---------------------------------------------------------------------------------------------------------------

**Laboratory/Institute:** Institute for Advanced Biosciences (INSERM U1209 /CNRS UMR 5309/Université Grenoble Alpes)
**Team:** Environmental epidemiology applied to development and respiratory health
**Supervisiors**: Aurélie Nakamura (postdoc in epidemiology; aurelie.nakamura@univ-grenoble-alpes.fr) and Johanna Lepeule (researcher in environmental epidemiology, HDR; johanna.lepeule@univ-grenoble-alpes.fr).
**Location:** IAB, Site Santé, Allée des Alpes. 38700 La Tronche (Grenoble).
**Start date**: January/February 2023

---------------------------------------------------------------------------------------------------------------

**Title**: **Associations between maternal tobacco smoking during pregnancy and placental DNA methylation using gene candidate and epigenome-wide approaches**

## Description

      Maternal tobacco smoking during pregnancy is a real burden and public health issue as its prevalence is estimated to be around 16% in Western Countries. Maternal tobacco smoking is related to numerous pregnancy complications affecting mothers and fetuses (such as extrauterine pregnancy, low intrauterine growth, prematurity, low birth weight for gestational age) but also to later child health, cognitive development and behavior (Zeitlin et al. 2015, Nakamura et al. 2020, Nakamura et al. 2021).

      A few underlying mechanisms have been proposed. They include alterations in epigenetic mechanisms such as DNA methylation (DNAm). DNA methylation does not change DNA sequences of nucleotides; can be replicated through cell divisions and can be either reversible or persist via biological memory [(Rousseaux et al. 2020)]. DNA methylation can be altered by environmental factors ranging from diet to maternal stress and to pollutants such as arsenic, persistent organic pollutant, endocrine disruptors, air pollutants, and tobacco smoke, especially during the earlier stages of the child's development as the epigenome undergoes considerable reprogramming during gametogenesis and the preimplantation embryonic stage (Abraham et al. 2018, Nakamura et al. 2021, Rousseaux et al. 2020). Epigenetic marks are tissue-specificity and highly specific to cell types in tissues. Therefore, part of DNA methylation levels measured are driven by the cell composition of the collected tissue sample. For some tissues, such as placenta, cell composition is more difficult to measure.

      In a recent study conducted by our team, on 568 pregnant women from the EDEN cohort study (Heude et al. 2015), either actively smoking during their pregnancy, formerly exposed to tobacco smoking, or not exposed to tobacco smoking during pregnancy (Rousseaux 2020), 152 differentially methylated regions (DMRs) were identified with "reversible" alterations of DNA methylation, which were only present in the placenta of current smokers, whereas 26 DMRs were also found altered in former smokers who had quit smoking prior to pregnancy and whose placenta had not been exposed directly to cigarette smoking. We showed that the 203 tobacco-induced DMRs identified were significantly enriched in epigenetic marks corresponding to enhancer regions and in regions controlling the monoallelic expression of imprinted genes. These data suggested that

tobacco smoking during pregnancy could impact the transcription of genes normally regulated by mechanisms involving DNA methylation as well as how it could affect the development and growth of the fetus.

Since the publication of this study, we received additional samples, giving us the potential of increasing statistical power in a replication study. As mentioned earlier, cell composition estimation is still a challenge and methods will be discussed.

The aim of this internship is to replicate our previous study; which involves estimating the associations between maternal tobacco smoking during pregnancy and DNAm in the EDEN cohort study, using both gene candidate and EWAS approaches.

## Candidate profile and required skills

- M2/Engineering degree in Public Health (Biostatistics, Epidemiology, etc.), Statistics or Bioinformatics, Biology with a strong background in statistics and/or R programming
- Interests in epigenetic epidemiology
- Statistics and/or epidemiology: multivariate regression analyses
- Programming: R or an equivalent programming language
- English: you should be able to read publications written in English
- French: not mandatory

For more information, please contact: aurelie.nakamura@univ-grenoble-alpes.fr.

## References

Abraham, E., Rousseaux, S., Agier, L., Giorgis-Allemand, L., Tost, J., Galineau, J., ... & EDEN mother-child cohort study group. (2018). Pregnancy exposure to atmospheric pollution and meteorological conditions and placental DNA methylation. Environment international, 118, 334-347.

Heude, B., Forhan, A., Slama, R., Douhaud, L., Bedel, S., Saurel-Cubizolles, M. J., ... & Thiebaugeorges, O. (2016). Cohort Profile: The EDEN mother-child cohort on the prenatal and early postnatal determinants of child health and development. International Journal of Epidemiology, 45(2), 353-363.

Nakamura, A.; Pryor, L.; Ballon, M.; Lioret, S.; Heude, B.; Charles, M.-A.; Melchior, M.; El-Khoury Lesueur, F. Maternal Education and Offspring Birth Weight for Gestational Age: The Mediating Effect of Smoking during Pregnancy. Eur. J. Public Health 2020, 30, 1001–1006.

Nakamura A, François O, Lepeule J, Epigenetic Alterations of Maternal Tobacco Smoking during Pregnancy: A Narrative Review, Int. J. Environ. Res. Public Health 2021;18(10);5083

Rousseaux, S.; Seyve, E.; Chuffart, F.; Bourova-Flin, E.; Benmerad, M.; Charles, M.-A.; Forhan, A.; Heude, B.; Siroux, V.; Slama, R. Immediate and Durable Effects of Maternal Tobacco Consumption Alter Placental DNA Methylation in Enhancer and Imprinted Gene-Containing Regions. BMC Med. 2020, 18, 1–20.

Yuan, V.; Price, E.M.; Del Gobbo, G.; Mostafavi, S.; Cox, B.; Binder, A.M.; Michels, K.B.; Marsit, C.; Robinson, W.P. Accurate Ethnicity Prediction from Placental DNA Methylation Data. Epigenet. Chromatin 2019, 12, 1–14.

Zeitlin, J.; Alexander, S.; Barros, H.; Blondel, B.; Delnord, M.; Durox, M.; Gissler, M.; Macfarlane, A.; Mohangoo, A. European Perinatal Health Report. In Core Indicators of the Health and Care of Pregnant Women and Babies in Europe in 2015; World Health Organization: Geneva, Switzerland, 2018; pp. 1–177.