Assortative Mating and Differential Fertility by Phenotype and Genotype across the 20th Century

Supplemental Information

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Contents:

- Text S1. Descriptives of the analytic and genotyped samples
- Text S2. Addressing concerns about mortality bias
- Text S3. Changing marriage and fertility patterns genome-wide
- Text S4. Marriage patterns and population structure

Text S5. Additional sensitivity analyses

Supplementary References

Tables S1 to S14

Figures S1 to S9

S1. Descriptives of the analytic and genotyped samples

Table S1 shows descriptive statistics for the entire sample of non-Hispanic white HRS respondents born between 1919 and 1955 versus the spousal subsample. Figure S1 shows densities for outcomes before and after standardization. Note that for CES-D, we first took the log of the mean CES-D plus one and then standardized. Figure S1 also shows a histogram of number of children ever born (NEB).

Figure S2 shows the raw and residualized polygenic scores. In general, the polygenic scores have approximately normal distributions, the largest exception being height. The density for height's polygenic score shows a local maxima around -3. Table S2 shows correlations between polygenic scores and their associated phenotypes after residualizing on the top 10 PCs.

Table S3 shows correlations from Figures 1A and 2A. Tables S4 and S5 show estimated coefficients for Equations 1 and 2 from the main text.

Figures S3 and S4 characterize the degree of intra-ethnic marriage in this sample. Taken together, Figure S3 suggests that while there is substantial intra-ethnic marriage in our sample (as evidenced by PC associations via a modified version of Equation 1) there are not significant shifts in these patterns over the window of birth cohorts examined here (see Figure S4).

S2. Addressing concerns about mortality bias

One potential concern with this exercise is mortality bias. Since HRS respondents had to survive until at least 2006 in order to be genotyped, the earlier cohorts in our analysis include generally longer lived respondents (1). We consider a number of additional analyses to address this possibility. First, we see if our results change when we allow second and higher order marriages to be included in the group in order to understand whether the processes of assortment substantially vary for higher order marriages. Adding these to the sample does not change the overall trends, though point estimates do fluctuate (see Table S6). We next compare the distribution of PGS scores for the six phenotypes in our analytic sample (i.e. where both spouses are still alive to be genotyped) with the sample of HRS respondents where one individual is genotyped but his/her spouse is not due to divorce, death, separation, never married status or simply missing genotype data for the spouse in Figure S5, below. While the distribution has more outliers in the non-spousal sample, the major measures of central tendency (i.e. median, the

2

interquartile range and 95% confidence intervals) appear to be almost identical. It should be reassuring that there is not differential selection by genotype into the spousal group. Finally, we also examined the PGS-phenotype correlations between the spouse and non-spouse sample, the latter of which consists of those who never married, divorced, or are widowed. These results are presented in Table S7. Of all the variables, only height has estimates for the spouse's data which does not fall into the 95% confidence interval for non-spouse's data.

S3. Changing genome-wide patterns of marriage and fertility

One possible explanation of any obtained results (or lack thereof) is that *genome-wide* patterns of genetic assortative mating are changing across birth cohorts. For example, the increasing rate of urbanization and the decline in co-ethnic marriage across the course of the 20th century may mean that genotypic similarity between spouses declines due to a decline in population structure. Figure S6 shows both GCTA GREML heritabilities (and 95% confidence intervals) as well as phenotype/polygenic score associations across two groups (those born 1937 and before versus those born 1938 and after). Here we show that overall genetic assortative mating, as indicated by the genome-wide genetic relatedness of spouses, does not differ significantly by birth cohort. Furthermore, genetic assortative mating, as measured by the algorithm suggested in Domingue et al. (2014), is 0.050 for the younger cohort and 0.047 for the older one (see Figure S7). These are quite similar to earlier results (0.045) and quite similar to each other (1).

Meanwhile, for fertility, as reported in Table S8, we observe an overall SNP-based heritability of 21%—higher than has been reported elsewhere (2)—and no significant differences when we split birth cohort along the median birth year. Thus, as in the case of marriage, we believe that any patterns we observe here are not driven by overall changes in the heritability of fertility.

S4. Marriage patterns and population structure

Building on what was mentioned in Section S1, we take a deeper look at spousal assortment on phenotypes, PGSs, and PCs. Contrary to the urbanization-modernization theory, the rural-urban split does not seem to be driving any differences in genetic assortment, as indicated by Table S9,

3

below. While there are some differences in point estimates, only the confidence intervals for the height estimates (both phenotype and genotype) do not overlap.

We calculated the correlation in principal components by birth cohort in Table S10, below. We calculated PCs three different ways for non-Hispanic whites. First, we calculated them for the entire sample and then examined the spousal correlation on the first four PCs by median birth year split. We find that when we do this, PC1 shows the largest difference between old and young pairs in spousal correlation. However, in this case it is the younger cohort who seem to mate assortatively to a greater degree on the first PC than the older cohort, contrary to the predictions of the modernization literature (though the confidence intervals overlap). When we recalculate PCs within each subsample and then compare the two groups (i.e. impute the younger sample PCs to the older group and vice versa), we do not see this pattern on PC1.

Figures S8 and S9 are updated versions of Figures 1 and 2 from the main text based on polygenic scores that are not residualized for population stratification. A comparison of these figures suggests that none of the main findings change. For example, the coefficient for the education polygenic score from Equation 1 in Figure 1 is -3.1e-3 while in Figure S8 it is -3.2e-3. Similarly, Figures 2 and S9 both report estimated coefficients from Equation 2 of approximately 3e-3 for the education polygenic score.

S5. Additional sensitivity analyses

Mating

A second potential concern with respect to the estimates underlying Figure 2 is the fact that the polygenic score is measured with error that may lead to attenuation bias. We used SIMEX to correct for potential attenuation bias (3). This worked as follows:

1. We first estimate heritabilities via GCTA for the four outcomes (4). Denote these h_{GCTA}^2 .

2. We then assume that, for each outcome

$$
y = g_t + e_1
$$

where g_t is the unobserved true polygenic score and is related to the heritability via the following expression:

$$
h_{GCTA}^2 = \frac{\text{Var}(g_t)}{\text{Var}(y)}.
$$

We then assume that

$$
g_o = g_t + e_2
$$

where g_0 is the observed polygenic score. The error terms (e_1 and e_2) are both assumed to be white-noise random errors (i.e. independent of g_t).

3. Usage of SIMEX requires an estimate for $Var(e_2)$. We obtain that by first noting that

$$
Var(g_t) = h_{GCTA}^2 Var(y)
$$

and then using

$$
Var(e_2) = Var(g_0) - h_{GCTA}^2 Var(y)
$$

by the assumption of independence with respect to e_2 .

4. This estimate for $Var(e_2)$ is then used in SIMEX to simulate predictors

$$
g_S \sim \text{Normal}[g_o, (1 + \lambda) \text{Var}(e_2)].
$$

For different values of λ (typically over a grid between 0 and 2), a trend in the estimates of the relevant covariates is established which is then extrapolated back to the case where $\lambda = -1$. Under certain assumptions (e.g., additive measurement error) that are reasonable in the context of polygenic scores, this is the unbiased estimator.

Results from this analysis are shown in Table S11. For computational reasons, we present conventional standard errors rather than Huber-White standard errors which adjust for the clustering of spousal pairs. As a result, we emphasize changes in the coefficients (which are independent of the clustering) and patterns in the SEs rather than interpretation of p-values. In all cases, the main effect of polygenic score and the interaction of polygenic score and birth year increase in magnitude after correction via SIMEX. This is accompanied by increases in the associated SE, so there is frequently not a dramatic change in the associated p-value. These analyses suggest that while measurement error in the polygenic scores will bias effect estimates toward the null, leading to underestimates of the true genetic dynamic, such random measurement error would not likely lead to a significant effect in the opposite direction but rather a false negative of zero estimated effect.

Fertility

We consider several sensitivity analyses meant to address certain potential concerns regarding the analyses presented in the main text. First, as above, there is measurement error in the left-

5

hand side variables that might lead to attenuation bias. While we use SIMEX as in the mating analysis, we also utilize the fact that NEB is measured with very little error. Thus, we reconsider Equation 2:

$PGS_i = b_0 + b_1 NEB_i + b_2$ birthyear_i + b₃NEB_i · birthyear_i + e_i.

The logic of the above equation is that, since there is minimal measurement error in the NEB, the above coefficients should be free of attenuation bias. Second, we consider a version of Equation 1 where, conditional on the predictors, the response is modeled as a Poisson variable. Finally, we consider estimates from Equation 1 based on a slightly different source of data. Waves 1 and 2 asked different questions regarding offspring which is why they were not used in the main paper. Here we re-estimate Equation 1 using a slightly different variable (denoted "all kids") capturing the number of living children (as opposed to strictly biological children; based on HwCHILD variables in RAND Fat Files) only for those respondents who are missing data on the measure derived from wave 3-11.

SIMEX results are shown in Table S12. The same pattern as above is observed in that magnitudes and SEs increase after SIMEX correction. Additional results from these analyses are shown in Table S13—reverse regression, Poisson regression and use of an alternative measurement of number of children. The statistically significant phenotypic results from the original analysis (BMI and education) are also significant here except for the reversed BMI result. The genotypic results are never significant in the original analyses or the sensitivity analyses, with the exception of the BMI result for total number of children ever born. In general, results do not seem overly sensitive to these changes in specification.

Sex-specific phenotypes

Table S14 presents analyses based on phenotypes that are standardized within-sex. Results are generally stable compared to those from Tables S4 and S5 where phenotypes are standardized across sex. The only difference in interpretation based on the interaction estimate would be in the mating analysis related to height (the estimate changes sign). However, in both analyses the interaction estimate is very near to zero. Thus, our analyses generally do not seem sensitive to sex-specific differences in phenotype. We only consider phenotypes since polygenic score distributions are comparable across sex.

6

Supplementary References

- 1. Domingue BW, Fletcher J, Conley D, Boardman JD (2014) Genetic and educational assortative mating among US adults. *Proc Natl Acad Sci USA* 111(22): 7996-8000.
- 2. Tropf FC, et al. (2015) Human fertility, molecular genetics, and natural selection in modern societies. *PLoS One* 10(6): e0126821.
- 3. Stefanski LA, Cook JR (1995) Simulation-extrapolation: the measurement error jackknife. *J Am Stat Assoc* 90(432): 1247-1256.
- 4. Yang J, et al. (2010) Common SNPs explain a large proportion of the heritability for human height. *Nat Genet* 42(7): 565-569.

Table S1: Sample means and standard deviations for HRS genotyped respondents in analytic sample (non-Hispanic Whites born between 1919 and 1955) and subsample with both spouses present in data. Due to the lack of NEB at waves 1 and 2, there is substantial missingness for that variable.

Table S2: Correlation of phenotype and polygenic scores for all non-Hispanic white genotyped respondents (N=8,865). The correlation between the raw CES-D variable (prior to the log transformation) was 0.058. All correlations have p-values less than 1e-8.

Table S4. Coefficient estimates from Equation 1.

Table S5. Coefficient estimates from Equation 2.

Table S6. Estimates of interaction coefficient from Equation 1 and associated quantities in the sample based on first marriages alone and then all spousal pairs.

Table S7: Polygenic Score-Phenotype correlations by marital status subsample.

	All		1937 and before		1938 and after	
Source	Variance	SE	Variance	SE	Variance	SE
V(G)	1.01	0.24	1.05	0.51	0.81	0.38
V(e)	3.78	0.24	4.11	0.51	3.54	0.38
Vp	4.79	0.08	5.16	0.12	4.35	0.09
V(G)/Vp	0.21	0.05	0.2	0.1	0.19	0.09
logL	-10467		-5321.3		-5271.1	
log _{LO}	-10479		-5323.6		-5274.3	
LRT	24.77		4.757		6.513	
df			1			
Pval	3.23E-07		0.0146		0.0054	
n	8160		4031		4268	

Table S8. GCTA heritability estimates for NEB for the entire sample and then for those born 1937 and before versus those born 1938 and after.

Table S9: Urban-Rural split on assortative mating.

Table S10: Correlations in PCs computed by different ranges of birth cohorts.

Table S11. Original versus SIMEX results for Equation1 focusing on polygenic scores.

Table S12. Original versus SIMEX results for Equation 2 focusing on polygenic scores.

Table S13. Further sensitivity analyses for interaction coefficients from Equation 2.

Figure S1. Estimated densities for phenotypes before (left) and after (right) standardization. Note that for CES-D, we first took the log of the mean CES-D plus one and then standardized. Bottom panel shows histogram for NEB.

Figure S2. Densities before (black) and after (red) residualization by 10 PCs. Normal curves with the observed mean and SD are shown in dashed lines.

Figure S3: Spousal correlations on principal components. Light gray bars represent correlations for principal components computed amongst the analytic sample (N=8865) while dark gray bars represent the principal components computed amongst all genotyped HRS respondents.

Figure S4. Spousal correlations in the first four PCs across birth cohorts; no significant differences are observed, suggesting that population structure shifts do not explain PGS changes in spousal intraclass correlations.

Figure S5: Distribution of polygenic scores for spousal and non-spousal genotyped samples in the HRS.

Figure S7: Spousal genome-wide relatedness (KING estimates) by birth cohort in the HRS.

Figure S8: Version of Figure 1 from main text, polygenic scores not residualized on top. 10 PCs with (A) using phenotypes and (B) using genotypes.

Figure S9: Version of Figure 2 from main text, polygenic scores not residualized on top. 10 PCs with (A) using phenotypes and (B) using genotypes.

