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

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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).

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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.

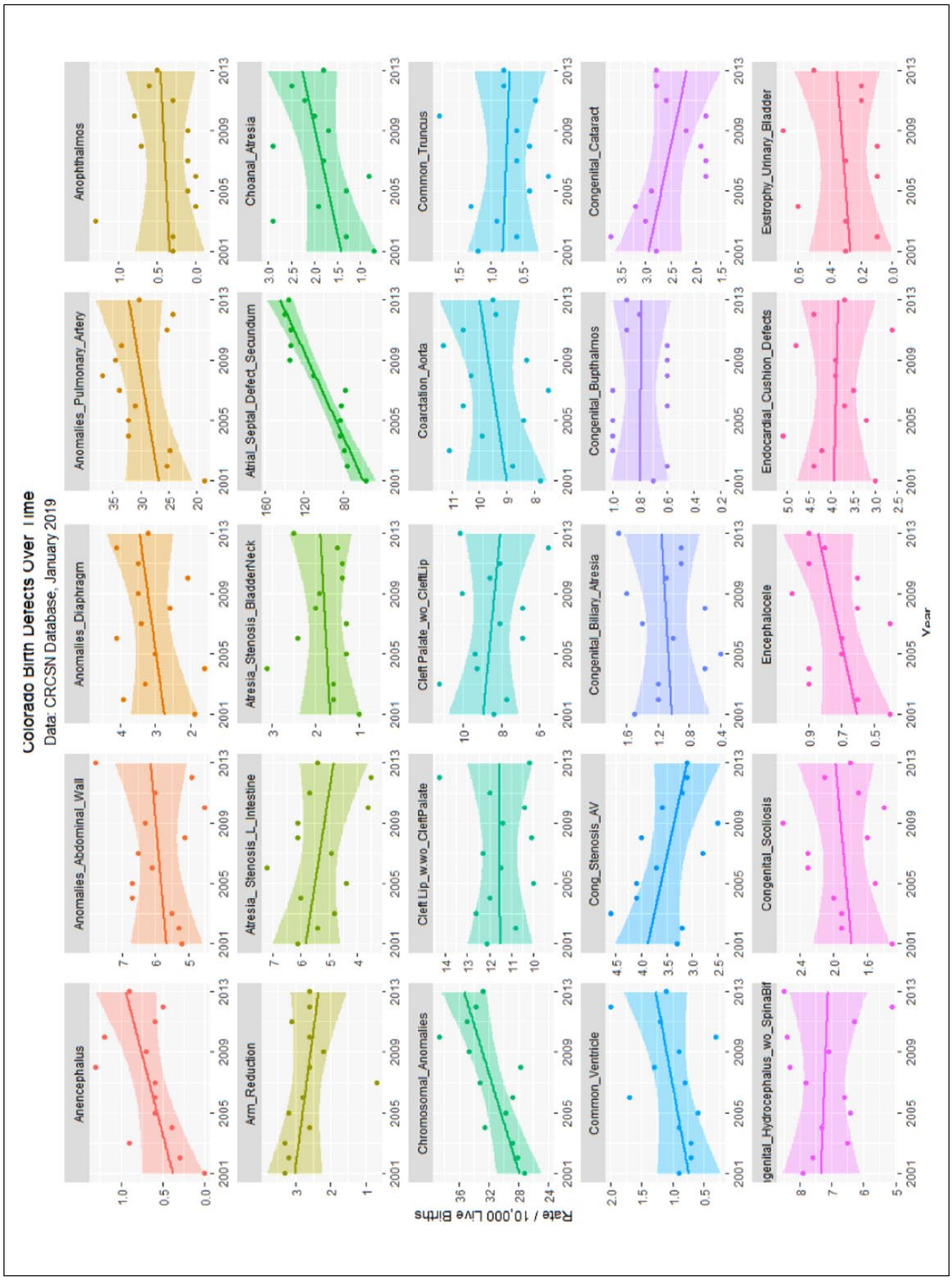

Figure 1. Colorado congenital defects A-E by time, regression lines fitted.

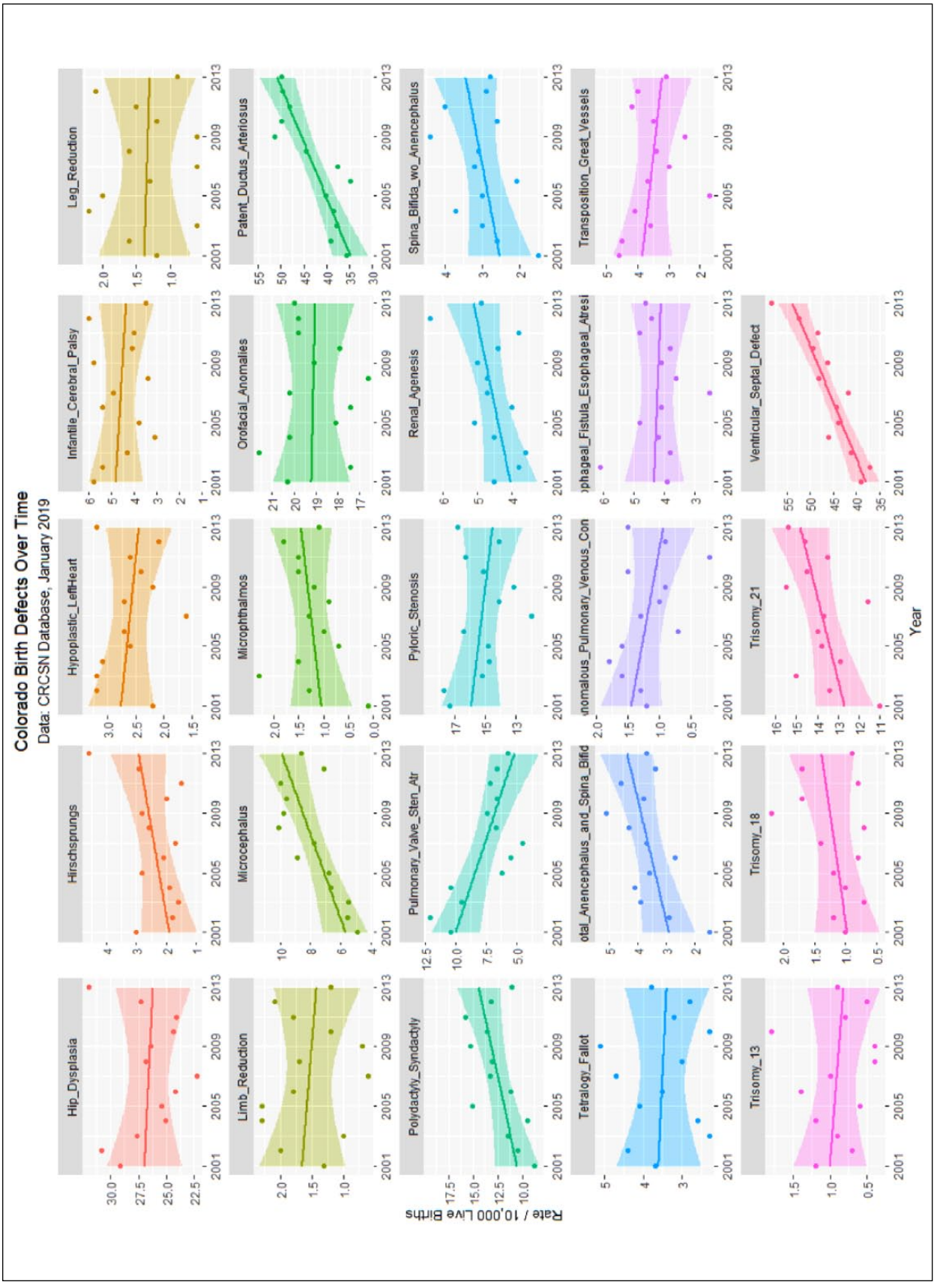

Figure 2. Colorado congenital defects H-V by time, regression lines fitted.

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

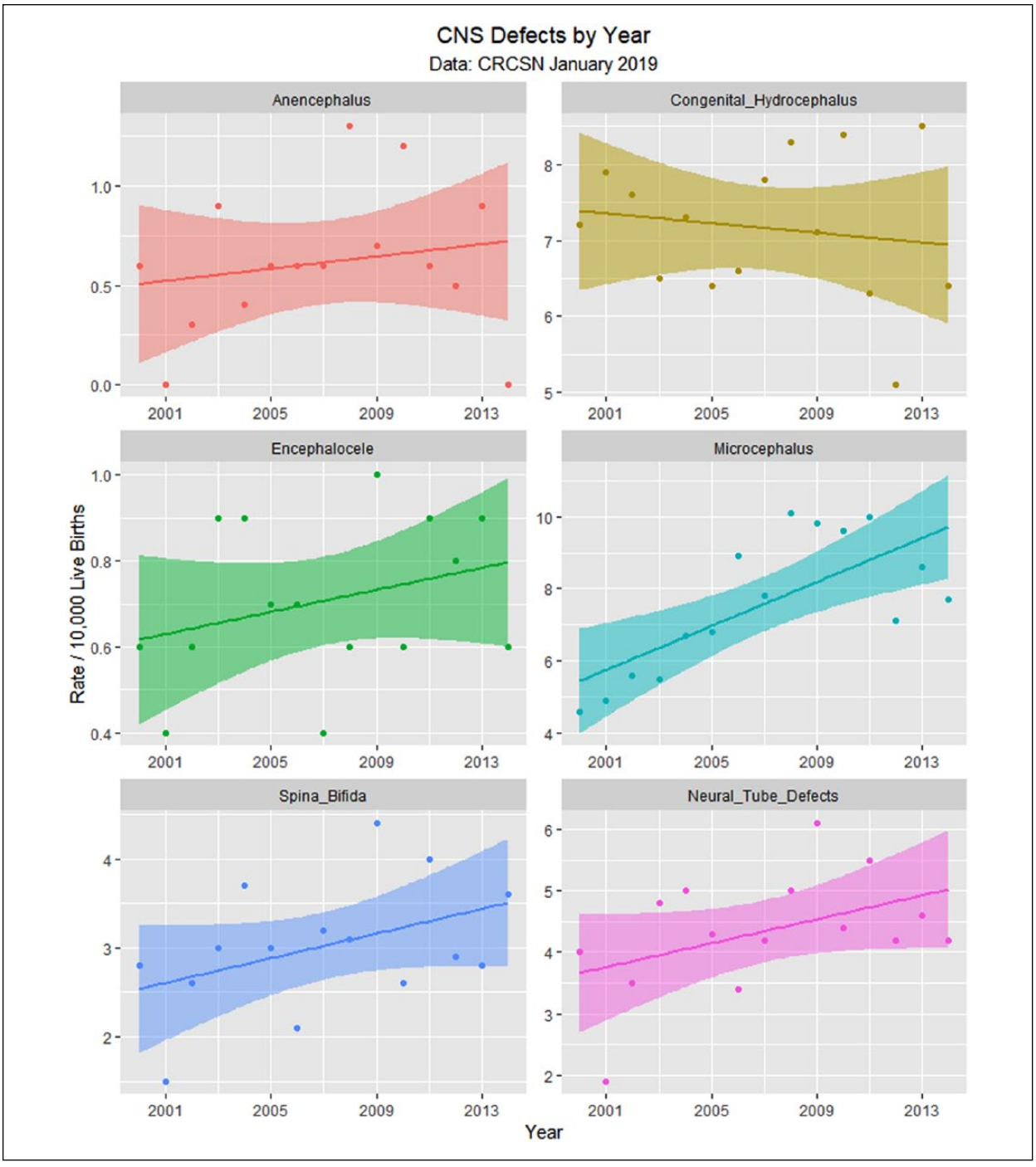

Figure 3. Central nervous system (CNS) defects by time.

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.

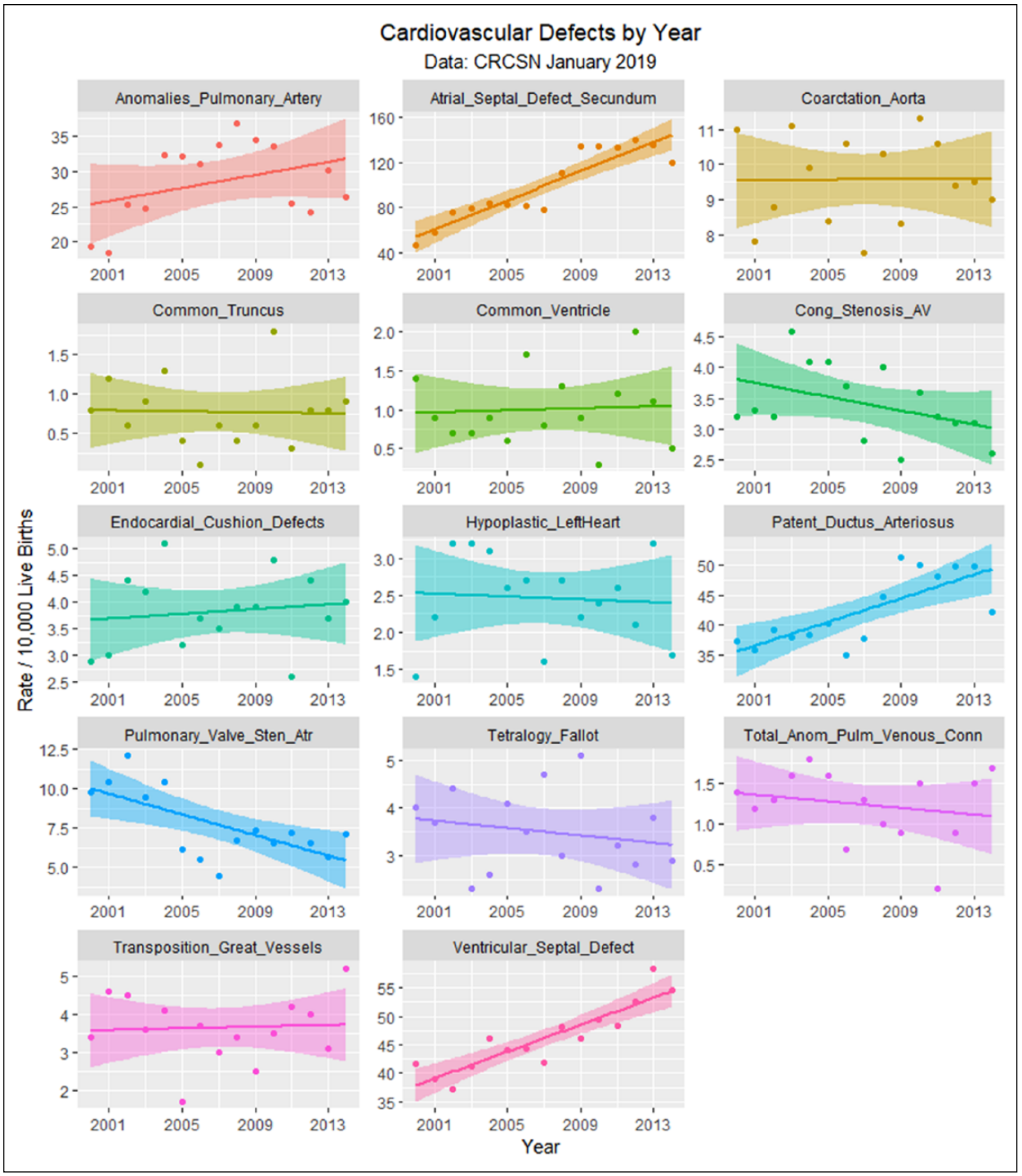

Figure 5. Cardiovascular defects by time.

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.

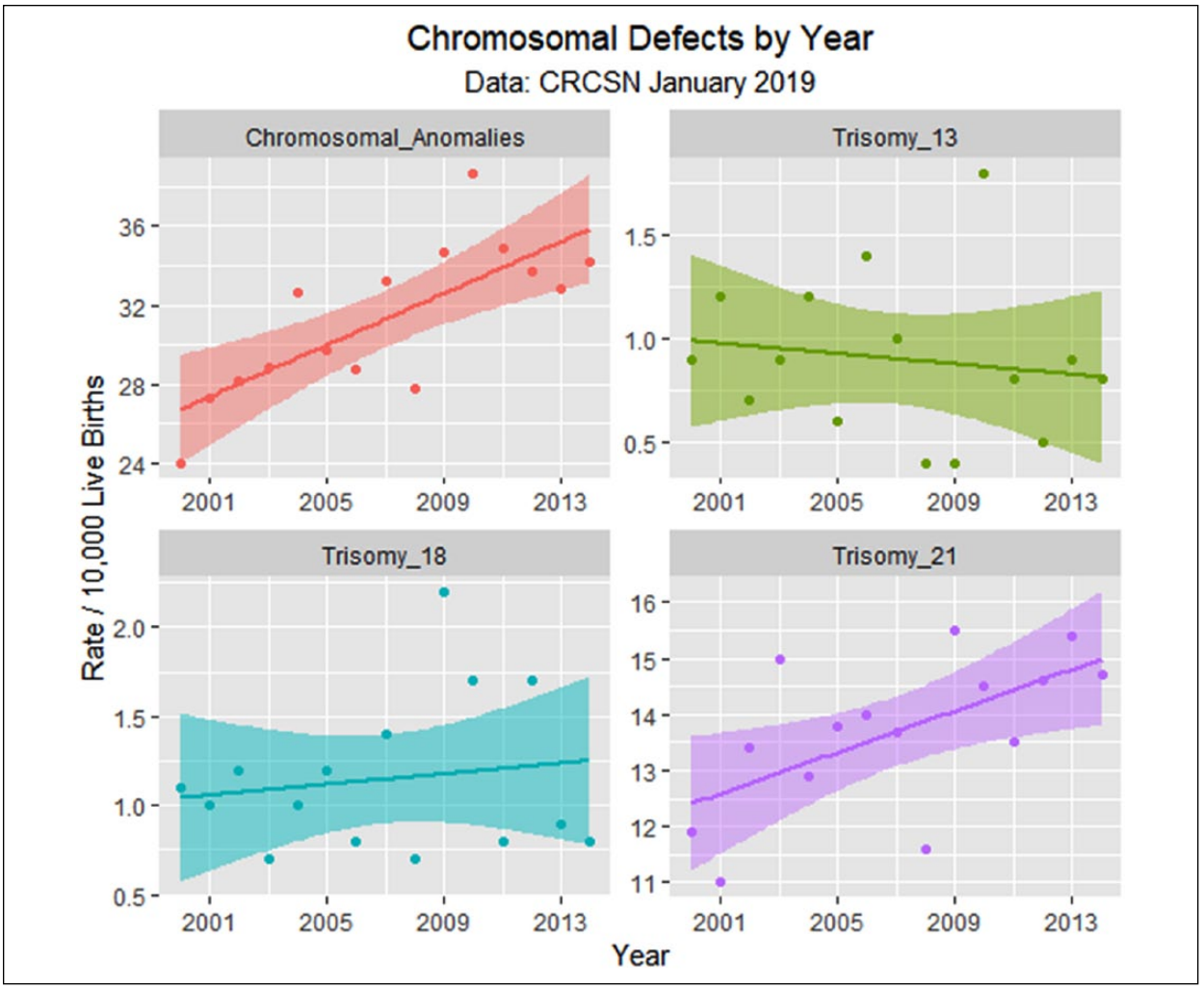

Figure 6. Chromosomal defects by time.

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.

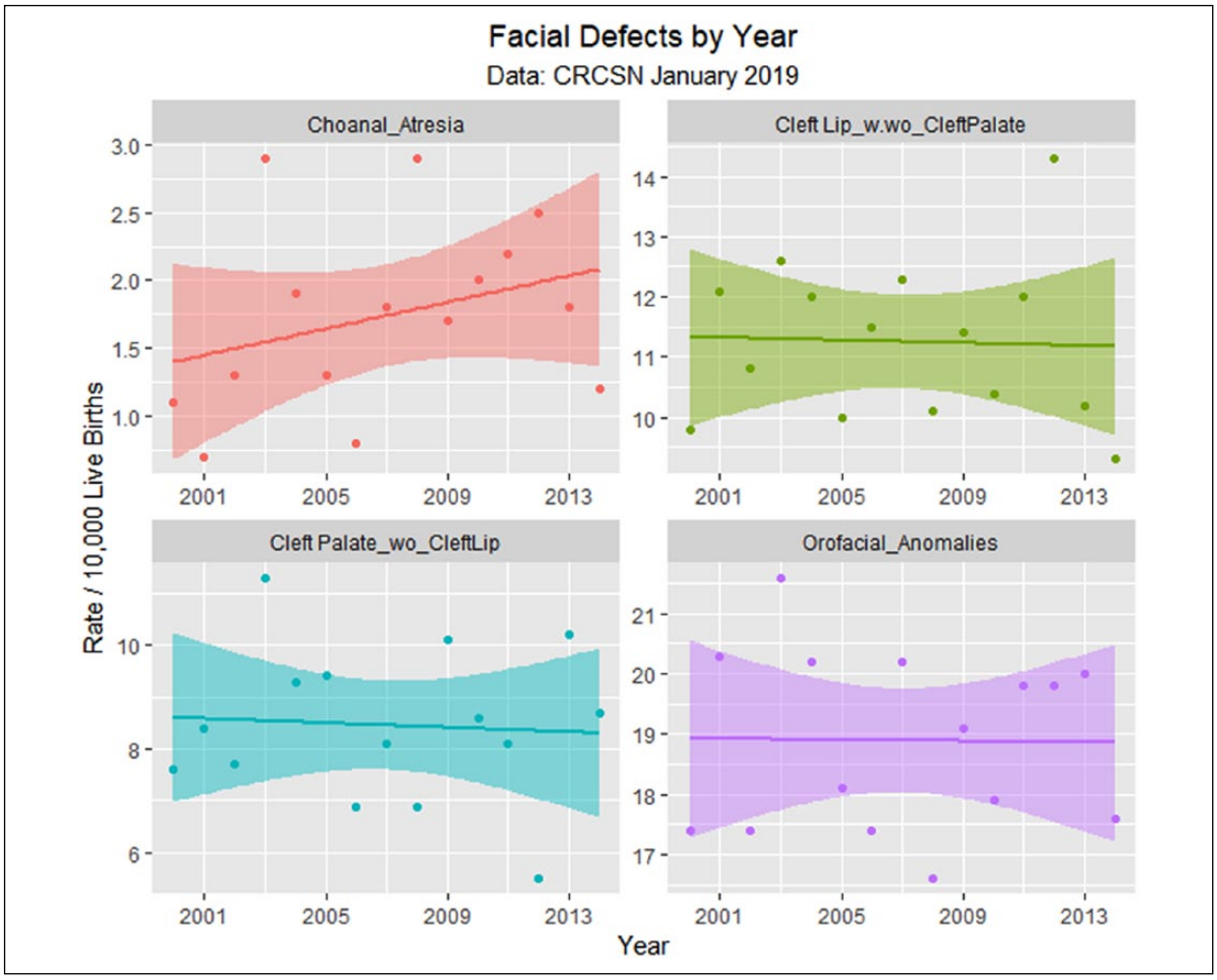

Figure 7. Face defects by time.

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.

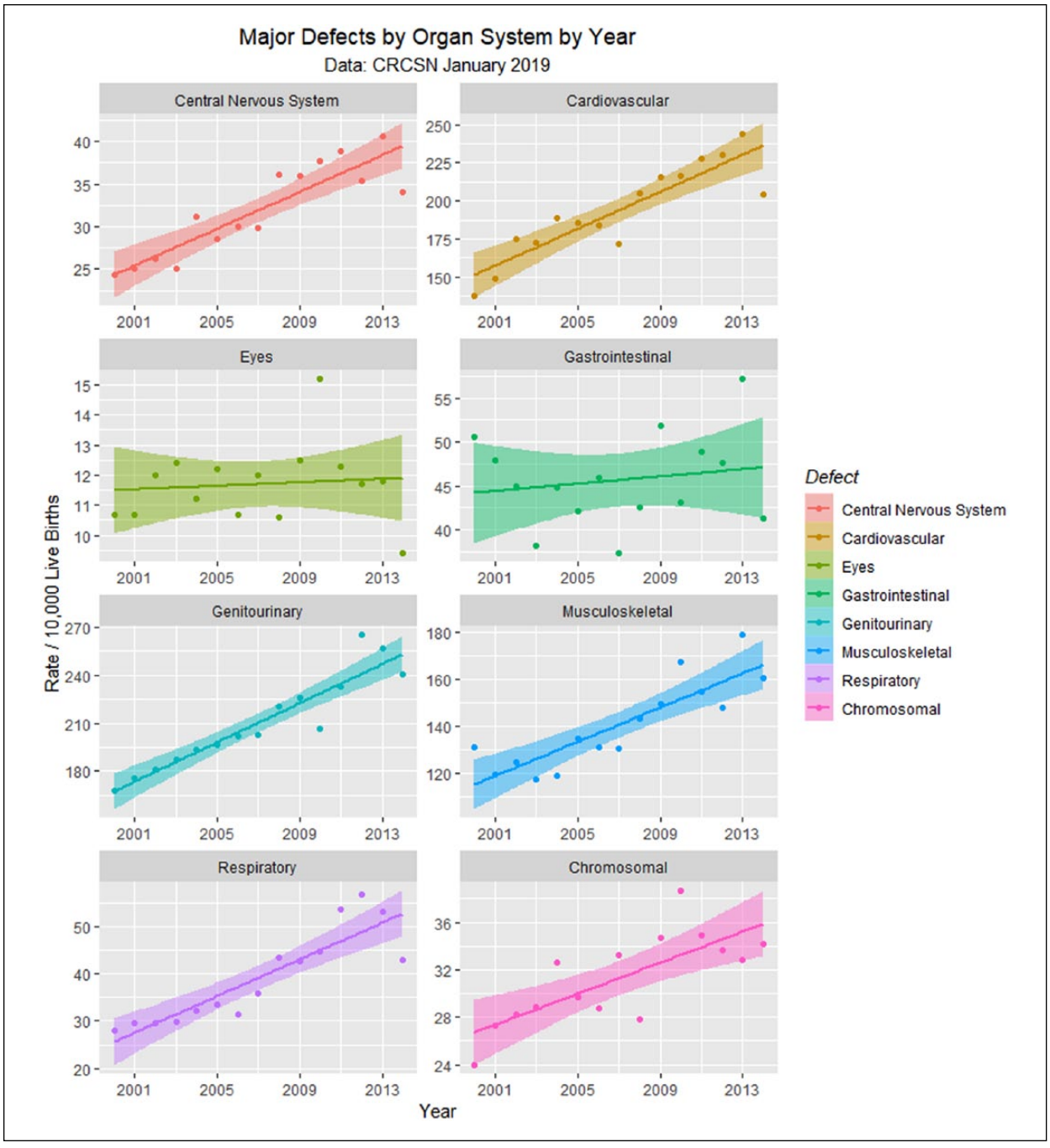

Figure 9. Major defects by time.

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

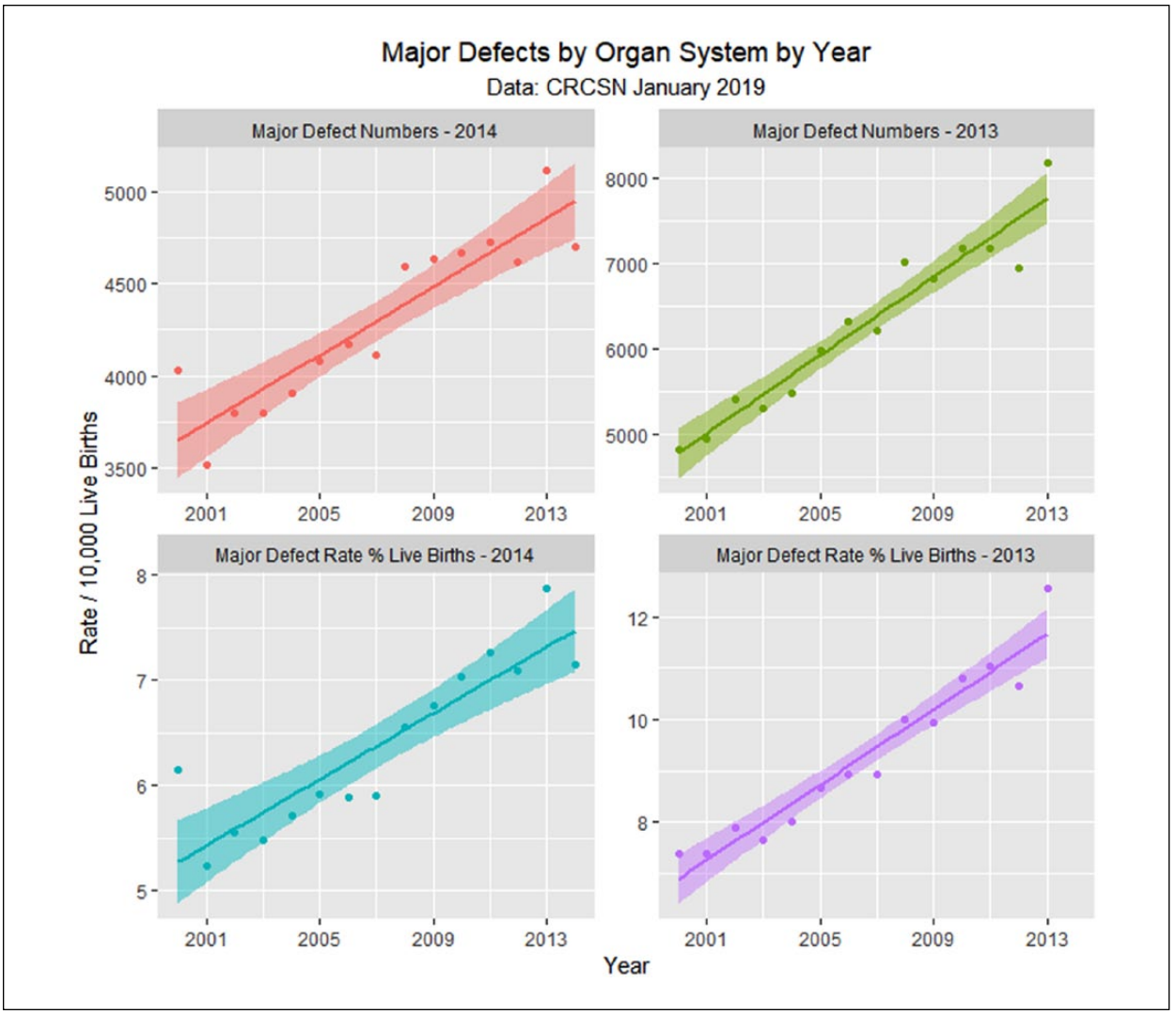

Figure 10. Total defects by time.

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.

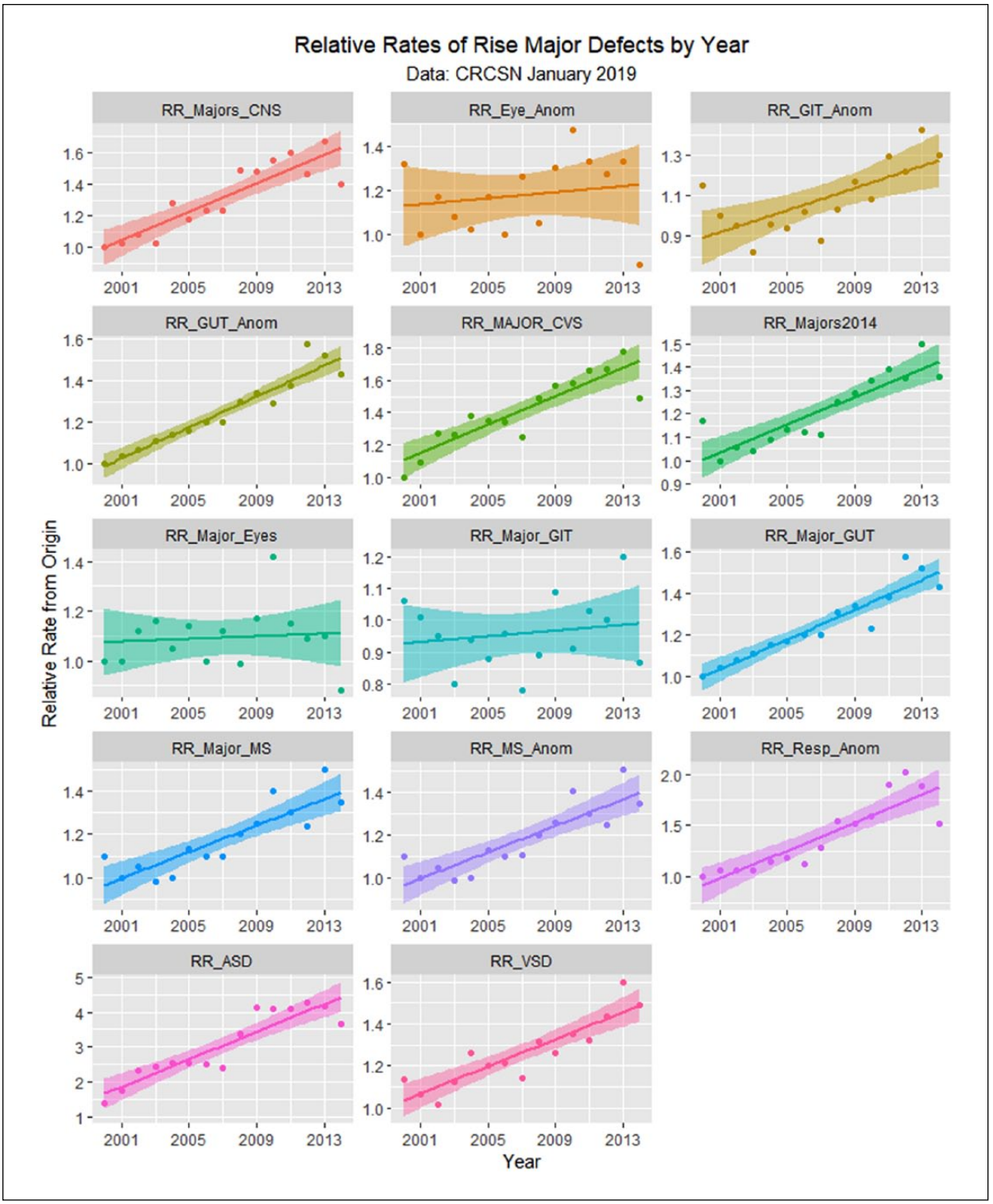

Figure 11. Relative rises in selected defects compared with baseline by time.

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.

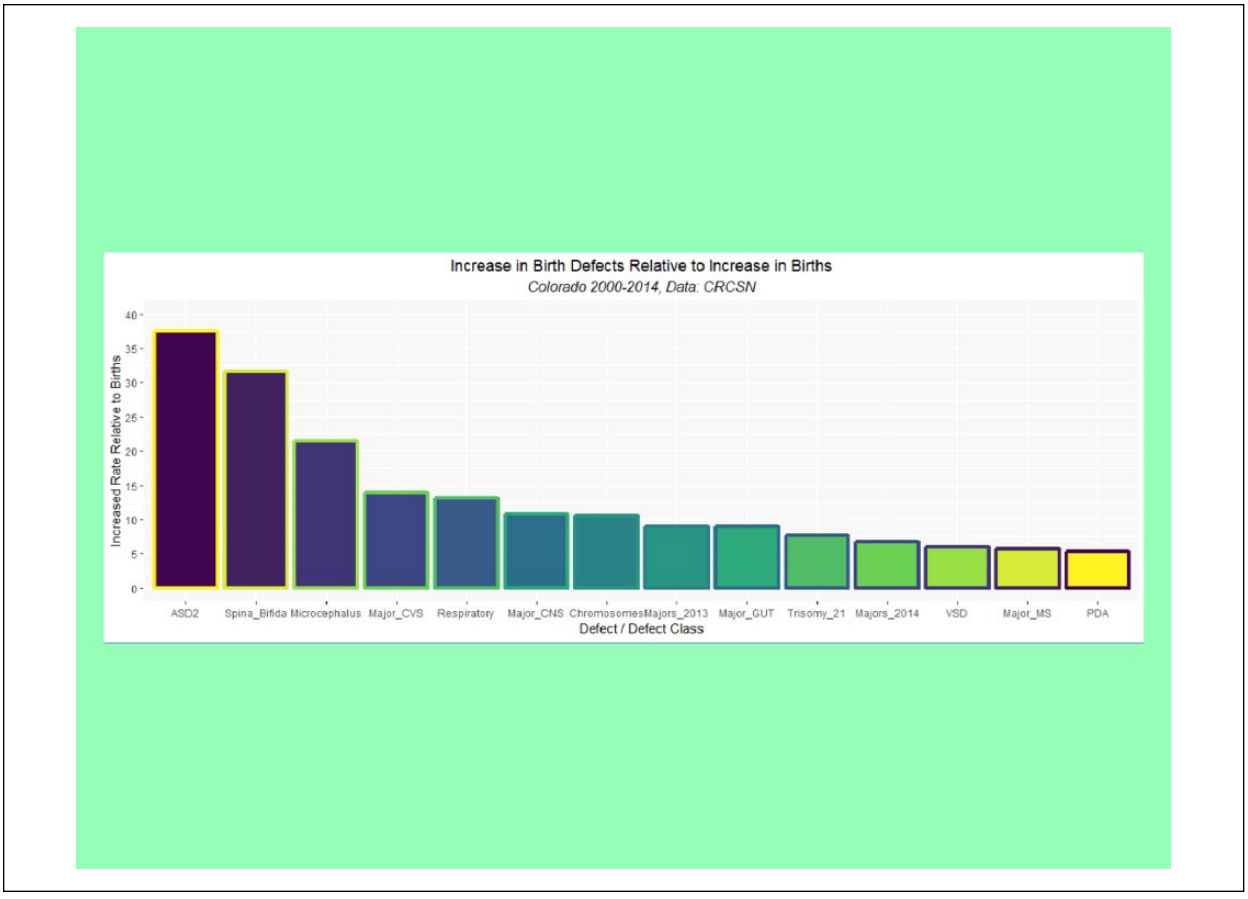

Figure 12. Rise in selected defects relative to rise in births by time.

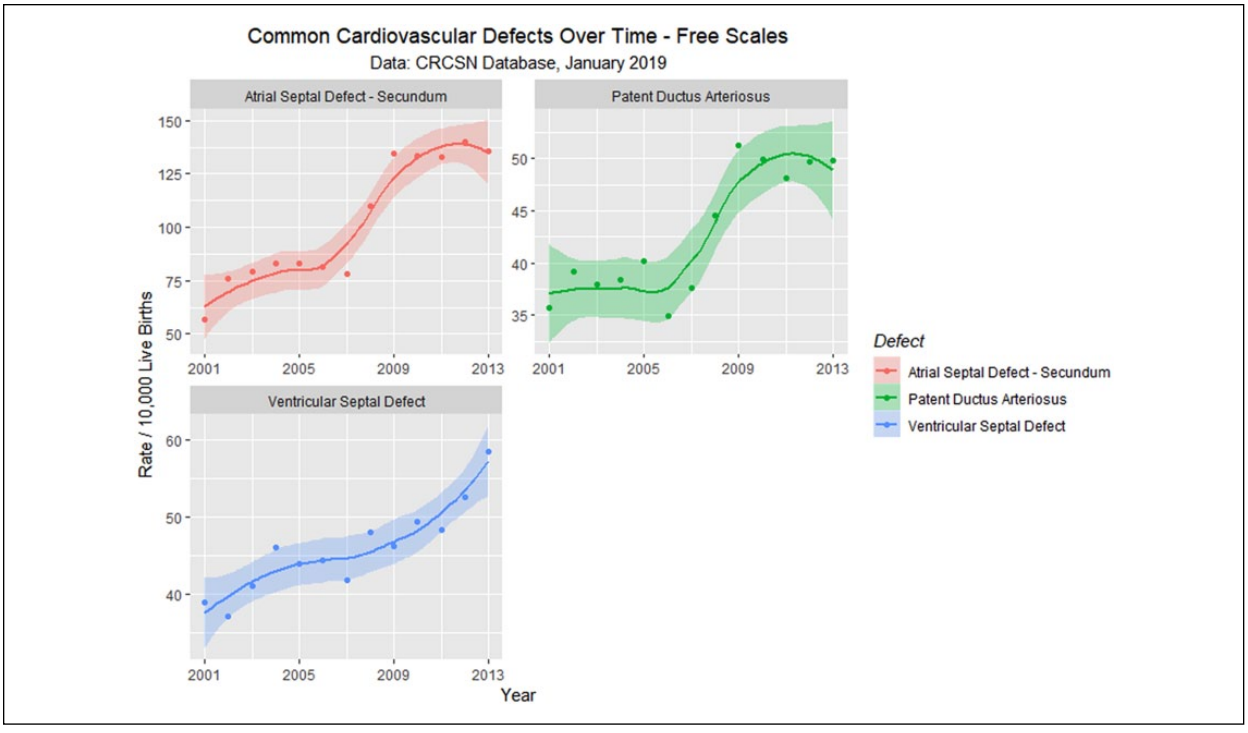

Figure 13. Atrial septal defect, ventricular septal defect, and patent ductus arteriosus—Loess curves by time.

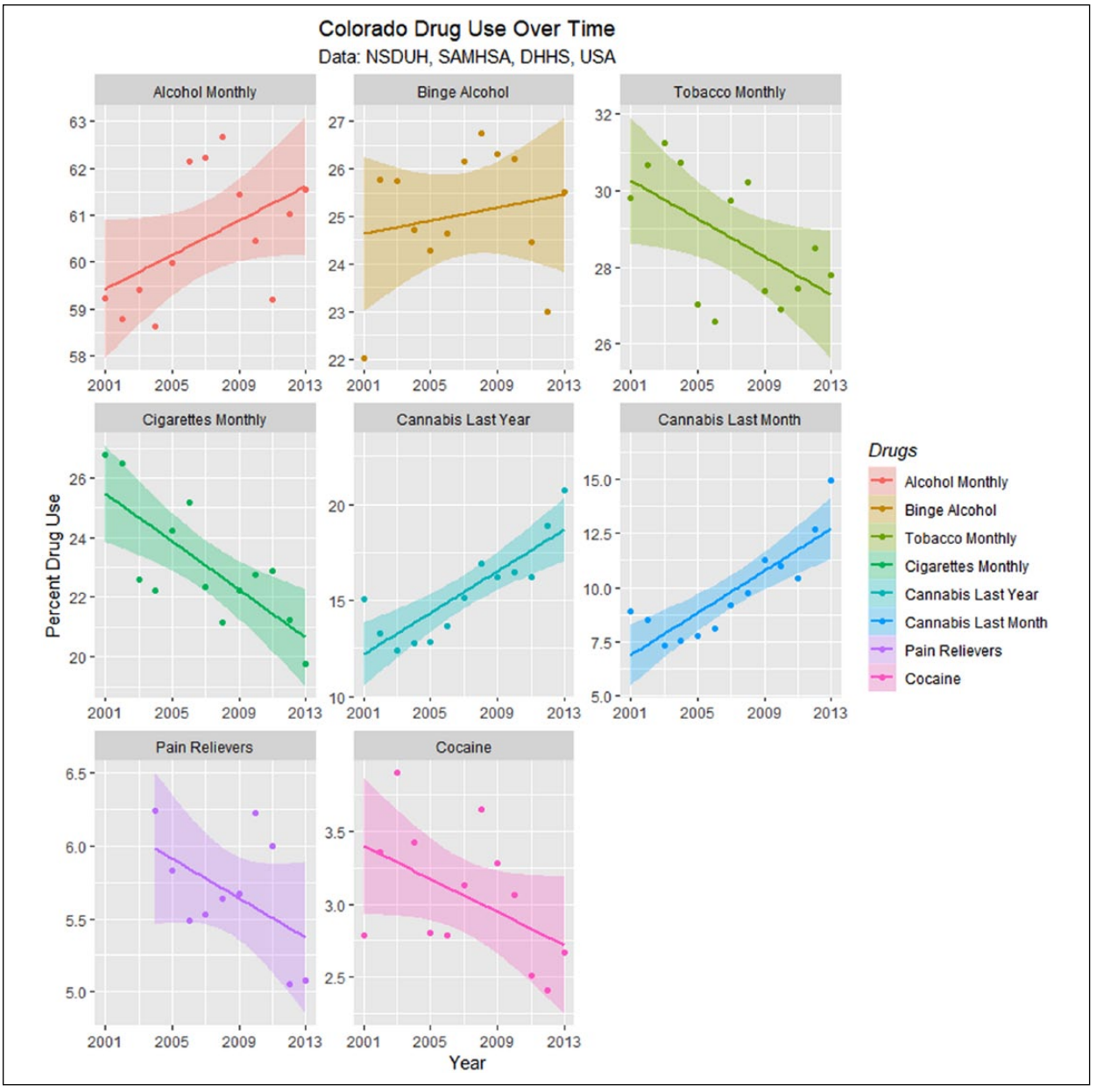

Figure 14. Drug use in Colorado from National Survey of Drug Use and Health (NSDUH) dataset by time with regression lines fitted.

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.

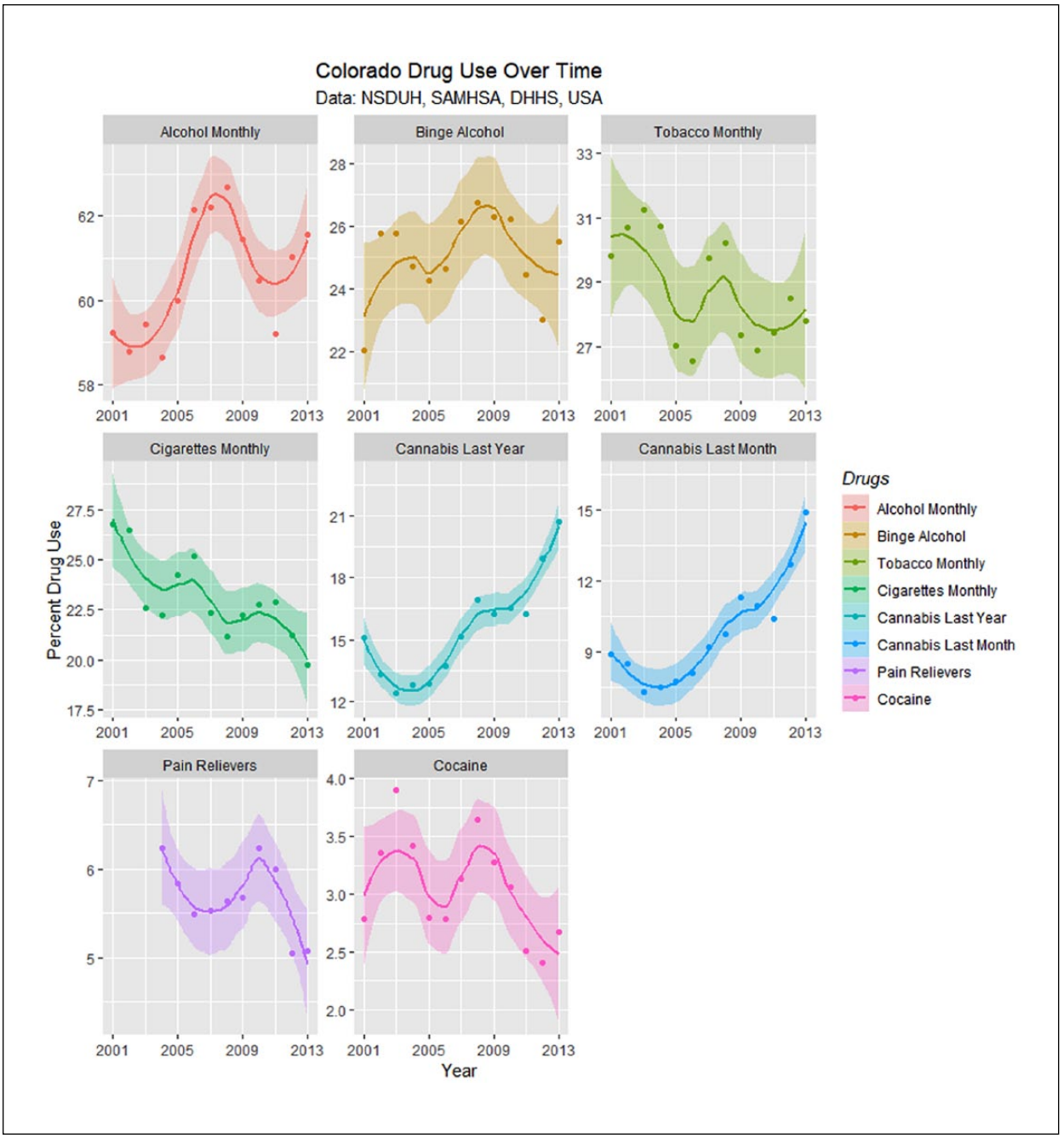

Figure 15. Drug use in Colorado from National Survey of Drug Use and Health (NSDUH) dataset by time with loess curves fitted.

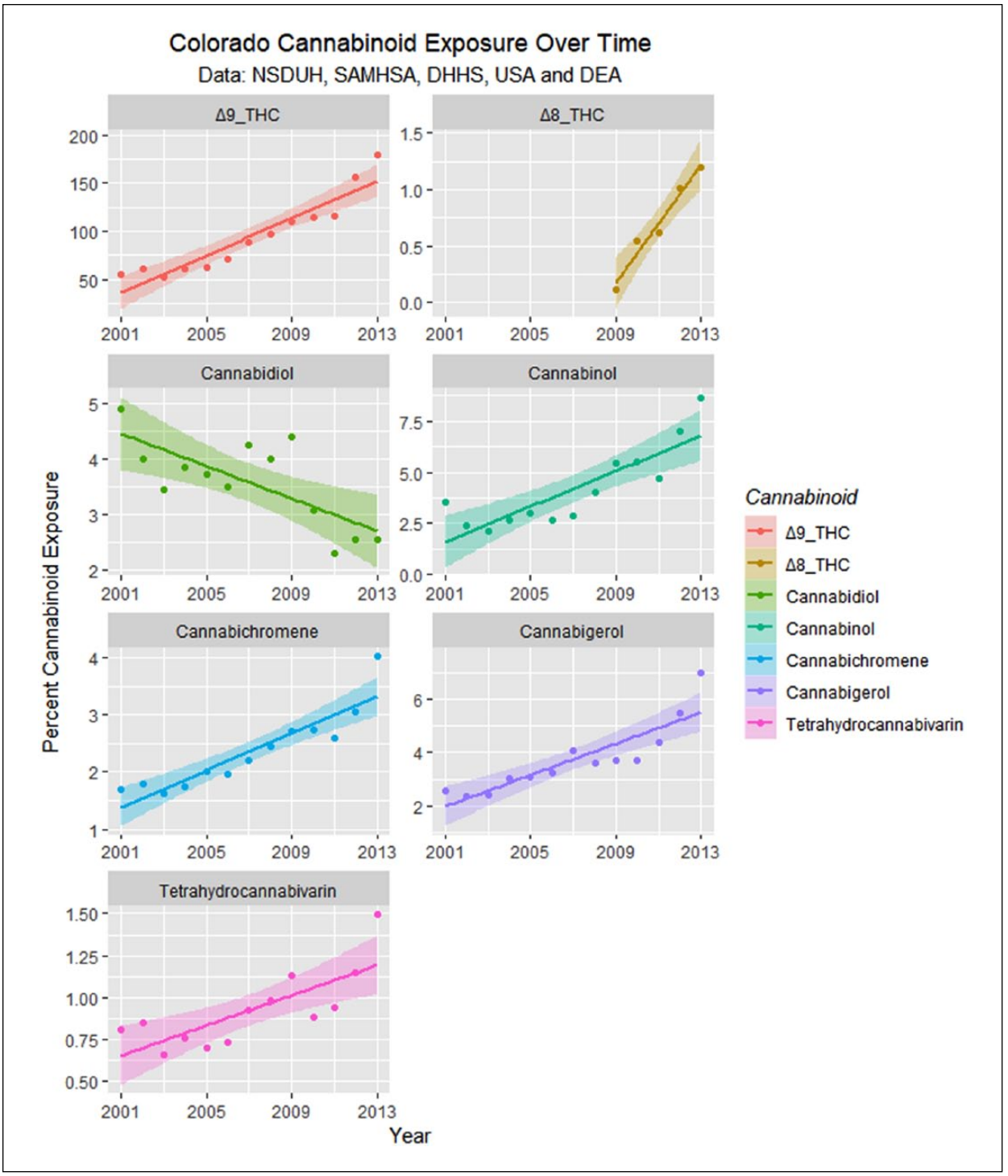

Figure 16. Cannabinoid exposure in Colorado from National Survey of Drug Use and Health (NSDUH) dataset by time with regression lines fitted.

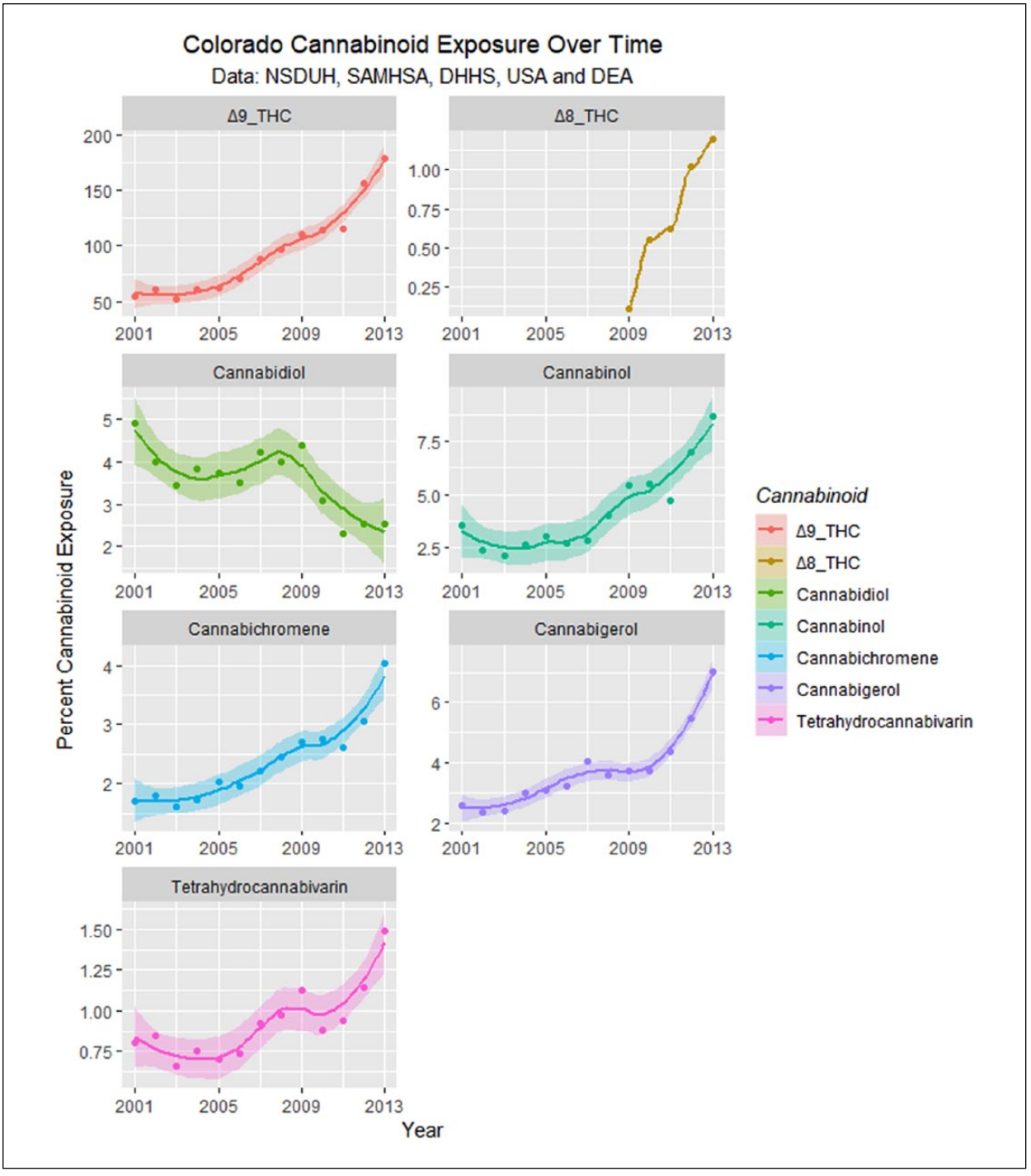

Figure 17. Cannabinoid exposure in Colorado from National Survey of Drug Use and Health (NSDUH) dataset by time with loess curves fitted.

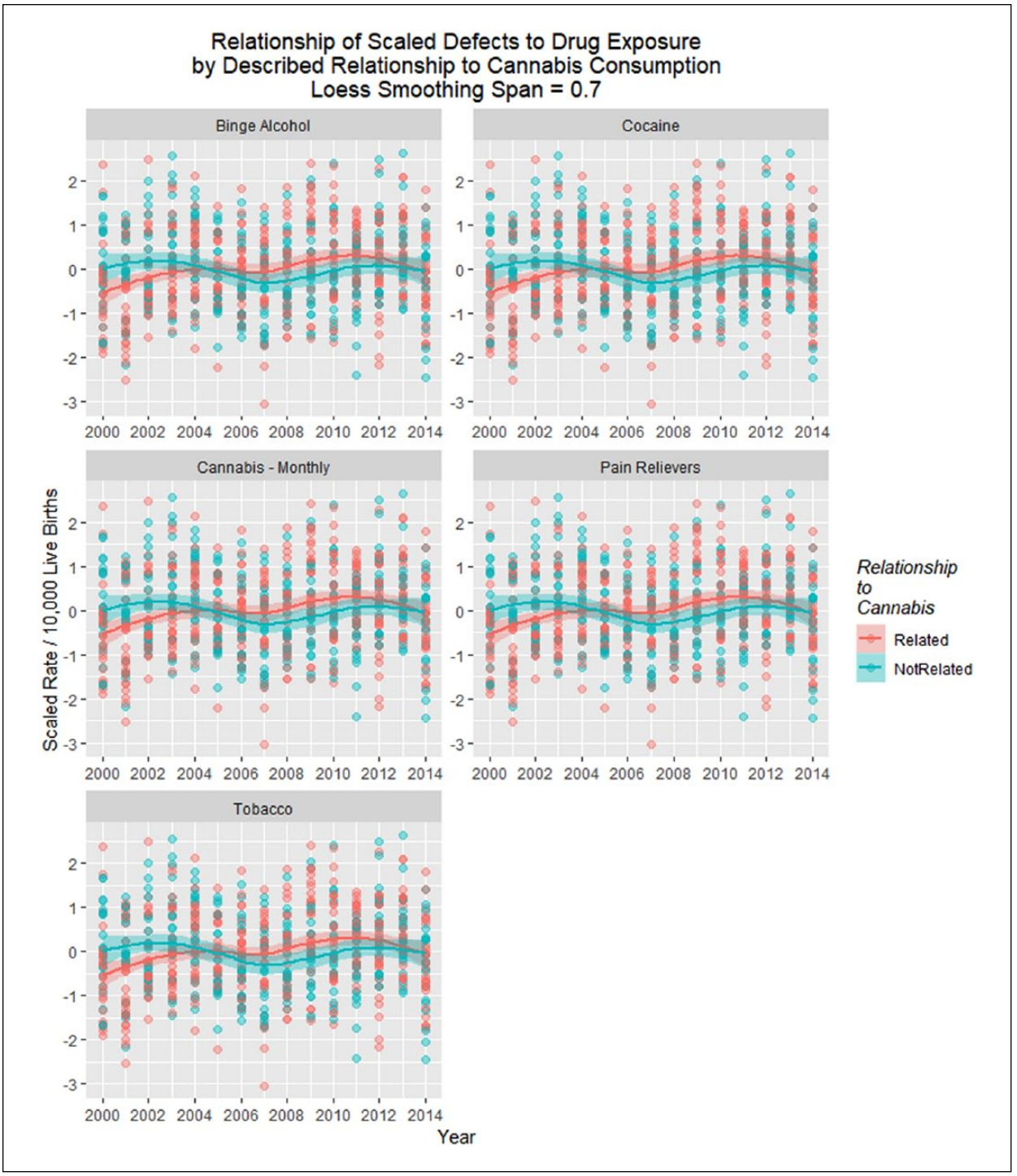

Figure 18. Scaled drug use in Colorado from National Survey of Drug Use and Health dataset by time with loess curves fitted.

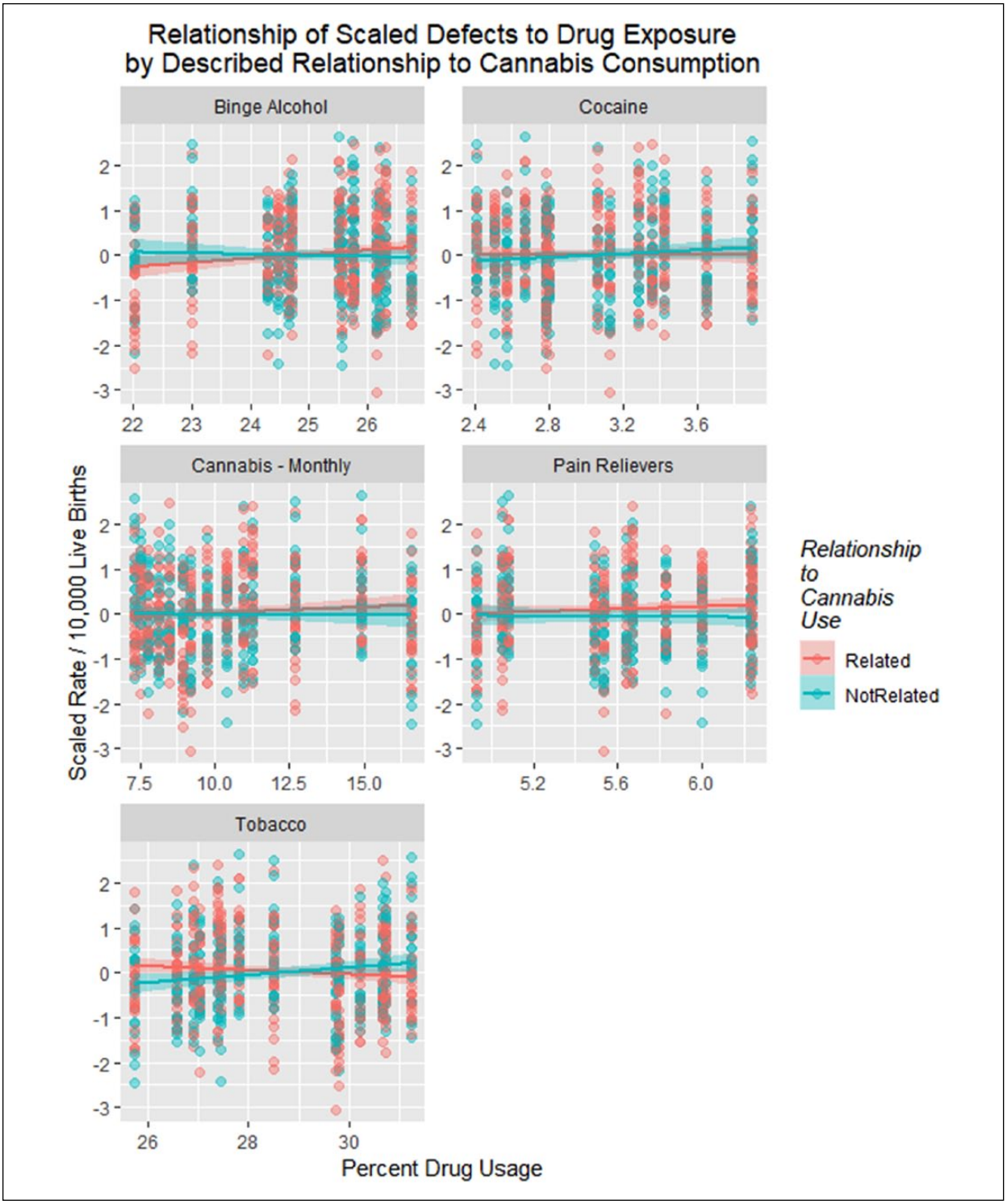

Figure 19. Scaled drug use in Colorado from National Survey of Drug Use and Health dataset by time with regression lines fitted.

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.

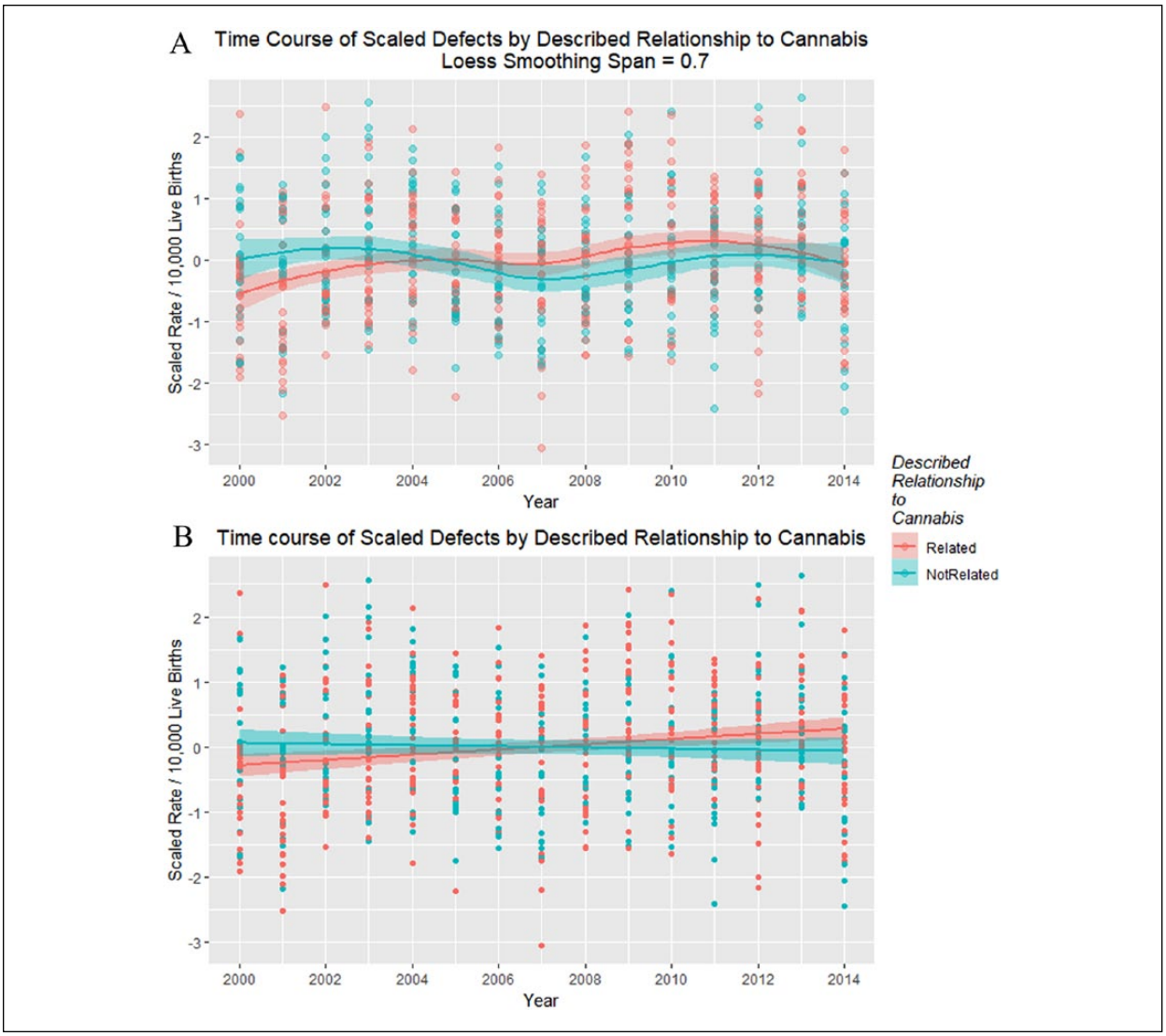

Figure 21. Scaled defects rate as a function of drug use exposure with (A) loess curves and (B) regression lines fitted.

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.

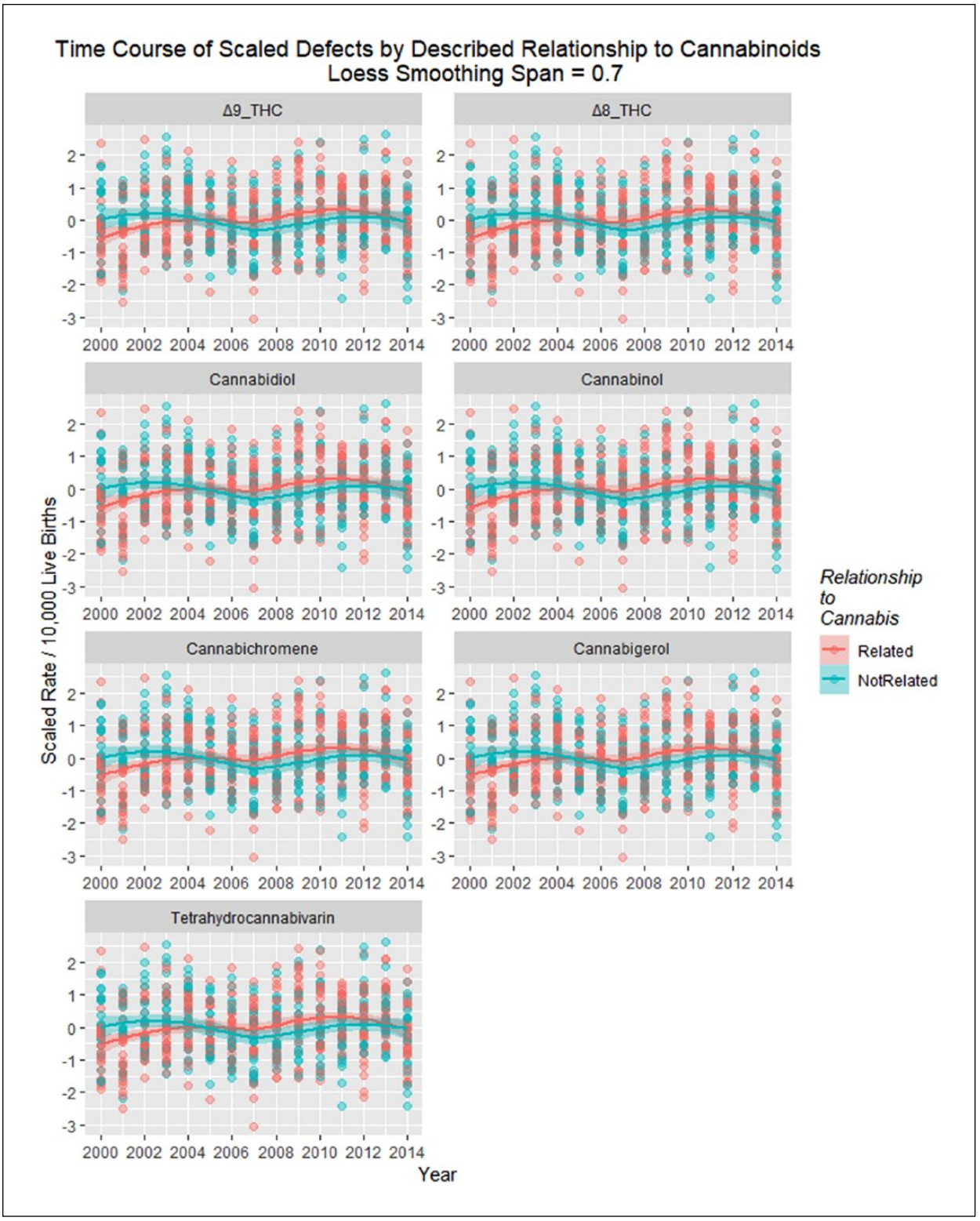

Figure 22. Scaled defects rate as a function of cannabinoid exposure with loess curves fitted. Facetted plot by cannabinoid.

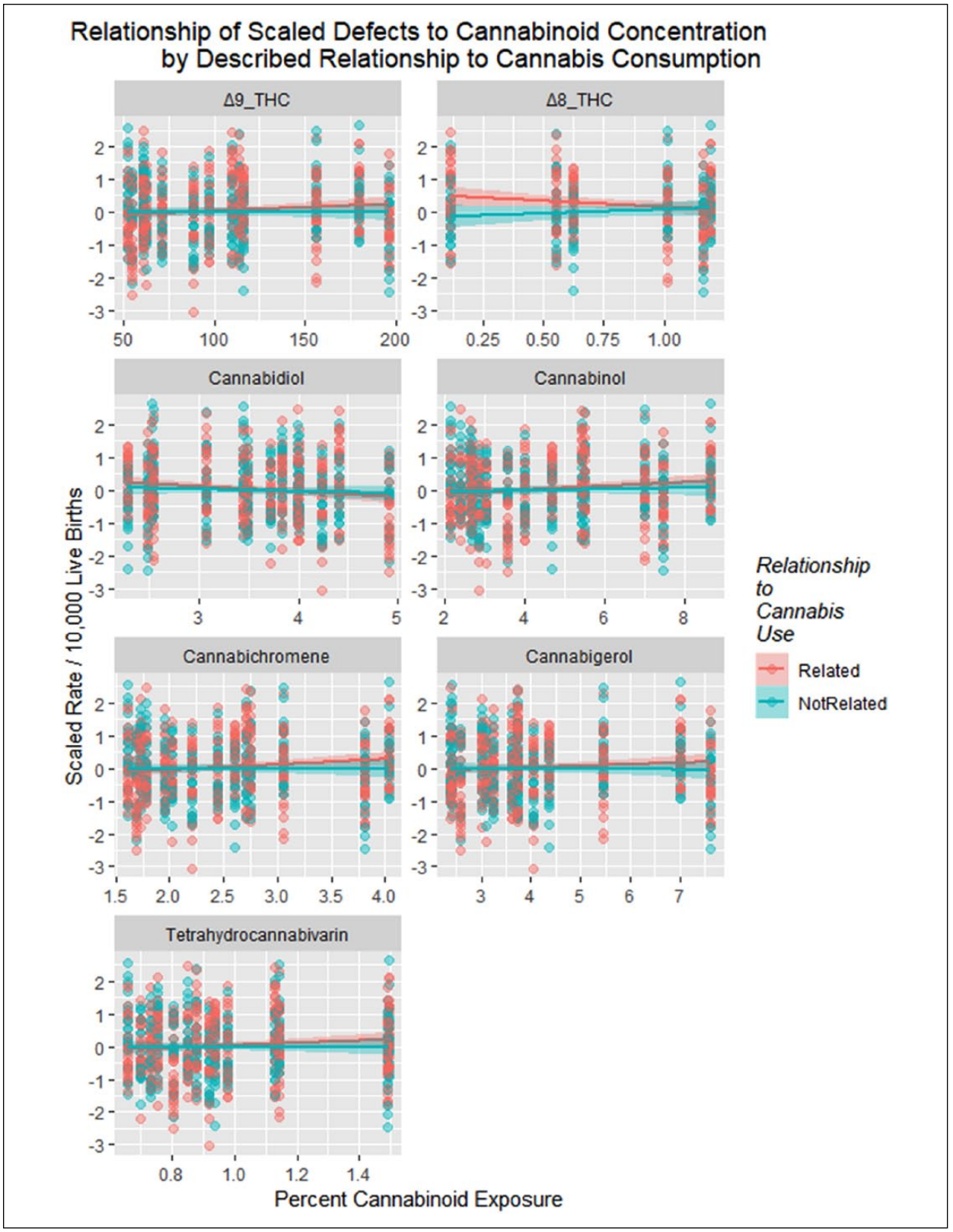

Figure 23. Scaled defects rate as a function of cannabinoid exposure with regression lines fitted. Facetted plot by cannabinoid.

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.

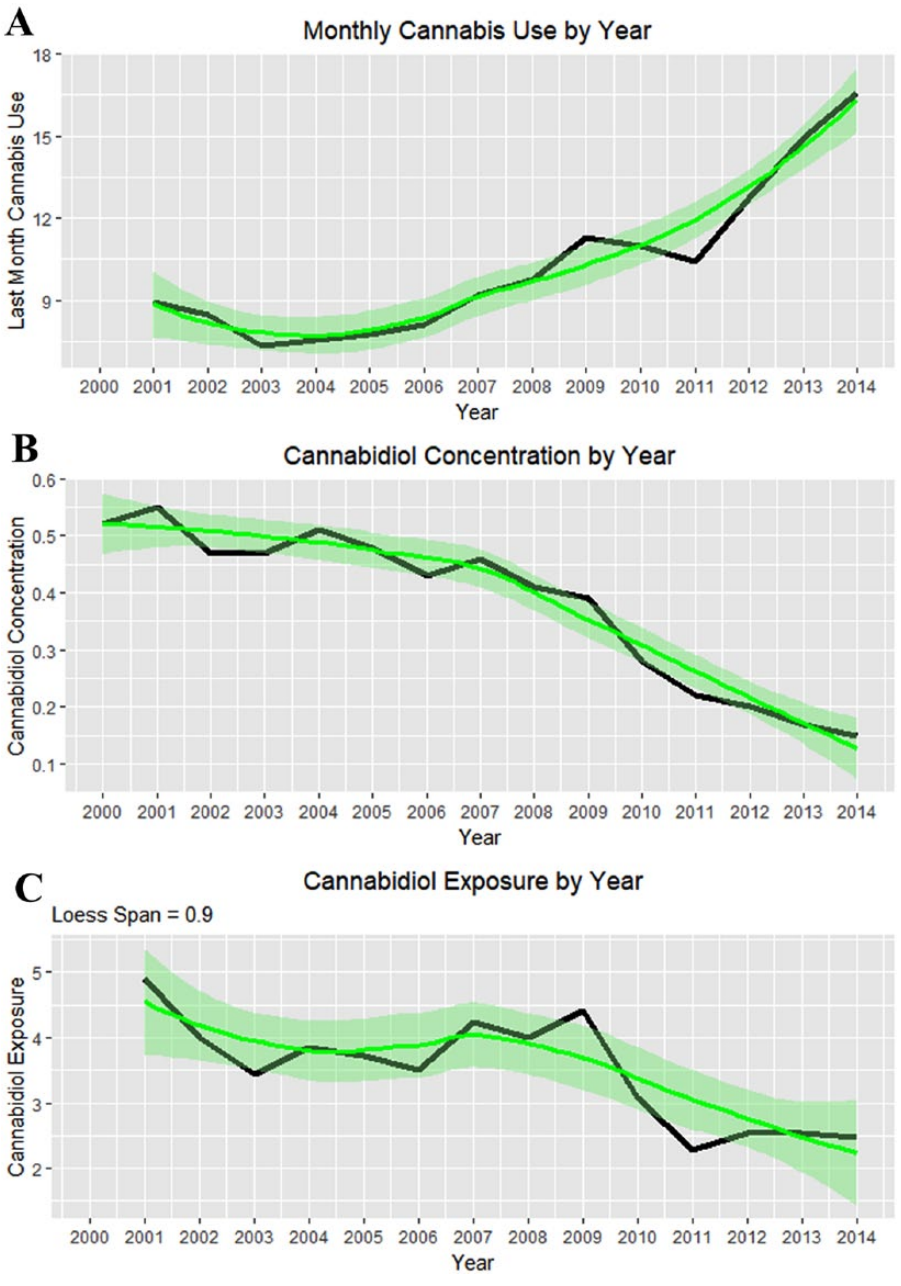

Figure 24. (A) Monthly cannabis use by year. (B) Cannabidiol concentration by year. (C) Cannabidiol exposure by year as the product of (A) and (B).

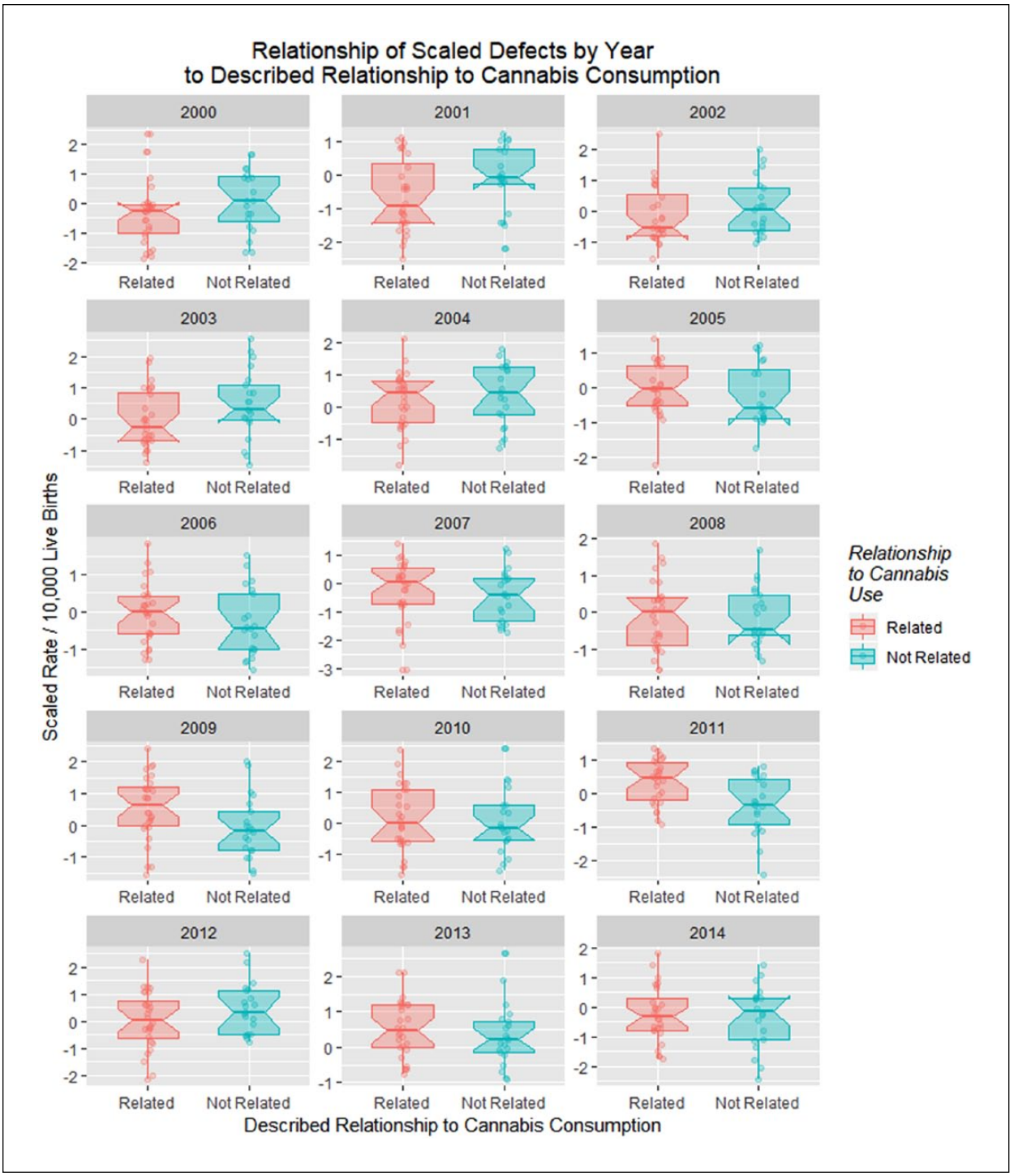

Figure 25. Relationship of scaled defects by year to described relationship to cannabis consumption from the published literature (see Discussion).

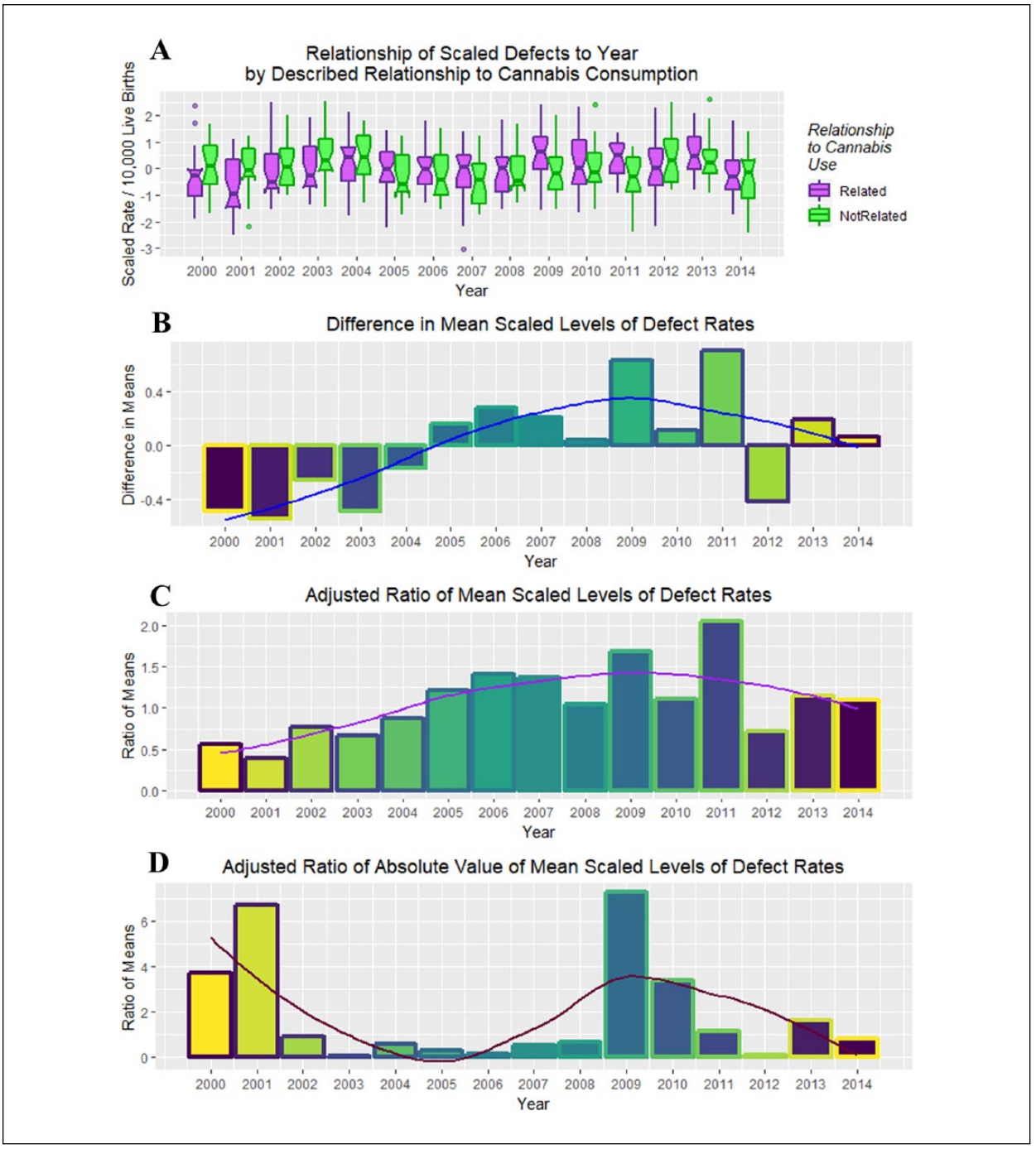

Figure 26. (A) Box plot of relationship of scaled defects to time by described relationship to cannabis use. (B) Difference between cannabis-related and non–cannabis-related rates of scaled scores. (C) Ratio of cannabis-related and non–cannabis-related scaled scores after adjustment by adding unity (1) 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.

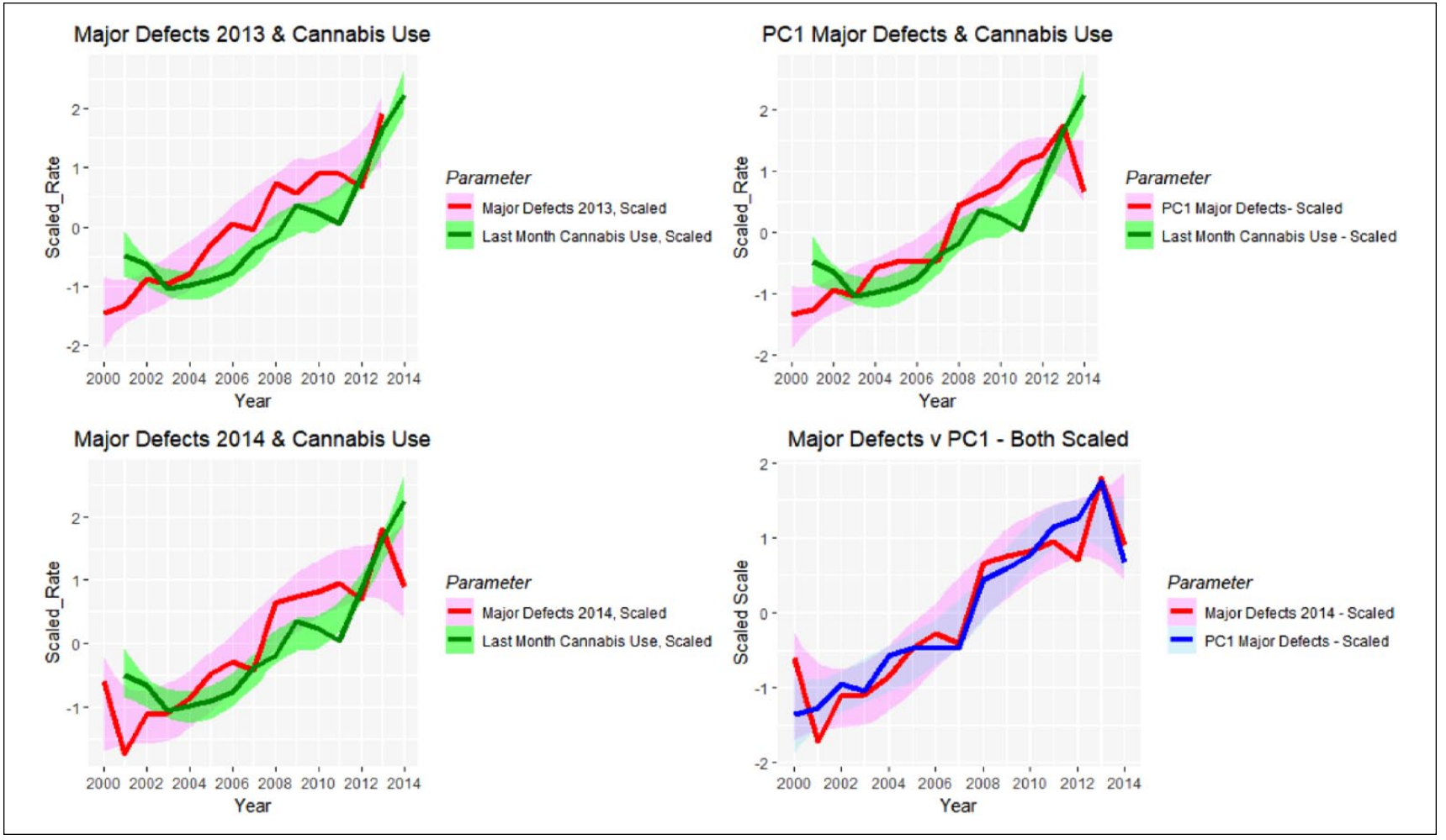

Figure 27. Line plots showing relationship between scaled (A) major defect rates 2013 and last month cannabis use; (B) major defect rates 2014 and last month cannabis use; (C) principal component 1 and last month cannabis use; (D) major defects 2014 and principal component 1 for 2014.

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.

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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.

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