Appendix Section B(2): CONCEPT PAPER TEMPLATE

DUNEDIN MULTIDISCIPLINARY HEALTH AND DEVELOPMENT STUDY

(The Dunedin Study)

CONCEPT PAPER TEMPLATE

(July 2024)

DUNEDIN STUDY CONCEPT PAPER

Provisional Paper Title:
Three reasons why we should not study one mental disorder at a time

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Please describe your proposal in 2-3 pages with sufficient detail for helpful review by addressing all areas outlined below.

Objective of the study:

Most research on mental disorders tries to find specific causes of specific disorders. For example, we ask: What genetic factors cause schizophrenia? What altered brain morphology causes ADHD? What type of child maltreatment causes depression? To answer such questions, the common strategy is to compare cases who have a specific disorder to controls, or to compare people who are located at different points on a quantitative dimension (such as 'externalizing' or 'internalizing'). But the search for causal specificity has been elusive. In fact, new evidence reveals that the major etiological factors are transdiagnostic. This is the conclusion that is emerging from genome-wide association studies, where the genetic risks for different disorders are highly correlated; from neuroimaging studies, where structural and functional alterations are shared by many forms of psychopathology; and from research in developmental psychopathology, which shows the same psychosocial risk factors for practically all disorders.

What is the reason that the search for specificity has been so elusive? We propose that one reason is that most disorders are more similar than they are distinct. But in trying to document and refute this alternative idea, a lot of research has turned to data that has limited the field's thinking about this idea. Most of the data analyzed is cross-sectional information about symptom-based categories of mental disorders that yields snapshots of individuals in one generation, and at a point in time. A developmental and inter-generational perspective offers an entirely different way of understanding why the search for specificity has been elusive. Here we present new and review previous data about why the search for specificity has been elusive and, along the way, why research on 'p' is valuable.

First, we will present evidence about assortative mating for mental disorders. We will document that it is ubiquitous and that cross-disorder assortative mating is common. This means that people with a psychiatric family history will be carrying risk genes and psychosocial risks for more than one disorder. Second, we will present evidence that mental disorders run in families, but that risk is transdiagnostic. That is, parents with a particular mental disorder do not necessarily have offspring with the same disorder; rather, they are likely to have offspring who may have many different disorders. Third, we will present evidence that, across the life course, individuals experience many different mental disorders and shift between internalizing, externalizing, and/or thought disorder families. Each of the points is illustrated with unique data, involving millions of individuals and families, and tens-of-million person-years. Our data come from the nationwide registries of Denmark and Norway and from the Dunedin Longitudinal Study.

The bottom line is that these data yield an easy-to-understand developmental and intergenerational perspective on why most mental disorders share so much in common, of 'p', and why the search for specificity has been elusive.

Data analysis methods[1]:

Denmark assortative mating data.

Study population. We use population-level administrative data from Denmark to study assortative mating. Since 1968, the Danish Civil Registration System has assigned all Danish residents a unique personal identification number, which identifies their interactions with government and private institutions. The personal identification number enables the linkage of administrative databases at the individual level and over time, as well as the linkage of family members. For our assortative mating analysis, the study population consists of all individuals born in Denmark between 1960-1970, who resided in Denmark at any point between 1980-2018. For each individual we identify all their opposite-sex partners (through cohabitation or marriage) between 1980-2018. The study population and the linkages between partners are identified through the population registers, which run from 1980 and contain yearly information on all residents in Denmark by January 1st each year.

Assessment of mental disorders**.** To assess the presence of mental disorders we link the focal individuals and their partners to (a) The Danish Psychiatric Central Register, which contains information on all inpatient treatment at psychiatric hospitals and wards in Denmark from 1970-1994, and (b) The Danish National Patient Register, which contains information on all contacts at psychiatric hospitals, wards and emergency rooms including both inpatient and outpatient contacts from 1995 and onwards. Focal individuals and their partners were classified as having a mental disorder if at any point between 1970-2018 they were registered with a diagnosis (primary or secondary) within the following diagnosis categories, according to ICD8 and ICD10: Externalizing behaviour in childhood or adolescence, substance abuse; mood, neurotic, and eating disorders; schizophrenia, bipolar disorder, and OCD; pervasive developmental disorders; personality disorders. We will report associations between partners.

Denmark parent-offspring resemblance data.

Study population. For the parent-offspring analysis, we study all children born in Denmark between 1985-1995. We link each focal child to their parents, identified through population registers which run from 1980, and contain yearly information on all residents in Denmark by January 1st each year.

Assessment of mental disorders. To assess the presence of mental disorders we link both parents and offspring to (a) The Danish Psychiatric Central Register, which contains information on all inpatient treatment at psychiatric hospital and wards in Denmark from 1970-1994, and (b) The Danish National Patient Register, which contains information on all contacts at psychiatric hospitals, wards and emergency rooms including both inpatient and outpatient contacts from 1995 and onwards. Offspring and their parents are classified as having a mental disorder if they were registered with a diagnosis (primary or secondary) within the following diagnosis categories, according to ICD8 and ICD10: Externalizing behavior in childhood or adolescence, substance abuse; mood, neurotic, and eating disorders; schizophrenia, bipolar disorder, and OCD; pervasive developmental disorders; personality disorders. We will report associations (ORs) between parents and offspring.

Norway assortative mating data.

Study population**.** We use population-level administrative data from primary-care settings in Norway, available from January 2006 until December 2019. For our assortative mating analysis, the study population consists of individuals born in Norway between February 1975 and January 1986. For each

[1] A key concern for the Dunedin Study is superficial analyses of data that simply identify differences or deficits between ethnic groups or other communities where inequities exist (e.g. persons with disabilities, Pasifika peoples, members of migrant and SOGIESC (Sexual Orientation, Gender Identify and Expression and Sexual Characteristics) communities). The cumulative effect of these types of studies is stigmatising and not of benefit. Any research that identifies differences must (a) incorporate information on the broader context (e.g. historical or political factors); (b) where possible undertake additional analyses to examine the source of the difference/s, and (c) include policy recommendations for its resolution.

individual we identify all their opposite-sex partners (through cohabitation or marriage) between 2006-2019.

Assessment of mental health conditions**.** All residents of Norway are assigned a primary-care physician (PCP). Access to specialist healthcare typically requires a referral from the PCP. Service is free for juveniles and highly subsidized for adults. To receive reimbursements, PCPs bill the Norwegian Health Economics Administration, sending at least one primary diagnosis or reason for the visit. Thus, it is unlikely that visits to PCPs go unreported. Information is coded according to the International Classification of Primary Care (ICPC-2)[10] and registered in a national database. ICPC-2 is divided into 17 chapters representing health conditions in different body systems. Using codes from ICPC-2 chapter P-Psychological, we study 14 mental-health conditions that had at least a 1% prevalence rate among adults, aged 20-50 years**:** substance abuse, ADHD, depression, acute stress reaction, anxiety, phobia, PTSD, somatization, psychosis, sleep disorder, sexual concerns, personality disorder, suicide/suicide attempt, mental disorders not otherwise specified. We will report associations between partners.

Norway parent-offspring resemblance data.

Study population. We use population-level administrative data from primary-care settings in Norway, available from January 2006 until December 2019. For the parent-offspring analysis, the study population consist of children born in Norway between February 2000 and December 2017. We link each focal child to their parents, as identified in the Norwegian Population Register.

Assessment of mental-health conditions. Among parents, we focus on the same 14 mental-health conditions we reported about in the assortative mating analysis and that had a prevalence across the 14-year observation window greater than 1%. Among the offspring, we focused on these same 14 conditions plus three additional mental-health conditions that had a prevalence greater than 1% among the population of children (continence issues; developmental delay/learning problems; stammering/stuttering/tic). We will report associations (ORs) between parents and offspring.

Dunedin longitudinal data.

Sample. We use data from the Dunedin Study to study the ebb and flow of mental disorders over the life course. The Dunedin Study is a longitudinal investigation of health and behavior in a complete birth cohort. Participants were all individuals born between April 1972 and March 1973 in Dunedin, New Zealand, who participated in the first assessment at age 3 years, representing 91% of participants who were eligible based on residence in the province. Assessments have been carried out at birth and ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, 38, and most recently, 45 years, when 94% of the 997 Study members still alive took part.

Mental health assessments. Beginning at age 11 years, participants were interviewed about past-year symptoms of mental disorders. At ages 11, 13, and 15 years, the following disorders were assessed: Externalizing disorders (i.e., attention-deficit/hyperactivity disorder and conduct disorder) and Internalizing disorders (i.e., depression, anxiety, and fears [including separation anxiety, overanxiety, social phobia, and simple phobia]). At ages 18, 21, 26, 32, 38, and 45 years, the following disorders were assessed: Externalizing disorders (ie, attention-deficit/hyperactivity disorder [at ages 18, 38, 45], conduct disorder, alcohol dependence, cannabis dependence, other drug dependence [at ages 26, 32, 38, 45], and tobacco dependence), Internalizing disorders (ie, depression, generalized anxiety disorder, fears [including social phobia, simple phobia, agoraphobia, and panic disorder], posttraumatic stress disorder [at ages 26, 32, 38, 45], and eating disorders [including bulimia and anorexia; at ages 18, 21, 26]]), and Thought disorders (i.e., obsessive-compulsive disorder, mania and schizophrenia [both at ages 21, 26, 32, 38, 45]). We report patterns of continuity and change, as previously described in Caspi et al. 2014 and Caspi et al. 2020, using new figures to illustrate the ebb and flow of mental health conditions.

Putting all the elements together.

We report a 3-generation analysis of mental disorders. In Dunedin, we have previously reported family histories of mental disorder (grouped into Internalizing, Externalizing, and Thought disorders) with data from the Dunedin Family Health History Study which collected information about each Study member's family from the Study member and from both of the Study member's parents (Caspi et al. 2014). In Norway we have constructed family histories of mental disorder (grouped into Internalizing, Externalizing and Thought disorders) using population-level administrative data. In Denmark, we are currently exploring the feasibility of constructing family histories. We report associations between mental disorders and estimate assortative mating, parent-offspring resemblance, and comorbidity among binary indicators

of Internalizing, Externalizing, and Thought disorders. Models are estimated in MPlus 8.4 using the weighted least-square means-and-variance-adjusted chi-square test (WLSMV), appropriate for use in models of binary data and/or R (v4.2.3) and the Lavaan package (v0.6-15) with pairwise deletion of missing data and the weighted least-square means-and-variance-adjusted chi-square test (WLSMV).

Variables needed at which ages:

Denmark: ICD mental health codes from inpatient and outpatient hospitals for the Danish population, 1970-2018.

Norway: ICPC2 mental health codes from primary-care settings for the Norwegian population, 2006-2019.

Dunedin: None. The data are a re-representation of Caspi et al. 2014 and 2020.

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

How the paper will contribute to Māori health advancement and/or equitable health outcomes[2]

This article is a 'thought piece' that draws on data from population registers in Denmark and Norway and from previously published findings from the Dunedin Study to illustrate why studying one mental disorder at a time is potentially blinding. With a new understanding of why it is so difficult to find disorder-specific causes of mental disorders, we will (a) spell out recommendations to reshape measurement and design practices in research settings in order to advance etiological research, and (b) spell out recommendations for assessment practices in clinical settings in order to deliver more effective treatments that can benefit the entire population, and vulnerable groups in particular. The goal of this article is to articulate these ideas as a set of tractable new directions for psychopathology research and clinical psychology.

References:

a. **Caspi A**, Houts RM, Ambler A, Danese A, Elliott ML, Hariri A, Harrington HL, Hogan S, Poulton R, Ramrakha S, Rasmussen LJH, Reuben A, Richmond-Rakerd L, Sugden K, Wertz J, Williams BS, Moffitt TE. Longitudinal assessment of mental health disorders and comorbidities across 4 decades among participants in the Dunedin birth cohort study. JAMA Network Open. 2020. PMID:32315069 PMCID: PMC7175086
b. Caspi, A., Houts, R. M., Belsky, D. W., Goldman-Mellor, S. J., Harrington, H., Israel, S., Meier, M. H., Ramrakha, S., Shalev, I., Poulton, R., & Moffitt, T. E. (2014). The p Factor: One General Psychopathology Factor in the Structure of Psychiatric Disorders? *Clinical Psychological Science*, *2*(2), 119-137. https://doi.org/10.1177/2167702613497473

[2] Helpful information can be found here: https://www.hrc.govt.nz/sites/default/files/2020-01/NZ%20Prioritisation-Framework-FA-web_0.pdf