ENVIRONMENTAL-RISK (E-RISK) LONGITUDINAL TWIN STUDY
CONCEPT PAPER FORM

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Provisional Paper Title: **Does polyvictimization exposure moderate a genetic propensity to psychopathology?**

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Objective of the study and its significance

It has long been recognized that exposure to traumatic stress or adversity is a strong risk factor for the development of later psychopathology. This relationship appears to transcend both exposure type and diagnostic boundaries, as multiple types of stressful experiences have each been connected to a broad array of psychiatric disorders (Scott, Smith, & Ellis, 2010; Vachon, Krueger, Rogosch, & Cicchetti, 2015; Schaefer et al., 2017). Interestingly, despite these robust associations, years of accumulated research suggest that not everyone exposed to these experiences will go on to develop psychiatric symptoms (Collishaw et al., 2007). This observation has led to an enduring interest in identifying individuals who are particularly susceptible or resilient to these experiences, and in understanding how risk/resilience factors might be manipulated to improve population health.

In the past decade, researchers studying mental illness have turned increasingly towards a "gene-environment interaction" perspective to explain this heterogeneity. This model suggests that an individual's susceptibility or resilience to the psychopathological effects of adverse environmental exposures is determined in large part by a variety of individual factors under genetic influence (e.g. temperament, personality, cognition, and/or stress reactivity). Recently, however, psychiatric genetics has moved beyond simplistic estimates of heritable and nonheritable determinants of psychopathology into studies that examine how the relative contribution of genetic and environmental risk factors changes as a function of the environmental context. This research has significant implications for etiological theories because it suggests that the influence of genetic propensity to disorder may become relatively stronger or weaker in particular contexts (e.g., those characterized by high versus low levels of traumatic stress).

There are three competing hypotheses to consider regarding the potential interaction of environmental stressors and genetic propensity. First, greater stress exposure may increase the heritability of psychiatric illness if it causes underlying differences in genetic risk variants to exert their pathological effects. This is the classic example of diathesis-stress demonstrated by early G x E studies such as Caspi et al. (2003), which reported that individuals with one or two copies of the short allele of the 5-HTT promoter polymorphism experienced greater levels of depressive symptoms *only* if they had also experienced

elevated levels of stressful life events. A second possibility is that greater stress exposure in adolescence may decrease the heritability of psychopathology. This pattern might occur in situations where the exposure is so traumatic that it overrides the effects of genetic predisposition, such that nearly everyone exposed to sufficient adversity will develop psychiatric symptoms (analogous to the finding that the heritability of intelligence is high in children born to affluent families, but close to zero in children born into poverty; Turkheimer, Haley, Waldron, D'Onofrio, & Gottesman, 2003). Finally, as suggested by data from the Minnesota Twin Study, it is possible that the effect of victimization exposure on the heritability of psychopathology changes as a function of the psychiatric spectra examined (Hicks, DiRago, Iacono, & McGue, 2009; Hicks, South, DiRago, Iacono, & McGue, 2009). For example, it is possible that high levels of environmental stress leads to increased heritability for externalizing disorders, but not internalizing disorders (or vice versa).

Although the number of studies examining how the effects of genetic propensity to mental disorder change across different environments has steadily increased in recent years, our understanding of gene-environment interplay in the etiology of mental illness remains limited in four important ways.

First, the majority of studies that examine how the effects of genetic propensity change with environmental adversity have considered a relatively limited range of exposures, defining "stress" or "adversity" as exposure to one or more common developmental risk factors, including poverty, negative parenting behaviors, and martial or family conflict. Substantially fewer studies have examined how exposure to serious trauma (such as severe physical, emotional, or sexual victimization) alters gene-environment interplay.

A second limitation of the existing literature concerns the range of outcomes studied. Although some previous studies have used scores on broader, hierarchical measures of psychopathology such as "internalizing" and "externalizing" symptoms as outcomes (e.g., Hicks, DiRago, et al., 2009; Hicks, South, et al., 2009), many others have examined only narrow psychiatric outcomes, such as depressive symptoms (e.g., Lau & Eley, 2008). This focus on narrow, disorder-specific outcomes is at odds with accumulating research indicating that the main effects of stressful life experiences like victimization are generalized rather than specific (Keyes et al., 2012; Schaefer et al., 2017; Vachon, Krueger, Rogosch, & Cicchetti, 2015), and, moreover, prevents researchers from testing for evidence of (non-)specificity in their moderation analyses.

A third limitation of the existing literature is not substantive, but methodological. The traditional bivariate biometric model (Purcell, 2002) used in several previous studies of gene-environment interplay (e.g., Hicks, DiRago, et al., 2009; Hicks, South, et al., 2009; Lau & Eley, 2008; Lau, Gregory, Goldwin, Pine, & Eley, 2007; South & Krueger, 2011; South & Krueger, 2008) has been shown to have several limitations, including risk of false-positive moderation results under certain conditions (Rathouz, Van Hulle, Rodgers, Waldman, & Lahey, 2008; van der Sluis, Posthuma, & Dolan, 2012). Thus, it is unclear whether the moderation effects reported in certain papers are "real" or spurious.

Finally, perhaps due in part to these issues, studies examining the interaction between genetic influences and environmental moderators using biometric twin models have so far returned mixed results. For example, two studies have reported that the variance in internalizing symptoms attributable to environmental influences increases in the context of increasing parental negativity (Feinberg, Button, Neiderhiser, Reiss, & Hetherington, 2007), and low socioeconomic status (South & Krueger, 2011), indicating that such exposures override the effects of genetic predisposition. However, other studies have found that the variance of internalizing symptoms attributable to genetic differences *increases* as a function of exposure to negative life events (Distel et al., 2011; Lau & Eley, 2008) and family conflict (Rice, Harold, Shelton, & Thapar, 2006), suggesting the opposite pattern. Finally, still others have reported increases in *both* genetic and nonshared environmental variance with increased exposure to the stressors of maternal punitive discipline (Lau & Eley, 2008) and low martial quality (South & Krueger, 2008). An analogous pattern of conflicting findings can also be seen in studies that measure genetic propensity directly using polygenic scores (PGSs). An initial study reported a significantly stronger impact of PGS on MDD risk in individuals exposed to childhood trauma, versus those without such an exposure (Peyrot et al., 2014). A second, however, reported the opposite finding (Mullins et al., 2016), and meta-analysis of

both cohorts indicated no interaction whatsoever (Peyrot et al., 2017).

The proposed study addresses each of these limitations directly. To examine whether existing moderation findings hold true for severe, traumatic exposures in addition to more "normative" forms of adversity, I propose examining how the relative contribution of genetic propensity to psychopathology changes as a function of adolescent victimization exposure. Victimization exposure in adolescence may also be a particularly powerful choice of moderator given work suggesting that it is likely a *causal contributor* to psychopathology (Schaefer et al., 2017). To better capture the broad and non-specific main effects of victimization, I will study the effects of genetic propensity and victimization exposure on general psychopathology (captured by the "p-factor", Caspi et al., 2014). Analysis of general psychopathology will allow me to examine whether the predictive power of genetic propensity to psychopathology changes as a function of victimization exposure. To address questions of specificity, I will repeat these analyses using Study members' scores on the constitutive spectra (Internalizing, Externalizing, and Thought Disorder) of general psychopathology as outcomes. Analysis of these factor scores will allow me to test whether the moderating effects of victimization exposure on genetic propensity differ across psychiatric spectra.

Finally, to increase confidence in the replicability of observed results, I propose testing whether victimization exposure moderates the effects of genetic propensity to psychopathology using three different approaches. First, I will test whether family history of psychopathology interacts with victimization to become a stronger predictor of psychopathology in Study members exposed to high levels of victimization stress. This analysis is often used as an initial test of gene-environment interaction, with family history of disorder serving as an approximation of an individual's genetic risk. A second approach involves the use of measured genetic risk (in the form of PGSs) in place of family history. This method has the advantage of using the participant's own genetic information, but may be underpowered to detect interaction effects given the small effect sizes of most PGSs. Finally, I will analyze differences in phenotypic variance attributable to genetic influences using biometric twin models. These approaches make use of phenotypic correlations between monozygotic and dizygotic twins to estimate heritability across a range of exposure levels.

Statistical analyses:

Family history of psychiatric disorder

To test whether family history of disorder is a stronger predictor of psychopathology at age 18 in Study members who were heavily victimized, I will run a linear regression analysis predicting Study members' scores on "p" at age 18 as a function of adolescent poly-victimization, family history of psychiatric disorder, and the interaction of poly-victimization and family history of psychiatric disorder, controlling for sex. A significant interaction between victimization and family history would indicate that the importance of family history in predicting psychopathology changes depending on the extent of victimization exposure. I will also include tests for "gene-environment" correlations between family history of psychopathology and poly-victimization (i.e. modeling poly-victimization as a function of family history; see Schaefer et al., 2017), as such an effect could potentially bias tests for interactions (Purcell, 2002).

Polygenic scores

To test whether measured genetic propensity to disorder is a stronger predictor of psychopathology at age 18 in Study members who were heavily victimized, I will model "p" as a function of adolescent poly-victimization, mental disorder polygenic scores (PGSs), and the interaction (poly-victimization x PGS), controlling for sex. I will also test for gene-environment correlations between measured genetic risk and poly-victimization and compute multiple-R^2 to assess what proportion of variance in "p" is explained by the polygenic risk score and adolescent poly-victimization independently, as well as their interaction.

I plan to test the model above using two different types of measured genetic risk.

(1) *Single PGSs*. Because there is currently no published GWAS of the "p-factor", I plan to select previously-published PGSs based on the available literature concerning the nature and correlates of "p",

and then test the extent to which the main effect of each PGSs predicts “p” in the E-risk sample before using these scores in tests of interactions.

One hypothesis regarding the nature of “p” is that it reflects a diffuse unpleasant affective state, such as neuroticism or negative emotionality (Lahey et al., 2017). Indeed, twin studies reveal common genetic influences on negative emotionality and a general factor of psychopathology (Tackett et al., 2013). Thus, I will test the extent to which a PGS for neuroticism is a reasonable “stand-in” for “p” (Okbay et al., 2016).

A second hypothesis is that “p” reflects the elements of thought disorder present at the extreme of nearly every form of severe mental illness (Caspi et al., 2014). Because schizophrenia is arguably the mental disorder most strongly associated with disordered thinking, I will also test the extent to which a schizophrenia PGS is a reasonable proxy for “p” (Ripke et al., 2014).

Finally, I will test the extent to which a cross-disorder PGS (based on results from the PGC cross-disorder GWAS; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013) is a reasonable proxy for “p”. Arguably the most “face valid” of the three, the PGC cross-disorder GWAS can be viewed as one of the first serious efforts to uncover genetic variants that contribute to the development of multiple forms of psychopathology (in this case, schizophrenia, bipolar disorder, major depression, ADHD, and autism).

(2) *Factor-analyzed PGSs for “p”.* Previous studies have indicated that “p” is predicted equally well by family histories of depression, anxiety, substance-use, and psychotic disorders (Caspi et al., 2014). Given that the p-factor is typically derived through confirmatory factor analysis of symptom-level data, an analogous method for deriving measured genetic propensity to “p” would be to factor-analyze all relevant single-trait PGSs to derive a single PGS reflecting measured genetic propensity to psychopathology. To date, the Psychiatrics Genomics Consortium has published GWASs of attention-deficit hyperactivity disorder (ADHD), anorexia nervosa (AN), autism-spectrum disorders (ASD), bipolar disorder (BPD), major depressive disorder (MDD), schizophrenia (SCZ). Thus, I will use these publications as the starting point for computing a factor-analyzed PGS aimed at capturing genetic propensity to general psychopathology.

Fig.1 shows the genetic correlations among multiple psychiatric disorder phenotypes. Genetic correlation is an estimate of the additive genetic effect that is shared between pairs of traits. The higher the genetic correlation, the more likely it is that the two traits share at least some of the same genes. The generally positive genetic correlations between each of the disorders studied is consistent with the notion that there exists some kind of shared genetic basis to general liability (“p”).

	ASD	AN	MDD	BIP	SCHZ	ADHD	CROSS
ASD	1						
AN	**0.03** (0.101) 0.769	1					
MDD	**0.215** (0.144) 0.135	0.137 (0.133) 0.3047	1				
BIP	0.044 (0.101) 0.660	0.112 (0.082) 0.174	**0.478** (0.106) <0.001	1			
SCHZ	0.14 (0.086) 0.102	**0.19** (0.045) <0.001	**0.508** (0.075) <0.001	**0.794** (0.039) <0.001	1		
ADHD	-0.164 (0.144) 0.253	0.192 (0.116) 0.099	0.236 (0.191) 0.215	0.265 (0.154) 0.085	**0.232** (0.089) 0.009	1	
CROSS	**0.363** (0.06) <0.001	**0.245** (0.067) <0.001	**0.709** (0.05) <0.001	**0.891** (0.035) <0.001	**0.913** (0.025) <0.001	**0.343** (0.106) 0.001	1

Figure 1*. Genetic correlations among psychiatric disorder phenotypes analyzed by GWAS (adapted from Bulik-Sullivan et al., 2015). From top to bottom in each cell: Correlation, (SE), p-value. Correlations in* ***bold*** *are significant at p <0.05. Darker blue signifies a stronger positive correlation; orange a negative correlation. ASD = autism spectrum disorder, AN = anorexia nervosa, MDD = major depressive disorder, BIP = bipolar disorder, SCHZ = schizophrenia, CROSS = cross-disorder.*

Behavioral genetic analyses

To test whether genetic influences on psychopathology increase under conditions of higher poly-victimization using a behavioral genetic approach, I will first compute a Cholesky bivariate twin model (which is functionally equivalent to the correlated-factors bivariate twin model computed in Study 2). This approach is commonly used in research on G x E interactions in psychopathology, and is appropriate when there is temporal ordering of the moderator (poly-victimization in adolescence) and phenotype (psychopathology in young adulthood). This model would account for the extent to which the same versus different genetic and environmental factors contribute to each construct. The bivariate model computed in Schaefer et al. (2017) indicates that there is substantial overlap in the genetic factors that account for variance in both victimization exposure and psychopathology (r_A = 0.75, 95% CI: 0.49, 1.00); this means that the genetic factors that predispose Study members to higher scores on “p” also predispose them to greater victimization exposure (gene-environment correlation, or r_{GE}). As mentioned above, it is important to account for this overlap because it might otherwise be misinterpreted as evidence of gene-by-environment interaction (Purcell, 2002). In the Cholesky decomposition, however, both the genetic and

environment paths shared across victimization and psychopathology and the genetic and environmental paths unique to psychopathology can be specified, which allows me to test whether they are each moderated by victimization exposure.

Although the bivariate approach to modeling genetic and environmental influences on psychopathology is commonly used, it also has several limitations, including risk of false-positive moderation results (van der Sluis et al., 2012). It is possible, however, to adopt a univariate approach that models the genetic and environmental contributions to the phenotype and controls for gene-environment correlation by regressing the phenotype on the moderator for both twins, and allowing these regression coefficients to vary across MZ and DZ twins. This model reduces the risk of false-positive GxE effects when the moderator and phenotype are correlated, and the moderator is also correlated across twins, which is the case for these data. However, it is also computationally more demanding, less parsimonious, and achieves less statistical power than a univariate model (van der Sluis et al., 2012). Consequently, I would compute both models in order to evaluate the replicability of findings across these different analytical approaches.

Variables (select references denoted by superscript):

Construct	E-Risk variable(s)	E-risk variable name(s)	Age(s)
Outcome			
Early-adult psychopathology	Factor scores	PBF_E1, INTCF_E, EXTCF_E, THDCF_E, INTBF_E1, EXTBF_E1, THDBF_E1	18
Main exposure			
Adolescent victimization	JVQ Items	JVQ1e18-JVQ6e18, JVQ8e18-JVQ11e18, JVQ15e18-JVQ17e18, JVQ20e18, JVQ25e18-JVQ28e18, JVQ38e18-JVQ40e18, polyvctze18	18
Childhood victimization	Maternal/Child report	eanseve12, pabevide12, pabsevtye12, pnseveritye12, sasevtye12, bullye12d, polyve512	5-12
Covariates			
Sex	-	sampsex	-
Genetic propensity			
Family history of psychopathology	Proportion of family members with valid data who have any disorder	FHANYPM12	12
Polygenic scores	Will be developed by Karen Sugden	Variable names to be assigned	

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Data Security Agreement

Provisional Paper Title	Does victimization exposure moderate the effects of genetic propensity to psychopathology?
Proposing Author	Jonathan D. Schaefer
Today's Date	1/23/2018

Please keep one copy for your records
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__X__ I am current on Human Subjects Training (CITI (www.citiprogram.org) or training in human subject protection through my post or courses.

__X__ My project is covered by Duke or King's IRB OR I have /will obtain IRB approval from my home institution.

__X__ I will treat all data as "restricted" and store in a secure fashion.

__X__ I will not share the data with anyone, including students or other collaborators not specifically listed on this concept paper.

__X__ I will not post data online or submit the data file to a journal for them to post. Some journals are now requesting the data file as part of the manuscript submission process. The E-Risk Study cannot be shared because the Study Members have not given informed consent for unrestricted open access. Speak to Terrie or Avshalom for strategies for dealing with data sharing requests from Journals.

_X___ Before submitting my paper to a journal, I will submit my draft manuscript and scripts for data checking, and my draft manuscript for co-author mock review, allowing three weeks.

__X__ I will submit analysis scripts and new variable documentation to project data manager after manuscript gets accepted for publication.

__X__ I will return all data files to the Data Manager after the project is complete. Collaborators and graduates of DPPP may not take a data file away from the DPPP office. The data remains the property of the Study and cannot be used for further analyses without express, written permission.

__X__ I will ensure geographical location information, including postcodes or geographical coordinates for the E-Risk study member's homes or schools, is <u>never</u> combined or stored with any other E-Risk data (family or twin-level data)

Signature: .....

CONCEPT PAPER RESPONSE FORM

A. To be completed by the proposing author

Proposing Author:

X I have read the E-Risk data-sharing policy guidelines and agree to follow them

Provisional Paper Title: Does victimization exposure moderate a genetic propensity to psychopathology?

Potential co-authors: Terrie Moffitt, Louise Arsenault, Daniel Belsky, Andrea Danese, Helen Fisher, HonaLee Harrington, Renate Houts, Leah Richmond-Rakerd, Margaret Sheridan, Jasmin Wertz, Avshalom Caspi

Potential Journals: TBD

Intended Submission Date (month/year): 7/2018

Please keep one copy for your records and return one to Louise (louise.arseneault@kcl.ac.uk)

B. To be completed by potential co-authors:

☐ Approved ☐ Not Approved ☐ Let's discuss, I have concerns

Comments:

Please check your contribution(s) for authorship:

☐ Conceptualizing and designing the longitudinal study

☐ Conceptualizing and collecting one or more variables

☐ Data collection

☐ Conceptualizing and designing this specific paper project

☐ Statistical analyses

☐ Writing

☐ Reviewing manuscript drafts

☐ Final approval before submission for publication

☐ Acknowledgment only, I will not be a co-author

If there's any other way I can contribute, please let me know.

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