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

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Provisional Paper Title: Antecedents and outcomes of social isolation across childhood

Date: 11th of December 2020

Objective of the study and its significance

Interpersonal connections provide emotional and physical support at all stages of life. Social isolation occurs when there is an absence or lack of these interpersonal connections and social relationships (Cacioppo et al., 2011). Research in adult populations has shown that social isolation is detrimental to physical and mental health (Hakulinen et al., 2016; Holt-Lunstad, 2017; Umberson & Montez, 2010). Individuals who experience social isolation are more likely to have symptoms of depression, cognitive decline, and even premature mortality compared to those who were not isolated (Cacioppo & Cacioppo, 2014; de Lange et al., 2020; Holt-Lunstad et al., 2010, 2015; Santini et al., 2020; Taylor et al., 2018). Mortality risk linked to social isolation has been shown to be comparable to the risk from smoking, obesity and air pollution (Holt-Lunstad et al., 2010; Pantell et al., 2013). Social isolation can also have detrimental effects on biological processes (de Lange et al., 2020; Yang et al., 2017). For example, an experimental study with adults suggested that longing for social interaction after induced social isolation influences brain neural pattern responses similar to that of craving food when hungry (Tomova et al., 2020). However, the majority of social isolation research has been conducted in adult populations, particularly older adults. Childhood experiences of social interaction could also be influential to later health outcomes. For example, childhood sociability has been associated with high levels of social support amongst adults and accounted for the buffering effect of social support on mental health problems later in life (Sehmi et al., 2020).

Social isolation in childhood and adolescence may be particularly detrimental as peer connections are becoming increasingly important and cognitive processes are rapidly developing (Orben et al., 2020). Findings from the Dunedin birth cohort have shown the independent association between chronic childhood social isolation and cardiovascular risk factors at age 26, greater depression levels and 60% increased risk of high inflammation at age 32 (Caspi et al., 2006; Danese et al., 2009). The National Child Development Study in Great Britain also found that children who were isolated at age 7-11 had higher levels of inflammation, lower SES and educational attainment, greater psychological distress and were more likely to be obese and smoke at age 44 (Lacey et al., 2014). These results from nationally representative cohort studies show the long-term influence of social isolation at a young age. However, to fully understand these poor outcomes later in life, and any factors that could contribute to experiencing social isolation in childhood, it is important to consider not only the emergence but the developmental pattern of social isolation over time.

To accurately capture changes in social isolation across time, we must account for within-person differences rather than measuring group averages. Studies that have used this "one size fits all" approach of taking average measures across time do not account for population heterogeneity in levels of social isolation. For example, Matthews and colleagues (2015) found little difference between average levels of social isolation at age 5 and at age 12. However, this approach does not take into account individual patterns of variation over time. Longitudinal growth mixture modelling (GMM) approaches can elucidate these patterns over time by

separating out individuals who fall into certain trajectory groups. Rather than taking an average trajectory of social isolation levels of all children simultaneously, GMM identifies groups or classes of children who have distinctly different starting levels and changes in social isolation over time. GMM research on topics related to social isolation such as peer victimisation and loneliness have shown that children follow distinct trajectories, rather than one overall trend, and the majority of this research has focused on the adolescent years (Oncioiu et al., 2020; Qualter et al., 2013; van Dulmen & Goossens, 2013). It is unknown if there are similar patterns of class membership for experiences of social isolation in childhood. Furthermore, children included in different trajectory groups may firstly have varying outcomes in young adulthood and secondly, have a different profile of antecedents that contribute to their trajectory group membership.

No research has explored antecedents of childhood trajectories of social isolation. The only research on social isolation antecedents to date found that child behavioural problems at age 5 were associated with social isolation at age 12 (Matthews et al., 2015). Similar work on loneliness found that child internalising problems and neuroticism at age 5 have been associated with loneliness at age 18 (Matthews et al., 2019). However, these studies only used average measures at one time point. Research examining trajectories of peer-victimisation and loneliness have highlighted antecedents and outcomes of trajectory membership. Parental antisocial behaviour and living in a non-intact family were associated with high-stable peer victimisation trajectories (Oncioiu et al., 2020). Furthermore, temperament, low social engagement and cognitive style have been associated with high-stable trajectories of loneliness from 5 to 17 years (Qualter et al., 2013). This study also found that those in the high-stable trajectory were more likely to report higher depression levels, visit the doctor and consume more alcohol at age 17. Another study reported that gender, ethnicity, SES, depression, social skills and aggression at age 7 were associated with high-increasing and high-stable loneliness trajectories (Schinka et al., 2013). They also found that these trajectories were associated with later deficits in social skills, depression, aggression and suicidal ideation at age 15. It's important to extend these findings to social isolation, as although loneliness and social isolation are similar constructs, they are distinct in two ways. First, in their subjective versus objective experience and second, in their overlapping but distinct genetic basis (de Lange et al., 2020; Matthews et al., 2016; Valtorta et al., 2016). Social isolation is known to be heritable (Matthews et al., 2016) and longitudinal research on other psychiatric traits has found genetic influence on developmental trajectories (Fontaine et al., 2010; Hannigan et al., 2018). Thus, the heritability and contribution of genetic and environmental influences could vary between class trajectories of social isolation. With a nationally representative cohort of twins regularly interviewed across 13 years, we can build on existing research by identifying childhood social isolation trajectories, and how these relate to outcomes at age 18 and antecedents at age 5, including genetic influence.

Aims

More than ever, the importance of developing and maintaining social relationships is emphasised. Now is a good time to better understand patterns of social isolation in childhood, identify antecedents that either increase likelihood, or prevent worsening, of social isolation and examine the influence of these trajectories on outcomes in young adulthood. The present study will:

a) identify developmental trajectories of social isolation using data at ages 5, 7, 10 and 12 years;
b) explore associations between trajectories of social isolation with antecedents including societal factors, home environment, parent characteristics, child neurodevelopment, child emotional and behavioural development and genetic predisposition, and;
c) test associations between trajectories of social isolation with mental health problems and service use, physical health and health risks, coping and functioning, and employment prospects in young adulthood.

It is anticipated that there will be distinct trajectories of social isolation, each with varying starting points and stability or change over time. Furthermore, it is expected that different trajectories of social isolation will be associated with different antecedents and outcomes. Please see **Table 1** for the full range of antecedents measured at age 5 and outcomes at age 18 included in the present study.

Table 1. Antecedents and outcomes of social isolation

	Domain	Variable	Measure in E-Risk	
Antecedents at age 5	**Social factors**	Urban residence: Classification of child's neighbourhood	Acorn Neighbourhood Classification based on 2001 CENSUS	(Newbury et al., 2016; Tanksley et al., 2020)
		Neighbourhood: Neighbourhood vandalism, problems with neighbours	Vandalism: graffiti and damage to property, cars broken into or stolen Neighbours: noise neighbours, arguments, loud parties, teenagers hanging around	(Bowes et al., 2009)
		School: Total number of children in school, percentage of children eligible for free school meals, average class size	Based on OFSTED data for schools attended by study participants	(Bowes et al., 2009)
		Family: Socio-economic disadvantage	Composite of parental income, education, and occupation	(Newbury et al., 2020)
	Home environment	Family structure variables, including mobility	For example, number of residence moves; biological father present in the home	(Jaffee et al., 2003)
		Exposure to domestic violence	Conflict Tactics Scales	(Bowes et al., 2009; Straus, 1979)
		Physical maltreatment	Multi-Site Child Development Project standardised protocol	(Jaffee et al., 2004)
		Social support	Time taken to reach closest family members; close friends in the immediate area	(Crush et al., 2018; Simons & Johnson, 1996)
		Stimulating activities	Been to the park; been to the cinema; been on a long walk	(Bowes et al., 2009)
		Maternal warmth	Maternal expressed emotion scales based on the five minute speech sample method	(Bowes et al., 2010; Caspi et al., 2004)
		Prosocial behaviours	CBCL	(Achenbach & Edelbrock, 1991)
	Parent characteristics	Maternal depression	DSM-IV Diagnostic Interview Schedule	(American Psychiatric Association, 1994)
		Maternal personality	Big Five Inventory (BFI)	(John, 1999)
		Parental antisocial behaviour and aggression	YASR, YABCL	(Jaffee et al., 2003)
		Parental alcoholism	2 items are taken from YASR and YABCL	(Achenbach, 1997)
	Child neurodevelopment	IQ	WPPSI Revised	(Wechsler, 1990)
		Executive functioning	Three tests: Mazes, a WPPSI subtest nonverbal analogue of the Stroop task, and Sentence Working memory	(Gerstadt et al., 1994; Grodzinsky & Diamond, 1992)
		Theory of mind	Battery of Theory of Mind tasks	(Hughes et al., 2000)

	Child emotional and behavioural development	Externalising problems: Antisocial behaviour, aggression and delinquency subscales	CBCL/TRF	(Achenbach & Edelbrock, 1991)
		Internalising problems: Anxiety, Withdrawn, and Somatic subscales	CBCL/TRF, with social isolation items excluded.	(Achenbach & Edelbrock, 1991)
		Hyperactivity/impulsivity: Attention-Deficit/Hyperactivity Disorder items, Inattentive, Impulsive, Hyperactive symptoms	CBCL/TRF	(Achenbach & Edelbrock, 1991)
		Temperament rating including: Negative Affect, Impulsivity, Approach, Sluggishness, Wariness, Under controlled, Inhibited, Shy	Interviewer rated 25 different behavioural characteristics	(Caspi et al., 1995)
	Genetic predisposition	Heritability of social isolation trajectory membership.	Bivariate twin model	(Fontaine et al., 2010; Matthews et al., 2016)
Outcomes at age 18 *Adapted from Matthews et al. (2019)*	**Mental health and service use**	Diagnosis of either depression, anxiety, ADHD, conduct disorder, PTSD, alcohol dependence or cannabis dependence	Past-year diagnosis according to DSM-IV or DSM-V criteria, assessed via structured clinical interview	(American Psychiatric Association, 1994, 2013)
		Psychosis symptoms	Items from the Structured Interview for Psychosis-Risk Syndromes (SIPS)	(Cannon et al., 2002; J. Newbury et al., 2019)
		Self-harm or suicide attempt	Reports of at least one instance of self-harm or suicide attempt between ages 12 and 18	(Matthews et al., 2019)
		Service use	Any visit to a GP, psychiatrist or counsellor/psychotherapist for mental health problems in past year	(Matthews et al., 2019)
	Physical health and health risks	BMI	Calculated from height and weight measurements taken by interviewers at the home visit	(Danese et al., 2009)
		C-reactive protein (CRP)	Collected via dried blood spots. mg/l values were log-transformed prior to analysis	(Danese et al., 2009, 2011)
		Physical activity	Daily physical activity during work/college or leisure time, measures using the Stanford Brief Activity Survey	(Taylor-Piliae et al., 2010)
		Daily smoking	At least one cigarette smoked daily	
	Coping and functioning	Loneliness	UCLA Loneliness Scale, Version 3	(Matthews et al., 2019)
		Life satisfaction	Global life satisfaction measured via the Satisfaction with Life Scale	(Diener et al., 1985)

	Coping with stress	Count of strategies used when experiencing stress in relation to finances, relationships, college or work. Four positively-coded items (For example, 'talk with other people about it', 'take steps to solve the problem') and four negatively-coded items ('withdraw or spend more time alone', 'obsess about problems') were combined, with higher scores reflecting more positive coping strategies	(Matthews et al., 2019)
	Problematic technology use	Compulsive use of digital technology such as internet, email, social networking, mobile phones and text messaging. Measured using an adapted version of the Compulsive Internet Use Scale	(Meerkerk et al., 2009)
	Sleep	The Pittsburgh sleep quality index	(Buysse et al., 1989)
Employment prospects	Not in employment, education or training	Participants' report of whether they were currently employed or studying	(Goldman-Mellor et al., 2016)
	Low qualifications	Based on attainment on the General Certificate of Secondary Education (GCSE), taken by UK students at age 14–15. Participants with either no qualifications or GCSE's at grades D–G were coded as having low qualifications	(Matthews et al., 2019)
	Job preparedness	Self-rating of professional and technical skills. For example, writing and computer programming. Self-rating of 'soft' skills. For example, communication and teamwork	(Goldman-Mellor et al., 2016)
	Optimism	Self-rated perceptions of participants' ability to get ahead in their careers	(Goldman-Mellor et al., 2016)
	Job search activities	Total number of job-seeking activities participants have undertaken. For example, applied for a job or looked at job vacancies pages	(Goldman-Mellor et al., 2016)

Statistical analyses

As a first step, we will identify class trajectories of social isolation using Growth Mixture Modelling (GMM) methodology in MPlus. These trajectories will be computed using social isolation combined report (mother and teacher) at ages 5, 7, 10 and 12. Single growth curve models and Latent Class Growth Analysis (LCGA) will be conducted as a preliminary step to assess the appropriate growth model (or curve) and estimated number of classes, respectively. We will use standard fit statistics (BIC, AIC, VLMR, Entropy values) to

identify the best fitting model for the final number of classes (or groups of individuals). The decision on the final model will be based on the following: incremental fit gain with each class, the proportion of the sample captured by each class and theoretical plausibility and meaningfulness.

From the GMM, posterior probabilities will be computed for each individual. These probabilities indicate how likely each individual is to be assigned to each identified class. Therefore, as a second step, we will use these probabilities to explore associations between all antecedents and outcomes, and class membership. The associations between class membership and antecedents or outcomes will be calculated using the "Standard Three-step Method" (van de Schoot et al., 2017). In step one, the number of classes will be determined by the GMM, independent of antecedents or outcomes. Step two, the most likely class membership (using posterior probabilities) is merged into the original dataset. Finally, step three, regression analyses will be used to estimate associations between class membership and the antecedents and outcomes. To test for independence of associations between the trajectories and outcomes, significant antecedents will be controlled for. Multiple testing corrections will be applied to all analyses.

As a final step, we will estimate the extent to which genetic and environmental influences contribute to social isolation trajectory class membership. Using a behavioural genetics approach, we will utilise the twin sample to estimate the heritability of class membership through partitioning the variance in additive genetic (A), common environment (C) and individual environment (E) influence on social isolation classes.

Note
In a later paper, we hope to expand on these behavioural genetic analyses by using genomic data collected in E-Risk.

Variables Needed at Which Ages (names and labels):

Study: E-Risk

Variables for all time points are included in a separate document:
Erisk_variables_KThompson_Dec2020.doc

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Data Security Agreement

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Today's Date	11th of December 2020

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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.

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