

## **Project Title**

Does cannabis increase the risk of neurodevelopmental delay via altered brain connectivity?

## **Investigators**

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## **Statement of Purpose**

This project will generate new knowledge on how prenatal cannabis exposure may put children at risk of neurodevelopmental conditions, via alterations to brain connectivity.

## **Project Summary**

Prenatal cannabis exposure (PCE) can alter fetal brain development and is associated with neurodevelopmental conditions such as autism. However, the mechanisms underlying this association remain unclear. Cannabis use has increased markedly in Canada over the past decade, raising significant concerns about the neurodevelopmental impacts of PCE.

Prospective studies of high-risk infants show that early signs and symptoms of neurodevelopmental conditions such as autism emerge within the first 2 years of life, and include developmental delays and brain changes in early infancy.

There is an urgent need to identify how PCE in the current Canadian context is associated with infant neurodevelopment to inform policy and support child health and wellbeing. Here, we propose to study infant neurodevelopment using MRI and development questionnaires, across the following aims:

**Aim 1a:** Is PCE associated with brain alterations measured by MRI at 3 months of age? **Aim 1b:** Are associations modified by prenatal alcohol use? We hypothesize that PCE is associated with lower volumes and reduced connectivity, particularly in frontal regions, and that concurrent prenatal alcohol exposure will exacerbate effects.

**Aim 2:** Do brain alterations at 3 months of age mediate the association between PCE and delays in development at 6 months? We hypothesize that lower volumes and reduced connectivity will mediate the association between PCE and developmental delays at 6 months.

**Exploratory Aim 3:** Do brain alterations at 3 months mediate the association between PCE and developmental delays or autism traits at 18 months? We hypothesize that lower volumes and reduced connectivity will mediate the association between PCE and delays in development and severity of autism traits.

The Alberta Cannabis in Pregnancy (ACP) study (led by co-PI Chaput) will recruit 1900 pregnant Albertans, with an overrepresentation of cannabis users. PCE will be prospectively measured during pregnancy using the first validated tool for measuring PCE (developed by co-PI Chaput). 75 cannabis exposed infants and 75 non exposed controls will be identified within the ACP study and recruited for neuroimaging at 3 months.

At 6 months, caregivers will complete the Ages and Stages Questionnaire (ASQ-3), a validated screening measure to identify delays in developmental milestones. Caregivers of children old enough will also complete the ASQ-3 and the Modified Checklist for Autism in Toddlers at 18 months.

We will examine brain connectivity differences between infants with PCE vs controls (Aim 1a), matching for infant sex, maternal education, income, and prenatal tobacco use, and assess the potential modifying effect of prenatal alcohol exposure. (Aim 1b). We will then conduct a mediation analysis with PCE, brain connectivity, and infant neurodevelopment at 6 months (Aim 2), and an exploratory mediation analysis of infant neurodevelopment (ASQ-3) and autism symptoms (M-CHAT) at 18 months (Aim 3). Sex will be included in all analyses.

Our novel, innovative study will generate new knowledge on how PCE alters infant brain connectivity, and how this may lead to developmental delays and risk of neurodevelopmental conditions, providing valuable data to inform policies and laying the foundation for larger future studies.