypes correlated with multiple allelic variants and these are passed quite reliably from one generation to the next (Drong et al. 2012; Goodarzi 2018(Wang et al. 2011; Cheng et al. 2018). Third, within-family shared tastes, preferences, resource constraints, will influence the offspring generation, particularly early in their lives, during infancy, early-childhood, and adolescence. This mechanism has been referred to as vertical cultural heredity (Boyd and Richerson 1988; Cavalli-Sforza and Feldman 1981) and could amplify the GxE impact on future generations.

a. Vertical cultural heritability of obesity

Individuals in obesogenic environments that increase susceptibility to the phenotype via tastes, preferences, behaviors (diet, exercise), and exposure to stressful settings, can reproduce similar environments to which related individuals will be exposed. In particular, offspring of parents with preferences for food and leisure associated with weight gain, are more likely to adopt similar preferences through constrained access to household resources, copying, imitation and other forms of ideational transmission (Jablonka and Lamb 2006). These influences begin to

¹² The mortality hazard models do not include BMI or obesity since their effects are statistically insignificant

operate before conception, are present during pregnancy, maintained during infancy and early childhood, and potentially reproduced during adolescence and adulthood. Thus, they generate a correlation between parental and child obesity predispositions (Adane et al. 2018; Agarwal et al. 2018; Archer 2015; Dabelea and Crume 2011; Heslehurst et al. 2019; Yajnik 2014). In late childhood and during adolescence the influence of parental effects on offspring may be augmented by other mechanisms, such as peer and other social networks, and teachers and mentors. These three types of influences are referred to as vertical, horizontal and oblique cultural inheritance, respectively. (Cavalli-Sforza and Feldman 1981; M. W. Feldman and Ramachandran 2018; Boyd and Richerson 1988). Together, they induce non-genetic heritability of obesity and result in a correlation of phenotypes across generations (Faenza et al. 2016; Fang et al. 2019; Lloyd et al. 2012; Mooyaart et al. 2019).¹³

b. Combined effects of sociocultural and genetic heritability

Because there is no evidence that obesity or BMI are phenotypes driven by positive or negative allelic selection, the future population gene pool is unlikely to change much other than by minor nudges from drift, migration, or assortative mating. However, one pathway through which today's population genetic propensities may influence future trends is via a combination of GxE and cultural heritability.

We pose the following scenario: suppose the parental generation, say born between 1945 and 1959, is abruptly exposed to an obesogenic environment absent in preceding generations and that all relevant exposures take place in utero, early childhood, and adolescence. As a result of the environmental change, obesity risks will increase for everybody, irrespective of genotype. In addition, however, when there are GxE interaction effects, obesity risks will increase above and beyond what is expected among parents whose genetic propensity alone would not have been translated into higher BMI obesity had there been no GxE. Let P_0 be this population of parents who become *obese solely by virtue of GxE effects*. The next generation will be exposed to three forces that increase obesity risks. First, they will experience higher risks by virtue of persistence of obesogenic environments (additive effects of E). Second, offspring who inherited higher

¹³ The coarse indicator of cultural transmission we use here may include more general influences that are referred in the literature as the 'symbolic inheritance system' (Jablonka and Lamb 2006).

genetic propensities for obesity, will experience added risks embedded in GxE effects. Third, since they are the descendants of P_0 , a parental subpopulation with increased obesity prevalence (traceable to GxE effects), their risk could increase due to vertical cultural heritability. This will change the genetic pool composition of the obese population among offspring because it will include, as happened in P_0 , individuals with lower average genetic propensity than in the preceding generation. Offspring with potentially higher obesity risks will attain reproductive ages, form couples, and bear their own offspring. Vertical cultural heritability will generate new obesogenic family settings to which offspring's offspring will be exposed. Thus, the initial excess obesity risk triggered by GxE interaction effects will produce two results. First, it will modify the genetic risk distribution (lower the mean and increase variance) among those who become obese in successive generations. Second, it will impart a self-sustaining upward shift on obesity prevalence in successive generations driven by sociocultural heritability (Cavalli-Sforza and Feldman M.W. 1981; Feldman and Ramachandran 2018).¹⁴

d. Simple model

To approximate the intergenerational impact of the GxE effects, we use the model described in Supplemental Material, Section IV. The main inference from this model is as follows: if there is an increase in the probability of obesity due to GxE effects that affects a subset of the parental generation at time t , the probability of obesity in the offspring generation $t + 1$ will experience two shifts. First, just as the parental generation did, they will be affected by an excess risk due to GxE effect (e.g. persistence of obesogenic environments). Second, there will be an added increase by virtue of cultural heritability: the subset of parents who, in the absence of the original GxE effect, would not have experienced obesity, will do so by virtue of GxE effects and, consequently, transmit preferences, tastes and behaviors that will boost their offspring obesity risks. How large can this latter increase be?

e. Empirical Results

We proceed as before, and compute sets of offspring probabilities of obesity by PRS (z-score) deciles. The first set are baseline probabilities, e.g. those that would be observed in the parent

¹⁴ A likely result of obesity GxE interactions is that the genetic composition of the obese population will progressively be more representative of the full spectrum of allelic variants associated with obesity, from those with the weakest to those with the strongest association. Overtime, the additive genetic variance of the phenotype will gradually diminish.

and offspring generation alike in the absence of GxE effects. The second set consists of probabilities that would be observed in the parental and offspring generation if there is a GxE effect and in the absence of cultural heritability. The third set includes the increased risk of obesity in the offspring generation associated with cultural heritability.

Figure 5 displays plots for these three sets using only the GxE effects estimated from HRS¹⁵. They are represented by the blue, purple and yellow line respectively. The green line displays the contribution of inheritance, e.g. just a fraction (about a third) of the GxE interaction effects corresponding to an intergenerational correlation $\theta=.3$ (see Supplemental Material, Section IV). The key observation is that differences between the second and third plots (purple vs yellow) are very small even at the extremes of the PRS distribution. That is, the increase in the offspring probability of obesity above and beyond what is expected because they and their parents share the same macro-obesogenic environment attributable to cultural heritability, is trivial. On average these differences are close to 0 and are very small even in top three deciles at about .025.¹⁶

V. Discussion

Obesity is a phenotype strongly related to important health outcomes and, in addition, has the potential of being reproduced across generations because of genetic and cultural heritability. The latter can amplify genetic impacts when there are significant GxE effects. Furthermore, these can alter the allelic composition of the population acquiring the phenotype in successive generations, dilute additive allelic effects, reduce genetic heritability, and augment the influence of cultural heritability.

The magnitude of GxE interactions matters for the plasticity embedded in the production of the trait as it affects the reproduction and survival of the organism that bears it. Even if obesity was not subject to assortative mating and had no effects on the net reproduction rate, its association with chronic conditions, disability, and mortality is sufficiently tight to make GxE relevant from a public health standpoint.

¹⁵ The fourth plot in the figure corresponds to the magnitude of increase due to cultural inheritance

¹⁶ This quantity, .025, could be contrasted with the intergenerational growth of the probability of obesity in the US population. In 1965 the US prevalence stood at about .13. Approximately twenty-five years later, when those born in 1965 became parents, it had risen to .23. And, in 2015, when the offspring generation were about to become parents, it attained a level of .40. Thus, the intergeneration growth in prevalence is of the order of .17. Contrast this with the maximum estimated increase due to sociocultural forces triggered by the GxE effect (.025)

Our empirical estimates indicate that current estimated GxE effects can only have a small influence on the trait's intergenerational transmission and that its aggregate impact on demographic outcomes of importance in population health is very small. GxE effects are of relevance only to the small fraction of individuals in the extremes of the genetic risk distribution. Because of this, they could be a useful guide for interventions in a small population segment. However, neither the future trajectory of the phenotype nor the aggregate impact on the population's prevalence of T2D and disability can be significantly affected by them. We conclude that, despite the excitement surrounding the detection of GxE effects on body size, they should be taken with a grain of salt as the magnitudes of estimates retrieved with very recent data is too small to have a noticeable influence on future trajectories of the phenotype or modify health outcomes that demographers and population health scientists are interested in.

It may well be, however, that the tools we use are too blunt to detect GxE with second order effects of importance. Even though these are the same tools employed to highlight first order impacts of GxE and should be well-known, it is worthwhile to repeat them. First, we ignored difficulties of estimation and interpretation of effects of genetic variants. The linear model including the PRS we and other researchers use is inconsistent with the standard population genetic model for phenotype determination. In the standard model the additive effects of loci are estimated separately whereas the GxE effects should be allele-specific. Thus, there is not one slope for GxE but potentially as many as there are candidate allelic variants. The PRS is just too crude a tool and causal interpretation of estimated effects PRS is problematic. In addition, we also ignored issues related to confounding, sample selection, insufficient statistical power, model misspecification, measurement error, and the difficulty to discriminate between quantitative and qualitative GxE.

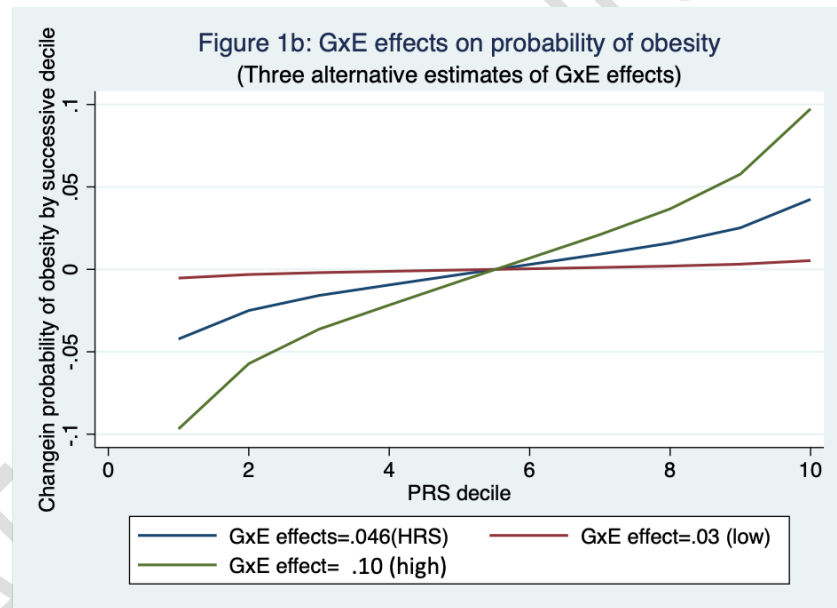
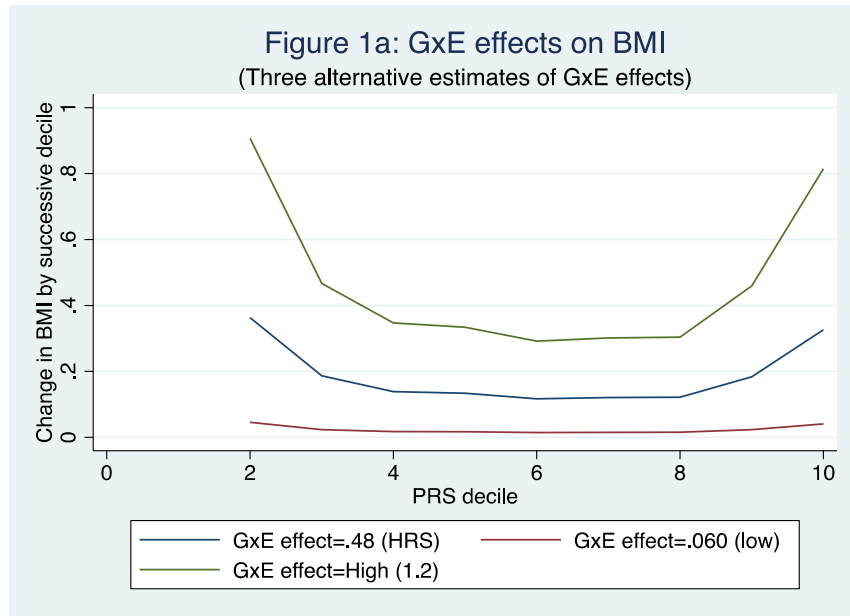
Second, the PRS scores from HRS and other similar studies includes a limited number of SNP's involved in shaping the phenotype. It is likely that many others could be identified and that the associated PRS will turn out to have much higher predictive power and possibly increase the magnitude of GxE effects.

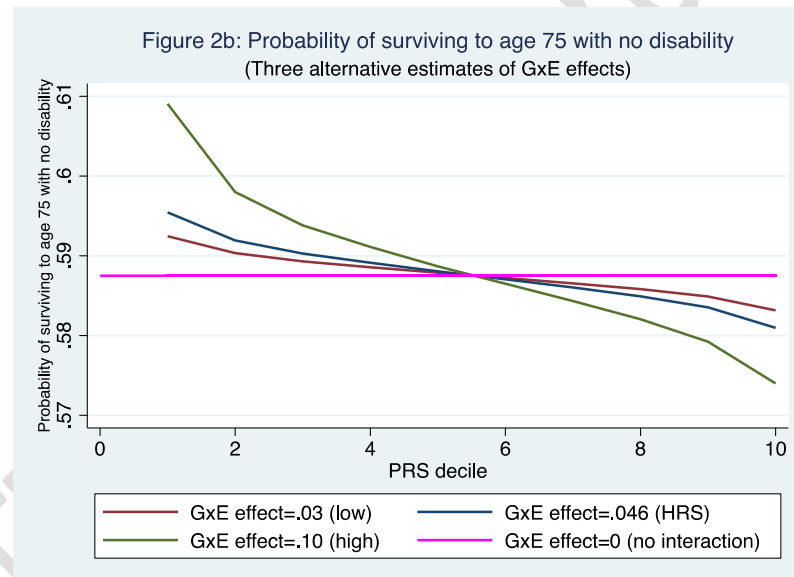
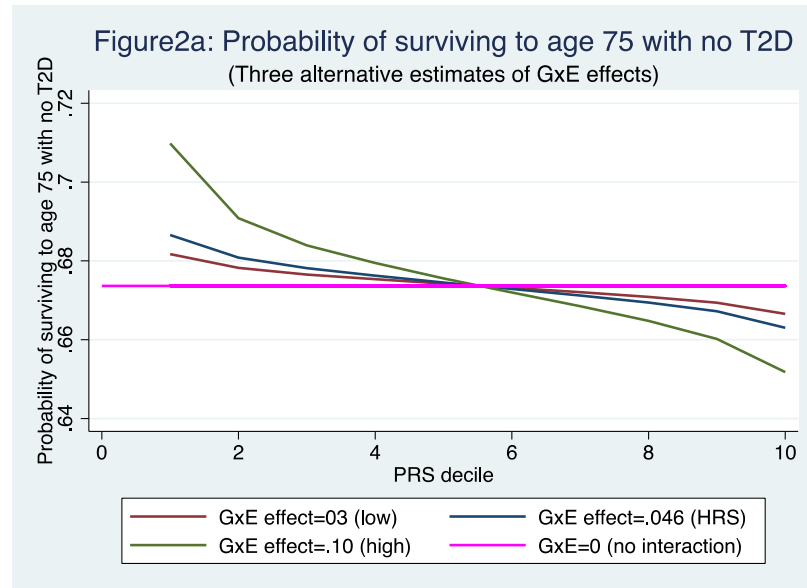
Third, the "E" in the GxE refers to cohorts born within discrete periods. In doing so, we followed recent studies in which birth cohort is used proxy for a "treatment", namely, exposure to environmental contexts within which the phenotype of interest is expressed. Employing birth cohort as "treatment" is justified on the grounds that it captures many transformations (in

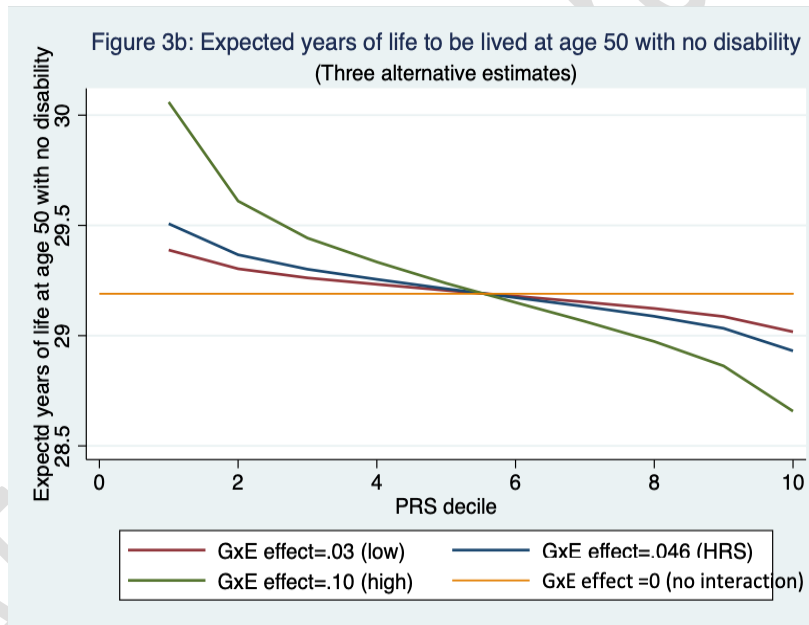
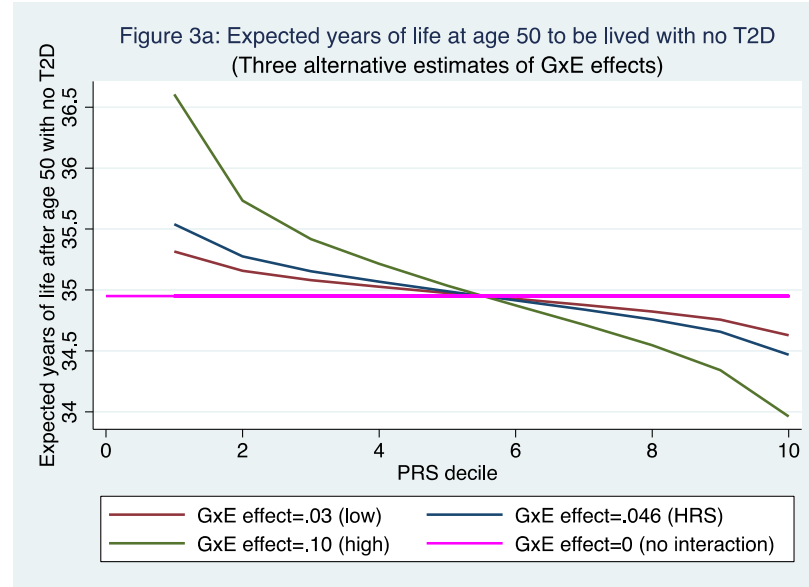
physical, ideological, legal, judicial, health, conditions) that may repress or relax constraints on the expression of a phenotype. But it is also an extremely vague and crude construct for we know next to nothing about the mechanisms (timing, duration, intensity of exposures, etc) linking it to the phenotype or genotype of interest. Just on this grounds, causal interpretation of estimates of GxE effects are problematic. Furthermore, and equally relevant, the actual birth cohorts we study represent not more than a White, elderly population living in the US.

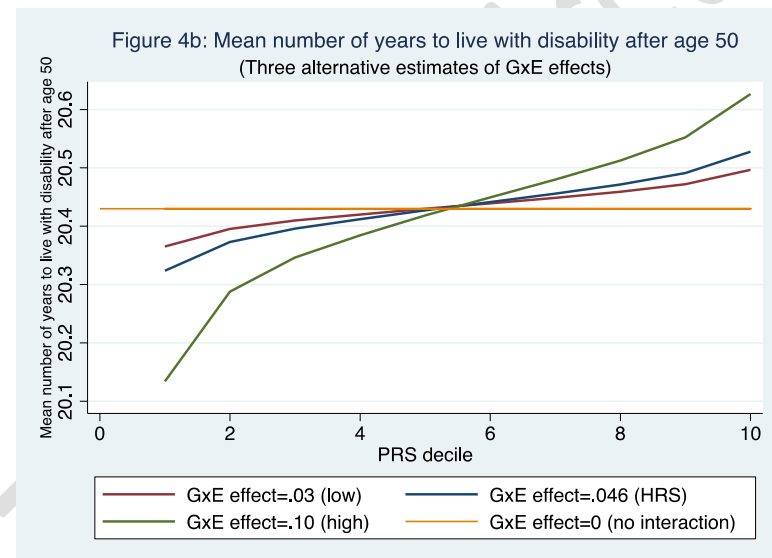
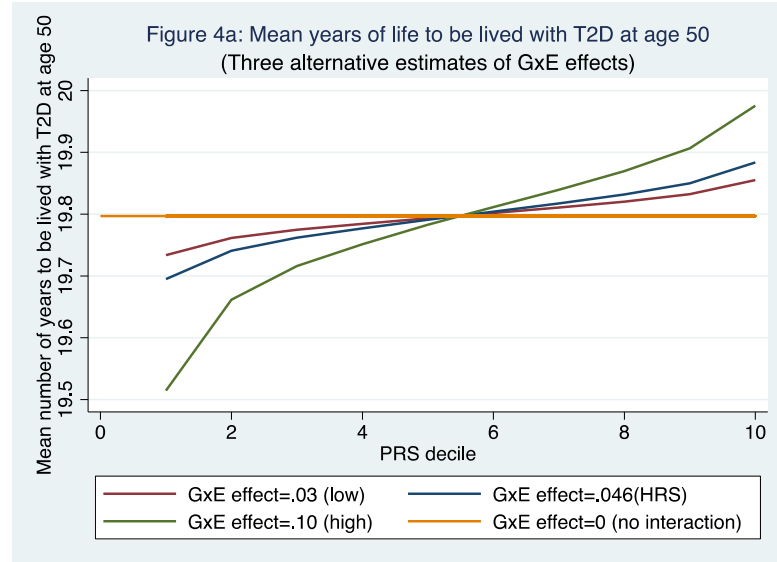
Fourth, we did not explore population distributional effects, only mean impacts. It remains to be studied if the GxE effects have influences on the timing of outcomes, namely, the population distribution of age of onset of obesity, T2D and disability.

A final caveat. Our inferences apply to the second order phenotypes we chose to examine, T2D and disability. It is possible that different results would have been obtained had we chosen to examine other health outcomes associated with BMI and obesity. This remains to be investigated but it is unlikely to be a deal breaker as T2D is by far the strongest second order outcome associated with BMI and obesity. By the same token, we study only one phenotype, obesity, and conclusions about the relevance of GxE should be confined only to it. The magnitude of GxE impacts could be more significant for other phenotypes that also cause deleterious health effects. For example, there are important GxE effects involving smoking behavior and environments that range from birth cohort to social contexts (Boardman et al. 2010; Domingue et al. 2016). Might it not be case that second order effects of these GxE effects (on lung and other cancers, COPD, CVD) are highly significant? This is certainly possible but to demonstrate it we should get into the habit of not halting a study of GxE after detecting first order effects. At least population health scientists should continue the search for impacts on second order phenotypes of interest, those located farther down a causal chain that begins with the first order phenotype. A comprehensive evaluation should include three steps: identification of GxE effects on first order phenotypes (obesity, smoking, drinking, exercising, etc), linkage between these and health-related second order phenotypes and, finally, evaluation of the accumulated health burden associated with the first order GxE effect in each of the second order phenotypes.



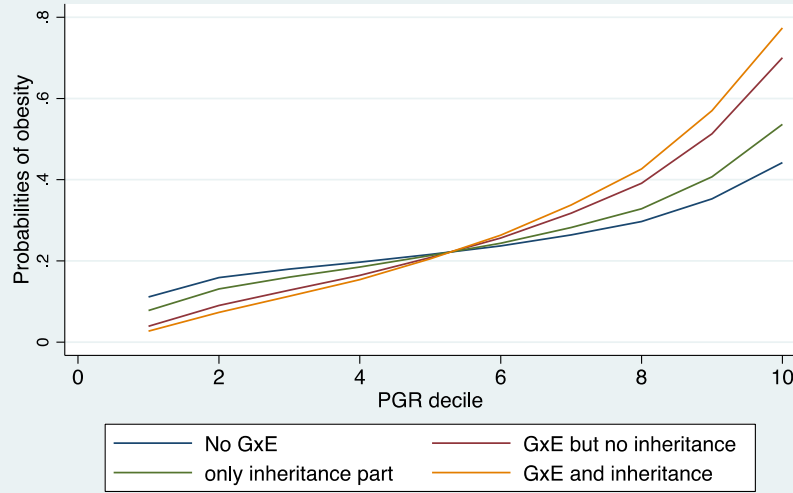






DRAFT- Do not circulate

Figure 5: Probabilities of obesity among offspring
(Three scenarios and contribution of sociocultural heritability)



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