ECOLE DOCTORALE PIERRE LOUIS DE SANTE PUBLIQUE A PARIS
EPIDEMIOLOGIE ET SCIENCES DE L'INFORMATION BIOMEDICALE

Directeur : Pierre-Yves Boëlle
Responsable pour Université de Paris : Isabelle Boutron

PROPOSITION DE SUJET DE THESE

SIGLE ET NOM DU LABORATOIRE : IPLESP- INSTITUT PIERRE LOUIS D'EPIDEMIOLOGIE ET DE SANTE PUBLIQUE
NOM DE L'EQUIPE : ERES- EQUIPE DE RECHERCHE EN EPIDEMIOLOGIE SOCIALE
DIRECTEUR DE THÈSE : JUDITH VAN DER WAERDEN
ADRESSE : 27 RUE CHALIGNY, 75012, PARIS

TITRE DE LA THÈSE : MATERNAL ADVERSE CHILDHOOD EXPERIENCES, PERINATAL MENTAL HEALTH AND CHILD DEVELOPMENT : INVESTIGATING THE CONTRIBUTIONS OF PSYCHOSOCIAL AND BIOLOGICAL MARKERS

CO-ENCADRANT EVENTUEL :
EQUIPE DU CO-ENCADRANT :
LABORATOIRE :

PRESENTATION DU SUJET

THE SCIENTIFIC CONTEXT OF THE PROJECT

Adverse childhood experiences (ACEs) represent a child's exposure to negative events, including multiple types of abuse, neglect, witnessing parental violence, and peer, community, and collective violence. Global estimates show that six in ten people in the general population have been exposed to at least one ACE [1]. *Within*-generation effects of adverse childhood experiences are well documented, with an increased risk for several health conditions, including perinatal mental health difficulties. A recent study found a 2.5-fold increase in the odds of prenatal depression for women with an ACE score greater than four as compared to women who had experienced fewer ACEs [2]. An association between a higher number of ACEs and postpartum depression has also been demonstrated [3,4].

Recent research suggests that the negative consequences associated with adverse childhood experiences can also be transmitted *between* generations. Children born to mothers with early-life adversity are equally at an increased risk for a multitude of poor health and developmental outcomes, including delayed achievement of developmental milestones and socioemotional and behavioral difficulties [6,7]. However, specificity between the exposures and outcomes remains unclear. Questions that have been left unaddressed are for instance whether the effects of different ACEs are distinct from each other or if they mainly operate in a cumulative fashion? Likewise, are the effects of adverse childhood experiences independent of the influence of other known risk factors in the broader social

and environmental context? Research examining the mechanisms by which the transmission of the consequences of maternal ACEs to child outcomes occurs is severely lacking [8].

The developmental origin of health and disease (DOHaD) theory posits that biological and genetic factors play a primary role in this transmission, by inducing physiological alterations in the developing fetus that can have long-lasting implications for subsequent physical and mental health. Potential biological pathways involved are immune pathways via cytokines, neurotrophic pathways via neurotrophins or chronic activation of the maternal HPA- axis and elevated cortisol levels [9, 10,11]. However, according to the bioecological model of child development, psychosocial factors in both the pre- and postnatal periods, are also important for understanding mechanisms of intergenerational transmission [12]. For example, maternal mental health symptoms partially mediated the relationship between maternal ACEs and offspring internalizing problems [13], but not for developmental delay at two years-of-age [14]. Overall, there is a need to simultaneously examine indices of biological and psychosocial risk from pregnancy and the postnatal period as potential mechanisms between maternal ACEs and different types of child development outcomes.

Understanding the antecedents and mechanisms that lead to the intergenerational transmission of risks associated with maternal ACEs can facilitate the development of preventive interventions that aim to break these continuities across generations.

RESEARCH OBJECTIVES

The first objective of this project is to examine the frequency and type of maternal ACEs among women from the French general population.
The second objective is to explore whether maternal ACEs are adversely associated, both independently and cumulatively, with children's socioemotional and cognitive development at age 5.5
The third objective is to assess to what extent this association can be attributed to prenatal and postnatal biological and psychosocial factors.

DATA SOURCES

This project will rely on data from the French EDEN mother–child cohort study, which aims to investigate the pre- and postnatal determinants of child health and development [15]. Pregnant women were recruited before 24 weeks of gestation from two maternity wards (Poitiers and Nancy University hospitals in France) between September 2003 and January 2006. Exclusion criteria were multiple pregnancies, history of diabetes, inability to speak and read French or plans to move out of the study region within the next 3 years. Among eligible women, 55% agreed to participate. Of the 2002 women recruited during pregnancy, birth data were available for 1899 mother-infant pairs. From pregnancy onwards, mothers and children were followed nine times (pregnancy, birth, 4, 8, 12, 24 months, 3, 4, 5.5 and 8 years) via face-to-face or self-completed questionnaires completed by the mothers. Data on the child's birth characteristics were collected directly from medical records. At the time of the child's

birth, several biological sources of data were collected including cord blood samples and maternal blood and hair samples. The study was approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomedicale (Ethics Committee, Kremlin Bicêtre Hospital) and by the Commission Nationale de l'Informatique et des Libertés (National Committee for Processed Data and Freedom (CNIL)). Written consent was obtained from the mother for herself at inclusion and for her newborn child after delivery.

Maternal psychopathology and stress: Multiple questionnaires were administered during pregnancy to evaluate different manifestations of prenatal stress exposure, including Adverse Childhood Experiences (ACEs) experienced prior to age 14. Prenatal maternal depression was measured with the Center for Epidemiologic Studies Depression Scale Revised, CES-D) and maternal anxiety with the STAI.

Child behavior: the Strengths and Difficulties Questionnaire (SDQ) was used to assess children's behavior. The SDQ is a validated parent reported questionnaire designed to assess the main psychopathological dimensions in 3- to 16-year-old youths. Internationally, it is the most widely used tool in the field of child psychiatric epidemiology. The SDQ consists of 25 items divided into 5 subscales (score range 0–10): symptoms of hyperactivity/inattention, conduct problems, emotional symptoms, peer relationship problems and prosocial behavior.

Cognitive development: the child's intelligence quotient (IQ) was assessed at 5.5 years using the Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III) administered by trained psychologists. IQ is the gold standard to evaluate overall cognitive skills. The core subtests of the battery were assessed to obtain the composite scores: verbal IQ, performance IQ, and full-scale IQ.

Biological markers: promising candidate biomarkers that have been tested in infant's cord blood and hair samples are cytokines (FN-γ, IL-1β, IL-6, IL-7, IL-8, IL-10, IL-15, IL-16, IL-17A, IL-23/IL-12p40, TNF-α, TNF-β), Neurotrophic factors (BDNF, β-NGF, NTN3) and corticosteroids (cortisol, cortisone).

The EDEN cohort provides rich information collected repeatedly on a range of individual and parental characteristics including health behaviors and family socio-economic factors that will be considered as potential covariates in our analyses.

METHODS

After creation of relevant indicators and detailing descriptive statistics of the study population, path analysis will be applied to test the direct and indirect effects of individual and cumulative maternal ACEs on child development at 5.5 years of age. In a primary step the unadjusted and adjusted associations between maternal ACEs and child developmental outcomes will be tested. To do so, we will estimate odds ratios/relative risks using conventional multivariable adjusted regression models. The nature (i.e. quantitative of qualitative) and distribution (i.e. normal or non-normal) of the variables will be

accounted for to determine the type of regression model to be used (i.e. logistic, linear, other). To provide meaningful results to clinicians, instrument specific binary high-risk cut-off scores will be used in logistic regression models. Sex specificity of associations will be tested in analyses for boys and girls separately.

In a second phase, we will quantify the effect of biological and psychosocial factors in the association between maternal ACEs and children's development. After identification of promising factors and the quantification of the strengths of their associations with both exposure and outcomes, a counterfactual-based mediation analysis will be used, allowing the identification of both the direct and indirect effects of maternal ACEs (exposure) on children's outcomes with the biological and psychosocial factors as the mediator(s). In this framework it is now also possible to include multiple mediators simultaneously (e.g. the mediation model proposed by Lange). Multiple imputation and Inverse probability weighting of analyses will be used to address potential problems of missing data and selective attrition

STATISTICAL POWER/NUMBER OF SUBJECTS

Among the 2,002 women included in the cohort, 1,907 mother–child pairs participated at the time of the child's birth. Number of participating mother–child pairs at ages 1, 2, 3, 5.5, and 8 years of the child were 1,717, 1,611, 1,527, 1,255, and 883, respectively. In order to test associations between mother's ACEs and children's behavioral outcomes, we will use the SDQ Total score at 5.5 years of age as the primary outcome, which is available for 1118 children.

PLANNING

1st semester: Literature review. First contact with the data
2nd semester: Analyses and writing of article 1
3rd semester: Submission of article 1, Analyses and writing of article 2
4th semester: Submission of article 2, revisions of article 1
5th semester: Writing of dissertation, revisions of article 2
6th semester: Writing, finalization and submission of dissertation, PhD defense

TOPICS OF ARTICLES

Paper I: The association between maternal adverse childhood experiences and child socioemotional and cognitive development at age 5.5
Paper II: Maternal adverse childhood experiences and child development: biological and psychosocial pathways of transmission

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PRÉREQUIS, FORMATION : MASTER DEGREE IN EPIDEMIOLOGY/ PUBLIC HEALTH/BIOSTATISTICS

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SPECIALITE DE LA THESE

Santé publique - Epidémiologie	☒
Santé publique - Epidémiologie clinique	☐

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