

## **Proposals for the Alicia Koplowitz Foundation PhD Fellowships**

We are pleased to offer two potential PhD projects for the FAK fellowships. Both are centered around the under-researched field of pediatric anxiety and related disorders. We propose two large-scale epidemiological investigations, taking advantage of the unique Swedish population-based registers. Project 1 examines the impact of anxiety, trauma-, and stressor-related disorders on educational and occupational outcomes. Project 2 focuses on environmental risk factors for these disorders. Both projects offer ample opportunities for a high caliber PhD thesis and a minimum of three publications.

### **PROJECT PROPOSAL NUMBER 1**

#### **Educational and occupational outcomes in anxiety, trauma-, and stressor-related disorders**

##### *Aims*

1. To examine the impact of anxiety, trauma-, and stressor-related disorders on academic achievement upon completion of the 9<sup>th</sup> grade at age 16 (school grades at the time of compulsory school graduation) and the highest level of education achieved, compared to general population controls and unaffected siblings.
2. To examine the impact of anxiety, trauma-, and stressor-related disorders on labor market entry and marginalization (receipt of disability pension, periods of sickness absence, or unemployment), compared to general population controls and unaffected siblings.
3. To examine the impact of having a child with anxiety, trauma, and stressor-related disorders on parental work impairment (receipt of disability pension, periods of sickness absence, or unemployment) compared to general population controls who have children of the same age without these disorders.

##### *Summary of methods*

This is a large-scale **epidemiological project**, which will include **three separate studies**, each tackling one of the aims described above. For all studies, we will link different population-based registers in Sweden using anonymous personal identification numbers. The nationwide registers that will be used for this project are: The Total Population Register, the Multi-Generation Register, the National Patient Register, the National School Register, and the Social Insurance Agency database.

A preliminary examination of the Swedish National Patient Register between 1997 and 2009 identified over 150,000 patients available for analyses. The breakdown is as follows:

Anxiety, Trauma, and Stress-Related Disorders	Number of patients (1997-2009)
All disorders	154,740
Agoraphobia and/or Panic Disorder	56,005
Social Anxiety Disorder	19,805
Specific Phobia	3,855
Generalized Anxiety Disorder	31,322
Acute Stress Disorder	62,741
Posttraumatic Stress Disorder	21,044

For this study, we will establish a new cohort up to 2013, which we estimate will include over 200,000 patients diagnosed across Sweden, providing ample statistical power for the proposed studies.

**Study 1** will include all Swedish residents graduating year 9 (15-16 years old). First, we will use logistic regression models to estimate the association between anxiety, trauma-, and stressor-related disorders and school performance comparing individuals exposed (those who received a diagnosis of anxiety, trauma-, and stressor-related disorders according to ICD-10 criteria) and unexposed subjects (those without a record of these disorders). Second, we will employ sibling comparison models to adjust for possible familial confounders (e.g., socioeconomic status, parental psychopathology, genetics). Specifically, we will compare full siblings discordant for the diagnoses, which will automatically exclude confounding of all shared environmental and a substantial proportion of genetic factors. Third, we will perform sensitivity analyses with subgroups of patients with anxiety, trauma-, and stressor-related disorders without the following comorbidities to examine their mediating effect on the outcomes: psychotic disorders (schizophrenia, bipolar disorder); neuropsychiatric disorders (obsessive-compulsive disorder [OCD], attention-deficit/hyperactivity disorder (ADHD), chronic tic disorders (CTD), pervasive developmental disorders, learning disabilities);

affective disorders (mood disorders except bipolar disorder) and substance use disorders. Fourth, we will perform sensitivity analyses including individuals who received their first diagnosis before graduating year 9 (15-16 years old).

**Study 2** will include all individuals alive and resident in Sweden aged 16-64. We will follow the exposed (affected) and unexposed (unaffected) individuals up until one of the following end-points: a) date of the work impairment outcome (receipt of disability pension, periods of sickness absence, or unemployment), b) date of death, c) date of first emigration, or d) end of the study period (31 December 2013), whichever comes first. As in Study 1, we will employ sibling comparison models to control for shared environmental and genetic confounders (e.g., education, region of residence, family situation, country of birth).

**Study 3** will include parents alive and living in Sweden at baseline (31 December 2001) who have offspring aged 6–25 years. We will follow the exposed (parents with affected children) and unexposed (parents with unaffected children) individuals up until one of the outcomes described in study 2. The statistical analyses and the covariates will be as described in Study 2.

## **PROJECT PROPOSAL NUMBER 2**

### **Perinatal and other environmental risk factors for anxiety, trauma-, and stressor-related disorders**

In this project, we will combine data from national Swedish registers to investigate the association between environmental risk factors, such as adverse perinatal events and reproductive cycle events in women, and these disorders. Our main aim is to identify environmental risk factors specifically implicated in the causation of anxiety, trauma-, and stressor-related disorders employing etiologically informative epidemiological designs.

#### *Aims*

1. To examine the association between a broad range of potential environmental risk factors (e.g., adverse perinatal events and reproductive cycle events in women) and lifetime anxiety, trauma-, and stressor-related disorders.
2. To apply quasi-experimental study designs to control for alternative explanations, such as shared environmental and genetic factors within families.

3. To compare monozygotic twins discordant for the exposure (i.e., one twin being exposed to the environmental risk factor while the other one is not) to further control for all genetic and a substantial part of the shared environmental factors.

### *Summary of methods*

This is an **epidemiological project** which will include **three separate studies**, each tackling one of the aims described above.

**Study 1** will investigate a broad range of potential environmental risk factors for anxiety, trauma-, and stressor related disorders, such as adverse perinatal events (e.g., preterm birth and birth complications, maternal metabolic disorders during pregnancy) and reproductive cycle events (e.g., pregnancy and postpartum) in women. A longitudinal cohort study design will be employed, whereby the cases will be compared to the rest of the total population. Measured confounders will be controlled for in the models (i.e., year of birth of the index person, sex, parity, and paternal/maternal age at childbirth). The contribution of common psychiatric comorbidities, e.g., neuropsychiatric disorders or depression, will be estimated.

**Study 2** will further investigate the associations from Study 1 by employing quasi-experimental study designs aimed at inferring causality from observational data. Using the Multi-Generation Register, we will identify relatives with various degrees of genetic and environmental distances to the index persons. This allows for a more robust control of unmeasured genetic, shared environmental, and other methodological confounders that could explain the observed associations.

**Study 3** will employ the discordant monozygotic (MZ) twin design, for the most robust control of genetic and shared environmental confounders. Because MZ twins share 100% of their genetic background and grow up largely in the same environment, any observed phenotypic differences between members of a MZ twin pair (e.g., differences in anxiety symptoms) may be attributable to non-shared environment (Vitaro, Brendgen, & Arseneault, 2009). For this study, we will employ data from the **Child and Adolescent Twin Study in Sweden (CATSS)** – a longitudinal twin study targeting all twins born in Sweden since July 1, 1992. Since 2004, parents of twins and the twins themselves since age 15 have been interviewed in connection with their 9<sup>th</sup> or 12<sup>th</sup> (CATSS-9/12; n=28,168 twins), 15<sup>th</sup> (CATSS-15; n=11,148 twins), 18<sup>th</sup> (CATSS-18; n=7,143 twins), and 24<sup>th</sup> (CATSS-24; starts autumn 2016) birthdays regarding the child's somatic and mental health. These comprehensive assessments include anxiety symptoms, measured with the Screen for Child Anxiety Related

Emotional Disorders, the Phobias questionnaire, and the Hospital Anxiety and Depression Scale. The twin register can be linked with Medical Birth Register to extract relevant information on perinatal and other risk factors. In addition, the CATSS study contains a wealth of information on parental and child factors that are highly relevant for the study (e.g., emotional abuse) (Anckarsater et al., 2011).

## **PhD SUPERVISORS**

**Prof David Mataix-Cols**, PhD, leads the Anxiety, Obsessive-Compulsive, and Related Disorders at the Department of Clinical Neuroscience, KI (<http://ki.se/en/cns/david-mataix-cols-research-group>). He is an internationally leading expert in the field of anxiety, obsessive-compulsive disorder (OCD) and related disorders. He also works as a consultant clinical psychologist at the OCD and Related Disorders Clinic for children and adolescents in SLSO/BUP. He is the coordinator of the Alicia Koplowitz Foundation advanced training fellowships and the new PhD fellowships hosted at the Karolinska Institutet.

**Dr Lorena Fernández de la Cruz**, PhD, Assistant Professor, is a clinical researcher specialized in the field of obsessive-compulsive disorder (OCD) and related disorders. She has clinically trained in Spain and the UK. She currently leads an epidemiological project on mortality and suicide in OCD, tics, and anxiety disorders. She has recently been appointed tutor for the Alicia Koplowitz Foundation fellows based at the Karolinska Institutet.

## **RESEARCH SETTING AND PRACTICAL ARRANGEMENTS**

The PhD student will become part of the Anxiety, Obsessive-Compulsive, and Related Disorders across the lifespan research group, led by Prof. Mataix-Cols. The group is part of the Department of Clinical Neuroscience (CNS) at Karolinska Institutet (KI). The proposed projects will be conducted in close collaboration with the Department of Insurance Medicine (Proposal number 1) and the Department of Medical Epidemiology and Biostatistics (Proposals number 1 and 2). The PhD student will have the necessary desk space as well as access to the Internet and to online library/data searches, the institution's network, and statistical software.

## **ADDITIONAL TRAINING ACTIVITIES**

Doctoral level courses related to the content and methodological skills needed for the development of the epidemiological projects described above will be available at KI (with no cost for the PhD student), such as:

- SAS (statistical package for epidemiological studies) for beginners
- Basic Course in Medical Statistics
- Epidemiology I: Introduction to epidemiology
- Epidemiology II: Design of epidemiological studies
- Epidemiology III: Analysis and interpretation of epidemiological data
- Biostatistics I: Introduction for epidemiologists
- Biostatistics II: Introduction for epidemiologists
- Biostatistics III: Survival analysis for epidemiologists
- Writing Science and Information Literacy
- To Communicate Science in Different Contexts

Additionally, the fellow will be able to attend other educational activities hosted at the Karolinska Institutet and the Child and Adolescent Psychiatry Research Centre, including our monthly Journal Club, trimestral KI OCD Sessions, and several series of periodic lectures at KI (e.g., KI Discovers, the Stockholm Psychiatry Lectures), among many others.

## **CLINICAL ACTIVITIES**

There is the possibility for the PhD student to obtain an honorary clinical contract to shadow clinical sessions at the OCD and Related Disorders Clinic for children and adolescents. However, the sessions will be in Swedish and therefore this option will be linked to the ability of the PhD student to quickly learn the basics of the Swedish language. The Swedish Government offers free Swedish Courses for Immigrants, which can be of help.

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