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

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An individualised risk calculator for psychopathology in young adults victimised during childhood

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Objective of the study:
The objective of this study is to build an individualised risk calculator to assist practitioners in identifying victimised children who are at the greatest risk of developing psychiatric disorder in young adulthood. This work partly builds upon analyses already undertaken in published E-Risk papers to identify factors associated with psychiatric outcomes in victimised children. Building and expanding on this work, we will aim to contribute to a clinical evidence base, and inform practice by generating a comprehensive prognostic tool – a 'risk calculator', which we hope will accurately predict individualised risk of psychiatric disorders in victimised children.

Background:
Child maltreatment, including physical abuse, sexual abuse, emotional abuse, neglect, and exposure to intimate partner violence, is a major public health problem worldwide. In the UK, research by the NSPCC has estimated that nearly 1 in 5 children experience some form of maltreatment [1]. Maltreatment can have profound and long-lasting adverse mental health consequences [2-5]. More specifically, individuals who report a history of childhood maltreatment or abuse have an increased risk of ADHD [6, 7], antisocial and delinquent behaviours [8, 9], mood disorders and suicidal behaviours [10-12], psychosis [13, 14] and various forms of substance abuse [15, 16]. Furthermore, bullying victimisation in childhood has been linked with increased risk of anxiety and depression [17,18], self-harm and suicidality [19], and psychotic symptoms [13]. The pleiotropic effect of victimisation exposure on mental health has been evidenced from non-specific associations with an overall general liability for psychopathology, or 'p factor' [20]. Furthermore, the co-occurrence of different types of abuse is also common, and individuals who report multiple forms of abuse tend to present more severe psychopathology compared to those reporting a single type [4, 21-23].

Although previous research consistently shows an increased risk of psychopathology among victimised children compared to their non-victimised peers [24], not all maltreated children experience such difficulties. Indeed, there is significant within-group variation in health and functioning among those victimised in youth, and a growing body of evidence suggests that the mental health of some of these individuals is relatively unaffected by their victimisation experiences [25-27]. These resilient children face the same stressors as their non-resilient counterparts, but achieve positive developmental outcomes in spite of the poor prognosis conferred by this adversity [28].

Recent research has attempted to identify specific individual or environmental markers that are associated with increased or reduced risk for psychopathology following exposure to maltreatment and victimisation

[2, 29]. The identification of important predictive factors would enable more specific classification of vulnerability for (or resilience against) later psychopathology among youth exposed to maltreatment or broader victimisation, particularly where these indicators can be easily measured within clinical settings. As discussed below, these proposed risk and protective factors have generally been organised under three main domains: (i) individual/child-level (e.g. genes, IQ, executive function, Theory of Mind, temperament, childhood psychopathology); (ii) family-level (e.g. maternal warmth, sibling relationships, family history of psychopathology, socio-economic status, social support); and (iii) community-level (e.g. social cohesion, neighbourhood deprivation, crime).

Individual-level factors
Previous studies have identified child cognitive and personality factors that may predispose maltreated or victimised children to psychiatric disorder, with much of the focus on difficulties with emotional expression and regulation [30-33]. At the same time, children classified as resilient following exposure to domestic violence have been characterised by easy temperament, with more positive mood and lower reactivity [34]. More specifically, higher conscientiousness, agreeableness and openness, and lower neuroticism, have been implicated in individuals exposed to childhood adversity who go on to show positive adaptive outcomes [35]. Prosocial behaviour has also been associated with a reduced likelihood of aggressive behaviour at an eighteen-month follow-up among physically abused children [36].

Previously in E-Risk, higher intelligence and more positive temperament has been observed in youth resilient to antisocial behaviour following maltreatment [37]. However, these individual factors failed to predict resilience when the child was exposed to multiple family and neighbourhood stressors in addition to maltreatment, implying that these characteristics may only be protective in the context of low-stress or normative caregiving environments [37]. In another representative community sample, resilient abused youth (defined by the absence of adult psychiatric disorder) showed lower neuroticism than their non-resilient peers, but did not differ from them on cognitive ability, suggesting that personality characteristics were more salient in relation to risk of psychopathology [38]. Alternatively, more specific social-cognitive factors, rather than overall ability, may be more important to the development of psychopathology in maltreated samples. For example, Theory of Mind deficits have been observed among a high-risk sample of adolescents in out-of-home care; these deficits were associated with decreased social competence, which, in turn, was associated with greater externalising psychopathology [39].

Family-level factors
Features of a child's home environment can confer both vulnerability for, and resilience against, psychopathology following victimisation. An insecure attachment style has been shown to partially account for a longitudinal association between childhood maltreatment and young-adult depressive symptoms [40]. Within a large female sample, an interaction effect showed that youth with a history of severe sexual abuse and higher parent authoritarianism had lower resilience against internalising symptoms in adulthood [41]. Another longitudinal study by Lansford et al. [42], having identified a specific sub-sample exposed to physical abuse during the first five years of life, found that low family socio-economic status, less proactive parenting, and lower parental monitoring or knowledge were associated with elevated levels of externalising and internalising problems over a nine-year time period among these children.

With regard to potential determinants of resilience, stable, sensitive, caring, and supportive family relationships can buffer against the risk for psychopathology, even among those who have previously experienced maltreatment [5, 29, 43, 44]. For example, Lansford et al. [42] reported that low family stress was protective against internalising problems among abused children. In addition, abused children whose parents showed low levels of unilateral decision making (i.e., exerted less control over their child's everyday activities) showed lower levels of externalising behaviour, similar to those of non-abused children. Elsewhere, perceived family support has been found to significantly relate to lower levels of internalising behaviours among physically-abused children, adjusting for child-reported teacher and peer support [45]. Furthermore, for sexual abuse, maternal support (where the mother is not the offending parent) is highlighted as a potential buffer against later mental health distress [46]. Indeed, within E-Risk itself, maternal warmth, sibling warmth and a positive home atmosphere were found to promote resilience against emotional and behavioural maladjustment for bullied children [47].

Community-level factors
Aspects of the wider social environment have also been found to contribute to poor mental health development in children. These include neighbourhood poverty and social disadvantage, residential

instability, exposure to community violence, and lack of participation in community activities [48-51]. In particular, low levels of social support have been found to moderate the longitudinal association between child abuse and adult levels of anxiety and depression [52]. Supportive and trusting neighbourly relationships have been found to promote positive parenting practices, which may in turn protect against adverse effects of maltreatment [53]. Indeed, in a previous E-Risk study, maltreated children who lived in neighbourhoods characterised by lower levels of crime, and higher levels of social cohesion and informal social control, were more likely to be resilient against the development of antisocial behaviour [37]. More subjective measures of neighbourhood satisfaction have also been associated with better psychiatric outcomes among those with a history of maltreatment [54]. Furthermore, a recent E-Risk study reported that higher levels of neighbourhood social cohesion were protective against psychotic symptoms at age 12 among children exposed to victimisation in early life [55]. However, in line with an ecological model, some interplay between different protective domains would be expected here; for example, children who were self-reliant within their families, and able to form supportive relationships with other adults in the community, such as teachers, were found to score more highly on a composite measure of resilience [56].

Significance of the study:
As outlined above, resilience following childhood victimisation has been observed across multiple domains [25, 26]. Indeed, multilevel ecological models have been proposed for maltreatment risk (and resilience), involving transactional relations between inter-related individual, family, and community characteristics [28, 57]. However, there are several outstanding knowledge gaps in the current literature, which this study aims to address.

First, although previous studies have tested protective factors for maltreatment, most have focused on a single protective factor at a time. However, resilience likely involves a constellation of risks across multiple domains of functioning. Thus, this study will build an ecological model that includes individual-, family-, and community-level risk factors for each individual, in order to capture a fuller picture of the diverse bio-psycho-social processes underlying victimisation resilience to psychopathology. Related to this, much of the previous research focuses on a single type of abuse or maltreatment [54]. In contrast, this study will use a broad measure for victimisation, and also test the sensitivity of findings across multiple types of victimisation (e.g. physical abuse, sexual abuse, emotional abuse/neglect, physical neglect).

Second, the majority of existing studies use cross-sectional designs and retrospective reports of child victimisation, prohibiting temporal inference about the direction of effects between victimisation and psychopathology. However, this study will capitalise on E-Risk's prospective design, ensuring that victimisation experiences in childhood precede later young-adult mental health. In particular, E-Risk's prospective measure of child victimisation combines repeated measures and multiple informants, and has proven validity. At the same time, despite the fact that retrospective and prospective reports of child maltreatment show only modest agreement in both the Dunedin [58] and E-Risk samples [24], both sources show significant associations with psychiatric problems, suggesting they both may be clinically useful, albeit in different ways. Therefore, we will also test the sensitivity of findings across prospective and retrospective measures of victimisation.

Third, previous studies often utilise highly selected clinical samples, with low levels of variation on child characteristics that could be important determinants of resilience (e.g., socio-economic status, IQ). By focusing on victimised individuals within a population-representative cohort of UK children, it is hoped that the findings of this study will be more generalisable to victimised children in the wider population.

Finally, although previous studies have examined psychiatric outcomes for victimised children, few have tested the predictive ability of these estimated models. Although logistic regression techniques can be used to compute the probability of developing a certain outcome (e.g. odds ratio), this still represents an explanatory rather than predictive model, as any observed associations are limited to the specific data in which the model was derived. They also describe the average probability of the outcome for a group rather than the prediction for individuals. Therefore, although certain individual, family and community factors may show a significant association with an outcome within a regression model, the extent to which these predictors can then be extrapolated to classify individual risk in new or unseen cases remains unclear. The best explanatory model may differ from the best predictive model, and studies have demonstrated that the odds ratio does not necessarily quantify the ability of a predictor to accurately classify an individual [59]. In order to prevent 'overfitting' of a multivariable regression model to a specific sample, additional penalties can be applied in 'regularised' regression models to reduce the variability of the regression estimates.

Furthermore, predictive accuracy can then be evaluated through internal validation by setting aside a subset of the data as a 'holdout' sample, which can be used to validate the proposed prediction model. Particular attention is paid to calibration, or the agreement between predicted and observed values, and discrimination, or the ability to distinguish between victimised youth who go on to develop psychopathology from those who do not [60].

Therefore, although some aspects of this study's design and analysis may overlap with previous aetiological research on maltreatment in E-Risk, our main aim is to advance existing knowledge about predictors of psychopathology following exposure to victimisation by moving from the averaged associations of regression models to more individualised prediction, in line with personalised medicine approaches. Research has begun to develop specific clinical prognostic models for psychiatric disorders such as psychosis [61] and bipolar disorder [62], in line with examples in general medicine for cardiovascular disease and cancer. By combining a series of important predictor variables, these 'risk calculators' allow clinicians to estimate the probability that a particular clinical outcome or diagnosis will arise for an individual [60, 62]. If available at initial clinical contact, this calculator could inform decision-making around the appropriate level of treatment response in victimised children.

Aims of the study:
This study will examine a variety of potential risk factors that confer vulnerability for, and/or resilience against, psychopathology in the face of childhood victimisation. The resulting multivariable prognostic model will be used to build a risk calculator, a practical tool to help clinicians and professionals identify children who are at the greatest risk of psychiatric disorder diagnosis in young adulthood following victimisation. The study's three main aims are:

1. To examine the role of individual-, family- and community-level factors as determinants of vulnerability and resilience for a range of psychiatric disorders at age 18, including externalising (ADHD, CD) and internalising disorders (anxiety, depression, PTSD, disordered eating), substance abuse (alcohol, smoking, and/or cannabis abuse or dependence), thought disorders (psychotic symptoms/experiences), as well as a dimensional psychopathology score (p factor), in children exposed to (i) any victimisation, or (ii) specific types of victimisation by 12 years of age.

2. To test whether the protective or risk factors identified within this group of victimised children are particularly important in explaining heterogeneity in the young-adult psychiatric outcomes of victimised children, compared to their non-victimised counterparts.

3. To generate a risk calculator based on the identified predictors of resilience and vulnerability, and evaluate its ability to accurately discriminate between victimised children with and without psychiatric disorder.

Statistical analyses:

Analyses will be conducted in STATA version 15, and will correct appropriately for familial clustering. These will be conducted in eight main steps:

1. Psychiatric outcome measures will be generated for use in subsequent analyses. Specifically, a categorical measure of 'any psychiatric disorder' will be derived at age 18; this will also be broken down into more specific diagnostic clusters (e.g. externalising, internalising, thought disorders), followed by individual disorder diagnoses, where appropriate. Categorical outcomes will be needed to build later predictive models (see below). To test the sensitivity of analyses using dimensional measures, we will use a previously-derived factor score capturing general liability for psychopathology (p factor), as well as factor scores for externalising, internalising and thought disorders (see Schaefer et al., in press [20]).

2. A series of univariate regression models will test group differences on age-18 psychiatric diagnoses between children defined as victimised or non-victimised at age 12. In follow-up analyses, group differences will also be examined based on each specific type of victimisation (i.e., physical abuse, sexual abuse, emotional abuse/neglect, physical neglect, bullying, or domestic violence).

3. Heterogeneity in these age-18 psychiatric diagnoses among (i) overall victimised children, and (ii) children exposed to specific types of victimisation will be explored, using scatterplots/bar graphs as

appropriate for descriptive purposes.

4. A series of bivariate regression models will be tested to examine whether various individual-, family- and community-level factors are associated with differences in age-18 psychiatric diagnoses within subsets of children exposed to (i) any victimisation or (ii) specific types of victimisation.

5. Significant predictors will be combined in multivariate explanatory regression models to predict differences in categorical (i.e., diagnoses) and dimensional (i.e., *p* factor) measures of psychopathology between (i) victimised youth and (ii) youth exposed to specific types of victimisation, to examine the relative unique contribution of each factor within our ecological model, over and above the other predictors.

6. The predictive accuracy of these explanatory models will then be tested. To ensure that a proposed model is not over-fitted to our specific data and can classify unseen cases, we will use internal validation methods (for example, *k*-fold cross validation or bootstrapping) to 'train' and 'test' the model using multiple separate subsets of the overall sample. Using this method, we will test: (i) discrimination (the model's ability to separate victimised youth with and without psychopathology at age 18), based on the *c*-statistic; and (ii) calibration (the agreement between the observed and predicted outcomes), by examining the intercept (*a*) and slope (*b*) of the calibration plot.

7. We will then test for statistical interactions between identified risk or protective factors and (i) any victimisation and (ii) specific types of victimisation exposure predicting the psychiatric diagnosis of interest, using the overall E-Risk sample to see if these factors are particularly important for victimised compared to non-victimised children.

8. As a final sensitivity analysis, the above steps will be re-run using a retrospective measure of child victimisation obtained at age 18.

Variables Needed at Which Ages (names and labels):

Study: E-Risk

Age 5:

FAMILYID	Unique family identifier
ATWINID	Twin A ID (ex chkdig)
BTWINID	Twin B ID (ex chkdig)
RORDERP5	Random Twin Order
RISKS	Sample Groups
COHORT	Cohort
SAMPSEX	Sex of Twins: In sample
ZYGOSITY	Zygosity
HOHSCM5	HoH Social Class (highest mum/dad)
ED56M5	How much total income did your household get from all sources
HHIEDM5	HoH Highest Ed Qual (highest mum/dad)
SETHNIC	Ethnicity of Twins
EXFUNCE5	Executive function – mean of Mazes, DayNight & SWM – Elder
TOMTOTE5	TOM total score – Elder
TOTEXTE5	Total Mum & Teacher Externalising Scale – Elder twin
INTISOE5	Internalising Scale – ex Soc Iso items (mum & teacher average)-P5-Elder
TOTPROE5	Total Mum & Teacher Prosocial Scale – Elder twin
SISOE5	Social isolation scale (mum & teacher average) – P5 - Elder
ADJE5	Temperament – P5 – Elder derived by Sara Jaffee
PARM5	Current partnership status – mother
P5ACORN	ACORN neighbourhood SES
NPROBM5	Perception of local environment
NCRIMM5	Neighbourhood personal victimisation
SOCCM5	Neighbourhood Informal Social Control
SCOHM5	Neighbourhood Social Cohesion
WARME5	Warmth towards elder twin

Age 7:

TOTEXTE7	Total Mum & Teacher Externalising Scale – Elder twin
TOTPROE7	Total Mum & Teacher Prosocial Scale – Elder twin
SISOE7	Social isolation scale (mum & teacher average) – P7 – Elder
SIBWRMM7	Sibling Warmth – Derived by Sara Jaffee
ATHOME7	Atmosphere at home
FSEC7M7	Food Situation – 7 scale Recoded
INTISOE7	Internalising Scale – ex Soc Iso items (mum & teacher average), in line with score derived by Tim at age 5

Age 10:

TOTEXTE10	Total Mum & Teacher Externalising Scale – Elder twin
TOTPROE10	Total Mum & Teacher Prosocial Scale – Elder twin
SISOE10	Social isolation scale (mum & teacher average) – P10 – Elder
LOWSC510E	Low Childhood Self-Control, 5-10, E-Twin
SIBWRM10	Sibling warmth (same as Bowes et al 2010)
ATHOME10	Atmosphere at home (same as Bowes et al., JCPP 2010)
MONEM10	Parental Monitoring – Elder Twin
KNOWEM10	Parental Monitoring (Knowledge Subscale) – P10 – Elder
CONTEM10	Parental Monitoring (Control Subscale) – P10 – Elder
WARME10	Warmth towards elder twin
BIOPARENTL10	Bio-parent living situation (to age 10)
FSEC7M10	Food Situation – 7 Scale Recoded
NMOVES510	N residence moves between ages 5 & 10
KIDSINFAMILY10	Number of children in the family, LHC siblings + 2
INTISOE10	Internalising Scale – ex Soc Iso items (mum & teacher average), in line with score derived by Tim at age 5

Age 12:

TOTEXTE12	Total Mum & Teacher Externalising Scale – Elder twin
TOTPROE12	Total Mum & Teacher Prosocial Scale – Elder twin
SISOE12	Social isolation subscale (mum and teacher average) – P12 – Elder
NSOCCOHL12	Number of social parents cohabiting with bio-parent (to age 12)
IQ12E	Pro-Rated IQ (INF & MR), 12E
FCEVIDE12	Foster care or non-parental care through age 12
MONEM12	Parental Monitoring (full scale) – P12 – Elder
KNOWEM12	Parental Monitoring (knowledge subscale) – P12 – Elder
CONTEM12	Parental Monitoring (control subscale) – P12 – Elder
BFIOE12	Openness to Experience Subscale (BFI) – Elder Twin
BFICE12	Conscientiousness Subscale (BFI) – Elder Twin
BFIEE12	Extroversion Subscale (BFI) – Elder Twin
BFIAE12	Agreeableness Subscale (BFI) – Elder Twin
BFINE12	Neuroticism Subscale (BFI) – Elder Twin
ADULTEC12	Adult Involvement – Elder
HOMEM12	State of the home – Mum Intv
CHSTIM12	Child Stimulation – Mum Intv
HAPPHM12	Happy Home – Mum Intv
CHAOSM12	Chaos in the home – Mum intv
EANSEVE12	Severity of emotional abuse/neglect of Elder twin, thru age 12, 2014
PABSEVTYE12	Physical abuse by 12, severity, Elder
PNSEVERITYE12	Physical neglect by 12, severity, Elder
SASEVTYE12	Sexual abuse by 12, severity, Elder
POLYVE512C	Extent of Polyvictim (Truncated @3), 5-12, E-Twin
EX_SVE12	Exposed to severe victimization (0/1), 5-12, E-Twin
EXPV_DV510	Exposure to domestic violence, 5 to 10, 012 coding (from HonaLee)
BULLSEVE12	Bullying victim to Age 12 – Elder
CTQCTOTM12	CTQ combined - types of abuse or neglect at mod/severe level (0-5)
ADHDANYE512	Any ADHD dx [incl meds] - P5-12 – Elder

ANYCDDX_EMT512	Any CD dx from 5 to 12, mum/tchr, Elder
MASCE12	Anxiety Scale – MASC – Elder
CDIE12	Depression Scale – CDI – Elder
SUB2EC12	Substance Use – Option 2 (Downgrade of Items 03 and 07) – Elder
SHARMSUICE12	Self-Harm/Suicidal Behaviour – P12 – Elder
PSYSYMP01E12	Psychosis Symptom Count – Verified Coding – 0, 1+ – Elder
FHSUIAM12	Anyone on list attempted suicide? – Twin's mum
FHSUICRSCR12	Fam Hist of suicide, Reeds score, Belsky 2012
FHANYPM12	Proportion of family members with valid data who have any disorder
INTISOE12	Internalising Scale – ex Soc Iso items (mum & teacher average), in line with score derived by Tim at age 5

Item LC5 from age 12 study booklet 'How many times have you changed addresses since twins turned 10?' (to be used to derive number of house moves up to 12)

Item LE31 from Life Events section of age 12 study booklet 'New stepchildren joined the family?'

Item LE32 from Life Events section of age 12 study booklet 'Had a baby?' (this and item LE31 to be used to extend number of children in the home up to age 12)

Age 18:

DXALCDEPE18	Alcohol dependent, dsm4_based – P18 – Elder
DXALCABUE18	Alcohol abuse, dsm4_based – P18 – Elder
DXMARJE18	Marijuana dependency, dsm4 – P18 – Elder
DXDRUGME18	Drug dependent (or on methadone maintenance), dsm4 – P18 – Elder
SMKDXFTNDE18	Fagerstrom Dx for Nicotine Dependence – P18 – Elder
CDMODE18	Moderate Conduct Disorder (>=5 count) – P18 - Elder
DXADHD5X_18E	DSM-5 ADHD Dx (based on >=5 Symp) [incl NEET & meds] – P18 – Elder
DXMDEE18	Major depressive episode, dsm4 – P18 – Elder
DXGADE18	Gen Anxiety Disorder, dsm4-based – P18 – Elder
DXPTSDCUE18	PTSD Current dx, DSM-IV – P18 – Elder
DXPTSDLFE18	PTSD Lifetime dx, DSM-IV – P18 – Elder
PSYSYMP01E18	Psychosis Symptom Count (0, 1+) – P18 – Elder
PSYEXPCE18	Psychotic Experiences (cat) – P18 – Elder
SUICATE18	Suicide attempted – P18 – Elder
SHARME18	Self-harm – P18 – Elder
SUIDEAE18	Any suicidal ideation 12-18 - Elder (derived by Jessie Baldwin)
CTQPNCCE18	Physical Neglect CTQ +/- P18 - Elder
CTQPACCE18	Physical Abuse CTQ +/- P18 - Elder
CTQENCCE18	Emotional Neglect CTQ +/- P18 - Elder
CTQEACCE18	Emotional Abuse CTQ +/- P18 - Elder
CTQSACCE18	Sexual Abuse CTQ +/- P18 - Elder
CTQCTOTE18	CTQ combined - types of abuse or neglect at mod/severe level (0-5) - P18 - Elder
Item EAT1	'Have you made yourself sick because you ate until felt uncomfortably full?'
Item EAT2	'Did you worry you had lost control over how much you eat?'
Item EAT3	'Did you lose more than one stone in a 3 month period?'
Item EAT4	'Did you believe yourself to be fat when others said you were too thin?'
Item EAT5	'Would you say that food dominated your life?'

Also, the 'p' factor score, and psychopathology cluster factor scores (i.e., externalising, internalising, thought disorders), derived in Jon Schaefer et al.'s *Clinical Psychology Science* paper (in press)

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Data Security Agreement

Provisional Paper Title	An individualised risk calculator for psychopathology in young adults victimised during childhood
Proposing Author	Alan Meehan
Today's Date	December 11th, 2017

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