

Concept Paper Form

Provisional Paper Title: The relationship between type, timing and duration of exposure to adverse childhood experiences and adolescent self-harm and depression
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Today's Date: 4/26/2022

Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

Objective of the study:

Self-harm and depression are both major public health concerns. Self-harm is one of the strongest risk factors for suicide and is a key concern in its own right as outlined in the national strategy for suicide prevention for England (Department of Health and Social Care, 2021; Hawton et al., 2012; Thapar et al., 2012). Depression is one of the most common mental health disorders in children and adolescents in the UK and carries increased risk of both suicide attempts and completed suicide, there is evidence of increasing depression among children and adolescents aged 5-15 years and young people aged 16-24 years (Pan and Brent, 2020; Haefner, 2016; Sadler et al., 2018; Office for National Statistics, 2020).

Adverse childhood experiences such as maltreatment (emotional, physical and sexual abuse, physical or emotional neglect, bullying), and household dysfunction (parental violence, separation, substance misuse, mental illness or criminal behaviour) are known to be associated with poor outcomes, including mental health problems, substance misuse, self-harm, suicidal ideation and suicide both in adolescence and early adulthood (Hammerton et al., 2015; Bomysoad and Francis, 2020; Bjorkenstam et al., 2017; Brown et al., 2018; Liu et al., 2018; Houtepen et al., 2020). Studies report a direct association between childhood adversity and risk for self-harm, and a dose-response relationship between the number of adversities experienced and self-harm and depression, whereby greater number of adversities confer an increased risk of self-harm and depression compared to those experiencing fewer adversities (Russell et al., 2021; Elmore and Crouch, 2020). The number of adversities experienced are commonly summed to obtain an overall score to investigate associations with subsequent mental health outcomes (Bomysoad and Francis, 2020; Houtepen et al., 2020).

This approach neglects the potentially important impact of individual adversities, duration of exposure to each adversity, the different pathways through which they may operate, and assumes each one contributes equally to poor outcomes. The effects of some types of adversities may be stronger for specific mental health problems, for example subtypes of child maltreatment (emotional

neglect and abuse) have stronger associations with self-injury compared to sexual abuse and physical neglect (Brown et al., 2018). A retrospective population-based study found the odds of suicide attempts were five-fold among those exposed to emotional abuse compared to 2-3 fold for other adversities such as parental separation/divorce, physical and sexual abuse and household substance abuse (Dube et al., 2001).

Furthermore, comorbidity of mental health problems are common among those exposed to multiple adversities, which may subsequently require a multifaceted approach to intervention (Van der Feltz-Cornelis et al., 2019). The co-occurrence of self-harm and psychiatric disorders is high, a review of 50 studies across 24 countries found 80% of adolescents and young people who self-harmed also had a psychiatric disorder, with depression being one of the most common disorders (Hawton et al., 2013). The co-occurrence of self-harm and depression carries increased risk for suicide attempts, in one study almost a half of 12-17 year olds with depression also reported self-harm and of those, 19% reported a suicide attempt, this was markedly reduced (0.4%) in those that only reported self-harm (Lawrence et al., 2015). Population-based cohort studies report higher all-cause mortality, suicide, burden of disease, and disability among those with depression and self-harm compared to those with depression alone (Björkholm et al., 2021; Aaltonen et al., 2019). The co-occurrence of self-harm and depression in association with specific adverse childhood experiences has not been studied using longitudinal prospective data where order of precedence of childhood adversities, self-harm and depression can be established.

It is important to understand the relationship between timing and duration of exposure to adversities and mental health outcomes for effective targeted intervention at key stages of the life course. Theories such as the accumulation of risk model suggests a dose-response relationship between duration of exposure and risk for poor outcomes, whereby cumulative exposure over the life course increases risk of poor outcomes (Kuh et al., 2003). The sensitive period hypothesis assumes there is a stronger relationship between an exposure and outcome during a specific period (i.e. early adolescence), however the critical period hypothesis posits that timing of an exposure, particularly in early childhood, may cause irreversible changes to development that have implications for later life health outcomes (Kuh et al., 2003). In such circumstances timely intervention is crucial for the prevention of poor outcomes in later life.

There has been some attention in the literature on testing these key life course hypotheses to untangle the relationship between timing and duration of exposure to adverse experiences and mental health outcomes in childhood (Dunn et al., 2018; Kuh et al., 2003). However, little is known about the longer-term impacts of prolonged exposure to multiple adversities at different stages of development (early childhood, middle childhood, and adolescence). The use of a longitudinal dataset spanning different developmental periods, with repeated measurements of childhood adverse experiences, social and demographic measures as well as mental health outcomes, may help elucidate the relationship between timing and duration of exposure to different adversities and later self-harm and depression.

The aims of this study are to:

1. Investigate the relationship between different types of adverse childhood experiences and a) self-harm, b) depression, c) co-occurring self-harm and depression during adolescence.
2. Investigate the relationship between timing and duration of exposure to adverse childhood experiences at three key stages of development (early life 0-5 years, middle childhood 6-10 years, adolescence 11-13 years) and a) self-harm, b) depression, and c) co-occurring self-harm and depression in adolescence.

Study design: Prospective population-based cohort study

Data sources: The primary data source is the Avon Longitudinal Study of Parents and Children (ALSPAC) which has unrivalled detail on prospective measures of adverse childhood experiences with multiple repeat measures over time (Boyd et al., 2013; Fraser et al., 2013; Houtepen et al., 2018). The E-Risk dataset will be used as a secondary data source to test the generalizability and replicability of findings across other cohorts, and in a nationally representative population. We appreciate that the timing of the exposure and outcome measures are slightly different across these two cohorts and thus replication will be attempted where assessment periods are comparable.

Data analysis methods:

Aim 1: A series of multinomial regression models (single unadjusted and multivariate adjusted models) will examine the relationship between each type of adverse childhood experience and a 4-category outcome at age 18: no self-harm or depression (reference group), self-harm only, depression only, and co-occurring self-harm and depression. Multivariate adjusted models will include the following confounders and covariates: sex, family socioeconomic status, neighbourhood deprivation, mother's age at delivery, mother's education, special educational needs, emotional and behavioural issues during early childhood, and also depression and self-harm at age 12. Early measures will be used where possible to ensure these additional factors precede the occurrence of adverse childhood experiences. Relative risk ratios (RR) with 95% confidence intervals will be estimated to make inferences about the relationship between each adverse childhood experience and risk of self-harm and depression. Gender differences and interaction effects will also be examined.

Aim 2: A structured life course modeling approach will be used to examine the relationship between timing and duration of exposure to adverse childhood experiences at three stages of development (early life 0-5 years, middle childhood 6-10 years, adolescence 11-13 years and where possible comparable age periods in E-Risk, e.g., 0-12 and >12-18) and outcomes in adolescence (at age 16 in ALSPAC and at age 18 in E-Risk).

The life course modeling approach will be based on the approach initially developed by Mishra et al (2009) and further refined by others (Smith et al., 2016; 2015). The accumulation of risk, critical and sensitive period hypotheses will be examined to determine which of these are best supported by the data, or whether this varies by the type of adversity being examined. Each hypothesis will be encoded into a variable, and the association between the encoded variables with the outcomes self-harm, depression, and co-occurring self-harm and depression will be examined, variables with the strongest association with the outcomes will then be selected. Confounders will also be added to the models.

Sensitivity analyses: Retrospective child reports of exposure to adverse experiences will be used as a sensitivity analysis to examine if outcomes differ by prospective or retrospective measures of adverse childhood experiences.

Note for all analyses using E-Risk data these will adjust for the clustered nature of the data (i.e., the non-independence of the twin observations).

Variables needed at which ages:

ACEs total score (ACESE512 - Adverse Childhood Experiences (ACEs) - [total] - thru P12 – ET)

Exposures (adverse childhood experiences) at any time between ages 0-12 years:

- Physical abuse (PABSEVTYE12 - Physical abuse by 12, severity, Elder)

- Sexual abuse (SASEVTYE12 - Sexual abuse by 12, severity, Elder)
- Emotional abuse and neglect (EANSEVE12 - Severity of Emotional abuse/neglect of Elder twin, thru age 12, 2014)
- Physical neglect (PNSEVERITYE12 - Physical neglect by 12, severity, Elder)
- Bullying (BULLSEVE12 - Bullying victim to Age 12 – Elder)
- Domestic violence (EXPV_DV510 - Exposure to DV, 5 to 10, 012 [Family level])
- Household substance abuse
 - o FHSUBPM12 - Proportion of family members with valid data who have problems with alcohol or drugs
 - o FHSUBAM12 - Anyone on list even had problems with alcohol or drugs? - Twin's Mum
 - o FHSUBBM12 - Anyone on list even had problems with alcohol or drugs? - Twin's Dad
- Parental mental health problems
 - o FHPSYHSUIC12 - Family History of psychiatric hospitalisation or suicide attempt, Belsky 2012
 - o FHANYAM12 - Anyone on list ever had any mental health problem? - Twin's Mum
 - o FHANYBM12 - Anyone on list ever had any mental health problem? - Twin's Dad
 - o FHHOSPAM12 - Anyone on list ever been hospitalized for any psychiatric disorder? - Twin's Mum
 - o FHHOSPBM12 - Anyone on list ever been hospitalized for any psychiatric disorder? - Twin's Dad
 - o FHSUIAM12 - Anyone on list attempted suicide? - Twin's Mum
 - o FHSUIBM12 - Anyone on list attempted suicide? - Twin's Dad
- Parental separation/divorce (PAR_SEP - any parent absent, as in Beckley et al 2018)
- Parental antisocial behavior (PAR_ASB – combination of mother and father antisocial behaviour from Beckley et al 2018)
- Retrospective measures of any of the above adversities (twin self-reports from Childhood Trauma Questionnaire)
 - o CTQPNCE18 - Physical Neglect CTQ Categories - P18 - Elder
 - o CTQPACE18 - Physical Abuse CTQ Categories - P18 - Elder
 - o CTQENCE18 - Emotional Neglect CTQ Categories - P18 - Elder
 - o CTQEACE18 - Emotional Abuse CTQ Categories - P18 - Elder
 - o CTQSACE18 - Sexual Abuse CTQ Categories - P18 - Elder

The above adversities also split separately by time period (which ever of the adversities are available by the following time periods), exposure between: 0-5 years, 6-10 years, and 11-12 years.

Physical & sexual abuse combined (older measure which was derived differently to the severity variables used above):

- HARM3EM5 - Child Harm 0-5 - Elder (3 code)
- HARME510 - Child Harm Phase 5-10 - Elder Twin
- HARME1012 - Child Harm Phase 10-12 - Elder Twin

Physical abuse only (newer measure):

- PABAGEE12 - Physical abuse by 12, age of onset, Elder (0=none, 1=0 to 7 yrs, 2=7 to 12 yrs)

Sexual abuse only (newer measure):

- SAAGEE12 - Sexual abuse by 12, age of onset, Elder (0=none, 1=0 to 7 yrs, 2=7 to 12 yrs)

Bullying:

- BU2E12 - Before you started school (under 5)? – Elder

- BU3E12 - While you were at primary school (5 - 10)? – Elder
- BU4E12 - After you started at secondary school (11 or over)? - Elder

Outcomes (at age 18 years):

Self-harm-

- SHARMSUICE18 - Suicide attempt or self harm - P18 – Elder
- SHARME18 – Any self harm - P18 – Elder
- SUICATE18 - Suicide attempted - P18 – Elder
- TOTSHE18 - Number of self harm events (incl suicide attempts) - P18 - Elder
- SHVARE18 - Types of self harm behaviour - P18 - Elder

Depression- Diagnostic Interview Schedule for DSM-IV (symptom count and diagnosis)

- MDESXE18 - MDE - Symptom scale - P18 - Elder
- DXMDEE18 - Major depressive episode, dsm4 - P18 - Elder

Confounders and other covariates:

- SAMPSEX - Sex of Twins: In sample
- SESWQ35 - Social Class Composite at age 5
- Deprivation deciles (Tony – could you provide IMD at age 5?)
- MOTHTBAGE – mother’s age at birth of twins
- HIEDM5 - Highest educational qualification mother
- CDIE12 - Depression Scale - CDI - Elder
- CDICATE12 - Clinically significant depression (CDI \geq 20) - P12 - Elder
- SE10M10 - Special education service or SENCO (age 10)
- SHARMSUICE12 - Self-Harm/Suicidal Behaviour - P12 – Elder)
- TOTINTE5 - Total Mum & Teacher Internalising Scale - Elder twin
- TOTEXTE5 - Total Mum & Teacher Externalising Scale - Elder twin

Significance of the Study (for theory, research methods or clinical practice):

Examining the relationship between timing and duration of exposure to adverse childhood experiences and self-harm and depression will provide support for key life course hypotheses on how exposures during stages of child and adolescent development impact later outcomes. It may be that those exposed in early life may have worse outcomes compared to those exposed at a different time point, or that those exposed for a longer period of time may have worse outcomes compared to those that have been exposed for a shorter period. It is important to understand the relationship between timing and duration of exposure to adversities and mental health outcomes for effective intervention at key stages of development to mitigate the impact of these adversities in later life.

This study will provide evidence on the relationship between each type of adverse childhood experience and self-harm, depression, and co-occurring self-harm and depression, as well as insights into the strength of association for each type of outcome. We hypothesise this will extend the evidence base by demonstrating that not all adversities contribute equally to poor outcomes, and identify key adversities that confer a greater risk of poor outcomes – which will subsequently require targeted intervention.

Understanding which adversities carry an increased risk of the occurrence of both self-harm and depression specifically has important clinical implications, this group may require more intensive support to address both self-harm and depression. Understanding the relationship between different adverse childhood experiences and self-harm and depression is an important aspect of public

health intervention to reduce the population burden of both self-harm and depression and their associated mortality.

Using two cohort datasets will enhance the replicability, generalizability and robustness of the study methodology and the findings, it will also provide strong evidence for clinical practice.

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Data Security Agreement

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<input checked="" type="checkbox"/>	I am current on Human Subjects Training (CITI (www.citiprogram.org) or equivalent)
<input checked="" type="checkbox"/>	My project is covered by the Duke/KCL ethics committee OR I have /will obtain ethical approval from my home institution.
<input checked="" type="checkbox"/>	I will treat all data as "restricted" and store in a secure fashion. My computer or laptop is: a) encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines) b) password-protected c) configured to lock-out after 15 minutes of inactivity AND d) has an antivirus client installed as well as being patched regularly.
<input checked="" type="checkbox"/>	I will not "sync" the data to a mobile device.
<input checked="" type="checkbox"/>	In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact Moffitt or Caspi.
<input checked="" type="checkbox"/>	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
<input checked="" type="checkbox"/>	I will not post data online or submit the data file to a journal for them to post. <i>Some journals are now requesting the data file as part of the manuscript submission process. Study participants have not given informed consent for unrestricted open access, so we have a managed-access process. Speak to Temi or Avshalom for strategies for achieving compliance with data-sharing policies of journals.</i>
<input checked="" type="checkbox"/>	I will delete all data files from my computer after the project is complete. Collaborators and trainees may not take a data file away from the office. This data remains the property of the Study and cannot be used for further analyses without an approved concept paper for new analyses.
<input checked="" type="checkbox"/>	I have read the Data Use Guidelines and agree to follow the instructions.

Signature: B.farooq