INTERNSHIP PROPOSAL, year 2026-2027

Supervisor Name (s): Judith VAN DER WAERDEN
Institution / Organization: Sorbonne Public Health Institute U1136, ESSMA (Épidémiologie Sociale, Santé Mentale et Addictions) team
Professional address: 27 rue Chaligny, 75571 Paris Cedex 12
E-mail address: judith.van-der-waerden@inserm.fr
Duration: 6 months

The internship will be located in (city, country): Paris, France

Description of the internship topic

Occupational exposures, maternal cytokines and perinatal depression: a network analysis to prioritise candidate inflammatory mediators

Background:

Perinatal depression is one of the most frequent complications of pregnancy and the postpartum period, with consequences for women, their families and child development[1]. As many women are employed during pregnancy, the work environment is a potentially modifiable source of risk. Occupational settings can expose pregnant women to chemical (e.g. solvents, metals), biological, physical, ergonomic and psychosocial hazards. Evidence linking these exposures to perinatal mental health remains limited, often relies on cross-sectional designs, and generally considers single exposures. In the EDEN cohort, we previously found that work-related stress during pregnancy was associated with persistent maternal depressive symptoms[2].

Maternal immune activation and low-grade inflammation are plausible biological pathways linking environmental exposures to perinatal depression. Women with perinatal depressive symptoms show elevated levels of pro-inflammatory cytokines such as IL-6[3], and socioeconomic disadvantage during pregnancy has been associated with altered maternal immune activity[4]. Several environmental chemicals are also known to affect immune function. Within the EXPRES project, 11 cytokines (IFN-γ, IL-1β, IL-6, IL-8, IL-10, TNF-α, IL-7, IL-12/23p40, IL-15, IL-16, IL-17A) have been measured in maternal serum in the EDEN and ELFE cohorts, and maternal occupational exposures have been characterised using job-exposure matrices (JEMs).

Before testing whether cytokines mediate the association between occupational exposures and perinatal depression, a key methodological question is which cytokines to study. Cytokines are strongly inter-correlated and act within interacting networks: testing each one separately as a mediator multiplies comparisons and ignores this dependence, whereas including all of them simultaneously in a mediation model is statistically unstable. Network analysis offers a data-driven way to address this question. By estimating the conditional associations between all variables simultaneously, graphical models describe how exposures, cytokines and depressive symptoms relate to each other after accounting for all other variables in the network[5,6]. Bridge centrality indices further identify the nodes that connect distinct communities of variables[7], here the cytokines linking occupational exposures to depression. This approach has been used to examine

links between inflammatory markers and depressive symptoms[8,9], but, to our knowledge, not yet in relation to occupational exposures in the perinatal period.

Objectives: The main objective is to estimate the network structure linking JEM-derived maternal occupational exposures during pregnancy, maternal serum cytokines and perinatal depression, in order to identify the cytokines to prioritise in subsequent mediation analyses. Specific objectives are to (i) describe the correlation structure of cytokines and occupational exposures, (ii) identify the cytokines bridging occupational exposures and perinatal depression, (iii) assess the accuracy and stability of the estimated networks, and (iv) assess the replicability of the network structure across the EDEN and ELFE cohorts.

Methods: Analyses will use data from the EDEN (n=2,002, recruited in 2003-2006)[10] and ELFE (n>18,000, recruited in 2011)[11] mother-child cohorts, restricted to women employed during pregnancy with available cytokine measures. Cytokines were measured with a multiplex electrochemiluminescence immunoassay (Meso Scale Discovery) in maternal serum sampled at 24-28 weeks of gestation in EDEN and before delivery in ELFE (1,023 women). Occupational exposures (e.g. solvents, organic compounds, other chemical compounds, heavy metals) were derived by applying JEMs to the occupation reported during pregnancy. Perinatal depression was measured with the Center for Epidemiologic Studies Depression scale during pregnancy and the Edinburgh Postnatal Depression Scale (EPDS) at 4, 8 and 12 months postpartum in EDEN, and with the EPDS at 2 months postpartum in ELFE.

Networks estimated in EDEN and ELFE will be compared, taking into account differences in sampling time and measurement instruments. The expected output is a ranked list of candidate cytokines, based on pre-specified criteria (bridge strength, stability, replication across cohorts), to be tested in counterfactual mediation analyses within EXPRES. As networks estimated from observational data reflect conditional associations, results will be interpreted as hypothesis-generating.

Activities to be conducted:

- Literature research in international bibliographic databases on occupational exposures, maternal inflammation and perinatal depression, and development of a conceptual framework (including a directed acyclic graph) to organize thinking, analysis and writing.
- Writing a data analysis plan, including pre-specified criteria for cytokine selection
- Management of the EDEN and ELFE data
- Estimation of network models and assessment of their accuracy and stability (R packages such as mgm, qgraph, bootnet, networktools)
- Writing of the dissertation according to the modalities defined by the university

A scientific publication of the results is possible.

Requested Competences/qualities:

- Capacity to work independently, sense of organization
- Familiarity with statistical analysis in R (or equivalent statistical software)
- Knowledge of basic statistical modelling, and interest in multivariate methods

- Interest in the biological pathways of mental health; prior knowledge of immunology is an asset but not required
- Good knowledge of English

Selected literature

1. Howard, L. M. & Khalifeh, H. Perinatal mental health: a review of progress and challenges. *World Psychiatry* **19**, 313–327 (2020).
2. van der Waerden, J. *et al.* Predictors of persistent maternal depression trajectories in early childhood: results from the EDEN mother–child cohort study in France. *Psychol Med* **45**, 1999–2012 (2015).
3. Osborne, L. M. *et al.* Innate immune activation and depressive and anxious symptoms across the peripartum: an exploratory study. *Psychoneuroendocrinology* **99**, 80–86 (2019).
4. Gilman, S. E. *et al.* Socioeconomic disadvantage, gestational immune activity, and neurodevelopment in early childhood. *Proc Natl Acad Sci USA* **114**, 6728–6733 (2017).
5. Epskamp, S., Borsboom, D. & Fried, E. I. Estimating psychological networks and their accuracy: a tutorial paper. *Behav Res Methods* **50**, 195–212 (2018).
6. Haslbeck, J. M. B. & Waldorp, L. J. mgm: estimating time-varying mixed graphical models in high-dimensional data. *J Stat Softw* **93**, 1–46 (2020).
7. Jones, P. J., Ma, R. & McNally, R. J. Bridge centrality: a network approach to understanding comorbidity. *Multivariate Behav Res* **56**, 353–367 (2021).
8. Fried, E. I. *et al.* Using network analysis to examine links between individual depressive symptoms, inflammatory markers, and covariates. *Psychol Med* **50**, 2682–2690 (2020).
9. Moriarity, D. P. *et al.* Inflammatory phenotype of depression symptom structure: a network perspective. *Brain Behav Immun* **93**, 35–42 (2021).
10. Heude, B. *et al.* Cohort profile: the EDEN mother-child cohort on the prenatal and early postnatal determinants of child health and development. *Int J Epidemiol* **45**, 353–363 (2016).
11. Charles, M. A. *et al.* Cohort profile: the French national cohort of children (ELFE): birth to 5 years. *Int J Epidemiol* **49**, 368–369j (2020).