

A close-up photograph of vibrant green cannabis leaves with serrated edges, filling the background of the slide. The lighting is soft, highlighting the texture of the leaves.

Drug Free Australia series – Media suppression of alarming cannabis harms

Episode 3 – Cannabis and birth defects

Birth defects

- A sampling of birth defects tracked

- hole in the heart
- spina bifida
- cleft lip and/or palate
- club foot
- autism
- limbleness
- gastroschisis
- all represent a significant physical, emotional and financial burden to cannabis users' families



ENVIRONMENTAL EPIGENETICS
Environmental Epigenetics, 2022, 8(1), 1-40
DOI: <https://doi.org/10.1093/epp/ckab021>
Research Article

Cannabinoid and substance relationships of European congenital anomaly patterns: a space-time panel regression and causal inferential study

Albert Stuart Reece^{1,2*} and Gary Kenneth Hulse^{1,2}

¹Division of Psychiatry, University of Western Australia, Crawley, Western Australia 6009, Australia, ²School of Medical and Health Sciences, Edith Cowan University, Joondalup, Western Australia 6027, Australia
*Correspondence address: Department of Psychiatry, University of Western Australia, Stirling Hwy, Crawley, Western Australia 6009, Australia. Tel: (617) 1364-6000, Fax: (617) 1364-4015, E-mail: stuart.reece@uq.edu.au

Abstract
With reports from Australia, Canada, USA, Hawaii and Colorado documenting a link between cannabis and congenital anomalies (CA), this relationship was investigated in Europe. Data on 90 CAs were accessed from Eurocat. Tobacco and alcohol consumption and median household income data were from the World Bank. Amphetamine, cocaine and last month and daily use of cannabis from the European Monitoring Centre for Drugs and Drug Addiction. Cannabis herb and resin Δ9-tetrahydrocannabinol concentrations were from published reports. Data were processed in R. Twelve thousand three hundred sixty CA rates were sourced across 16 nations of Europe. Nations with a higher or increasing rate of daily cannabis use had a 71.7% higher median CA rates than others [median 4 interquartile range 2.13 (0.58, 6.30) v. 1.24 (0.16, 5.49)10000 live births ($p = 4.74 \times 10^{-6}$; minimum F-value (minF) = 1.52]. Eighty nine out of 90 CAs in bivariate association and 74/90 CAs in additive panel inverse probability weighted space-time regression were cannabis related. In inverse probability weighted interactive panel models lagged to zero, two, four and six years, 76, 51, 50 and 29 CAs had elevated mFVs ($>2.46 \times 10^3$) for cannabis metrics. Cardiovascular, central nervous, gastrointestinal, genital, immunology, limb, face and chromosomal/genetic systems along with the multisystem VACTERL syndromes were particularly vulnerable targets. Data reveal that cannabis is related to many CAs and fulfil epidemiological criteria of causality. The triple convergence of rising cannabis use prevalence, intensity of daily use and Δ9-tetrahydrocannabinol concentration in herb and resin is powerfully implicated as a primary driver of European teratogenicity, confirming results from elsewhere.

Key words: tobacco; alcohol; cannabis; cannabinoid; cancer; carcinogenesis; mutagenesis; oncogenesis; genotoxicity; epigenotoxicity; chromosomal toxicity

Introduction
Whilst it is often said that prenatal cannabis exposure has relatively benign implications in postnatal life [1-3], recent independent reports from Hawaii [4], Colorado [5], Canada [6, 7], Australia [8] and USA [9-11] indicate that dozens of congenital anomalies (CA; birth defects) are likely epidemiologically causally associated with rising rates of community cannabis consumption. Systems that are particularly affected include the cardiovascular, gastrointestinal, chromosomal, gastrointestinal limb and body wall systems. Concerns regarding prenatal exposure were provided with heightened salience by reports from many places indicating increased use of cannabis and cannabinoid products by pregnant women in recent times [12], by rates of cannabis use in pregnancy amongst teenagers as high as 20% [13], by increased use of cannabis in pregnancy since the COVID-19 pandemic [13] and by reports that 69% of cannabis dispensaries positively recommended cannabis use to women whilst pregnant [14]. Moreover, recent reports note a qualitative convergence of rising rates of cannabis use, Δ9-tetrahydrocannabinol (THC) potency, intensity of daily use and cannabis use disorder in Europe, suggesting that the modern era is actually experiencing a confluence of concerning teratogenic trends [15, 16].

The implications of cannabinoid genotoxicity are further highlighted with the recent data suggesting that multiple cancers of (breast, pancreas, thyroid, liver and acute lymphoid and myeloid leukaemia) are also epidemiologically causally related to cannabis use [17, 18] and, with the formal experimental demonstration in mice, that epigenetic programming actually controls the organism wide ageing epigenomic cassettes [19]. The recent demonstration that cannabis is a major driver of the rise in USA paediatric cancer rates underscores the transgenerational nature of this mutagenesis [17, 20]. These data together indicate that cannabinoid related epigenetic disturbances likely have broad public health implications for diverse communities extending to carcinogenesis on the one hand and pan-systemic ageing on the other and including transgenerational effects.

Key to any consideration of the possible causal relationships of cannabis with mutagenesis and teratogenesis is the elucidation

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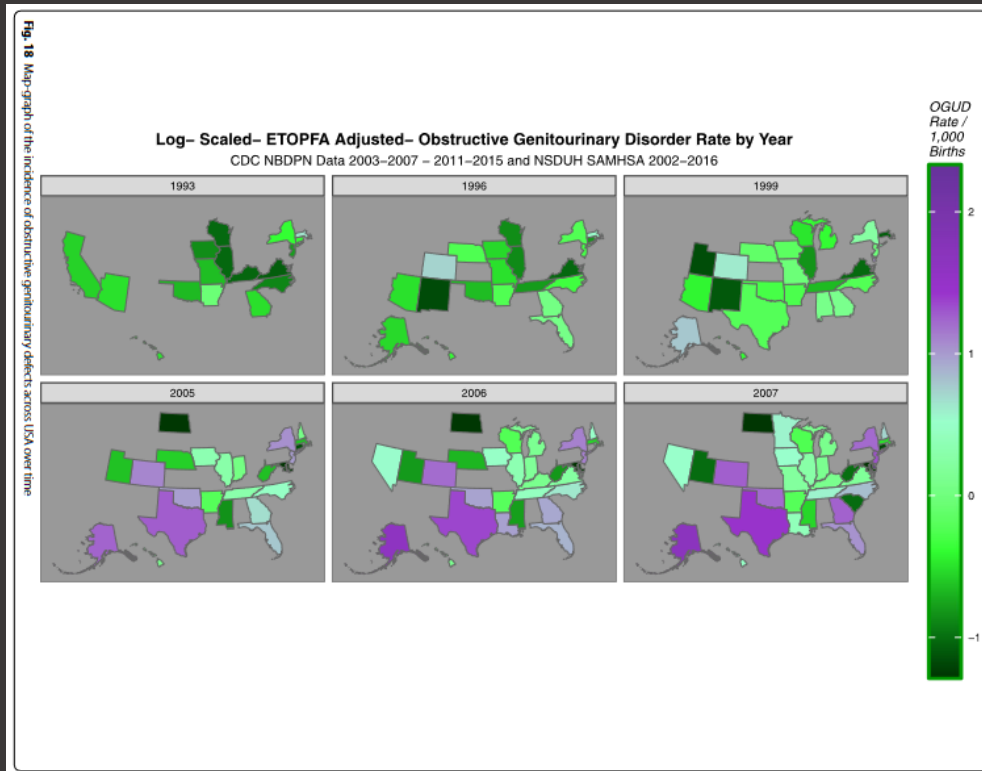
Differing cannabis use

- USA States and European countries – differing regimes
 - all cannabis prohibited
 - cannabis use decriminalised
 - medicinal cannabis use legalised
 - recreational cannabis use legalised
- All with differing:
 - population percentages using cannabis
 - THC and other cannabinoid levels
 - disease burden – in this case it is birth defects



Population studies

- 50 States in the USA



Reece and Hulce *BMC Pediatrics* (2021) 21:47
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RESEARCH Open Access

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Abstract
Background: Cannabinoids including cannabidiol have recognized genotoxic activities but their significance has not been studied broadly epidemiologically across the teratological spectrum. We examined these issues including contextual space-time relationships and formal causal inferential analysis in USA.
Methods: State congenital anomaly (CA) rate (CAR) data was taken from the annual reports of the National Birth Defects Prevention Network 2001–2005 to 2011–2015. Substance abuse rates were from the National Survey of Drug Use and Health a nationally representative longitudinal survey of the non institutionalized US population with 74.1% response rate. Drugs examined were cigarettes, monthly and binge alcohol, monthly cannabis and analgesic and cocaine abuse. Early termination of pregnancy for abortion (ETOPFA) rates were taken from the published literature. Cannabinoid concentrations were from Drug Enforcement Agency ethnicity and income data were from the US Census Bureau. Inverse probability weighted (IPW) regressions and geotemporospatial regressions conducted for selected CAs.
Results: Data on 18,328,529 births from an aggregated population of 2,377,483,589 for mid year analyses 2005–2013 comprising 12,611 CAs for 62 CAs was assembled and ETOPFA corrected (ETOPFACAR) where appropriate. E-Values for ETOPFACARs by substance trends were elevated for THC (40 CAs), cannabis (35 CAs), tobacco (11 CAs), cannabidiol (8 CAs), monthly alcohol (5 CAs) and binge alcohol (2 CAs) with minimum E-Values descending from 16.55, 1.55x10⁷, 555.10, 7.53x10¹³, 0.30 and 20.98. Cardiovascular, gastrointestinal, chromosomal, limb reductions, urinary, face and body wall (A)s particularly affected. Highest v. lowest substance use quartile CAR prevalence ratios 2.84 (95%CI 2.44, 3.31), 4.85 (4.08, 5.77) and 1.92 (1.63, 2.27) and attributable fraction in exposed 0.28 (0.27, 0.28), 0.57 (0.51, 0.62) and 0.47 (0.38, 0.55) for tobacco, cannabis and cannabidiol. Small intestinal stenosis or atresia and obstructive genitourinary defect were studied in detail in lagged IPW pseudo randomized causal regressions and spatiotemporal models confirmed the causal role of cannabinoids. Spatiotemporal predictive modeling demonstrated

*Correspondence: stuart.reece@qld.gov.au
¹School of Medical and Health Sciences, Edith Cowan University, Joondalup, WA 6022, Australia
Full list of author information is available at the end of the article

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Population studies

- 16 countries in Europe

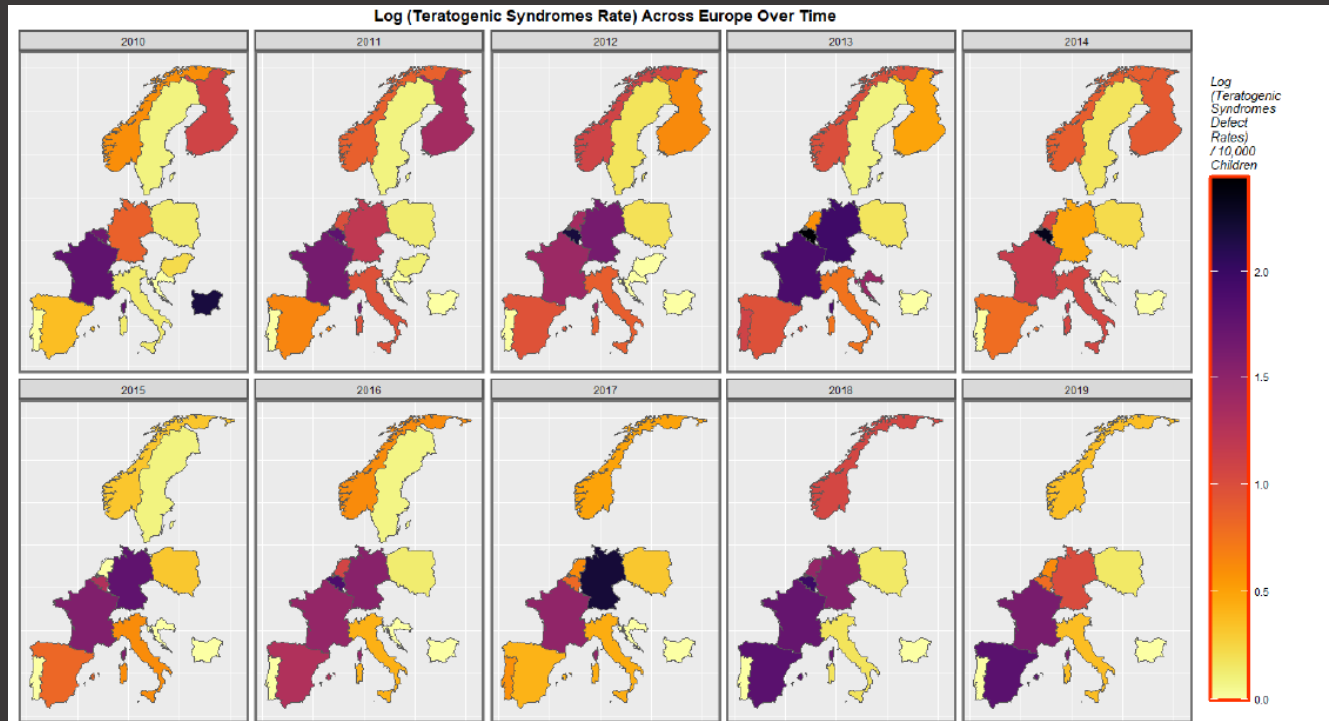


Figure 7. Log (Teratogenic Syndrome Rates) in selected European nations. Sequential map-graph of the log rate of teratogenic syndromes over time in selected European nations.

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US population

• Results for birth defects

- tobacco 11
- alcohol 5

• Cannabis constituents (cannabinoids)

- THC 40
- Cannabidiol (CBD) 8

• Cannabis causal in 45 of 62 birth defects in all in the US data



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BMC Pediatrics

RESEARCH Open Access

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¹School of Medical and Health Sciences, Edith Cowan University, Joondalup, WA 6022, Australia
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Europe - population

- What the data shows

“Eighty-nine out of 90 Congenital Anomalies in bivariate association and 74/90 Congenital Anomalies in additive panel inverse probability weighted space-time regression were cannabis related.”

“Twelve thousand three hundred sixty Congenital Anomaly rates were sourced across 16 nations of Europe. Nations with a higher or increasing rate of daily cannabis use had a 71.77% higher median Congenital Anomaly rates than others”



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Key to any consideration of the possible causal relationships of cannabis with mutagenesis and teratogenesis is the elucidation

Autism

“Using two independent datasets and two categorization methods we confirmed that **medical, decriminalized and legal cannabis regimes are associated with higher rates of ASD than illegal ones.** Findings are consistent with molecular, cellular and epigenetic mechanisms.”



Clinical Pediatrics: Open Access
Research Article

Effect of Cannabis Legalization on US Autism Incidence and Medium Term Projections

Albert Stuart Reace^{1*}, Gary Kenneth Hulse^{2,3}

¹Division of Psychiatry, University of Western Australia, Crawley, Western Australia 6009, Australia; ²School of Medical and Health Sciences, Edith Cowan University, Joondalup, Western Australia, 6027, Australia

ABSTRACT

Objective: In that cannabis use has been linked with the development of autism spectrum disorder like conditions in genetically exposed children, we set out to explore the extent to which using cannabis use might contribute to the rising autism epidemic.

Methods: Datasets from US Department of Education Individuals with Disabilities Act (IDEA), National Survey of Drug Use and Health, and CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network were investigated. Data on legal status was derived from SAMHSA.

Results: IDEA had N=1,023 and ADDM N=67. Modelling of IDEA consistently showed that models quadratic-in-time outperformed linear-only models (ANOVA $p < 2.0 \times 10^{-9}$). In both datasets liberalization of cannabis legislation was associated with increased ASD ($p < 10^{-6}$ and $p < 0.03$ respectively). Slopes of ASD vs. time, Cannabis vs. time and ASD vs. cannabis curves were shown to be related via graphical analysis by profinite plots and tangents (entanglement=0.3326). CDC's ADDM network quoted US autism incidence 168/10,000 in 2014. IDEA projections indicated rates 108.37, 131.67 and 166.49 in cannabis-legal, medical and decriminalized states rising exponentially to 283.37, 396.91 and 455.24 by 2030.

Conclusions: ASD is the commonest form of cannabis-associated clinical neurology. Using two independent datasets and two categorization methods we confirmed that medical, decriminalized and legal cannabis regimes are associated with higher rates of ASD than illegal ones. Findings are consistent with molecular, cellular and epigenetic mechanisms. Forwardly quadratic regression curves became exponential when projected forwards to 2030, predict a lower quantum than the 2014 ADDM CDC figure, and indicate a 60% excess of cases in legal states by 2030.

Keywords: Cannabis; Cannabinoids; Cannabidiol; Cannabinol; Cannabidiolomene; Tetrahydrocannabinol

Abbreviations: ADDM: Autism and Developmental Difficulties Monitoring from CDC; ASD: Autism Spectrum Disorder; CB1R: Cannabinoid Type 1 Receptor; CDC: Centers for Disease Control; IDEA: US Department of Education Individuals with Disabilities Act; NSDUH: National Survey of Drug Use and Health; Robt: Rebound, a guidance molecule receptor for annual growth cones and arterial endothelial tips; SAMHSA: Substance Abuse and Mental Health Services Administration; Slt: Slt1-3, arterial and venous guidance molecule and ligand for Robt; * : An additive operator for regression calculations; †: Tilde, a middle sign separating the two sides of a regression calculation; ‡: Asterisk, an operator used in regression calculations to indicate additive and interactive relationships.

INTRODUCTION

Recent reports from several sources indicate that the incidence of Autism Spectrum Disorder (ASD) has been growing significantly in most USA jurisdictions in recent decades [1-3]. Although the cause is not completely understood, periconceptual and postnatal exposures including genetic and epigenetic factors are believed to play an important role [4-6]. Older parents, affected siblings, time between births, exposure to some drugs, particularly anticonvulsants and SSRI antidepressants and folate deficiency

Correspondence to: Albert Stuart Reace, Division of Psychiatry, University of Western Australia, Crawley, Western Australia 6009, Australia, Tel: (617) 3544-4000; Fax: (617) 3544-4015; Email: stuart.reace@uq.edu.au

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<https://www.researchgate.net/publication/336583893>
Effect of Cannabis Legalization on US Autism Incidence and Medium Term Projections

Limbleness

- Limb reduction and limbleness

“The limb disorders that were positively associated with cannabis exposure on bivariate analysis were: club foot, hip dysplasia, limb, **limb reductions**, polydactyly and syndactyly.”

“ . . . syndactyly, polydactyly and **reduction deformity of the upper limbs** were first identified in the Hawaiian series. **Reduction of the lower limbs** was a positive finding in the USA series.”



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The implications of cannabinoid genotoxicity are further highlighted with the recent data suggesting that multiple cancers of (breast, pancreas, thyroid, liver and acute lymphoid and myeloid leukaemia) are also epidemiologically causally related to cannabis use [17, 18] and, with the formal experimental demonstration in mice, that epigenetic programming actually controls the organism wide ageing epigenomic cassette [19]. The recent demonstration that cannabis is a major driver of the rise in USA paediatric cancer rates underscores the transgenerational nature of this mutagenesis [17, 20]. These data together indicate that cannabinoid related epigenetic disturbances likely have broad public health implications for diverse communities extending to carcinogenesis on the one hand and pan-systemic ageing on the other and including transgenerational effects.
Key to any consideration of the possible causal relationships of cannabis with mutagenesis and teratogenesis is the elucidation

In the food chain

- Hemp used as fodder for cattle raises the question of cannabinoids passed to humans through the food chain

“Interestingly, recent reports from France and Germany, where cannabis use is rising, relate to ‘outbreaks’ of **babies borne without limbs** but no such reports have been issued from nearby Switzerland where cannabis is not allowed to enter the food chain.”



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Research Article

Cannabinoid and substance relationships of European congenital anomaly patterns: a space-time panel regression and causal inferential study

Albert Stuart Reece^{1,2*} and Gary Kenneth Hulse^{1,2}

¹Division of Psychiatry, University of Western Australia, Crawley, Western Australia 6009, Australia, ²School of Medical and Health Sciences, Edith Cowan University, Joondalup, Western Australia 6027, Australia
*Correspondence address: Department of Psychiatry, University of Western Australia, Stirling Hwy, Crawley, Western Australia 6009, Australia.
Tel: (617) 1384-6000, Fax: (617) 1384-4015, E-mail: stuart.reece@uq.edu.au

Abstract
With reports from Australia, Canada, USA, Hawaii and Colorado documenting a link between cannabis and congenital anomalies (CA), this relationship was investigated in Europe. Data on 90 CAs were accessed from Eurocat. Tobacco and alcohol consumption and median household income data were from the World Bank. Amphetamine, cocaine and last month and daily use of cannabis from the European Monitoring Centre for Drugs and Drug Addiction. Cannabis herb and resin Δ9-tetrahydrocannabinol concentrations were from published reports. Data were processed in R. Twelve thousand three hundred sixty CA rates were sourced across 16 nations of Europe. Nations with a higher or increasing rate of daily cannabis use had a 71.7% higher median CA rates than others [median, interquartile range 2.13 (0.58, 6.30) v. 1.24 (0.15, 5.49) 10000 live births ($p = 4.94 \times 10^{-16}$; minimum F-value (minF) = 1.52]. Eighty-nine out of 90 CAs in bivariate association and 74/90 CAs in additive panel inverse probability weighted space-time regression were cannabis related. In inverse probability weighted interactive panel models lagged to zero, two, four and six years, 76, 51, 50 and 29 CAs had elevated mFVs ($>2.06 \times 10^3$) for cannabis matrix, cardiovascular, central nervous, gastrointestinal, genital, immunology, limb, face and chromosomal-genetic systems along with the multisystem VACTERL syndromes were particularly vulnerable targets. Data reveal that cannabis is related to many CAs and fulfil epidemiological criteria of causality. The triple convergence of rising cannabis use prevalence, intensity of daily use and Δ9-tetrahydrocannabinol concentration in herb and resin is powerfully implicated as a primary driver of European teratogenicity, confirming results from elsewhere.

Key words: tobacco; alcohol; cannabis; cannabinoid; cancer; carcinogenesis; mutagenesis; oncogenesis; genotoxicity; epigenotoxicity; chromosomal toxicity

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Next episode

- More detail in future episodes:

- Cannabis and cancer
- Cannabis and birth defects
- **Cannabidiol (CBD), cancer and birth defects**
- Cannabis and pain
- Cannabis and driving
- Hemp and psychoactive metabolites
- Cannabis and psychosis
- Cannabis and violence/homicide
- Cannabis and suicide
- Cannabis – its other harms

