Concept Paper Form

Provisional Paper Title: Can a warm and supportive adult protect against mental health problems in the context of childhood adversity? A discordant twin study
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P.I. Sponsor: Helen Fisher   (if the proposing author is a student or colleague of an original PI)
Today's Date: 11th Jan 2022

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

Objective of the study:

Adverse childhood experiences are associated with mental health difficulties at the population level[1]. However, individual differences exist in children's responses to adversity, and some exposed children do not develop mental health problems[2]. This resilience to childhood adversity may in part be explained by the presence of protective factors. In particular, a warm and supportive adult presence has been identified as a potential protective factor against poor mental health outcomes after adverse childhood experiences (ACEs)[3–5] and bullying victimisation[6]. However, it is not clear if a warm and supportive adult presence has an environmentally mediated effect in the context of ACEs, as most existing research has not accounted for the possibility of genetic confounding, which is a requirement for establishing causality.

Genetic confounding could arise if genetic influences on mental health problems affect a child's exposure to a warm and supportive adult, via gene-environment correlation (rGE)[7]. Three types of rGE may operate in this context. Firstly, passive rGE (the association between an inherited genotype and the environment a child is raised in) may mean that a child whose parents have mental health problems may be less likely to receive warmth and support from them, whilst also inheriting genes which predispose them to psychopathology. Secondly, reactive rGE (the association between genetically influenced behaviour and reactions from those in the environment) may mean that a child who is more withdrawn or disruptive is less likely to elicit a warm, supportive response from adults in their environment. Thirdly, active rGE (the association between genetically influenced traits

and environments which an individual selects) may lead a child who is feeling anxious or overwhelmed to seek out solitary environments where adult warmth and support is not easily accessed. In these ways, it is possible that those children who are more vulnerable to mental health difficulties may be less likely to receive support from caring adults. If this is the case, adult warmth and support might be linked to positive mental health outcomes due to genetic confounding, rather than a causal protective effect.

In this study, we propose to use the co-twin control design to test whether the presence of a warm and supportive adult protects against mental health difficulties in children exposed to adversity, independent of genetic confounding. First, we will examine the associations between warm and supportive adult involvement and mental health difficulties during late childhood and early adulthood, in the context of adverse childhood experiences (objective 1). Second, we will use discordant twin models to test whether warm and supportive adult involvement protects against mental health difficulties in the context of adversity, independent of genetic confounding (objective 2).

Data analysis methods:

Initial analysis:
As an initial step, we will examine the relationship between ACEs and three mental health outcomes: (i) emotional problems at age 12, (ii) behavioural problems at age 12 (sum of the aggression and delinquency scales), and (iii) the p-factor at age 18. These models will be used to identify the cut-off for the number of ACEs which confers an elevated risk of mental health problems, for sample selection in the later analyses (see below). We will estimate these associations using generalised estimating equation (GEE) models with an exchangeable correlation structure to account for familial clustering.

Objective 1:
We will next use GEE linear regressions (accounting for familial clustering) to test the protective effects of warm and supportive adult involvement on mental health difficulties, among children exposed to ACEs between birth and age 12. To define ACE exposure, we will use the minimum ACE score (e.g., 1+ ACEs, 2+ ACEs) that is associated with higher levels of mental health problems in the initial analysis. First, in the Study members exposed to ACEs, we will test whether maternal warmth (average of assessments at ages 5-10) predicts fewer emotional problems and behavioural problems at age 12. Second, in the Study members exposed to ACEs, we will test whether the presence of a supportive adult (assessed at age 12) is associated with fewer emotional problems and behavioural problems at age 12. Third, we will repeat the above regression analyses testing whether maternal warmth and the presence of a supportive adult predicts a lower p-factor score at age 18.

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Objective 2:

We will use mixed effects discordant twin models to examine whether the presence of a warm and supportive adult has an environmentally driven protective effect on mental health problems. Among twin pairs exposed to ACEs (which are predominantly assessed at the family-level), we will test whether twins with greater levels of maternal warmth and adult support demonstrate better mental health outcomes than their co-twins. To rule out confounding from the non-shared environment, we will further adjust the discordant twin models for earlier mental health difficulties assessed at the individual level. In the first instance, we will focus on both MZ and DZ twins, but if the sample size of MZ twins is sufficient, we will conduct a sensitivity analysis on MZ twins only to completely rule out genetic confounding.

Notes:
- We have chosen to focus on the p-factor at age 18 (rather than internalising and externalising problems) because it captures liability to any form of psychopathology[9] and research has suggested that (i) ACEs have non-specific associations with a wide range of psychiatric disorders[10], and (ii) effects of protective factors are likely to generalise across different types of psychopathology[4].
- For the discordant twin models, we are confident that there is sufficient within-twin pair variation in maternal warmth, emotional and behavioural problems at age 12, and the p-factor at age 18 as these variables have previously been examined in discordant twin analyses in this cohort.[6,8] However, we will check for within-twin pair variation in the adult involvement measure which, to our knowledge, has not been used in discordant twin models before.

<u>Variables needed at which ages:</u>

FAMILYID	Unique family identifier
TWINAID	Twin A ID (ex chkdig)
BTWINID	Twin B ID (ex chkdig)
RISKS	Sample Groups
COHORT	Cohort
SAMPSEX	Sex of Twins: In Sample
ZYGOSITY	Zygosity
TORDER	True Twin Order
TPAIRFLT	Filter for twin-pair level data

Age 5
Protective factors

WARME5	Warmth towards elder twin
WARMY5	Warmth towards younger twin

Potential confounders – prior mental health and social class

TOTAGGE5	Total Mum & Teacher Aggression Behaviour Scale – Elder twin
TOTAGGY5	Total Mum & Teacher Aggression Behaviour Scale – Younger twin
TOTDELE5	Total Mum & Teacher Deliquency Scale – Elder twin
TOTDELY5	Total Mum & Teacher Deliquency Scale – Younger twin
TOTEMOE5	Total Mum & Teacher Emotional Scale (Ex Somatic) – Elder twin
TOTEMOY5	Total Mum & Teacher Emotional Scale (Ex Somatic) – Younger twin
SESWQ35	Social Class Composite

Age 10
Protective factors

| WARME10 | Warmth towards elder twin |
| WARMY10 | Warmth towards younger twin |

Age 12
Mental health outcomes

TOTAGGE12	Total Mum & Teacher Aggression Behaviour Scale – Elder twin
TOTAGGY12	Total Mum & Teacher Aggression Behaviour Scale – Younger twin
TOTDELE12	Total Mum & Teacher Deliquency Scale – Elder twin
TOTDELY12	Total Mum & Teacher Deliquency Scale – Younger twin
TOTEMOE12	Total Mum & Teacher Emotional Scale (Ex Somatic) – Elder twin
TOTEMOY12	Total Mum & Teacher Emotional Scale (Ex Somatic) – Younger twin

ACEs

| ACESTOTE512 | Adverse Childhood Experiences (ACEs) – [total] – thru P12 – ET |
| ACESTOTY512 | Adverse Childhood Experiences (ACEs) – [total] – thru P12 – YT |

Protective factors

| ADULTEC12 | Adult Involvement – Elder |
| ADULTYC12 | Adult Involvement – Younger |

Age 18
Mental health outcomes (p-factor)

| PH_E | P: Hierarchical, E-Twin |
| PH_Y | P: Hierarchical, Y-Twin |

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

The findings from this study could inform interventions to prevent mental health problems in young people exposed to adversity. If warm and supportive adult involvement has an environmentally mediated protective effect, this would suggest that interventions which boost adult warmth and support amongst children exposed to adversity could prevent them from developing mental health problems. Such interventions might include programmes to promote positive parenting, and community support such as parenting groups and recreation programmes. However, if the association between warm and supportive adult

involvement and resilience to psychopathology is genetically confounded, then interventions that boost adult warmth and support may not prevent children exposed to adversity from developing mental health problems. Instead, interventions may be better placed addressing other protective factors that could prevent children exposed to adversity from developing psychopathology.

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Data Security Agreement

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☒	I am current on Human Subjects Training (CITI (www.citiprogram.org) or equivalent)
☒	My project is covered by the Duke ethics committee OR I have /will obtain ethical approval from my home institution.
☒	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.
☒	I will not "sync" the data to a mobile device.
☒	In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact Moffitt or Caspi.
☒	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
☒	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. 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 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.
☒	I have read the Data Use Guidelines and agree to follow the instructions.

Signature: