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

Proposing Author: Katherine N Thompson

Author's affiliation, phone, and e-mail address:
Social, Genetic and Developmental Psychiatry Centre,
Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK,
+447951027945,
katherine.n.thompson@kcl.ac.uk

Sponsoring Investigator: Louise Arseneault

Proposed co-authors: Timothy Matthews, Bridget Bryan, Jessica Agnew-Blais, Candice Odgers, Andrea Danese, Louise Arseneault, E-Risk co-investigators

Provisional Paper Title: Bidirectional associations between childhood social isolation and ADHD

Date: 10th of February 2022

Objective of the study and its significance

Children become socially isolated when they lack positive social relationships and connections that typically provide companionship, guidance, and support[1–3]. A growing body of evidence indicates that childhood social isolation constitutes a risk factor for poor health in adulthood[4–7]. Recent work from our group showed that social isolation in childhood could also be a valuable indicator of co-occurring mental health problems[8]. Specifically, we found associations between attention deficit hyperactivity disorder (ADHD) symptoms and social isolation across different points in childhood. ADHD is characterised by a pattern of inattention and/or hyperactivity-impulsivity that interferes with daily functioning[9] and has been associated with poor functional outcomes and comorbid mental health disorders[10]. Here, we aim to clarify the nature of the association between social isolation and ADHD throughout childhood.

The relationship between childhood social isolation and ADHD could be bidirectional. Children with mental health problems could become isolated through withdrawal from social settings. As a broad example, around half of a sample of adolescents undergoing inpatient psychiatric treatment reported that they would rather be alone and they were concerned about peer problems when returning to school[13]. In E-Risk, childhood ADHD symptoms have been associated with later social isolation[14,15]. This could occur through withdrawal from social situations or experiencing negative responses from surroundings. On the other hand, previous research has shown that social isolation can lead to later mental health difficulties[4]. Isolation in childhood could also influence ADHD symptoms by modifying how much exposure children gain to social experiences associated with developing self control[11,12]. Longitudinal research demonstrated that childhood ADHD was associated with later exposure to abuse/neglect (not specific to isolation) when comorbid with conduct disorder, indicating that disruptive behaviours could evoke long term responses from a person's environment[16]. Therefore, outward negative or anti-social behaviours could be a mechanism by which children with ADHD become excluded from their peers. One study reported that childhood ADHD symptoms accompanied with high rates of aggression were associated with social problems years later[17]. It is also possible that children with ADHD who gain support systems to learn prosocial behaviours could be protected from becoming isolated[18]. We aim to distinguish the direction of the association between social isolation and ADHD, whilst identifying any mediating effects of antisocial and prosocial behaviour in childhood.

Social isolation could be differentially associated with hyperactive and inattentive ADHD symptoms. Being hyperactive and impulsive could evoke a negative response from peers or other people in their environment. Research in schools has shown that children were more likely to exclude hyperactive peers than low-achieving peers for reasons of effective group functioning[19]. Whereas children with inattentive symptoms may withdraw from social situations through being disengaged[20] and miss key developmental opportunities at school . Here, we will explore bidirectional associations across childhood between social isolation and

hyperactivity and inattentive ADHD symptoms, separately.

We will consider the modifying effect of sex, socioeconomic status (SES), and informant (teacher or parent) on the bidirectional association between social isolation and ADHD. For sex, boys are more likely than girls to be diagnosed with ADHD and experience more severe symptoms[21]. Girls and boys have been shown to have different developmental trajectories of ADHD symptoms[22] and girls who meet diagnostic criteria for ADHD are more prosocial and have lower levels of conduct problems than boys[23]. For SES, children from higher income families may have more available capital for social activities and could be less isolated as they gain more opportunities for involvement in sports clubs[24], music groups, and special needs programmes to support social engagement for children with difficulties[25]. For informant, parents and teachers witness child behaviour in environments with substantially different structures (home or school). Schools provide more routine and social opportunities; therefore, teachers and parents are likely to witness different types and levels of social isolation and ADHD symptoms. Longitudinal studies of ADHD symptoms have shown that informant agreement (parents and teachers reporting similar levels/types of symptoms) is low for hyperactive symptoms (r = 0.23) and slightly higher for inattention (r = 0.47)[26]. This level of agreement is similar for social isolation (r = ~0.30)[8]. Research has even shown that the relationship between ADHD and peer relationship difficulties is dependent on using either parent or teacher report[27]. Here we will conduct sensitivity analyses assessing bidirectional associations between social isolation and ADHD whilst stratifying for sex, SES, and informant.

Aims

1. The present study will explore differing directional associations between social isolation and ADHD symptoms in childhood.
   a. We hypothesise that there are significant associations between earlier ADHD and later social isolation, which will be consistent across ages 5, 7, 10, and 12.
   b. We hypothesise that associations differ based on if we are examining hyperactive/impulsive, inattentive, or combined hyperactive and inattentive ADHD symptoms from age 5 to 12.
   c. We hypothesise different directional associations according to sex, SES, and informant from age 5 to 12.

We originally aimed to better understand this association through exploring the role of genetic factors on the longitudinal association between social isolation and ADHD. However, the E-Risk data is underpowered to support the complexity of these analyses. Instead, where associations are found in Aim 1, we will assess other mediating mechanisms that could explain the association between social isolation and ADHD.

2. Where directional associations are found, we will explore potential mediators for the association between social isolation and ADHD symptoms.
   a. We hypothesise that antisocial behaviours (e.g., aggression) at age 7/10 mediate the association between ADHD at age 5 and social isolation at age 12.
   b. We hypothesise that prosocial behaviours (e.g., helping other children) at age 7/10 mediate the association between ADHD at age 5 and social isolation at age 12.

Statistical analyses

Phase 1: Bidirectional influences

We will compute a random intercept cross-lagged panel model (RI-CLPM) to assess bidirectional effects between social isolation and ADHD across 5 to 12 years. The RI-CLPM[40], is an extension of the traditional cross-lagged panel model which models directed associations between two variables over time. The RI-CLPM further separates out change within an individual over time (within-person) and change between individuals over time (between-person). To start with, we will use social isolation and ADHD sum scores or symptom counts as raw variables in the RI-CLPM. This is shown in **Figure 1** whereby the between-person effects are modelled by the random intercept in blue, and the within person effects in red. Here, we are most interested in the within person cross-lag effects. For example, deviation from an individual's expected level of social isolation will be followed by deviation in the individual's expected level of ADHD symptoms at the next occasion in the same direction. As a second step, and if we have enough power based on missing data, an additional measurement model section will be added to the RI-CLPM, which is represented by a factor of symptoms items, rather than computing a sum/total score[41]. **Figure 2** shows the addition of the measurement model in yellow. The measurement model overcomes the limitation that sum scores assume all items equally and consistently contribute to a disorder[42]. Additionally, the inclusion of latent factors rather than raw scores negates any measurement error[43]. In both models, the most parsimonious model will be chosen. We will use 6 items from the CBCL to measure social isolation and DSM symptom counts to measure hyperactive/impulsive and inattentive ADHD symptoms.

To assess differences in effects based on reporter, parallel models will be computed using parent and teacher report items, separately. Multiple group version of RI-CLPM[41] will be used to assess differences in bidirectional relationships based on sex and SES. The similarity of the within-person effects can then be compared across different groups. These can be thought of as moderation or interaction effects, where dependent on what group a participant resides, this leads to differences in the relationship between social isolation and ADHD. Separate models will be computed for hyperactive/impulsive, and inattentive ADHD symptoms. As a sensitivity analysis, residual coefficients will be used to establish bidirectional relationships between ADHD and social isolation whilst completely separating out symptoms of hyperactivity and inattention. Hyperactivity will be regressed on inattention and vice versa to calculate the residual at each time point, these residuals will then be used in the RI-CLPM. All models will be tested to see if effects remain consistent or stable across childhood, where parameters from one time point to the next are constrained to be equal to obtain the most parsimonious model.

Phase 2: Mediation analyses

Phase 2 was previously planned to understand how genetic factors play a role in the longitudinal relationship between social isolation and ADHD. However, due to the complexity of the models involved, we are not well-powered enough to conduct this in E-Risk, or likely any twin sample. Therefore, we will use other methods to better understand why children with ADHD become isolated, or why isolated children are more at risk of developing ADHD behaviours. Where significant effects are found in **phase 1**, we plan to conduct mediation analyses to assess if antisocial and prosocial behaviours account for the relationship between ADHD and social isolation. We expect that there will be significant associations between early ADHD and later social isolation. Thus, longitudinal SEM mediation models[44] will be computed to assess if composite prosocial and antisocial behaviours at age 7 and 10 mediate the longitudinal relationship between ADHD at age 5 and social isolation at age 12. Mediation models will be conducted for prosocial and antisocial behaviours separately to begin with. Both will be included in the final model if they show significant effects separately.

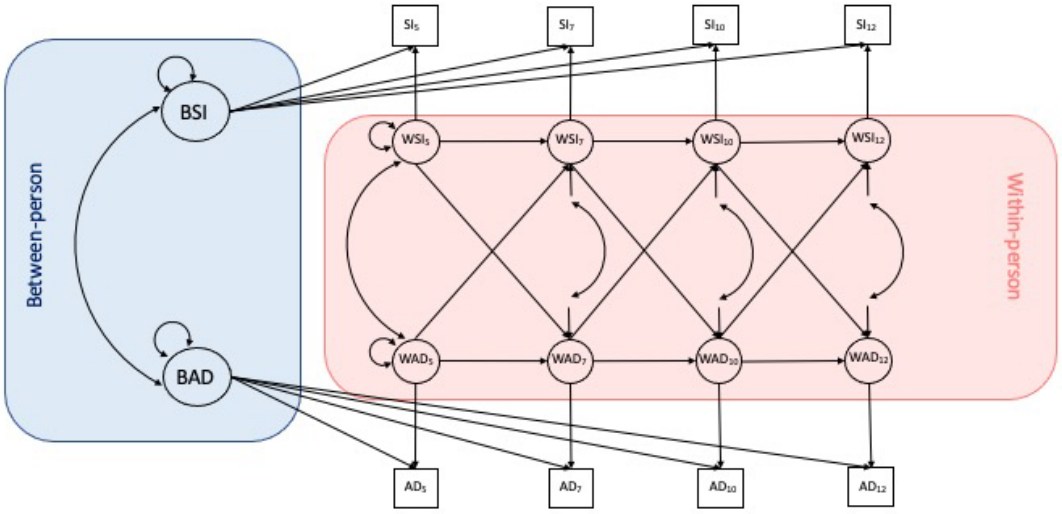

Figure 1. RI-CLPM for the longitudinal relationship between social isolation (SI) and ADHD symptoms (AD). Time point of assessment is indicated in the subscript. AD: ADHD symptom raw sum score; WAD: within-person factor of ADHD symptoms; BAD: between-person ADHD symptoms; SI: social isolation symptoms raw sum score; WSI: within-person factor of social isolation symptoms; BSI: between-person social isolation symptoms.

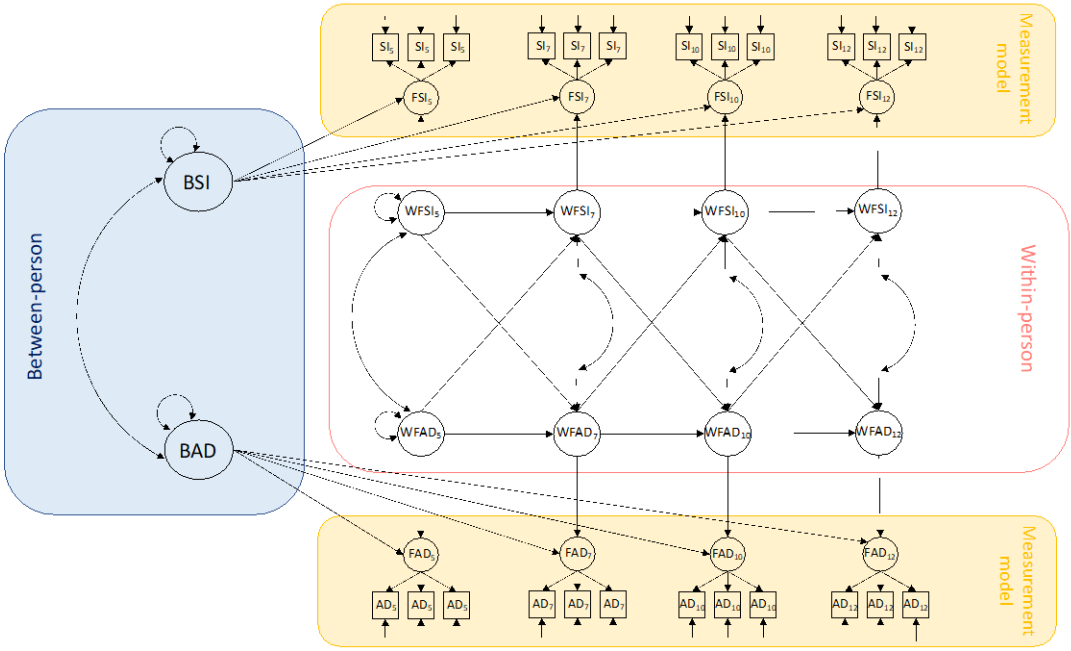

Figure 2. RI-CLPM for the longitudinal relationship between social isolation (SI) and ADHD symptoms (AD), including a measurement model component. Time point of assessment is indicated in the subscript. AD: ADHD symptom items; FAD: factor of ADHD symptoms; WFAD: within-person factor of ADHD symptoms; BAD: between-person ADHD symptoms; SI: social isolation symptom items; FSI: factor of social isolation symptoms; WFSI: within-person factor of social isolation symptoms; BSI: between-person social isolation symptoms.

Variables Needed at Which Ages (names and labels):

Study: E-Risk

Demographic variables
FAMILYID ID Family
ATWINID ID Twin 1
SAMPSEX Sex of twins
RORDERP5 Random order variable
ZYGOSITY Zygosity
SETHNIC Ethnicity of twins
SESWQ35 SES

Age 5
Social isolation variables
All six raw age 5 social isolation items (pe2m5, pe4m5, pe7m5, pe11m5, pe13m5, pe25m5) for mother and teacher, elder only.
SISOE5 Social isolation elder
SISOET5 Social isolation elder teacher
SISOEM5 Social isolation elder mother
ADHD variables
All raw age 5 inattention ADHD items (PE81M5, PE82M5, PE83M5, PE86M5, PE87M5, PE88M5, PE89M5, PE90M5, PE91M5) for mother and teacher, elder only (to create factors)
All raw age 5 hyperactivity ADHD items (PE84M5, PE85M5, PE96M5, PE97M5, PE92M5, PE93M5, PE94M5, PE95M5, PE64M5) for mother and teacher, elder only (to create factors)
INEM5 Inattention symptom count mother elder
HYEM5 Hyperactivity/impulsivity symptom count mother elder
INET5 Inattention symptom count teacher elder
HYET5 Hyperactivity/impulsivity symptom count teacher elder
TADHDEM5 total ADHD symptom count mother elder
TADHDET5 total ADHD symptom count teacher elder
Prosocial behaviours
All raw age 5 CBCL prosocial items (PE98M5, PE99M5 , PE100M5, PE101M5, PE102M5, PE103M5, PE104M5, PE105M5, PE106M5, PE107M5) for mother and teacher, elder only (to create factors)
PROEM5
Antisocial behaviours
All raw age 5 CBCL antisocial subscale items: aggression, delinquency, conduct (PE37M5, PE38M5, PE41M5, PE42M5, PE43M5, PE44M5, PE45M5, PE46M5, PE50M5 PE53M5 PE56M5 PE58M5 PE61M5 PE62M5 PE64M5 PE65M5 PE66M5 PE69M5 PE47M5 PE51M5 PE52M5 PE54M5 PE55M5 PE57M5 PE59M5 PE60M5 PE63M5 PE67M5 PE68M5 PE70M5 PE71M5 PE39M5 PE40M5 PE49M5 PE72M5 PE73M5 PE74M5 PE75M5 PE76M5 PE77M5 PE78M5 PE79M5 PE80M5) for mother and teacher, elder only (to create factors)
ASBEM5

Age 7
Social isolation variables
All six raw age 7 social isolation items (pe2m7, pe4m7, pe7m7, pe11m7, pe13m7, pe25m7) for mother and teacher, elder only (to create factors)
SISOE7 Social isolation elder
SISOET7 Social isolation elder teacher
SISOEM7 Social isolation elder mother
ADHD variables
All raw age 7 inattention ADHD items (PE81M7, PE82M7, PE83M7, PE86M7, PE87M7, PE88M7, PE89M7, PE90M7, PE91M7) for mother and teacher, elder only (to create factors)
All raw age 7 hyperactivity ADHD items (PE84M7, PE85M7, PE96M7, PE97M7, PE92M7, PE93M7, PE94M7, PE95M7, PE64M7) for mother and teacher, elder only (to create factors)
INEM7 Inattention symptom count mother elder
HYEM7 Hyperactivity/impulsivity symptom count mother elder
INET7 Inattention symptom count teacher elder

HYET7 Hyperactivity/impulsivity symptom count teacher elder
TADHDEM7 total ADHD symptom count mother elder
TADHDET7 total ADHD symptom count teacher elder

Prosocial behaviours

All raw age 7 CBCL prosocial items (PE98M7, PE99M7, PE100M7, PE101M7, PE102M7, PE103M7, PE104M7, PE105M7, PE106M7, PE107M7) for mother and teacher, elder only (to create factors)
PROEM7

Antisocial behaviours

All raw age 7 CBCL antisocial subscale items: aggression, delinquency, conduct (PE37M7, PE38M7, PE41M7, PE42M7, PE43M7, PE44M7, PE45M7, PE46M7, PE50M7 PE53M7 PE56M7 PE58M7 PE61M7 PE62M7 PE64M7 PE65M7 PE66M7 PE69M7 PE47M7 PE51M7 PE52M7 PE54M7 PE55M7 PE57M7 PE59M7 PE60M7 PE63M7 PE67M7 PE68M7 PE70M7 PE71M7 PE39M7 PE40M7 PE49M7 PE72M7 PE73M7 PE74M7 PE75M7 PE76M7 PE77M7 PE78M7 PE79M7 PE80M7) for mother and teacher, elder only (to create factors)
ASBEM7

Age 10

Social isolation variables

All six raw age 10 social isolation items (pe2m10, pe4m10, pe7m10, pe11m10, pe13m10, pe25m10) for mother and teacher, elder only (to create factors)
SISOE10 Social isolation elder
SISOET10 Social isolation elder teacher
SISOEM10 Social isolation elder mother

ADHD variables

All raw age 10 inattention ADHD items (PE81M10, PE82M10, PE83M10, PE86M10, PE87M10, PE88M10, PE89M10, PE90M10, PE91M10) for mother and teacher, elder only (to create factors)
All raw age 10 hyperactivity ADHD items (PE84M10, PE85M10, PE96M10, PE97M10, PE92M10, PE93M10, PE94M10, PE95M10, PE64M10) for mother and teacher, elder only (to create factors)
INEM10 Inattention symptom count mother elder
HYEM10 Hyperactivity/impulsivity symptom count mother elder
INET10 Inattention symptom count teacher elder
HYET10 Hyperactivity/impulsivity symptom count teacher elder
TADHDEM10 total ADHD symptom count mother elder
TADHDET10 total ADHD symptom count teacher elder

Prosocial behaviours

All raw age 10 CBCL prosocial items (PE98M10, PE99M10, PE100M10, PE101M10, PE102M10, PE103M10, PE104M10, PE105M10, PE106M10, PE107M10) for mother and teacher, elder only (to create factors)
PROEM10

Antisocial behaviours

All raw age 10 CBCL antisocial subscale items: aggression, delinquency, conduct (PE37M10, PE38M10, PE41M10, PE42M10, PE43M10, PE44M10, PE45M10, PE46M10, PE50M10 PE53M10 PE56M10 PE58M10 PE61M10 PE62M10 PE64M10 PE65M10 PE66M10 PE69M10 PE47M10 PE51M10 PE52M10 PE54M10 PE55M10 PE57M10 PE59M10 PE60M10 PE63M10 PE67M10 PE68M10 PE70M10 PE71M10 PE39M10 PE40M10 PE49M10 PE72M10 PE73M10 PE74M10 PE75M10 PE76M10 PE77M10 PE78M10 PE79M10 PE80M10) for mother and teacher, elder only (to create factors)
ASBEM10

Age 12

Social isolation variables

All six raw age 12 social isolation items (pe2m12, pe4m12, pe7m12, pe11m12, pe13m12, pe25m12) for mother and teacher, elder only (to create factors)
SISOE12 Social isolation elder
SISOET12 Social isolation elder teacher
SISOEM12 Social isolation elder mother

ADHD variables

All raw age 12 inattention ADHD items (PE81M12, PE82M12, PE83M12, PE86M12, PE87M12, PE88M12, PE89M12, PE90M12, PE91M12) for mother and teacher, elder only (to create factors)
All raw age 12 hyperactivity ADHD items (PE84M12, PE85M12, PE96M12, PE97M12, PE92M12, PE93M12, PE94M12, PE95M12, PE64M12) for mother and teacher, elder only (to create factors)

INEM12 Inattention symptom count mother elder
HYEM12 Hyperactivity/impulsivity symptom count mother elder
INET12 Inattention symptom count teacher elder
HYET12 Hyperactivity/impulsivity symptom count teacher elder
TADHDEM12 total ADHD symptom count mother elder
TADHDET12 total ADHD symptom count teacher elder

Prosocial behaviours

All raw age 12 CBCL prosocial items (PE98M12, PE99M12, PE100M12, PE101M12, PE102M12, PE103M12, PE104M12, PE105M12, PE106M12, PE107M12) for mother and teacher, elder only (to create factors) PROEM12

Antisocial behaviours

All raw age 12 CBCL antisocial subscale items: aggression, delinquency, conduct (PE37M12, PE38M12, PE41M12, PE42M12, PE43M12, PE44M12, PE45M12, PE46M12, PE50M12 PE53M12 PE56M12 PE58M12 PE61M12 PE62M12 PE64M12 PE65M12 PE66M12 PE69M12 PE47M12 PE51M12 PE52M12 PE54M12 PE55M12 PE57M12 PE59M12 PE60M12 PE63M12 PE67M12 PE68M12 PE70M12 PE71M12 PE39M12 PE40M12 PE49M12 PE72M12 PE73M12 PE74M12 PE75M12 PE76M12 PE77M12 PE78M12 PE79M12 PE80M12) for mother and teacher, elder only (to create factors)
ASBEM12

References cited:

1. Cacioppo, J. T., Hawkley, L. C., Norman, G. J. & Berntson, G. G. Social isolation. *Ann. N. Y. Acad. Sci.* **1231**, 17–22 (2011).
2. Cohen, S. & Wills, T. A. Stress, social support, and the buffering hypothesis. *Psychol. Bull.* **98**, 310–357 (1985).
3. Weiss, R. S. *Loneliness: The experience of emotional and social isolation*. xxii, 236 (The MIT Press, 1973).
4. Caspi, A., Harrington, H., Moffitt, T. E., Milne, B. J. & Poulton, R. Socially Isolated Children 20 Years Later: Risk of Cardiovascular Disease. *Arch. Pediatr. Adolesc. Med.* **160**, 805 (2006).
5. Danese, A. *et al.* Adverse Childhood Experiences and Adult Risk Factors for Age-Related Disease: Depression, Inflammation, and Clustering of Metabolic Risk Markers. *Arch. Pediatr. Adolesc. Med.* **163**, (2009).
6. Lacey, R. E., Kumari, M. & Bartley, M. Social isolation in childhood and adult inflammation: Evidence from the National Child Development Study. *Psychoneuroendocrinology* **50**, 85–94 (2014).
7. Loades, M. E. *et al.* Rapid Systematic Review: The Impact of Social Isolation and Loneliness on the Mental Health of Children and Adolescents in the Context of COVID-19. *J. Am. Acad. Child Adolesc. Psychiatry* **59**, 1218-1239.e3 (2020).
8. Thompson, K. *et al.* Trajectories of childhood social isolation in a nationally representative cohort: Associations with antecedents and early adulthood outcomes. *JCPP In Press* (2021).
9. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 5th edn*. (Washington, DC: American Psychiatric Association, 2013).
10. Erskine, H. E. *et al.* Long-Term Outcomes of Attention-Deficit/Hyperactivity Disorder and Conduct Disorder: A Systematic Review and Meta-Analysis. *J. Am. Acad. Child Adolesc. Psychiatry* **55**, 841–850 (2016).
11. McBride, S. & Preyde, M. Loneliness and Social Isolation in a Sample of Youth Hospitalized for Psychiatric Illness. *Child Adolesc. Soc. Work J.* (2020) doi:10.1007/s10560-020-00723-y.
12. Matthews, T. *et al.* Social Isolation and Mental Health at Primary and Secondary School Entry: A Longitudinal Cohort Study. *J. Am. Acad. Child Adolesc. Psychiatry* **54**, 225–232 (2015).
13. Agnew-Blais, J. C. *et al.* Young adult mental health and functional outcomes among individuals with remitted, persistent and late-

onset ADHD. *Br. J. Psychiatry* **213**, 526–534 (2018).

14. Sasser, T. R., Kalvin, C. B. & Bierman, K. L. Developmental trajectories of clinically significant attention-deficit/hyperactivity disorder (ADHD) symptoms from grade 3 through 12 in a high-risk sample: Predictors and outcomes. *J. Abnorm. Psychol.* **125**, 207–219 (2016).
15. Campbell, S. B., Halperin, J. M. & Sonuga-Barke, E. J. S. A Developmental Perspective on Attention-Deficit/Hyperactivity Disorder (ADHD). in *Handbook of Developmental Psychopathology* (eds. Lewis, M. & Rudolph, K. D.) 427–448 (Springer US, 2014). doi:10.1007/978-1-4614-9608-3_22.
16. Stern, A. *et al.* Associations between abuse/neglect and ADHD from childhood to young adulthood: A prospective nationally-representative twin study. *Child Abuse Negl.* **81**, 274–285 (2018).
17. Humphreys, K. L. *et al.* Friendship and social functioning following early institutional rearing: The role of ADHD symptoms. *Dev. Psychopathol.* **31**, 1477–1487 (2019).
18. Velő, S. *et al.* The Association between Prosocial Behaviour and Peer Relationships with Comorbid Externalizing Disorders and Quality of Life in Treatment-Naïve Children and Adolescents with Attention Deficit Hyperactivity Disorder. *Brain Sci.* **11**, 475 (2021).
19. Gasser, L., Grütter, J., Torchetti, L. & Buholzer, A. Competitive classroom norms and exclusion of children with academic and behavior difficulties. *J. Appl. Dev. Psychol.* **49**, 1–11 (2017).
20. Milich, R., Balentine, A. C. & Lynam, D. R. ADHD combined type and ADHD predominantly inattentive type are distinct and unrelated disorders. *Clin. Psychol. Sci. Pract.* **8**, 463–488 (2001).
21. Arnett, A. B., Pennington, B. F., Willcutt, E. G., DeFries, J. C. & Olson, R. K. Sex differences in ADHD symptom severity. *J. Child Psychol. Psychiatry* **56**, 632–639 (2015).
22. Murray, A. L. *et al.* Sex differences in ADHD trajectories across childhood and adolescence. *Dev. Sci.* **22**, e12721 (2019).
23. Mowlem, F., Agnew-Blais, J., Taylor, E. & Asherson, P. Do different factors influence whether girls versus boys meet ADHD diagnostic criteria? Sex differences among children with high ADHD symptoms. *Psychiatry Res.* **272**, 765–773 (2019).
24. Musić Milanović, S. *et al.* Socioeconomic disparities in physical activity, sedentary behavior and sleep patterns among 6- to 9-year-old children from 24 countries in the WHO European region. *Obes. Rev.* **22**, e13209 (2021).
25. Kelly, B. *et al.* The association between socioeconomic status and autism diagnosis in the United Kingdom for children aged 5–8 years of age: Findings from the Born in Bradford cohort. *Autism* **23**, 131–140 (2019).
26. Murray, A. L., Booth, T., Ribeaud, D. & Eisner, M. Disagreeing about development: An analysis of parent-teacher agreement in ADHD symptom trajectories across the elementary school years. *Int. J. Methods Psychiatr. Res.* **27**, e1723 (2018).
27. Milledge, S. V. *et al.* Peer relationships and prosocial behaviour differences across disruptive behaviours. *Eur. Child Adolesc. Psychiatry* **28**, 781–793 (2019).
28. Larsson, H., Chang, Z., D'Onofrio, B. M. & Lichtenstein, P. The heritability of clinically diagnosed attention deficit hyperactivity disorder across the lifespan. *Psychol. Med.* **44**, 2223–2229 (2014).
29. Matthews, T. *et al.* Social isolation, loneliness and depression in young adulthood: a behavioural genetic analysis. *Soc. Psychiatry Psychiatr. Epidemiol.* **51**, 339–348 (2016).
30. Kendler, K. S. & Baker, J. H. Genetic influences on measures of the environment: a systematic review. *Psychol. Med.* **37**, 615–626 (2007).
31. Plomin, R., DeFries, J. C. & Loehlin, J. C. Genotype-environment interaction and correlation in the analysis of human behavior.

Psychol. Bull. **84**, 309–322 (1977).

32. Battaglia, M. *et al.* Trajectories of pain and anxiety in a longitudinal cohort of adolescent twins. *Depress. Anxiety* **37**, 475–484 (2020).
33. Fontaine, N. M. G., Rijsdijk, F. V., McCrory, E. J. P. & Viding, E. Etiology of Different Developmental Trajectories of Callous-Unemotional Traits. *J. Am. Acad. Child Adolesc. Psychiatry* **49**, 656–664 (2010).
34. Hannigan, L. J. *et al.* Genetics of co-developing conduct and emotional problems during childhood and adolescence. *Nat. Hum. Behav.* **2**, 514–521 (2018).
35. Hatoum, A. S., Rhee, S. H., Corley, R. P., Hewitt, J. K. & Friedman, N. P. Etiology of Stability and Growth of Internalizing and Externalizing Behavior Problems Across Childhood and Adolescence. *Behav. Genet.* **48**, 298–314 (2018).
36. Kwong, A. S. F. *et al.* Polygenic risk for depression, anxiety and neuroticism are associated with the severity and rate of change in depressive symptoms across adolescence. *J. Child Psychol. Psychiatry* jcpp.13422 (2021) doi:10.1111/jcpp.13422.
37. Takahashi, Y., Pease, C. R., Pingault, J.-B. & Viding, E. Genetic and environmental influences on the developmental trajectory of callous-unemotional traits from childhood to adolescence. *J. Child Psychol. Psychiatry* **62**, 414–423 (2021).
38. Pingault, J.-B. *et al.* Genetic and Environmental Influences on the Developmental Course of Attention-Deficit/Hyperactivity Disorder Symptoms From Childhood to Adolescence. *JAMA Psychiatry* **72**, 651 (2015).
39. Torvik, F. A. *et al.* Explaining the association between anxiety disorders and alcohol use disorder: A twin study. *Depress. Anxiety* **36**, 522–532 (2019).
40. Hamaker, E. L., Kuiper, R. M. & Grasman, R. P. P. P. A critique of the cross-lagged panel model. *Psychol. Methods* **20**, 102–116 (2015).
41. Mulder, J. D. & Hamaker, E. L. Three Extensions of the Random Intercept Cross-Lagged Panel Model. *Struct. Equ. Model. Multidiscip. J.* **28**, 638–648 (2021).
42. Fried, E. I. & Nesse, R. M. Depression sum-scores don't add up: why analyzing specific depression symptoms is essential. *BMC Med.* **13**, 72 (2015).
43. Bollen, K. A. & Pearl, J. Eight Myths About Causality and Structural Equation Models. in *Handbook of Causal Analysis for Social Research* (ed. Morgan, S. L.) 301–328 (Springer Netherlands, 2013). doi:10.1007/978-94-007-6094-3_15.
44. Selig, J. P. & Preacher, K. J. Mediation Models for Longitudinal Data in Developmental Research. *Res. Hum. Dev.* **6**, 144–164 (2009).
45. Malanchini, M. *et al.* Reading self-perceived ability, enjoyment and achievement: A genetically informative study of their reciprocal links over time. *Dev. Psychol.* **53**, 698–712 (2017).
46. Allegrini, A. *et al.* Developmental co-occurrence of psychopathology dimensions in childhood: between and within person processes. (2021) doi:10.31234/osf.io/t486z.

Data Security Agreement

Provisional Paper Title	Bidirectional associations between childhood social isolation and ADHD
Proposing Author	Katherine N Thompson
Today's Date	10th of February 2022

Please keep one copy for your records
(Please initial your agreement)

__KT__ I am familiar with the King's College London research ethics guidelines (https://www.kcl.ac.uk/innovation/research/support/ethics/about/index.aspx) and the MRC good research practice guidelines (https://www.mrc.ac.uk/research/policies-and-guidance-for-researchers/good-research-practice/)

__KT__ My project has ethical approval from my institution.

__KT__ My computer is (a) encrypted at the hard drive level, (b) password-protected, (c) configured to lock after 15 minutes of inactivity, AND (d) has an antivirus client which is updated regularly.

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

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

_KT___ I will not merge data from different files or sources, except where explicit approval has been given by the PI.

__KT__ 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 the study PI for strategies for dealing with data sharing requests from Journals.

__KT_ 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.

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

_KT___ **For projects using location data:** I will ensure geographical location information, including postcodes or geographical coordinates for the E-Risk study member's homes or schools, is never combined or stored with any other E-Risk data (family or twin-level data)

_KT___ **For projects using genomic data:** I will only use the SNP and/or 450K data in conjunction with the phenotypes that have been approved for use in this project at the concept paper stage.

Signature: 

CONCEPT PAPER RESPONSE FORM

A. To be completed by the proposing author

Proposing Author: Katherine N Thompson

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

Provisional Paper Title: Bidirectional associations between childhood social isolation and ADHD

Potential co-authors: Timothy Matthews, Bridget Bryan, Jessica Agnew-Blais, Candice Odgers, Andrea Danese, Louise Arseneault, E-Risk co-investigators

Potential Journals: Psychological medicine/ Child Development/ Research on Child and Adolescent Psychopathology Journal

Intended Submission Date (month/year): Spring 2022

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

Signature: .....