NOT ENOUGH KNOWN

Any changes to legislation concerning Cannabidiol (CBD) availability cannot currently be an informed decision

1. All medical preparations regulated by the Australian TGA have been subject to rigorous science and testing, to which CBD has not generally been subject
2. CBD is a known chromosomal clastogen, epigenotoxin and mitochondrial toxin, causing DNA damage and chromosomal aberrations. This demands caution.
3. CBD is already known to cause physical disease and safety risks, while being implicated in autism and birth defects
4. False advertising regarding imaginary benefits from CBD is already proliferating a substance within Australia about which little is known
5. In the US there are many issues with the manufacture of CBD which provide sound warnings against a less regulated environment
6. There are many questions that have not yet been answered regarding CBD
7. We simply do not know enough about CBD to be rescheduling the substance

Central Issues
&
Compiled Evidence

DRUG FREE AUSTRALIA

7 CENTRAL ISSUES FOR THE AUSTRALIAN TGA

1. **All medical preparations regulated by the Australian TGA have been subject to rigorous science and testing, to which CBD has not generally been subject**

   CBD preparations are currently used in Australia for medical conditions, real or imagined, and therefore should be subject, like any other medicine, to the strictures applied to every other medicine within this country

   Epidiolex is the only CBD preparation that has met FDA testing standards in the US, and which meets TGA strictures in Australia. GW Pharmaceuticals has done its due diligence in getting its product approved, so why should other CBD products be allowed to skirt requirements?

   Government instrumentalities should never make the health of Australians subject to the commercial vested interests of cannabis lobbyists motivated by profits rather than health. Any lobbyist interested in the health of Australians will readily accede to the TGA strictures applied to the availability of new and untested medicines

2. **CBD is a known chromosomal clastogen, epigenotoxin and mitochondrial toxin, causing DNA damage and chromosomal aberrations. This genotoxicity demands caution.**

   Such damage done by CBD is well-established and uncontroversial

3. **CBD is already known to cause physical disease and safety risks, while being implicated in autism and birth defects**

   CBD has recently been strongly implicated in links between cannabis and autism, birth defects and pediatric cancers in population studies, where a mechanism of causation has been proposed

   CBD presents an established risk to pregnant women, to those driving or involved in machine

operation, while adulterated CBD products may negatively affect drug tests

Recent research indicates that oral CBD had adverse reactions that are shared with THC. The same research also challenges the widely held belief that CBD is not intoxicating

Adverse reactions to CBD include:
- hepatocellular injury (liver injury) with inflammation or damage to cells
- somnolence and sedation
- suicidal behavior and ideation
- hypersensitivity reactions - allergic reactions
- negative interaction with anti-epilepsy drugs
- interactions with immunosuppressive drugs used in transplants or chemotherapy and with Warfarin
- impaired kidney function and caused anemia

It is very important that CBD retain its Schedule 4 status given that there is not enough known about the substance at this early stage of more limited availability

4. False advertising regarding imaginary benefits from CBD is already proliferating a substance within Australia about which little is known

The marijuana industry has touted commercial CBD as a "wonder drug." They may claim it is perfectly safe and legal and can be used for all that ails you or makes you uncomfortable physically. People are consuming large amounts under the misapprehension that it is safe to do so. It is not safe to do so. It has negative side effects and may interfere with the functioning of other medications

The US has seen a steady stream of such fraudulent claims for the healing properties of CBD, in common with the many overblown claims for medical cannabis in general. False claims for CBD have included a positive effect on cancers, Alzheimer's, psychiatric disorders and diabetes

The upshot of this false advertising is the proliferation of a substance to very large numbers of Australians so affected, while little is yet known about the short and long-term effects of the substance

5. **In the US there are many issues with the manufacture of CBD which provide sound warnings against the less regulated environment the TGA is considering**

   A JAMA research letter indicates false labelling for many CBD products available online, with 21% containing THC, many products mislabeled with either higher or lesser amounts of CBD than advertised. Products claiming to contain no heavy metals or insecticides have been found with significant amounts of both

6. **There are many questions that have not yet been answered regarding CBD**

   What are the effects of long-term daily CBD use?
   What level of intake triggers the known risks associated with CBD?
   How do different methods of consumption affect intake (e.g., oral consumption, topical, smoking or vaping)?
   What is the effect of CBD on the developing brain (such as on children who take CBD)?
   What are the effects of CBD on the developing fetus or breastfed newborn?
   How does CBD interact with herbs and other plant materials?
   Does CBD cause male reproductive toxicity in humans, as has been reported in studies of animals

7. **We simply do not know enough about CBD to be rescheduling the substance**

The evidence supporting these central issues is found in the following pages

Table of Contents

CENTRAL ISSUES FOR THE AUSTRALIAN TGA - 1

All medical preparations regulated by the Australian TGA have been subject to rigorous science and testing, to which CBD has not generally been subject

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Government instrumentalities should never make the health of Australians subject to the commercial vested interests of cannabis lobbyists motivated by profits rather than health. Any lobbyist interested in the health of Australians will readily accede to the TGA strictures applied to the availability of new and untested medicines

Crude CBD preparations do not measure up as medicine

Given that CBD within Australia will in most cases be used for medical purposes, ie as a medicine, all CBD products ***must*** be held to the same standards as any other medicine, as described below:

Criteria for the acceptance of a drug for medical use

All active ingredients have to be identified and their chemistry determined. They have to be tested for purity with limits set for all impurities including pesticides, microbe & fungi and their products. These tests have to be validated and reproduced if necessary in an official laboratory.

The cannabis plant contains some 400 chemicals, a multiplicity of ingredients that vary with habitat – impossible to standardise and often contaminated with microbes, fungi or pesticides.[1]

[1] Jenike MA. Drug Abuse. In Rubenstein E, Federman DD (eds) *Scientific American Medicine*, Scientific American Inc. 1993. Therapeutic Uses of Cannabis, BMA, 1997.

Animal testing will include information on fertility, embryo toxicity, immuno-toxicity, mutagenic and carcinogenic potential. Risks to humans, especially pregnant women and lactating mothers, will be evaluated.

Adequate safety and efficacy trials must be carried out. They must state the method of administration and report on the results from different groups, i.e. healthy volunteers, patients, special groups of the elderly, people with liver and kidney problems and pregnant women. Adverse drug reactions (ADR) have to be stated and include any effects on driving or operating machinery.

The drug must be accepted by qualified experts. Their detailed reports need to take account of all the relevant scientific literature and the potential of the drug to cause dependence.

(Text, which has been reduced, taken from "One Cannot Vote for a Medicine – National Drug Prevention Alliance, UK – used with permission)

The unseemly haste with which commercial CBD manufacturers seek down-regulation is exposed by the rigour required in certifying any medicine.

Drug Free Australia asserts that there are other agendas at play behind some of the push for the normalisation of CBD use, which is clearly the push for the normalisation and legalisation of recreational cannabis use within Australia.

High costs for Epidiolex approval

A pure form of CBD (Epidiolex) has been approved by the FDA as a medicine for two rare disorders to be used only under proper medical protocols. In the US, other CBD products sold as medicines, or food or food supplements, that are not approved by their FDA are black-market and are illegally trafficked and sold. In addition, CBD cosmetics must be properly labeled under FDA law and not be adulterated by deleterious substances.

Black market CBD products have not been evaluated by the FDA to determine if they are effective or safe for any medical use, and if safe, what the proper dosage would be. In addition, they are not administered with any federally approved medical protocols as are prescription drugs and there may be no warnings for how they interact with other drugs, or whether they have dangerous side effects.

In Australia, Epidiolex has been used for Phase 3 clinical trials for childhood epilepsies, and GW Pharmaceuticals has borne the costs of research and development of its products which in 2020 cost in excess of $45,000,000 https://www.globenewswire.com/news-release/2020/05/11/2031373/0/en/GW-Pharmaceuticals-plc-Reports-First-Quarter-2020-Financial-Results-and-Operational-Progress.html. In addition to R&D costs, Epidiolex in the US is subject to approval costs.

> After completion of the required clinical testing, an NDA is prepared and submitted to the FDA. The FDA approval of the NDA is required before marketing of the product may begin in the U.S. The NDA must include the results of all pre-clinical, clinical, and other testing and a compilation of data relating to the product's pharmacology, chemistry, manufacture, and controls. The cost of preparing and submitting an

NDA is substantial. Under federal law, the submission of most NDAs is additionally subject to a substantial application user fee, for fiscal year 2018 $2,421,495, and the manufacturer and/or sponsor under an approved NDA are also subject to annual program fees, for fiscal year 2018 $304,162.

Given that CBD products in Australia will be used chiefly for medical purposes, Drug Free Australia asks why other CBD producers should not be held to the same costs and standards in developing their products.

Australia must not be captive to vested-interest commercial players

In early 2016 cannabis was a TGA Schedule 9 Prohibited Substance for very good reason. Cannabis is causal, or associated with, a long list of unacceptable harms including:

- Cannabis is an established gateway to other dangerous drugs, adding an additional gateway beyond the two existing legal drugs
- Cannabis users are 50% more likely to develop alcohol use disorder
- Cannabis use is associated with a doubling the chance of psychosis, or 500% chance for those using high THC cannabis
- Cannabis use is associated with a greater risk of depression
- Cannabis use is associated with anxiety
- Cannabis is associated with Amotivational Syndrome
- Cannabis use is associated with a 3 fold risk of suicidal ideation
- VIOLENCE AND AGGRESSION are a documented part of its withdrawal syndrome, with Alex Berenson's book "Tell Your Children" well-documenting the linkage to violent murders
- Brain Function
    - Verbal learning is adversely affected
    - Organisational skills are adversely affected
    - Cannabis causes loss of coordination
    - Associated memory loss can become permanent
    - Cannabis is associated with attention problems
- Drivers are 16 times more likely to hit obstacles
- Miscarriage is elevated with cannabis use
- Fertility is adversely affected
- Newborns are adversely affected with appearance, weight, size, hormonal function, cognition and motor function adversely affected through to adulthood
- Cannabis use causes bronchitis
- Testicular cancer is associated with cannabis use
- Cannabis is also associated with cardio-vascular stroke and heart attack, with chance of myocardial infarction 5 times higher after one joint

According to the most authoritative 2017 review on cannabis by the US National Institutes of Health, medical cannabis can treat:

- Chronic pain – modest effect only
- Nausea – with most other available options more effective
- Multiple Sclerosis (MS) – modest effect only
- AIDS wasting – with many other better options available
- Tourette Syndrome
- Post Traumatic Stress Disorder (PTSD)

- Traumatic brain injury, intracranial haemorrhage
- Childhood Epilepsy (these latter conditions were confirmed in US Epidiolex trials which were completed after the 2017 NIH review)

Yet medical cannabis still carries every one of the harms of recreational use listed above.

CBD has been falsely positioned as the wholly benign non-psychoactive healing component of cannabis by commercial interests not particularly beholden to an honest accounting of the product, and yet, as per Section 3 of this document, CBD does in fact share in some of the harms thought to be mostly caused by THC, including being implicated, according to correlations of cannabinoids analysed in US DEA cannabis seizures, with rising autism and gastroschisis rates in that country. This is no small thing. While this finding awaits a lot more study, it does demand caution regarding the medical uses of CBD.

In light of too many unknowns at a time when CBD is still a novelty being glibly marketed as benign when it clearly is not, Australia cannot afford to be held captive by commercial interests which do not have the welfare of Australians at heart. It is the TGA that has been entrusted with safeguarding the welfare of Australians, and it thereby cannot afford to reschedule CBD.

Epidiolex's CBD must be on a level playing field

In light of all the above, all CBD preparations must be treated like any other medicine where the onus is on its manufacturers to demonstrate that they are safe and effective.

CENTRAL ISSUES FOR THE AUSTRALIAN TGA – 2

CBD is a known chromosomal clastogen, epigenotoxin and mitochondrial toxin, causing DNA damage and chromosomal aberrations. This genotoxicity demands caution.

Such damage done by CBD is well-established and uncontroversial

Care must be taken with genotoxic CBD

CBD has been sold to the Australian public as the benign healing component of cannabis. Yet research has shown that CBD is a known chromosomal clastogen, epigenotoxin and mitochondrial toxin which causes DNA damage and chromosomal aberrations as per:
Epigenetics. 2019 Nov;14(11):1041-1056. doi: 10.1080/15592294.2019.1633868. Epub 2019 Jul 11.

Epigenetics

Impacts of Cannabinoid Epigenetics on Human Development: Reflections on Murphy et. al. "Cannabinoid Exposure and Altered DNA Methylation in Rat and Human Sperm" Epigenetics 2018; 13: 1208-1221.

--Manuscript Draft--

Manuscript Number:	KEPI-2019-0152R1
Full Title:	Impacts of Cannabinoid Epigenetics on Human Development: Reflections on Murphy et. al. "Cannabinoid Exposure and Altered DNA Methylation in Rat and Human Sperm" Epigenetics 2018; 13: 1208-1221.
Article Type:	Review
Manuscript Classifications:	Development; DNA Methylation; Histone Modifications; Immunobiology; In Utero Development
Abstract:	Recent data from the Kollins lab ("Cannabinoid exposure and altered DNA methylation in rat and human sperm" Epigenetics 2018; 13: 1208-1221) indicated epigenetic effects of cannabis use on sperm in man parallel those in rats and showed substantial shifts in both hypo- and hyper- DNA methylation with the latter predominating. This provides one likely mechanism for the transgenerational transmission of epigenomic instability with sperm as the vector. It therefore contributes important pathophysiological insights into the probable mechanisms underlying the epidemiology of prenatal cannabis exposure potentially explaining diverse features of cannabis-related teratology including effects on the neuraxis, cardiovasculature, immune stimulation, secondary genomic instability and carcinogenesis related to both adult and pediatric cancers. The potentially inheritable and therefore multigenerational nature of these defects needs to be carefully considered in the light of recent teratological and neurobehavioural trends in diverse jurisdictions such as USA nationally, Hawaii, Colorado, Canada, France and Australia, particularly relating to mental retardation, age related morbidity and oncogenesis including inheritable cancerogenesis. Increasing demonstrations that the epigenome can respond directly and in real time and retain memories of environmental exposures of many kinds implies that the genome-epigenome is much more sensitive to environmental toxicants than has been generally realized. Issues of long-term multigenerational inheritance amplify these concerns. Further research particularly on the epigenomic toxicology of many cannabinoids is also required.

Also: https://jglobal.jst.go.jp/en/detail?JGLOBAL_ID=201902279906393186

Low doses of widely consumed cannabinoids (cannabidiol and cannabidivarin) cause DNA damage and chromosomal aberrations in human-derived cells

Chiara Russo[1] · Franziska Ferk[2] · Miroslav Mišík[2] · Nathalie Ropek[2] · Armen Nersesyan[2] · Doris Mejri[2] · Klaus Holzmann[2] · Margherita Lavorgna[1] · Marina Isidori[1] · Siegfried Knasmüller[2]

Received: 16 May 2018 / Accepted: 2 October 2018 / Published online: 19 October 2018

Abstract
Cannabidiol (CBD) and cannabidivarin (CBDV) are natural cannabinoids which are consumed in increasing amounts worldwide in cannabis extracts, as they prevent epilepsy, anxiety, and seizures. It was claimed that they may be useful in cancer therapy and have anti-inflammatory properties. Adverse long-term effects of these drugs (induction of cancer and infertility) which are related to damage of the genetic material have not been investigated. Therefore, we studied their DNA-damaging properties in human-derived cell lines under conditions which reflect the exposure of consumers. Both compounds induced DNA damage in single cell gel electrophoresis (SCGE) experiments in a human liver cell line (HepG2) and in buccal-derived cells (TR146) at low levels (≥ 0.2 µM). Results of micronucleus (MN) cytome assays showed that the damage leads to formation of MNi which reflect chromosomal aberrations and leads to nuclear buds and bridges which are a consequence of gene amplifications and dicentric chromosomes. Additional experiments indicate that these effects are caused by oxidative base damage and that liver enzymes (S9) increase the genotoxic activity of both compounds. Our findings show that low concentrations of CBD and CBDV cause damage of the genetic material in human-derived cells. Furthermore, earlier studies showed that they cause chromosomal aberrations and MN in bone marrow of mice. Fixation of damage of the DNA in the form of chromosomal damage is generally considered to be essential in the multistep process of malignancy, therefore the currently available data are indicative for potential carcinogenic properties of the cannabinoids.

CBD genotoxicity is uncontroversial

Drug Free Australia Fellow, Dr Stuart Reece, a Professor at the University of Western Australia, has confirmed that the genotoxicity of CBD is non-controversial. Dr Reece is well-published in areas such as cannabis teratology and epigenetics.

Original Article

Cannabis Teratology Explains Current Patterns of Coloradan Congenital Defects: The Contribution of Increased Cannabinoid Exposure to Rising Teratological Trends

Clinical Pediatrics
1–39

DOI: 10.1177/0009922819861281
journals.sagepub.com/home/cpj
SAGE

Albert Stuart Reece, MBBS (Hons), FRCS (Ed), FRCS (Glas), FRACGP, MD (UNSW)[1,2] and Gary Kenneth Hulse, BBSc (Hons), MBSc, PhD[1,2]

Abstract
Rising Δ9-tetrahydrocannabinol concentrations in modern cannabis invites investigation of the teratological implications of prenatal cannabis exposure. Data from Colorado Responds to Children with Special Needs (CRCSN), National Survey of Drug Use and Health, and Drug Enforcement Agency was analyzed. Seven, 40, and 2 defects were rising, flat, and falling, respectively, and 10/12 summary indices rose. Atrial septal defect, spina bifida, microcephalus, Down's syndrome, ventricular septal defect, and patent ductus arteriosus rose, and along with central nervous system, cardiovascular, genitourinary, respiratory, chromosomal, and musculoskeletal defects rose 5 to 37 times faster than the birth rate (3.3%) to generate an excess of 11753 (22%) major anomalies. Cannabis was the only drug whose use grew from 2000 to 2014 while pain relievers, cocaine, alcohol, and tobacco did not. The correlation of cannabis use with major defects in 2014 (2019 dataset) was $R = .77$, $P = .0011$. Multiple cannabinoids were linked with summary measures of congenital anomalies and were robust to multivariate adjustment.

In an e-mail to Drug Free Australia dated 27June 2019 Dr Reece confirmed that the CBD effect on mitochondria is highly significant, well recognised and non-controversial. He further stated that it is now accepted that mitochondrial toxicity can become reflected in genotoxicity also through the balance mechanisms between mitochondria and nucleus, which is also non-controversial.

The genotoxicity of CBD is admitted in authorised prescribing information with the US FDA and with the European Medicines Commission. It even appears on the labels of hemp oil marketed by Woolworths.

It is crucial that more be known about CBD before any decision is made to loosen strictures.

CENTRAL ISSUES FOR THE AUSTRALIAN TGA – 3

CBD is already known to cause physical disease and safety risks, while being implicated in autism and birth defects

CBD has recently been strongly implicated in links between cannabis and autism, birth defects and pediatric cancers in population studies, where a mechanism of causation has been proposed

CBD presents an established risk to pregnant women, to those driving or involved in machine operation, while adulterated CBD products may negatively affect drug tests

Recent research indicates that oral CBD had adverse reactions that are shared with THC. The same research also challenges the widely held belief that CBD is not intoxicating

Adverse reactions to CBD include:
- **hepatocellular injury (liver injury) with inflammation or damage to cells**
- **somnolence and sedation**
- **suicidal behavior and ideation**
- **hypersensitivity reactions - allergic reactions**
- **negative interaction with anti-epilepsy drugs**
- **interactions with immunosuppressive drugs used in transplants or chemotherapy and with Warfarin**
- **impaired kidney function and caused anemia**

It is very important that CBD retain its Schedule 4 status given that there is not enough known about the substance at this early stage of more limited availability

Drug Free Australia acknowledges use of some information below from CIVEL, one of our US affiliates

CBD implicated in population studies regarding autism

The often-voiced claim that CBD is benign, presenting no significant harms to a patient, needs to be reassessed in the light of an evolving science on CBD.

In a recent letter to the New England Medical Journal, Drug Free Australia Fellow, Dr Stuart Reece, and his research colleague, Dr Gary Hulse wrote the following:

> As one of the major cannabinoids and a high-dose ligand at CB1R's cannabidiol is implicated in the close spatial (northeast USA), temporal (recent years) and demographic (young adults) association between cannabis use and mental illness chronicled by SAMHSA and the nationwide surge in autism recently linked to cannabidiol.

They cited the following study found at Appendix A:
https://www.longdom.org/open-access/effect-of-cannabis-legalization-on-us-autism-incidence-and-medium-term-projections.pdf

Clinical Pediatrics: Open Access

OPEN ACCESS Freely available online

Research Article

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

Albert Stuart Reece[1,2]*, Gary Kenneth Hulse[1,2]

[1]Division of Psychiatry, University of Western Australia, Crawley, Western Australia 6009, Australia; [2]School 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 gestationally exposed children, we set out to explore the extent to which rising 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=87. Modelling of IDEA consistently showed that models quadratic-in-time out-performed linear-only models (ANOVA $p<2.0x10^{-16}$). In both datasets liberalization of cannabis legislation was associated with increased ASD ($p<10^{-9}$ and $p<0.05$ respectively). Slopes of: ASD *vs.* time, Cannabis *vs.* time and ASD *vs.* cannabis curves were shown to be related on graphical analysis by geofacet plots and tanglegrams (entanglement=0.3326). CDC's ADDM network quoted US autism incidence 168/10,000 in 2014. IDEA projections indicated rates 108.57, 131.67 and 166.49 in cannabis-illegal, -medical and -decriminalized states rising exponentially to 282.37, 396.91 and 455.54 by 2030.

Conclusion: ASD is the commonest form of cannabis-associated clinical teratology. 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. Formerly quadratic regression curves become 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; Cannabichromene; 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; Robo: Roundabout, a guidance molecule receptor for axonal growth cones and arterial endothelial tips; SAMHSA: Substance Abuse and Mental Health Services Administration; Slit: Slits 1-3, arterial and axonal guidance molecule and ligand for Robo; + : 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 include additive and interactive relationships.

CBD is more strongly implicated in autism prevalence than THC, and cannabis moreso than opiates according to this study. This has been established from DEA cannabis seizures which establishes the strength of THC and various other cannabinoids in cities across the US correlated against increases in autism in those US States that have legalised access to recreational and medical cannabis.

It is clear from early correlational population studies that CBD is not beyond question, and it is incumbent on the TGA to await further data before rescheduling CBD.

CBD also implicated in growing birth defect prevalence

Reece and Hulse, in their aforementioned letter to the New England Journal of Medicine assert the following:

> Cannabidiol is a known chromosomal clastogen, epigenotoxin (https://www.ncbi.nlm.nih.gov/pubmed/31293213) and mitochondrial toxin and was linked to the 29% surge in Colorado birth defects (https://www.ncbi.nlm.nih.gov/pubmed/31288542), led by cardiovascular defects, just as in Canada; and the pattern of rise of Downs syndrome, anotia and absent arms in Alaska and Oregon (https://www.nbdpn.org/ar.php); and parts of France after it was added to the food supply; or the emergence of new cannabis-related defects like atrial septal defect in Colorado, Alaska, Oregon, Kentucky and Hawaii (https://www.nbdpn.org/ar.php).

While cannabis is implicated in growing rates of gastroschisis (a birth defect where babies are born with their intestines outside the body) in States and countries which are legalising cannabis for medical and recreational use, it is CBD moreso than THC that appears causal in these population studies. https://www.ncbi.nlm.nih.gov/pubmed/30725103

Format: Abstract

JAMA Surg. 2019 Apr 1;154(4):366-367. doi: 10.1001/jamasurg.2018.4694.

Gastroschisis and Autism-Dual Canaries in the Californian Coalmine.

Reece AS[1,2], Hulse GK[1,2].

Author information

Comment in
Gastroschisis and Autism-Dual Canaries in the Californian Coalmine-Reply. [JAMA Surg. 2019]

Comment on
Incidence of Gastroschisis in California. [JAMA Surg. 2018]

PMID: 30725103 DOI: 10.1001/jamasurg.2018.4694

[Indexed for MEDLINE]

In an e-mail to Drug Free Australia dated 21 January 2019 Dr Stuart Reece, one of the researchers that uncovered the association between cannabis and gastroschisis, stated that “The order of potency for both gastroschisis and autism is CBD>THC>Opioids.

This statistical finding alone suggests more study needs to be done on CBD’s relationship to birth defects, given the known DNA damage it has been demonstrated to cause.

CBD correlations with pediatric cancers

Reece and Hulse also noted in the aforementioned letter to NEJM the correlations between CBD use and pediatric cancers. They stated that:

> Total pediatric cancer (inheritable genotoxicity) has increased 42% from 1975 and is 54% higher in Caucasian-Americans than in African-Americans, patterns which follow historical cannabis-cannabidiol use.

They cited their data source as
https://seer.cancer.gov/explorer/application.php?site=1&data_type=1&graph_type=1&compareBy=race&chk_sex_1=1&chk_sex_3=3&chk_sex_2=2&chk_race_1=1&chk_age_range_15=15&chk_data_type_1=1&advopt_precision=1&advopt_display=1&showDataFor=sex_1_and_age_range_15_and_data_type_1.)

and a study is in progress.

CBD symptoms similar to THC

Research published in the journal Cannabis and Cannabinoid Research shows that more than 40% of children with epilepsy who were given CBD orally had adverse events that included THC like symptoms. The research challenged the widely accepted premise that CBD is not intoxicating. https://www.thehealthyhomeeconomist.com/cbd-oil-dangers/#comment-643247 There is evidence that CBD is biotransformed to metabolites that have similar effects as THC. See https://www.tandfonline.com/doi/abs/10.1081/TXR-120026915

Pharmacology and Toxicology of Major Constituents of Marijuana—On the Metabolic Activation of Cannabinoids and Its Mechanism

Ikuo Yamamoto, Kazuhito Watanabe, Tamihide Matsunaga, Toshiyuki Kimura, Tatsuya Funahashi & Hidetoshi Yoshimura

Pages 577-589 | Published online: 12 Nov 2003

Download citation https://doi.org/10.1081/TXR-120026915

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Abstract

Many oxidative metabolites of tetrahydrocannabinols (THCs), active components of *Cannabis sativa* L. (*Cannabinaceae*), were pharmacologically potent, and 11-hydroxy-THCs, 11-oxo-Δ^8-THC, 7-oxo-Δ^8-THC, 8β,9β-epoxyhexahydrocannabinol (EHHC), 9α,10α-EHHC and 3'-hydroxy-Δ^9-THC were more active than THC in pharmacological effects such as catalepsy, hypothermia and barbiturate synergism in mice, indicating that these metabolites are active metabolites of THCs. Cannabidiol (CBD), another major component, was biotransfomred to two novel metabolites, 6-hydroxymethyl-Δ^9-THC and 3-pentyl-6, 7, 7a, 8, 9, 11a-hexahydro-1, 7-dihydroxy-7,10-dimethyldibenzo[b,d]oxepin (PHDO) through 8R,9-epoxy-CBD and 8S, 9-epoxy-CBD as intermediates, respectively, identified by us. Both metabolites have some pharmacological effects comparable to Δ^9-THC. Cannabinol (CBN), the other major component, was mainly metabolized to 11-hydroxy-CBN by hepatic microsomes of animals including humans. The pharmacological effects of the metabolite were higher than those of CBN demonstrating that 11-hydroxylation of CBN is an activation pathway of the cannabinoid as is the case in THCs. Tolerance developed to catalepsy, hypothermia and pentobarbital-induced sleep prolonging effects of Δ^8-THC and its active metabolite, 11-hydroxy-Δ^8-THC. Reciprocal cross-tolerance also developed to pharmacological effects and the magnitude of tolerance development produced by the metabolite was significantly higher than that by Δ^8-THC indicating that 11-hydroxy-Δ^8-THC has important role not only in the pharmacological effects but also its tolerance development of Δ^8-THC. THCs and their metabolites competed with the specific binding of CP-55,940, an agonist of cannabinoid receptor, to synaptic membrane from bovine cerebral cortex. The Ki value of THCs and their metabolites were closely parallel to their pharmacological effects in mice. A novel cytochrome P450 (cyp2c29) was purified and identified for the first time by us as a major enzyme responsible for the metabolic activation of Δ^8-THC at the 11-position in the mouse liver. cDNA of cyp2c29 was cloned from a mouse cDNA library and its sequence was determined. All of major P450s involving the metabolic activation of Δ^8-THC at the 11-position are belonging to CYP2C subfamily in mammalian liver.

Even US pro-cannabis magazine says further studies needed

Concerning the transformation of orally-ingested CBD into THC, even the US Hemp Connoisseur magazine https://hcmagazine.com/does-cbd-convert-to-thc-when-ingested-the-findings-from-one-study-conclude-it-is-possible/ recognizes that more study is needed. They write:

> Much research has involved the administration of THC and CBD to patients for symptoms such as fibromyalgia, Crohn's disease and insomnia, but researchers have been circumspect in declaring their results and have called for further testing. Watanabe's research, though conducted on mice, may hold true for humans – but that must be the subject of future studies. As Georgetown University Medical School's Dr. Robert du Pont pointed out, there are an estimated 400 components in the cannabis plant, making it difficult to determine exactly which component is providing relief when cannabis is ingested for medical reasons.3
>
> Could anomalies in results have resulted from the way gastric juices break down CBD within the human body? In a 2016 study published in Cannabis and Cannabinoid Research, by John Merrick and associates, it was noted that, "In recent epilepsy research, pediatric subjects receiving orally administered CBD showed a relatively high incidence of adverse events (≤44%), with somnolence (≤21%) and fatigue (≤17%) among the most common."4 This led the researchers to more closely investigate the accepted premise that CBD is non-psychoactive. They came to the conclusion that, "Gastric fluid without enzymes converts CBD into the psychoactive components Δ9-THC and Δ8-THC, which suggests that the oral route of administration may increase the potential for psychomimetic adverse effects from CBD."

FDA advise against CBD use in pregnancy

The FDA strongly advises that during pregnancy and while breastfeeding women should not use CBD or THC. They may put themselves or their baby at serious risk by using these marijuana products (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6024459/). CBD products may also be contaminated with substances that may pose a risk to the fetus or breastfed baby such as pesticides, heavy metals, bacteria, and fungus. Studies in laboratory animals show male reproductive toxicity, including in the male offspring of CBD-treated pregnant females. This includes decrease in testicular size, inhibition of sperm development, and decreased testosterone.

There is not adequate data on the developmental risks associated with Epidiolex use in pregnant women. Administration of CBD to pregnant animals produced evidence of developmental toxicity such as increased embryofetal mortality in rats and decreased fetal body weights in rabbits; decreased growth, delayed sexual maturation, long-term neurobehavioral changes, and adverse effects on the reproductive system in rat offspring.

There are not good data on the presence of cannabidiol or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Epidiolex and any

potential adverse effects on the breastfed infant from Epidiolex or from the underlying maternal condition.

Epidiolex prescribing information not on general CBD labelling

Epidiolex, as a tested CBD medication, has side-effects and contraindications which are not listed on loosely regulated CBD products. This alone is adequate reason to maintain the current Schedule 4 status for CBD products.

The FDA prescribing information for CBD is found at:
https://www.epidiolex.com/sites/default/files/pdfs/EPIDIOLEX_Full_Prescribing_Information_04_16_2020.pdf

The prescribing information is relevant to all CBD products.

Drug Contraindications

CBD oil may potentially interact in a negative way with anti-epilepsy drugs such as:

1. carbamazepine (Tegretol)
2. phenytoin (Dilantin)
3. phenobarbital (Luminal, Solfoton, Tedral)
4. primidone (anti-seizure)

Further to those listed by the FDA, there are interactions with CBD and immunosuppressive drugs used in transplants or chemotherapy and there are interactions with Warfarin as there may be the potentiation of anticoagulant effects with marijuana, including CBD.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5789126/

Common Side effects

The most common side effects of CBD can include:

- Sleepiness
- Decreased appetite
- Diarrhea
- Change in liver function
- Fatigue/Malaise/Asthenia (weakness or lack of energy)
- Rash
- Insomnia/Sleep disorder/Poor quality sleep
- Infections
- CBD also interacts with some other seizure medicines
- Nausea or vomiting
- Dizziness
- Anxiety or depression
- Changes in appetite/weight

Glaucoma

A recent study suggests that CBD doesn't lower eye pressure but raises it. High eye pressure is the primary risk factor for glaucoma, a leading cause of blindness. Glaucoma damages the optic nerve at the back of the eye. Glaucoma is linked to a buildup of pressure inside the eye. The increased

pressure can damage the nerve, leading to permanent vision loss.
https://www.aao.org/eye-health/news/cbd-oil-may-worsen-glaucoma

Driving and machine operation

TAKING CBD CAN BE DANGEROUS WHEN DRIVING OR USING MACHINERY. Recent FDA studies show that CBD can cause sleepiness, sedation that may make operating a motor vehicle or machinery dangerous after consuming CBD products.

Drug Tests

CBD may affect drug test results. A truck driver lost his job when he tested positive for THC on a drug test after being told by the manufacturer that a CBD product had no THC. (Horn v. Medical Marijuana, 383 F.Supp.3d 114 (WD NY 2019).

Adverse Reactions

CBD has known health risks based on FDA clinical studies in humans and other clinical reports. The known adverse reactions include:

1. Hepatocellular Injury (liver injury) - inflammation or damage to cells
2. Somnolence and Sedation
3. Suicidal Behavior and Ideation
4. Hypersensitivity Reactions - allergic reactions
5. Negative interaction with anti-epilepsy drugs such as Tegretol, Dilantin, Luminal, Solfoton, Tedral, Primidone (anti-seizure)
6. Interactions with immunosuppressive drugs used in transplants or chemotherapy and with warfarin.
7. CBD use can impair kidney function and cause anemia.

Adverse reactions include suicidal ideation and depression

The FDA-listed Adverse Reactions include THC-like symptoms such as suicidal ideation, depression and anxiety. Their advice is as follows:

> Antiepileptic drugs (AEDs), including EPIDIOLEX, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with an AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.
>
> Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27863 AED-treated patients was 0.43%, compared to 0.24% among 16029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as 1 week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5±100 years) in the clinical trials analyzed. Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

Table 2: Risk of Suicidal Thoughts or Behaviors by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients
Epilepsy	1.0	3.4	3.5
Psychiatric	5.7	8.5	1.5
Other	1.0	1.8	1.9
Total	2.4	4.3	1.8

The relative risk for suicidal thoughts or behavior was higher in clinical trials in patients with epilepsy than in clinical trials in patients with psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing EPIDIOLEX or any other AED must balance the risk of suicidal thoughts or behaviors with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

It is clear that the looser controls of a Schedule 3 drug will not adequately address issues of suicidal ideation and depression caused by CBD. This is best monitored by a prescribing doctor.

CENTRAL ISSUES FOR THE AUSTRALIAN TGA – 4

False advertising regarding imaginary benefits from CBD is already proliferating a substance within Australia about which little is known

The marijuana industry has touted commercial CBD as a "wonder drug." They may claim it is perfectly safe and legal and can be used for all that ails you or makes you uncomfortable physically. People are consuming large amounts under the misapprehension that it is safe to do so. It is not safe to do so. It has negative side effects and may interfere with the functioning of other medications

The US has seen a steady stream of such fraudulent claims for the healing properties of CBD, in common with the many overblown claims for medical cannabis in general. False claims for CBD have included a positive effect on cancers, Alzheimer's, psychiatric disorders and diabetes

The upshot of this false advertising is the proliferation of a substance to very large numbers of Australians so affected, while little is yet known about the short and long-term effects of the substance

Drug Free Australia acknowledges use of some information below from AALM, one of our US affiliates

Claims of therapeutic benefit = CBD as a medicine

False claims for CBD have been proliferated worldwide with commercial profit being one motive, and the legalisation of recreational cannabis use being another. Neither have an overwhelming interest in an accurate accounting of the health benefits and deficits of using CBD.

In the US groups such as Americans Against Legalizing Marijuana (AALM) are taking action against false claims, insisting that the FDA get involved. The FDA has responded thus:

> In particular, we continue to be concerned at the number of drug claims being made about products not approved by the FDA that claim to contain CBD or other cannabis-derived compounds. Among other things, the FDA requires a cannabis product (hemp-derived or otherwise) that is marketed with a claim of therapeutic benefit, or with any other disease claim, to be approved by the FDA for its intended

use before it may be introduced into interstate commerce. This is the same standard to which we hold any product marketed as a drug for human or animal use. Cannabis and cannabis-derived products claiming in their marketing and promotional materials that they're intended for use in the diagnosis, cure, mitigation, treatment, or prevention of diseases (such as cancer, Alzheimer's disease, psychiatric disorders and diabetes) are considered new drugs or new animal drugs and must go through the FDA drug approval process for human or animal use before they are marketed in the U.S. Selling unapproved products with unsubstantiated therapeutic claims is not only a violation of the law, but also can put patients at risk, as these products have not been proven to be safe or effective. This deceptive marketing of unproven treatments raises significant public health concerns, as it may keep some patients from accessing appropriate, recognized therapies to treat serious and even fatal diseases. https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-signing-agriculture-improvement-act-and-agencys

FDA letter to Curaleaf provides examples

In a letter dated 22 July 2019 (https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/curaleaf-inc-579289-07222019) the FDA confronted the medical claims for CBD by Curaleaf where such claims had little or no evidentiary basis. The FDA confronted the claims as follows:

Unapproved New and Misbranded Human Drug Products

Based on our review of your website, your "CBD Lotion," "CBD Pain-Relief Patch," "CBD Tincture," and "CBD Disposable Vape Pen" products are drugs under section 201(g)(1) of the FD&C Act, 21 U.S.C. 321(g)(1), because they are intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease and/or intended to affect the structure or any function of the body.

Examples of claims observed on your website and social media accounts in April 2019 that establish the intended use of your products as drugs include, but may not be limited to, the following:

On your product webpage for CBD Disposable Vape Pen (Relieve):
• "[F]or chronic pain."

Additional claims observed on your website in June 2019 include, but are not limited to, the following:

On your webpage titled "Can CBD Oil be Used for ADHD?"
• "CBD oil is becoming a popular, all-natural source of relief used to address the symptoms of many common conditions, such as chronic pain, anxiety . . . ADHD."
• "The Benefits of CBD Oil for ADHD . . . It's not unusual for people with ADHD to feel anxious and on the edge. CBD is known for its anti-anxiety properties that can promote relaxation and stress relief. It can also help to restore focus and ability to concentrate on specific tasks, as well as reduce impulsivity."

On your webpage titled “How to Use CBD Oil for Anxiety”
• “CBD can successfully reduce anxiety symptoms, both alone and in conjunction with other treatments.”
• “CBD oil can be used in a variety of ways to help with chronic anxiety.”

On your webpage titled “CBD Benefits: Top 5 Research-Backed Benefits of CBD”
• “CBD has also been shown to be effective in treating Parkinson’s disease.”
• “CBD has been linked to the effective treatment of Alzheimer’s disease . . ..”
• “CBD is being adopted more and more as a natural alternative to pharmaceutical-grade treatments for depression and anxiety.”
• “CBD can also be used in conjunction with opioid medications, and a number of studies have demonstrated that CBD can in fact reduce the severity of opioid-related withdrawal and lessen the buildup of tolerance.”
• “CBD has been demonstrated to have properties that counteract the growth of spread of cancer.”
• “CBD was effective in killing human breast cancer cells.”
• “Heart disease is one of the leading causes of death in the United States each year, and CBD does a number of things to deter it. The two most important of these are the ability to lower blood pressure, and the ability to promote good cholesterol and lower bad cholesterol.”

On your webpage titled “What are the Benefits of Hemp-Derived CBD Oil?”
• “What are the benefits of CBD oil? . . . Some of the most researched and well-supported hemp oil uses include . . . Anxiety, depression, post-traumatic stress disorders, and even schizophrenia . . . Chronic pain from fibromyalgia, slipped spinal discs . . . Eating disorders and addiction . . ..”

In a California case, the plaintiffs claim that the defendant company made false claims that CBD could help the symptoms of autism and that could treat illnesses such as hepatitis, cancer and Tourette syndrome. Dasilva v. Infinite Product Company, 2:19-cv-10148.

In a California case, the plaintiffs claim that that the defendant company products were mislabeled as dietary supplements or that they contain the illegal dietary ingredient CBD. Under federal law, it is illegal to use CBD as a dietary supplement. The plaintiffs claim that the company engaged in false and deceptive practices and that their products could not be sold legally. Colette et al. v. CV Sciences Inc., 2:19-cv-10227.

Medical claims require medical supervision

Drug Free Australia maintains that medical claims made for drugs derived from cannabis, a previously Schedule 9 substance in Australia, must remain subject to TGA testing strictures and remain at a medico’s discretion for prescription. Too little is yet known about the various cannabinoids while too much is known about the harms of the plant from which they derive.

CENTRAL ISSUES FOR THE AUSTRALIAN TGA – 5

In the US there are many issues with the manufacture of CBD which provide sound warnings against the less regulated environment the TGA is considering

A JAMA research letter indicates false labelling for many CBD products available online, with 21% containing THC, many products mislabelled with either higher or lesser amounts of CBD than advertised. Products claiming to contain no heavy metals or insecticides have been found with significant amounts of both

Drug Free Australia acknowledges use of information below from CIVEL, one of our US affiliates

False labelling of CBD, incorrect percentages

The Food and Drug Administration (FDA) has issued several warning letters to firms that market Commercial CBD that they are selling CBD illegally. These products are not approved by FDA for the diagnosis, cure, mitigation, treatment, or prevention of any disease. The FDA has also tested the chemical content of cannabinoid compounds in CBD, and many were found to not contain the levels of CBD they claimed to contain (See the 2016 warning letters section at https://www.fda.gov/news-events/public-health-focus/warning-letters-and-test-results-cannabidiol-related-products). consumers should beware purchasing and using any such products.

The Journal of the American Medical Association (JAMA) published a research letter showing the results of “undercover” purchases of CBD from Internet sources. Of 84 samples obtained and tested, THC was detected in 21%. There were other defects in the mislabeled products noted by the undercover agents. For example, 26% of the 84 products contained less CBD than labeled. With respect to CBD, 42.85% of products were under-labeled 26.19% were over-labeled and only 30.95% were accurately labeled. Accuracy of labeling depended on product type, with vaporization liquid most frequently mislabeled 87.50% and oil most frequently labeled accurately 45.00%. Concentration of unlabeled cannabinoids was generally low however, THC was detected in 21.43% cannabidiolic acid 15.48% and cannabigerol 2.38%. This yielded a good deal of information suggesting that open-source CBD bought on the Internet is not a very reliable or safe product if one is planning to use it for medical purposes or in foods (https://www.nbcnews.com/health/health-news/fda-ftc-send-warning-letters-three-cbd-marketers-false-claims-n990251, https://jamanetwork.com/journals/jama/article-abstract/2661569?redirect=true)

On December 8, 2017, the Utah Poison Control Center (UPCC) notified the Utah Department of Health (UDOH) of reports of emergency department visits associated with reported exposure to products labeled as CBD. Patients experienced adverse reactions, including altered mental status, seizures, confusion, loss of consciousness, and hallucinations. These reactions prompted concern for potential adulteration with a synthetic cannabinoid. Sale of CBD is currently illegal in Utah, although CBD is readily available online and in shops. This investigation highlights the hazards of consuming unregulated products labeled as CBD (Notes from the Field: Acute Poisonings from a Synthetic Cannabinoid Sold as Cannabidiol- Utah, 2017–2018 MMWR Weekly May 25, 2018/67(20);587–588 https://www.cdc.gov/mmwr/volumes/67/wr/mm6720a5.htm?s_cid=mm6720a5_w).

A Johns Hopkins researcher reports that the vast majority of edible marijuana products sold in a sample of medical marijuana dispensaries carried labels that overstated or understated the amount of THC. The results of the study suggest some medical marijuana patients could be unintentionally overdosing or are being cheated by mislabeled products. ”If this study is representative of the medical cannabis market, we may have hundreds of thousands of patients buying cannabis products that are mislabeled,” says experimental psychologist Ryan Vandrey, PhD, an associate professor of psychiatry and behavioral sciences at the Johns Hopkins University School of Medicine. People could suffer from overdosing side effects, including extreme anxiety and psychotic reactions. The study collected 75 different edible marijuana products - baked goods, beverages, and candy/chocolates - representing 47 different brands from Washington state and California. Only 13 products were accurately labeled. They also tested the products for cannabidiol, or CBD, another of the active ingredients in marijuana believed to have medical benefit, which may also help reduce the side effects of THC. Testing showed 44 products (59%) had detectible levels of CBD, but the average ratio of THC to CBD was 36-to-1. Only one product had a 1-to-1 ratio, which some research suggests is associated with fewer side effects and improved clinical benefit compared with higher ratios of THC to CBD. What the testing indicates that a lot of what’s available in the edible cannabis market may have very little CBD.
(https://www.socialworktoday.com/news/dn_062315.shtml).

Another report published by the National Institute of Health showed that products were mislabeled with 26% containing less CBD than labeled and 43% containing more, indicating a high degree of variability and poor standardization of online products. Notably, the oil-based products were more likely to be accurate (45% compared to 25% for tincture and 12.5% for vaporization liquid) and had a smaller percentage of deviation. Oil based products also had a higher range of concentration. In addition to CBD mislabeling, THC was detected in 21% of samples. This study also notes that products containing THC could have sufficient enough concentrations to produce intoxication in children (Inadequate Regulation Contributes to Mislabeled Online Cannabidiol Products https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6024459/).

Given the growing understanding of harms caused by CBD, the TGA needs to maintain a tight regulation of CBD medications, and avoid the looseness of regulation in other countries worldwide.

CBD with lead and other contaminants

Lead toxicity has been associated with behavioral handicaps, reading disability, antisocial and hyperactive behavior, juvenile delinquency, and impaired cognition. In addition, preclinical studies suggest an association with drug addiction; e.g., animals treated with lead either pre- or post-natally self-administer opiates at a much higher rate. (https://pubmed.ncbi.nlm.nih.gov/18755453/).

In a Florida case, the plaintiff bought CBD (hemp oil) products relying on the manufacture's advertising that the products had "No Heavy Metals or Insecticides." He became curious and had the products tested by the same laboratory used by the manufacturer. The products failed the laboratory's testing for heavy metals, including copper, nickel and lead and also for total yeast and mould. The Complaint notes that lead can cause poisoning, speech and language problems, anti-social behaviors, brain damage, reproductive problems and brain damage. Mould can cause allergic and respiratory problems and yeasts can cause infection in people with compromised immune systems. Davis v. CBD American Shaman, Case 0:20-cv-60897 (SD FL 2020)

If other CBD products in Australia were to undergo the same testing rigour as GW Pharmaceutical's Epidiolex, all the above issues would not exist.

CENTRAL ISSUES FOR THE AUSTRALIAN TGA – 6

There are many questions that have not yet been answered regarding CBD

- **What are the effects of long-term daily CBD use?**
- **What level of intake triggers the known risks associated with CBD?**
- **How do different methods of consumption affect intake (e.g., oral consumption, topical , smoking or vaping)?**
- **What is the effect of CBD on the developing brain (such as on children who take CBD)?**
- **What are the effects of CBD on the developing fetus or breastfed newborn?**
- **How does CBD interact with herbs and other plant materials?**
- **Does CBD cause male reproductive toxicity in humans, as has been reported in studies of animals?**

Not enough yet known to down-schedule cannabinoids

In light of CBD being a constituent of a previous Schedule 9 Prohibited Substance that was slated as such for its many harms, Drug Free Australia contends that too little is yet known about CBD to be changing its status in Australia.

The questions listed above all impact the health and well-being of Australians and must be answered before any moves are made to reschedule CBD.

CENTRAL ISSUES FOR THE AUSTRALIAN TGA – 7

We simply do not know enough about CBD to be rescheduling the substance

APPENDIX A – CBD & AUTISM, BIRTH DEFECT STUDIES

Clinical Pediatrics

OPEN ACCESS Freely available online

Research Article

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

Albert Stuart Reece[1,2]*, Gary Kenneth Hulse[1,2]

[1]Division of Psychiatry, University of Western Australia, Crawley, Western Australia 6009, Australia; [2]School 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 gestationally exposed children, we set out to explore the extent to which rising 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=87. Modelling of IDEA consistently showed that models quadratic-in-time out-performed linear-only models (ANOVA $p<2.0x10^{-16}$). In both datasets liberalization of cannabis legislation was associated with increased ASD ($p<10^{-9}$ and $p<0.05$ respectively). Slopes of: ASD *vs.* time, Cannabis *vs.* time and ASD *vs.* cannabis curves were shown to be related on graphical analysis by geofacet plots and tanglegrams (entanglement=0.3326). CDC's ADDM network quoted US autism incidence 168/10,000 in 2014. IDEA projections indicated rates 108.57, 131.67 and 166.49 in cannabis-illegal, -medical and -decriminalized states rising exponentially to 282.37, 396.91 and 455.54 by 2030.

Conclusion: ASD is the commonest form of cannabis-associated clinical teratology. 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. Formerly quadratic regression curves become 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; Cannabichromene; 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; Robo: Roundabout, a guidance molecule receptor for axonal growth cones and arterial endothelial tips; SAMHSA: Substance Abuse and Mental Health Services Administration; Slit: Slits 1-3, arterial and axonal guidance molecule and ligand for Robo; + : 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 include additive and interactive relationships.

INTRODUCTION

Recent reports from several sources indicate that the incidence of Autistic 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 perigestational 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 folic acid deficiency

Correspondence to: Albert Stuart Reece, Division of Psychiatry, University of Western Australia, Crawley, Western Australia 6009, Australia, Tel: (617) 3844-4000; Fax: (617) 3844-4015, E-mail: stuart.reece@bigpond.com

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have all been implicated [4-6]. So too has cannabinoid exposure [7,8].

This opens the possibility that the recent rise in the use of cannabinoids across the USA may be linked to the disturbing rise in the prevalence of autism [9]. Such a link achieves public health importance in the light of large numbers of pregnant American women who are exposed to cannabis, reaching 161,000 in 2017 [10], the frequent recommendation of cannabis dispensaries to pregnant users to consume cannabis during gestation [11], and the positive test or affirmation of cannabis use by 25% of Californian teenage mothers [12].

The USA provides a useful opportunity to epidemiologically assess the putative association of cannabis in autism pathogenesis as the Substance Abuse and Mental Health Services Administration (SAMHSA) report strong negative trends for all other drug use in USA, but strong upward trends in cannabis use across the country [10, 13]. This has the effect at the epidemiological level of isolating the effect of cannabis in statistical analyses.

Given that a number of leading USA public health organisations have published data showing that pro-cannabis legalization paradigms are associated with increased rates of cannabis use [14], we investigated if these trends in individual states cannabis use were associated with increased incidence of ASD. The reader should note that it is our view that a putative link between prenatal cannabis use and ASD is already established by both mechanistic and longitudinal epidemiological studies which have been published in the literature. The question we set out to address was to what extent these putative relationships might be reflected in the extant epidemiological data on this subject.

METHODS

Data

Data on autism incidence rates at eight years of age was obtained from two sources. The major source was the US Department of Education Individuals with Disabilities Act (IDEA) Network and was sourced from [3]. The Network for Autism and Developmental Disabilities Monitoring (ADDM) based at CDC was also accessed from [2,3]. The IDEA dataset includes 1,023 points in 51 US states including the District of Columbia at annual intervals from 1991-2011. The ADDM dataset includes 87 data points 2000-2014 in selected states in eight cycles at two yearly intervals. As one metric is derived from schools and the other from clinical services the two rates used are not directly comparable.

Data on drug use was sourced from the National Survey of Drug Use and Health (NSDUH), which is an annual household survery conducted by SAMHSA [10]. Data on the legal status of cannabis in the various US states was derived from two sources, firstly an internet search of historical sources, and secondly an address by the Director of SAMHSA on 4th February 2019 [15] which provided details on the legal status of cannabis by state at that time.

Statistics

Desktop R from CRAN v3.5.2 was used for all analyses which were done in R Studio 1.1.463, performing regressions and preparing graphs and maps. Continuous variables were log transformed to optimize normality assumptions as guided by the Shapiro test. Linear regression was conducted in the classical manner by progressive manual model reduction by deletion of the least significant term. Model diagnostics were checked in each case in R. Geofacetted graphs were prepared using the geofacet package v0.1.9 and tanglegrams (interacting dendrograms) were prepared using dendextend v0.1.9 and cluster v2.0.7.1 and factoextra v1.0.5 amongst other packages. Bivariate choropleth maps were prepared using the colorplaner package v0.1.4 and ggplot2 v3.1.0. The R function predict in the stats package which comes with Base R was used for simple model forward projections. $p<0.05$ was considered significant.

Ethics

Ethical permission to undertake this study was granted from the Human Research Ethics Committees of the Southcity Medical Centre and the University of Western Australia.

RESULTS

Figure 1 presents choropleth maps of cannabis use, ASD and both cannabis and autism together across USA by state. Figure 1C is a bivariate choropleth map. Purple and pink shading indicate regions where both cannabis and autism are high such as California, Oregon and Vermont. Most of the bivariate map is green indicating that both signals are simultaneously low.

The time courses of both cannabis and autism (IDEA data) are presented for each US state in Supplementary Figures 1-4. Supplementary Figure 1 shows the time course of autism in 25 states with names from A to M plotted on an ordinate axis which is constant throughout. Supplementary Figure 2 shows a similar plot for the remaining 24 states with names from M to W. Supplementary Figure 3 shows the last month cannabis use rate for states over time for the alphabetically first 25 US states A to M. Supplementary Figure 4 shows similar cannabis use data for states M to W.

Figure 2 is a geofacetted plot showing the time course of autism rates and cannabis use, both of which have been scaled to make them comparable. The advantage of this format is that the data for each state appears separately and overplotting does not occur. Readers who may be interested in a particular American state can readily examine the pattern in their state and how this compares to that seen in nearby states. The figure clearly shows evidence of rising cannabis use rates and concurrently rising autism states in most states. This pattern is emphasized by the inclusion of regression lines for each plot.

Figure 3 shows the IDEA data categorized by legal status firstly by data from SAMHSA (A) and secondly using historical documentation of when each state transitioned into medical or legal use derived from an internet search (B). In each case the figures show clear separation of the autism rate in each legal category. This graphical demonstration suggests analysis by transformed autism rate over time.

Table 1 presents some of the regressions from Figure 3A, many of which achieve high levels of statistical significance. Figure 3A appears to be of quadratic form and one notes in Table 1 that the R-squared values are higher for regressions quadratic in time rising from about 0.78 to about 0.82. This superiority is confirmed at Anova testing (AIC-linear=321.89, AIC-Quadratic=272.30, dF=1, $F=185.63$, $p<2.0\times10^{-16}$).

Table 2 presents the results of the linear regressions from Figure 3B.

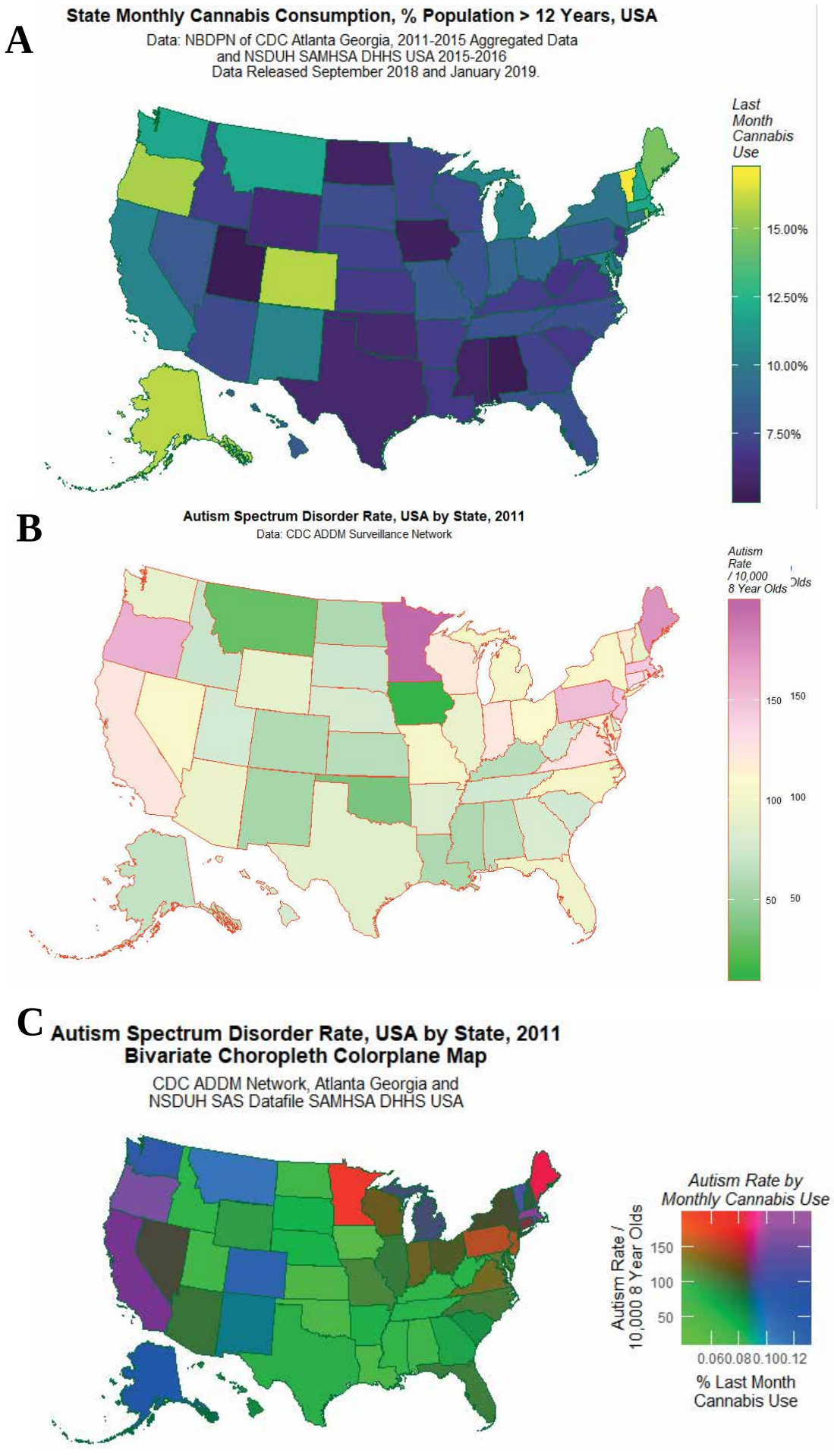

Figure 1: Maps of A: Cannabis Use, B: Autism, C: Cannabis use and autism together by USA state.

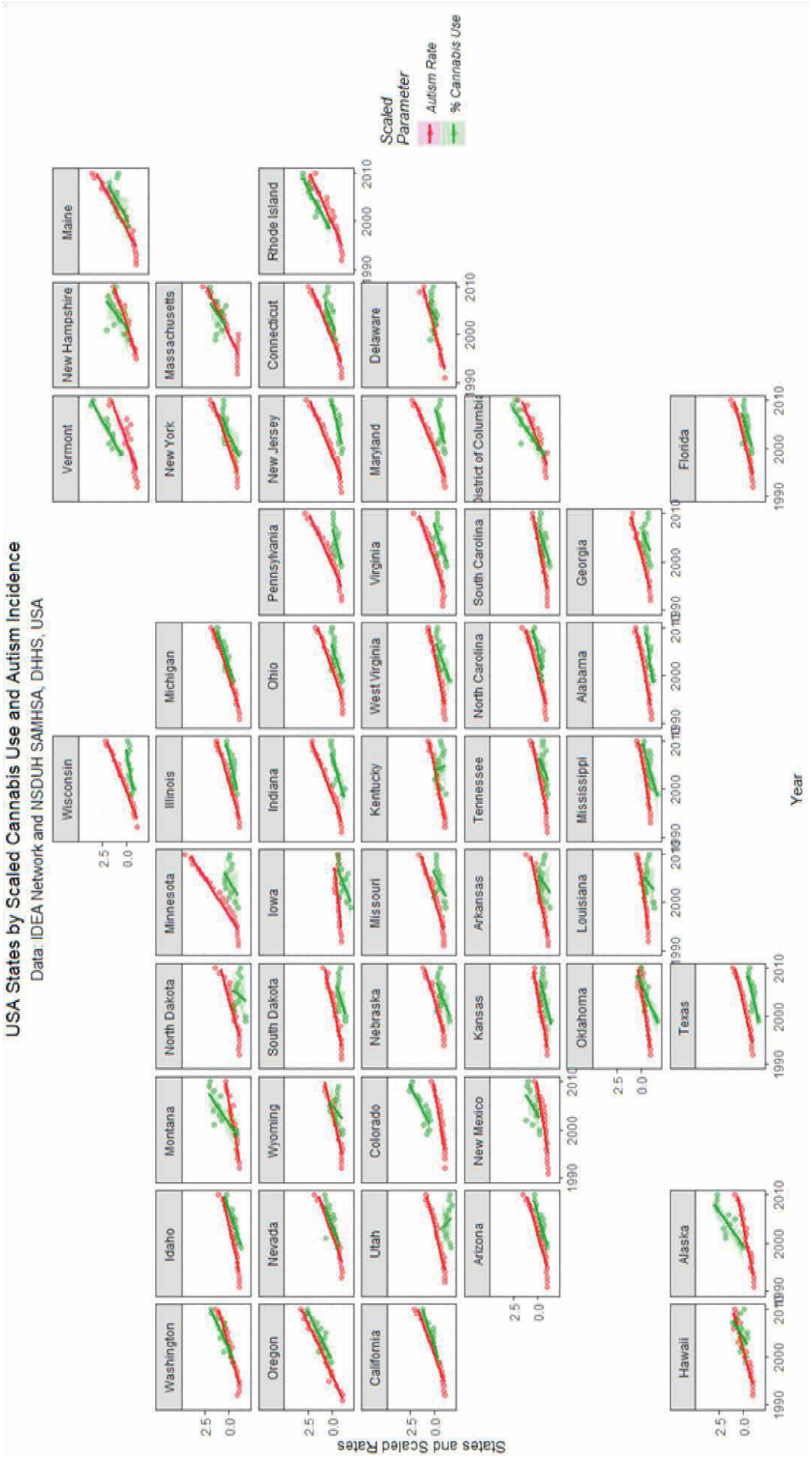

Figure 2: Geo-facetted charts of cannabis use and autism by US State.

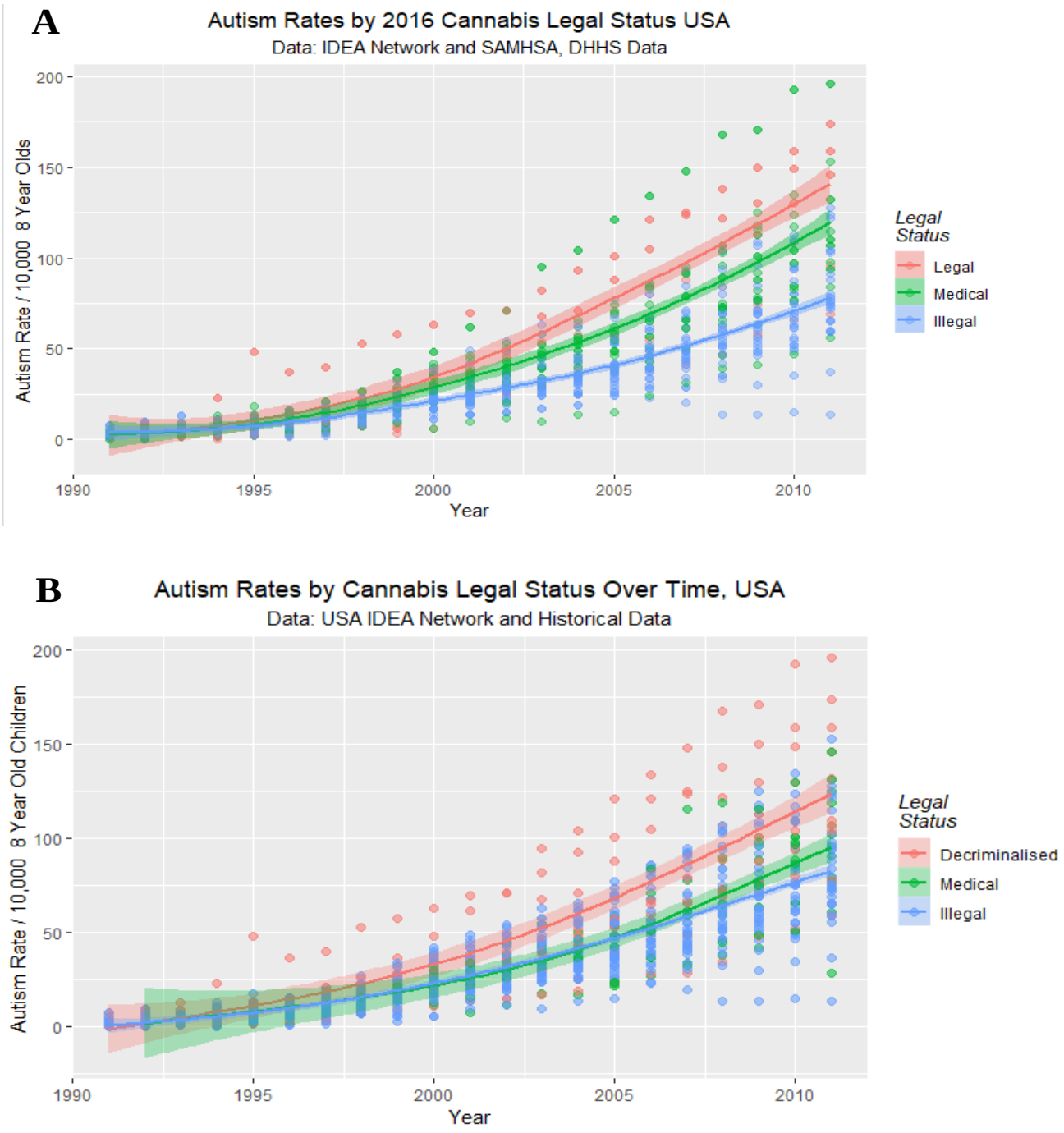

Figure 3: Graphs of Autism by US state by cannabis legal status using A: SAMHSA described legal status and B: historical legal status.

Again quadratic models are superior (ANOVA: AIC-linear=306.43, AIC-Quadratic=255.23, dF=3, F=51.19, $p<2.0x10^{-16}$).

Figure 4 shows some graphical dissections of the ADDM data on autism incidence. Figure 4A shows the ASD rate over time for the fifteen states in the CDC ADDM network with individual regression lines of best fit. Figure 4B shows similar data with a loess localized polynomial curve fitted to all the states as one whole dataset. Figure 4C presents the same data with a single least squares regression line for all the data. Figure 4D is a similar plot but this time with the states categorized into states where cannabis is illegal and states where cannabis is legal for medical or recreational use. Panel D illustrates a dichotomized stratification of legal status which is shown in Table 3 to be significant.

Since it has been shown that cannabis legalization is associated with more widespread cannabis use [14] it is of interest to consider the relationship between the slope of the cannabis use curves and the slopes of the autism rise. Figure 5 is a geofacetted plot which presents the very important data of the autism rate as a function of community uptake of cannabis by state. Several important features stand out from this graph. States charted in red and pink, particularly Maine, Minnesota, Oregon and Ohio seem either to have higher levels of autism or to be rising more steeply. Secondly in most cases the slopes of the regression lines showing the relation between the autism rate and cannabis use rate is positive irrespective of the legal status of cannabis. This is a very important finding indeed.

This finding is so important that it is again investigated in Figure 6 which compares the slopes of the regression lines by state for autism against time squared against each line's intercept on a single plot. This is a common plot used by statisticians to investigate models.

Table 1: Linear Regression of IDEA Database on 2018 Cannabis Status.

Parameter	Parameters				Model			
	Est.	Std. Error	t value	Pr (>|t|)	Adj. R Sq	F	df	P
IDEA								
Linear Models								
Log (Autism_Rate)~Status								
Status Medical	0.2031	0.0826	2.46	0.01	0.0047	3.418	21,020	0.03317
Status Legal	0.1785	0.1052	1.696	0.09				
Log (Autism_Rate)~Time+Status								
Year	0.1806	0.003	60.947	<2.0E-16	0.7855	1249	31,019	<2.0E-16
Status Medical	0.2001	0.0383	5.221	0.00				
Status Legal	0.1494	0.0489	3.059	0.00				
*Log (Autism_Rate)~Time * Status*								
Year	0.1661	0.0043	38.27	<2.0E-16	0.7896	768.1	51,017	<2.0E-16
Year: Status Legal	0.0334	0.0083	4.003	0.00				
Status Legal	-66.59	16.67	-3.994	0.00				
Year: Status Medical	0.0235	0.0065	3.632	0.00				
Status Medical	-46.88	12.96	-3.616	0.00				
Quadratic Models								
Log(Autism_Rate)~(Time)²+Status								
Time	36.7204	0.5433	67.585	<2.0E-16	0.8192	1159	41,018	<2.0E-16
(Time)²	-7.5797	0.5487	-13.815	<2.0E-16				
Status_Medical	0.1995	0.0352	5.67	9.80E-06				
Status_Legal	0.1433	0.0449	3.194	0.00				
*Log(Autism_Rate)~(Time)² * Status*								
Time	33.6271	0.7911	42.504	<2.0E-16	0.8242	600	81,014	<2.0E-16
(Time)²	-6.4559	0.8011	-8.058	2.2E-15				
Status_Medical	0.1855	0.0349	5.322	1.30E-07				
Status_Legal	0.1253	0.0446	2.809	0.0051				
Time: Status_Legal	5.0561	1.1815	4.28	2.1E-0.5				
(Time)²: Status_Medical	-2.5638	1.1928	-2.149	0.0319				
Time: Status_Legal	7.1735	1.5269	4.698	3.OE-0.6				

Table 2: Linear Regression of IDEA Database on Historical Cannabis Status.

Parameter	Parameters				Model			
	Est.	Std.Error	t value	Pr (>|t|)	Adj. R Sq	F	df	P
IDEA-Historical Data								
Linear Models								
Autism~Year								
Year	5.026	0.1136	44.257	<2.0E-16	0.644	1959	11,081	<2.0E-16
Autism~Year Status*								
Year	4.2146	0.1238	34.0467	<2.0E-16	0.7129	538.4	51,077	<2.0E-16
Status Medical	-4539.2	569.84	-7.9658	0.00				
Status Decriminalised	-4539.2	569.84	-7.9658	0.00				
Year: Status Medical	2.2761	0.2847	7.9947	0.00				
Year: Status Decriminalised	2.2761	0.2847	7.9947	0.00				
Log (Autism)~Year								
Year								
Log (Autism)~Year Status*								
Year	0.1821	0.003	60.2368	<2.0E-16	0.7766	1255	31,079	<2.0E-16
Year: Status Medical	0.0001	0	5.6809	0.00				
Year: Status Decriminalised	0.0001	0	5.6809	0.00				
Quadratic Models								

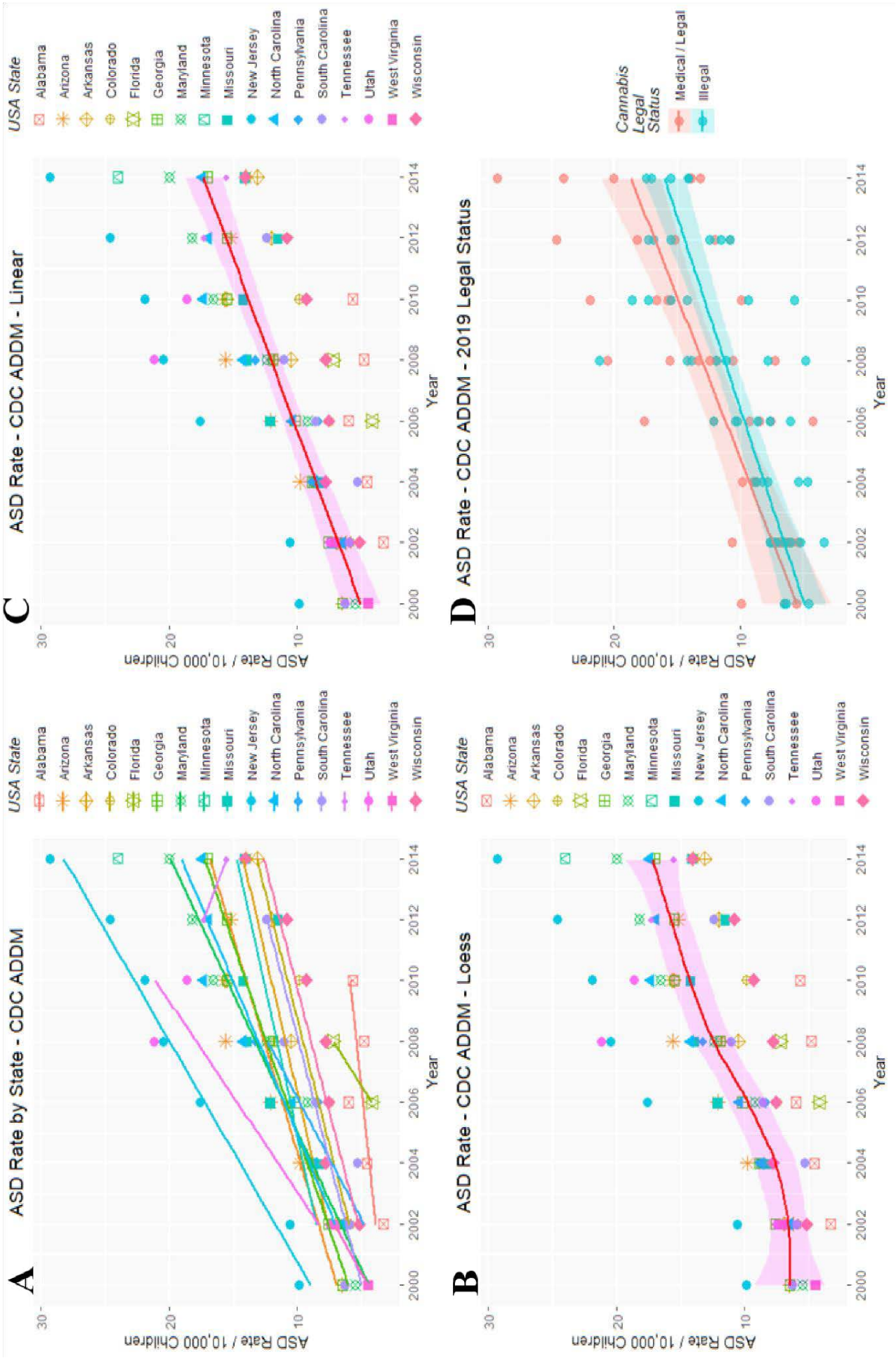

Figure 4: Graphs of Autism from the CDC ADDM network A: by US state, B: with a loess curve of best fit applied, C: with a straight line least squares regression line fitted, and D: categorized into dichotomous cannabis legal status groups.

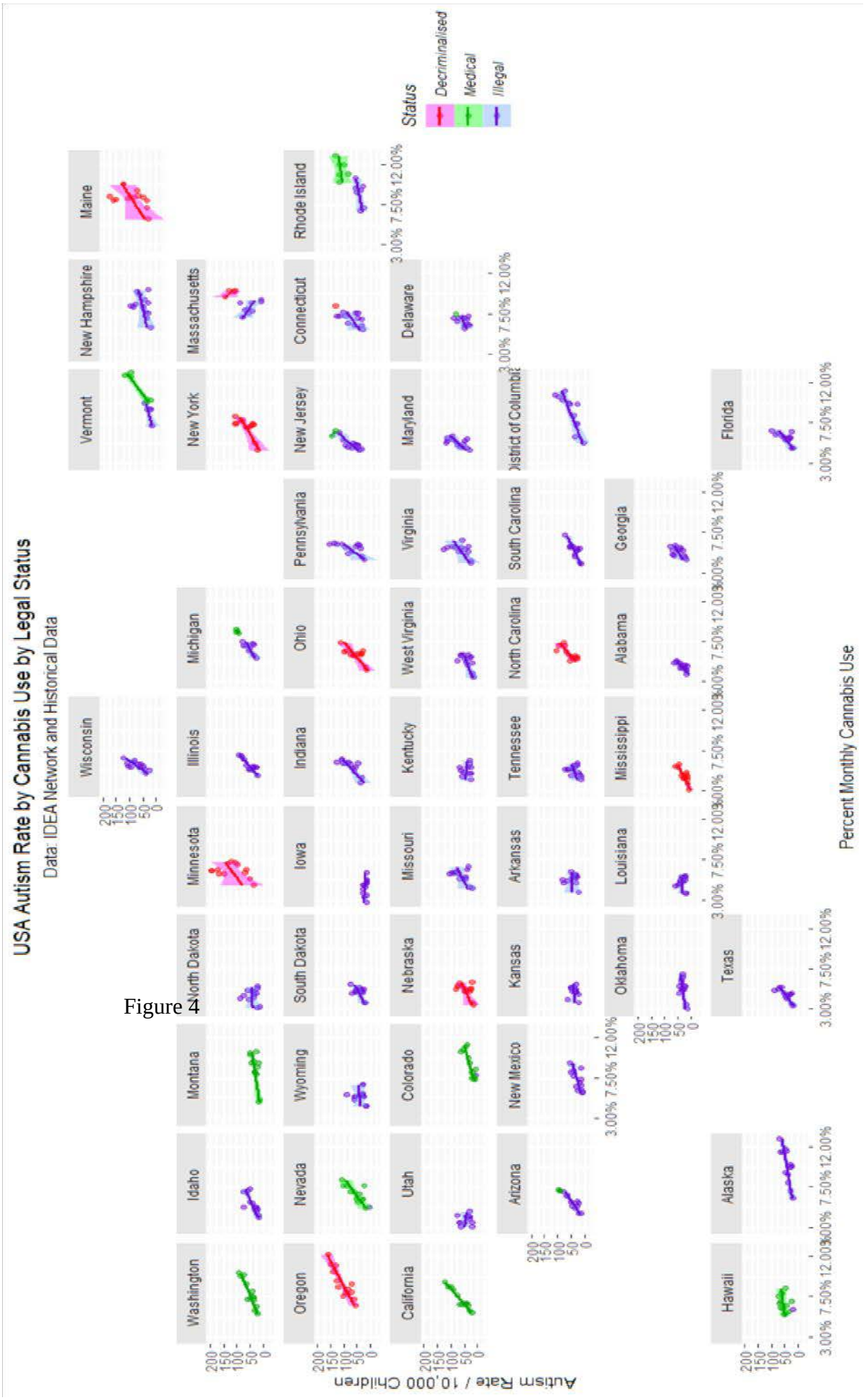

Figure 4

Figure 5: Geofacetted charts of autism rates as a function of cannabis consumption rates by US state.

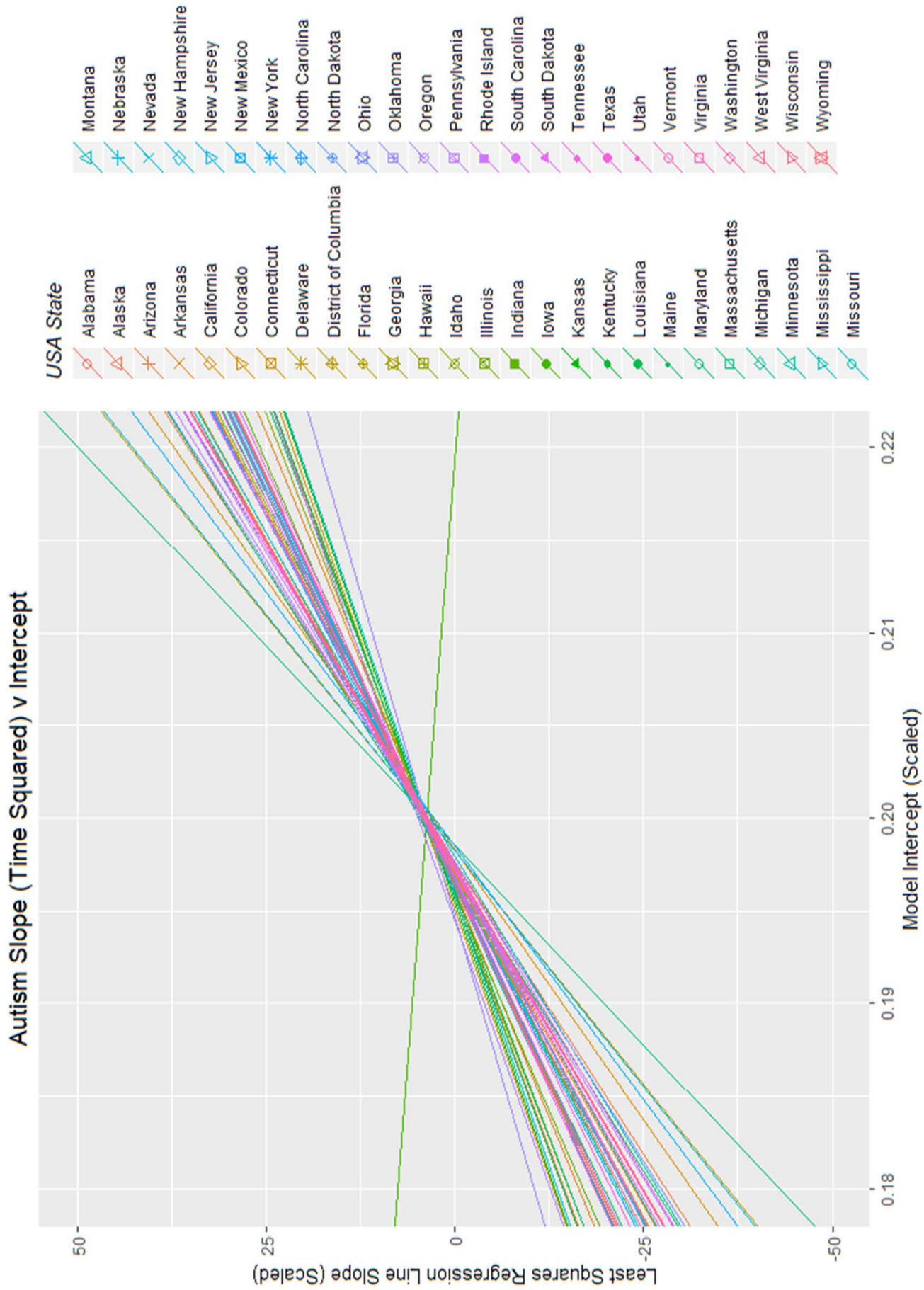

Figure 6: Graph comparing the slopes of the regression lines of autism against the square of time by US state. The regression line for Iowa stands out as a notable exception.

The negative slope in Iowa stands out prominently when the data is presented in this manner. The slope of the autism rate against time (squared) is noted to be positive in 48 of 49 states.

If cannabis use and autism were causally related it might be reasonable to suppose that the rates of rise of the slopes of the two regression lines might be roughly parallel. Figure 7 plots two interacting cluster dendrograms classifying the slope of the autism

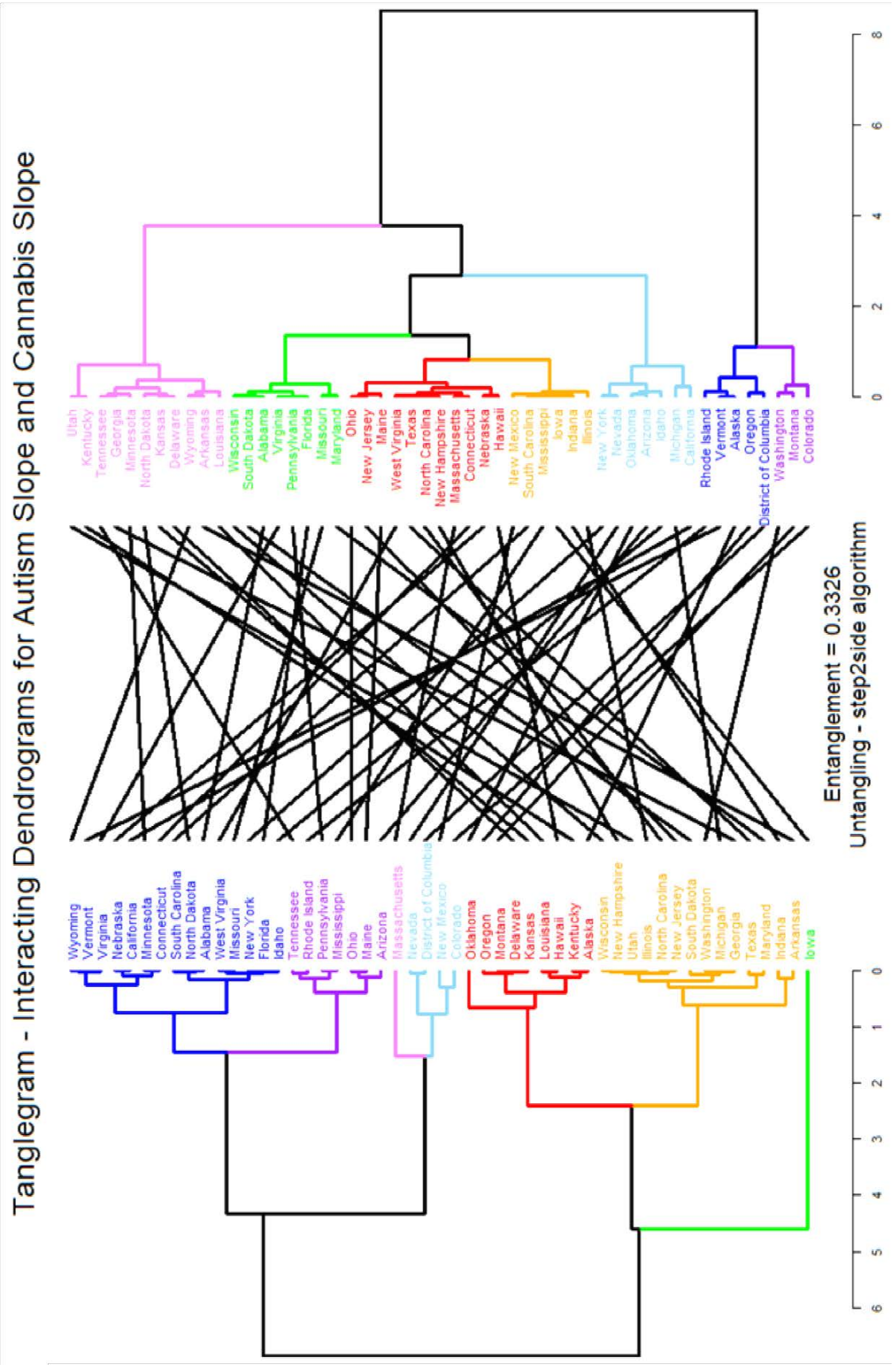

Figure 7: Tanglegram ./ Interacting Dendrograms showing the classification of slopes of the regression lines for autism (left dendrogram) with the regression line slopes for cannabis (right dendrogram). Compared using Wards algorithm to maximize agglomerative coefficient. After disentangling the tanglegram with the step2side algorithm the entanglement coefficient is 0.3326 indicating fair to moderate entanglement of the two parameters.

regression lines on the left and cannabis use regression slope on the right. The dendrograms have been drawn using Ward's algorithm to perform hierarchical clustering which achieved the highest agglomerative coefficient (AC=0.9727 v 0.9657 from the complete method with all the others lower). When an untangling algorithm (step 2 side) is applied to these two dendrograms the two are shown to be fairly-to-moderately entangled (entanglement coefficient=0.3326). This coefficient is a measure of the statistical relationship between the two dendrograms.

Figure 8 again presents the IDEA autism frequency data by time together with the various applicable quadratic equations for the curves of best fit for each legal condition. In each case the curve of best fit is shown for each legal category of cannabis use.

One notes that ascertainment of rates of autism can be very delayed after birth and it is not uncommon to wait until children are eight years of age before finalizing such a diagnosis. This introduces a protracted delay into case finding and tracking of the epidemic. Hence the IDEA dataset finishes in 2011, but we are already at 2019 at the time of writing.

Since the IDEA dataset is so rich it lends itself to simple forward projections. This has been done using the predict function from the stats package in R. Figure 9 shows that the previously quadratic curves now appear to be exponential, and this is confirmed on formal testing (equations presented on the figure for each legal category; R-squared for exponential models for decriminalization, medicalization and illegal status are 0.9671, 0.9719 and 0.9385

Table 3: Linear Regression of ADDM Database on Historical Cannabis Status.

Parameter	Parameters				Model			
	Est.	Std. Error	t value	Pr (>|t|)	Adj. R Sq	F	df	P
IDEA-Historical Data								
Linear Models								
Log (Autism_Rate) ~ Status								
Status_Medical/Legal	0.179	0.0995	1.7987	0.0756	0.0253	3.235	1,85	0.0756
Log (Autism_Rate) ~ Time+Status								
Year	0.079	0.0076	10.3666	<2.0E-16	0.5673	57.38	2,84	<2.0E-16
Status_Medical/Legal	0.1361	0.0664	2.0482	0.0437				
*Log (Autism_Rate) ~ Time*Status*								
Year	0.079	0.0076	10.3666	<2.0E-16	0.5673	57.38	2,84	<2.0E-16
Status_Medical/Legal	0.1361	0.0664	2.0482	0.0437				

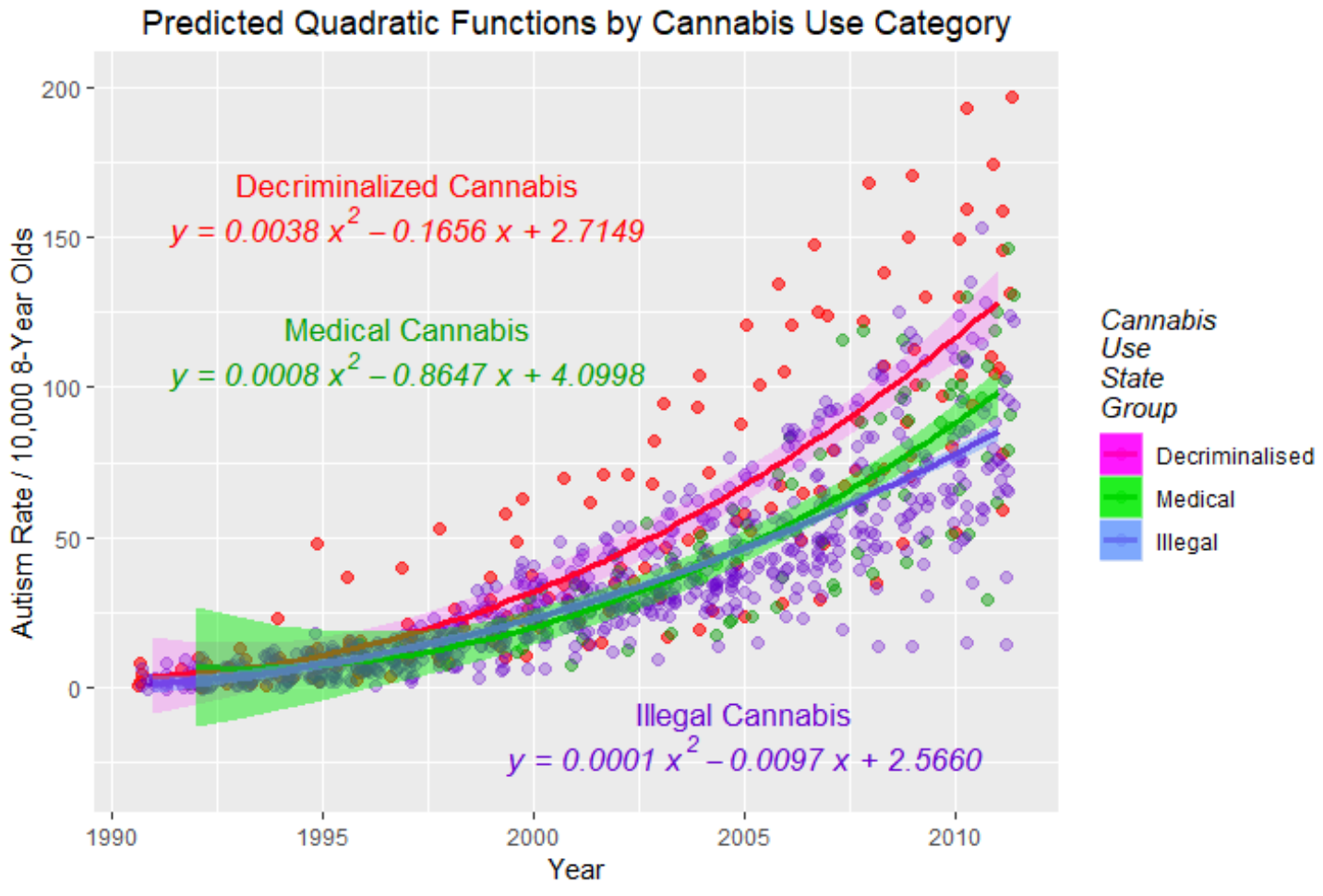

Figure 8: Graph of IDEA autism with historical legal status showing quadratic equations for the best fit regression lines.

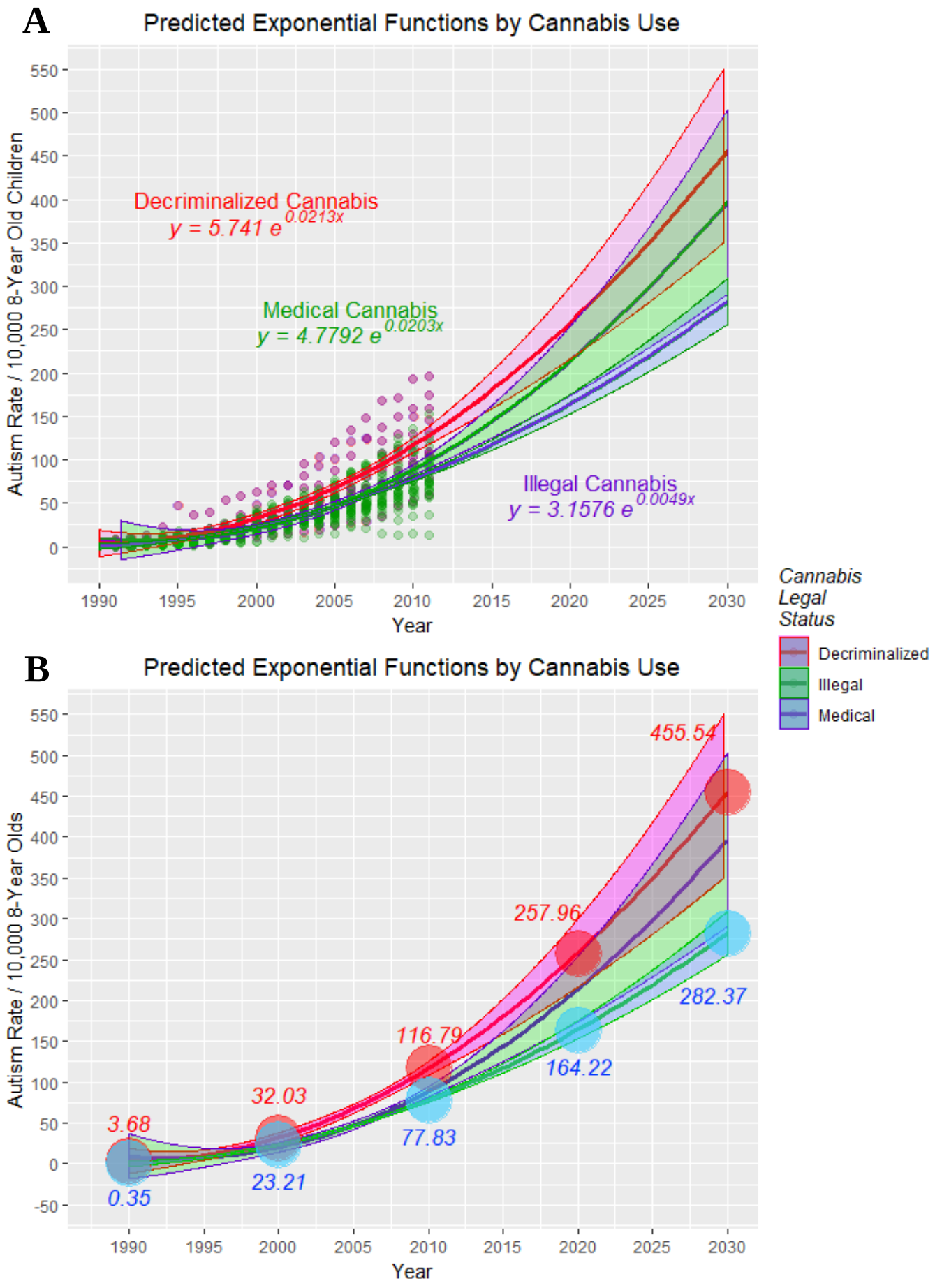

Figure 9: Projections of ASD to 2030 based on presently available IDEA data. A: Includes exponential equations of best fit, B: Placing numbers on the calculated curves at decadal points.

Table 4: Linear Regression of IDEA Database on Historical Cannabis Status.

Year	Decriminalised	Medical	Illegal
1990	3.68	9.4	0.35
1991	3.98	7.89	1.21
1992	4.84	6.96	2.38
1993	6.26	6.6	3.87
1994	8.25	6.81	5.68
1995	10.8	7.6	7.81
1996	13.92	8.97	10.25
1997	17.6	10.9	13.01
1998	21.85	13.41	16.09
1999	26.66	16.5	19.49
2000	32.03	20.16	23.21
2001	37.97	24.39	27.24
2002	44.47	29.2	31.59
2003	51.54	34.58	36.26
2004	59.17	40.53	41.24
2005	67.36	47.06	46.55
2006	76.12	54.17	52.17
2007	85.44	61.85	58.11
2008	95.33	70.1	64.36
2009	105.78	78.93	70.94
2010	116.79	88.33	77.83
2011	128.37	98.3	85.04
2012	140.51	108.85	92.56
2013	153.22	119.97	100.41
2014	166.49	131.67	108.57
2015	180.33	143.94	117.05
2016	194.72	156.79	125.85
2017	209.69	170.21	134.96
2018	225.21	184.2	144.4
2019	241.31	198.77	154.15
2020	257.96	213.91	164.22
2021	275.18	229.63	174.6
2022	292.96	245.92	185.31
2023	311.31	262.78	196.33
2024	330.22	280.22	207.67
2025	349.7	289.24	219.32
2026	369.74	316.82	231.3
2027	390.34	335.99	243.59
2028	411.51	355.72	256.2
2029	433.34	376.03	269.13
2030	455.54	396.91	282.37

whilst those for quadratic models are 0.8205, 0.7949 and 0.7990 respectively; ANOVA testing is not suitable as degrees of freedom are equal in all models). One notes the very high applicable R-squared (0.94 – 0.97) for each legal condition implying that the curves of best fit account for nearly all the variance in the trend model.

When these curves are projected outwards into the medium term the data shown in Figure 9B and Table 4 is obtained. Data in Table 4 is highlighted at each decadal point to make it easier to discern the longitudinal trends. One notes a report from the CDC [2] that the 2014 incidence of ASD in the ADDM network was 1.68%. This is a little above the estimates presented in Table 4 for all three legal conditions, suggesting that the estimates presented there are somewhat underestimates.

Figure 9A presents the applicable exponential equations for the predicted curves and the known data on its left hand side. Figure 9B highlights the growth in ASD rates for the two extreme groups decriminalization and illegal status. Indeed one notes that in 2030 the two rates are predicted to be 455.54/10,000 compared to 282.37/10,000 or 60.75% larger under the decriminalization regime.

It is noted again that these calculations somewhat underestimate the most recent CDC ADDM estimate of ASD incidence of 1.68% in 2014 [2]. This in turn implies that these modest projection calculations likely err on the conservative side. As mentioned although these modest projections extend out to 2030, one notes that we are already at 2019. The lag in data acquisition reflects the time needed to diagnose ASD which are often not finalized until 8 years of age. This also gives us pause since if it is accepted that many of the causes of ASD occur during gestational or prenatal life which then this implies that most of the input of genetic and environmental causes have already occurred at this point, since 2019 plus 8 years is 2027 which is almost 2030 already.

DISCUSSION

The USA appears to be undergoing a significant social transformation in recent years in relation to addiction in general and to cannabis use in particular. Indeed America's addiction epidemics have been at the heart of two recent Surgeons General's reports to the nation [16,17].

The present study confirms that increased rates of US state cannabis use related to increasingly liberal paradigms (medical cannabis, decriminalization and drug legalization) are associated with subsequent increased rates of ASD. Importantly, this correlation was consistently replicated using different indices of ASD are used (IDEA and ADDM) and when different metrics of cannabis legal status are employed (SAMHSA and historical survey data).

This study also demonstrates that most states show a positive relationship between the slope of the cannabis: time and the ASD: time curves on linear regression, geofacet and ggplot2 analysis; Iowa being a notable and prominent exception. Tanglegram analysis confirms that the two slopes are related in a fair to moderate way.

One notes that a few exceptions to the overall pattern do exist in some states. We feel that this may reflect the operation of other complex factors since it seems clear that many environmental and hereditary factors may well interfere with brain development.

The rich IDEA dataset also lends itself to medium term extrapolation. The historically quadratic ASD epidemics appear to be undergoing exponential transformation at present. The projection calculated is numerically somewhat below the latest CDC ADDM figure of 1.68% in 2014, but nevertheless shows that by 2030 the rate of ASD in cannabis decriminalized states is likely to be more than 60% higher than that in states where cannabis is not legal in any respect. The real nature of the cannabis effect is likely more significant than suggested by this analysis, as cannabis use is reported to be rising even in jurisdictions where it is presently illegal [10]. Notwithstanding the provisional nature

of any such projections, it is important to note that much of what will likely occur with autism incidence 2019-2027 has already been set in place given the long incubation time and time to diagnosis of autistic and developmental delays and their largely prenatal and perinatal aetiology.

We show here that at the state level there is a relationship between increased cannabis use and increasing rates of autism; that the slopes of the two epidemics are related; that the epidemic is presently undergoing a transformation from a quadratic growth phase to an exponential growth phase; and noted that this is consistent with numerous mechanistic studies indicating that cannabis is implicated in many key neurodevelopmental processes including myelination, proliferation and migration of foetal neuroblasts, axonal steering and path finding, synapse formation, exuberant outgrowth of the relatively massive human neocortex, fasciculation of white matter fibre tracts and oligodendrocyte physiology, neural stem cell niche maintenance, mitochondrial energetic and metabolic functions, dendritogenesis, microglial and immune maturation, synaptic pruning, and maintenance of the integrity of the genome, epigenome and epitranscriptome [18-44].

Moreover prenatal cannabis exposure has also been linked with many defects of cortical and executive functioning including reduced visual processing, attention span and concentration in all four longitudinal studies which examine this question [45-49]. One impressive longitudinal New Zealand study of 1,037 children followed from birth to age 38 years found progressive, serious and dose-related declines in IQ and a global decline in all measures of executive cortical functioning, which accrued with continued use and were obvious to external observers [45]. Cannabis has been shown to impair synapse formation [19,22] and induce dendritic pruning [21] which has been causally linked with the mechanisms of forgetting [50,51] and to adversely affect the slit/robo ratio [18,52,53] a key messenger-ligand pair controlling the extent of exuberant mammalian neocortical development [54,55]. All of these widespread neurocognitive cannabis-induced defects are consistent with its multifarous known mechanisms of action and its intimate involvement in virtually every step of brain and neural network formation.

Overall therefore our results, together with increasing reports from clinicians practising in high-cannabis areas of US [56,57] suggest that an increase in ASD is likely to be one of the more serious, and the commonest implications of increasing the availability of cannabis to the general population and particularly to both male and female adults of reproductive potential.

Reports from the National Births Defects Prevention Network of CDC have previously implicated cannabis use in causing anencephaly, gastroschisis, diaphragmatic hernia and oesophageal stenosis with or without tracheo-oesophageal fistula [58,59]. The American Academy of Pediatrics position statement on the aetiology of non-inherited heart disease previously noted that cannabis is associated with a doubling of the incidence of ventricular septal defect and Ebsteins anomaly [60]. And a large registry-controlled Hawaiian study in 2007 found that the incidence of 21 congenital defects was more common after cannabis exposure [61]. This novel study whose findings were much more serious than others, has since been validated by the latest American experience with atrial septal defect, the experience of many congenital anomalies in Colorado, and a recent experience of phocomelia in France [9].

However since ASD is more common than any of these other disorders it seems likely that it will become by far the most common issue with cannabis teratogenesis and cannabis neuroteratogenesis.

There is a lengthy delay period between birth and diagnosis of ASD. Indeed, given that we are now in 2019 in eight years' time the year will be 2027, so given that much of the aetiology of ASD is believed to occur in or around birth, it would seem that much of this medium term trajectory has already been determined.

It is of interest to consider the generalizability of present findings. Several considerations are pertinent. Firstly USA is a large nation so its experience carries significant epidemiological weight. By many metrics USA is the world's leading nation and exercises considerable financial and cultural prowess. The bulk of cannabis sales occurs over the internet and it is a matter of record that many providers in California, Colorado, Canada and elsewhere have large mail order businesses [62]. Mail order seizures from Colorado show that interstate trafficking ranks in the thousands of kilograms [62]. California is said to grow eight times more cannabis than is consumed intrastate. NSDUH data indicate that in 2017 161,000 pregnant women in USA consumed cannabis and for 69,000 this was reported to be daily or near daily use [10,13]. Of particular concern it was recently reported that 69% of cannabis dispensaries in Colorado recommended cannabis use to pregnant females [11]. Almost 25% of pregnant females in California recently tested positive or admitted to cannabis use [12]. All these factors point in the same direction and indicate that US trends are likely to have both direct and indirect effects to spread the experience of a cannabis-autism link both within and outside the United States.

The present study has various strengths and weaknesses. Its strengths relate to the use of two major datasets for autism diagnosis and the use of two systems for the categorization of cannabis legal status. Moreover the study is set in the US which arguably has the best data on these parameters. Also the IDEA dataset is of not inconsiderable size being over 1,000 data points. The shortcomings of the study relate to its epidemiological and ecological design. Individual participant level data was not available to this work. These issues would be corrected by the conduct of a prospective case-control design study where data relevant to these matters could be collected prospectively. Since self-report is a generally unreliable basis on which to conduct such investigations more objective measures are required. In this regard the work of the group of David employing hair analysis to assess neonatal toxicological exposure is relevant [63]. It should be noted that it is possible that the cannabis industry may have indirect effects on brain growth and development, as the widespread use of highly potent pesticides to protect cannabis cultivars from animal predation is reported [64]. For example a number of citations have been made of carbofuran use, a highly potent and exquisitely toxic pesticide which has been banned in USA and many nations [64-68].

CONCLUSION

A substantial literature establishes that brain formation occurs by a complex and intricately orchestrated choreographed "dance" of molecules, genes and epigenetic regulation with new neuroblasts and glial cells coming "on line" and being wired into the expanding neural circuit. The evidence of this study suggests but does not prove that these delicate and spatiotemporally precisely coordinated events are materially, seriously and permanently impaired by prenatal cannabis exposure in the parents.

Our study has shown that ASD is more common in states which host

more liberal legislative paradigms (decriminalization, legalization and medicalization) relating to cannabis use. This relationship is robust to consideration with different datasets and with different methods of legal status assignment. Extrapolation of current quadratic ASD trends shows exponentiation of the epidemic, with the rate of ASD in cannabis-legal states likely 60% greater than those in cannabis-illegal states by 2030 under conservative assumptions. These epidemiological level findings are consistent with basic sciences mechanisms which have demonstrated that cannabinoids are critically involved in numerous key aspects of brain and neurological development. Together with the increasingly common presentation of such cases to clinicians practising in localities which see significant numbers of cannabis exposed patients these findings suggest that the autism epidemic will continue to accelerate in the medium term and that the increasing availability of cannabis is likely to have common and unforeseen and potentially serious long-term neurodevelopmental complications. Further detailed mechanistic case-control investigations are required.

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CONFLICT OF INTEREST:

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CLINICAL TRIAL REGISTRATION:

Not applicable.

CONTRIBUTORS STATEMENT PAGE

Dr Reece designed the study, performed the statistical analysis and wrote the first draft.

Prof. Hulse reviewed the manuscript for important intellectual content and revised the draft. He also provided administrative, research support and assisted with statistical advice and oversight.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Cannabis Teratology Explains Current Patterns of Coloradan Congenital Defects: The Contribution of Increased Cannabinoid Exposure to Rising Teratological Trends

Albert Stuart Reece, MBBS (Hons), FRCS (Ed), FRCS (Glas), FRACGP, MD (UNSW)[1,2] and Gary Kenneth Hulse, BBSc (Hons), MBSc, PhD[1,2]

Abstract

Rising Δ9-tetrahydrocannabinol concentrations in modern cannabis invites investigation of the teratological implications of prenatal cannabis exposure. Data from Colorado Responds to Children with Special Needs (CRCSN), National Survey of Drug Use and Health, and Drug Enforcement Agency was analyzed. Seven, 40, and 2 defects were rising, flat, and falling, respectively, and 10/12 summary indices rose. Atrial septal defect, spina bifida, microcephalus, Down's syndrome, ventricular septal defect, and patent ductus arteriosus rose, and along with central nervous system, cardiovascular, genitourinary, respiratory, chromosomal, and musculoskeletal defects rose 5 to 37 times faster than the birth rate (3.3%) to generate an excess of 11 753 (22%) major anomalies. Cannabis was the only drug whose use grew from 2000 to 2014 while pain relievers, cocaine, alcohol, and tobacco did not. The correlation of cannabis use with major defects in 2014 (2019 dataset) was $R = .77$, $P = .0011$. Multiple cannabinoids were linked with summary measures of congenital anomalies and were robust to multivariate adjustment.

Keywords

delta9-tetrahydrocannabininol, cannabidiol, epigenetic genotoxicity, congenital teratogenicity, congenital cardiovascular malformations

Introduction

While the teratogenic activities of cannabis have been investigated since the 1960s,[1,2] substantially higher levels of Δ9-tetrahydrocannabinol of currently used cannabis[3] suggests that the neonatal epidemiology of former years requires reexamination.[4,5]

Urgency for epidemiological reassessment achieves particular currency in view of recent US data indicating that 24% of pregnant Californian teenagers test positive for cannabinoids,[6] that 69% of pregnant Coloradan mothers have cannabis recommended to them by cannabis dispensaries,[7] and that 161 000 pregnant women across the United States admitted to cannabis use during their pregnancy.[8]

In such a context, experience from flagship states such as Colorado, which has been a pioneer in US cannabis use and also supports a detailed and public database of congenital defects, is invaluable to ascertain current trends and likely future directions. Cannabis was permitted for medicinal use from November 2000 and was decreed legal in November 2011 with full effect from 2014.

Colorado also has one other considerable advantage that greatly simplifies the statistical analysis of its data, as during the period 2000 to 2014, nationally representative datasets indicate that the use of other drugs was static or falling. In this sense, therefore, the Coloradan context is ideal from a statistical and public health perspective to ascertain current teratological trends while statistically isolating the effect of rising cannabinoid exposure to facilitate the study of prenatal cannabis exposure (PCE).

[1]University of Western Australia, Crawley, Western Australia, Australia
[2]Edith Cowan University, Joondalup, Western Australia, Australia

Corresponding Author:
Albert Stuart Reece, 39 Gladstone Road, Highgate Hill, Brisbane, Queensland, Australia.
Email: stuart.reece@bigpond.com

This study explores the presence of any overall trends in the pattern of Coloradan congenital anomalies data and investigates the extent to which ecologically documented drug use trends explained some of this variance.

Methods

Data

Data on birth defects in Colorado were taken from the Colorado Responds to Children with Special Needs (CRCSN) online database as single data points in January 2019.[9] Total 2013 defect data were taken from the April 2018 CRCSN dataset. Data on drug use were taken from the National Survey of Drug Use and Health (NSDUH) conducted annually by the Substance Abuse and Mental Health Administration (SAMHSA).[8] Data on cannabinoid concentration were taken from the National Drug Enforcement Agency seizures[10,11] and multiplied by annual cannabis use to derive state-wide cannabinoid exposure.

Relationship to Cannabis

Defects were classified as cannabis-related if strong published evidence had previously identified a relationship to cannabis exposure. Papers from Centers for Disease Control and Prevention (CDC) and National Birth Defects Prevention Network (NBDPN) have established that anencephaly,[12,13] diaphragmatic hernia, esophageal atresia with or without tracheoesophageal fistula, and gastroschisis are cannabis-related.[12] A joint statement by the American Academy of Pediatrics and the American Heart Association linked Ebstein's anomaly and ventricular septal defect (VSD) with cannabis use.[14] A large 2007 epidemiological study from Hawaii also linked encephalocele, hypoplastic left heart, syndactyly, reduction deformity of the upper limbs, hydrocephaly, cleft lip and cleft palate both separately and together, anotia/microtia, tetralogy of Fallot, pyloric stenosis, microcephaly, pulmonary valve atresia and/or stenosis, large bowel or rectal atresias or stenosis, obstructive genitourinary defect, polydactyly, atrial septal defect (ASD), and trisomy 21 with PCE.[15] Although this study is an outlier in terms of the literature, this list of defects was accepted as being cannabis-related in view of its high predictive value and pointed real-world applicability particularly in the United States (see Results and Discussion sections).

Statistics

Data were processed in "R" v3.5.2 and "R Studio" v1.1.463 from the Central "R" Archive Network. Model reduction was conducted by the classical method with progressive removal of the least significant term. Models were compared by analysis of variance (ANOVA). Model parameters were compared with the "purrr" and "broom" packages. Regression line slope change was assessed with the "segmented" package. Differing quantitative scales were adjusted using the "scales" package. The "nlme" package was used for mixed-effects regression. Principal components analysis was conducted using the "psych" package. $P < .05$ was considered significant.

Ethics

The study was approved by the Human Research Ethics Committees of South City Medical Centre and the University of Western Australia.

Results

The January 2019 CRCSN dataset consists of annual numbers and rates on 49 defects for each of the years 2000 through 2014 and comprises 746 data points together with 180 data points relating to 13 summary indices by major organ system. These defects are graphed by time in Figures 1 and 2.

Table 1 lists the slope and confidence intervals of these time-dependent changes. Seven defects are noted to be significantly rising and 2 significantly falling. Table 2 repeats this exercise for the major defect summary groups. Nine of 11 slopes are noted to be rising. Supplementary Figures 1 and 2 (available online) present loess curves for these data.

Since the data are rather difficult to mentally digest en masse, Figures 3 to 8 present data grouped by organ system. Figure 9 illustrates the summary data by organ system.

Figure 10 shows the numbers of defects as a total number and as a percentage of live born babies. The total figure in the April 2018 CRCSN dataset is noted to be substantially higher than that in the January 2019 CRCSN dataset. Figure 11 shows the relative rise from baseline of the various categories with the origin of each dataset forming the baseline comparator for that group.

Supplementary Table 1 (available online) shows the summaries of regression models for these major defects and defect classes. Table 3 lists the number of cases in each group by year, sums the total, compares it with the calculated total based on 15 times (2000:2014) the lowest rate in either 2000 or 2001, calculates the absolute and relative case excess, and compares it with the rise in births from 2000 to 2014 of 3.3069%. These relative case excesses are then graphed in order in Figure 12.

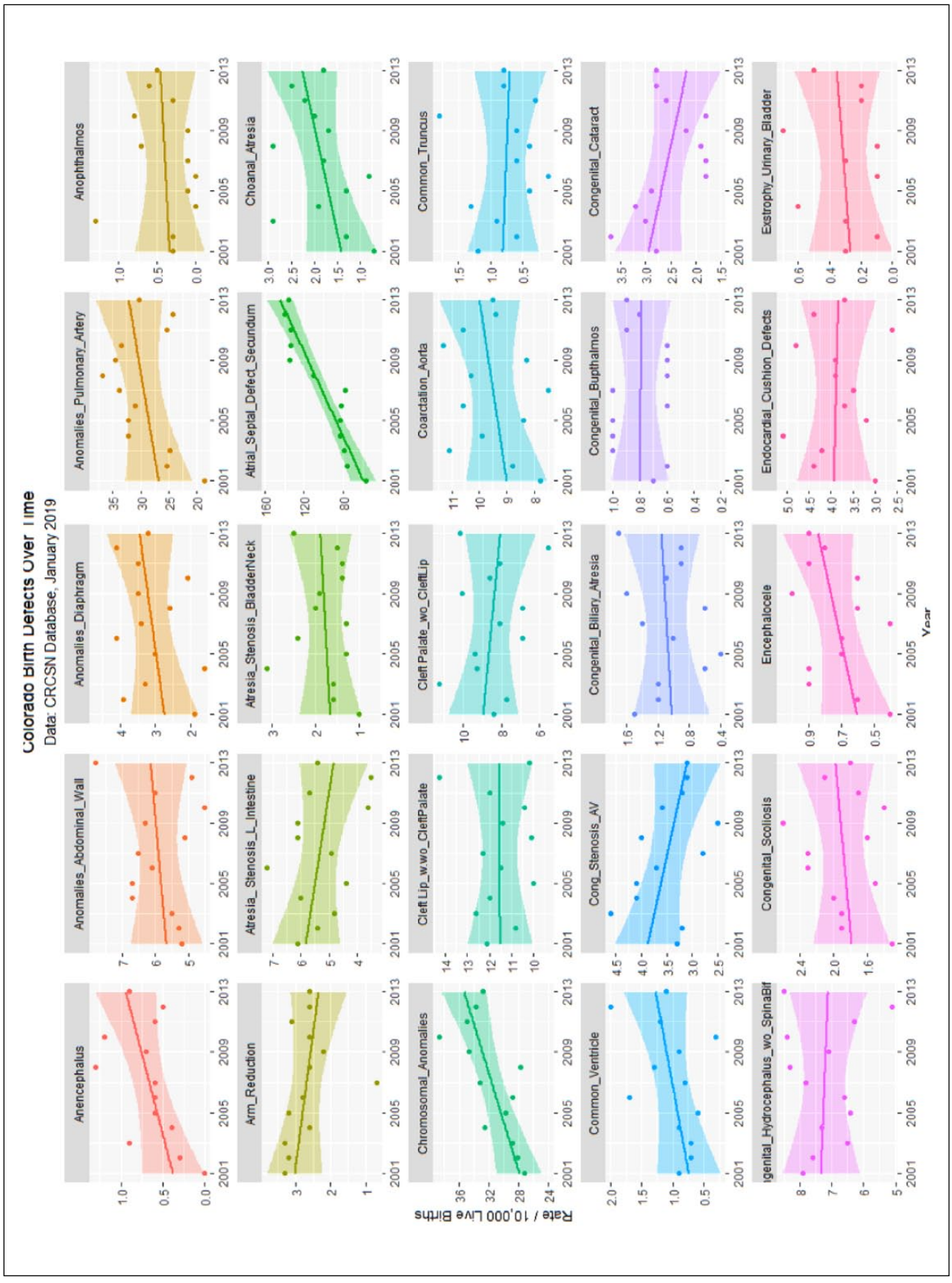

Figure 1. Colorado congenital defects A-E by time, regression lines fitted.

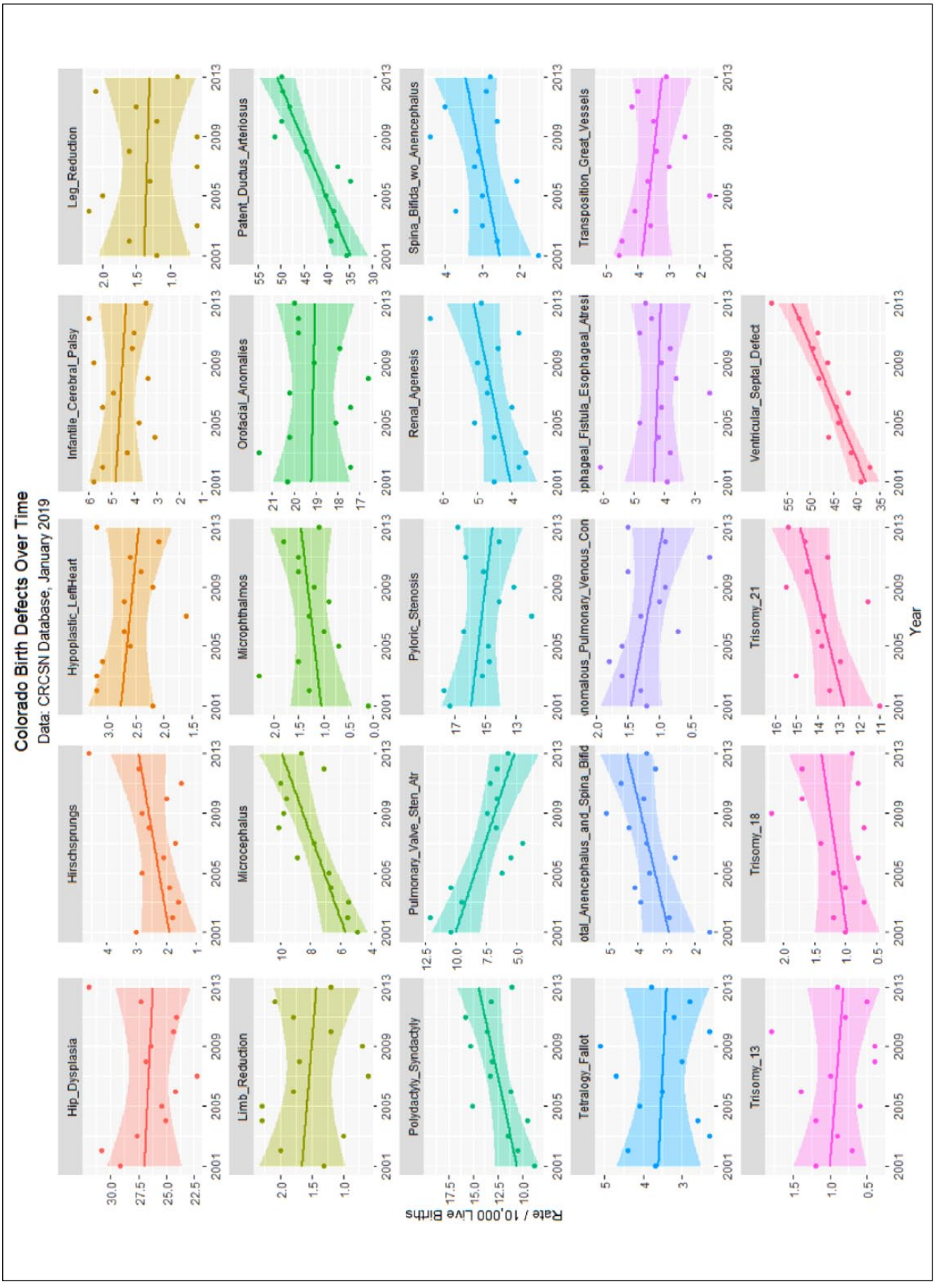

Figure 2. Colorado congenital defects H-V by time, regression lines fitted.

Table 1. Time-Dependent Trends of CRCSN Defects.

Defect	Term	β-Estimate	Standard Error	*t*	*P*	Lower CI	Upper CI
Atrial septal defect secundum	Year	6.4518	0.7943	8.1229	.0000	4.7359	8.1677
Ventricular septal defect	Year	1.1825	0.1623	7.2866	.0000	0.8319	1.5331
Patent ductus arteriosus	Year	0.9925	0.2382	4.1660	.0011	0.4778	1.5072
Chromosomal anomalies	Year	0.6543	0.1545	4.2357	.0010	0.3206	0.9880
Anomalies pulmonary artery	Year	0.4621	0.3210	1.4396	.1736	−0.2314	1.1556
Microcephalus	Year	0.3046	0.0812	3.7519	.0024	0.1292	0.4801
Trisomy 21	Year	0.1850	0.0673	2.7480	.0166	0.0396	0.3304
Renal agenesis	Year	0.0961	0.0394	2.4378	.0299	0.0109	0.1812
Total anencephalus and spina bifida	Year	0.0843	0.0467	1.8052	.0942	−0.0166	0.1852
Hirschsprung's	Year	0.0754	0.0457	1.6485	.1232	−0.0234	0.1741
Spina bifida without anencephalus	Year	0.0693	0.0405	1.7094	.1111	−0.0183	0.1568
Anomalies abdominal wall	Year	0.0507	0.0528	0.9610	.3541	−0.0633	0.1647
Choanal atresia	Year	0.0489	0.0405	1.2086	.2483	−0.0385	0.1364
Microphthalmos	Year	0.0296	0.0305	0.9723	.3486	−0.0362	0.0955
Endocardial cushion defects	Year	0.0221	0.0434	0.5106	.6182	−0.0716	0.1158
Anencephalus	Year	0.0154	0.0224	0.6847	.5056	−0.0331	0.0638
Trisomy 18	Year	0.0150	0.0267	0.5619	.5838	−0.0427	0.0727
Anophthalmos	Year	0.0139	0.0218	0.6402	.5332	−0.0331	0.0609
Encephalocele	Year	0.0129	0.0110	1.1654	.2648	−0.0110	0.0367
Transposition great vessels	Year	0.0107	0.0540	0.1983	.8458	−0.1060	0.1274
Congenital biliary atresia	Year	0.0096	0.0273	0.3538	.7291	−0.0492	0.0685
Exstrophy urinary bladder	Year	0.0072	0.0166	0.4304	.6770	−0.0305	0.0448
Common ventricle	Year	0.0064	0.0284	0.2266	.8242	−0.0548	0.0677
Coarctation aorta	Year	0.0032	0.0768	0.0418	.9673	−0.1628	0.1692
Congenital scoliosis	Year	0.0029	0.0234	0.1222	.9046	−0.0477	0.0534
Polydactyly syndactyly	Year	−0.0014	0.1724	−0.0083	.9935	−0.3738	0.3710
Leg reduction	Year	−0.0018	0.0324	−0.0551	.9569	−0.0717	0.0682
Congenital buphthalmos	Year	−0.0032	0.0157	−0.2043	.8413	−0.0372	0.0308
Common truncus	Year	−0.0032	0.0267	−0.1205	.9059	−0.0608	0.0544
Orofacial anomalies	Year	−0.0046	0.0921	−0.0504	.9606	−0.2036	0.1943
Hypoplastic left heart	Year	−0.0096	0.0367	−0.2631	.7966	−0.0888	0.0695
Cleft Lip with/without cleft palate	Year	−0.0114	0.0828	−0.1381	.8923	−0.1903	0.1674
Limb reduction	Year	−0.0125	0.0330	−0.3785	.7112	−0.0838	0.0588
Trisomy 13	Year	−0.0125	0.0235	−0.5311	.6043	−0.0633	0.0383
Tracheoesophageal fistula esophageal atresia stenosis	Year	−0.0146	0.0475	−0.3086	.7625	−0.1172	0.0879
Anomalies diaphragm	Year	−0.0146	0.0543	−0.2697	.7917	−0.1320	0.1027
Total anomalous pulmonary venous connection	Year	−0.0204	0.0262	−0.7768	.4512	−0.0770	0.0363
Cleft palate without cleft lip	Year	−0.0214	0.0916	−0.2340	.8186	−0.2193	0.1764
Atresia stenosis bladder neck	Year	−0.0304	0.0391	−0.7759	.4517	−0.1149	0.0542
Congenital hydrocephalus without spina bifida	Year	−0.0318	0.0584	−0.5443	.5954	−0.1579	0.0944
Tetralogy Fallot	Year	−0.0389	0.0524	−0.7425	.4710	−0.1522	0.0743
Arm reduction	Year	−0.0414	0.0381	−1.0881	.2963	−0.1237	0.0408
Cong stenosis aortic valve	Year	−0.0568	0.0337	−1.6866	.1155	−0.1295	0.0160
Hip dysplasia	Year	−0.0639	0.1674	−0.3819	.7087	−0.4256	0.2977
Congenital cataract	Year	−0.0689	0.0346	−1.9903	.0680	−0.1437	0.0059
Atresia stenosis large intestine	Year	−0.0936	0.0641	−1.4594	.1682	−0.2321	0.0449
Infantile cerebral palsy	Year	−0.1325	0.0730	−1.8158	.0925	−0.2901	0.0251
Pyloric stenosis	Year	−0.2529	0.1057	−2.3912	.0326	−0.4813	−0.0244
Pulmonary valve stenosis atresia	Year	−0.3271	0.1009	−3.2417	.0064	−0.5452	−0.1091

Abbreviations: CRCSN, Colorado Responds to Children with Special Needs; CI, confidence interval.

Table 2. Time-Dependent Trends of CRCSN Major Defect Classes.

Defect	Term	β-Estimate	Standard Error	*t*	*P*	Lower CI	Upper CI
Major Defects Number 2013	Year	228.4791	17.7906	12.8427	.000000	189.7167	267.2415
Major Defects Number 2014	Year	92.9179	11.5577	8.0395	.000002	67.9489	117.8868
Major Defects Rate 2014	Year	15.6757	2.2823	6.8684	.000011	10.7451	20.6063
Major Genitourinary Defects	Year	6.1111	0.6297	9.7052	.000000	4.7508	7.4714
Major Cardiovascular Defects	Year	6.0657	0.8369	7.2476	.000006	4.2576	7.8738
Major Musculoskeletal Anomalies	Year	3.6582	0.5886	6.2149	.000031	2.3866	4.9298
Major Musculoskeletal Defects	Year	3.6329	0.5912	6.1449	.000035	2.3556	4.9101
Respiratory Anomalies	Year	1.9304	0.2758	6.9991	.000009	1.3345	2.5262
Chromosomal Anomalies	Year	0.6543	0.1545	4.2360	.000973	0.3210	0.9880
Major Gastrointestinal Defects	Year	0.2061	0.3224	0.6393	.533760	−0.4903	0.9025
Major Eyes Defects	Year	0.0289	0.0807	0.3585	.725688	−0.1454	0.2032

Abbreviations: CRCSN, Colorado Responds to Children with Special Needs; CI, confidence interval.

En passant one notes that the rate of rise of the 2 common cardiac defects ASD (secundum type) and patent ductus arteriosus (PDA) appears to rise sigmoidally across this time period of the cannabis legalization process (Figure 13). One notes that the quartic model accounts for the time-dependent variance significantly better than the linear model for both ASD (ANOVA $F = 6.6319$, degrees of freedom [df] = 3, $P = .0096$) and PDA (ANOVA $F = 5.413$, df = 3, $P = .018$).

Since both the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists concur that drug use in the peripartum period is harmful to the fetus,[16,17] it is reasonable to consider the potential role of drug use by the parents in a possible epidemiological association with this overall increasing defect profile.

Drug use in Colorado is presented from the SAMHSA NSDUH data as least squares regression lines in Figure 14, and the slopes of these lines are summarized in Table 4. Only the slopes of the cannabis curves are seen to be rising; the slopes of the tobacco, cigarette, cocaine, and pain reliever curves are falling significantly.

Figure 15 presents these drug use data with loess curves. Formal testing for change of regression slope for monthly cannabis use showed a significant change in 2007 from .0293 to .11917 (Davies test, $k = 3$, $P = .0002$).

Monthly cannabinoid exposure was calculated by multiplying the concentration of Federal cannabis seizures by within-state monthly cannabis use. These data are presented as regression lines and loess curves in Figures 16 and 17.

Because many of the 49 defects had different quantitative rates, they were scaled to mean of 0 and standard deviation of 1 using the "scales" package. The time-dependent plots shown in Figure 18 were obtained.

A similar exercise was conducted, illustrated in Figure 19, which charts the scaled defect rate as a linear temporal function of the various drug exposures. Increasing levels of binge alcohol, cocaine, cannabis, and pain relievers are all noted to be linked to higher rates of congenital defects. These relationships are demonstrated in Table 5. One notes that the quartic model for cannabis has a higher *F* value and lower model *P* value than that for opioid pain relievers (7.83 vs 4.422 and 3.5×10^{-7} vs 3.4×10^{-5}).

Table 6 compares the defect rates against multiple drug exposure in additive models and increasingly complex interactive mixed-effects models with defect as the random variable. Terms including cannabis exposure persisted in final models.

As described in Methods, defects were assigned to be either cannabis-related or not based on reports in the published literature. However, as the Hawaiian report of pyloric stenosis being cannabis-linked[15] has not been confirmed elsewhere, this condition was removed from the cannabis-associated group. Moreover, 2 reports from CDC/NBDPN indicate that PCE is linked with anencephaly.[12,13] Several drugs linked with anencephaly are similarly linked with spina bifida, which is accepted to be a prototypical neural tube closure defect so that it seems likely that cannabis may also be linked with spina bifida with or without anencephaly. Graphs showing the effect of these 2 adjustments are included as Supplementary Figures 3 to 6 (available online).

Figure 20 shows the time relationship of the 49 scaled defects by the above-described relationship to cannabis. These data are shown on single plots with both loess curves and linear regression lines in Figure 21.

A model quartic-in-time was superior to a linear-only model (ANOVA $F = 4.6099$, df = 5, $P = .0004$).

Table 7 shows that the results of both linear and quartic models are significant with cannabis terms remaining

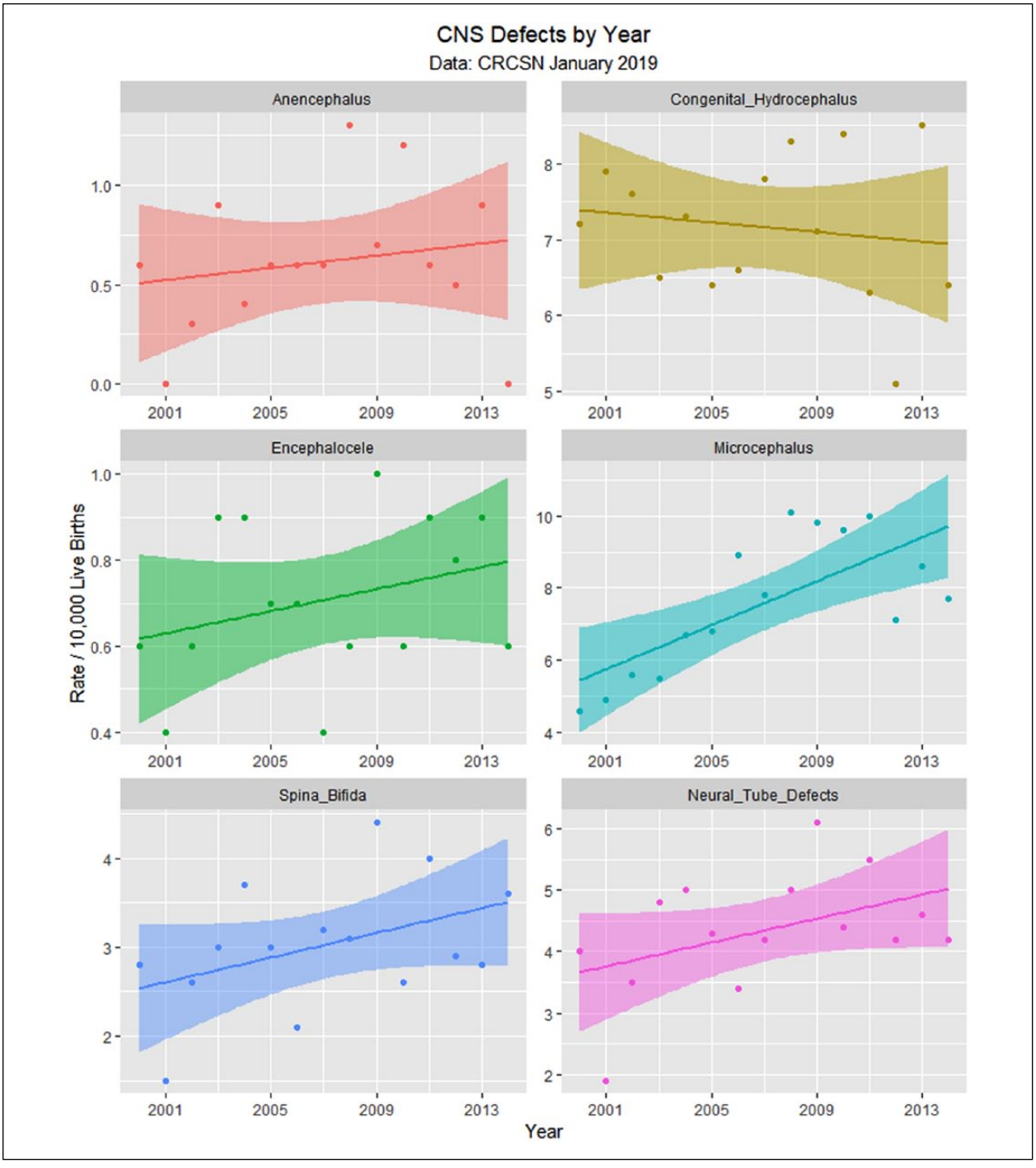

Figure 3. Central nervous system (CNS) defects by time.

in final models both as a factor and in interaction with time and time-squared.

Figure 22 shows the time relationship of exposure to various cannabinoids with regression lines, and loess curves are shown in Supplementary Figure 7 (available online).

Figure 23 shows the defects charted against cannabinoid exposure. These relationships are formalized in Table 8.

Figure 24 illustrates the complex relationship between monthly cannabis use, falling cannabidiol concentration, and the population exposure to cannabidiol.

Figure 25 is a point and box plot graph of the movement of cannabis-related versus nonrelated defects for each year to address the complex relationship of cannabidiol exposure.

Figure 4. Neural tube defects by time.

Figure 26A shows these 2 rates side by side from 2000 to 2014. The difference between the 2 groups is plotted in Figure 26B, and their adjusted ratio (adjusted by adding unity [1] to numerator and denominator) appears in Figure 26C. Figure 26D shows the ratio of the absolute values of the cannabis-related and non–cannabis-related values, which correlates broadly with cannabidiol exposure (Figure 24C, $R = 0.4857$, $P = .0783$). These measures clearly peaked in 2009-2010 when cannabidiol exposure also peaked.

Figure 9 and Table 2 showed that defects in 5 major organ systems are rising: central nervous system, cardiovascular, genitourinary, musculoskeletal, and respiratory systems. These 5 may then be combined by principal component analysis. A scree plot (Supplementary Figure 8, available online) shows that 1 principal component—PC1—was sufficient to combine these data and accounted for 90% of the variance. Together with total rates from the CRCSN dataset, this produces 3 summary statistics, the totals for 2013, 2014, and PC1.

Figure 27 charts these parameters against each other along with the monthly cannabis exposure. A close visual relationship is immediately apparent. These correlations are presented formally in Table 9.

Table 10 summarizes the regression of all scaled defects against various drug combinations.

Table 11 is a regression summary for all scaled defects against various cannabinoids.

Table 12 presents final regression models of various key summary parameters against the indicated combinations of drugs and cannabinoids in linear and/or time-quartic models.

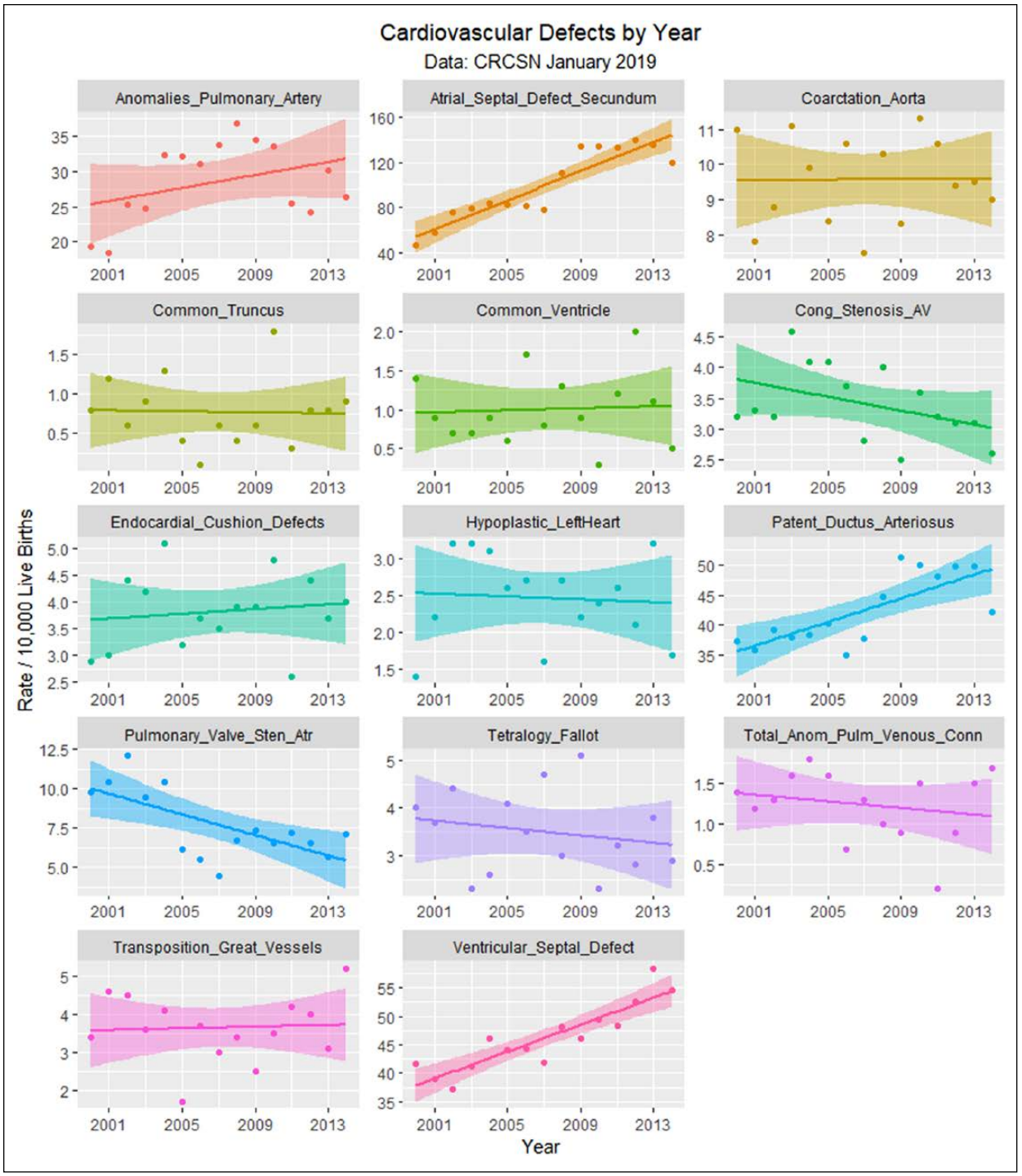

Figure 5. Cardiovascular defects by time.

Discussion

This study portrays a detailed picture of congenital defects in the state of Colorado based on the latest intrastate defect registry data from CRCSN and provides compelling evidence that the generally rising pattern both of individual defects and of systems levels summary and total measures closely parallels the rise in cannabis use in Colorado in the context of static or falling levels of other drug use.

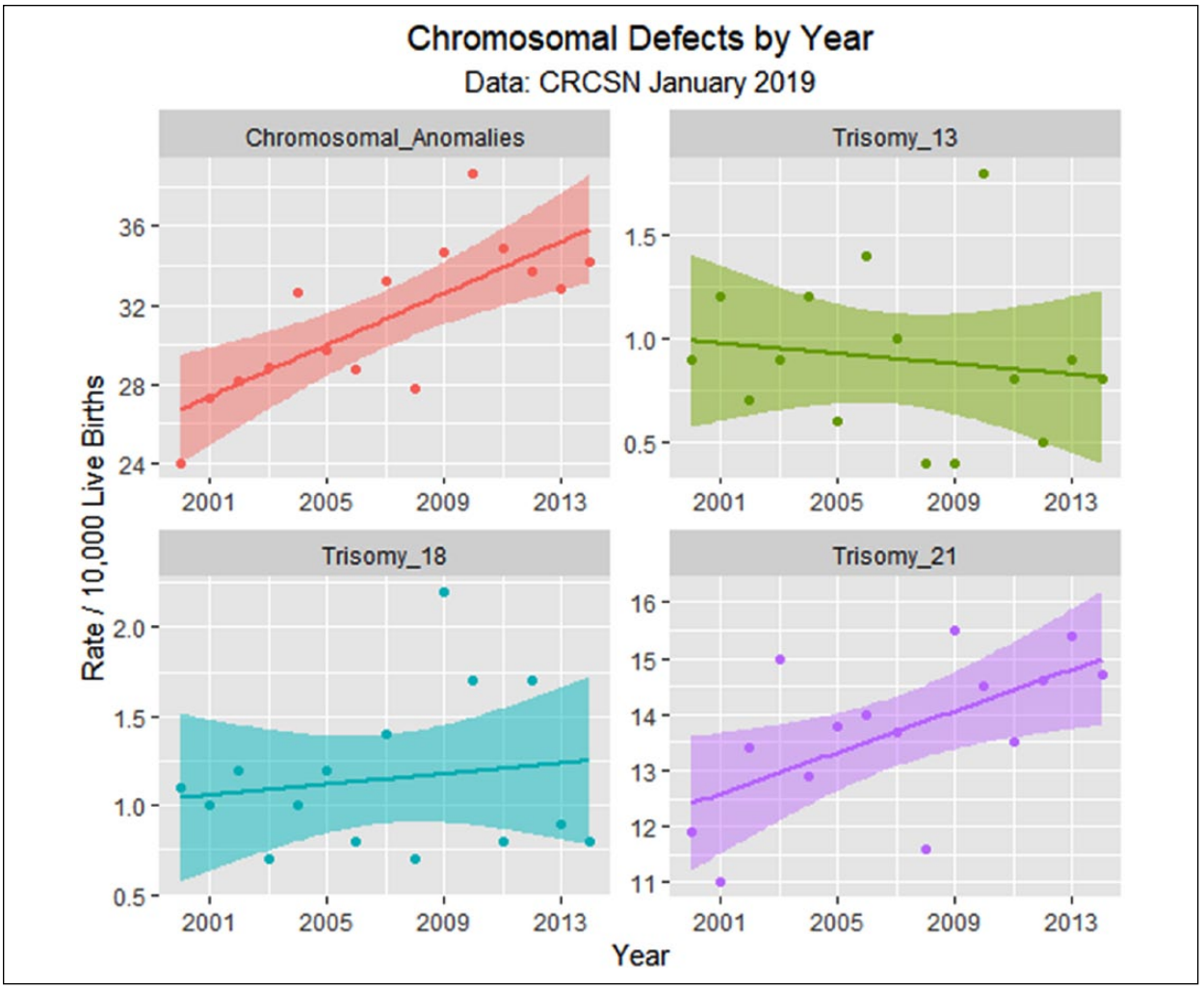

Figure 6. Chromosomal defects by time.

While there is substantial heterogeneity in the trend of birth defects in Colorado, the overall trend of the CRCSN dataset is upward, a trend that closely parallels cannabis use during the progression of that state toward cannabis legalization. This is reflected in some of the most common birth defects such as ASD, PDA, VSD, and Down's syndrome and also in summary measures such as central nervous, cardiovascular, respiratory, chromosomal, and genitourinary defects, the overall total defects in both 2013 and 2014 and on principal component analysis. Indeed, ASD and PDA showed an uptick temporally associated with rising cannabis use. Cannabis use showed a statistically significant rise about 2007 related to the movement toward cannabis legalization. Moreover, the relationship to cannabis use was robust to multivariate adjustment with all other drug use. Data implicated several cannabinoids including Δ9-tetrahydrocannabinol, Δ8-tetrahydrocannabinol, tetrahydrocannabivarin, cannabinol, and cannabidiol. Although the relationship with cannabidiol is temporally complex, data show that the relative elevation of cannabis-related defects compared with non–cannabis-related defects peaked in 2009 to 2010 when cannabidiol exposure was peaking.

It should be underscored again that the reported changes are all at the associational level only: such a study cannot by itself establish or interrogate causal pathways.

Moreover, as has been described elsewhere, numerous published mechanistic reports link PCE with molecular pathways to teratogenesis and form a critical backdrop and highly pertinent context to the present report.[18-23] This confluence of strong mechanistic links together with the present compelling teratological profile in the situation where the use of other drugs is uniformly static or falling strengthens the argument that causal pathways may be operating in clinical populations.

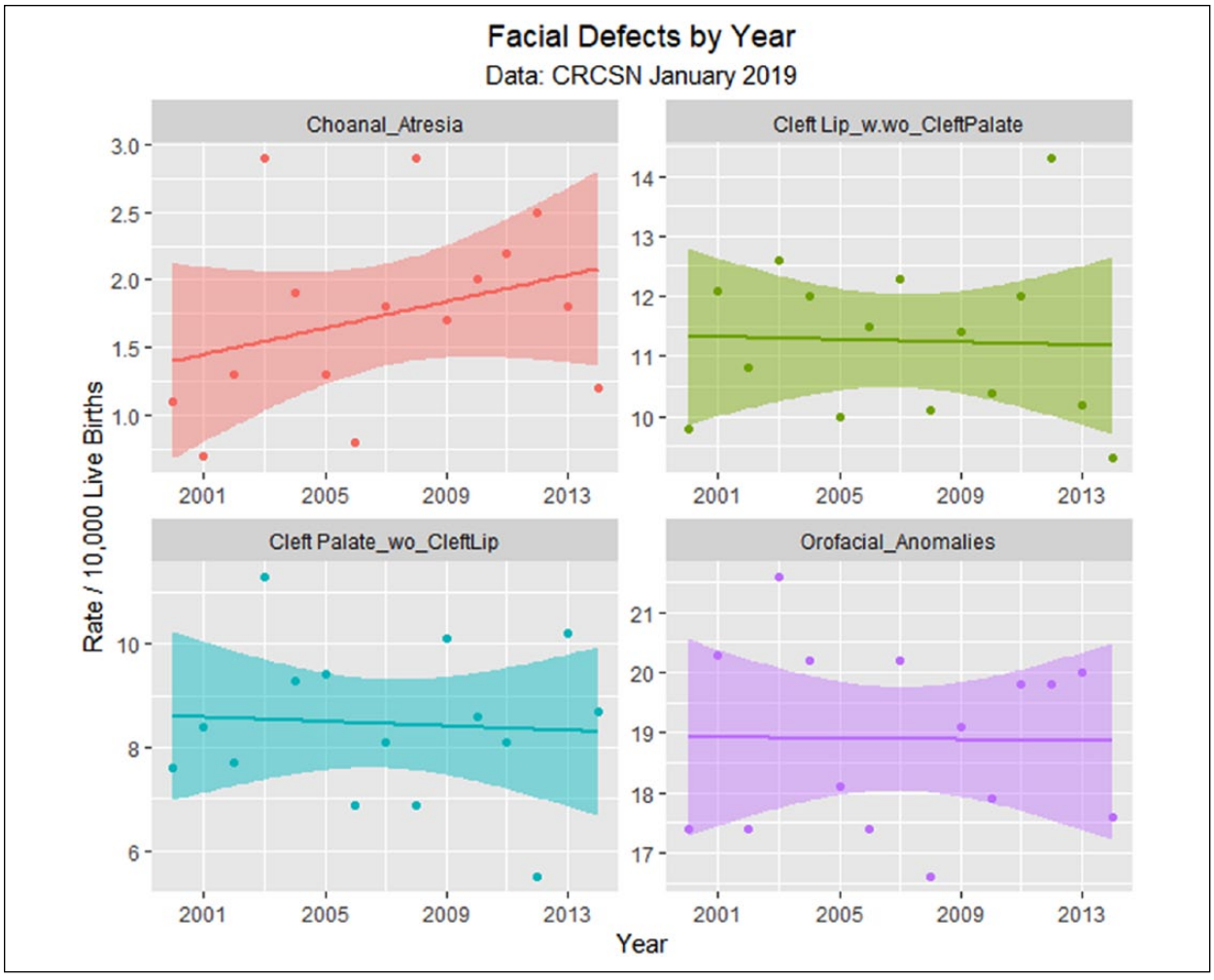

Figure 7. Face defects by time.

Space precludes detailed consideration of possible teratogenic mechanisms, but these have been addressed elsewhere.[18-23] Neurotoxic mechanisms include withdrawal of glutamate receptors from synapses,[24] misconstruction of synapses from disruption of neurexin-neuroligin synaptic scaffolding,[25] excessive dendritic and spine pruning,[26] mitochondrial impairment,[27] stem cell inhibition,[28] CB1R-mediated neuraxis inflammation,[29] and cytoskeletal impairment and motility disruption.[30] Cardiovascular toxic mechanisms include inflammatory vasculitis and CB1R signaling to CB1R-rich endovascular and endocardial tissues.[31,32] Importantly, cannabis has been described as blocking both notch[33,34] and robo-slit receptor-ligand[35] signaling, which are important as both neuronal and vascular guidance cues,[36] and critically involved in heart and brain morphogenesis.[36] Cannabis induces severe epigenetic disruption[22,37-39] and has long been known to stimulate micronucleus formation and genetic anomalies secondary to chromosomal missegregation.[22,40]

The present work did not have access to Coloradan early termination of pregnancy for anomaly data. Since many of the defects mentioned are known to be carefully sought by prenatal screening programs and have high applicable termination rates, the present results represent underestimates and set a lower bound for effect, which is likely to be greatly exacerbated by incorporation of the complete dataset.

Some discussion of the attribution of cannabis association to the listed defects is appropriate. Many of the defects listed as cannabis-associated have been attributed as such based on the large population survey of Forrester and Merz from Hawaii in 2007.[15] While this article is an outlier in the clinical cannabis-related teratogenesis literature, albeit highly concordant with previous animal studies,[1,2] its very uniqueness places it in a

Figure 8. Limb defects by time.

signal position to face the most stringent test of predictive theories, namely, the test of prediction of future trends. By this test, the Forrester-Merz article towers above the remainder of the literature. It alone predicts the increased incidence of ASD, Downs' syndrome, microcephaly, and chromosomal defects found in the present study. Moreover, this is the only study that explains the current pattern of cannabis-related defects such as ASD, Down's syndrome, VSD, encephalocele, limb reductions, anotia, and gastroschisis across the high cannabis-using states of the United States[41] and recently reported elevated rates of limb defects in France in hemp-fed cattle and babies.[42,43] As noted above, pyloric stenosis was omitted from the cannabis-related group as it has not been independently verified by other studies, and spina bifida is believed to share much in common with other neural tube closure defects such as anencephalus so this has been included.

Four of 4 longitudinal studies of cortical executive functioning following PCE indicate serious deficits in cerebral associational function.[44-48] Data on these deficits are not included within the CRCSN dataset, which therefore forms an additional disease burden to that described above. However, one notes that there has been a movement in Colorado for several years to declare a state of medical emergency related to a rapidly accelerating renaissance of autistic spectrum disorders in that community.[49] Importantly, rapid growth of autism in Colorado may shortly overshadow the classical anomalies described in the present report, which again suggests that this work describes a lower bound of cannabis teratogenesis.

Taken together, these various data imply that the full spectrum of cannabis-associated defects is potentially much broader than has previously been delineated. It may still be expanding.

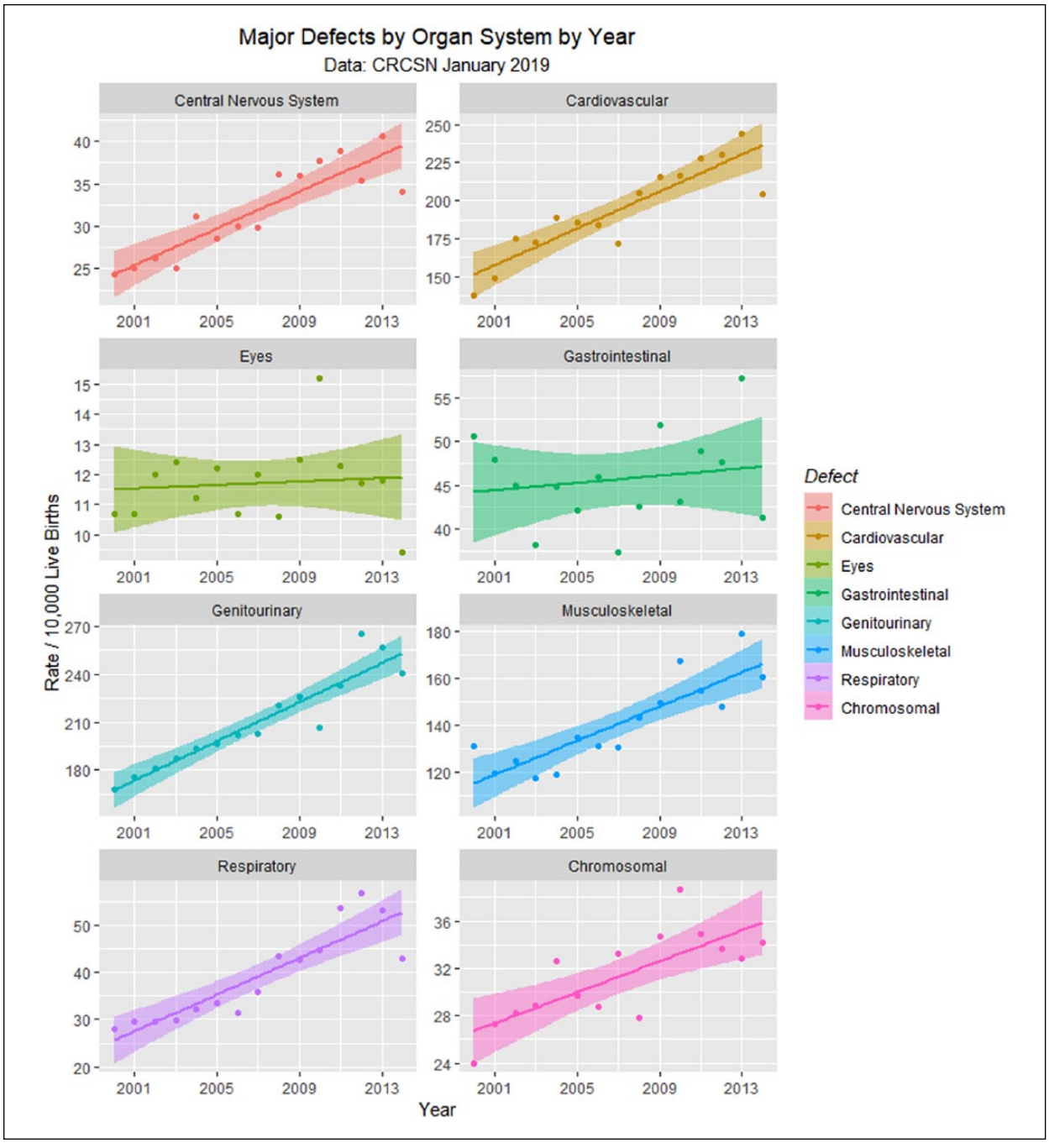

Figure 9. Major defects by time.

A major finding of this statistical study was that models quartic in time outperformed strictly linear models. This suggests a feed-forward–type positive-feedback process.

In October 2018, the CRCSN revised their total database from 2000 to 2014 without explanation in a manner that mainly affected the total congenital anomalies. The previous historical totals from 2000 to 2013 appear as indicated.

This study has several strengths. Colorado is unusual among the United States in that it makes extracts from its birth defects register publicly available. Colorado is also unusual as it is one of the only states with legal cannabis to do so. This study also utilizes the very large

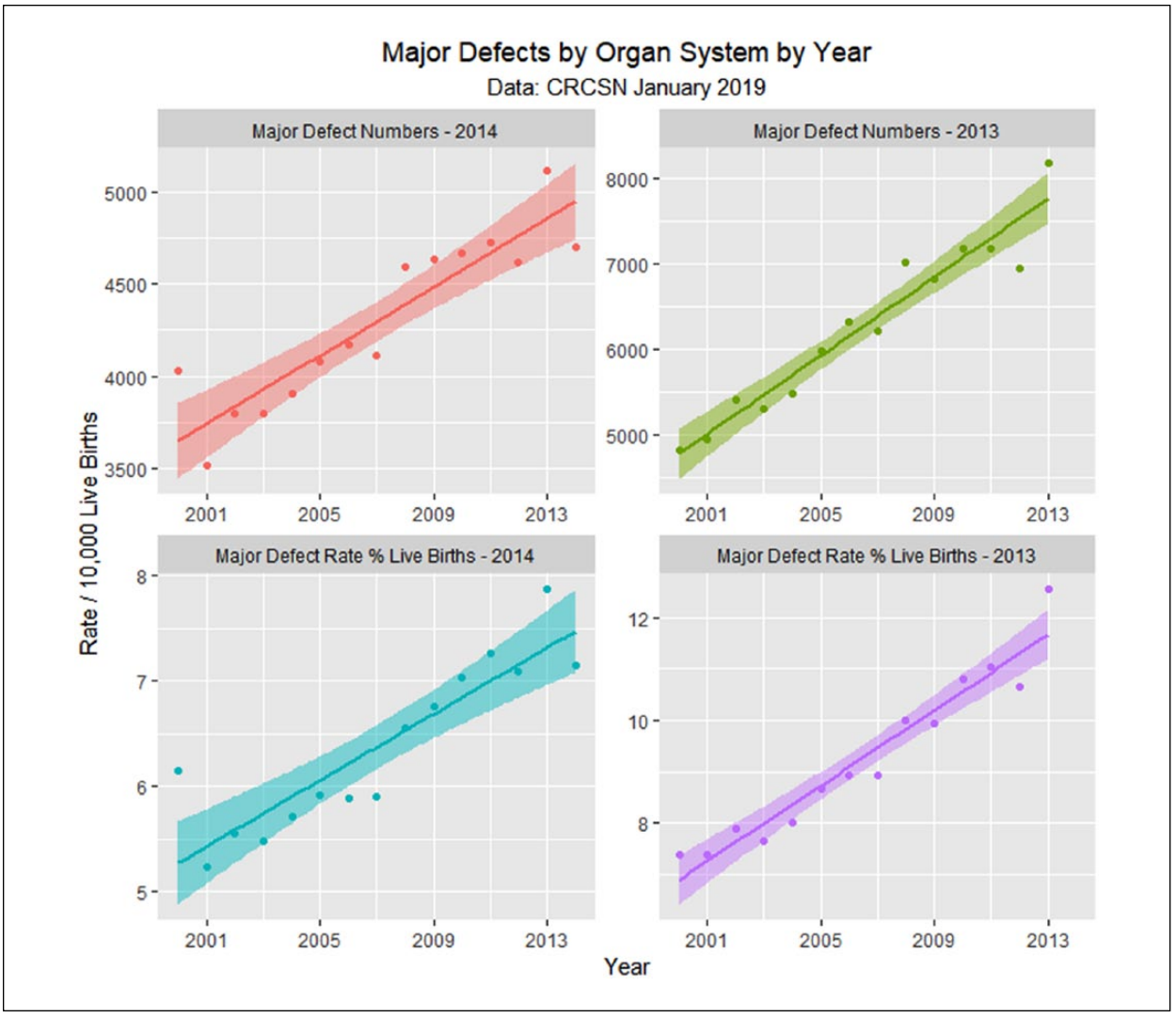

Figure 10. Total defects by time.

nationally representative NSDUH dataset to assess intrastate drug exposure. Limitations include the lack of individual-level drug use data, which might be available to a case-control study. Due to the uncertainties involved with self-report studies,[6] we would suggest that future studies employ objective evidence of drug exposure such as hair analysis.[50]

Conclusion

An excess of 11 753 to 20 152 birth defects occurred in Colorado from 2000 to 2014, which represents a 6.7- to 9.4-fold excess of growth in defects compared with growth in births. Defects in 6 of 8 major organ systems increased significantly in frequency. While other drug use was falling over this period, cannabis use alone rose. Cannabis and many cannabinoids were shown to be associationally linked with this rise with correlation coefficients up to 0.78, were confirmed on bivariate analysis, and were robust to multivariate adjustment. In the context of multiple mechanistic pathways, causality is strongly implied. Longitudinal case-control series denominated by an objective measures of drug use are indicated.

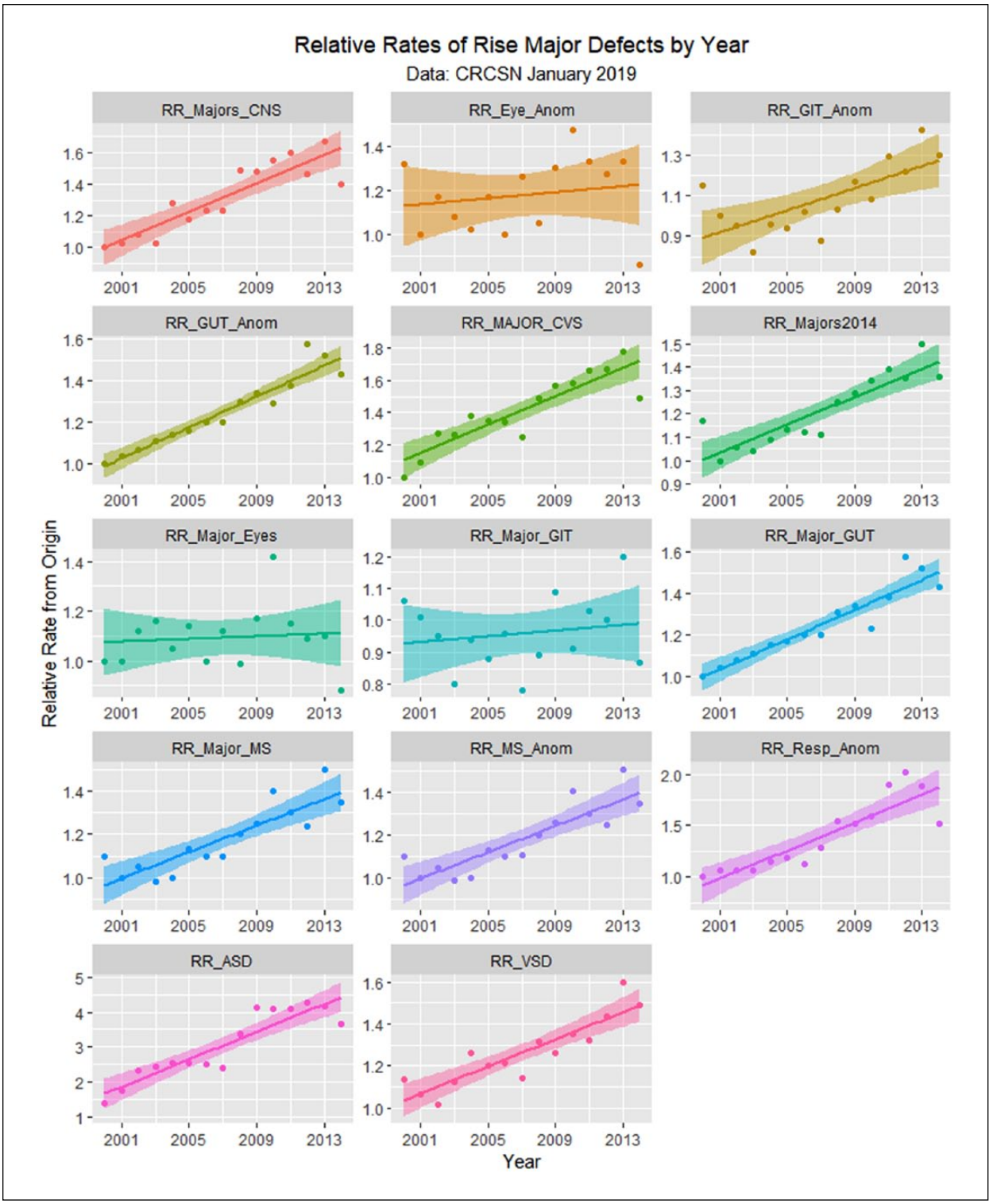

Figure 11. Relative rises in selected defects compared with baseline by time.

Table 3. Case Excess.

Population		Specific Defects						Major Systems						Total	
Year	Births	Microcephalus	Spina_ Bifida	Atrial_Septal_ Defect_ Secundum	Patent_ Ductus_ Arteriosus	Ventricular_ Septal_Defect	Trisomy_21	Major_ CNS	Major_ CVS	Resp_ Anom	Major_ GUT2	Major_ MS	Chromosomal_ Anomalies	Majors_N_2014	Majors_N_2013
2000	65429	30	18	299	244	272	78	159	898	184	1101	860	157	4026	4830
2001	67006	33	10	382	239	261	74	168	999	199	1176	800	183	3514	4942
2002	68420	38	18	518	268	254	92	179	1196	203	1240	856	193	3795	5406
2003	69325	38	21	548	263	285	104	174	1194	207	1297	814	200	3797	5311
2004	68491	46	25	568	263	316	88	213	1295	221	1322	814	223	3909	5482
2005	68929	47	21	571	277	303	95	197	1280	230	1355	929	205	4080	5978
2006	70732	63	15	578	247	314	99	212	1303	223	1430	927	204	4168	6325
2007	69580	55	23	553	266	296	97	212	1218	254	1434	927	235	4111	6213
2008	70024	71	22	770	312	337	81	253	1436	303	1543	1004	195	4592	7010
2009	68603	67	30	922	352	317	106	246	1478	293	1550	1025	238	4637	6826
2010	66339	64	17	887	331	328	96	250	1434	296	1444	1112	257	4666	7171
2011	65026	65	26	866	313	314	88	253	1483	348	1515	1008	227	4728	7174
2012	65173	46	19	912	324	342	95	231	1498	370	1744	966	220	4619	6939
2013	64996	56	18	880	324	380	100	264	1585	345	1668	1164	213	5117	8165
2014	65817	51	24	785	277	359	97	224	1346	282	1581	1058	225	4704	
Total	1013890	770	307	10039	4300	4678	1390	3235	19643	3958	21400	14264	3175	64463	87772
Calculated total	981435	450	150	4485	3660	3915	1110	2385	13470	2760	16515	12000	2355	52710	67620
Case excess	32455	320	157	5554	640	763	280	850	6173	1198	4885	2264	820	11753	20152
% Excess	3.3069%	71.11%	104.67%	123.84%	17.49%	19.49%	25.23%	35.64%	45.83%	43.41%	29.58%	18.87%	34.82%	22.30%	29.80%
Excess relative to births	1.00	21.50	31.65	37.45	5.29	5.89	7.63	10.78	13.86	13.13	8.94	5.71	10.53	6.74	9.01

Abbreviations: CNS, central nervous system; CVS, cardiovascular system.

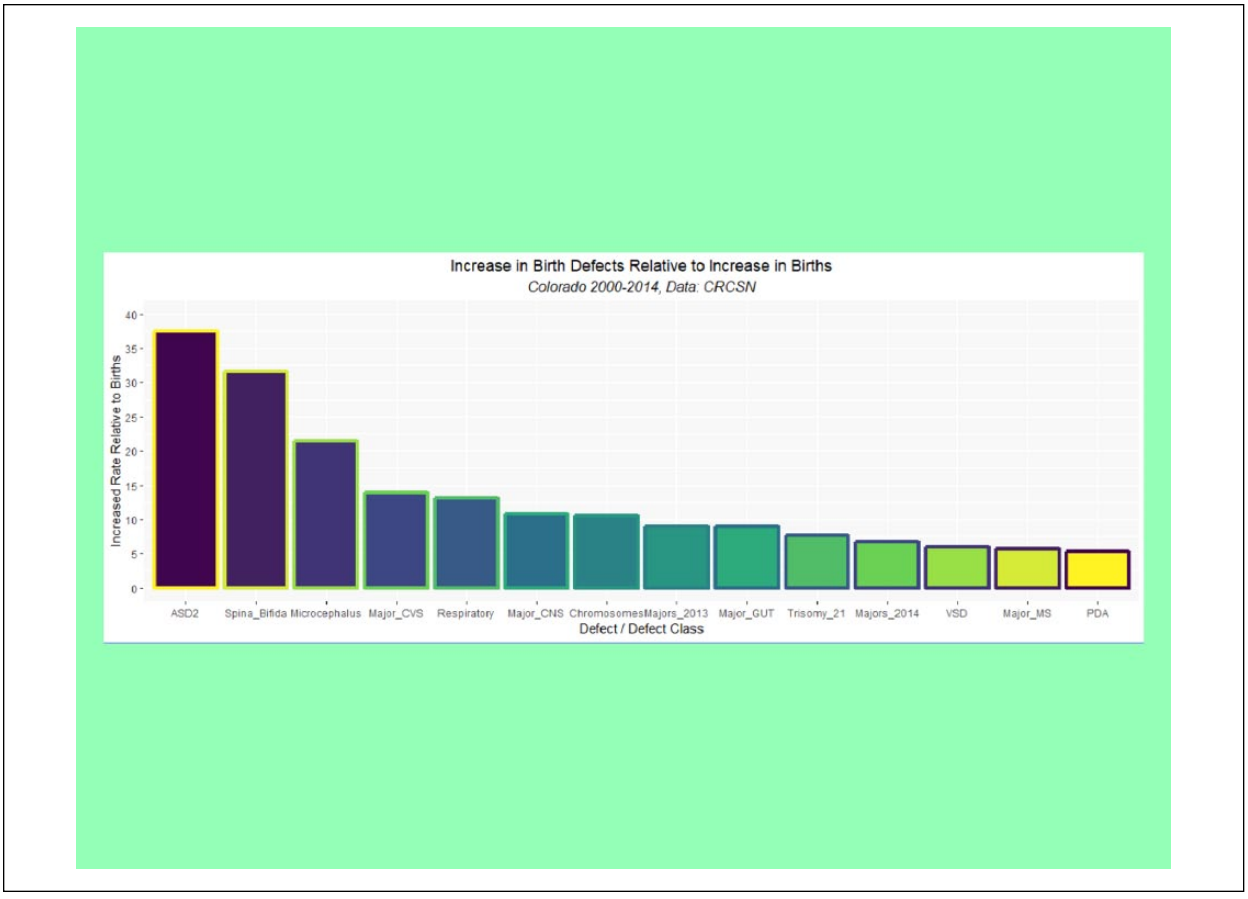

Figure 12. Rise in selected defects relative to rise in births by time.

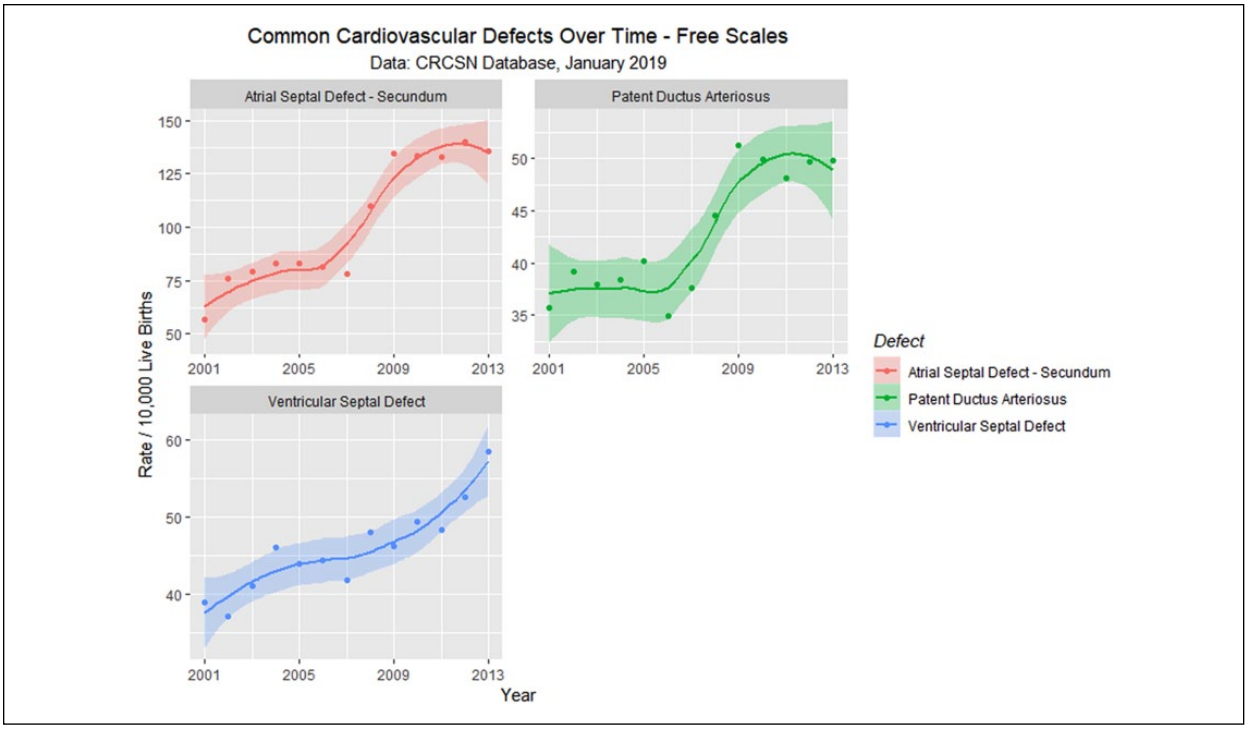

Figure 13. Atrial septal defect, ventricular septal defect, and patent ductus arteriosus—Loess curves by time.

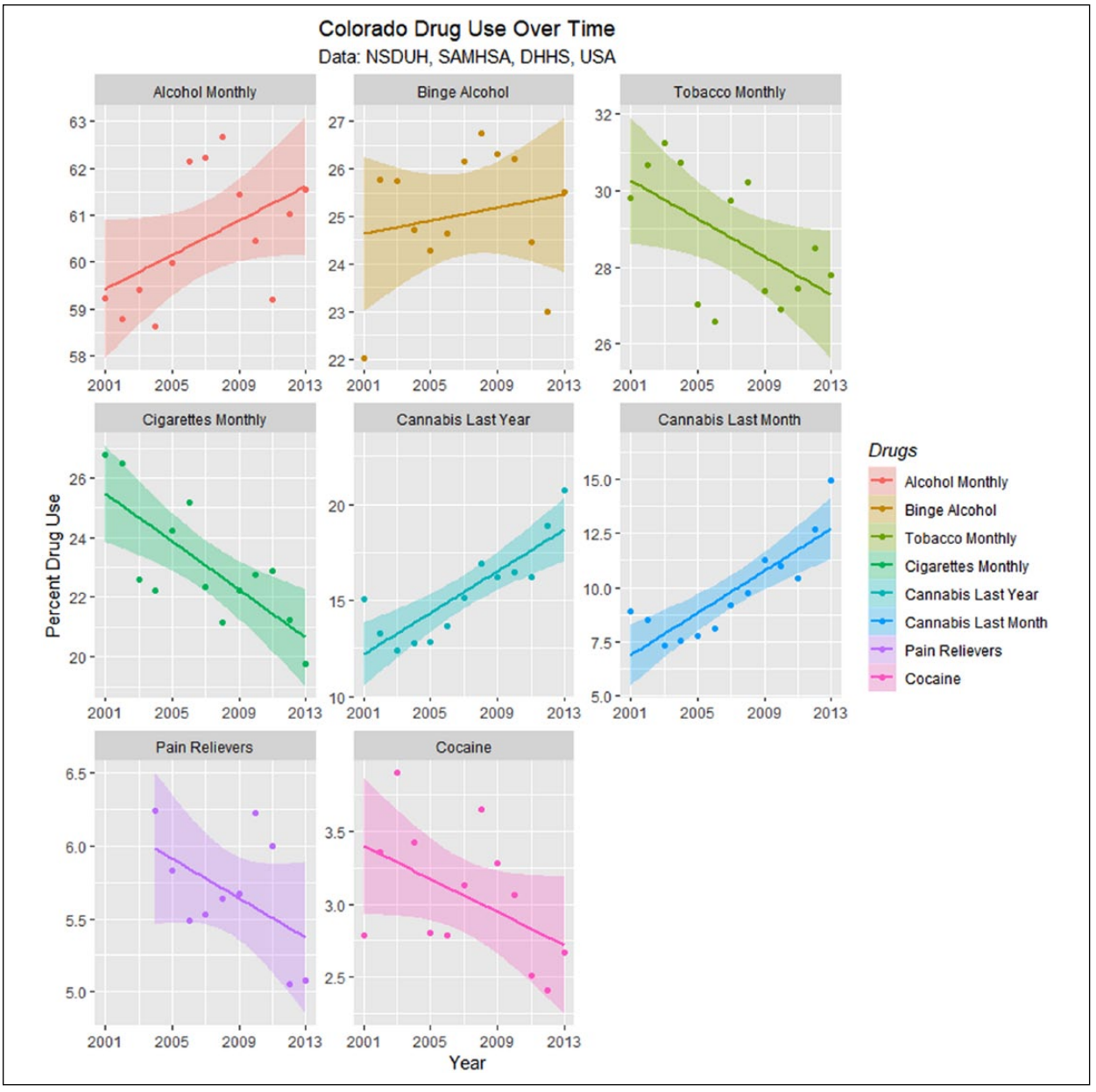

Figure 14. Drug use in Colorado from National Survey of Drug Use and Health (NSDUH) dataset by time with regression lines fitted.

Table 4. Regression Slope Trend Estimates for Drug Use—NSDUH.

Drugs	Term	β-Estimate	Standard Error	*t*	*P*	Lower CI	Upper CI
Cannabis—Annual	Year	0.6509	0.1107	5.8808	.0001	0.4097	0.8921
Cannabis—Monthly	Year	0.5822	0.0960	6.0671	.0001	0.3731	0.7913
Alcohol Monthly	Year	0.1498	0.0825	1.8159	.0925	−0.0284	0.3281
Binge Alcohol	Year	0.0703	0.0896	0.7842	.4481	−0.1250	0.2656
Cocaine Annual	Year	−0.0592	0.0260	−2.2795	.0417	−0.1158	−0.0026
Pain Relievers	Year	−0.0849	0.0358	−2.3698	.0419	−0.1660	−0.0039
Tobacco Monthly	Year	−0.2859	0.0933	−3.0651	.0098	−0.4892	−0.0827
Cigarettes Monthly	Year	−0.3743	0.0817	−4.5838	.0005	−0.5507	−0.1979

Abbreviations: NSDUH, National Survey of Drug Use and Health; CI, confidence interval.

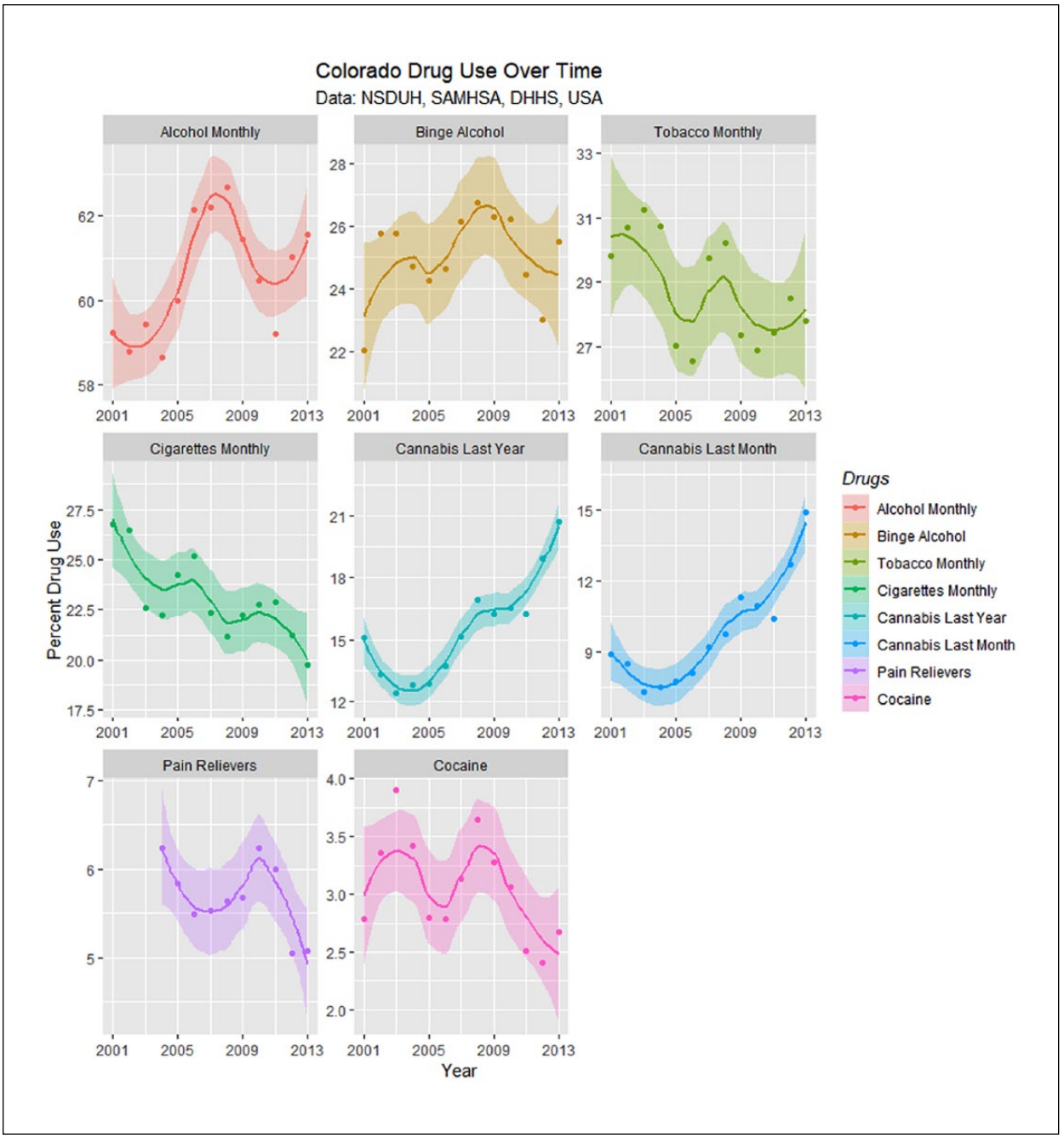

Figure 15. Drug use in Colorado from National Survey of Drug Use and Health (NSDUH) dataset by time with loess curves fitted.

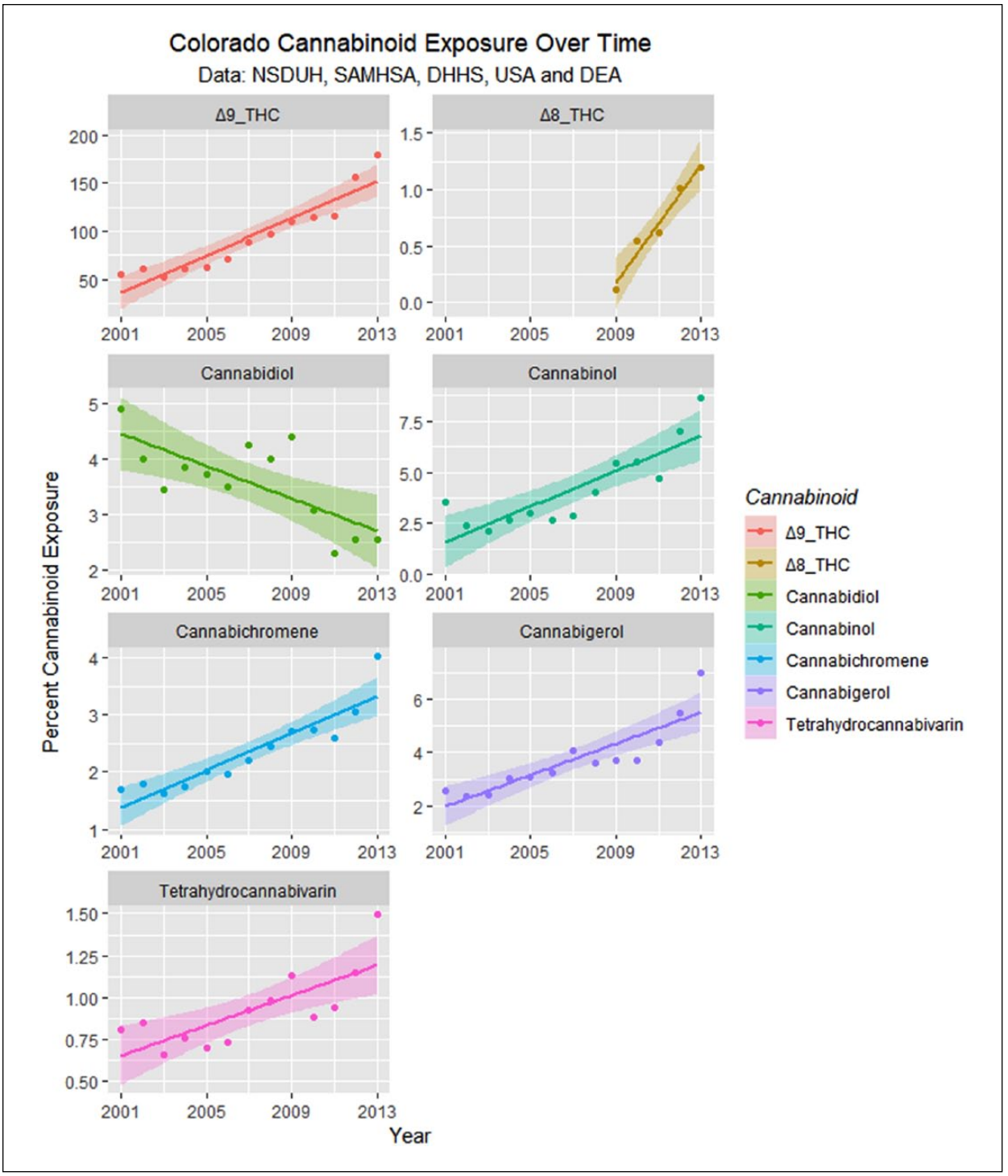

Figure 16. Cannabinoid exposure in Colorado from National Survey of Drug Use and Health (NSDUH) dataset by time with regression lines fitted.

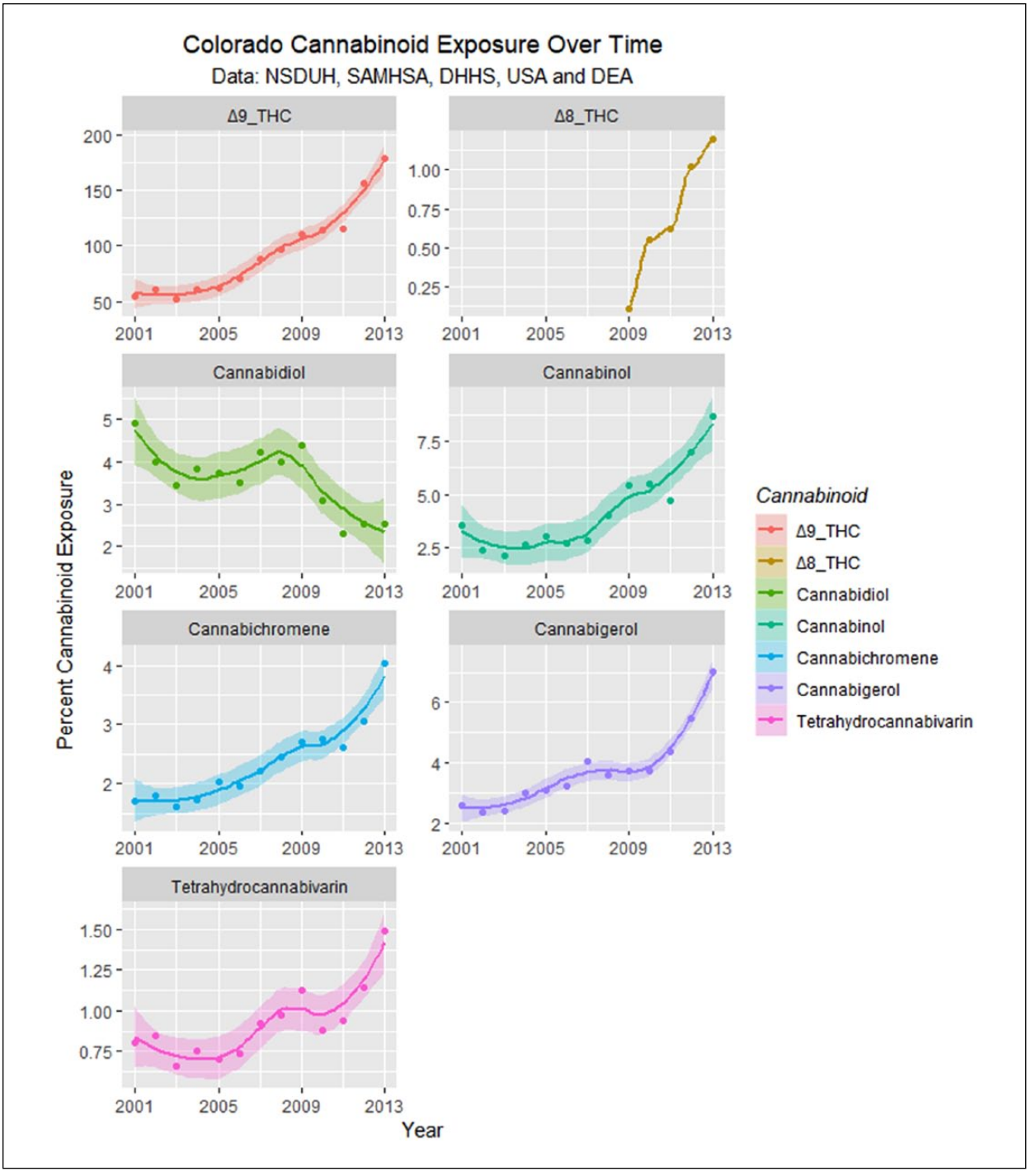

Figure 17. Cannabinoid exposure in Colorado from National Survey of Drug Use and Health (NSDUH) dataset by time with loess curves fitted.

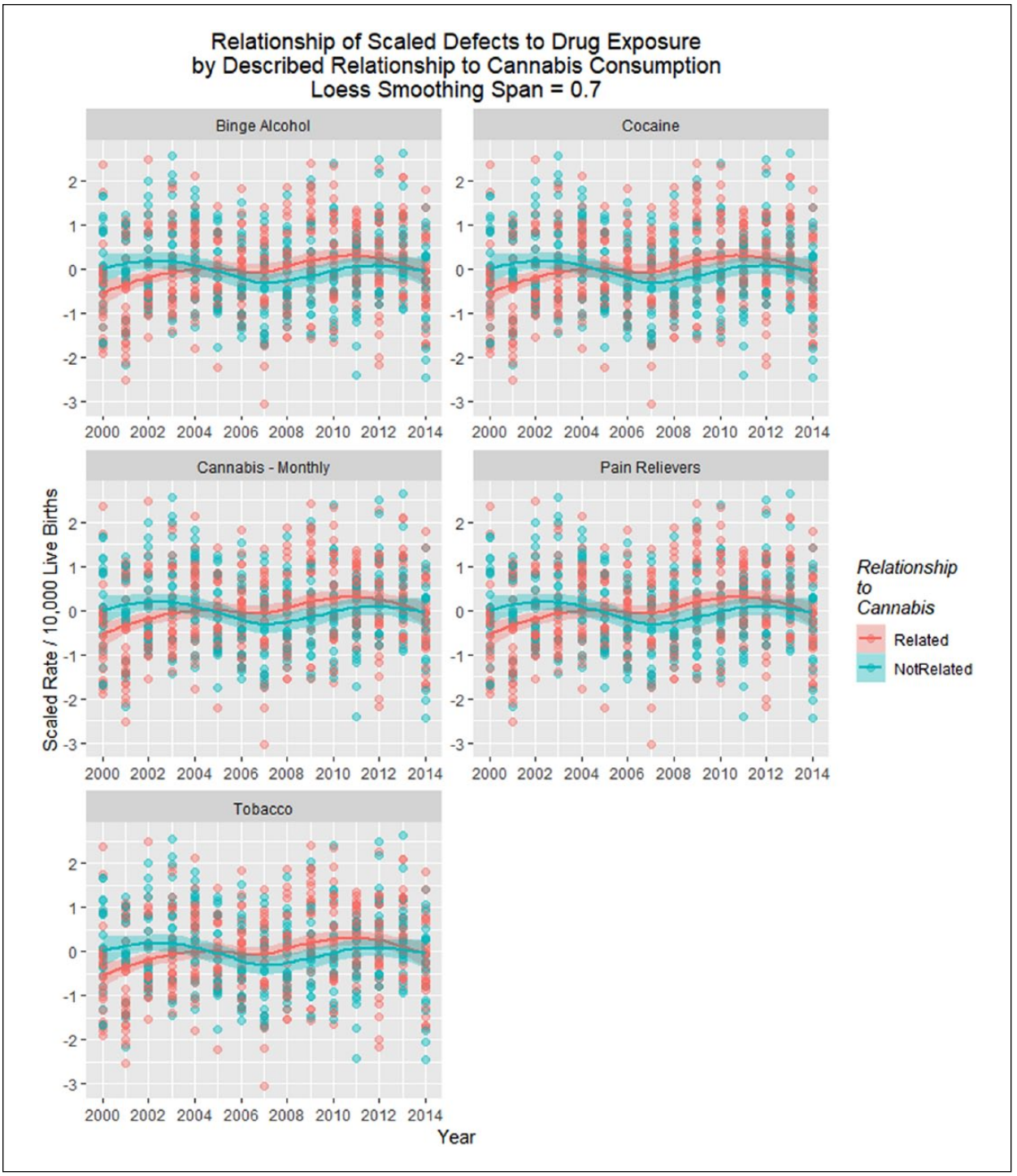

Figure 18. Scaled drug use in Colorado from National Survey of Drug Use and Health dataset by time with loess curves fitted.

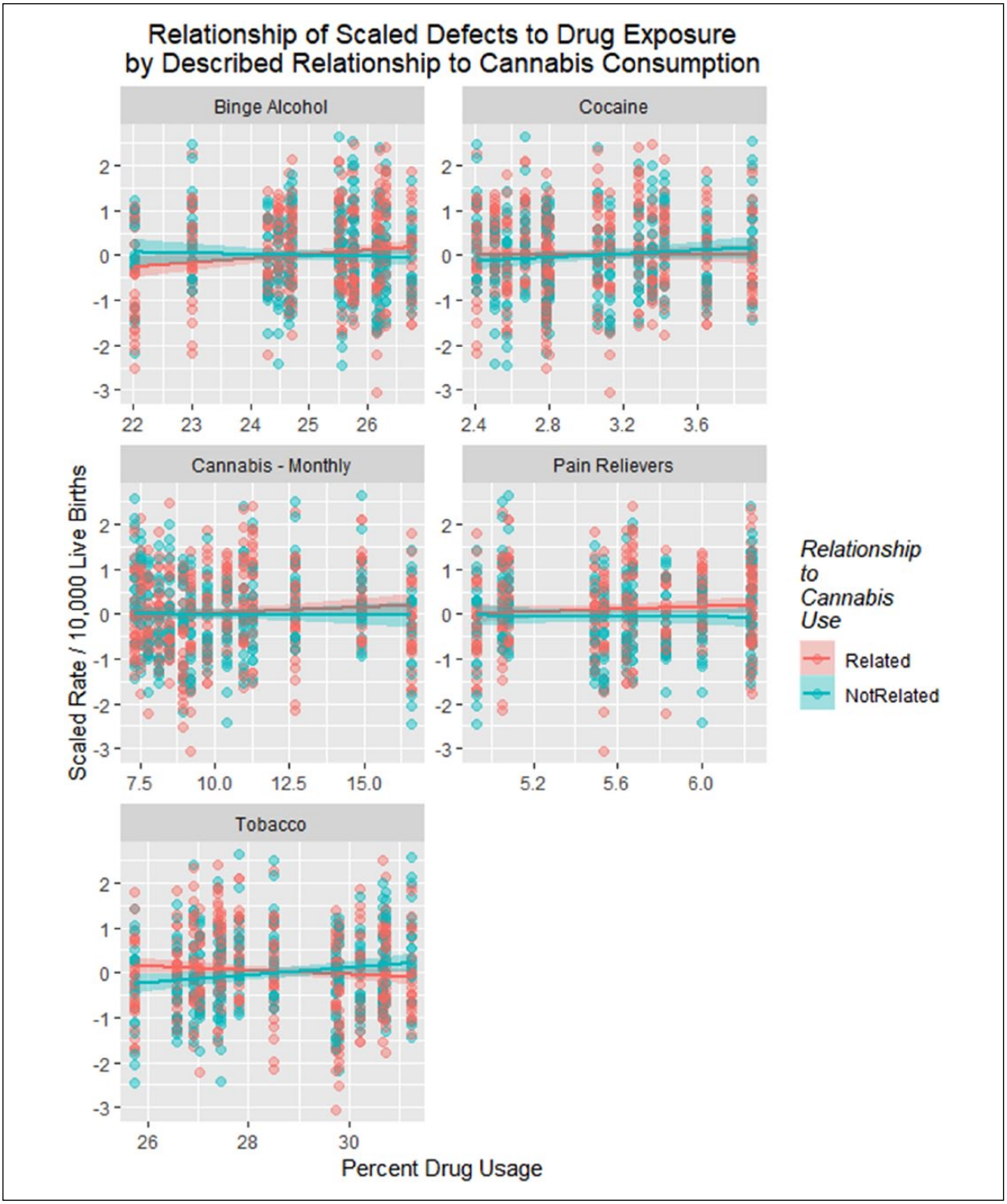

Figure 19. Scaled drug use in Colorado from National Survey of Drug Use and Health dataset by time with regression lines fitted.

Table 5. Regression Slopes for All Scaled Defects by Drug Classes.

Parameter					Model			
Parameter	Estimate	Standard Error	*t*	Pr(>|*t*|)	Adjusted R^2	*F*	df	*P*
Linear models								
Cannabis								
Cannabis_Monthly	−9.4175	4.3409	−2.169	0.0304	0.005634	2.932	2680	.05395
Year:Cannabis_Monthly	0.0047	0.0021	2.173	0.0301				
Opioids								
Year	0.3486	0.1756	1.985	0.0477	0.009133	2.644	3532	.04856
Pain_Relevers	112.5612	62.2827	1.807	0.0713				
Year:Pain_Relevers	−0.0559	0.0310	−1.804	0.0718				
Quartic models								
Tobacco								
(Year)^3: Tobacco	5.1567	1.7701	2.913	0.0037	0.04503	5.02	8674	4.55E-06
(Year)^3	−145.182	51.2001	−2.836	0.0047				
Alcohol								
NS								
Cannabis								
(Year)^2	−13.6307	3.5007	−3.894	0.00011	0.0477	7.833	5677	3.51E-07
(Year)^3	4.8938	1.5169	3.226	0.00132				
(Year)^4	−9.6683	1.6810	−5.751	1.3E-08				
Cannabis_Monthly	0.2002	0.0710	2.822	0.00492				
Opioids								
Year	−610.237	228.352	−2.672	0.0078	0.04869	4.422	8527	3.39E-05
(Year)^4	−309.336	103.395	−2.992	0.0029				
(Year)^2: Pain_Relevers	83.360	35.953	2.319	0.0208				
(Year)^4: Pain_Relevers	69.235	22.935	3.019	0.0027				
Cocaine								
(Year)^2	32.2730	14.3249	2.253	0.0246	0.04574	5.087	8674	3.67E-06
(Year)^2: Cocaine	−13.2694	5.0409	−2.632	0.0087				

Abbreviation: df, degrees of freedom.

Table 6. Regression Slopes for All Scaled Defects Against Various Drugs—Mixed-Effects Models.

	Parameter					Model		
Parameter	Value	Standard Error	df	*t*	*P*	AIC	BIC	LogLik
Additive model								
Rate~Year+Cannabis_Monthly+Opioids+Tobacco+Cocaine+BingeAlc								
Opioids	0.3479	0.1560	278	2.2311	.0265	848.7998	867.4013	−419.3999
Year	0.0448	0.0214	278	2.0954	.0370			
Increasing levels of interactive models								
*Rate~Year*Cannabis_Monthly+Opioids+Tobacco+Cocaine+BingeAlc*								
Opioids	0.4003	0.1756	278	2.2796	.0234	863.8158	882.4173	−426.9079
Year:Cannabis_Monthly	0.0000	0.0000	278	2.0248	.0438			
*Rate~Year*Cannabis_Monthly*Opioids+Tobacco+Cocaine+BingeAlc*								
Year	6.3170	1.6760	273	3.7689	.0002	861.0326	898.0704	−420.5163
Opioids	2489.7840	680.8430	273	3.6569	.0003			
Year: Opioids	−1.2360	0.3390	273	−3.6495	.0003			
Cannabis_Monthly: Opioids	−392.6320	114.0330	273	−3.4431	.0007			
Year: Cannabis_Monthly: Opioids	0.1950	0.0570	273	3.4470	.0007			
Cannabis_Monthly	2101.5210	617.6850	273	3.4023	.0008			
Year: Cannabis_Monthly	−1.0440	0.3060	273	−3.4071	.0008			

(continued)

Table 6. (continued)

	Parameter					Model		
Parameter	Value	Standard Error	df	*t*	*P*	AIC	BIC	LogLik
*Rate~Year*Cannabis_Monthly*Tobacco+Opioids+Cocaine+BingeAlc*								
Year: Cannabis_Monthly	−0.0030	0.0009	275	−4.0238	.0001	875.2932	904.9767	−429.6466
Cannabis_Monthly: Tobacco	0.2550	0.0637	275	4.0089	.0001			
Year	5.5130	1.4606	275	3.7741	.0002			
Tobacco	396.3240	105.2453	275	3.7657	.0002			
Year: Tobacco	−0.1990	0.0527	275	−3.7677	.0002			
*Rate~Year+Cannabis_Monthly*Opioids*Tobacco+Cocaine+BingeAlc*								
Opioids: Tobacco	−0.4067	0.1071	272	−3.7971	.0002	866.9679	907.6728	−422.4839
Cannabis_Monthly: Opioids: Tobacco	0.1857	0.0530	272	3.5015	.0005			
Cannabis_Monthly: Opioids	−4.4878	1.2866	272	−3.4882	.0006			
Cannabis_Monthly	18.7962	5.6135	272	3.3484	.0009			
Cannabis_Monthly: Tobacco	−0.7761	0.2343	272	−3.3130	.0010			
Cocaine	−1.5894	0.5995	272	−2.6510	.0085			
Opioids	6.2896	3.0387	272	2.0698	.0394			

Abbreviations: df, degrees of freedom; AIC, Akaike information criterion; BIC, Bayesian information criterion; LogLik, log likelihood.

Figure 20. Scaled defects rate as a function of drug use exposure with regression lines fitted in facetted plot by relationship to cannabis use, after omission of pyloric stenosis and inclusion of spina bifida.

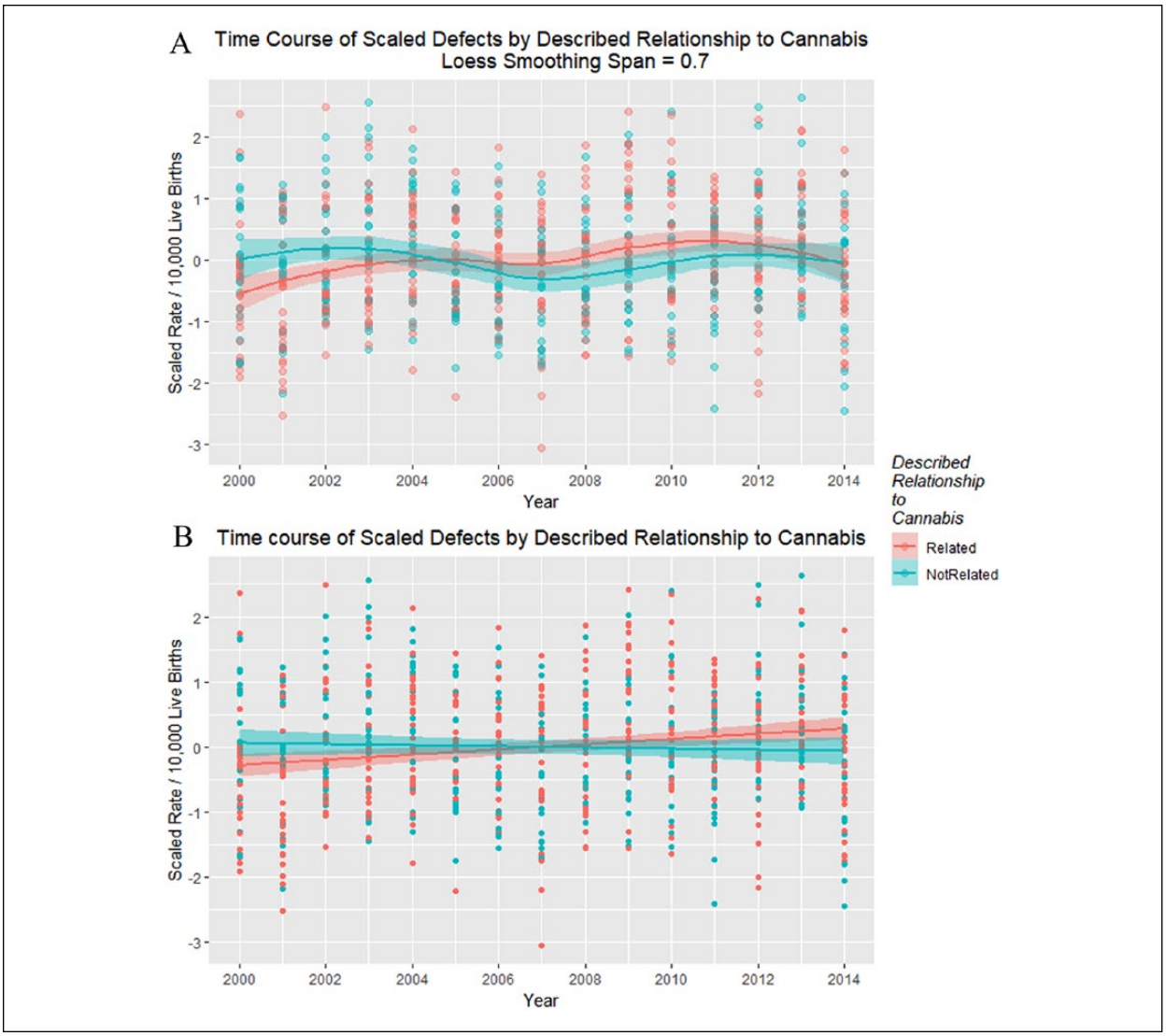

Figure 21. Scaled defects rate as a function of drug use exposure with (A) loess curves and (B) regression lines fitted.

Table 7. Comparisons of Cannabinoid Models Linear and Quartic in Time for All Scaled Defects.

Parameter					Model			
Parameter	Estimate	Standard Error	*t*	Pr(>|*t*|)	Adjusted R^2	*F*	df	*P*
Linear models								
*Defect_Rate ~ Year * Cannabis_Related*								
Year: Cannabis_Related	0.0402	0.0108	3.712	0.0002	0.01523	4.763	3727	.002697
Cannabis_Related	−98.8011	33.3927	−2.959	0.0032				
Quartic-in-time models								
*Defect_Rate ~ I(poly(Year, n=4)) * Cannabis_Related*								
(Year)^4	−4.7042	1.4591	−3.224	0.0013	0.03908	4.711	8722	1.20E-05
Year: Cannabis_Related	5.7531	1.9252	2.988	0.0029				
(Year)^2: Cannabis_Related	−4.8258	1.9287	−2.502	0.0126				

Abbreviation: df, degrees of freedom.

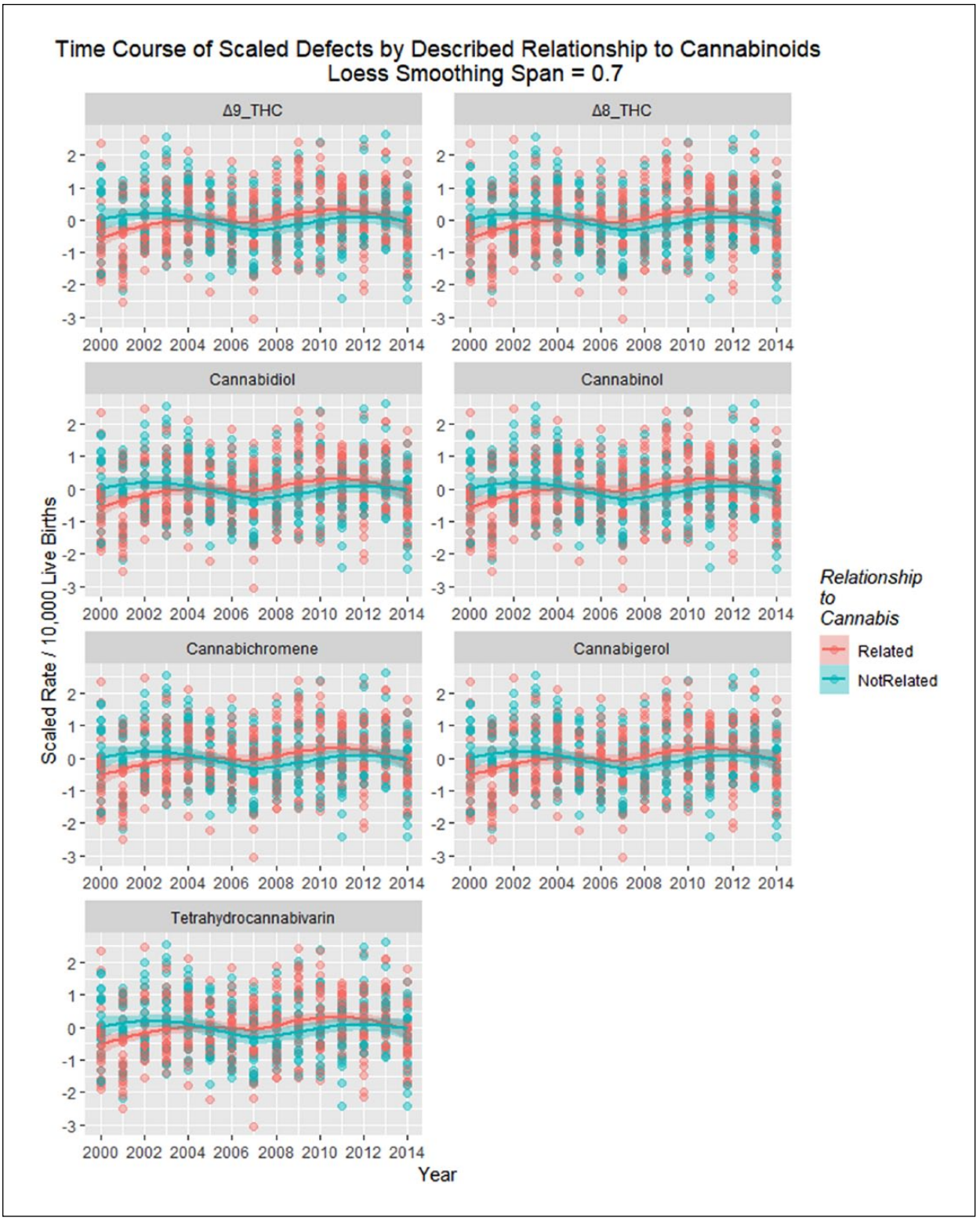

Figure 22. Scaled defects rate as a function of cannabinoid exposure with loess curves fitted. Facetted plot by cannabinoid.

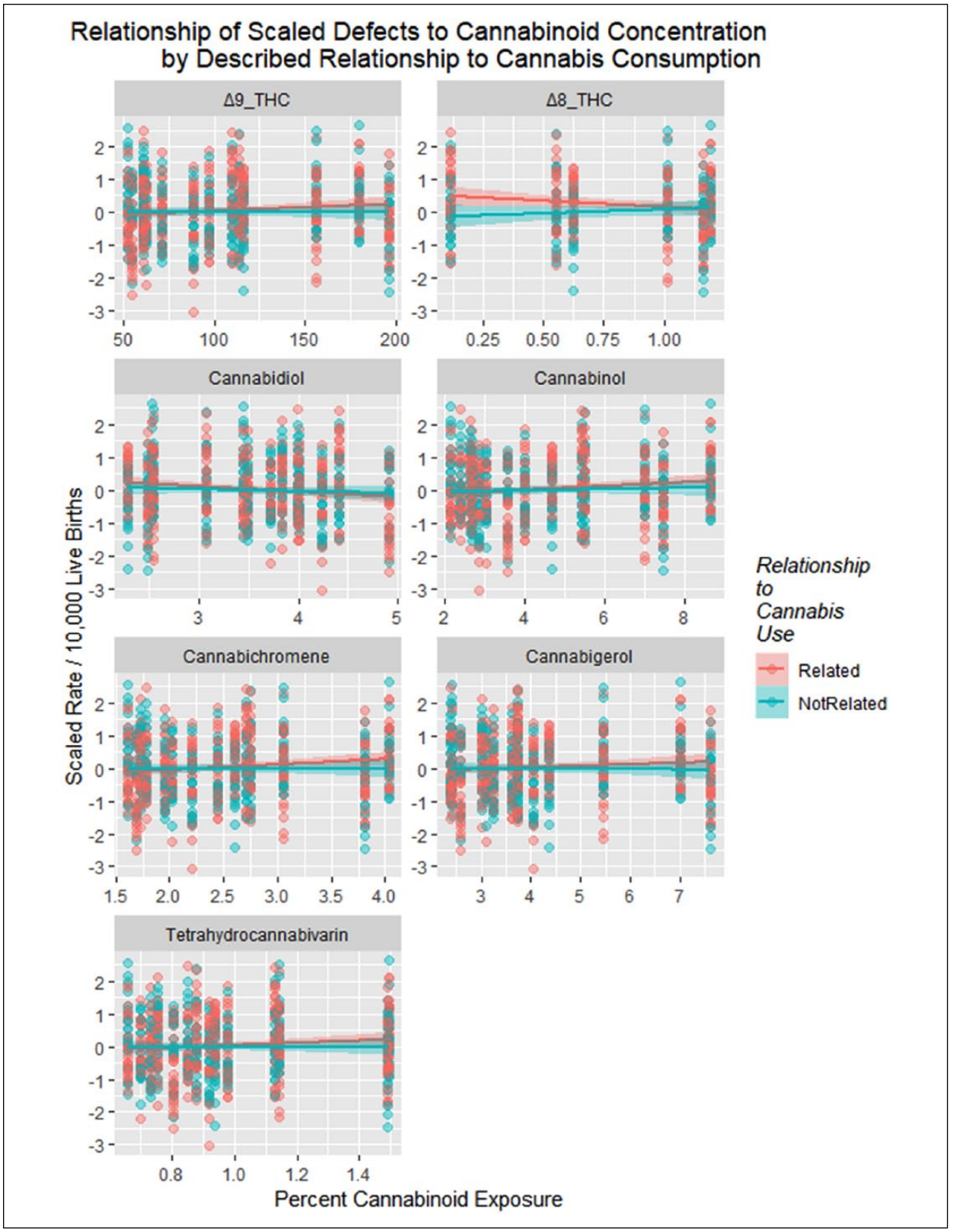

Figure 23. Scaled defects rate as a function of cannabinoid exposure with regression lines fitted. Facetted plot by cannabinoid.

Table 8. Rises in Defects by Cannabinoid Exposure—Models Linear and Quartic in Time.

Parameter					Model			
Parameter	Estimate	Standard Error	*t*	Pr(>|*t*|)	Adjusted R^2	*F*	df	*P*
Linear models								
d8_THC								
Year	−0.2870	0.1131	−2.537	.0117	0.0169	3.496	2289	.03162
Year:d8_THCMON	0.0005	0.0002	2.209	.0280				
Quartic models								
d9_THC								
Year: d9_THC	0.8892	0.3821	2.327	.0203	0.0431	4.84	8674	8.15E-06
(Year)^4	−20.9952	9.1100	−2.305	.0215				
Year	−99.5298	49.4149	−2.014	.0444				
CBD								
(Year)^3	55.9750	22.1400	2.528	.0117	0.0489	5.378	8674	1.42E-06
(Year)^3: CBD	−14.8342	5.9146	−2.508	.0124				
CBN								
(Year)^4	−6.6144	1.2950	−5.108	4.3E-07	0.0477	7.832	5577	3.52E-07
(Year)^2	−8.8041	2.0599	−4.274	2.2E-05				
(Year)^3	4.8154	1.5064	3.197	.0015				
CBN	0.1645	0.0583	2.821	.0049				
CBG								
NS								
THCV								
(Year)^4	−8.0989	1.4039	−5.769	1.2E-08	0.04671	7.683	5677	4.88E-07
(Year)^2	−8.4791	2.0250	−4.187	3.2E-05				
THCV	0.9907	0.3681	2.691	.0073				
(Year)^3	3.7194	1.4095	2.639	.0085				

Abbreviation: df, degrees of freedom.

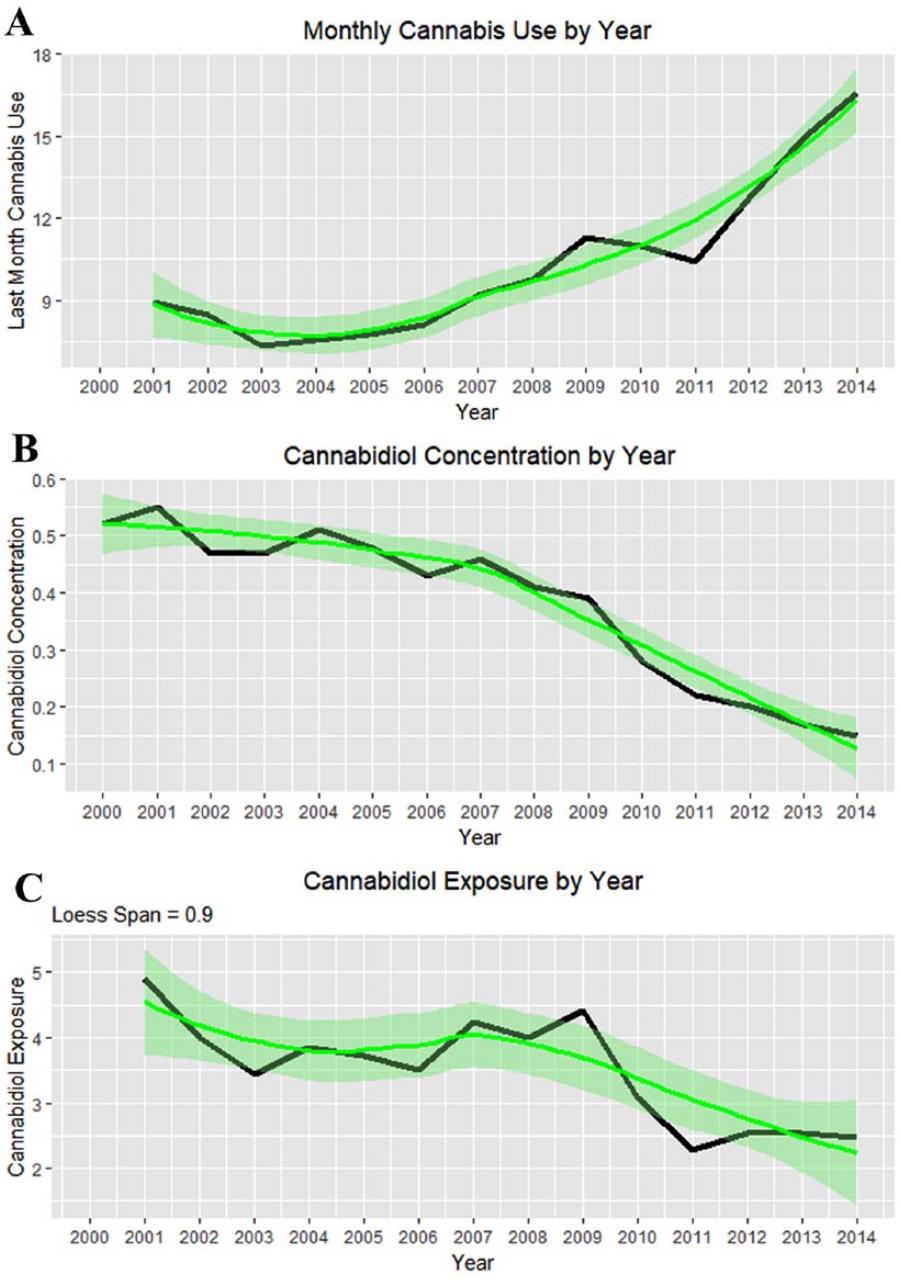

Figure 24. (A) Monthly cannabis use by year. (B) Cannabidiol concentration by year. (C) Cannabidiol exposure by year as the product of (A) and (B).

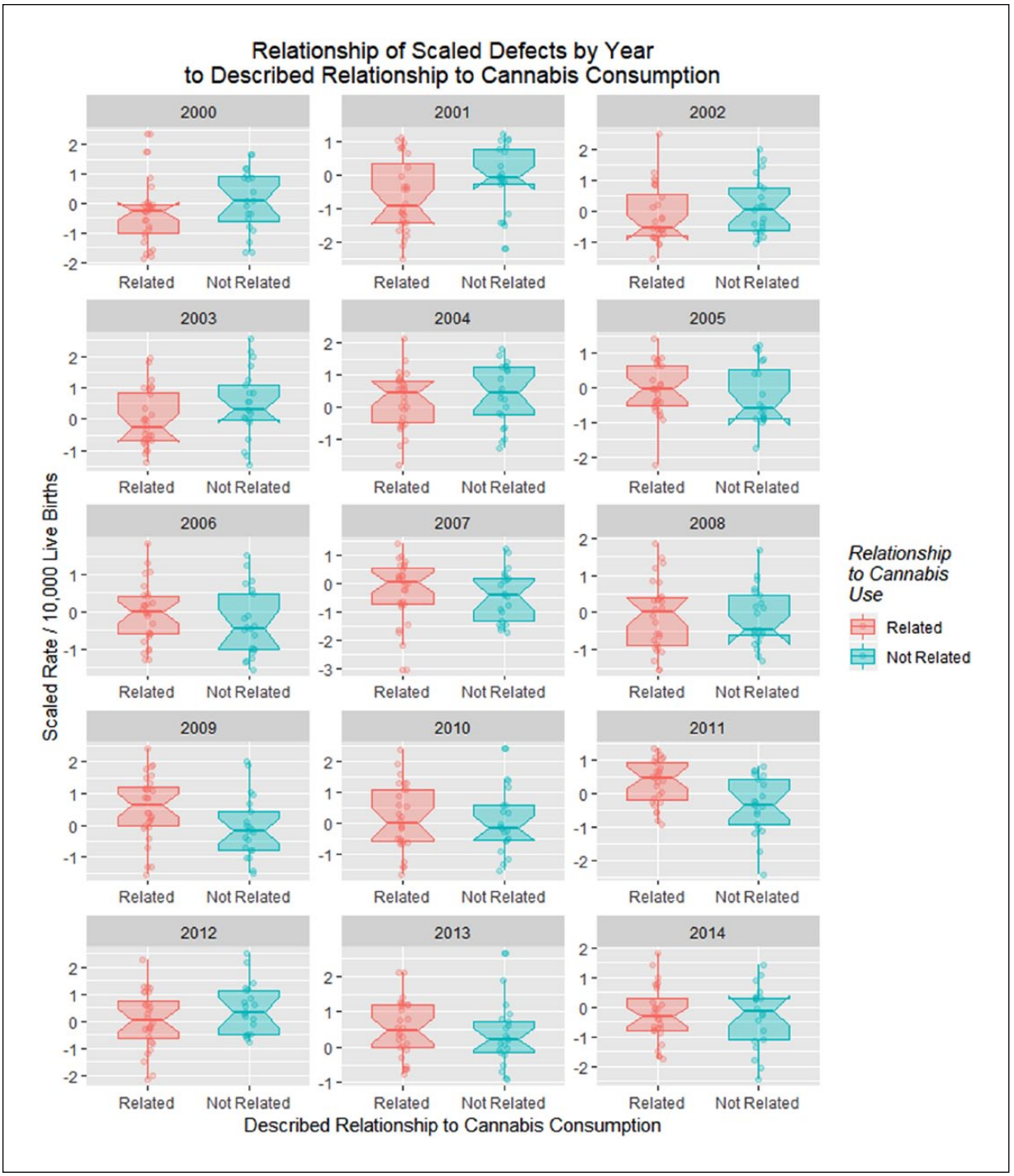

Figure 25. Relationship of scaled defects by year to described relationship to cannabis consumption from the published literature (see Discussion).

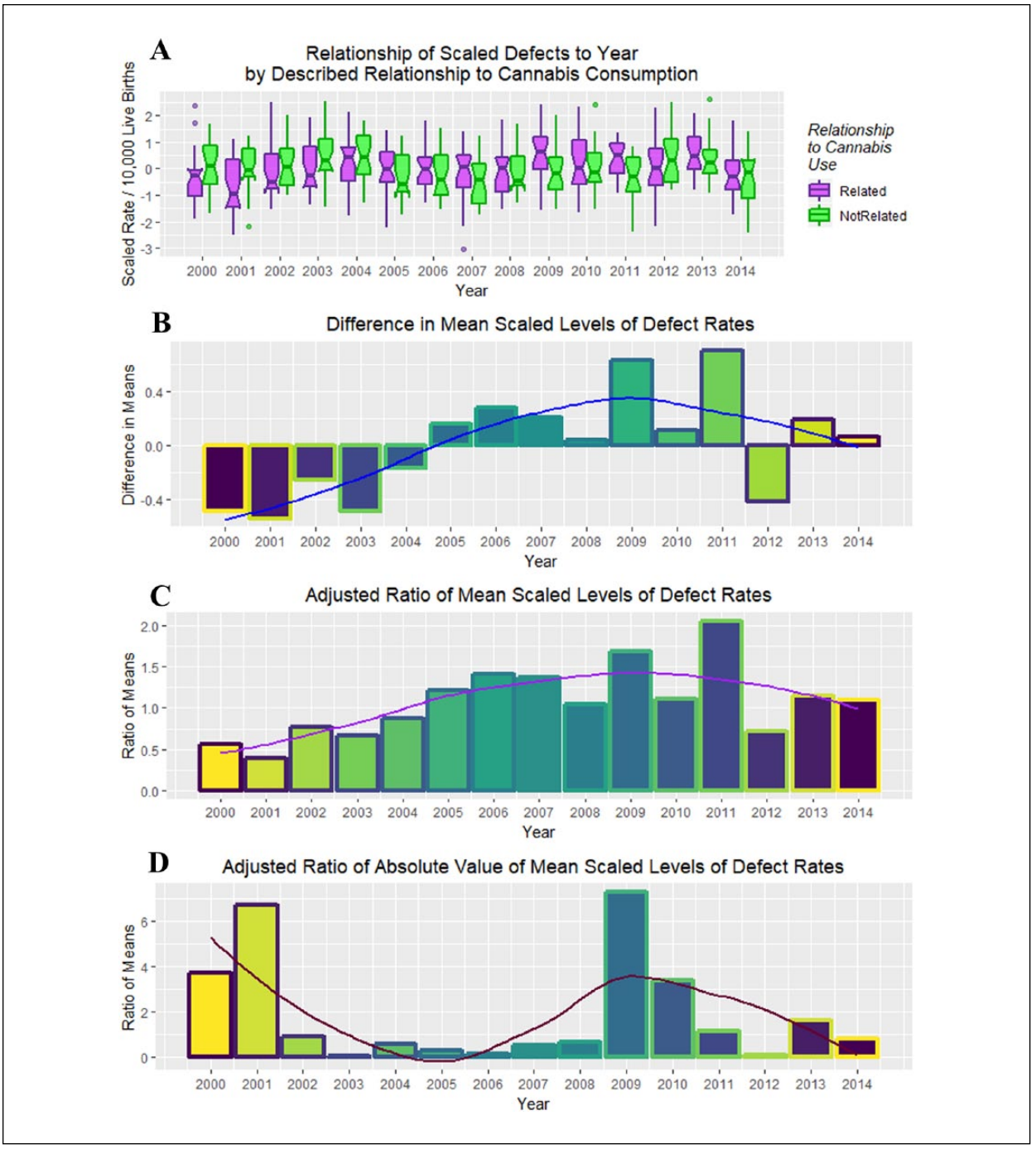

Figure 26. (A) Box plot of relationship of scaled defects to time by described relationship to cannabis use. (B) Difference between cannabis-related and non–cannabis-related rates of scaled scores. (C) Ratio of cannabis-related and non–cannabis-related scaled scores after adjustment by adding unity (1) to both scores. (D) The ratio of the absolute value of the cannabis-related defects to that of the absolute value of cannabis-unrelated defects.

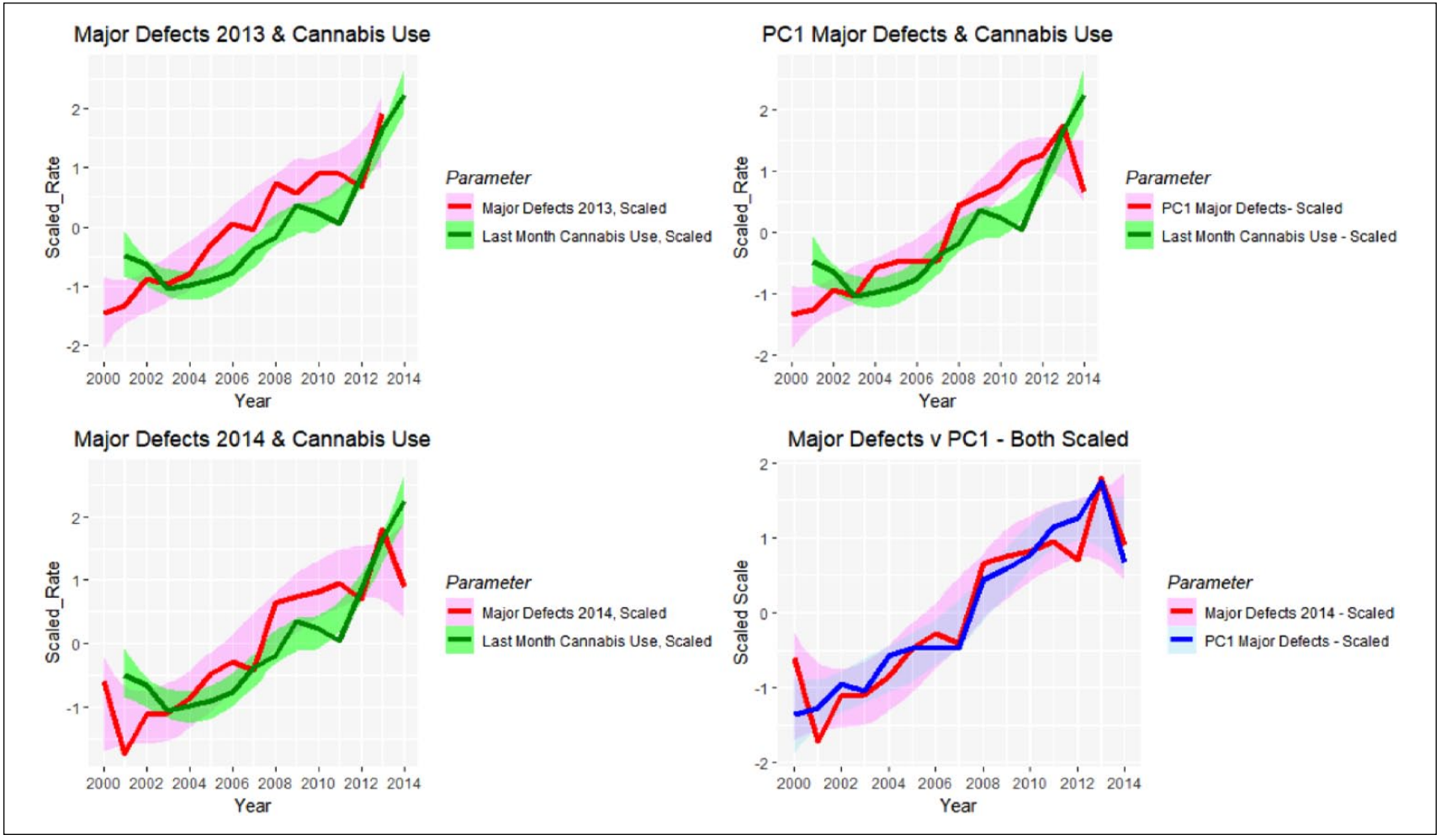

Figure 27. Line plots showing relationship between scaled (A) major defect rates 2013 and last month cannabis use; (B) major defect rates 2014 and last month cannabis use; (C) principal component 1 and last month cannabis use; (D) major defects 2014 and principal component 1 for 2014.

Table 9. Correlation Coefficients—Major Summary Indices With Cannabis Use (see Figure 27).

Group 1	Group 2	*t*	df	*P*	*R*	Lower CI	Upper CI
Major Defects 2014	Cannabis_Monthly	4.2597	12	.0011	0.7758	0.4169	0.9255
Major Defects 2013	Cannabis_Monthly	5.1534	11	.0003	0.8409	0.5402	0.9512
PC1	Cannabis_Monthly	4.2722	12	.0011	0.7767	0.4187	0.9258
Majors Defects 2014	PC1	11.035	13	5.7E-08	0.9505	0.8542	0.9838

Abbreviations: df, degrees of freedom; CI, confidence interval.

Table 10. Linear Regression of Major Summary Indices by NSDUH Drug Exposure.

Parameter					Model			
Parameter	Estimate	Standard Error	*T*	Pr(>|*t*|)	Adjusted R^2	*F*	df	*P*
Linear models								
*Majors2014~Year+Tobacco*Cannabis_Monthly+Opioids+Binge_Alcohol+Cocaine*								
Cannabis_Monthly	1.2139	0.1678	7.234	.0002	0.8656	22.48	3,7	.0005718
Tobacco: Cannabis_Monthly	0.4423	0.1116	3.964	.0054				
Opioids	0.3683	0.1373	2.683	.0314				
*Majors2014~Year*Δ9-THC+CBDM+Tobacco+Opioids*								
Δ9-THC	253.3969	94.7077	2.676	.0281	0.7856	19.33	2,8	.0095
Year: Δ9-THC	−0.1257	0.0471	−2.668	.0284				
*PC1~Year+Tobacco*Cannabis_Monthly+Opioids+Binge_Alcohol+Cocaine*								
Cannabis_Monthly	1.2404	0.1962	6.322	.0004	0.8221	16.4	3,7	.001508
Tobacco: Cannabis_Monthly	0.4829	0.1305	3.701	.0076				
Opioids	0.3957	0.1605	2.465	.0431				
*Major_CNS~Year+Tobacco*Cannabis_Monthly+Opioids+Binge_Alcohol+Cocaine*								
Cannabis_Monthly	1.1631	0.2332	4.988	.0016	0.6956	8.619	3,7	.00949
Opioids	0.6071	0.1908	3.182	.0154				
Tobacco: Cannabis_Monthly	0.4133	0.1551	2.665	.0322				
*Major_CVS~Year+Tobacco*Cannabis_Monthly+Opioids+Binge_Alcohol+Cocaine*								
Cannabis_Monthly	1.1303	0.2331	4.85	.0019	0.6951	8.599	3,7	.009549
Tobacco: Cannabis_Monthly	0.4770	0.1550	3.077	.0179				
Opioids	0.4469	0.1907	2.344	.0516				
Quartic-in-time models								
*PC1~I(poly(Year, n=4))*Δ9-THC+CBDM+Tobacco+Opioids*								
Δ9-THC	0.6793	0.1625	4.181	.0024	0.6223	17.48	1,9	.0095
*Majors2014~(poly(Year, n=4))*Cannabis_Monthly+Tobacco+Opioids+Binge_Alcohol+Cocaine*								
(Year)^4: Cannabis_Monthly	−20.4192	0.9427	−21.66	.0294	0.9982	609.9	9,1	.03141
Year: Cannabis_Monthly	302.1905	14.3060	21.12	.0301				
Cannabis_Monthly	−58.0400	2.8018	−20.71	.0307				
(Year)^3: Cannabis_Monthly	99.9858	4.8684	20.54	.0310				
(Year)^2: Cannabis_Monthly	−209.6725	10.3174	−20.32	.0313				
Year	340.6153	16.8783	20.18	.0315				
(Year)^2	−270.0904	13.4573	−20.07	.0317				
(Year)^3	119.3061	6.4290	18.56	.0343				
(Year)^4	−40.3087	2.4539	−16.43	.0387				
*PC1~I(poly(Year, n=4))*Cannabis_Monthly+Tobacco+Opioids+Binge_Alcohol+Cocaine*								
Year: Cannabis_Monthly	−5.7912	1.1506	−5.033	.0024	0.8062	11.4	4,6	.005744
(Year)^2: Cannabis_Monthly	5.0229	1.0371	4.843	.0029				
(Year)^3: Cannabis_Monthly	2.9675	0.8060	3.682	.0103				
(Year)^4: Cannabis_Monthly	−1.6296	0.6479	−2.515	.0456				

(continued)

Table 10. (continued)

Parameter					Model			
Parameter	Estimate	Standard Error	*T*	Pr(>|t|)	Adjusted R^2	*F*	df	*P*
*Major_CNS~I(poly(Year, n=4))*Cannabis_Monthly+Tobacco+Opioids+Binge_Alcohol+Cocaine*								
Year: Cannabis_Monthly	−5.6711	1.5086	−3.759	.0094	0.5964	4.694	4,6	.04649
(Year)^2: Cannabis_Monthly	4.2187	1.3598	3.102	.0211				
(Year)^3: Cannabis_Monthly	2.6681	1.0568	2.525	.0450				
*Major_CVS~I(poly(Year, n=4))*Cannabis_Monthly+Tobacco+Opioids+Binge_Alcohol+Cocaine*								
Cannabis_Monthly	−54.5060	3.3030	−16.5	.0385	0.997	373	9,1	.04016
Year: Cannabis_Monthly	274.4250	16.8670	16.27	.0391				
(Year)^2: Cannabis_Monthly	−192.5180	12.1640	−15.827	.0402				
(Year)^4: Cannabis_Monthly	−17.3420	1.1110	−15.604	.0407				
Year	309.6860	19.8990	15.562	.0409				
(Year)^3: Cannabis_Monthly	84.3810	5.7400	14.701	.0432				
(Year)^2	−228.2030	15.8660	−14.383	.0442				
(Year)^3	103.9890	7.5800	13.719	.0463				
(Year)^4	−28.4810	2.8930	−9.844	.0644				

Abbreviations: NSDUH, National Survey of Drug Use and Health; df, degrees of freedom.

Table 11. Linear Regression of Major Summary Indices Against Selected Cannabinoids.

Parameter					Model			
Parameter	Estimate	Standard Error	*T*	Pr(>|t|)	Adusted R^2	*F*	df	*P*
Quartic-in-time models								
Additive models								
Majors2014~poly(Year, n=4)+Δ9-THC+CBD+CBN+THCV								
Δ9-THC	0.8746	0.1535	5.699	.0001	0.7077	32.48	1,12	9.9E-05
PC1~poly(Year, n=4)+Δ9-THC+CBD+CBN+THCV								
Year	2.5605	0.5875	4.358	.0024	0.9582	60.67	5,8	3.8E-06
(Year)^4	−0.8531	0.2711	−3.147	.0137				
(Year)^2	−1.0638	0.4303	−2.472	.0386				
CBN	0.4179	0.1789	2.336	.0477				
Major_CVS~poly(Year, n=4)+Δ9-THC+CBD+CBN+THCV								
(Year)^4	−1.5260	0.3572	−4.273	.0027	0.9149	28.97	5,8	6.4E-05
(Year)^2	−1.9670	0.5670	−3.469	.0085				
Year	2.3018	0.7741	2.974	.0178				
CBN	0.5051	0.2357	2.143	.0645				
Majors2013~poly(Year, n=4)+Δ9-THC+CBD+CBN+THCV								
CBD	−1.3975	0.3085	−4.530	.0062	0.9718	60.04	7,5	.0002
THCV	1.1978	0.2796	4.284	.0078				
(Year)^4	1.9973	0.4900	4.076	.0096				
(Year)^3	−2.4039	0.6190	−3.884	.0116				
(Year)^2	−3.5165	1.0913	−3.222	.0234				
CBN	0.8580	0.2758	3.111	.0265				
Year	−8.0678	2.6757	−3.015	.0296				

(continued)

Table 11. (continued)

Parameter					Model			
Parameter	Estimate	Standard Error	*T*	Pr(>|*t*|)	Adusted R^2	*F*	df	*P*
Interactive models								
*PC1~poly(Year, n=4)*Δ9-THC+CBD+CBN+THCV*								
Year: Δ9-THC	−2.1082	0.3168	−6.655	.0006	75.94	75.94	7,6	2.0E-05
CBD	−0.3900	0.0713	−5.469	.0016				
CBN	0.5980	0.1536	3.894	.0080				
THCV	0.4206	0.1444	2.914	.0268				
*Majors2013~poly(Year, n=4)*LMCann+Tob+Opioids+Binge_Alcohol+Cocaine*								
(Year)^3	4.5310	0.9640	4.700	.0053	0.8206	11.29	4,5	.0102
Year	3.0367	0.9432	3.219	.0235				
(Year)^2	−2.9994	1.1589	−2.588	.0490				
*Majors2013~poly(Year, n=4)*Δ9-THC+CBD+CBN+THCV*								
Δ9-THC	3.7695	0.0983	38.354	.0166	0.9999	14750.0	11,1	.0064
CBD	−1.2900	0.0356	−36.203	.0176				
(Year)^4: Δ9-THC	9.4066	0.2628	35.801	.0178				
Year: Δ9-THC	−31.1351	0.9101	−34.211	.0186				
(Year)^4	23.1233	0.7273	31.791	.0200				
(Year)^2	40.8303	1.3204	30.923	.0206				
(Year)^3: Δ9-THC	−23.2475	0.8131	−28.59	.0223				
CBN	1.0334	0.0472	21.908	.0290				
Year	−4.7978	0.3662	−13.103	.0485				

Abbreviation: df, degrees of freedom.

Table 12. Linear Regression of Major Defect Indices Against Drugs and Cannabinoids Together.

Parameter					Model			
Parameter	Estimate	Standard Error	*t*	Pr(>|*t*|)	Adjusted R^2	*F*	df	*P*
Linear models								
*Majors2014~Year*Δ9-THC+CBDM+Tobacco+Opioids*								
Δ9-THC	253.3969	94.7077	2.676	.0281	0.7856	19.33	2,8	.0008648
Year:Δ9-THC	−0.1257	0.0471	−2.668	.0284				
Quartic-in-time models								
*Majors2014~poly(Year, n=4)*Δ9-THC+CBDM+Tobacco+Opioids*								
(Year)^3: Δ9-THC	3.8734	1.1020	3.515	.0126	0.7258	7.619	4,6	.01561
(Year)^2: Δ9-THC	−5.4212	1.5780	−3.435	.0139				
Year: Δ9-THC	4.0698	1.3505	3.013	.0236				
(Year)^4: Δ9-THC	−1.7240	0.8807	−1.958	.0980				
*PC1~poly(Year, n=4)*Δ9-THC+CBDM+Tobacco+Opioids*								
Δ9-THC	0.6793	0.1625	4.181	.0024	0.6223	17.48	1,9	.002374
*Major_CNS~poly(Year, n=4)*Δ9-THC+CBDM+Tobacco+Opioids*								
(Year)^2: Δ9-THC	−6.4699	1.7370	−3.725	.0098	0.6103	4.915	4,6	.04217
Year: Δ9-THC	4.8429	1.4866	3.258	.0173				
(Year)^3: Δ9-THC	2.7165	1.2130	2.239	.0664				
*Major_CVS~poly(Year, n=4)*Δ9-THC+CBDM+Tobacco+Opioids*								
Δ9-THC	0.5267	0.1820	2.894	.0178	0.4244	8.374	1,9	.01777
*Majors2013~poly(Year, n=4)*Δ9-THC+CBDM+Tobacco+Opioids*								
(Year)^3: Δ9-THC	4.7555	1.0784	4.410	.0070	0.7843	9.179	4,5	.01592

(continued)

Table 12. (continued)

Parameter					Model			
Parameter	Estimate	Standard Error	*t*	Pr(>|*t*|)	Adjusted R^2	*F*	df	*P*
Year: Δ9-THC	3.3902	1.2164	2.787	.0386				
(Year)^2: Δ9-THC	−3.6253	1.3525	−2.680	.0438				

Abbreviation: df, degrees of freedom.

Author Contributions

ASR did the background research, analyzed data and wrote the first draft. GKH provided supervision, provided administrative, professional and academic support of several types, provided meaningful intellectual input and co-wrote the final draft of this paper.

Declaration of Conflicting Interests

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ORCID iD

Albert Stuart Reece https://orcid.org/0000-0002-3256-720X

Supplemental Material

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Summary of Cannabis Genotoxicity Papers

There are several principal pathways to inheritable genotoxicity, mutagenicity and teratogenesis induced by cannabis which are known and well established at this time including the following. These three papers discuss different aspects of these effects.

1) **Stops Brain Waves and Thinking** The brain has both stimulatory and inhibitory pathways. GABA is the main brain inhibitory pathway. Brain centres talk to each other on gamma (about 40 cycles/sec) and theta frequencies (about 5 cycles/sec), where the theta waves are used as the carrier waves for the gamma wave which then interacts like harmonics in music. The degree to which the waves are in and out of phase carries information which can be monitored externally. GABA (γ-aminobutyric acid) inhibition is key to the generation of the synchronized firing which underpins these various brain oscillations. These GABA transmissions are controlled presynaptically by type 1 cannabinoid receptors (CB1R's) and CB1R stimulation shuts them down. This is why cannabis users forget and fall asleep.

2) **Blocks GABA Pathway and Brain Formation** GABA is also a key neurotransmitter in brain formation in that it guides and direct neural stem cell formation and transmission and development and growth of the cerebral cortex and other major brain areas. Gamma and theta brain waves also direct neural stem cell formation, sculpting and connectivity. Derangements then of GABA physiology imply that the brain will not form properly. Thin frontal cortical plate measurements have been shown in humans prenatally exposed to cannabis by fMRI. This implies that their brains can never be structurally normal which then explains the long lasting and persistent defects identified into adulthood.

3) **Epigenetic Damage** DNA not only carries the genetic hardware of our genetic code but it also carries the software of the code which works like traffic lights along the sequence of DNA bases to direct when to switch the genes on and off. This is known as the "epigenetic code". Fetal alcohol syndrome is believed to be due to damage to the software epigenetic code. The long lasting intellectual, mood regulation, attention and concentration defects which have been described after in utero cannabis exposure in the primary, middle and high schools and as college age young adults are likely due to these defects. Epigenetics "sets in stone" the errors of brain structure made in (2) above.

4) **Arterial Damage**. Cannabis has a well described effect to damage arteries through (CB1R's) (American Heart Association 2007) which they carry in high concentration (Nature Reviews Cardiology 2018). In adults this causes heart attack (500% elevation in the first hour after smoking), stroke, severe cardiac arrhythmias including sudden cardiac death; but in developing babies CB1R's acting on the developing heart tissues can lead to at least six major cardiac defects (Atrial- ventricular- and mixed atrio-ventricular and septal defects, Tetralogy of Fallot, Epstein's deformity amongst others), whilst constriction of various babies' arteries can lead to serious side effects such as gastroschisis (bowels hanging out) and possibly absent limbs (in at least one series).

5) **Disruption of Mitotic Spindle**. When cells divide the separating chromosomes actually slide along "train tracks" which are long chains made of tubulin. The tubulin chains are called "microtubules" and the whole football-shaped structure is called a "mitotic spindle". Cannabis inhibits tubulin formation, disrupting microtubules and the mitotic spindle causing the separating chromosomes to become cut off in tiny micronuclei, where they eventually become smashed up and pulverized into "genetic junk", which leads to foetal malformations, cancer and cell death. High rates of Down's syndrome, chromosomal anomalies and cancers in cannabis exposed babies provide clinical evidence of this.

6) **Defective Energy Generation & Downstream DNA Damage** DNA is the crown jewel of the cell and its most complex molecule. Maintaining it in good repair is a very energy

intensive process. Without energy DNA cannot be properly maintained. Cannabis has been known to reduce cellular energy production by the cell's power plants, mitochondria, for many decades now. This has now been firmly linked with increased DNA damage, cancer formation and aging of the cells and indeed the whole organism. As it is known to occur in eggs and sperm, this will also damage the quality of the germ cells which go into forming the baby and lead directly to damaged babies and babies lost and wasted through spontaneous miscarriage and therapeutic termination for severe deformities.

7) **Cancer induction** Cannabis causes 12 cancers and has been identified as a carcinogen by the California Environmental Protection agency (2009). This makes it also a mutagen. 4 of these cancers are inheritable to children; i.e. inheritable carcinogenicity and mutagenicity. All four studies in testicular cancer are strongly positive (elevation by three fold). Carcinogen = mutagen = teratogen.

8) **Colorado's Teratology Profile**. From the above described teratological profile we would expect exactly the profile of congenital defects which have been identified in Colorado (higher total defects and heart defects, and chromosomal defects) and Ottawa in Canada (long lasting and persistent brain damage seen on both functional testing and fMRI brain scans in children exposed in utero) where cannabis use has become common. Gastroschisis was shown to be higher in all seven studies looking at this; and including in Canada, carefully controlled studies. Moreover in Australia, Canada, North Carolina, Colorado, Mexico and New Zealand, gastroschisis and sometimes other major congenital defects cluster where cannabis use is highest. Colorado 2000-2013 has experienced an extra 20,152 severely abnormal births above the rates prior to cannabis liberalization which if applied to the whole USA would equate to more than 83,000 abnormal babies live born annually (and probably about that number again therapeutically aborted); actually much more since both the number of users and concentration of cannabis have risen sharply since 2013, and cannabis has been well proven to be much more severely genotoxic at higher doses.

9) **Cannabidiol is also Genotoxic** and tests positive in many genotoxicity assays, just as tetrahydrocannabinol does.

10) **Births defects registry data needs to be open and transparent and public.** At present it is not. This looks too much like a cover up.