A Geospatiotemporal and Causal Inference Epidemiological Exploration of Substance and Cannabinoid Exposure as Drivers of Rising US Pediatric Cancer Rates

Short Title:

Geospatiotemporal Cannabinoid Exposure and Total Pediatric Cancer Incidence

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Abstract

Background. Age-adjusted US total pediatric cancer incidence rates (TPCIR) rose 49% 1975-2015 for unknown reasons. Prenatal cannabis exposure has been linked with several pediatric cancers which together comprise the majority of pediatric cancer types. We investigated whether cannabis use was related spatiotemporally and causally to TPCIR.

Methods. State-based age-adjusted TPCIR data was taken from the CDC Surveillance, Epidemiology and End Results cancer database 2003-2017. Drug exposure was taken from the nationally-representative National Survey of Drug Use and Health, response rate 74.1%. Drugs included were: tobacco, alcohol, cannabis, opioid analgesics and cocaine. This was supplemented by cannabinoid concentration data from the Drug Enforcement Agency and ethnicity and median household income data from US Census.

Results. TPCIR rose while all drug use nationally fell, except for cannabis which rose. TPCIR in the highest cannabis use quintile was greater than in the lowest (β-estimate=1.31 (95%C.I. 0.82, 1.80), $P=1.80x10^{-7}$) and the time:highest two quintiles interaction was significant (β-estimate=0.1395 (0.82, 1.80), $P=1.00x10^{-14}$). In robust inverse probability weighted additive regression models cannabis was independently associated with TPCIR (β-estimate=9.55 (3.95, 15.15), P=0.0016). In interactive geospatiotemporal models including all drug, ethnic and income variables cannabis use was independently significant (β-estimate=45.67 (18.77, 72.56), P=0.0009). In geospatial models temporally lagged to 1,2,4 and 6 years interactive terms including cannabis were significant. Cannabis interactive terms at one and two degrees of spatial lagging were significant (from β-estimate=3954.04 (1565.01, 6343.09), P=0.0012). The interaction between the cannabinoids THC and cannabigerol was significant at zero, 2 and 6 years lag (from β-estimate=46.22 (30.06, 62.38), $P=2.10x10^{-8}$). Cannabis legalization was associated with higher TPCIR (β-estimate=1.51 (0.68, 2.35), P=0.0004) and cannabis-liberal regimes were associated with higher time:TPCIR interaction (β-estimate=$1.87x10^{-4}$, ($2.9x10^{-5}$, $2.45x10^{-4}$), P=0.0208). 33/56 minimum e-Values were >5 and 6 were infinite.

Conclusion. Data confirm a close relationship across space and lagged time between cannabis and TPCIR which was robust to adjustment, supported by inverse probability

66 weighting procedures and accompanied by high e-Values making confounding unlikely and
67 establishing the causal relationship. Cannabis-liberal jurisdictions were associated with
68 higher rates of TPCIR and a faster rate of TPCIR increase. Data inform the broader general
69 consideration of cannabinoid-induced genotoxicity.
70

Introduction

CDC Surveillance, Epidemiology and End Results (SEER) data from 9 US cancer registries indicates that the age-adjusted total Pediatric (age less than twenty years) cancer incidence rate (TPCIR) has risen 49.0% from 12.96 to 19.32 / 100,000 from 1975-2015 [1]. Cancer incidence is U-shaped across the pediatric age range being higher in the under 5 years and over 14 years age groups [2]. Leukaemias, brain and nervous system, neuroblastoma, soft tissue sarcoma, lymphoma and testicular cancer are amongst the commonest pediatric cancers [2, 3].

Notwithstanding a generally falling mortality rate from childhood cancer, the TPCIR incidence is acknowledged to be rising since the records of collated cancer registries were first published in 1975 [2]. The cause of this unprecednted increase is at present unclear. Moreover major ethnic differentials are evident for tumours such as All Childhood Cancer (ACC), acute lymphatic leukaemia (ALL) and brain and testicular cancers where the rates in African-American patients vary from 20-70% of those in the Caucasian-American community [2]. Again the reasons for such large ethnic disparities are unknown. It therefore appears that several of the major questions relating to the aetiopathogenesis of pediatric cancer are outstanding.

Whilst in adult populations the relationship between cannabis use and cancer incidence is controversial with both positive and negative reports in existence [4, 5], amongst pediatric populations the situation is much clearer. It was noted by the California Environmental Protection Agency in a very detailed literature review that five of six studies reported a positive relationship [6-11]. Parental cannabis use has been linked with acute lymphatic leukaemia, acute myeloid leukaemia, childhood astrocytoma, rhabdomyosarcoma and neuroblastoma [2, 7-12]. Together these comprise 60-70% of the total cancers seen in children younger than 14 years and those between 15 and 20 years [2]. In such a context it becomes plausible that the rise in cannabis use since the 1960's may be a primary driver of total pediatric cancer.

Testicular cancer is a particularly interesting case. It is well established that testicular cancer occurs mainly in younger men with an age peak at 30-34 years and 20% of cases occur in the pediatric age range [1]. The testes houses the germ cells and cannabinoids are known to have

myriad direct effects on the reproductive tract in both sexes [13-17]. There is great uniformity in studies of the cannabis-testicular cancer link as all four studies found a risk elevation of over two-fold [18-21] with an overall risk for current, weekly and chronic smokers of non-seminomatous germ cell tumours estimated in meta-analysis of 2.59 (95%C.I. 1.60-4.19) [22]. Since pediatric cancer often results from inherited genetic errors [23, 24] this implies that major genetic errors in germ cells are induced by parental cannabis exposure.

Adding to concerns related to the potentially genotoxic actions of prenatal cannabinoid exposure (PCE) is an increasing interest in elevation of many birth defects following PCE in Hawaii, Colorado, Canada and Australia [25-28]. A recent report noted a three-fold rise in total congenital defects in the northern Territories of Canada where more cannabis is smoked [28]. Downs syndrome, due to a major genetic trisomic error, has also been found to be elevated following PCE in Hawaii, Colorado and Australia [25-27] and this syndrome has an established link with childhood ALL with 6-10% of Downs syndrome children being affected by this malignancy [29, 30].

As discussed below the physiology and pathophysiology of both the endocannabinoid system and the impacts of diverse exogenous phytocannabinoids is presently being studied in great detail and major impacts on reproductive health, genetic and physiological quality of gametes, epigenetic effects on both DNA methylation and histone synthesis and signalling, immunomodulatory and mitochondriopathic effects, and transgenerational inheritable epigenetic effects in both man and mouse are well established and have been demonstrated by a number of investigators [15, 17, 31-38].

Concerns are heightened by the recent demonstration that 69% of cannabis dispensaries in Colorado recommended cannabis use to pregnant patients for various symptoms in a recent telephone survey [39] and that in 2017 an estimated 161,000 women used cannabis whilst pregnant across USA [40, 41].

Taken together these data suggest that an improved understanding of cannabis-related carcinogenesis in the closely defined pediatric context might well lead to important insights into cannabis-related genotoxicity more generally [42, 43]. Moreover the advent of

sophisticated geospatial analysis together with some of the formal techniques of causal inference analysis implies that sophisticated and modern analytical procedures could be brought to bear on these important and increasingly topical issues. Techniques such as inverse probability weighting and e-Values are designed to formally investigate causal, as opposed to merely associational, relationships.

The objective of this study was to determine if the rise in pediatric cancers across USA paralleled the recent rise in the use of cannabis when considered formally across space and time, and if the relationship met the criteria for causal inference when assessed by strict quantitative criteria.

Methods

Data. Annual data on age-adjusted rates of pediatric cancer cases occurring in patients less than 20 years old was accessed from the publicly available SEER*Explorer website [1]. Data on state-based pediatric cancer rates was accessed via the SEER*Stat software from the SEER / NCI database [44]. Drug use data was accessed from the nationally representative National Survey of Drug Use and Health (NSDUH) conducted by the Substance Abuse and Mental Health Services Administration (SAMHSA) [45]. This survey reports a 74.1% response rate [46]. Data on the following drug variables was collated: monthly cigarette use; annual alcohol use disorder, monthly cannabis use, annual analgesic abuse and annual cocaine use. Data on ethnic composition and median household income by state and year was accessed via the tidycensus package in R from the US Census Bureau. The ethnicities for which data was collected were: Caucasian American, African American, Hispanic American, Asian American, American Indian / Alaskan Native American, Native Hawaiian / Pacific Islander American. Data on national cannabinoid concentrations for Δ9-tetrahydrocannabinol (THC), cannabinol, cannabigerol and cannabichromene was obtained from various published reports [47-49]. Data on cannabis legal status was adduced from an internet search [50].

Derived Data. Given the clear differences in drug use by ethnicity it was considered important to formally take ethnic cannabis use into account in regression modelling. Data on the frequency of cannabis use by ethnicity was available at the national level from the SAMHSA Substance Abuse and Mental Health Data Archive (SAMHDA) Restricted Use Data Analysis System (RDAS) [45]. For each ethnicity and for each year the percentage of the ethnicity using cannabis at the midpoint of the indicated frequency were multiplied together and summed to gain an ethnic cannabis use index. Hence if fraction x of an ethnicity used cannabis from 20-30 days per month then x would be multiplied by 25. This was repeated and summed across all use frequencies to obtain a specific ethnic cannabis use index for that year. This index was multiplied by the state cannabis use rate and the THC concentration in that year to derive an estimate of the ethnic exposure to THC in each state. Similarly the concentration of selected cannabinoids was multiplied by the state cannabis use rate to derive a state based exposure to that cannabinoid. Cannabis use quintiles were defined in each year and concatenated to form strata across all years.

Missing data. The total pediatric cancer rate for Wyoming 2008 was absent. This was imputed as the mean of its rate in 2007 and 2009. The rate of analgesic use was missing for all states in 2015. This was imputed as the mean of the state rates for 2014 and 2016.

Statistics. R version 4.0.2 (2020-06-22) from CRAN was used for data analysis and accessed via the RStudio 1.2.5042 (2009-2020) GUI. Data analysis was performed in September 2020. Graphs and map-graphs were drawn using packages ggplot, albersusa and sf. Covariates were log-transformed to approximate normality based on the Shapiro-Wilks test. Linear, mixed effects, panel, robust marginal structural models and spatial models were studied using packages base, nlme, plm, survey and splm (spatial panel linear models) respectively [51-53]. In each case model reduction was performed by the classical technique of serial deletion of the least significant term. A variety of modelling procedures was employed for the following reasons. Mixed effects regression was useful for state-wise study of data, for inverse probability weighted corrections, and for generation of standard deviations which can be input to eValue calculations. Panel regression modelling was well suited to the time series sequential nature of the dataset, can be inverse probability weighted and allowed the use of both lagging and instrumental variables. Robust regression was conducted to examine the robust effects after inverse probability weighting. Spatiotemporal regression was performed as the data are inherently distributed across space and time and there was good evidence from the models for both spatial and temporal autocorrelation (see Results). As the models also produce a variance estimate their output is well suited to the calculation of e-Values. Inverse probability weighting was conducted with the ipw package and e-Values for regression models were calculated with the package EValue. Tests for trend were conducted with the chi squared test in Base. T-tests were conducted for parametric group comparisons and were two tailed. $P<0.05$ was considered significant throughout.

Panel analysis utilized the pooling technique, a time effect, the random method of Swarmy, the instrumental method of Amemiya and were inverse probability weighted. Robust structural models were conducted by state and were inverse probability weighted.

Spatial analysis. Interstate geospatial linkages were made on the “queen” basis of shared edges or corners and compiled with the poly2nb function from package spdep. They were edited as described so that no state, such as Alaska or Hawaii, was left geospatially isolated (as shown in Results). Model specification of spatial models was undertaken from the

general full model to the specific [54]. That is to say the standard spatiotemporal regression model was conducted using the splm function spreml (spatial panel random effects maximum likelihood) including spatial autocorrelation after Kapoor, Kelejian and Prucha [55], random effects, serial correlation in the residual errors and spatial autocorrelation, coded as sem2srre in spreml models [52]. Significance of the final model parameters phi, psi, rho and lambda which quantify random error, serial correlation in the residuals, spatial error correlation and spatial autocorrelation respectively, confirmed that this maximal structure was appropriate (see Results tables). The spatial error adjustment of Kapoor, Kelejian and Prucha takes into account spatial correlation in both the exposure and the outcome and this was considered to be reflective of the real world situation in this case [54]. spreml models do allow the use of both spatial and temporal lagging which has been utilized as described. At the time of writing splm and spreml spatial models do not allow the use of instrumental variables or inverse probability weighting which implies the need for supplementary techniques.

Causal inference. Two techniques of causal inference were employed. Inverse probability weights were constructed for the exposure of interest, monthly cannabis exposure, as a function of the other drug variables which were our primary variables of interest. These weights were used to weight mixed effects, panel and robust regression models appropriately. The effect of this procedure is to equalize exposure across study groups and has also been validated for continuous exposures as considered here. Such techniques are said to create pseudo-randomized groups from which causal inferences can properly be made. We also calculated e-Values which are a measure of the association required of any unmeasured potential confounder variable with both the exposure and the outcome to discount the reported results. In the literature minimum (of the two) e-Values above 1.25 are commonly considered of relevance [56].

Data availability. All data, including R code, inverse probability weights, geospatial weights, and source datasets, has been made publicly available through the Mendeley data base repository and may be accessed at this URL: http://dx.doi.org/10.17632/cnwv9hdspd.1 .

Ethics. The datasets used were all publicly available and de-identified. No reference has been made at any point to individually identifiable data. The present work was approved by the University of Western Australia Human Research Ethics Committee on June 7th 2019 (No. RA/4/20/4724).

263 Results
264
265 Inspection of the SEER*Explorer website shows that at the national level that age-adjusted
266 rates of several cancers in the pediatric age group (younger than 20 years) are rising including
267 all cancer and acute lymphatic leukaemia which is the commonest tumour. The annotation
268 on the SEER website is made from the JoinPoint program which also comes from NCI and
269 CDC. These tumours are listed in Table 1 and illustrated in Figure 1 using data based on 9
270 US cancer registries 1975-2017. Supplementary Figure 1 shows other cancers which are
271 mostly rising utilizing data from 21 US cancer registries 2000-2017.
272
273 Figure 2 shows national drug exposure data from NSDUH 2003-2017 and US Census bureau
274 median household income data. It is important to note that exposure to most classes of drugs
275 is dropping with the notable exception of cannabis. Since SAMHSA NSDUH data could be
276 temporally matched to the CDC SEER cancer database for the years 2003-2017, this became
277 the period of analysis.
278
279 Figure 3 shows the concentration of various cannabinoids found in federal cannabis seizures
280 1980-2017 [47-49].
281
282 Figure 4 shows the age-adjusted state-based TPCIR plotted as a function of exposure to the
283 various substances listed. The regression line for cannabis is noted to be weakly and non-
284 significantly positive.
285
286 Figure 5 shows plots of the TPCIR rate against selected cannabinoids. The regression lines
287 for THC and cannabigerol appear to be strongly positive.
288
289 Figure 6 shows the TPCIR as a function of ethnic cannabis exposure. In each case the
290 regression line appears to be strongly positive and up-sloping.
291
292 Table 2 lists applicable results from linear regression against time, cannabis, THC, various
293 substances, cannabinoids and ethnicity. Many results are significant with the notable
294 exception of cannabis.
295

Figure 7 shows the result of assessing the TPCIR as a function of cannabis use quintiles both cross-sectionally (boxplots) and over time (scatterplots). Panel A appears to show a rising trend with cannabis use quintile. One notes in particular that the notches of the fourth and fifth quintiles do not overlap those of Quintiles 1 and 2 which indicates significance. In Panel B the highest two quintiles seem to be above the lower ones over time. Panel C and D look at the data dichotomized into the two highest quintiles compared to the three lower ones. Again in Panel C it is clear that the notches of the upper quintiles do not overlap those of the lower ones. Panel D shows that this holds true over time. Raw mean quintile data with standard errors appears in Supplementary Table 1.

When comparing the highest and lowest quintile of cannabis use the TPCIR in the highest quintiles is significantly greater than that in the lowest quintile (t=5.038, df=299.6, $P=8.15x10^{-7}$). Comparing the two dichotomized cannabis quintile groups they are also significantly different (t=5.641, df=673.6, $P=2.4810^{-8}$). The chi squared test for trend across the quintiles does not reach significance (Chi.Squ.=465.4, df=420, P=0.0623). When these data are examined by linear regression the significant results shown in Table 3 are found.

Table 3.: Linear Regressions on Quintiles

Parameter Estimates			Model Parameters			
Parameter	**Estimate (C.I.)**	**P-Value**	**R-Squared**	**F**	**dF**	**P-Value**
Quintiles						
lm(Cancer_Rate ~ Quintile)						
Quintile 2	0.2 (-0.29, 0.69)	0.4242	0.04527	9.34	4,745	2.27E-07
Quintile 3	0.14 (-0.35, 0.63)	0.5655				
Quintile 4	0.72 (0.23, 1.2)	0.0042				
Quintile 5	1.31 (0.82, 1.8)	1.8E-07				
Dichotomized Quintiles						
lm(Cancer_Rate ~ Dichotomized_Quintiles)						
Upper_2_Quintiles	0.9 (0.58, 1.22)	3.9E-08	0.0383	30.9	1,748	3.86E-08
Dichotomized Quintiles Over Time						
lm(Cancer_Rate ~ Year + Dichotomized_Quintiles)						
Upper_2_Quintiles	0.9 (0.59, 1.2)	1.1E-08	0.111	47.8	2,747	<2E-16
lm(Cancer_Rate ~ Year : Dichotomized_Quintiles)						
Lower_3_Quintiles	0.139 (0.1, 0.17)	1.2E-14	0.111	47.7	2,747	<2E-16
Upper_2_Quintiles	0.1395 (0.1, 0.17)	1.0E-14				

Table 4 presents results from increasingly complex robust inverse probability weighted marginal structural models. Results for additive, interactive with drugs only, interactive including drugs, race and income and interactive including cannabinoids, drugs, race and income models are shown. It is particularly noteworthy that in a simple additive robust model (listed first in the table) cannabis is independently highly significant (β-estimate=9.55 95%C.I. (3.95, 15.15), P = 0.0016).

Since these robust models are not accompanied by a model variance it is necessary to also use a mixed effects model system in order to be able to calculate e-Values subsequently. Mixed effects modelling was also conducted after inverse probability weighting. Again a series of increasingly complex models is shown progressing through additive, drug-interactive, full models including drugs, income and ethnicity, and a full model including the two cannabinoids THC and cannabigerol. Importantly in the first three models cannabis is independently highly statistically significant (from β-estimate=79.27 (56.77, 101.78), P = $1.2x10^{-11}$).

Since the data are gridded in space and time they are well suited for panel linear modelling, a technique which, in addition to inverse probability weighting, allows the added refinements of instrumental variables and temporal lagging. Temporal lagging is pathophysiologically important in such studies as it is likely that any procarcinogenic or environmental exposure takes some time to work before the clinical and epidemiological impact of genotoxicity becomes evident. Again a series of increasingly complex models is presented at increasing lags. Cannabis is again highly significant in many terms, including being independently significant in additive models (from β-estimate=5.31 (1.68, 8.95), P = 0.0042).

Data is also evidently oriented in space and time and is thus eminently suited for formal spatiotemporal analysis. Map-graphs of the data over the 16 years 2002-2017 are shown in Figure 8. Figure 9 shows the geospatial relationships between the contiguous American states and the manner in which links to Hawaii and Alaska have been edited in to define the final spatial neighbourhood network based on “queen” (edge and corner) contiguity. This neighbourhood sparse weights matrix is utilized in all the spatial regressions which follow.

Table 7 shows the initial results from a series of additive and increasingly complex unlagged interactive spatiotemporal models. The table includes the log of the maximum likelihood

ratio (Log.Lik.) at model optimization, and the specifically geospatial model coefficients phi, psi, rho and lambda (see Methods). Since all four of these parameters are generally highly significant this confirms that the full model specification (denoted 'sem2srre' in splm::spreml) is appropriate. The Table also lists the standard deviation of each model which is a required input for E-Value calculation. Again cannabis is noted to be independently highly significant in each model.

Table 8 shows the results of models lagged first just with cannabis and then for all drugs. Interactive terms including cannabis continue to be highly significant. Interactive terms including cannabis are significant from β-estimate=658.72 (396.60, 920.84), $P = 8.40x10^{-7}$ for cigarettes: cannabis: alcohol interaction at 2 years of lag.

Table 9 presents results of models lagged in space for cannabis and in time for the other drugs.

Table 10 presents the results of temporally lagged interactive space-time models including the two cannabinoids THC and cannabigerol. Cannabigerol is independently significant at 2 lags, and the THC:cannabigerol interaction is significant at zero, two and six lags.

As mentioned in Methods, well described ethnic disparities exist for many tumours including total cancer. However it is important to consider to what extent such drug use disparities might account for the known epidemiology of TPCIR . Table 11 presents an interactive geospatial regression of the TPCIR against THC exposure of five races as indicated with highly significant results.

Table 11.: Spatially- and Temporally- Lagged Spatiotemporal Models

Parameter			Model				
Parameter	**Estimate (C.I.)**	**P-Value**	**LogLik**	**S.D.**	**Model Parameter**	**Estimate**	**P-Value**
Cancer Incidence as a Function of Racial Cannabis Exposure							
spreml(Cancer_Rate ~ NHWhite_THC_Exp + NHBlack_THC_Exp * Hispanic_THC_Exp *Asian_THC_Exp * AIAN_THC_Exp)							
Afric-Am._THC_Exp: Hispan.Am_THC_Exp	1.74 (1.18, 2.29)	1.1E-09	-1532.27	1.9803	phi	0.3887	0.0001
Afric-Am._THC_Exp: Hispan.Am_THC_Exp: Asian-Am._THC_Exp: AIAN-Am._THC_Exp	0.15 (0.09, 0.21)	1.9E-06			psi	0.1542	0.0005
Asian-Am._THC_Exp: AIAN-Am._THC_Exp	0.89 (0.37, 1.41)	0.0008			rho	-0.4676	0.0002
Afric-Am._THC_Exp: Hispan.Am_THC_Exp: Asian-Am._THC_Exp	-1.11 (-1.55, -0.67)	8.8E-07			lambda	0.4215	8.1E-06
Afric-Am._THC_Exp: Hispan.Am_THC_Exp: AIAN-Am._THC_Exp	-0.2 (-0.28, -0.13)	4.8E-08					
Caucasian-American_THC_Exposure	-1.27 (-1.65, -0.89)	5.0E-11					

E-Values are an important way of quantitating the magnitude of co-association required of any unmeasured confounder with both the exposure and outcome variables to explain away the observed effects. Table 12 presents selected E-Value calculations from linear, mixed effects and geospatial models presented in preceding Tables. The key variable to observe is the final number at the right hand side representing the minimum E-Value, and should be read in the light of the observation by one of its originators that E-Values in the literature over approximately 1.25 are considered noteworthy [56]. In general terms the E-Values fall in the sequence geospatial models > mixed effects models > linear models, related partly to the much smaller model variance of more complex models.

Table 12 lists 56 E-Values related to cannabis or cannabinoids of which 24 are larger than 1,000. Of the 33 E-Values originating from geospatial models, 20 are larger than 1,000. The table lists six minimum e-Values of infinity, three deriving from mixed effects models and three from geospatial models.

Given the above compelling data demonstrating a link between rising rates of cannabis exposure and rising TPCIR an obvious extension of this study was whether the increasing use, availability and concentration of cannabis associated with more liberal legal paradigms [57]was associated with elevated TPCIR . One important caveat on such an investigation is that since the data only run to 2017 and many populous states had not yet been affected by the cannabis legalization movement, it may be considered that the data is premature for a full determination of this potential effect. Figure 10A shows the rate of TPCIR under various legal paradigms. Whilst the few states involved with full cannabis legalization at that time were associated with broad confidence interval bands there is a clear impression in this Figure that the rate under decriminalization appeared to be at a higher levels than others. Figure 10B dichotomizes the data into liberal paradigms vs. traditional policies of cannabis being considered illegal. Separation of the two regression lines towards the right hand side of the graph gives a clear impression for a significant interaction between time and dichotomized legal status.

These differences are formally assessed in Table 13 by linear regression. Decriminalized and legal status are both confirmed to be significant on their own (upper table segment). In interaction with time decriminalized status is significant (middle table segment). Dichotomized legal status is also found to be significant in interaction with time (lower table

segment, β-estimate=1.87×10^{-4}, (2.9×10^{-5}, 2.45×10^{-4}), P=0.0208). Table 12 lists the minimum E-Values associated with these changes as 1.60 and 1.98 for cannabis decriminalization and full cannabis legalization respectively (at the bottom of the Linear Regression part of Table 12).

Discussion

Main Results

The main results of this study confirmed that total Pediatric cancer rates have risen significantly nationally across USA and this trend holds for the commonest pediatric malignancies the leukaemias, Non-Hodgkins lymphoma, localized and distant sarcoma and testicular cancer. It was important to note across this period that the use of tobacco, alcohol use disorders, cocaine and analgesic abuse declined as measured in major national surveys whilst cannabis use alone was rising. The level of cannabinoids identified in Federal seizure data also rose for most cannabinoid analytes. TPCIR rose strongly and significantly as a function of cannabinoid exposure, but only weakly and non-significantly in bivariate analysis in relation to cannabis itself. TPCIR was significantly higher in the two highest cannabis use quintiles both overall and across time. Inverse probability weighting was used to equilibrate cannabis exposure across the cohort. Indices of ethnic cannabinoid exposure and seizure cannabinoid concentrations were variously used as instrumental variables to adjust panel models.

Cannabis use was independently associated with TPCIR in additive robust marginal structural, mixed effects, panel and geospatiotemporal models. Cannabis use was independently associated with TPCIR in interactive mixed effects and geospatial models. Cannabis use was linked with TPCIR in various interactions in linear models, robust marginal, mixed effects, panel and geospatial models. Cannabis was independently linked with TPCIR in geospatial models lagged to zero, 1 and 6 years and featured in interactions lagged to 1,2,4 and 6 years. When the cannabinoids THC and cannabigerol were studied they were also linked with TPCIR at high levels of statistical significance at zero, 2, 4 and six years of lag.

On sensitivity analysis 49 of 56 minimum e-Values were above 1.25 which is a quoted threshold for likely causal relationships. Similarly 31 of 33 geospatial e-Values were above this threshold. The highest finite minimum e-Value was 4.14×10^{89}. Six minimum e-Values were infinity.

The recent trend to cannabis liberalization was associated with elevated TPCIR both as a group and as an acceleration of the time-dependent trend in cannabis-liberal states.

Our interpretation of these highly consistent and concordant findings obtained by several methodologies with instrumental variables, controlling for ethnic cannabinoid exposure, utilizing robust regression techniques, inverse probability weighting with high levels of association across both space and time together with very high e-Values is that the relationship of cannabinoid exposure to total pediatric cancer incidence fulfills the criteria of causality and explains the increasing rates of pediatric cancer under cannabis-liberal legislative paradigms, and that this statement is especially true for THC and cannabigerol the two cannabinoids which show the most consistent rises over time.

Hence our study is closely concordant with other published series on the link between pediatric cancer and cannabis use [7-11].

Statistical Comments

It is worth considering briefly the incisive logical power of space-time regression. To say that two variables are statistically associated carries a certain weight. To say that two variables are closely associated when their distribution is considered across both space and time simultaneously is strongly suggestive of a presumptively causal relationship.

Nineteen spatiotemporal models were presented. In seventeen the spatial error coefficient rho was significant. In eighteen the spatial error autocorrelation coefficient lambda was significant. And spatial errors adjusted in the manner of Kapoor, Kelejian and Prucha consistently had higher precision than those adjusted by the algorithm of Baltagi. Together this is indisputable evidence of effects operating in a spatially distributed manner, and represents in the data analytical environment a reflection of the orchestrated campaign across USA to legalize cannabis which operated in a coordinated manner from the west coast eastwards.

Some comments in relation to casual inference and causal assignment are pertinent. Inverse probability weighting is a method which is well established to correct for inconsistent exposures amongst groups. It is enjoys a strong theoretical and epidemiological evidence

base [58]. Its effect is to even out exposures between groups and creates pseudo-randomized populations from which causal implications can appropriately be drawn. Similarly E-Values were recently introduced in a formal way to quantitate extraneous confounding from unmeasured covariates and provides a quantitative magnitude to the level of association required of unknown factors with both the exposure and the outcome to remove the impact of any described association [59].

Mechanisms

Of pivotal importance in linking associational findings with causal pathways is the issue of biological plausibility and the cellular and molecular pathways which might connect the exposure of interest with the outcome of concern. The subject of the pro-oncogenic activities and potential of cannabis, cannabis smoke and cannabinoids is complex major papers have addressed this issue [14, 26, 28, 32, 34-36, 42, 60-66]. In this paper we will provide a brief and concise overview of what presently seem to be some of the most important pathways which are likely to be implicated. They will be described under nine headings of: gametotoxicity, genotoxicity, epigenotoxicity, mitochondriopathy, immunomodulation, pro-aging, endovascular ischaemia – hypoxia, sympathetically mediated effects on stem cell niches and non-linearity of the dose-response genotoxic effect curve. These domains are not independent but are themselves interdependent and intricately intertwined. Whilst most of the following observations have been experimentally defined the logical sequence has been filled out where this seems reasonable and concordant with the evidence base.

Cannabinoids have been detected in seminal fluid and have been linked with DNA nicking and fragmentation, abnormal sperm nuclear size, gross abnormalities of sperm morphology including sperm fragmentation, disordered DNA packing and re-packing, disorders of protamine synthesis, histone-protamine substitution and major disruption of sperm DNA methylation [15-17, 31, 37, 61, 67, 68]. Cannabinoids have been found in Graafian follicle and oviduct fluid and have been linked with oocyte nuclear blebbing, nuclear bridging, chromosomal fragmentation and large scale oocyte loss after the second meiotic cell division [14, 15, 17]. Cannabis smoke is known to contain all of the carcinogens of tobacco smoke

including many tars and carcinogens including aromatic amines, polycyclic hydrocarbons, and tars [69]. Cannabinoid exposure has been linked with nuclear bleb and chromosomal bridge formation, chromosomal mis-segregation at the anaphase separation, micronucleus formation [70], transposon activation and chain and ring chromosome formation [14, 32, 34]. Cannabidiol, Cannabinol and THC have been implicated in in chromosomal translocation formation to the same level seen with cytotoxic drugs [13]. Cannabidiol and cannabidivarin have been shown to cause double stranded DNA breaks, micronucleus formation and nuclear buds and bridges in human cells which is worse under oxidative stress [66]. Cannabinoid-induced micronucleus formation is very important as it has been identified as a major engine of catastrophic damage to the genetic material and one-step chromothripsis, chromoanagensis and oncogenic transformation [60, 71, 72]. Cannabinoid exposure has been linked with large scale perturbation of DNA methylation, gross defects in histone synthesis – which necessarily leave DNA more open and available for transcription which is a pro-oncogenic state – altered histone signalling, and an inhibition of ATP supply to genetic and epigenetic processes – most of which are energy dependent – and an inhibition of epigenetic substrate supply [31, 33, 35, 37, 61, 73]. Together these changes may be expected to advance the "epigenetic clock" which is believed to be one of the key determinants of cellular aging [74, 75]. The profound implications of major epigenetic reprogramming were highlighted by a recent paper noting that despite the short half life of immune cells in the circulation – just a few days - the cellular basis for long lasting immunity is actually epigenetic changes in long lived myeloid precursor cells which record metabolic and immune activation responses in the coordinated patterns of their enhancers, promoters, long non-coding RNA's, DNA methylation and histone codes which determine chromatin conformation and the assembly of topologically transcriptionally active domains which functionally facilitate secondary responses to infection and vaccines [76, 77].

The outer mitochondrial membrane not only possess CB1R's, but indeed the whole of the cannabinoid signalling transduction machinery found in the plasmalemma also resides in the inner and outer mitochondrial membrane and within the intermembrane space so that cannabinoids are an important direct modulator of metabolic state [78-82]. Several adverse mitochondrial processes are well described including a reduction in the transmembrane potential across the inner mitochondrial membrane, a reduced synthesis of key oxidative phosphorylation substrates including the F1-ATPase, increased electron shunting via

uncoupling protein 2 activation, gross mitochondrial damage and swelling and impairment of mitonuclear cross-talk and mitonuclear genomic coordination [17, 83-87].

There is a rich literature describing both the pro- and anti- inflammatory actions of cannabinoids. In this context the proinflammatory CB1R-mediated activities seem to be especially important [88] as chronic inflammation is a well established cause of cancers in many tissue beds and occurs by many mechanisms. One pathway of particular interest is that cytoplasmic inflammation stimulates the transposons or "jumping genes" of the genome, to start "jumping" mobile segments and creating genomic havoc. Micronucleus disruption releases double stranded DNA into the cytoplasm where it potently stimulates the cytoplasmic GMP-AMP – STimulator of INterferon Gamma (cGAS-STING) pathway which further intracytoplasmically stimulates inflammation via interferon-γ and innate immune signalling and destabilizes the genome [89-91]. The immunosuppressive activities of cannabinoids may depress the immune response to the developing field change and nascent tumours. This cycle could potentially explain the many case reports of cancers occurring in adults at a younger age than usual and with increased aggressiveness in heavily cannabis exposed patients [92-95].

Cannabis exposure has been found to accelerate organismal cardiovascular aging clinically [96]. Cannabinoids are known to inhibit stem cell division [34, 97]. This combination of impaired stem cell activity, reduction of mitochondrial energy generation and a pro-inflammatory milieu are all hallmarks of cellular ageing and the senescence-associated secretory phenotype [98-100] of growth factors and cytokines which is presumably stimulated and a key hallmark of aging. Aging of course is the leading risk factor for most adult tumours. In the light of the foregoing cellular changes it would seem that the quality of cannabinoid-exposed gametes may be broadly seen as defective and they may thus be said in general terms to likely be "aged" in metabolic, epigenetic and genetic terms. Cannabinoids are known to have important effects on the microvasculature and can induce tissue ischaemia [101-104] which is an important determinant of the hypoxic microenvironment which stimulates genomic instability and oncogenesis and promotes nascent and mature tumour growth. Cannabis addiction is known to feature periods of cannabinoid withdrawal marked by agitation and manifest sympathetic hyperstimulation [105]. Sympathetic stimulation has been shown to have direct adverse activities on the stem cell niche of the hair follicle [106] and likely acts similarly in other stem cell niches.

Arguably the most concerning feature of this literature is the apparent threshold effect beyond which genotoxic and mitochondriopathic changes emerge relatively abruptly. This implies that the exponential dose-effect curve seen in many genotoxic assays for cannabinoids [35, 62, 107, 108] can appear to be functionally an abrupt discontinuity in the dose-response curve at the epidemiological level. At the community level this implies that a doubling of daily cannabis use, as has been documented in USA in recent years [109], might reasonably be linked with a disproportionate response in genotoxic downstream sequaelae such as congenital anomalies including transgenerationally transmissible carcinogenesis.

From this brief overview it is apparent that a plethora of cellular oncogenic mechanisms exist linking exposure to cannabis smoke, cannabis and cannabinoids to the processes of carcinogenesis.

In 1965 Hill described nine criteria as being required of any association in order to assign causality to the relationship. Strength of association, consistency amongst studies, specificity, temporal sequence, coherence with known data, biological plausibility a biological response or dose-response curve, analogy with similar situations elsewhere and experimental confirmation were key features [110]. It will be noted that the above analysis, including the published literature and the cited experimentally demonstrated mechanistic links, fulfill all of these criteria for the relationship between cannabis exposure and TPCIR .

Generalizability

Our data are population level data derived from publicly available datasets from one of the world's most technologically advanced nations. The underlying population is also substantial. Given that our findings are robust to various different methods, fulfill criteria for causality and are consistent with the majority of the published work in the area we believe that our findings are robust and widely generalizable. However as it is clear that cannabis use is in a state of flux worldwide at the present with rises in the prevalence of use, intensity of use, and concentration of product we feel that it is important that on-going studies be conducted in this area to monitor the situation at higher levels of geospatial resolution.

Future Directions

Further extensions of this work might include detailed dissection of the molecular and cellular level of the pathways mentioned particularly relating to mitochondrial cannabinoid signalling, mitochondrial electron leaks and shunts, free oxyradical flux, perturbation of mitonuclear cross-talk, cannabinoid induced disruption of metabolic supply of epigenetic substrates, cannabinoid-related disruption of histone synthesis and signalling and the histone code generally, cannabinoid epigenotoxicity generally and heritable and transgenerational epigenotoxicity specifically, proinflammatory cannabinoid actions, microvascular-disrupting and hypoxia-inducing actions, chromosomal mis-segregation and anaphase disruption and the interaction of cannabinoids with the cGAS-STING cytoplasmic signalling pathway. Research into cannabinoid interactions with the germ cells, oocytes and sperm, is clearly of primary and foundational importance to these concerns and should be up-prioritized on research agendas. Analytically higher resolution space-time modelling based on more detailed datasets from CDC and SAMHSA is an obvious task for the near future. The incorporation of instrumental variables and inverse probability weights into the space-time and spatiotemporally lagged models of plm, splm and similar software would allow all the questions of interest to be addressed in a single modelling framework without the need for multiple model types as was necessitated in the present report and would likely only require minimal resources to enable the required programming code to be written for this very impressive, sophisticated and highly flexible software to be further optimized.

Strengths and Limitations.

Our study has several strengths including using data from a very populous nation, the use of publicly available datasets, the use of different statistical techniques, the application of inverse probability weighting and e-Values, two mechanisms well established in the causal epidemiological literature, the use of geospatiotemporal regression techniques with complex random error structures, the use of models lagged both spatially and temporally, the use of a variety of covariates, consideration of substance-exposure indices which is often absent from many studies, the use of various instrumental variables, the availability of a relatively lengthy

panel data series for 15 years, and correction for ethnic cannabis exposure as a major underlying confounding factor. The absence of geospatial techniques from much of cancer epidemiology appears to be a major knowledge gap which the present study begins to redress. It may also be argued that for research enterprises to consume significant public resources but never be able to provide actual causal advice to their host community at once stretches public credulity and tests their patience, particularly when well established methodologies are available which can be used to fill this major knowledge gap. The deliberate application of the techniques of formal causal inference in this study thus comprises a major strength. The study's major limitation relates to the unavailability of individual patient-level data which is a common limitation amongst epidemiological studies. Due to the complexity of the present analysis we have not considered further subgroup analyses, either of individual tumours, or by fascinating sex or ethnic incidence differences. All of this remains to be done at higher geospatial resolution by subsequent investigators.

Conclusion

In summary our study confirms previous reports in the literature linking cannabis exposure with pediatric and testicular cancer [7-11, 18-22] and answers both our opening hypotheses affirmatively. We extend and amplify earlier reports in many ways including with the use of national cancer census data and widely cited nationally representative drug use surveys, the application of geospatial techniques and the formal techniques of causal inference to the data series and various technical refinements including the use of several sets of instrumental variables and various forms of inverse probability-weighted and spatially weighted regression matrices and robust, panel and linear multivariable techniques. After including socioeconomic, ethnic and drug use variables we find robust associations across space and time for cannabis use and TPCIR and that cannabis, and particularly the cannabinoids THC and cannabigerol, are independently and interactively associated with TPCIR both in *de novo* space-time grids and in spatially and temporally lagged models. Moreover very high e-Values clearly indicate that the relationship cannot be explained away by unmeasured, unknown or hypothetical confounding variables. This analysis is consistent with five previously reported series comprising the majority of the published literature in the field [7-11], dozens of potential experimentally described mechanistic pathways and fulfill the paradigmatic Hill criteria of causality [110]. Findings are also consistent with reports of

690 elevated rates of congenital anomalies following prenatal cannabis exposure [25-28, 42, 43]
691 and thus are broadly concordant conceptually with wide ranging and far reaching heritable
692 cannabinoid-related genotoxicity. Our analysis also begins to provide insights into the
693 previously mysterious major differences in cancer incidence between various ethnicities by
694 indicating that varying ethnic exposures to cannabinoids are of particular concern. It is
695 important that this thread be further explored in the future. Such formal demonstration of
696 strong evidence of a presumptively genotoxic cannabis-cancer causal link is highly relevant
697 for the ongoing and currently controversial story of the relationship of cannabis use with
698 malignant tumourigenesis in adults. Strong evidence of a robust causal relationship of
699 cannabis exposure to pediatric and thus transgenerational inheritable genotoxicity carries far
700 reaching implications for the ongoing public debate relating to the most appropriate forms of
701 regulation of cannabis and cannabinoids. Moreover the present analysis powerfully informs
702 the broader discussion regarding cannabis-related genotoxicity as it relates to adult
703 tumourigenesis and many congenital anomalies encountered at birth [25-28, 42, 60, 61].
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Declarations

Ethics Approval and Consent to Participate

The Human Research Ethics Committee of the University of Western Australia provided ethical approval for the study to be undertaken 7th June 2019 (No. RA/4/20/4724). Ethics approval was not required to access the data in the first instance. However Ethical approval provided permission to access, analyze and publish all the data obtained.

Consent for Publication

Not applicable.

Availability of Data and Materials

All data generated or analysed during this study are included in this published article and its supplementary information files. No permissions are required to access the data which was used and collated in this study, e.g. NSDUH study. Data including shapefiles and R programming script is made publicly available on the Mendeley Data Archive at this URL: URL: http://dx.doi.org/10.17632/cnwv9hdspd.1 .

Competing Interests

The authors declare that they have no competing interests.

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data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Authors' Contributions

ASR assembled the data, designed and conducted the analyses, and wrote the first manuscript draft. GKH provided technical and logistic support, co-wrote the paper, assisted with gaining ethical approval, provided advice on manuscript preparation and general guidance to study conduct.

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References

1. **SEER Explorer** [https://seer.cancer.gov/explorer/application.html]

2. National Cancer Institute: **An Analysis of the National Cancer Institute's Investment in Pediatric Cancer Research**. In. https://www.cancer.gov/types/childhood-cancers/research/pediatric-analysis.pdf: National Cancer Institute, National Institutes of Health; 2013: 1-20.

3. **Cancers that Develop in Children** [https://www.cancer.org/cancer/cancer-in-children/types-of-childhood-cancers.html]

4. Volkow ND, Baler RD, Compton WM, Weiss SRB: **Adverse Health Effects of Marijuana Use**. *New England Journal of Medicine* 2014, **370**(23):2219-2227.

5. Hashibe M, Straif K, Tashkin DP, Morgenstern H, Greenland S, Zhang ZF: **Epidemiologic review of marijuana use and cancer risk**. *Alcohol (Fayetteville, NY* 2005, **35**(3):265-275.

6. Tomar R.S., Beaumont J., Hsieh J. C. Y., Reproductive and Cancer Hazard Assessment Branch, Office of Environmental Health Hazard Assessment, Californian Environmental Protection Agency: **Evidence on the Carcinogenicity of Marijuana Smoke**. *California Health Department* August 2009, **1**(1):1-150.

7. Kuijten RR, Bunin GR, Nass CC, Meadows AT: **Gestational and familial risk factors for childhood astrocytoma: results of a case-control study**. *Cancer Res* 1990, **50**(9):2608-2612.

8. Robison LL, Buckley JD, Daigle AE, Wells R, Benjamin D, Arthur DC, Hammond GD: **Maternal drug use and risk of childhood nonlymphoblastic leukemia among offspring. An epidemiologic investigation implicating marijuana (a report from the Childrens Cancer Study Group)**. *Cancer* 1989, **63**(10):1904-1911.

9. Trivers KF, Mertens AC, Ross JA, Steinbuch M, Olshan AF, Robison LL, Children's Cancer G: **Parental marijuana use and risk of childhood acute myeloid leukaemia: a report from the Children's Cancer Group (United States and Canada)**. *Pediatric and perinatal epidemiology* 2006, **20**(2):110-118.

10. Grufferman S, Schwartz AG, Ruymann FB, Maurer HM: **Parents' use of cocaine and marijuana and increased risk of rhabdomyosarcoma in their children**. *Cancer Causes Control* 1993, **4**(3):217-224.

11. Wen WQ, Shu XO, Steinbuch M, Severson RK, Reaman GH, Buckley JD, Robison LL: **Paternal military service and risk for childhood leukemia in offspring**. *Am J Epidemiol* 2000, **151**(3):231-240.

12. Reece AS: **Chronic toxicology of cannabis**. *Clinical Toxicology* 2009, **47**(6):517-524.

13. Dalterio S, Badr F, Bartke A, Mayfield D: **Cannabinoids in male mice: effects on fertility and spermatogenesis**. *Science* 1982, **216**(4543):315-316.

14. Morishima A: **Effects of cannabis and natural cannabinoids on chromosomes and ova**. *NIDA Res Monogr* 1984, **44**:25-45.

15. Chioccarelli T, Cacciola G, Altucci L, Lewis SE, Simon L, Ricci G, Ledent C, Meccariello R, Fasano S, Pierantoni R *et al*: **Cannabinoid receptor 1 influences chromatin remodeling in mouse spermatids by affecting content of transition protein 2 mRNA and histone displacement**. *Endocrinology* 2010, **151**(10):5017-5029.

16. Rossato M, Pagano C, Vettor R: **The cannabinoid system and male reproductive functions**. *Journal of neuroendocrinology* 2008, **20 Suppl 1**:90-93.

17. Rossato M, Ion Popa F, Ferigo M, Clari G, Foresta C: **Human sperm express cannabinoid receptor Cb1, the activation of which inhibits motility, acrosome reaction, and mitochondrial function**. *The Journal of clinical endocrinology and metabolism* 2005, **90**(2):984-991.

18. Callaghan RC, Allebeck P, Akre O, McGlynn KA, Sidorchuk A: **Cannabis Use and Incidence of Testicular Cancer: A 42-Year Follow-up of Swedish Men between 1970 and 2011**. *Cancer Epidemiol Biomarkers Prev* 2017, **26**(11):1644-1652.

19. Daling JR, Doody DR, Sun X, Trabert BL, Weiss NS, Chen C, Biggs ML, Starr JR, Dey SK, Schwartz SM: **Association of marijuana use and the incidence of testicular germ cell tumors**. *Cancer* 2009, **115**(6):1215-1223.

20. Lacson JC, Carroll JD, Tuazon E, Castelao EJ, Bernstein L, Cortessis VK: **Population-based case-control study of recreational drug use and testis cancer risk confirms an association between marijuana use and nonseminoma risk**. *Cancer* 2012, **118**(21):5374-5383.

21. Trabert B, Sigurdson AJ, Sweeney AM, Strom SS, McGlynn KA: **Marijuana use and testicular germ cell tumors**. *Cancer* 2011, **117**(4):848-853.

22. Gurney J, Shaw C, Stanley J, Signal V, Sarfati D: **Cannabis exposure and risk of testicular cancer: a systematic review and meta-analysis**. *BMC Cancer* 2015, **15**:897.

23. Grobner SN, Worst BC, Weischenfeldt J, Buchhalter I, Kleinheinz K, Rudneva VA, Johann PD, Balasubramanian GP, Segura-Wang M, Brabetz S *et al*: **The landscape of genomic alterations across childhood cancers**. *Nature* 2018, **555**(7696):321-327.

24. Ma X, Liu Y, Liu Y, Alexandrov LB, Edmonson MN, Gawad C, Zhou X, Li Y, Rusch MC, Easton J *et al*: **Pan-cancer genome and transcriptome analyses of 1,699 Pediatric leukaemias and solid tumours**. *Nature* 2018, **555**(7696):371-376.

25. Forrester MB, Merz RD: **Risk of selected birth defects with prenatal illicit drug use, Hawaii, 1986-2002**. *Journal of toxicology and environmental health* 2007, **70**(1):7-18.

26. Reece A.S., Hulse G.K.: **Cannabis Teratology Explains Current Patterns of Coloradan Congenital Defects: The Contribution of Increased Cannabinoid Exposure to Rising Teratological Trends**. *Clinical Pediatrics* 2019, **58**(10):1085-1123.

27. **Broad Spectrum Epidemiological Contribution of Cannabis, Tobacco and Alcohol to the Teratological Profile of Northern New South Wales: Geospatial and Causal Inference Analysis *In Review*** [https://www.researchsquare.com/article/rs-53395/v1]

28. Reece AS, Hulse GK: **Canadian Cannabis Consumption and Patterns of Congenital Anomalies: An Ecological Geospatial Analysis**. *J Addict Med* 2020.

29. Birger Y, Shiloh R, Izraeli S: **Mechanisms of Leukemia Evolution: Lessons from a Congenital Syndrome**. *Cancer Cell* 2019, **36**(2):115-117.

30. Labuhn M, Perkins K, Matzk S, Varghese L, Garnett C, Papaemmanuil E, Metzner M, Kennedy A, Amstislavskiy V, Risch T *et al*: **Mechanisms of Progression of Myeloid Preleukemia to Transformed Myeloid Leukemia in Children with Down Syndrome**. *Cancer Cell* 2019, **36**(2):123-138 e110.

31. Murphy SK, Itchon-Ramos N, Visco Z, Huang Z, Grenier C, Schrott R, Acharya K, Boudreau MH, Price TM, Raburn DJ *et al*: **Cannabinoid exposure and altered DNA methylation in rat and human sperm**. *Epigenetics* 2018.

32. Zimmerman AM, Zimmerman S., Raj A.Y.: **Effects of Cannabinoids on spermatogenesis in mice**. In: *Marihuana and medicine.* edn. Edited by Nahas G.G., Sutin K.M., Harvey D.J., Agurell S. Totowa, N.J, USA.: Humana Press; 1999: 347-358.

33. Zimmerman AM, Raj AY: **Influence of cannabinoids on somatic cells in vivo**. *Pharmacology* 1980, **21**(4):277-287.

34. Zimmerman S, Zimmerman AM: **Genetic effects of marijuana**. *The International journal of the addictions* 1990, **25**(1A):19-33.

35. Tahir SK, Zimmerman AM: **Influence of marihuana on cellular structures and biochemical activities**. *Pharmacology, biochemistry, and behavior* 1991, **40**(3):617-623.

36. Graham JDP: **Cannabis and Health**. In: *Cannabis and Health. Volume 1*, 1 edn. Edited by Graham JDP. London, New York, San Francisco: Academic Press; 1976: 271-320.

37. Mon MJ, Haas AE, Stein JL, Stein GS: **Influence of psychoactive and nonpsychoactive cannabinoids on cell proliferation and macromolecular biosynthesis in human cells**. *Biochemical pharmacology* 1981, **30**(1):31-43.

38. Watson CT, Szutorisz H, Garg P, Martin Q, Landry JA, Sharp AJ, Hurd YL: **Genome-Wide DNA Methylation Profiling Reveals Epigenetic Changes in the Rat Nucleus Accumbens Associated With Cross-Generational Effects of Adolescent THC Exposure**. *Neuropsychopharmacology* 2015.

39. Dickson B, Mansfield C, Guiahi M, Allshouse AA, Borgelt LM, Sheeder J, Silver RM, Metz TD: **Recommendations From Cannabis Dispensaries About First-Trimester Cannabis Use**. *Obstet Gynecol* 2018, **131**(6):1031-1038.

40. Young-Wolff KC, Tucker L, Alexeeff S, et al.: **Trends in self-reported and biochemically tested marijuana use among pregnant females in california from 2009-2016**. *JAMA* 2017, **318**(24):2490-2491.

41. Volkow ND, Han B, Compton WM, McCance-Katz EF: **Self-reported Medical and Nonmedical Cannabis Use Among Pregnant Women in the United States**. *JAMA* 2019, **322**(2):167-169.

42. Reece A.S., Hulse G.K.: **Cannabis in Pregnancy – Rejoinder, Exposition and Cautionary Tales**. *Psychiatric Times* 2020, **In Press**.

43. Reece AS: **Known Cannabis Teratogenicity Needs to be Carefully Considered**. *British Medical Journal* 2018, **362**:k3357.

44. **National Program of Cancer Registries and Surveillance, Epidemiology, and End Results SEER*Stat Database: NPCR and SEER Incidence – U.S. Cancer Statistics Public Use Research Database, 2019 submission (2001-2017), United States Department**

of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute. Released June 2020. Available at www.cdc.gov/cancer/public-use.

[www.cdc.gov/cancer/public-use.]

45. **Substance Abuse and Mental Health Data Archive (SAMHDA)** [https://www.datafiles.samhsa.gov/]

46. **National Survey of Drug Use and Health 2018, NSDUH** [https://www.samhsa.gov/data/all-reports]

47. ElSohly MA, Mehmedic Z, Foster S, Gon C, Chandra S, Church JC: **Changes in Cannabis Potency Over the Last 2 Decades (1995-2014): Analysis of Current Data in the United States**. *Biol Psychiatry* 2016, **79**(7):613-619.

48. Chandra S, Radwan MM, Majumdar CG, Church JC, Freeman TP, ElSohly MA: **New trends in cannabis potency in USA and Europe during the last decade (2008-2017)**. *European archives of psychiatry and clinical neuroscience* 2019, **269**(1):5-15.

49. ElSohly MA, Ross SA, Mehmedic Z, Arafat R, Yi B, Banahan BF, 3rd: **Potency trends of delta9-THC and other cannabinoids in confiscated marijuana from 1980-1997**. *Journal of forensic sciences* 2000, **45**(1):24-30.

50. **Legality of cannabis by U.S. jurisdiction** [https://en.wikipedia.org/wiki/Legality_of_cannabis_by_U.S._jurisdiction]

51. **Package 'plm'** [https://cran.r-project.org/web/packages/plm/plm.pdf]

52. Millo G: **Maximum likelihood estimation of spatially and serially correlated panels with random effects**. *Computational Statistics & Data Analysis* 2014, **71**:914-933.

53. Millo G., Piras G.: **splm: Spatial Panel Data Models in R**. *Journal of Stastistical Software* 2012, **47**(1):1-38.

54. Croissant Y., Millo G.: **Panel Data Econometrics with R**, vol. 1. Hoboken, New JErsey, USA; West Sussex, U.K.: Wiley and Sons; 2019.

55. Kapoor M., Kelejian H.H., Prucha I.R.: **Panel Data Models with Spatially Correlated Error Components**. *Journal of Econometrics* 2007, **140**(1):97-130.

56. VanderWeele T.J., Ding P., Mathur M.: **Technical Considerations in the Use of the E-Value**. *Journal of Causal Inference* 2019, **7**(2):1-11.

57. Hasin DS, Sarvet AL, Cerda M, Keyes KM, Stohl M, Galea S, Wall MM: **US Adult Illicit Cannabis Use, Cannabis Use Disorder, and Medical Marijuana Laws: 1991-1992 to 2012-2013**. *JAMA Psychiatry* 2017, **74**(6):579-588.

58. Wal W, Geskus R: **ipw: An R Package for Inverse Probability Weighting**. *Journal of Statistical Software* 2011, **43**.

59. VanderWeele TJ, Ding P: **Sensitivity Analysis in Observational Research: Introducing the E-Value**. *Ann Intern Med* 2017, **167**(4):268-274.

60. Reece AS, Hulse GK: **Chromothripsis and epigenomics complete causality criteria for cannabis- and addiction-connected carcinogenicity, congenital toxicity and heritable genotoxicity**. *Mutat Res* 2016, **789**:15-25.

61. Reece AS, Hulse GK: **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**. *Epigenetics* 2019:1-16.

62. Tahir SK, Trogadis JE, Stevens JK, Zimmerman AM: **Cytoskeletal organization following cannabinoid treatment in undifferentiated and differentiated PC12 cells**. *Biochem Cell Biol* 1992, **70**(10-11):1159-1173.

63. Piatti E, Rizzi R, Re F, Chiesara E: **Genotoxicity of heroin and cannabinoids in humans**. *Pharmacol Res* 1989, **21 Suppl 1**:59-60.

64. Lopes CF, de Angelis BB, Prudente HM, de Souza BV, Cardoso SV, de Azambuja Ribeiro RI: **Concomitant consumption of marijuana, alcohol and tobacco in oral squamous cell carcinoma development and progression: recent advances and challenges**. *Arch Oral Biol* 2012, **57**(8):1026-1033.

65. Kopjar N, Fuchs N, Žunec S, Mikolić A, Micek V, Kozina G, Lucić Vrdoljak A, Brčić Karačonji I: **DNA Damaging Effects, Oxidative Stress Responses and Cholinesterase Activity in Blood and Brain of Wistar Rats Exposed to Δ(9)-Tetrahydrocannabinol**. *Molecules* 2019, **24**(8).

66. Russo C, Ferk F, Mišík M, Ropek N, Nersesyan A, Mejri D, Holzmann K, Lavorgna M, Isidori M, Knasmüller S: **Low doses of widely consumed cannabinoids (cannabidiol and cannabidivarin) cause DNA damage and chromosomal aberrations in human-derived cells**. *Archives of toxicology* 2019, **93**(1):179-188.

67. Hembree W.C. III, Nahas G.G., Zeidenberg P., Huang H.F.S.: **Changes in Human Spermatozoa Associated with High Dose Marijuana Smoking**. In. Edited by Nahas GG, Sutin K.M., Harvey D.J., Agurell S., vol. 1. Totowa, New York: Humana Press 1999: 367-378.

68. Huang H.F.S., Nahas G.G., Hembree W.C.: **Effects of Marijuana Inhalantion on Spermatogenesis of the Rat**. In: *Marijuana in Medicine. Volume 1*, edn. Edited by Nahas GG, Sutin K.M., Harvey D.J., Agurell S. Totowa, New York: Human Press 1999: 359-366.

69. British Lung Foundation: **Cannabis: A Smoking Gun**. In. London; 2005.

70. Hall W, Degenhardt L: **Adverse health effects of non-medical cannabis use**. *Lancet* 2009, **374**(9698):1383-1391.

71. Liu S, Kwon M, Mannino M, Yang N, Renda F, Khodjakov A, Pellman D: **Nuclear envelope assembly defects link mitotic errors to chromothripsis**. *Nature* 2018, **561**(7724):551-555.

72. Zhang C-Z, Spektor A, Cornils H, Francis JM, Jackson EK, Liu S, Meyerson M, Pellman D: **Chromothripsis from DNA damage in micronuclei**. *Nature* 2015, **522**(7555):179-184.

73. McClean DK, Zimmerman AM: **Action of delta 9-tetrahydrocannabinol on cell division and macromolecular synthesis in division-synchronized protozoa**. *Pharmacology* 1976, **14**(4):307-321.

74. Horvath S: **DNA methylation age of human tissues and cell types**. *Genome Biol* 2013, **14**(10):R115.

75. Bocklandt S, Lin W, Sehl ME, Sanchez FJ, Sinsheimer JS, Horvath S, Vilain E: **Epigenetic predictor of age**. *PLoS ONE* 2011, **6**(6):e14821.

76. de Laval B, Maurizio J, Kandalla PK, Brisou G, Simonnet L, Huber C, Gimenez G, Matcovitch-Natan O, Reinhardt S, David E *et al*: **C/EBPβ-Dependent Epigenetic Memory Induces Trained Immunity in Hematopoietic Stem Cells**. *Cell Stem Cell* 2020, **26**(5):793.

77. Mantovani A, Netea MG: **Trained Innate Immunity, Epigenetics, and Covid-19**. *New England Journal of Medicine* 2020, **383**(11):1078-1080.

78. Hebert-Chatelain E, Reguero L, Puente N, Lutz B, Chaouloff F, Rossignol R, Piazza PV, Benard G, Grandes P, Marsicano G: **Cannabinoid control of brain bioenergetics: Exploring the subcellular localization of the CB1 receptor**. *Mol Metab* 2014, **3**(4):495-504.

79. Hebert-Chatelain E, Desprez T, Serrat R, Bellocchio L, Soria-Gomez E, Busquets-Garcia A, Pagano Zottola AC, Delamarre A, Cannich A, Vincent P *et al*: **A cannabinoid link between mitochondria and memory**. *Nature* 2016, **539**(7630):555-559.

80. Bartova A, Birmingham MK: **Effect of delta9-tetrahydrocannabinol on mitochondrial NADH-oxidase activity**. *J Biol Chem* 1976, **251**(16):5002-5006.

81. Sarafian TA, Habib N, Oldham M, Seeram N, Lee RP, Lin L, Tashkin DP, Roth MD: **Inhaled marijuana smoke disrupts mitochondrial energetics in pulmonary epithelial cells in vivo**. *American journal of physiology* 2006, **290**(6):L1202-1209.

82. de Luis DA, Ballesteros M, Lopez Guzman A, Ruiz E, Munoz C, Penacho MA, Iglesias P, Maldonado A, San Martin L, Izaola O *et al*: **Polymorphism G1359A of the cannabinoid receptor gene (CNR1): allelic frequencies and influence on cardiovascular risk factors in a multicentre study of Castilla-Leon**. *J Hum Nutr Diet* 2015.

83. Badawy ZS, Chohan KR, Whyte DA, Penefsky HS, Brown OM, Souid AK: **Cannabinoids inhibit the respiration of human sperm**. *Fertil Steril* 2009, **91**(6):2471-2476.

84. Sarafian TA, Kouyoumjian S, Khoshaghideh F, Tashkin DP, Roth MD: **Delta 9-tetrahydrocannabinol disrupts mitochondrial function and cell energetics**. *American journal of physiology* 2003, **284**(2):L298-306.

85. Canto C, Menzies KJ, Auwerx J: **NAD(+) Metabolism and the Control of Energy Homeostasis: A Balancing Act between Mitochondria and the Nucleus**. *Cell Metab* 2015, **22**(1):31-53.

86. Bino T, Chari-Bitron A, Shahar A: **Biochemical effects and morphological changes in rat liver mitochondria exposed to 1 -tetrahydrocannabinol**. *Biochim Biophys Acta* 1972, **288**(1):195-202.

87. Wang J, Yuan W, Li MD: **Genes and pathways co-associated with the exposure to multiple drugs of abuse, including alcohol, amphetamine/methamphetamine, cocaine, marijuana, morphine, and/or nicotine: a review of proteomics analyses**. *Molecular neurobiology* 2011, **44**(3):269-286.

88. Bileck A, Ferk F, Al-Serori H, Koller VJ, Muqaku B, Haslberger A, Auwarter V, Gerner C, Knasmuller S: **Impact of a synthetic cannabinoid (CP-47,497-C8) on protein expression in human cells: evidence for induction of inflammation and DNA damage**. *Archives of toxicology* 2016, **90**(6):1369-1382.

89. Ablasser A, Chen ZJ: **cGAS in action: Expanding roles in immunity and inflammation**. *Science* 2019, **363**(6431):eaat8657.

90. Bakhoum SF, Ngo B, Laughney AM, Cavallo JA, Murphy CJ, Ly P, Shah P, Sriram RK, Watkins TBK, Taunk NK *et al*: **Chromosomal instability drives metastasis through a cytosolic DNA response**. *Nature* 2018, **553**(7689):467-472.

91. Dou Z, Ghosh K, Vizioli MG, Zhu J, Sen P, Wangensteen KJ, Simithy J, Lan Y, Lin Y, Zhou Z *et al*: **Cytoplasmic chromatin triggers inflammation in senescence and cancer**. *Nature* 2017, **550**(7676):402-406.

92. Van Hoozen BE, Cross CE: **Marijuana. Respiratory tract effects**. *Clinical reviews in allergy & immunology* 1997, **15**(3):243-269.

93. Kothadia JP, Chhabra S, Marcus A, May M, Saraiya B, Jabbour SK: **Anterior mediastinal mass in a young marijuana smoker: a rare case of small-cell lung cancer**. *Case Rep Med* 2012, **2012**:754231.

94. Graef S, Choo CG, Warfield A, Cullen M, Woolhouse I: **Small cell lung cancer in a 26-year-old man with significant Cannabis exposure**. *J Thorac Oncol* 2011, **6**(1):218-219.

95. Donald PJ: **Marijuana smoking--possible cause of head and neck carcinoma in young patients**. *Otolaryngol Head Neck Surg* 1986, **94**(4):517-521.

96. Reece A.S., Norman A, Hulse G.K.: **Cannabis Exposure as an Interactive Cardiovascular Risk Factor and Accelerant of Organismal Ageing – A Longitudinal Study**. *BMJ - Open* 2016, **In Press**.

97. Noonan M.A., A.J. E: **Regulation of Adult Neurogenesis by Cannabinoids**. *Chemistry Today* 2006, **24**(5):84-88.

98. Wiley CD, Campisi J: **From Ancient Pathways to Aging Cells-Connecting Metabolism and Cellular Senescence**. *Cell Metab* 2016, **23**(6):1013-1021.

99. Wiley CD, Velarde MC, Lecot P, Liu S, Sarnoski EA, Freund A, Shirakawa K, Lim HW, Davis SS, Ramanathan A *et al*: **Mitochondrial Dysfunction Induces Senescence with a Distinct Secretory Phenotype**. *Cell Metab* 2016, **23**(2):303-314.

100. Baker DJ, Alimirah F, van Deursen JM, Campisi J, Hildesheim J: **Oncogenic senescence: a multi-functional perspective**. *Oncotarget* 2017, **8**(16):27661-27672.

101. Pacher P, Steffens S, Hasko G, Schindler TH, Kunos G: **Cardiovascular effects of marijuana and synthetic cannabinoids: the good, the bad, and the ugly**. *Nat Rev Cardiol* 2018, **15**(3):151-166.

102. Mathew RJ, Wilson WH, Humphreys D, Lowe JV, Wiethe KE: **Middle cerebral artery velocity during upright posture after marijuana smoking**. *Acta psychiatrica Scandinavica* 1992, **86**(2):173-178.

103. Inal T, Kose A, Koksal O, Armagan E, Aydin SA, Ozdemir F: **Acute temporal lobe infarction in a young patient associated with marijuana abuse: An unusual cause of stroke**. *World J Emerg Med* 2014, **5**(1):72-74.

104. Wolff V, Armspach JP, Beaujeux R, Manisor M, Rouyer O, Lauer V, Meyer N, Marescaux C, Geny B: **High frequency of intracranial arterial stenosis and cannabis use in ischaemic stroke in the young**. *Cerebrovascular diseases (Basel, Switzerland)* 2014, **37**(6):438-443.

105. Bahji A, Stephenson C, Tyo R, Hawken ER, Seitz DP: **Prevalence of Cannabis Withdrawal Symptoms Among People With Regular or Dependent Use of Cannabinoids: A Systematic Review and Meta-analysis**. *JAMA Netw Open* 2020, **3**(4):e202370.

106. Zhang B, Ma S, Rachmin I, He M, Baral P, Choi S, Gonçalves WA, Shwartz Y, Fast EM, Su Y *et al*: **Hyperactivation of sympathetic nerves drives depletion of melanocyte stem cells**. *Nature* 2020, **577**(7792):676-681.

107. Koller VJ, Ferk F, Al-Serori H, Misik M, Nersesyan A, Auwarter V, Grummt T, Knasmuller S: **Genotoxic properties of representatives of alkylindazoles and aminoalkyl-indoles which are consumed as synthetic cannabinoids**. *Food Chem Toxicol* 2015, **80**:130-136.

108. Vela G, Martin S, Garcia-Gil L, Crespo JA, Ruiz-Gayo M, Fernandez-Ruiz JJ, Garcia-Lecumberri C, Pelaprat D, Fuentes JA, Ramos JA *et al*: **Maternal exposure to delta9-tetrahydrocannabinol facilitates morphine self-administration behavior and changes regional binding to central mu opioid receptors in adult offspring female rats**. *Brain Res* 1998, **807**(1-2):101-109.

109. United National Office of Drugs and Crime: **World Drug Report 2019**. In. Edited by World Health Organization Office of Drugs and Crime, vol. 1-5. Geneva, Switzerland: United National World Health Organization; 2019: https://wdr.unodc.org/wdr2019/index.html.

110. Hill AB: **The Environment and Disease: Association or Causation?** *Proc R Soc Med* 1965, **58**:295-300.

TABLES

Table 1.: SEER-Nominated Time Trends of Various Pediatric and Adult Cancers

Cancer	Observed Trend	Delayed Trend
All Pediatric Cancers (<20 Years)	Rising	Rising
Pediatric ALL - Acute Lymphatic Leukaemia	Rising	
Pediatric AML - Acute Myeloid Leukaemia	Rising	
Pediatric Brain Cancer	Stable	Rising
Pediatric NHL - Non-Hodgkins Lymphoma	Rising	Rising
Sarcoma - All Age	Stable	
Sarcoma <20 Year - Localized	Rising	
Sarcoma <20 Year - Distant	Rising	
Sarcoma All Age - Localized	Rising	
Sarcoma All Age - Distant	Rising	
Sarcoma All Age	Rising	
Pediatric Testes < 20 Years	Stable	Stable
Testes < 50 Years	Rising	Rising
Testes All Age	Rising	Rising

Table 2.: Linear Models: TPCIR Against Time, Cannabis, Cannabinoids and Ethnicity

Parameter Estimates			Model Parameters			
Parameter	**Estimate (C.I.)**	**Pr(>|t|)**	**R-Squared**	**F**	**dF**	**P**
lm(Cancer_Rate ~ Time)						
Year	0.14 (0.1, 0.17)	3.8E-14	0.0725	59.6	1,748	3.80E-14
lm(Cancer_Rate ~ Cannabis)						
mrjmon	1.00 (-1.22, 3.22)	0.3800	-0.0003	0.78	1,748	0.3770
lm(Cancer_Rate ~ Δ9THC)						
Δ9THC	0.33 (0.15, 0.5)	0.0002	0.0169	13.8	1,748	0.0002
lm(Cancer_Rate ~ Exposure * Drug)						
Drug_Rate: Cannabis	4.63 (2.11, 7.15)	0.0003	0.0207	9.82	9,3740	5.39E-15
Drug_Rate: Alcohol	-3.22 (-6.21, -0.22)	0.0356				
Drug_Rate: Analgesics	-6.63 (-10.51, -2.75)	0.0008				
Cocaine	-1.06 (-1.63, -0.49)	0.0003				
Cannabis	-1.32 (-1.89, -0.74)	0.0000				
Drug_Rate	-3.63 (-4.86, -2.4)	0.0000				
lm(Cancer_Rate ~ Exposure * Cannabinoid)						
Cannabinol	6.54 (5.07, 8.01)	< 2E-16	0.0402	18.9	7,2992	<2E-16
Cannabigerol	7.65 (5.91, 9.38)	< 2E-16				
Drug_Rate	2.14 (1.55, 2.73)	0.0000				
Cannabichromene	3.86 (0.29, 7.42)	0.0340				

Drug_Rate: Cannabichromene	-3.02 (-5.4, -0.63)	0.0130				
lm(Cancer_Rate ~ Ethnic_THC_Exposure * Ethnicity)						
Ethnic_THC_Exposure	0.14 (0.07, 0.21)	0.0001	0.0021	2.57	6,4493	0.0174
Asian-Am_THC_Exposure	0.28 (0.02, 0.55)	0.0360				

Table 4.: Robust Generalized Linear Regression Models

Parameter	Estimate (C.I.)	P-Value
Additive Model		
svyglm(Cancer_Rate ~ Cigarettes + Cannabis + Analgesics + Alcohol + Cocaine)		
Cannabis	9.55 (3.95, 15.15)	0.0016
Alcohol	-19.69 (-27.68, -11.7)	1.5E-05
Interactive Model		
svyglm(Cancer_Rate ~ Cigarettes * Cannabis * Analgesics * Alcohol + Cocaine)		
Cigarettes: Cannabis: Analgesics	268.42 (91.87, 444.96)	0.0046
Cigarettes: Analgesics	-59.54 (-92.24, -26.84)	0.0009
Full Interactive Model		
svyglm(Cancer_Rate ~ Cigarettes * Cannabis * Analgesics * Alcohol + Cocaine + 6_Races + Income)		
White	8.1 (6.04, 10.17)	4.2E-09
Hispanic	0.74 (0.37, 1.11)	0.0004
Asian	0.77 (0.38, 1.16)	0.0004
Cigarettes: Alcohol: Analgesics	331.59 (121.58, 541.61)	0.0038
Cigarettes: Cannabis: Analgesics	2537.45 (833.94, 4240.95)	0.0060
Cigarettes	52.94 (15.62, 90.27)	0.0086
Alcohol: Analgesics	871 (196.96, 1545.04)	0.0158
Cannabis: Alcohol	543.49 (110.37, 976.6)	0.0189
Cigarettes: Cannabis	-268.79 (-471.82, -65.76)	0.0136
Alcohol	-119.12 (-207.37, -30.87)	0.0120
Cannabis: Alcohol: Analgesics	-4989.69 (-8616.76, -1362.61)	0.0106

AIAN	-6.66 (-11.36, -1.95)	0.0087
Cigarettes: Analgesics	-500.17 (-808.72, -191.63)	0.0030
Full Interactive Model with Cannabinoids		
svyglm(Cancer_Rate ~ Cigarettes * Δ9THC * Cannabigerol * Alcohol + Analgesics + Cocaine + 6_Races + Income)		
White	7.87 (5.73, 10.02)	1.9E-08
Cocaine	25.98 (12.75, 39.21)	0.0005
Asian	0.68 (0.31, 1.06)	0.0010
Hispanic	0.59 (0.23, 0.94)	0.0026
Cigarettes: Δ9THC: Analgesics	34.32 (13.53, 55.11)	0.0026
Cigarettes: Cannabigerol	270.35 (104.12, 436.59)	0.0030
Cigarettes: Δ9THC	2.93 (0.58, 5.28)	0.0195
Δ9THC: Cannabigerol	29.24 (4.95, 53.53)	0.0239
AIAN	-5.96 (-11.16, -0.75)	0.0311
Cigarettes: Δ9THC: Alcohol	-13.34 (-24.92, -1.77)	0.0300
Cigarettes: Δ9THC: Cannabigerol	-103.55 (-181.75, -25.34)	0.0136
Cannabigerol	-115.2 (-189.34, -41.06)	0.0043
Cigarettes: Analgesics	-87.59 (-127.51, -47.66)	1.2E-04

Table 5.: Mixed Effects Regression Models

Parameters			Model Parameters			
Parameter	**Estimate (C.I.)**	**P-Value**	**SD**	**AIC**	**BIC**	**logLik**
Additive Model						
lme(Cancer_Rate ~ Cigarettes + Cannabis + Analgesics + Alcohol + Cocaine)						
Cannabis	5.34 (0.07, 10.6)	0.0472	3.43138	3884.77	3912.46	-1936.39
Analgesics	-11.02 (-18.65, -3.39)	0.0048				
Interactive Model						
lme(Cancer_Rate ~ Cigarettes * Cannabis * Analgesics * Alcohol + Cocaine)						
Cannabis	72.88 (49.6, 96.15)	1.4E-09	3.31033	3781.12	3836.4	-1878.56
Cigarettes	43.36 (27.68, 59.04)	8.2E-08				
Alcohol: Analgesics	1523.99 (970.61, 2077.38)	9.3E-08				
Cigarettes: Cannabis: Analgesics	2788.19 (1676.17, 3900.2)	1.1E-06				
Cannabis: Alcohol: Analgesics	-4554.93 (-6709.17, -2400.69)	3.8E-05				
Cigarettes: Analgesics	-539.08 (-790.18, -287.99)	2.9E-05				
Analgesics	-87.43 (-121.63, -53.23)	6.9E-07				
Alcohol	-82.06 (-113.58, -50.54)	4.3E-07				
Cigarettes: Cannabis	-284.5 (-376.55, -192.45)	2.3E-09				
Full Interactive Model						
lme(Cancer_Rate ~ Cigarettes * Cannabis * Analgesics * Alcohol + Cocaine + 6 Races + Income)						
White	11.8 (8.45, 15.14)	1.1E-11	3.18221	3715.57	3784.61	-1842.79
Cannabis	79.27 (56.77, 101.78)	1.2E-11				
Asian	2.54 (1.8, 3.27)	2.6E-11				
Cigarettes: Alcohol: Analgesics	1636.35 (1108.24, 2164.46)	2.1E-09				

Cigarettes	45.74 (30.44, 61.04)	7.2E-09				
Cigarettes: Cannabis: Analgesics	2525.7 (1488.65, 3562.75)	2.2E-06				
Alcohol: Analgesics	959.4 (425.8, 1493)	4.5E-04				
Cannabis: Alcohol: Analgesics	-4264.85 (-6314.08, -2215.61)	5.1E-05				
Alcohol	-93.44 (-124.44, -62.43)	5.5E-09				
Cigarettes: Analgesics	-766.56 (-1011.12, -521.99)	1.4E-09				
Cigarettes: Cannabis	-290.63 (-373.83, -207.42)	1.7E-11				
Income	-9.44 (-12.02, -6.87)	1.7E-12				
Full Interactive Model with Cannabinoids						
lme(Cancer_Rate ~ Cigarettes * Δ9THC * Cannabigerol * Alcohol + Analgesics + Cocaine + 6 Races + Income)						
White	15.39 (11.82, 18.96)	1.8E-16	3.16296	3743.28	3798.56	-1859.64
Asian	2.46 (1.76, 3.16)	1.2E-11				
Cigarettes: Cannabigerol: Alcohol	4741.19 (3077.86, 6404.51)	3.3E-08				
Cigarettes: Δ9THC	26.57 (15.54, 37.6)	2.8E-06				
Δ9THC: Alcohol	14.95 (7.74, 22.16)	5.4E-05				
Hispanic	0.7 (0.14, 1.26)	1.4E-02				
Cigarettes: Cannabigerol	-663.69 (-971.24, -356.13)	2.7E-05				
Income	-7.76 (-10.11, -5.41)	1.9E-10				
Cigarettes: Δ9THC: Alcohol	-240.65 (-304.57, -176.72)	4.6E-13				

Table 6.: Panel Regression Models

Model Specification		Parameters			Model Parameters				
Instrumental Variables	**Lagged Parameter**	**Parameter**	**Estimate (C.I.)**	**P-Value**	**Adj. R-Squared**	**Chi.Squ.**	**F**	**dF**	**P**
		Additive model							
		plm(Cancer_Rate ~ Cigarettes + Cannabis + Analgesics + Alcohol + Cocaine)							
		Cannabis	5.31 (1.68, 8.95)	0.0042	0.0790	80.6858		3	<2.2E-16
		Analgesics	-9.3 (-14.93, -3.67)	0.0012					
		Cigarettes	-4.53 (-7.15, -1.92)	0.0007					
		Interactive model							
		plm(Cancer_Rate ~ Cigarettes * Cannabis * Analgesics * Alcohol + Cocaine)							
		Cigarettes: Cannabis	24.47 (11.37, 37.57)	0.0003	0.0663	83.1987		4	<2.2E-16
		Cocaine	-11.93 (-22.84, -1.02)	0.0321					
		Analgesics	-8.25 (-14.2, -2.3)	0.0066					
		Cigarettes	-5.83 (-8.92, -2.73)	0.0002					
		Interactive Full model							
		plm(Cancer_Rate ~ Cigarettes * Cannabis * Analgesics * Alcohol + Cocaine + 6_Races + Income)							
		White	8.57 (7.18, 9.96)	<2.2E-16	0.1927	23.5694		13,736	<2.2E-16
		Asian	0.92 (0.67, 1.17)	2.0E-12					
		Hispanic	0.71 (0.47, 0.94)	7.1E-09					
		Cigarettes	69.38 (39.16, 99.59)	7.9E-06					
		Cigarettes: Alcohol: Analgesics	1169.92 (598.17, 1741.68)	6.7E-05					
		Cannabis: Alcohol	719.64 (352.45, 1086.83)	1.3E-04					

		Cigarettes: Cannabis :Analgesics	2926.99 (1407.72, 4446.25)	0.0002					
		Analgesics	58.43 (22.7, 94.17)	0.0014					
		Alcohol: Analgesics	709.96 (139.61, 1280.31)	0.0149					
		Cannabis: Alcohol: Analgesics	-5916.9 (-9125.97, -2707.83)	0.0003					
		Cigarettes: Cannabis	-345.82 (-521.51, -170.13)	1.2E-04					
		Alcohol	-153.51 (-219.89, -87.13)	6.8E-06					
		Cigarettes: Analgesics	-716.53 (-1007.91, -425.15)	1.8E-06					
		Interactive Full model - 2 Lags							
	Cigarettes, 2	***plm(Cancer_Rate ~ Cigarettes * Cannabis * Analgesics * Alcohol + Cocaine + 6_Races + Income)***							
	Cannabis, 2	White	9.28 (7.88, 10.67)	<2.2E-16	0.2014		33.9397	7,642	2.0E-01
	Analgesics, 2	Asian	0.96 (0.71, 1.22)	2.1E-13					
	Alcohol, 2	Hispanic	0.67 (0.41, 0.94)	9.4E-07					
	Cocaine, 2	Cigarettes	18.29 (9.29, 27.29)	7.6E-05					
		Cigarettes: Alcohol: Analgesics	513.89 (96.6, 931.17)	0.0161					
		Cigarettes: Analgesics	-92.64 (-154.24, -31.03)	0.0033					
		Cigarettes: Alcohol	-95.72 (-146.79, -44.65)	0.0003					
		Interactive Full model - 4 Lags							
		plm(Cancer_Rate ~ Cigarettes * Cannabis * Analgesics * Alcohol + Cocaine + 6_Races + Income)							
	Cigarettes, 4	White	8.71 (6.97, 10.46)	<2.2E-16	0.1990		17.6055	12,537	<2.2E-16
	Cannabis, 4	Hispanic	0.85 (0.54, 1.16)	7.3E-08					
	Analgesics, 4	Asian	0.72 (0.4, 1.05)	1.7E-05					
	Alcohol, 4	Cigarettes: Cannabis	233.66 (115.14, 352.18)	1.3E-04					
	Cocaine, 4	Cigarettes: Alcohol: Analgesics	1975.86 (855.19, 3096.52)	0.0006					
		Cannabis: Alcohol: Analgesics	1972.91 (573.99, 3371.83)	0.0059					
		Alcohol	105.37 (17.01, 193.73)	0.0198					
		AIAN	-8.33 (-14.85, -1.8)	0.0127					
		Alcohol: Analgesics	-647.54 (-1104.4, -190.68)	0.0057					
		Cannabis: Alcohol	-376.97 (-619.06, -134.87)	0.0024					
		Cigarettes: Alcohol	-286.48 (-462.48, -110.48)	0.0015					
		Cigarettes: Cannabis: Analgesics	-1300.25 (-2003.68, -596.83)	0.0003					

		Interactive Full model - 5 Lags							
		plm(Cancer_Rate ~ Cigarettes * Cannabis * Analgesics * Alcohol + Cocaine + 6_Races + Income)							
THC	Cigarettes, 5	White	6.7228 (5.29, 8.15)	<2.2E-16	0.2302	233.988		10	<2.2E-16
Cannabigerol	Cannabis, 5	Hispanic	0.652 (0.41, 0.89)	7.2E-08					
Cannabinol	Analgesics, 5	Asian	0.6755 (0.42, 0.93)	2.6E-07					
Cannabichromene	Alcohol, 5	Cigarettes: Cannabis	28.717 (14.28, 43.16)	0.0001					
	Cocaine, 5	Cigarettes: Cannabis: Alcohol: Analgesics	8122.4789 (3192.57, 13052.39)	0.0012					
		Cannabis: Analgesics	463.7354 (130.9, 796.57)	0.0063					
		Cigarettes: Cannabis: Analgesics	-1099.2482 (-1927.82, -270.68)	0.0093					
		Cannabis: Alcohol: Analgesics	-3523.9404 (-5495.28, -1552.6)	0.0005					
		AIAN	-9.4157 (-14.03, -4.81)	0.0001					
		Cigarettes	-5.1117 (-7.44, -2.78)	1.7E-05					
		Interactive Full Model with Racial Cannabis Exposure as Instrumental Variables							
THC Exposure		***plm(Cancer_Rate ~ Cigarettes * Cannabis * Analgesics * Alcohol + Cocaine + 6_Races + Income)***							
In:		White	0.7294 (-11.72, 25.62)	<2.2E-16	0.2300	232.721		9	<2.2E-16
Caucas-Am.		Asian	0.1306 (-9.77, 11.17)	9.2E-08					
African-Am.		Hispanic	0.1202 (-9.65, 10.91)	1.6E-07					
Hispan-Am.		Cigarettes: Cannabis: Alcohol: Analgesics	731.4135 (3112.74, 3129.47)	2.0E-05					
Asian-Am.		Cannabis: Analgesics	35.5327 (136.48, 152.42)	4.8E-05					
AIAN-Am.		Cocaine	4.9629 (7.98, 18.41)	0.0078					
NHPI-Am.		AIAN	2.3266 (-1.45, -16.93)	7.9E-05					
		Cannabis: Alcohol: Analgesics	378.1363 (-1752.55, -1770.82)	3.2E-06					
		Cigarettes: Analgesics	9.4453 (-37.01, -56.39)	7.7E-07					

Table 7.: Introductory Spatiotemporal Models

Parameter			Model				
Parameter	**Estimate (C.I.)**	**P-Value**	**LogLik**	**S.D.**	**Model Parameter**	**Estimate**	**P-Value**
Additive Model							
spreml(Cancer_Rate ~ Cigarettes + Cannabis + Alcohol + Analgesics + Cocaine)							
Cannabis	5.16 (2.26, 8.06)	0.0005	-1541.00	1.9451	phi	0.3170	0.0002
Analgesics	-4.6 (-9.18, -0.02)	0.0490			psi	0.1480	0.0007
Cigarettes	-2.72 (-4.85, -0.59)	0.0124			rho	-0.4959	2.2E-05
					lambda	0.4598	8.2E-08
3-Way Interactive model							
spreml(Cancer_Rate ~ Cigarettes * Cannabis * Alcohol + Analgesics + Cocaine)							
Cannabis	20.68 (7.02, 34.33)	0.0030	-1541.24	1.9495	phi	0.3466	0.0002
Cigarettes: Alcohol	48.6 (2.75, 94.46)	0.0378			psi	0.1488	0.0006
Cigarettes: Cannabis	-46.18 (-84.76, -7.6)	0.0190			rho	-0.5248	2.4E-06
Alcohol	-25.69 (-44.01, -7.37)	0.0060			lambda	0.4837	1.3E-09
4-Way Interactive model							
spreml(Cancer_Rate ~ Cigarettes * Cannabis * Alcohol * Analgesics + Cocaine)	phi		0.3169				0.0002
Cannabis	5.42 (2.34, 8.5)	0.0006	-1540.34	1.9470	psi	0.1479	0.0007
Alcohol	-8.18 (-14.61, -1.74)	0.0128			rho	-0.4896	3.1E-05
Cigarettes: Analgesics	-31.81 (-56.07, -7.54)	0.0102			lambda	0.4514	2.1E-07

Interactive Full Model - 0 Lags							
spreml(Cancer_Rate ~ Cigarettes * Cannabis * Alcohol * Analgesics + Cocaine+ 6_Races+Income)							
Cigarettes	28.41 (12.48, 44.34)	0.0005	-1520.55	1.8458	phi	0.1709	0.0017
Cannabis	45.67 (18.77, 72.56)	0.0009			psi	0.1079	0.0138
White	5.24 (3.38, 7.1)	0.0000			rho	-0.4106	0.0029
Cigarettes: Cannabis: Alcohol	840.86 (416.29, 1265.44)	0.0001			lambda	0.3643	0.0006
Alcohol: Analgesics	638.1 (283.09, 993.12)	0.0004					
Asian-American	0.6 (0.23, 0.97)	0.0015					
Hispanic-American	0.45 (0.11, 0.79)	0.0089					
Cigarettes: Cannabis: Analgesics	966.38 (184.69, 1748.06)	0.0154					
AIAN-American	-8.3 (-15.42, -1.18)	0.0224					
Cigarettes: Analgesics	-240.1 (-391.42, -88.77)	0.0019					
Cannabis: Alcohol: Analgesics	-2613.19 (-4248.03, -978.35)	0.0017					
Cigarettes: Cannabis	-235.06 (-381.19, -88.92)	0.0016					
Alcohol	-79.04 (-114.93, -43.14)	1.6E-05					

Table 8.: Time-Lagged Spatiotemporal Models

Lagged Variables	Parameter			Model				
	Parameter	Estimate (C.I.)	P-Value	LogLik	S.D.	Model Parameter	Estimate	P-Value
	Full model - 2 Lags - Just Lagging Cannabis							
	spreml(Cancer_Rate ~ Cigarettes * Cannabis * Alcohol * Analgesics + Cocaine+ 6_Races+Income)							
Cannabis, 2	Caucasian-American	5.3 (3.63, 6.97)	5.3E-10	-1329.42	1.8583	phi	0.1690	0.0037
	Asian-American	0.63 (0.31, 0.95)	1.3E-04			psi	0.1476	0.0018
	Hispanic-American	0.54 (0.21, 0.86)	0.0013			rho	-0.4435	8.3E-04
	AIAN-American	-11.33 (-18.34, -4.32)	0.0015			lambda	0.4234	9.1E-06
	Full model - 4 Lags - Just Lagging Cannabis							
	spreml(Cancer_Rate ~ Cigarettes * Cannabis * Alcohol * Analgesics + Cocaine+ 6_Races+Income)							
Cannabis, 4	Caucasian-American	4.81 (2.92, 6.7)	6.1E-07	-1130.71	1.8616	phi	0.2095	0.0031
	Asian-American	0.67 (0.31, 1.03)	0.0003			psi	0.1134	0.0356
	Hispanic-American	0.55 (0.18, 0.92)	0.0037			rho	-0.5410	3.0E-05
	Cigarettes: Cannabis: Analgesics	261.1 (19.06, 503.15)	0.0345			lambda	0.4597	9.1E-07
	Cannabis: Analgesics	-107.34 (-193.09, -21.6)	0.0141					
	AIAN-American	-12.1 (-19.56, -4.64)	0.0015					
	Full model - 6 Lags - Just Lagging Cannabis							
	spreml(Cancer_Rate ~ Cigarettes * Cannabis * Alcohol * Analgesics + Cocaine+ 6_Races+Income)							
Cannabis, 6	Caucasian-American	7.54 (3.96, 11.12)	3.6E-05	-936.96	1.9697	phi	0.2705	0.0022
	Asian-American	0.95 (0.34, 1.54)	0.0020			psi	0.0992	0.1012

	Cannabis	8.49 (1.47, 15.5)	0.0177			rho	0.4222	0.0006
	Hispanic-American	0.7 (0.11, 1.29)	0.0202			lambda	-0.4083	0.0059
	Cannabis: Analgesics	-47.05 (-79.05, -15.03)	0.0040					
	Full Model - 1 Temporal Lag							
	spreml(Cancer_Rate ~ Cigarettes * Cannabis * Alcohol * Analgesics + Cocaine+ 6_Races+Income)							
Cigarettes, 1	Caucasian-American	5.42 (3.72, 7.12)	4.6E-10	-1426.33	1.8466	phi	0.1684	0.0027
Alcohol, 1	Asian-American	0.67 (0.33, 1)	0.0001			psi	0.1408	0.0016
Cannabis, 1	Hispanic-American	0.56 (0.22, 0.9)	0.0014			rho	-0.4380	0.0009
Analgesics, 1	Cannabis	7.88 (1.7, 14.06)	0.0125			lambda	0.4226	1.2E-05
Cocaine, 1	Cigarettes: Cannabis: Alcohol	182.23 (29.55, 334.9)	0.0193					
	AIAN-American	-9.03 (-16.1, -1.96)	0.0123					
	Cannabis: Alcohol	-114.28 (-198.3, -30.27)	0.0077					
	Full Model - 2 Temporal Lags							
	spreml(Cancer_Rate ~ Cigarettes * Cannabis * Alcohol * Analgesics + Cocaine+ 6_Races+Income)							
Cigarettes, 2	Caucasian-American	9.62 (6.82, 12.43)	1.7E-11	-1317.36	1.8519	phi	0.1408	0.0083
Alcohol, 2	Cigarettes: Cannabis: Alcohol	658.72 (396.6, 920.84)	8.4E-07			psi	0.1469	0.0018
Cannabis, 2	Asian-American	1.32 (0.75, 1.89)	6.4E-06			rho	0.3276	0.0126
Analgesics, 2	Alcohol: Analgesics	306.67 (143.27, 470.07)	0.0002			lambda	-0.2888	0.0462
Cocaine, 2	Hispanic-American	0.69 (0.26, 1.12)	0.0016					
	Income	-2.15 (-4.22, -0.08)	0.0415					
	Cannabis: Alcohol: Analgesics	-1810.02 (-2618.86, -1001.18)	1.2E-05					
	Cigarettes: Alcohol	-133.02 (-184.5, -81.54)	4.1E-07					
	Full Model - 4 Temporal Lags							
	spreml(Cancer_Rate ~ Cigarettes * Cannabis * Alcohol * Analgesics + Cocaine+ 6_Races+Income)							
Cigarettes, 4	Caucasian-American	5.25 (3.17, 7.33)	7.6E-07	-1129.73	1.8795	phi	0.1863	0.0058
Alcohol, 4	Cigarettes: Cannabis: Alcohol	472.69 (145.49, 799.88)	0.0046			psi	0.1341	0.0127

Cannabis, 4	Asian-American	0.56 (0.16, 0.95)	0.0055			rho	-0.4598	0.0040
Analgesics, 4	Hispanic-American	0.5 (0.13, 0.87)	0.0085			lambda	0.4021	8.6E-04
Cocaine, 4	Cigarettes: Alcohol: Analgesics	603.85 (143.88, 1063.82)	0.0101					
	Cigarettes: Alcohol	-80.89 (-138.89, -22.89)	0.0063					
	AIAN-American	-10.99 (-18.8, -3.18)	0.0058					
	Cigarettes: Cannabis: Alcohol: Analgesics	-3668.28 (-6170.15, -1166.42)	0.0041					
	Full Model - 6 Temporal Lags							
Cigarettes, 6	***spreml(Cancer_Rate ~ Cigarettes * Cannabis * Alcohol * Analgesics + Cocaine+ 6_Races+Income)***							
Alcohol, 6	Caucasian-American	4.28 (2.17, 6.4)	7.4E-05	-938.093	1.9015	phi	0.2238	0.0053
Cannabis, 6	Asian-American	0.5 (0.13, 0.87)	0.0089			psi	0.1218	0.0448
Analgesics, 6	Hispanic-American	0.51 (0.12, 0.91)	0.0115			rho	-0.5495	7.7E-05
Cocaine, 6	AIAN-American	-11.64 (-19.61, -3.66)	0.0042			lambda	0.5042	1.8E-07

Table 9.: Spatially- and Temporally- Lagged Spatiotemporal Models

Lagged Variables	Parameter			Model				
	Parameter	Estimate (C.I.)	P-Value	LogLik	S.D.	Model Parameter	Estimate	P-Value
	Full Model - 1 Spatial & 1 Temporal Lag							
	spreml(Cancer_Rate ~ Cigarettes * Cannabis * Alcohol * Analgesics + Cocaine+ 6_Races+Income)							
Cigarettes, 1	Caucasian-American	4.49 (2.56, 6.41)	4.9E-06	-1422.64	1.8639	phi	0.1534	0.0041
Alcohol, 1	Hispanic-American	0.61 (0.26, 0.96)	0.0006			psi	0.1284	0.0043
Cannabis, Sp1	Cannabis: Analgesics	110.36 (37.53, 183.19)	0.0030			rho	-0.3379	0.0408
Analgesics, 1	Cigarettes: Cannabis: Alcohol	1688.83 (336.9, 3040.77)	0.0143			lambda	0.3229	0.0134
Cocaine, 1	Asian-American	0.46 (0.09, 0.83)	0.0146					
	Cannabis: Alcohol: Analgesics	-885.51 (-1625.8, -145.21)	0.0191					
	AIAN-American	-10.01 (-17.08, -2.94)	0.0055					
	Analgesics	-18.96 (-29.31, -8.61)	0.0003					
	Full Model - 2 Spatial & 2 Temporal Lags							
	spreml(Cancer_Rate ~ Cigarettes * Cannabis * Alcohol * Analgesics + Cocaine+ 6_Races+Income)							
Cigarettes, 2	Caucasian-American	8.03 (5.67, 10.39)	2.6E-11	-1319.97	1.8579	phi	0.0990	0.0324
Alcohol, 2	Asian-American	1.02 (0.53, 1.51)	5.2E-05			psi	0.1426	0.0032
Cannabis, Sp2	Hispanic-American	0.66 (0.33, 0.99)	9.0E-05			rho	-0.2287	0.3086
Analgesics, 2	Analgesics	55.5 (26.18, 84.81)	0.0002			lambda	0.2307	0.2080
Cocaine, 2	Cigarettes: Cannabis: Alcohol: Analgesics	3954.04 (1565.01, 6343.08)	0.0012					
	Cocaine	15.51 (1.58, 29.44)	0.0291					
	Cigarettes: Cannabis: Analgesics	-749.24 (-1219.42, -279.07)	0.0018					

	Alcohol: Analgesics	-377.69 (-553.03, -202.35)	2.4E-05					
	Full Model - 4 Spatial & Temporal Lags							
	spreml(Cancer_Rate ~ Cigarettes * Cannabis * Alcohol * Analgesics + Cocaine+ 6_Races+Income)							
Cigarettes, 4	Caucasian-American	5.18 (3.29, 7.07)	7.7E-08	-1133.35	1.8790	phi	0.1850	0.0049
Alcohol, 4	Asian-American	0.59 (0.25, 0.93)	0.0008			psi	0.1286	0.0176
Cannabis, Sp4	Hispanic-American	0.52 (0.16, 0.87)	0.0045			rho	-0.4868	0.0004
Analgesics, 4	Alcohol: Analgesics	-27.25 (-54.07, -0.43)	0.0464			lambda	0.4290	2.5E-05
Cocaine, 4	AIAN-American	-10.96 (-18.4, -3.51)	0.0039					

Table 10.: Spatially- and Temporally- Lagged Spatiotemporal Models

Lagged Variables	Parameter			Model				
	Parameter	Estimate (C.I.)	P-Value	LogLik	S.D.	Model Parameter	Estimate	P-Value
	Cannabinoids							
	Cannabinoids as Main Effects							
	spreml(Cancer Rate ~ Cigarettes * THC * Cannabigerol * Alcohol + Analgesics + Cocaine)							
	Caucasian-American	4.83 (2.77, 6.89)	4.5E-06	-1511.96	1.8350	phi	0.2050	0.0009
	Cigarettes: Alcohol	334 (171.12, 496.88)	0.0001			psi	0.0889	0.0450
	Alcohol: Analgesics	312 (149.91, 474.09)	0.0002			rho	-0.4495	0.0003
	Cigarettes: Δ9THC: Analgesics	391 (181.28, 600.72)	0.0003			lambda	0.3639	0.0001
	Δ9THC: Alcohol	116 (51.71, 180.29)	0.0004					
	Cigarettes: Δ9THC: Cannabigerol: Alcohol	4810 (2124.8, 7495.2)	0.0004					
	Δ9THC: Cannabigerol	109 (41.58, 176.42)	0.0016					
	Analgesics	96.5 (35.74, 157.26)	0.0018					
	Asian-American	0.57 (0.19, 0.94)	0.0029					
	Δ9THC: Cannabigerol: Alcohol: Analgesics	5640 (1680.8, 9599.2)	0.0052					
	Hispanic-American	0.41 (0.07, 0.76)	0.0193					
	Cigarettes: Δ9THC	9.01 (0.6, 17.42)	0.0359					
	AIAN-American	-8.84 (-16.13, -1.55)	0.0175					
	Cigarettes: Δ9THC: Cannabigerol: Alcohol: Analgesics	-18100 (-29977.6, -6222.4)	0.0028					
	Cigarettes: Δ9THC: Cannabigerol	-385 (-612.36, -157.64)	0.0009					
	Δ9THC: Cannabigerol: Alcohol	-1480 (-2346.32, -613.68)	0.0008					
	Δ9THC: Analgesics	-130 (-199.78, -60.22)	0.0003					
	Cigarettes: Δ9THC: Alcohol	-384 (-583.92, -184.08)	0.0002					
	Cigarettes: Analgesics	-383 (-563.32, -202.68)	3.2E-05					

	Alcohol	-137 (-197.96, -76.04)	1.1E-05					
	Cannabinoids as Main Effects - 2 Lags							
	spreml(Cancer_Rate ~ Cigarettes * THC * Cannabigerol * Alcohol + Analgesics + Cocaine)							
THC, 2	Caucasian-American	4.63 (2.53, 6.72)	1.5E-05	-1320.47	1.8880	phi	0.1976	0.0021
Cannabigerol, 2	Cannabigerol	21.6 (9.29, 33.9)	0.0006			psi	0.1322	0.0052
	THC: Alcohol	10.25 (4.12, 16.37)	0.0010			rho	-0.3332	0.0881
	Asian-American	0.56 (0.17, 0.95)	0.0053			lambda	0.3037	0.0500
	Cannabigerol: Alcohol: Analgesics	1176.24 (308.66, 2043.82)	0.0079					
	Hispanic-American	0.47 (0.1, 0.84)	0.0117					
	AIAN-American	-10.84 (-18.51, -3.17)	0.0056					
	Cannabigerol: Alcohol	-288.07 (-474.04, -102.11)	0.0024					
	THC: Cannabigerol: Analgesics	92.38 (39.25, 145.5)	0.0007					
	Cannabinoids as Main Effects - 4 Lags							
	spreml(Cancer_Rate ~ Cigarettes * THC * Cannabigerol * Alcohol + Analgesics + Cocaine)							
THC, 4	Caucasian-American	4.31 (2.26, 6.36)	3.9E-05	-1126.72	1.8642	phi	0.1876	0.0047
Cannabigerol, 4	Cigarettes: THC	2.87 (1.47, 4.27)	5.9E-05			psi	0.1223	0.0246
	Asian-American	0.64 (0.26, 1.03)	0.0010			rho	-0.4917	0.0007
	Hispanic-American	0.58 (0.21, 0.95)	0.0021			lambda	0.3940	0.0004
	Cigaretes: Cannabigerol: Alcohol	668.38 (191.09, 1145.67)	0.0061					
	Cigarettes	-3.45 (-5.85, -1.04)	0.0050					
	AIAN-American	-11.66 (-19.15, -4.17)	0.0023					
	Cannabigerol: Alcohol	-329.3 (-523.66, -134.95)	0.0009					
	Cannabinoids as Main Effects - 6 Lags							
	spreml(Cancer_Rate ~ Cigarettes * THC * Cannabigerol * Alcohol + Analgesics + Cocaine)							
THC, 6	Cigarettes: THC	28.16 (18.61, 37.71)	7.6E-09	-918.382	1.8922	phi	0.2868	0.0023
Cannabigerol, 6	THC: Cannabigerol	46.22 (30.06, 62.38)	2.1E-08			psi	0.1197	0.0495

	Asian-American	0.67 (0.21, 1.12)	0.0039			rho	-0.5066	0.0004
	Caucasian-American	3.19 (1.01, 5.38)	0.0042			lambda	0.3707	0.0007
	Cocaine	18.22 (3.99, 32.46)	0.0121					
	Cigarettes: Cannabigerol: Alcohol	724.22 (143.74, 1304.71)	0.0145					
	AIAN-American	-10.25 (-18.78, -1.73)	0.0184					
	Cannabigerol: Alcohol	-329.39 (-580.71, -78.07)	0.0102					
	Cigarettes: THC: Cannabigerol	-177.1897 (-248.1, -106.28)	9.7E-07					
	THC	-7.21 (-9.86, -4.55)	1.1E-07					
	Cigarettes	-29.01 (-39.21, -18.82)	2.4E-08					

Table 12.: Spatially- and Temporally- Lagged Spatiotemporal Models

Parameter	Estimate (C.I.)	R.R. (C.I.)	E-Values
LINEAR REGRESSION			
Cancer Rate Over Time			
Year	0.14 (0.1, 0.17)	1.06 (1.04, 1.08)	1.31, 1.27
Cancer Rate by Δ9THC			
Δ9THC	0.33 (0.15, 0.5)	1.15 (1.07, 1.23)	1.55, 1.33
Cancer Rate by Drug Rate			
Drug_Rate: Cannabis	4.63 (2.11, 7.15)	6.83 (2.41, 19.41)	13.15, 4.25
Cancer Rate by Cannabinoid Over Time			
Cannabinol	6.54 (5.07, 8.01)	15.54 (8.39, 28.78)	30.58, 16.27
Cannabigerol	7.65 (5.91, 9.38)	24.71 (11.96, 51.02)	48.91, 23.41
Drug_Rate	2.14 (1.55, 2.73)	2.45 (1.91, 3.14)	4.34, 3.24
Cannabichromene	3.86 (0.29, 7.42)	5.04 (1.14, 22.44)	9.54, 1.51
Cancer Rate by Ethnic Cannabis Exposure			
Ethnic_THC_Exposure	0.14 (0.07, 0.21)	1.06 (1.03, 1.09)	1.31, 1.20
Asian-Am_THC_Exposure	0.28 (0.02, 0.55)	1.12 (1.01, 1.26)	1.50, 1.10
Legal Status			
Decriminalized	0.85 (0.44, 1.26)	1.42 (1.20, 1.69)	2..20, 1.69
Liberal	0.663 (0.35, 0.98)	1.32 (1.15, 1.50)	1.96, 1.58
Legal	1.3286 (0.47, 2.19)	1.73 (1.21, 2.45)	2.86, 1.72
Cancer by Legal Status			
Decriminalized	0.78 (0.37, 1.19)	1.38 (1.16, 1.64)	2.11, 1.60
Legal	1.51 (0.68, 2.35)	1.87 (1.33, 2.66)	3.16, 1.98
Cancer by Year * Status			

Year: Decriminalized	0.0003 (0.0001, 0.0005)	1.00013 (1.00004, 1.00021)	1.011, 1.006
Cancer by Year * Dichotomized_Status			
Year: Liberal	0.0002 (0, 0.0004)	1.00008 (1.00001, 1.00015)	1.0090, 1.0035
MIXED EFFECTS REGRESSION			
Additive Model			
Cannabis	5.34 (0.07, 10.6)	4.11 (1.02, 16.59)	7.70 , 1.18
Interactive Drugs Model			
Cannabis	72.88 (49.6, 96.15)	5.02E+08 (8.45E+05, 2.97E+11)	1.01E+09, 1.69E+06
Cigarettes: Cannabis: Analgesics	2788.19 (1676.17, 3900.2)	Infinity (2.40E+200, Infinity)	Infinity, Infinity
Full Interactive Model			
Cannabis	79.27 (56.77, 101.78)	7.00E+09 (1.14E+07, 4.31E+12)	1.40E+09, 2.27E+07
Cigarettes: Cannabis: Analgesics	2525.7 (1488.65, 3562.75)	Infinity (1.38E+185, Infinity)	Infinity, Infinity
Full Interactive Model with Cannabinoids			
Cigarettes: Cannabigerol: Alcohol	4741.19 (3077.86, 6404.51)	Infinity (Infinity, Infinity)	Infinity, Infinity
Δ9THC: Alcohol	14.95 (7.74, 22.16)	73.78 (9.31, 584.34)	147.07, 18.12
Cigarettes: Δ9THC	26.57 (15.54, 37.6)	2.09E+03 (87.97, 4.95E+04)	4.18E+03, 175.45
GEOSPATIAL REGRESSION			
Additive Model			
Cannabis	5.16 (2.26, 8.06)	11.18 (2.89, 43.30)	21.84,. 5.22
3-Way Interactive model			
Cannabis	20.68 (7.02, 34.33)	1.55E+04 (26.85, 9.01E+06)	3.11E+04, 53.19
4-Way Interactive model			
Cannabis	5.42 (2.34, 8.5)	12.61 (2.99, 53.07)	24.71, 5.45
Interactive Full Model - 0 Lags			
Cannabis	45.67 (18.77, 72.56)	6.00E+10 (1.07E+04, 3.45E+15)	1.20E+120, 5.15E+04
Cigarettes: Cannabis: Alcohol	840.86 (416.29, 1265.44)	1.09E+180 (2.07E+89, 5.78E+270)	Infinity, 4.14E+89
Cigarettes: Cannabis: Analgesics	966.38 (184.69, 1748.06)	8.18E+206 (7.64E+39, Infinity)	Infinity, 1.52E+40

Time Lagged Models			
Full model - 4 Lags - Just Lagging Cannabis			
Cigarettes: Cannabis: Analgesics	261.1 (19.06, 503.15)	8.26E+39 (0.07, 9.56E+80)	1.65E+40, 1.00
Full model - 6 Lags - Just Lagging Cannabis			
Cannabis	8.49 (1.47, 15.5)	50.45 (1.98, 1.28E+03)	100.41, 3.39
Full Model - 1 Temporal Lag			
Cannabis	7.88 (1.7, 14.06)	48.60 (2.32, 1.016E+03)	96.68, 4.07
Cigarettes: Cannabis: Alcohol	182.23 (29.55, 334.9)	1..00E+39 (2.45E+06, 4.07E+71)	1.99E+39, 4.91E+06
Full Model - 2 Temporal Lags			
Cigarettes: Cannabis: Alcohol	658.72 (396.6, 920.84)	3.76E+140 (5.65E+84, 2.53E+196)	7.58E+140, 1.13E+85
Full Model - 4 Temporal Lags			
Cigarettes: Cannabis: Alcohol	472.69 (145.49, 799.88)	9.42E+126 (2.81E+30, 3.15E+223)	1.88E+127, 5.62E+30
Space-Time Lagged Models			
Full Model - 1 Spatial & 1 Temporal Lag			
Cannabis: Analgesics	110.36 (37.53, 183.19)	2.51E+23 (9.78E+07, 6.48E+38)	5.03E+23, 1.95E+08
Cigarettes: Cannabis: Alcohol	1688.83 (336.9, 3040.77)	Infinity (1.033E+72, Infinity)	Infinity, 2.07E+72
Full Model - 2 Spatial & 2 Temporal Lags			
Cigarettes: Cannabis: Alcohol: Analgesics	3954.04 (1565.01, 6343.08)	Infinity (Infinity, Infinity)	Infinity, Infinity
Cannabinoid Models			
Cannabinoids as Main Effects			
Cigarettes: Δ9THC: Analgesics	391 (181.28, 600.72)	1.62E+84 (1.65E+39, 1.59E+129)	3.24E+84, 3.30E+39
Δ9THC: Alcohol	116 (51.71, 180.29)	1.11E+25 (1.68E+11, 7.41E+38)	2.23E+25, 3.36E+11
Cigarettes: Δ9THC: Cannabigerol: Alcohol	4810 (2124.8, 7495.2)	Infinity (Infinity, Infinity)	Infinity, Infinity
Δ9THC: Cannabigerol	109 (41.58, 176.42)	2.45E+23 (7.67E+08, 7.83E+37)	4.90E+23, 1.54E+09
Δ9THC: Cannabigerol: Alcohol: Analgesics	5640 (1680.8, 9599.2)	Infinity (Infinity, Infinity)	Infinity, Infinity
Cigarettes: Δ9THC	9.01 (0.6, 17.42)	87.15 (1.35, 5.61E+03)	173.80, 2.04

Cannabinoids as Main Effects - 2 Lags			
Cannabigerol	21.6 (9.29, 33.9)	3.32E+04 (89.18, 1.23E+07)	6.64E+04, 177.84
THC: Alcohol	10.25 (4.12, 16.37)	139.58 (7.34, 2.65E+03)	278.66, 14.15
Cannabigerol: Alcohol: Analgesics	1176.24 (308.66, 2043.82)	1.66E+246 (9.51E+64, Infinity)	Infinity, 1.91E+65
Cannabinoids as Main Effects - 4 Lags			
Cigarettes: THC	2.87 (1.47, 4.27)	4.06 (2.06, 8.04)	7.58, 3.52
Cigarettes: Cannabigerol: Alcohol	668.38 (191.09, 1145.67)	5.01E+141 (5.21E+40, 4.82E+242)	1.00E+142, 1.04E+41
Cannabinoids as Main Effects - 6 Lags			
Cigarettes: THC	28.16 (18.61, 37.71)	7.61E+05 (7.76E+03, 7.46E+07)	1.52E+06, 1.55E+04
THC: Cannabigerol	46.22 (30.06, 62.38)	4.50E+09 (1.92E+06, 1.06E+13)	9.01E+09, 3.84E+06
Cigarettes: Cannabigerol: Alcohol	724.22 (143.74, 1304.71)	1.82E+151 (1.84E+30, 1.80E+272)	3.64E+151, 3.68E+30
Ethnicity Models			
Cancer Incidence as a Function of Racial Cannabis Exposure			
Afric-Am._THC_Exp: Hispan.Am_THC_Exp	1.74 (1.18, 2.29)	2.22 (1.72, 2.86)	3.86, 2.86
Afric-Am._THC_Exp: Hispan.Am_THC_Exp: Asian-Am._THC_Exp: _AIAN-Am._THC_Exp	0.15 (0.09, 0.21)	1.51 (1.18, 1.91)	2.38, 1.66
Asian-Am._THC_Exp: AIAN-Am._THC_Exp	0.89 (0.37, 1.41)	1.06 (1.04, 1.10)	1.34, 1.24

Table 13.: Linear Regressions for Legal Status

Parameter Estimates			Model Parameters			
Parameter	**Estimate (C.I.)**	**P-Value**	**R-Squared**	**F**	**dF**	**P-Value**
Cancer by Status						
lm(Cancer_Rate ~ Legal_Status)						
Decriminalized	0.78 (0.37, 1.19)	2.0E-04	0.0268	7.88	3,746	3.49E-05
Legal	1.51 (0.68, 2.35)	4.0E-04				
Cancer by Year * Status						
lm(Cancer_Rate ~ Year * Legal_Status)						
Year	0.13 (0.09, 0.16)	4.3E-11	0.0809	17.5	4,745	1.01E-13
Year: Decriminalized	0.0003 (0.0001, 0.0005)	4.4E-03				
Cancer by Year * Dichotomized_Status						
lm(Cancer_Rate ~ Year * Dichotomized_Status)						
Year	0.128 (0.09, 0.16)	9.8E-12	0.0778	32.6358	2,747	2.58E-14
Year: Liberal	0.0002 (0, 0.0004)	2.1E-02				

Figure Captions

Figure 1.: Pediatric Cancers 1975-2017, CDC SEER Explorer Dataset, USA National Level, data derived from 9 cancer registries.

Figure 2.: Drug use over time. Data from NSDUH 2002-2017, SAMHSA.

Figure 3.: Cannabinoid concentrations in Federal Seizures of Cannabis over time, Drug Enforcement Agency data [47-49].

Figure 4.: Total pediatric cancer incidence rate as a function of drug exposure.

Figure 5.: Total pediatric cancer incidence rate as a function of estimated state level cannabinoid exposure.

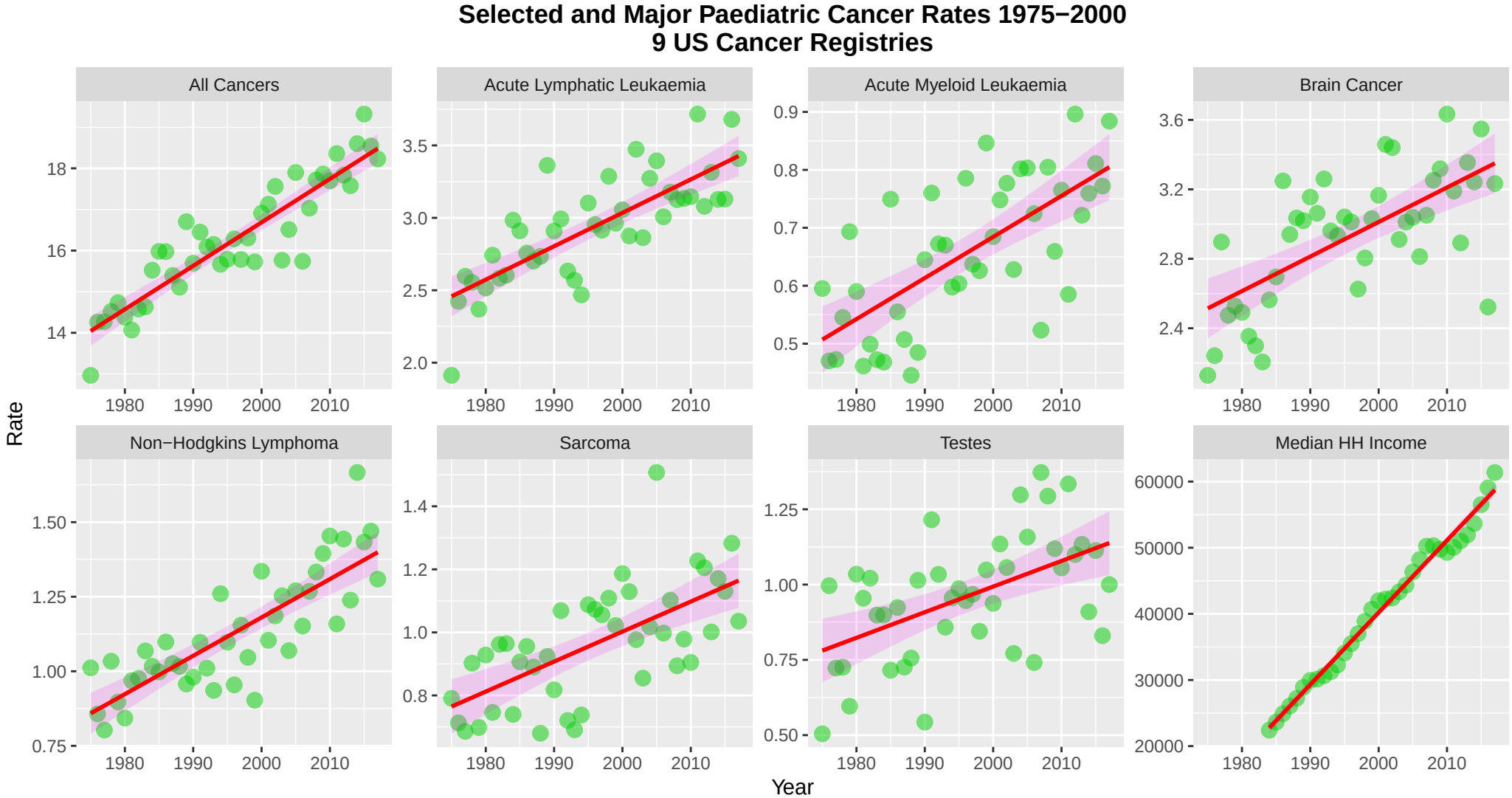
Figure 6.: Total pediatric cancer incidence rate as a function of estimated ethnic THC exposure.

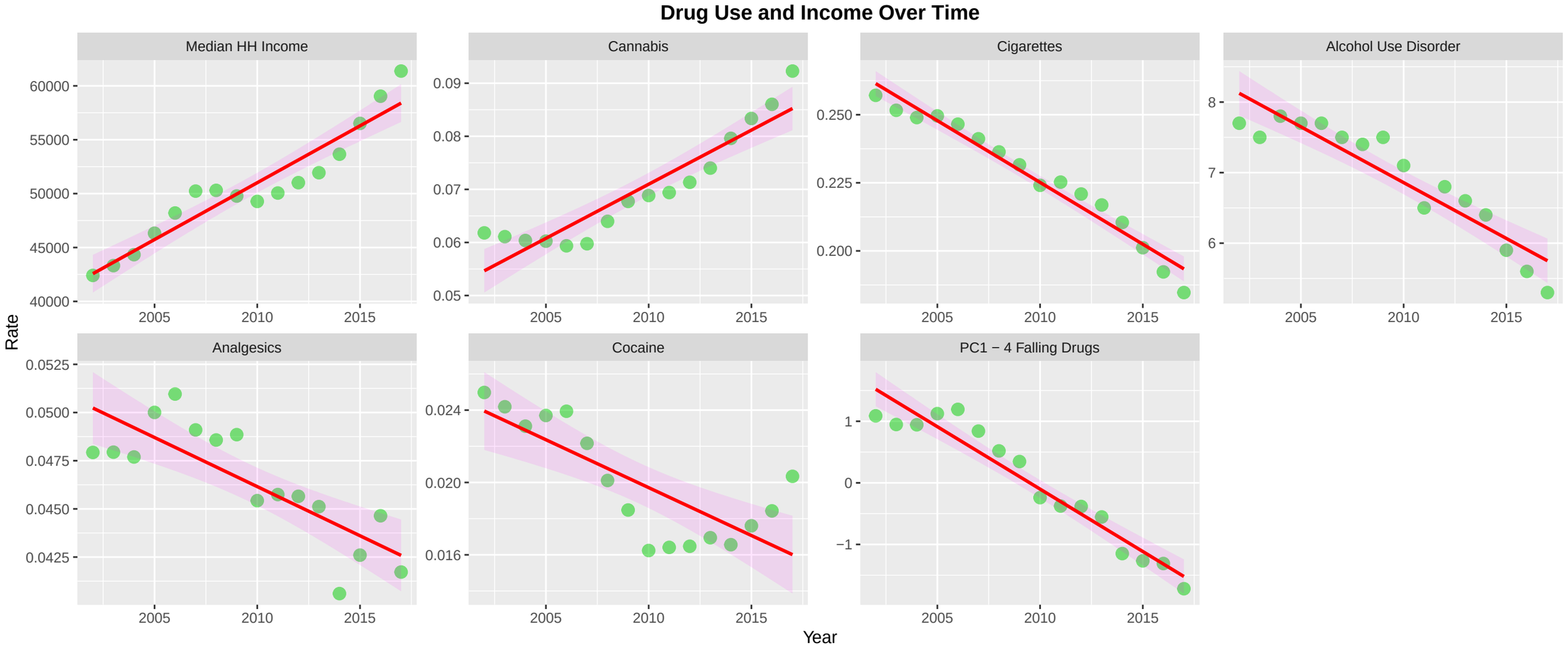
Figure 7.: Total pediatric cancer incidence rate by cannabis use quintiles. (A) Boxplot over aggregated time. (B) Scatterplot over time by cannabis use quintiles. (C) Boxplot by dichotomized cannabis use quintiles, highest two quintiles vs. the lowest three. Note non-over-lapping notches indicating significant differences. (D) Scatterplot over time of total pediatric cancer incidence rate by dichotomized cannabis use quintiles.

Figure 8.: Map graph of total pediatric cancer incidence rate by state over time sequence, by year.

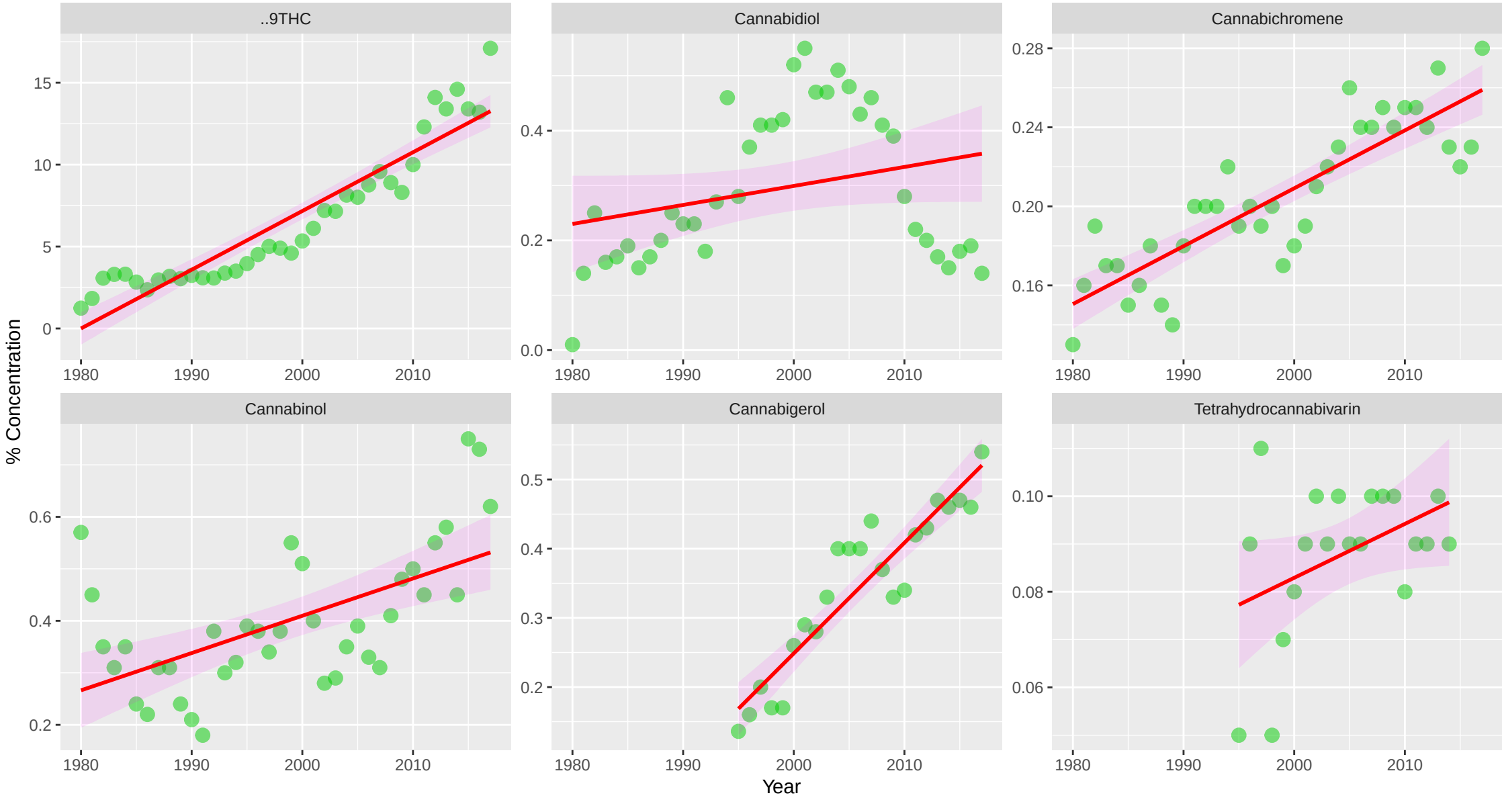
Figure 9.: Geospatial linkages used for geospatiotemporal regression analyses. Note Alaska and Hawaii elided arithmetically onto continental USA. (A) Edited spatial links. (B) Final links.

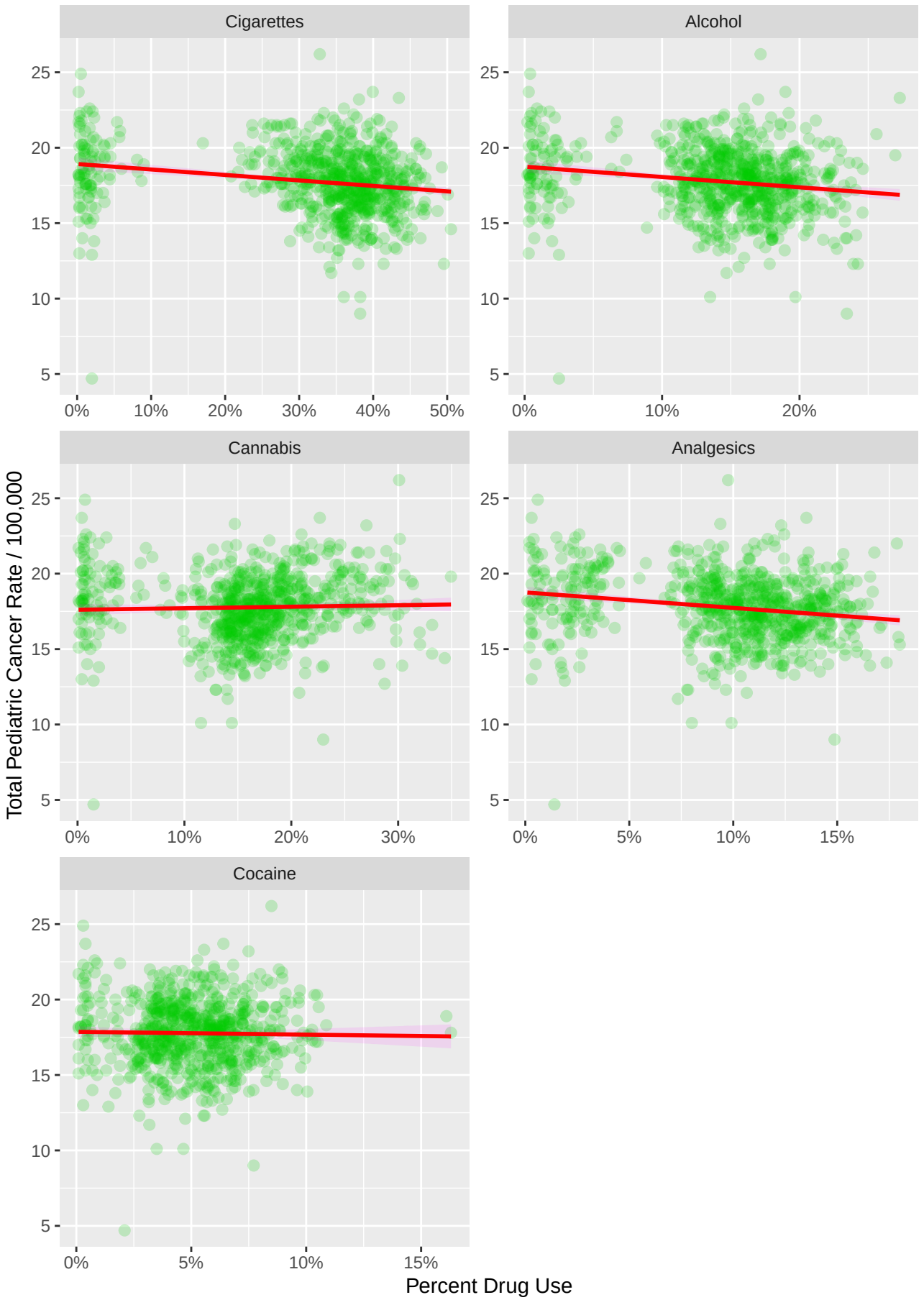
Figure 10: Effect of Cannabis Legal Status on total pediatric cancer incidence rate. (A) Scatterplot of legal statuses over time. (B) Scatterplot of legal status over time dichotomized as illegal status vs. liberal regimes.

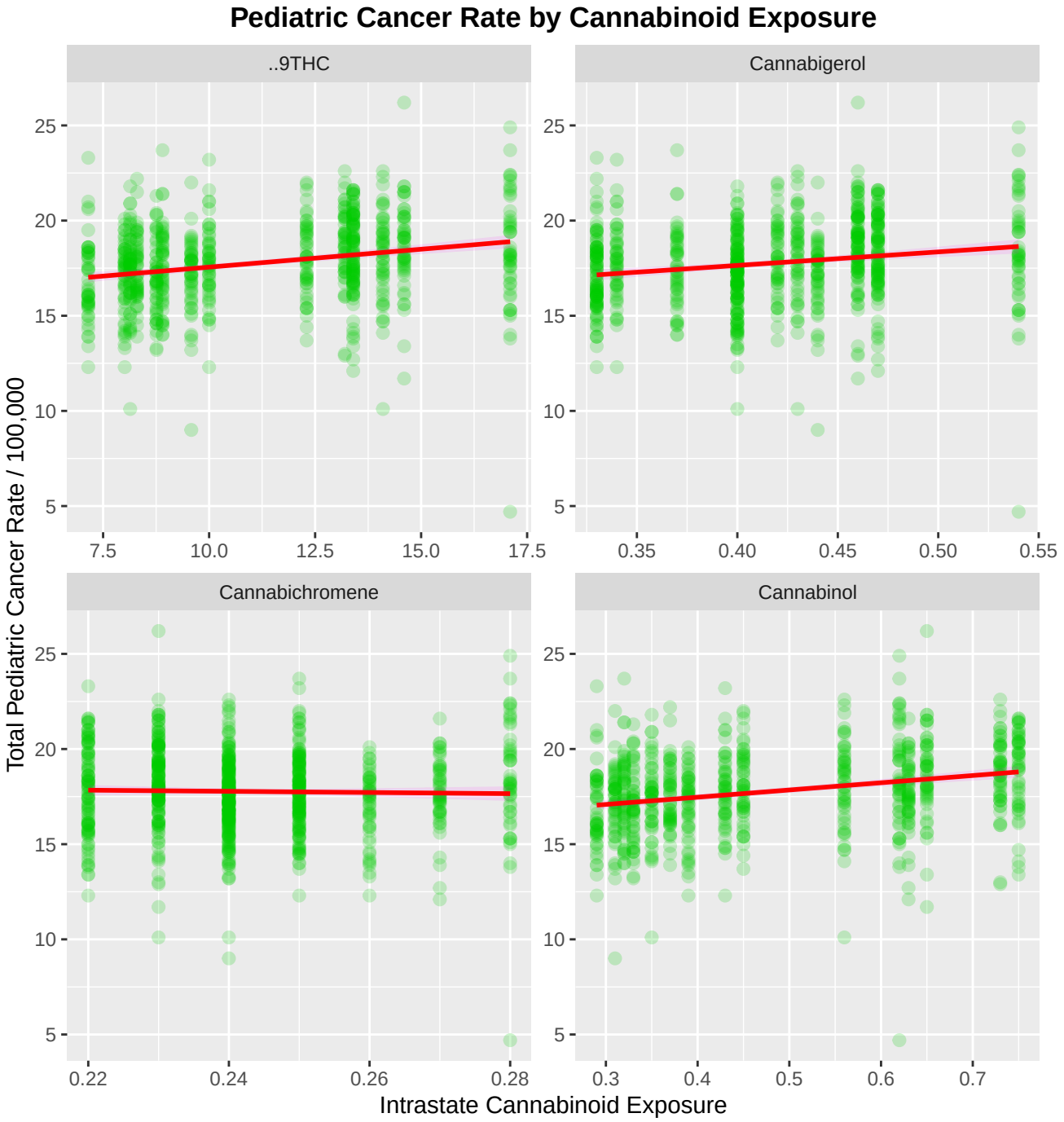

Selected and Major Paediatric Cancer Rates 1975−2000
9 US Cancer Registries
All Cancers
Acute Lymphatic Leukaemia
Acute Myeloid Leukaemia
Brain Cancer
Non−Hodgkins Lymphoma
Sarcoma
Testes
Median HH Income
Rate
Year

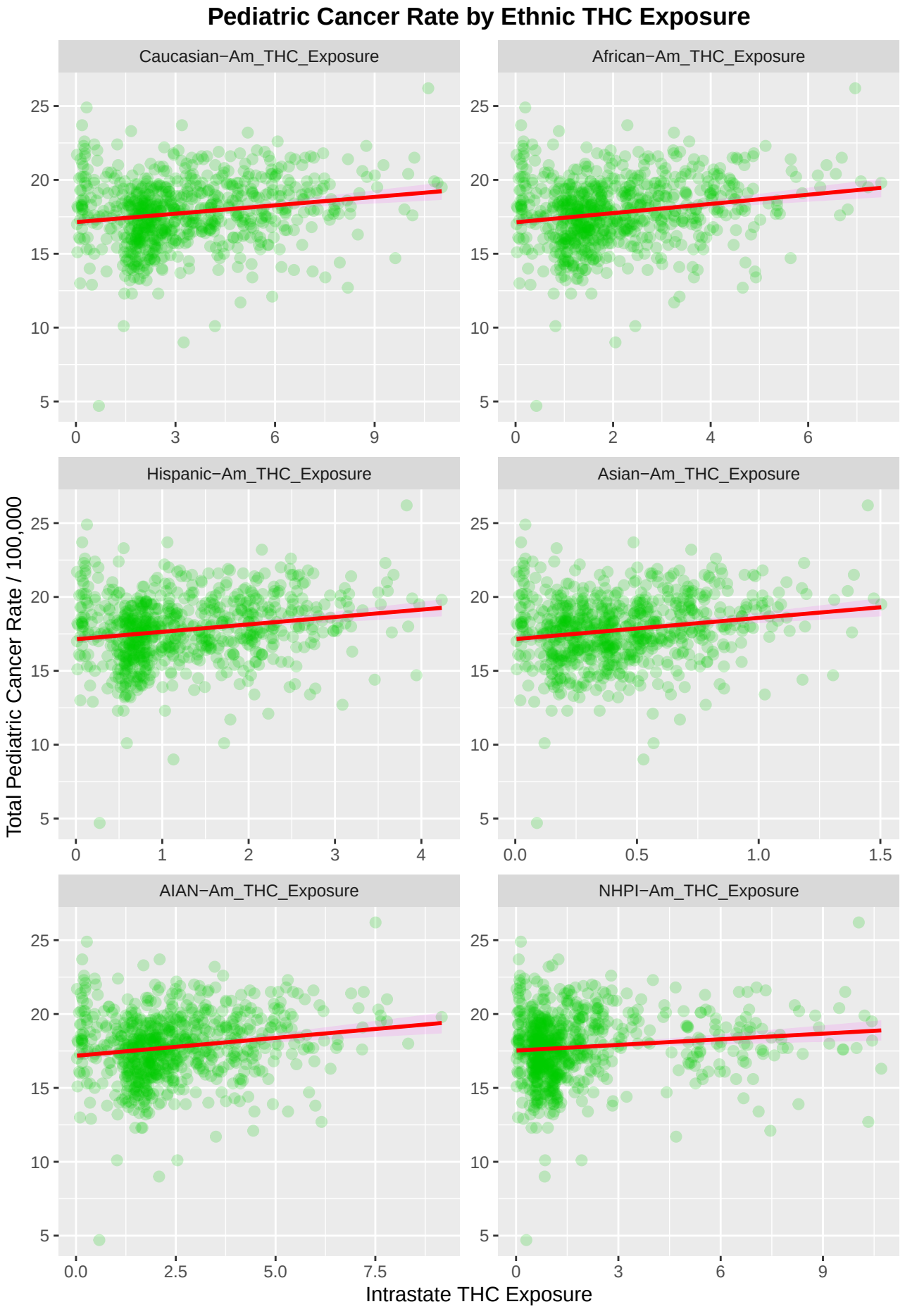

Drug Use and Income Over Time
Median HH Income
Cannabis
Cigarettes
Alcohol Use Disorder
Analgesics
Cocaine
PC1 − 4 Falling Drugs
Rate
Year
60000
55000
50000
45000
40000
0.09
0.08
0.07
0.06
0.05
0.250
0.225
0.200
8
7
6
0.0525
0.0500
0.0475
0.0450
0.0425
0.024
0.020
0.016
1
0
−1
2005
2010
2015

US National Cannabinoid Concentration Trends
DEA Seizure Analyses



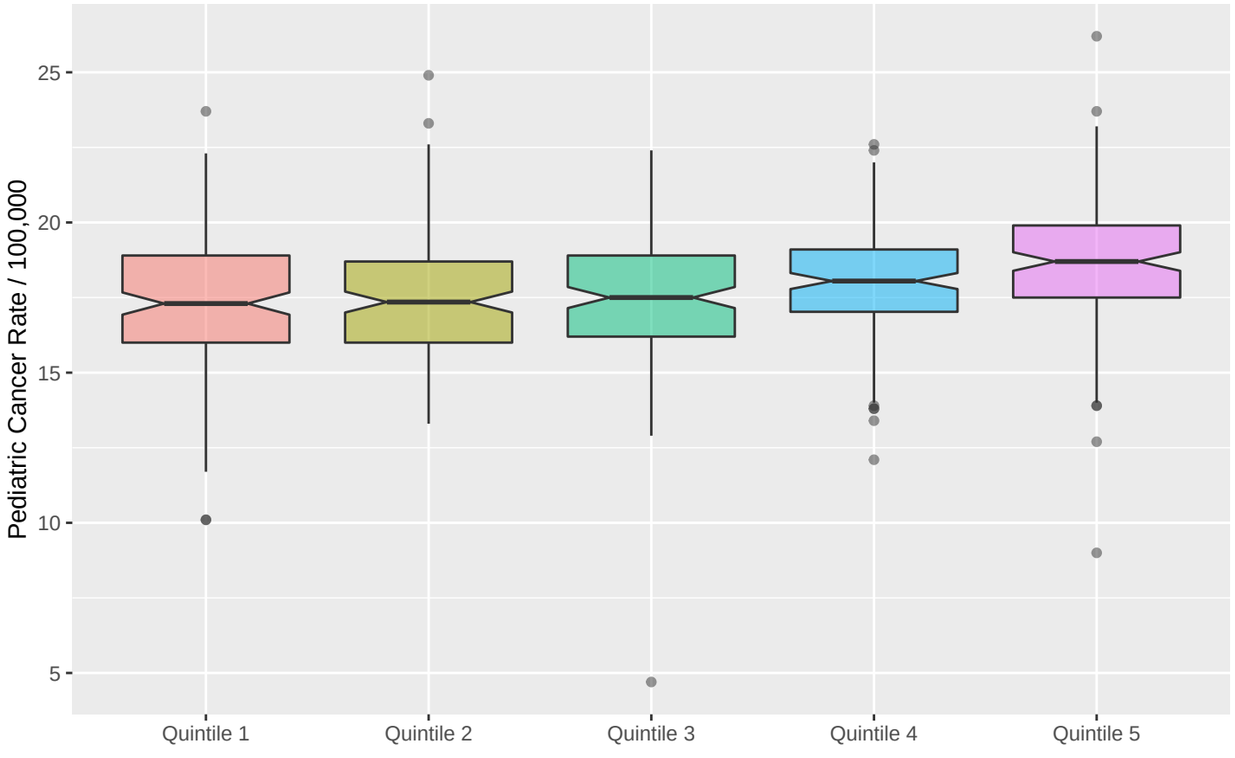

Pediatric Cancer Rate by Substance Exposure
Cigarettes
Alcohol
Cannabis
Analgesics
Cocaine
Total Pediatric Cancer Rate / 100,000
Percent Drug Use
25
20
15
10
5
0%
10%
20%
30%
40%
50%
5%
15%


Pediatric Cancer Rate by Cannabinoid Exposure
..9THC
Cannabigerol
Cannabichromene
Cannabinol
Total Pediatric Cancer Rate / 100,000
Intrastate Cannabinoid Exposure
25
20
15
10
5
7.5
10.0
12.5
15.0
17.5
0.35
0.40
0.45
0.50
0.55
0.22
0.24
0.26
0.28
0.3
0.4
0.5
0.6
0.7

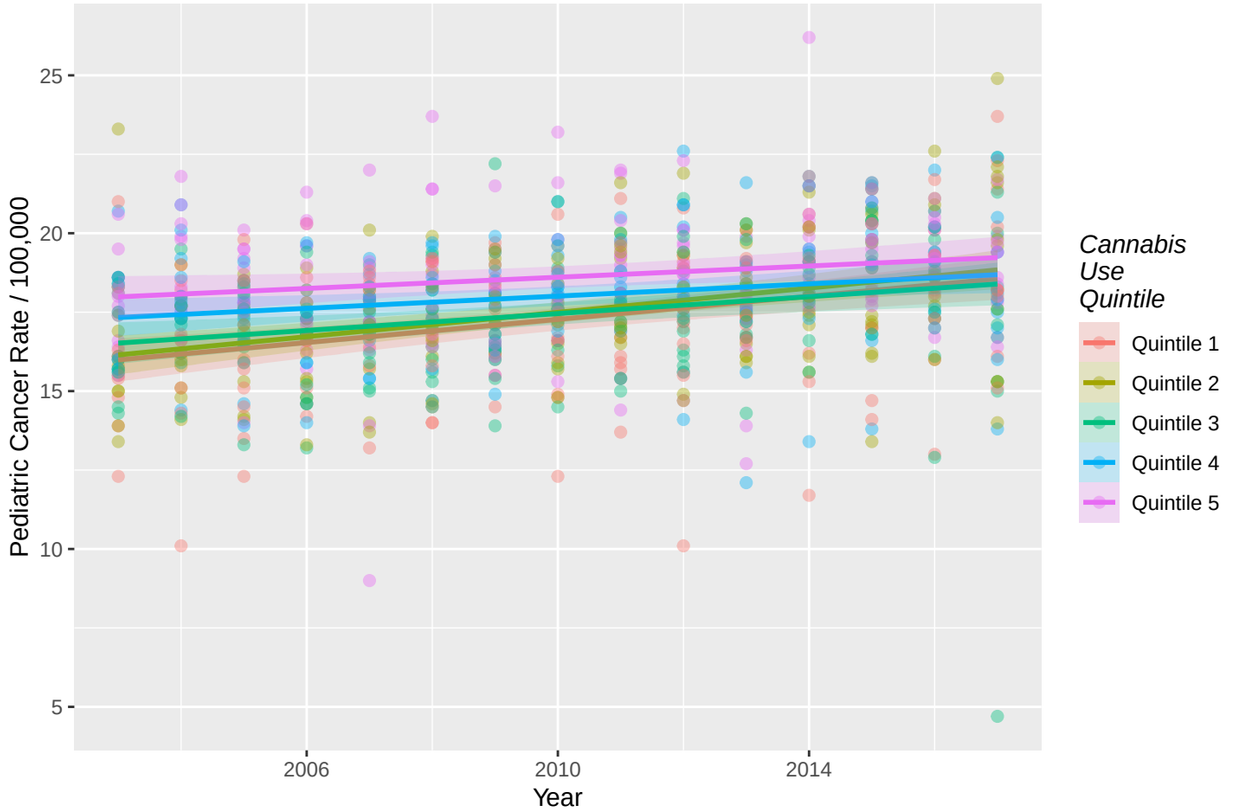

Pediatric Cancer Rate by Ethnic THC Exposure
Caucasian−Am_THC_Exposure
African−Am_THC_Exposure
Hispanic−Am_THC_Exposure
Asian−Am_THC_Exposure
AIAN−Am_THC_Exposure
NHPI−Am_THC_Exposure
Total Pediatric Cancer Rate / 100,000
Intrastate THC Exposure

Pediatric Cancer Rate by Quintiles of Cannabis Use

Data − NCI SEER Program and NSDUH, SAMHSA

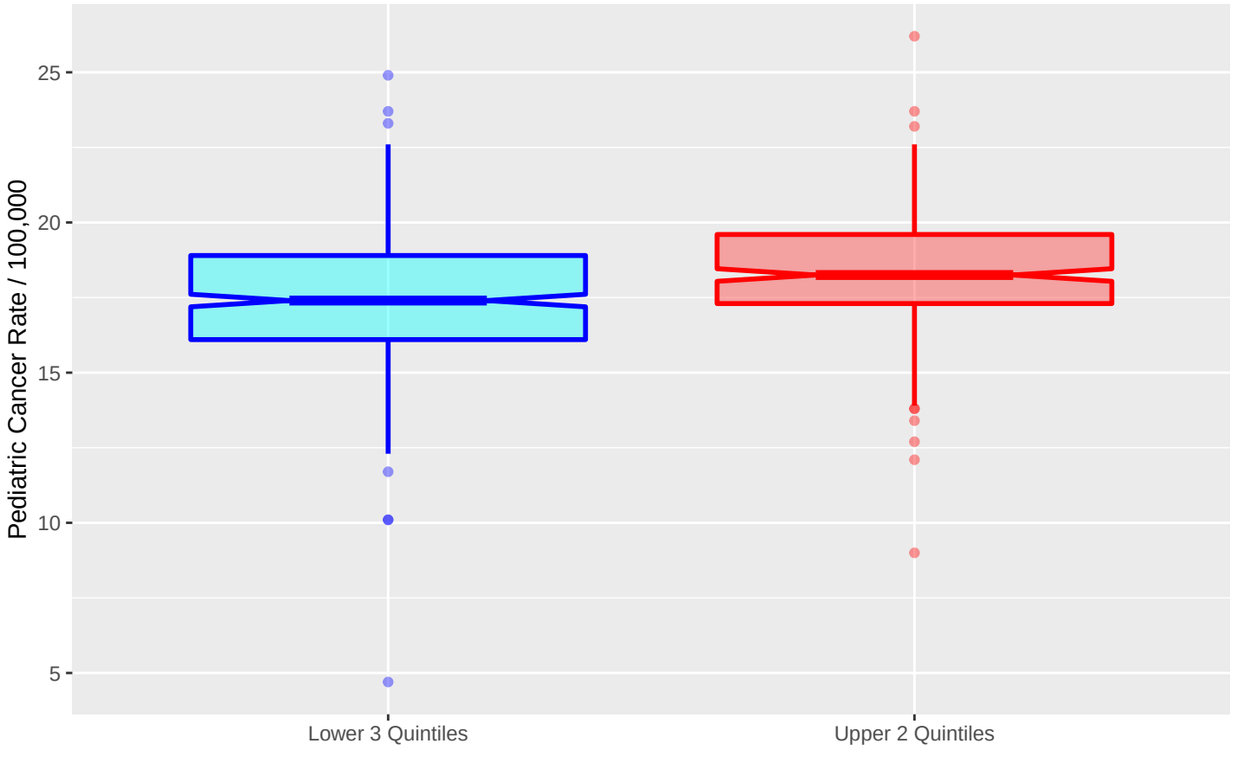


US Pediatric Cancer Rates by Cannabis Use Quintile

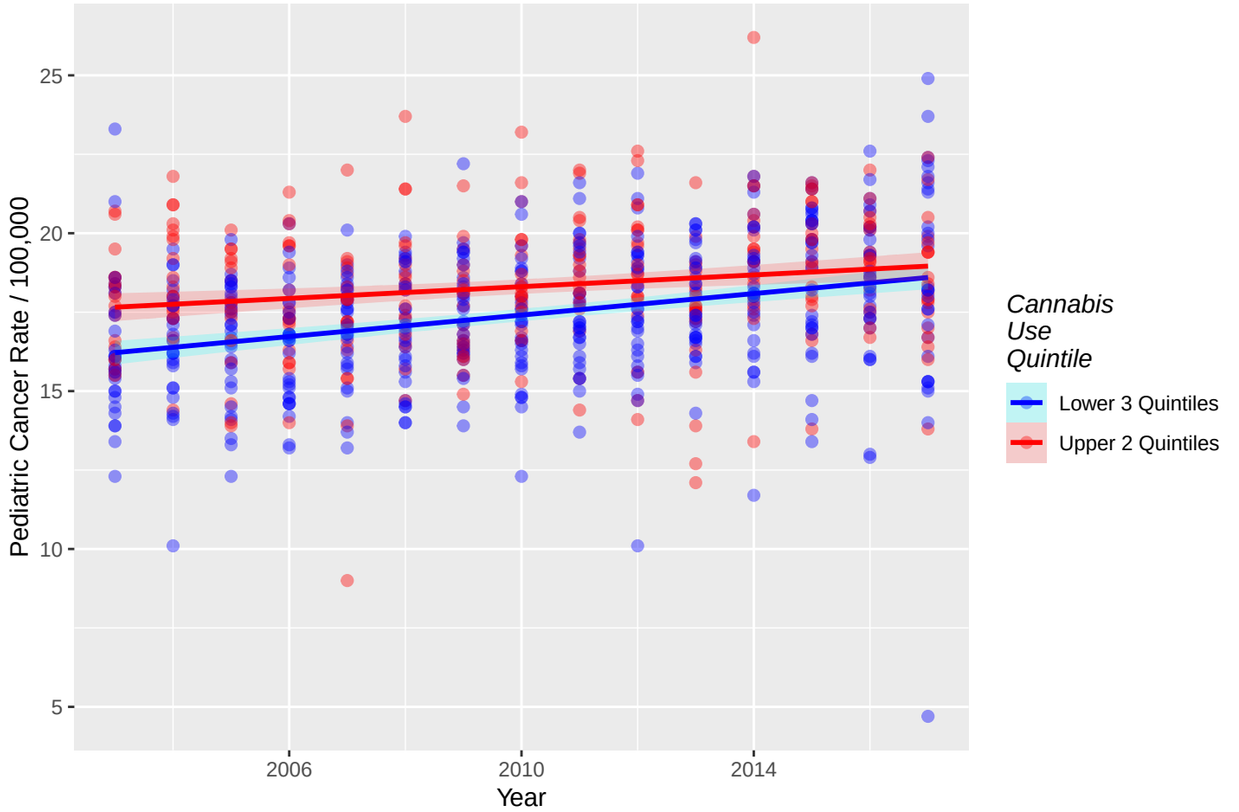


Pediatric Cancer Rate by Quintiles of Cannabis Use

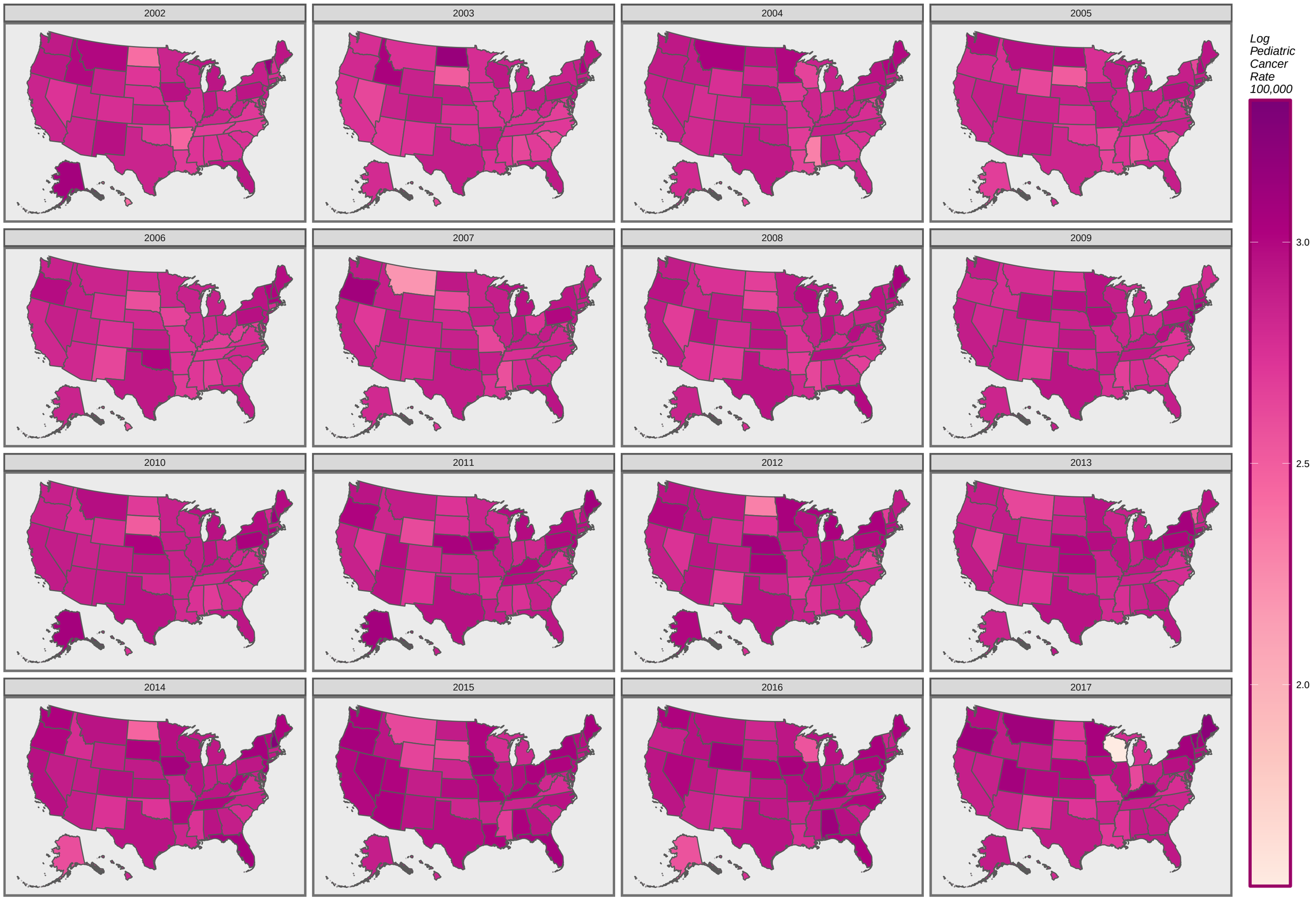
Data − NCI SEER Program and NSDUH, SAMHSA



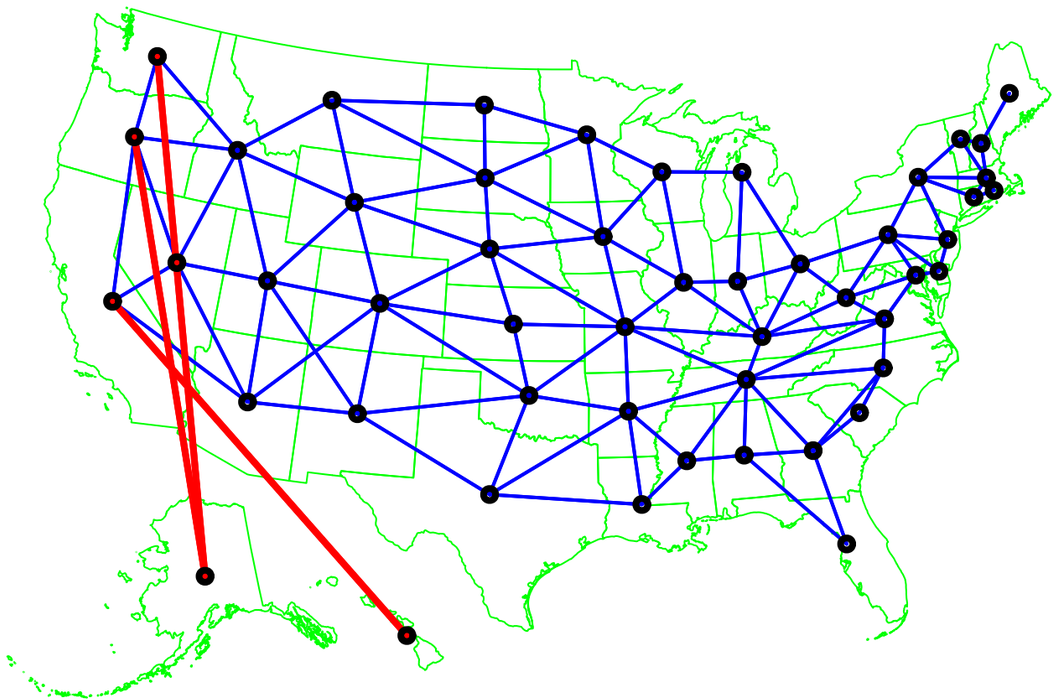
US Pediatric Cancer Rates by Cannabis Use Quintile − Dichotomized



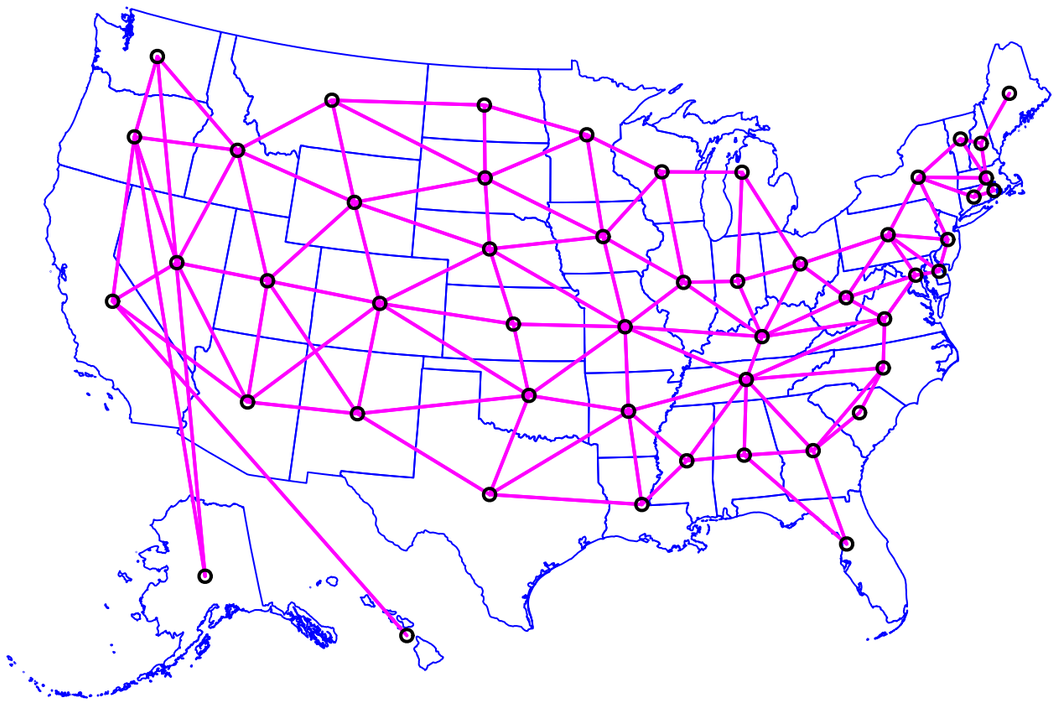
Log (Rates) of Paediatric Cancer US States 2002−2017

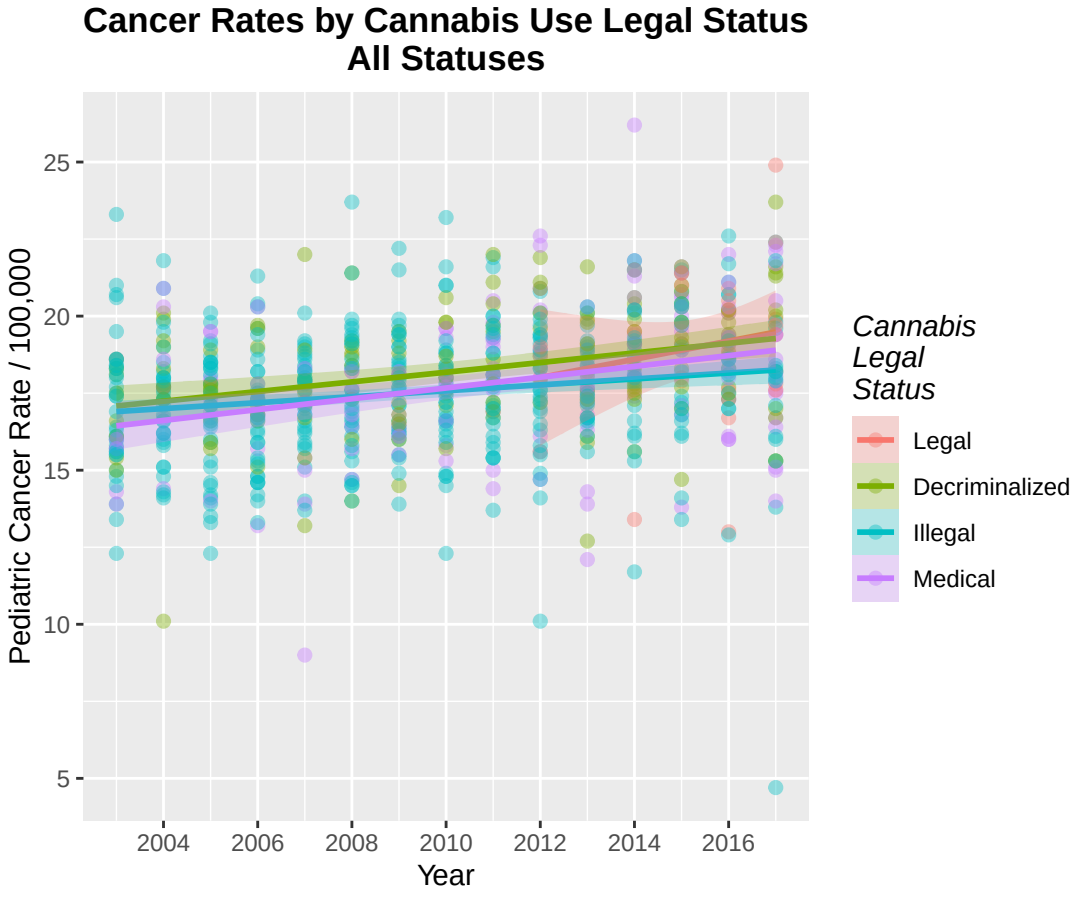


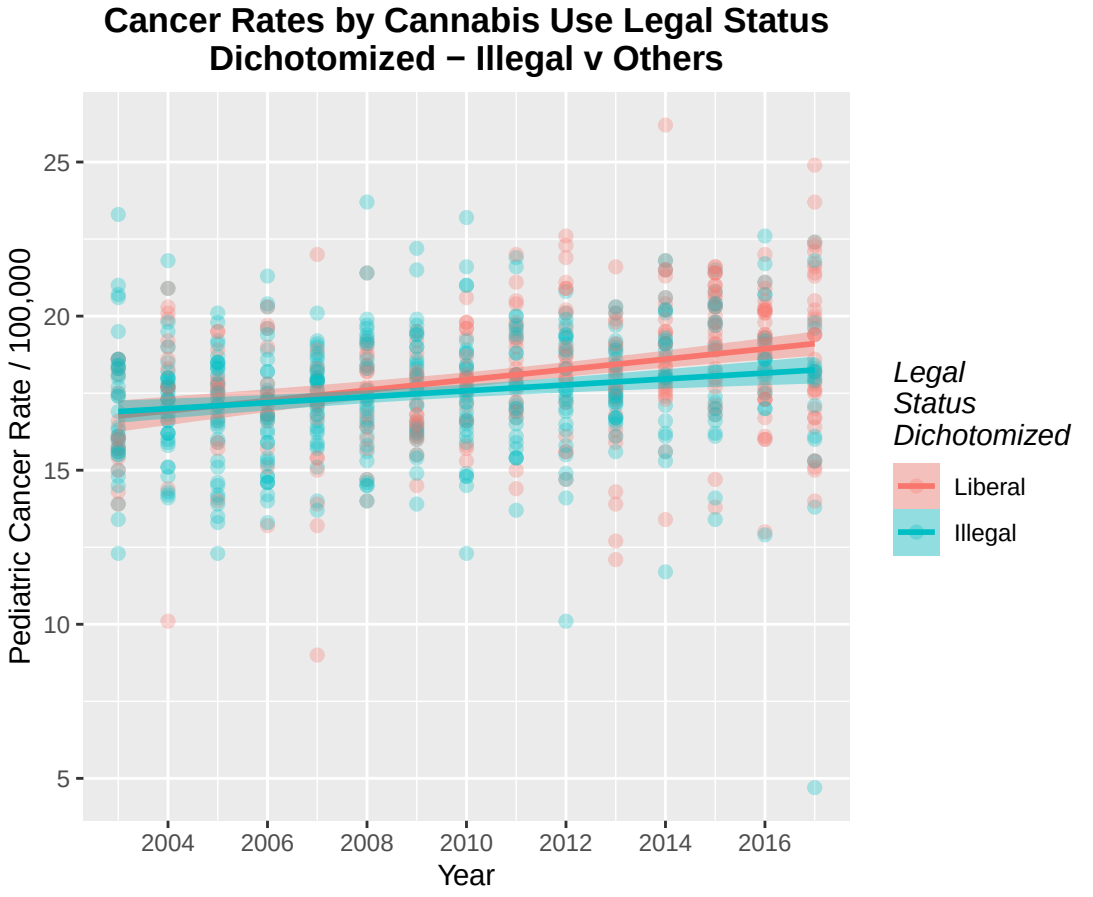
Additional Links to State Neighbourhood Linkage Network for US Pediatric Cancer Network Dataset



Final Links to State Neighbourhood Linkage Network for US Pediatric Cancer Network Dataset




Cancer Rates by Cannabis Use Legal Status
All Statuses
Pediatric Cancer Rate / 100,000
25
20
15
10
5
2004
2006
2008
2010
2012
2014
2016
Year
Cannabis Legal Status
Legal
Decriminalized
Illegal
Medical


Cancer Rates by Cannabis Use Legal Status
Dichotomized − Illegal v Others
Pediatric Cancer Rate / 100,000
25
20
15
10
5
2004
2006
2008
2010
2012
2014
2016
Year
Legal Status Dichotomized
Liberal
Illegal

Supplementary Table 1.: Cannabis Quintile Data

Quintile	Cannabis Exposure	Cancer Rates
Quintiles		
Quintile 1	0.1101 (0.0038)	17.2941 (0.1913)
Quintile 2	0.1349 (0.0042)	17.4933 (0.1763)
Quintile 3	0.1552 (0.0044)	17.4381 (0.1806)
Quintile 4	0.1731 (0.005)	18.0087 (0.1581)
Quintile 5	0.2304 (0.0062)	18.6060 (0.1767)
Dichotomized Quintiles		
Lower Quintiles	0.1331 (0.0025)	17.4076 (0.1055)
Upper Quintiles	0.2018 (0.0043)	18.3073 (0.1196)

Selected and Major Paediatric Cancer Rates Over Time
21 US Cancer Registries