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Analysis of genetic similarity among friends and schoolmates in the National Longitudinal Study of Adolescent to Adult Health (Add Health)

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Genetic similarity among friends and schoolmates

Abstract

It has been long known that human relationships are genetically stratified. Whether genetic similarity among those in a relationship is due to complex ancestral patterns linked to historical migration, macro-level social structures in modern society, or individual-level peer selection remains unsettled. We use data from 9,500 adolescents from the the National Longitudinal Study of Adolescent to Adult Health to examine genetic similarity among school-based friends. While friends have correlated genotypes, both at the whole-genome level as well as at trait-associated loci (via polygenic scores), the results suggest that macro-level forces, such as school assignment, are a prime source of genetic similarity between friends. Further, we find evidence consistent with the existence of social genetic effects as an individual's educational attainment is strongly associated with the polygenic scores of those in their broader social environment (e.g., school) and of their friends (net of their own score). In contrast, individual BMI and height are largely unassociated with the genetics of peers.

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Introduction

The degree to which genetics are implicated in the formation and consequences of social relationships is of growing interest to the new field of sociogenomics (1). Analysis of human genomes linked by marriage suggests that married couples are more genetically similar to one another as compared to randomly chosen individuals from the population. This genetic similarity is observed in comparisons of genotypes across generic polymorphic loci (2–4) and in comparisons of trait-associated variants (5–7). The degree of genetic similarity between spouses is modest—overall genetic similarity is roughly 1/3 the amount of educational similarity (2)—but has potential implications for statistical and medical genetic models of inheritance (8,9). Marriages arise from a range of social processes. In modern Western settings in which individuals tend to choose their spouses themselves, a key social process in marriage is social network development: people tend to marry other people who they know. We tested if the same genetic similarity observed in married couples could be observed in social networks formed before marriage: adolescent friendships.

We analyzed data from the National Longitudinal Study of Adolescent to Adult Health (Add Health). Add Health surveyed 90,118 US adolescents aged 12-18 in 1994-1995 using a school-based sampling frame. As part of the survey, students were asked to list the names of their friends. Responses were collated within schools to identify social ties between individuals and their friends (10). Of the adolescents surveyed, 20,745 were enrolled in a longitudinal study that included in-home interviews with the adolescents and their parents and that followed the adolescents prospectively across four assessments spanning 14 years. At the most recent assessment in 2008, ~12,000 Add Health participants provided DNA for genotyping and genome-wide single-nucleotide polymorphism (SNP) data were assayed. We linked these genetic data with social network information from the original school-based surveys along with information about personal characteristics and social environments accumulated across Add Health follow-up. Complete details on the data are in Section 1 of the Supplemental Information (SI).

Our analysis proceeded in three steps. In Step 1, we tested if friends were more genetically similar to one another than to randomly selected peers. In Step 2, we sought to disentangle potential sources of any genetic similarity between friends. In Step 3, we evaluated a potential implication of genetic similarity among friends: social genetic effects, or the effect of the genetics of one's social peers on one's own phenotype.

Results

1. Are friends more genetically similar to one another than they are to randomly selected peers?

We tested if friends were more genetically similar to one another as compared to random pairs of individuals using two approaches. First, we tested if genomes of friends were more similar as compared to genomes of random pairs of individuals. We used KING (11) to compute

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genetic kinships between all pairs of Add Health participants. We then compared kinships among friends to kinships among random pairs of individuals to estimate the degree of genetic similarity among friends (2). To address potential confounding of analysis by ancestry, we considered only pairs of individuals with the same self-identified race.

Estimates of genetic similarity among friends were positive for all race/ethnicity groups (**Table 1**). KING estimates of genetic similarity among non-Hispanic white friends were about 2/3 the magnitude of previous KING estimates of genetic similarity among non-Hispanic white spouses (friend similarity=0.030, CI=0.022-0.037; in Ref 1, spousal similarity =0.045). Results based on a secondary metric of overall genetic similarity were largely similar (see Section 2 of SI).

Our second analysis tested if friends were more similar to one another on specific trait-related genetic dimensions. We analyzed polygenic scores for three phenotypes: height, body-mass index, and educational attainment. Polygenic scores are genome-wide summaries of genetic influence. They are computed by weighting alleles at loci across the genome according to their association with a phenotype of interest and then summing weighted allele counts across loci. We computed polygenic scores based on weights from published genome-wide association studies (GWAS) (12–14) using established methods (15). Because GWAS the original were performed on non-Hispanic whites, we restricted polygenic score analysis to this population as population stratification may dilute genetic associations (16). To correct for any residual population stratification, we adjusted polygenic score analyses for the first 10 principal components computed from the genome-wide SNP data (17). Further details are reported in the SI.

We first confirmed polygenic scores were associated with their respective phenotypes (all polygenic score-phenotype correlations were ~0.25; see Section 1 of SI). Next, for each score, we computed associations of an Add Health participant's polygenic score with the average polygenic score among their friends. Polygenic scores for body-mass index and educational attainment were positively correlated among friends (r=0.06 for body-mass index polygenic score; r=0.07 for education polygenic score; **Table 2**). Polygenic scores for height were not (r=0.01). In contrast, phenotypes were more strongly correlated between friends, especially for educational attainment (r=0.4 for educational attainment, r<0.15 for height and BMI). With the exception of BMI, correlations among polygenic scores between friends were smaller than published correlations between polygenic scores among spouses (5), especially for height. Associations were similar amongst same-sex friends (SI Section 2).

2. Why are friends more genetically similar to one another than they are to randomly selected peers?

We considered two hypotheses. One hypothesis is that friends are more genetically similar to one another because they form their friendships partly because they share similar phenotypes and family backgrounds (e.g. being short or tall, heavy or slim, well-educated families or poorly-educated families). This process is called "social homophily" (18–21).

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Genetic similarity among friends and schoolmates

Because phenotypes that influence human social tie formation tend to be heritable (22), the first hypothesis suggests that social homophily can generate genetic similarity between friends. A second hypothesis is that friends are more genetically similar because they form their friendships within socially stratified environments (e.g. living in the same community, attending the same school). We refer to this process as social structuring (23). Because genetic factors influence selection into social environments (24), the second hypothesis suggests that social structuring can generate genetic similarity between friends even without explicit selection on phenotypic similarity. Social structuring and social homophily are not mutually exclusive and may indeed be complementary processes. We tested for evidence of social structuring processes by estimating genetic similarity at the level of the social environment. Then, in cases where we found evidence of social structuring, we tested for complementary homophily by re-estimating genetic similarity between friends within social environments.

To test the social structuring hypothesis, we asked about the degree to which schoolmates were genetically similar using the same technique as above with friends (but replacing being in the same school with being friends as the relevant pair-level indicator). Add Health participants who were schoolmates were genetically more similar—roughly half the genetic similarity of friends, in fact—to one another as compared to random pairs of individuals (e.g., for white school-mates=0.016, CI=0.014-0.017; see **Table 1**).

We therefore repeated our analysis of genetic similarity among friends, this time comparing friend-level similarity to random pairs of individuals selected from within their social environment. Within-school analysis tested if genetic similarity among friends observed in our original analysis was fully explained by the social structuring hypothesis. Friend-level genetic similarity was substantially reduced when the analysis compared friends to random pairs of individuals from within the same school (KING-estimated within-school friend similarity=0.016, CI=0.007-0.022; **Figure 1A**).

We next repeated polygenic score analysis. Within-school polygenic score analysis tested correlations between Add Health participants' polygenic scores and the average polygenic scores of their friends after adjusting for the school-average polygenic score (i.e. school-level fixed effects). Even within schools, friends had more similar BMI polygenic scores as compared to random pairs of schoolmates. In contrast, friends' polygenic scores for educational attainment were no more similar than random pairs of schoolmates (**Figure 1B**; results were comparable outside of the saturation school, see Section 3 of SI).

3. Are there social genetic effects among friends?

Social genetic effects refer to influence of genotypes in a focal organism's social environment on the focal organism's phenotype (25). Social genetic effects may take several forms (1). We tested (a) social-genetic main effects – if friend genotypes were associated with a focal individual's phenotype net of that focal individual's own genotype; and (b) social epistasis—if the association between a focal individual's own genotype and phenotype varied depending of the genotypes of their social (i.e. schoolmate?) environment.

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Genetic similarity among friends and schoolmates

First, we tested if average friend polygenic scores predicted the focal Add Health participant's height, BMI, and educational attainment measured at the Wave IV Add Health follow-up, 13 years after social network information was collected (we also examined associations with observable outcomes at Wave 1, see Section 4 of SI). Friend polygenic scores for BMI and educational attainment, but not height, were associated with Add Health participants' respective phenotypes at the Wave IV assessment (for BMI b=0.04, p=0.06; for educational attainment b=0.15, p<0.001).

Next, we tested if any social genetic main effects might be accounted for by social genetic correlation, i.e. similar polygenic scores among friends. This analysis included statistical adjustment for the focal participant's own polygenic score. After adjusting for the focal participant's polygenic score, social genetic main effects were reduced but, for educational attainment, remained statistically significant (social genetic main effect b=0.02 BMI; b=0.13, p<0.001 for educational attainment). These social genetic main effects are summarized in **Figure 2**.

For educational attainment, the effect of friend PGS was largely mediated by an individual's own verbal ability and high-school GPA (social genetic main effect b=0.04, p=0.04). This suggests that individuals with certain profiles are seeking out specific friends, making it difficult to determine whether it is the characteristics of the individual or the friend that are relevant.

We also tested social genetic main effects at the school level after accounting for the individual's own polygenic score. Findings were similar in nature (but stronger in magnitude) to those at the friend-level (school-level social genetic main effect b=0.06, p<0.001 for BMI; b=0.21, p<0.001 for educational attainment). Add Health participants who attended schools with other students who had higher polygenic scores tended to complete more education over the subsequent 13 years even after accounting for their own polygenic score.

To test if school-level social genetic main effects might account for social genetic main effects among friends, we re-estimated friend-level social genetic main effects using the within-school design. This analysis included statistical adjustment for school-average polygenic scores using school fixed effects. For educational attainment, friend-level social genetic main effects remained statistically significant even after accounting for school-level social genetic main effects (within-school social genetic main effect b=0.08, p=0.004). Based on recent work (7), we considered the robustness of our findings to the inclusion of information about overall genetic relatedness. Results are similar to those reported here (section 4 of SI). Results were similar when we considered estimates outside of the saturation school and with only mutual friendship nominations. Finally, we considered results based on only those students attending schools with more than 80% self-identified white respondents. Estimates were slightly attenuated but qualitatively similar.

We additionally tested for "social epistasis", i.e. variability in genetic main effects according to the genetic composition of a focal individual's social environment. We tested social epistasis as interaction between Add Health participant's own polygenic scores and average

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polygenic scores for their friends and schoolmates. We found no evidence of social epistasis in these tests (results are in Section 4 of SI).

Discussion

We present novel evidence for positive genetic similarity amongst friends from a nationally representative sample of adolescents in the US. Our findings echo and extend earlier work suggesting that adult friends exhibit overall genetic similarity (26) and that adolescents exhibit similarity on some candidate genes (27,28). This conclusion is supported by evidence of genetic similarity as measured both at the genome-wide level (although we may be underpowered to detect genome-wide similarities, Ref 7) and by polygenic scores. We also observe the clustering of specific genetic polymorphisms across schools. We estimate that roughly a small proportion (~3%, **Table 2**) of the variation in the educational attainment polygenic score is between schools. However, net of this school clustering, certain genetic composites, in particular the polygenic score for BMI, were associated with the genotype of the individual's friends. It is possible that genetically similar individuals actively select into friendships because of common observable traits with genetic origins; it is also possible that genes shape environments. Educational tracks, for example, are not assigned randomly (29), have long-lasting consequences, and are potential sources for friend formation. If educational tracks are a source of further environmental concentration within grades, they may be a mechanism leading to the observed association between friends' genotypes.

Social, or indirect, genetic effects are accounted for in evolutionary theory (30,31) and have been observed among animals (32–34) and siblings (35,36). In mice, evidence of social genetic effects has been found for a broad variety of phenotypes, ranging from psychological phenotypes (e.g., anxiety) to biomedical phenotypes such as wound healing (25). If the effect of a certain allele may extend beyond the organism that carries it, estimates of direct genetic effects may be biased when social genetic effects are unaccounted for (25). Thus, evidence for the existence of social genetic effects would raise important questions about the meaning and interpretation of genetic "effects." However, it is difficult to identify causes for effects propagated via social networks. Animal studies can use aspects of randomization (25), but this is not generally possible in most studies of human social interaction (although there are exceptions; see Ref 37). Previous attempts to identify causal effects (38) have been met with skepticism (39). In observational studies of friends, the fundamental problem is that the friendship bond is endogenous (with respect to the characteristics of the individuals in the friendship), so it is challenging to disentangle the effects of the friendship from the effects of the individuals who engage in it (40).

Results from our analyses suggest the possibility of social genetic effects. Of the traits we consider (educational attainment, height, and BMI), the clearest null finding related to social genetic effects comes from the phenotype—height—that seems least likely to be influenced by broader social processes, at least in contemporary US society. Interpretation of the findings

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related to BMI and educational attainment is challenging given the difficulties of causal inference in network settings. We distinguish between two hypothetical types of social genetic effects: "broad" and "narrow" effects. Broad effects occur if the genotypes of one's peers—broadly constructed as those in the same school—predict one's own phenotype. We observe evidence consistent with the existence of broad effects in that the genetic endowments of community members of a focal individual predict that individual's genotype. However, there are likely confounding factors that we are unable to address. The genetics of one's broad set of peers could be associated with a historical set of processes regarding school funding, for example, and/or the set of policies and social forces that have led to high levels of residential segregation by ancestry in the US (41).

In contrast, narrow effects occur when the genotypes of one's peers, narrowly constructed here to indicate friends, predict one's own trait. That is, narrow social genetic effects are a type of peer effect. Previous work has suggested the possibility of peer effects on traits such as BMI (38), but, again, causal inference is demanding (39). A number of alternative mechanisms could account for our evidence of social genetic effects, specifically friendship selection and friendship as a proxy for the broader social environment. We examined these issues empirically, but it would be premature to draw a firm conclusion on this point. Given that students are not randomly assigned to schools and that, once in schools, students are not randomly assigned to friendships, we are unable to fully distinguish between these mechanisms. In order to be more definitive, future research may require exogenous mechanisms underlying social contact (37).

This study contributes to what is currently known about the genetic ecology that exists in human societies. We have provided specific evidence about both gene-environment correlations and the potential for social genetic effects, and noted that the joint existence of these two genetic features could produce important feedback loops. If the genetics of one's social environment matter *and* the relevant genetics are stratified across environments, then being in certain environments might substantially modulate genetic signals. More work is needed to document both features in humans before such modulations can be unambiguously documented, but their possible existence challenges simple notions of genetic "effects."

Methods & Materials

Data

The National Longitudinal Study of Adolescent to Adult Health (Add Health) is a nationally representative cohort drawn from a probability sample of 80 US high schools and 52 US middle schools (in roughly 90 US communities), representative of US schools in 1994–95 with respect to region, urban setting, school size, school type, and race or ethnic background. About 15,000 respondents (or 96%) consented to genotyping during the Wave 4 interview in 2008–09 for purposes of approved Add Health Wave 4 research. Of those who consented to

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genotyping, ~12,000 (or 80%) agreed to have their DNA archived for future testing (see SI for a comparison of genotyped and non-genotyped respondents). DNA extraction and genotyping on this archived sample using two platforms yielded a sample of 9,520 Add Health members with GWAS data consisting of 631,990 SNPs. The SI contains additional details on the genotyping process.

In the in-school survey (which was administered to every student in the participating schools, not only the Add Health study members who are prospectively followed into adulthood), as well as in the in-home surveys at waves 1 and 2, students were asked to nominate up to 5 of their male friends and 5 female friends. We accept a nomination in either direction (i.e. "undirected" friendships) as evidence of a friendship between two individuals. Of those with genetic data, only 4997 people were in a friendship pair with another genotyped respondent. We focus largely on friendship nominations within race/ethnicity. Of the 7016 friendship pairs between genotyped respondents, ~90% were within race/ethnicity. We emphasize two additional caveats. First, related respondents (as identified by measures of genetic similarity) were not included in the analyses. Second, one school—a so called "saturated school" in the Add Health data—contributed a disproportionate number of friend pairs to the sample of non-Hispanic white respondents. Results reported are robust to the removal of this school.

Measures

To measure genetic similarity, we use a kinship measures (KING; 11) that has been the focus of earlier research (2,3). We construct principal components using all genotyped respondents. We construct polygenic scores for anthropometric traits (BMI, height) and educational attainment. To construct these scores, we utilize publicly available genome-wide association study results (12–14) derived from large consortia studies (that did not include Add Health) of populations of European descent. Polygenic scores do not typically generalize across racial groups (16), so we focus these analyses on respondents who identify as non-Hispanic and white. Since self-identified race may still contain genetic heterogeneity (e.g., Ref 42) that may lead to bias when using the polygenic scores, we exclude respondents (N=12) who have values on PC 1 larger than the minimum value on this PC for a self-identified black, Asian, or Hispanic respondent or a value for PC 2 larger than the minimum value on this PC for self-identified Asian respondents.

We use information from Wave 4 (when respondents were 24–32 years old) on years of education completed, BMI, and height (see additional details on all measures in SI).

Methods

Overall Genetic Similarity

We first consider a measure of genetic similarity amongst friends used previously to study genetic similarity amongst spouses (2,3). We compute the area between the 45 degree line and the P-P plot (given two CDFs F and G, the P-P plot is the set of points (F(x),G(x)) for all x)

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comparing the density of genetic similarity between friends with the density of genetic similarity for all dyads.

Targeted Genetic Similarity

We first consider a baseline model for some polygenic score G_i of the form

$$G_i=a+b\bullet\mu_F(G_i)+e_i. \text{ (M1)}$$

where $\mu_F(G_i)$ is the mean of G_i for all an individual's friends. The coefficient b captures the degree to which being friends is associated with levels of overall genetic similarity. Motivated by previous studies of the Add Health social networks (43,44), we next consider the role of genetic clustering into schools in the observed degree of friend genetic similarity via

$$G_i=a+b\bullet\mu_F(y_i)+c\bullet\mu_S(G_i)+e_i. \text{ (M2)}$$

where $\mu_S(G_i)$ is the mean of G_i for all other individual's at the school of individual i. We interpret attenuation in estimates of b going from M1 to M2 as evidence for the importance of social structure, specifically school assignment, in observed genetic similarity amongst friends. We adjust all standard errors for clustering of students into schools (45).

Turning to our analysis of social genetic effects, we first consider models of the (potentially confounded) effect of the social genome on an individual's phenotype (P_i) net of the individual's own polygenic score (PGS_i). The social genome will be characterized via $\mu_F(G_i)$ and $\mu_S(G_i)$ as above. We first consider

$$P_i=a+b\bullet PGS_i+c\bullet\mu_F(G_i)+e. \text{ (M3)}$$

We construe this as a test of "narrow" social genetic effects of friends. In contrast, we also consider measures of "broad" social genetic effects:

$$P_i=a+b\bullet PGS_i+c\bullet\mu_S(G_i)+e, \text{ (M4)}$$

Again, all standard errors are adjusted for clustering into schools.

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Genetic similarity among friends and schoolmates

Table 1. Similarity estimates based on overall estimates of genetic similarity (KING) and when using schoolmate status (attend same school?) in place of friendship status in calculation of similarity.

Group	N people	N friend pairs	Friend Similarity	95% CI	Schoolmate Similarity	95% CI
White	3030	4851	0.030	0.022,0.037	0.016	0.014,0.017
Black	669	562	0.046	0.030,0.065	0.032	0.024,0.039
Asian	234	285	0.173	0.126,0.192	0.035	0.029,0.037
Hispanics	495	497	0.132	0.109,0.148	0.103	0.098,0.107

Genetic similarity among friends and schoolmates

Table 2. Correlations between social genotype (columns) and individual genotypes/phenotypes (rows) and ICC of individual genotypes within schools among non-Hispanic white respondents.

	Correlations, Individual and		ICCs
	Mean friend PGS	Mean schoolmate PGS	School
Edu PGS	0.074	0.140	0.029
BMI PGS	0.059	0.034	0.007
Height PGS	0.013	0.066	0.010
Education	0.153	0.244	0.154
BMI	0.037	0.065	0.017
Height	0.039	0.039	0.021

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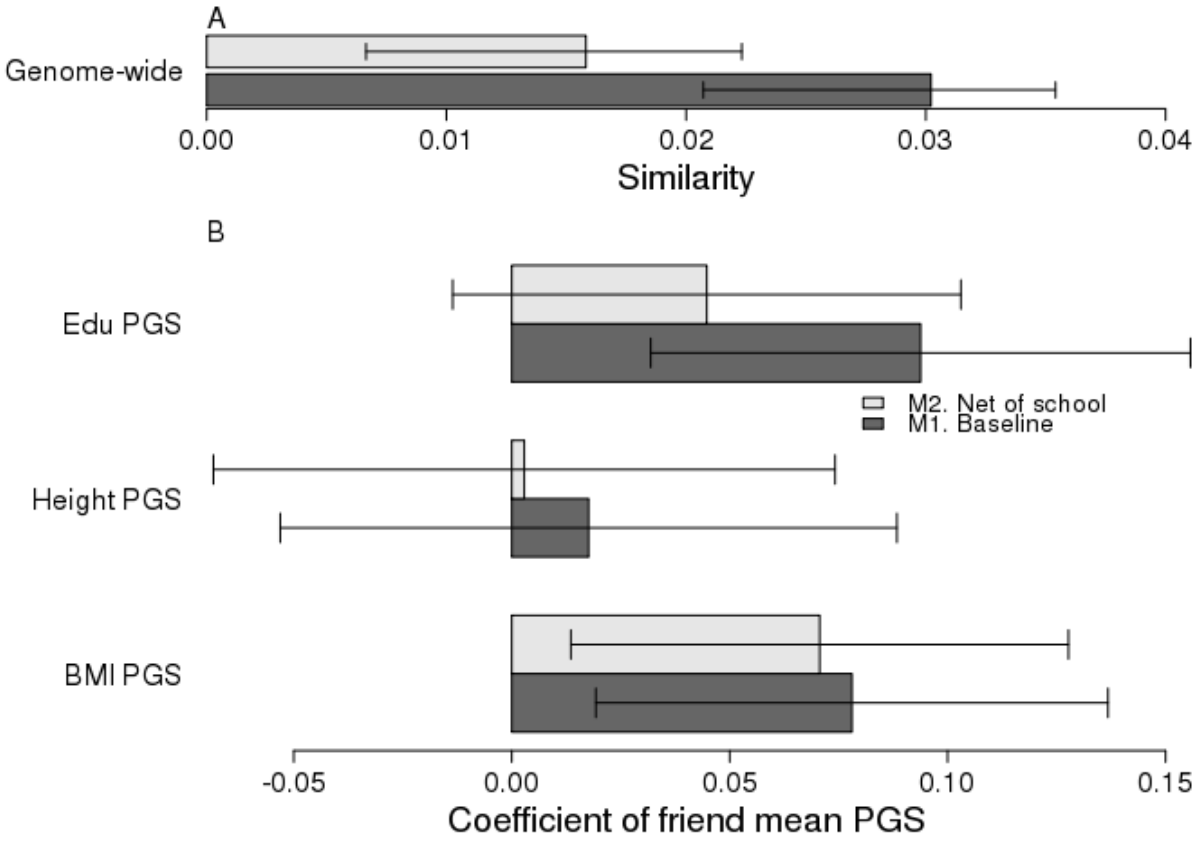
Figure 1. A. Genetic similarity between friends before and after accounting for genetic similarity of schoolmates. B. Comparison of genetic prediction between friends before (M1) and after (M2) adjusting for the genetic makeup of their school (via mean PGS).



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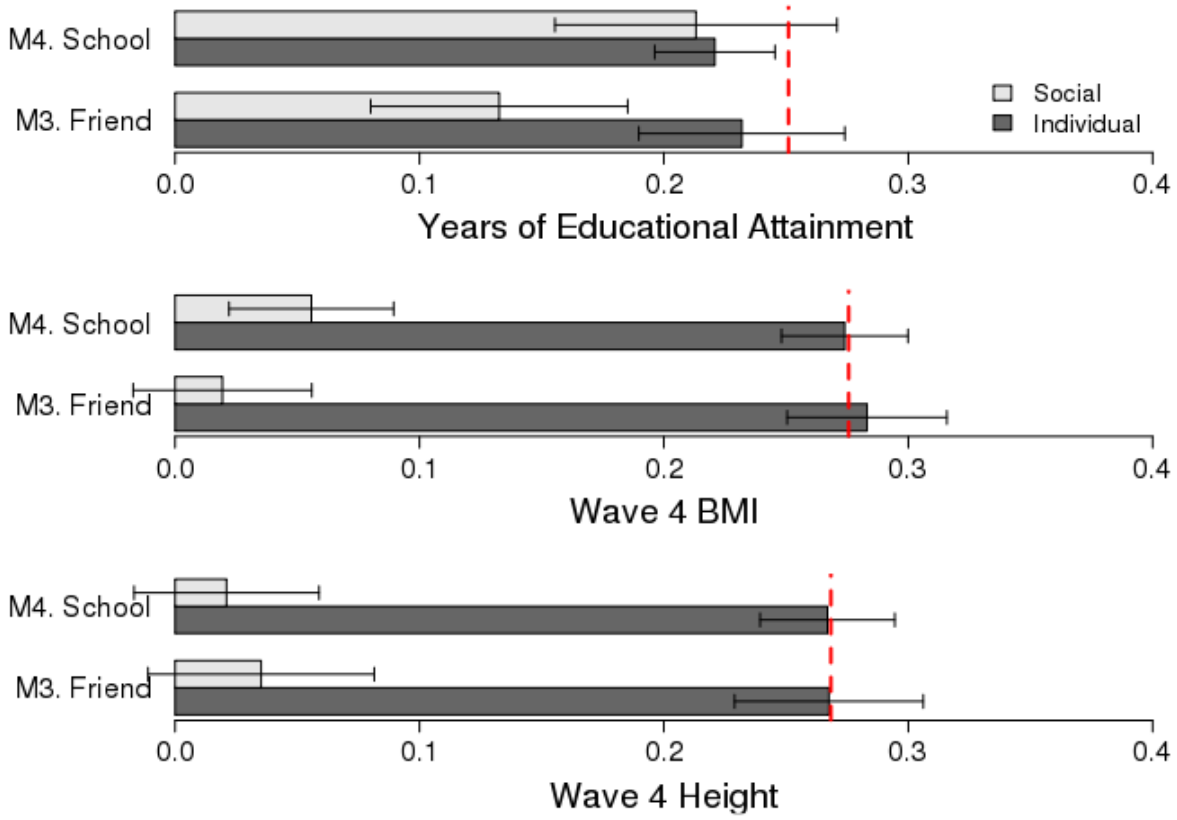
Figure 2. Social Genetic Effects: Effect of friend and school mean PGS net of one's own PGS for educational attainment, BMI, and height (all measured at Wave 4) on associated outcome. Outcomes are standardized as are social genotypes. The red line is the baseline effect of own PGS on the outcome in a null model with no other predictors. Estimates are based on a sample of unrelated respondents. SEs robust to school clustering.