Human Heredity

Hum Hered , DOI: 10.1159/000549053
Received: January 2, 2025
Accepted: October 13, 2025
Published online: November 28, 2025

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ISSN: 0001-5652 (Print), eISSN: 1423-0062 (Online)
https://www.karger.com/HHE
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Generalized Stable Population and Agent-Based Models of phenotypic transmission in human populations, with an application to body size

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Shortitle: Models of human obesity
Keywords: Obesity, genetic inheritance, assortative mating, fertility differentials, stable populations models

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Abstract

Introduction: We show that generalizations of stable population (GSPM) and agent-based models (ABM) are useful tools to simulate trajectories of human phenotypes. Although mathematically very different, both classes of models can simultaneously account for multiple determinants of the population distribution of a phenotype across time and space. These include genetic transmission, assortative mating, differential fertility, vertical and horizontal cultural heredity, gene-environments interactions (GxE), and environmental feedback. We propose an application to obesity, a condition that has spread rapidly around the globe, increasing the risk of adult chronic illnesses and mortality. ***Methods:*** We choose Body Mass Index as the target phenotype, and formulate GSPM and ABM models that include genetic inheritance, GxE, assortative mating, and fertility differentials. We exclude, in this version, the role of vertical cultural heredity. The GSPM is built on time-varying stochastic matrices that trace the trajectory of the phenotype by groups. The ABM models the behavior of individual agents integrating a stochastic component modifying each agent's behavior. ***Results:*** There are four key results. First, differential fertility dominates the phenotype's time trajectory, followed by assortative mating and GxE. Second, contrary to research in other phenotypes, the impact of assortative mating cannot offset the influence of fertility differentials. Third, concerning the formal representation of the transmission process, we show that the use of simple Mendelian models to represent complex phenotypes can produce badly biased inferences. Fourth, despite their mathematical differences, the GSPM and ABM produce virtually identical results. ***Conclusions:*** Modelling phenotypes with complex genetic transmission and heavily dependent on regimes of fertility differentials, assortative mating and GxE ought not to rely on excessive simplifications, as has traditional been done in past research. Both, the GSPM and ABM are useful, accessible, and effective tools to introduce more realism in the modelling of these phenotypes, and can be used as guides for policy interventions.

1 Introduction

There is a rich tradition in population genetics establishing the foundations of models for the diffusion of a phenotype in human populations (1; 2; 3; 4; 5; 6). The nature of these models is heterogeneous, reflecting differences in the problems they address. The majority of these models are designed to assess influences of selection, drift, and mutation on the time and space distribution of a trait. In some cases, they also consider adaptation to changing environments (7). These models introduce consideration of substrate processes that are the raw materials on which selection, drift and mutation work: genotypic and phenotypic transmission of the phenotype, assortative mating, differential fitness (net fertility), and migration. As expected, the complexity increases in tandem with the number of substrate processes considered. To circumvent reduced mathematical tractability without ignoring relevant processes, simplifying assumptions are introduced. Thus, for example, in most cases the trait is binary, not continuous. Genetic transmission is a function of a single or handful of bi-allelic loci (6; 8; 9; 10; 11; 12). Mating is for the most part assumed to be completely random or completely endogamous by phenotype, seldom by social groups or a combination thereof. Differential fitness (net reproduction) is usually defined as a simple function of the phenotype, invariant over time and space. With some exceptions, these models assume that there are no gene-environment interactions, GxE. Finally, we know of no applications considering feedback mechanisms whereby the prevalence of the phenotype itself alters some of or all the substrate processes.

Ours is by no means the first attempt to model some of these processes and we follow the tracks left by other researchers who made important contributions in this area (13; 14; 15; 16; 17; 18; 19; 20). However, and to the best of our knowledge, these substrate processes have not been jointly modeled in the demographic, epidemiological or population health literature.

In this paper we introduce two novel contributions. First, we propose a Generalized Stable Population Model (GSPM) defined by stochastic and time-varying transition matrices to generate the population distribution by phenotype over time and space. This class of models is a generalization of classic stable populations models used in demography (21; 22; 23; 24; 25; 26) We know of only one application of a deterministic form of GSPM focusing on the evolution of IQ under variable assortative mating regimes (27). The GSPM we propose here is more general because it depends on stochastic and changing transition matrices that better represent the substrate processes, particularly genetic transmission.

A second contribution is verification that, despite differences in the treatment of randomness, results from the GSPM are very similar to those of an Agent Based Model (ABM) when input parameters are properly calibrated. This is a very important result because ABM can handle vastly more complex processes than GSPM without ramping up the number of simplifying assumptions. If ABMs produce the same or similar results as do GSPM, they could be deployed to represent higher order complexity even if they cannot be rendered with formal expressions as GSP can.

2 Models' domains

Models for the time (space) diffusion of a trait must include a minimum of three domains.

2.1 Assortative mating (AM)[1]

The nature of the population's mating regime is crucial for the evolution of polygenic traits. Mating, or reproductive pair formation, can occur by phenotype, social homogamy (e.g. population stratification), or a combination of these. The difference between these mechanisms is consequential for the propagation of the trait.

An AM regime driven by phenotype modulates the impact of genetic transmission. To the extent that couples that resemble each other phenotypically are more likely to be genetically similar (28; 29; 30), AM will influence therefore both their offspring's genotype and phenotype distributions. When the phenotype is influenced by only a few loci with strong penetrance, the impact of AM on the trait's evolution will be stronger. Instead, when genetic value is assessed with Polygenic Risk Scores (PRS), the linkages between AM and genetic heredity are relaxed[2]. When mating is random relative to the phenotype, genotypic frequencies will remain constant across generations, and the trait's evolution will be a function of other forces.

AM does not only, or mainly, takes place by phenotype, but also according to social groups' homogamy rules. AM by social homogamy can modulate vertical cultural transmission (VCT) of the phenotype because membership in social groups results in shared environments that might influence the phenotype (33; 5). Furthermore, social homogamy creates conditions under which phenotypic distributions are influenced by indirect genetic effects (IGE) (34; 35; 36). IGE and VCT can be integrated in both GSPM and ABM (see section S6 in SuppMat). When the AM regime is a blend of both phenotypical and social homogamy rules, they will produce feedback and could strengthen the impact of GT on the phenotype (see Section 5 for a model application to obesity).

A highly controversial issue in social and health sciences is whether changes in the AM regime can offset the impact of net fertility differentials. For example, it is known that there are strong net fertility differentials between populations with high and low IQ (27) or large and small body sizes (37; 38; 39; 30). These differentials need not be associated with the genotype or phenotype but could be a result of shared social conditions. Under what conditions can alterations of the regimes (phenotypical or social homogamy) significantly alter the phenotype trajectories? We address this issue in Section 5.

2.2 Genetic transmission (GT)

There are two strategies to introduce GT in a model. The first is to invoke Mendelian segregation rules and assume that the phenotype is dichotomous and fully determined by one or few of bi-allelic loci. This strategy is

[1] We use the term "assortative mating" to refer to non-random pairing of individuals. It can be driven by phenotypical similarity, but also by membership in social groups (social endogamy), residential proximity, kinship, cultural affinity or other distinctive traits. It rarely occurs by genotype.

[2] AM can also increase gametic linkage disequilibrium (GLD), the association between distant loci (31; 32), thus augmenting even further the genetic variance of the trait.

appropriate for monogenic phenotypes but unrealistic for most phenotypes of interest to social and health scientists, such as Body Mass Index (BMI), Type 2 Diabetes (T2D), height, education, IQ, etc... In Section 5.6 we show that, at least in the case of obesity, this sort of model can lead to misleading inferences

A second strategy is to exploit current advances in genetic computing and meta-analyses of massive genetic data bases (GWAS). These studies have powered the construction of Polygenic Risk Scores (PRS) that capture effects of many hundreds of loci and render unnecessary simplifying assumptions about genotypes.

2.3 Net fertility differentials

We adopt the standard demographic definition of net reproduction rate of a reproductive couple i, NRR_i, assume that individual members of the pair are of the same age, and define the quantity as follows:

$$NRR_i = \int_a^b g_i(x)\kappa_i(x)dx \tag{2.1}$$

where $g_i(x)$ is the fertility rate of pair i at exact age x, $\kappa_i(x)$ is the couple's members joint probability of surviving to age x and a and b are the initial and final ages of reproduction. We simplify expression (2.1) to be $f_i = \text{INT}_i \cdot \kappa(A)$, where INT_i is the integral of the function $g_i(x)$ and A is mean age at childbearing[3].

2.4 Gene-Environment Interactions (GxE)

A phenotype trajectory can shift when genetic effects on a phenotype change more than trivially with environmental conditions. Examples of phenotypes associated with GxE interactions in social and health sciences are body size (BMI and obesity), intelligence (IQ), and educational attainment. The GSPM and ABM we propose below integrate a component for GxE.

3 GSPM

Stable population models were first formulated in continuous time and continuous age (21; 25; 23) and then for discrete time and discrete age (22; 24; 26). The latter are also referred as the Leslie matrices approach. Throughout we use this term interchangeably with GSPM.

3.1 GSPM for a binary trait depending on a single bi-allelic locus

We begin with the simplest model for a binary, 0/1, phenotype, ϕ, depending on a bi-allelic locus. At first, we assume only one social group and age invariance, e.g. only one age[4]. In the absence of selection, drift and mutation, the trajectory of the phenotype will be a function on AM, GT and DF.

3.1.1 Assortative mating

When there is only one social group, AM can only be by phenotype. If this is binary, we introduce a 2x4 mating matrix where cells represent the mating probabilities of individuals (ij) at reproductive ages:

$$M = \begin{pmatrix} m_{11} & m_{12} & 0 & 0 \\ 0 & 0 & m_{21} & m_{22} \end{pmatrix} \tag{3.1}$$

where m_{ij} (for i, j = 0/1) is the probability that an individual with phenotype i pairs up with one of phenotype j[5]. These quantities should reflect the population's observed mating rules and this can be accomplished with two different strategies: using an observed matrix M or estimating a one-parameter function from an incomplete M. In the latter case we proceed as follows:

Let π_i be the fraction of individuals in phenotypic category i and $0 \le \omega \le 1$ be a parameter that determines AM so that when its value is 0 the mating is completely random by phenotype and 1 when is completely endogamous. The probabilities of (i, i) pairs are

$$m_{ii} = \pi_i + (1 - \pi_i) \cdot \omega \tag{3.2}$$

with $m_{ij} = (1 - \omega) \cdot \pi_j$. This strategy allows the researcher to compare trajectories produced by different values of a single parameter, ω.

3.1.2 Genetic transmission

When the phenotype is determined by a bi-allelic locus, the offspring's probabilities of inheriting the phenotype depend on parental phenotypes and can be defined by standard Mendelian segregation rules. In particular, let H be a 4x2 heredity matrix containing the probabilities $h_{ij,k}$ that parents (ij) (for i = 0/1 and j = 0/1) produce an offspring of phenotype k, (k = 0/1).

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[3] It is well-known that concentrating all fertility at the mean age of childbearing, does not bias results of a stable population model; it only limits the features of a phenotypical trajectory that can be studied.

[4] Extensions are in Supplementary Materials, Section S2.

[5] The definition allows for non-symmetric probabilities, e.g. $m_{ij} \neq m_{ji}$.

$$H = \begin{pmatrix} h_{11,1} & h_{11,2} \\ h_{12,1} & h_{12,2} \\ h_{21,1} & h_{21,2} \\ h_{22,1} & h_{22,2} \end{pmatrix} \quad (3.3)$$

Assuming dominance f so that when $f = 1$ then $\phi = 1$, these probabilities are:

- Parents (1,1)

$$h_{11,1} = 1 - \frac{6f}{9} + \frac{7f^2}{9} - \frac{2f^3}{9} \quad (3.4)$$

- Parents (1,2) or (2,1)

$$h_{12,1} = h_{21,1} = \frac{3}{9} + \frac{2f}{9} + \frac{3f^2}{9} - \frac{2f^3}{9} \quad (3.5)$$

- Parents (2,2)

$$h_{22,1} = \frac{1}{9} + \frac{2f}{9} - \frac{f^2}{9} - \frac{2f^3}{9} \quad (3.6)$$

3.1.3 Net fertility differentials by phenotype (FD)

We define a 4x4 diagonal matrix F containing net reproduction rates f_{ij} or the number of offspring born to the pair at the end of their reproductive life.

$$F = \begin{pmatrix} f_{11} & 0 & 0 & 0 \\ 0 & f_{12} & 0 & 0 \\ 0 & 0 & f_{21} & 0 \\ 0 & 0 & 0 & f_{22} \end{pmatrix} \quad (3.7)$$

3.1.4 Full model

If the initial parental population in generation 0 is represented by a 2x1 vector $P(0)$ (where the elements represent the proportion of individuals with each phenotype), the population distribution by phenotype in generation T is given by a 2x1 vector $P(T)$:

$$P(T) = \Sigma^T \times P(0) \quad (3.8)$$

where Σ^T is the Tth power of the matrix product $M \times F \times H$. This matrix's rows consist of conditional probabilities that phenotypic pairs (ij) at time T=0 will leave descendants at time T of either phenotype. When Σ is primitive and irreducible, the chain has a stationary distribution that reflects the embedded properties of M, F, and H.[6]

3.2 GSPM for a continuous phenotype

We describe a model for a continuous phenotype ϕ that can, without loss of generality, be treated as categorical with K disjoint categories. In the absence of selection, drift, and mutation, three matrices and a vector of a population's phenotypic distribution are needed to fully specify the model[7].

3.2.1 Assortative mating

When there is only one social group of interest, assortative mating can only occur by phenotype. We define a matrix M of order $K \times K^2$,

$$M = \begin{pmatrix} m_{11} & \cdots & m_{1K} & 0 & \cdots & 0 & 0 & \cdots & 0 & \cdots & 0 & \cdots & 0 \\ 0 & \cdots & 0 & m_{21} & \cdots & m_{2K} & 0 & \cdots & 0 & \cdots & 0 & \cdots & 0 \\ 0 & \cdots & 0 & 0 & \cdots & 0 & m_{31} & \cdots & m_{3K} & \cdots & 0 & \cdots & 0 \\ \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots & \cdots \\ 0 & \cdots & 0 & 0 & \cdots & 0 & 0 & \cdots & 0 & \cdots & m_{K1} & \cdots & m_{KK} \end{pmatrix} \quad (3.9)$$

where entries m_{ij} are the probabilities that an individual in category i mates with an individual in category j[8]. As was the case of the simpler model, M can be either an observed matrix or, alternatively, its cells determined with the aid of a model and a handful of parameters estimated from observables. When AM is by a phenotype in K-categories,we have:

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[6] A generalization of this model with social groups is in section S2 of SuppMat.

[7] A GSPM can accommodate a very large number of categories and, as K increases, its results will converge to those of the continuous case. The ABM model can handle more naturally a real valued phenotype without resorting to extrapolations for large T.

[8] The above definition assumes that the matrix is not (but can be) symmetric, namely, m_{ij} may be different from m_{ji}.

$$m_{ij} = (1 - \omega_{ij}) \cdot \pi_j$$
$$m_{ii} = \pi_i + (1 - \pi_i) \cdot \overline{\omega_i} \quad (3.10)$$

where $0 \leq \omega_{ij} \leq 1$ is a measure of the preference that those in category i have for those in category j and $\overline{\omega_i}$ is the average of ω_{ij} over all j. If preferences are symmetric, e.g. $\omega_{ij} = \omega_{ji}$ there will be $K - 1$ parameters to estimate empirically. Furthermore, if are preferences invariant by social group, expression (3.10) reduces to

$$m_{ij} = (1 - \omega) \cdot \pi_j$$
$$m_{ii} = \pi_i + (1 - \pi_i) \cdot \omega \quad (3.11)$$

3.2.2 Genetic transmission

Define a $K^2 \times K$ hereditary matrix that donates a phenotype to each pair's offspring. In the case of a K-category phenotype:

$$H = \begin{pmatrix} h_{11,1} & h_{12,1} & \dots & h_{1K,1} \\ h_{11,K} & h_{12,2} & \dots & h_{1K,2} \\ \dots & \dots & \dots & \dots \\ h_{11,K} & h_{12,K} & \dots & h_{1K,K} \\ \dots & \dots & \dots & \dots \\ h_{K1,K} & h_{K2,K} & \dots & h_{KK,K} \end{pmatrix} \quad (3.12)$$

where $h_{ij,k}$ is the probability that pair (ij) produces an offspring with phenotype k. As was the case for M, the H matrix is not assumed to be symmetric. A general approach to define the entries of H proceeds in two steps. First, we estimate the relation between the continuous phenotype, ϕ, and a continuous measure of genetic value such as a Polygenic Risk Score (PRS) for the phenotype. This can be expressed as

$$\phi = \alpha + \beta \cdot PRS + \epsilon_\phi \quad (3.13)$$

where ϕ is a continuous phenotype, PRS is a continuous, synthetic (e.g. multiple loci) measure of genetic value for the phenotype expressed as a $\mathcal{N}(0,1)$ normal variate, α is the value of ϕ at the mean of $PRS = 0$, β is genetic penetrance or the effect of PRS, and ϵ_ϕ is a stochastic, $\mathcal{N}(0, \sigma_\phi)$ normal variate.

The initial parental generation, G0, is composed of Z individuals of which $Z/2$ are females. They are assigned a PRS randomly and subsequently we allocate them into K phenotypic categories according to the following rule: let $PRS(k^*) < PRS(k^* + 1)$ be the boundaries of an interval $[PRS(k^*), PRS(k^* + 1)]$ defining the k^*th phenotype category. Let $\mu(k^*) = (\phi - \alpha - \beta \cdot PRS(k^*))$ and $\mu(k^* + 1) = (\phi - \alpha - \beta \cdot PRS(k^* + 1))$. An observation is classified in category k^* with probability $p(k^*)$ expressed by

$$p(k^*) = \begin{cases} 1 & if\ \Phi\big(\mu(k^*)\big) \leq RN < \Phi\big(\mu(k^* + 1)\big) \\ 0 & otherwise \end{cases} \quad (3.14)$$

where RN is a random number in [0,1] and $\Phi(.)$ is the cumulative normal distribution function $\mathcal{N}(0,1)$. We begin with generation G0 of Z/2 males and females and allocate them into phenotypic categories according to expression 3.14.

The second step is to specify a mechanism of heredity whereby parents classified in categories (ij) 'pass on' a PRS to their offspring. Unless there is evidence to the contrary, we adhere to the standard assumption, namely, that the genetic value of an offspring is the average of the genetic values of parents plus a stochastic component:

$$PRS_{ij} = \frac{PRS_i + PRS_j}{2} + \epsilon_{PRS} \quad (3.15)$$

and ϵ_{PRS} is a $\mathcal{N}(0, \sigma_{PRS})$ random variate. As a result of the foregoing definitions, H is stochastic and will change from one generation to the next.

3.2.3 Net fertility differential by phenotype

The following $K^2 \times K^2$ diagonal matrix is the net fertility matrix:

$$F = \begin{pmatrix} f_{11} & 0 & \dots & 0 \\ 0 & f_{12} & \dots & 0 \\ \dots & \dots & \dots & \dots \\ 0 & 0 & \dots & f_{KK} \end{pmatrix} \quad (3.16)$$

where entries correspond to net fertility rates are entries in the matrix F defined in expression (2.1).

Finally, we compute the matrix product $M \times F$ to generate the expected number of offspring to each (ij) pair and allocate them to phenotypic categories using (3.14).

3.2.4 Final model

The matrix H is time-(generation) dependent and the population distribution by phenotype at time T is recursively defined,

$$P(T + 1) = M \times F \times H(T) \times P(T) \quad (3.17)$$

where $P(T)$ is a $K \times 1$ vector of the population in generation T classified in K phenotypic categories. $P(T)$ does not necessarily converge to a stationary distribution as $T \to \infty$ and it cannot be rendered in a closed form expression[9].

4 ABM for a continuous phenotype

4.1 Why is an ABM necessary?

The GSPM approach has an important disadvantage, namely, it cannot represent individual behavior(s). As a consequence, it is not flexible enough to easily integrate domains we do not considered in this paper. For example, inclusion of horizontal heredity via peer networks, influencers, or residential location renders the GSPM cumbersome.

An ABM approach is useful when the dynamic of a system cannot be transparently translated into a formal representation (such as the Leslie matrices underpinning the GSPM). Because an ABM always focuses on agents' behaviors, not on categories of individuals, it is flexible enough to integrate them in social groups, place them in residential areas, create interactions between them, and represent complex feedback mechanisms. An example of a model with some of these properties was developed by Giabanelli and colleagues and validated using data from the National Longitudinal Study of Youth (NLSY) (18) (see also (15; 20; 40; 19; 16; 41)). Because our final goal is to represent all relevant substrate process, including those we ignore in this paper (vertical and horizontal cultural heredity and indirect genetic effects (IGE)), and because this cannot be accomplished by tractable extensions of GSPM, it behooves us to verify that an ABM resting on a specification exactly identical to those of the GSPM matrix approach generates approximately the same results and inferences as those from GSPM.

4.2 ABM algorithm

The design of the ABM is based on the same rules of the matrix approach. The only difference is that these rules apply to single (simulated) individuals or "agents" rather than to categories or groups represented by matrices.

The ABM moves by steps ('tics'). In our model these correspond to pair formation and reproduction plus assignment of genotypes over multiple generations[10]. The ABM begins with Z individual agents of whom Z/2 are female. In the next tic or step, these agents are randomly assigned both a genotype (PRS) and phenotype (described later).

Agents then seek a partner among those allowed by the rules of the AM regime. Thus, for example, when ϕ is categorized in K categories, an agent who, by virtue of her phenotype, is in category i will pair with an agent whose phenotype is j with probability defined by expressions (3.10) or (3.11). Partners' assignment depends on the pool of eligible partners at a given tic[11]. Once pairs are formed, they become the new agents whereas the original ones are discarded.

In the next tic, pairs bear offspring according to net fertility rules, e.g. entries of matrix F in expression (3.16). Reproduction takes place only once in the lifetime of the pair. After offspring have been assigned to parental pairs, the latter are discarded and offspring become new agents.

Offspring are then endowed with genotypes, g, according to a GT mechanism. The genotype g can be (i) a set of allelic values for one or more biallelic loci or (ii) a single value that is a function of the parental g's. In the first case the offspring inherits a genotype according to Mendelian segregation rules. Thus, in the case of a biallelic locus, the offspring can have three possible genotypes; the assignment does not include a stochastic component. In the second case, the offspring receives the average of parental values g modified by a random component, as in expression (3.15).

Finally, each offspring' phenotype is defined using their genotypes and corresponding parameters in expression (4.1) As in the case of GSPM, offspring' phenotypes are defined as a function of genotype (and, when appropriate, a random component). To determine the agent's categorical or continuous phenotype, we specify a function linking genotype, g, and phenotype, ϕ, values:

$$\phi = \zeta(g) \tag{4.1}$$

where g can be defined as either a categorical variable representing different genotypes for one or a combination of loci or, alternatively, a continuous measure of genetic value reflecting the impact of hundreds of loci such as a

[9] In section S1 of SuppMat, we describe extensions to include social groups.

[10] Although in our application pair formation is by phenotype, the ABM can easily accommodate multiple social groups. See section S2 in SuppMat.

[11] In our model, all agents are able to find a partner.

Polygenic Risk Score[12]. The function ζ can map a genotype onto a categorical phenotype, or alternatively, a continuous value of g maps to a continuous value of ϕ (expression (5.3)).
The ABM proceeds with the next generation until reaching the *Gth* generation. The results are summarized and stored as outcomes associated with each of the *G* generations corresponding to one ABM realization. A new realization begins with *Z* new agents (or G0) and subsequent generations. In the end, we produce a total of *R* realizations of *G* generations each, containing generation-specific distributions of outcomes of interest, e.g. obesity prevalence or mean and variance of BMI.

5 Empirical application: the case of Body Mass Index (BMI) and obesity

We use GSPM and ABM to assess alternative trajectories of a population's BMI distribution and obesity prevalence and estimate the impacts of genetic transmission, GxE, assortative mating by phenotype, and differential net fertility.

5.1 The obesity epidemic

The human obesity epidemic is a result of a heterogeneous set of factors that vary across time and space. There is agreement that an accounting framework of the epidemic should include distal macro-determinants, such as modern food production and distribution and built-in environments, micro-conditions such as individual preferences and choices responsible for caloric intake and expenditures, and proximate pathways such as molecular mechanisms that regulate energy management, tissue growth, composition, and storage (42)[13].
Although this accounting framework is valuable, it places less emphasis on background processes that influence the spatial diffusion and intergenerational transmission of the phenotype. We model four of these: (i) genetic transmission (GT), (ii) gene-environment interactions (GxE), (iii) assortative mating (AM), and (iv) net fertility differentials (FD). We shall use BMI and WHO-defined obesity categories as phenotypes[14]. To simplify, we leave out vertical cultural heredity[15].
We address the following questions:
1. How sensitive is population obesity prevalence to changes in phenotypic assortative mating? Do changes in assortative mating significantly alter genetic heritability of the trait? Can assortative mating be an important modifier of obesity trends?
2. What is the impact of differential fertility by phenotype? Can reductions of assortative mating offset effects of differential fertility by BMI or obesity status?
3. How strong is the contribution of vertical genetic transmission? How large can the impact of gene-environments interactions (GxE) be on future trends of the phenotype?

5.2 GSPM with random and time dependent $\boldsymbol{H(t)}$

We employ WHO classification scheme and define four obesity categories: underweight (BMI ≤ 18.5), normal weight (18.5 < BMI ≤ 25), overweight (25 < BMI ≤ 30), and obese (BMI ≥ 30)[16]. Let $O(t+1)$ be a 4x1 vector with obesity category frequencies for the $(t+1)$ generation defined recursively as:

$$P(t+1) = M \times F \times H(t) \times P(t) \tag{5.1}$$

where $P(t+1)$ and $P(t)$ are population vectors by phenotype, M is a 4x16 matrix of mating probabilities of pairing between obesity categories that produces 16 classes of couples, F is a 16x16 matrix of fertility rates for the 16 classes of couples and, finally, H is a 16x4 matrix of genetic heritability, containing the probabilities of offspring allocation by BMI category status conditional on the parental BMI category. The mating and fertility matrices, M and F, are fixed and deterministic, whereas H changes across generations and has a stochastic component.

5.2.1 Assortative mating

Past research suggests that AM by body size has increased jointly with the prevalence of obesity (37). To reflect this, we specify assortative mating rules by phenotype and choose a particular case of expression (3.10) to define a one-parameter continuous function, ω ∈ [0,1]. We assume all members of the population find a partner. When

[12] Once an agent is assigned a value of ϕ, she can be classified in discrete categories of the phenotype. This facilitates handling of assortative mating (see expressions (3.10) and (3.11)).
[13] For a recent and very thorough overview of determinants of obesity, see 'Causes of Obesity: Theories, Conjectures and Evidence', The Royal Society of London, October 17-19, 2022: https://royalsociety.org/science-events-andlectures/2022/10/causes-obesity
[14] https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
[15] In section SuppMat we briefly describe extensions to include VCH.
[16] For some analyses, the categories "underweight" and "normal" were merged together, as, in some populations, underweight individuals – as per WHO definition – are rare.

$\omega = 0$, the mating regime is completely random and when $\omega = 1$, the mating regime is completely endogamous, e.g. individuals only mate within their BMI category. Other ω values within the closed interval [0,1] define mixed regimes. Let π_i, be the ith entry of the column vector $P(t)$ corresponding to the fraction of individuals in BMI category i. The probability that an individual belonging to category i mates with a partner in the same category is:

$$p_{ii} = \pi_i + (1 - \pi_i) \cdot \omega \quad (5.2)$$

Because the sum of over all j of p_{ij} must add up to 1, the probability of mating with individuals from a different BMI category ($i \neq j$) is

$$p_{ij} = (1 - \omega) \cdot \pi_j \quad (5.3)$$

These probabilities fully specify the matrix M.

To determine a realistic, empirically robust range for the parameter ω, we carried out an extensive meta-analysis of studies with information on assortative mating by BMI and obesity in multiple countries. A full empirical justification of the range of values for ω is in Table S1 of SuppMat.

Importantly, our meta-analysis and inferences about AM enable us to generate alternative estimates of ω by observed phenotype (BMI categories). Due to lack of information, the models we used to estimate ranges for the parameter ω did not control for social class, a dimension along which AM also takes, even more frequently than it does by phenotype. To the extent that there is an empirical association between social class and phenotype, AM indicators by phenotype will also reflect AM by social class. Since in most high-and middle-income countries, BMI is negatively associated with social class, the range of ω we use in this paper may exaggerate the influence of phenotype on pair formation.

5.2.2 Net fertility differentials

We assume a strictly positive association between fertility and BMI[17] and define a continuous, one-parameter function, $\varphi \in [0,1]$. A couple whose members are in BMI categories i and j will produce a number of offspring given by

$$f_{ij} = 2 + (i + j - 6) \cdot \frac{\varphi}{2} \quad (5.4)$$

The magnitude of the differential is maximized when couples with two individuals in categories (i, j = 4) have 3 children whereas couples consisting of two underweight individuals (i,j = 1) have none. When there are no fertility differentials, all couples have two offspring. The values f_{ij} from equation (5.4) fully specify the entries of the diagonal fertility matrix R[18].

As in the case of ω, the range of values for φ was defined after carrying out an extensive meta-analysis of existing studies and from empirical estimates using secondary data sources available to us. The description of procedures used to narrow down a range of representative values of ϕ is in SuppMat (see Table S2).

A word of caution is needed when evaluating the role of φ in the simulation results. Due to lack of suitable information, the models we use to estimate empirical values of φ, do not include controls for social class. To the extent that higher fertility and obesity are more prevalent in lower social classes, the range for φ we use in the simulation may be an overestimate of population fertility differentials by phenotype only.

5.2.3 Genetic transmission: BMI as a complex polygenic trait

We consider BMI as a polygenic phenotype and assume multiple loci with variable penetrance, whose effects on the phenotype of interest (BMI) are summarized by a BMI polygenic risk score (PRS). Because the offspring' PRS depends on her parents' PRS and a random component (see Section 3.2) the entries of the matrix $H(t), \forall t$ are random and, importantly, depend on t. To define the initial numerical values for the entries of matrix $H(t)$, namely, $H(0)$, we use the joint distributions of PRS and BMI observed in Z/2 = 1,568 intact couples (Z = 3,136 individ uals) with DNA information in the 2006 wave of the Health & Retirement Study (HRS)[19].These individuals play the role of generation 0, G0, and we will use their PRS as well as the observed relation between their PRS and

[17] This reflects what is observed in high- and middle-income countries. The relation is the result of the joint association between fertility, social class and BMI that offsets the negative correlation between fecundity and obesity.

[18] Recall that f_{ij}s are net fertility rates and represent number of offspring per pair who themselves will survive to reproduce.

[19] Health and Retirement Study, RAND HRS Longitudinal File 2023, public use dataset. Produced by the RAND Center for the Study of Aging (Santa Monica, CA.) with funding from the National Institute on Aging and the Social Security Administration and distributed by the University of Michigan with funding from the National Institute on Aging (grant number NIA U01AG009740).

BMI to determine the offspring's (generation G1) values of PRS and BMI (and corresponding BMI category)[20]. This is done in five steps listed below:

- Couples in generation G0: we use the set of Z/2 = 1,568 intact couples in the 2006 HRS' wave including their information on BMI and PRS. We then assign to each couple a random number of children following a Poisson distribution with mean 2. Thus, at least initially, there is no association between realized fertility and BMI (obesity). The set of offspring defines generation G1.
- Allocation of offspring' PRS in G1: after fusion of gametes, the zygote genome is composed of approximately half of maternal and paternal genes. To reflect this, we compute G1's PRS as the arithmetic mean of their G0 parents' plus a random term to represent inherent stochasticity as in 5.5. The random component is scaled so that the offspring PRS distribution is normal (0,1), as is that of their parents'.

$$PRS_{off} = \frac{PRS_{par1} + PRS_{par1}}{2} + \epsilon_{PRS_{off}} \tag{5.5}$$

where $\epsilon_{PRS_{off}}$ is a $\mathcal{N}(\mu = 0, \sigma_{off} = 0.7)$ normal random variate.

- Assignment of offspring' BMI in G1: This is done using estimated parameters for a simple linear relation between BMI and PRS observed in the G0 sample[21]. The estimated relation is

$$BMI = 27.796 + \beta \times PRS + \epsilon_{BMI} \tag{5.6}$$

where ϵ_{BMI} is a $\mathcal{N}(\mu = 0, \sigma_{BMI} = 4.55)$ random variate and $\beta = 1.0715$. The value of σ is scaled so that the variance of the BMI distribution is identical to the observed one in G0. We then assign obesity categories to members of G1 according to their predicted BMI. This last step defines matrix $H(0)$.

- Couple formation in G1: After classifying members of G1 by BMI categories, we pair them up according to the mating rules, that is, a fraction (1 − ω) of the total target couples pair up randomly and then match the remaining individuals within their BMI category (endogamously).
- Assignment of offspring in G1: we assign to each couple in G1 a number of offspring (G2) according to differential fertility rules. These will become generation G2[22].

Subsequent generations are computed by repeatedly applying the steps described above.

5.2.4 GxE interactions

To reflect the presence of GxE in well-defined environments and subpopulations, we will also allow increases of the parameter for penetrance in equation (5.6), $\beta = 1.0715$. To do so, we will define the penetrance parameter as :

$$\beta' = \beta \cdot (1 + p) \tag{5.7}$$

with p attaining values 0, 0.1, and 0.2[23].

Because the distributions of PRS and BMI in each generation after G0 are functions of random normal variates ϵPRS and ϵBMI, we assign values of PRS and BMI to individuals in a generation by independently drawing a random variable from normal distributions, $\mathcal{N}(0, \sigma_{PRS})$ and $\mathcal{N}(0, \sigma_{BMI})$ (see Section 3.2).The collection of distributions by obesity categories defines a single realization of the sequence of matrices $(H(0), H(1), H(2), \dots, H(T))$ associated with one combination of param eters or set of rules. We repeat this process 20 times gathering 20 different realizations of the matrices associated with those rules. To summarize results of these 20 realizations, we compute means and standard deviations of the outcomes of interest (BMI and PRS distributions and obesity prevalence)[24].

5.3 Specification of the ABM

The agent-based model (ABM) was developed using NetLogo to simulate generational dynamics of BMI under different GT, AM, and FD. The simulation of any generation of agents moves by tics and each tic refers to one of two steps: mating and reproduction. First, we create an initial sample of Z= 7100 agents and randomly allocate them by sex (with .5 probability of being a female). Each agent is randomly assigned a PRS for BMI, a BMI, and a

[20] Our results will thus depend on the strength of the observed association between PRS and BMI. To eliminate this dependence, we generate alternative results by varying the strength parameter within an empirically supported range.

[21] The correlation of BMI and the PRS for BMI in the sample of 3,136 individuals is ρ = 0.23.

[22] The expression for f_{ij} from equation (5.4) may result in a fractional number of children, between n and n+1, say $n + \nu$, where $0 \leq \nu \leq 1$. In order to convert this figure to an integer we randomly assign integer n with probability $1 - \nu$ and n+1 with probability ν.

[23] A review of a limited number of very recent studies shows that increased penetrance due to GxE can be as high as .4. The values we use here are in the middle of a range (.05-.40) (43; 44).

[24] We assign 6 different values to ω and 3 each to φ and p thus producing 54 combinations of rules. For each of these we collect 20 realizations.

BMI category determined by the PRS. Second, these initial agents proceed to find a mate according to the GSPM's AM rules (5.3) and generate offspring according to expression (5.4). Each offspring is then assigned a PRS following expression (5.5) and a phenotype (BMI) according to expression (5.6) (see definitions in Section 3.1) These new agents constitute generation G1, and the algorithm is repeated, e. g., agents in G1 replicate actions in G0, that is, seek a partner, reproduce and endow their offspring with genetic and/or phenotypic characteristics. We do this for G generations and results are summarized in each case. The set of results for all G generations constitute one realization or replica of the ABM. We produce R = 300 replicas of a single population that reflects the influence of rules and of stochastic behaviors. This set of replicas of one population is characterized by distributions of outcomes of interest and their parameters, means, medians, variances, etc.

5.4 Results

5.4.1 GSPM

Because the distribution by obesity categories in GSPM and ABM is a function of individuals' PRS and BMI influenced by a random component, there might not be a steady state, e.g. a generation after which all outcomes of interest become invariant. As a consequence, our assessments will use distributions in the 10th generation[25].

Figures 1 and 2, from the GSPM and ABM respectively, display values of obesity prevalence in the 10th generation as a function of the AM parameter, ω, for multiple combinations of GT and FD[26]. To avoid cluttering we only plot mean values attained across replicas in each case and ignore the (overlapping) confidence intervals associated with each series. Because the results for GSPM and ABM are very similar, we discuss them jointly[27].

[Figure 1 about here]

[Figure 2 about here]

When φ is greater than 0 (green and blue lines), obesity prevalence levels increase linearly as one moves from a random mating regime to one that is fully endogamous. A steady state is reached when there are no fertility differentials and is identical to the initial distribution. Second, changes in FD have the largest impact on obesity prevalence. Thus, the maximum difference in prevalence due to differential fertility occurs in a completely endogamous regime (about .15 or the distance between red and blue line at ω = 1.0) whereas the minimum is about (.05−.07) (distance between the red and blue lines at ω = 0). Instead, differences induced by AM are at most .07 and differences induced by GT (changes in p) are in the range (.01 − .04).

Does AM offset the effects of FD on the trait's trajectory? As an illustration, consider a state defined by ω = .5, φ = 0 and p = .20. When occupying this state, the system produces a prevalence level of about .32. If fertility differential increased to the maximum (φ = 1), the system would reach a prevalence of about .44. To offset this increase we could alter the mating regime by introducing maximum randomness or setting ω = 0. If we do so, the system produces a minimum prevalence of about .40. That is, the maximum offsetting effect of the AM regime is equivalent to about one third (.04/.12) of the total effect of fertility. Finally, the case when there is no FD (red lines) is peculiar as neither ω nor p are relevant and the state is only dependent on the mechanism of genetic transmission. Importantly, both figures reveal the existence of significant interaction effects. These are explored below.

In summary, the largest impact is exerted by FD. AM plays no direct role as its additive (direct) effects are not much larger than those of genetic transmission. This is inconsistent with claims in the obesity literature that highlight the role that AM may have played in driving the recent spread of obesity. Indeed, our finding casts doubts on the possibility that AM could have had in the past or will have in the future any discernible influence on the global obesity epidemic.

5.5 Relation between input parameters and phenotype trajectories

A useful way to summarize the above results is to model outcomes of interest (prevalence of obesity and parameters of the BMI and PRS distributions) as functions of input parameters. Because results from both the matrix and ABM approach depend on microsimulation (with 20 replicas, in the case of Leslie matrices and about

[25] Because in our results, the obesity prevalence across generations is monotonically increasing (with FD) or relatively steady (without FD), inferences are the same irrespective of the generation we choose to focus on.

[26] Obesity prevalence in G0 is 0.32.

[27] Section S4 in SuppMat displays plots means and variances of the BMI and PRS continuous distributions.

300 in the case of ABM), we can estimate the average relation between selected outcomes and input parameters. We estimate the following models

$$\ln(O_{ij}) = \alpha_i + \Sigma_k(\beta_{ik} \times Z_{ik}) \quad (5.8)$$

where $\ln(O_{ij})$ is the log of the outcome i, namely, mean BMI or PRS, obesity prevalence and standard deviations of BMI and PRS for the jth simulation, Z_{ik} is the value of the kth ancillary parameter (ω for AM, φ for FD and p for GT) used in the simulation i, α_i is an outcome-specific constant, and β_{ik}s are effects of the input parameter k on outcome i[28].

Table 1 displays estimates of parameters and measures of fit in linear models for (the logs of) prevalence of obesity, mean BMI, and mean PRS observed in the 10th generation (results for the standard deviations of BMI and PRS are displayed in Supplementary Materials, Table S3).

[Table 1 about here]

Estimates from the ABM and Leslie matrices models have the same signs, comparable statis tical significance levels, and similar magnitude. The strongest direct effect is associated with FD: a change from a regime with no fertility differential ($\varphi = 0$) to one with the maximum value ($\varphi = 1$) implies a relative change of obesity prevalence of 15 and 23 percent (second row, first two columns) in a population with an initial prevalence of about .30. On the other hand, the changes in BMI are equivalent to increases of 2.4 to 3.7 percent (second row, third and fourth columns) in a population with an average BMI equal to 28. These changes translate into increases in body weight of 4.6 and 7.6 kilograms, a fairly large shift for any one individual to experience. Changes in p exert a weaker (prevalence) or no effect (BMI and PRS), roughly equivalent to one third of the effects of FD. Finally, the magnitude of the direct effect of AM is trivial in all cases (albeit statistically significant in the ABM simulations).

As suggested by Figures 1 and 2, there are several strong first order interaction effects. The effects of fertility differentials become larger with increases in assortative mating and penetrance. For example, the proportional increase in prevalence associated with maximum fertility differentials grows from .23 (ABM) or .15 (GSPM) in a random mating regime to about .31 (ABM) or .29 (matrix) in a fully endogamous ones, or additional relative increases in prevalence of the order of 9 and 15 percent. These are large changes and suggest that non-linearities and higher order effects are likely to be an important part of observed time trends of BMI and obesity.

The most important take away message from these results is that, contrary to widely accepted claims in the obesity literature, AM is unlikely to have ever been in the past or be in the future a driver of the obesity epidemic. It could have been an important determinant but only in localized populations and even there only transiently.

In the section below, we show that a much more sweeping conclusion can be reached, one that applies to phenotype other than obesity, namely, that the role of AM relative to other domains, cannot be accurately assessed unless the GT domain is properly modeled.

5.6 Consequences of simplifications

In sections 1 and 2 we stated without proof that a GSPM that represents GT with one or a handful of loci can lead to misleading inferences, even when all other components are well-specified. In this section we show that this is indeed the case[29].

Again, we focus on four WHO defined BMI categories and assume there is one biallelic locus, the dominant allele has dominance f, and the recessive allele induces BMI < 30. We use expressions in Section 2.1 and simulate the trajectory of the phenotype using alternative matrices M, H, and F (section S3 in SuppMat describes in more detail the model specification). Because the system has a steady state solution, we focus on steady state prevalence of the phenotype (BMI ≥ 30). Results are in Figures 3 and 4.

[Figure 3 about here]

[28] Because the PRS is in standard units and can attain negative values we do not use its logarithmic value.

[29] It is well-known that only rare forms of obesity are monogenic and that a one bi-allelic locus for the phenotype is, in most cases, inappropriate. This section contrast results from a monogenic and a polygenic model only to demonstrate the existence of bias induced by the simplified model.

Figure 3 displays steady state obese prevalence rates in two extreme AM regimes and five FD regimes ($\varphi = 0, .25, \ldots, 1$) as a function of dominance, f. As expected, increases if FD translate into increases in obesity prevalence, irrespective of dominance and AM. In a random AM regime (top panel), differences in prevalence induced by fertility differentials are maximum at low levels of f small and lowest under full dominance. In neither case does obesity prevalence attain 100 percent, e.g the dominant allele never reaches fixation.

In a fully endogamous regime (bottom panel), relationships are not linear and the maximum differences across FD regimes are attained when there is full dominance. In particular, when there are no fertility differentials, obesity prevalence drifts to 0 and the recessive allele reaches fixation. This occurs because when the obesity allele is dominant in a fully endogamous regime, couples whose members are obese may produce offspring who are not, but the reverse cannot happen. For all f lower than some threshold value (that depends on φ[30]), obesity prevalence is always larger under endogamy than under random mating whereas for values above that threshold, the opposite is true. Importantly, for high values of φ, obesity prevalence is insensitive to the AM regime if f is large, e.g. exceeds .60 or so.

What can we conclude about the role of AM *vis-a-vis* other domains such as FD?

Figure 4 helps to sort out the magnitude of effects of shifts in AM and FD on phenotypic prevalence under variable levels of dominance. The y-axis is the ratio of a change from endogamous to random mating under maximum DF to the change from no DF to maximum DF under an endogamous regime, that is to say, the power of the mating regime to offset increases in DF[31]. Thus, a value above (below) 1 means that the AM shift reduces prevalence by more (less) that what the change in FD increased it. It is clear from this figure that AM has important effects only under weak dominance, e.g. f < .50. When dominance increases, the role of AM wanes until it becomes trifling when f = 1. Also, note that for values of f over .737, the offsetting becomes negative, which means that, when FD is maximum, shifting from an endogamous to a random regime increases prevalence even more.

[Figure 4 about here]

We draw three conclusions. First, even in a simple Mendelian model, the influence of AM on the phenotype prevalence relative to that of FD is a tight function of allelic dominance. In particular, changes in AM can significantly offset effects of FD but only under weak dominance. Thus, inferences about the possible moderating effects of less endogamous AM regimes are questionable in the absence of precise knowledge about allelic dominance. If the heredity mechanism is derived only from observed parental and offspring phenotype frequencies at a given point in time (with no knowledge of f) models' inferences could be incorrect.

Second, we know from results in the previous section that when the phenotype is polygenic, the effects of genetic values are weak and there is a stochastic component, inferences will be at odds with those we obtain assuming simple Mendelian segregation of a single (or even a handful) of allelic loci.

Third, unlike the case of a continuous phenotype determined by a PRS, the simple Mendelian segregation model converges to a steady state and can lead to the disappearance of the phenotype. This is unlikely to happen when the phenotype is a function $\zeta(g)$ of the genotype g.

5.7 Feedback

We use our results from the polygenic model to investigate a policy relevant issue that involves a feedback mechanisms[32].

There is widespread agreement that an important factor driving the obesity epidemic is the post-1950 worldwide diffusion of obesogenic environments (45; 46). In some cases, settings can be modified with policies that alter individual behaviors, preferences, or environmental exposures. Commonly, implementation of policies usually takes place in response to the dynamic of the system itself, e.g., as feedback effect. For example, an intervention to curb the increase of obesity may result from forecast or projections suggesting that obesity prevalence could in the short run exceed some threshold value beyond which health expenditures cannot be sustained.

[30] For instance, $f_{lim}(\varphi = 0) = 0.5;\ f_{lim}(\varphi = 0.5) = 0.63;\ f_{lim}(\varphi = 1) = 0.73$.

[31] Or $offsetting = \frac{prev(\varphi=1,\omega=1) - prev(\varphi=1,\omega=0)}{prev(\varphi=1,\omega=1) - prev(\varphi=0,\omega=1)}$

[32] We hasten to add that our inferences are tentative as they rely on a model with simplifying assumptions. See section 6.

Changes in obesity associated with such policy can be simulated using our models by a reduction of p in expression (5.7) or a change in the constant of the regression converting a PRS into a BMI[33]. In what follows, we assume a reduction in *p* as much has been made of the contribution of GxE interactions on the recent acceleration of obesity prevalence around the world. What is the influence of AM and FD on obesity prevalence? On the time it takes to reach a lower target level?

Figure 5 displays plots of the trajectory of the phenotype before and after an intervention that reduces p to -0.5 when obesity prevalence attains or surpasses .40. Although all but one combination of regimes experience reductions, they follow different paths[34]. The largest and fastest impact (change from .40 to about .36 in 2 generations) is associated with a regime of high net fertility and full endogamy. The next largest is when AM is fully random and fertility highest (from .39 to .37 in 3 generations). Further, note that the post-intervention fall in prevalence takes 3 and 4 generations to run its course in the first and second scenario r, respectively, and when it does it levels off at around .36, a rather elevated value. This result suggests that any policy intervention that targets GxE interactions, will be insufficient to cause more than a modest change[35].

[Figure 5 about here]

6 Discussion

There are two major takeaways from the paper. The first is related to our contribution to the understanding of the transmission of the phenotype. The second is about modelling strategies. We address these in turn.

Our results lead to a handful of potentially useful inferences. First, and unlike empirical results from other phenotypes, we find that fertility differentials by obesity categories are central to the story. By contrast, assortative mating plays a secondary role, especially when the phenotype is polygenic. This result undermines the conjecture that assortative mating by BMI could have driven past or could drive future trends of the obesity epidemic, both in populations that are in the midst of it and in those in the initial stages of the epidemic (see also Supplementary Materials for added reasons to suspect a weak role of AM)[36]. However, while AM does not exert a significant *direct* influence, it modifies the influence of fertility differentials and vertical genetic heritability.

Second, even though we use rather low values of excess genetic penetrance (*p*) to reflect the impact of GxE interaction, its role is not trivial. In fact, it augments the impact of fertility differentials and through it, reinforces the power of potential interventions designed to eliminate or reduce exposure of some subgroups to obesogenic environments. In addition, its influence could be felt in areas we did not fully explore. For example, a GxE interaction that emerges in generation G0 may have important effects on genotypic composition, couples' distribution by obesity category, and genetic heritability of the phenotype, that will be subsequently expressed in G1.

In addition to empirical results, the paper made some inroads on modelling the transmission of phenotypes. First, we argued that commonly used simplifying assumptions are dangerous and can lead us astray and showed that there are differences between the simple Mendelian model and the one embedded in the use of a PRS. This confirms that the manner in which we represent vertical genetic heritability is highly consequential. When there are no FD, the model for a single allele under Mendelian segregation rules leads to a scenario in which the obese subpopulation disappears. Instead, when BMI is assumed to be polygenic, the system attains a stationary state (with some noise) and the prevalence of obesity remain close to those that existed in G0. The impacts and relations between FD and AM rules are very different depending on whether or not the trait is monogenic.

Second, , we show that, at least with the domains we are able to model, inferences from a matrix and ABM approach are very close. This is an important result for the matrix approach relies on simplifications that the ABM approach avoids. The fact that they can be used interchangeably is strong evidence supporting the use of the ABM model to include substrate process that matrix approaches cannot represent. This is highly relevant for

[33] Strictly speaking, the interventions will change the social/physical setting, not the GxE interaction parameter, p. However, we can alter p in such a way that effects on the phenotype are equivalent to those generated by changes in settings.

[34] In a population where there is no GxE, to begin with, there will be no policy effect.

[35] The fact that in some scenarios the drop in prevalence occurs before attaining .40 is dues to the fact we are plotting the average of multiple realization of the simulation.

[36] Hedrick's formal representation shows that AM can contribute some, but not much, to aggregate genetic variance via GLD. Our simulation assuming a single locus, suggests that its total contribution via increased homozygosity must be a relatively minor player in the growth of global obesity.

current research in population genetics that attempts to include non-genetic, e.g. cultural, transmission of phenotypes(see section on limitations below) . GSMP is supported by a well-understood mathematical machinery, one in which it is possible to formally demonstrate properties of a system represented by multiple domains and parameters. Whether the system attains a steady state, oscillates or is explosive can be determined *ex ante* by knowing key relations between domains represented by matrices. This is because this kind of mathematical representation is a generalization of Markov chains whose properties are well known.
But GSPM have an important drawback. As the dimensions to represent a system increase, complications in the translation of those dimensions into matrix language becomes difficult and, beyond some point, it is simply intractable. A clear example of this is when we wish to include the influence of social networks (kinship, peers), a key component of the cultural transmission of a phenotype. As shown repeatedly in various fields, cultural transmission may be so strong that it swamps genetic inheritance, assortative mating, or fertility differentials. To include the influence of social networks in a GSPM is a non-starter. Even if one could introduce simplifying assumptions to ease translation into matrix language, some of them may have to be hardly credible thus rendering the whole exercise pointless. ABM can handle social networks. In fact, that's why they were developed for, to represent interacting agents. But, beyond narrow research areas, ABM models have not been widely accepted. Some have argued that because they do not have an exact mathematical representation, beyond what is needed to specify agents' behaviors, the results are difficult to interpret. In some research areas, they are strongly discouraged as, it is claimed, they require pulling parameters out of thin air, choosing values that have no empirical basis. But this is a misplaces critique. It may well be that some existing applications use parameter values that are poorly justified but that's not a limitation of the ABM model but of the researcher(s). In our application we use empirically grounded parameters which requires painstaking empirical searches and meta-analysis. If one is unwilling or not able to do this, neither ABM nor any other simulation procedure will do.
What we showed empirically is that GSPM and ABM produce the same results even if they do not share the same principles. This means that one could use ABM when GSPM are infeasible and still rely on the theoretical machinery of GSPM to anchor, anticipate, or justify results.
Further, this approach can be applied to many phenotypes, that could be modelled as we modeled BMI. Among the most relevant are IQ, educational attainment, height, non-cognitive skills, age at first birth, age at menopause, birthweight and other health outcomes.
The paper has two shortcomings. First, it excludes vertical cultural heredity, a domain in which first Cavalli Sforza-Feldman (33), on one hand, and Boyd and Richerson (5) on the other, and then more recently, Feldman and colleagues (8; 9; 10; 11; 12) have made important contributions (see also (47; 48)). The household 'niche' to which children are exposed is crafted by parents, close kin and caregivers. To the extent that these are similar in body type, they may also share traits (behaviors, preferences, values) that modify obesity risks directly such as household settings or indirectly via teaching and socialization (47). Vertical cultural transmission can modulate the effects of AM and those can be much stronger than those that prevail under regimes that only depend on genetic transmission. Furthermore, ignoring this domain makes it difficult to assess the impact of indirect genetic effects (IGE) and could lead to underestimates of the impact of GxE interactions when the environments is the household setting.
Second, the model only represents situations in which the relation between fertility and obesity is positive, e.g the observed pattern in populations that are in advanced stages of the obesity epidemic. A more realistic model should include both regimes simultaneously, one in which the initial stages are characterized by an inverse relation that is reversed once the population attains certain levels of obesity prevalence. This may turn out to be a powerful feedback mechanism that only an ABM model can handle efficiently.
Despite these limitations, there is value in our contribution. Because we rely on empirically derived, not guessed, input parameters that represent well the relations between substrate processes included in the model, our assessment of their influence is empirically anchored and defensible.

7 Acknowledgments
We are thankful to Samuel H. Preston, Shripad Tuljapurkar, and Thorkild Sorensen for careful reading of earlier versions of the manuscript and very helpful comments. We also acknowledge support from the Instituto de Economía, Geografía y Demografía (IEGD) of the Consejo Superior de Investigaciones Científicas (CSIC), Spain.

8 Statement of ethics
The empirical data used in the paper, The Health and Retirement Study (HRS), was accessed from a public source at the University of Michigan. Our study was granted an exemption by the University of Wisconsin-Madison

Institutional Review Board (project: Demographic models and hypothesis testing of delayed effects on adult mortality; Alberto Palloni, PI No 2017-1226).

9 Conflict of Interest Statement

The authors have no conflicts of interest to declare.

10 Funding Sources

This project received funding from the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme (grant agreement No 788582). Beltrán-Sánchez acknowledges support from the National Institute of Child Health and Human Development (P2C-HD041022) to the California Center for Population Research at the University of California, Los Angeles (UCLA). The paper reflects only the authors' view and the Research Executive Agency and the Commission are not responsible for any use that may be made of the information it contains.

11 Author Contributions

AP had the original idea and wrote the first draft of the paper. NA and AGA designed the stable population and Agent Based models, respectively, performed data analysis on simulation results, and contributed to the writing of the final version. SD wrote an alternative version of the Agent Based Models whose results are not included in the final version of the paper. HBS participated in discussions leading to the final version of the stable population model, read several versions of the manuscript, and provided critical comments.

12 Data Availability Statement

The simulation codes uses for Leslie matrices and ABM, are available in https://github.com/hirambeltran/Intergen_transmission_body_size. The public version of the Health and Retirement Study data used for estimation of relations between BMI and Polygenic Score, are available to download from the Institute of Research Survey (ISR) University of Michigan-Ann Arbor https://hrs.isr.umich.edu/ Further enquiries can be directed to the corresponding author.

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Figures text

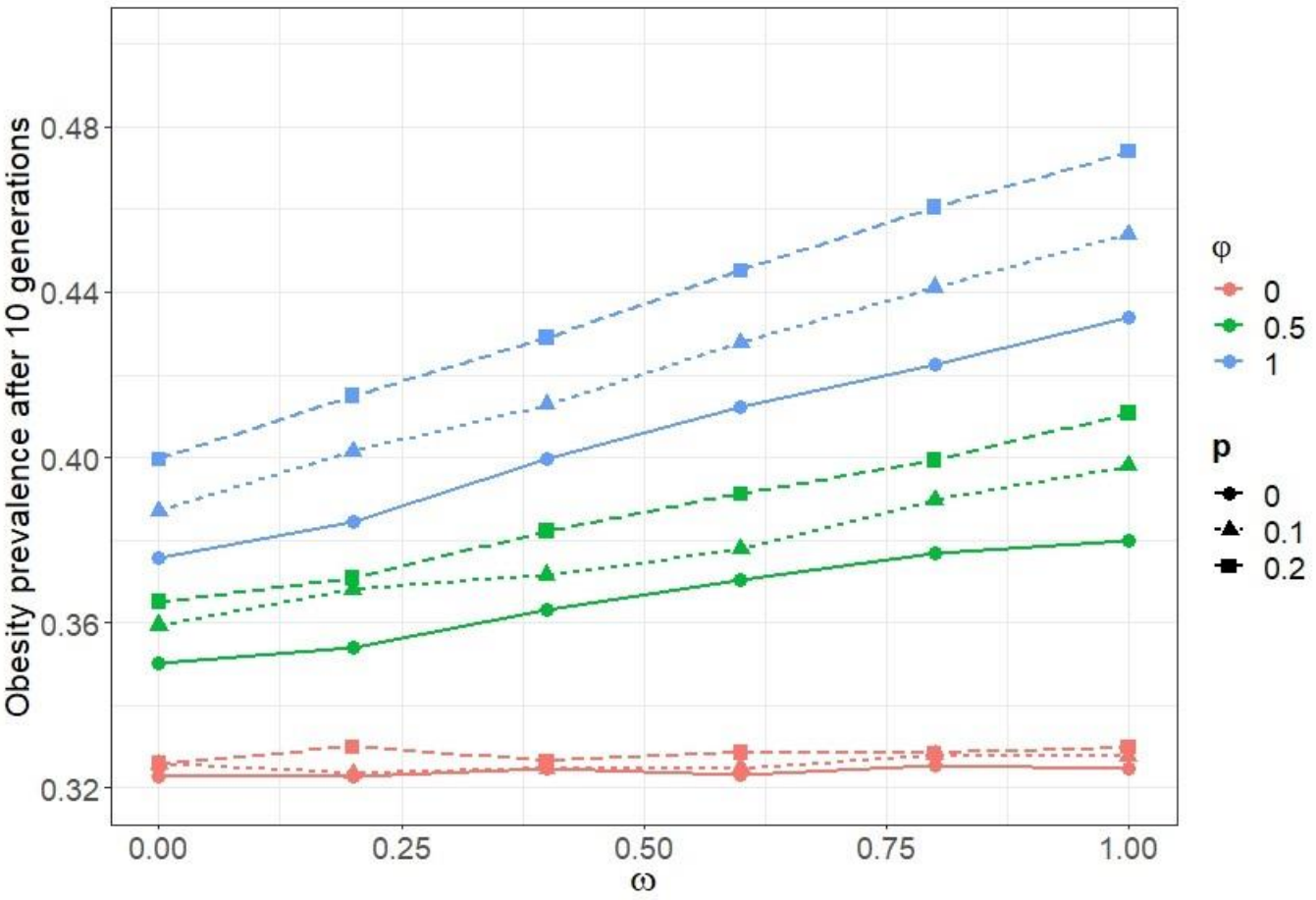
Figure 1: Prevalence of obesity after 10 generations as a function of AM (ω), fertiity differentials(φ), and genetic penetrance (p), Leslie matrices.
Description: Obesity prevalence increases with AM, but only when fertility differentials exist. It reads as follows: after 10 generations, when φ=0.5, ω=0.8 and p=0.2, the average obesity prevalence attained across various simulations using Leslie matrices is 0.40.

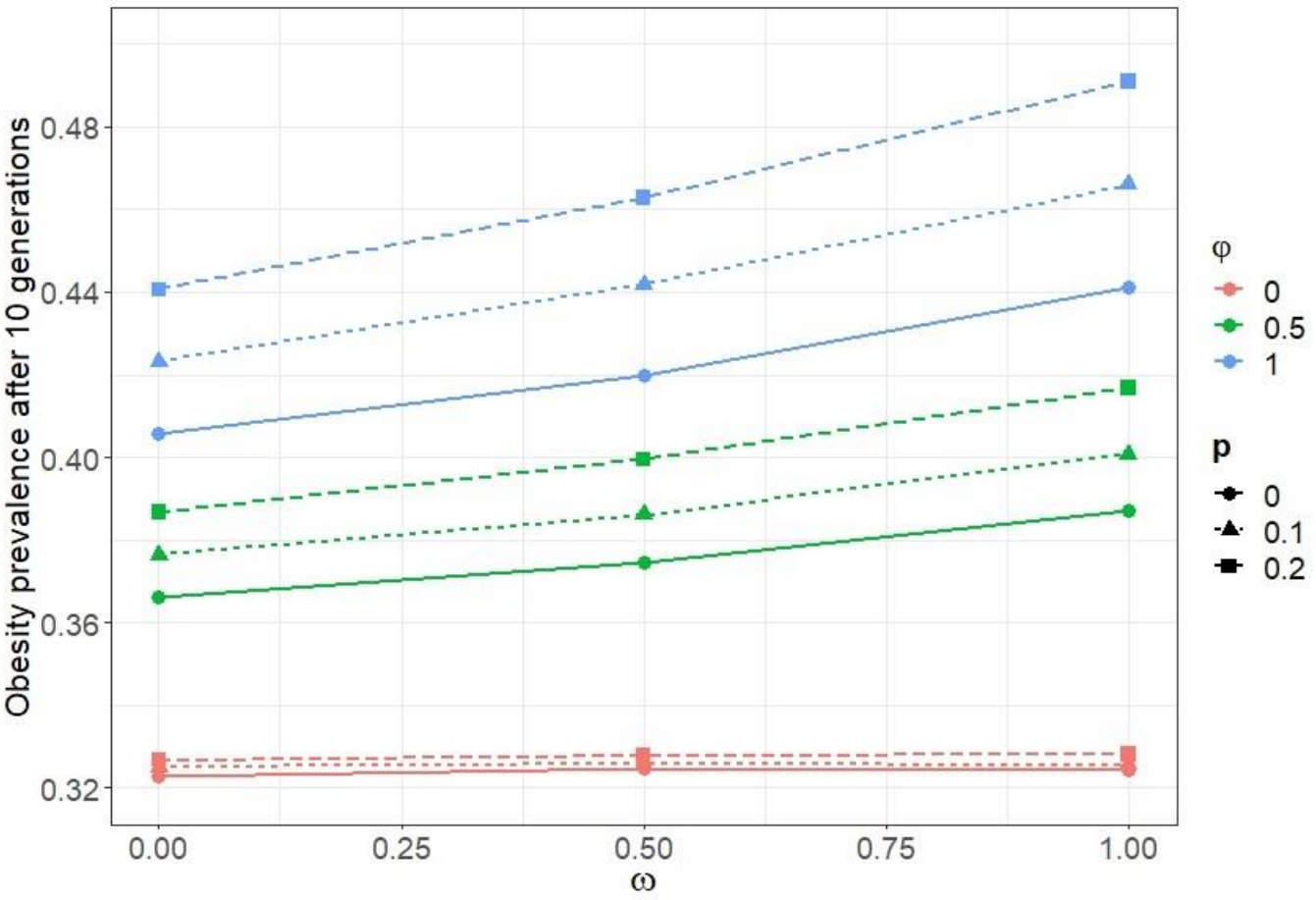
Figure 2: Prevalence of obesity after 10 generations as a function of AM (ω), fertility differentials (φ), and genetic penetrance (p), Agent-Based Models.
Description: Obesity prevalence increases with AM, but only when fertility differentials exist. It reads as follows: after 10 generations, when φ=0.5, ω=0.5 and p=0.1, the average obesity prevalence attained across various simulations using an Agent-Based Model is 0.39.

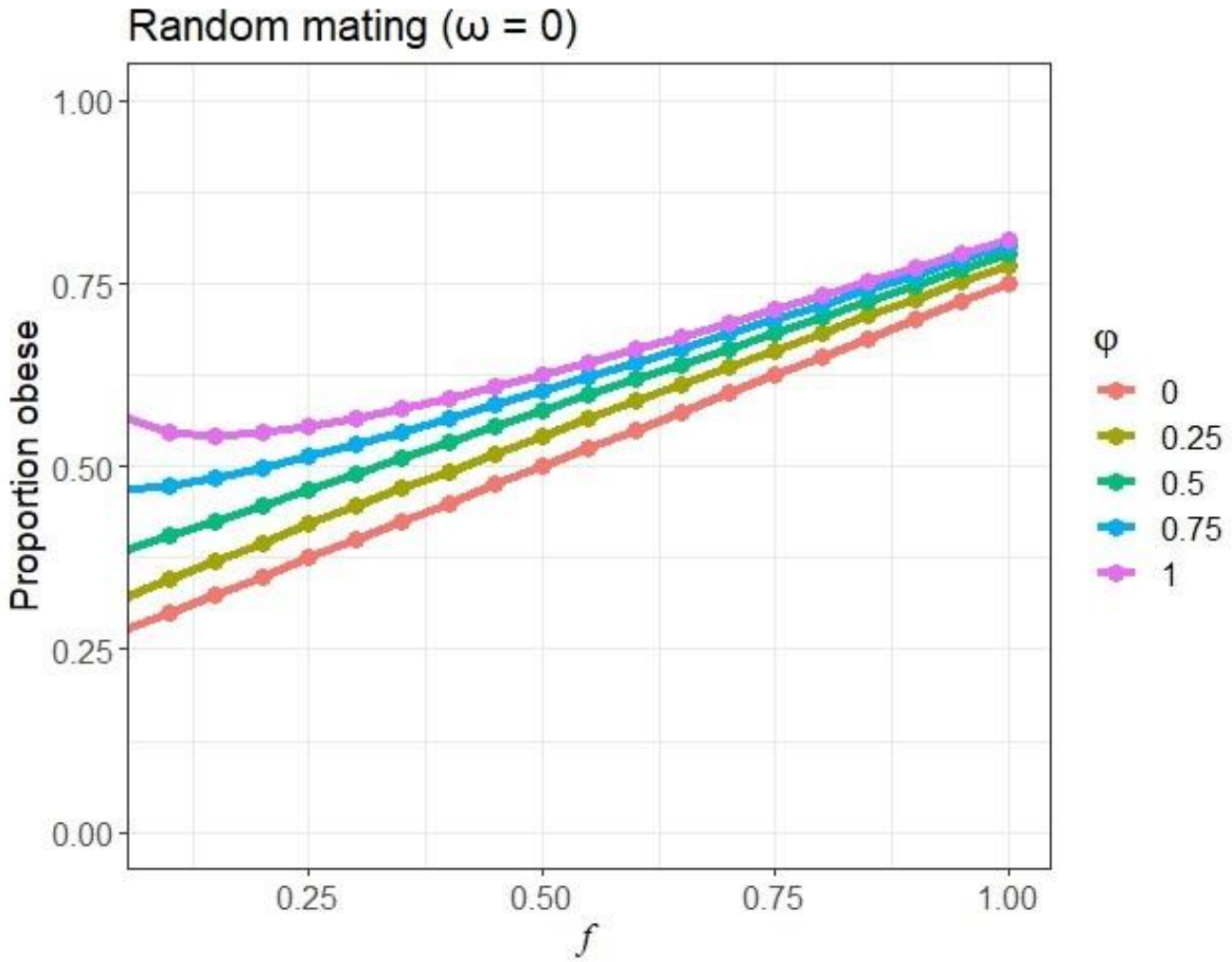
Figure 3: Steady state obesity prevalence for two extreme mating regimes, five FD regimes and dominance f
Description: The figure represents the obesity prevalence that the system attains under different combinations of assortative mating (ω), differential fertility (ϕ) and dominance (f). For instance, when f=0.9 and ϕ=0.25, the obesity prevalence will eventually reach 0.73 when mating is random (upper panel) and 0.5 when mating is endogamous (lower panel).

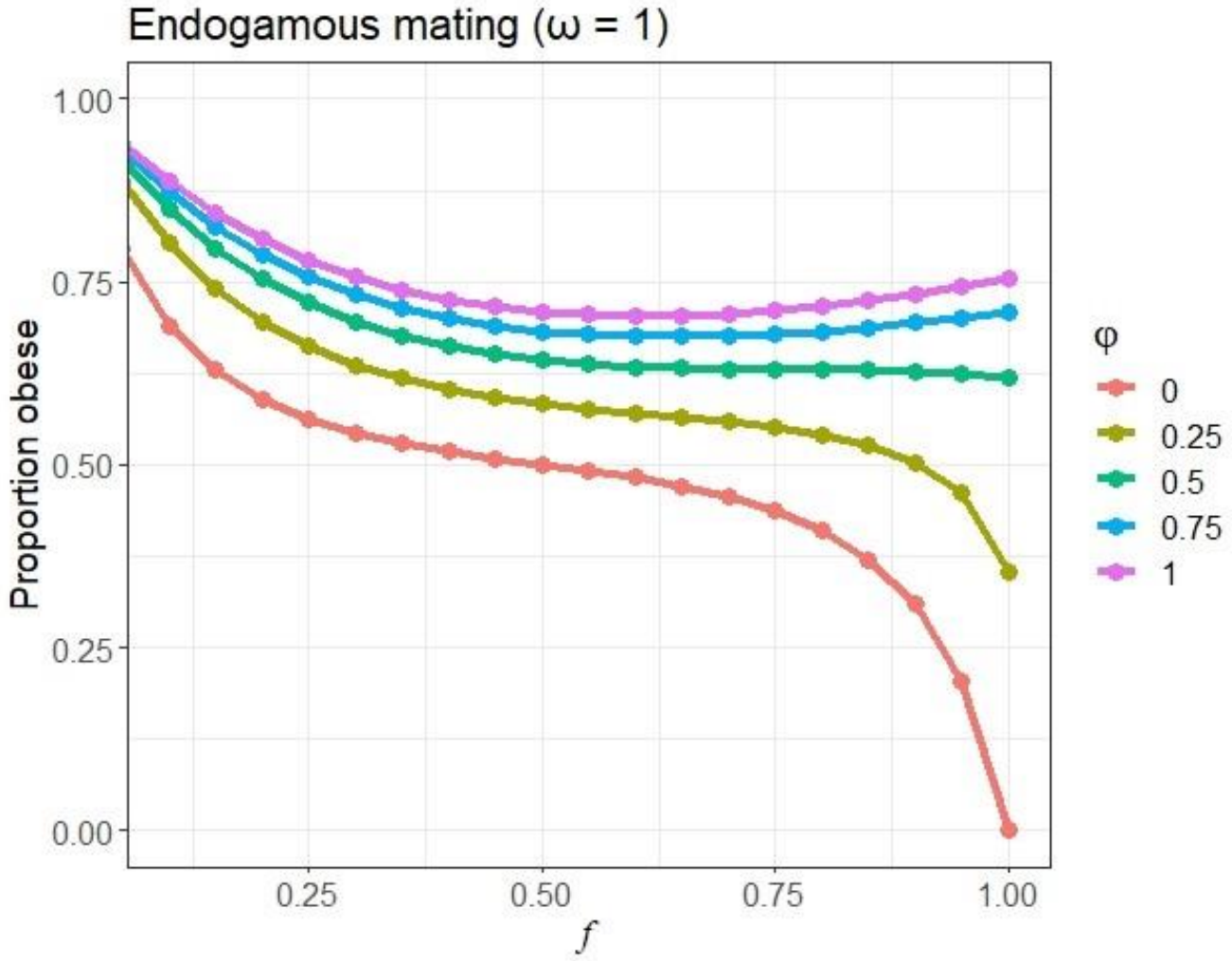
Figure 4: Ratio of changes in phenotypic prevalence due to changes in AM (ω = 1 → 0, with φ = 1) relative to those due to increases in FD (φ = 0 → 1, with ω = 1) as a function of dominance (f)
Description: The figure represents the capacity of reducing obesity prevalence induced by increases in differential fertility by reducing assortative mating. When the offsetting is greater than 1 (f < ~0.27), it means that, by removing assortative mating, obesity is reduced more than what it increased by increasing fertility differentials. Offsetting between 0 and 1 (~0.27 < f < ~0.73) means that, while obesity can be reduced by removing assortative mating, it does not fully compensate increases in differential fertility. Negative offsetting (f > ~0.73) means reducing assortative mating produces further increases in prevalence.

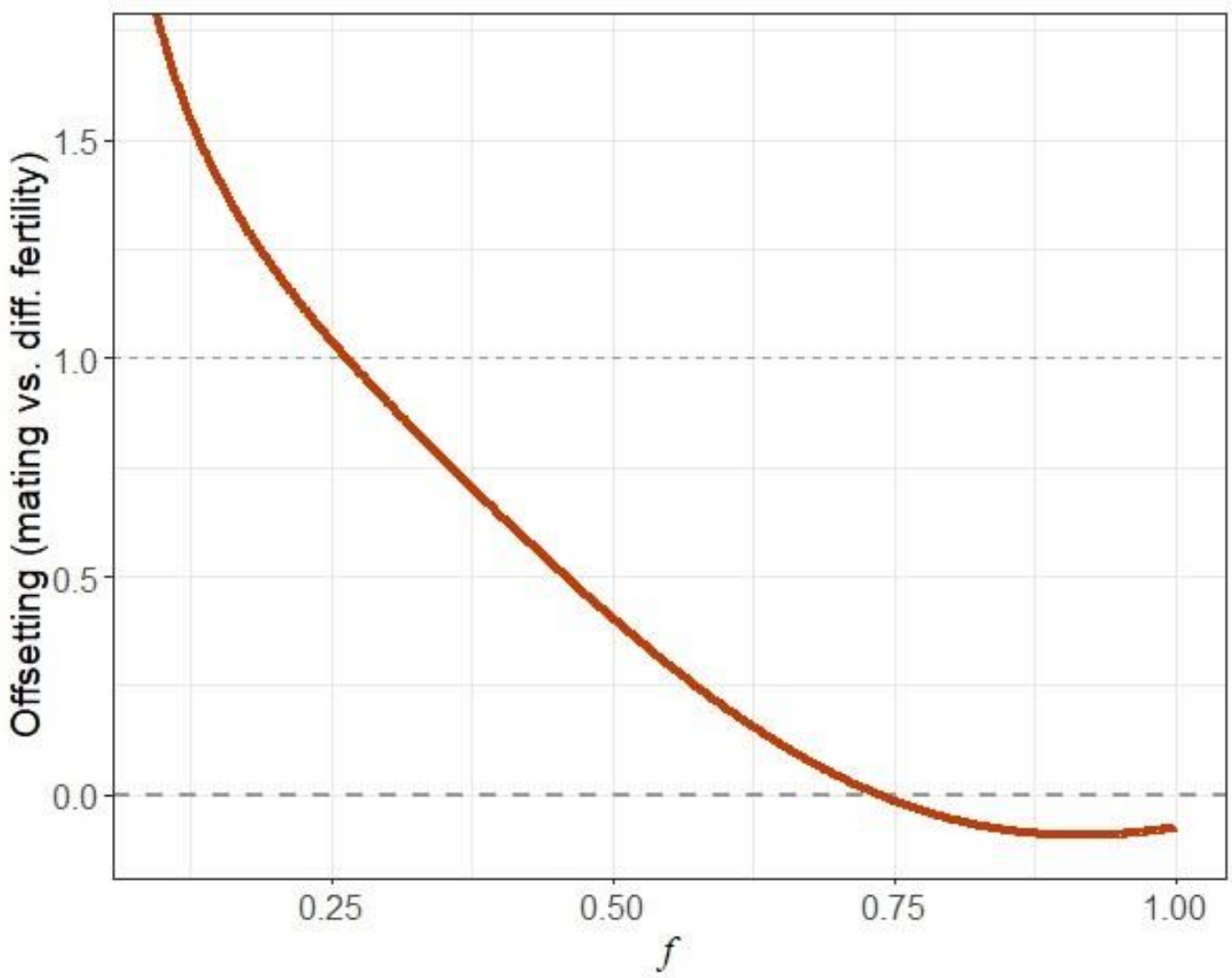
Figure 5: Evolution of the prevalence of obesity in 10 generations as a function of AM (ω), differential fertility (φ) and genetic penetrance (p): results of an intervention.
Description: Obesity prevalence for different generations in conditions where an intervention happens when prevalence reaches 40 %, reducing p to -0.5. The curve corresponding to $\omega = 1$, $\varphi = 1$, p=0.2 is the first to be intervened, at generation 7, which produces a drop in prevalence of 4 points in two generations.











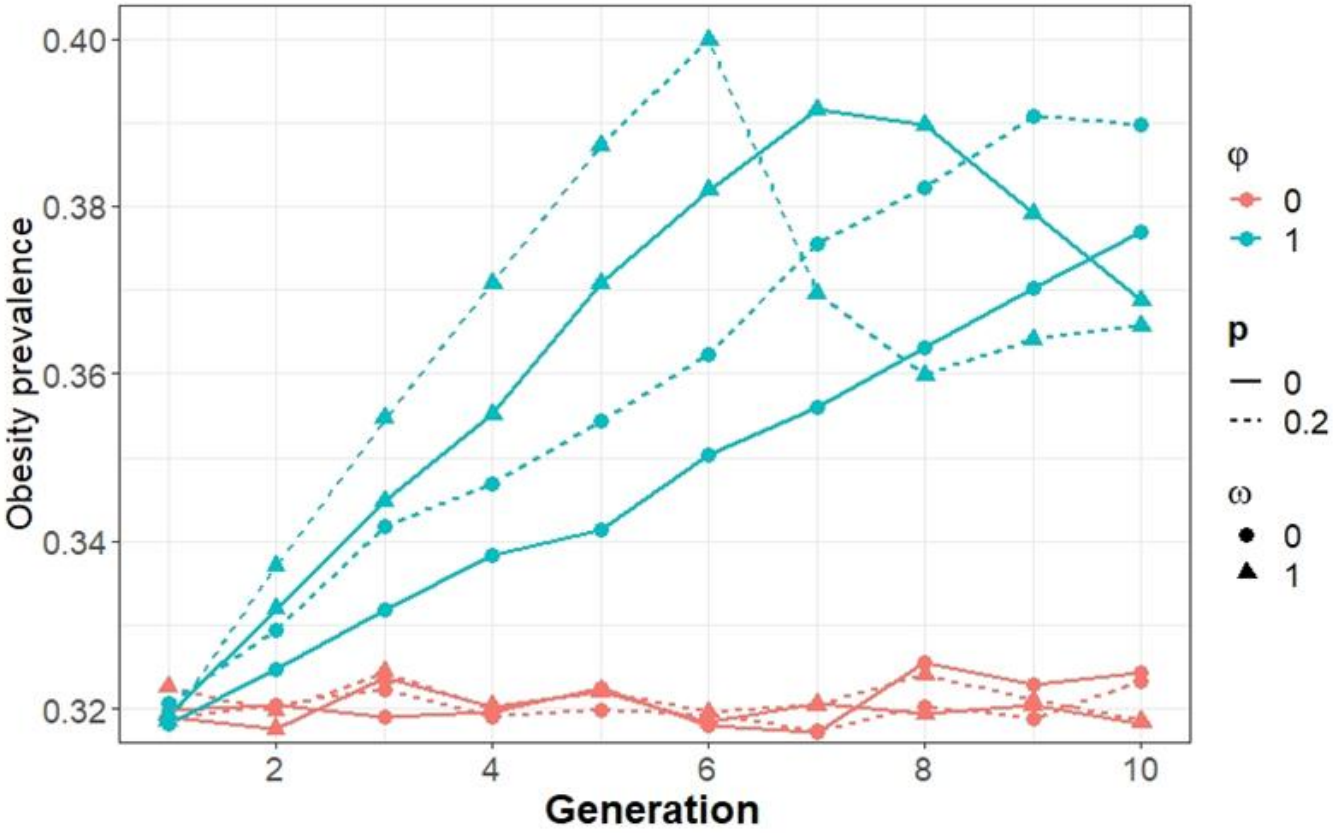


Table 1. Coefficients of regression of three outcomes for ABM and Leslie matrices

	log(prev.)		**log(mean BMI)**		**Mean PRS**	
	ABM	**LM**	**ABM**	**LM**	**ABM**	**LM**
Constant	-1.177***	-1.129***	3.325***	3.325***	.009***	.008
$\beta(\omega)$	**.006*** **	**.011***	**.001****	.001	**.015*** **	.005
$\beta(\varphi)$	**.225*** **	**.152*** **	**.037*** **	**.024*** **	**.978*** **	**.635*** **
$\beta(p)$	**.068*** **	**.064****	.001	.002	.013	-.029
$\beta(\omega \times \varphi)$	**.082*** **	**.140*** **	**.015*** **	**.024*** **	**.410*** **	**.674*** **
$\beta(\omega \times p)$	.019	.034	.002	.003	.032	.136
$\beta(\varphi \times p)$	**.360*** **	**.262*** **	**.072*** **	**.047*** **	**.799*** **	**.576*** **
$\beta(\omega \times \varphi \times p)$	**.113*** **	**.118***	**.030*** **	**.037*** **	**.342*** **	.244
N	7,944	1,080	7,944	1,080	7,944	1,080
R^2	.982	.963	.989	.976	.993	.988
Adj. R^2	.982	.962	.989	.976	.993	.988
RSE	.019	.022	.003	.003	.046	.051
df	7,936	1,072	7,936	1,072	7,936	1,072

The N for LM models corresponds to 54 combinations of parameter values and 20 replicas for each of them. The N for ABM models corresponds to 27 combinations of parameter values and about 300 replicas for each.