

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

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**Objective of the study and its significance**

Social isolation, or the absence of positive relationships,<sup>1</sup> can negatively impact mental health across the lifespan.<sup>2</sup> Recent research has highlighted the complexity of this relationship, with studies showing concurrent, longitudinal, and bidirectional associations between social isolation and a range of mental health problems.<sup>3-5</sup> Common underlying genetic influences are also known to contribute to the co-occurrence of social isolation and mental health problems.<sup>6</sup> Social isolation arises from an individual's social environment, but how an individual responds to that environment can reflect genetic predisposition.<sup>7</sup> Thus, environmental exposures or events can be influenced by heritable characteristics that come with mental health.<sup>8</sup> It is unclear, however, if a modifiable environmental pathway exists between social isolation and mental health problems in young people, after accounting for pre-existing genetic effects.

Our first aim is to disentangle genetic and environmental influences on social isolation across childhood. Genetic risk can manifest across a wide range of social behaviours.<sup>9,10</sup> Social isolation at age 18 is partly heritable, whereby ~40% of the variance in social isolation is due to genetic factors.<sup>6</sup> The contribution of genetic and environmental factors to social isolation has not yet been studied in childhood and could differ from adulthood for three reasons. First, the social isolation phenotype in childhood differs to that in adulthood. Young children are typically surrounded by parents and siblings, therefore, rather than defined by an absence of any relationships as in adulthood, childhood isolation occurs from limited connections with parents or other children.<sup>11</sup> Second, genetic influences on social isolation change over time. Behaviour throughout development is continuously changing, and this could reflect variation in both stable and time-specific genetic influences on social isolation over time.<sup>12,13</sup> Third, heritable characteristics which make people vulnerable to isolation (withdrawal/exclusion) exert stronger effects as they get older, when social interactions become more complex and demanding. As children get older, they develop autonomy, complex relationships, and independence in social situations. Identifying the period where the environment has the strongest impact could provide avenues for timely targeted interventions. Moreover, understanding the extent to which genetic and environmental factors play a role in social isolation across multiple points in childhood can provide insight into age-related changes in genetic overlap with mental health problems.

Our second aim is to explore the genetic and environmental overlap between social isolation and mental health across time. The same heritable characteristics could be involved in experiencing social isolation and mental health problems. Previous work in E-Risk showed social isolation has substantial genetic overlap with depression at age 18,<sup>6</sup> suggesting the genetic predisposition for feeling depressed could also drive individuals to remove themselves or be excluded from social groups. In other work, polygenic scores (PRS) for major depressive disorder, attention deficit hyperactivity disorder (ADHD), and autism significantly predicted

experiences of social isolation in adolescence.<sup>10</sup> Interestingly, these associations were stronger as the child got older and differed according to parent or teacher reports of childhood social isolation. The effect size and extent to which it increased by age also varied across disorder PRS, suggesting substantial variation in genetic overlap with social isolation for each disorder. Genetic influences can contribute to initial experiences, but also to how a disorder changes over time and influences other behaviours.<sup>14–20</sup> As an example, genetic influences of ADHD account for ~81% of the variance in change in hyperactive/impulsive symptoms, and nonadditive genetic influences account for ~54% of the variation in the developmental course of inattentive symptoms.<sup>21</sup> By longitudinally modelling the association between social isolation and different aspects of mental health, we can examine how genetic associations or shared heritability between social isolation and mental health changes across development.

Our third aim is to test for key environmental modifiers involved in the association between social isolation and mental health. Regardless of genetic influence, the association between isolation and mental health can occur from unique environmental experiences. Research has typically assessed this association in one direction; social isolation predicting later poor mental health.<sup>11</sup> However, our recent work showed that whilst controlling for stable characteristics (i.e., genetic influence), social isolation can be an outcome of mental health symptoms.<sup>4</sup> One explanation for this potential bidirectional association could be experiencing abuse; either within the home setting or at school. Within the family context, physical or sexual abuse could make children withdraw from social contact and hugely impact their later mental health.<sup>22</sup> Similarly, if children are isolated and spend less time with peers outside the home, they could be more at risk of maltreatment from abusive family members.<sup>23</sup> Within the school context, several studies have reported intertwined links between mental health problems, bullying, and social isolation.<sup>24–28</sup> For example, children excluded from peer groups may be more at risk of being bullied which could exacerbate later mental health problems. In E-Risk, bullying victimisation has shown to have a distinctly environmental effect on mental health problems.<sup>29</sup> The directionality and distinction from genetic processes in the association between social isolation and mental health problems can be tested by assessing differences between monozygotic (MZ) twins. MZ twins share all their genes yet can differ in their experiences of social isolation and mental health problems. This approach makes it possible to directly test if mental health problems predict social isolation, and vice versa, whilst accounting for any genetic confounding. Here, we will assess the environmental modifying effect of abuse in the home and bullying victimisation at school. Establishing this environmental mechanism through accounting for genetic overlap will provide a window to guide prevention programmes for both mental health and social isolation.

### **Research questions**

Using a developmental approach, we aim to explore the extent to which the association between social isolation and mental health problems is genetically and environmentally driven.

1. To what extent do genetic and environmental influences on social isolation vary through childhood across ages 5, 7, 10, and 12?
2. What is the role of genetic and environmental influences on the overlap between social isolation and mental health problems (depression, anxiety, conduct problems, and psychotic experiences) across time?
3. Are there distinct childhood experiences that explain the longitudinal association between social isolation and mental health problems?
  - a. Is social isolation at age 12 associated with mental health problems at age 18 when accounting for genetic factors?
    - i. Does this environmental association remain when accounting for childhood experiences of physical/sexual abuse and bullying victimisation?
  - b. Are mental health problems at age 12 associated with social isolation at age 18 when accounting for genetic factors?
    - i. Do this environmental association remain when accounting for childhood experiences of physical/sexual abuse and bullying victimisation?

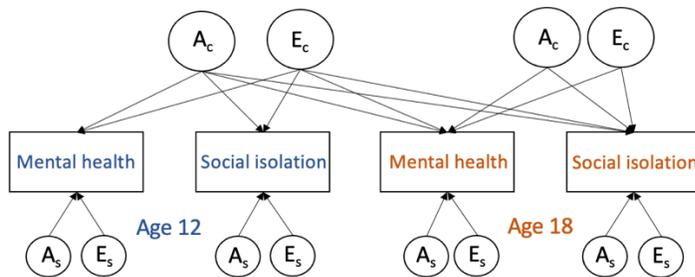
## Statistical analyses

### Step 1: Heritability of childhood social isolation

We will use a multivariate Cholesky decomposition to test if relative influences (ACE) on social isolation change across childhood. Social isolation will be measured using 6 items from the CBCL.

### Step 2: Longitudinal genetic overlap between social isolation and mental health problems

If genetic effects are found in step 1, we will explore the extent to which genetic, shared environmental, and individual environmental influences explain the association between social isolation and mental health problems. We will use the **independent pathway model (IPM)** to look at common and specific genetic effects that influence social isolation and mental health at ages 12 and 18 (e.g., **Figure 1**). We can then see how much of additive genetic (A), common environment (C), and individual environment (E) contribute to the longitudinal correlations between social isolation and mental health. To measure mental health in childhood, we will use diagnostic measurement of four mental health difficulties at age 12 as identified in previous research: anxiety, depression, conduct disorder, and psychotic experiences. Separate models will be conducted for each mental health problem. Please note, the investigation into psychotic experiences may be propped depending on power analyses. As a sensitivity analysis, we will check for reporter differences in our models.



**Figure 1.** Example of longitudinal independent pathway model showing additive genetic influences (A) and non-shared environmental influences (E). Subscript C denotes common influences and subscript S denotes time and variable specific, residual influences.

### Step 3: Environmental mechanisms involved in the association between social isolation and mental health problems

First, we will assess the longitudinal association between social isolation and mental health, whilst controlling for genetic effects. This will be conducted for both directions of association: age 12 social isolation predicting age 18 mental health, and age 12 mental health predicting age 18 isolation. To separate the genetic and environmental effects, we will **use multilevel modelling** that simultaneously estimates the family-wide (between-twin pair) and unique (within-twin pair) effects of social isolation (age 12) on mental health (age 18). And vice versa, effects of mental health (age 12) on isolation (age 18). By using **monozygotic twins only**, we will test whether the associations are primarily environmental as the genetic relatedness between MZ twins is controlled for. Second, we will add in the modifying effect of physical/sexual abuse and bullying victimisation, separately. Both maltreatment variables (physical/sexual abuse and bullying victimisation) will be a composite score of these experiences across ages 5 to 12.

Regression equations as follows:

$$\text{MZdiff\_isoaltion\_18} \sim \text{MZdiff\_mentalhealth\_12} + \text{MZdiff\_bullying\_comp12}$$

$$\text{MZdiff\_mentalhealth\_18} \sim \text{MZdiff\_isolation\_12} + \text{MZdiff\_bullying\_comp12}$$

$$\text{MZdiff\_isoaltion\_18} \sim \text{MZdiff\_mentalhealth\_12} + \text{MZdiff\_abuse\_comp12}$$

$$\text{MZdiff\_mentalhealth\_18} \sim \text{MZdiff\_isolation\_12} + \text{MZdiff\_abuse\_comp12}$$

Variables Needed at Which Ages (names and labels):

#### Study: E-Risk

#### Demographic variables

FAMILYID ID Family

ATWINID ID Twin A

BTWINID ID Twin B

SAMPSEX Sex of twins  
RORDERP5 Random order variable  
ZYGOSITY Zygoty  
SETHNIC Ethnicity of twins  
SESWQ35 SES  
Index of multiple deprivation (IMD) decile at age 12 and 18 elder and younger

### **Age 5**

#### **Social isolation**

SISOE5 Social isolation elder  
SISOET5 Social isolation elder teacher  
SISOEM5 Social isolation elder mother  
SISOY5 Social isolation younger  
SISOYT5 Social isolation younger teacher  
SISOYM5 Social isolation younger mother

### **Age 7**

#### **Social isolation**

SISOE7 Social isolation elder  
SISOET7 Social isolation elder teacher  
SISOEM7 Social isolation elder mother  
SISOY7 Social isolation younger  
SISOYT7 Social isolation younger teacher  
SISOYM7 Social isolation younger mother

### **Age 10**

#### **Social isolation**

SISOE10 Social isolation elder  
SISOET10 Social isolation elder teacher  
SISOEM10 Social isolation elder mother  
SISOY10 Social isolation younger  
SISOYT10 Social isolation younger teacher  
SISOYM10 Social isolation younger mother

### **Age 12**

#### **Social isolation**

SISOE12 Social isolation elder  
SISOET12 Social isolation elder teacher  
SISOEM12 Social isolation elder mother  
SISOY12 Social isolation younger  
SISOYT12 Social isolation younger teacher  
SISOYM12 Social isolation younger mother

#### **Anxiety**

MASCE12 Anxiety scale elder self-report  
MASCCATE12 Extreme anxiety elder  
MASCY12 Anxiety scale younger self-report  
MASCCATY12 Extreme anxiety younger

#### **Depression**

CDIE12 Depression scale CDI elder  
CDICATE12 Clinically significant depression elder  
CDIY12 Depression scale CDI younger  
CDICATY12 Clinically significant depression younger

#### **Conduct disorder**

CONEC12 Conduct problems computer task elder  
CONYC12 Conduct problems computer task younger

DXCD\_EMT12 Diagnosis of conduct disorder mother or teacher elder  
DXCD\_YMT12 Diagnosis of conduct disorder mother or teacher younger

**Psychotic experiences**

PSYSYMP01E12 Age-12 childhood psychotic symptoms elder  
PSYSYMPE12 Psychotic symptom count elder  
PSYSYMP01Y12 Age-12 childhood psychotic symptoms younger  
PSYSYMPY12 Psychotic symptom count younger

**Age 18**

**Social isolation**

SOCISOE18 Social isolation elder  
SOCISOY18 Social isolation younger

**Anxiety**

GADSXE18 Generalised Anxiety Disorder scale elder  
GADSXY18 Generalised Anxiety Disorder scale younger  
DXGADE18 Generalised Anxiety Disorder diagnosis elder  
DXGADY18 Generalised Anxiety Disorder diagnosis younger

**Depression**

MDESXE18 Depression symptom scale elder  
DXMDEE18 Depressive episode elder  
MDESXY18 Depression symptom scale younger  
DXMDEY18 Depressive episode younger

**Conduct disorder**

CDSXE18 conduct disorder scale elder  
CDMODE18 moderate conduct disorder elder  
CDSXY18 conduct disorder scale younger  
CDMODY18 moderate conduct disorder younger

**Psychosis**

PSYSYMP01E18 Psychotic symptoms categorical elder  
PSYSYMPE18 Psychotic symptoms elder  
PSYEXPE18 Psychotic experiences full count elder  
PSYEXPCE18 Psychotic experiences categorical elder  
PSYSYMP01Y18 Psychotic symptoms categorical younger  
PSYSYMPY18 Psychotic symptoms younger  
PSYEXPY18 Psychotic experiences full count younger  
PSYEXPCY18 Psychotic experiences categorical younger

**Childhood maltreatment**

PABSEVTYE12 Physical abuse in childhood elder  
PABSEVTTY12 Physical abuse in childhood younger  
SASEVTYE12 Sexual abuse in childhood elder  
SASEVTTY12 Sexual abuse in childhood younger  
BULLSEVE12 Bullying elder  
BULLSEVY12 Bullying younger  
ExpV\_DV510 Family domestic violence 5 through 10

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