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# Association between Paternal Cannabinoid Use and Congenital Heart Defects in Offspring

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## ABSTRACT

Cannabis consumption in Canada is rising for both recreational and therapeutic purposes. Research shows that cannabis can impact sperm quality, motility, and volume by binding to receptors on sperm. However, the link between paternal cannabis use and congenital heart defects (CHD) in offspring has not been studied. This ecological study examined Canadian national data on male-household cannabis use and CHD rates per 10,000 births from 2010 to 2020, sourced from Statistics Canada and the Canadian Congenital Anomalies Surveillance System. Using RStudio, Shapiro-Wilk, Spearman's rank correlation coefficient, and multivariate linear regressions were performed to analyze the relationship, adjusting for household smoking. A p-value below 0.05 was deemed statistically significant. Shapiro-Wilk tests showed that the CHD data did not meet normality ($p = 0.004427$), while paternal cannabis and smoking data did ($p = 0.09368$, $p = 0.3399$). Spearman's tests found no significant link between paternal cannabis use and CHD in offspring ($R^2 = 0.0251$). However, multivariate regressions indicated a correlation between paternal cannabis use and a higher risk of CHD in offspring ($\beta_1 = 0.04742$, $R^2 = 0.1507$). This study, the first to explore this correlation with aggregated data, suggests that paternal cannabis use may be associated with an increased risk of CHD, providing important insights for Canadians.

## Introduction

Congenital heart defects (CHDs) are structural abnormalities of the heart that are present at birth. The part of the heart that CHDs can affect varies, with the most common CHD being a ventricular septal defect (VSD), in which there is a hole in the ventricular septum (Botto, Correa, & Erickson, 2001). CHDs affect nearly 1% of births per year –around 3,500 births in just Canada alone (Hoffman & Kaplan, 2002; Reller et al., 2008). Among infants born with a CHD, there is a 25% probability of having a CHD that is considered a critical CHD (Oster et al., 2013). Moreover, an estimated 69% of infants born with a critical CHD are predicted to survive to 18 years of age (Oster et al., 2013). CHDs are the most common type of birth defect.

The cause of CHDs among most infants is unknown. However, many risk factors have been identified such as genetic and environmental factors (Ferencz et al., 1985). Chromosomal alterations have been shown to contribute to the development of CHDs, as indicated by recent studies highlighting the role of single nucleotide polymorphisms and submicroscopic copy number abnormalities (Schott et al., 1998; Garg et al., 2003). Environmental factors such as the mother's diet, medication use, and previous health conditions such as obesity or diabetes have been found to have a relationship with an increased risk of CHDs in offspring (Yang et al., 2022; Obermann-Borst et al., 2011; Turunen et al., 2024). Other environmental factors such as maternal smoking have been shown to be strongly associated with increased risk of septal defects (Malik et al., 2008).

Research indicates that exposure to cannabis during pregnancy can result in adverse birth outcomes, including preterm birth, being small for gestational age, and low birth weight, suggesting a negative impact on fetal growth (Duko et al., 2023; Brar et al., 2021; Hurd et al., 2005; El Marroun et al., 2009). Importantly, phytocannabinoid's are able to pass through the placenta (Rokeby et al., 2023). With the legalization of cannabis in Canada, a recent cross-

sectional study has shown that cannabis use has increased by 13% among pregnant women (Myran et al., 2023). This trend has prompted an increase in investigations into the effects of maternal cannabis use on the risk of CHDs.

While multiple studies have been conducted to test the relationship between maternal cannabis use and the prevalence of CHDs in infants, the association between paternal cannabis use and the rate of CHDs in the offspring remains understudied. Cannabis has been shown to alter sperm quality, motility, and volume through marijuana's affinity for binding to receptors on the structure of sperm (Slotkin et al., 2020).

The objective of this study was to examine if there is an association between paternal cannabis use and CHDs in offspring. This study adapted an ecological study design using aggregate paternal cannabis use and CHD data at the country level for Canada. This is the first study to utilize aggregated data to uncover the potential association between paternal cannabis use and CHDs in offspring.

## Methods

Paternal cannabis use data was taken from Statistics Canada's analysis of trends from years 2010 to 2020, with exceptions for 2014 and 2016 due to insufficient data (Government of Canada, Statistics Canada, 2018). Reported data on cannabis use was combined through nine national surveys from 2010. Variations in response rates and sample sizes of the nine surveys, ranging from 10,076 to 36,984 participants, have been accounted for in Statistics Canada's data analysis. Given the limited availability of paternal cannabis data for more recent years, data from the Canadian Cannabis Survey was incorporated for the years 2017, 2019, and 2020. This allowed for more statistically powerful tests to be done. National congenital heart defect data spanning from 2006 to 2020 was obtained from the Canadian Congenital Anomalies Surveillance System (CCASS) data tool. CCASS is a surveillance system designed to capture the majority of congenital anomalies, including congenital heart defects. CCASS's data tool was extracted from two primary sources: the Canadian Institute for Health Information's Discharge Abstract Database (CIHI-DAD) and Quebec's database, the Maintenance et exploitation des données pour l'étude de la clientèle hospitalière (MED-ÉCHO). The reported data on congenital heart defects includes both live births and stillbirths from the population, with the rate of confirmed congenital heart defects presented as a percentage per 10,000 births.

Potential confounding variables were adjusted for in the main analysis for selected congenital heart defect characteristics. Selected characteristics included smoking use because of their known significant association with congenital heart defects (Bolin et al., 2022). Smoking data was taken from the Canadian Alcohol and Drug Use Survey (CADUMS) for the years 2010 to 2012, and the Canadian Tobacco, Alcohol and Drugs Survey (CTADS) 2013 to 2017. Data for 2019 and 2020 was also taken from the Canadian Tobacco and Nicotine Survey (CTNS).

Shapiro-Wilk tests were performed to assess the normality of the reported data for CHDs, paternal cannabis use, and smoking use. The Shapiro-Wilk test evaluates whether a dataset follows a normal distribution and if it's parametric or not. A p-value below the significance threshold indicates a deviation from normality. Additionally, Levene's test was used to check for any difference in variances of different CHD reported data in the CCASS. Different CHD reported data included nationwide data on Coarctation of Aorta, Endocardial cushion defects, Hypoplastic Left Heart Syndrome, Tetralogy of Fallot, and Transposition of Great Arteries. Spearman's rank correlation coefficient tests were then conducted to assess the relationship between CHDs and paternal cannabis use. Multivariate linear regressions were then performed to analyze the relationship between paternal cannabis use and CHDs while adjusting for confounding variables. An $\alpha$ value of 0.05 was used to analyze all the p-values creating a 95% confidence interval.

The Shapiro-Wilk, Levene, Spearman's rank correlation coefficient, and multivariate linear regression tests were visualized and calculated in R Studio using R version 4.3.2 and ggplot2. Tables were created with Excel.

## Results

The results of the ecological study revealed that there is no significant relationship between paternal cannabis use and CHDs ($R^2$ = 0.0251). However, in the multivariate linear regression, paternal cannabis use was shown to have an increased risk of CHDs in offspring ($\beta_1$ = 0.04742, $R^2$ = 0.1507).

**Table 1.** Results of Shapiro-Wilk Tests for Paternal Cannabis Use, Smoking Use and Congenital Heart Defects

| Variable | *P*-value[1] |
|---|---|
| Paternal Cannabis Use | 0.0936 |
| Smoking Use | 0.3399 |
| Congenital Heart Defects | **0.0044** |

[1]All *p*-values in boldface are significant at better than the .05 level for a two-tailed test.

Table 1 displays the outcomes of the Shapiro-Wilk tests. The p-values obtained from testing paternal cannabis use and smoking data all exceeded the significance threshold ($p > 0.05$), suggesting weak to moderate normality. Conversely, the p-value for CHDs data fell below the significance threshold ($p < 0.05$), indicating that there is evidence to reject the null hypothesis of normality, and that CHDs significantly deviates from a normal distribution.

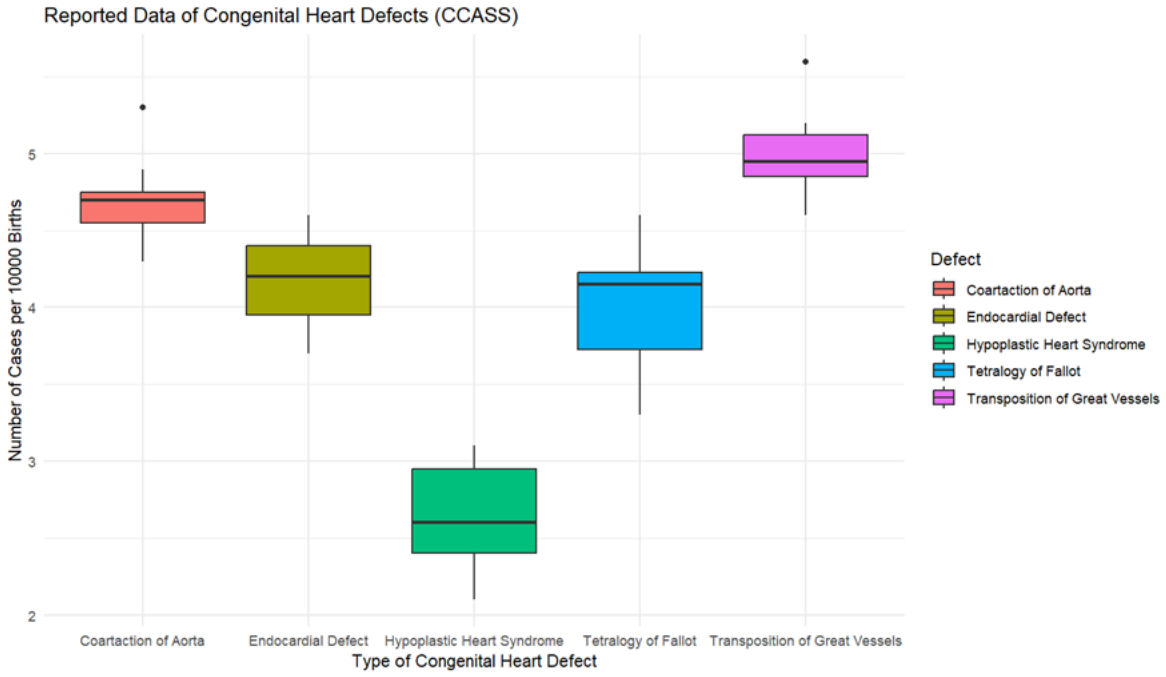


**Figure 1.** Visualization of the data of the data for different types of CHDs reported in the CCASS over the years 2010 to 2013, 2015, 2017, and 2019 to 2020.

Figure 1 illustrates the distribution of measurements for six CHDs: Coarctation of Aorta, Endocardial cushion defects, Hypoplastic Left Heart Syndrome, Tetralogy of Fallot, and Transposition of Great Arteries. Outliers represented by a point outside the whiskers are shown. Reported data of Coarctation of Aorta had an outlier of 5.3 cases

per 10,000 births (2017). Reported data for Transposition of Great Vessels had an outlier of 5.6 cases per 10,000 births (2015).

**Table 2**. Summary of The Reported Data for Each Congenital Heart Defect (CCASS

| Congenital Heart Defect | Min. | 1st Qu. | Median | Mean | 3rd Qu. | Max. |
|---|---|---|---|---|---|---|
| Coarctation of Aorta | 4.3 | 4.55 | 4.7 | 4.7 | 4.75 | 5.3 |
| Endocardial cushion defects | 3.7 | 3.95 | 4.2 | 4.162 | 4.4 | 4.6 |
| Hypoplastic Left Heart Syndrome | 2.1 | 2.4 | 2.6 | 2.65 | 2.95 | 3.1 |
| Tetralogy of Fallot | 3.3 | 3.725 | 4.15 | 4 | 4.225 | 4.6 |
| Transposition of Great Arteries | 4.6 | 4.85 | 4.95 | 5 | 5.125 | 5.6 |

Table 2 displays the summary of data found in the CCASS. The table includes the minimum, first quartile (Q1), median, mean, third quartile (Q3), and maximum values for each defect.

**Table 3**. Results of Levene's Test for Homogeneity of Variance in Reported Data for Different Congenital Heart Defects

| Degrees Of Freedom | *F*-Value | *P*-Value |
|---|---|---|
| 4 | 0.5716 | 0.685 |

Table 3 illustrates the results of the Levene's Test. The p-value was not significant, indicating that there is not enough evidence to reject the null hypothesis ($p = 0.685$). There is no significant difference between the reported data of Coarctation of Aorta, Endocardial cushion defects, Hypoplastic Left Heart Syndrome, Tetralogy of Fallot, and Transposition of Great Arteries.

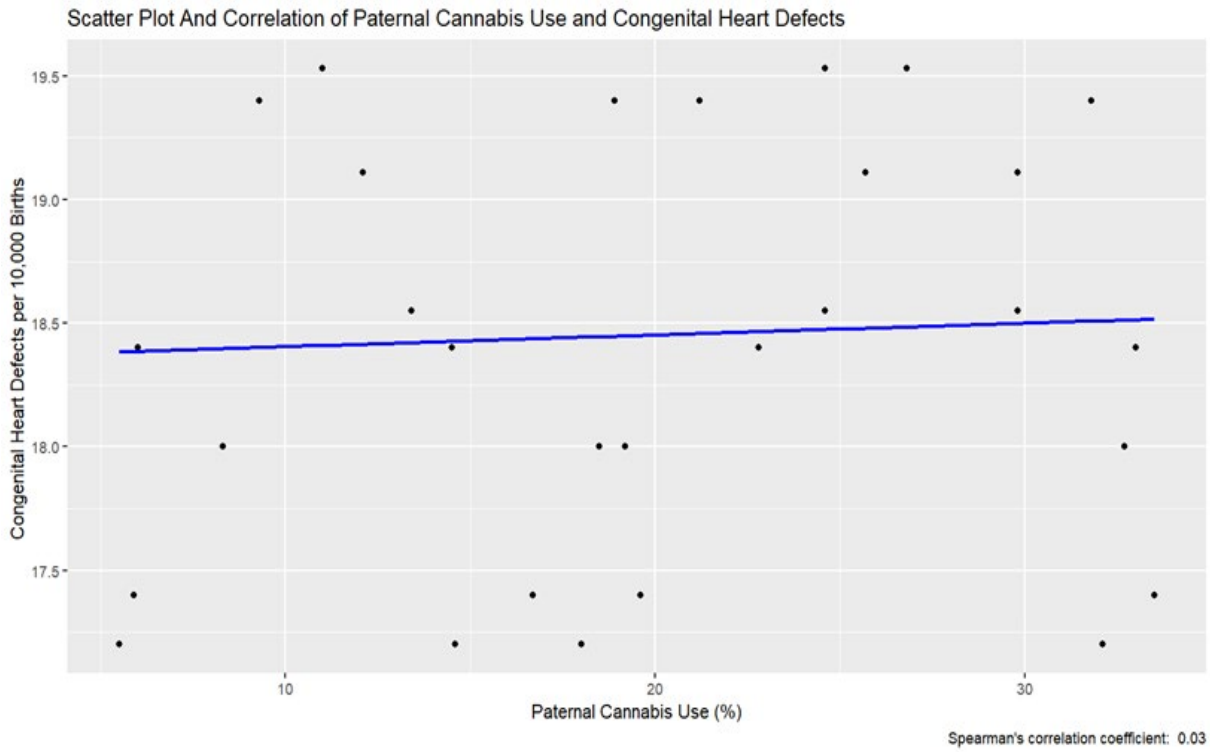


**Figure 2**. Results of Spearman's Rank Correlation Coefficient Test Between the Variables of Paternal Cannabis Use and Congenital Heart Defects

Figure 2 visualizes data points of reported data of the national percentage of paternal cannabis use and confirmed cases of CHDs per 10,000 births in Canada. The correlation coefficient of 0.03 shows that there is a mild increase of CHDs in offspring with paternal cannabis use in the population. A p-value of 0.9639 was returned and implied that there was no evidence to reject the null hypothesis. Spearman Rank Correlation Coefficient tests suggest that there is no significant association between paternal cannabis use and CHDs in offspring.

**Table 4.** Results of Multivariate Linear Regression for Paternal Cannabis Use, Smoking Use and Congenital Heart Defects

| Variable | Multiple $R^2$ | $\beta_1$ | *P*-Value |
|---|---|---|---|
| Paternal Cannabis Use | 0.1507 | 0.0337 | 0.0937 |

Table 4 illustrates the results of multivariate linear regressions. The confounding variable of smoking use was adjusted for using aggregated data. The multiple $R^2$ value was indicative of a mild to moderate linear correlation between paternal cannabis use, smoking use, and CHDs. The correlation coefficient of paternal cannabis use suggests that for every one percent increase in paternal cannabis use, there is an associated increase of 30 cases of CHDs. The results were not significant ($p = 0.0937$) suggesting that there is no association between paternal cannabis use and CHDs.

## Discussion

Outcomes of Shapiro-Wilk in Table 1 showed that the reported data for paternal cannabis use, and smoking use follow a normal distribution. While the reported data for CHDs was observed to deviate from normality and was non-parametric. This suggested non-parametric tests to be used such as Spearman's rank correlation coefficient and Levene's tests.

There were no differences in variation between Coarctation of Aorta, Endocardial cushion defects, Hypoplastic Left Heart Syndrome, Tetralogy of Fallot, and Transposition of Great Arteries as seen in Figure 1. Table 2 illustrates the box plot by providing the measurements recorded. The significant similarities in variation suggested that there should not be a significant difference between the different types of CHDs and that a Spearman's test would be suitable for the purposes of this study.

From Table 3, a mild to moderate positive linear correlation between paternal cannabis use and CHDs can be drawn. This can also be seen in Figure 2 visualizing the scatter plot. This trend was also discussed in the Baltimore-Washington Infant Study (Ferencz et al., 1985). However, it should be noted that the number of people who reported illicit drug use was extremely small, and the interpretation of this study should be proceeded with caution (Patel & Burns, 2013). Additionally, multivariate linear regressions conducted to adjust for the confounding variable of smoking showed that there was also a mild to moderate positive correlation as shown in Table 4. The p-value of this model was not significant suggesting that there is no association between paternal cannabis use and CHDs in offspring while adjusting for smoking use.

There are several strengths in this study. Ecological studies are useful when disease data at the individual level is not available and individual level of exposure is either difficult or impossible to obtain (Lawson & Lee, 2017). Ecological studies are more useful for generating and testing hypotheses because they use aggregate data (Rytkönen et al., 2003). The conclusion that there is no association between paternal cannabis use and CHDs can be indicative but not causal. However, the findings that hint at a positive correlation would justify the need for further toxicological approach for investigating the adverse effects of paternal cannabis on sperm. This study uses aggregate data from nine different nationwide surveys on cannabis, the Canadian Cannabis Survey, and the CCASS with an ecological approach. Reported sample sizes for surveys on cannabis use are considerably large and the CCASS has the ability to report for most CHDs found in babies born in hospitals. This increases the statistical power and reliability of tests performed using the aggregate data. Although the data coverage in this study was Canada, findings of this correlation can be translatable for other high cannabis use countries such as Papua New Guinea and the United States (Cannabis Use by Country, 2024). There is a need to assess the effects of paternal cannabis use on public health in countries with the legalization of cannabis.

## Conclusion

In this ecological study investigating the relationship between paternal cannabis use and CHDs in offspring using aggregated data for Canada, while a mild to moderate positive correlation between paternal cannabis use and CHDs was observed, this association did not reach statistical significance after adjusting for confounding variables such as smoking use. Despite the suggestive increase in the risk of CHDs with paternal cannabis use, indicated by Spearman tests and linear regressions, the results of multivariate linear regression analysis showed a non-significant p-value ($p = 0.0937$). The strengths of the study lie in the utilization of comprehensive aggregate data from multiple nationwide surveys on cannabis use and the extensive CHD data captured by the Canadian Congenital Anomalies Surveillance System (CCASS). However, limitations such as the lack of adjustment for additional confounding factors and the inherent constraints of ecological studies should be acknowledged. Further research, including more detailed analyses such as cohort studies or animal studies, is warranted to validate these findings and uncover potential causal mechanisms underlying the relationship between paternal cannabis use and CHDs in offspring.

## Limitations

There are also several limitations to this study. First, while smoking use was adjusted, other potential confounding factors were not considered in the study, for example, age. diabetes and socioeconomic status. Maternal age has been found to be a risk factor for CHDs (Nørregaard et al., 2023). Lower degrees of maternal socioeconomic status are modestly associated with CHDs (Miao et al., 2021). The use of aggregated data and inferences based on the analysis cannot be directly transferred to the individual level. This is because of the "ecologic fallacy". The inherent limitation of an ecological study is that it uses aggregate data and cannot incorporate individual data.

The population-based ecological analysis also did not consider population migration. It must also be noted that there are limitations to CHD data. Not all regions have hospitals limiting the data to more urban areas with more access to better healthcare. Data for the years 2014, 2016, and 2019 were also not included because no surveys on cannabis use were conducted by the Canadian government during those years. The results would be more compelling if the physiological tests agreed with the practical data used. Additionally, since data was taken at a national level, and when scaled down to individuals, the results may vary. Further research is required to conclusively determine the effects of paternal cannabis use and CHDs in offspring.

Despite these limitations, the analyses showed that there is no significant correlation between paternal cannabis use and CHDs. These results contrast with previous studies that suggest that there is a significant correlation. However, the sample sizes for those reports are extremely small (Patel & Burns, 2013). Future studies could attempt to test the results of this study through animal studies or cohort studies. The trends for more specific CHDs such as septal defects should be explored.

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