

## Editorial

# Special Issue editorial: Leveraging genetically informative study designs to understand the development and familial transmission of psychopathology

Sylia Wilson<sup>1</sup>  and Soo Hyun Rhee<sup>2</sup> 

<sup>1</sup>Institute of Child Development, University of Minnesota, Minneapolis, MN, USA and <sup>2</sup>Department of Psychology and Neuroscience, Institute for Behavioral Genetics, University of Colorado Boulder, Boulder, CO, USA

Experiences in infancy, childhood, and adolescence, both positive and negative, set the stage for later adaptive and maladaptive development (Cicchetti, 2017; McLaughlin et al., 2022). It is now widely recognized that most forms of psychopathology first emerge in early childhood and adolescence, and that even psychopathology that onsets in adulthood is often presaged by earlier symptoms and problematic behaviors evident much earlier (see Casey et al., 2014; Kim-Cohen et al., 2003; Paus et al., 2008). Recent reviews and meta-analyses of the prevalence and age of onset of mental disorders around the world find that approximately a quarter of children and adolescents have experienced a mental disorder in the past year, one-third to one-half have experienced a mental disorder by 18 years, and peak age of onset is 14.5 years (Merikangas et al., 2022; Solmi et al., 2022). An extensive body of research seeking to understand those factors conferring risk for developing psychopathology or promoting adaptation has been conducted. A fundamental question is how and to what extent parents, parenting, and the rearing environment, as well as other key contextual factors, such as peers, schools, and geopolitical and sociocultural contexts, contribute to adaptive and maladaptive child outcomes. Familial risk is of particular importance, with approximately 15% to 23% of children worldwide living with a parent affected by psychopathology or substance use (Leijdesdorff et al., 2017), and these children at several-fold higher risk for developing psychopathology themselves, including anxiety, depression, attention problems, disruptive behavior, and substance use (Fisher, 2017; Hill et al., 2011; King et al., 2009; McAdams et al., 2015; Weissman et al., 2016).

### Genetic and environmental influences on adaptive and maladaptive development

Fundamental to research on the development and familial transmission of psychopathology is well established evidence that varied forms of psychopathology are genetically influenced to at least some extent (Polderman et al., 2015; Turkheimer, 2000). The estimated proportion of phenotypic variance attributable to genetic differences among individuals ranges from 37% for depression to over 70% for ADHD (Nikolas & Burt, 2010; Sullivan et al.,

2000). At the same time, it is abundantly clear that aspects of the environment are also critical in shaping the onset, expression, course, and severity of psychopathology. Differentiating genetic from environmental influences and identifying those aspects of the rearing and larger environments that are *causal* influences is necessary to understand the development and determinants of psychopathology and mechanisms of familial transmission. Doing so requires moving beyond correlational studies to study designs that are genetically and causally informative. Typical family studies of nuclear (biologically related) families and parent-child dyads can establish associations and identify potential explanatory factors, including parenting impairment and familial adversity, for the development and familial transmission of psychopathology. However, because the rearing environment (including parenting) is completely confounded with genetic influences in samples of biologically related families, even the best family studies are limited in their causal inference – they cannot account for or rule out genetic confounding to isolate nongenetically influenced environmental contributors.

Although parents, families, and the rearing environment clearly contribute to child development, the last several decades have seen accumulating evidence that genes can and do help to shape the environments experienced by children, including the rearing environment (Kendler & Baker, 2007). In their classic paper, Scarr and McCartney (1983) outlined a theory of development in which genes help to dictate experiences. Individuals' genotypes influence the environments to which they are exposed in multiple ways. Passive gene-environment correlation occurs when parents provide rearing environments to their biological children that are influenced by genes shared by parent and child (e.g., parents with a genetic liability to anxiety model fear responses to their temperamentally fearful children). Evocative gene-environment correlation occurs when children evoke responses from their environments that are influenced by their genotype (e.g., children with a genetic liability toward disruptive behavior elicit harsh reactions from parents and teachers). Active gene-environment correlation occurs when children selectively attend to or place themselves in environments that are genetically influenced (e.g., adolescents with a genetic liability toward disordered eating behaviors seeking out "pro-ana" social media). Determining which aspects of the development and familial transmission of psychopathology are genetically influenced and which are due to environmental influences – and to which specific aspects of the environment – is critical for informing etiological

**Corresponding author:** Sylia Wilson, email: [syliaw@umn.edu](mailto:syliaw@umn.edu)

**Cite this article:** Wilson, S. and Rhee, S. H. (2022). Special Issue editorial: Leveraging genetically informative study designs to understand the development and familial transmission of psychopathology. *Development and Psychopathology* 34: 1645–1652, <https://doi.org/10.1017/S0954579422000955>

models of psychopathology, ascertaining causal mechanisms, identifying those children, parents, and families at greatest risk, and developing and implementing the most targeted and effective preventive-intervention efforts. Interventions that target putative environmental factors (e.g., parental modeling, the quality of parent- or teacher-child relationships, social media) that fail to appropriately account for genetic influences on these environmental exposures will be less or even not at all effective. The complex interplay of genes and environment over time and development, and in different familial and sociocultural contexts, highlights the need for genetically informative research that can account for genetic confounding to identify causal environmental risk factors.

### Aims of this Special Issue

In this Special Issue, we have brought together a collection of papers that leverage genetically informative study designs to further our understanding of the development and familial transmission of psychopathology. In so doing, we seek to highlight for developmental psychopathology researchers the usefulness of these approaches for understanding etiology and causal mechanisms, provide an overview of classic and state-of-the-art genetically informative approaches and quantitative methods, and consider challenges and opportunities for genetically informative research as the field continues to advance. These papers illustrate many of the fundamental developmental psychopathology principles first introduced by Cicchetti (Cicchetti & Rogosch, 1996; Cicchetti, 1984, 1993; Cicchetti & Toth, 2009), including a focus on both normal and abnormal developmental processes that are evident during infancy, childhood, and adolescence; equifinality and multifinality, or the different developmental pathways that may lead to both adaptive and maladaptive functioning, including competent adaptation despite genetic liability or exposure to environmental adversity; and the importance of taking a multiple levels of analysis approach and an interdisciplinary perspective to understanding the development and familial transmission of psychopathology.

The papers in this Special Issue also illustrate several tenets of behavior genetics that may be less familiar to developmental psychopathologists, though the concepts themselves are readily integrated into a comprehensive understanding of child development within larger familial and sociocultural contexts. Behavior genetics is the study of genetic variation in psychological phenotypes (including both adaptive and maladaptive behaviors/symptomatology). Developmental psychopathology has long recognized the role of genes in child development – the field of developmental psychopathology has been interdisciplinary since its inception, integrating across embryology, epidemiology, genetics, neuroscience, philosophy, psychiatry, psychoanalysis, clinical, developmental, experimental, and physiological psychology, and sociology (Cicchetti, 1990). In fact, because developmental psychopathology explicitly emphasizes a multiple levels of analysis approach, researchers seeking to understand “the whole organism” (Sroufe & Rutter, 1984) within their contexts, and thus working at different levels, must develop theories that are consistent across all levels of inquiry (Cicchetti & Dawson, 2002). Collectively, the papers in this Special Issue highlight the importance of genetic influences on the development and familial transmission of psychopathology. At the same time, these papers also speak to important nuances in the relative influences of genes and environments, identify specific nongenetically influenced aspects of parenting and the rearing environment, and point to peer and other

sociocultural contexts that also influence adaptive and maladaptive development.

### Genetically informative approaches to the development and familial transmission of psychopathology in this Special Issue

In their comprehensive overview of genetically informative approaches, Sellers *et al.* (2022) describe many of the study designs used by papers in this Special Issue, highlighting the critical role of these approaches for understanding genetic and environmental influences on the etiology and course of psychopathology. In particular, they emphasize the potential for “genetic confounding” on putative environmental factors and the advantages of genetically informative approaches for elucidating potentially causal environmental processes in the development and familial transmission of psychopathology – after accounting for genetic influences. Of note, their review covers traditional quantitative behavior genetics approaches, including classic twin family and adoption study designs, as well as extended designs, such as children of twins, discordant siblings (including twins), maternal and paternal exposure during pregnancy, and assisted reproductive technology study designs, and more recently developed molecular genetics approaches, including polygenic scores derived from genome-wide association studies (GWAS) and Mendelian randomization. Their overview of the different approaches, including assumptions, strengths, and limitations of each, summarized in a comprehensive table, will be extremely useful to developmental psychopathologists and other researchers in outlining how the field stands to benefit from using systematic, complementary, genetically informative approaches to understand the development and familial transmission of psychopathology.

#### Classic twin family and adoption studies

Several papers in this Special Issue use classic twin family and adoption study designs. Twins and adoptive families can be thought of as a type of quasi- or “natural” experiment (Cook *et al.*, 1979; McGue *et al.*, 2010; Rutter, 2007; Shadish *et al.*, 2002) in which genes and family environments systematically (and quasi-randomly) vary, allowing comparisons across varying proportions of shared genes and environments and among biologically related and unrelated family members who do and do not also share their family environments. Twin and adoption studies allow estimation of the relative proportion of genetic and environmental influences on a behavioral trait, typically operationalized as A (additive genetic influences, the effects of individual genes summed across loci), C (shared environmental influences, that which makes members of the family similar to one another), and E (nonshared environmental influences, that which makes members of the family dissimilar, as well as any measurement error). Twin and adoption studies take advantage of differences in genetic relatedness of family members to estimate ACE using biometric models – monozygotic (“identical”) twins share 100% of segregating genes, dizygotic (“fraternal”) twins share 50% of segregating genes on average and, by definition, 100% of the shared environment and 0% of the nonshared environment. Adoptive parents and children siblings share 0% of their genes and 100% of the shared environment.

In a twin sample prospectively assessed over multiple assessments in the Wisconsin Twin Project, Planalp *et al.* (2022) examined the predictive role of a key early temperamental trait, behavioral inhibition, for later social anxiety in adolescence, finding evidence of bidirectional associations between behavioral

inhibition and social anxiety. Bivariate biometric models indicated genetic influences on shared variance between childhood behavioral inhibition and adolescent social anxiety, as well as unique variance in adolescent social anxiety, with the remaining variance explained by nonshared environmental influences. In the twin subsample in the Adolescent Brain Cognitive Development Study, Waller et al. (2022) found that higher callous-unemotional traits were associated with lower parental acceptance, more family conflict, and more parental psychopathology. Using bivariate biometric models, they found evidence of overlap in genetic and nonshared environmental influences on callous-unemotional traits and family conflict. In extended gene-by-environment interaction models, they found that the magnitude of nonshared environmental influences on callous-unemotional traits was greater among children with lower parental acceptance and greater parental psychopathology.

The adoption study design is optimal for examining environmental influences of parenting on children because it includes adoptive parents and their nonbiologically related adopted children, thus ruling out passive gene-environment correlation. However, a study examining adoptees and their adoptive parents cannot rule out genetic influences on familial transmission entirely, as adopted children's genotypes may evoke parental and familial experiences via evocative gene-environment correlation. In the Colorado Adoption Project, Gresko et al. (2022) found that parent-child relationship quality and adolescent orientation to parents were associated with adolescent substance use among both adoptive and nonadoptive families, indicating evidence for environmental influences, not passive gene-environmental correlation. Moreover, sibling associations for parenting were comparable across adoptive and nonadoptive sibling pairs, suggesting evidence against evocative gene-environment correlation. Leve et al. (2022) addressed children's genetic risk in the Early Growth and Development Study. The inclusion of biologically related birth parents, in addition to nonbiologically related adoptive parents, allowed them to consider the implications of parenting by adoptive parents among children at higher and lower genetic risk due to birth parent psychopathology. They found that structured parenting was associated with fewer behavior problems among children with higher genetic risk, but more behavior problems among children with lower genetic risk. These papers highlight the usefulness of classic twin family and adoption studies for understanding nongenetically influenced environmental (causal) effects during childhood and adolescence, the importance of disambiguating environmental influences from passive and evocative gene-environment correlation, and the implications for interventions that consider children's genetic liability, as specific aspects of parenting may be differently effective or even harmful for some children.

### *Extended twin family studies*

Many of the papers in this Special Issue use extended twin family designs that incorporate aspects of classic twin family and adoption study designs. The nuclear twin family model directly incorporates twins' biological parents into the classic twin model, allowing disambiguation of shared environmental influences into sibling level (i.e., what increases similarity between twins but not between parents and their children) and parent-child level (i.e., what increase similarity between twins and their parents) and examination of passive gene-environment correlation. Hyde et al. (2022) examined child executive function and mechanisms of familial transmission in the Michigan Twins Neurogenetics Study using

both twin family and nuclear twin family approaches. They found modest genetic and large nonshared environmental influences on child executive functioning and no evidence of shared environmental influences or passive gene-environment correlation. Bivariate biometric models also indicated little evidence of evocative gene-environment correlation, significant shared environmental overlap between both warm and harsh parenting and child executive functioning (i.e., either passive gene-environment correlation or environmental mediation), and some overlap of nonshared environmental influences on harsh parenting and child executive functioning, after accounting for genetic confounds. O'Connor et al. (2022) used the nuclear twin family study in the Michigan State University Twin Registry to examine disordered eating among pre-early puberty girls. They found that sibling level, but not parent-child level, shared environmental influences and nonshared environmental influences accounted for disordered eating, with no evidence of direct or indirect (via passive gene-environment correlation) genetic influences.

Burt et al. (2022) introduced a novel genetically informative study design that included nonbiologically related step-parents (primarily step-fathers) in the Nonshared Environment and Adolescent Development study. This approach incorporates aspects of adoption studies (i.e., rearing by a nonbiologically related step-parent) as well as classic family studies (i.e., rearing by a biologically related parent). They found that paternal depression was associated with adolescent depression and behavior problems for both biological and nonbiological step-fathers, indicating environmental influences accounted for this association. The association between paternal depression and child psychopathology was mediated by father-child conflict, even in "blended" families, in which one child was biologically related to the father and the other was not.

The children of twins study design takes advantage of the fact that children of monozygotic twins are as genetically related to their parents as they are to their parents' co-twins in order to examine familial transmission. In the Twin and Offspring Study in Sweden, Marceau et al. (2022) examined the familial transmission of internalizing and externalizing symptom severity (i.e., comorbid symptoms) and directionality (i.e., preponderance of internalizing versus externalizing symptoms). By placing their findings from this children of twins study (i.e., parents are twins) in the context of their work in a classic twin family study design (i.e., children are twins), they concluded that the familial transmission of severity and directionality are likely due to direct phenotypic transmission and/or nonpassive (evocative or active) gene-environment correlation and severity was also likely due to passive gene-environment correlation. Taken together, these papers highlight the usefulness of extended twin family approaches, especially when used in conjunction with other twin family and adoption study designs, for understanding environmental influences on children and adolescents. They also highlight several potential points of intervention in the rearing environment that show evidence of nongenetically influenced environmental (causal) mediation of associations between parental and child/adolescent functioning or psychopathology.

### *Discordant twin/sibling studies*

Some papers in this Special Issue leveraged discordant twin/sibling study designs. These designs allow the approximation of an experiment when random assignment is not ethical or feasible (e.g., to family adversity) by considering twins and siblings who are

discordant for or who differ in some type of exposure. The co-twin control study design increases causal inference by accounting for all genetic and environmental influences shared by twins in a twin pair – whether measured or unmeasured. This allows greater control of confounds than possible in the usual studies of singletons, which typically attempt to account for such confounding by including measured covariates in models – necessarily limited to the constructs researchers think to measure and the psychometric properties of those measures – and are unlikely to account for all confounds.

Using the co-twin control study design in the Child and Adolescent Twin Study in Sweden, O'Reilly *et al.* (2022) examined the potential protective influence of sports participation, physical activity, and friendship quality on substance use and self-harm behavior in adolescence. After controlling for shared familial (genetic and environmental) liability, they found suggestive evidence for the potentially causal effects of sports participation and friendship quality on increased adolescent substance use but protective effects of sports participation, physical activity, and friendship quality on decreased self-harm behaviors. Knopik *et al.* (2022) used the sibling-control study design in the Missouri Mothers and Their Children study to examine potentially causal effects of maternal smoking during pregnancy on executive functioning in early-mid adolescence. Comparing siblings discordant for prenatal exposure to maternal smoking allows the isolation of effects of maternal smoking accounting for any other family or contextual risk shared by siblings. They found little evidence of direct effects of prenatal exposure to maternal smoking on executive functioning after accounting for shared confounding and other child and family risk factors. These papers highlight the potential for discordant twin/sibling studies for increasing causal inference by accounting for both measured and unmeasured familial liability shared by twins/siblings. Isolating causal risk and protective factors or ruling out causal effects has critical prevention–intervention implications, as intervening on non-causal factors (e.g., maternal smoking) will be ineffective if other preventive–intervention efforts are not also applied (e.g., identifying at-risk families indexed by maternal smoking, addressing familial and contextual risk factors).

### *Molecular genetics approaches*

As Balbona *et al.* (2022) and Plomin *et al.* (2022) review, the third wave of genetics research has moved beyond statistical inference of ACE estimates in biometric models of twins and adoptees. Advances in direct measures of genetic influences have led to increasingly accurate polygenic scores for an increasingly broad range of relevant behavioral traits. Polygenic scores are derived in genotyped data as associations with a measured behavioral trait aggregated across millions of variants over the entire genome. Critically, once polygenic scores have been derived, they can then be computed for any individual with genotyped data.

The “DNA revolution” has revitalized interest in gene–environment interactions – variation in genetic susceptibility to environmental influences that may lead to adaptive or maladaptive development – now using polygenic scores as measured genetic effects. Plomin *et al.* (2022) illustrated this approach in the Twins Early Development Study, finding evidence for gene (polygenic scores for ADHD and neuroticism)–environment (parental discipline, family risk, family socioeconomic status) interaction effects on child behavior, emotional, and peer relationship problems, though only a small proportion of additional variance was accounted for beyond main effects. Su *et al.* (2022) examined

whether the genetic influences on childhood impulsivity, an early precursor of alcohol use, are moderated by the family environment in the Adolescent Brain Cognitive Development Study. There was no main effect of a polygenic score for alcohol use disorder and little evidence of an interaction between the polygenic score and the family environment. These papers usher in a new era of using molecular genetics approaches when considering the ways in which children and adolescents may respond differently to their environments (“goodness of fit” and differential susceptibility to the environment, Belsky, 1997; Boyce & Ellis, 2005; Chess & Thomas, 2013) or how individual vulnerability may be triggered by exposure to a stressor (diathesis–stress model, Monroe & Simons, 1991). Continued attention to the “*envirome*,” including careful measurement and deep phenotyping of potentially relevant familial and socio-cultural factors, will help to advance our understanding of the development and familial transmission of psychopathology.

Using both adolescent polygenic scores and familial risk for alcohol use disorder as indicators of genetic liability in the Collaborative Study on the Genetics of Alcoholism, Stephenson *et al.* (2022) examined whether social relationship factors promote alcohol resistance among adolescents at higher familial risk. Results were largely null and there was little support for this hypothesis except that higher father–child relationship quality was associated with later age of alcohol initiation, and greater social competence was associated with lower resistance to heavy episodic alcohol use. Saunders *et al.* (2022) took a Mendelian randomization approach that leveraged natural and random variation in the ALDH2 and ADH1B genes (common only in East/North-East Asian ancestry populations) and the adoption study design in the Sibling Interaction and Behavior Study. They found robust evidence that one ALDH2 variant is associated with lower alcohol use (but not later age of initiation) in adolescence, but not protective against other substance use, inconsistent with the gateway hypothesis. They also found that peer (but not biologically unrelated parental or sibling) alcohol use was associated with adolescent alcohol use across ALDH2 variants, consistent with environmental influences. Of note, the protective effect of the ALDH2 variant was attenuated in this Minnesota sample relative to earlier studies and in other samples in East Asian countries, suggestive of the influence of sociocultural contexts on adolescent alcohol use. Given that family history of and genetic loading for alcohol use disorder are well established risk factors for substance use in adolescence and adulthood, factors that promote alcohol resistance even among individuals at high familial and genetic risk are especially important. These papers highlight how we can use such information to identify at-risk children and adolescents, including those who show resistance in the presence of familial and genetic risk, to identify mechanisms of risk and promote adaptive outcomes.

Polygenic scores can also be used to examine how genetic influences are transmitted through families and from parent to child, and specifically “genetic nurture,” or the influence of parents’ genes not transmitted to their children on their children (i.e., passive gene–environment correlation). Kuo *et al.* (2022) used polygenic scores for externalizing behavior in both parents and children in the Collaborative Study on the Genetics of Alcoholism. They found evidence of genetic nurture, with parents’ polygenic scores for externalizing behavior associated with adolescent externalizing behavior after accounting for adolescents’ polygenic scores, as well as evidence of evocative gene–environment correlation, with adolescents’ polygenic scores associated with lower parent–child communication, less parent–child closeness, and lower parental knowledge, after accounting for parents’ polygenic scores. This paper highlights

the usefulness of using polygenic scores in both parents and children to understand parents' direct genetic influences on their children, as well as on the rearing environments they provide to their children, and children's genetic influences on the parenting they receive. In their comprehensive review of molecular genetics approaches to understanding parental genetic and environmental influences, Balbona et al. (2022) describe their recently developed, state-of-the-art approach, which situates polygenic scores within the structural equation modeling framework used in traditional quantitative behavior genetics approaches. Their SEM (structural equation modeling)-PGS (polygenic score) approach leverages polygenic scores that are and are not transmitted from parent to child in order to estimate nongenetically influenced environmental (causal) variance, even when the polygenic score has poor predictive validity, and can be applied not only in samples of trios of parents and a child, but also in samples with other relative pairs, including parent-child, spouses, and sibling pairs. Their figures, in particular, will be extremely useful in illustrating key constructs and the logic of their approach, and highlight the advantages of the SEM-PGS approach for understanding parental genetic and environmental influences on their children.

### Challenges and opportunities for genetically informative research

Collectively, the papers in this Special Issue highlight the need for and advantages of genetically informative study designs for understanding the development and familial transmission of psychopathology. They also highlight several challenges and opportunities. Some challenges, including issues of sample size and power and sample ascertainment and generalizability, are not limited to genetically informative research. Some challenges, including a lack of sample sociodemographic and global diversity, are particularly salient for behavior genetics research and require particular care and attention. Notwithstanding these challenges, the opportunities of genetically informative study designs for advancing our understanding, and, in so doing, informing the most targeted and effective prevention-intervention efforts for children, adolescents, and families are unmatched.

### Sample ascertainment and representativeness

As is true for research in general, careful attention to sample size and power is critical for genetically informative research. This is of particular importance for extended twin family studies. Including additional family members and generations allows more accurate estimates of various relevant sources of genetic and environmental influences and estimation of additional hypothesized pathways. However, increasingly complex models also require increasingly large samples, as power to detect some pathways, including gene-environment interaction, is often quite low. Because polygenic scores computed in larger samples account for greater variance, accuracy is improved for polygenic scores from GWAS conducted in sample sizes heretofore unheard of (now over a million participants for some behavioral traits). To meet the needs for increasingly larger samples, genetically informative studies are increasingly moving toward consortium-wide efforts of teams of investigators linking together existing and ongoing studies, with considerable promise for advancing developmental psychopathology research in new and exciting ways. However, this also means identifying appropriate replication samples can become increasingly difficult, an issue researchers must consider when planning their replication attempts (e.g., maintaining holdout samples).

Amassing large samples can be challenging, especially for researchers working in lower income or less highly resourced countries. There is a rich history of highly influential twin family studies in the United States and Canada, Western Europe, and Australia, but as yet fewer in Africa, Asia, Eastern Europe, and Central and South America – though a recent review highlighted twin family registries in 25 countries from six continents (Hur et al., 2019). Global and sociodemographic representation are important because ensuring that findings from genetically informative research are generalizable requires samples that are representative of the larger population. In addition, important questions about the representativeness of twins and adoptive families to singletons and nonadoptive families have also been raised. Twins have been found to be similar to singletons in psychopathology and substance use (Kendler & Prescott, 2007), brain development (barring serious pre-/perinatal complications; Knickmeyer et al., 2011; Ordaz et al., 2010), personality (Johnson et al., 2002), and cognitive ability (Christensen et al., 2006). Adoptive families do differ on average from nonadoptive families in lower rates of psychopathology and substance use and greater socioeconomic advantage, though not in aspects of family functioning (McGue et al., 2007), and these factors must be appropriately measured, modeled, and taken into consideration when interpreting findings from adoption studies. Polygenic scores, which can be computed for any individual with genotyped data, offer an opportunity to extend genetically informative research beyond twin and adoptive families.

Most twin family studies pay close attention to issues of sample ascertainment in order to develop a representative sample. Using birth records (which are publicly available in some, though not all, states in the United States or accessible to researchers in some European countries with hospital or population registries) allows the identification of (almost all) twin births, and these samples are more representative than the typical volunteer-based community samples in variation and range of socioeconomic indicators (e.g., income, education, rurality/urbanicity). However, because many of these resulting samples are local representative of twins born in the 20<sup>th</sup> century only in some United States and European countries, many are also quite homogeneous in race/ethnicity (i.e., predominantly non-Hispanic White). Note also that birth and hospital records may not be available for all infants, including those without access to prenatal or medical care, and some state policies are idiosyncratic in ways that exclude some infants (e.g., reflecting outdated and paternalistic views, birth records in Minnesota state that do not list a birth father are not made publicly available). To the extent development and psychopathology are influenced by geopolitical and sociocultural factors, twin, adoption, and family studies from a restricted set of locations and samples with restricted range in relevant sociodemographic factors will not model these influences or their role for the development and familial transmission of psychopathology in the larger population adequately. Fortunately, the fundamental importance of sociodemographically representative samples in genetically informative research (including both twin family and adoption studies and GWAS) is increasingly recognized, and great strides have been made in the last several decades toward this end around the world. Future research must continue and accelerate these efforts.

### The need for equitable genetically informative research and minimizing potential for harm

GWAS has thus far been conducted primarily in samples of European ancestry – about 79%, even though people of European

ancestry make up only 16% of the global population (Martin et al., 2019). Functionally, this means the derivation of polygenic scores is primarily conducted in European ancestry samples, with a recent review of polygenic score research conducted in 2008 through 2017 finding that 67% of studies included participants of European ancestry exclusively and 19% included participants of East Asian ancestry exclusively (Duncan et al., 2019). The predictive accuracy of polygenic scores derived among participants of European ancestry is lower when then computed in non-European ancestry samples (e.g., Duncan et al., 2019; Martin et al., 2019). This has important implications for polygenic score research, which must currently balance the tension between excluding participants of ancestry groups for whom polygenic scores have not yet been derived versus using less accurate polygenic scores within those groups, with the consequent difficulty in interpretation of results. Fortunately, these issues are at the forefront of psychiatric and behavior genetics research, and advances are being made rapidly to develop both large, ancestrally diverse samples and new theoretical models and trans-ancestry analyses (e.g., Wang et al., 2020). Developing consortia of diverse samples from around the world, and particularly establishing and supporting equitable partnerships between high-income and low- and middle-income countries, is fundamental to these efforts (Martin et al., 2022).

The need for equitable research and to minimize potential for harm is of course crucial for all science, but takes on particular importance for genetically informative research, given the historical and contemporary use of behavior genetics research to support racist, stigmatizing, and/or discriminatory agendas, particularly in the domains of intelligence and violence (Berryessa & Cho, 2013; Hayden, 2013; Martschenko et al., 2019; Wedow et al., 2022). All researchers, and especially behavior genetics researchers, must be mindful of and anticipate the ethical, legal, social, and policy contexts in which their research will be received, both within and outside of academia. Many people – both laypeople and scientists – continue to fall victim to longstanding misunderstandings of behavior genetics research. The idea that genetic influences are necessarily immutable and intractable to environmental interventions persists despite abundant evidence to the contrary. The misinterpretation of genetic determinism and misapplications of behavior genetics findings can have important policy implications that may affect children, parents, and families directly, such as calls to end the Head Start Program. Although we cannot determine definitively how research will be used once it is in the public domain, we do bear a responsibility to take every measure possible in developing our research questions, designing our studies, conducting the research, and interpreting and disseminating the findings in ways that minimize the potential for harm as much as possible.

## Conclusions

It is now abundantly clear that human behavior, including psychopathology, is influenced by both genes and the environment. Attending to both genetic and environmental influences, including the family and sociocultural contexts in which children develop, is fundamental for developmental psychopathology research. No single genetically informative study design or approach is optimal for addressing all relevant research questions. However, using complementary approaches, each with their own advantages and disadvantages, allows the accumulation of scientific knowledge. Even aspects of human behavior that are strongly genetically influenced do not imply immutability. However, determining genetic and

environmental influences on the development and familial transmission of psychopathology is critical for determining causal mechanisms, identifying at-risk children, parents, and families, and developing and implementing the most targeted and effective preventive-intervention efforts. Genetically informative research that accounts for genetic confounding to identify causal environmental risk factors allows the development of prevention and intervention approaches targeting true causal environmental risk factors that will be most effective in promoting adaptive outcomes for children, parents, and families.

**Acknowledgements.** We would like to thank the Reviewers for their time and effort in reviewing the papers included in this Special Issue.

**Funding statement.** Research reported in this article was supported by the National Institute on Drug Abuse of the National Institutes of Health under award numbers R01DA054087 (SW, SHR) and R01AG046938 (SHR).

**Conflicts of interest.** None.

## References

- Balbona, J. V., Kim, Y., & Keller, M. C. (2022). The estimation of environmental and genetic parental influences. *Development and Psychopathology*.
- Belsky, J. (1997). Variation in susceptibility to environmental influence: An evolutionary argument. *Psychological Inquiry*, 8(3), 182–186.
- Berryessa, C. M., & Cho, M. K. (2013). Ethical, legal, social, and policy implications of behavioral genetics. *Annual Review of Genomics and Human Genetics*, 14(1), 515–534.
- Boyce, W. T., & Ellis, B. J. (2005). Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. *Development and Psychopathology*, 17(2), 271–301. <https://doi.org/10.1017/S0954579405050145>
- Burt, S. A., Clark, D. A., & Neiderhiser, J. M. (2022). Illuminating the origins of the intergenerational transmission of psychopathology with a novel genetically-informed design. *Development and Psychopathology*.
- Casey, B. J., Oliveri, M. E., & Insel, T. (2014). A neurodevelopmental perspective on the research domain criteria (RDoC) framework. *Biological Psychiatry*, 76(5), 350–353.
- Chess, S., & Thomas, A. (2013). *Goodness of fit: Clinical applications, from infancy through adult life*. Routledge.
- Christensen, K., Petersen, I., Skytthe, A., Herskind, A. M., McGue, M., & Bingley, P. (2006). Comparison of academic performance of twins and singletons in adolescence: Follow-up study. *BMJ*, 333(7578), 1095.
- Cicchetti, D. (1984). The emergence of developmental psychopathology. *Child Development*, 55(1), 1–7.
- Cicchetti, D. (1990). A historical perspective on the discipline of developmental psychopathology. In J. Rolf, A. Masten, D. Cicchetti, K. Nuechterlein, & S. Weintraub (Eds.), *Risk and protective factors in the development of psychopathology* (pp. 2–28). Cambridge University Press.
- Cicchetti, D. (1993). Developmental psychopathology: Reactions, reflections. *Developmental Review*, 13(4), 471–502.
- Cicchetti, D. (2017). Biological and behavioral effects of early adversity on multiple levels of development [Special issue]. *Development and Psychopathology*, 29, 1517–1986.
- Cicchetti, D., & Dawson, G. (2002). Multiple levels of analysis. *Development and Psychopathology*, 14(3), 417–420.
- Cicchetti, D., & Rogosch, F. A. (1996). Equifinality and multifinality in developmental psychopathology. *Development and Psychopathology*, 8(4), 597–600.
- Cicchetti, D., & Toth, S. L. (2009). The past achievements and future promises of developmental psychopathology: The coming of age of a discipline. *Journal of Child Psychology and Psychiatry*, 50(1–2), 16–25.
- Cook, T. D., Campbell, D. T., & Day, A. (1979). *Quasi-experimentation: Design & analysis issues for field settings* (Vol. 351). Houghton Mifflin Boston.
- Duncan, L., Shen, H., Gelaye, B., Meijssen, J., Ressler, K., Feldman, M., Peterson, R., & Domingue, B. (2019). Analysis of polygenic risk score usage

- and performance in diverse human populations. *Nature Communications*, 10(1), 3328. <https://doi.org/10.1038/s41467-019-11112-0>
- Fisher, S. D. (2017). Paternal mental health: Why is it relevant? *American Journal of Lifestyle Medicine*, 11(3), 200–211.
- Gresko, S., Rieselbach, M., Corley, R. C., Reynolds, C. A., & Rhee, S. H. (2022). Associations between parenting characteristics and adolescent substance use: A genetically informed, longitudinal adoption study. *Development and Psychopathology*.
- Hayden, E. C. (2013). Taboo genetics. *Nature*, 502(7469), 26–28.
- Hill, S. Y., Tessner, K. D., & McDermott, M. D. (2011). Psychopathology in offspring from families of alcohol dependent female probands: A prospective study. *Journal of Psychiatric Research*, 45(3), 285–294.
- Hur, Y.-M., Bogl, L. H., Ordonana, J. R., Taylor, J., Hart, S. A., Tuvblad, C., Ystrom, E., Dalgård, C., Skytthe, A., & Willemssen, G. (2019). Twin family registries worldwide: An important resource for scientific research. *Twin Research and Human Genetics*, 22(6), 427–437.
- Hyde, L. W., Tomlinson, R. C., Weigard, A., Klump, K. L., & Burt, S. A. (2022). The role of parenting in the intergenerational transmission of executive functioning: A genetically informed approach. *Development and Psychopathology*.
- Johnson, W., Krueger, R. F., Bouchard, T. J., & McGue, M. (2002). The personalities of twins: Just ordinary folks. *Twin Research and Human Genetics*, 5(2), 125–131.
- 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., & Prescott, C. A. (2007). *Genes, environment, and psychopathology: Understanding the causes of psychiatric and substance use disorders*. Guilford Press.
- Kim-Cohen, J., Caspi, A., Moffitt, T. E., Harrington, H., Milne, B. J., & Poulton, R. (2003). Prior juvenile diagnoses in adults with mental disorder: Developmental follow-back of a prospective-longitudinal cohort. *Archives of General Psychiatry*, 60(7), 709–717. <https://doi.org/10.1001/archpsyc.60.7.709>
- King, S. M., Keyes, M., Malone, S. M., Elkins, I., Legrand, L. N., Iacono, W. G., & McGue, M. (2009). Parental alcohol dependence and the transmission of adolescent behavioral disinhibition: A study of adoptive and non-adoptive families. *Addiction*, 104(4), 578–586.
- Knickmeyer, R. C., Kang, C., Woolson, S., Smith, J. K., Hamer, R. M., Lin, W., Gerig, G., Styner, M., & Gilmore, J. H. (2011). Twin-singleton differences in neonatal brain structure. *Twin Research and Human Genetics*, 14(3), 268–276.
- Knopik, V. S., Micalizzi, L., Marceau, K., Loviska, A. M., Yu, L., Bien, A. C., Doner, E., Evans, A., Palmer, R. H. C., & Heath, A. C. (2022). The roles of familial transmission and smoking during pregnancy on executive function skills: A sibling comparison study. *Development and Psychopathology*.
- Kuo, S., Poore, H. E., Barr, P., Chirico, I., Aliev, F., Bucholz, K. K., Chan, G., Kamarajan, C., Kramer, J., McCutcheon, V. V., Plawewski, M. H., & Dick, D. M. (2022). The role of parental genotype in the intergenerational transmission of externalizing behavior: Evidence for genetic nurturance. *Development and Psychopathology*.
- Leijdesdorff, S., van Doesum, K., Popma, A., Klaassen, R., & van Amelsvoort, T. (2017). Prevalence of psychopathology in children of parents with mental illness and/or addiction: An up to date narrative review. *Current Opinion in Psychiatry*, 30(4), 312–317.
- Leve, L. D., Anderson, D., Harold, G. T., Neiderhiser, J. M., Natsuaki, M. N., Shaw, D. S., Ganiban, J. M., & Reiss, D. (2022). Developmental profiles of child behavior problems from 18 months to 8 years: The protective effects of structured parenting vary by genetic risk. *Development and Psychopathology*.
- Marceau, K., Yu, L., Knopik, V. S., Ganiban, J. M., & Neiderhiser, J. M. (2022). Intergenerational transmission of psychopathology: An examination of symptom severity and directionality. *Development and Psychopathology*.
- Martin, A. R., Kanai, M., Kamatani, Y., Okada, Y., Neale, B. M., & Daly, M. J. (2019). Clinical use of current polygenic risk scores may exacerbate health disparities. *Nature Genetics*, 51(4), 584–591. <https://doi.org/10.1038/s41588-019-0379-x>
- Martin, A. R., Stroud, R. E., Abebe, T., Akena, D., Alemayehu, M., Atwoli, L., Chapman, S. B., Flowers, K., Gelaye, B., & Gichuru, S. (2022). Increasing diversity in genomics requires investment in equitable partnerships and capacity building. *Nature Genetics*, 54(6), 740–745.
- Martschenko, D., Trejo, S., & Domingue, B. W. (2019). Genetics and education: Recent developments in the context of an ugly history and an uncertain future. *AERA Open*, 5(1), 2332858418810516.
- McAdams, T. A., Rijsdijk, F. V., Neiderhiser, J. M., Narusyte, J., Shaw, D. S., Natsuaki, M. N., Spotts, E. L., Ganiban, J. M., Reiss, D., & Leve, L. D. (2015). The relationship between parental depressive symptoms and offspring psychopathology: Evidence from a children-of-twins study and an adoption study. *Psychological Medicine*, 45(12), 2583–2594.
- McGue, M., Keyes, M., Sharma, A., Elkins, I., Legrand, L., Johnson, W., & Iacono, W. G. (2007). The environments of adopted and non-adopted youth: Evidence on range restriction from the Sibling Interaction and Behavior Study (SIBS). *Behavior Genetics*, 37(3), 449–462.
- McGue, M., Osler, M., & Christensen, K. (2010). Causal inference and observational research: The utility of twins. *Perspectives on Psychological Science*, 5(5), 546–556.
- McLaughlin, K. A., Ellis, B. J., & Cicchetti, D. (Eds.) (2022). Dimensions of early experience and adaptive and maladaptive development [Special issue]. *Development and Psychopathology*, 34, 447–754.
- Merikangas, K. R., Nakamura, E. F., & Kessler, R. C. (2022). Epidemiology of mental disorders in children and adolescents. *Dialogues in Clinical Neuroscience*, 11(1), 7–20.
- Monroe, S. M., & Simons, A. D. (1991). Diathesis-stress theories in the context of life stress research: Implications for the depressive disorders. *Psychological Bulletin*, 110(3), 406–425. <https://doi.org/10.1037/0033-2909.110.3.406>
- Nikolas, M. A., & Burt, S. A. (2010). Genetic and environmental influences on ADHD symptom dimensions of inattention and hyperactivity: A meta-analysis. *Journal of Abnormal Psychology*, 119, 1–17.
- O'Connor, S., Mikhail, M., Anaya, C., Haller, L., Burt, S. A., McGue, M., Iacono, W. G., & Klump, K. L. (2022). Exploring the possibility of parents' broad internalizing phenotype acting through passive gene-environment correlations on daughters' disordered eating. *Development and Psychopathology*.
- O'Reilly, L. M., Elam, K., Adams, S., Pettersson, E., Klonsky, E. D., Larsson, H., Lundstrom, S., Lichtenstein, P., D'Onofrio, B. M., & Quinn, P. D. (2022). Examining protective factors for substance use problems and self-harm behavior during adolescence: A longitudinal co-twin control study. *Development and Psychopathology*.
- Ordaz, S. J., Lenroot, R. K., Wallace, G. L., Clasen, L. S., Blumenthal, J. D., Schmitt, J. E., & Giedd, J. N. (2010). Are there differences in brain morphology between twins and unrelated singletons? A pediatric MRI study. *Genes, Brain and Behavior*, 9(3), 288–295.
- Paus, T., Keshavan, M., & Giedd, J. N. (2008). Why do many psychiatric disorders emerge during adolescence? *Nature Reviews Neuroscience*, 9(12), 947–957.
- Planalp, E. M., Goldsmith, H. H., Hilton, E., Phan, J., Sarkisian, K., Carroll, I., & Lemery-Chalfant, K. (2022). Childhood inhibition predicts adolescent social anxiety: Findings from a longitudinal twin study. *Development and Psychopathology*.
- Plomin, R., Gidziela, A., Malanchini, M., & von Stumm, S. (2022). Gene-environment interaction using polygenic scores: Do polygenic scores for psychopathology moderate predictions from environmental risk to behavior problems? *Development and Psychopathology*.
- Polderman, T. J., Benyamin, B., De Leeuw, C. A., Sullivan, P. F., Van Bochoven, A., Visscher, P. M., & Posthuma, D. (2015). Meta-analysis of the heritability of human traits based on fifty years of twin studies. *Nature Genetics*, 47(7), 702–709.
- Rutter, M. (2007). Proceeding from observed correlation to causal inference: The use of natural experiments. *Perspectives on Psychological Science*, 2(4), 377–395. <https://doi.org/10.1111/j.1745-6916.2007.00050.x>
- Saunders, G. R. B., McGue, M., Iacono, W. G., & Vrieze, S. I. (2022). Longitudinal effects and environmental moderation of ALDH2 and ADH1B gene variants on substance use from age 14 to 40. *Development and Psychopathology*.
- Scarr, S., & McCartney, K. (1983). How people make their own environments: A theory of genotype greater than environment effects. *Child Development*, 54(2), 424–435. <https://doi.org/10.2307/1129703>

- Sellers, R., Riglin, L., Gordon, H. W., & Thapar, A. (2022). Using genetic designs to identify likely causal environmental contributions to psychopathology. *Development and Psychopathology*.
- Shadish, W. R., Cook, T. D., & Campbell, D. T. (2002). *Experimental and quasi-experimental designs for generalized causal inference*. Houghton, Mifflin and Company.
- Solmi, M., Radua, J., Olivola, M., Croce, E., Soardo, L., Salazar de Pablo, G., Il Shin, J., Kirkbride, J. B., Jones, P., & Kim, J. H. (2022). Age at onset of mental disorders worldwide: Large-scale meta-analysis of 192 epidemiological studies. *Molecular Psychiatry*, 27(1), 281–295.
- Sroufe, L. A., & Rutter, M. (1984). The domain of developmental psychopathology. *Child Development*, 55(1), 17–29.
- Stephenson, M., Aliev, F., Kuo, S. I.-C., Edwards, A. C., Pandey, G., Su, J., Kamarajan, C., Dick, D., & Salvatore, J. E. (2022). The role of adolescent social relationships in promoting alcohol resistance: Interrupting the intergenerational transmission of alcohol misuse. *Development and Psychopathology*.
- Su, J., Trevino, A., Jamil, B., & Aliev, F. (2022). Genetic risk of alcohol use disorders and childhood impulsivity: Examining the role of parenting and family environment. *Development and Psychopathology*.
- Sullivan, P. F., Neale, M. C., & Kendler, K. S. (2000). Genetic epidemiology of major depression: Review and meta-analysis. *American Journal of Psychiatry*, 157, 1552–1562.
- Turkheimer, E. (2000). Three laws of behavior genetics and what they mean. *Current Directions in Psychological Science*, 9(5), 160–164.
- Waller, R., Perlstein, S., Hawes, S. W., Vazquez, A., Pacheco-Colon, I., Lehman, S., Parent, J., & Byrd, A. L. (2022). Genetic versus environmental influences on callous-unemotional traits in preadolescence: The role of parenting and parental psychopathology. *Development and Psychopathology*.
- Wang, Y., Guo, J., Ni, G., Yang, J., Visscher, P. M., & Yengo, L. (2020). Theoretical and empirical quantification of the accuracy of polygenic scores in ancestry divergent populations. *Nature Communications*, 11(1), 1–9.
- Wedow, R., Martschenko, D., & Trejo, S. (2022). *Scientists must consider the risk of racist misappropriation of research*. Scientific American.
- Weissman, M. M., Berry, O. O., Warner, V., Geleroff, M. J., Skipper, J., Talati, A., Pilowsky, D. J., & Wickramaratne, P. (2016). A 30-year study of 3 generations at high risk and low risk for depression. *JAMA Psychiatry*, 73(9), 970–977.