Document Version
Peer reviewed version

1 **The nature of nurture: Widespread covariation of early environmental**
2 **exposures and trait-associated polygenic variation**
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Abstract

Although gene-environment correlation is recognized and investigated by family studies and recently by SNP-heritability studies, the possibility that genetic effects on traits capture environmental risk factors or protective factors has been neglected by polygenic prediction models. We investigated covariation between trait-associated polygenic variation identified by genome-wide association studies (GWAS) and specific environmental exposures, controlling for overall genetic relatedness using a genomic-relatedness-matrix restricted maximum-likelihood model. In a UK-representative sample (N=6,710), we find widespread covariation between offspring trait-associated polygenic variation and parental behavior and characteristics relevant to children's developmental outcomes – independently of population stratification. For instance, offspring genetic risk for schizophrenia was associated with paternal age (R^2=0.002; P=1e-04), and offspring education-associated variation was associated with variance in breastfeeding (R^2=0.021; P=7e-30), maternal smoking during pregnancy (R^2=0.008; P=5e-13), parental smacking (R^2=0.01; P=4e-15), household income (R^2=0.032; P=1e-22), watching television (R^2=0.034; P=5e-47), and maternal education (R^2=0.065; P=3e-96). Education-associated polygenic variation also captured covariation between environmental exposures and children's inattention/hyperactivity, conduct problems, and educational achievement. The finding that genetic variation identified by trait GWAS partially captures environmental risk factors or protective factors has direct implications for risk prediction models and the interpretation of GWAS findings.

Significance Statement

Environmental exposures are among the best predictors of health and educational outcomes. Models that estimate the effect of environmental exposures on developmental outcomes typically ignore genetic factors, or focus on gene-environment interaction (whether individuals' response to environmental exposures depends on their genotype). Here we test gene-environment correlation (whether individuals' exposure to environments depends on their genotype). Using a method that tests specific genetic effects while controlling for background genetic effects, we estimate covariation between children's genetic liability/propensity for core developmental outcomes and a wide range of environmental exposures. Findings suggest that genetic variants associated with traits, such as educational attainment, body-mass index, and schizophrenia, also capture environmental risk and protective factors.

58 \body
59 **Introduction**
60 Environmental exposures are among the best early predictors of developmental
61 outcomes. For instance, maternal smoking during pregnancy, socioeconomic
62 deprivation, and time spent watching television and playing video games are
63 associated with lower academic achievement (1–9). Harsh parental physical
64 discipline such as hitting has been linked to increased emotional and behavioral
65 problems including aggression in adolescence (10–14). Paternal age is a risk factor
66 for a range of disorders and subclinical phenotypes including low academic
67 achievement (15), with the link to autism spectrum disorders and schizophrenia most
68 robustly replicated (16–21). Breastfeeding and higher parental socio-economic status
69 (education, income, occupation) are protective factors for a range of outcomes
70 including educational achievement (7, 8, 22).

71

72 Evidence from many family, twin, and adoption studies converges in showing that
73 individuals' exposure to environments partially depends on their genotype (i.e.
74 genotype-environment correlation). This includes both parenting characteristics and
75 broad socio-economic variables; all are partially heritable (23–28). In the past
76 decade, quantitative genetic research of this type has been extended to explore
77 genetic and environmental contributions to correlations between environmental
78 factors and children's outcomes (29–32). Some new designs such as the children-of-
79 twins designs make it possible to tease apart different types of genotype-
80 environment correlation and identify environmental influences free of genetic
81 confounds (33–37). These designs are limited by the extent to which environmental
82 variables differ between close relatives.

83

84 Converging evidence for gene-environment correlation comes more recently from
85 'single-nucleotide-polymorphism (SNP)-heritability' studies that estimate overall
86 genetic influences from genome-wide DNA differences in unrelated individuals.
87 These studies have shown that variation in individuals' social deprivation, household
88 income, stressful life events, and family socio-economic status partially reflects
89 individual' differences across genome-wide common genetic variants measured on
90 SNP arrays (38–44). There have also been a few reports of extending SNP
91 heritability analysis to estimate genetic correlations between environmental
92 measures and measures of children's developmental outcomes (38–40).

93

94 Gene-environment correlation is recognized and investigated by family studies and
95 recently by SNP-heritability studies. However, the possibility that genetic effects on
96 traits capture environmental risk factors or protective factors has been neglected by
97 polygenic prediction models, which use trait-associated genetic variants identified by
98 genome-wide association studies (GWAS) to estimate genetic trait propensities for
99 individual-level trait prediction.

100

101 Here we tested whether genetic variation identified by trait GWAS capture variation
102 in environmental risk factors or protective factors. Specifically, as children's
103 environments and genetic propensities are both 'provided by' their parents, these are
104 expected to correlate because parents pass on genetic variants to their offspring that
105 influence parents' environment-providing behaviors. Therefore, we examine to what
106 extent offspring trait-associated alleles covary with parental traits and behaviors
107 previously reported to be environmental risk or protective factors for important child
108 outcomes. We also tested to what extent offspring genetic trait propensities
109 contribute to the correlation between parenting characteristics and children's
110 developmental outcomes.

111
112

113 First, we conducted a systematic investigation of covariation between children's
114 genetic propensities for specific developmental outcomes and a wide range of
115 environmental exposures, previously shown to be risk or protective factors for these
116 outcomes (SI Appendix, Methods S3). We focus on genetic propensities – that is,
117 individual-specific genomic profiles of trait-associated alleles – for three core
118 developmental outcomes: educational attainment (45), body mass index (BMI) (46),
119 and schizophrenia (47). These traits from three important domains of child
120 development: social-cognitive, mental health, and physical health, each are robust
121 predictors of mortality and life expectancy, with substantial associated societal and
122 personal burden (48–55). They were chosen because of the availability of statistically
123 powerful GWAS summary statistics for these traits (56).

125 Second, we tested whether the environmental exposures predicted children's
126 developmental outcomes (as would be expected based on previous literature) and to
127 what extent these associations are captured by children's polygenic propensities for
128 education, BMI, and schizophrenia. For this, we examined associations between the
129 environmental exposures and three developmental outcomes assessed at age 16 in
130 our sample: educational achievement, inattention-hyperactivity symptoms, and
131 conduct problems (SI Appendix, Methods S3).

133 We used a sample of 6,710 unrelated individuals, drawn from the Twins Early
134 Development Study (TEDS), for whom genotype data and a wide range of specific
135 environmental exposure measures and developmental outcomes from birth to
136 adolescence are available. TEDS is a multivariate longitudinal study that recruited
137 over 11 000 twin pairs born in England and Wales in 1994, 1995 and 1996 (57, 58),
138 shown to be representative of the UK population (38, 59).

140 We created genome-wide polygenic scores for trait-associated genetic variants for
141 each individual in the sample using summary statistics from the independent
142 genome-wide association study (GWAS) of years of education (EDU) (45), BMI (46),
143 and schizophrenia (SCZ) (47). We used a Bayesian approach (60) that estimates
144 posterior mean effect size of each marker by using a point-normal mixture prior on
145 effect sizes and linkage disequilibrium information (*Materials and Methods*).

147 Because of the salience of possible population stratification when investigating the
148 genetic effect on differences in environmental exposures, we estimated the effect of
149 the polygenic scores while controlling for overall genetic relatedness in the form of a
150 genomic-relatedness-matrix restricted maximum-likelihood model. Specifically, we fit
151 the effects of all SNPs as random effects, while estimating the fixed effects of the
152 polygenic scores (*Materials and Methods*).

154 **Results**
155 To estimate the univariate effect of each polygenic score on the environmental
156 exposures, we fit a series of single-score models, which reveal significant trait-
157 associated polygenic effects across a wide range of environmental exposures. Figure
158 1a (and SI Appendix, Table S1) shows the estimated variance explained by each
159 polygenic score for each of the environmental measures. Environmental factors
160 varied significantly as a function of trait-associated polygenic variation, independently
161 of population stratification. This provides evidence for trait-associated genotype-
162 environment correlation. However, given the robust evidence for extensive pleiotropy
163 across complex traits (61), we aimed to isolate the effects of each trait-associated
164 polygenic score using a multi-score model. To test the trait-specificity of the
165 polygenic effects on environmental exposures, we jointly modelled the three scores
166 for years of education, BMI, and schizophrenia, allowing us to estimate the effects of
167 each polygenic score while adjusting for the effects of the others. Figure 1b (and SI

168   Appendix, Table S2) shows that the multi-score models revealed some attenuation of
169   the polygenic score effects compared to the single-score models, suggesting that the
170   effects of the three scores on environmental exposures are non-independent.
171   Specifically, the effects of BMI-associated polygenic variation on several
172   environmental measures (including watching television and parental education) were
173   no longer significant.
174
175   Breastfeeding duration was positively associated with offspring education polygenic
176   score, adjusted for BMI and schizophrenia polygenic scores (R^2=0.021, beta=0.144;
177   P=7e-30). Figure 2a displays children's adjusted education polygenic score as a
178   function of whether and for how long they were breastfed. Children who were
179   breastfed had, on average, an education polygenic score approximately one third
180   standard deviation higher (Hedges' g = 0.30) than children who were not breastfed (t
181   =-11.55, df= 5664.2, P=1.6e-30).
182
183   Maternal smoking during pregnancy was negatively associated with offspring
184   education polygenic score adjusted for BMI and schizophrenia polygenic scores
185   (R^2=0.008, beta=0.090; P=5e-13; Figure 2b). Children exposed to maternal smoking
186   prenatally had, on average, an education polygenic score approximately one quarter
187   standard deviation lower (Hedges' g = 0.26) than children whose mothers did not
188   smoke (t =7.93, df=1556.3; P=4e-15).
189
190   Other effects of education-associated polygenic variation on environmental
191   exposures included: 3.3% in household income (beta=0.181, P=1e-22), 6.5% in
192   maternal education level (beta=0.255, P=3e-96), 1% in parental smacking (beta= -
193   0.10, P=4e-15), and 3.4% in television watching in the household (beta= -0.184,
194   P=5e-47).
195
196   Offspring genetic risk for schizophrenia was positively associated with paternal age,
197   even when adjusting for education and BMI-associated polygenic variation
198   (R^2=0.002, beta=0.049; P=1e-04). Figure 2c shows children's adjusted genetic risk
199   for schizophrenia as a function of paternal age. Children whose father was aged over
200   45 at their birth had, on average, a genetic risk score for schizophrenia over one
201   quarter standard deviation (Hedges' g = 0.26) higher than children whose father was
202   under the age of 26 at their birth (t=-3.01, df=411.91; P=3e-03).
203
204   Next, we examined the extent to which associations between environmental
205   exposures and developmental outcomes are explained by trait-associated polygenic
206   variation for education, BMI, and schizophrenia (SI Appendix, Fig. S3). We examined
207   associations between environmental exposures and three developmental outcomes:
208   educational achievement, inattention-hyperactivity symptoms, and conduct problems.
209   Of the three polygenic scores, only the education polygenic score captured
210   covariation between environmental exposures and the three developmental
211   outcomes (SI Appendix, Table S3).
212
213   On average education-associated polygenic variation explained 15% of the
214   associations between the environmental measures and children's developmental
215   outcomes. For example, the education polygenic score explained 23% (P=1.2e-18)
216   of the beta = 0.19 covariance between child educational achievement and
217   breastfeeding. Education-associated polygenic variation also captured 6% (P=1.9e-
218   05) and 7% (P=4.4e-06) of the associations between parental slapping/smacking and
219   conduct problems and hyperactivity/inattention problems (beta=0.20 for both).
220

Discussion

We report evidence for covariation between trait-associated polygenic variation and early environmental exposures independently of population stratification. We show that a wide range of parental, neighborhood, and parent-child perinatal characteristics, representing key early life 'environmental' influences, present at birth or early in life, correlate with offspring genetic propensity – specifically, with the allele frequency at loci associated with education, BMI, and schizophrenia. We also demonstrate that covariance between environments and important developmental outcomes are partially captured by education-associated polygenic variation.

The present study combines family and molecular data. In addition to replicating the general finding that individuals' environmental exposures vary as a function of their genotype, the current findings suggest that trait GWAS are detecting genetic variants associated with parental characteristics and their correlation with child outcomes.

Importantly, the association between exposures and outcomes was by no means entirely captured by offspring trait-associated polygenic variation. There are three likely, non-mutually exclusive, explanations for this. First, a substantial proportion of the exposure-outcome associations is likely due to non-genetic factors. Second, polygenic scores intrinsically underestimate the total genetic effects on the exposure-outcome associations because they are limited to the additive effects of common variants on a particular trait that the discovery GWAS was powered to detect. Third, we only measure offspring polygenic variation, but offspring phenotype can be influenced not only by transmitted but also by non-transmitted parental alleles via parental phenotype (i.e. child exposure).

The education-associated polygenic variation showed the strongest and most consistent correlations with environmental exposures. This is consistent with research showing associations between educational attainment and many parental behaviors and characteristics (e.g. 12, 31, 63). Moreover, the multi-polygenic score models showed that the association between BMI-associated polygenic variation and environmental exposures such as television watching and parental education are explained by education-associated genetic variations. This suggests the potential for multi-polygenic models for isolating polygenic effects, provided the underlying discovery GWAS are similarly powered. The finding of an association between paternal age and offspring genetic risk for schizophrenia is consistent with previous evidence for older fathers' elevated risk for conceiving a child who will go on to develop schizophrenia (18, 19, 63). Although the current findings provide evidence for the relevance of gene-environment correlation for polygenic trait prediction methods, they are not informative about the mechanisms involved.

The observed associations could arise from passive or active gene-environment correlation, or via environmentally-mediated genetic effects, all of which are non-mutually exclusive. Figure 3 illustrates these possibilities schematically. Many of the observed associations between offspring genotype and environment-providing parental characteristics are outside of the offspring's influence (e.g. parental age and education level at child birth) and are therefore likely to result from passive gene-environment correlation. That is, parental genetic propensities that were passed down to offspring also influence environment-providing parental behavior (through both path a and b Figure 3). However, some of the investigated parental behaviors could partially be evoked by offspring genetic propensities (through paths c, and d in Figure3; e.g. breastfeeding, watching television). Finally, genetic correlations could arise as a result of environmentally-mediated genetic effects (e.g. if education-associated genetic variation influenced mothers' predisposition to smoke during pregnancy, and prenatal exposure to nicotine had an environmental effect on

276 offspring attention problems, this could result in offspring education-associated
277 polygenic variation being associated with maternal smoking pregnancy as well as
278 capturing part of its correlation with offspring attention problems).
279
280 The design of the current study is unable to distinguish environmentally-mediated
281 genetic effects, passive-, and evocative gene-environment correlations. One way to
282 investigate the contributions of these different mechanisms would be to use samples
283 incorporating parental genotype data. In analyses of such samples, confounding of
284 offspring genotype by parental genotypes could be accounted for. Provided that
285 paternal, maternal, and offspring genotype and phenotype data were available in a
286 single sample, cross-generational effects of genetic and environment could be further
287 disentangled (see Figure 3 for schematic illustration).
288
289 Nurture has a genetic component; trait-associated alleles in the offspring explain
290 variation in environment-providing parental behaviors, and their covariation with
291 offspring developmental outcomes. This provides evidence that the observed effects
292 from GWAS are not only reflecting direct trait effects. This evidence resonates with
293 the hypothesis that trait GWAS capture variation in risk factors as well as direct
294 genetic effects on the trait (64). Here we showed that polygenic scores derived from
295 trait GWAS predict variation in variables beyond the target trait, including variables
296 often presumed to be environmental in origin such as parenting. This suggests
297 incorporating genetic variants associated with environmental risk or predictive factors
298 into polygenic prediction models might improve trait prediction.
299
300 In summary, we show that genetic variation identified by trait GWAS partially
301 captures environmental risk or protective factors, indicating that some of the same
302 genetic variation underlies both traits and environments. In contrast to the conceptual
303 dichotomy often imposed between traits and environments, this finding implies that
304 the pleiotropy widely found in phenome-genome associations also crosses over to
305 the realm of environments and manifests across generations. Findings illustrate the
306 relevance of gene-environment correlation for polygenic prediction models, and that
307 combining family and molecular data might help reveal mechanisms by which genetic
308 variation is translated into phenotypic variation.
309
310 **Materials and Methods**
311 We used genome-wide SNP and environment-wide phenotype data from 6,710
312 unrelated individuals drawn from the UK-representative Twins Early Development
313 Study (57, 58),. We processed the 6,710 genotypes using stringent quality control
314 procedures followed by imputation of SNPs to the Haplotype Reference Consortium
315 reference panel (65) (SI Appendix, Methods S1). This included removing one
316 individual from any pair of individuals with an estimate SNP marker relatedness
317 >0.05. After quality control, 7,581,516 genotyped or well-imputed (info >.70) variants
318 remained.
319 *Polygenic scores*
320 For each individual in the sample, we created polygenic scores for years of
321 education, schizophrenia, and BMI. After coordinating overlapping markers between
322 each of the three GWA summary statistics and the target data by excluding markers
323 due to nucleotide inconsistencies or low minor allele frequency (<1%), we retained
324 5,690,632 for the years of education (45), 5,781,731 for schizophrenia (47), and
325 1,810,667 for BMI (46). We constructed polygenic scores as the effect-size weighted
326 sums of individuals' trait-associated alleles across all SNPs. We used LDpred (60),
327 which places a prior on the markers' effect sizes and adjusts summary statistics for
328 linkage disequilibrium (LD) between markers. For each trait, we created score using
329 three different priors on the fraction of causal markers, 0.01, 0.1, and 1.0, from which
330 the one yielding the largest R^2 in the single-polygenic score models was then entered

331 into the multi-polygenic score model. For details on the polygenic score construction
332 see SI Appendix, Methods S2.
333 To account for population stratification, we adjusted the polygenic predictors by the
334 first 30 principal components generated from genotype data prior to the analysis. We
335 used the top 30 PCs as well as genotyping array and plate to create a
336 N*P matrix Z of eigenvectors across the P selected principal components. We then
337 regressed the genetic polygenic predictor onto the eigenvectors as $S = \mu + Z\beta + e$,
338 where μ is the mean and β is a P×1 vector of the regression coefficients, and e is the
339 residual error.
340 **_Single-score and multi-score genomic-relatedness-matrix restricted_ maximum-**
341 **_likelihood models_**
342 When estimating genetic effects on environmental exposures, the possibility of
343 population stratification is especially salient. This is because genetic and common
344 environment effects, even if uncorrelated, may be confounded as close relatives
345 share both genes and their environment to a greater extent than other individuals.
346 We control this type of confounding because, under only population stratification, we
347 would not expect an association between polygenic predictors and environmental
348 measures within the mixed effect model of equations 1 and 2. This is because they
349 account for population stratification by both regressing PCs from the polygenic
350 predictors (see above), and fitting a relationship matrix estimated from the SNP
351 markers (see below).
352 To estimate the degree to which trait-associated polygenic variation captures
353 variation in environmental measures, we estimated the relationship between the
354 polygenic scores and the environmental measures, while controlling for net genetic
355 relatedness by fitting the effects of all the SNPs as random effects by a mixed linear
356 model.
357 Single-score model (Eq. 1): $var(y) = \mu + S_i\beta + A\sigma_g^2 + I\sigma_e^2$
358 Multi-score model (Eq. 1): $var(y) = \mu + S_{BMI}\beta + S_{SCZ}\beta + S_{EDU}\beta + A\sigma_g^2 + I\sigma_e^2$
359 y is an n × 1 vector containing the level of environmental exposure, with n being the
360 sample size. β is a vector of fixed effects estimating the effects of the polygenic
361 predictor, independently of overall genetic relatedness g.
362 In the single-score model (Eq. 1), S_i is a vector containing individuals' polygenic
363 score for one of i ∈ {years of education (EDU) (45), Body Mass Index (BMI) (46),
364 schizophrenia (SCZ) (47)}; adjusted for 30 principal components, genotyping array
365 and plate (see section above). g is an n × 1 vector of the total genetic effects of the
366 individuals, independently of β, with g~N(0,Aσ^2g), and A is interpreted as the genetic
367 relationship matrix (GRM) between individuals (MAF >0.01; relatedness <0.05 as
368 described above). The genomic relationship of each pair of subjects j and k is
369 calculated as Ajk = 1N∑Ni=1(xij−2pi)(xik−2pi)/2pi(1−pi) with x_{ij} being the number of
370 copies of the reference allele for the ith SNP of the jth individual and p_i being the
371 frequency of the reference allele (66).
372
373
374 In the multi-score model (Eq. 2), the effects of the three polygenic predictors are
375 being estimated jointly, thereby allowing to the effect of each polygenic predictor
376 independently of each other and of overall genetic relatedness g.
377
378 The genetic relatedness matrix accounts for population stratification in the
379 environmental exposure, because it is equivalent to fitting all the principal
380 components within the model. Equations 1 and 2 were estimated using the restricted
381 maximum likelihood (REML) approach implemented in the _reml_ function in GCTA
382 v1.26.0 (56).
383 **_Decomposition of covariance between environmental exposures and_**
384 **_developmental outcomes_**

We fit structural equation models to decompose the covariance between environmental exposures and developmental outcomes into effects of the three polygenic scores and residual covariance (SI Appendix, Fig. 3). The total covariance estimated as $Cov_{total} = (a * d) + (b * e) + (c * f) + g$ was decomposed into the effect of the education score: $Cov_{EDU} = (a * d)$, that of the BMI score: $Cov_{BMI} = (b * e)$, that of the schizophrenia score $Cov_{SCZ} = (c * f)$, and residual covariance g. We used maximum likelihood estimation with robust (Huber-White) standard errors. The analyses were conducted using the *lavaan* package in R (68).

Multiple testing correction
P-values obtained for each statistic were corrected for multiple testing using the Šidák correction (69). The Šidák adjusted alpha level is equal to1-(1-alpha)^(1/k), where k is the number of tests. The total number of tests was: 357, with 153 (3 scores * 3 priors * 17 exposures) tests for the single-polygenic score models, 51 (3 scores * 17 exposures) tests for the multi-polygenic score model, and 153 (3 scores * 17 exposures * 3 outcomes) test for the decomposition of covariance models. The multiple comparison adjustments were applied to alpha = 0.05. Hence, the corrected 'experimentwise' alpha level was 1-(1-0.05)^(1/357) = 1.44e-04.

Environmental exposures and child outcome measures
For a detailed description of all measures see the SI Appendix, Methods S3.

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617

618 **Figure Legends**
619
620 **Figure 1**
621 **a** *Single-polygenic score models: Associations between polygenic scores and*
622 *environmental exposures*
623 Single-predictor effects of polygenic scores for years of education, BMI, and
624 schizophrenia on the environmental exposures.
625 **b** *Multi-polygenic score models: Joint estimation of effects of polygenic scores on*
626 *environmental exposures*
627 Effects of polygenic scores for years of education, BMI, and schizophrenia on the
628 environmental exposures while adjusting for other predictors, respectively.
629 Color gradients represent effect sizes as standardized coefficients, i.e. standard
630 deviations change in the environmental exposure, per standard deviation increase in
631 the polygenic predictor, while adjusting for the other polygenic predictors in the
632 model, respectively (see SI Appendix, Tables S1-3 for full statistics). Single asterisk
633 indicates uncorrected $P < 0.05$, double asterisks indicate multiple testing corrected P
634 < 0.05 (see Materials & Methods).
635
636 **Figure 2**
637 **a** *Offspring adjusted education polygenic score (standardized) by level of*
638 *breastfeeding:* Education polygenic score was adjusted for schizophrenia and BMI
639 polygenic scores. Positive association ($R^2=0.021$, beta=0.144; P=7e-30). Children
640 who were breastfed had, on average, an education polygenic score approximately
641 one third standard deviation higher (Hedges' $g = 0.30$) than children who were not
642 breastfed (t =-11.55, df= 5664.2, P=1.6e-30).
643 **b** *Offspring adjusted education polygenic score (standardized) by level of maternal*
644 *smoking during pregnancy:* Education polygenic score was adjusted for
645 schizophrenia and BMI polygenic scores. Negative association ($R^2=0.008$,
646 beta=0.090; P=5e-13). Children exposed to maternal smoking prenatally had, on
647 average, an education polygenic score approximately one quarter standard deviation
648 lower (Hedges' $g = 0.26$) than children whose mothers did not smoke (t =7.93,
649 df=1556.3; P=4e-15).
650 **c** *Offspring adjusted schizophrenia polygenic score (standardized) by paternal age at*
651 *birth of offspring:* Genetic risk for schizophrenia was adjusted for education and BMI
652 polygenic scores. Positive association ($R^2=0.002$, beta=0.049; P=1e-04). Children
653 whose father was aged over 45 at their birth had, on average, a genetic risk score for
654 schizophrenia over one quarter standard deviation (Hedges' $g = 0.26$) higher than
655 children whose father was under the age of 26 at their birth (t=-3.01, df=411.91;
656 P=3e-03).
657 Horizontal lines and bars represent means and 95% confidence intervals. Violin
658 shapes represent probability density of the data.
659
660 **Figure 3**
661 *Schematic illustration of cross-generational effects within family triad*
662 Because of the lack of parental genotype data, the present study was unable to
663 distinguish passive and evocative gene-environment correlation.
664 Passive gene-environment correlation: $a_{m,p}*b_{m,p}$.
665 Evocative gene-environment correlation: $c_{m,p}*b_{m,p}$
666 Offspring phenotype can be influenced by both the transmitted paternal and maternal
667 alleles (red arrows), and by non-transmitted alleles via parental phenotype (green
668 arrows). Provided that paternal, maternal, and offspring genotype and phenotype
669 data were available in a single sample, the effect of parental trait-associated alleles
670 on offspring phenotype independently of genetic sharing between parents and
671 offspring (green arrows) could be estimated (70–72). A testable assumption for

672   investigating these mechanisms is there is no correlation between parental
673   genotypes and between each parent's haplotypes (i.e. assortative mating) (yellow
674   arrows).