Genetics of Experience: Genetically Sensitive Approaches to Measuring Childhood Environment

Hanscombe, Ken

Awarding institution:
King's College London

Genetics of Experience:
Genetically Sensitive Approaches to Measuring Childhood Environment

Ken B. Hanscombe, MSc

MRC Social, Genetic and Developmental Psychiatry Centre
Institute of Psychiatry
King's College London

A thesis submitted to King's College London
for the degree of Doctor of Philosophy (PhD)
2012

Abstract of Thesis

Environmental experience is not free of genetic influence. Through genetically-influenced behaviours, genes can influence exposure to certain environments: gene-environment correlation. Particular genotypes may also be more or less sensitive to the effects of the environment: gene-environment interaction. Embedding measured environmental experiences and the childhood outcomes they correlate with into genetically sensitive designs is a powerful approach to unravelling the mechanisms at the interface between nature and nurture.

This thesis explored children's environmental experience using data spanning 14 years of the population-based Twins Early Development Study (TEDS). Bivariate twin model fitting showed a significant genetic component linking children's heritable experience of the chaotic home and their academic achievement. Genes confound a previously assumed environmental effect. The continuous moderation model revealed greater variation in the IQ of children from low socioeconomic status (SES) families. This greater variation was the result of SES moderation of the environmental, not genetic, effect on IQ. Longitudinal twin model fitting showed a bi-directional cross-lagged effect between disruptive behaviour and children's experience of the chaotic home. The effect of household chaos on disruptive behaviour was environmentally mediated, and in the reverse process, disruptive behaviour did not account for the heritable component of home chaos. Multivariate twin modelling revealed a substantial common genetic liability between behaviour (internalizing, externalizing, and cognitive ability) and the psychosocial experience of peer victimization. Statistical genetic techniques using whole-genome data confirmed that victimization is a typical complex trait with a common genetic liability.

The approach taken here was to explore gene-environment mechanisms at the interface between nature and nurture using a variety of childhood experiences rather than focusing on one particular environment. The examples of home chaos, SES, and peer victimization highlight the ubiquity of gene-environment interplay in a range of childhood experiences. Child-driven effects on the environment result in a genetic component to experience.

Table of Contents

List of Tables

List of Figures

Acknowledgements

I would like to thank my supervisors, Robert Plomin and Claire Haworth, as well as Oliver Davis and Sara Jaffee, for their guidance, encouragement and friendship. I must also thank my calm and composed office mate Sania Shakoor, constant friend Maciej Trzaskowski, the TEDS team and families, and all the other students and staff at the SGDP for their support.

Thank you to my parents, and especially to my mum for all the sacrifices she made to give me the best chance possible. Most of all thank you to my wife, Ewa, for her love, companionship, and belief in my ability.

Publications

Haworth, C. M. A., Davis, O. S. P., **Hanscombe, K. B.**, Kovas, Y., Dale, P. S., & Plomin, R. (In Press). Understanding the science-learning environment: A genetically sensitive approach. *Learning and Individual Differences*. doi: 10.1016/j.lindif.2012.07.018

Hanscombe, K. B., Trzaskowski, M., Haworth, C. M. A., Davis, O. S. P., Dale, P. S., & Plomin, R. (2012). Socioeconomic Status (SES) and Children's Intelligence (IQ): In a UK-Representative Sample SES Moderates the Environmental, Not Genetic, Effect on IQ. *PLoS One, 7*(2). doi: 10.1371/journal.pone.0030320

*Jaffee, S. R., ***Hanscombe, K. B.**, Haworth, C. M. A., Davis, O. S. P., & Plomin, R. (2012). Chaotic homes and children's disruptive behaviour: A longitudinal cross-lagged twin study. *Psychological Science, 23*(6), 643-650. doi: 10.1177/0956797611431693
*Joint first authorship

Hanscombe, K. B., Haworth, C. M. A., Davis, O. S. P., Jaffee, S. R., & Plomin, R. (2011). Chaotic homes and school achievement: a twin study. *Journal of Child Psychology and Psychiatry, 52*(11), 1212-1220. doi: 10.1111/j.1469-7610.2011.02421.x

Hanscombe, K. B., Haworth, C. M. A., Davis, O. S. P., Jaffee, S. R., & Plomin, R. (2010). The nature (and nurture) of children's perceptions of family chaos. *Learning and Individual Differences, 20*(5), 549-553. doi: 10.1016/j.lindif.2010.06.005

Viding, E., **Hanscombe, K. B.**, Curtis, C. J., Davis, O. S. P., Meaburn, E. L., & Plomin, R. (2010). In search of genes associated with risk for psychopathic tendencies in children: a two-stage genome-wide association study of pooled DNA. *Journal of Child Psychology and Psychiatry, 51*(7), 780-788. doi: 10.1111/j.1469-7610.2010.02236.x

Submitted for Publication

Hanscombe, K. B., Haworth, C. M. A., Davis, O. S. P., Petrill, S., Dale, P. S., Plomin, R. & Kovas, K. (Submitted). Why do spatial abilities predict mathematical performance?

Trzaskowski, M., Eley, T. C., Wellcome Trust Case Control Consortium 2, Davis, O. S. P., Docherty, S. J., **Hanscombe, K. B.**, Meaburn, M. L., Haworth, C. M. A., Price, T., Plomin, R. (Submitted). First genome-wide association study on anxiety-related behaviours in childhood.

Harlaar, N., Meaburn, M. L., Hayiou-Thomas, M. E., Wellcome Trust Case Control Consortium 2, Davis, O. S. P., Docherty, S. J., **Hanscombe, K. B.**, Haworth, C. M. A., Price, T., Trzaskowski, M., Dale, P. S., Plomin, R. (Submitted). Genome-wide association study of language ability of 12-year-olds.

1 Measuring the Nature of Nurture

1.1 Genetic effects on "environmental risk": The long reach of the gene

Environmental influences are potential risk factors for cognitive and behavioural development (Pike, Iervolino, Eley, Price, & Plomin, 2006). But, are these "environmental risks" environmental? Four decades ago, Dawkins (1976) described genetic effects on the environment as the normal expectation under evolution by natural selection:

> "The phenotypic effects of a gene are normally seen as all the effects that it has on the body in which it sits. This is the conventional definition. But we shall now see that the phenotypic effects of a gene need to be thought of as *all the effects that it has on the world*."

Behavioural genetics, which aims to explain why individuals in a population differ from one another, has shown this expectation to be true in humans: genes affect *exposure* and *sensitivity* to environmental experience (Kendler, Jaffee, & Romer, 2011; Plomin, DeFries, McClearn, & McGuffin, 2008). For example, in a female sample, genes found to affect anxiety also increased exposure to depressogenic environmental influences and sensitivity to adverse life events (Eaves, Silberg, & Erkanli, 2003). Genetic influence on the environment requires that previously assumed "environmental" influences on behaviour be revisited – e.g., parenting on children's choice of peers (Pike & Eley, 2009).

Study designs that are sensitive to genetically influenced exposure and sensitivity to experience lead to a radically different view of the individual in their environment, and of how genes and experiences affect complex behaviour (Davis, Haworth, Lewis, & Plomin, 2012). In a recent study of environmental risk, Pike et al. (2006) noted that the phenotypic "examination of environmental risk–outcome associations can be taken a step further by exploring the genetic and environmental mediation of these links." Quantitative genetics is the toolkit used to provide an overview of genetic and environmental influences on behaviour.

1.2 The intersection between genes and environment: Quantitative genetic methods

Quantitative genetics provides a theory and set of methods to partition the population variation for a particular trait into fractions attributable to genetic and environmental factors. It aims to unravel the nature and nurture of individual differences, or what

makes one person different from another. In the classical twin design, comparison of the resemblance between identical (monozygotic, MZ) twins and non-identical (dizygotic, DZ) twins provides an estimation of the genetic and environmental contributions to variance within a trait and covariance between traits (Plomin et al., 2008). Most of the human genome is identical from person to person, but a small proportion of it varies. If we just concentrate on the DNA that varies between humans, MZ twins are 100% identical. DZ twins, on the other hand, are only 50% identical on average. So it follows that the extent to which MZ twins are more alike than DZ twins on any particular trait is a function of their greater genetic relatedness.

Derived from quantitative genetic theory, the twin model partitions the variance of a trait, or the covariance between traits, into an additive genetic component (A), a shared (common) environmental component (C), and a non-shared environmental component (E). The effect of the C component is to make reared together children similar on the trait of interest; C accounts for DZ twin correlations greater than half the MZ twin correlations. Both C and A contribute to sibling similarity, or between-family variation. E represents elements of the environment that uniquely affect reared-together siblings and therefore contributes to differences between twins, or within-family variation. The relative contribution of additive genetic variation to the total variation is called the *heritability* – A / (A+C+E). Any measurement error is included in the E term (Rijsdijk & Sham, 2002). A more detailed description of the twin method, path analysis, and the use of structural equation modelling (SEM) to model twin data and estimate variance components are presented in **Chapter 2**. The assumptions of the twin model are described at the end of this section.

The partitioning of trait variation may not be as simple as described above, however. The boundary between genetic and environmental effects is often blurred – there is potentially crosstalk between A, C, and E. We describe here two important gene-environment (GE) phenomena and the twin model fitting approaches used to measure them: GE correlation and GE interaction. If GE effects are present and not explicitly modelled, they will complicate interpretation of the latent variance components, or worse still, lead to complete misinterpretation of the data (Evans, Gillespie, & Martin, 2002; Purcell, 2002).

1.2.1 Gene-environment correlation

It is often thought that the environment a person experiences simply happens to them, that the direction of effect is environment → person. This is not the case. People have an effect on and are affected by their environment (Bell, 1968). The direction of effects

is a two-way interaction between a person and their physical and psychosocial experience: environment ←→ person. Research in epidemiology recognizes the continuum between physical and social aspects of the environment (Yen & Syme, 1999); environmental psychology – which typically sees the person and their environment as independent – acknowledges the personal selection of environments as "the confounding problem" (p.323, Winkel, Saegert, & Evans, 2009). Consider the example of number of books in the home. Books are bought and placed on shelves by people, and so the number of books in the home must correlate with personal characteristics (Plomin & Bergeman, 1991). People are exposed to particular environments, select experiences, engage with artefacts, and communicate with other people in their environment, in part based on their genetic propensities. In this way genes become correlated with the environment – a phenomenon called gene-environment (GE) correlation (Plomin, DeFries, & Loehlin, 1977; Scarr & McCartney, 1983).

GE correlation is conceptualized as one of three types: passive, evocative, or active. Passive GE correlation happens because a child inherits both their genotype and environment from their parents. Evocative GE correlation happens when other people react to a person's genetically influenced characteristics. Active GE correlation is the result of a person engaging other people or interacting with artefacts because of their heritable predispositions (Plomin et al., 2008). Consider the example of a child from a quiet neighbourhood whose parents provide a structured home environment (passive). The child attends a good school (passive/evocative) and often asks questions in class (active). Later, the student joins the school electronics club (active) and is invited to do an internship at a tech start-up (evocative).

Measured environments in a genetically sensitive design

Treating a measured environment as the dependent variable in a genetically sensitive design, such as the twin design, blurs the boundary between genes and the environment. Comparing the correlation in measured environment between identical twin pairs and non-identical twin pairs reveals that environmental experience is just like any other complex trait (Figure 1.1) – even the "environment" shows genetic influence (Kendler & Eaves, 1986; Plomin & Bergeman, 1991; Plomin et al., 1977).

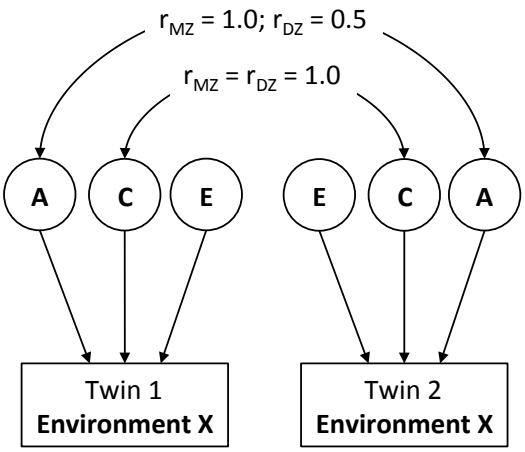


Figure 1.1 Classical twin design with measured environment as dependent variable
A, C, E = genetic, shared environmental, non-shared environmental variance components. Significant A suggests the environment is heritable.

A significant genetic component in Figure 1.1 indicates GE correlation. However, the twin model does not distinguish between passive, evocative, and active GE correlation but rather captures all three modes of correlation. Far from rare, genetic influence on the environment is pervasive, e.g., television watching, stressful life events, experience of parenting – heritable environments are ubiquitous (Jaffee & Price, 2007; Kendler & Baker, 2007). What does this mean for so-called "environmental" risk factors?

Genetic mediation: A potential confound

If the environment itself is heritable, then there is a potential confound in observed environmental effects on childhood outcomes. The link between a heritable environment and a heritable outcome may in fact be genetic. In other words, genes may mediate the association between measured environment and childhood outcome. For example, given the confounding of genetic and environmental effects within biological families, any study of the effects of family and socioeconomic background on children's developmental outcomes needs to consider the possibility that child and parental genotypes influence both background and outcome (Rowe & Rodgers, 1997). It is possible to quantify this mediation with the genetic correlation, r_g (Neale & Cardon, 1992): the correlation between latent genetic variance components in a bivariate twin model (Figure 1.2).

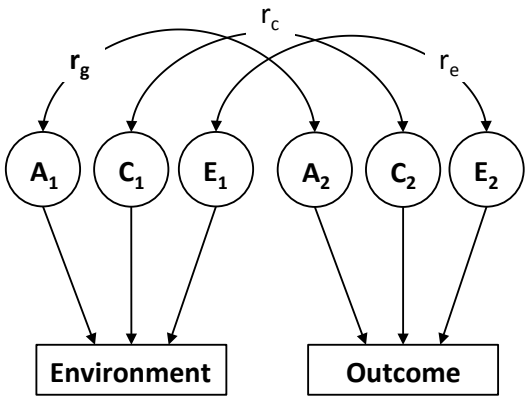


Figure 1.2 Genetic mediation of "environmental" effects
r_g = genetic correlation; A, C, E = genetic, shared environmental, non-shared environmental variance components

Child-specific measures of the environment are needed in order to partition the covariation between environment and outcome. Studies that have included a measured family-wide environment as mediator of within-family similarity implicitly assume that there are no genetic effects on the family-wide environment – i.e. no GE correlation (Turkheimer, D'Onofrio, Maes, & Eaves, 2005). Where individual-specific measures of the environment are not available, it is generally not possible to draw conclusions about the nature of the effect of family-wide environment on the outcome (Purcell & Koenen, 2005), although there have been recent statistical advances (Price & Jaffee, 2008). A family-wide measure is obligatorily-shared because a single account is given for all children in the family. It is not shared environmental in effect, and it is potentially not free of genetic influence. The unknown presence of GE correlation in family-wide measures also has consequences for their use in studies of environmental moderation of genetic influence.

1.2.2 Gene-environment interaction

Gene-environment (GE) interaction is observed when genetic effects on a phenotype depend on the environment in which they are expressed. In other words, sensitivity to the environment is under genetic influence (Eaves, Last, Martin, & Jinks, 1977). Figure 1.3 (reproduced from Purcell, 2002) shows the effect on a phenotype of three genotypes (at a single locus), at different levels of an environmental moderator. With each additional *A* allele, a unit increase in the level of the environment corresponds to an increase of β in the phenotype. At low levels of the environment, the three genotypes are indistinguishable on the phenotype; at high levels, the three genotypes are quite

distinct: homozygote *AA* is highest, homozygote *aa* is lowest, and the heterozygote is intermediate on the phenotype.

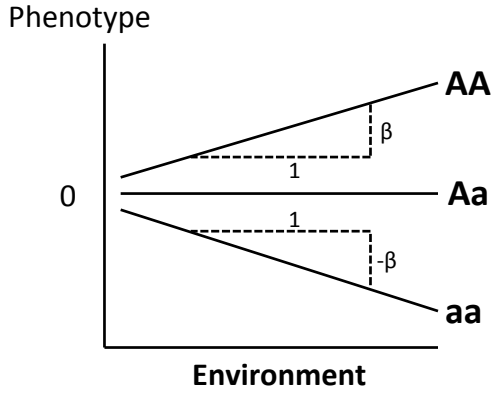


Figure 1.3 Genetic effects as a linear function of a moderator environment
AA, Aa, aa = three genotypes at a single locus; β = change in the phenotype for a unit change in the environmental moderator

Figure 1.3 shows the simplest case of environmental moderation of genetic effect: a single locus gives rise to different phenotypes dependent on the level of the environment. When considered in aggregate, what effect do all such quantitative trait loci – sensitive to the level of the environment – have on population variance components? GE interaction at the level of the population would look like differences in the heritability of the phenotype as a function of the moderating environment (Rutter, Moffitt, & Caspi, 2006). How do we model GE interaction in the twin design?

Different effects in different groups: Heterogeneity

An early approach to testing for GE interaction regresses identical twin pair phenotype differences (which estimate non-shared environmental effect) onto phenotype sums (which estimate genetic and shared environmental effect) – any correlation suggests potential GE interaction (Jinks & Fulker, 1970). However, this approach has a number of limitations including sensitivity to non-normality. A more recent approach using structural equation modelling proceeds by splitting the sample into groups based on the putative moderator – e.g., high versus low, or exposed versus not exposed – and applying the classical univariate twin model to the phenotype of interest within each group (Neale & Cardon, 1992). Figure 1.4 illustrates the logic: variance components are estimated for variable X, within groups high and low on the measured environment.

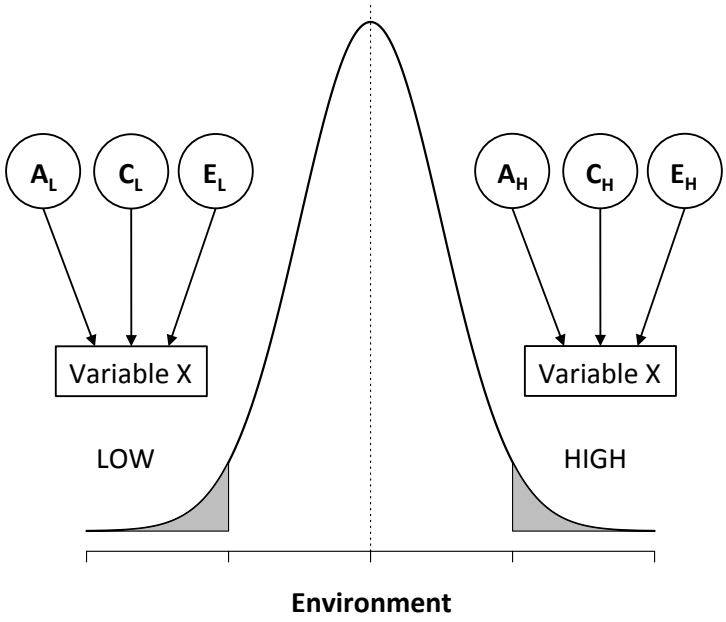


Figure 1.4 Variance components by level of moderating environment – high or low
A, C, E = genetic, shared environmental, non-shared environmental variance components; Environment = putative moderating environment; GE interaction is indicated if $A_L \neq A_H$

Comparing the difference in fit between this model and one in which variance components are estimated for the groups combined – i.e., equating the A, C, and E variance components across groups – is a test of whether there is a significant difference in the variance components by group, i.e., heterogeneity. In particular, GE interaction is indicated when equating A across groups significantly worsens model fit (e.g., in Figure 1.4, $A_L \neq A_H$). Sex-limitation analyses, which estimate variance components separately for males and females, are a specific type of heterogeneity analysis widely used in studies of twin data (Neale, Røysamb, & Jacobson, 2006).

However, the heterogeneity model potentially has several problems, especially for testing GE interaction (Purcell, 2002). Notably, there is a reduction in power both because of the assignment of a single value of the moderator to each group – most apparent when falsely dichotomizing the moderator – and because selecting extremes necessarily reduces sample size. Secondly, heterogeneity modelling cannot disentangle GE interaction and GE correlation: greater heritability in a particular group could be due to the environment moderating the effect of genes (interaction), or the environment controlling gene frequency (correlation). Using the full quantitative distribution of the environmental moderator, and modelling variance components under continuous moderation, overcomes these problems.

All levels of the measured environment: Continuous moderation

Purcell (2002) proposed a model that can be used to measure GE interaction with a quantitative moderator and phenotype of interest. When the putative moderator is a measure of the environment, the continuous moderator model allows the measure of potential main effects of the environment on the phenotype of interest, as well as simultaneously estimating moderating effects – effects on the variance components of the phenotype. Figure 1.5 shows the inclusion of the environmental moderator. The genetic path coefficient (environmental paths not shown) becomes a linear combination of an un-moderated component, and a moderated component that captures the effect of the environment on the additive genetic variance and accounts for potential GE interaction. The model in effect slightly adjusts the path estimates for each individual (each twin pair in the case of a family-wide moderator).

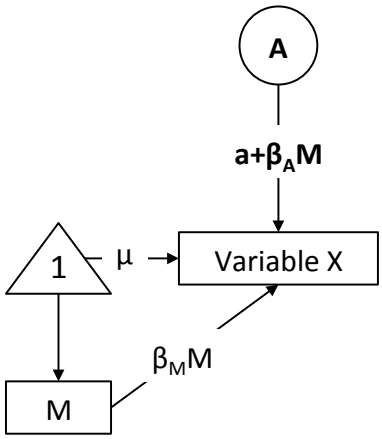


Figure 1.5 Continuous moderation of the additive genetic variance component
A = additive genetic variance component; a = un-moderated component of the genetic path coefficient. β_A = moderated component of the genetic path coefficient; μ = mean level of Variable X; M = putative moderating environment; GE interaction is indicated if $\beta_A \neq 0$

The continuous moderator model is described in detail in **Chapter 4**, but it is worth noting here that this model handles GE correlation by simply partialling out any genetic effect on the environment that is correlated with genetic effect on the phenotype. The model has several extensions including a bivariate variation that explicitly measures both GE interaction and GE correlation – an extension that requires twin-specific measures on the both the moderator and the phenotype (Purcell, 2002). For example, the continuous moderator model has been used to show that genetic effects on depressive symptoms in adolescence are moderated by maternal punitive discipline and negative life events (GE interaction), as well as being correlated with the genetic effects on these environments (GE correlation) (Lau & Eley, 2008). While the basic continuous moderator model (shown in Figure 1.5 and used in **Chapter 4**) does not attempt to

quantify any potential GE correlation, any observed GE interaction is unequivocally moderation of the genetic variance component, independent of any genetic effect that may be correlated with the moderator. However, it has been shown that several alternative models explain equally well, apparent GE interaction as determined by the bivariate continuous moderator model, without the inclusion of moderation of the genetic variance component – i.e., suggesting no GE interaction is present (Rathouz, Van Hulle, Rodgers, Waldman, & Lahey, 2008). **Chapter 4** highlights further considerations when modelling GE interaction.

1.2.3 Assumptions of the twin method

The twin method and model fitting procedures make several necessary assumptions concerning the nature of the genetic and environmental causes of behaviour, the shared environments experienced by twins, the minimal impact of GE effects, non-assortative (random) mating in the population, and the generalizability of the results of twin studies to the singleton population (Martin, Boomsma, & Machin, 1997; Plomin et al., 2008). The assumption that resemblance due to shared environmental influences is equal for MZ and DZ twin pairs, is explicit in the twin model fitting – latent C components correlate 1.0. The assumptions if violated will have a variety of effects on the variance components of the phenotype under study; how justified each of the assumptions of the classical twin model are depend on the phenotype. Where tested the assumptions are generally upheld, and if not, it is often possible to account for violations in the modelling – notably the modelling of GE effects (Martin et al., 1997; Rijsdijk & Sham, 2002; Visscher, Hill, & Wray, 2008). It is worth noting that other quantitative genetic methods with different assumptions, for example the adoption method, arrive at similar conclusions about the relative importance of the A, C and E variance components (Plomin et al., 2008).

Other assumptions relate directly to the specification of the twin model and distributional properties of the twin data. At the level of the family it is assumed that the phenotype is multivariate normal, and that means and variances are homogeneous across twin birth order and zygosity. Perhaps most critical in the context of the present thesis is the assumption that, where GE effects are not modelled, GE interaction and GE correlation have minimal effect on the phenotype (Rijsdijk & Sham, 2002).

Biased estimates with un-modelled GE effects

Purcell (2002) demonstrated, with covariance algebra proof, the outcome of un-modelled GE interplay on population variance components. The biased estimates are

summarized in Table 1.1. For example, if genetic effects depend on shared experiences (GE interaction) this will increase the resemblance of MZ twins (100% similar genetically) compared to DZ twins (50% similar genetically) and will inflate the A estimate. In contrast, when particular genotypes are more common in certain environments (GE correlation), this looks like greater similarity between siblings due to shared environment. C will be inflated in the presence of GE correlation because the actual genetic similarity between DZ twins will be more than the assumed 50%.

Table 1.1 Biased variance component estimates with un-modelled gene-environment (GE) interaction and correlation

Interplay	**Biased estimate**	
	GE Interaction	*GE Correlation*
A-C	A	C
A-E	E	A

The **Interplay** column indicates the presence of un-modelled GE effects between genes and shared environment (A-C), and between genes and non-shared environment (A-E). Under the **Biased estimate** label is the variance component that is inflated for either un-modelled GE interaction, or un-modelled GE correlation. A, C, E = genetic, shared, and non-shared environmental variance components; GE = gene-environment

With un-modelled GE effects, genetic and environmental variance components are not simply averaged over the population – instead they are systematically biased. Given the expected pervasiveness of GE effects (Rutter et al., 2006), failure to account for GE phenomena is problematic for understanding the nature of genetic and environmental effects (Evans et al., 2002). One of the aims of this thesis is add to the body of literature on the pervasiveness of these effects in childhood environments and to highlight the biases in their assumed absence.

1.3 Measured genotypes and the environment: Molecular genetic methods

If measured environments are themselves complex traits, we should be able to apply standard molecular genetic methods to map genes to the environment, just as we associate genes with any other complex trait (Hirschhorn & Daly, 2005). This proposition is not as odd as it at first seems: Quantitative genetic studies suggest that it is the genetic effects on heritable behaviours that explain the heritability of environmental measures (Saudino & Plomin, 1997). Thus, genetic variation associated with heritable environmental measures represents shared genetic liability underlying both problem behaviour and the environment it predisposes to. Although a few associations with candidate genes have been reported (e.g., GABRA2 and marital status;

Dick et al., 2006), so far there have been no replicated associations for experiences reported by the most powerful and up to date molecular genetic method, genome-wide association. If environments are like typical complex traits, we expect many variants of small effect size to account for their genetic variation (Park et al., 2010; Visscher, Brown, McCarthy, & Yang, 2012).

Using measured genetic variation to explain phenotypic variation

The current state of genome-wide association studies (GWASs) is the recognition that beyond simply surveying hundreds of thousands of SNPs for associations with a particular phenotype – essentially one SNP at a time – whole-genome data can be used to reveal the genetic architecture of complex traits. A new technique uses the measured genotypes on a genome-wide genotyping array to estimate the relatedness among every pair of individuals in an unrelated population. The extent to which this genetic relationship matrix predicts phenotypic variation is the estimate of genetic variation in the trait due to common genetic variation in the genome: genome-wide complex trait analysis (GCTA; Yang, Lee, Goddard, & Visscher, 2011). GCTA has been used to establish the importance of genetic factors in both height and intelligence (Davies et al., 2011; Yang et al., 2010). Using measured genetic variation to explain environmental variaiton would confirm the quantitative genetic finding that common genetic variation explains individual variation in experience of the environment – GE correlation (Jaffee & Price, 2007; Kendler & Baker, 2007).

1.4 Aims of this thesis

This thesis aims to contribute to the study of GE effects in childhood with a series of studies on environmental experience and childhood outcomes embedded in genetically sensitive designs. "Models, of course, are never true, but fortunately it is only necessary that they be useful. For this it is usually needful only that they not be grossly wrong" (p.2, Box, 1979). Each chapter provides a small extension to the literature on GE effects, highlighting the utility of modelling the environment as a multifactorial trait in order to understand the nature of "environmental risk" for complex behaviour.

Chapter 2 describes the large population-based twin sample, the Twins Early Development Study (TEDS), and the particular environments and childhood outcomes studied in this thesis. **Chapter 3** illustrates the hidden assumption in the link between environment and childhood outcome: that "environments" have environmentally-mediated effects on the cognitive, academic and behavioural outcomes with which they are associated. With the example of environmental confusion in the home, so called

family chaos, this chapter describes the phenomenon of genetically-influenced exposure to the environment, and genetically mediated links between experience of the environment and outcome: GE correlation. This chapter draws attention to the fact that the absence of child-driven genetic effects is implicitly assumed in studies that use family-wide measures, for example parent or teacher reports.

Chapter 4 describes an investigation of the possibility that the genetic and environmental effects on children's intelligence (IQ), from infancy through adolescence, depend on the level of their parents' socioeconomic status (SES). This chapter uses two quantitative genetic designs to test whether genetic effects depend on the environment. The results in our large UK-representative sample do not replicate the widely reported moderation of the genetic effect on IQ by SES – a GE interaction. We show with exact simulation the sample sizes that are needed for a range of interaction effect sizes, and the performance of the continuous moderator model. We compare and contrast our result with past studies investigating SES moderation of IQ and suggest potential causes for the differences – differences that apply to the investigation of GE interaction for any trait.

Longitudinal designs address direction of causation in child development; twin models augment this information with the ability to look at genetic and environmental aspects of stability and change. In **Chapter 5** we include measured experiences to simultaneously explore the behavioural origin of the genetic effect on a heritable environment, and to test the environmental mediation of the chaotic home environment and disruptive behaviour. **Chapter 6** extends this by incorporating multiple behaviours to try to account for the total genetic effect on a heritable environment. This study is a snapshot of the genetic and environmental links between behaviour and environment in early adolescence. Finally, **Chapter 7** describes the use of whole-genome data to take GE correlation to its logical conclusion: to test the environment for association with specific genetic variants.

2 Sample, Measures, and Statistical Procedures

2.1 Sample

The Twins Early Development Study (TEDS)

All analyses described in this PhD thesis were performed on data from the Twins Early Development Study (TEDS: Oliver & Plomin, 2007; Trouton, Spinath, & Plomin, 2002). TEDS is a population-based longitudinal study of over 10,000 pairs of twins. The Office for National Statistics (ONS) provided the sampling frame: mothers of all live-born twins in England and Wales, 1994 - 1996. Subsamples of the TEDS twins have been tested on a variety of measures – including cognitive and academic abilities, home, school and peer environment, and problematic behaviour – at ages 2, 3, 4, 7, 9, 10, 12, 14, and currently at age 16. Comparison to census data from the ONS indicates that the sample has remained representative of the United Kingdom (UK) population (Kovas, Haworth, Dale, & Plomin, 2007). The subsamples that participate at each age also remain representative of the larger TEDS sample.

Zygosity was assigned to the twins using a parent-rated instrument that yielded 95% accuracy when compared to zygosity established from DNA markers (Price et al., 2000); uncertainties were followed up with DNA marker testing. A subsample of over 3000 twins have been genotyped on the Affymetrix Genome-Wide Human SNP Array 6.0 and are part of the Wellcome Trust Case Control Consortium 2 (WTCCC2) investigating genome-wide associations in quantitative traits.

Ethical approval for the Twins Early Development Study has been provided by the King's College London ethics committee (reference: 05/Q0706/228). The parents of the twins provide informed written consent at each wave of assessment. Sample sizes are reported for each study.

2.2 Measures

Assessment

The TEDS twins have been assessed with a variety of methods at each wave of assessment including parent-administered tests, in-home observations, telephone interviews, postal questionnaires, and Internet-based assessments. The assessment procedures (and their validation in the TEDS sample where appropriate) are fully described elsewhere (Haworth et al., 2007; Oliver & Plomin, 2007; Trouton et al., 2002).

Environmental measures

2.2.1 Socioeconomic status, SES

As indices of SES, we used parental education, occupation, and family income. We assessed parental education and occupation (mother's and father's highest educational qualification and job status) at first contact with the families, when the twins were 18 months old, and again when the twins were 7 years old; we assessed family income at age 9. From these measures we created three indices: SES index 1, parental education and occupation acquired at contact (age 18 months); SES index 2, parental education and occupation acquired at age 7; and SES index 3, parental income assessed at age 9. All composites were created as a unit-weighted sum of the contributing scales, i.e., first mapped to a standard normal distribution with the rank-based van der Waerden transformation (Lehmann, 1975), then summed, and finally standardized again. The correlations between these three SES estimates are 0.77 for SES index 1 and 2, 0.55 for SES index 1 and 3, and 0.57 for SES index 2 and 3.

2.2.2 Confusion, Hubbub and Order Scale, CHAOS

At age 9 and 12, the twin's perceptions of noise, order, and routine in their family home were assessed using a short version of the Confusion, Hubbub, and Order Scale (CHAOS; Matheny, Wachs, Ludwig, & Phillips, 1995). The CHAOS scale has been widely used and has good psychometric properties; the original full-length inventory had high internal consistency (Cronbach's alpha, $\alpha = 0.79$) and stability across a 12-month period (r=0.74: Dumas et al., 2005). CHAOS was administered as part of a larger battery of measures in a booklet mailed to each of the twins at ages 9 and 12. The short form of CHAOS assesses the level of routine, noise, and general environmental confusion with six items: 'I have a regular bedtime routine' (scoring reversed), 'You can't hear yourself think in our home', 'It's a real zoo in our home', 'We are usually able to stay on top of things' (scoring reversed), 'There is usually a television turned on somewhere in our home', and 'The atmosphere in our house is calm' (scoring reversed). The children rated the extent to which they agree: 'Not True', 'Quite True', or 'Very True'. At both age 9 ($\alpha = 0.58$) and age 12 ($\alpha = 0.57$), a mean of the individual items was used as an overall score, with higher scores indicating greater chaos. Our internal-consistency reliability is moderate and acceptable, although slightly lower than others have found for parent ratings of the same short version in younger samples (e.g., 0.68, Hart, Petrill, Deater-Deckard, & Thompson, 2007; 0.63, Petrill, Pike, Price, & Plomin, 2004). Child-reported CHAOS correlated 0.43 between ages 9 and 12. Parent-reported CHAOS when the children were age 9 and 12 correlated 0.53 and 0.55 respectively with

the corresponding child reports, supporting the validity of the child reports. Child-rated CHAOS at both ages was normally distributed.

2.2.3 Peer victimization

We measured children's self-reports of peer victimization at age 12 using the Multidimensional Peer Victimization Scale (Mynard & Joseph, 2000). The scale assesses physical victimization, verbal victimization, social manipulation, and property damage, with 16 items. A factor analysis with varimax rotation on the 16 items confirmed the presence of these four subscales in the TEDS sample. The subscales, calculated as a mean of the four contributing items, had high internal-consistency reliability (α = 0.79 – 0.81) and were highly correlated (r = 0.50 – 0.62). As is often found with behavioural scales (which record endorsements), the four subscales and the victimization total score were all positively skewed. We transformed the data to a standard normal distribution (Lehmann, 1975), based on the assumption that the underlying risk for exposure to victimization was normally distributed.

Cognitive and academic measures

2.2.4 General cognitive ability, g

At all ages described below, a unit-weighted composite of verbal and nonverbal cognitive tests was used as an index of g. We mapped all verbal and nonverbal cognitive tests to a standard normal distribution (Lehmann, 1975), summed the contributing scales, and standardized the final g composite. This score was identical to a first principal component extracted from the balanced test battery.

Ages 2, 3, and 4

In early childhood, parent-administered tests and parent-reported observations were used to assess verbal and nonverbal cognitive abilities at age 2, 3, and 4. These measures have been validated against standard tests administered by a trained tester (Oliver et al., 2002; Saudino et al., 1998).

Nonverbal cognitive performance was assessed using age-appropriate versions of the Parent Report of Children's Abilities (PARCA; Oliver et al., 2002; Saudino et al., 1998). The PARCA is an hour-long test comprising three types of parent-administered tasks: a "find the pair" task, a drawing task, and a matching task. Some items are novel; others are adapted from previously well-validated tests such as the McCarthy Scales of Children's Abilities (McCarthy, 1972) or the Bayley Scales of Infant Development (BSID-II; Bayley, 1993). Together, the administered items are designed to assess

number, shape, size, conceptual grouping and orientation skills. This parent-administered component is supplemented by a small number of parent report items anchored on concrete behaviours and requiring simple yes or no answers. Some of these items are novel; others are adapted from previously well-validated assessments such as the Minnesota Child Development Inventory (MCDI; Ireton & Thwing, 1974) and the Ages and Stages Questionnaires (Bricker, Squires, & Mounts, 1995). The complete PARCA, including novel and previously well-validated items, has been validated in an independent sample (Saudino et al., 1998) and in the TEDS sample (Oliver et al., 2002).

The verbal component of the early childhood battery included vocabulary and grammar as assessed by parent reports for the CDI-III, an extension of the short form of the MacArthur Communicative Development Inventories: Words and Sentences (Fenson et al., 2000). The MCDI has been shown to have excellent internal consistency and test–retest reliability, as well as concurrent validity with tester-administered measures (Fenson et al., 2000).

Age 7

At age 7, verbal and nonverbal abilities were tested by telephone (Petrill, Rempell, Oliver, & Plomin, 2002). Prior to the telephone call, parents were sent a booklet of test items along with instructions indicating, for example, that the test booklet should not be opened prior to the telephone interview and that the twins should not be in the same room for the duration of the call. The booklet contained two tests of verbal cognitive abilities and two nonverbal tests. The verbal tests consisted of the Similarities subtest and the Vocabulary subtest from the Wechsler Intelligence Scale for Children (WISC-III-UK; Wechsler, 1992). The nonverbal tests were the Picture Completion subtest from the WISC-III-UK and Conceptual Grouping from the McCarthy Scales of Children's Abilities (McCarthy, 1972).

Age 9

Nine-year-old participants received a test booklet containing two verbal and two nonverbal tests that, like the tests in early childhood, were administered under the supervision of the parent (guided by an instruction booklet rather than a telephone interview). The verbal tests comprised vocabulary and general knowledge tests adapted from the multiple-choice version of the WISC-III-UK (Wechsler, 1992). The nonverbal tests included a Puzzle test adapted from the Figure Classification subtest of the Cognitive Abilities Test 3 (CAT3; Smith, Fernandes, & Strand, 2001). The second nonverbal test was a Shapes test also adapted from the CAT3 Figure Analogies subtest

that assesses inductive and deductive reasoning. Details are reported by Davis et al. (2008).

Age 10

Children at age 10 participated in web-based testing. Widespread access to inexpensive and fast internet connections in the UK has made online testing an attractive possibility for collecting data on the large samples necessary for genetic research. The advantages and potential pitfalls of data collection over the Internet have been reviewed (Birnbaum, 2004). For older children, most of whom are competent computer users, it is an interactive and enjoyable medium. Through adaptive branching, it allows the use of hundreds of items to test the full range of ability, while requiring individual children to complete only a relatively small number of items to ascertain their level of performance. In tests where it is appropriate, streaming voiceovers can minimize the necessary reading. In addition, the tests can be completed over a period of several weeks, allowing children to pace the activities themselves, although they are not allowed to return to items previously administered. Finally, it is possible to intersperse the activities with games. All of these factors help to maintain children's engagement with the tests. Participants at age 10 were tested on two verbal tests: WISC-III-PI Multiple Choice Information (General Knowledge) and WISC-III-PI Vocabulary Multiple Choice (Wechsler, 1992). Two nonverbal reasoning tests were also administered: WISC-III-UK Picture Completion (Wechsler, 1992) and Raven's Standard Progressive Matrices (Raven, Court, & Raven, 1996). Details are reported in Haworth et al. (2007).

Age 12

At age 12 we again used Web-based assessment of general cognitive ability. The tests administered were updated versions of the same tests used at age 10, with the addition of more difficult age-appropriate items. We administered two verbal ability tests: WISC-III-PI Information Multiple Choice (General Knowledge) and WISC-III-PI Vocabulary Multiple Choice (Kaplan, Fein, Kramer, Delis, & Morris, 1999). We also administered two nonverbal tests: Raven's Progressive Matrices (Raven et al., 1996) and WISC-III-UK Picture Completion (Wechsler, 1992).

Age 14

At age 14 we measured general cognitive ability with one verbal and one non-verbal web-based test. The verbal test used was WISC-III-PI Vocabulary Multiple Choice (Kaplan et al., 1999); the nonverbal test used was Raven's Progressive Matrices (Raven

et al., 1996). Both measures were the age-appropriate versions of those tests used at earlier ages.

2.2.5 School Achievement

The assessment of school performance at age 12 was based on teacher ratings using UK National Curriculum (NC) criteria (Qualifications and Curriculum Authority (QCA); http://curriculum.qca.org.uk/). These criteria provide curriculum and assessment guidelines followed by all teachers in the UK state school system. The validity of teacher ratings has been demonstrated (Hoge & Coladarci, 1989); for example, in the current sample teacher assessments are highly correlated with standardized tests of reading and mathematics (Kovas et al., 2007). Teachers rated the children on each component of English, mathematics and science on a scale from 1 to 8, with an additional level 9 for exceptional performance. This is a behaviourally-anchored rating scale based on concrete targets; the QCA provides teachers with vignettes in order to standardize their assessments. As the children get older, different levels of the scale will come to represent the average expected performance. Children at age 12 have just begun Key Stage 3 of the UK NC, covering the ages 11-14. At age 11 most pupils are expected to achieve level 4 in the teacher assessments; at age 14, most pupils are expected to achieve level 5. Children's performance is based on class work and homework, and takes account of written, practical and oral work.

We calculated a mean score for each of the three subjects from teacher-rated NC levels of English (Speaking and listening; Reading; Writing), mathematics (Using and applying numbers; Number and algebra; Shape, space and measures; Handling data) and science (Scientific enquiry; Life processes and living things; Materials and their properties; Physical processes) performance.

Behavioural measures

2.2.6 Strengths and Difficulties Questionnaire, SDQ

The Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997, 2001) is a brief screening measure of children's problem behaviours. Parents reported whether each of five items on five subscales – prosocial behaviour, hyperactivity, conduct problems, peer problems, anxiety (or emotional problems) – were 'Not True', 'Somewhat True', or 'Definitely True' of their child. **Chapter 5** uses the conduct problems and hyperactivity subscales at age 9 (conduct $\alpha = 0.57$; hyperactivity $\alpha = 0.76$) and age 12 (conduct $\alpha = 0.55$; hyperactivity $\alpha = 0.76$). **Chapter 6** uses the age 12 subscales hyperactivity, conduct problems, peer problems ($\alpha = 0.62$), and anxiety ($\alpha = 0.67$); internal-

consistency reliability of the four subscales combined was $\alpha = 0.80$. We did not include the prosocial subscale as absence of prosocial behaviour is not necessarily "problem" behaviour. The moderate internal-consistency reliability for conduct problems does not seem to be specific to our sample: A paper exploring the validity and reliability of the SDQ scale in a Dutch sample (N=562, mean age 12.3 years) found the same internal consistency ($\alpha = 0.55$) for the conduct problems subscale (Muris, Meesters, & van den Berg, 2003).

2.2.7 Moods and Feelings Questionnaire, MFQ

At age 12, the twins completed self reports of the 11-item short form of the Moods and Feelings Questionnaire (MFQ) designed to study depression in children and adolescents (Angold et al., 1995). Two items were removed from the standard 13-item short form MFQ because these were repeated in the SDQ scale. The twins responded 'Not True', 'Quite True', or 'Very True' to 11 statements about their feelings and action over the previous 2 weeks. The MFQ scale showed high internal consistency reliability in the TEDS sample at age 12 ($\alpha = 0.85$).

2.2.8 Antisocial Process Screening Device, APSD

We measured parent-rated antisocial behaviour at age 12 with the Antisocial Process Screening Device (APSD; Frick & Hare, 2001). Parents responded 'Not True', 'Somewhat True', or 'Very True', to a series of statements on each child's behaviour over the previous 3 months. The APSD is a 20-item questionnaire with three subscales: impulsivity ($\alpha = 0.64$), callous-unemotional traits ($\alpha = 0.49$), and narcissism ($\alpha = 0.66$). Overall internal-consistency reliability was high ($\alpha = 0.76$).

2.2.9 Childhood Asperger Syndrome Test, CAST

At age 12 we measured autistic-like traits with parent ratings of the Childhood Asperger Syndrome Test (CAST (Scott, Baron-Cohen, Bolton, & Brayne, 2002; Williams et al., 2005). Parents respond 'Yes' or 'No' to items describing their children's behaviour over the previous 3 months. The CAST is a 30-item questionnaire assessing three aspects of autistic-like behaviour: social ($\alpha = 0.49$), non-social ($\alpha = 0.47$), and communication ($\alpha = 0.60$). Overall internal consistency reliability was moderate ($\alpha = 0.69$).

2.3 Statistical procedures

2.3.1 Twin model fitting

The twin design compares the phenotypic resemblance of identical (monozygotic, MZ) twins to the phenotypic resemblance of non-identical (dizygotic, DZ) twins in order to partition the variance on a trait into sources of genetic and environmental variation. The coefficient of genetic relatedness is 1.0 between MZ twins, and on average 0.5 between dizygotic twins, who share 50% of their segregating alleles. The twin model attributes the similarity of reared-together twins to additive genetic (A) and shared environmental (C) factors, and the differences between them to non-shared environmental (E) factors (Plomin et al., 2008). By definition, co-twins in both MZ and DZ pairs are correlated 1.0 for C factors – this is known as the equal environment assumption. The assumptions of the twin design are described in **Chapter 1**; detailed descriptions and attempts to validate them are described in detail elsewhere (Boomsma, Busjahn, & Peltonen, 2002).

The proportion of total phenotypic variation accounted for by genetic factors is indexed by the heritability statistic, h^2 = A/(A+C+E). An estimate of heritability – as well as the relative proportion of variance accounted for by shared and non-shared environmental factors – can be derived using Falconer's formulae applied to intra-class twin correlations (coefficients of twin similarity; Shrout & Fleiss, 1979):

$$h^2 = 2(r_{MZ} - r_{DZ})$$
$$c^2 = r_{MZ} - h^2$$
$$e^2 = 1 - h^2 + c^2$$

However, these formulae provide no confidence intervals around the estimates, and can only consider twin pairs for whom both twins in the pair have data. Structural equation modelling, using full information maximum likelihood, addresses these shortcomings and provides the basis for a variety of more sophisticated models. Path analysis provides a set of tracing rules for calculating expected variances and covariances, and an intuitive visualization of the variance-covariance structure among observed and latent variables.

Path analysis

Sewell Wright proposed the method of path analysis to decompose the covariation among traits given a specific model of causation (Wright, 1918). The path diagram in Figure 2.1 summarizes the classic twin ACE model for a single trait, Variable X.

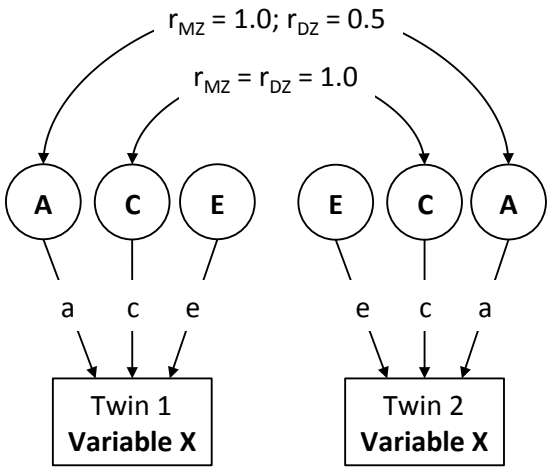


Figure 2.1 Path diagram of the univariate ACE model.
The measured Variable X is regressed on the latent additive genetic (A), shared environmental (C), and non-shared environmental (E) variance components; a, c, and e are partial regression coefficients. The variance in Variable X is given by $a^2 + c^2 + e^2$. The covariance between twins is given by $a^2 + c^2$ for MZ twins, and $0.5a^2 + c^2$ for DZ twins. Single-head arrows represent regression and double-headed arrows correlation; rectangles are measured variables; circles are latent variables.

Path tracing rules can be used to derive the variance within an observed variable and the covariance between variables (Wright, 1934):

1. No loops allowed – do not pass through the same variable twice.
2. No tracing backward, then forward.
3. One double-headed arrow per route.

The covariation between measured traits is the sum of all legitimate routes (or path chains); a path chain is the product of the coefficients traced from one variable to another. In Figure 2.1, the covariance for MZ twins = $(a*r_{MZ}*a) + (c*r_{MZ}*c) = a^2 + c^2$. By definition, the E component does not contribute to covariation within twin pairs. The variation of a given variable is the covariation of that variable with itself. By design the variance of the latent variables is 1 – the double-headed arrow showing the covariance of 1 is typically omitted. Using the sum of all legitimate routes formula for covariation, in Figure 2.1, the total variation of Variable X = $(a*1*a) + (c*1*c) + (e*1*e) = a^2 + c^2 + e^2$.

Structural equation model fitting

Structural equation modelling (SEM) provides a method to decompose the covariance between measured (or observed) variables and latent (or unobserved) variables. We used the matrix optimization and SEM package OpenMx (Boker et al., 2011) in the open-source programming language R (www.R-project.org; R Development Core Team, 2011) to fit structural equation models to the phenotypic covariance structure between

twins. The fit of a particular model to the data is summarized by a fit statistic, negative two times the log likelihood (-2lnL); the difference in fit between two nested models has a chi-square (χ^2) distribution. Using this difference in fit as the critical value in a χ^2 test, with degrees of freedom (df) equal to the difference in number of parameters estimated, provides a likelihood ratio or goodness-of-fit test. With large samples, such as TEDS, the χ^2 goodness-of-fit test penalizes simpler models (that estimate less parameters). For this reason, several alternate indices of fit that favour parsimony are preferred. Two indices often used in twin analyses (and throughout this thesis) are Akaike's information criterion (AIC = (-2lnL) - 2df; Akaike, 1987), and the Bayesian information criterion (BIC = (-2lnL) - ln(n)*df; Raftery, 1995). The BIC in particular favours simpler models in large samples. In comparing two models, lower AIC and BIC values indicate a better fit of the model to the data.

2.3.2 Extensions to the basic twin model

The univariate twin model outlined above and summarized in Figure 2.1 can be extended in several ways. Each of the multivariate models described below is an a priori account of the common and specific variance among multiple phenotypes; all include an expansion of the covariance matrix to accommodate combinations of within and across twin and trait covariances. It is also possible to model separate parameter estimates for subgroups and test their equality within the model – a so-called heterogeneity model. Examples of heterogeneity modelling include sex-differences analyses, the modelling of separate parameters on a given trait for males and females, and interaction analyses, the modelling of separate parameters on the trait of interest for groups high and low on a putative moderator.

Multivariate models

Multivariate data provides an expanded variance-covariance matrix; the additional across-twin across-trait covariances allow the partitioning of the covariance between traits (as well as the variance within traits) into genetic and environmental sources. Multivariate twin modelling aims to explain sources of common and specific variance among multiple phenotypes according to some a priori model of causation. Each of the models introduced below is described in more detail within each chapter.

Cholesky decomposition

In a Cholesky decomposition, variable order matters. The first trait has an effect on all traits after it. The residual (genetic and environmental) variance components of the

second trait are uncorrelated with the first trait, and have effects only on the traits that come after the second. The residual variance components in the third trait are uncorrelated with the first and second trait, and have effects only on the traits after the third variable, and so on. Figure 2.2 shows the path diagram for the bivariate case. A common misinterpretation of the variance components A_1, C_1, and E_1 is that they represent the common variation between Variables X and Y. A_1, C_1, and E_1 are in fact the total (genetic and environmental sources of) variation in X; onto these Y is regressed. A_2, C_2, and E_2 are then the residual genetic and environmental variance in Y, uncorrelated with Variable X (Loehlin, 1996).

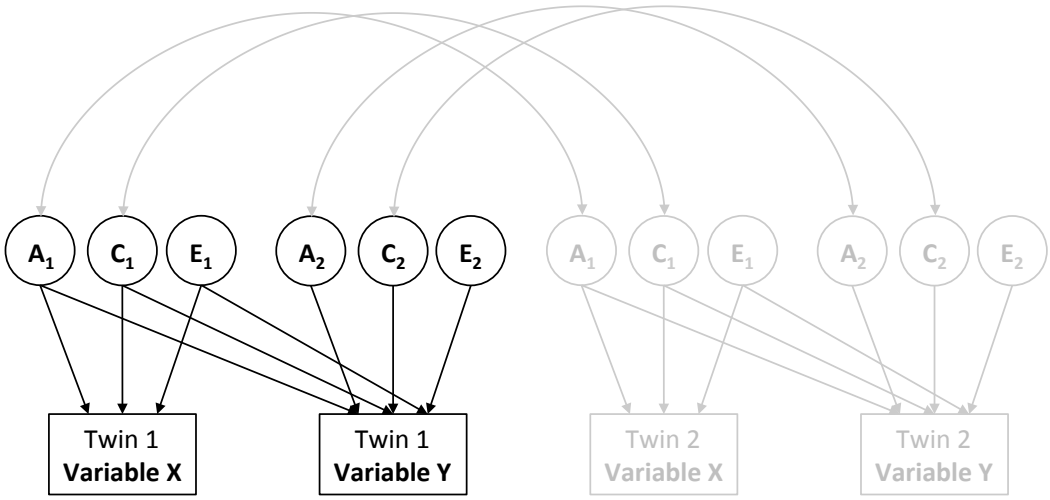


Figure 2.2 Cholesky decomposition of two variables
The greyed-out co-twin variables are included here for completeness – these are typically left off the path diagram for simplicity.

Common pathway model

The common pathway model (Figure 2.3) decomposes the common variance among multiple phenotypes at one or more latent factors (as well as the residual variance within each trait) into sources of genetic and environmental variance. The latent factor represents a phenotypic common factor, e.g., a psychometric factor such as general cognitive ability (g) underlying a diverse set of cognitive abilities.

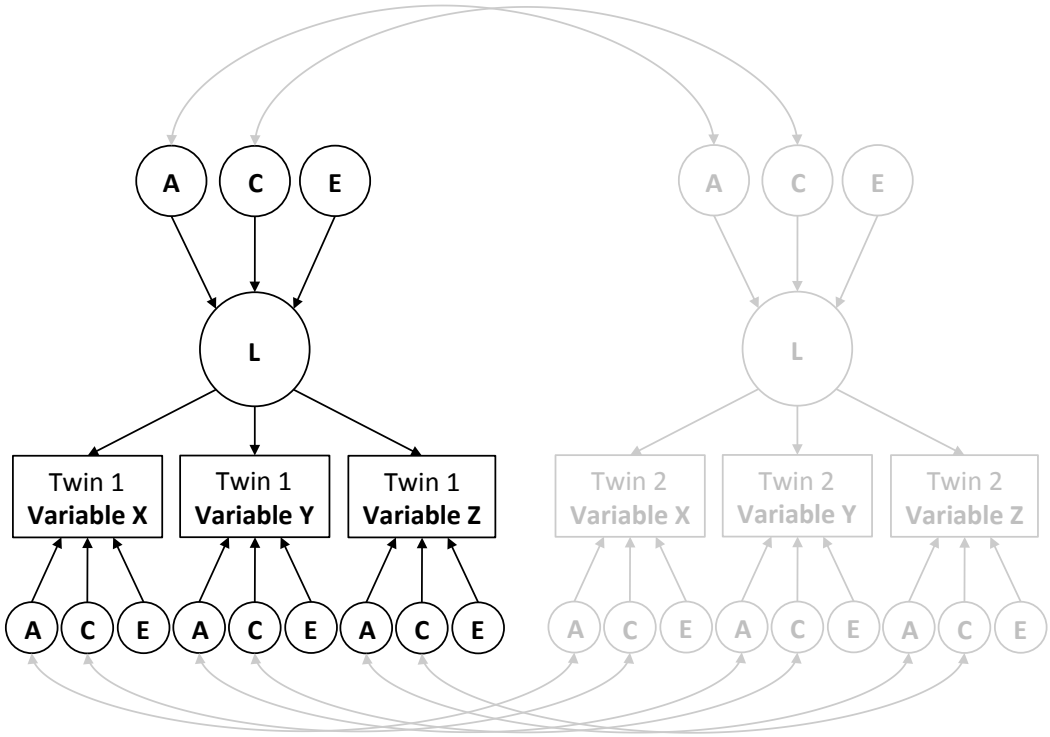


Figure 2.3 Common pathway model with a single latent factor
Each measured variable loads onto the common factor whose variance is decomposed into sources of common genetic and environmental influence. The residual variance, variation specific to each variable, is also partitioned into genetic and environmental influences. The greyed-out co-twin variables are included here for completeness – these are typically left off the path diagram for simplicity.

Heterogeneity models

Sex-limitation modelling, described below, is one application of the heterogeneity model. **Chapter 4** illustrates the model's application to gene-environment interaction – the estimation of genetic and environmental variance components in a trait of interest at different levels of a potential environmental moderator. Figure 2.4 shows the full sex-limitation model which is used to explicitly test the presence of qualitative and/ or quantitative sex differences: differences in type and/ or magnitude of genetic and environmental effects in males and females. These are genetic and environmental factors affecting the variance in the trait, measured in males and females, after correction for mean differences in the trait. The presence of qualitative sex differences is indicated if the coefficient of genetic relatedness in DZ opposite-sex pairs is significantly less than 0.5, or if the coefficient of environmental relatedness is significantly less than 1.0. The number of observed statistics (means, variances, and covariances) allows the estimation of only one of these parameters. The presence of quantitative effects is indicated if the genetic and environmental path coefficient for males (a_m, c_m, e_m) cannot be equated to those for females (a_f, c_f, e_f). Variance differences between males and females can be accounted for with the inclusion of a scalar

multiplier, which allows for the estimation of a single set of genetic and environmental coefficients (a, c, e) by scaling the variance up or down in one sex.

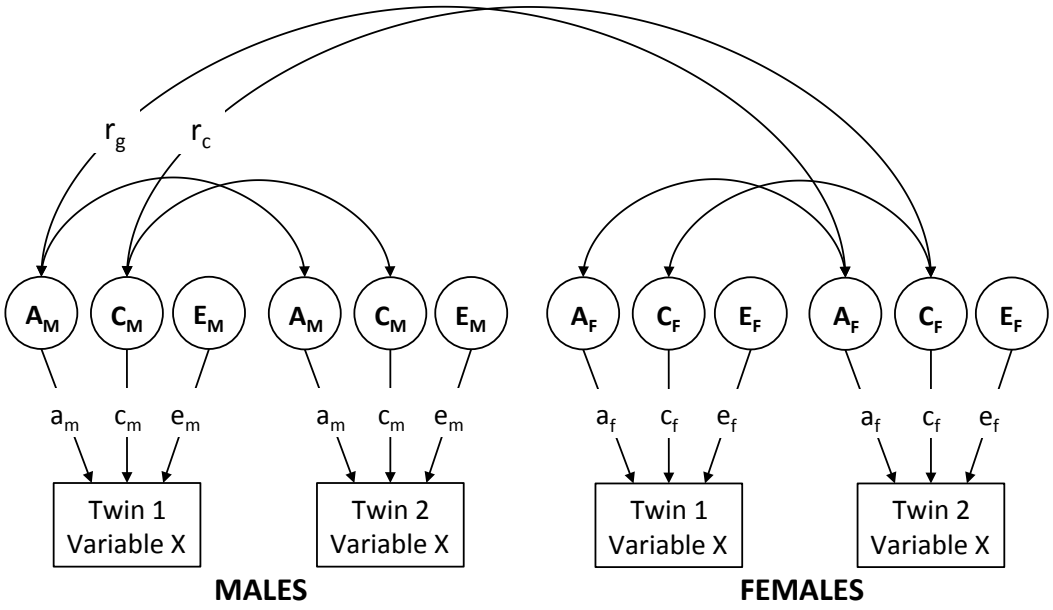


Figure 2.4 Full univariate sex-limitation model
This model includes both same-sex and opposite-sex pairs. r_g is the coefficient of genetic relatedness in DZ opposite-sex pairs; r_c is the coefficient of environmental relatedness in the DZ opposite-sex pairs; a_m, c_m, and e_m are the genetic and environmental coefficients in males; a_f, c_f, and e_f are the genetic and environmental coefficients in females.

2.3.4 Molecular and statistical genetics

Genome-Wide Association Study (GWAS)

A genome-wide association study (GWAS) tests hundreds of thousands of single nucleotide polymorphisms (SNPs) for association with a given trait. In a case-control study, this is simply testing if a particular allele (at a given locus) appears more often among cases than controls. In **Chapter 7** we have performed a GWAS on a quantitative trait using SNPTEST (Wellcome Trust Case Control, 2007). As part of the Wellcome Trust Case Control Consortium 2 (WTCCC2) we genotyped 3,747 individuals from TEDS (no co-twins were included) on the Affymetrix Genome-Wide Human SNP Array 6.0, which assays about 1 million SNPs. After SNP quality control (QC) – exclusion of SNPs with call rate < 0.98, minor allele frequency (MAF) < 0.01, and Hardy Weinberg Equilibrium (HWE) p-value < 1×10^{-20} – we had 688,025 genotyped SNPs. We also excluded outlying individuals based on call rate, heterozygosity, relatedness and ancestry, which left a sample size of 3,154. We used EIGENSTRAT to derive principal components from the genomic data, and included these population axes as covariates in our test of association to account for population structure (Price et al.,

2006). We also included age and sex as covariates in the analyses. We imputed missing genotypes, bringing the total number of SNPs to 1,721,433 (1,033,408 imputed, 688,025 genotyped), and fitted an additive model for each SNP (Balding, 2006).

Testing for association at many thousands of loci introduces a multiple testing burden and the need for multiple test correction. The accepted genome-wide significance threshold is a p-value = 5×10^{-8}, i.e., $0.05 / 1 \times 10^{6}$ (a million independent tests). This is a conservative correction – given the non-independence of the loci due to linkage disequilibrium – but necessary: at a p-value = 0.05, a million independent tests would produce up to 50,000 false positives.

Genome-wide Complex Trait Analysis (GCTA)

Genome-wide complex trait analysis (GCTA; Yang et al., 2011) is a tool that estimates the genetic variance explained by all SNPs on a given genotyping platform, and the common variation in the genome tagged by the genotyped SNPs. The aggregate additive genetic effect of all SNPs is fitted as a random effect in a mixed linear model explaining phenotypic variation. Using unrelated individuals avoids inflation of the phenotypic correlation due to shared environment. We estimated the pairwise genetic relationships among these individuals using 688,025 SNPs, and excluded one member of any pair which had a relatedness > 0.025. Our final sample size for the GCTA analysis was about 2700 (individuals with phenotype data).

3 Chaotic Homes and School Achievement: A Gene-Environment Correlation Study[1]

3.1 Abstract

Chaotic homes predict poor school performance. However, we know that genes affect both children's experience of household chaos and their school achievement. To what extent is the relationship between high levels of noise and environmental confusion in the home, and children's school performance, mediated by heritable child effects? This is the first study to explore the genetic and environmental pathways between household chaos and academic performance. We assessed children's perceptions of family chaos at ages 9 and 12 and their school performance at age 12 in more than 2300 twin pairs. Using child-specific measures in a multivariate genetic analysis made it possible to investigate the genetic and environmental origins of the covariation between children's experience of chaos in the home and their school achievement. Children's experience of family chaos and their school achievement are significantly correlated in the expected negative direction (r = -0.26). As expected, shared environmental factors explained a large proportion (63%) of the association. However, genetic factors accounted for a significant proportion (37%) of the association between children's experience of household chaos and their school performance. The association between chaotic homes and poor performance in school, previously assumed to be entirely environmental in origin, is in fact partly genetic. How children's home environment affects their academic achievement is not simply in the direction environment → child → outcome. Instead, genetic factors that influence children's experience of the disordered home environment also affect how well they do at school. The relationship between the child, their environment, and their performance at school is complex: both genetic and environmental factors play a role.

[1] Chapter adapted from:

Hanscombe, K.B., Haworth, C.M.A., Davis, O.S.P., Jaffee, S.R., & Plomin R. (2010). The nature (and nurture) of children's perceptions of family chaos. *Learning and Individual Differences, 20*(5), 549-553. doi: 10.1016/j.lindif.2010.06.005

Hanscombe, K.B., Haworth, C.M.A., Davis, O.S.P., Jaffee, S.R., & Plomin R. (2011). Chaotic homes and school achievement: A twin study. *Journal of Child Psychology and Psychiatry, 52(11)*, 1212-1220. doi: 10.1111/j.1469-7610.2011.02421.x

3.2 Introduction

Children who do better at school tend to come from homes that are quieter, more organized, and have a predictable routine, regardless of socio-economic status (Evans, 2006). Children living in the environmental confusion and unpredictability of high levels of family chaos (i.e. noise, disorder, and human traffic) have lower expectations, lack of persistence and a tendency to withdraw from academic challenge (Brown & Low, 2008). The level of family chaos affects early reading skill, even after considering other home environmental factors relevant to children's mastery of reading (Johnson, Martin, Brooks-Gunn, & Petrill, 2008). It would be reasonable to conclude that home chaos has an environmental effect on school outcomes, but there is a potential confound – genes.

We know that school achievement is heritable; genes explain about half of the variation in academic ability (Kovas et al., 2007; Petrill & Wilkerson, 2000). What about the home environment? With a genetically-sensitive design such as the twin design, we can explore the genetic and environmental contributions to a particular "environment". When twins are asked to rate the level of chaos in their home, identical twins who share all their genes are more similar in their experience than are non-identical twins, suggesting that genes influence chaos (Hanscombe, Haworth, Davis, Jaffee, & Plomin, 2010). Genetic influence on an environmental measure, known as gene-environment correlation (Jaffee & Price, 2007; Kendler & Eaves, 1986; Plomin et al., 1977), means that the environment is not a passive event that just happens to us - we elicit reactions and construct the environment around us in part due to our genetic propensities.

Nevertheless, it seems reasonable to assume that the effect of home chaos on school performance is mediated environmentally, for example, by way of its effect on children's ability to complete their homework due to interruptions and distractions. However, it has been difficult to assess the origins of the association between home chaos and school performance because child-specific measures of chaos are needed to investigate this question. Given that children's perception of chaos in their home shows genetic influence, it is possible that the association is, in part, mediated genetically in the sense that common genes affect both chaos and achievement. Using a genetically-sensitive design, it is possible to estimate the relative roles of genes and environments on the relationship between chaos and achievement. Knowing how nature and nurture work together in educationally relevant environments will inform the design of targeted interventions that could improve both child welfare and academic performance. In this study we used the twin design to investigate the genetic and environmental contributions to the link between child reports of family chaos and their teacher-reported school achievement.

Chaos is typically measured by parent reports

Parents' reports of chaos in the home predict children's behaviour problems (Coldwell, Pike, & Dunn, 2006), lower cognitive test scores (Hart et al., 2007; Petrill et al., 2004), and poor school performance (Brody & Flor, 1997). However, family-wide descriptions of the home environment provided by a parent cannot inform us about factors important for individual differences in the experiences of each child. That is, parent reports are not child-specific because they give just one account of the home for all the children living in it. This view of the home environment – that it is the same for all children living in it – is limited because it doesn't take into account the influence that each child exerts on their environment, including the genetic contribution to their experience through their behaviour. A child's environment has an impact on the child, but the child can also have an impact on their environment: there is a two-way relationship. Using measures of the experience of each individual within a genetically-sensitive design has revealed that people's genes affect their experience (Kendler & Baker, 2007; Plomin & Bergeman, 1991). For example, aspects of the home environment (e.g. parental involvement and responsivity) measured on each child in the home were used to show that genetic factors explain about a quarter of the relationship between these characteristics of the home and standardized test-assessed achievement (Cleveland, Jacobson, Lipinski, & Rowe, 2000). For this reason, it is important to assess child-specific experiences of environmental noise and disorganisation in the home, to supplement the family-wide measures. This approach allows the investigation of genetic and environmental influences on environmental confusion and routine at home, and its association with outcomes such as school achievement.

Using child-specific measures we have shown that genetic factors do explain a significant proportion of individual differences in children's perceptions of chaos in the home between the ages of 9 and 12 in the present sample (Hanscombe et al., 2010). Around 20% of the variation in experience of chaos is driven by heritable factors. What does it mean to say that an environment is heritable? Genetic influence on behaviours that affect exposure to, or experience of, the environment is called gene-environment (GE) correlation (Jaffee & Price, 2007; Kendler & Eaves, 1986; Plomin et al., 1977). There are three possible mechanisms: passive GE correlation happens because the environment children experience reflects their parents' genetically influenced behaviour – children inherit both their parents' genes and environment; evocative GE correlation is the result of people in the children's environment reacting to the children's genetically influenced behaviour or characteristics; active GE correlation arises when children

directly seek out, select and modify their environment to suit their genetic propensities. The "environment" is not something that simply happens to us. Instead, we seek environmental niches, modify our surroundings, select social interactions and engage other people in ways that are consistent with our genetic predispositions (Scarr & McCartney, 1983).

Given that both school achievement and home chaos show genetic influence, and that there is a correlation between them, we hypothesized that genetic factors would contribute to the association between chaotic homes and school achievement. We have measured school achievement at age 12; this age marks the transition to secondary school, the stage at which children are making choices about the subjects they will go on to study, as well as the age at which some children begin to drop out of school. Our aim was to assess the relative contribution of genetic and environmental factors to the association between chaos in the home and school achievement, using child-specific measures in a multivariate genetically sensitive twin design. We compared the resemblance of identical and non-identical twins to find the genetic and environmental sources of covariation between chaos in the home and school achievement. Because children rated chaos in their homes and teachers rated school achievement, we could rule out the confounding effects of having the same rater describe both environment and outcome.

3.3 Methods

3.3.1 Sample

The Twins Early Development Study (TEDS) sample is described in **Chapter 2**. Only the 1994 and 1995 birth cohorts were tested at age 9; all three birth cohorts were included in the 12-year wave of testing. The analyses in this chapter are based on a subsample of 7,394 twin pairs in which we had data for at least one twin in a pair. Of these, 2,337 complete pairs had data on chaos in the home at both 9 and 12 years; 3,040 complete pairs had data on school performance. In the analyses described below, we were able to make use of all available data using full-information maximum likelihood procedures.

3.3.2 Measures

The analyses in this chapter used child-rated environmental confusion in the home at age 9 and 12, the Confusion Hubbub and Order Scale (CHAOS; Matheny et al., 1995), and teacher-rated National Curriculum (NC) English, mathematics, and science at age

12. The child-rated home CHAOS and teacher-rated school achievement measures are described in **Chapter 2**.

3.3.3 Twin model fitting

We used the structural equation modelling package OpenMx (Boker et al., 2011) in R (R Development Core Team, 2011; www.R-project.org) to partition the covariation between child-reported CHAOS and teacher-reported school achievement into sources of genetic and environmental covariation. **Chapter 2** describes the univariate model and the extension to multivariate data. The specific multivariate model we fitted in this study derived one latent factor for home chaos, and one latent factor for school achievement. Given that our aim was to assess the origin of the association between middle childhood chaos and school achievement, combining measures in a factor analysis provided a neat way to summarize the data to address this aim.

Common pathway model

We fitted a common pathway model to the data. The common pathway model reduces the data in several measured variables to a specified number of latent phenotypic factors derived by maximum likelihood factor analysis. Both the common variation at the latent phenotypic factors, and the residual variation in each measured variable, is then partitioned into genetic (A), shared environmental (C) and non-shared environmental (E) sources of variation. We fitted a model with two factors: the first factor, "Chaos 9-12 yr", represented children's ratings of chaos in the home between age 9 and 12; the second factor, "School Ach. 12 yr", indexed school achievement at age 12 from teacher ratings of English, mathematics and science (Figure 3.1 summarizes the fitted model).

3.4 Results

3.4.1 Phenotypic analysis

The phenotypic correlation between child-reported CHAOS and teacher-reported school achievement was significant and negative (r_p = -0.26, 95% CI=-0.30 – -0.22), indicating that greater home chaos, as perceived by the child, is associated with worse performance in school. Table 3.1 shows the phenotypic correlations among chaos at age 9 and 12, and English, mathematics and science at age 12. English, mathematics and science were highly correlated at age 12 in the TEDS sample.

Table 3.1 Phenotypic correlations between family chaos and school achievement

		9-year	12-year			
		CHAOS	*CHAOS*	*English*	*Mathematics*	*Science*
year	*CHAOS*	1 N=3123				
12-year	*CHAOS*	0.43 N=2484	1 N=5503			
	English	-0.16 N=1249	-0.18 N=3205	1 N=3843		
	Mathematics	-0.17 N=1208	-0.16 N=3153	0.80 N=3738	1 N=3785	
	Science	-0.18 N=1201	-0.15 N=3143	0.82 N=3718	0.82 N=3721	1 N=3775

Note: N based on one randomly selected member from each twin pair.

Descriptive statistics and an analysis of variance by sex and zygosity for each of the five measures are presented in Table 3.2. The combined effect of zygosity and sex accounted for 1% or less of the variance for all five measures (R^2=0.00–0.01). For all subsequent analyses, the scores for males and females were combined.

Because similarity due to age and sex can contribute to phenotypic twin similarity and inflate estimates of C, the measures were corrected for the effects of age and sex, as is standard practice in the analysis of twin data (McGue & Bouchard, 1984). Age- and sex-corrected twin correlations by zygosity are shown in Table 3.3.

Along the diagonal in Table 3.3 are the within-trait twin correlations; below the diagonal are the cross-trait twin correlations. Doubling the difference between the MZ and DZ correlations within any trait gives an indication of the heritability. Within-trait across-twin correlations suggest modest heritability for family chaos (average h^2=0.22) and moderate heritability for teacher-rated NC achievement (average h^2=0.53). Genetic model-fitting analyses described below provided a more comprehensive use of the data, and the possibility to fit a multivariate model with quantifying fit statistics.

Table 3.2 Means, standard deviations, and analysis of variance by sex and zygosity

Assessment	Measure	Male		Female		MZ		DZ		ANOVA				
		M	SD	M	SD	M	SD	M	SD	Sex	Zyg.	Sex*Zyg.	R^2	N
9-year	*CHAOS*	0.77	0.39	0.71	0.38	0.74	0.39	0.75	0.38	<0.01	0.62	0.48	0.01	3123
12-year	*CHAOS*	0.69	0.34	0.64	0.34	0.67	0.34	0.67	0.34	<0.01	0.33	0.42	<0.01	5503
	English	4.28	0.96	4.43	0.88	4.32	0.91	4.34	0.95	<0.01	0.04	0.25	0.01	3843
	Mathematics	4.42	1.05	4.35	0.98	4.34	1.00	4.42	1.03	0.15	0.10	0.20	<0.01	3785
	Science	4.48	0.96	4.43	0.91	4.41	0.92	4.49	0.95	0.45	0.04	0.36	<0.01	3775

Assessment=age of assessment; M=mean; SD=standard deviation; MZ=monozygotic twins; DZ= dizygotic twins; Sex=p-value associated with sex effect on means; Zyg.=p-value associated with effect of zygosity on means; R^2=proportion of the total variance explained by sex and zygosity; ANOVA=Analysis of variance performed using one randomly selected member of each twin pair; N=number of randomly selected individuals (1 member of each twin pair) included in ANOVA analysis. Grey highlight indicates assessment at age 9.

Table 3.3 Twin correlations and cross-twin correlations by zygosity, and ACE parameter estimates for chaos and achievement at ages 9 and 12

			Twin 2							
			9-year	12-year				Twin model estimates		
			1.	*2.*	*3.*	*4.*	*5.*	**A**	**C**	**E**
Twin 1	9-year	*1. CHAOS*	**0.66/0.51**					0.26 (0.18–0.34)	0.39 (0.32–0.45)	0.35 (0.32–0.38)
	12-year	*2. CHAOS*	0.46/0.41	**0.63/0.56**				0.15 (0.09–0.21)	0.48 (0.43–0.53)	0.37 (0.34–0.39)
		3. English	-0.20/-0.14	-0.21/-0.13	**0.80/0.53**			0.56 (0.50–0.62)	0.25 (0.19–0.31)	0.19 (0.17–0.21)
		4. Mathematics	-0.20/-0.11	-0.17/-0.10	0.68/0.49	**0.76/0.53**		0.49 (0.43–0.56)	0.28 (0.21–0.34)	0.23 (0.21–0.25)
		5. Science	-0.23/-0.14	-0.19/-0.14	0.71/0.49	0.69/0.51	**0.76/0.57**	0.44 (0.38–0.50)	0.34 (0.28–0.40)	0.22 (0.20–0.24)

Along the diagonal in bold are the within-trait cross-twin correlations (MZ/DZ); below the diagonal are the cross-trait cross-twin correlations (MZ/DZ). A, C, and E= proportion of phenotypic variance attributable to genetic, shared environmental, and non-shared environmental factors respectively (95% confidence intervals shown in parentheses)

3.4.2 Genetic analyses

Variance components derived from univariate ACE models shown in Table 3.3, suggest that the difference between child-ratings of CHAOS at 9 and 12 years are not significant, as indicated by overlapping confidence intervals (CI). For example the A component at age 9 = 0.26 (95% CI = 0.18–0.34), and at age 12 = 0.15 (95% CI = 0.09–0.21)). As a measure of long-term chaos, we combined the two measures into a single latent factor in our model. Figure 3.1 summarizes the common-pathway ACE model fitted to CHAOS at age 9 and 12, and English, mathematics and science at age 12. The A, C, and E variance components for the family chaos and school achievement factors are consistent with the univariate estimates in Table 3.3.

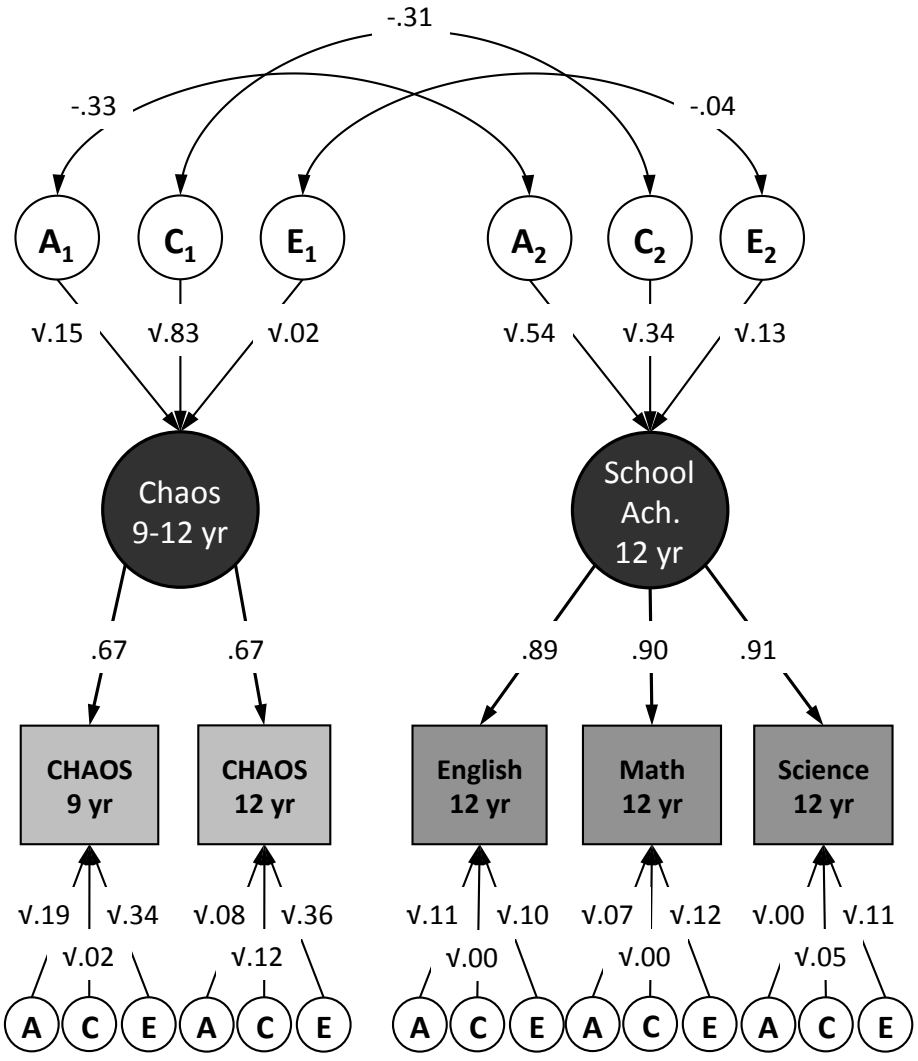


Figure 3.1 Chaotic homes and school achievement
The genetic (A), shared (C) and non-shared (E) environmental relationship between latent factors representing child-reported CHAOS in the home between ages 9 and 12 (Chaos 9-12 yr) and teacher-reported school achievement at age 12 (School Ach. 12yr)

Compared to the saturated model (-2lnL=88604.36, df=39938), and a saturated model with means and variances constrained to be equal across twin and zygosity (Δ-2lnL=55.26, Δdf=30, BIC=-133696.10), the common pathway model did not provide a significantly worse account of the data (Δ-2lnL=177.28, Δdf=99, BIC=-133942.50). Considering model fit, the common pathway model provided a parsimonious account of the relationship between chaos and school achievement (more detail in footnote to Table 3.4).

Table 3.4 shows the genetic and environmental correlations between the latent A, C and E components of variance. Both the shared environmental and the genetic correlation are significant and in the expected negative direction (r_C = -0.31, 95% CI = -0.43 – -0.19; r_A = -0.33, 95% CI = -1.00 – -0.10). These correlations indicated that both shared environmental and genetic factors associated with household chaos were also associated with school achievement.

The proportion of the phenotypic correlation explained by genetic and environmental factors – bivariate heritability and environmentality, respectively – is also shown in Table 3.4. The covariation between family chaos and school achievement is largely shared environmental in origin (63%), however genetic factors also explain a significant proportion (37%) of the phenotypic correlation. Non-shared environmental factors are unique to each trait and do not contribute to the association between experience of chaos and school achievement.

Table 3.4 Genetic and environmental correlations and bivariate estimates from the common pathway model

Measure	Correlations			
	r_A	r_C	r_E	r_P
CHAOS and Achievement	-0.33 (-1.00 – -0.10)	-0.31 (-0.43 – -0.19)	-0.04 (-1.00 – 1.00)	-0.26 (-0.30 – -0.22)
	Variance components of common factors			
	A	**C**	**E**	
CHAOS	0.15 (0.02 – 0.28)	0.83 (0.72 – 0.93)	0.02 (0.00 – 0.07)	
Achievement	0.54 (0.48 – 0.60)	0.34 (0.28 – 0.39)	0.13 (0.11 – 0.14)	
	Mediation of r_P			
	$a_x a_y r_A / r_P$	$c_x c_y r_C / r_P$	$e_x e_y r_E / r_P$	
CHAOS and Achievement	0.37 (0.12 – 0.62)	0.63 (0.41 – 0.84)	0.01 (-0.07 – 0.08)	

r_A= genetic correlation; r_C= shared environment correlation; r_E= non-shared environment correlation; r_P= phenotypic correlation; $a_x a_y r_A / r_P$= proportion of phenotypic correlation mediated by genetic factors; $c_x c_y r_C / r_P$= proportion of the phenotypic correlation mediated by shared environmental factors; $e_x e_y r_E / r_P$= proportion of the phenotypic correlation mediated by non-shared environmental factors; 95% confidence intervals in parentheses.

Model fit | **1.** ***Saturated***: -2LL=88604.36 (df=39938); **2.** ***Means/variances equal across twin and zygosity***: Δ-2LL=55.26 (Δdf=30), *p*-value<0.01, Akaike's information criterion (AIC)=-8723.61, Bayesian information criterion (BIC)=-133696.10; **3.** ***Common pathway***: Δ-2LL=177.28 (Δdf=99), *p*-value<0.01, AIC=8707.64, BIC=-133942.50

3.5 Discussion

Consistent with previous studies using parental reports, we confirmed that children's experience of household chaos was associated with how well they performed in school. The more disorganized, noisy and confusing children perceived their homes to be, the poorer their performance in school. Environmental factors that make siblings more alike – shared environments – explained the largest part of the chaos-school achievement relationship. This might be expected considering chaos is after all a measure of the home environment, but noteworthy nonetheless given the recent rethinking about the effects of the shared environment (Burt, 2009). Remarkably, however, over a third of the association between children's perceptions of family chaos and their teacher-rated achievement was accounted for by common genetic factors.

Environmental confusion at home predicts poor performance in school

Using a genetically-sensitive design made it possible to characterize the influence of home environment on school achievement. By controlling for genetic effects, we have shown that about two thirds of the association between the experience of home chaos and school achievement is due to shared environmental factors. What could these shared experiences be? Obvious candidates are the elements of the scale itself, such as the items "I have a regular bedtime routine", and "There is usually a television turned on somewhere in our home". A previous study has found that the elements of the household chaos scale that tap order and routine (as opposed to noise) predict early reading skill (Johnson et al., 2008). This is supported by evidence that children living in unstable chaotic homes withdraw from academic challenge – an effect partially mediated by disrupted and inconsistent sleep patterns (Brown & Low, 2008). Poor sleep hygiene – irregular sleeping patterns including difficulty getting to sleep, staying asleep and excessive tiredness – is predictive of poor school performance (Bruni et al., 2006). Another characteristic of the chaotic home, immoderate television watching, both directly predicts poor school performance and is significantly associated with disrupted sleep patterns (Li et al., 2007; Sharif, Wills, & Sargent, 2010; Van den Bulck, 2004). Of course, all of these "environments" are components of the heritable CHAOS scale, and are therefore likely themselves to be partly genetic in origin.

Genetically driven experience: G→E correlation

The surprising finding here, however, is that the association between chaos and school achievement is not entirely environmental in origin. A common set of genetic factors explains a third of the association between the children's heritable experience of

household chaos and their school achievement. But whose genes explain this relationship: the parents' or the child's? If parents who create chaotic home environments also do not encourage schoolwork or take an interest in homework because of their genetic predisposition, the GE correlation between home and school is passive; parental genes bridge the children's experience of environmental confusion at home and their school performance. That is to say, children get their genes as well as their genetically influenced environment from their parents.

However, passive GE correlation on its own is only one step removed from a scenario in which the child, a blank slate, is entirely at the mercy of their nurture. Given that by the age of 12 we might expect that children are having some input into their routine at home and commitment to school, it seems likely that the genetic link between home and school is at least in part due to the child's genes: an active (or reactive) child-driven process. For example, if children are particularly uncooperative about going to bed, turning off the television, or sitting down to meals, their parents may abandon attempts to impose structure on their environment. Similarly, the children's teachers may have to spend more time managing the children's behaviour than teaching them. Modifying the child's behaviour might allow parents to successfully implement regular routines and allow teachers to more effectively educate the child.

Another possibility is that some children become socially withdrawn as a way of filtering out the excess noise and confusion in chaotic homes (Evans, Rhee, Forbes, Mata Allen, & Lepore, 2000). Moreover, children in chaotic homes may be inappropriately extending this filtering to potentially beneficial social interactions and carrying it over to the classroom. If under the influence of genetic factors, a "tuning out" strategy could explain the common genetic link between household chaos and school achievement. Notably however, children's accounts of environmental confusion and disorder in the home predict school achievement even after accounting for problem behaviour and inattention in the present sample. The many potential behavioural mediators of the genetic link between chaotic homes and poor school performance are a rich area for exploration.

Finally, given that the present study measured perceptions of the environment by questionnaire, children's perceptions of the chaos in their homes could have been influenced by additional cognitive, affective and personality factors for genetic reasons. However, environments that are not measured by questionnaire are still found to be heritable (Plomin & Bergeman, 1991).

Implications and future directions

This study highlights the importance of supplementing family-wide measures with individual-specific measures for the study of factors relevant to school achievement, and developmental outcomes in general. Child-specific measures within the genetically informative twin design provide a means to quantify the contribution of the child's (and their parents') genes to their environment and its link to academic outcomes. To the extent that the link between chaotic homes and academic achievement is the result of shared experiences like unstructured television watching and irregular sleeping patterns, imposing structure will be beneficial. However, a common genetic contribution to the link between family chaos and low school performance suggests that additional targets for intervention may be found in as yet unidentified genetically driven behaviours of the child or their parents.

The present study focused on latent genetic and environmental factors linking family chaos and school achievement. However, underlying the genetic effect on experience of the chaotic home and its link to school achievement will be specific genetic variants. Isolating these variants and tracing out their effects, may tell us something about what behaviours or propensities underlie the heritable effect in children's experience of high levels of chaos in the home, and their poor performance in the classroom. If the common environmental component of the association between chaotic homes and school achievement represents a causative effect of home chaos on achievement - a possibility still to be tested - then imposing structure and order are obvious interventions. Future work to understand the shared environmental link between the experience of organization and routine at home and academic achievement will be informative about which routines and patterns are amenable to intervention. However, targeting behaviours like different children's perceptions and coping response when immersed in particular environments, may be a complementary strategy. Although the sample is representative of the UK population, the generalizability of the findings to populations in other countries, with different demographics, may be limited.

There are many potential background variables that could influence noise and routine at home and school achievement. These background variables are typically not twin-specific, but rather family-wide measures (e.g. socioeconomic status, SES) that could have an effect on the mean level of family chaos and achievement, as well as a moderating effect on both measures and the link between them. Because "correction" for obligatorily-shared measures would have the same effect on both twins in a family, and our goal was to understand individual differences, we focused on the link between

CHAOS as measured and school achievement in a genetically-sensitive design; that is, on the origins of the covariation within pairs in context.

The environments we find ourselves in give opportunities to act out our genetic predispositions, to re-shape our surroundings, and to select new environments and social interactions informed by our experience. We infuse the psychosocial environment of home with our particular blend of genetic preferences, and, as it turns out, some of the very same ingredients are evident in our school performance.

4 Socioeconomic Status and Children's Intelligence: A Gene-Environment Interaction Study†

4.1 Abstract

The environment can moderate the effect of genes – a phenomenon called gene-environment (GxE) interaction. Several studies have found that socioeconomic status (SES) modifies the heritability of children's intelligence. Among low-SES families, genetic factors have been reported to explain less of the variance in intelligence; the reverse is found for high-SES families. The evidence however is inconsistent. Other studies have reported an effect in the opposite direction (higher heritability in lower SES), or no moderation of the genetic effect on intelligence. Using 8716 twin pairs from the Twins Early Development Study (TEDS), we attempted to replicate the reported moderating effect of SES on children's intelligence at ages 2, 3, 4, 7, 9, 10, 12 and 14: i.e., lower heritability in lower-SES families. We used a twin model that allowed for a main effect of SES on intelligence, as well as a moderating effect of SES on the genetic and environmental components of intelligence. We found greater variance in intelligence in low-SES families, but minimal evidence of GxE interaction across the eight ages. A power calculation indicated that a sample size of about 5000 twin pairs is required to detect moderation of the genetic component of intelligence as small as 0.25, with about 80% power – a difference of 11% to 53% in heritability, in low- (-2 standard deviations, SD) and high-SES (+2 SD) families. With samples at each age of about this size, the present study found no moderation of the genetic effect on intelligence. However, we found the greater variance in low-SES families is due to moderation of the environmental effect – an environment-environment interaction. In a UK-representative sample, the genetic effect on intelligence is similar in low- and high-SES families. Children's shared experiences appear to explain the greater variation in intelligence in lower SES.

4.2 Introduction

A key construct for understanding the interplay between nature and nurture is genotype-environment (GxE) interaction: Genes can have different effects on a phenotype depending on the environment, and environments can have different effects depending

† Chapter adapted from Hanscombe, K.B., Trzaskowski, M., Haworth, C.M.A., Davis, O.S.P., Dale, P. S., & Plomin, R. (2012). Socioeconomic status (SES) and children's intelligence (IQ): In a UK-representative sample SES moderates the environmental, not genetic, effect on IQ. *PLoS ONE 7(2)*, e30320. doi: 10.1371/journal.pone.0030320

on genes (Kendler, 2011; Kendler & Eaves, 1986; Kendler & Gardner, 2010; Plomin et al., 1977; Rutter, 2007a; Rutter et al., 2006). Twin and adoption studies divide the population variation in a trait, e.g. height, into fractions attributable to genetic and environmental factors. The net genetic contribution to population variation, i.e., what makes one person different from another, can be expressed as a *heritability* statistic (h^2). However, if the effects of genes and environments do not simply "add up", i.e., if there exists a GxE interaction, heritability will depend on the level of the moderating environment.

The education, occupation and income of parents – indices of the families' socioeconomic status (SES) – have been found to moderate the heritability of their children's intelligence (Fischbein, 1980; Rowe, Jacobson, & van den Oord, 1999; Tucker-Drob, Rhemtulla, Harden, Turkheimer, & Fask, 2010; Turkheimer, Haley, Waldron, D'Onofrio, & Gottesman, 2003). The most recent twin study in this area reported significant moderation of the genetic component of children's intelligence (IQ, or general cognitive ability, g) by their parents' SES (Tucker-Drob et al., 2010): a GxE interaction in which heritability of intelligence *increased* with SES. Focusing on early cognitive development, the study found an increasing heritability of the change in IQ between the ages of 10 months and 2 years as a function of SES. Although SES was measured as a continuous variable, the magnitude of genetic moderation found suggested an increase in the heritability of IQ from 5% in low-SES families (-2 standard deviations, SD), to 50% in high-SES families (+2 SD).

It is reasonable to consider the possibility that heritability of intelligence is higher in higher SES families because such families seem likely to provide more opportunities to realize differences in children's genetic potentials. Conversely, in lower SES families, genetic differences might be restrained by poverty. Two theories, the *bioecological model* (Bronfenbrenner & Ceci, 1994) and the *environmental disadvantage hypothesis* (Scarr, 1992; Scarr-Salapatek, 1971), predict this direction of GxE interaction effect – greater genetic contribution to IQ in high-SES families. It is important to note that these theories make predictions about how children will react to the environment they experience in the "real" world, but the interactions reported are statistical and model-dependent (Kendler & Gardner, 2010). However appealing these reports may be, the moderating effect of SES is not consistently found. Several studies are either less conclusive (Scarr, 1981), find no moderation of the heritability of IQ by level of SES (Grant et al., 2010; van der Sluis, Willemsen, de Geus, Boomsma, & Posthuma, 2008), or find a trend in the opposite direction – greater heritability of children's IQ in lower-

SES families (Asbury, Wachs, & Plomin, 2005). Table 4.1 summarises the previous studies.

At least three design differences could play a role in the inconsistent findings: first, statistical GxE interaction has been investigated with a variety of methods with different power to detect an interaction; second, the age range investigated has covered infancy (10 months; Tucker-Drob et al., 2010) to adulthood (49 years; van der Sluis et al., 2008) – age groups which may not be directly comparable; third, the samples have been drawn from different demographics (representing different points on the SES distribution), or different countries in which socioeconomic status may be more or less a factor for children's intelligence. Given the large range of ages studied and the variety of SES indices used, the present study set out to replicate the reported increasing heritability with increasing SES at each of eight ages from early childhood to adolescence in a large UK-representative sample by systematically applying the continuous moderator model (Purcell, 2002). The continuous moderator model can be used to measure potential SES moderation of the genetic and environmental influences typically found by the classic twin design (effects on the variance components of IQ), after accounting for main effects of the measured environment (effects on the mean level of IQ). The twin model typically divides the trait variance into additive genetic (A) and shared environmental (C) influences that explain twin similarity, and non-shared environmental (E) influences that explain twin differences. Figure 4.1 and the method section describe how the continuous moderator model incorporates moderation of each of these terms.

For several power-related reasons, the moderation of environmental factors (in particular experiences shared by children reared together - *shared environment*, C) may be particularly important in explaining the inconsistent reports of GxE interaction. The continuous moderator model, used by several of the studies investigating GxE interaction, has demonstrated low power to distinguish between moderation of the genetic (A) and shared environmental (C) variance components. Purcell (2002) notes that specificity of the model is an issue – an observation made by the first study to report SES moderation of the heritability of IQ using this model (Turkheimer et al., 2003, p. 627): "Although the models indicate that the (β_A, β_C, and β_E) interactions jointly contributed significant variance to differences in (IQ), the models were less able to distinguish which of the individual interactions with A, C, and E was most important." (β_A, β_C, and β_E represent SES moderation of the genetic, shared, and non-shared environmental influences on IQ.) Nonetheless, the full model, which simultaneously takes into account all influences on a trait (moderated and un-

moderated, genetic and environmental), tends to recover the true parameter values in simulated data (Purcell, 2002). Regardless of which terms have been found to be significant and what decisions have been made about the presence or absence of particular moderating effects, because of the difficulty distinguishing between genetic and environmental moderation, estimates from the full model are preferable to those derived from a model in which individual terms have been fixed to zero.

A more general power consideration is that twin studies use the same information to estimate the genetic and shared environmental influence on a trait with the result that large samples are required to detect moderate shared environment (Burt, 2009). Moreover, the relative contribution of the shared environment to population variation in a variety of traits including IQ has been shown to decrease with age (Bergen, Gardner, & Kendler, 2007; Davis, Haworth, & Plomin, 2009; Haworth et al., 2009).

Using a large population-based United Kingdom (UK) twin sample, with longitudinal data on IQ from infancy to adolescence, we aimed to address these age, population, and power concerns. We set out to replicate the finding that SES modifies the genetic effect on children's intelligence with three indices of SES: parental education and occupation measured when the twins were 18 months old; the same composite of education and occupation measured when the twins were 7 years old; and family income measured when the twins were 9 years old. The possibility that the environmental disadvantage hypothesis applies to academic achievement and reading measures has also been studied. However, because achievement and reading are quite different from IQ, and studies of them are no more conclusive about the presence or absence of GxE interaction, in the present study we choose to focus on IQ only. Given the inconsistency in the literature, we hypothesized that we would not find consistent GxE interaction from childhood to adolescence.

Table 4.1 Gene-environment (GxE) Interaction Twin Studies of SES and Cognitive Measures

Country	Number of pairs	Age	Analytical model	SES measure	Cognitive measure	GxE *Higher h^2 in higher SES*	Heritability *Low SES - High SES*
UK (Asbury et al., 2005)	~1000 MZ, ~1000 DZ	4 years	Extended DF analysis	Parental education & occupation, and age of mother at birth of first child	Verbal factor	No	81% - 49% [a]
					Non-verbal factor	No	21% - 42% [a]
⊘Sweden (Fischbein, 1980)	94 MZ, 229 DZ	12 years	Stratification and inspection of twin correlations	Parental education & occupation	Verbal test (opposites)	Yes	48% - 76%
					Non-verbal test (logic)	Yes	21% - 96%
US (Grant et al., 2010)	1774 MZ, 1429 DZ	16-30 years	**Continuous moderator**	Parental education	Armed Forces Qualification Test	No	56% - 45%
US (Rowe et al., 1999)	1909 (176 MZ, 347 DZ, 795 full-sib, 269 half-sib, 118 cousins, 204 unrelated)	16 years	Extended DF analysis	Parental education	Peabody Picture Vocabulary (verbal IQ)	Yes	26% - 74%
⊘US (Scarr, 1981)	96 MZ, 69 DZ	10-15 years	Stratification and inspection of twin correlations	Parental education and occupation (census tract data)	Composite of 5 tests	No[e]	52% - 50%
⊘US	503 Black pairs, 275	6-18 years	Stratification and	Parental education and	Composite of 5	Yes	~0% - 27%

(Scarr-Salapatek, 1971)	White pairs [d]		inspection of twin correlations	occupation (census tract data)	tests	Yes	~0% - 40%
US (Tucker-Drob et al., 2010)	188 MZ, 562 DZ	10 months & 2 years	**Continuous moderator**	Parental education, occupation & income	Bayley Mental Development Index	Yes[c]	5% - 50%
US (Turkheimer et al., 2003)	114 MZ, 205 DZ	7 years	**Continuous moderator**	Parental education & occupation	WISC IQ	Yes	10% - 72% (based on twin correlations from a median split - not the continuous moderator parameters)
Netherlands (van der Sluis et al., 2008)	130 MZ, 144 DZ	26 & 49 years	**Continuous moderator**	Parental education	WAIS IQ	No	- [b]

⊘ indicates studies considered to have unreliable estimates based on small samples and/or non-standard zygosity assignment.

[a] 15% cut-offs for low and high SES (non-significant estimates for 25%, 33% and 50% cut-offs also reported in original paper)

[b] Not reported

[c] GxE significant for change in mental ability from 1 to 2 years

[d] No zygosity information; MZ and DZ twin correlations estimated from data (number of same- and opposite-sex twins pairs)

[e] Results averaged over 5 tests and 2 ethnic groups

4.3 Methods

4.3.1 Sample

The TEDS sample is described in **Chapter 2**. The present study investigated the moderating role of parental SES on children's intelligence or IQ (measured as general cognitive ability, *g*) at ages 2, 3, 4, 7, 9, 10, 12, and 14. Analyses were performed on a subsample of 8716 twin pairs (2996 monozygotic (MZ); 5720 dizygotic (DZ)) for whom we had IQ data for at least one twin at any age, and with at least one index of SES. Subsets of these data were assessed at each age. In the analyses described below, we used all the available data with full-information maximum likelihood procedures.

4.3.2 Measures

The analyses in this chapter used the general cognitive ability and socioeconomic status measures described in **Chapter 2**. The correlations between the eight IQ scores are shown in Table 4.2.

Table 4.2 Phenotypic correlations between IQ measures

Age	2	3	4	7	9	10	12	14
2								
3	0.64							
	(0.62 – 0.66)							
4	0.54	0.69						
	(0.52 – 0.56)	(0.67 – 0.71)						
7	0.25	0.26	0.30					
	(0.22 – 0.28)	(0.23 – 0.29)	(0.27 – 0.33)					
9	0.19	0.23	0.26	0.43				
	(0.15 – 0.23)	(0.19 – 0.27)	(0.22 – 0.30)	(0.40 – 0.46)				
10	0.20	0.21	0.23	0.42	0.56			
	(0.16 – 0.24)	(0.17 – 0.25)	(0.19 – 0.27)	(0.38 – 0.45)	(0.53 – 0.59)			
12	0.16	0.20	0.24	0.45	0.52	0.59		
	(0.12 – 0.20)	(0.16 – 0.24)	(0.21 – 0.27)	(0.42 – 0.48)	(0.49 – 0.55)	(0.56 – 0.62)		
14	0.17	0.19	0.19	0.44	0.47	0.51	0.61	
	(0.12 – 0.22)	(0.14 – 0.24)	(0.15 – 0.23)	(0.40 – 0.48)	(0.43 – 0.51)	(0.47 – 0.55)	(0.58 – 0.64)	

Correlations are based on one randomly selected member of each twin pair.

4.3.3 Statistical analysis

This chapter used structural equation modelling with twin data on IQ and SES. Twin model fitting is described in **Chapter 2**. Below is a description of an extension to the classic univariate ACE model to include moderation of the genetic and environmental variance components of the measured trait.

Univariate GxE model

We used the basic continuous GxE model (Purcell, 2002) to estimate the moderating effect of SES on IQ. This model allows the putative moderator to have a main effect on the trait, as well as a moderating effect on any or all of the residual A, C, and E components of the trait. Figure 4.1 summarizes the structural equation model for a single twin.

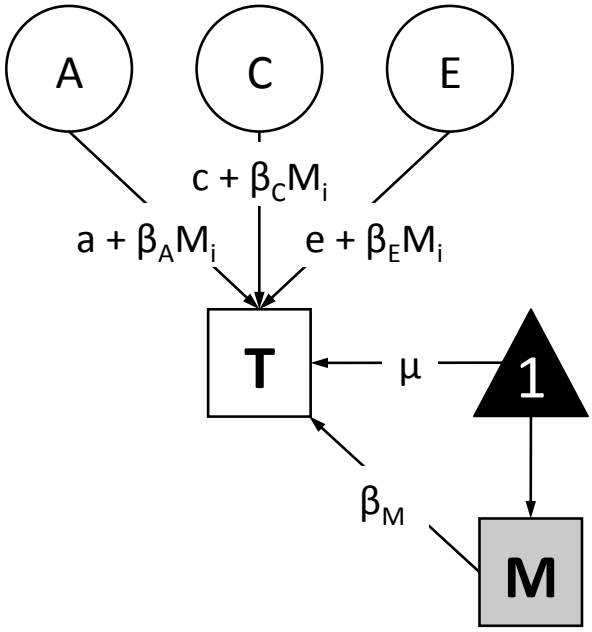


Figure 4.1 Continuous moderator model

The measured moderator (M) has a mediating or main effect (β_M) on the trait (T), as well as a potential moderating effect on the variance components of the residual (after the main effect has been partialled out). A, C, E = additive genetic, shared environmental, and non-shared environmental variance components (of residual T); a, c, e = un-moderated elements of genetic, shared, and non-shared path coefficients; β_A, β_C, β_E = moderated elements of the genetic, shared, and non-shared path coefficients; M_i = measured moderator level for the ith twin pair (both twins in a pair have the same value for obligatorily-shared moderators like SES); μ = the mean of the trait (T); 1 = the constant by which μ is multiplied, values of the trait are given by $1\mu + \beta_M$

The mean of trait (T) is given by $\mu + \beta_M M$, where β_M represents the phenotypic regression coefficient. The main effect of the measured environment (M) on the trait is assessed by estimating the value of β_M. In the present study the trait is IQ and the

moderator is SES. The residual variance in the trait is then partitioned into latent A, C and E components; the effect of each of these components on the trait is also expressed as a linear function of the moderator. For example, the additive genetic path coefficient is made up of both an un-moderated element (a) and a moderated element ($\beta_A M_i$), where M_i represents the family-wide moderator value for the *i*th twin pair. The significance of the moderating effect of SES is tested by asking whether β_A is significantly different from zero. Likewise, the C and E path coefficients (β_C and β_E respectively) indicate the moderating effect of SES on the shared and non-shared environmental components of the residual variance in IQ and their significance is tested against zero.

One limitation of the basic GxE model is that it cannot detect potential moderation of any genetic variation in common between the measured environment and the trait, and SES is phenotypically correlated with IQ. It is well established that "environmental" measures are to some extent heritable – a phenomenon known as genotype-environment correlation (Jaffee & Price, 2007; Kendler & Baker, 2007; Plomin & Bergeman, 1991; Plomin et al., 1977). In the present study however, SES is the same for both members of a twin pair (they are children in the same household), so that the extent of genetic influence on SES cannot be assessed in our twin design. Nonetheless, any unmeasured genetic variation in SES that also explains variation in IQ is partialled out as part of the basic GxE model (and included in the β_M term in the means model).

4.3.4 Power estimation

We used exact data simulation with the continuous moderator model to estimate power to detect GxE moderation, and in particular, moderation of the latent genetic (A) component. For all power calculations we used the MASS (Venables & Ripley, 2002) and OpenMx (Boker et al., 2011) packages, in the statistical computing environment R (www.R-project.org; R Core Development Team, 2011). For a range of sample sizes, effect sizes, a given genetic and environmental effect, a normally distributed moderator, and a specified moderation, we simulated data to which we fitted the basic continuous moderator model (Purcell, 2002) and obtained a fit statistic, -2lnL. We then fitted a (constrained) model with the moderator term dropped, and calculated the difference in fit, Δ-2lnL which distributes as chi-square. We repeated this procedure 1000 times for each set of initial values, and plotted the distribution of chi-square statistics. Given that we simulated a significant non-zero moderation then dropped this term in the

constrained model, the power to detect a particular effect size was the percentage of these replicates whose chi-square value was greater than 3.84 (the critical value for a 1df chi-square test, with significance value of p=0.05).

In order to generate outcome data under continuous moderation, we first sampled N random values for MZ pairs and N for DZ pairs from a standard normal distribution. This was our obligatorily-shared moderator (SES in the present study). Then, for each level of the moderator we drew a single pair from a multivariate standard normal distribution. The variance-covariance matrix for each randomly sampled pair was specified by (the covariance structure of the basic continuous moderator model),

MZ twin pairs

$$\begin{bmatrix} (a+\beta_A M_i)^2+(c+\beta_C M_i)^2+(e+\beta_E M_i)^2 & (a+\beta_A M_i)^2+(c+\beta_C M_i)^2 \\ (a+\beta_A M_i)^2+(c+\beta_C M_i)^2 & (a+\beta_A M_i)^2+(c+\beta_C M_i)^2+(e+\beta_E M_i)^2 \end{bmatrix}$$

DZ twin pairs

$$\begin{bmatrix} (a+\beta_A M_i)^2+(c+\beta_C M_i)^2+(e+\beta_E M_i)^2 & 0.5*(a+\beta_A M_i)^2+(c+\beta_C M_i)^2 \\ 0.5*(a+\beta_A M_i)^2+(c+\beta_C M_i)^2 & (a+\beta_A M_i)^2+(c+\beta_C M_i)^2+(e+\beta_E M_i)^2 \end{bmatrix}$$

where M_i was the value of the moderator for the *i*th twin pair; a, c, and e are the un-moderated path coefficients; and β_A, β_C, β_E, and are the moderated path coefficients.

4.4 Results

The means, standard deviations, and analysis of variance by sex and zygosity for IQ at every age are presented in Table 4.3. There was no indication of any differences by zygosity or sex. In general, we find no significant effect of sex for intelligence (Davis et al., 2008). For all subsequent analyses, we considered the IQ scores for males and females together.

Because similarity due to age and sex can contribute to phenotypic similarity and inflate estimates of C, as is standard practice in twin analyses (McGue & Bouchard, 1984), all verbal and nonverbal scales were corrected for the effects of age and sex before conducting twin analyses. Correlations between IQ measured at each age are presented in Table 4.2. Correlations are high between ages 2, 3, and 4 (0.54-0.69), and between ages 7, 9, 10, 12, and 14 (0.42-0.61); across these two age ranges, IQ correlations are more moderate (0.19-0.30).

Below, results are presented for continuous moderation analyses of IQ moderated by three indices of SES: *SES index 1*, Parental education and occupation acquired at first contact (age 18 months); *SES index 2*, Parental education and occupation at age 7; and *SES index 3*, Parental income at age 9. At the end of this section, we present results for a discontinuous analysis, i.e., IQ as a function of stratified SES.

Table 4.3 Means, standard deviations, and analysis of variance by sex and zygosity for IQ

	All		MZ		DZ		Female		Male		ANOVA			
Age	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*zyg*	*sex*	*zyg*sex*	R^2
2	16.77	6.84	16.24	6.93	17.04	6.77	17.87	6.76	15.63	6.73	<0.01	<0.01	0.01	0.03
3	20.05	6.75	19.62	7.05	20.30	6.57	20.88	6.49	19.18	6.91	<0.01	<0.01	0.56	0.02
4	11.20	2.51	10.98	2.58	11.32	2.47	11.34	2.43	11.05	2.60	<0.01	<0.01	0.56	0.01
7	9.63	2.23	9.49	2.20	9.71	2.25	9.66	2.21	9.60	2.26	<0.01	0.32	0.63	<0.01
9	18.31	3.50	18.14	3.50	18.42	3.49	18.26	3.50	18.37	3.49	0.03	0.46	0.22	<0.01
10	28.30	5.56	27.98	5.63	28.49	5.51	28.00	5.53	28.68	5.58	0.02	<0.01	0.67	0.01
12	22.84	4.16	22.56	4.15	23.00	4.16	22.65	4.17	23.08	4.14	<0.01	<0.01	0.15	0.01
14	27.26	4.05	27.10	4.01	27.36	4.08	27.30	4.02	27.21	4.10	0.11	0.53	0.16	<0.01

MZ = monozygotic; DZ = dizygotic; M = mean; SD = standard deviation; ANOVA = analysis of variance; zyg/ sex/ zyg*sex = p-value associated variance attributable to zygosity/ sex/ the zygosity*sex interaction; R^2 = variance explained by the ANOVA model

Table 4.4 Phenotypic correlations between SES and IQ

Age	Phenotypic correlation	N
SES index 1: parent education and occupation at 18 months		
2	0.08 (0.05 – 0.11)	5110
3	0.17 (0.14 – 0.20)	4657
4	0.18 (0.16 – 0.20)	6726
7	0.32 (0.30 – 0.35)	4703
9	0.31 (0.27 – 0.34)	2966
10	0.26 (0.22 – 0.30)	2419
12	0.33 (0.30 – 0.35)	3972
14	0.37 (0.34 – 0.40)	2592
SES index 2: Parent education and occupation at age 7		
7	0.29 (0.26 – 0.32)	4512
9	0.25 (0.22 – 0.29)	2610
10	0.22 (0.18 – 0.26)	2069
12	0.31 (0.28 – 0.34)	3588
14	0.33 (0.29 – 0.36)	2294
SES index 3: Family income at age 9		
9	0.23 (0.20 – 0.26)	2959
10	0.17 (0.13 – 0.21)	2097
12	0.23 (0.19 – 0.27)	1822
14	0.26 (0.21 – 0.31)	1339

N = number of pair-wise observations (based on one randomly selected member from each twin pair); 95% confidence intervals shown in parentheses. All correlations significant at $p < .001$

Table 4.5 Intra-class correlations (coefficients of twin similarity) for IQ by zygosity for twins with SES

Age	ICC (95% CI)		N	
	MZ	*DZ*	*MZ*	*DZ*
SES index 1				
2	0.91 (0.90-0.92)	0.76 (0.75-0.77)	1677	3315
3	0.95 (0.95-0.96)	0.84 (0.82-0.85)	1200	2374
4	0.89 (0.88-0.90)	0.71 (0.69-0.73)	1238	2460
7	0.68 (0.65-0.71)	0.49 (0.46-0.52)	1264	2284
9	0.75 (0.72-0.78)	0.58 (0.54-0.61)	863	1495
10	0.73 (0.69-0.76)	0.50 (0.45-0.54)	685	1197
12	0.66 (0.62-0.70)	0.42 (0.37-0.47)	777	1242
14	0.60 (0.54-0.65)	0.37 (0.31-0.43)	563	894
SES index 2				
7	0.66 (0.64-0.69)	0.49 (0.46-0.52)	1614	2851
9	0.75 (0.72-0.77)	0.57 (0.53-0.60)	964	1595
10	0.74 (0.70-0.77)	0.50 (0.45-0.54)	744	1281
12	0.66 (0.62-0.69)	0.43 (0.39-0.46)	1310	2133
14	0.60 (0.55-0.64)	0.35 (0.30-0.40)	812	1201
SES index 3				
9	0.76 (0.73-0.78)	0.58 (0.55-0.61)	1084	1816

10	0.73 (0.69-0.76)	0.49 (0.44-0.53)	773	1285
12	0.65 (0.60-0.69)	0.42 (0.37-0.46)	685	1072
14	0.61 (0.55-0.66)	0.33 (0.27-0.40)	510	712

ICC (95% CI) = intra-class correlation coefficient (95% confidence interval); MZ = monozygotic; DZ = dizygotic; N = number of complete cases, i.e. number of pairs in which both twins have IQ data. NB. The formal estimation of variance components, using full information maximum likelihood structural equation modelling, included data from incomplete cases.

Table 4.6 Genetic and environmental parameter estimates for IQ moderated by SES - full continuous moderator model

	Parameters	*Age*							
		2	*3*	*4*	*7*	*9*	*10*	*12*	*14*
SES index 1	*a*	0.52	0.45	0.54	0.60	0.60	0.67	0.69	0.67
	c	0.78	0.84	0.74	0.46	0.57	0.47	0.30	0.01
	e	0.31	0.23	0.35	0.57	0.48	0.51	0.56	0.61
SES index 1 moderation of the genetic and environmental components of IQ	β_A	0.01	0.00	-0.03	0.03	0.01	-0.10	0.02	-0.01
	β_C	-0.04	0.01	-0.03	-0.04	-0.06	0.05	-0.05	0.19
	β_E	-0.01	0.00	0.01	-0.01	0.00	0.02	-0.01	0.00
	β_M	0.09	0.17	0.17	0.31	0.29	0.24	0.32	0.37
SES index 2	*a*				0.59	0.56	0.66	0.71	0.66
	c				0.47	0.60	0.49	0.24	0.17
	e				0.57	0.49	0.50	0.56	0.62
SES index 2 moderation of the genetic and environmental components of IQ	β_A				0.04	0.01	-0.01	0.01	-0.07
	β_C				-0.06	-0.06	-0.05	-0.09	0.13
	β_E				0.00	0.00	0.00	-0.01	0.02
	β_M				0.28	0.24	0.21	0.31	0.32
SES index 3	*a*					0.59	0.66	0.76	0.70
	c					0.60	0.50	0.16	0.20
	e					0.48	0.51	0.55	0.61
SES index 3 moderation of the genetic and environmental components of IQ	β_A					-0.01	-0.04	-0.02	0.05
	β_C					-0.05	-0.04	-0.16	-0.16
	β_E					0.00	0.01	0.00	-0.03
	β_M					0.23	0.17	0.25	0.29

4.4.1 SES index 1: Parental education and occupation at contact (age 18 months)

Phenotypic correlations between SES (a unit-weighted composite of parental education and occupation acquired at contact) and IQ are presented in Table 4.4. From infancy to adolescence we found an increasing correlation between SES and IQ, from .08 to .37, as expected from the literature. A graphical summary of the continuous moderation analyses is presented in Figure 4.2. This visual summary of the SES moderation of IQ across the eight ages suggests three conclusions. First, the total variation in IQ changed with SES level: at ages 2, 4, 9, and 10 we found greater variance in low-SES families; at ages 3, 7 and 12 only small differences; and at age 14, greater variance at both ends of the SES distribution than around the mean.

Second, except for a large drop in the A contribution with increasing SES at age 10, we found no substantial change in A across the eight ages: little or no change at ages 2, 3, 9, and 14, and small increases with increasing SES at ages 7 and 12. This suggests no consistent GxE interaction. Moreover, it should be noted that the only substantial GxE interaction at age 10 is in the opposite direction from that suggested in the literature: heritability is greater in low-SES families.

Third, differences in C were somewhat more consistent: at ages 2, 4, 7, 9, and 12, there was a drop in C with increasing SES. This suggests the presence of greater C in low-SES families.

Intra-class correlations (coefficients of twin similarity; Shrout & Fleiss, 1979) are presented in Table 4.5. Doubling the differences between the MZ and DZ correlations provides a rough estimate of the heritability of IQ. These estimates show the expected pattern of increasing heritability with age, from 30% at age 2 to 46% at age 14. The extent to which MZ correlations are not explained by heritability provides an estimate of shared environment. These estimates show the expected pattern of decreasing shared environmental influence with age, from 61% at age 2 to 14% at age 14

Table 4.6 shows the parameter estimates at each age derived from the full GxE interaction model with full information maximum likelihood estimation. Squaring the path estimate and dividing by the sum of the squared paths gives the standardized variance component: e.g., heritability or $h^2 = (a + \beta_A M)^2 / ((a + \beta_A M)^2 + (c + \beta_C M)^2 + (e + \beta_E M)^2)$. (A formal test of the significance of each moderated term in the interaction model, at each age, is shown in Supplementary Table C.1, **Appendix C**.)

At ages 3, 7, and 12 the best-fitting model, as indicated by AIC, was one with no moderation of either genetic or environmental components. At age 2, the best fitting model, as indicated by AIC, was one with no genetic moderation. The p-value showing model fit for individually dropped parameters suggests only moderation of the C term is

significant (β_C = -.04). At age 4, the best-fitting model was one with moderation of both A and C terms (β_A = -.03, β_C = -.03). At age 9, moderation of only the C term was significant (β_C = -.06). Age 10 showed a significant decrease in A with increasing SES (β_A = -.10). At age 14, the best fitting model, as indicated by AIC, suggested significant moderation of the C term (β_C = -.19)

All significant genetic and environmental moderation was in the direction of greater variance in IQ explained at lower levels of SES.

.

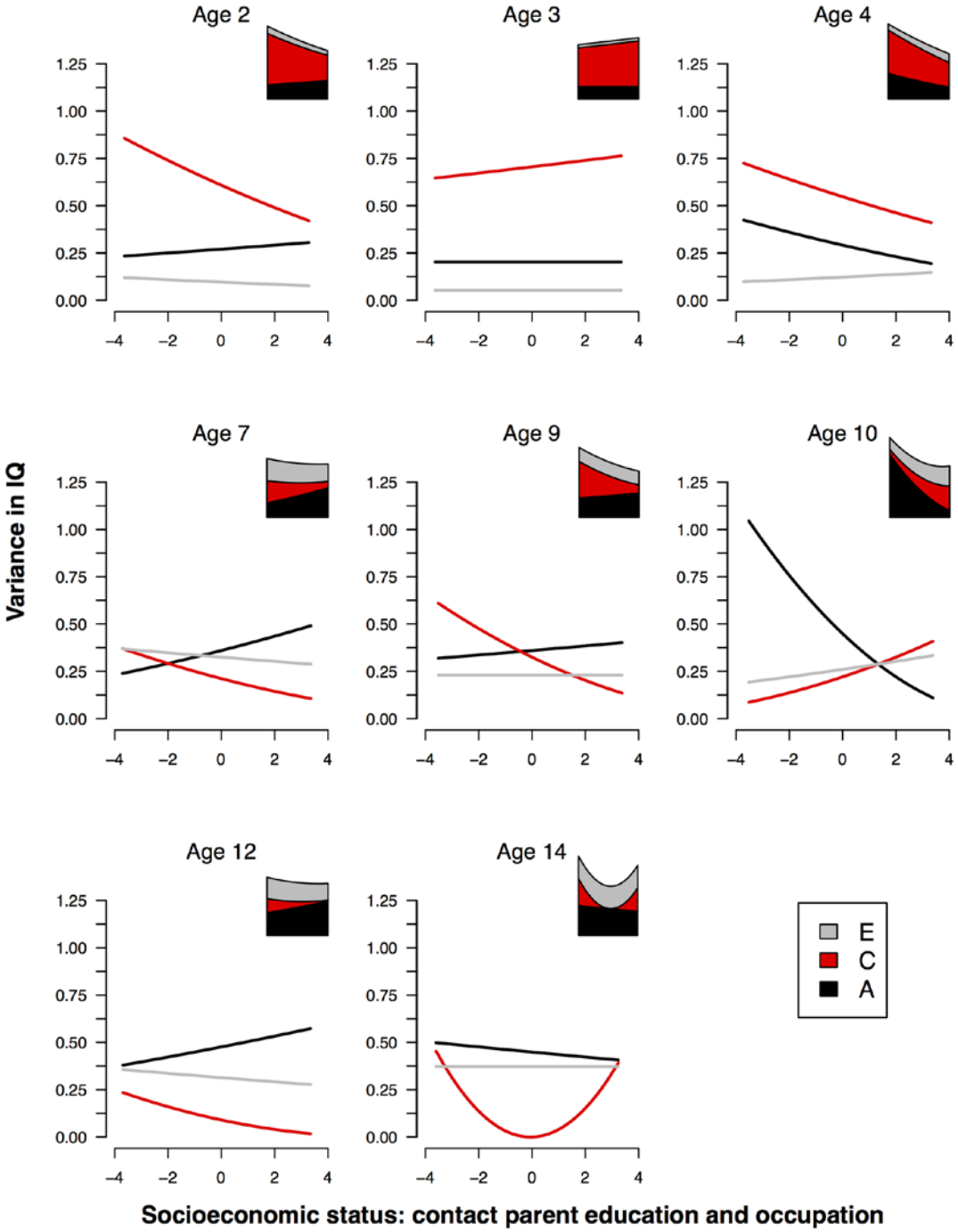


Figure 4.2 Unstandardized IQ variance components by SES index 1
Unstandardized genetic and environmental variance components for IQ as a function of first contact parental education and occupation (SES index 1). To the top right of each graph is a stacked plot showing the total variance in IQ as a function of SES.

4.4.2 SES index 2: Parental education and occupation at age 7

Phenotypic correlations between SES (a unit-weighted composite of parental education and occupation assessed at age 7) and IQ show a similar pattern of increasing correlation with age, and are in the range 0.22 - 0.33 (Table 4.4). Intra-class correlations for twins with data on 7-year parental education and occupation are presented in Table 4.5. Rough estimates of variance components calculated by doubling the differences between the MZ and DZ correlations are similar to estimates for twins with SES index 1 data.

A graphical summary of the continuous moderation analyses is presented in Figure 4.3. Inspection of the visual summary of the interaction analyses reveals a consistent increase in the effect of the shared environment on IQ with decreasing SES, coupled with an increase in the variance in IQ in low-SES families - most notably at ages 9, 10 and 12.

Table 4.6 shows the parameter estimates at each age derived from the full GxE interaction model with full information maximum likelihood estimation. (A formal test of the significance of each moderated term in the interaction model, at each age, is shown in Supplementary Table C.2, **Appendix C**.)

At ages 7 and 14, the best fitting model as indicated by AIC was one with no moderation of genetic or environmental components of intelligence. At all other ages (9, 10, and 12) the best fitting model included only moderation of the C component (β_C = -.06, β_C = -.05, and β_C = -.09 respectively).

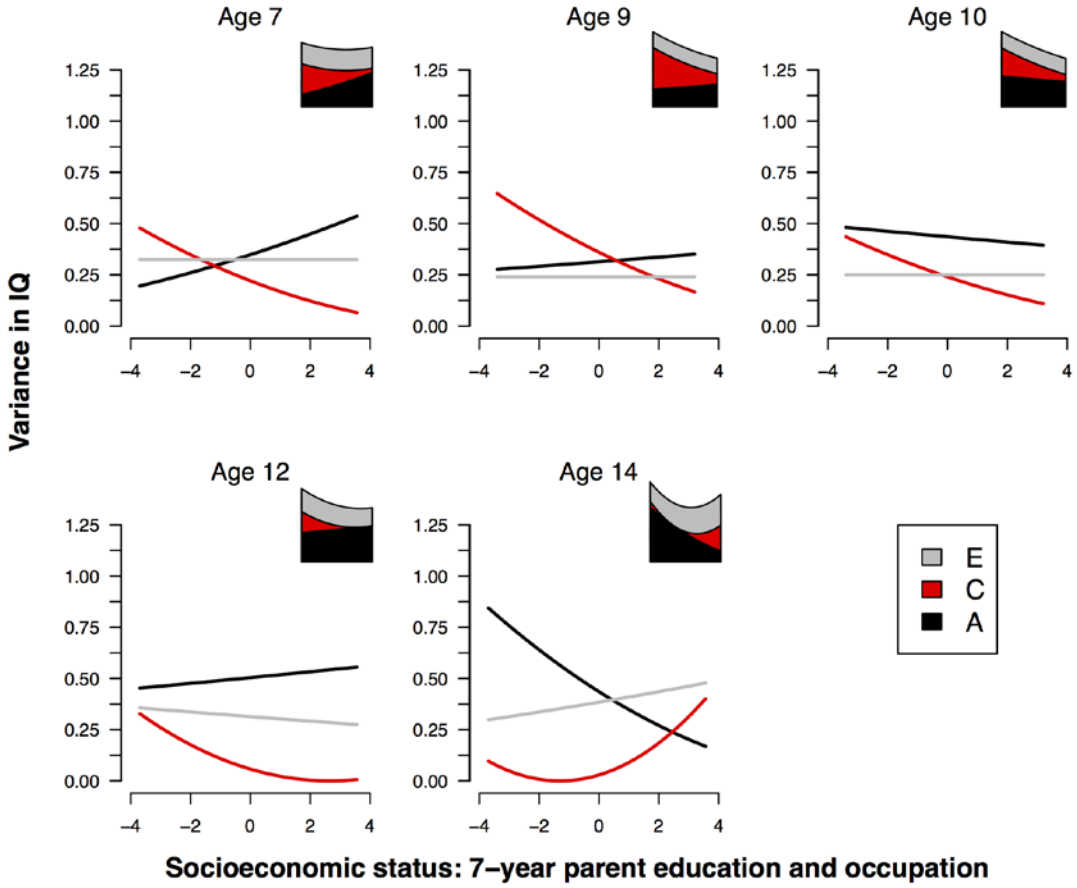


Figure 4.3 Unstandardized IQ variance components by SES index 2
Unstandardized genetic and environmental variance components for IQ as a function of 7-year parental education and occupation (SES index 2). To the top right of each graph is a stacked plot showing the total variance in IQ as a function of SES.

4.4.3 SES index 3: Parental income at age 9

Phenotypic correlations between SES (family income at age 9) and IQ are presented in Table 4.4. As for SES indices 1 and 2, we find a pattern of increasing correlation between IQ and SES index 3 with age, with correlations in the range 0.17 - 0.26. Intra-class correlations by zygosity for twins with 9-year family income data are presented in Table 4.5. Again, rough estimates of variance components found by doubling the differences between the MZ and DZ correlations are similar to estimates for twins with SES index 1 and 2 data.

A graphical summary of the continuous moderation analyses at ages 9, 10, 12 and 14 is presented in Figure 4.4. As for the other indices of SES, the visual summary of the interaction analyses reveals an increase in the variance in IQ in low-SES families, an increase in the effect of the shared environment on IQ with decreasing SES, and inconsistent differences in genetic effect.

Table 4.6 shows the parameter estimates at each age derived from the full GxE interaction model with full information maximum likelihood estimation. (A formal test of the significance of each moderated term in the interaction model, at each age, is shown in Supplementary Table C.3, **Appendix C**.)

At all ages (9, 10, 12, and 14), the best fitting model as indicated by AIC includes (in addition to the main effect of SES) only moderation of the shared environmental component (β_C = -.05, β_C = -.04, β_C = -.16, and β_C = -.16 respectively).

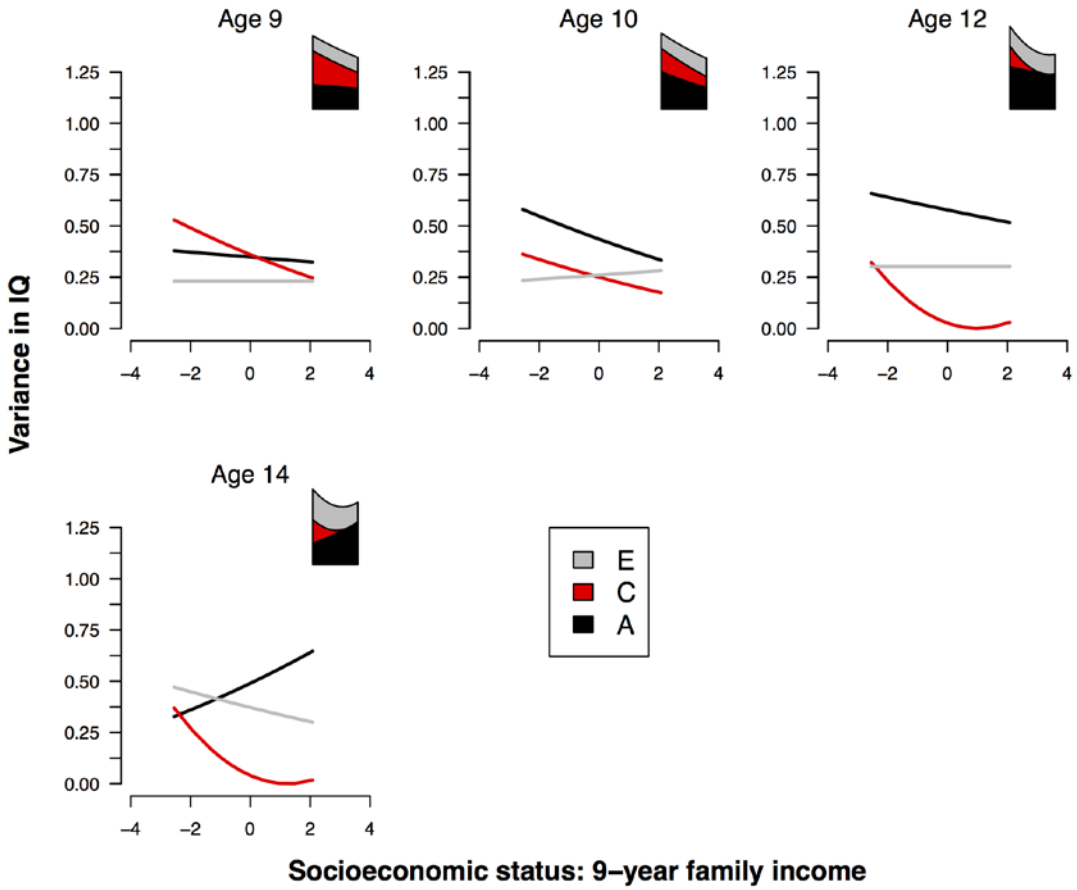


Figure 4.4 Unstandardized IQ variance components by SES index 3
Unstandardized genetic and environmental variance components for IQ as a function of 9-year family income (SES index 3). To the top right of each graph is a stacked plot showing the total variance in IQ as a function of SES.

4.4.4 What is the most parsimonious account of the moderating effect of SES?

Summarized in Table 4.7 are the best-fitting models at each age, for each of the three indices of SES. The best-fitting model as indicated by AIC is marked. It should be noted that at each age, in testing the significance of each parameter in the model, AIC suggests very little difference between each of the accounts of the data (see last column in Supplementary Table C.1, Supplementary Table C.2, and Supplementary Table C.3,

Appendix C). Accepting this small difference, three results are worth highlighting. First, the only significant GxE interaction with SES index 1 found for IQ at age 10 (higher heritability in low-SES families) disappears with the more proximal measures of SES at ages 7 and 9. Second, the best fitting model indicates no interaction of any kind at three ages for SES index 1 (ages 3, 7, and 12), and for two ages for SES index 2 (ages 7 and 14). Third, moderation of the shared environmental component of IQ is indicated at four of eight ages for SES index 1, three of five ages for SES index 2, and four of four ages for SES index 3. Thus, the most consistent result across ages and across the three indices of SES is moderation of the influence of shared environment on children's intelligence - an *environment*-environment interaction.

Table 4.7 Summary of best fitting model (as indicated by AIC) for three indices of SES

§Best fitting model	SES index 1								SES index 2					SES index 3			
	2	*3*	*4*	*7*	*9*	*10*	*12*	*14*	*7*	*9*	*10*	*12*	*14*	*9*	*10*	*12*	*14*
ace β_A β_C β_E β_M																	
$\beta_A = 0$	O																
$\beta_C = 0$																	
$\beta_E = 0$			O														
$\beta_A = \beta_C = 0$																	
$\beta_A = \beta_E = 0$					⊙			⊙		⊙	⊙	⊙		⊙	⊙	⊙	⊙
$\beta_C = \beta_E = 0$						*											
$\beta_A = \beta_C = \beta_E = 0$		☒		☒			☒		☒				☒				

§Best fitting model as indicated by Akaike's information criterion (AIC). For example, $\beta_A = 0$ means significant moderation of C and E; $\beta_A = \beta_C = 0$ means significant moderation of β_E only; $\beta_A = \beta_C = \beta_E = 0$ means no moderation of A, C, or E variance components. SES index 1 = a composite of parental education and occupation acquired when the TEDS twins were 18 months old; SES index 2 = a composite of parental education and occupation acquired when the TEDS twins were 7 years old; SES index 3 = family income measured when the TEDS twins were 9 years old; a, c, e = un-moderated genetic, shared, and non-shared environmental path coefficients; β_A, β_C, β_E = moderated genetic, shared, and non-shared environmental path coefficients; β_M = main effect of moderator on mean of IQ; O = includes C moderation; ⊙ = C moderation only; * = A moderation only; ☒ = no moderation.

4.4.5 *Performance of the continuous moderator model with simulated data*

In order to estimate power of the continuous model to detect genetic moderation under conditions of genetic moderation only, we set parameters as follows; $a = c = e = 1$; $\beta_C = \beta_E = 0$. We simulated a range of genetic moderation (β_A) between 0.05 and 0.50. We generated 1000 replicates for a range of sample sizes, with equal numbers of MZ and DZ twin pairs. Figure 4.5 shows that a sample size of about 2500 pairs of MZ and DZ twins each is needed to detect an effect size (genetic moderation) of between 0.25 and 0.30 with 80% power. A genetic moderation of 0.25 translates to a difference in heritability of about 11% at -2SD of the moderator to about 53% at +2SD of the moderator (at the simulated parameter values).

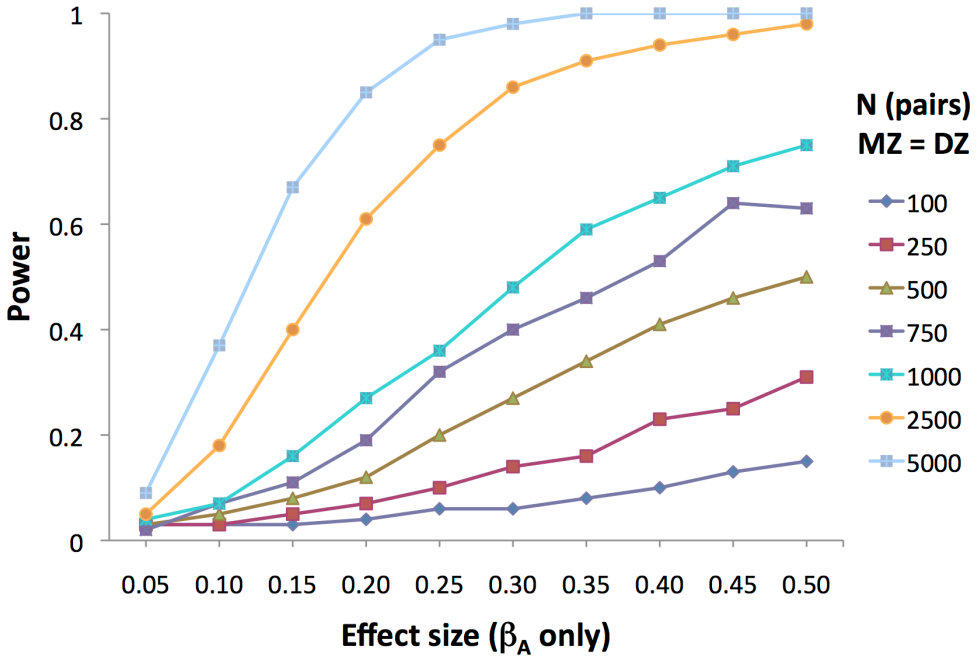


Figure 4.5 Power to detect GxE when only genetic moderation is simulated
Power to detect the presence of a genetic moderation with the continuous moderator model (genetic moderation only simulated). Equal number of MZ and DZ twin pairs simulated (N = 500, means 500 MZ and 500 DZ pairs). N = sample size; MZ = monozygotic; DZ = dizygotic; β_A = moderated element of genetic path coefficient

Second, to explore how the model performed when moderation of all three terms is present, we simulated data with parameters set as follows: $a = c = e = 1$; and, $\beta_C = \beta_E = \beta_A$ = a range of values between 0.05 and 0.50. Again, we generated 1000 replicates for each sample and effect size, and estimated the model's ability to detect the presence of the genetic moderation only, i.e. a 1df test. Figure 4.6 is more informative about model performance than power per se. With equal moderation of the genetic, shared, and non-

shared environmental components, above a moderation of 0.30 (moderated coefficient 30% of the un-moderated coefficient, i.e., $\beta_A = 0.30^*a$) the model does not perform well when assessing the significance of just the genetic moderation (a 1df test). Purcell's (2002) simulations suggest that this would also be the case when testing only moderation of the shared environment.

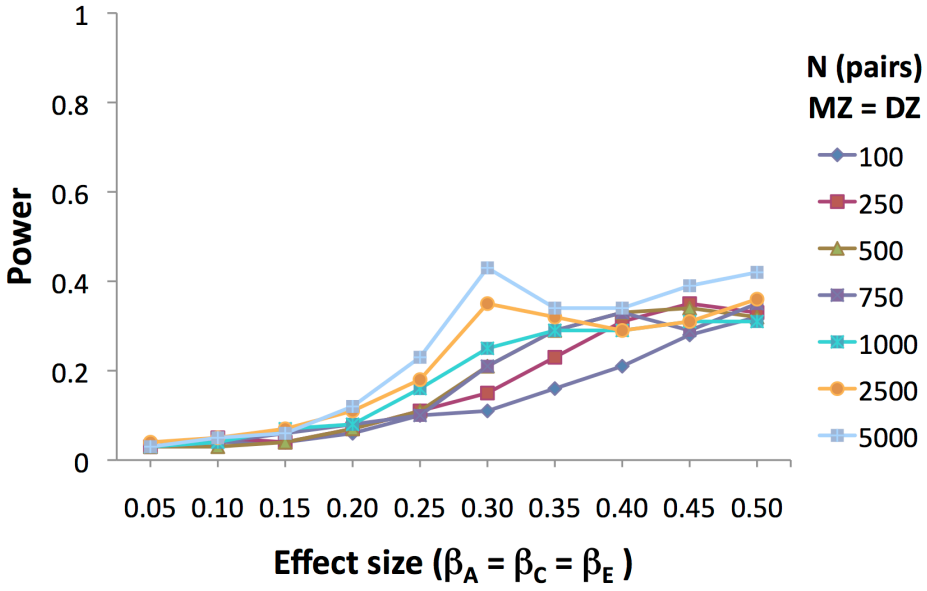


Figure 4.6 Power to detect GxE when genetic and environmental moderation are simulated
Power to detect the presence of a genetic moderation with the continuous moderator model (equal genetic, shared and non-shared environmental moderation simulated). Equal number of MZ and DZ twin pairs simulated (N = 500, means 500 MZ and 500 DZ pairs). N = sample size; MZ = monozygotic; DZ = dizygotic; β_A, β_C, β_E = moderated elements of genetic, shared environmental, and non-shared environmental path coefficients

The simulations summarized in Figure 4.5 and Figure 4.6 perhaps illustrate the best and worst case scenario for the continuous moderator model. In the case of genetic moderation only, the model performs well, and increasing sample size increases power to detect genetic moderation. However, as noted by Purcell (2002), the model does not do well at distinguishing between genetic and shared environmental moderation when both are present, and one proceeds by testing one term at a time.

4.4.6 Discontinuous analysis of low-SES versus high-SES groups

Because several studies explored GxE interaction by comparing ACE estimates, or twin correlations, in low-and high-SES groups (see Table 4.1), we compared results of our continuous moderator analysis with the results for a discontinuous analysis. We estimated variance components in low- and high-SES groups, and tested whether these

could be equated – a *heterogeneity* analysis. Although these discontinuous analyses have usually ignored variance differences between groups by using twin correlations (which standardize variances between groups), heterogeneity analysis provided components of raw variance which we present along with the standardized estimates to highlight the difference between components of raw and standardized variance.

We present results for age 9 IQ, which showed the most consistent C interaction across the three SES indices. We split the sample into quartiles and compared the variance components derived for the top and bottom 25% of the SES distribution. In Figure 4.7, rows 1, 2, and 3 show age 9 IQ components as a function of SES indices 1, 2, and 3 respectively; in the left column are the components of raw variance, in the right hand column are the standardized estimates. The unstandardized estimates show greater total variance for the low-SES groups and this excess variance can be attributed to greater shared environment for the low-SES group. Shared environment is significantly greater in the low-SES group for SES indices 1 (low-SES C=.40 [95% confidence interval (CI)=.27-.53]; high-SES C=.19 [95% CI=.08-.31]) and 2 (low-SES C=.48 [.34-.62]; high-SES C=.25 [.13-.37]). Equating C in low- and high-SES groups significantly reduced model fit (SES index 1: Δ-2lnL=5.45, Δdf=1, ΔAIC=3.45, p=.02; SES index 2: Δ-2lnL=3.572, Δdf=1, ΔAIC=5.57, p=.02). In contrast, heritability estimates are identical for the low- and high-SES groups. The standardized estimates also show greater C in the low-SES group for SES indices 1 and 2; however, standardizing the variance components in the two groups artificially increases estimates of A in the high-SES group.

In summary, this discontinuous analysis of low-SES versus high-SES groups generally confirms the results of our continuous moderator analysis for the largest interaction effect, despite a great loss in power for the discontinuous analysis (Purcell, 2002).

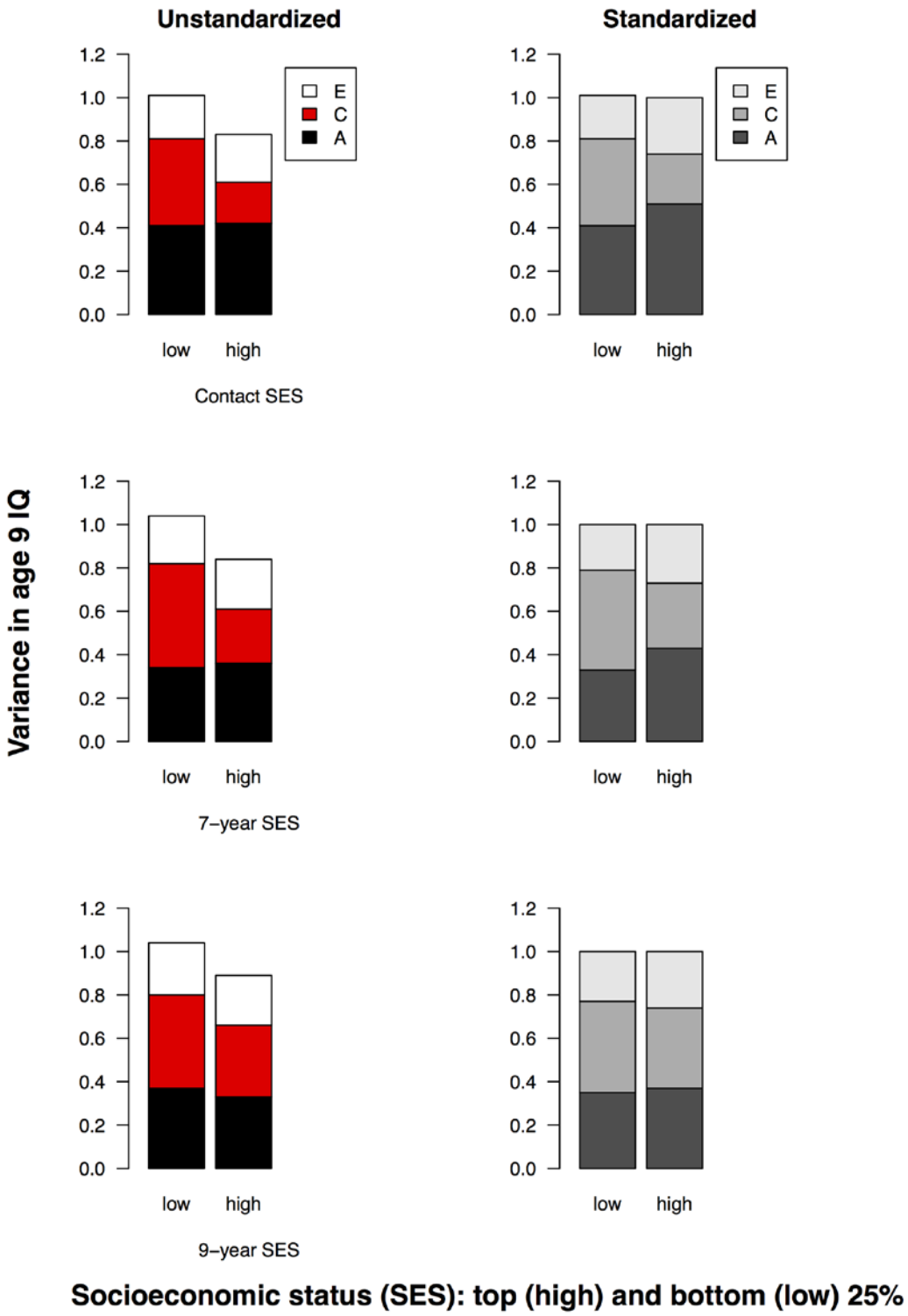


Figure 4.7 Age 9 IQ in low- and high-SES groups – heterogeneity analysis
Variance components of 9-year IQ in low- and high-SES families (bottom and top 25% of SES distribution). Top, middle, and bottom rows show IQ as a function of 18-month, 7-year, and 9-year SES respectively (SES indices 1, 2, and 3). In the left column are the unstandardized estimates; in the right column are the standardized estimates.

4.5 Discussion

We attempted to replicate the finding that parental SES moderates the heritability of children's intelligence, with a greater genetic contribution to IQ in high-SES families compared to low-SES families. In a large UK-representative sample, we did not find evidence for the presence of such a gene-environment interaction across childhood and adolescence. At only one of the eight ages, age 10, did we find a significant moderation of the genetic contribution to IQ. However, the GxE interaction was in the opposite direction from that predicted by the environmental disadvantage hypothesis, and moreover, was not significant with a more proximal measure of parental education and occupation. Instead, using three different indices of SES, at eight ages from infancy through adolescence the emerging pattern appears to be one of *environment*-environment interaction rather than *gene*-environment interaction: shared experiences explain more of the variance in children's performance on IQ tests in more disadvantaged backgrounds.

Environmental moderation of shared experiences

How can the present finding of SES moderation of the shared environmental effect on IQ, be reconciled to the reports of SES moderation of the genetic component of IQ? An increase in the contribution of C in lower-SES families would seem to require a reduction in the relative contribution of A because environmental and genetic variance components are complementary, and explain 100% of the variance. However, this is only the case for standardized components that are forced to sum to 100% regardless of total variance differences. Our most consistent finding is that total IQ variance is greater in lower-SES families, which must be caused by greater A, C, or E components of variance in lower-SES families. Although the power demands are daunting to disentangle A and C sources of this increased variance in lower-SES families, data from our large sample suggests that the source is C rather than A. The genetic effect does not differ for low- and high-SES groups using unstandardized estimates (A, C, and E) that take into account the greater total variance in the low-SES group, but the relative contribution of genes – heritability or $h^2 = A/(A+C+E)$ – is lower in low-SES families because the shared environmental effect increases.

Children from low-SES families face many physical and psychosocial environmental handicaps for their cognitive development (Evans, 2004). For example, low-SES children are read to less, have fewer books, less access to computers, and tend to watch more television. Parents tend to be less responsive to children in low-SES families, participate less in their children's school activities, and are more authoritarian. Children from more disadvantaged backgrounds tend to experience more instability,

come from noisier, more crowded homes, and live in disadvantaged neighbourhoods with poorer facilities and inferior schools (for a recent review of the correlates of low-SES see Evans, 2004). To the extent that children growing up together experience these environments similarly, their cumulative effects are captured by the C component in a twin model; experiences such as these seem likely to contribute to the observed greater variation in the cognitive ability performance of children from low-SES families.

Sampling, age differences, and power to detect C

What factors contribute to the inconsistency in the literature (Table 4.1)? We suggest three possibilities: sampling, age range, and power to distinguish moderation by A and C. First, a general concern is that sampling from different ranges of a putative moderator distribution (low, medium, or high levels), can lead to different conclusions about the presence or absence of a GxE interaction (Eaves, 2006). Factors that are additive across the entire range of a moderator may appear to be interacting within small windows at the extremes of a dose-response curve (Kendler, 2011). However, it is also possible a different gene-environment dynamic exists at the extremes of SES (Scarr, 1992). Children from average- and high-SES families receive adequate educational resources, parent-child interaction, and orderly homes within safe neighbourhoods. However, below a certain threshold of environmental quality, children's experience could begin to have a negative impact on their cognitive ability. For example, the National Collaborative Perinatal Project oversampled families from an extremely impoverished background, with a quarter of the families on incomes below the poverty line (Turkheimer et al., 2003). Extreme levels of the environment, however, cannot be the sole reason for the inconsistent reports; the same team replicated the GxE interaction found in the National Collaborative Perinatal Project (Turkheimer et al., 2003), in a sample representative of the US population (Tucker-Drob et al., 2010).

Differences between countries is another possible sampling issue for two overlapping reasons: the relationship of the SES measures to each other, and their relationship to IQ. First, the traditional measures of SES – family income, parental education, and occupational status (Bradley & Corwyn, 2002) – may differ in relation to each other by population group (Braveman et al., 2005) and may also depend on country-specific political and historical background (Uher, Dragomirecka, Papezova, & Pavlova, 2006). The extent to which income, education, and occupation successfully capture financial, human, and social capital and their effect on child development are discussed thoroughly elsewhere (Bradley & Corwyn, 2002). In the present study, we combined education and occupation to better capture a broader construct of SES, and

benefitted from being able to compare the measure at two ages; we treated income separately as we only had this measure from age 9 on.

Second, the magnitude and nature of the effect of SES on children's IQ could differ in different countries (Uher et al., 2006), such as the UK versus the US. Although this possibility has not been systematically tested, inspection of the studies in Table 4.1 is consistent with the hypothesis of differences between European and US samples. Within the European studies, only one reported an increasing heritability of IQ with SES (Fischbein, 1980); this finding was based on estimates of twin correlations from a small sample. Among the US samples, with the exception of inconclusive results in a study with very small sample size (Scarr, 1981), the only non-replication of the greater heritability with increasing SES finding was in an older sample, with an age range of 16 to 30 years (Grant et al., 2010).

We believe that sample age is a particularly important factor in the inconsistent findings. Because heritability increases and shared environmental influence decreases from childhood to adulthood (Davis et al., 2009; Haworth et al., 2009), developmental differences in moderation could be expected. Two of the four studies in Table 4.1 that do not find greater heritability of IQ in higher SES are in older samples, ranging in age from 16 to 49 years (Grant et al., 2010; van der Sluis et al., 2008). The third non-replication was based on a small sample and unreliable estimates (Scarr, 1981). The last of the four non-replications involved an earlier analysis in the TEDS sample. This earlier analysis found no significant moderation of the heritability of age 4 IQ by SES, but did find moderation of the genetic effect by family chaos and parent-child communication (Asbury et al., 2005). Using the continuous moderator model, the present study suggests that SES does in fact moderate the relative contributions of A and C to variance in age 4 IQ – we suggest this is driven by a moderation of C.

Detecting modest shared environmental effects in the presence of larger genetic and non-shared environmental effects requires large twin samples (Martin, Eaves, Kearsey, & Davies, 1978). This difficulty is compounded by the fact that the shared environmental contribution to general cognitive ability diminishes with age. We suggest moderation of the shared environmental effect on IQ could go undetected in smaller samples and that it could be misinterpreted as genetic moderation given the low power of the continuous moderator model to distinguish between moderation of the genetic and shared environmental variance components. Even with a relatively large sample, as in the present study, comparing the fit of nested models yields little difference in their ability to explain the data, as indicated by the small AIC differences at every age and for

every SES index (Supplementary Table C.1, Supplementary Table C.2, and Supplementary Table C.3, **Appendix C**).

Several quantitative genetic approaches have been used to investigate moderation of the genetic effect on IQ. These include the heterogeneity model (e.g., splitting the sample into groups "low" versus "high" on the moderator), regression models with an interaction term (e.g. extended DF regression), and the continuous moderator model. The continuous moderator model is the most powerful approach, allowing the use of full information maximum likelihood to estimate potential moderation of latent variance components while simultaneously controlling for the confounding effects of gene-environment correlation. Because the interactions tested by the various approaches are *statistical* in nature, they are necessarily dependent on measurement scale, analytical model, and the assumptions underlying the model. Establishing a mechanism for moderation of the effect of genes, such as a change in gene expression, is several steps removed from finding moderation as a latent genetic population variance component (Kendler, 2011). Likewise, statistical moderation of a shared environmental component needs to be experimentally investigated to understand the real-world mechanisms behind the moderation.

Conclusion

The notion that heritability may be lower in lower-SES families is appealing, in part because of its environmental implications: If heritability is lower in lower-SES families, it suggests that environmental interventions might be more effective in boosting cognitive development for children in lower-SES families. The present study, which is based on a large UK-representative sample of children followed longitudinally, leads to a similar implication. Although the genetic influence on IQ is the same in lower-SES families, shared environmental influence appears to be greater in lower-SES families, suggesting that family-based environmental interventions might be more effective in these families. However, two further aspects of the results temper the policy implications of this finding. First, shared environmental influence is found in both lower- and higher-SES families and the difference in shared environmental influence between them is modest. Second, shared environmental influences on IQ decline from childhood to adulthood so that these influences might not have an impact in the long run.

5 Chaotic Homes and Disruptive Behaviour: Investigating Genetic Mediation and Direction of Causation‡

5.1 Abstract

Chaotic home lives are correlated with behaviour problems in children. In the study reported here, we tested whether there was a cross-lagged relation between children's experience of chaos and their disruptive behaviours (conduct problems and hyperactivity-inattention). Using genetically informative models, we then tested for the first time whether the influence of household chaos on disruptive behaviour was environmentally mediated and whether genetic influences on children's disruptive behaviours accounted for the heritability of household chaos. We measured children's perceptions of household chaos and parent ratings of children's disruptive behaviour at ages 9 and 12 in a sample of 6,286 twin pairs from the Twins Early Development Study (TEDS). There was a phenotypic cross-lagged relation between children's experiences of household chaos and their disruptive behaviour. In genetically informative models, we found that the effect of household chaos on subsequent disruptive behaviour was environmentally mediated. However, genetic influences on disruptive behaviour did not explain why household chaos was heritable.

5.2 Introduction

Although the child's social environment – comprising day-to-day interactions between children and caregivers – has long been a focus of research on children's development, researchers have only more recently begun to study the child's physical environment (Evans, 2006; Evans, Gonnella, Marcynyszyn, Gentile, & Salpekar, 2005). This research has shown that children raised in chaotic homes – characterized by noise, over-crowding, and a lack of order – tend to score lower on tests of cognitive ability and self-regulatory capabilities, have poorer language abilities, and score higher on measures of problem behaviours and learned helplessness than children who are raised in less chaotic environments (Evans et al., 2005; Hanscombe, Haworth, Davis, Jaffee, & Plomin, 2011). These associations have been demonstrated prospectively and controlling for family-wide characteristics (e.g., income, maternal depression) that could potentially confound the association (Deater-Deckard et al., 2009; Dumas et al., 2005).

‡ Chapter adapted from §Jaffee, S.R., §Hanscombe, K.B., Haworth, C.M.A., Davis, O.S.P., & Plomin R. (2012). Chaotic homes and children's disruptive behaviour: A longitudinal cross-lagged twin study. *Psychological Science*. doi:10.1177/0956797611436349

§*Joint first authorship*

Researchers have identified a number of mechanisms by which being raised in chaotic homes could lead to relatively poor cognitive and behavioural outcomes in children. Parents in more crowded homes are less verbally responsive with their children than parents in less crowded homes, and this accounts for the relatively low complexity of their own speech and, plausibly, their children's speech (Evans, Maxwell, & Hart, 1999). Children – like adults – may respond to household chaos by learning to filter out unwanted stimuli and may then generalize this strategy to other settings (e.g., the classroom) in which it is less adaptive.

Although household chaos may be a cause of children's poor developmental outcomes, it may also result from children's behaviour. On the face of things, this seems counterintuitive. Household chaos was originally conceptualized as a measure of the physical environment, comprising background noise, crowding, and foot traffic in the home (Wohlwill & Heft, 1987). However, features of the physical and social environment fall along a continuum, with one extreme reflecting inanimate, non-responsive, background sources of stimulation (which are unlikely to be influenced by the child, e.g., traffic noise) and the other reflecting responsive, animate, and focal sources of stimulation (which is more likely to be influenced by the child, e.g., parental speech) (Wachs, 1989). Some features of the environment will therefore combine characteristically physical and social elements. For example, the television could be turned on at high volume because a child has ignored repeated requests to turn it down. The decibel level in a home could be high because children have not heeded requests to take noisy play outdoors.

The Confusion, Hubbub, and Order Scale (CHAOS; Matheny et al., 1995) is a widely-used measure of household chaos that combines physical and social elements. Items include, 'It's a real zoo in our home' and 'You can't hear yourself think in our home' – conditions that could be generated by a child's behaviour. Indeed, the CHAOS measure captures a broad construct of chaotic living conditions, characterized not only by factors such as noise and crowding, but also by qualities such as a lack of structure and routine (Evans et al., 2005). The fact that the CHAOS measure potentially captures effects of children on their environment raises questions about whether household chaos is a cause of children's disruptive behaviour or whether disruptive children create or perceive chaotic environments.

Recent quantitative genetics research has shown that although environmental factors largely explain why some children are more likely than others to perceive their homes as chaotic, genetic factors account for a significant 22% of the variation in these perceptions (Hanscombe et al., 2010). But can these factors be identified? This would

entail demonstrating that (a) some characteristic of the child predicts household chaos, (b) that characteristic is genetically influenced, and (c) genetic influences on that characteristic also account for genetic variation in household chaos.

We hypothesized that children's disruptive behaviour problems (e.g., conduct problems and hyperactivity-inattention), which are genetically influenced traits, would partially account for the heritability of household chaos. Given moderately strong correlations between social disadvantage and disruptive behaviour problems (Duncan & Brooks-Gunn, 1997), disruptive children may experience their environments as being noisy, crowded, and lacking in structure. Additionally, it is possible that children's disruptive behaviour partly creates an environment that is noisy, in which it is difficult to concentrate, and in which children refuse to adhere to rules or routines related to television viewing, bedtimes, or mealtimes.

Results from other studies have identified parent- and child-driven effects in the relationship between children's disruptive behaviours and aspects of the family environment, such as parent-child conflict (Burt, McGue, Krueger, & Iacono, 2005) and parental negativity (Larsson, Viding, Rijsdijk, & Plomin, 2008). Thus, we also hypothesize that household chaos would have an environmentally mediated effect on children's disruptive behaviour.

5.3 Method

5.3.1 Sample

The TEDS sample is described in **Chapter 2**. The present study includes data from the 9- and 12-year TEDS assessments. The 1994 and 1995 birth cohorts were tested at age 9; all three birth cohorts were tested at age 12. In this study, the sample comprises 6286 pairs (2255 monozygotic (MZ) pairs; 2051 dizygotic (DZ) same-sex pairs; 1980 DZ opposite-sex pairs) for whom data were available from at least one twin in a pair, on at least one measure. All available data were used in the genetic analyses described below using full information maximum likelihood estimation.

5.3.2 Measures

Children's reports of their experience of noise, disorder and routine at home (Confusion, Hubbub, and Order Scale (CHAOS); Matheny et al., 1995), and parent reports or their conduct problems and hyperactivity-inattention (Strengths and Difficulties Questionnaire (SDQ); Goodman, 1997) were collected when the twins were 9 and 12 years. The CHAOS and SDQ scales, and their psychometric properties at age 9 and 12, are described in **Chapter 2**.

5.3.3 Analyses

Phenotypic analyses

To test the cross-lagged effect of CHAOS at age 9 on disruptive behaviour (conduct problems or hyperactivity-inattention) at age 12, we performed an ordinary least squares regression of the form,

$$Y_{\text{age 12}} = b_0 + b_1 Y_{\text{age 9}} + b_2 X_{\text{age 9}} + \varepsilon$$

where Y represents disruptive behaviour and X represents CHAOS. To test for the reverse process, we reversed the variable order: CHAOS scores at age 12 were regressed on CHAOS scores at age 9 and disruptive behaviour at age 9. The coefficient b_2 measures the cross-lagged relation between disruptive behaviour and CHAOS; b_1 measures the effect within trait across time; b_0 is the intercept. (This procedure was followed separately for conduct problems and hyperactivity-inattention.)

Genetic analyses

We used Cholesky decomposition models implemented in the OpenMx library (Boker et al., 2011), in the statistical computing environment R (R Development Core Team, 2011), to decompose the covariance structure of the relationship between disruptive behaviours and CHAOS at ages 9 and 12. All available data were included in the models using full information maximum likelihood. Figure 5.1 shows a path diagram of the Cholesky decomposition used to model the cross-lagged effects of a pair of traits.

In a Cholesky decomposition, each subsequent observed variable is regressed on the latent A, C, and E variance components of all the previous observed variables. In Figure 5.1, V_1 explains the total variance in Trait 1 (i.e., $A_1 + C_1 + E_1$). Traits 2, 3, and 4 are regressed on the latent variable V_1; in other words, the variance component V_1 takes precedence in explaining variance in these three measured traits. V_2 then explains the residual variance in Trait 2 ($A_2 + C_2 + E_2$), that is, variance not correlated with V_1. V_2 also has next priority in explaining variance in Trait 3 and Trait 4. V_3 and V_4 explain residual variance in Traits 3 and 4, respectively, and are uncorrelated with each other or with V_2 and V_1. The total genetic variation in Trait 4 is estimated by squaring and summing the genetic paths (*a*41-*a*44) from the A components of V (A_1 through A_4) to Trait 4. Similarly, shared and unique environmental variation in Trait 4 is estimated by squaring and summing the paths from all C and E components, respectively.

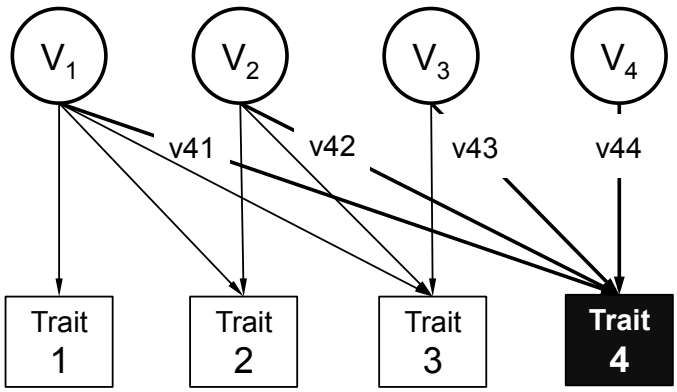


Figure 5.1 Four variable Cholesky decomposition
Measured traits (Traits 1–4) are regressed on corresponding latent variables (V_1–V_4). V_1 is the total variation in Trait 1 and takes precedence in explaining variance in Traits 2, 3, and 4. V_2 is the residual variance in Trait 2 and has next priority in explaining variance in Traits 3 and 4. V_3 is the residual variance in Trait 3 and has next priority to explain variance in Trait 4. V_4 explains residual variance in Trait 4. Each measured trait is regressed on all preceding latent variables, and all latent variables are uncorrelated. The total variation in Trait 4 is estimated by squaring and summing the paths from V_1 through V_4 to Trait 4 (v41 through v44, respectively). V_1 through V_4 can be decomposed into additive genetic (A), shared environmental (C), and non-shared environmental (E) components. For example, the total additive genetic variance in Trait 4 would be explained by the squared and summed paths a41 through a44 from latent variables A_1 through A_4.

To determine whether genetic influences on disruptive behaviours at age 9 account for genetic influences on CHAOS at age 12 (controlling for CHAOS at age 9), we ordered the traits in the Cholesky decomposition so that Trait 1 was CHAOS at age 9, Trait 2 was disruptive behaviour at age 9, Trait 3 was disruptive behaviour at age 12, and Trait 4 was CHAOS at age 12 (Figure 5.2). The degree to which the path between Trait 2 and Trait 4 accounted for the total genetic variation in CHAOS at age 12 – $a42^2/(a41^2 + a42^2 + a43^2 + a44^2)$ – addresses the substantive research question.

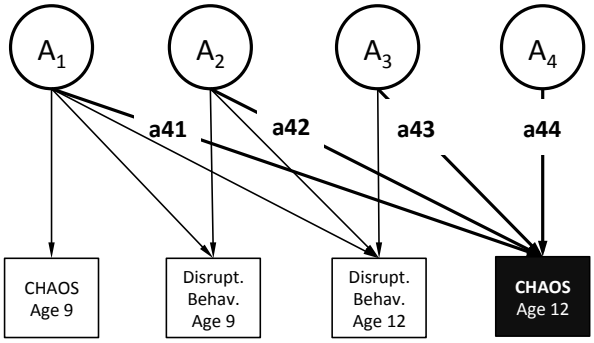


Figure 5.2 Origin of the genetic effect on CHAOS at age 12
A_1 through A_4 = latent genetic variance components; a41 through a44 = partial (genetic) regression coefficients. Proportion of genetic variation in CHAOS at age 12 explained by (residual) genetic variation in disruptive behaviour at age 9 = $a42^2/(a41^2 + a42^2 + a43^2 + a44^2)$.

Similarly, to determine whether environmental influences on CHAOS at age 9 accounted for environmental influences on disruptive behaviours at age 12 (controlling for disruptive behaviour at age 9), we ordered the traits so that Trait 1 was disruptive behaviour at age 9, Trait 2 was CHAOS at age 9, Trait 3 was CHAOS at age 12, and Trait 4 was disruptive behaviour at age 12 (Figure 5.3).

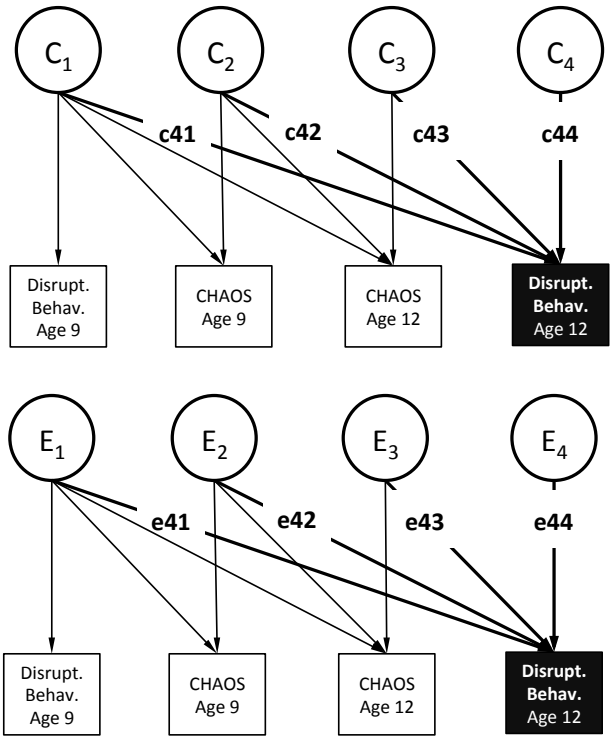


Figure 5.3 Origin of the environmental effect on disruptive behaviour at age 12
C_1 through C_4 = latent shared environmental variance components; $c41$ through $c44$ = partial (shared environmental) regression coefficients; E_1 through E_4 = latent non-shared environmental variance components; $e41$ through $e44$ = partial (non-shared environmental) regression coefficients; Disrupt. Behav. = disruptive behaviour. The proportion of shared environmental variation in disruptive behaviour at age 12 explained by (residual) shared environmental variation in CHAOS at age 9 = $c42^2/(c41^2 + c42^2 + c43^2 + c44^2)$. The same calculation can be applied to the non-shared environment.

The full bivariate cross-lagged model was achieved by running the Cholesky decompositions with these alternative trait orderings (Luo, Haworth, & Plomin, 2010).

5.4 Results

5.4.1 Descriptive Statistics

Descriptive statistics and analyses of variance are presented in Table 5.1. Across all measures, at both ages, there was no indication of substantial sex or zygosity differences: main and interactive effects of sex and zygosity accounted for 6% or less of the variance in CHAOS, conduct problems, or hyperactivity-inattention. Because similarity due to age and sex can contribute to phenotypic twin similarity and inflate

estimates of C, the measures were corrected for the effects of age and sex, as is standard practice in the analysis of twin data (McGue & Bouchard, 1984).

Phenotypic correlations among CHAOS and disruptive behaviour are shown in Table 5.2. Correlations within trait across time were moderate for CHAOS (0.45) and high for disruptive behaviours (conduct = 0.56; hyperactivity-inattention = 0.66); correlations between CHAOS and disruptive behaviour across trait and time were modest (0.20 - 0.24).

Table 5.1 Means for the Key Variables and Results of Sex × Zygosity Analyses of Variance (ANOVA)

							ANOVA		
	n	Overall	Female	Male	MZ	DZ	Sex (*p*)	Zygosity (*p*)	Sex × Zygosity (*p*)	R^2
CHAOS age 9	3,136	4.46 (2.32)	4.31 (2.26)	4.63 (2.37)	4.44 (2.33)	4.48 (2.31)	< .01	.79	.47	< .01
Conduct age 9	3,264	1.26 (1.42)	1.10 (1.30)	1.44 (1.53)	1.27 (1.46)	1.25 (1.40)	< .01	.49	.05	.02
Hyper. age 9	3,261	3.18 (2.34)	2.74 (2.08)	3.68 (2.51)	3.27 (2.29)	3.13 (2.37)	< .01	.03	.75	.04
CHAOS age 12	5,501	4.01 (2.05)	3.91 (2.06)	4.12 (2.03)	4.01 (2.04)	4.01 (2.05)	< .01	.79	.07	< .01
Conduct age 12	5,592	1.32 (1.45)	1.21 (1.38)	1.44 (1.51)	1.30 (1.42)	1.33 (1.46)	< .01	.50	.28	.01
Hyper. age 12	5,591	2.81 (2.25)	2.30 (2.01)	3.38 (2.37)	2.82 (2.20)	2.80 (2.28)	< .01	.38	.70	.06

Standard deviations are given in parentheses. The statistics in this table were calculated using data from one randomly selected member of each twin pair. CHAOS = Confusion, Hubbub, and Order Scale; ANOVA = analysis of variance.

Table 5.2 Phenotypic (Pearson's) Correlations and Intra-class Twin Correlations

	CHAOS age 9	Conduct age 9	Hyper. age 9	CHAOS age 12	Conduct age 12	Hyper. age 12
Phenotypic correlations[a]						
Conduct age 9	.27 (3,109)					
Hyper. age 9	.25 (3,106)	.49 (3,261)				
CHAOS age 12	.45 (2,489)	.23 (2,587)	.20 (2,584)			
Conduct age 12	.21 (2,522)	.56 (2,625)	.35 (2,622)	.26 (5,448)		
Hyper. age 12	.24 (2,521)	.42 (2,624)	.66 (2,621)	.24 (5,447)	.47 (5,591)	
Intra-class correlations by sex and zygosity						
MZ (all)	.66 (.63–.69)	.80 (.78–.82)	.73 (.70–.76)	.65 (.62–.67)	.77 (.75–.79)	.75 (.73–.77)
DZ (all)	.52 (.49–.56)	.49 (.46–.53)	.15 (.11–.19)	.56 (.54–.58)	.49 (.46–.51)	.27 (.23–.30)
MZ male	.64 (.58–.69)	.81 (.78–.83)	.75 (.71–.78)	.61 (.56–.65)	.75 (.72–.78)	.75 (.72–.78)
DZ male	.55 (.48–.61)	.52 (.45–.58)	.16 (.08–.25)	.57 (.52–.62)	.50 (.44–.55)	.24 (.18–.30)
MZ female	.68 (.64–.72)	.79 (.76–.81)	.71 (.67–.75)	.68 (.64–.71)	.79 (.77–.81)	.76 (.73–.78)
DZ female	.56 (.50–.62)	.57 (.52–.63)	.15 (.07–.23)	.61 (.57–.65)	.55 (.50–.59)	.30 (.25–.36)
DZ same sex	.56 (.51–.60)	.55 (.51–.59)	.16 (.10–.22)	.60 (.56–.62)	.53 (.49–.56)	.28 (.24–.32)
DZ opposite sex	.49 (.44–.54)	.44 (.39–.49)	.14 (.08–.20)	.52 (.49–.56)	.44 (.40–.48)	.25 (.21–.30)

For phenotypic correlations, the number of observations is given in parentheses; for intra-class correlations, 95% confidence intervals are given in parentheses. Pearson's correlations were calculated using one randomly selected member of each twin pair. CHAOS = Confusion, Hubbub, and Order Scale.
[a]All phenotypic correlations were significant ($p < .001$)

5.4.2 Phenotypic Evidence for Cross-Lagged Effects

Standardized parameter estimates from a series of ordinary least squares regression analyses showed evidence of cross-lagged effects. As described in the methods above, both age 9 measures were entered simultaneously. Both conduct problems ($\beta = 0.07$, $p < 0.001$) and hyperactivity-inattention ($\beta = 0.08$, $p < 0.001$) at age 12 were significantly predicted by CHAOS at age 9, even after controlling for the effects of conduct problems and hyperactivity-inattention at age 9. The reverse was also true: CHAOS at 12 was predicted by conduct problems ($\beta = 0.12$, $p < 0.001$) and hyperactivity-inattention ($\beta = 0.09$, $p < 0.001$) at age 9, even after controlling for the effects of CHAOS at age 9. These were analyses run separately for conduct problems and hyperactivity-inattention.

5.4.3 Genetically Sensitive Analyses

We performed full sex-limitation univariate analyses on disruptive behaviour and CHAOS at ages 9 and 12 to estimate the genetic and environmental variance components separately for males and females. Overall, the models estimating genetic and environmental parameters separately for males and females did not provide a significantly better fit to the data than the more parsimonious scalar model, which estimates one value of A, C and E for both males and females by accounting for sex differences in the phenotypic variance. Although sex-limitation modelling suggested a lower genetic (or shared environmental) correlation in opposite-sex pairs compared to same-sex pairs for hyperactivity-inattention at age 9, the ACE estimates for males and females were similar and had over-lapping confidence intervals. We explored this potential difference in the multivariate analyses described in the following section. ACE estimates derived from the univariate scalar models showed genetic and unique environmental factors accounted for significant variance in all three measures at 9 and 12 years. Shared environmental factors accounted for significant variance in CHAOS and conduct problems at 9 and 12 years, but not hyperactivity-inattention.

5.4.4 Multivariate Analyses of the Links between CHAOS and Disruptive Behaviour

Because of the limited evidence of sex differences in univariate estimates, all multivariate analyses were conducted for males and females combined (with the inclusion of a scalar to account for phenotypic variance differences in boys and girls). However, we also applied the same multivariate analyses to males and females separately. Conclusions drawn from the separated-by-sex analyses are limited because

comparisons are made between groups (sexes) with different phenotypic variances. Nonetheless, we have noted below if the multivariate results changed when analysed separately by sex. Details of these sex-specific analyses are included in Supplementary Table D.1 and Supplementary Table D.2 in **Appendix D**.

The salient results from our multivariate modelling of the cross-lagged relationship between CHAOS and disruptive behaviour are presented below. Standardized (un-squared) partial regression coefficients show the effect of latent genetic components of disruptive behaviour on CHAOS (Figure 5.2) and latent environmental effects of CHAOS on disruptive behaviour (Figure 5.3). Supplementary Table D.3 and Supplementary Table D.4 in **Appendix D** include point estimates and 95% confidence intervals for all path estimates.

5.4.5 What Explains Genetic Influences on CHAOS at 12 Years?

The total genetic variation in CHAOS at age 12 can be derived by squaring and summing the paths that lead from the genetic factors (A_1 through A_4) to CHAOS at age 12 (Figure 5.2). In the relationship between conduct problems and CHAOS, the total genetic variation on CHAOS at age 12 is given by the formula = $0.13^2 + 0.00^2 + 0.03^2 + 0.34^2 = 0.1334$, or 13%. Of this total genetic variation, about 13% was carried over from genetic influences on CHAOS at age 9 ($0.13^2/0.1334$), and 87% was specific to CHAOS at age 12 ($0.34^2/0.1334$). Less than 1% was explained by genetic influences on conduct problems at ages 9 and 12; these paths (from A_2 and A_3) were not statistically significant (i.e., 95% confidence intervals included 0). Similar to the results for conduct problems, genetic influences on hyperactivity-inattention at ages 9 and 12 explained a non-significant 2% of the genetic variation in CHAOS at 12 years. When separated by sex, results were similar for both males and females and comparable to the combined analyses.

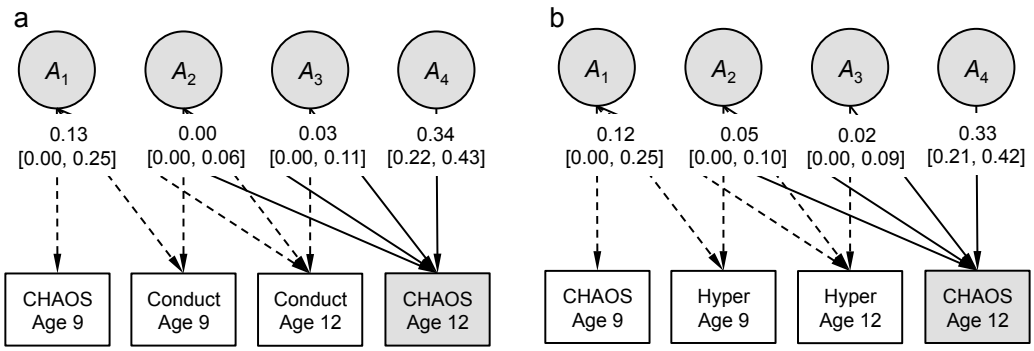


Figure 5.4 Genetic effects of disruptive behaviour on home chaos
Separate models are shown for the effects of (a) conduct and (b) hyperactivity-inattention, with both analyses controlling for the genetic effects of CHAOS scores at age 9. A_1 captures the total genetic variation in CHAOS scores at age 9; A_2, A_3, and A_4 are the residual genetic variances in disruptive behaviour at age 9, disruptive behaviour at age 12, and CHAOS scores at age 12, respectively. Standardized (unsquared) path coefficients and 95% confidence intervals are shown.

5.4.6 What Explains Environmental Influences on Disruptive Behaviour Problems?

Figure 5.5 shows the shared (C) and non-shared (E) environmental influences of CHAOS on disruptive behaviour at age 12, after accounting for the effects of disruptive behaviour at age 9. Shared environmental factors accounted for 28% of the variation in conduct problems at age 12. Shared environmental influences on CHAOS at ages 9 and 12 explained 13% and 10% of this total variation, respectively. Results of the univariate scalar model showed that shared environmental influences on hyperactivity-inattention at 12 years were statistically non-significant. However, multivariate analyses – which benefit from the additional information of covariances between traits – suggested a small shared environmental component in hyperactivity-inattention at 12 (about 5%) whose only significant contribution was from shared environmental influences on hyperactivity-inattention at 9.

Although unique environmental factors accounted for 22% of the variation in conduct problems at age 12 and 25% of the variation in hyperactivity-inattention, virtually none of this variation was explained by unique environmental influences on CHAOS at ages 9 or 12.

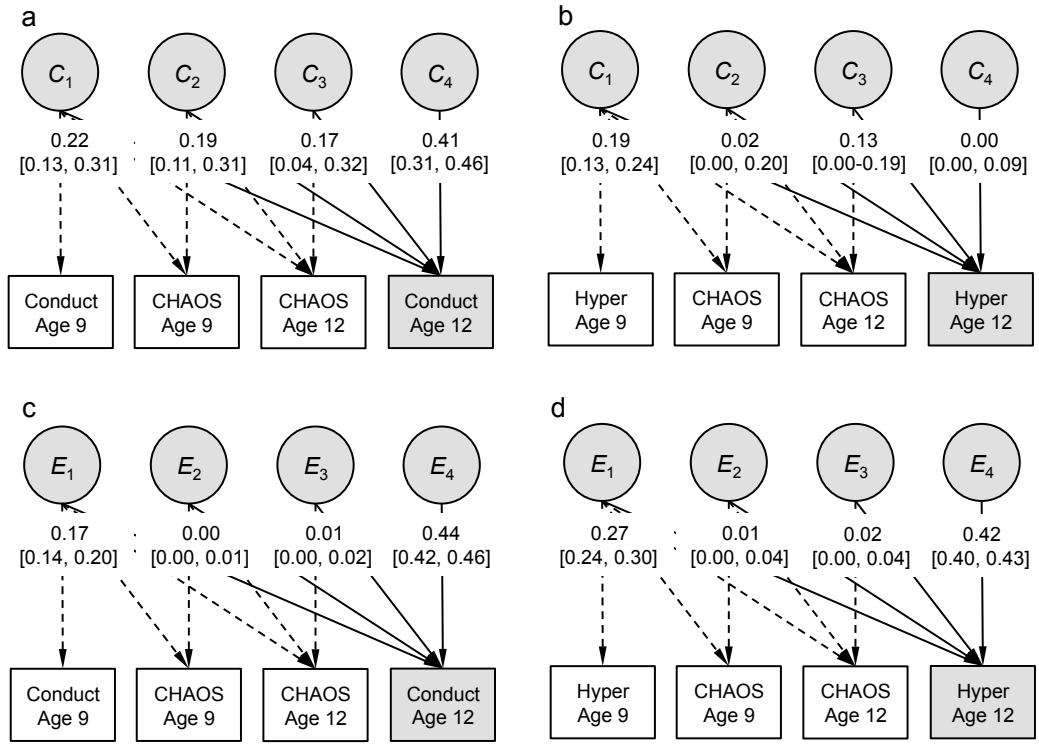


Figure 5.5 Shared (*C*) and non-shared (*E*) environmental effects of home chaos on disruptive behaviour

Separate models are shown for the effects on conduct at age 12 (a, c) and hyperactivity-inattention at age 12 (b, d). All analyses controlled for the corresponding disruptive behaviour at age 9. C_1 and E_1 refer to the total environmental variance in disruptive behaviour at age 9; C_2, C_3, and C_4 and E_2, E_3, and E_4 refer to the residual environmental variance in CHAOS scores at age 9, CHAOS scores at age 12, and disruptive behaviour at age 12, respectively. Standardized (unsquared) path coefficients and 95% confidence intervals are shown.

Sex-specific multivariate analyses suggested a non-significant difference between boys and girls in the shared environmental link between CHAOS at 9 and conduct problems at 12. However, given neither of these variables show univariate sex differences, separating the sample by sex may simply reduce power to detect environmental effects.

5.5 Discussion

Consistent with previous reports from TEDS, our analyses identified genetic and environmental influences on measures of household chaos, conduct problems, and hyperactivity-inattention at ages 9 and 12. The goal of our analyses was to identify the developmental origins of those genetic and environmental influences. Specifically, we tested whether genetic influences on disruptive behaviours at age 9 explained genetic variation in CHAOS at age 12 and whether environmental influences on CHAOS at age 9 explained environmental variation in disruptive behaviours at age 12.

We found that shared environmental influences on CHAOS at age 9 uniquely accounted for 13% of the shared environmental variation in conduct problems at age

12, suggesting that some of the cross-lagged effect of CHAOS on subsequent conduct problems was environmentally mediated. This finding suggests that encouraging parents to adopt stable routines and to minimize extraneous noise in the house could complement other techniques used in parent-training programs to prevent children's disruptive behaviours, such as reinforcing children's prosocial behaviours and reducing the use of harsh, coercive discipline.

Although genetic influences on disruptive behaviours were substantial, they accounted for little of the genetic variation in CHAOS at age 12. Although other researchers have identified similarly small contributions of disruptive behaviours to the heritability of the family environment (Burt et al., 2005; Larsson et al., 2008), our findings could be due to how CHAOS was measured. The fact that CHAOS was reported by each twin in a pair generates two possibilities for what it means for CHAOS to be heritable. One possibility is that genetic influences on CHAOS reflect genetically-based individual differences among children (e.g., disruptive behaviour problems) that elicit a chaotic environment. A second possibility is that genetic influences on CHAOS reflect genetically-based differences in children's perceptions of the environment. If the latter, then the degree to which children differ in their reports of household chaos may have more to do with how attentive or sensitive they are to their surroundings – characteristics that are not necessarily captured by children's disruptive behaviours as well as they might be by a measure of stress reactivity, for example. In reality, genetic influences on CHAOS are likely to reflect both genetically-based differences in children's behaviours as well as their perceptions.

Although the genetic cross-lagged analysis provides a direct estimate of the genetic and environmental influences on the cross-lagged paths – which was our goal – it does not allow for the simultaneous estimation of both cross-lagged paths in the same model (Luo et al., 2010). In contrast, the model developed by Burt et al. (2005) estimates a fully cross-lagged model of the relationship among the phenotypes. Although the cross-lagged model reported by Burt et al. (2005) has the advantage of being economical (in that it models the bi-directional relationship in a single run), it does not directly decompose the stability (across time, within trait) and cross-lagged (across time, across trait) effects into ACE components. Estimates of the ACE effects transmitted along stable and cross-lagged paths are simply scalar multiples of the ACE effects at the earlier time point, constrained to be in the ACE proportions at the earlier time point (Luo et al., 2010). Because we required direct estimates of genetic and environmental influences on the cross-lagged paths to answer our focal research questions, we opted to use the Cholesky approach. A second limitation was that the

internal consistency reliability of the CHAOS measures was only moderate. However, parent and child reports of CHAOS were highly correlated, providing additional validity for the measure.

In conclusion, although individual differences in reports of environmental confusion were partly genetic in origin, this genetic variance was not accounted for by the heritable component of children's disruptive behaviour. In addition, the effects of environmental confusion on children's disruptive behaviours were environmentally mediated. Noisy, crowded homes characterized by a lack of routine may undermine children's ability to regulate emotions and behaviour and may provide children with opportunities to act out.

6 Peer Victimization and Problem Behaviour: Origin of the Genetic Effect on a Heritable Environment

6.1 Abstract

Peer victimization is a heritable experience: genes influence children's likelihood of being bullied. Heritable psychosocial experience is thought to reflect genetically-influenced behaviours that drive exposure to particular environments. We asked: if we examine a broad cross-section of heritable behaviours in adolescence – internalizing problems, externalizing problems, and general cognitive ability – just how much of the genetic effect on concurrent victimization could we account for? We assessed 5625 12-year old twins from the UK population-representative Twins Early Development Study (TEDS) on a range of problem behaviours, general cognitive ability, and their self-reported experiences of peer victimization. The victimization scale we used was a 16-item continuous measure with four subscales: physical victimization, verbal victimization, social manipulation, and property damage. We found that, when considered separately, internalizing problems (e.g., depression, anxiety), externalizing problems (e.g., conduct problems, hyperactivity-inattention), and general cognitive ability, all accounted for part of the genetic variation in victimization. However, when considered together, these behaviours account for about half of the genetic variance in victimization. A substantial proportion of the genetic risk for victimization is shared with the genetic risk for internalizing and externalizing behaviours, and low cognitive ability. The present study cannot conclude that this particular set of behaviours causes bullying. Instead, given that the genetic effect on the experience of victimization is largely shared with this set of behaviours, the result is consistent with the idea that it is through heritable behaviours that psychosocial environmental experiences come to be heritable. The residual variation in victimization is partly due to genetic variance unique to victimization, and partly due to experiences that children growing up together do not share – non-shared environment.

6.2 Introduction

At school, being the victim of bullying by peers is a common experience. About 17% of school-aged children in a large US-representative sample reported being bullied in a recent World Health Organization survey (Nansel et al., 2001). The experience of being victimized is more than mild peer conflict: it involves regular attempts to cause injury or distress in an individual in a less powerful social role than the perpetrator(s) (Boulton & Underwood, 1992). Bullying can be direct (e.g., hitting, name calling) or indirect (e.g.,

social exclusion, telling lies about an individual); it takes place in different contexts around the school which may not be visible to teachers (e.g., playgrounds, corridors); and it has different direct/ indirect patterns in primary and secondary school (Rivers & Smith, 1994). The most remarkable fact however, is that the experience of peer victimization is heritable: whether or not a child is victimized by their peers is influenced by their genes (Ball et al., 2008; Beaver, Boutwell, Barnes, & Cooper, 2009).

In a UK-based study of 10-year-old same-sex twins (N = 1,116 pairs), mothers reported whether each of their children were bullied within the last two years, and if as a result, they suffered physical or psychological harm. From these reports a categorical severity of victimization was attributed to each twin in a pair: never, moderately or severely victimized. Comparing the similarity of the identical twins on their severity of victimization to the similarity of the non-identical twins, suggested that the underlying risk to victimization was highly heritable – about 70% (Ball et al., 2008). This finding has been replicated in a smaller US sample (N = 536 pairs), across a wider age range (grade 7–12, age 12–18), albeit with a more moderate heritability – about 45% (Beaver et al., 2009).

Peoples' characteristics and behaviours in the social world, whether they are conscious or not, direct them towards particular experiences (Scarr & McCartney, 1983). When we measure environmental experiences, they invariably show genetic influence (Kendler & Baker, 2007). This phenomenon – gene-environment (GE) correlation – was the focus of **Chapter 3**. In this chapter we direct our attention to the origin of the heritable effect on the environment – the heritable behaviours that underlie the exposure to particular experiences. If heritable behaviour drives experience, can we map the behavioural context within which children are victimized? To what extent will a concurrent measure of the known behavioural correlates of victimization, and the experience of victimization, be accounted for by a common set of genes?

Peer victimization has been associated with a variety of maladaptive behaviours. A recent review of the literature on peer victimization and mental health problems in childhood found that bullied children show increased levels of both internalizing (e.g. anxiety, depression) and externalizing (e.g. conduct problems) behaviours (Arseneault, Bowes, & Shakoor, 2010). In a large non-clinical sample of children (N=6437), the risk for non-clinical psychotic symptoms reported at age 12 showed a 2-fold increase among children bullied between the ages of 8 and 10 (Schreier et al., 2009). Bullied children's academic adjustment is also affected. Victimized children perceive their classrooms as unsupportive environments and generally like their school less than children who are not bullied (Wang, Iannotti, & Luk, 2011). Although the relationship between peer

victimization and problem behaviour is typically studied in the direction victimization → problem behaviour, there are studies that have looked at early behaviour problems predicting later victimization. For example, teacher ratings of internalizing, externalizing, and hyperactive-inattentive behaviour of children age 5-6 predicted victimization three years later, even after controlling for concurrent behaviour problems (Schwartz, McFadyen-Ketchum, Dodge, Pettit, & Bates, 1999).

In the present study, we shifted perspective to answer a different question: Instead of asking whether a particular behaviour is the cause or consequence of peer victimization, we investigated to what extent a single set of pleiotropic genes contributed to risk for victimization and a cross-section of correlated behaviours – internalizing, externalizing, and general cognitive ability. Using child reports of a continuous measure of peer victimization, we aimed to establish first the correlational structure between internalizing behaviours, externalizing behaviours, general cognitive ability and peer victimization in a UK-representative sample of adolescents. Second, with the use of multivariate twin modelling, we assessed the extent to which these heritable behaviours share a common genetic liability with peer victimization. We hypothesized that this cross-section of heritable behaviour would account for a significant proportion of the heritability of victimization.

6.3 Method

6.3.1 Sample

The TEDS sample is described in **Chapter 2**. All three cohorts, 1994-1996, were included in the 12-year assessment. The analyses in this chapter are based on a subsample of 5625 twin pairs (2035 MZ, 3590 DZ) for whom we had victimization data for at least one twin in a pair, on at least one of the victimization subtypes. In the analyses described below, we made use of all available data using full information maximum likelihood procedures.

6.3.2 Measures

The analyses described in this chapter used child-reported peer victimization measured with the Multi-Dimensional Peer Victimization Scale (Mynard & Joseph, 2000). General cognitive ability at age 12 was calculated as the unit-weighted sum of two verbal and two nonverbal tests: WISC-III-PI Information Multiple Choice (General Knowledge) and WISC-III-PI Vocabulary Multiple Choice (Kaplan et al., 1999), and Raven's Progressive Matrices (Raven et al., 1996) and WISC-III-UK Picture Completion (Wechsler, 1992) respectively. Internalizing and externalizing behaviours were measured

with child-rated depressive symptoms on the Moods and Feelings Questionnaire (MFQ; Angold et al., 1995); parent-rated conduct and peer problems, anxiety and inattention assessed with the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997); parent-reported autistic-like traits assessed with the Childhood Asperger Syndrome Test (CAST; Scott et al., 2002); and parent-reported antisocial behaviour measured with the Antisocial Process Screening Device (APSD; Frick & Hare, 2001). The content, scale construction, and psychometric properties of these questionnaires are described in detail in **Chapter 2**. All model-fitting analyses were performed on the age- and sex- corrected measures transformed to a standard normal distribution (Lehmann, 1975).

6.3.3 Analyses

We examined the twin correlations for victimization and the behavioural measures, and the correlational structure between them, in the open-source statistical computing language R (R Core Team, 2011). Using the classical twin design, we fitted a series of multivariate models to each combination of behavioural scale and victimization outcome, and to all the behavioural correlates and victimization simultaneously. Twin model-fitting analysis uses matrix algebra to specify the correlational structure (between twins and between traits) in terms of genetic and environmental parameters (the model). **Chapter 2** describes the univariate ACE model and the multivariate extension used in this chapter, the Cholesky decomposition. We used the R package OpenMx (Boker et al., 2011) to derive the maximum likelihood estimates of the genetic and environmental variance components.

6.4 Results

Results presented below are from analyses performed on all traits transformed to a standard normal distribution, using a rank-based transformation (Lehmann, 1975). Structural equation twin modelling on continuous data assumes that the data are (multivariate) normally distributed; transformation to a normal distribution is consistent with the idea that underlying the observed trait is a normally distributed liability.

6.4.1 Descriptive Statistics

The means and standard deviations by sex and zygosity of victimization and the set of measured behaviours are shown in Table 6.1. As expected with a very large sample, even relatively small differences are found to be significant. For example, among the victimization subscales, physical, social and property damage show significant mean differences by sex ($p < 0.01$). Cohen's d (a measure of effect size; Cohen, 1988) suggests

only physical victimization and property damage show small to medium size differences in mean between males and females. Mean differences by sex and zygosity are small for all other measures.

Behavioural genetic analyses are concerned with individual differences, or variation. As such, twin model fitting is performed on the residual of each trait after correcting for any mean effect of sex. Potential sex differences in the genetic and environmental factors affecting the variation in each trait were explicitly tested for and are reported in the univariate twin model fitting described below.

Table 6.1 Means, standard deviations, and test of mean differences by sex and zygosity

	All			Sex						Zygosity					
				F		M				MZ		DZ			
	n	*m*	*sd*	*m*	*sd*	*m*	*sd*	**p*	*d*	*m*	*sd*	*m*	*sd*	*p*	*d*
Physical	5600	0.00	1.00	0.17	0.68	-0.19	1.24	<0.01	0.37	0.04	0.97	-0.02	1.01	0.03	0.06
Verbal	5601	0.00	1.00	0.07	0.92	-0.08	1.07	0.51	0.14	0.00	0.98	-0.01	1.00	0.72	0.01
Social	5600	0.01	1.00	-0.05	1.09	0.08	0.88	<0.01	-0.14	0.04	1.01	0.00	1.00	0.12	0.04
Property	5600	0.00	1.01	0.21	0.72	-0.24	1.21	<0.01	0.46	0.06	1.00	-0.04	1.01	0.00	0.09
Vocabulary	4364	0.01	0.99	0.02	1.01	-0.02	0.96	0.34	0.04	-0.03	0.99	0.03	0.98	0.04	-0.06
Gen. Knowledge	4667	0.00	1.01	0.03	1.03	-0.04	0.98	0.22	0.07	-0.09	0.99	0.05	1.02	<0.01	-0.14
Pic. Completion	4243	0.00	1.00	0.01	0.98	-0.01	1.02	0.46	0.02	-0.05	1.02	0.03	0.99	0.01	-0.08
Raven's Matrices	4528	0.00	1.01	-0.01	0.99	0.00	1.03	0.96	0.00	-0.04	0.99	0.02	1.02	0.10	-0.05
Hyperactivity	5581	0.00	0.99	-0.04	0.92	0.06	1.06	<0.01	-0.10	-0.02	1.00	0.02	0.99	0.19	-0.04
Conduct	5581	0.00	0.99	0.05	0.87	-0.05	1.11	0.03	0.11	-0.01	1.01	0.01	0.98	0.41	-0.02
Peer Problems	5581	0.00	0.99	0.13	0.84	-0.14	1.12	<0.01	0.28	0.00	1.01	0.01	0.99	0.70	-0.01
Anxiety	5581	0.01	0.99	-0.06	1.10	0.08	0.86	<0.01	-0.14	0.00	1.02	0.02	0.98	*0.65	-0.02
Depression	5549	0.01	1.01	0.03	0.95	-0.02	1.06	0.33	0.05	0.02	1.02	0.00	1.00	0.55	0.02
Aut. Non-social	5574	0.00	1.01	0.14	0.87	-0.16	1.12	<0.01	0.30	-0.07	1.00	0.04	1.01	0.00	-0.11
Aut. Social	5580	0.00	0.99	0.01	0.88	-0.01	1.10	0.35	0.02	-0.08	0.99	0.05	0.99	0.00	-0.12
Callous	5584	0.00	1.00	0.03	0.95	-0.03	1.05	0.25	0.07	0.02	1.00	-0.01	1.00	0.36	0.03
Narcissism	5582	0.01	1.00	0.13	0.82	-0.13	1.15	<0.01	0.26	0.00	0.98	0.01	1.01	0.63	-0.01
Impulsivity	5569	0.00	1.00	-0.02	0.91	0.03	1.10	<0.01	-0.06	0.00	1.01	0.00	1.00	0.98	0.00

Descriptives based on a random selection of one member of each twin pair. Grey highlight indicates victimization subscales. F = female; M = male; MZ = monozygotic; DZ = dizygotic; n = sample size; m = mean; sd = standard deviation; p = p-value associated with a mean difference test (* = non-parametric test); d = effect size (Cohen's d): 0.20-0.30 small, about 0.50 medium, > 0.80 large. - indicates males > females.

6.4.2 Phenotypic structure

The phenotypic correlations between victimization and the behavioural subscales are shown in Table 6.2. All behaviour-victimization correlations are significant except for the victimization and the non-verbal cognitive ability subscale picture completion and the CAST social subscale. The correlations between the victimization and cognitive ability subscales are negative and small (-0.05 – -0.12); correlations with all other behaviours are positive and small to moderate (SDQ: 0.18 – 0.35, MFQ: 0.33 – 0.38, CAST: 0.10 – 0.14, APSD: 0.06 – 0.19). Correlations among the victimization subscales are positive and moderate to high (0.45 – 0.61).

Table 6.2 Pearson's phenotypic correlations between victimization and behavioural measures

	PHYSICAL	VERBAL	SOCIAL	PROPERTY
Physical	1.00	0.61	0.47	0.53
Verbal	0.61	1.00	0.57	0.50
Social	0.47	0.57	1.00	0.45
Property	0.53	0.50	0.45	1.00
Vocabulary	-0.06	-0.06	-0.10	-0.05
Gen. Knowledge	-0.06	-0.05	-0.12	-0.07
Pic. Completion	-0.02 (0.16)	-0.02 (0.34)	-0.06	-0.02 (0.26)
Raven's Matrices	-0.06	-0.07	-0.10	-0.05
Hyperactivity	0.20	0.23	0.24	0.18
Conduct	0.26	0.29	0.27	0.23
Peer Problems	0.33	0.35	0.28	0.30
Anxiety	0.21	0.29	0.29	0.20
Depression	0.34	0.38	0.38	0.33
Aut. Non-social	0.14	0.13	0.10	0.13
Aut. Social	0.03 (0.02)	0.02 (0.22)	0.01 (0.35)	0.02 (0.24)
Callous	0.11	0.09	0.10	0.06
Narcissism	0.16	0.17	0.14	0.14
Impulsivity	0.15	0.18	0.19	0.14

All correlations are significant at $p < 0.01$ except where shown in parentheses. Grey highlight indicates correlations among victimization subscales.

A correlation matrix provides accurate point estimates of pairwise correlations but gives little sense of the overall relationship among the variables. Visual analysis of quantitative information provides a complementary tool to standard summary statistics (Davis & Plomin, 2010). To get an impression of the overall relationship among the measured variables, we used a dendrogram to represent the phenotypic similarity (or more precisely dissimilarity) and a scatterplot of the result of a multi-dimensional scaling (MDS) to two dimensions (Figure 6.1). We calculated dissimilarities among the variables

by subtracting every element in the correlation matrix from 1. MDS maps these dissimilarities to a set of points such that the distance between the points is approximately equal to the trait dissimilarities – in this case, reducing the 18 traits to positions in two 2-dimensional space. In a dendrogram, more dissimilar traits branch off from each other earlier (or share a more distant root). In Figure 6.1, the general cognitive ability subtypes are most dissimilar from victimization and the other behaviours: in the scatterplot, the first axis separates victimization, peer problems, internalizing and externalizing behaviours, from general cognitive ability; this is also the earliest branch in the dendrogram. The four victimization subtypes are most closely related to peer problems, and the internalizing traits of depression and anxiety. The second MDS axis separates victimization, peer problems and internalizing behaviours, from the externalizing, autistic-like and hyperactive behaviours. The dendrogram also shows peer problems and internalizing behaviours share the most recent branch with the victimization subtypes.

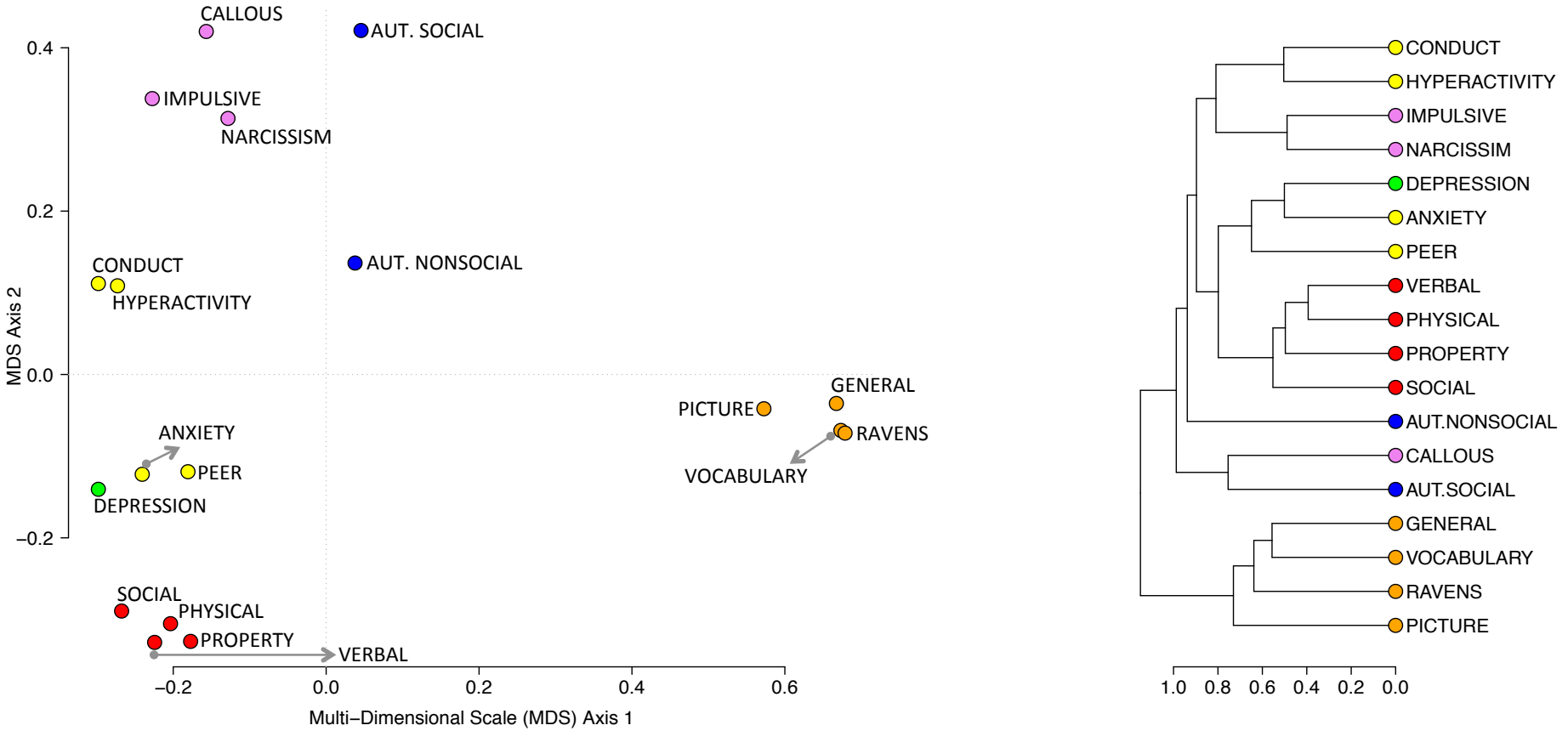


Figure 6.1 Phenotypic similarity of victimization and measured behavioural correlates
The figures provide a complementary account of the correlational structure among the variables. On the left is a scatterplot of the result of a multidimensional scaling; distance between points corresponds to dissimilarity between the variables. On the right a dendrogram; more distant relationships branch off earlier. Note. Distances are derived from a correlation matrix: a correlation of +1 is most "similar", and –1 most "dissimilar".

6.4.3 Univariate twin modelling

Twin intra-class correlations (coefficients of twin similarity; Shrout & Fleiss, 1979) for the subscales of victimization and each behavioural measure are presented in Table 6.3. Heritability is estimated by doubling the difference between the MZ and DZ correlations – victimization and all the other behavioural traits show substantial genetic influence.

Table 6.3 Intra-class twin correlations

	ICC (95 % CI)	
	MZ	*DZ*
Physical	0.48 (0.42-0.52)	0.28 (0.25-0.31)
Verbal	0.55 (0.52-0.58)	0.32 (0.29-0.35)
Social	0.53 (0.50-0.56)	0.28 (0.25-0.31)
Property	0.44 (0.41-0.48)	0.22 (0.19-0.25)
Vocabulary	0.43 (0.39-0.47)	0.30 (0.26-0.33)
Gen. Knowledge	0.57 (0.54-0.60)	0.43 (0.40-0.46)
Pic. Completion	0.48 (0.44-0.52)	0.33 (0.30-0.37)
Raven's Matrices	0.49 (0.45-0.52)	0.30 (0.27-0.34)
Hyperactivity	0.47 (0.44-0.51)	0.18 (0.15-0.21)
Conduct	0.46 (0.43-0.50)	0.24 (0.21-0.27)
Peer Problems	0.43 (0.39-0.47)	0.25 (0.22-028)
Anxiety	0.42 (0.38-0.46)	0.19 (0.16-0.22)
Depression	0.49 (0.46-0.53)	0.34 (0.31-0.37)
Aut. Nonsocial	0.71 (0.68-0.73)	0.31 (0.28-0.34)
Aut. Social	0.72 (0.70-0.74)	0.34 (0.31-0.36)
Callous	0.86 (0.85-0.87)	0.69 (0.67-0.71)
Narcissism	0.78 (0.76-0.80)	0.49 (0.47-0.52)
Impulsivity	0.81 (0.79-0.82)	0.46 (0.44-0.49)

ICC = intra-class twin correlation; 95% CI = 95% confidence interval

We also performed univariate sex-limitation modelling which provides a maximum likelihood test of the presence of quantitative and qualitative sex differences. Sex limitation modelling is described in **Chapter 2**, under heterogeneity models. For all age 12 variables a scalar model fitted the data best (or no worse than the full sex-limited model). In other words, once the phenotypic variance difference between sexes was taken into account, we found that the same genetic and environmental factors affected both males and females, and to the same degree (full univariate sex-limitation result for the victimization subscales are included in Supplementary Table E.1, **Appendix E**). Table 6.4 shows the univariate genetic and environmental variance components for each of the victimization subcales.

Table 6.4 ACE variance components for victimization from the univariate model

	Physical	Verbal	Social	Property
A	0.27 (0.18-0.36)	0.37 (0.28-0.45)	0.42 (0.34-0.51)	0.31 (0.22-0.41)
C	0.22 (0.15-0.29)	0.18 (0.11-0.25)	0.09 (0.02-0.16)	0.11 (0.04-0.19)
E	0.51 (0.48-0.54)	0.45 (0.43-0.48)	0.48 (0.46-0.52)	0.57 (0.54-0.61)

A, C, E = standardized genetic, shared, and non-shared variance components

6.4.4 How much genetic variation in victimization is shared with problem behaviour?

In the multivariate analyses described below we also included a scalar multiplier to account for phenotypic variance differences between sexes. This allowed the estimate of a single A, C and E covariance matrix for males and females. When we modelled the covariation between each behavioural scale and peer victimization separately, each accounted for a small fraction of the genetic component of peer victimization (Table 6.5). A Cholesky decomposition of a unit-weighted composite of each scale (IQ, SDQ, MFQ, CAST, APSD) simultaneously predicting a unit-weighted composite of victimization, showed that victimization shares a large common genetic liability with the behavioural predictors. Expressing the residual genetic variation in the victimization composite (0.22, 95% CI = 0.14-0.29) as a fraction of the total genetic variation in victimization (0.38, 95% CI = 0.31-0.46) shows that a little under half of the genetic variation is accounted for by the measured behavioural scales (1.00 – 0.22/0.38 = 0.42). This does not imply causation – the variables in the multivariate model could have been arranged in any order, to provide a mathematically equivalent solution. Choosing to place victimization last simply draws attention to the genetic variation unique to victimization, if any, after accounting for genetic risk in common with concurrent heritable behaviour.

Table 6.5 Residual genetic variation in victimization from a Cholesky decomposition

Behaviour	Residual genetic variation			
	Physical Victimization	**Verbal Victimization**	**Social Manipulation**	**Property Damage**
IQ	0.22 (0.00-0.32)	0.12 (0.00-0.19)	0.19 (0.00-0.22)	0.10 (0.00-0.17)
SDQ	0.15 (0.04-0.23)	0.11 (0.04-0.17)	0.19 (0.11-0.22)	0.10 (0.00-0.17)
MFQ	0.17 (0.08-0.25)	0.14 (0.07-0.19)	0.20 (0.15-0.22)	0.11 (0.00-0.17)
CAST	0.25 (0.17-0.33)	0.12 (0.04-0.19)	0.18 (0.10-0.22)	0.12 (0.00-0.18)
APSD	0.23 (0.15-0.31)	0.15 (0.07-0.20)	0.20 (0.15-0.22)	0.11 (0.00-0.17)

In each row is the result of a Cholesky decomposition with the subscales of the behaviour scale listed in the first column predicting variation in each of the four victimization subscales – only residual genetic variation in the victimization subscales is shown. IQ = general cognitive ability; SDQ = Strengths and Difficulties Questionnaire; MFQ = Moods and Feelings Questionnaire; CAST = Childhood Asperger Syndrome Test; APSD = Antisocial Process Screening Device

The Cholesky decomposition can also be converted to the equivalent correlated factor solution. The correlated factor solution gives a correlation between corresponding latent genetic (and environmental) variance components, for every pair of traits. A genetic correlation can be interpreted as the probability that genes found to be associated with one trait will be associated with the other. Table 6.6 shows the genetic correlations between each of the behavioural measures and the peer victimization subscales. In general, the genetic correlations in Table 6.6 track the phenotypic correlations (Table 6.2). For example, they are negative and small (or not significant) except notably with the social manipulation and vocabulary (-0.23) and general knowledge (-0.30), and property damage and general knowledge (-0.25). The IQ subscales have a negative correlation with victimization (-0.09 – -0.30). The behavioural problems phenotypes are positively correlated with victimization, the largest correlation – besides the peer problems subscale – is with the internalizing behaviour depression (0.40 – 0.60). It was expected that peer problems would have a high correlation with victimization (0.64 with verbal victimization). Nonetheless, the range of genetic correlations between peer problems and the other victimization subtypes (0.48 – 0.55) was no more than the relationship between those victimization subtypes and conduct problems (0.40 – 0.55) or depression (0.40 – 0.60), suggesting the peer problems scale did not capture the full victimization experience. The genetic correlations in Table 6.6 do not show the genetic variation in victimization independent of the behavioural traits – this is shown by the residual variation in the victimization in the Cholesky decomposition. The genetic correlations do however give a sense of the genetic landscape (similar to the phenotypic landscape in Figure 6.1) between victimization and the measured behavioural scales

simultaneously. A Cholesky decomposition answers the key question of how much of the genetic variation in victimization is independent of the behavioural measures, but, because of the built in order of the model, it does not at a glance give a picture of the genetic back background.

Table 6.6 Genetic correlations among measures of general cognitive ability, internalizing and externalizing behaviour, and peer victimization at age 12

	PHYSICAL	VERBAL	SOCIAL	PROPERTY
Physical		0.78 (0.67-0.90)	0.68 (0.56-0.80)	0.77 (0.60-0.94)
Verbal	0.78 (0.67-0.90)		0.65 (0.56-0.75)	0.60 (0.58-0.72)
Social	0.68 (0.56-0.80)	0.65 (0.56-0.75)		0.65 (0.63-0.77)
Property	0.77 (0.60-0.94)	0.60 (0.58-0.72)	0.65 (0.63-0.77)	
Vocabulary	-0.09 (-0.38-0.17)*	-0.12 (-0.35-0.11)*	-0.23 (-0.45--0.02)	-0.22 (-0.26-0.04)*
Gen. Knowledge	-0.23 (-0.37-0.01)*	-0.21 (-0.41--0.01)	-0.30 (-0.50--0.11)	-0.25 (-0.48--0.02)
Pic. Completion	0.09 (-0.20-0.38)*	0.15 (-0.09-0.40)*	-0.04 (-0.25-0.19)*	0.08 (-0.18-0.37)*
Raven's matrices	-0.03 (-0.25-0.20)*	-0.11 (-0.31-0.08)*	-0.15 (-0.33-0.01)*	0.01 (-0.22-0.21)*
Hyperactivity	0.55 (0.39-0.74)	0.51 (0.39-0.65)	0.46 (0.35-0.57)	0.40 (0.27-0.55)
Conduct	0.37 (0.19-0.56)	0.41 (0.26-0.56)	0.39 (0.26-0.55)	0.26 (0.08-0.43)
Peer Problems	0.50 (0.31-0.71)	0.64 (0.62-0.82)	0.48 (0.32-0.66)	0.55 (0.36-0.71)
Anxiety	0.39 (0.19-0.59)	0.49 (0.34-0.65)	0.37 (0.22-0.50)	0.35 (0.17-0.53)
Depression	0.60 (0.41-0.80)	0.55 (0.39-0.72)	0.47 (0.32-0.61)	0.40 (0.22-0.58)
Aut. Non-social	0.09 (-0.02-0.20)*	0.11 (0.03-0.21)	0.16 (0.08-0.24)	0.15 (0.12-0.24)
Aut. Social	0.03 (-0.08-0.16)*	-0.04 (-0.13-0.06)*	-0.01 (-0.10-0.08)*	-0.03 (-0.14-0.07)*
Callous	0.01 (-0.13-0.15)*	0.04 (-0.08-0.15)*	0.02 (-0.09-0.13)*	0.08 (0.03-0.22)
Narcissism	0.13 (0.01-0.26)	0.11 (0.01-0.21)	0.12 (0.03-0.22)	0.02 (-0.10-0.14)*
Impulsivity	0.25 (0.14-0.38)	0.23 (0.14-0.33)	0.25 (0.17-0.34)	0.17 (0.07-0.29)

* = Confidence intervals include zero, indicating non-significant genetic correlations

6.5 Discussion

In the present study we found that peer victimization at age 12 had a small to moderate positive correlation with a range of problem behaviours including internalizing and externalizing traits: more behaviour problems correlated with greater peer victimization. General cognitive ability showed a small negative correlation with victimization – lower general cognitive ability was associated with greater peer victimization. Phenotypically, in the present sample at age 12, victimization appears to be more closely related to internalizing behaviours. Our central aim was to account for the genetic component of the psychosocial experience of peer victimization. We found that each of the behavioural scales considered separately explained a small fraction of the genetic variation in victimization. When considered simultaneously, the heritable behaviours accounted for about half of the genetic effect on victimization.

Using a set of behavioural correlates we have shown that in adolescence, the heritable psychosocial experience of victimization has substantial common genetic risk with a subset of concurrent behaviour problems. While this study cannot conclude that the set of measured behaviours cause victimization, the observation of overlapping genetic factors is consistent with the idea that it is through heritable behaviours that particular genotypes come to be associated with particular environments (Scarr & McCartney, 1983). Genetic mediation between an environmental experience and a behavioural outcome, suggests genetically-driven exposure to experience (Kendler & Eaves, 1986; Plomin et al., 1977).

The present study suggests that when considering the effects of peer victimization in childhood on mental health (Arseneault et al., 2010), as well as the effects of problem behaviours on the likelihood of victimization (Schwartz et al., 1999), we have to take into account the genetic confound. The behavioural context of victimization – internalizing, externalizing behaviours, hyperactivity-inattention, and poor academic adjustment – is at least in part the result of an underlying genetic liability. Do genetic factors predispose some children to actively behave in a way that makes them more vulnerable to bullies, do their heritable behaviours evoke bullying behaviour in their peers, or are they more inclined to feel powerless and perceive particular experiences as acts of bullying? These remain open questions to be tested. However, recognizing that both the genetic and environmental components of behaviour are mutable, genetic mediation may suggest new avenues to victimization intervention – addressing problem behaviours may be a complementary strategy to current bullying interventions. One possibility might be friendship networks. Although choice of friends is almost certainly also under genetic influence (Fowler, Settle, & Christakis, 2011),

fostering larger friendships groups or buddy systems might support children at risk for victimization. Friendship has been shown to moderate the effects of problem behaviour on likelihood of peer victimization (Schwartz et al., 1999).

The analyses we performed were not intended to conclude that the particular set of cognitive, internalizing, and externalizing behaviours measured here cause bullying. Instead, establishing that there is a large common genetic liability for victimization and the set of measured behaviours at a particular age is a starting point for addressing the key question of whether it is through heritable behaviour that exposure to environmental experience comes under genetic influence (GE correlation). An alternative explanation of the result is that the pleiotropic genes underlying victimization and behaviour are simply a confounding factor and the observed phenotypic covariation of behaviour and victimization is spurious. This explanation seems unlikely given the body of research on reciprocal effects between victimization and behaviour across development (Arseneault et al., 2010). Given that the genetic effect on the experience of victimization is largely shared with the cross-section of behaviour measured in this study, the result is consistent with the idea that it is partly through these heritable behaviours that psychosocial environmental experiences come to be heritable. In other words, because children's environmental experience reflects the ways in which they tend to behave, and their behaviour is influenced by their genetic predispositions, particular genes will be more common in certain environments. In this way children come to select and shape their environment, in part, for genetic reasons (Scarr & McCartney, 1983). After accounting for the overlap between the behaviours we measured and peer victimization, we found that the remainder was due to a unique genetic component (genes specific to victimization experience) and a unique environmental component (experiences that children growing up together do not share).

A possible limitation in the present study is the use of child reports of victimization. However, a study of school children suggests that about half of children victimized in primary school, and about two thirds of those bullied in secondary school, did not report these instances of bullying to someone at home (Rivers & Smith, 1994). It seems possible that child-self reports actually capture occurrences of victimization that are not known to parents or teachers. Another consideration may be that something about being a twin, in particular an identical twin, actually elicits peer victimization. Assuming that non-identical twins are no different to any other pair of siblings, we find no mean difference in the level of victimization experienced by identical and non-identical twins in the present sample.

In conclusion, the results of the present study highlight the GE correlation phenomenon in peer victimization. The common genetic risk between victimization and problem behaviours is the result of a mediating set of pleiotropic genes. Victimization, like other heritable psychosocial experiences, can be viewed as an *extended phenotype* (Dawkins, 1982) – an example of genetic effects beyond the skin.

7 Whole-Genome Data Explains Environmental Experience: Molecular Genetics of Peer Victimization

7.1 Abstract

Twin studies typically show genetic influence on environmental experiences – a phenomenon called gene-environment correlation. Obvious personal characteristics such as height and weight are heritable, but so too are the psychosocial experiences we select and shape. The quantitative genetic evidence indicating substantial genetic influence suggests that molecular genetic techniques applied to a measure of the environment should confirm the quantitative genetic findings, and it should be possible to identify the genes responsible for this heritability. We measured the psychosocial experience of peer victimization in a sample of more than 2700 12-year-olds from the Twins Early Development Study (TEDS) for whom we had whole-genome data. After quality control and we had genetic information for 688,025 genotyped single nucleotide polymorphisms (SNPs). We performed a discovery stage genome-wide association study (GWAS) and, using Genome-wide Complex Trait Analysis (GCTA), estimated the genetic variance of victimization explained by common variation in the genome. The discovery stage GWAS yielded a suggestive locus for future replication on chromosome 20. Considering all the SNPs on the array simultaneously explained a significant proportion of the variation in victimization. For two of the victimization subtypes SNP effects in aggregate gave an estimate equal to the twin estimate for heritability. Finally, we used identity-by-state (IBS), a measure of allele sharing between individuals, to explore the genetic architecture of peer victimization. Heritable childhood experiences are simply 'extended phenotypes' with the properties of other complex traits: common variants explain their genetic variation.

7.2 Introduction

Quantitative genetic studies show that environmental experiences are heritable – a phenomenon called gene-environment (GE) correlation (Jaffee & Price, 2007; Kendler & Baker, 2007; Plomin & Bergeman, 1991). From a statistical genetics perspective, if genes drive exposure to the environment, then genotypes will not be randomly distributed across the environment. If people select particular environments because of their genetic propensities (GE correlation), the result will be greater numbers of particular genotypes in certain environments. Equivalently, it could be said that environments control gene frequency (Purcell, 2002). If genotype is correlated with environment, we should be able to apply standard molecular genetic methods to map

genes to the environment, just as we associate genes with any other complex trait (Hirschhorn & Daly, 2005).

A few candidate gene associations for environmental measures have already been reported, but are yet to be replicated (e.g., Dick et al., 2006). These are typically measured in the context of gene-environment (GE) interaction, genetically-influenced sensitivity to the environment – interactions that have been proposed as a source of missing heritability (Thomas, 2010). However, as well as the perennial problem of failure to replicate candidate gene associations (Duncan & Keller, 2011; Hewitt, 2012; Ioannidis, 2003), it is arguably more difficult to select plausible biological candidates for environments than well-characterized physiological phenotypes.

In this study we focus on the phenomenon of GE correlation, analysing the environment itself as the phenotype of interest in a genome-wide association study (GWAS). GWASs provide an unbiased survey of the genome for risk variants and incorporate rigorous multiple test correction (McCarthy et al., 2008). We chose the psychosocial experience of adolescent peer victimization as the target heritable environment. In **Chapter 6** we used the twin method to replicate two previous studies that have shown bullying to be a heritable environmental experience (Ball et al., 2008; Beaver et al., 2009). Given the association between peer victimization and parenting and home environment (Zimmerman, Glew, Christakis, & Katon, 2005), behaviour problems (Brendgen et al., 2011), and psychopathology (Arseneault et al., 2010), it is critical to understand the genetic and environmental aetiology of peer victimization in order to unravel these associations, and potentially find new inroads to intervention.

Our aim in the present study was to leverage the power of whole-genome data to support the quantitative genetic finding of GE correlation in victimization. In this chapter we report molecular genetic analyses using measured genotypes in more than 2700 children with self-reports of the experience of peer victimization. First, we surveyed the genome for any large single variant effects on victimization, and second, we used measured genotypes to estimate the heritability of the psychosocial experience of peer victimization. Finally, we compared the genetic architecture of victimization to other typical complex traits.

7.3 Methods

7.3.1 Sample

The Twins Early Development Study (TEDS) is described in **Chapter 2**. This chapter describes analyses performed on a subset of 3154 individuals who were genotyped as part of the Wellcome Trust Case Control Consortium 2 (WTCCC2), on the Affymetrix

Human Array 6.0 Gene chip. This subsample contained no known relatives (i.e. no co-twins).

7.3.2 Measures

The measures used in the present study are described in **Chapter 2**. This chapter describes analyses performed on child self-reports of the psychosocial experience of peer victimization (Mynard & Joseph, 2000) assessed at age 12.

7.3.3 Genome-wide association

One approach to genetic association is to compare the frequency of polymorphic markers in individuals with different disease states, e.g., cases versus controls, or in the present study, bullied versus not-bullied children (Balding, 2006). Recognizing however that peer victimization is a quantitative trait encompassing a range of experience – and that, in general, common dichotomous disorders are quantitative traits (Plomin, Haworth, & Davis, 2009) – we looked for genetic association across the full range of peer victimization scores. We had child self-reported victimization ratings at age 12 for 2,706 of the 3,154 children that passed genotyping quality control (QC). Genome-wide association analyses were performed using a frequentist test of association, SNPTEST 's Score Test which reduces to a Armitage Trend Test under an additive model. Sex and the first 10 principal components from a population stratification analysis were included as covariates in the association test. Population stratification analysis was performed using EIGENSTRAT (Price et al., 2006). Association results were filtered by SNP quality using the following thresholds: genomic location (autosomal and non-mitochondrial), minor allele frequency (MAF) < 0.01, call rate < 0.98, Hardy Weinberg Equilibrium (HWE) p-value < 1×10^{-20}. After SNP QC and imputation using HapMap, we had a total of 1,721,433 SNPs (1,033,408 imputed, 688,025 genotyped).

7.3.4 Genome-wide Complex Trait Analysis (GCTA)

The current state of GWAS is the recognition that beyond simply surveying hundreds of thousands of SNPs for associations with a particular phenotype – essentially, one SNP at a time – whole-genome data can be used in aggregate to explain the genetic component of complex traits. Genome-wide Complex Trait Analysis (GCTA; Yang et al., 2011) was used to estimate the genetic variance in adolescent experience of peer victimization. First, a genetic relationship matrix (GRM) is derived which summarizes the degree of relatedness for all possible pairs among the 2,706 individuals with victimization and genetic data at age 12. Using only genotyped SNPs to calculate the

GRM provides a baseline estimated of the phenotypic variation explained by common genetic variation; including imputed SNPs would increase the genetic variance explained by including many more common variants. In subsequent calculation using the GRM, a cut-off of genome-wide relatedness < 0.025 ensures that no relatives above eighth cousins are included.

GCTA and other statistical genetic approaches (So, Li, & Sham, 2011) have begun to confirm the importance of genetic influence for human behaviour as revealed by quantitative genetic methods. Height (Yang et al., 2010) and intelligence (Davies et al., 2011) are both highly heritable. Typical GTCA estimates are about half the quantitative genetic heritability estimate.

7.3.5 Collaboration with a physicist – Professor Stephen Hsu

Genome-wide genotypes can provide an estimate of the genetic variation explained by common variation, but they also reveal more about typical complex traits. Professor Stephen Hsu has proposed a method that uses whole-genome data to answer a related set of questions about complex trait architecture, in particular, "How different genetically are two individuals at different points in a phenotype distribution?" (McMahon, Hanscombe, Vattikuti, Lee, Chang, Chow, Plomin, Davey Smith, & Hsu, paper in preparation). To illustrate the major result of the approach in relation to the heritable psychosocial experience of peer victimization, we selected the extremes from the victimization distribution and used identity-by-state (IBS, see Figure 7.1).

Figure 7.1 Identity-by-state (IBS) between two individuals at a single locus

At each bi-allelic locus, pairs of individuals are IBS = 0, 1, or 2. Between two individuals *i* and *j* there are three genotype combinations that correspond to two alleles shared IBS, four that correspond to one allele shared IBS, and two possibilities of no allele sharing.

		j		
		AA	AB	BB
i	AA	2	1	0
	AB	1	2	1
	BB	0	1	2

This method differs from GCTA in that it starts by ranking all individuals on their trait scores, then for every pair of individuals, walks along their genomes summing up the number of SNP differences at polymorphic loci. (Note: IBS – used in the present chapter to summarize allele sharing between individuals – is similar to, but not exactly the same as, the allele sharing method proposed by Stephen Hsu. The result given below is a preliminary exploration of the data using the IBS calculation.)

7.4 Results

7.4.1 A discovery stage GWAS

Figure 7.2 shows Manhattan plots of genome-wide evidence for association for the four victimization subscales. On the right of each scatter plot is a complementary quantile-quantile (QQ) plot showing evidence of enrichment for low p-values, reflecting the pattern seen in each of the genome-wide signal plots. The genome-wide signal plots and QQ plots for each of the victimization subscales suggest possible true risk variants for victimization that would require replication in an independent sample. Because the linkage peak on chromosome 20 stood out across all four victimization subtypes – and was significant for the property damage subscale - we performed a GWAS on a unit-weighted sum of all the subscales. Figure 7.3 shows the genome-wide signal plot for the victimization composite.

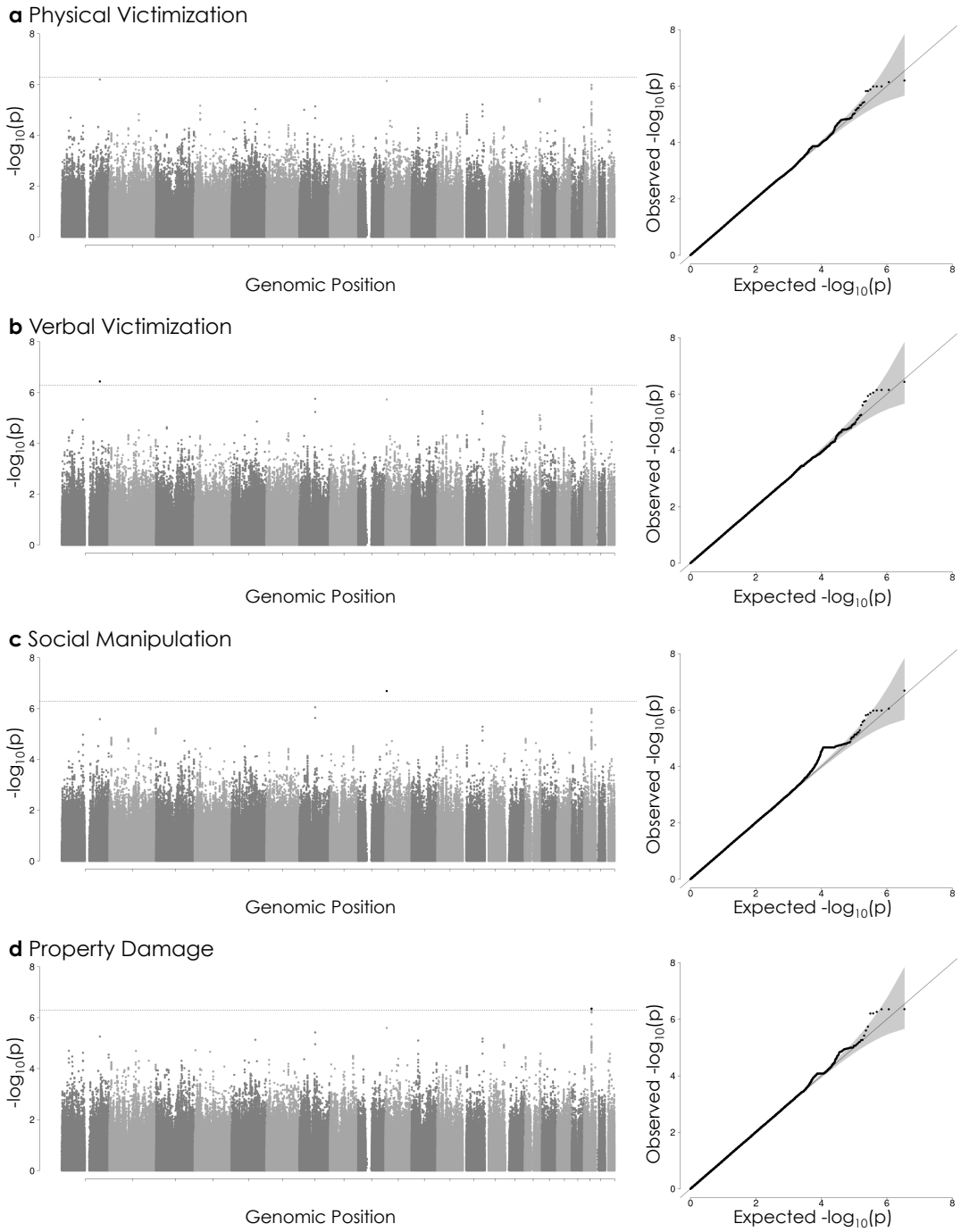


Figure 7.2 Manhattan and quantile-quantile (QQ) plots for peer victimization subscales
The dotted lines in each Manhattan plot (left) indicate genome-wide significance (p-value = 5 x 10^{-7}). In each QQ plot (right), p-values from the association test are plotted against quantiles from expected distribution under the null hypothesis of no association. Deviation above the line y = x for low p-values – or large $-\log_{10}(p)$ – suggest true susceptibility loci. Grey bands indicate 95% confidence intervals.

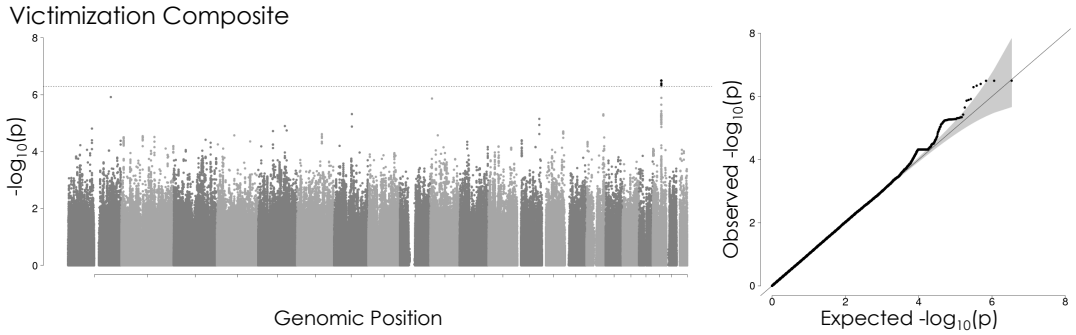


Figure 7.3 Manhattan plot and QQ plot for peer victimization composite
The dotted lines (left) indicates genome-wide significance (p-value = 5 x 10^{-7}). The QQ plot (right) shows p-values from the association test (observed) plotted against the expected distribution under the null hypothesis of no association. Deviation above the line y = x for low p-values – or large -$\log_{10}$(p) – suggests true susceptibility loci. Grey band indicates 95% confidence intervals.

The linkage peak on chromosome 20 is associated with the Zinc fingers and homeoboxes 3 (ZHX3) gene. The top ranked genotyped SNP (rs4812488, chromosome 20, p-value=4.02 x 10^{-7}) from the GWAS on the victimization composite is located in an intron of ZHX3. A regional plot showing linkage disequilibrium around this top SNP is included in **Appendix F** (Supplementary Figure F.1). The discovery stage is only the first stage in a GWAS and a replication stage is necessary to name associated genes with any confidence. A table of the top 10 "hits" from each subscale is included in the **Appendix F**.

7.4.2 SNP effects in aggregate

Table 7.1 shows the GCTA estimates of genetic variation explained by common variants in the four victimization subtypes. Very large samples are needed to calculate genetic variation and, as expected, this was reflected in the relatively large standard errors.

Table 7.1 Genetic variation explained by measured SNPs

	V(G)/V(P)	SE	N	QG h^2
Physical victimization	0.24	0.12	2706	0.27 (0.18-0.36)
Verbal victimization	0.35	0.13	2707	0.37 (0.28-0.45)
Social manipulation	0.15	0.12	2705	0.42 (0.34-0.51)
Property damage	0.04	0.12	2705	0.31 (0.22-0.41)

V(G)/V(P) = proportion of phenotypic variation accounted for by common genetic variation; SE = standard error; N = sample size; QG h^2 = quantitative genetic estimate of heritability derived from a univariate twin model

The GCTA estimate of phenotypic variation explained by common genetic variation was essentially the same as the quantitative genetic estimate for physical and verbal victimization. The estimate for social manipulation was closer to half the quantitative genetic estimate – similar to GCTA estimates for height and weight. However, for property damage the estimated proportion of genetic variation was non-significant.

IBS differences as a function of phenotype

Figure 7.4 is a visual summary of the basic approach we took to estimate genetic difference as a function of phenotypic difference, and the major result.

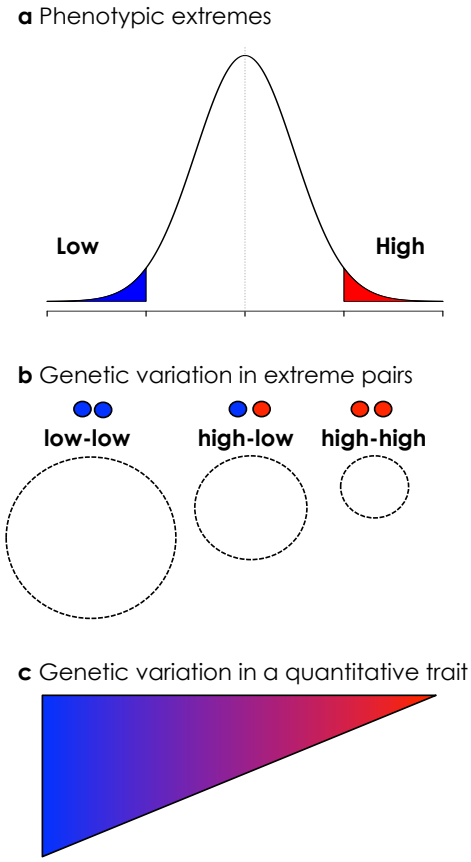


Figure 7.4 Genetic differences as a function of phenotype
a. Selection of the extremes of a normal phenotypic distribution, top and bottom ~10% – 300 high and 300 low. **b.** Forming pairs from the extremes of the distribution is informative. The dotted circles represent the greater genetic variation among the average pair in which individual *i* and *j* are selected one from the phenotypic extremes: low-low, low-high, and high-high. **c.** The triangle represents genetic variation across the entire quantitative distribution of the trait. We observed decreasing genetic variation towards the high (or optimal) end of the trait (i.e. less victimization, or greater intelligence).

For peer victimization – as we have found for the genetic architectures of height and intelligence (McMahon, Hanscombe, Vattikuti, Lee, Chang, Chow, Plomin, Davey Smith, & Hsu, paper in preparation) – there are a greater number of SNP differences associated with the phenotype for two individuals further apart on the phenotypic distribution. Second, there are more genotypes that correspond to below average on the phenotype. On the composite peer victimization score (a unit-weighted sum of all four subscales), the average number of SNPs between a pair of individuals from the extremes is 316,668 low-low, 316,613 high-low, 316,559 high-high (For comparison to height and intelligence, high corresponds to the trait optimal, i.e., less victimization).

7.5 Discussion

Our discovery stage genome-wide association study showed some promising evidence for SNP association with peer victimization. Of course, these results need to be followed up with a replication study. Inflated p-values suggest that true susceptibility loci for victimization are among the common variants tagged by the Affymetrix Human 6.0 Array. Remarkably, when considered in aggregate, we found that we were able to explain a substantial amount of the quantitative genetic estimate for the heritability of three of the four victimization subtypes. As expected for a typical complex trait, we found that the more dissimilar two children are in their experience of victimization the more different they are genetically – a similar pattern to that seen for other typical complex traits.

Considering whole-genome data one SNP at a time and in aggregate confirmed the quantitative genetic finding that peer victimization is heritable (**Chapter 6**; Ball et al., 2008; Beaver et al., 2009), and appears to be a typical complex trait. This confirmation of genetic contribution to the experience of peer victimization highlights the non-independence of the individual and their environment (Scarr & McCartney, 1983). Viewing the child as an active participant in their environment could open up new possibilities for intervention. One previous study found that the teacher-child relationship moderated the effects of victimization on children's aggressive behaviour (Brendgen et al., 2011). Of course the teacher-child relationship is influenced by the (genetic) predispositions of both parties – only certain children actively form a positive relationship with the teacher – but knowing the positive effect it could have is a reason to foster these relationships with at-risk children. The friendship choices children make may be positive and protective, but may also be detrimental. Knowing that genotypes are correlated among friends (Fowler et al., 2011), a possible intervention could be to rearrange children during school or class activities which may give them the opportunity to form new relationships with peers they may not ordinarily seek out. The quality of parent-child interactions and the family environment are associated with victimization (Zimmerman et al., 2005), but parent-child and family environment dynamics exist before the child begins school and are both affected by children's heritable predispositions (Bell, 1968; Hanscombe et al., 2011; Pike & Eley, 2009). The link between parental discipline and children's extra-familial friendship quality has already been shown in a twin study to be largely genetic in origin (Pike & Eley, 2009). On the other hand, genetically-sensitive studies also provide the best evidence for the importance of the environment. For example, parent-child attachment style in infancy – an important early parent-child dynamic – is found to have negligible genetic influence

and is environmentally linked to maternal sensitivity (Bokhorst et al., 2003; Fearon et al., 2006). There is likely a complex pattern of feedback between psychosocial experiences like victimization and co-occurring behaviour problems. Both quantitative and molecular genetic designs can add to our understanding of the role of the child.

The present study described only the discovery stage of a GWAS. In order to select and follow up particular SNPs that may further illuminate the genetic pathways to victimization a replication study is needed. The ZHX3 gene implicated in the present study has no obvious biological relevance for peer victimization, but with further molecular genetic analysis of victimization (and environmental experience in general) genetic mappings to environmental experience could change the way we understand the individual in their environment. There is no obvious explanation why GCTA explains none of the variance in the property damage subscale, especially considering the GWAS results for this subscale. Sample size and number of SNPs are considerations, but these were adequate for the other measures. It may be that the program simply failed to generate an interpretable estimate for this subscale. The estimate for the social manipulation subscale is a little under half the twin estimate. This is as found for height and intelligence (Davies et al., 2011; Yang et al., 2010), and is expected with decreasing allele frequency of causal variants of small effect. The estimates of genetic variance in physical and verbal victimization show no missing heritability. This suggests they are completely explained by the common variation on the chip and a powerful enough association study should link measured genetic variation to phenotypic variation. In combination, the tools of molecular genetics in the present study suggest that genes influence exposure to psychosocial environmental experience, confirming the quantitative genetic finding of GE correlation.

8 Discussion

This thesis used the approaches of quantitative and molecular genetics to explore the nature of environmental experience in childhood and the origin of its links to developmental outcomes. **Chapter 3** and **Chapter 4** described investigations of the two main gene-environment (GE) phenomena explored using the classical twin design – GE correlation and GE interaction, respectively. **Chapter 3** revealed that the link between noise and routine in the home and school performance – previously assumed to be environmentally mediated – is in fact partially genetically mediated. By using individual-specific accounts of experience, we highlighted that family-wide accounts alone cannot give a complete picture of the effect of children's environmental experience on developmental outcomes. Across middle childhood the nature of the genetic effect on exposure to particular experiences may be a combination of passive, evocative and active GE correlation suggesting that there are opportunities to address both children's and their parents heritable behaviours. Moreover, because genetic effects on environmental experiences are ubiquitous (Kendler & Baker, 2007), the entire range of apparently physical environmental risks for children (Evans, 2006), potentially capture child and parent effects.

The findings of **Chapter 3** imply that studies not including child-specific accounts of experience are limited in the conclusions they can draw about the effects of children's experience on developmental outcomes (Evans et al., 2002). This study also has implications for education. Identifying the behavioural manifestations of academic achievements shared genetic risk with children's exposure to chaos in the home could indicate new approaches to the process of educating children in the classroom. At least it should be recognized that children bring something to the experience of education: the same teaching approach may have different effects on two different children.

More generally, genetic risk for environmental exposure, GE correlation, is critical where environments have been shown to pose particular risk. For example, because environments play a principal role in the cause of sporadic cancer (Lichtenstein et al., 2000), understanding why particular genotypes occur at a greater frequency in certain environments (GE correlation) will have far-reaching implications for epidemiology. This has led to a call for a more comprehensive view of environmental exposure – measurement of the entire "exposome", just as GWAS covers the genome – if epidemiologists are to unravel the genetic and environmental paths to disease (Rappaport & Smith, 2010).

Chapter 4 showed the absence of evidence that socioeconomic status (SES) moderates the genetic effect on children's intelligence (IQ) in a UK-representative sample. What we did find was that phenotypic variation in children's IQ – i.e., the spread of children's scores on general cognitive ability – is greater in lower-SES families. Using three indices of SES, the pattern we saw from infancy through adolescence was a larger shared environmental component to IQ in lower-SES families. One possibility, suggested by a survey of the studies that have failed to replicate GE interaction in IQ as a function of SES, is that SES has a different effect on the genetic and environmental components of IQ in the UK and Europe compared the US. Another possibility, given the known low specificity of the continuous moderator model (Purcell, 2002), is that previous reports have misinterpreted an *environment*-environment interaction as gene-environment interaction. The most highly-cited report of SES moderation of the genetic effect on IQ noted this possibility (Turkheimer et al., 2003). Moreover, Purcell (2002) showed using simulated data that standardization of the variance components is problematic for interpretation. We demonstrated with a heterogeneity analysis of real population data that standardization can lead to an artifactual change in the genetic variance component – a spurious gene-environment interaction. Finally, considering the lack of consensus among studies attempting to replicate the SES moderation of the genetic effect on IQ, we also demonstrated (with exact data simulation) the large sample sizes that are needed to generate power to detect moderating effects.

Given our lack of replication, SES moderation of the genetic effect on IQ (or GE interaction in IQ as a function of SES) does not appear to be a source of heritability in IQ. GE interaction as a function of other potential environmental moderators remains a possible source of (missing) heritability in IQ (Thomas, 2010). Power to detect these interactions will be prohibitive; main effects themselves have so far eluded detection – no replicated genome-wide significant variants have been found for IQ. It is worth noting that GE interaction may not contribute to heritability at all. Making certain assumptions regarding the frequency of causal variants (as predicted by population genetic theory), and incomplete linkage disequilibrium between typed markers on commercial arrays and the causal variants themselves, Yang et al. (2010) show that the explained variation for height can be scaled up to the quantitative genetic estimate for heritability of height.

The predictions of the *bioecolological theory* (Bronfenbrenner & Ceci, 1994) and the *environmental disadvantage hypothesis* (Scarr, 1992; Scarr-Salapatek, 1971) do not appear to apply to the genetic effect on IQ as a function of SES in a UK-representative sample. Data from the TEDS sample from infancy through adolescence shows no constraint or

restriction of children's genetic potentials in the adverse environment of low SES. Instead it appears that the shared experiences of low SES increase the variation in children's IQ performance. Said differently, the resources available to children (and their parents) in higher-SES families buffer them against the negative environmental effects of low-SES – effects that are evidently experienced similarly by children growing up together. The non-replication of the previously reported SES moderation of the genetic component of IQ, along with the power calculation indicating the very large sample sizes that are needed to detect GE interaction with the twin model, and the known low specificity of the continuous moderation model, imply that caution is required in interpretation of GE interaction.

Chapter 5 explored genetic and environmental mediation of the link between environmental risk and behaviour across time. This chapter explored the genetic and environmental mediation between disruptive behaviour and the chaotic home environment with a longitudinal twin design that captured cross-lagged effects. Complementary Cholesky factorization allowed decomposition of bi-directional phenotypic effects across time (Luo et al., 2010). We found that neither conduct problems nor hyperactivity-inattention explained any of the heritable effect in children's experience of the chaotic home at age 12, after taking into account the effect of their earlier experience of the chaotic home. Although the expectation is that environments come to be heritable through heritable behaviours (Jaffee & Price, 2007), and disruptive behaviours seem like plausible candidates for genetic effects on environmental confusion in the home, they did not account for any of the genetic effect on the chaotic home. Asking somewhat the reverse question, to what extent is the effect of the chaotic home on disruptive behaviour actually environmental, we found that the chaotic home did in fact have a shared environmental link to conduct problems at age 12, explaining about a quarter of the shared environmental component after accounting for the effects of earlier conduct problems. Hyperactivity-inattention had no significant shared environmental component. The non-shared environmental component of both behaviours and the chaotic home were unique to each trait and each age. One caveat worth noting here is that the Cholesky approach to this problem is conservative in that we are only looking at residuals (on all the measures) after taking into account the effect of the earliest trait. While the alternative approach used by Burt et al. (2005) does not give precedence to any one trait, it does not allow the decomposition of the cross-lagged paths – our aim in **Chapter 5**.

Chapter 5 highlighted the possibility that children's perceptions of the environment – an aspect of children's environmental experience that is not measured by

parent or teacher reports – are also a potential source of genetic influence. Child self-reports meant that genetic influence on exposure to environmental confusion in the home included children's subjective experience or interpretation. The ability to control for the genetic effect on children's experience of home chaos using child-specific accounts, meant that unlike using obligatorily-shared (parent or teacher) reports we could with certainty say that the effect of early home chaos on disruptive behaviour was environmentally mediated. The implication for research – similar to the implication of **Chapter 3** for chaotic home and school achievement – is that all previous measures of family-wide experience are worth re-assessing from the child's perspective.

Chapter 6 took explanation of the heritable component of a genetically influenced environment (one of the questions asked in **Chapter 5**) a step further. It took a broader palette of behaviours and asked to what extent they explain the genetic component of a heritable environment. Underlying the psychosocial environmental experience of victimization and a cross-section of behavioural correlates at age 12 – cognitive ability, externalizing behaviour, and internalizing behaviour – we found a large common genetic liability. This chapter was a cogent demonstration of the generalist effect of genes, beyond cognitive abilities (Plomin & Kovas, 2005), to include behaviour and all the effects genes have on the psychosocial world.

As this study was in effect a snapshot of children's behaviour and their experience of victimization at a particular age, we cannot conclude that this cross-section of heritable behaviour is the source of the common genetic component. It is however consistent with the expectation that the environmental experience comes to be heritable as a result of genetic influences on behaviour that drive the exposure to the experience. Of course correlation does not mean causation (Rutter, 2007b). In **Chapter 6** we showed the genetic influence on victimization was partially correlated with the genetic influence on a variety of behaviours including internalizing and externalizing behaviours, and general cognitive ability. One possibility is that the genetic association seen here is the genetic influence on the correlated heritable behaviours that increase the likelihood of exposure to victimization, i.e., genetic influence → behaviour → victimization. Of course the reverse may also be true, i.e., genetic influence → victimization → behaviour, but this is obviously not likely for example for the autistic-like traits. Another possibility is that the same set of pleiotropic genes affect problem behaviour and increase risk of exposure to risky environments, i.e., behaviour ← genetic influence → victimization. Mapping of the actual causal variants may be one way to unravel the developmental paths between behaviour and experience.

Chapter 7 confirmed the quantitative genetic finding that genes influence environmental experiences. A discovery stage GWAS indicated enrichment for low p-values for SNP associations with victimization, evidence that genetic variation measured on the array tagged true causal variants. For complex traits in general, the SNP associations that have been found so far only account for a small fraction of the heritability as determined by quantitative genetic studies (Maher, 2008). A variety of possibilities have been suggested to explain the problem of "missing heritability". One explanation is that the quantitative genetic estimates are in fact wrong. New approaches using whole-genome data in aggregate however have begun to produce the expected result – after accounting for SNP frequency and low linkage disequilibrium between marker and causal SNPs – explaining about half of the quantitative genetic estimate (Davies et al., 2011; Yang et al., 2010). With measured whole-genome data, we were able to estimate the genetic variance in the experience of peer victimization explained by common variation. One surprising finding was that the genetic variance estimates for physical and verbal victimization matched our quantitative genetic estimates (in the same sample), suggesting that with sufficient power we should be able to completely map the genetic risk for peer victimization. It is worth noting that this is the estimate of genetic variance in the victimization subscales using only genotyped SNPs to construct the genetic relationship matrix used in the GCTA calculation. This in effect sets a lower bound for the genetic variance in the trait that might be explained by common variation in the genome; using imputed SNPs is expected to increase the explanatory capacity of the method.

The implication of the results of the molecular and statistical genetic analyses in **Chapter 7** is that the many potential uses of whole-genome data to gain insight into the genetic architecture of complex traits can be applied equally well to measures of environmental experience. As is expected for a typical complex trait, we found that genetic differences are greater among individuals further apart on the peer victimization distribution again confirming the genetic influence on experience of peer victimization. Follow-up of specific risk-associated variants will ultimately reveal whether the genetic risk for exposure to victimization is direct or indirect (mediated through heritable behaviour) – just as the fat mass and obesity associated (FTO) gene was found to be only indirectly associated with type 2 diabetes through its effect on body mass index (BMI) (Frayling et al., 2007).

Accepting that environmental experiences are themselves *extended phenotypes* opens up a whole new raft of possibilities for "the environment". Every childhood experience assumed to be environmental becomes a target for a GWAS. Another

exciting possibility with the use of molecular genetic techniques to investigate GE correlation, is their application to psychosocial experiences for which heritability estimates are not known because individual specific reports have not been possible, e.g., SES in childhood. GWAS, and other techniques that measure SNP effects in aggregate, do not require individual-specific measures. Genetic effects on family-wide measures of the environment will require new statistical developments to incorporate these obligatorily-shared experiences into the twin design (Price & Jaffee, 2008).

This thesis applied complementary quantitative and molecular genetic and techniques to the analysis of environmental experience. Viewing environmental exposure and sensitivity as the extended effect of genes beyond the individual recognizes that children are agents in their experience (Plomin & Bergeman, 1991; Scarr & McCartney, 1983). The twin design used in the large UK-representative TEDS twin sample demonstrates that genetically sensitive designs are a vital tool for understanding the nature of "environmental risk" and its effect on developmental outcomes. The assumed absence of GE effects leads to misinterpretation of risk. A comprehensive grasp of environmental exposure and the non-random distribution of genotypes across the environment (GE correlation) will inform epidemiology (Rappaport & Smith, 2010); pharmacogenetics already recognizes differential genetic sensitivity (GE interaction) to pharmacological intervention (Hunter, 2005). This thesis showed the pervasiveness of genetic effects on experience. Taking these effects into account can reveal where environment truly mediates association between experience and outcome, or where genetic effects confound this relationship. We also revealed a potential environment-environment interaction, a phenomenon we expect may account for inconsistency in low powered studies of environmental moderation of genetic effects. Understanding how people come to select and shape their experiences, and that they may be differentially sensitive to them, is a step in the direction of personalized education and medicine.

References

Akaike, H. (1987). Factor analysis and AIC. *Psychometrika, 52*, 317-332.

Angold, A., Costello, E. J., Messer, S. C., Pickles, A., Winder, F., & Silver, D. (1995). Development of a short questionnaire for use in epidemiological studies of depression in children and adolescents. *International Journal of Methods in Psychiatric Research, 5*(4), 237-249.

Arseneault, L., Bowes, L., & Shakoor, S. (2010). Bullying victimization in youths and mental health problems: 'much ado about nothing'? *Psychological Medicine, 40*(5), 717-729. doi: 10.1017/S0033291709991383

Asbury, K., Wachs, T. D., & Plomin, R. (2005). Environmental moderators of genetic influence on verbal and nonverbal abilities in early childhood. *Intelligence, 33*(6), 643-661. doi: 10.1016/j.intell.2005.03.008

Balding, D. J. (2006). A tutorial on statistical methods for population association studies. *Nature Review Genetics, 7*(10), 781-791. doi: 10.1038/nrg1916

Ball, H. A., Arseneault, L., Taylor, A., Maughan, B., Caspi, A., & Moffitt, T. E. (2008). Genetic and environmental influences on victims, bullies and bully-victims in childhood. *Journal of Child Psychology and Psychiatry, 49*(1), 104-112. doi: 10.1111/J.1469-7610.2007.01821.X

Bayley, N. (1993). *Bayley Scales of Infant Development*. New York, NY: The Psychological Corporation.

Beaver, K. M., Boutwell, B. B., Barnes, J. C., & Cooper, J. A. (2009). The Biosocial Underpinnings to Adolescent Victimization Results From a Longitudinal Sample of Twins. *Youth Violence and Juvenile Justice, 7*(3), 223-238. doi: 10.1177/1541204009333830

Bell, R. Q. (1968). A reinterpretation of the direction of effects in socialization *Psychological Review, 75*, 81-95.

Bergen, S. E., Gardner, C. O., & Kendler, K. S. (2007). Age-related changes in heritability of behavioral phenotypes over adolescence and young adulthood: A meta-analysis. *Twin Research and Human Genetics, 10*(3), 423-433. doi: 10.1375/twin.10.3.423

Birnbaum, M. H. (2004). Human research and data collection via the internet. *Annual Review of Psychology, 55*, 803-832. doi: 10.1146/annurev.psych.55.090902.141601

Boker, S., Neale, M., Maes, H., Wilde, M., Spiegel, M., Brick, T., . . . Fox, J. (2011). OpenMx: An Open Source Extended Structural Equation Modeling Framework. *Psychometrika, 76*(2), 306-317. doi: 10.1007/S11336-010-9200-6

Bokhorst, C. L., Bakermans-Kranenburg, M. J., Fearon, R. M., van Ijzendoorn, M. H., Fonagy, P., & Schuengel, C. (2003). The importance of shared environment in mother-infant attachment security: a behavioral genetic study. *Child Development, 74*(6), 1769-1782.

Boomsma, D., Busjahn, A., & Peltonen, L. (2002). Classical twin studies and beyond. *Nature Reviews Genetics, 3*(11), 872-882. doi: 10.1038/nrg932

Boulton, M. J., & Underwood, K. (1992). Bully Victim Problems among Middle School-Children. *British Journal of Educational Psychology, 62*, 73-87.

Box, G. E. P. (1979). Some Problems of Statistics and Everyday Life. *Journal of the American Statistical Association, 74*(365), 1-4.

Bradley, R. H., & Corwyn, R. F. (2002). Socioeconomic status and child development. *Annual Review of Psychology, 53*, 371-399. doi: 10.1146/annurev.psych.53.100901.135233

Braveman, P. A., Cubbin, C., Egerter, S., Chideya, S., Marchi, K. S., Metzler, M., & Posner, S. (2005). Socioeconomic status in health research: one size does not fit all. *Journal of the American Medical Association, 294*(22), 2879-2888. doi: 10.1001/jama.294.22.2879

Brendgen, M., Boivin, M., Dionne, G., Barker, E. D., Vitaro, F., Girard, A., . . . Perusse, D. (2011). Gene-environment processes linking aggression, peer victimization, and the teacher-child relationship. *Child Development, 82*(6), 2021-2036. doi: 10.1111/j.1467-8624.2011.01644.x

Bricker, D., Squires, J., & Mounts, L. (1995). *Ages and Stages Questionnaire: A parent-completed, child-monitoring system*. Baltimore: Brookes.

Brody, G., & Flor, D. (1997). Maternal psychological functioning, family processes, and child adjustment in rural, single-parent, African American families. *Developmental Psychology, 33*(6), 1000-1010. doi: 10.1037/0012-1649.33.6.1000

Bronfenbrenner, U., & Ceci, S. J. (1994). Nature-nurture reconceptualized in developmental perspective: A bioecological model. *Psychological Review, 101*(4), 568-586. doi: 10.1037//0033-295X.101.4.568

Brown, E. D., & Low, C. M. (2008). Chaotic living conditions and sleep problems associated with children's responses to academic challenge. *Journal of Family Psychology, 22*(6), 920-923. doi: 10.1037/a0013652

Bruni, O., Ferini-Strambi, L., Russo, P. M., Antignani, M., Innocenzi, M., Ottaviano, P., . . . Ottaviano, S. (2006). Sleep disturbances and teacher ratings of school achievement and temperament in children. *Sleep Med, 7*(1), 43-48. doi: 10.1016/j.sleep.2005.09.003

Burt, S. A. (2009). Rethinking environmental contributions to child and adolescent psychopathology: A meta-analysis of shared environmental influences. *Psychological Bulletin, 135*(4), 608-637. doi: 10.1037/a0015702

Burt, S. A., McGue, M., Krueger, R. F., & Iacono, W. G. (2005). How are parent-child conflict and childhood externalizing symptoms related over time? Results from a genetically informative cross-lagged study. *Development and Psychopathology, 17*(1), 145-165.

Cleveland, H. H., Jacobson, K. C., Lipinski, J. J., & Rowe, D. C. (2000). Genetic and Shared Environmental Contributions to the Relationship between the Home Environment and Child and Adolescent Achievement. *Intelligence, 28*(1), 69-86.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences*. Hillsdale, New Jersey: Lawrence Erlbaum Associates.

Coldwell, J., Pike, A., & Dunn, J. (2006). Household chaos - links with parenting and child behaviour. *Journal of Child Psychology and Psychiatry, 47*(11), 1116-1122. doi: 10.1111/j.1469-7610.2006.01655.x

Davies, G., Tenesa, A., Payton, A., Yang, J., Harris, S. E., Liewald, D., . . . Deary, I. J. (2011). Genome-wide association studies establish that human intelligence is highly heritable and polygenic. *Molecular Psychiatry, 16*(10), 996-1005. doi: 10.1038/mp.2011.85

Davis, O. S., Haworth, C. M., Lewis, C. M., & Plomin, R. (2012). Visual analysis of geocoded twin data puts nature and nurture on the map. *Molecular Psychiatry*. doi: 10.1038/mp.2012.68

Davis, O. S., & Plomin, R. (2010). Visualizing genetic similarity at the symptom level: the example of learning disabilities. *Behavioral and Brain Sciences, 33*(2-3), 155-157. doi: 10.1017/S0140525X10000749

Davis, O. S. P., Arden, R., & Plomin, R. (2008). g in middle childhood: Moderate genetic and shared environmental influence using diverse measures of general cognitive ability at 7, 9 and 10 years in a large population sample of twins. *Intelligence, 36*, 68-80. doi: 10.1016/j.intell.2007.01.006

Davis, O. S. P., Haworth, C. M. A., & Plomin, R. (2009). Dramatic increase in heritability of cognitive development from early to middle childhood: an 8-year longitudinal study of 8,700 pairs of twins. *Psychological Science, 20*(10), 1301-1308. doi: 10.1111/j.1467-9280.2009.02433.x

Dawkins, R. (1976). *The Selfish Gene*. New York: Oxford University Press.

Dawkins, R. (1982). *The Extended Phenotype: The Long Reach of the Gene*. Oxford: Oxford University Press.

Deater-Deckard, K., Mullineaux, P. Y., Beekman, C., Petrill, S. A., Schatschneider, C., & Thompson, L. A. (2009). Conduct problems, IQ, and household chaos: a longitudinal multi-informant study. *Journal of Child Psychology Psychiatry*. doi: 10.1111/j.1469-7610.2009.02108.x

Dick, D. M., Agrawal, A., Schuckit, M. A., Bierut, L., Hinrichs, A., Fox, L., . . . Begleiter, H. (2006). Marital status, alcohol dependence, and GABRA2: evidence for gene-environment correlation and interaction. *Journal of Studies on Alcohol, 67*(2), 185-194.

Dumas, J. E., Nissley, J., Nordstrom, A., Smith, E. P., Prinz, R. J., & Levine, D. W. (2005). Home Chaos: Sociodemographic, Parenting, Interactional, and Child Correlates. *Journal of Clinical Child and Adolescent Psychology, 34*(1), 93-104. doi: 10.1207/s15374424jccp3401_9

Duncan, G. J., & Brooks-Gunn, J. (1997). *Consequences of growing up poor*. New York: Russell Sage Foundation.

Duncan, L. E., & Keller, M. C. (2011). A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *American Journal of Psychiatry, 168*(10), 1041-1049. doi: 10.1176/appi.ajp.2011.11020191

Eaves, L. J. (2006). Genotype x Environment Interaction in Psychopathology: Fact or Artifact? *Twin Research and Human Genetics, 9*(1), 1-8. doi: 10.1375/183242706776403073

Eaves, L. J., Last, K., Martin, N. G., & Jinks, J. L. (1977). A progressive approach to non-additivity and genotype-environmental covariance in the analysis of human differences. *British Journal of Mathematical and Statistical Psychology, 30*(1), 1-42.

Eaves, L. J., Silberg, J., & Erkanli, A. (2003). Resolving multiple epigenetic pathways to adolescent depression. *Journal of Child Psychology and Psychiatry, 44*(7), 1006-1014.

Evans, D. M., Gillespie, N. A., & Martin, N. G. (2002). Biometrical genetics. *Biological Psychology, 61*(1-2), 33-51.

The meaning and efficacy of social withdrawal as a strategy for coping with chronic residential crowding, 4, 20 Cong. Rec. 335-342 (2000).

Evans, G. W. (2004). The environment of childhood poverty. *American Psychologist, 59*(2), 77-92. doi: 10.1037/0003-066X.59.2.77

Evans, G. W. (2006). Child development and the physical environment. *Annual Review of Psychology, 57*, 423-451. doi: 10.1146/annurev.psych.57.102904.190057

Evans, G. W., Gonnella, C., Marcynyszyn, L. A., Gentile, L., & Salpekar, N. (2005). The role of chaos in poverty and children's socioemotional adjustment. *Psychological Science, 16*(7), 560-565.

Evans, G. W., Maxwell, L. E., & Hart, B. (1999). Parental language and verbal responsiveness to children in crowded homes. *Developmental Psychology, 35*(4), 1020-1023.

Fearon, R. M., van Ijzendoorn, M. H., Fonagy, P., Bakermans-Kranenburg, M. J., Schuengel, C., & Bokhorst, C. L. (2006). In search of shared and nonshared environmental factors in security of attachment: a behavior-genetic study of the association between sensitivity and attachment security. *Developmental Psychology, 42*(6), 1026-1040.

Fenson, L., Pethick, S., Renda, C., Cox, J. L., Dale, P. S., & Reznick, J. S. (2000). Short-form version of the MacArthur Communicative Development Inventories. *Applied Psycholinguistics, 21*, 95-116.

Fischbein, S. (1980). IQ and social class. *Intelligence, 4*(1), 51-63.

Fowler, J. H., Settle, J. E., & Christakis, N. A. (2011). Correlated genotypes in friendship networks. *Proceedings of the National Academy of Sciences of the United States of America, 108*(5), 1993-1997. doi: 10.1073/pnas.1011687108

Frayling, T. M., Timpson, N. J., Weedon, M. N., Zeggini, E., Freathy, R. M., Lindgren, C. M., . . . McCarthy, M. I. (2007). A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science, 316*(5826), 889-894. doi: 10.1126/science.1141634

Frick, P. J., & Hare, R. D. (2001). *The Antisocial Process Screening Device (APSD)*. Toronto, Canada: Multi-Health Systems.

Goodman, R. (1997). The Strengths and Difficulties Questionnaire: A research note *Journal of Child Psychology and Psychiatry, 38*(5), 581-586.

Goodman, R. (2001). Psychometric properties of the strengths and difficulties questionnaire. *Journal of American Academic Child and Adolescent Psychiatry, 40*(11), 1337-1345.

Grant, M. D., Kremen, W. S., Jacobson, K. C., Franz, C., Xian, H., Eisen, S. A., . . . Lyons, M. J. (2010). Does Parental Education have a Moderating Effect on the Genetic and Environmental Influences of General Cognitive Ability in Early Adulthood? *Behavior Genetics, 40*(4), 438-446. doi: 10.1007/s10519-010-9351-3

Hanscombe, K. B., Haworth, C. M., Davis, O. S., Jaffee, S. R., & Plomin, R. (2011). Chaotic homes and school achievement: a twin study. *Journal of Child Psychology and*

Psychiatry and Allied Disciplines, 52(11), 1212-1220. doi: 10.1111/j.1469-7610.2011.02421.x

Hanscombe, K. B., Haworth, C. M. A., Davis, O. S. P., Jaffee, S. R., & Plomin, R. (2010). The nature (and nurture) of children's perceptions of family chaos. *Learning and Individual Differences, 20*(5), 549-553. doi: 10.1016/j.lindif.2010.06.005

Hart, S. A., Petrill, S. A., Deater-Deckard, K., & Thompson, L. A. (2007). SES and CHAOS as environmental mediators of cognitive ability: A longitudinal genetic analysis. *Intelligence, 35*(3), 233-242. doi: 10.1016/j.intell.2006.08.004

Haworth, C. M. A., Harlaar, N., Kovas, Y., Davis, O. S. P., Oliver, B. R., Hayiou-Thomas, M. E., . . . Plomin, R. (2007). Internet cognitive testing of large samples needed in genetic research. *Twin Research and Human Genetics, 10*(4), 554-563.

Haworth, C. M. A., Wright, M. J., Luciano, M., Martin, N. G., de Geus, E. J. C., van Beijsterveldt, C. E. M., . . . Plomin, R. (2009). The heritability of general cognitive ability increases linearly from childhood to young adulthood. *Molecular Psychiatry, 15*(11), 1112-1120. doi: 10.1038/mp.2009.55

Hewitt, J. K. (2012). Editorial policy on candidate gene association and candidate gene-by-environment interaction studies of complex traits. *Behavior Genetics, 42*(1), 1-2. doi: 10.1007/s10519-011-9504-z

Hirschhorn, J. N., & Daly, M. J. (2005). Genome-wide association studies for common diseases and complex traits. *Nature Review Genetics, 6*(2), 95-108.

Hoge, R. D., & Coladarci, T. (1989). Teacher-based judgments of academic achievement: A review of literature. *Review of Educational Research, 59*(3), 297-313.

Hunter, D. J. (2005). Gene-environment interactions in human diseases. *Nature Reviews Genetics, 6*(4), 287-298.

Ioannidis, J. P. (2003). Genetic associations: false or true? *Trends Mol Med, 9*(4), 135-138. doi: 10.1016/S1471-4914(03)00030-3

Ireton, H., & Thwing, E. (1974). *The Minnesota Child Development Inventory*. Minneapolis, MN: Behavior Science Systems.

Jaffee, S. R., & Price, T. S. (2007). Gene-environment correlations: a review of the evidence and implications for prevention of mental illness. *Molecular Psychiatry, 12*(5), 432-442.

Jinks, J. L., & Fulker, D. W. (1970). Comparison of the biometrical genetical, MAVA, and classical approaches to the analysis of human behavior. *Psychological Bulletin, 73*, 311-349.

Johnson, A. D., Martin, A., Brooks-Gunn, J., & Petrill, S. A. (2008). Order in the House! Associations among Household Chaos, the Home Literacy Environment, Maternal Reading Ability and Children's Early Reading. *Merrill-Palmer Quarterly-Journal of Developmental Psychology, 54*(4), 445-472.

Kaplan, E., Fein, D., Kramer, J., Delis, D., & Morris, R. (1999). *WISC-III as a Process Instrument (WISC-III-PI)*. New York: The Psychological Corporation.

Kendler, K. S. (2011). A conceptual overview of gene environment interaction and correlation in a developmental context. In K. S. Kendler, S. R. Jaffee & D. Romer (Eds.), *The Dynamic Genome and Mental Health: The Role of Genes and Environment in Youth Development* (pp. 5-28). Oxford: Oxford University Press.

Kendler, K. S., & Baker, J. H. (2007). Genetic influences on measures of the environment: a systematic review. *Psychological Medicine, 37*(5), 615-626.

Kendler, K. S., & Eaves, L. J. (1986). Models for the joint effects of genotype and environment on liability to psychiatric illness. *American Journal of Psychiatry, 143*, 279-289.

Kendler, K. S., & Gardner, C. O. (2010). Interpretation of interactions: guide for the perplexed. *British Journal of Psychiatry, 197*(3), 170-171. doi: 10.1192/bjp.bp.110.081331

Kendler, K. S., Jaffee, S. R., & Romer, D. (2011). *The dynamic genome and mental health : the role of genes and environments in youth development*. Oxford ; New York: Oxford University Press.

Kovas, Y., Haworth, C. M. A., Dale, P. S., & Plomin, R. (2007). *The genetic and environmental origins of learning abilities and disabilities in the early school years* (Vol. 72).

Larsson, H., Viding, E., Rijsdijk, F. V., & Plomin, R. (2008). Relationships between parental negativity and childhood antisocial behavior over time: A bidirectional effects model in a longitudinal genetically informative design. *Journal of Abnormal Child Psychology, 36*(5), 633-645.

Lau, J. Y., & Eley, T. C. (2008). Disentangling gene-environment correlations and interactions on adolescent depressive symptoms. *Journal of Child Psychology and Psychiatry, 49*(2), 142-150.

Lehmann, E. L. (1975). *Nonparametrics: Statistical methods based on ranks*. San Francisco, CA: Holden-Day.

Li, S., Jin, X., Wu, S., Jiang, F., Yan, C., & Shen, X. (2007). The impact of media use on sleep patterns and sleep disorders among school-aged children in China. *Sleep, 30*(3), 361-367.

Lichtenstein, P., Holm, N. V., Verkasalo, P. K., Iliadou, A., Kaprio, J., Koskenvuo, M., . . . Hemminki, K. (2000). Environmental and heritable factors in the causation of cancer - analyses of cohorts of twins from Sweden, Denmark, and Finland. *New England Journal of Medicine, 343*(2), 78-85. doi: 10.1056/NEJM200007133430201

Loehlin, J. C. (1996). The Cholesky approach: A cautionary note. *Behavior Genetics, 26*(1), 65-69.

Luo, Y. L., Haworth, C. M., & Plomin, R. (2010). A novel approach to genetic and environmental analysis of cross-lagged associations over time: the cross-lagged relationship between self-perceived abilities and school achievement is mediated by genes as well as the environment. *Twin Res Hum Genet, 13*(5), 426-436. doi: 10.1375/twin.13.5.426

Maher, B. (2008). Personal genomes: The case of the missing heritability. *Nature, 456*(7218), 18-21. doi: 10.1038/456018a

Martin, N. G., Boomsma, D., & Machin, G. (1997). A twin-pronged attack on complex traits. *Nature Genetics, 17*(4), 387-392. doi: 10.1038/ng1297-387

Martin, N. G., Eaves, L. J., Kearsey, M. J., & Davies, P. (1978). The power of the classical twin study. *Heredity, 40*, 97-116. doi: 10.1038/hdy.1978.10

Matheny, A. P., Wachs, T. D., Ludwig, J. L., & Phillips, K. (1995). Bringing order out of chaos: Psychometric characteristics of the Confusion, Hubbub and Order Scale. *Journal of Applied Developmental Psychology, 16*, 429-444.

McCarthy, D. (1972). *McCarthy Scales of Children's Abilities*. New York: The Psychological Corporation

McCarthy, M. I., Abecasis, G. R., Cardon, L. R., Goldstein, D. B., Little, J., Ioannidis, J. P., & Hirschhorn, J. N. (2008). Genome-wide association studies for complex traits: consensus, uncertainty and challenges. *Nat Rev Genet, 9*(5), 356-369.

McGue, M., & Bouchard, T. J. (1984). Adjustment of twin data for the effects of age and sex. *Behavior Genetics, 14*(4), 325-343. doi: 10.1007/BF01080045

Muris, P., Meesters, C., & van den Berg, F. (2003). The Strengths and Difficulties Questionnaire (SDQ) - Further evidence for its reliability and validity in a community sample of Dutch children and adolescents. *European Child and Adolescent Psychiatry, 12*(1), 1-8. doi: 10.1007/s00787-003-0298-2

Mynard, H., & Joseph, S. (2000). Development of the Multidimensional Peer-Victimization Scale. *Aggressive Behavior, 26*, 169-178. doi: 10.1002/(SICI)1098-2337(2000)26:2<169::AID-AB3>3.0.CO;2-A

Nansel, T. R., Overpeck, M., Pilla, R. S., Ruan, W. J., Simons-Morton, B., & Scheidt, P. (2001). Bullying behaviors among US youth - Prevalence and association with psychosocial adjustment. *Jama-Journal of the American Medical Association, 285*(16), 2094-2100.

Neale, M. C., & Cardon, L. R. (1992). *Methodology for genetic studies of twins and families*. Dordrecht: Kluwer Academic Publications.

Neale, M. C., Røysamb, E., & Jacobson, K. (2006). Multivariate genetic analysis of sex limitation and G x E interaction. *Twin Res.Hum.Genet, 9*(4), 481-489.

Oliver, B. R., Dale, P. S., Saudino, K. S., Petrill, S. A., Pike, A., & Plomin, R. (2002). The validity of parent-based assessment of non-verbal cognitive abilities of three-year olds. *Early Child Development and Care, 172*, 337-348. doi: 10.1080/03004430212713

Oliver, B. R., & Plomin, R. (2007). Twins' Early Development Study (TEDS): A multivariate, longitudinal genetic investigation of language, cognition and behavior problems from childhood through adolescence. *Twin Research and Human Genetics, 10*(1), 96-105.

Park, J. H., Wacholder, S., Gail, M. H., Peters, U., Jacobs, K. B., Chanock, S. J., & Chatterjee, N. (2010). Estimation of effect size distribution from genome-wide association studies and implications for future discoveries. *Nature Genetics, 42*(7), 570-U139. doi: 10.1038/ng.610

Petrill, S. A., Pike, A., Price, T. S., & Plomin, R. (2004). Chaos in the home and socioeconomic status are associated with cognitive development in early childhood: Environmental mediators identified in a genetic design. *Child Development, 32*(5), 445-460.

Petrill, S. A., Rempell, J., Oliver, B., & Plomin, R. (2002). Testing cognitive abilities by telephone in a sample of 6-to 8-year-olds. *Intelligence, 30*(4), 353-360.

Petrill, S. A., & Wilkerson, B. (2000). Intelligence and achievement: A behavioral genetic perspective. *Educational Psychology Review, 12*(2), 185-199.

Pike, A., & Eley, T. C. (2009). Links between parenting and extra-familial relationships: nature or nurture? *Journal of Adolescence, 32*(3), 519-533. doi: 10.1016/j.adolescence.2008.07.002

Pike, A., Iervolino, A. C., Eley, T. C., Price, T. S., & Plomin, R. (2006). Environmental risk and young children's cognitive and behavioral development. *International Journal of Behavioral Development, 30*(1), 55-66.

Plomin, R., & Bergeman, C. S. (1991). The nature of nurture: Genetic influence on "environmental" measures. *Behavioral and Brain Sciences, 14*(3), 373-385.

Plomin, R., DeFries, J. C., & Loehlin, J. C. (1977). Genotype-Environment Interaction and Correlation in Analysis of Human-Behavior. *Psychological Bulletin, 84*(2), 309-322. doi: 10.1037/0033-2909.84.2.309

Plomin, R., DeFries, J. C., McClearn, G. E., & McGuffin, P. (2008). *Behavioral genetics*. New York: Worth Publishers.

Plomin, R., Haworth, C. M., & Davis, O. S. (2009). Common disorders are quantitative traits. *Nature Reviews Genetics, 10*(12), 872-878. doi: 10.1038/nrg2670

Plomin, R., & Kovas, Y. (2005). Generalist genes and learning disabilities. *Psychological Bulletin, 131*(4), 592-617. doi: 10.1037/0033-2909.131.4.592

Price, A. L., Patterson, N. J., Plenge, R. M., Weinblatt, M. E., Shadick, N. A., & Reich, D. (2006). Principal components analysis corrects for stratification in genome-wide association studies. *Nature Genetics, 38*(8), 904-909. doi: 10.1038/ng1847

Price, T. S., Freeman, B., Craig, I. W., Petrill, S. A., Ebersole, L., & Plomin, R. (2000). Infant zygosity can be assigned by parental report questionnaire data. *Twin Research, 3*, 129-133.

Price, T. S., & Jaffee, S. R. (2008). Effects of the family environment: gene-environment interaction and passive gene-environment correlation. *Developmental Psychology, 44*(2), 305-315.

Purcell, S. (2002). Variance components models for gene-environment interaction in twin analysis. *Twin Research and Human Genetics, 5*(6), 554-571. doi: 10.1375/twin.5.6.554

Purcell, S., & Koenen, K. C. (2005). Environmental mediation and the twin design. *Behavior Genetics, 35*(4), 491-498. doi: DOI 10.1007/s10519-004-1484-9

Raftery, A. E. (1995). Bayesian model selection in social research. *Sociological Methodology, 25*, 111-163.

Rappaport, S. M., & Smith, M. T. (2010). Epidemiology. Environment and disease risks. *Science, 330*(6003), 460-461. doi: 10.1126/science.1192603

Rathouz, P. J., Van Hulle, C. A., Rodgers, J. L., Waldman, I. D., & Lahey, B. B. (2008). Specification, testing, and interpretation of gene-by-measured-environment interaction models in the presence of gene-environment correlation. *Behavior Genetics, 38*(3), 301-315.

Raven, J. C., Court, J. H., & Raven, J. (1996). *Manual for Raven's Progressive Matrices and Vocabulary Scales*. Oxford: Oxford University Press.

Rijsdijk, F. V., & Sham, P. C. (2002). Analytic approaches to twin data using structural equation models. *Briefings in bioinformatics, 3* 119-133.

Rivers, I., & Smith, P. K. (1994). Types of Bullying Behavior and Their Correlates. *Aggressive Behavior, 20*(5), 359-368.

Rowe, D. C., Jacobson, K. C., & van den Oord, E. J. (1999). Genetic and environmental influences on vocabulary IQ: parental education level as moderator. *Child Development, 70*(5), 1151-1162.

Rowe, D. C., & Rodgers, J. L. (1997). Poverty and behaviour: Are environmental measures nature or nurture? *Developmental Review, 17*, 358-375.

Rutter, M. (2007a). Gene-environment interdependence. *Developmental Science, 10*(1), 12-18. doi: 10.1111/j.1467-7687.2007.00557.x

Rutter, M. (2007b). Proceeding From Observed Correlation to Causal Inference: The Use of Natural Experiments. *Perspectives on Psychological Science, 2*(4), 377-395. doi: 10.1111/j.1745-6916.2007.00050.x

Rutter, M., Moffitt, T. E., & Caspi, A. (2006). Gene-environment interplay and psychopathology: multiple varieties but real effects. *Journal of Child Psychology & Psychiatry, 47*(3-4), 226-261. doi: 10.1111/j.1469-7610.2005.01557.x

Saudino, K. J., Dale, P. S., Oliver, B., Petrill, S. A., Richardson, V., Rutter, M., . . . Plomin, R. (1998). The validity of parent-based assessment of the cognitive abilities of 2-year-olds. *British Journal of Developmental Psychology, 16*, 349-363.

Saudino, K. J., & Plomin, R. (1997). Cognitive and temperamental mediators of genetic contributions to the home environment during infancy. *Merrill-Palmer Quarterly-Journal of Developmental Psychology, 43*(1), 1-23.

Scarr, S. (1981). *Race, social class, and individual differences in I.Q.* Hillsdale, NJ: Lawrence Erlbaum Associates.

Scarr, S. (1992). Developmental theories for the 1990s: Development and individual differences. *Child Development, 63*(1), 1-19. doi: 10.2307/1130897

Scarr, S., & McCartney, K. (1983). How people make their own environments: A theory of genotype → environment effects. *Child Development, 54*(2), 424-435.

Scarr-Salapatek, S. (1971). Race, Social Class, and IQ. *Science, 174*(4016), 1285-1295. doi: 10.1126/science.174.4016.1285

Schreier, A., Wolke, D., Thomas, K., Horwood, J., Hollis, C., Gunnell, D., . . . Harrison, G. (2009). Prospective study of peer victimization in childhood and psychotic symptoms in a nonclinical population at age 12 years. *Archives of General Psychiatry, 66*(5), 527-536. doi: 66/5/527 [pii]
10.1001/archgenpsychiatry.2009.23

Schwartz, D., McFadyen-Ketchum, S., Dodge, K. A., Pettit, G. S., & Bates, J. E. (1999). Early behavior problems as a predictor of later peer group victimization: moderators and mediators in the pathways of social risk. *Journal of Abnormal Child Psychology, 27*(3), 191-201.

Scott, F. J., Baron-Cohen, S., Bolton, P., & Brayne, C. (2002). The CAST (Childhood Asperger Syndrome Test): preliminary development of a UK screen for mainstream primary-school-age children. *Autism, 6*(1), 9-31.

Sharif, I., Wills, T. A., & Sargent, J. D. (2010). Effect of visual media use on school performance: a prospective study. *Journal of Adolescent Health, 46*(1), 52-61. doi: 10.1016/j.jadohealth.2009.05.012

Shrout, P. E., & Fleiss, J. (1979). Intraclass correlations: Uses in assessing rater reliability. *Psychological Bulletin, 86*(2), 420-428.

Smith, P., Fernandes, C., & Strand, S. (2001). *Cognitive Abilities Test 3 (CAT3)*. Windsor: nferNELSON.

So, H. C., Li, M., & Sham, P. C. (2011). Uncovering the total heritability explained by all true susceptibility variants in a genome-wide association study. *Genetic Epidemiology, 35*(6), 447-456. doi: 10.1002/gepi.20593

Team, R. D. C. (2011). R: A language and environment for statistical computing. R Foundation for Statistical Computing. Retrieved from http://www.R-project.org/

Thomas, D. (2010). Gene-environment-wide association studies: emerging approaches. *Nature Reviews Genetics, 11*(4), 259-272. doi: 10.1038/nrg2764

Trouton, A., Spinath, F. M., & Plomin, R. (2002). Twins Early Development Study (TEDS): A multivariate, longitudinal genetic investigation of language, cognition and behavior problems in childhood. *Twin Research, 5*(5), 444-448.

Tucker-Drob, E. M., Rhemtulla, M., Harden, K. P., Turkheimer, E., & Fask, D. (2010). Emergence of a Gene x Socioeconomic Status Interaction on Infant Mental Ability Between 10 Months and 2 Years. *Psychological Science, 22*(1), 125-133. doi: 10.1177/0956797610392926

Turkheimer, E., D'Onofrio, B. M., Maes, H. H., & Eaves, L. J. (2005). Analysis and interpretation of twin studies including measures of the shared environment. *Child Development, 76*(6), 1217-1233.

Turkheimer, E., Haley, A., Waldron, M., D'Onofrio, B., & Gottesman, I. I. (2003). Socioeconomic status modifies heritability of IQ in young children. *Psychological Science, 14*(6), 623-628. doi: 10.1046/j.0956-7976.2003.psci_1475.x

Uher, R., Dragomirecka, E., Papezova, H., & Pavlova, B. (2006). Use of socioeconomic status in health research. *Journal of the American Medical Association, 295*(15). doi: 10.1001/jama.295.15.1770-a

Van den Bulck, J. (2004). Television viewing, computer game playing, and Internet use and self-reported time to bed and time out of bed in secondary-school children. *Sleep, 27*(1), 101-104.

van der Sluis, S., Willemsen, G., de Geus, E. J. C., Boomsma, D. I., & Posthuma, D. (2008). Gene-environment interaction in adults' IQ scores: measures of past and present environment. *Behavior Genetics, 38*(4), 348-360. doi: 10.1007/s10519-008-9212-5

Venables, W. N., & Ripley, B. D. (2002). *Modern Applied Statistics with S. Fourth edition* (Fourth edtion ed.). New York, NY: Springer.

Visscher, P. M., Brown, M. A., McCarthy, M. I., & Yang, J. (2012). Five years of GWAS discovery. *American Journal of Human Genetics, 90*(1), 7-24. doi: 10.1016/j.ajhg.2011.11.029

Visscher, P. M., Hill, W. G., & Wray, N. R. (2008). Heritability in the genomics era--concepts and misconceptions. *Nature Reviews Genetics, 9*(4), 255-266. doi: 10.1038/nrg2322

Wachs, T. D. (1989). The nature of the physical microenvironment: An expanded classification system. *Merrill-Palmer Quarterly, 35*, 399-419.

Wang, J., Iannotti, R. J., & Luk, J. W. (2011). Peer victimization and academic adjustment among early adolescents: moderation by gender and mediation by perceived classmate support. *Journal of School Health, 81*(7), 386-392. doi: 10.1111/j.1746-1561.2011.00606.x

Wechsler, D. (1992). *Wechsler intelligence scale for children - Third Edition UK (WISC-IIIUK) Manual*. London: The Psychological Corporation.

Wellcome Trust Case Control, C. (2007). Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature, 447*(7145), 661-678.

Williams, J., Scott, F., Stott, C., Allison, C., Bolton, P., Baron-Cohen, S., & Brayne, C. (2005). The CAST (Childhood Asperger Syndrome Test): Test accuracy. *Autism, 9*(1), 45-68.

Winkel, G., Saegert, S., & Evans, G. W. (2009). An ecological perspective on theory, methods, and analysis in environmental psychology: Advances and challenges. *Journal of Environmental Psychology, 29*(3), 318-328. doi: 10.1016/j.jenvp.2009.02.005

Wohlwill, J., & Heft, H. (1987). The physical environment and the development of the child. In D. Stokol & I. Altman (Eds.), *Handbook of environmental psychology* (pp. 281-328). New York: Plenum.

Wright, S. (1918). On the Nature of Size Factors. *Genetics, 3*(4), 367-374.

Wright, S. (1934). The method of path coefficients. *Annals of Mathematical Statistics, 5*, 161-215.

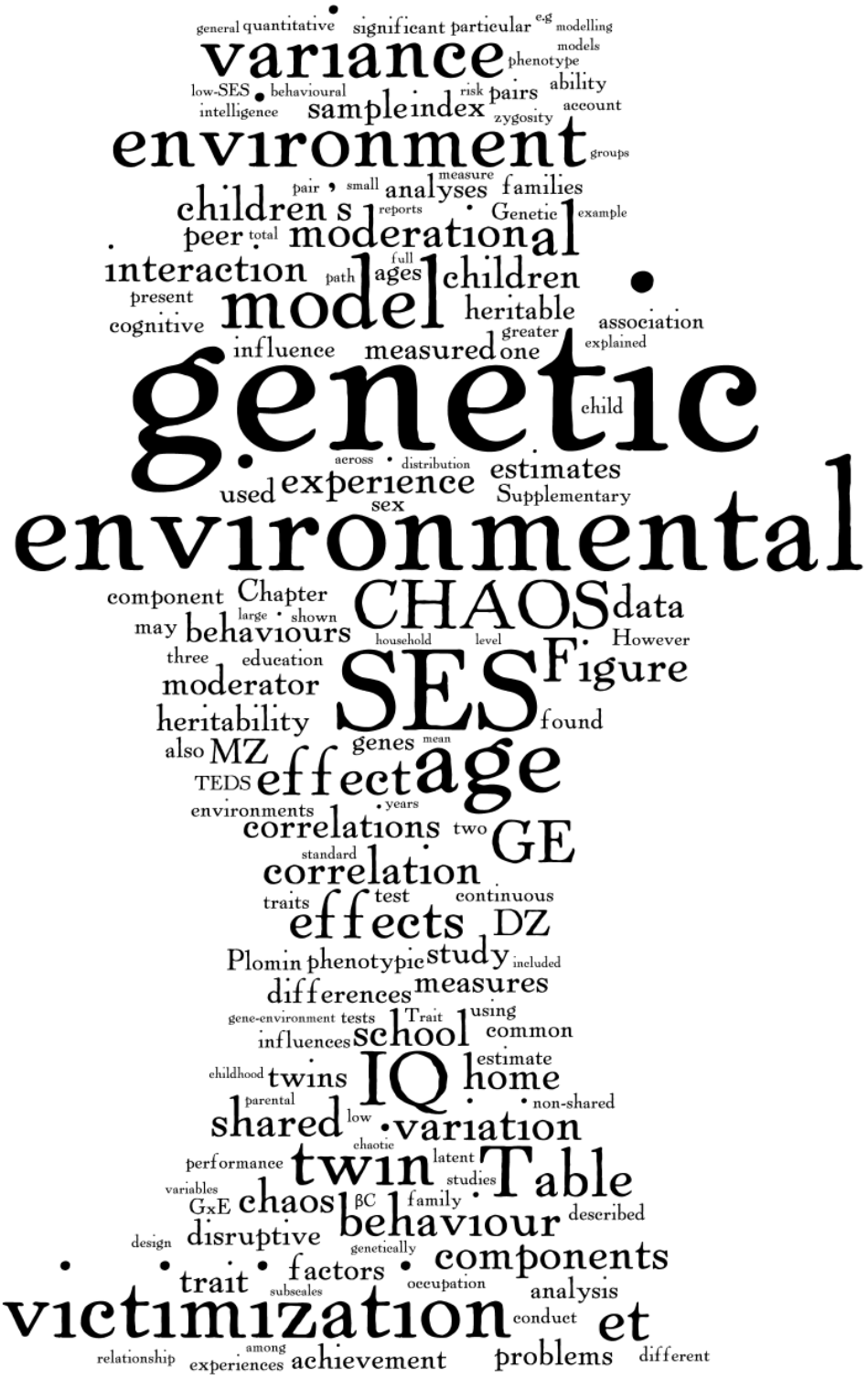
Yang, J., Benyamin, B., McEvoy, B. P., Gordon, S., Henders, A. K., Nyholt, D. R., . . . Visscher, P. M. (2010). Common SNPs explain a large proportion of the heritability for human height. *Nature Genetics, 42*(7), 565-569. doi: 10.1038/ng.608

Yang, J., Lee, S. H., Goddard, M. E., & Visscher, P. M. (2011). GCTA: a tool for genome-wide complex trait analysis. *American Journal of Human Genetics, 88*(1), 76-82. doi: 10.1016/j.ajhg.2010.11.011

Yen, I. H., & Syme, S. L. (1999). The social environment and health: a discussion of the epidemiologic literature. *Annual Review of Public Health, 20*, 287-308. doi: 10.1146/annurev.publhealth.20.1.287

Zimmerman, F. J., Glew, G. M., Christakis, D. A., & Katon, W. (2005). Early cognitive stimulation, emotional support, and television watching as predictors of subsequent bullying among grade-school children. *Archives of Pediatrics and Adolescent Medicine, 159*(4), 384-388. doi: 10.1001/archpedi.159.4.384

Appendix A Visual representation of thesis



Supplementary Figure A.1 The most frequently used words in the present thesis
This figure was generated using a word cloud tool at www.wordle.net

Appendix B Questionnaires for Chapter 2

Supplementary Table B.1 Confusion, Hubbub, and Order Scale (CHAOS)
Instruction: Please answer these questions about your home. Think about how things have been in the last 3 months. [Child-rated]
Rating: Not true/ Quite true/ Very true

1r	I have a regular bedtime routine
2	You can't hear yourself think in our home
3	It's a real zoo in our home
4r	We are usually able to stay on top of things
5	There is usually a television turned on somewhere in our home
6r	The atmosphere in our house is calm

r = item reversed

Supplementary Table B.2 Multi-dimensional Peer Victimization
Instruction: Below is a list of things that some children do to other children. How often during this school year has another pupil done these things to you? [Child-rated]
Rating: Not at all/ Once/ More than once

*	*Physical victimization*
1	Punched me
5	Kicked me
9	Hurt me physically in some way
13	Beat me up
	Verbal victimization
2	Called me names
6	Made fun of me because of my appearance
10	Made fun of me for some reason
14	Swore at me
	Social manipulation
3	Tried to get me into trouble with my friends
7	Tried to make my friends turn against me
11	Refused to talk to me
15	Made other people not talk to me
	Property damage
4	Took something of mine without permission
8	Tried to break something of mine
12	Stole something from me
16	Deliberately damaged some property of mine

* Questionnaire order

Supplementary Table B.3 Antisocial Process Screening Device (ASPD)
Instructions: Please give your answers on the basis of each child's behaviour over the last 3 months. [Parent-rated]
Rating: Not true/ Somewhat true/ Very true

*	*Impulsivity*
1	Blames others for his/her mistakes
4	Acts without thinking of the consequences
9	Gets bored easily
13	Engages in risky or dangerous activities
17	Does not plan ahead or leaves things until the "last minute"
	Callous-unemotional
3r	Is concerned about how well he/she does at school
7r	Is good at keeping promises
12r	Feels bad or guilty when he/she does something wrong
18r	Is concerned about feelings of others
19	Does not show feelings or emotions
20r	Keeps the same friends
	Narcissism
5	His/her emotions seem shallow and not genuine
8	Brags excessively about his/her abilities, accomplishments, or possessions
10	Uses or cons other people to get what he/she wants
11	Teases, makes fun of other people
14	Can be charming at times but in ways that seem insincere or superficial
15	Becomes angry when corrected or punished
16	Seems to think he/she is better than other people
2	Engages in illegal activities
6	Lies easily and skilfully

* Questionnaire order; r = item reverse

Supplementary Table B.4 Childhood Asperger Syndrome Test (CAST)
Instruction: Please give your answers on the basis of each child's behaviour over the last 3 months. [Parent-rated]
Rating: Yes/ No

*	*Social*
1r	Does s/he join in playing games with other children easily?
2r	Does s/he come up to you spontaneously for a chat?
3r	Is it important to him/ her to fit in with the peer group?
11r	Does s/he have friends, rather than just acquaintances?
12r	Does s/he often bring you things s/he is interested in to show you?
17r	Are people important to him/ her?
19r	Does s/he play imaginatively with other children, and engage in role-play?
21r	Does s/he make normal eye contact?
23	Is his/ her social behaviour very one-sided and always on his/ her own terms?
25r	Does s/he prefer imaginative activities such as play- acting or story-telling, rather than numbers or lists of facts?
28r	Does s/he care how s/he is perceived by the rest of the group?
	Non-social
4	Does s/he appear to notice unusual details that others miss?
6	Does s/he like to do things over and over again, in the same way all the time?

9r	Does s/he mostly have the same interests as his/ her peers?
10	Does s/he have an interest which takes up so much time that s/he does little else?
15	Does s/he appear to have an unusual memory for details?
22	Does s/he have any unusual or repetitive movements?
27	Does s/he try to impose routines on him/ herself, or on others, in such a way that it causes problems?
	Communication
5	Does s/he tend to take things literally?
7r	Does s/he find it easy to interact with other children?
8r	Can s/he keep a two-way conversation going?
13r	Does s/he enjoy joking around?
14	Does s/he have difficulty understanding the rules for polite behaviour?
16	Is his/her voice unusual (e.g. overly adult, flat, or very monotonous)?
18r	Is s/he good at turn-taking in conversation?
20	Does s/he often do or say things that are tactless or socially inappropriate?
24	Does she/ he sometimes say 'you' or 's/he' when s/he means 'I'?
26	Does s/he sometimes lose the listener because of not explaining what s/he is talking about?
29	Does s/he often turn conversations to his/ her favourite subject rather than following what the other person wants to talk about?
30	Does s/he have odd or unusual phrases?

* Questionnaire order; r = item reversed

Supplementary Table B.5 Moods and Feeling Questionnaire (MFQ)
Instruction: These questions are about how you might have been feeling or acting recently. For each question, please tick the box you think shows how much you have felt or acted in this way in the past two weeks. [Child-rated]
Rating: Not True/ Quite True/ Very True

1	I didn't enjoy anything at all
2	I felt so tired I just sat around and did nothing
3	I felt I was no good anymore
4	I cried a lot
5	I found it hard to think properly or concentrate
6	I hated myself
7	I was a bad person
8	I felt lonely
9	I thought nobody really loved me
10	I thought I could never be as good as other kids
11	I did everything wrong

Supplementary Table B.6 Strengths and Difficulties Questionnaire (SDQ)
Instruction: Please give your answers on the basis of each child's behaviour over the last 3 months. [Parent-rated]
Rating: Not true/ Quite True/ Very True

*	*Prosocial*
1	Considerate of other people's feelings
4	Shares readily with other children (food, games, pens etc.)
9	Helpful if someone is hurt, upset or feeling ill
17	Kind to younger children
20	Often volunteers to help others (parents, teachers, children)
	Hyperactivity
2	Restless, overactive, cannot stay still for long
10	Constantly fidgeting or squirming
15	Easily distracted, concentration wanders
21r	Thinks thing out before acting
25r	Sees tasks through to the end, good attention span
	Anxiety
3	Often complains of headaches, stomach aches or sickness
8	Many worries, often seems worried
13	Often unhappy, downhearted or tearful
16	Nervous or clingy new situations, easily loses confidence
24	Many fears, easily scared
	Conduct
5	Often has temper tantrums or hot tempers
7r	Generally obedient, does what adults request
12	Often fights with other children and bullies them
18	Often lies or cheats
22	Steals from home, school or elsewhere
	Peer problems
6	Rather solitary, tends to play alone
11r	Has at least one good friend
14r	Generally liked by other children
19	Picked on or bullied by other children
23	Get on better with adults than with other children

* Questionnaire order; r = item reversed

Appendix C Supplementary tables for Chapter 4

Supplementary Table C.1 Continuous moderator model fit for IQ by SES index 1 – parental education and occupation at 18 months.

Age	Model	Δ-2lnL	Δdf	p-value	AIC
2	$ace\ \beta_A \beta_C \beta_E\ \beta_M$	--	--	--	2667.258
	$\beta_A = 0$	1.298	1	0.254	2666.556
	$\beta_C = 0$	10.493	1	*0.001	2675.752
	$\beta_E = 0$	3.330	1	0.068	2668.588
	$\beta_A = \beta_C = 0$	10.768	2	*0.005	2674.027
	$\beta_A = \beta_E = 0$	3.378	2	0.184	2666.637
	$\beta_C = \beta_E = 0$	11.992	2	*0.002	2675.250
	$\beta_A = \beta_C = \beta_E = 0$	13.743	3	*0.003	2675.001
3	$ace\ \beta_A \beta_C \beta_E\ \beta_M$	--	--	--	795.956
	$\beta_A = 0$	0.010	1	0.921	793.966
	$\beta_C = 0$	0.216	1	0.641	794.172
	$\beta_E = 0$	0.210	1	0.646	794.167
	$\beta_A = \beta_C = 0$	0.225	2	0.894	792.181
	$\beta_A = \beta_E = 0$	0.223	2	0.894	792.180
	$\beta_C = \beta_E = 0$	0.381	2	0.827	792.337
	$\beta_A = \beta_C = \beta_E = 0$	0.466	3	0.926	790.422
4	$ace\ \beta_A \beta_C \beta_E\ \beta_M$	--	--	--	4490.210
	$\beta_A = 0$	5.018	1	*0.025	4493.228
	$\beta_C = 0$	4.946	1	*0.026	4493.156
	$\beta_E = 0$	1.312	1	0.252	4489.522
	$\beta_A = \beta_C = 0$	23.583	2	*0.000	4509.793
	$\beta_A = \beta_E = 0$	5.068	2	0.079	4491.278
	$\beta_C = \beta_E = 0$	8.138	2	*0.017	4494.347
	$\beta_A = \beta_C = \beta_E = 0$	24.109	3	*0.000	4508.319
7	$ace\ \beta_A \beta_C \beta_E\ \beta_M$	--	--	--	5340.294
	$\beta_A = 0$	1.283	1	0.257	5339.577
	$\beta_C = 0$	1.432	1	0.231	5339.727
	$\beta_E = 0$	0.547	1	0.459	5338.841
	$\beta_A = \beta_C = 0$	1.459	2	0.482	5337.753
	$\beta_A = \beta_E = 0$	1.292	2	0.524	5337.586
	$\beta_C = \beta_E = 0$	1.448	2	0.484	5337.743
	$\beta_A = \beta_C = \beta_E = 0$	1.460	3	0.692	5335.754
9	$ace\ \beta_A \beta_C \beta_E\ \beta_M$	--	--	--	2834.482

	$\beta_A = 0$	0.049	1	0.826	2832.530
	$\beta_C = 0$	5.255	1	*0.022	2837.737
	$\beta_E = 0$	0.169	1	0.681	2832.651
	$\beta_A = \beta_C = 0$	11.526	2	*0.003	2842.001
	$\beta_A = \beta_E = 0$	0.536	2	0.765	2831.018
	$\beta_C = \beta_E = 0$	7.199	2	*0.027	2837.682
	$\beta_A = \beta_C = \beta_E = 0$	11.529	3	*0.009	2840.011
10	$ace\ \beta_A \beta_C \beta_E\ \beta_M$	--	--	--	2638.801
	$\beta_A = 0$	3.912	1	*0.047	2640.713
	$\beta_C = 0$	1.086	1	0.297	2637.888
	$\beta_E = 0$	1.726	1	0.189	2638.528
	$\beta_A = \beta_C = 0$	10.489	2	*0.005	2645.291
	$\beta_A = \beta_E = 0$	3.924	2	0.141	2638.725
	$\beta_C = \beta_E = 0$	1.884	2	0.389	2636.686
	$\beta_A = \beta_C = \beta_E = 0$	11.329	3	*0.010	2644.131
12	$ace\ \beta_A \beta_C \beta_E\ \beta_M$	--	--	--	4597.302
	$\beta_A = 0$	0.304	1	0.581	4595.607
	$\beta_C = 0$	0.316	1	0.574	4595.618
	$\beta_E = 0$	0.959	1	0.327	4596.261
	$\beta_A = \beta_C = 0$	0.317	2	0.853	4593.619
	$\beta_A = \beta_E = 0$	1.199	2	0.549	4594.501
	$\beta_C = \beta_E = 0$	1.054	2	0.590	4594.357
	$\beta_A = \beta_C = \beta_E = 0$	1.435	3	0.697	4592.738
14	$ace\ \beta_A \beta_C \beta_E\ \beta_M$	--	--	--	3105.441
	$\beta_A = 0$	0.000	1	0.976	3103.442
	$\beta_C = 0$	6.471	1	*0.011	3109.912
	$\beta_E = 0$	0.020	1	0.886	3103.462
	$\beta_A = \beta_C = 0$	6.539	2	*0.038	3107.981
	$\beta_A = \beta_E = 0$	0.035	2	0.983	3101.476
	$\beta_C = \beta_E = 0$	6.473	2	*0.039	3107.914
	$\beta_A = \beta_C = \beta_E = 0$	6.744	3	0.084	3106.086

Model fit for twins with 18-month parental education and occupation. Grey highlight rows show best fitting model as indicated by AIC; * = significantly worse model fit as indicated by p-value

Supplementary Table C.2 Continuous moderator model fit for IQ by SES index 2 - parental education and occupation at age 7

Age	Model	Δ-2lnL	Δdf	p-value	AIC
7	$ace\ \beta_A \beta_C \beta_E\ \beta_M$	--	--	--	5154.816
	$\beta_A = 0$	1.545	1	0.214	5154.361

	$\beta_C = 0$	2.512	1	0.113	5155.328
	$\beta_E = 0$	0.094	1	0.760	5152.910
	$\beta_A = \beta_C = 0$	2.762	2	0.251	5153.579
	$\beta_A = \beta_E = 0$	2.409	2	0.299	5153.226
	$\beta_C = \beta_E = 0$	3.126	2	0.209	5153.942
	$\beta_A = \beta_C = \beta_E = 0$	3.126	3	0.373	5151.942
9	$ace\ \beta_A \beta_C \beta_E\ \beta_M$	--	--	--	2530.328
	$\beta_A = 0$	0.185	1	0.667	2528.513
	$\beta_C = 0$	4.656	1	*0.031	2532.984
	$\beta_E = 0$	0.023	1	0.879	2528.351
	$\beta_A = \beta_C = 0$	9.504	2	*0.009	2535.832
	$\beta_A = \beta_E = 0$	0.210	2	0.900	2526.538
	$\beta_C = \beta_E = 0$	5.267	2	0.072	2531.595
	$\beta_A = \beta_C = \beta_E = 0$	9.834	3	*0.020	2534.162
10	$ace\ \beta_A \beta_C \beta_E\ \beta_M$	--	--	--	2221.107
	$\beta_A = 0$	0.128	1	0.720	2219.235
	$\beta_C = 0$	1.279	1	0.258	2220.386
	$\beta_E = 0$	0.122	1	0.727	2219.229
	$\beta_A = \beta_C = 0$	6.166	2	*0.046	2223.273
	$\beta_A = \beta_E = 0$	0.476	2	0.788	2217.583
	$\beta_C = \beta_E = 0$	1.281	2	0.527	2218.388
	$\beta_A = \beta_C = \beta_E = 0$	7.650	3	*0.054	2222.757
12	$ace\ \beta_A \beta_C \beta_E\ \beta_M$	--	--	--	4174.114
	$\beta_A = 0$	4.280	1	*0.039	4176.394
	$\beta_C = 0$	0.826	1	0.364	4172.940
	$\beta_E = 0$	0.891	1	0.345	4173.005
	$\beta_A = \beta_C = 0$	2.681	2	0.262	4172.795
	$\beta_A = \beta_E = 0$	0.896	2	0.639	4171.010
	$\beta_C = \beta_E = 0$	1.042	2	0.594	4171.156
	$\beta_A = \beta_C = \beta_E = 0$	5.021	3	0.170	4173.135
14	$ace\ \beta_A \beta_C \beta_E\ \beta_M$	--	--	--	2769.711
	$\beta_A = 0$	3.975	1	*0.046	2771.686
	$\beta_C = 0$	3.653	1	*0.056	2771.364
	$\beta_E = 0$	1.718	1	0.190	2769.429
	$\beta_A = \beta_C = 0$	5.748	2	0.056	2771.460
	$\beta_A = \beta_E = 0$	4.012	2	0.135	2769.723
	$\beta_C = \beta_E = 0$	4.500	2	0.105	2770.211
	$\beta_A = \beta_C = \beta_E = 0$	5.751	3	0.124	2769.462

Model fit for twins with 7-year parental education and occupation. Grey highlighted rows show best fitting model as indicated by AIC; * = significantly worse model fit as indicated by p-value

Supplementary Table C.3 Continuous moderator model fit for IQ by SES index 3 - family income at age 9

Age	Model	Δ-2lnL	Δdf	p-value	AIC
9	*ace* $\beta_A \beta_C \beta_E \beta_M$	--	--	--	2971.476
	$\beta_A = 0$	0.088	1	0.767	2969.563
	$\beta_C = 0$	3.950	1	*0.047	2973.425
	$\beta_E = 0$	0.124	1	0.724	2969.600
	$\beta_A = \beta_C = 0$	11.933	2	*0.003	2979.409
	$\beta_A = \beta_E = 0$	0.138	2	0.933	2967.614
	$\beta_C = \beta_E = 0$	5.061	2	*0.080	2972.537
	$\beta_A = \beta_C = \beta_E = 0$	12.181	3	*0.007	2977.656
10	*ace* $\beta_A \beta_C \beta_E \beta_M$	--	--	--	2309.272
	$\beta_A = 0$	0.902	1	0.342	2308.174
	$\beta_C = 0$	0.808	1	0.369	2308.080
	$\beta_E = 0$	0.579	1	0.447	2307.851
	$\beta_A = \beta_C = 0$	12.190	2	*0.002	2317.462
	$\beta_A = \beta_E = 0$	0.940	2	0.625	2306.212
	$\beta_C = \beta_E = 0$	2.517	2	0.284	2307.790
	$\beta_A = \beta_C = \beta_E = 0$	12.680	3	*0.005	2315.952
12	*ace* $\beta_A \beta_C \beta_E \beta_M$	--	--	--	2196.403
	$\beta_A = 0$	0.262	1	0.609	2194.665
	$\beta_C = 0$	0.802	1	0.371	2195.205
	$\beta_E = 0$	0.005	1	0.943	2194.408
	$\beta_A = \beta_C = 0$	7.627	2	*0.022	2200.029
	$\beta_A = \beta_E = 0$	0.515	2	0.773	2192.918
	$\beta_C = \beta_E = 0$	0.988	2	0.610	2193.391
	$\beta_A = \beta_C = \beta_E = 0$	9.540	3	*0.023	2199.943
14	ace $\beta_A \beta_C \beta_E \beta_M$	--	--	--	1734.714
	$\beta_A = 0$	1.565	1	0.211	1734.279
	$\beta_C = 0$	3.091	1	*0.079	1735.805
	$\beta_E = 0$	2.634	1	0.105	1735.348
	$\beta_A = \beta_C = 0$	3.095	2	0.213	1733.808
	$\beta_A = \beta_E = 0$	2.779	2	0.249	1733.493
	$\beta_C = \beta_E = 0$	4.618	2	*0.099	1735.332
	$\beta_A = \beta_C = \beta_E = 0$	5.814	3	0.121	1734.527

Model fit for twins with 9-year family income. Grey highlighted rows show best fitting model as indicated by AIC; * = significantly worse model fit as indicated by p-value

Appendix D Supplementary material for Chapter 5

Potential sex differences in the effect of CHAOS on disruptive behaviour

In addition to the main analyses, we applied the same multivariate modelling approach to boys and girls separately. These separated-by-sex analyses were less powerful because of the reduction in sample size. However, there are two of results worth highlighting. First, the pattern of effects is largely the same for males and females. Second, although the variance components for disruptive behaviour at age 12 are similar for males and females, there is a difference in the aetiology of the effect of CHAOS on disruptive behaviour.

Of the total genetic variation in conduct at 12 (females A = 52%, males = 49%), none was due to A effects on CHAOS at 9 and 12 years in females, and about 30% was due to A effects on CHAOS at 9 and 12 years in males. The reverse pattern was true for the shared environment. Of the total shared environmental variation in conduct at 12 (females C = 28%, males = 26%), about 30% was due to C effects on CHAOS at 9 and 12 years in females, and about 12% was due to C effects on CHAOS at 9 and 12 years in males. None of the non-shared environmental effect (females E = 20%, males = 25%) was due to E effects on CHAOS at 9 and 12 years in either females or males.

Of the total genetic variation in hyperactivity at 12 (females A = 70%, males = 72%), none was due to A effects on CHAOS at 9 and 12 years in females, and about 11% was due to A effects on CHAOS at 9 and 12 years in males. Estimates of total shared environmental effects on hyperactivity at 12 years were very small, about 4% for females and about 6% in males. Non-shared environmental effects on hyperactivity at 12 years were equal in boys and girls (24%), and were not due to E effects on CHAOS at 9 and 12 years.

Supplementary Table D.1 Separated-by-sex CHAOS-conduct analyses

	MALES				FEMALES			
Latent genetic effects on CHAOS at 12:								
Standardized a paths								
	CHAOS 9	Conduct 9	Conduct 12	CHAOS 12	CHAOS 9	Conduct 9	Conduct 12	CHAOS 12
CHAOS 9	.44 (.24-.58)				.45 (.29-.57)			
Conduct 9	.12 (.00-.33)	.74 (.65-.82)			.12 (.00-.29)	.64 (.55-.70)		
Conduct 12	.12 (.00-.35)	.50 (.38-.60)	.48 (.35-.58)		.04 (.00-.21)	.58 (.48-.67)	.42 (.26-.52)	
CHAOS 12	.16 (.00-.35)	.00 (.00-.09)	.06 (.00-.20)	.10 (.00-.35)	.14 (.00-.34)	.00 (.00-.08)	.00 (.00-.11)	.36 (.13-.47)
Latent environmental effects on Conduct at 12:								
Standardized c paths								
	Conduct 9	CHAOS 9	CHAOS 12	Conduct 12	Conduct 9	CHAOS 9	CHAOS 12	Conduct 12
Conduct 9	.50 (.35-.60)				.60 (.51-.68)			
CHAOS 9	.41 (.24-.64)	.53 (.18-.66)			.42 (.30-.56)	.55 (.38-.65)		
CHAOS 12	.48 (.30-.69)	.30 (.00-.52)	.49 (.28-.58)		.40 (.29-.51)	.42 (.24-.60)	.44 (.15-.56)	
Conduct 12	.26 (.07-.41)	.13 (.00-.46)	.12 (.00-.42)	.40 (.00-.49)	.19 (.05-.30)	.24 (.12-.48)	.16 (.00-.35)	.40 (.00-.49)
Standardized e paths								
	Conduct 9	CHAOS 9	CHAOS 12	Conduct 12	Conduct 9	CHAOS 9	CHAOS 12	Conduct 12
Conduct 9	.43 (.40-.46)				.46 (.43-.49)			
CHAOS 9	.00 (.00.05)	.60 (.56-.64)			.01 (.00-.05)	.57 (.53-.57)		
CHAOS 12	.00 (.00-.03)	.02 (.00-.08)	.63 (.60-.66)		.00 (.00-.03)	.02 (.00-.07)	.57 (.54-.59)	
Conduct 12	.19 (.14-.24)	.00 (.00-.04)	.00 (.00-.02)	.46 (.43-.49)	.15 (.11-.15)	.00 (.00-.02)	.02 (.00-.04)	.42 (.40-.45)

Standardized (un-squared) path estimates shown

Supplementary Table D.2 Separated-by-sex CHAOS-hyperactivity/inattention analyses

	MALES				FEMALES			
Latent genetic effects on CHAOS at 12:								
Standardized a paths								
	CHAOS 9	Hyperactivity 9	Hyperactivity 12	CHAOS 12	CHAOS 9	Hyperactivity 9	Hyperactivity 12	CHAOS 12
CHAOS 9	.40 (.20-.55)				.45 (.30-.58)			
Hyperactivity 9	.26 (.11-.54)	.80 (.65-.84)			.27 (.14-.44)	.77 (.69-.80)		
Hyperactivity 12	.46 (.26-.84)	.51 (.11-.60)	.50 (.00-.59)		.18 (.02-.35)	.51 (.43-.57)	.65 (.60-.68)	
CHAOS 12	.19 (.00-.32)	.01 (.00-.11)	.00 (.00-.28)	.10 (.00-.35)	.12 (.00-.32)	.06 (.00-.16)	.02 (.00-.11)	.35 (.15-.46)
Latent environmental effects on Hyperactivity at 12:								
Standardized c paths								
	Hyperactivity 9	CHAOS 9	CHAOS 12	Hyperactivity 12	Hyperactivity 9	CHAOS 9	CHAOS 12	Hyperactivity 12
Hyperactivity 9	.21 (.13-.29)				.21 (.13-.29)			
CHAOS 9	.69 (.48-.76)	.00 (.00-.49)			.68 (.44-.75)	.00 (.00-.52)		
CHAOS 12	.52 (.33-.70)	.00 (.00-.67)	.53 (.00-.60)		.61 (.42-.72)	.19 (.00-.60)	.36 (.00-.55)	
Hyperactivity 12	.11 (.01-.20)	.00 (.00-.24)	.16 (.00-.24)	.00 (.00-.13)	.22 (.10-.29)	.04 (.00-.23)	.09 (.00-.22)	.00 (.00-.16)
Standardized e paths								
	Hyperactivity 9	CHAOS 9	CHAOS 12	Hyperactivity 12	Hyperactivity 9	CHAOS 9	CHAOS 12	Hyperactivity 12
Hyperactivity 9	.50 (.46-.54)				.55 (.51-.59)			
CHAOS 9	.00 (.00-.03)	.60 (.56-.64)			.00 (.00-.03)	.57 (.53-.60)		
CHAOS 12	.00 (.00-.02)	.03 (.00-.08)	.63 (.60-.66)		.00 (.00-.02)	.02 (.00-.07)	.57 (.54-.59)	
Hyperactivity 12	.24 (.20-.28)	.00 (.00-.05)	.03 (.00-.06)	.43 (.40-.46)	.26 (.22-.30)	.03 (.00-.06)	.02 (.00-.04)	.41 (.38-.43)

Standardized (un-squared) path estimates shown

Supplementary Table D.3 Cholesky decomposition of the cross-lagged relationship between parent-rated conduct and child-rated CHAOS (standardized un-squared path estimates)

Component	9-year		12-year	
	CHAOS	*Conduct*	*Conduct*	*CHAOS*
A_1	.49 (.39-.56)	.14 (.03-.25)	.07 (.00-.18)	.13 (.00-.25)
C_1	.65 (.59-.70)	.31 (.24-.39)	.30 (.22-.38)	.59 (.51-.67)
E_1	.58 (.56-.61)	.00 (.00-.03)	.00 (.00-.02)	.02 (.00-.06)
A_2		.71 (.66-.76)	.54 (.47-.59)	.00 (.00-.06)
C_2		.41 (.32-.49)	.05 (.00-.17)	.10 (.00-.20)
E_2		.45 (.43-.47)	.17 (.14-.20)	.00 (.00-.02)
A_3			.46 (.38-.52)	.03 (.00-.11)
C_3			.43 (.34-.48)	.13 (.00-.24)
E_3			.44 (.42-.46)	.01 (.00-.03)
A_4				.34 (.22-.43)
C_4				.37 (.19-.47)
E_4				.60 (.58-.62)

	Conduct	*CHAOS*	*CHAOS*	*Conduct*
A_1	.73 (.68-.78)	.09 (.03-.16)	.02 (.00-.08)	.54 (.47-.60)
C_1	.52 (.45-.58)	.39 (.30-.50)	.45 (.35-.55)	.22 (.13-.31)
E_1	.45 (.43-.47)	.00 (.00-.04)	.00 (.00-.02)	.17 (.14-.20)
A_2		.48 (.38-.56)	.13 (.00-.27)	.00 (.00-.07)
C_2		.52 (.40-.60)	.39 (.24-.52)	.19 (.11-.31)
E_2		.58 (.56-.61)	.02 (.00-.06)	.00 (.00-.01)
A_3			.34 (.21-.43)	.04 (.00-.17)
C_3			.39 (.22-.49)	.17 (.04-.32)
E_3			.60 (.58-.62)	.01 (.00-.02)
A_4				.46 (.38-.52)
C_4				.41 (.31-.46)
E_4				.44 (.42-.46)

In each row are the standardized (un-squared) path coefficients (and 95% confidence interval) leading from the latent variance component in column 1 to the measured trait labelled at the top of each column. Variance components with subscript 1 explain variance in measured trait 1 (column 2); subscripts 2, 3, and 4 denote variance components explaining residual variation in measured traits 2, 3, and 4 (columns 3, 4, and 5). A, C, and E = genetic, shared, and non-shared environmental variance components**;** CHAOS = CHAOS; conduct = conduct problems.

Supplementary Table D.4 Cholesky decomposition of the cross-lagged relationship between parent-rated hyperactivity and child-rated CHAOS (standardized un-squared estimates)

Component	9-year		12-year	
	CHAOS	*Hyperactivity*	*Hyperactivity*	*CHAOS*
A_1	.47 (.38-.56)	.20 (.12-.29)	.23 (.14-.34)	.12 (.00-.25)
C_1	.66 (.60-.71)	.21 (.16-.26)	.19 (.13-.24)	.58 (.50-.67)
E_1	.59 (.56-.61)	.00 (.00-.01)	.01 (.00-.04)	.02 (.00-.06)
A_2		.79 (.76-.81)	.53 (.49-.57)	.05 (.00-.10)
C_2		.02 (.00-.11)	.13 (.00-.20)	.41 (.00-.51)
E_2		.54 (.51-.57)	.27 (.24-.30)	.00 (.00-.01)
A_3			.60 (.56-.63)	.02 (.00-.09)
C_3			.00 (.00-.19)	.00 (.00-.50)
E_3			.41 (.40-.43)	.03 (.00-.06)
A_4				.33 (.21-.42)
C_4				.00 (.00-.26)
E_4				.60 (.58-.62)

	Hyperactivity	*CHAOS*	*CHAOS*	*Hyperactivity*
A_1	.82 (.79-.84)	.12 (.07-.16)	.09 (.04-.13)	.58 (.54-.61)
C_1	.22 (.17-.26)	.65 (.57-.70)	.59 (.46-.68)	.19 (.13-.24)
E_1	.54 (.51-.57)	.00 (.00-.01)	.00 (.00-.01)	.27 (.24-.30)
A_2		.46 (.37-.54)	.10 (.00-.21)	.09 (.00-.19)
C_2		.00 (.00-.32)	.05 (.00-.55)	.02 (.00-.20)
E_2		.59 (.56-.61)	.02 (.00-.06)	.01 (.00-.04)
A_3			.34 (.22-.42)	.04 (.00-.15)
C_3			.40 (.21-.50)	.13 (.00-.19)
E_3			.60 (.58-.62)	.02 (.00-.04)
A_4				.60 (.56-.63)
C_4				.00 (.00-.09)
E_4				.42 (.40-.43)

See note to Table D.3. hyperactivity = hyperactivity/inattention.

Appendix E Supplementary tables for Chapter 6

Supplementary Table E.1 Peer victimization univariate sex-limitation model fitting

Model	-2lnL	df	Δ-2lnL	Δdf	p-value	AIC	BIC
Physical Victimization							
Full sex-limitation	23953.95	9469	--	--	--	5015.95	-58347.29
Sub-model 1	23958.82	9470	4.87	1	0.03	5018.82	-58351.11
Sub-model 2	25699.81	9473	1745.87	4	0.00	6753.81	-56636.19
Sub-model 3	23960.66	9472	6.71	3	0.08	5016.66	-58366.66
Verbal Victimization							
Full sex-limitation	25478.42	9470	--	--	--	6538.42	-56831.51
Sub-model 1	25478.42	9471	0.00	1	1.00	6536.42	-56840.20
Sub-model 2	25680.03	9474	201.61	4	0.00	6732.03	-56664.67
Sub-model 3	25482.59	9473	4.17	3	0.24	6536.60	-56853.41
Social Manipulation							
Full sex-limitation	25792.84	9468	--	--	--	6856.84	-56499.71
Sub-model 1	25792.84	9469	0.00	1	0.99	6854.84	-56508.40
Sub-model 2	25975.59	9472	182.75	4	0.00	7031.59	-56351.73
Sub-model 3	25810.52	9471	17.69	3	0.00	6868.52	-56508.10
Property Damage							
Full sex-limitation	24469.38	9468	--	--	--	5533.38	-57823.17
Sub-model 1	24469.38	9469	0.00	1	0.98	5531.38	-57831.86
Sub-model 2	25856.66	9472	1387.27	4	0.00	6912.66	-56470.66
Sub-model 3	24471.15	9471	1.76	3	0.62	5529.15	-57847.48

All sub-models are compared to the full sex-limitation model. *Full sex-limitation* = coefficient of genetic relatedness estimated (i.e. allowed to deviate from 0.5) and ACE parameters estimated separately for males and females; *Sub-model 1* = Test of qualitative sex differences. Coefficient of genetic relatedness fixed to 0.5 in opposite-sex pairs; *Sub-model 2* = Test of both qualitative and quantitative sex differences. Coefficient of genetic relatedness fixed to 0.5 in opposite-sex pairs and ACE parameters equated across males and females; *Sub-model 3* = Test of phenotypic variance differences. Single set of ACE parameters estimated for males and females with a scalar multiplier applied to one sex to account for phenotypic variance differences; -2lnL = minus twice the log likelihood; df = degrees of freedom; Δ-2lnL = difference in minus twice the log likelihood; Δdf = difference in degrees of freedom; p-value = significance of chi square test; AIC = Akaike's information criterion; BIC = Bayesian information criterion

Appendix F Top hits and regional plot for Chapter 7

Supplementary Table F.1 Physical Victimization "top hits" from a GWAS

dbSNP rsID	Chr	Position	B	A	Frequency B	Beta	SE	P-value
rs3762399	1	198268749	C	A	0.9208894	0.2362	0.047421	6.33E-07
rs7098843	10	7692685	G	C	0.9398663	0.26139	0.052751	7.22E-07
rs6513714	20	39349815	T	A	0.3789276	0.12633	0.025853	1.03E-06
rs6129801	20	39349851	T	C	0.6211101	-0.12629	0.02585	1.03E-06
rs6072328	20	39347410	T	C	0.6211002	-0.1263	0.025851	1.03E-06
rs4812488	20	39349574	T	C	0.6217937	-0.12506	0.025861	1.33E-06
rs6072329	20	39348929	G	A	0.621988	-0.12435	0.025835	1.49E-06
rs12480916	20	39365770	T	G	0.6210289	-0.1242	0.025819	1.51E-06
rs11648191	16	78154576	T	C	0.1227212	-0.17656	0.038155	3.70E-06
rs8053967	16	78159191	T	A	0.1222988	-0.17778	0.038541	3.97E-06

Grey rows indicate imputed SNPs. dbSNP rsID = single nucleotide polymorphism database reference; Chr = chromosome; Position = base pair position; B and A = alleles at the SNP; Beta = SNPTEST codes allele A as 0 and allele B as 1 and this defines the meaning of the beta's and there se's. For example, when using the additive model the beta estimates the increase in log-odds that can be attributed to each copy of allele B; SE = standard error associated with Beta; P-value = probability value

Supplementary Table F.2 Verbal Victimization "top hits" from a GWAS

dbSNP rsID	Chr	Position	B	A	Frequency B	Beta	SE	P-value
rs3762399	1	198268749	C	A	0.9208894	0.24123	0.047434	3.67E-07
rs6513714	20	39349815	T	A	0.3789276	0.12829	0.025868	7.08E-07
rs6072328	20	39347410	T	C	0.6211002	-0.12825	0.025866	7.12E-07
rs6129801	20	39349851	T	C	0.6211101	-0.12823	0.025865	7.13E-07
rs4812488	20	39349574	T	C	0.6217937	-0.12718	0.025877	8.88E-07
rs12480916	20	39365770	T	G	0.6210289	-0.12638	0.025836	1.00E-06
rs6072329	20	39348929	G	A	0.621988	-0.12565	0.025847	1.17E-06
rs2371211	7	82209720	T	A	0.1611041	0.16318	0.03415	1.77E-06
rs7098843	10	7692685	G	C	0.9398663	0.25157	0.052782	1.88E-06
rs6029632	20	39393756	G	A	0.6160431	-0.12124	0.02575	2.50E-06

Grey rows indicate imputed SNPs. See footnote to Supplementary Table F.1

Supplementary Table F.3 Social Manipulation "top hits" from a GWAS

dbSNP rsID	Chr	Position	B	A	Frequency B	Beta	SE	P-value
rs7098843	10	7692685	G	C	0.9398663	0.27405	0.052744	2.04E-07
rs2371211	7	82209720	T	A	0.1611041	0.16779	0.034133	8.85E-07
rs6513714	20	39349815	T	A	0.3789276	0.1263	0.02585	1.03E-06
rs6072328	20	39347410	T	C	0.6211002	-0.12627	0.025849	1.03E-06
rs6129801	20	39349851	T	C	0.6211101	-0.12625	0.025847	1.04E-06
rs4812488	20	39349574	T	C	0.6217937	-0.12542	0.025857	1.23E-06
rs12480916	20	39365770	T	G	0.6210289	-0.12445	0.025817	1.43E-06
rs6072329	20	39348929	G	A	0.621988	-0.12418	0.02583	1.53E-06
rs6956744	7	82209312	T	G	0.1569329	0.162	0.034306	2.34E-06
rs3762399	1	198268749	C	A	0.9208894	0.22275	0.0474	2.61E-06

Grey rows indicate imputed SNPs. See footnote to Supplementary Table F.1

Supplementary Table F.4 Property Damage "top hits" from a GWAS

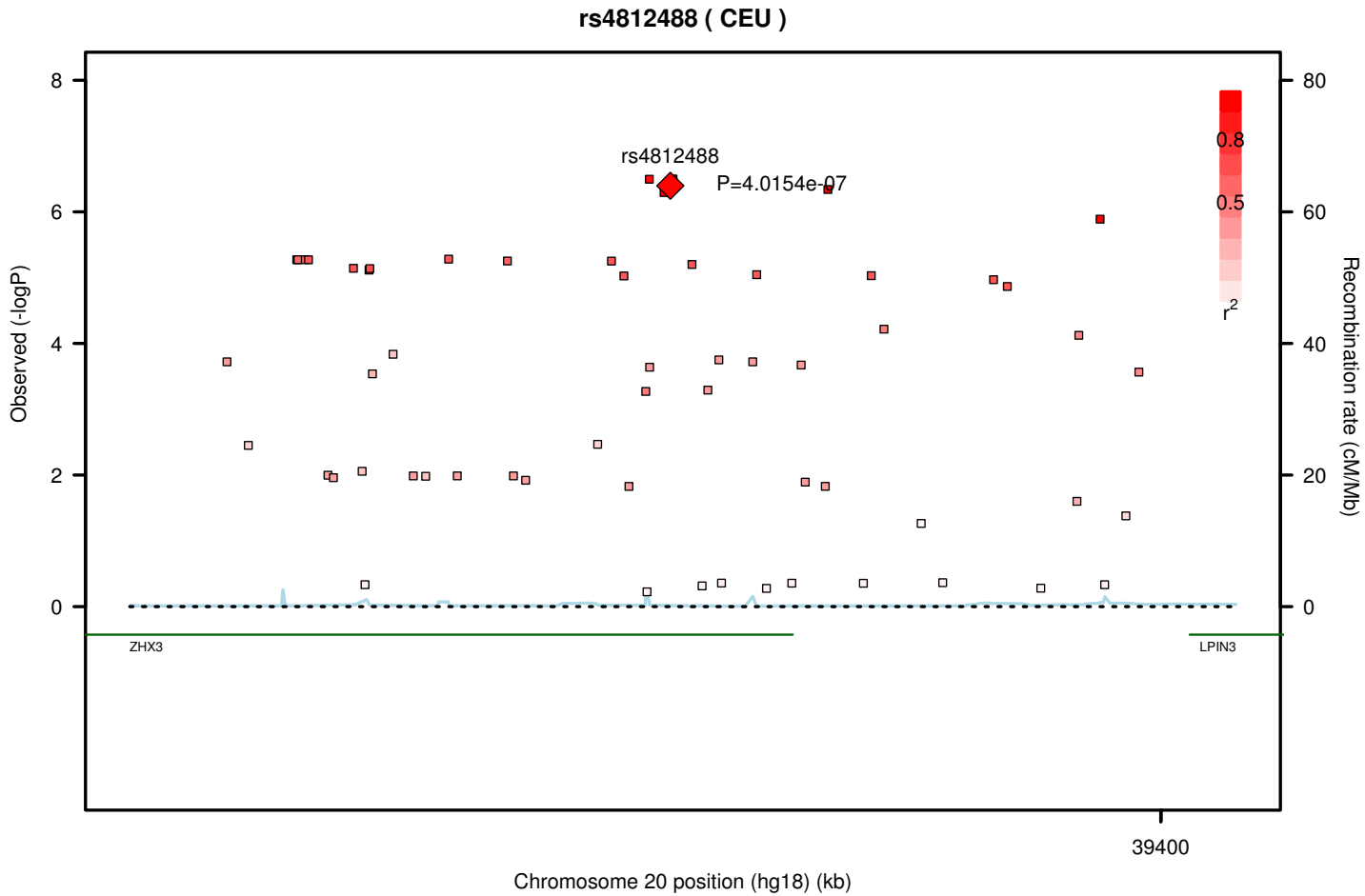
dbSNP rsID	Chr	Position	B	A	Frequency B	Beta	SE	P-value
rs6513714	20	39349815	T	A	0.3789276	0.13048	0.025834	4.40E-07
rs6072328	20	39347410	T	C	0.6211002	-0.13045	0.025833	4.42E-07
rs6129801	20	39349851	T	C	0.6211101	-0.13043	0.025831	4.43E-07
rs4812488	20	39349574	T	C	0.6217937	-0.12944	0.02584	5.47E-07
rs6072329	20	39348929	G	A	0.621988	-0.12866	0.025813	6.22E-07
rs12480916	20	39365770	T	G	0.6210289	-0.12857	0.0258	6.25E-07
rs6029632	20	39393756	G	A	0.6160431	-0.12274	0.025716	1.82E-06
rs7098843	10	7692685	G	C	0.9398663	0.24816	0.052714	2.51E-06
rs2371211	7	82209720	T	A	0.1611041	0.15768	0.034106	3.78E-06
rs6029526	20	39106032	T	A	0.5353215	-0.11389	0.025031	5.37E-06

Grey rows indicate imputed SNPs. See footnote to Supplementary Table F.1

Supplementary Table F.5 Victimization Composite "top hits" from a GWAS

dbSNP rsID	Chr	Position	B	A	Frequency B	Beta	SE	P-value
rs6513714	20	39349815	T	A	0.3789276	0.13221	0.025859	3.17E-07
rs6072328	20	39347410	T	C	0.6211002	-0.13218	0.025857	3.19E-07
rs6129801	20	39349851	T	C	0.6211101	-0.13215	0.025855	3.20E-07
rs4812488	20	39349574	T	C	0.6217937	-0.13109	0.025866	4.02E-07
rs12480916	20	39365770	T	G	0.6210289	-0.13026	0.025825	4.56E-07
rs6072329	20	39348929	G	A	0.621988	-0.12979	0.025839	5.08E-07
rs3762399	1	198268749	C	A	0.9208894	0.2302	0.047423	1.21E-06
rs6029632	20	39393756	G	A	0.6160431	-0.12461	0.02574	1.29E-06
rs7098843	10	7692685	G	C	0.9398663	0.25486	0.052762	1.36E-06
rs6029526	20	39106032	T	A	0.5353215	-0.1185	0.025053	2.24E-06

Grey rows indicate imputed SNPs. See footnote to Supplementary Table F.1



Supplementary Figure F.1 Regional plot showing the top genotyped SNP in peer victimization
rs4812488 is in an intron of the Zinc Finger and homeoboxes 3 (ZHX3) gene on chromosome 20. Lipin-3 (LPIN3) is within 50kb. It appears in the top 10 SNPs of all four victimization subtypes, and is genome-wide significant in property damage subscale and the victimization composite