

European epidemiological patterns of cannabis- and substance-related congenital cardiovascular anomalies: geospatiotemporal and causal inferential study

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Abstract

As prenatal and community cannabis exposures have recently been linked with congenital heart disease (CHD), it was of interest to explore these associations in Europe in a causal framework and space-time context. Congenital anomaly data from Eurocat, drug-use data from the European Monitoring Centre for Drugs and Drug Addiction, and income from the World Bank. Countries with rising daily cannabis use had in general higher congenital anomaly rates over time than those without (time: status interaction: β -Est. = 0.0267, $P = 0.0059$). At inverse probability-weighted panel regression, cannabis terms were positive and significant for CHD, severe CHD, atrial septal defect, ventricular septal defect, atrioventricular septal defect, patent ductus arteriosus, tetralogy of Fallot, vascular disruptions, double outlet right ventricle, transposition of the great vessels, hypoplastic right heart, and mitral valve anomalies from 1.75×10^{-19} , 4.20×10^{-11} , $<2.2 \times 10^{-16}$, $<2.2 \times 10^{-16}$, 1.58×10^{-12} , 4.30×10^{-9} , 4.36×10^{-16} , 3.50×10^{-8} , 5.35×10^{-12} , $<2.2 \times 10^{-16}$, 5.65×10^{-5} and 6.06×10^{-10} . At spatial regression, terms including cannabis were positive and significant for this same list of anomalies from 0.0038, 1.05×10^{-10} , 0.0215, 8.94×10^{-6} , 1.23×10^{-5} , 2.05×10^{-5} , 1.07×10^{-6} , 8.77×10^{-5} , 9.11×10^{-6} , 0.0001, 3.10×10^{-7} and 2.17×10^{-7} . 92.6% and 75.2% of 149 E-value estimates and minimum E-values were in high zone >9; 100.0% and 98.7% >1.25. Data show many congenital cardiac anomalies exhibit strong bivariate relationships with metrics of cannabis exposure. Causal inferential modelling for the twelve anomalies selected demonstrated convincing evidence of robust relationships to cannabis which survived adjustment and fulfilled epidemiological criteria for causal relationships. Space-time regression was similarly confirmatory. Epigenomic pathways constitute viable potential mechanisms. Given exponential genotoxic dose-response effects, careful and astute control of cannabinoid penetration is indicated.

Key words: tobacco; alcohol; cannabis; cannabinoid; cancer; cancerogenesis; mutagenesis; oncogenesis; genotoxicity; epigenotoxicity; transgenerational inheritance

Introduction

Cardiovascular anomalies form the commonest group of congenital anomalies (CAs) [1–3]. Following on from recent reports in HI, CO, Canada, Australia and the USA [4–8], as well as preliminary reports from Europe [9], it was of interest to study how the European pattern of cardiac congenital anomalies (CCAs) would behave when investigated in a formal causal inferential analytical framework and in the space-time context from which the native data were drawn.

The earliest report of this association from HI, USA identified hypoplastic left heart syndrome, tetralogy of Fallot, pulmonary valve stenosis or atresia, ventricular septal defect (VSD) and atrial septal defect (ASD) as being significantly related to prenatal cannabis exposure [4]. In Canada, the total cardiovascular defects were linked with community cannabis consumption [7]. In CO, USA, pulmonary artery anomalies, ASD, patent ductus arteriosus

(PDA) and VSD were significantly cannabis related [5]. In Australia, ASD, VSD, PDA and tetralogy of Fallot were more common in a high cannabis using area, while the transposition of the great vessels was of borderline significance [6]. In the report from the USA, interrupted aortic arch, hypoplastic left heart syndrome, aortic valve stenosis, VSD, pulmonary valve atresia, total anomalous pulmonary return, tetralogy of Fallot, coarctation of the aorta, ASD and single ventricle were all related to Δ^9 -tetrahydrocannabinol (THC) exposure, and the transposition of the great vessels was related to cannabidiol exposure [8, 10].

Morphogenesis of the heart and great vessels is very complex. The heart at first forms from the fusion of the two dorsal aortae which become pulsatile. This fused dorsal heart tube then folds, twists and turns to provide the somewhat twisted shape of the adult heart. The heart forms from cells in six cardiogenic fields, the primary, secondary and lateral heart fields, the proepicardium,

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the neural crest and parts of the great vessels are formed from the somites of the pharyngeal arches [11].

Genes that are important to heart development and are known as the core regulatory network are MEF2, NKX2, GATA, Tbx and Hand-1 and Hand-2 [11]. Impairment of Hand-1 expression leads to left ventricular anomalies. Impairments of Hand-2 lead to right ventricular anomalies [11]. Genes that are important in arteriogenesis include sonic hedgehog/vascular endothelial growth factor/notch/Eph-4/Ephrin-B2 [11]. Genes that are important in venogenesis include COUP-TFII/notch/Eph-4.

Moreover, the recent availability of detailed epigenomic resources describing lists of genes altered both in cannabis dependence and in cannabis withdrawal [12] indicates that it should be possible to gain a fair degree of mechanistic insight into the pathways which may be acting to generate the observed profile of teratological disturbances.

Cannabis is used widely by young people in the reproductive age group. Indeed, one recent study reported that 24% of pregnant Californian teenagers recently tested positive for cannabis [13], a situation that appears to have deteriorated since the COVID-19 pandemic commenced [14]. It was recently reported that an estimated 169 000 American women used cannabis while pregnant [15–18]. Moreover, it was recently reported that 69% of Coloradoan cannabis dispensaries actively recommended cannabis preparations for many of the side effects of pregnancy, such as insomnia, tiredness, anxiety and nausea [19], which interestingly is the identical group of indications for which thalidomide was also recommended in about 1958 [20].

The European Network of Population-Based Registries for the Epidemiological Surveillance of Congenital Anomalies (EUROCAT) [21] database tracks 95 birth defects across time which provides unusual detail and depth to analyses of body systems. It also provides a category for system-wide anomalies such as total congenital heart disease (CHD). Importantly, the total CA rate (CAR) includes live births, stillbirths and cases where early termination for anomaly was practised, all combined together so that it represents a total overall picture across all classes of births. The European Monitoring Centre for Drugs and Drug Addiction has a very detailed dataset of various metrics of cannabis use, which combined with a recent epidemiological analysis of cannabis use patterns across Europe [22] means that in-depth and detailed analyses can be conducted in this population.

One of our particular concerns going into this analysis was that many cannabinoids have shown a very clear exponential genotoxic dose–response relationship relating to diverse mutagenic and DNA-damaging activities [23–33], as well as the basic metabolic reactions on which genomic and epigenomic stability depends [34–39]. Moreover, recent epidemiological studies have confirmed that at the highest environmental doses of cannabis, a sharp jump is observed in the rates of many CAs [10]. Since a number of European countries have recently experienced a major increase in all of cannabis use prevalence, daily cannabis use intensity and cannabinoid potency [22, 40] it would appear that community cannabinoid exposure has increased rapidly there in recent years. Furthermore, there is some indication that cannabinoids are entering the food chain in countries such as France based on large crops of cannabis grown in parts of that nation and accompanying teratological outbreaks of major limb deformities in both bovine and human babies [41–43]. For these reasons, we are concerned that the sharp increase in cannabinoid penetration into the community colliding with the well-defined genotoxic dose–response curve [25–29, 33, 38] may well lead to further major genotoxic outcomes reflected in patterns of disease in whole populations.

The present study set out to study the following hypotheses and study questions: (i) Is there a bivariate relationship between exposure to various metrics of cannabis exposure and some cardiac CAs? (ii) Are these relationships robust to multivariable adjustment? (iii) Do these relationships fulfill quantitative criteria for causality? (iv) Was this confirmed at space-time analysis? (v) To what extent do epigenomic mechanisms potentially explain these observations? These hypotheses were formulated prior to the study analysis being performed.

Methods

Data

Data on all available CARs were downloaded by each individual year for each of 14 nations from the EUROCAT website [21] and analysed. The total CAR includes anomaly rates among live births, stillbirths and cases where early termination for anomaly was practised, all combined together so that it represents a total overall picture across all classes of births. The nations selected were chosen on the basis of the availability of their CA data for most of the years 2010–2019. National tobacco (percent daily tobacco use prevalence) and alcohol (litres of pure alcohol consumed per capita annually) use data were downloaded from the World Health Organization [44]. Drug use data for cannabis, amphetamines and cocaine were taken from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) [45]. Data relate to both sexes considered together. Last month cannabis use data were also supplemented by data on the THC content of cannabis herb and resin provided in recently published reports [22]. Data on daily cannabis use were also available from the EMCDDA and were collated in recent reports [22]. Median household income data (in \$USD) were taken from the World Bank [46].

National Assignment

Nations were categorized as being either high and rising daily cannabis use or low and/or falling daily cannabis use based on a recent European epidemiological study (see [Supplementary Fig. S4](#)) [22]. Thus, Belgium, Croatia, France, Germany, Italy, Netherlands, Norway, Portugal and Spain were categorized as nations experiencing increasing daily use, while Bulgaria, Finland, Hungary, Poland and Sweden were nations which were experiencing low or falling levels of daily cannabis use.

Derived Data

The availability of several metrics of cannabis use, exposure and consumption made it possible to calculate various derived metrics. Hence, last month cannabis use prevalence data were multiplied by the THC content of cannabis herb and resin to derive compound metrics. These metrics were also multiplied by imputed daily cannabis use prevalence rates to derive further compound metrics for both cannabis herb and resin.

Data Imputation

Missing data were completed by linear interpolation. This was particularly the case for daily cannabis use. Fifty-nine data points on daily cannabis use from the EMCDDA were available for these 14 nations across this period. Linear interpolation expanded this dataset to 129 data points (further details are provided in the Results section). Data on cannabis resin THC concentration were not available for Sweden. However, it was noted that the resin to herb THC concentration was almost constant in nearby Norway at 17.7, so this ratio was applied to the Swedish cannabis herb THC concentration data to derive estimates of Swedish cannabis resin THC concentration. Similarly, data for the cannabis resin THC con-

centration in Poland were not available. The resin to herb THC concentration ratio of nearby Germany was used to estimate the resin THC content in Poland from the known Polish herb THC concentrations. Since geospatial analytical techniques do not tolerate missing data, the dataset was completed by the last observation carried forwards or backwards for Croatia in 2018 and 2019 and Netherlands in 2010. It was not appropriate to use multiple imputation methods for this dataset as multiple imputations cannot be applied in panel or spatial multivariable regression techniques.

Statistics

Data were processed in R Studio version 1.4.1717 based on R version 4.1.1 from the Comprehensive R Archive Network and the R Foundation for Statistical Computing [47]. The analysis was conducted in December 2021. Data were manipulated using dplyr from the tidyverse [48]. Data were log-transformed where appropriate to improve compliance with normality assumptions based on the results of the Shapiro–Wilks test. Graphs were drawn in ggplot2 from tidyverse. Maps were drawn using ggplot2, sf (simple features) [49] and both custom colour palettes and palettes taken from the viridis and viridisLite packages [50].

Bivariate maps were drawn with package colorplaner [51]. All illustrations are original and have not been published previously. Linear regression was conducted in Base R. Mixed-effects regression was performed using package nlme [52]. In all multivariable models, model reduction was by the classical technique of serial deletion of the least significant term to yield a final reduced model which is the model presented. Multiple linear models were processed in a single pass using combined techniques from R packages purrr and broom [48, 53, 54]. The overall effect of covariates in multivariable models may be quantified as the marginal effect. In this case, the overall marginal effect was calculated using the R package margins [55].

Covariate Selection

The presence of multiple different metrics for cannabis consumption and exposure created a problem for analysis as it was not clear which was the most appropriate metric to employ for any particular model. Indiscriminate use of excessive covariates in a multivariable model would unnecessarily consume degrees of freedom and thereby restrict the ability to assess interactions. This issue was formally addressed by the use of random forest regression using the R package ranger [56] with variable importance being formally assessed via the R package vip (variable importance plot) [57]. The most predictive covariates from this process were entered into the regression modelling equations. The tables from this analysis are presented in the Results section.

Panel and Geospatial Analysis

Panel analysis was conducted using R package plm [58] across both space and time simultaneously using the ‘twoways’ effect. The spatial weights matrix was calculated using the edge and corner ‘queen’ relationships using R package spdep (spatial dependency) [59]. Geospatial modelling was conducted using the spatial panel random effects maximum likelihood (spremml) function from the package spml which allows detailed modelling and correction of model error structures [60, 61]. Such models may produce four model coefficients of interest which are useful in determining the most appropriate error structure for the model. These coefficients are phi, the random error effect; psi,

the serial correlation effect; rho, the spatial coefficient, and theta, the spatial autocorrelation coefficient. In each case, the most appropriate error structure was chosen for each spatial model generally taking care to preserve the model error specification across related models. The appropriate error structure was determined by the backward methods from the full general model to the most specific model, as has been described [62]. Both panel and geospatial models were temporally lagged as indicated by 1–2 years.

Causal Inference

The formal tools of causal inference were used in this analysis. Inverse probability weighting (ipw) is the technique of choice to convert a purely observational study into a pseudo-randomized study from which it is appropriate to make causal inferences [63]. All multivariable panel models presented herein were inverse probability weighted. ipw was performed using the R package ipw. Similarly, E-values (expected values) quantify the correlation required for some hypothetical unmeasured confounder covariate with both the exposure of concern and the outcome of interest in order to explain away some apparently causal relationship [64–66]. It therefore provides a quantitative measure of the robustness of the model to extraneous covariates which have not been accounted for within the measured parameters. E-values have a confidence interval associated with them and the 95% lower bound of this confidence interval is reported herein. E-value estimates >1.25 are said to indicate causality [67] with E-values >9 being described as high [68]. E-values were calculated from the R package E-value [69]. Both ipw and E-values are foundational and pivotal techniques used in formal causal inferential methods in order to allow causal relationships to be assessed from real-world observational studies.

Data Availability

Raw datasets, including 3800 lines of computation code in R, have been made freely available through the Mendeley data repository at the following URLs: 10.17632/tysn37t426.1 and 10.17632/nm3tgcvvzd.1. This study was not pre-registered in the Open Science Framework.

Ethics

Ethical approval for this study was provided by the Human Research Ethics Committee of the University of Western Australia number RA/4/20/4724 on 24 September 2021.

Results

Supplementary Table ST1 provides an overview of study data. As shown, total CAR data were derived from 14 nations for 24 cardiovascular anomalies for the years 2010–2019. The total CAR includes stillborn and early termination of pregnancy for anomaly rates in addition to babies born normally alive and is a critical metric required to properly assess trends in CARs. The total sample size of the whole Eurocat database for these nations was 77 410 rates. Drug and cannabis use and exposure rates are also shown in this table including various compound metrics. Median household income is also shown.

Daily cannabis use data across the various jurisdictions of Europe were largely incomplete as indicated in Supplementary Table ST2 where only 59 raw data points are shown. These data were completed by linear interpolation, as shown in

Supplementary Table ST3, so that 129 points were finally available for analysis.

Figures 1–3 show the rates of the various CAs against the use of the different substances. Eight CAs are shown in each figure which has been split into three parts to accommodate all 24 CAs. From these figures, it is apparent that tobacco exposure is for the most part negatively related to CAR. Regression line slopes for alcohol are mostly flat or negative but generally weak. Regression line slopes for amphetamine are mostly flat or somewhat positive. The lines of best fit for cocaine are generally positive, and some, such as CHD, double outlet right ventricle and mitral valve anomalies, are quite strongly so. The cannabis exposure metric chosen in this graph is daily cannabis use interpolated. For most anomalies, the regression line is flat or weakly positive. However, for some anomalies such as CHD, double outlet right ventricle and mitral valve anomalies, the regression line indicates strong and robust obviously positive associations.

Figures 4–6 chart the bivariate relationships of the different cannabis metrics with the spectrum of CARs. Some of the steepest positively sloped lines are for atrioventricular septal defect (AVSD), severe CHD, double outlet right ventricle, pulmonary valve atresia, transposition of the great vessels and hypoplasia of the right heart which are all seen as a function of cannabis resin THC concentration.

Figure 7 shows a graphical map of the CHD rate across Europe during this decade. Many European nations are darkly shaded, indicating relatively high rates of CHD. Figure 8 depicts the rates of severe CHD which appears to have a more varied pattern. Figures 9–12 illustrate the rates for ASD, VSD, PDA and Ebstein's anomaly, respectively.

Patterns of daily cannabis use are illustrated in Fig. 13 which indicates increases in Spain, Netherlands, Belgium, France and Norway, reductions in Poland and little change in Bulgaria.

Figure 14 is a bivariate colorplane plot showing the bivariate relationship between CHD and the compound cannabis metric last month cannabis use $\times$ resin THC concentration $\times$ daily use interpolated. The areas covered by Spain and France are seen to obviously turn from tan and brown in 2010 to purple and crimson in 2019, indicating that they have moved up into the high cannabis metric—high CHD zone of the colorplane (shown in the key at the right hand side of the graph).

A similar change occurs across France and Spain for severe CHD as indicated in Fig. 15.

For the relationship between cannabis herb and CHD, the map is noted to have turned increasingly purple with time as nations more into the higher zone on both covariates (Fig. 16). Similar comments apply to the relationship between severe CHD and cannabis herb THC concentration, as shown in Fig. 17.

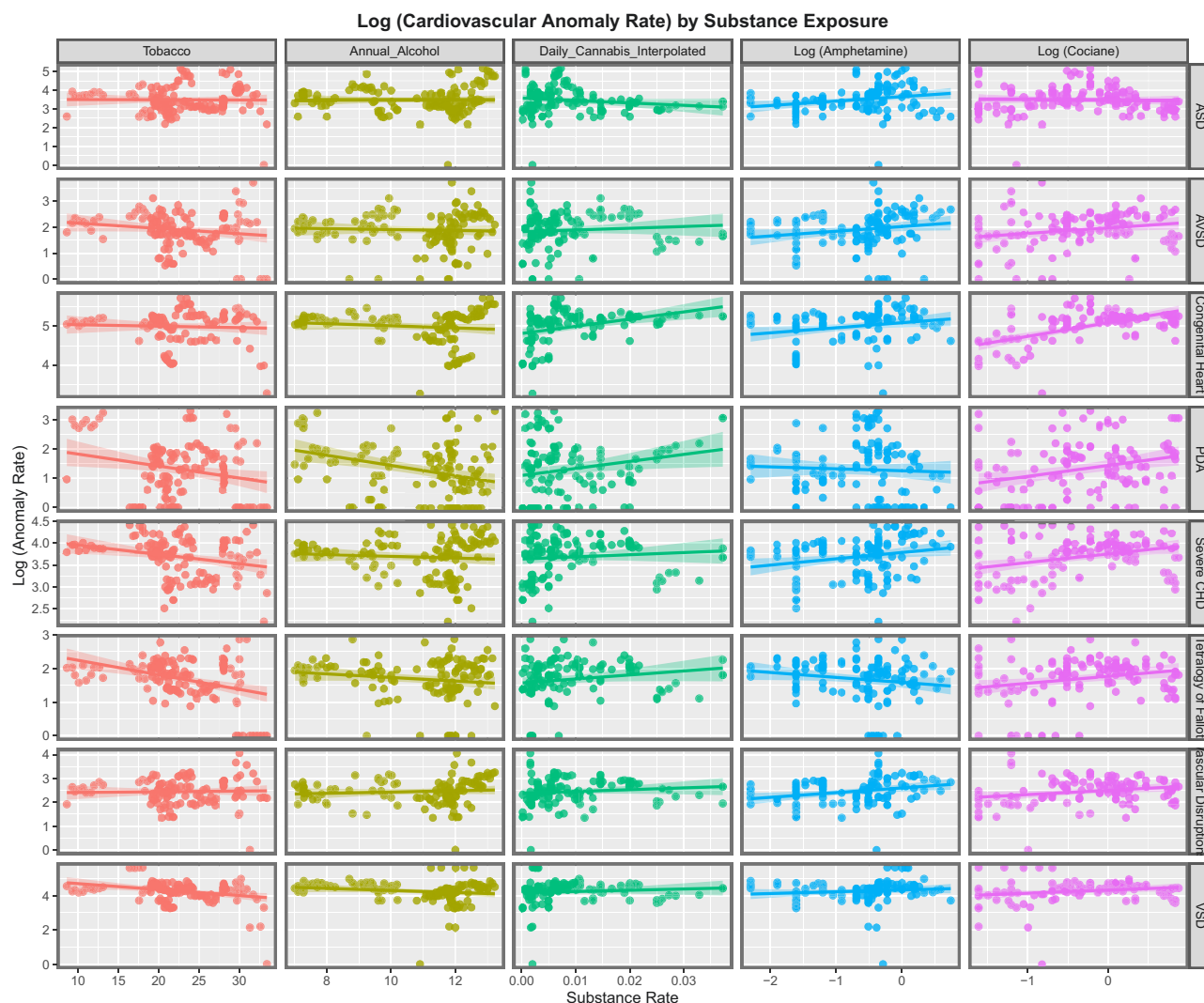


Figure 1: Panelled scatterplot of log (rates of selected CCAs) against rates of substance exposure—1

Figure 18 shows the bivariate relationship between severe CHD and cannabis resin THC concentration. Here, the map is noted to turn pink and purple across most countries across the decade.

Figure 19 shows the relationship between AVSD and cannabis resin THC concentration. The area for France changes shades of purple across the period. The areas covered by Germany and Norway appear to change in their blue-purple hues across this period.

When the relationship between transposition of the great vessels and cannabis resin THC concentration is considered, the map is also noted to have become more purple generally (Fig. 20).

Based on recent findings reported in major epidemiological reviews [22], it is possible to categorize European nations into increasing and high daily use and low or decreasing daily use groups. A panelled series of these defects across the decade are shown in Fig. 21. For most anomalies, there is a significant overlap between the areas covered by both sets of nations. However, for some anomalies, such as CHD, double outlet right ventricle, hypoplastic left heart syndrome, mitral valve anomalies and tricuspid valve stenosis or atresia, the rate in the nations with increasing daily use is higher than those which do not have

this feature. Mixed-effects regression with anomaly as the random effect confirms that the time: daily use rate interaction is significantly higher in the countries with increasing cannabis use (β -Est. = 0.267, t = 2.756, P = 0.059; model AIC = 5317.51, Log-Lik. = -2652.75).

The slopes of 275 of these regression lines for each anomaly and each substance are provided in Supplementary Table ST4 using a purrr-broom simultaneous multigroup analytical workflow. From this list, the 69 models with positive and significant regression coefficients were selected out and are shown in Table 1. The table is ordered in descending order of minimum E-values (mEV). It is of interest therefore that the first 30 terms in this table all relate to cannabis exposure metrics. Of the 69 terms, 15 relate to cocaine, 5 to amphetamines, 1 to alcohol and 48 (69.6%) to various cannabis metrics. It is noted that the E-value estimates descend from 1.35×10^{19} , and the mEVs decline from 4.78×10^{10} .

Table 1 lists both P-values and E-values. By analogy with the genomic and epigenomic literature, it is therefore possible to present these data for graphical consideration as a 'volcano plot' which plots the negative logarithm of the P-value against the fold change in the anomaly rate quantified by the E-value. Figure 22

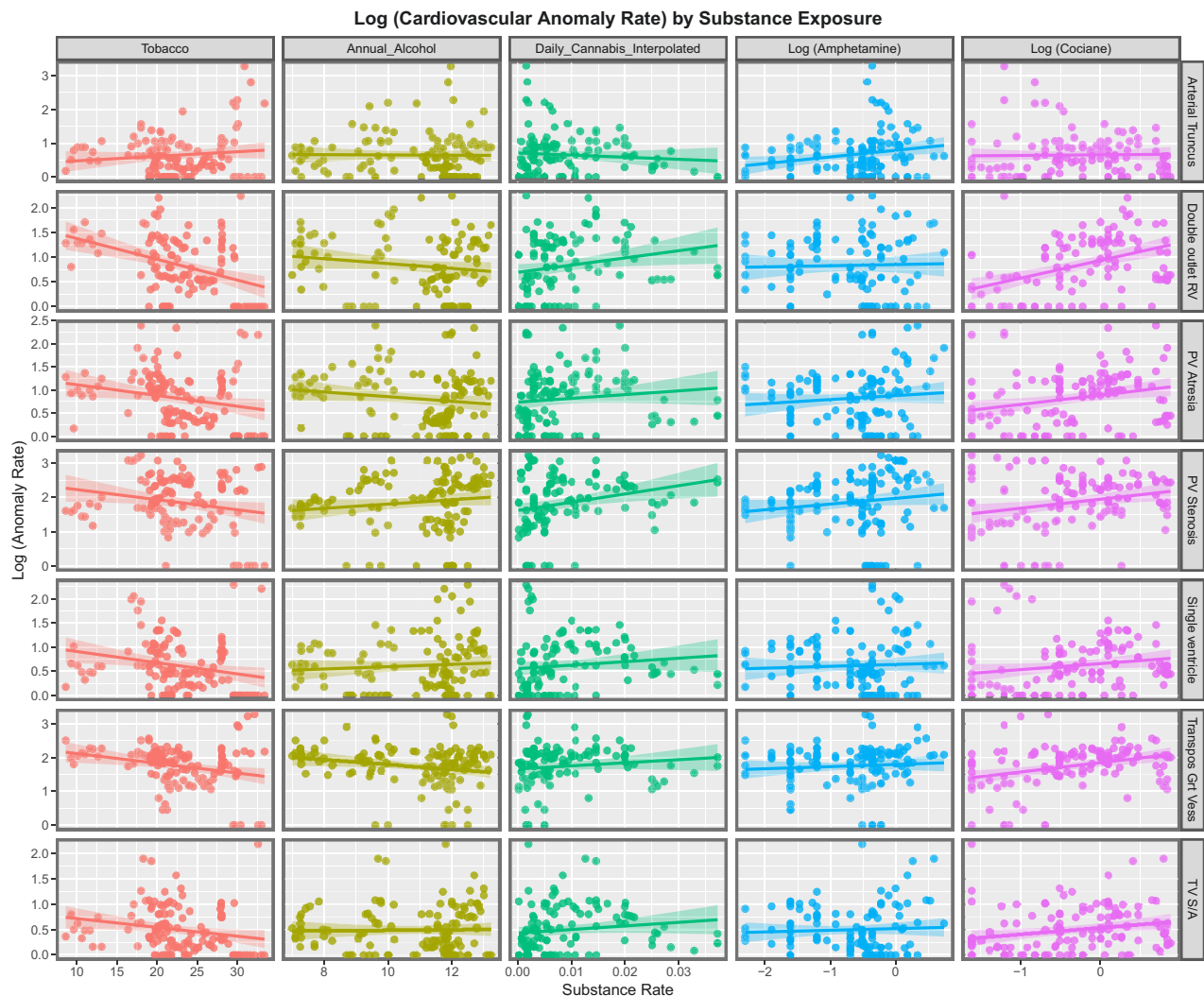


Figure 2: Panelled scatterplot of log (rates of selected CCAs) against rates of substance exposure—2

presents such a plot for the E-value estimate itself, and Fig. 23 presents a similar plot for the mEV. In these figures, strong signals are indicated for CHD and mitral valve anomalies and many other CAs as indicated.

Given these impressive results at bivariate analysis, it is of interest to investigate how all of these variables compare in multivariable regression techniques. Given that there are so many primary and compound cannabis metrics, it is not entirely clear which covariates are most suitable to use, given that the regression equations to be employed have a very finite number of degrees of freedom.

The issue of covariate selection was addressed formally using random Forrest regression in the ranger package in tandem with the variable importance package vip to create tables of relative variable importance. These tables are presented as Supplementary Tables S5–S16 for the 12 CAs in which we were most interested.

As the data are well suited to panel regression, this format was chosen to perform multiple regression analyses on these data. All panel regression models were inverse probability weighted which is an important step that transfers the analysis from merely an observational study into a pseudo-randomized analytical and interpretive context.

Supplementary Table S17 shows the result of panel regression of the CHD dataset against the group of covariates indicated in the table. Additive, interactive and models that lagged temporally to 1 and 2 years are presented. In each case, several terms including cannabis have positive regression coefficients and are highly statistically significant.

This same pattern of results is continued across all of the selected CAs, namely severe CHD, ASD, VSD, AVSDs, patient ductus arteriosus, tetralogy of Fallot, vascular disruption, double outlet right ventricle, transposition of the great arteries, hypoplastic right heart syndrome and mitral valve anomalies, as shown in Supplementary Tables S18–S28. In all cases, all multivariable panel models are inverse probability weighted to allow causal relationships to be formally assessed.

Having made the important above observations, the next issue was whether these relationships would persist when formal space-time modelling was undertaken in a fashion which allows random effects, serial correlation, spatial correlation and spatial autocorrelation in the error structure to be formally considered. Geospatial links were derived, edited and finalized, as indicated in Supplementary Fig. S1, and these formed the basis of the sparse spatial weights matrix which was then employed in the R package spml to conduct formal spatiotemporal regression.

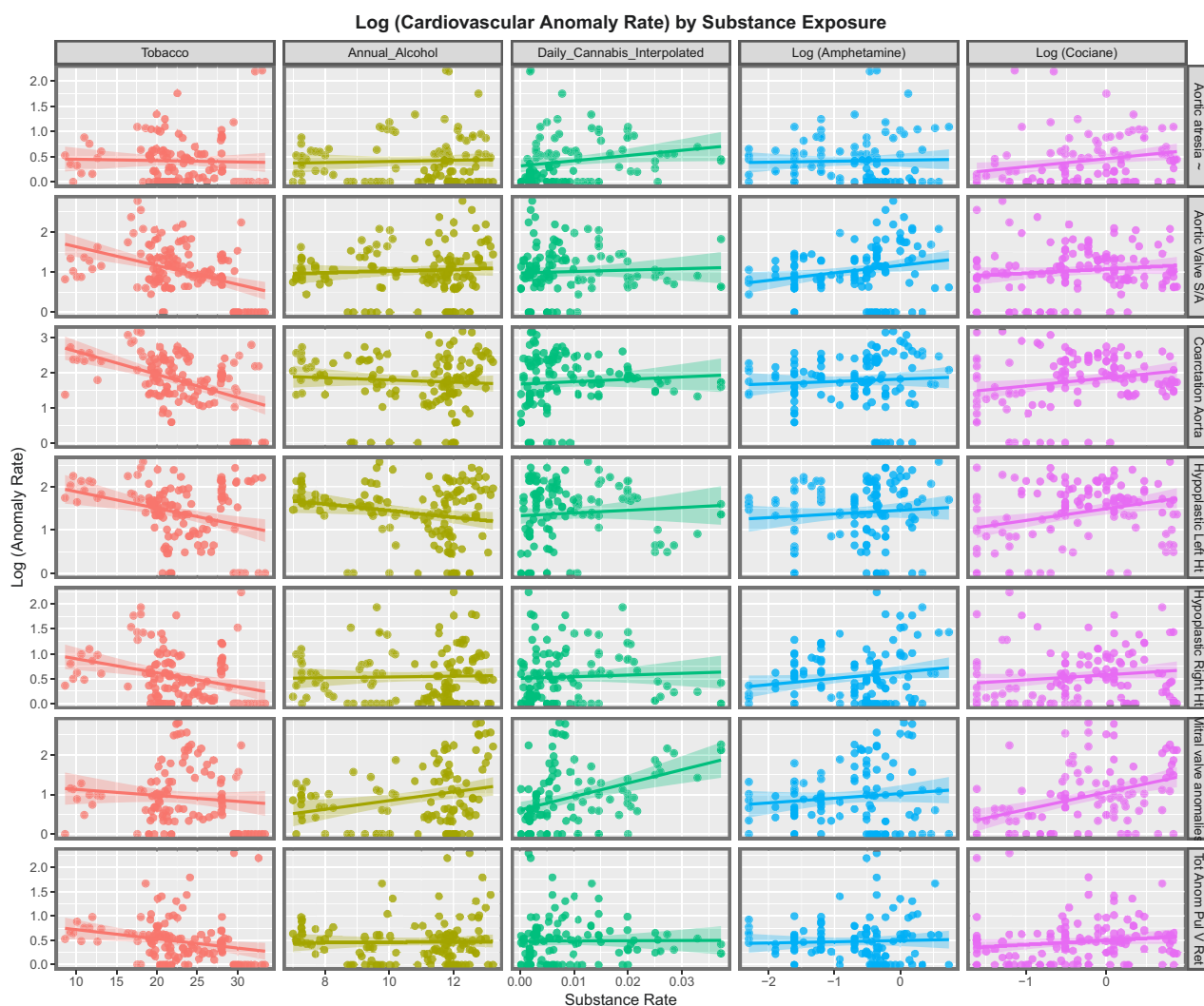


Figure 3: Panelled scatterplot of log (rates of selected CCAs) against rates of substance exposure—3

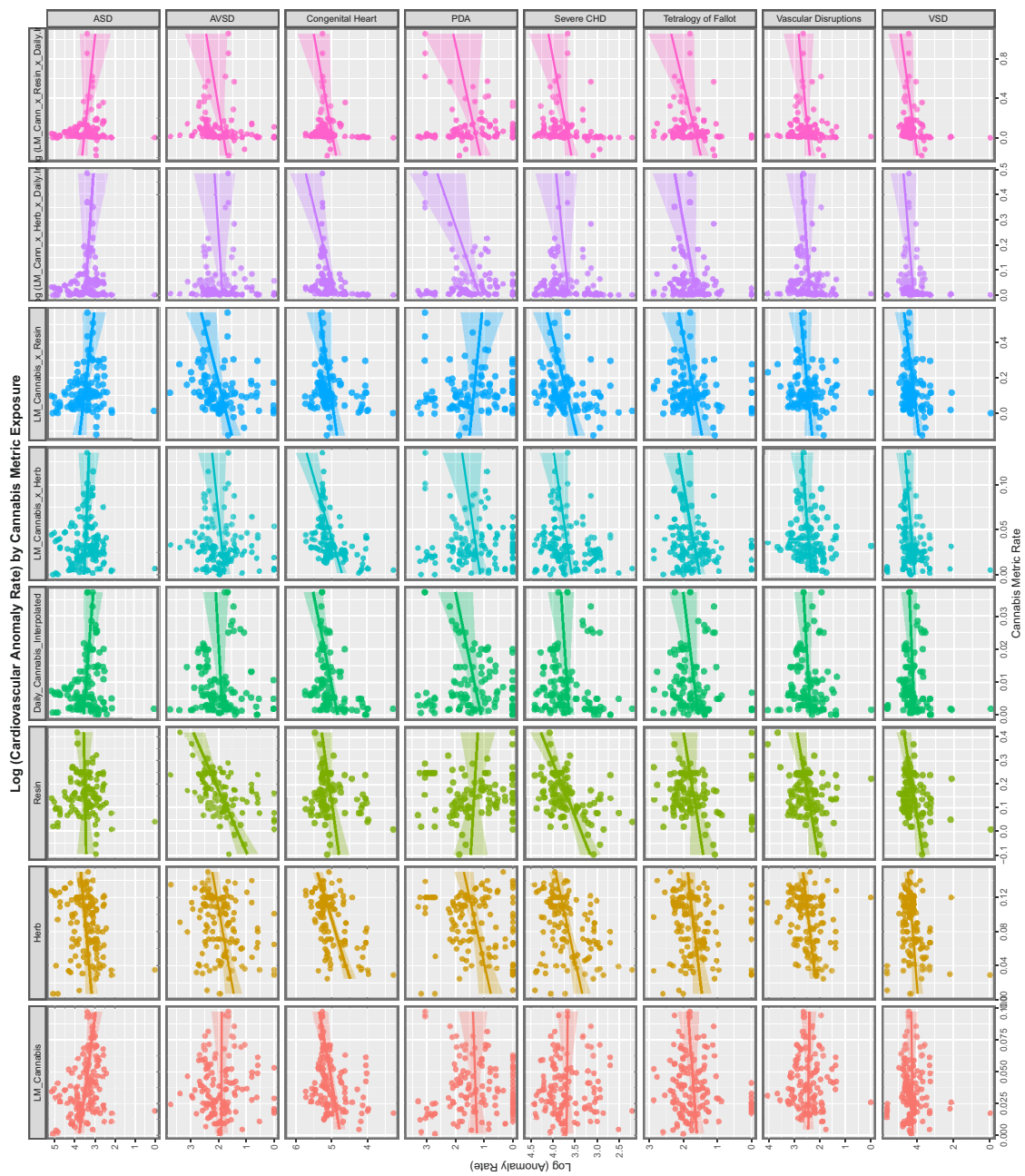


Figure 4: Panelled scatterplot of log (rates of selected CCAs) against rates of cannabis metric exposure—1

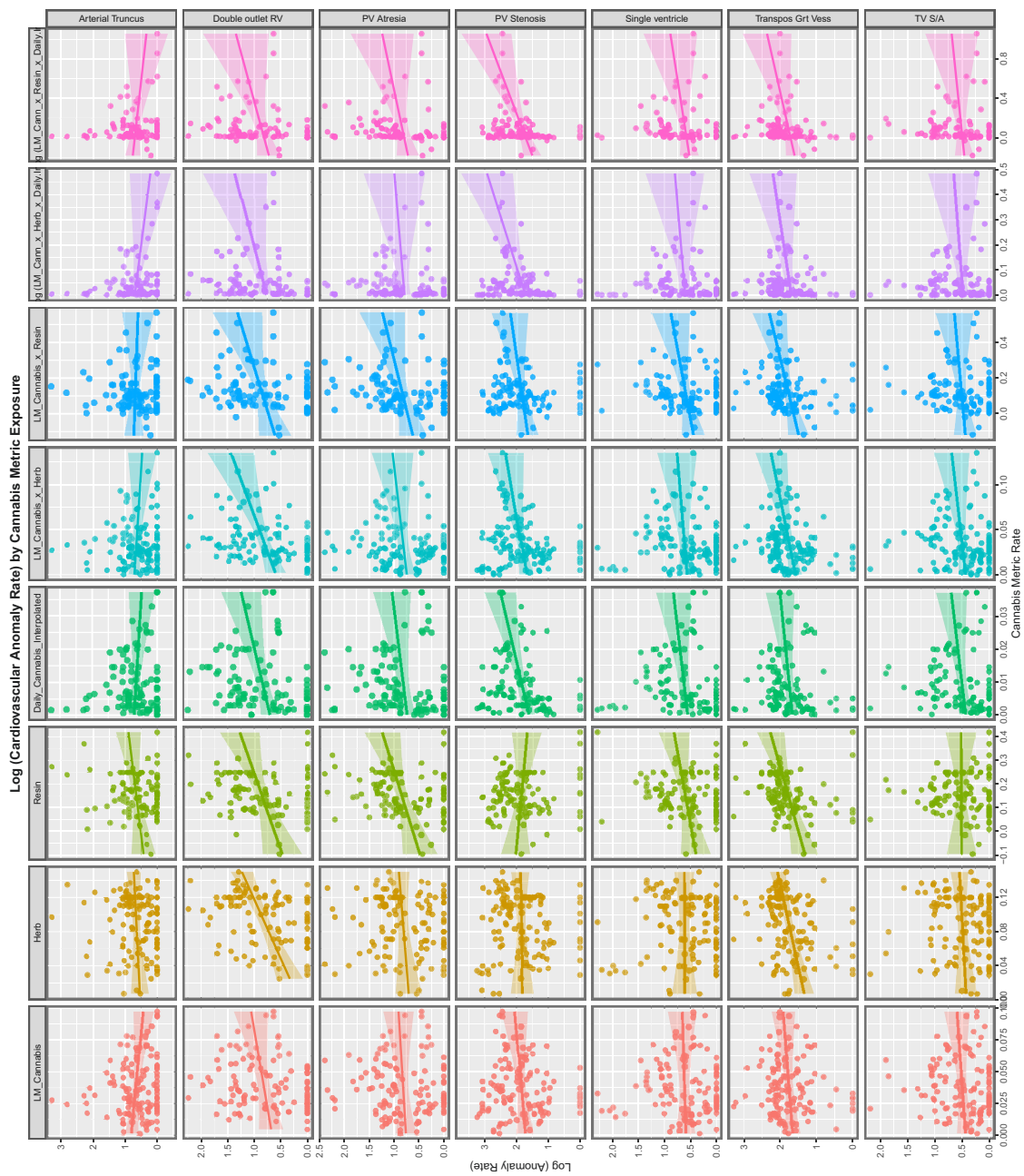


Figure 5: Panelled scatterplot of log (rates of selected CCAs) against rates of cannabis metric exposure—2

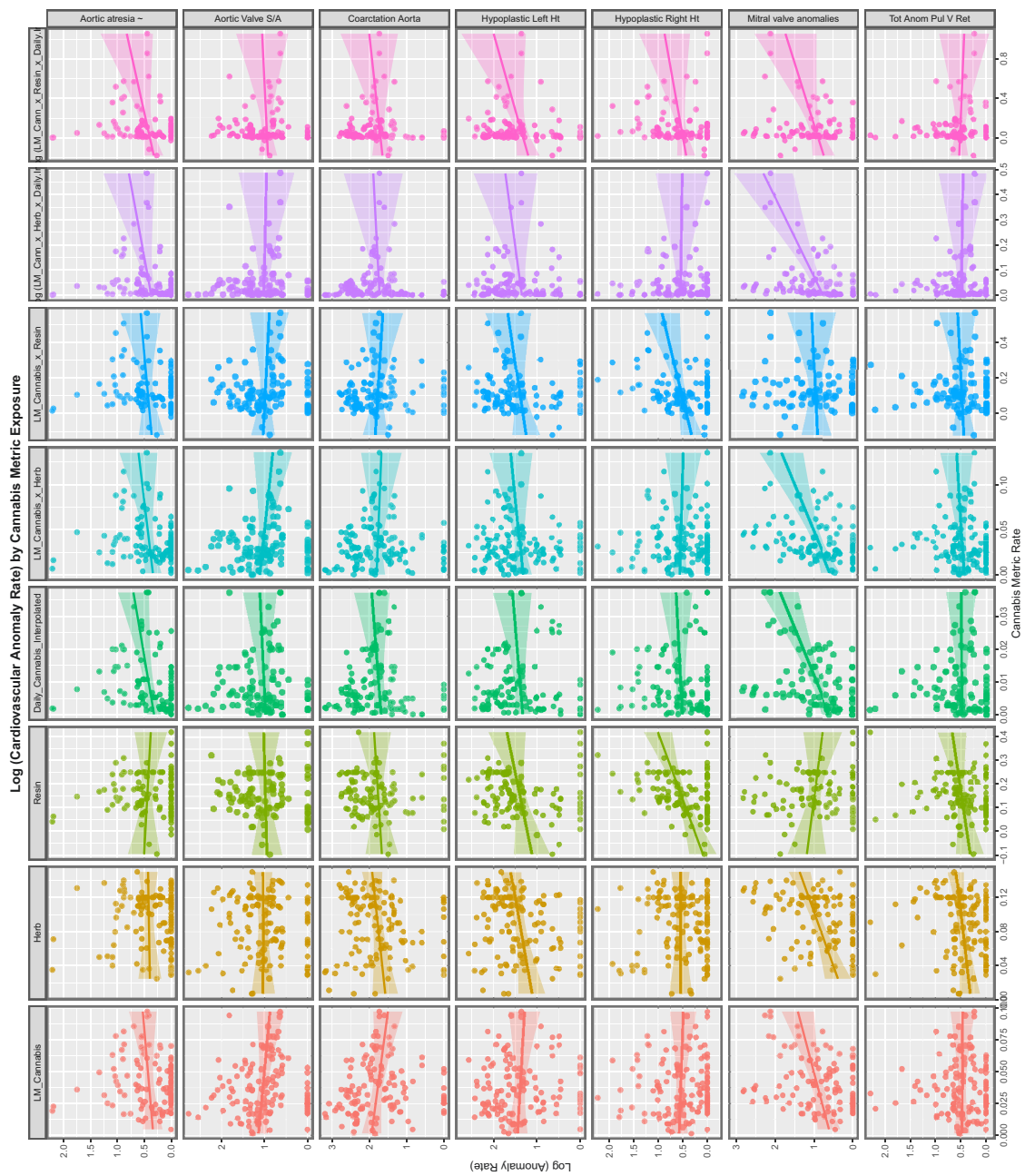


Figure 6: Panelled scatterplot of log (rates of selected CCAs) against rates of cannabis metric exposure—3

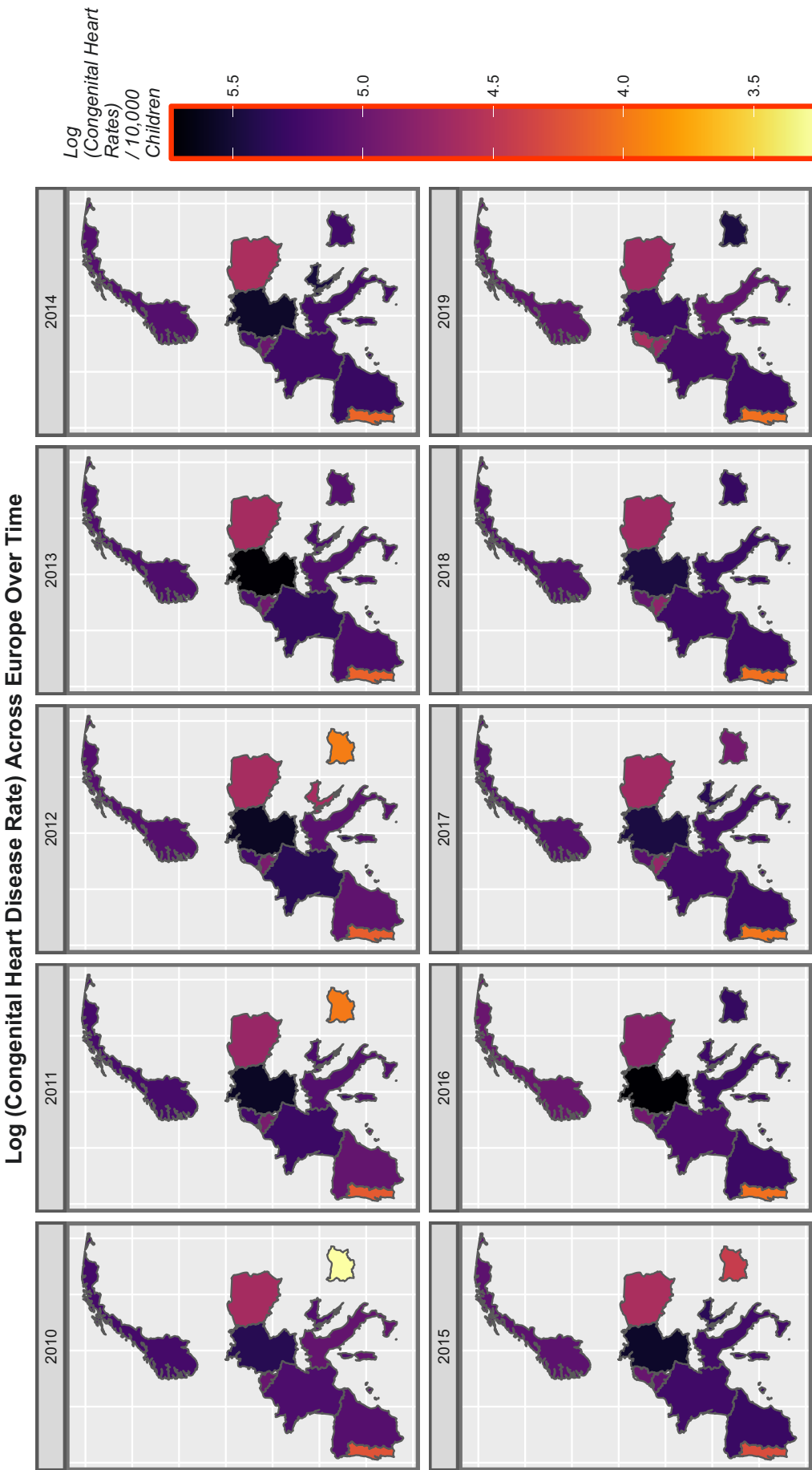


Figure 7: Sequential map-graphs of log (rates of CHD) across selected European countries over time, 2010–2019

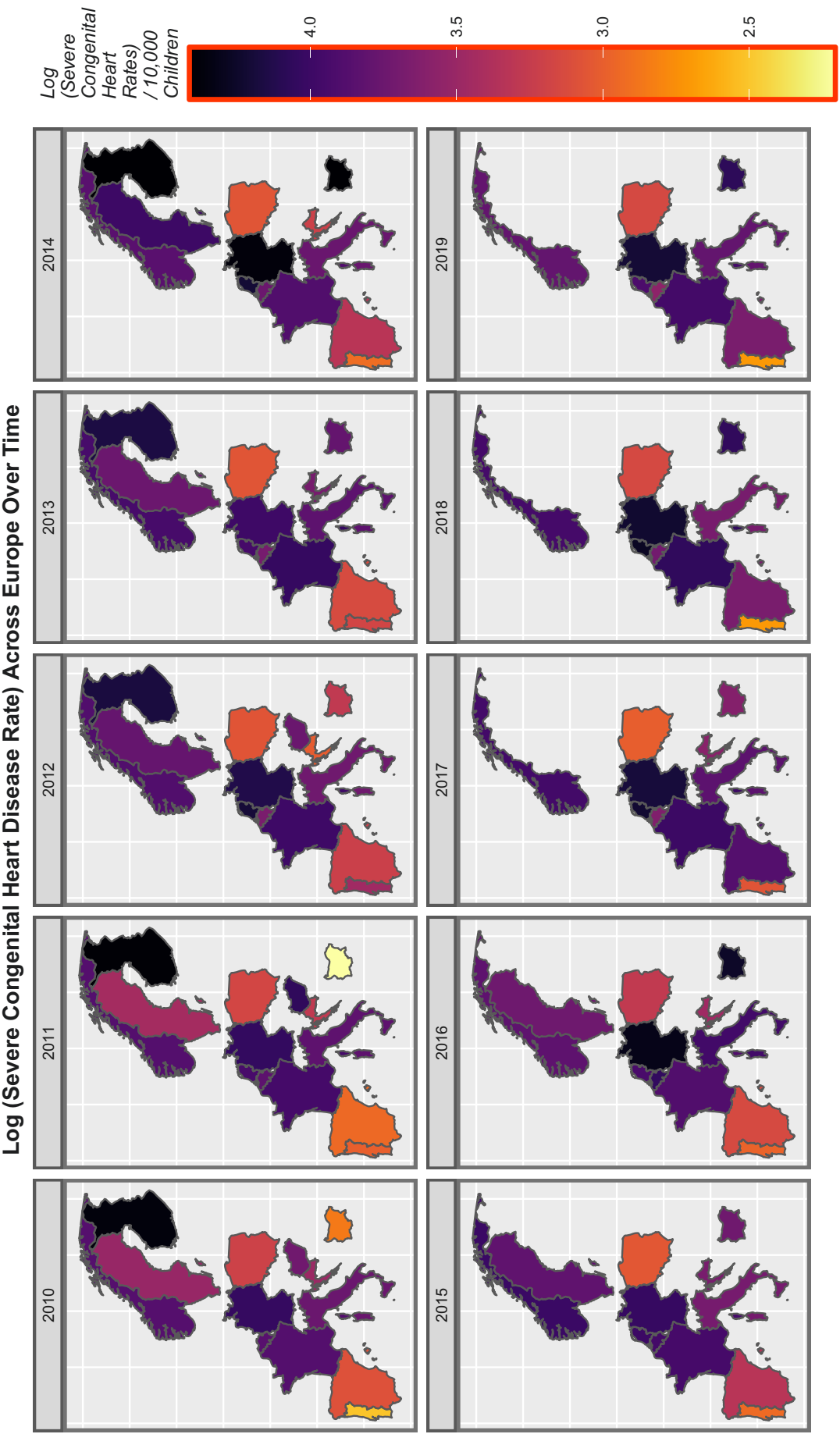


Figure 8: Sequential map-graphs of log (rates of severe CHD) across selected European countries over time, 2010–2019

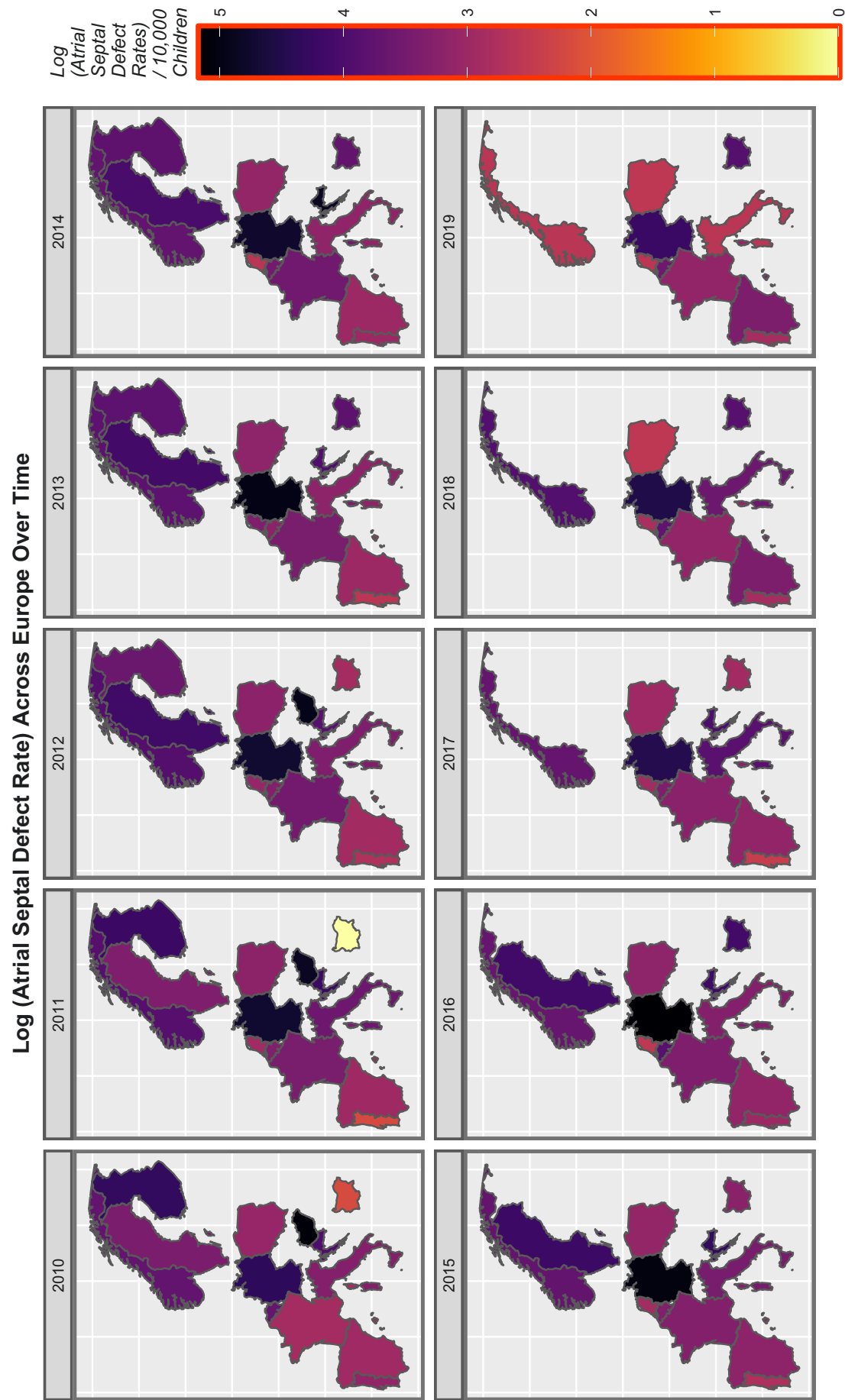


Figure 9: Sequential map-graphs of log (rates of ASD) across selected European countries over time, 2010–2019

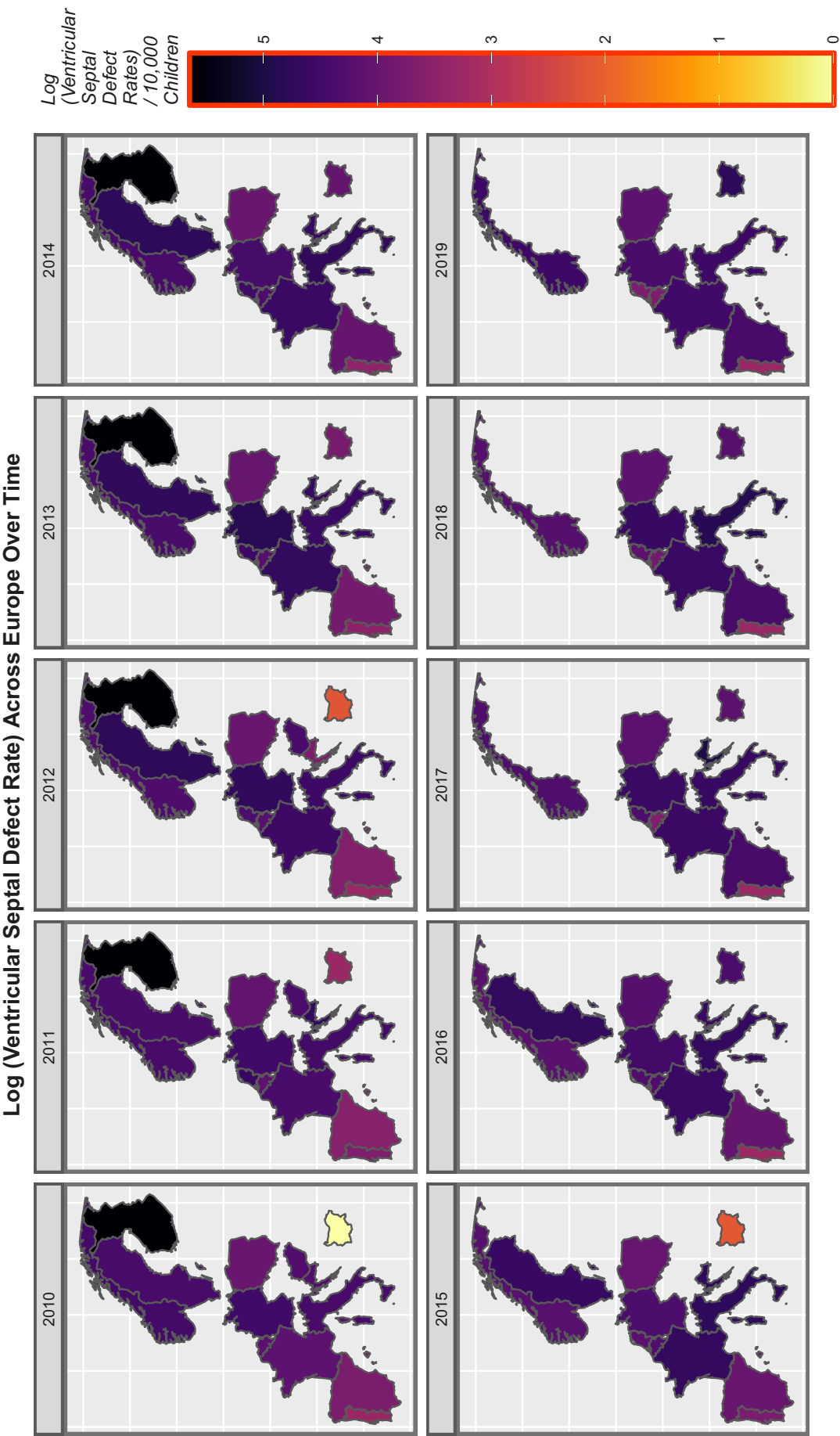


Figure 10: Sequential map-graphs of log (rates of VSD) across selected European countries over time, 2010–2019

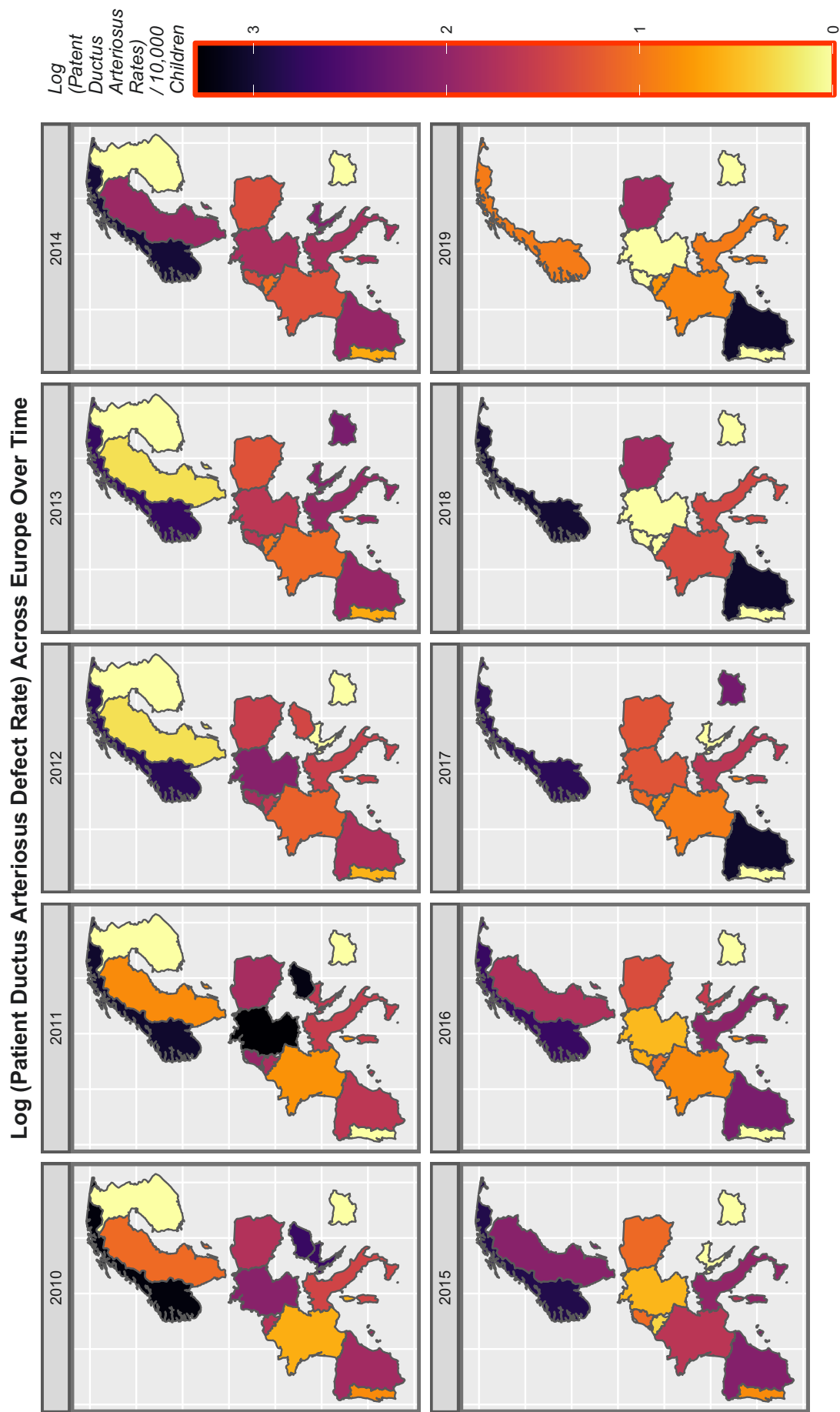


Figure 11: Sequential map-graphs of log (rates of PDA) across selected European countries over time, 2010–2019

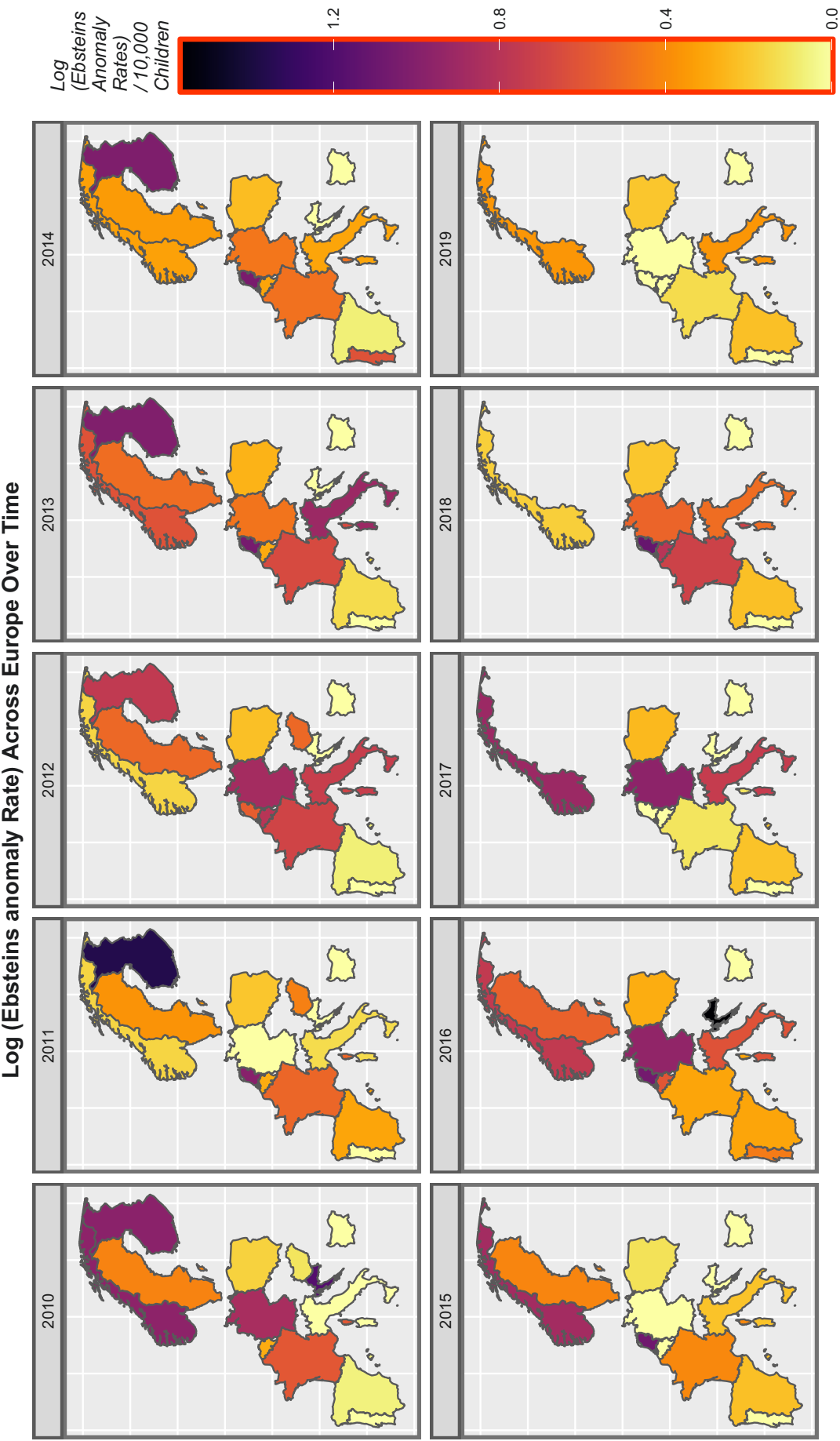


Figure 12: Sequential map-graphs of log (rates of Ebsteins anomaly) across selected European countries over time, 2010–2019

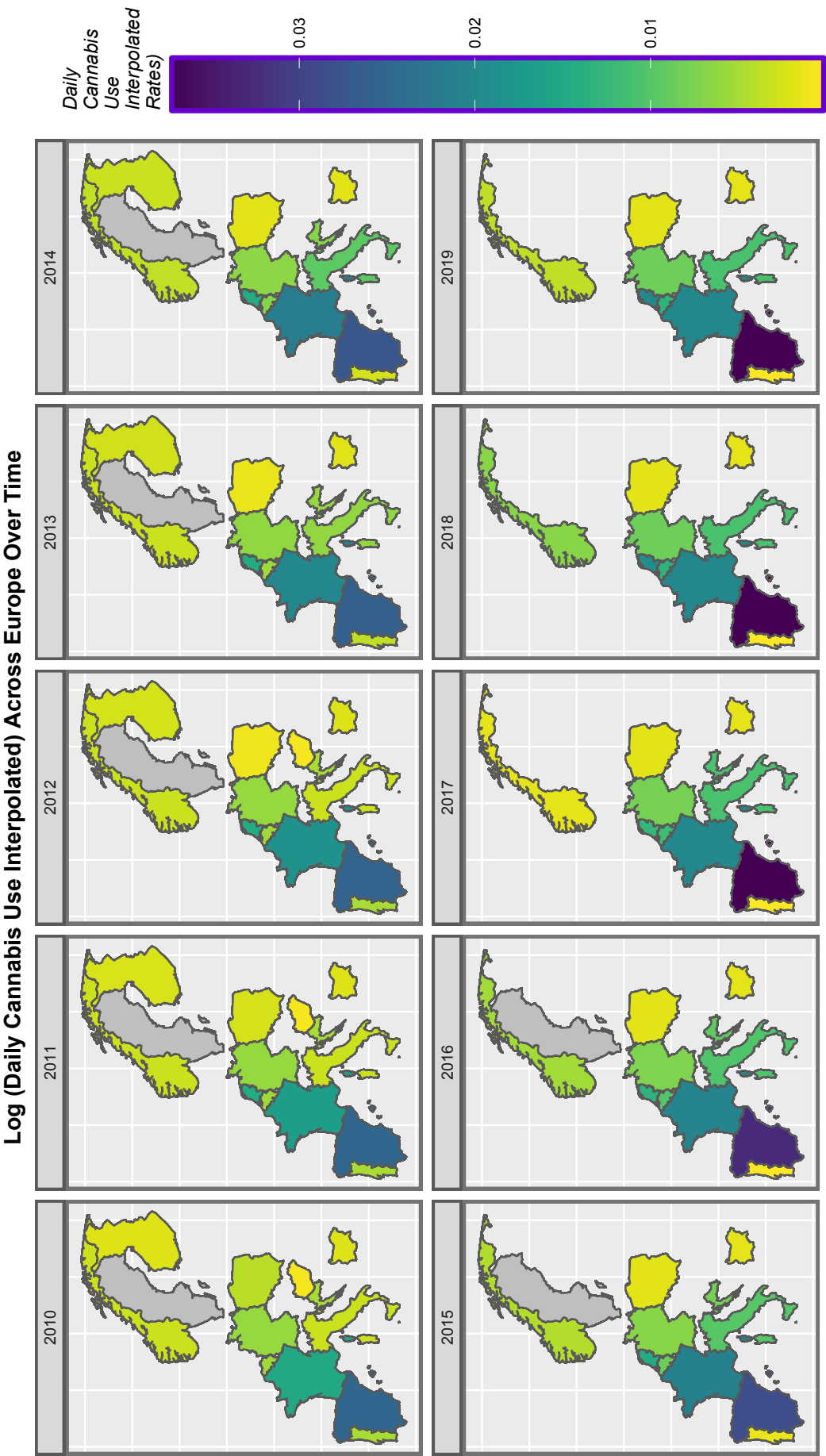


Figure 13: Sequential map-graphs of rates of daily cannabis use interpolated across selected European countries over time, 2010–2019

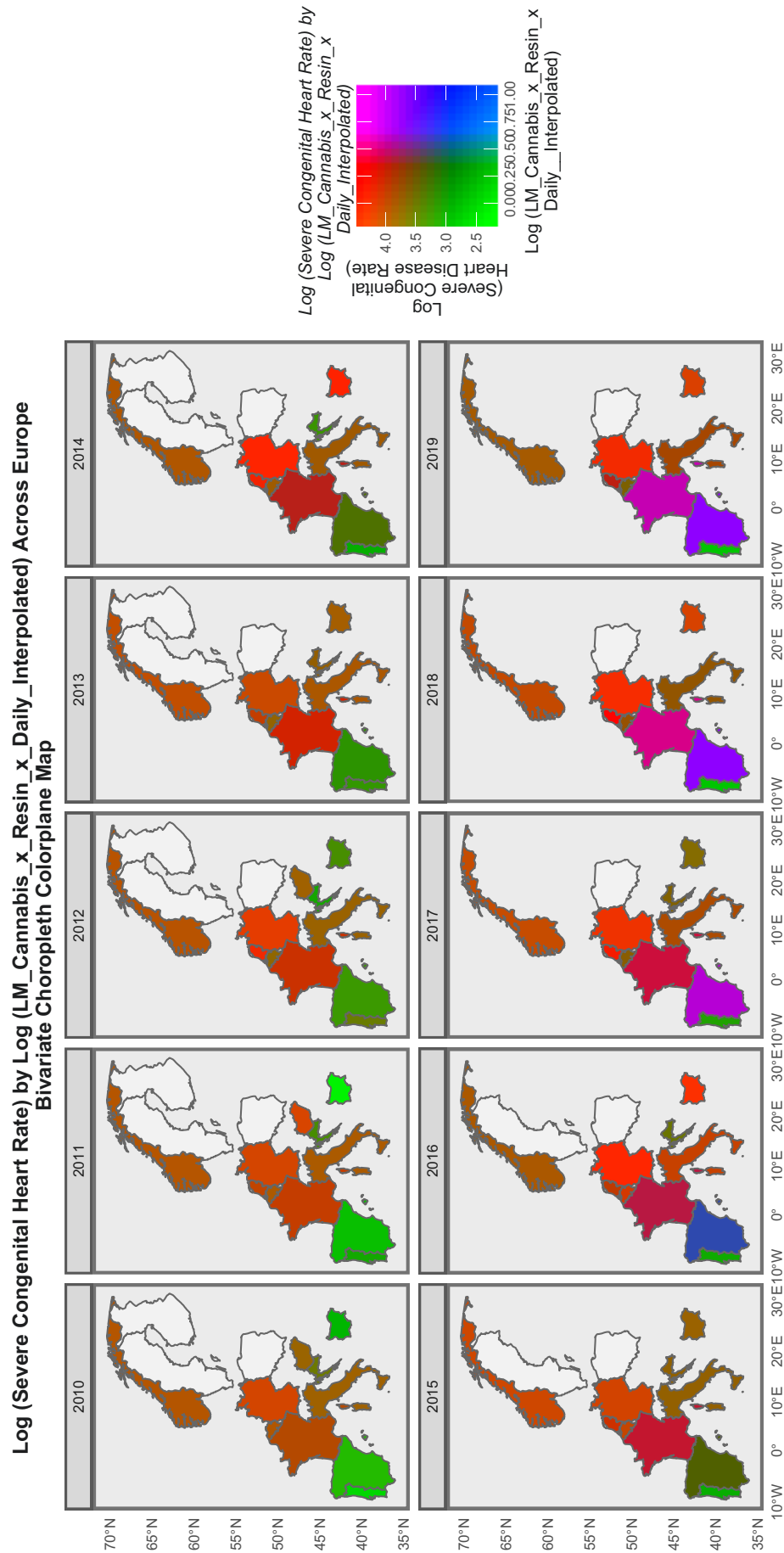


Figure 15: Bivariate colorplane sequential map-graphs of log (rates of severe CHD) by last month cannabis use: cannabis resin THC concentration: daily cannabis use interpolated across selected European countries over time, 2010–2019

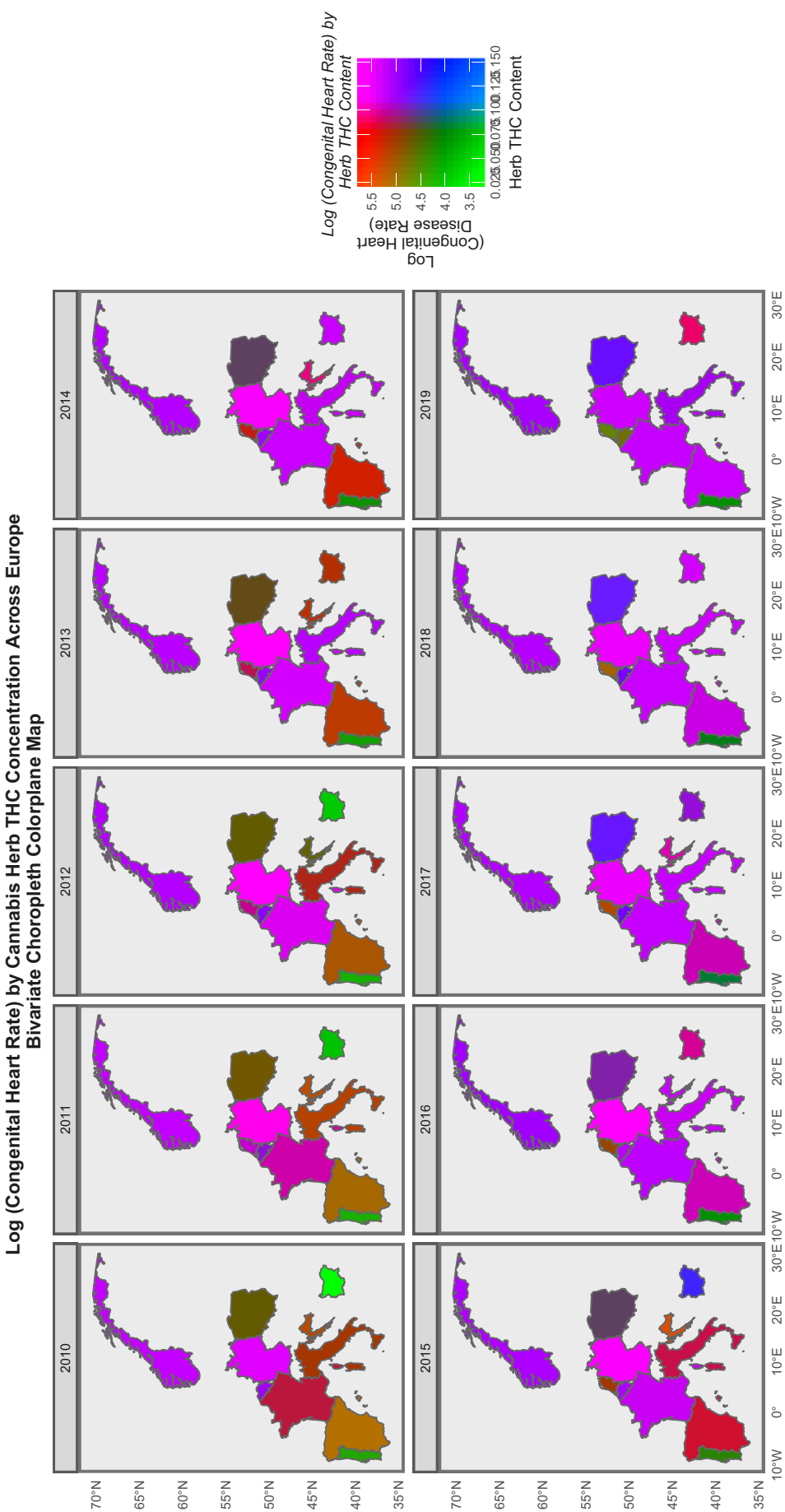


Figure 16: Bivariate colorplane sequential map-graphs of log (rates of CHD) by cannabis herb THC concentration across selected European countries over time, 2010–2019

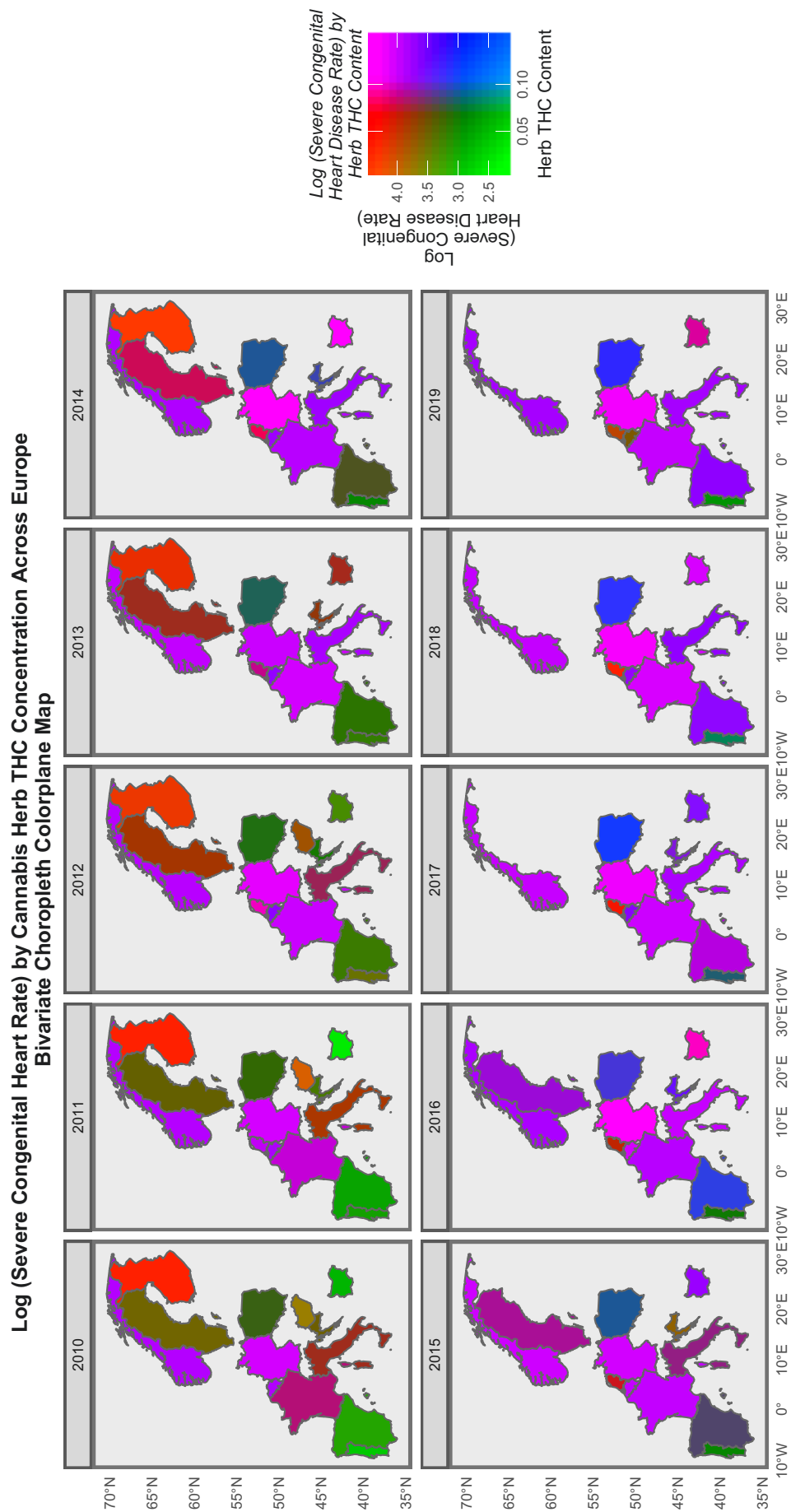


Figure 17: Bivariate colorplane sequential map-graphs of log (rates of severe CHD) by cannabis herb THC concentration across selected European countries over time, 2010–2019

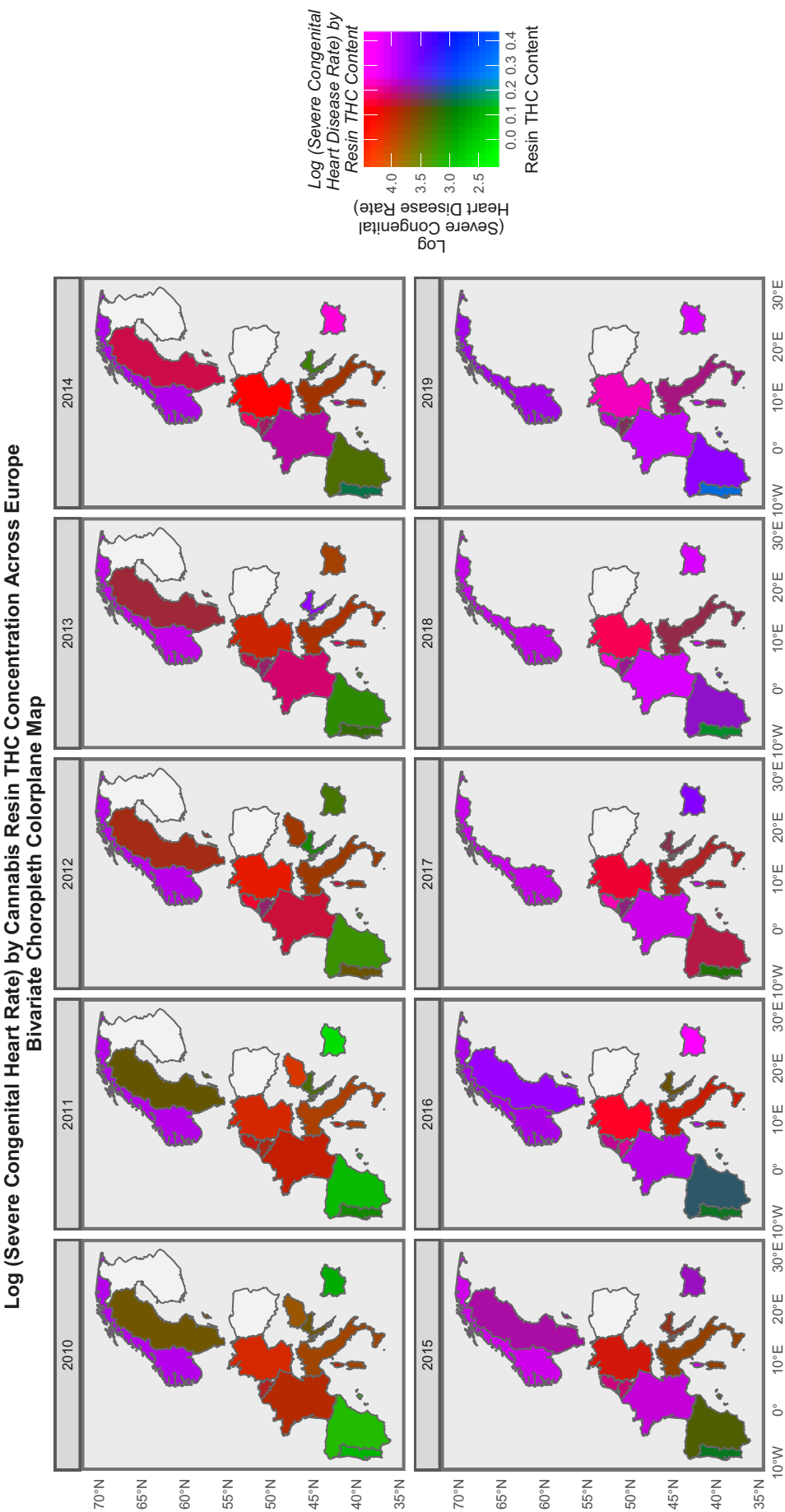


Figure 18: Bivariate colorplane sequential map-graphs of log (rates of severe CHD) by cannabis resin THC concentration across selected European countries over time, 2010–2019

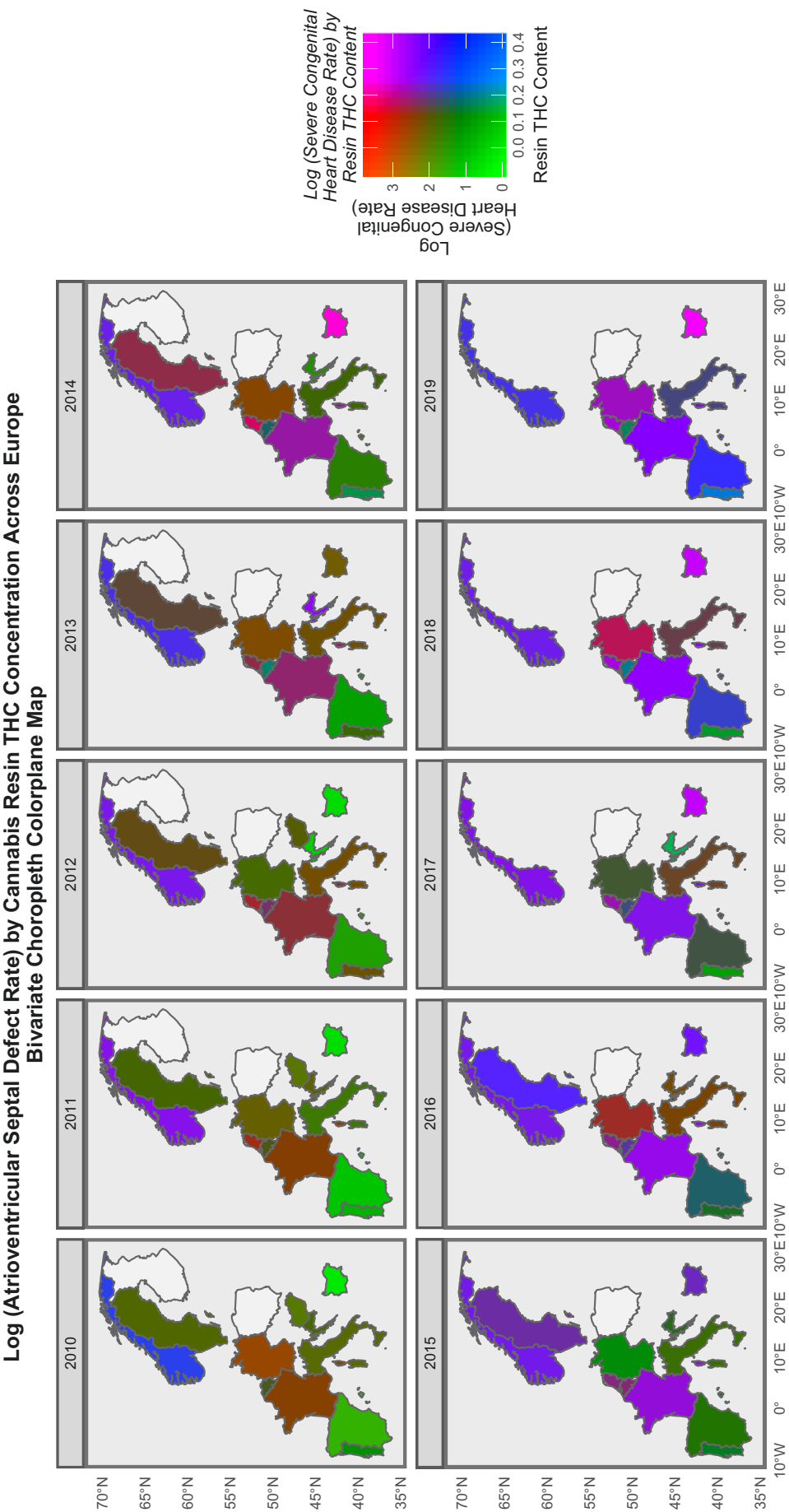


Figure 19: Bivariate colorplane sequential map-graphs of log (rates of AVSD) by cannabis resin THC concentration across selected European countries over time, 2010–2019

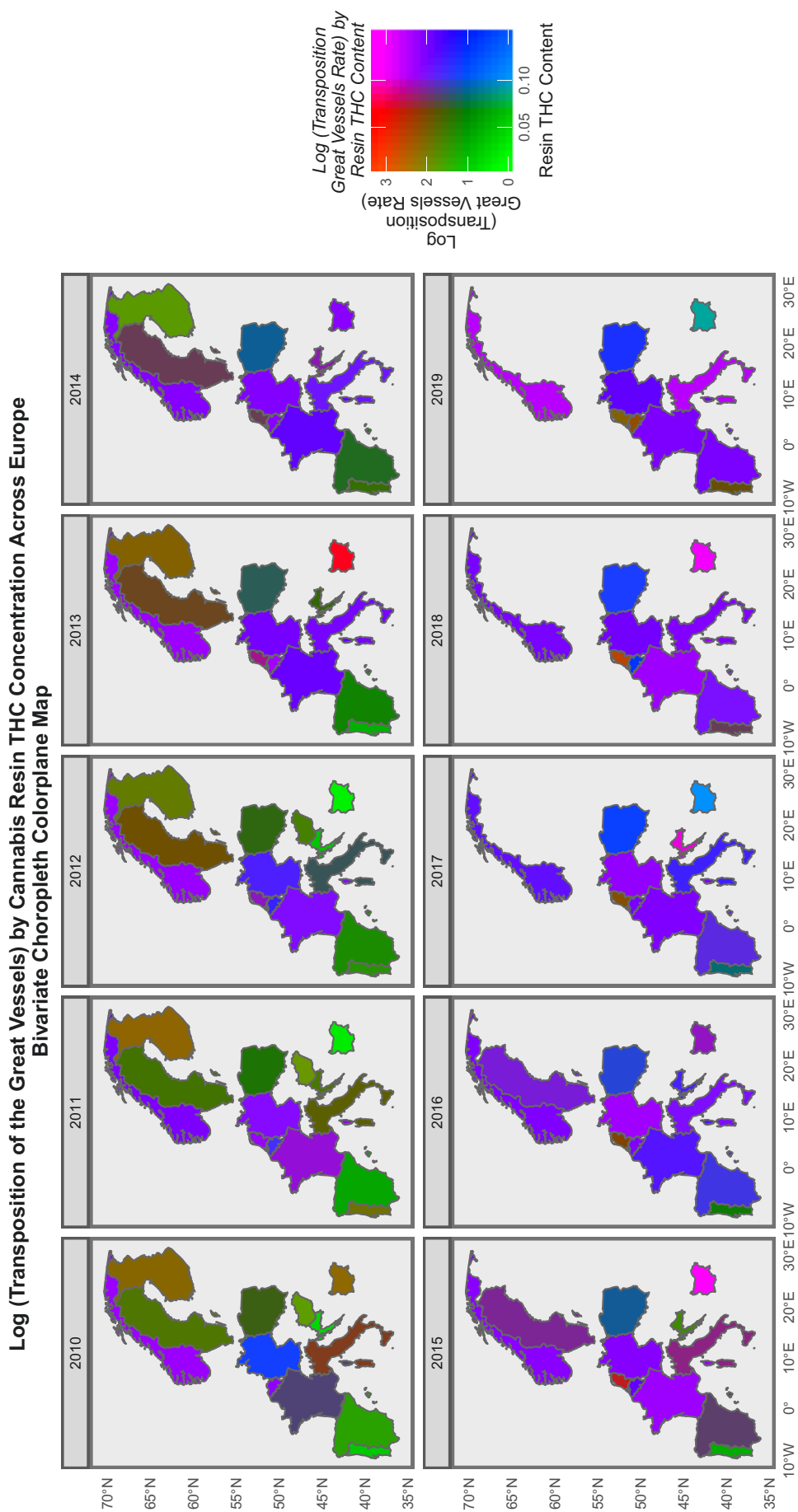


Figure 20: Bivariate colorplane sequential map-graphs of log (rates of transposition of the great vessels) by cannabis resin THC concentration across selected European countries over time, 2010–2019

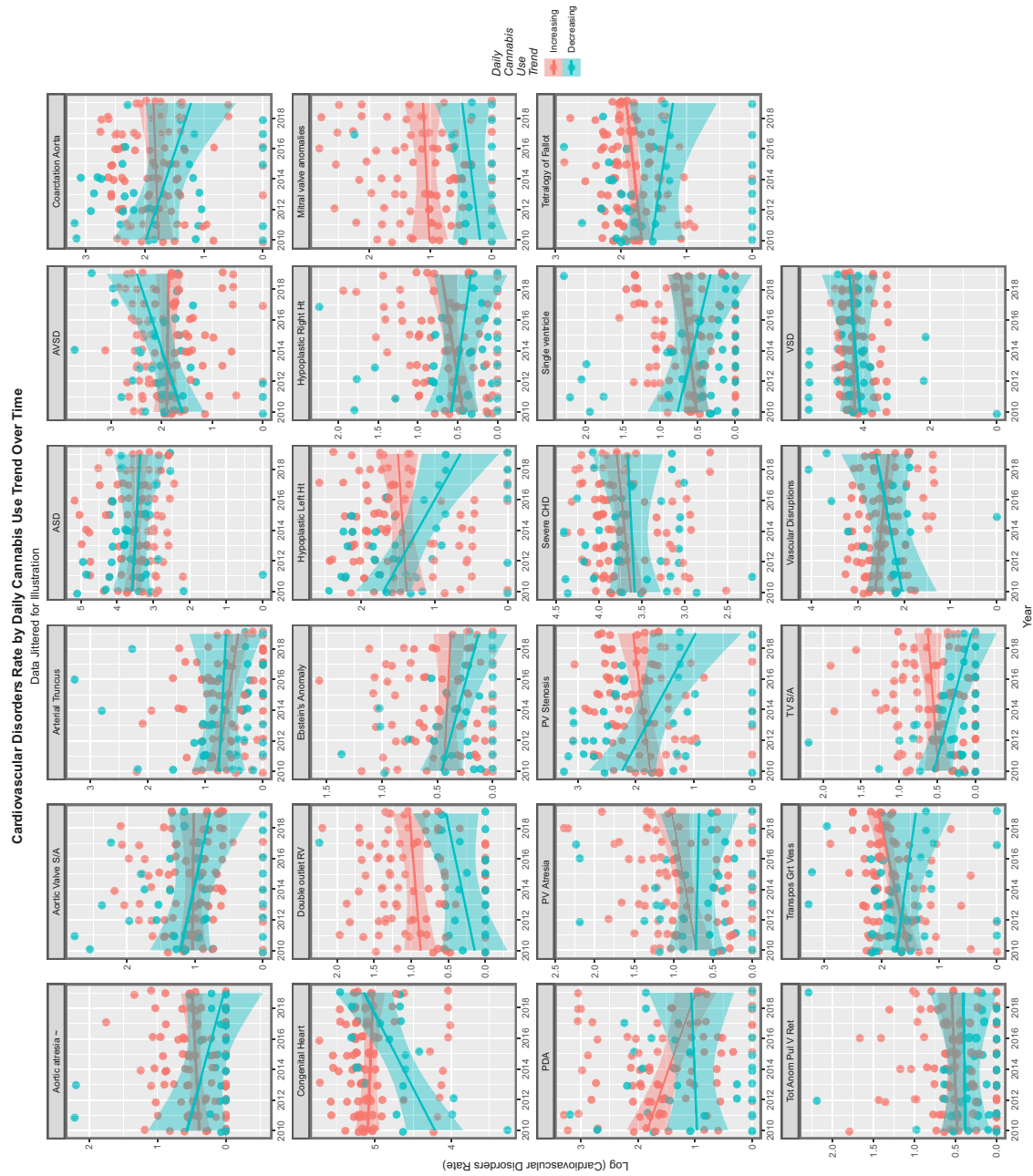


Figure 21: Log rates of CCAs by daily cannabis use status by CA. See Methods section for categorization of nations

Table 1: Significant positive slopes from bivariate regression

Anomaly	Substance	Mean Anomaly Rate	Estimate	Std. Error	Sigma	t-statistic	P-Value	E-Value Estimate	E-Value Lower Bound
Mitral valve anomalies	Daily.interpol.	1.5003	33.8128	7.7588	0.7097	4.3580	3.07E-05	1.35E+19	4.78E+10
Congenital heart	Daily.interpol.	79.9062	18.6127	4.5313	0.4145	4.1076	7.94E-05	1.1196E+18	3.96E+09
Congenital heart	Herb	79.9062	7.2519	1.1476	0.3801	6.3192	6.48E-09	6.95E+07	3.22E+05
Congenital heart	LMCannabis_Herb	79.9062	7.4271	1.5650	0.4052	4.7459	6.58E-06	3.51E+07	3.63E+04
PV stenosis	Daily.interpol.	4.0360	24.2371	8.3771	0.7863	2.8933	0.0046	3.0404E+12	1.77E+04
Double outlet RV	Herb	1.1079	7.1871	1.6528	0.5474	4.3485	3.18E-05	3.09E+05	1.43E+03
Mitral valve anomalies	LMCannabis_Herb	1.5003	9.3952	2.8340	0.7337	3.3151	0.0013	2.30E+05	236.98
Severe CHD	Herb	21.6609	4.2206	1.0939	0.4253	3.8582	1.85E-04	1.67E+04	171.06
Mitral valve anomalies	Herb	1.5003	7.8448	2.1992	0.7283	3.5671	5.45E-04	3.61E+04	166.84
Congenital heart	LM_Cannabis	79.9062	5.9088	1.9991	0.4290	2.9557	0.0039	5.55E+05	138.14
PDA	Daily.interpol.	2.6743	23.9286	10.1280	0.9506	2.3626	0.0199	17.732.087.319	102.52
Double outlet RV	Daily.interpol.	1.1079	14.5709	6.3435	0.5802	2.2970	0.0236	16.820.336.693	58.96
Double outlet RV	LMCannabis_Herb	1.1079	6.3564	2.2113	0.5725	2.8745	0.0049	4.88E+04	49.96
Transpos Grt Vess	Herb	3.2853	5.1077	1.5361	0.5973	3.3251	0.0012	4.79E+03	48.76
AVSD	Resin	4.0167	3.7361	0.7343	0.6601	5.0878	1.59E-06	344.49	47.12
Severe CHD	Resin	21.6609	2.1476	0.4264	0.3833	5.0361	1.98E-06	326.92	44.70
AVSD	Herb	4.0167	5.3712	1.7549	0.6824	3.0607	0.0027	2.58E+03	26.03
Mitral valve anomalies	LM_Cannabis	1.5003	8.6035	3.4940	0.7498	2.4624	0.0154	6.85E+04	16.60
Mitral valve anomalies	LM_Cannabis_x_Herb.THC_x_Daily.Inter-pol.	1.5003	3.1648	0.8621	0.7260	3.6710	3.82E-04	105.14	12.24
PDA	Herb	2.6743	6.5630	2.3969	0.9320	2.7382	0.0071	1.21E+03	11.95
Congenital heart	LM_Cannabis_x_Herb.THC_x_Daily.Inter-pol.	79.9062	1.7086	0.5033	0.4239	3.3947	9.71E-04	77.87	8.94
Hypoplastic right heart	Resin	0.6757	1.7823	0.5256	0.4725	3.3908	9.83E-04	61.40	8.01
Vascular disruptions	Herb	6.6675	4.0369	1.6751	0.5548	2.4100	0.0177	1.50E+03	6.42
Aortic atresia ~	Daily.interpol.	0.5067	10.3538	4.9896	0.4564	2.0751	0.0404	1.849078.395	5.99
Transpos Grt Vess	LMCannabis_Herb	3.2853	4.9262	2.1275	0.6107	2.3155	0.0223	3.08E+03	5.70
VSD	Resin	41.6464	2.0114	0.7053	0.6341	2.8517	0.0052	35.36	4.39
PDA	LM_Cannabis_x_Herb.THC_x_Daily.Inter-pol.	2.6743	3.0256	1.1046	0.9430	2.7390	0.0072	36.56	4.04
PV stenosis	LM_Cannabis_x_Herb.THC_x_Daily.Inter-pol.	4.0360	2.4987	0.9251	0.7898	2.7009	0.0080	35.08	3.85
Severe CHD	LMCannabis_Resin	21.6609	0.9713	0.3439	0.4118	2.8244	0.0057	16.59	3.28
Transpos Grt Vess	Resin	3.2853	1.8158	0.6963	0.6259	2.6077	0.0104	27.51	3.28
Congenital heart	Cocaine	79.9062	0.3536	0.0489	0.3649	7.2278	8.21E-11	4.26	3.21
AVSD	LMCannabis_Resin	4.0167	1.6005	0.5954	0.7129	2.6883	0.0084	14.91	2.88
Tetralogy of Fallot	LMCannabis_Herb	3.0532	4.5496	2.1449	0.6157	2.1211	0.0360	1.66E+03	2.76
Vascular disruptions	Resin	6.6675	1.5929	0.6530	0.5622	2.4393	0.0166	25.84	2.72
VSD	Herb	41.6464	3.7183	1.7168	0.6675	2.1658	0.0323	317.46	2.65
PV stenosis	LM_Cannabis_x_Resin.THC_x_Daily.Inter-pol.	4.0360	1.1697	0.4095	0.7664	2.8562	0.0052	7.49	2.47
Double outlet RV	Cocaine	1.1079	0.3591	0.0716	0.5341	5.0147	2.17E-06	3.09	2.26

(continued)

Table 1: (Continued)

Anomaly	Substance	Mean Anomaly Rate	Estimate	Std. Error	Sigma	t-statistic	P-Value	E-Value Estimate	E-Value Lower Bound
Double outlet RV	Resin	1.1079	1.5674	0.6900	0.5941	2.2715	0.0254	21.56	2.14
Mitral valve anomalies	Cocaine	1.5003	0.4350	0.0943	0.7032	4.6137	1.12E-05	2.91	2.11
PV atresia	Resin	1.0993	1.4785	0.6617	0.5948	2.2343	0.0276	18.69	1.98
Transpos Grt Vess	Cocaine	3.2853	0.2772	0.0735	0.5902	3.7714	2.53E-04	2.44	1.76
Severe CHD	Cocaine	21.6609	0.1970	0.0532	0.4272	3.7043	3.22E-04	2.41	1.74
VSD	LMCannabis_Resin	41.6464	1.1863	0.5373	0.6434	2.2078	0.0294	10.18	1.72
Transpos Grt Vess	LMCannabis_Resin	3.2853	1.1583	0.5274	0.6316	2.1961	0.0303	10.09	1.69
ASD	Herb	21.0695	3.7614	1.8527	0.7204	2.0302	0.0445	230.98	1.66
Hypoplastic left heart	Cocaine	2.3072	0.2725	0.0833	0.6689	3.2713	0.0014	2.25	1.59
PDA	Cocaine	2.6743	0.3709	0.1147	0.9214	3.2329	0.0016	2.24	1.58
Hypoplastic right heart	LMCannabis_Resin	0.6757	0.8725	0.4068	0.4871	2.1446	0.0343	9.68	1.58
PV atresia	Cocaine	1.0993	0.2021	0.0710	0.5702	2.8465	0.0052	2.11	1.45
Vascular disruptions	Log(Amphetamine)	6.6675	0.1969	0.0711	0.5502	2.7687	0.0067	2.12	1.43
Congenital heart	LM.Cannabis_x_Resin.THC_x_DailyInter-pol.	79.9062	0.5114	0.2390	0.4449	2.1397	0.0349	5.14	1.41
PV stenosis	Cocaine	4.0360	0.2636	0.0969	0.7779	2.7213	0.0075	2.06	1.40
Tetralogy of Fallot	Cocaine	3.0532	0.2061	0.0758	0.6087	2.7190	0.0075	2.06	1.40
Aortic atresia ~	Cocaine	0.5067	0.1607	0.0604	0.4507	2.6583	0.0091	2.11	1.40
VSD	LM.Cannabis_x_Resin.THC_x_DailyInter-pol.	41.6464	0.7413	0.3499	0.6547	2.1188	0.0366	5.05	1.38
ASD	DailyInterpol.	21.0695	0.2363	0.0893	0.7122	2.6454	0.0093	2.04	1.38
Arterial truncus	Log(Amphetamine)	0.9427	0.1964	0.0753	0.6009	2.6065	0.0103	2.03	1.37
Severe CHD	Log(Amphetamine)	21.6609	0.1434	0.0550	0.4387	2.6060	0.0103	2.03	1.36
Aortic valve S/A	Log(Amphetamine)	1.4907	0.1865	0.0751	0.5987	2.4842	0.0144	1.99	1.32
Coarctation aorta	Cocaine	3.6130	0.2296	0.0926	0.7433	2.4804	0.0145	1.98	1.32
AVSD	Cocaine	4.0167	0.2100	0.0861	0.6916	2.4383	0.0162	1.97	1.30
Vascular disruptions	LM.Cannabis_x_Herb.THC:	6.6675	0.1776	0.0744	0.5550	2.3862	0.0188	2.01	1.29
	LM.Cannabis_x_Resin.THC_x_DailyInterpol.								
Congenital heart	Log(Amphetamine)	79.9062	0.1314	0.0563	0.4354	2.3341	0.0215	1.96	1.26
Mitral valve anomalies	Annual_Alcohol	1.5003	0.1100	0.0383	0.7425	2.8744	0.0049	1.55	1.26
TV S/A	Cocaine	0.5907	0.1273	0.0553	0.4438	2.3028	0.0230	1.92	1.24
VSD	Cocaine	41.6464	0.1833	0.0831	0.6671	2.2071	0.0292	1.89	1.20
Tetralogy of Fallot	LM.Cannabis_x_Resin.THC_x_DailyInter-pol.	3.0532	0.7043	0.3548	0.6639	1.9850	0.0499	4.69	1.13
AVSD	Log(Amphetamine)	4.0167	0.1810	0.0873	0.6961	2.0732	0.0403	1.85	1.13
Ebstein's anomaly	Cocaine	0.4327	0.0924	0.0460	0.3691	2.0101	0.0467	1.82	1.08

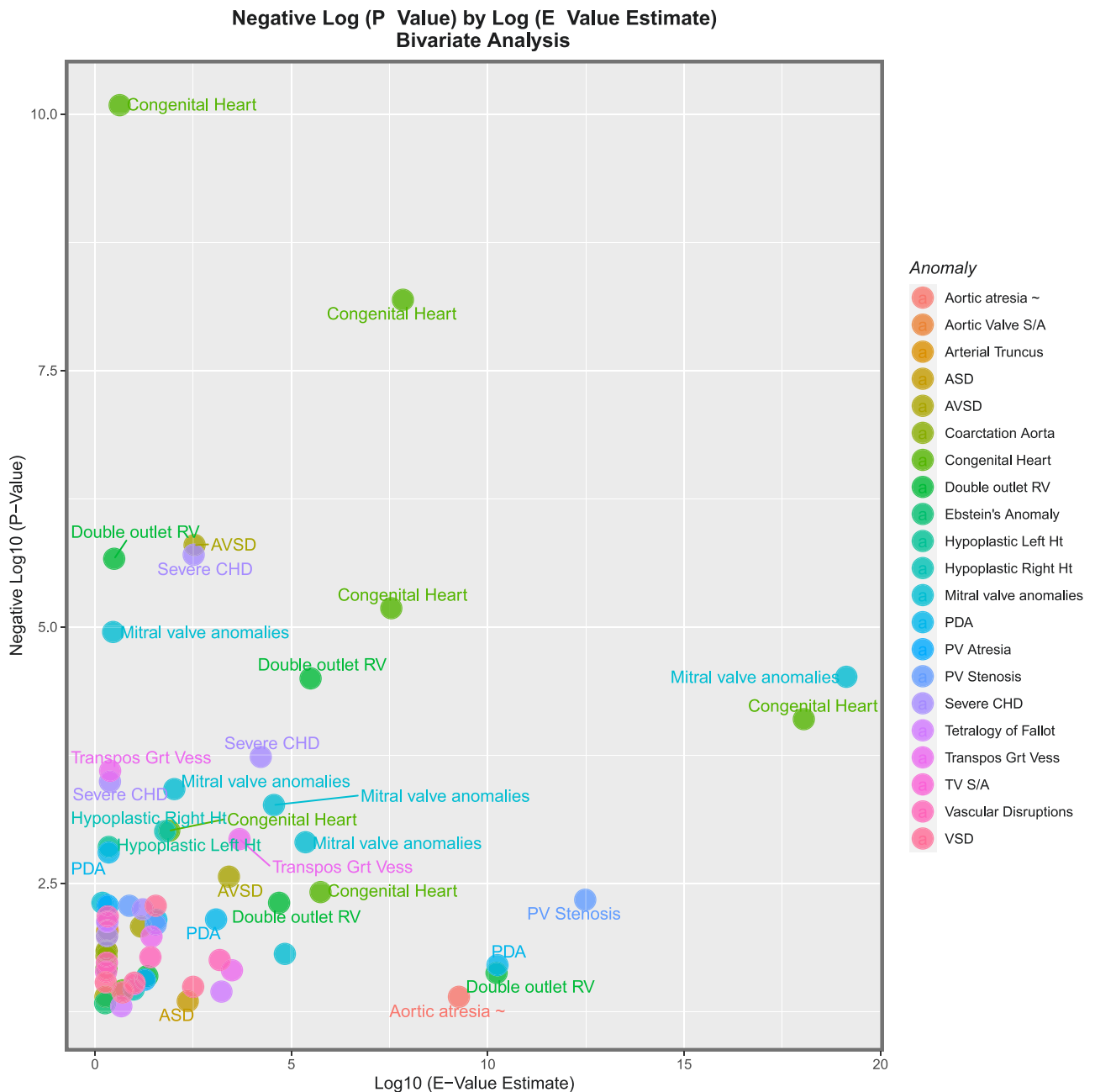


Figure 22: Volcano plot of negative log of P-values against log of E-value estimates for bivariate regressions

Tables 2–13 present the results of final reduced models for each of the 12 anomalies cited in the preceding paragraphs immediately above. In virtually all models terms including cannabis metrics persist in the final models, have positive regression coefficients and are statistically significant usually at high levels.

Tables 14 and 15 present the E-values to emerge from these positive and significant cannabis-related terms in the panel and spatial regression model sets, respectively.

These lists are then combined into the lists of 149 E-values derived from both sets of models, as shown in Table 16. It was found that 138/149 (92.6%) of the E-value estimates were >9 and so in the high zone, and all 149 exceeded the cut-off for causality at 1.25 [67]. 112/149 (75.2%) mEVs exceeded 9 and so fell in the high zone [68], and 147/149 mEVs (98.7%) exceeded the threshold for causality at 1.25 [67].

Table 17 lists these E-values by CA. Table 18 summarizes these data by CA listed in descending order of median mEV. This table is of interest for several reasons and is considered further in the Discussion section below.

These multivariable data are also similarly suited to illustration by Volcano plots as was done earlier for the bivariate results.

The multivariable data for the E-value estimates are shown in Supplementary Fig. S2. In this plot, the presence of the tetralogy of Fallot far to the right forces all the points to the left side of the graph and makes the remainder of the graph difficult to interpret clearly. A similar problem occurs when the mEVs are considered, as shown in Supplementary Fig. S3.

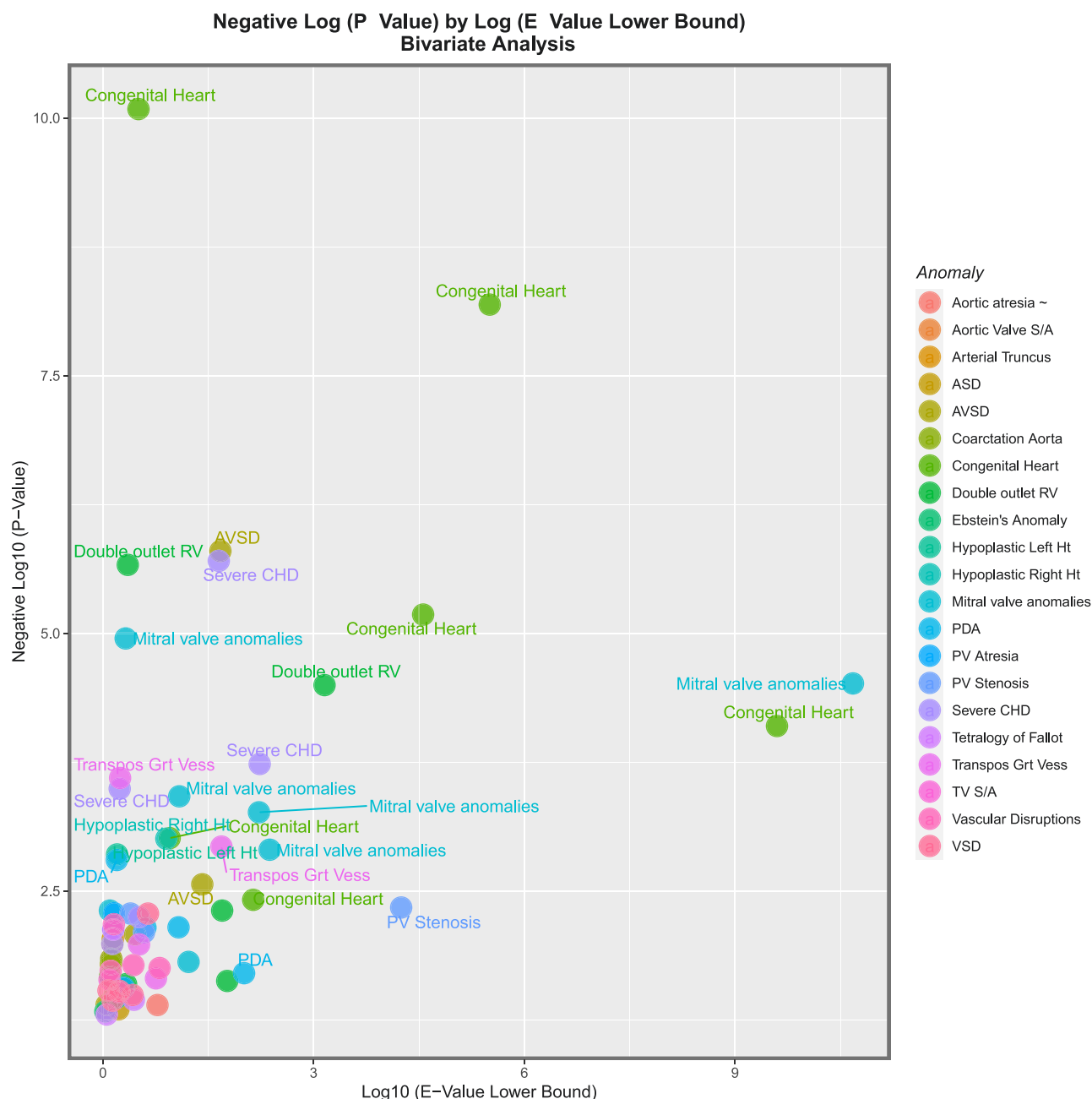


Figure 23: Volcano plot of negative log of P-values against log of mEV for bivariate regressions

Discussion

Main Results

Study data indicate that 17 of the 23 congenital cardiac anomalies demonstrated strong bivariate relationships with different metrics of cannabis exposure. Twelve of these anomalies were selected for detailed study in inverse probability weight panel regression models and in spatiotemporal models. In all twelve cases cannabis metrics persisted after adjustment in multivariable panel and spatial models. The use of ipw in panel models moved the analysis from a merely observational paradigm into a pseudorandomized paradigm from which it is both proper and appropriate to draw causal conclusions. When models were assessed for uncontrolled confounding E-values were noted to be very high throughout effectively excluding alternative explanations on quantitative

grounds. The present results for ASD, VSD, AVSD, PDA and transposition of the great vessels are consistent with those previously reported in other series [4–9, 70].

Interestingly a companion paper to this one has shown that the VACTERL syndrome (Vertebral, anorectal, cardiac, tracheo-esophageal fistulae/esophageal atresia, renal and limb anomalies) was strongly and causally linked with European cannabinoid exposure which is itself consistent with cannabis-induced inhibition of the sonic hedgehog pathway as has previously been demonstrated [32, 71]. Since cardiac abnormalities are part of the VACTERL syndrome this finding confirms current study findings. The commonest cardiac anomalies seen in VACTERL syndrome are VSD and tetralogy of Fallot, two of the anomalies described herein [71–73].

In this respect the present results closely paralleled similar studies recently published from Canada, Australia, HI, CO, and the USA [4–9, 70]. They are also consistent with the wide spectrum of genotoxic activities which have been demonstrated experimentally for cannabis and cannabinoids.

The seventeen anomalies which showed strong bivariate relationships to cannabis exposure metrics were: (i) congenital heart defects, Severe CHD, Double outlet right ventricle, Transposition of great vessels, Single ventricle, VSD, ASD, AVSD, Tetralogy of Fallot, Ebstein's anomaly, Pulmonary valve stenosis, Pulmonary valve atresia, Mitral valve anomalies, Hypoplastic right heart, Aortic atresia/interrupted aortic arch, PDA as only CHD in term infants (≥ 37 weeks) and Vascular disruption anomalies.

The six anomalies which did not show a bivariate relationship to cannabis exposure were: (ii) arterial truncus, tricuspid valve stenosis and atresia, aortic valve stenosis or atresia, coarctation of the aorta, hypoplastic left heart, total anomalous pulmonary venous return.

The twelve anomalies for which extended inverse probability weighted panel regression and space-time modelling was undertaken were: (iii) congenital heart defects, Severe CHD, Double outlet right ventricle, Transposition of great vessels, VSD, ASD, AVSD, Tetralogy of Fallot, Mitral valve anomalies, Hypoplastic right heart, PDA as only CHD in term infants (≥ 37 weeks) and Vascular disruption anomalies.

Table 2: Final multivariate geospatial regression models for CHD

Parameter Values			Model Parameters		
Parameter	Estimate (CI)	P-Value	Parameter	Value	Significance
<i>Additive</i>					
Rate ~ Tobacco + Alcohol + LM.Cannabis_x_Herb.THC_x_Daily.Interpol. + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + Herb + LM.Cannabis_x_Herb.THC + Amphetamines + Cocaine + Income					
Herb.THC	2.09 (0.67, 3.5)	0.0038	psi	0.84099	<2.2E-16
Cocaine	0.17 (0.05, 0.29)	0.0045	rho	-0.61126	3.03E-08
			lambda	0.62061	4.97E-10
<i>Interactive</i>					
Rate ~ Tobacco * LM.Cannabis_x_Herb.THC_x_Daily.Interpol. + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. * Herb + LM.Cannabis_x_Herb.THC + Alcohol + Amphetamines + Cocaine + Income					
Herb.THC	2.09 (0.67, 3.5)	0.0038	psi	0.84099	<2.2E-16
Cocaine	0.17 (0.05, 0.29)	0.0045	rho	-0.61126	3.03E-08
			lambda	0.6261	4.97E-10
<i>1 Lag</i>					
Rate ~ Tobacco,1) * LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + LM.Cannabis_x_Herb.THC_x_Daily.Interpol.,1) + Herb + LM.Cannabis_x_Herb.THC,1) + Alcohol,1) + Amphetamines,1) + Cocaine,1) + Income,1)					
Herb.THC	2.17 (0.1, 4.23)	0.0401	psi	0.85902	<2.2E-16
			rho	0.62929	1.20E-07
			lambda	-0.4748	0.0018
<i>2 Lags</i>					
Rate ~ Tobacco,2) + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. * LM.Cannabis_x_Herb.THC_x_Daily.Interpol.,2) + Herb + LM.Cannabis_x_Herb.THC,2) + Alcohol,2) + Amphetamines,2) + Cocaine,2) + Income,2)					
Herb.THC	1.91 (0.25, 3.56)	0.0238	psi	0.88721	<2.2E-16
Cocaine	-0.16 (-0.29, -0.03)	0.0158	rho	-0.5633	2.83E-05
			lambda	0.6436	2.11E-09

Table 3: Final multivariate geospatial regression models for severe CHD

Parameter Values			Model Parameters		
Parameter	Estimate (CI)	P-Value	Parameter	Value	Significance
<i>Additive</i>					
Rate ~ Tobacco + Alcohol + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + LM.Cannabis_x_Herb.THC_x_Daily.Interpol. + Herb + LM.Cannabis_x_Resin.THC + Amphetamines + Cocaine + Income					
Herb	4.22 (2.54, 5.9)	8.22E-07	psi	0.3942	1.34E-04
Income	0 (0, 0)	5.29E-05	rho	-0.5169	1.10E-04
LM.Cannabis_x_Resin.THC	1.19 (0.56, 1.82)	0.0002	lambda	0.3181	0.0240
Tobacco	0.03 (0.02, 0.05)	0.0004			
Cocaine	0.17 (0.06, 0.29)	0.0040			
LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	-2.7 (-3.77, -1.63)	8.39E-07			
<i>Interactive</i>					
Rate ~ Tobacco * LM.Cannabis_x_Resin.THC_x_Daily.Interpol. * LM.Cannabis_x_Herb.THC_x_Daily.Interpol. + Herb * LM.Cannabis_x_Resin.THC + Alcohol + Herb + Amphetamines + Cocaine + Income					
Herb	7.47 (5.2, 9.74)	1.05E-10	psi	0.3091	0.0042
Income	0 (0, 0)	1.42E-05	rho	-0.3024	0.0058

(continued)

Table 3: (Continued)

Parameter Values			Model Parameters		
Parameter	Estimate (CI)	P-Value	Parameter	Value	Significance
LM.Cannabis_x_Resin.THC	2.95 (1.58, 4.32)	2.35E-05			
Tobacco	0.04 (0.02, 0.06)	3.87E-05			
Cocaine	0.21 (0.09, 0.32)	0.0005			
Herb: LM.Cannabis_x_Resin.THC	-18.6 (-33.38, -3.82)	0.0138			
Tobacco: LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	-0.1 (-0.15, -0.05)	0.0003			
<i>1 Lag</i>					
Rate ~ Tobacco,1) + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. * LM.Cannabis_x_Resin.THC,1) * LM.Cannabis_x_Herb.THC_x_Daily.Interpol. + Herb,1) + Alcohol,1) + Amphetamines,1) + Cocaine,1) + Income,1)					
Income	0 (0, 0)	9.59E-05	psi	0.7862	<2.2E-16
LM.Cannabis_x_Resin.THC: LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	5.2 (1.57, 8.83)	0.0050	rho	0.6708	1.73E-15
Alcohol	0.09 (0.02, 0.15)	0.0091	lambda	-0.5679	2.68E-08
Herb	2.43 (0.12, 4.74)	0.0391			
LM.Cannabis_x_Resin.THC	-1.45 (-2.42, -0.48)	0.0035			
<i>2 Lags</i>					
Rate ~ Tobacco,2) * LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + LM.Cannabis_x_Resin.THC,2) + LM.Cannabis_x_Herb.THC_x_Daily.Interpol. + Herb,2) + Alcohol,2) + Amphetamines,2) + Cocaine,2) + Income,2)					
Tobacco	0.06 (0.04, 0.09)	1.08E-05	psi	0.4317	0.0004
Income	0 (0, 0)	7.82E-08			
LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	9.27 (3.23, 15.31)	0.0026			
Herb	2.93 (0.42, 5.44)	0.0221			
Tobacco: LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	-0.28 (-0.51, -0.06)	0.0143			
LM.Cannabis_x_Herb.THC: LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	-4.14 (-6.9, -1.38)	0.0032			

Table 4: Final multivariate geospatial regression models for ASD

Parameter Values			Model Parameters		
Parameter	Estimate (CI)	P-Value	Parameter	Value	Significance
<i>Additive</i>					
Rate ~ Tobacco + Alcohol + Daily.Interpol. + LM.Cannabis_x_Herb.THC_x_Daily.Interpol. + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + Herb + Amphetamines + Cocaine + Income					
Herb	3.88 (-0.56, 8.31)	0.0865	psi	0.66684	<2.2E-16
<i>Interactive</i>					
Rate ~ Tobacco + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. * LM.Cannabis_x_Herb.THC_x_Daily.Interpol. + Daily.Interpol. + Herb + Alcohol + Amphetamines + Cocaine + Income					
No significant parameters remaining in the final model					
<i>1 Lag</i>					
Rate ~ Tobacco + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. * LM.Cannabis_x_Herb.THC_x_Daily.Interpol. + Daily.Interpol. + Herb + Alcohol + Amphetamines + Cocaine + Income					
Tobacco: Daily.Interpol.	8.56 (1.29, 15.83)	0.0210	psi	0.80977	<2.2E-16
Daily.Interpol.	-209.01 (-381.79, -36.23)	0.0177			
<i>2 Lags</i>					
Rate ~ Tobacco * Daily.Interpol. + LM.Cannabis_x_Herb.THC + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + Alcohol + Amphetamines + Cocaine + Income					
Tobacco	0.13 (0.04, 0.21)	0.0028	psi	0.78396	<2.2E-16
Income	0 (0, 0)	0.0053			
Daily.Interpol.	210 (31.44, 388.56)	0.0215			
Tobacco: Daily.Interpol.	-7.99 (-15.32, -0.66)	0.0324			
Cocaine	-0.38 (-0.67, -0.08)	0.0135			

Table 5: Final multivariate geospatial regression models for VSD

Parameter Values			Model Parameters		
Parameter	Estimate (CI)	P-Value	Parameter	Value	Significance
<i>Additive</i>					
Rate ~ Tobacco + Alcohol + Daily.Interpol. + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + LM.Cannabis_x_Herb.THC + Resin + Herb + Amphetamines + Cocaine + Income					
Herb	4.95 (1.91, 8)	0.0014	psi	0.4909	7.62E-06

(continued)

Table 5: (Continued)

Parameter Values			Model Parameters		
Parameter	Estimate (CI)	P-Value	Parameter	Value	Significance
Cocaine	0.31 (0.12, 0.5)	0.0016	rho	−0.6133	7.46E-07
Resin	1.76 (0.17, 3.35)	0.0296	lambda	0.5634	1.06E-06
Amphetamines	−0.2 (−0.37, −0.03)	0.0209			
LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	−0.98 (−1.71, −0.26)	0.0079			
<i>Interactive</i>					
Rate ~ Tobacco * Daily.Interpol. + LM.Cannabis_x_Herb.THC + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + LM.Cannabis_x_Herb.THC_x_Daily.Interpol. + Alcohol + Amphetamines + Cocaine + Income					
LM.Cannabis_x_Herb.THC	17.3 (9.66, 24.94)	8.94E-06	psi	0.4735	6.35E-05
Income	0 (0, 0)	0.0058	rho	−0.5867	4.97E-07
LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	−4.63 (−7.33, −1.93)	0.0008	lambda	0.5404	1.94E-06
<i>1 Lag</i>					
Rate ~ Tobacco,1) * Daily.Interpol.,1) + LM.Cannabis_x_Herb.THC,1) + LM.Cannabis_x_Resin.THC_x_Daily.Interpol.,1) + Alcohol,1) + LM.Cannabis_x_Herb.THC_x_Daily.Interpol.,1) + Amphetamines,1) + Cocaine,1) + Income,1)					
LM.Cannabis_x_Herb.THC	10.81 (4.89, 16.73)	0.0003	psi	0.5464	1.31E-10
			rho	0.5562	3.30E-05
			lambda	0.3306	0.0462
<i>2 Lags</i>					
Rate ~ Tobacco,2) + Daily.Interpol.,2) + LM.Cannabis_x_Herb.THC,2) + LM.Cannabis_x_Resin.THC_x_Daily.Interpol.,2) + Alcohol,2) + LM.Cannabis_x_Herb.THC_x_Daily.Interpol.,2) + Amphetamines,2) + Cocaine,2) + Income,2)					
Tobacco	0.04 (0, 0.07)	0.0352	psi	0.4333	0.0003
Daily.Interpol.	45.5 (9.24, 81.76)	0.0137	rho	−0.5302	0.0004
LM.Cannabis_x_Herb.THC	18.6 (10.03, 27.17)	2.15E-05	lambda	0.5682	6.71E-06
Income	0 (0, 0)	0.0012			
LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	−7.13 (−12.05, −2.21)	0.0046			
Cocaine	−0.42 (−0.7, −0.13)	0.0043			
Alcohol	−0.1 (−0.17, −0.03)	0.0032			

Table 6: Final multivariate geospatial regression models for AVSD

Parameter Values			Model Parameters		
Parameter	Estimate (CI)	P-Value	Parameter	Value	Significance
<i>Additive</i>					
Rate ~ Tobacco + Alcohol + Daily.Interpol. + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + LM.Cannabis_x_Herb.THC + Resin + Herb + Amphetamines + Cocaine + Income)					
Herb	4.95 (1.91, 8)	0.0014	psi	0.4909	7.62E-06
Cocaine	0.31 (0.12, 0.5)	0.0016	rho	−0.6133	7.46E-07
Resin	1.76 (0.17, 3.35)	0.0296	lambda	0.5634	1.06E-06
Amphetamines	−0.2 (−0.37, −0.03)	0.0209			
LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	−0.98 (−1.71, −0.26)	0.0079			
<i>Interactive</i>					
Rate ~ Tobacco * Resin * LM.Cannabis_x_Resin.THC + Alcohol + Amphetamines + Cocaine + Income					
Tobacco: Resin	0.52 (0.29, 0.75)	1.23E-05	psi	0.401	1.49E-05
Income	0 (0, 0)	0.0015			
Cocaine	0.37 (0.08, 0.67)	0.0133			
Resin	−6.16 (−11.98, −0.34)	0.0378			
Tobacco: LM.Cannabis_x_Resin.THC	−0.15 (−0.24, −0.06)	0.0013			
<i>2 Lags</i>					
Rate ~ Tobacco,2) * Resin,2) + LM.Cannabis_x_Resin.THC,2) + LM.Cannabis_x_Resin.THC_x_Daily.Interpol.,2) + Herb,2) + Daily.Interpol.,2) + Alcohol,2) + Amphetamines,2) + Cocaine,2) + Income,2)					
Income	0 (0, 0)	0.0020	psi	0.4191	0.0006
Tobacco: Resin	0.25 (0.03, 0.47)	0.0289	rho	0.5425	0.0004
			lambda	−0.5980	8.42E-05

Table 7: Final multivariate geospatial regression models for PDA

Parameter Values			Model Parameters		
Parameter	Estimate (CI)	P-Value	Parameter	Value	Significance
Additive					
Rate ~ Tobacco + Alcohol + Daily.Interpol. + LM.Cannabis_x_Herb.THC + LM.Cannabis_x_Herb.THC_x_Daily.Interpol. + LM.Cannabis + Amphetamines + Cocaine + Income					
LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	5.83 (2.33, 9.32)	0.0011	psi	0.59171	1.43E-12
Cocaine	0.48 (0.17, 0.79)	0.0026	rho	-0.61788	7.19E-08
LM.Cannabis	-30.65 (-45.35, -15.94)	4.41E-05	lambda	0.6049	2.06E-09
Interactive					
Rate ~ Tobacco * Daily.Interpol. + LM.Cannabis + Alcohol + LM.Cannabis_x_Herb.THC_x_Daily.Interpol. + Amphetamines + Cocaine + Income					
LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	6.45 (3.45, 9.46)	2.50E-05	psi	0.36814	0.000342
Tobacco: Daily.Interpol.	7.94 (3.04, 12.85)	0.0015	rho	-0.68835	5.12E-12
Daily.Interpol.	-168.25 (-292.36, -44.13)	0.0079	lambda	0.66996	2.47E-15
Alcohol	-0.16 (-0.25, -0.08)	0.0001			
Tobacco	-0.07 (-0.11, -0.04)	9.56E-05			
LM.Cannabis	-29.84 (-42.83, -16.84)	6.76E-06			
1 Lag					
Rate ~ Tobacco,1) * Daily.Interpol.,1) + LM.Cannabis_x_Herb.THC,1) + LM.Cannabis,1) + LM.Cannabis_x_Herb.THC_x_Daily.Interpol.,1) + Alcohol,1) + Daily.Interpol.,1) + Amphetamines,1) + Cocaine,1) + Income,1)					
Tobacco: Daily.Interpol.	9.38 (4.9, 13.86)	4.13E-05	psi	0.3964	0.000433
LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	7.55 (2.63, 12.47)	0.0026	rho	0.72302	<2.2E-16
LM.Cannabis_x_Herb.THC	-17.48 (-29.69, -5.28)	0.0050	lambda	-0.63094	9.92E-11
Daily.Interpol.	-220.55 (-334.75, -106.35)	0.0002			
Tobacco	-0.13 (-0.18, -0.09)	1.02E-09			
2 Lags					
Rate ~ Tobacco,2) * Daily.Interpol.,2) + LM.Cannabis_x_Herb.THC,2) + LM.Cannabis,2) + LM.Cannabis_x_Herb.THC_x_Daily.Interpol.,2) + Alcohol,2) + Daily.Interpol.,2) + Amphetamines,2) + Cocaine,2) + Income,2)					
Tobacco: Daily.Interpol.	2.52 (1.05, 3.99)	0.0008	psi	0.45343	2.48E-05
LM.Cannabis_x_Herb.THC	15.77 (3.67, 27.88)	0.0107	rho	0.71484	<2.2E-16
LM.Cannabis	-32.01 (-49.41, -14.61)	0.0003	lambda	-0.6013	5.76E-09
Alcohol	-0.22 (-0.3, -0.14)	9.40E-08			

Table 8: Final multivariate geospatial regression models for tetralogy of Fallot

Parameter Values			Model Parameters		
Parameter	Estimate (CI)	P-Value	Parameter	Value	Significance
Additive					
Rate ~ Tobacco + Alcohol + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + Herb + Daily.Interpol. + Herb + Amphetamines + Cocaine + Income					
Cocaine	0.25 (0.13, 0.37)	6.77E-05	rho	-0.5927	6.13E-09
Herb	3.18 (1.06, 5.31)	0.0033	lambda	0.5414	3.29E-07
Tobacco	-0.02 (-0.04, -0.01)	0.0023			
Amphetamines	-0.22 (-0.32, -0.12)	1.24E-05			
Interactive					
Rate ~ Tobacco * Resin + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + Alcohol + Amphetamines + Cocaine + Income					
Tobacco: Resin	0.43 (0.23, 0.62)	1.44E-05	rho	-0.6819	5.55E-14
Income	0 (0, 0)	7.88E-05	lambda	0.61208	6.66E-11
Alcohol	-0.05 (-0.09, -0.01)	0.0232			
Amphetamines	-0.18 (-0.29, -0.08)	0.0004			
Tobacco	-0.08 (-0.12, -0.04)	0.0003			
Resin	-10.3 (-15.49, -5.11)	0.0001			
1 Lag					
Rate ~ Tobacco,1) * Herb,1) + Resin,1) + Alcohol,1) + Amphetamines,1) + Cocaine,1) + Income,1)					
Cocaine	0.27 (0.15, 0.39)	7.90E-06	psi	-0.24715	0.0132
Tobacco: Herb	0.96 (0.49, 1.42)	5.26E-05			
Amphetamines	-0.16 (-0.27, -0.04)	0.0066			
Herb	-17.03 (-28.64, -5.42)	0.0040			
Tobacco	-0.12 (-0.17, -0.07)	1.80E-06			
2 Lags					
Rate ~ Tobacco,2) * LM.Cannabis_x_Herb.THC,2) + LM.Cannabis_x_Resin.THC_x_Daily.Interpol.,2) * LM.Cannabis_x_Herb.THC_x_Daily.Interpol.,2) + Alcohol,2) + Amphetamines,2) + Cocaine,2) + Income,2)					

(continued)

Table 8: (Continued)

Parameter Values			Model Parameters		
Parameter	Estimate (CI)	P-Value	Parameter	Value	Significance
Tobacco: LM.Cannabis_x_Herb.THC	0.59 (0.35, 0.82)	1.07E-06	rho	−0.6367	1.58E-08
Cocaine	0.29 (0.11, 0.46)	0.00115	lambda	0.5254	2.40E-05
Amphetamines	−0.24 (−0.36, −0.13)	5.82E-05			
LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	−5.14 (−7.5, −2.78)	2.00E-05			
Tobacco	−0.04 (−0.05, −0.02)	1.93E-06			

Table 9: Final multivariate geospatial regression models for vascular disruptions

Parameter Values			Model Parameters		
Parameter	Estimate (CI)	P-Value	Parameter	Value	Significance
Additive					
Rate ~ Tobacco + LM.Cannabis_x_Herb.THC_x_Daily.Interpol. + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + Resin + Daily.Interpol. + Alcohol + Amphetamines + Cocaine + Income					
Alcohol	0.12 (0.08, 0.16)	1.23E-08	rho	0.7048	<2.2E-16
LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	2.1 (1.05, 3.15)	8.77E-05	lambda	−0.4902	6.17E-06
Income	0 (0, 0)	0.0001			
Cocaine	0.24 (0.09, 0.39)	0.0021			
LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	−4.63 (−7.45, −1.81)	0.0013			
Interactive					
Rate ~ Tobacco + LM.Cannabis_x_Herb.THC_x_Daily.Interpol. * LM.Cannabis_x_Resin.THC_x_Daily.Interpol. * Resin + Daily.Interpol. + Alcohol + Amphetamines + Cocaine + Income					
Alcohol	0.12 (0.08, 0.16)	1.23E-08	rho	0.7048	<2.2E-16
LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	2.1 (1.05, 3.15)	8.77E-05	lambda	−0.4902	6.17E-06
Income	0 (0, 0)	0.0001			
Cocaine	0.24 (0.09, 0.39)	0.0021			
LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	−4.63 (−7.45, −1.81)	0.0013			
1 Lag					
Rate ~ Tobacco + LM.Cannabis_x_Herb.THC_x_Daily.Interpol. + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + Resin + Daily.Interpol. + Alcohol + Amphetamines + Cocaine + Income					
Income	0 (0, 0)	1.04E-05	rho	0.66669	1.83E-12
Alcohol	0.1 (0.05, 0.14)	3.48E-05	lambda	−0.5336	7.94E-06
Amphetamines	0.13 (0.03, 0.23)	0.0139			
LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	0.59 (0.06, 1.11)	0.0284			
2 Lags					
Rate ~ Tobacco + LM.Cannabis_x_Herb.THC_x_Daily.Interpol. + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + Resin + Daily.Interpol. + Alcohol + Amphetamines + Cocaine + Income					
Alcohol	0.11 (0.06, 0.16)	2.03E-05	rho	0.69361	2.72E-15
Income	0 (0, 0)	0.0001	lambda	−0.5337	7.84E-06
LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	1.13 (0.47, 1.79)	0.0008			

Table 10: Final multivariate geospatial regression models for double outlet right ventricle

Parameter Values			Model Parameters		
Parameter	Estimate (CI)	P-Value	Parameter	Value	Significance
Additive					
Rate ~ Tobacco + Alcohol + Daily.Interpol. + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + LM.Cannabis_x_Herb.THC + LM.Cannabis_x_Herb.THC_x_Daily.Interpol. + Herb + Resin + LM.Cannabis_x_Resin.THC + LM.Cannabis_x_Herb.THC_x_Daily.Interpol. + Amphetamines + Cocaine + Income					
Income	0 (0, 0)	5.64E-13	psi	0.19608	0.0393
LM.Cannabis_x_Herb.THC	5.13 (1.23, 9.03)	0.0099			
Interactive					
Rate ~ Tobacco * LM.Cannabis_x_Herb.THC + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + LM.Cannabis_x_Herb.THC_x_Daily.Interpol. + Daily.Interpol. + Alcohol + Amphetamines + Cocaine + Income					
Income	0 (0, 0)	6.71E-08	psi	0.1731	0.0712
LM.Cannabis_x_Herb.THC	29.6 (4.51, 54.69)	0.0208			
Tobacco	0.05 (0, 0.1)	0.0497			
Tobacco: LM.Cannabis_x_Herb.THC	−1.01 (−2.02, 0)	0.0499			

(continued)

Table 10: (Continued)

Parameter Values			Model Parameters		
Parameter	Estimate (CI)	P-Value	Parameter	Value	Significance
<i>2 Lags</i>					
Rate ~ Tobacco * LM.Cannabis_x_Herb.THC + Daily.Interpol. * LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + Alcohol + Amphetamines + Cocaine + Income					
Income	0 (0, 0)	<2.2E-16	psi	-0.1072	0.331
LM.Cannabis_x_Herb.THC	12.8 (7.14, 18.46)	9.11E-06			
Alcohol	0.06 (0.01, 0.11)	0.0207			
Daily.Interpol.: LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	-40.5 (-73.04, -7.96)	0.0146			

Table 11: Final multivariate geospatial regression models for transposition of the great vessels

Parameter Values			Model Parameters		
Parameter	Estimate (CI)	P-Value	Parameter	Value	Significance
<i>Additive</i>					
Rate ~ Tobacco + Alcohol + Daily.Interpol. + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + LM.Cannabis_x_Herb.THC + LM.Cannabis_x_Herb.THC_x_Daily.Interpol. + Herb + Amphetamines + Cocaine + Income					
Income	0 (0, 0)	5.64E-13	psi	0.1961	0.0393
LM.Cannabis_x_Herb.THC	5.13 (1.23, 9.03)	0.0099			
<i>Interactive</i>					
Rate ~ Tobacco * LM.Cannabis_x_Resin.THC + Resin * Herb + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + Alcohol + Amphetamines + Cocaine + Income					
Herb	3.41 (1.49, 5.33)	0.0005	rho	-0.7757	<2.2E-16
Cocaine	0.21 (0.09, 0.33)	0.0005	lambda	0.6425	1.99E-13
Income	0 (0, 0)	0.0235			
Tobacco	0.02 (0, 0.05)	0.0455			
Alcohol	-0.07 (-0.11, -0.03)	0.0004			
<i>1 Lag</i>					
Rate ~ Tobacco * LM.Cannabis_x_Resin.THC + Resin * LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + Alcohol + Amphetamines + Cocaine + Income					
Income	0 (0, 0)	0.0020	rho	-0.7509	<2.2E-16
Tobacco	0.03 (0, 0.06)	0.0308	lambda	0.6706	6.45E-14
Cocaine	0.15 (0.01, 0.28)	0.0343			
Resin	0.94 (0.06, 1.82)	0.0370			
Alcohol	-0.07 (-0.12, -0.03)	0.0011			
<i>2 Lags</i>					
Rate ~ Tobacco * LM.Cannabis_x_Resin.THC + Resin * LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + Alcohol + Amphetamines + Cocaine + Income					
LM.Cannabis_x_Resin.THC	1.16 (0.58, 1.74)	0.0001	rho	-0.7579	6.87E-16
Alcohol	-0.08 (-0.12, -0.04)	3.85E-05	lambda	0.6752	4.76E-15
Income	0 (0, 0)	9.61E-07			

Table 12: Final multivariate geospatial regression models for hypoplastic right heart

Parameter Values			Model Parameters	
Parameter	Estimate (CI)	P-Value	Parameter	Value
<i>Additive</i>				
Rate ~ Tobacco + Alcohol + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + LM.Cannabis_x_Herb.THC_x_Daily.Interpol. + LM.Cannabis_x_Herb.THC + Amphetamines + Cocaine + Income				
Alcohol	0.08 (0.04, 0.13)	0.0005	Least squares	
LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	2.68 (1.53, 3.83)	5.22E-06	SD	0.3951
LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	-7.03 (-9.93, -4.13)	2.10E-06		
Cocaine	0.22 (0.06, 0.39)	0.0066		
Income	0 (0, 0)	2.28E-05		
<i>Interactive</i>				
Rate ~ Tobacco,1) * LM.Cannabis_x_Herb.THC_x_Daily.Interpol., 1) + LM.Cannabis_x_Herb.THC,1) + LM.Cannabis_x_Resin.THC_x_Daily.Interpol., 1) + Alcohol,1) + Daily.Interpol.,1) + Amphetamines,1) + Cocaine,1) + Income,1)				
Income	0 (0, 0)	3.32E-08	Least squares	
LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	2.84 (1.75, 3.93)	3.10E-07	SD	0.3914
Alcohol	0.06 (0.02, 0.1)	0.0064		
LM.Cannabis_x_Herb.THC_x_Daily.Interpol.: LM.Cannabis_x_Herb.THC	-57.4 (-79.74, -35.06)	5.02E-07		

(continued)

Table 12: (Continued)

Parameter Values			Model Parameters	
Parameter	Estimate (CI)	P-Value	Parameter	Value
1 Lag				
Rate ~ Tobacco * LM.Cannabis_x_Herb.THC_x_Daily.Interpol. + LM.Cannabis_x_Herb.THC + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + Alcohol + Daily.Interpol. + Amphetamines + Cocaine + Income				
Income	0 (0, 0)	1.37E-06	Least squares	
LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	2.79 (1.28, 4.31)	0.0003	SD	0.4160
Alcohol	0.07 (0.02, 0.12)	0.0053		
Daily.Interpol.	35.17 (9.24, 61.1)	0.0079		
LM.Cannabis_x_Herb.THC	7.88 (0.62, 15.14)	0.0333		
LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	-11.66 (-17.57, -5.75)	0.0001		
2 Lag				
Rate ~ Tobacco * LM.Cannabis_x_Herb.THC_x_Daily.Interpol. + LM.Cannabis_x_Herb.THC + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + Alcohol + Daily.Interpol. + Amphetamines + Cocaine + Income				
LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	5.24 (3.12, 7.36)	1.09E-06	Least squares	
Income	0 (0, 0)	4.19E-05	SD	0.4106
Daily.Interpol.	98.5 (50.87, 146.13)	5.10E-05		
LM.Cannabis_x_Herb.THC	13.6 (4.53, 22.67)	0.0035		
Cocaine	-0.34 (-0.65, -0.03)	0.0295		
LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	-22 (-30.55, -13.45)	4.22E-07		

Table 13: Final multivariate geospatial regression models for mitral valve anomalies

Parameter Values			Model Parameters		
Parameter	Estimate (CI)	P-Value	Parameter	Value	Significance
Additive					
Rate ~ Tobacco + Alcohol + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + LM.Cannabis_x_Herb.THC + Daily.Interpol. + Amphetamines + Cocaine + Income					
Income	0 (0, 0)	0.0005	psi	0.4569	2.28E-07
Alcohol	0.12 (0.05, 0.2)	0.0015	rho	0.6040	3.16E-06
			lambda	-0.7052	1.56E-10
Interactive					
Rate ~ Tobacco * Daily.Interpol. + LM.Cannabis_x_Herb.THC + LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + Alcohol + Amphetamines + Cocaine + Income					
Alcohol	0.25 (0.19, 0.31)	4.69E-16	rho	0.6192	9.08E-11
Tobacco: Daily.Interpol.	6.77 (4.21, 9.33)	2.17E-07	lambda	-0.7536	<2.2E-16
Amphetamines	0.14 (0.02, 0.26)	0.0185			
LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	-0.73 (-1.37, -0.09)	0.0260			
Daily.Interpol.	-130.64 (-193.93, -67.35)	5.22E-05			
Tobacco	-0.15 (-0.19, -0.11)	<2.2E-16			
1 Lag					
Rate ~ Tobacco * Daily.Interpol. + LM.Cannabis_x_Herb.THC * LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + Alcohol + Amphetamines + Cocaine + Income					
Alcohol	0.25 (0.19, 0.31)	1.41E-15	rho	0.6812	6.99E-16
Tobacco: Daily.Interpol.	6.27 (3.6, 8.94)	4.14E-06	lambda	-0.7776	<2.2E-16
Amphetamines	0.2 (0.08, 0.33)	0.0011			
LM.Cannabis_x_Herb.THC:	30.04 (9.68, 50.4)	0.0038			
LM.Cannabis_x_Resin.THC_x_Daily.Interpol.					
LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	-3.04 (-4.78, -1.3)	0.0006			
Daily.Interpol.	-127.56 (-192.42, -62.7)	0.0001			
Tobacco	-0.15 (-0.19, -0.11)	1.41E-15			
2 Lags					
Rate ~ Tobacco * Daily.Interpol. + LM.Cannabis_x_Herb.THC * LM.Cannabis_x_Resin.THC_x_Daily.Interpol. + Alcohol + Amphetamines + Cocaine + Income					
Alcohol	0.25 (0.18, 0.32)	1.01E-12	rho	0.6404	2.70E-11
Tobacco: Daily.Interpol.	4.88 (1.58, 8.18)	0.0038	lambda	-0.7388	<2.2E-16
Amphetamines	0.21 (0.07, 0.36)	0.0044			
LM.Cannabis_x_Herb.THC:	40.2 (9.02, 71.37)	0.0115			
LM.Cannabis_x_Resin.THC_x_Daily.Interpol.					
Daily.Interpol.	-90.59 (-171.28, -9.9)	0.0278			
LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	-3.95 (-6.36, -1.53)	0.0014			
Tobacco	-0.14 (-0.18, -0.1)	2.04E-11			

Table 14: E-values from panel models

No.	Cardiovascular Anomaly	Model Type	Term	P-Value	E-Value Estimate	Lower Bound E-Value
1	Cong. heart disease	Additive	Herb.THC	1.93E-16	3.38E + 12	1.26E + 10
2	Cong. heart disease	Interactive	Herb.THC	9.29E-10	3.95E + 14	2.95E + 10
3	Cong. heart disease	Interactive	LM.Cannabis_x_Herb.THC	6.23E-03	5.19E + 13	2.14E + 04
4	Cong. heart disease	Interactive	LM.Cannabis_x_Herb.THC_x_Daily.Interpol.: LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	1.91E-02	5.56E + 20	9.39E + 03
5	Cong. heart disease	1 Lag	Herb.THC	1.75E-19	8.06E + 19	3.88E + 16
6	Cong. heart disease	2 Lags	Herb.THC	1.15E-05	6.66E + 08	1.86E + 05
7	Cong. heart disease	2 Lags	Herb.THC: LM.Cannabis_x_Herb.THC	4.14E-11	4.37E + 59	3.41E + 44
8	Severe cong. heart disease	Additive	LM.Herb.THC.Daily.Interpol	4.43E-02	4.92E + 00	1.24
9	Severe cong. heart disease	Additive	LM.Herb.Daily.Intpltd	4.74E-02	5.25E + 13	3.67
10	Severe Cong. Heart Disease	Additive	LM.Herb.THC	1.48E-03	7.57E + 06	850.24
11	Severe cong. heart disease	Interactive	LM.Resin.Daily.Interpol	4.20E-11	4.84E + 13	1.30E + 10
12	Severe cong. heart disease	Interactive	Herb.THC	1.31E-05	3.89E + 07	2.94E + 05
13	Severe cong. heart disease	Interactive	LM.Resin	9.62E-07	2.33E + 04	686.08
14	Severe cong. heart disease	Interactive	Tobacco: LM.Herb.THC.Daily.Interpol	3.85E-08	2.49	2.03
15	Severe cong. heart disease	Interactive	LM.Resin.Daily.Interpol: LM.Herb.THC.Daily.Interpol	1.22E-13	108.11	42.72
16	Severe cong. heart disease	1 Lag	LM.Resin	0.0003	616.49	29.73
17	Severe cong. heart disease	1 Lag	Herb.THC	0.0078	6.74E + 03	18.81
18	Severe cong. heart disease	1 Lag	LM.Resin: LM.Herb.THC.Daily.Interpol	0.0005	1.80E + 06	1.03E + 03
19	Severe cong. heart disease	2 Lags	LM.Resin	7.23E-06	1.31E + 03	91.92
20	Severe cong. heart disease	2 Lags	Herb.THC	4.41E-02	3.46E + 03	2.10
21	Severe cong. heart disease	2 Lags	LM.Resin.Daily.Interpol: LM.Resin	4.42E-02	4.08E + 05	2.76
22	ASD	Additive	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	0.0133	4.91	1.81
23	ASD	Additive	Herb	0.0013	1.79E + 04	81.68
24	ASD	Interactive	Herb	2.32E-12	3.59E + 05	1.76E + 04
25	ASD	1 Lag	LM.Cannabis_x_Herb.THC	8.72E-15	7.28E + 09	6.31E + 07
26	ASD	2 Lags	LM.Cannabis_x_Herb.THC	<2.2E-16	9.01E + 15	2.54E + 13
27	ASD	4 Lags	LM.Cannabis_x_Herb.THC	0.0168	2.51E + 08	90.06
28	VSD	Additive	LM.Cannabis_x_Herb.THC	<2.2E-16	2.38E + 06	1.96E + 05
29	VSD	Interactive	LM.Cannabis_x_Herb.THC	<2.2E-16	2.38E + 06	1.96E + 05
30	VSD	1 Lag	LM.Cannabis_x_Herb.THC	<2.2E-16	3.04E + 06	2.58E + 05
31	VSD	2 Lags	LM.Cannabis_x_Herb.THC	2.7E-14	1.60E + 21	4.97E + 16
32	AVSD	Additive	Resin	4.05E-10	897.5	155.66
33	AVSD	Interactive	LM.Cannabis_x_Resin.THC	8.05E-07	1.67E + 24	1.86E + 15
34	AVSD	Interactive	Tobacco: Resin	4.26E-07	5.56	3.48
35	AVSD	Interactive	Tobacco: Resin: LM.Cannabis_x_Resin.THC	0.0026	263.77	11.38
36	AVSD	1 Lag	LM.Cannabis_x_Resin.THC	0.0042	4.17E + 08	1.18E + 03
37	AVSD	1 Lag	Tobacco: Resin	1.11E-07	5.64	3.62
38	AVSD	2 Lags	Tobacco: Resin	1.58E-12	1.54	1.44
39	PDA	Additive	Daily.Interpol.	4.3E-09	5.07E + 49	3.15E + 34
40	PDA	Additive	LM.Cannabis_x_Herb.THC	0.0158	2.80E + 03	8.07
41	PDA	Interactive	LM.Cannabis_x_Herb.THC	3.27E-05	3.64E + 05	1.52E + 03
42	PDA	Interactive	LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	0.0449	1.48	1.07
43	PDA	Interactive	Tobacco: Daily.Interpol.	8.61E-10	243.5	59.42
44	PDA	1 Lag	LM.Cannabis_x_Herb.THC	7.29E-14	8.51E + 14	4.28E + 11
45	PDA	1 Lag	Tobacco: Daily.Interpol.	1.39E-08	2.93E + 08	7.61E + 05
46	PDA	2 Lags	LM.Cannabis_x_Herb.THC	2.33E-07	7.34E + 11	6.85E + 07
47	PDA	2 Lags	Tobacco: Daily.Interpol.	0.0042	3.30E + 05	111.26
48	Tetralogy of Fallot	Additive	Daily.Interpol.	5.96E-09	3.79E + 19	3.72E + 13
49	Tetralogy of Fallot	Interactive	Daily.Interpol.	2.1E-09	Infnty	4.28E + 135
50	Tetralogy of Fallot	Interactive	LM.Cannabis_x_Herb.THC	0.0159	1.19E + 05	17.74
51	Tetralogy of Fallot	Interactive	LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	4.68E-07	36.96	12.31
52	Tetralogy of Fallot	1 Lag	LM.Cannabis_x_Herb.THC: LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	2.59E-10	1.24E + 04	1.08E + 03
53	Tetralogy of Fallot	2 Lags	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	4.36E-16	3.78E + 03	868.53
54	Tetralogy of Fallot	2 Lags	Resin	0.0460	474.56	1.71
55	Tetralogy of Fallot	2 Lags	LM.Cannabis_x_Herb.THC	3.86E-08	1.04E + 25	1.04E + 17

(continued)

Table 14: (Continued)

No.	Cardiovascular Anomaly	Model Type	Term	P-Value	E-Value Estimate	Lower Bound E-Value
56	Vascular disruptions	Additive	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	4.85E-05	52.93	11.26
57	Vascular disruptions	Additive	Resin	9.68E-03	44.48	3.89
58	Vascular disruptions	Interactive	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	1.56E-06	3.81E + 03	212.19
59	Vascular disruptions	Interactive	Resin	0.0038	62.36	5.91
60	Vascular disruptions	Interactive	LM.Cannabis_x_Herb.THC_x_Daily.Interpol.: LM.Cannabis_x_Resin.THC_x_Daily.Interpol.: Resin	1.27E-05	4.00E + 17	1.77E + 10
61	Vascular disruptions	1 Lag	LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	6.72E-04	1.09E + 05	255.77
62	Vascular disruptions	1 Lag	LM.Cannabis_x_Resin.THC	9.61E-04	4.79E + 03	54.91
63	Vascular disruptions	2 Lags	LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	1.76E-04	1.48E + 03	55.25
64	Vascular disruptions	2 Lags	Resin	3.50E-08	6.79E + 04	2.43E + 03
65	Double outlet right ventricle	Interactive	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	0.0005	3.52E + 08	1.08E + 04
66	Double outlet right ventricle	Interactive	Herb	6.33E-05	1.34E + 05	740.60
67	Double outlet right ventricle	Interactive	LM.Cannabis_x_Herb.THC: LM.Cannabis_x_Resin.THC	9.88E-05	2.08E + 32	7.82E + 16
68	Double outlet right ventricle	Interactive	Tobacco: LM.Cannabis_x_Resin.THC_x_Daily.Interpol.: LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	5.35E-12	4.53E + 04	3.72E + 03
69	Double outlet right ventricle	2 Lags	LM.Cannabis_x_Herb.THC	0.0030	9.24E + 13	1.74E + 05
70	Double outlet right ventricle	2 Lags	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	0.0052	3.92E + 03	22.14
71	Double outlet right ventricle	2 Lags	Herb: Resin	0.0138	5.10E + 24	5.89E + 05
72	Transposition great vessels	Additive	Herb	0.0003	9.44E + 07	8.52
73	Transposition great vessels	Additive	LM.Cannabis_x_Resin.THC	0.0002	1.61E + 03	50.46
74	Transposition great vessels	Interactive	Herb	0.0013	5.06E + 04	121.42
75	Transposition great vessels	Interactive	Tobacco: Resin	0.0002	3.72	2.28
76	Transposition great vessels	Interactive	LM.Cannabis_x_Resin.THC: Resin	8.46E-05	7.77E + 39	7.81E + 20
77	Transposition great vessels	1 Lag	Herb	<2.2E-16	3.11E + 06	2.02E + 05
78	Transposition great vessels	2 Lags	LM.Cannabis_x_Resin.THC	0.0034	1.41E + 03	19.41
79	Transposition great vessels	2 Lags	Herb	0.0056	4.74E + 09	1.68E + 03
80	Transposition great vessels	2 Lags	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	0.0437	54.68	1.59
81	Hypoplastic right heart	Additive	Resin	0.0050	1.11E + 03	14.31
82	Hypoplastic right heart	Additive	LM.Cannabis_x_Herb.THC	0.0265	5.02E + 07	17.69
83	Hypoplastic right heart	Interactive	LM.Cannabis_x_Resin.THC	0.0052	9.24	2.67
84	Hypoplastic right heart	1 Lag	Resin	5.65E-05	25.73	7.38
85	Hypoplastic right heart	2 Lags	Resin	0.0009	25.49	5.44
86	Mitral valve anomalies	Additive	Daily.Interpol.	6.06E-10	6.92E + 21	4.76E + 15
87	Mitral valve anomalies	Interactive	Daily.Interpol.	7.46E-09	2.31E + 18	5.81E + 12
88	Mitral valve anomalies	Interactive	LM.Cannabis_x_Herb.THC	0.0189	6.44E + 05	19.02
89	Mitral valve anomalies	1 Lag	Tobacco: Daily.Interpol.	1.27E-13	9.27	6.31
90	Mitral valve anomalies	2 Lags	Herb	0.0155	8.04E + 03	10.85

Table 15: E-values from geospatial models

No.	Regression	Anomaly	Model Type	Term	P-Value	E-Value Estimate	Lower Bound E-Value
1	Spatial	Cong. heart disease	Additive	Herb.THC	0.0038	1.20E + 05	70.68
2	Spatial	Cong. heart disease	Interactive	Herb.THC	0.0038	1.20E + 05	70.68
3	Spatial	Cong. heart disease	1 Lag	Herb.THC	0.0401	801.09	1.98
4	Spatial	Cong. heart disease	2 Lags	Herb.THC	0.0238	144.6	2.95
5	Spatial	Severe cong. heart disease	Additive	Herb	8.22E-07	8.11E + 07	7.77E + 04
6	Spatial	Severe cong. heart disease	Additive	LM.Cannabis_x_Resin.THC	0.0002	281.87	20.47
7	Spatial	Severe cong. heart disease	Interactive	Herb	1.05E-10	1.19E + 13	1.61E + 09
8	Spatial	Severe cong. heart disease	Interactive	LM.Cannabis_x_Resin.THC	2.35E-05	2.21E + 05	1.03E + 03
9	Spatial	Severe cong. heart disease	1 Lag	LM.Cannabis_x_Resin.THC: LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	0.0050	2.18E + 05	3.06
10	Spatial	Severe cong. heart disease	1 Lag	Herb	0.0391	1.20E + 11	3.67E + 03
11	Spatial	Severe cong. heart disease	2 Lags	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	0.0026	2.74E + 11	1.60E + 04
12	Spatial	Severe cong. heart disease	2 Lags	Herb	0.0221	6.71E + 03	5.99
13	Spatial	ASD	1 Lag	Tobacco: Daily.Interpol.	0.0210	4.41E + 07	25.77

(continued)

Table 15: (Continued)

No.	Regression	Anomaly	Model Type	Term	P-Value	E-Value Estimate	Lower Bound E-Value
14	Spatial	ASD	2 Lags	Daily.Interpol.	0.0215	1.54E + 139	1.07E + 21
15	Spatial	VSD	Additive	Herb	0.0014	33.67	1.99
16	Spatial	VSD	Additive	Resin	0.0296	5.88E + 03	43.32
17	Spatial	VSD	Interactive	LM.Cannabis_x_Herb.THC	8.94E-06	1.16E + 17	4.81E + 09
18	Spatial	VSD	1 Lag	LM.Cannabis_x_Herb.THC	0.0003	9.50E + 09	4.91E + 05
19	Spatial	VSD	2 Lags	Daily.Interpol.	0.0137	3.41E + 57	1.44E + 12
20	Spatial	VSD	2 Lags	LM.Cannabis_x_Herb.THC	2.15E-05	4.45E + 23	8.06E + 12
21	Spatial	AVSD	Additive	Herb	0.0014	5.88E + 03	43.32
22	Spatial	AVSD	Additive	Resin	0.0296	33.65	1.99
23	Spatial	AVSD	Interactive	Tobacco: Resin	1.23E-05	4.06	2.56
24	Spatial	AVSD	2 Lags	Tobacco: Resin	0.0289	2.37	1.26
25	Spatial	PDA	Additive	LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	0.0011	4.73E + 03	44.81
26	Spatial	PDA	Interactive	LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	2.50E-05	3.21E + 05	1.23E + 03
27	Spatial	PDA	Interactive	Tobacco: Daily.Interpol.	0.0015	5.09E + 06	576.84
28	Spatial	PDA	1 Lag	Tobacco: Daily.Interpol.	4.13E-05	1.11E + 13	5.74E + 05
29	Spatial	PDA	1 Lag	LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	0.0026	1.37E + 16	3.82E + 08
30	Spatial	PDA	2 Lags	Tobacco: Daily.Interpol.	0.0008	7.25E + 09	344.71
31	Spatial	PDA	2 Lags	LM.Cannabis_x_Herb.THC	0.0107	66.55	8.12
32	Spatial	Tetralogy of Fallot	Additive	Herb	0.0033	2.95E + 07	503.90
33	Spatial	Tetralogy of Fallot	Interactive	Tobacco: Resin	1.44E-05	26.76	7.86
34	Spatial	Tetralogy of Fallot	1 Lag	Tobacco: Herb	5.26E-05	13.11	4.83
35	Spatial	Tetralogy of Fallot	2 Lags	Tobacco: LM.Cannabis_x_Herb.THC	1.07E-06	62.87	15.34
36	Spatial	Vascular disruptions	Additive	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	8.77E-05	293.63	23.91
37	Spatial	Vascular disruptions	Interactive	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	8.77E-05	293.63	23.91
38	Spatial	Vascular disruptions	1 Lag	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	0.0284	6.95	1.58
39	Spatial	Vascular disruptions	2 Lags	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	0.0008	24.97	5.19
40	Spatial	Double outlet right ventricle	Additive	LM.Cannabis_x_Herb.THC	0.0099	7.76E + 04	25.13
41	Spatial	Double outlet right ventricle	Interactive	LM.Cannabis_x_Herb.THC	0.0208	1.63E + 27	2.73E + 04
42	Spatial	Double outlet right ventricle	2 Lags	LM.Cannabis_x_Herb.THC	9.11E-06	2.54E + 12	1.18E + 07
43	Spatial	Transposition great vessels	Additive	LM.Cannabis_x_Herb.THC	0.0099	7.77E + 04	25.13
44	Spatial	Transposition great vessels	Interactive	Herb	0.0005	4.95E + 03	61.38
45	Spatial	Transposition great vessels	1 Lag	Resin	0.0370	15.34	1.53
46	Spatial	Transposition great vessels	2 Lags	LM.Cannabis_x_Resin.THC	0.0001	12.51	4.51
47	Spatial	Hypoplastic right heart	Additive	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	5.22E-06	960.35	67.27
48	Spatial	Hypoplastic right heart	Interactive	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	3.10E-07	1.48E + 03	118.27
49	Spatial	Hypoplastic right heart	1 Lag	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	0.0003	6.18E + 07	7.55
50	Spatial	Hypoplastic right heart	1 Lag	Daily.Interpol.	0.0079	901.95	32.41
51	Spatial	Hypoplastic right heart	1 Lag	LM.Cannabis_x_Herb.THC	0.0333	5.17E + 33	1.34E + 09
52	Spatial	Hypoplastic right heart	2 Lags	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	1.09E-06	2.21E + 13	4.19E + 04
53	Spatial	Hypoplastic right heart	2 Lags	Daily.Interpol.	5.10E-05	2.22E + 05	2.10E + 03
54	Spatial	Hypoplastic right heart	2 Lags	LM.Cannabis_x_Herb.THC	0.0035	1.17E + 95	2.06E + 49
55	Spatial	Mitral valve anomalies	Interactive	Tobacco: Daily.Interpol.	2.17E-07	9.91E + 05	7.03E + 03
56	Spatial	Mitral valve anomalies	1 Lag	Tobacco: Daily.Interpol.	4.14E-06	1.58E + 06	4.93E + 03
57	Spatial	Mitral valve anomalies	1 Lag	LM.Cannabis_x_Herb.THC: LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	0.0038	3.71E + 28	2.81E + 09
58	Spatial	Mitral valve anomalies	2 Lags	Tobacco: Daily.Interpol.	0.0038	3.97E + 04	49.19
59	Spatial	Mitral valve anomalies	2 Lags	LM.Cannabis_x_Herb.THC: LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	0.0115	5.36E + 35	2.03E + 08

Table 16: List of all E-values

No.	E-Value Estimate	Lower Bound E-Value
1	Infinity	4.28E + 135
2	1.54E + 139	2.06E + 49
3	1.17E + 95	3.41E + 44
4	4.37E + 59	3.15E + 34
5	3.41E + 57	1.07E + 21
6	5.07E + 49	7.81E + 20
7	7.77E + 39	1.04E + 17
8	5.36E + 35	7.82E + 16
9	5.17E + 33	4.97E + 16
10	2.08E + 32	3.88E + 16
11	3.71E + 28	4.76E + 15
12	1.63E + 27	1.86E + 15
13	1.04E + 25	3.72E + 13
14	5.10E + 24	2.54E + 13
15	1.67E + 24	8.06E + 12
16	4.45E + 23	5.81E + 12
17	6.92E + 21	1.44E + 12
18	1.60E + 21	4.28E + 11
19	5.56E + 20	2.95E + 10
20	8.06E + 19	1.77E + 10
21	3.79E + 19	1.30E + 10
22	2.31E + 18	1.26E + 10
23	4.00E + 17	4.81E + 09
24	1.16E + 17	2.81E + 09
25	1.37E + 16	1.61E + 09
26	9.01E + 15	1.34E + 09
27	8.51E + 14	3.82E + 08
28	3.95E + 14	2.03E + 08
29	9.24E + 13	6.85E + 07
30	5.25E + 13	6.31E + 07
31	5.19E + 13	1.18E + 07
32	4.84E + 13	7.61E + 05
33	2.21E + 13	5.89E + 05
34	1.19E + 13	5.74E + 05
35	1.11E + 13	4.91E + 05
36	3.38E + 12	2.94E + 05
37	2.54E + 12	2.58E + 05
38	7.34E + 11	2.02E + 05
39	2.74E + 11	1.96E + 05
40	1.20E + 11	1.96E + 05
41	9.50E + 09	1.86E + 05
42	7.28E + 09	1.74E + 05
43	7.25E + 09	7.77E + 04
44	4.74E + 09	4.19E + 04
45	6.66E + 08	2.73E + 04
46	4.17E + 08	2.14E + 04
47	3.52E + 08	1.76E + 04
48	2.93E + 08	1.60E + 04
49	2.51E + 08	1.08E + 04
50	9.44E + 07	9.39E + 03
51	8.11E + 07	7.03E + 03
52	6.18E + 07	4.93E + 03
53	5.02E + 07	3.72E + 03
54	4.41E + 07	3.67E + 03
55	3.89E + 07	2.43E + 03
56	2.95E + 07	2.10E + 03
57	7.57E + 06	1.68E + 03
58	5.09E + 06	1.52E + 03
59	3.11E + 06	1.23E + 03
60	3.04E + 06	1.18E + 03

(continued)

Table 16: (Continued)

No.	E-Value Estimate	Lower Bound E-Value
61	2.38E + 06	1.08E + 03
62	2.38E + 06	1.03E + 03
63	1.80E + 06	1.03E + 03
64	1.58E + 06	868.53
65	9.91E + 05	850.24
66	6.44E + 05	740.60
67	4.08E + 05	686.08
68	3.64E + 05	576.84
69	3.59E + 05	503.90
70	3.30E + 05	344.71
71	3.21E + 05	255.77
72	2.22E + 05	212.19
73	2.21E + 05	155.66
74	2.18E + 05	121.42
75	1.34E + 05	118.27
76	1.20E + 05	111.26
77	1.20E + 05	91.92
78	1.19E + 05	90.06
79	1.09E + 05	81.68
80	7.77E + 04	70.68
81	7.76E + 04	70.68
82	6.79E + 04	67.27
83	5.06E + 04	61.38
84	4.53E + 04	59.42
85	3.97E + 04	55.25
86	2.33E + 04	54.91
87	1.79E + 04	50.46
88	1.24E + 04	49.19
89	8.04E + 03	44.81
90	6.74E + 03	43.32
91	6.71E + 03	43.32
92	5.88E + 03	42.72
93	5.88E + 03	32.41
94	4.95E + 03	29.73
95	4.79E + 03	25.77
96	4.73E + 03	25.13
97	3.92E + 03	25.13
98	3.81E + 03	23.91
99	3.78E + 03	23.91
100	3.46E + 03	22.14
101	2.80E + 03	20.47
102	1.61E + 03	19.41
103	1.48E + 03	19.02
104	1.48E + 03	18.81
105	1.41E + 03	17.74
106	1.31E + 03	17.69
107	1.11E + 03	15.34
108	960.35	14.31
109	901.95	12.31
110	897.5	11.38
111	801.09	11.26
112	616.49	10.85
113	474.56	8.52
114	293.63	8.12
115	293.63	8.07
116	281.87	7.86
117	263.77	7.55
118	243.5	7.38
119	144.6	6.31
120	108.11	5.99

(continued)

Table 16: (Continued)

No.	E-Value Estimate	Lower Bound E-Value
121	66.55	5.91
122	62.87	5.44
123	62.36	5.19
124	54.68	4.83
125	52.93	4.51
126	44.48	3.89
127	36.96	3.67
128	33.67	3.62
129	33.65	3.48
130	26.76	3.06
131	25.73	2.95
132	25.49	2.76
133	24.97	2.67
134	15.34	2.56
135	13.11	2.28
136	12.51	2.10
137	9.27	2.03
138	9.24	1.99
139	6.95	1.99
140	5.64	1.98
141	5.56	1.81
142	4.92	1.71
143	4.91	1.59
144	4.06	1.58
145	3.72	1.53
146	2.49	1.44
147	2.37	1.26
148	1.54	1.24
149	1.48	1.07

For these reasons, these figures have been re-plotted at higher magnification as [Figs 24](#) and [25](#) which address the E-value estimates and the mEVs, respectively. As compared to the earlier bivariate analysis, it is now apparent that ASD, VSD, tetralogy of Fallot, severe CHD, transposition of the great vessels and mitral valve anomalies accompany CHD in the upper reaches of these plots.

The E-value list may also be listed in order of the environmental exposure to intoxicant, as shown in [Table 19](#). When the exposures are categorized into three primary exposures as daily cannabis exposure interpolated and herb and resin THC concentrations, the outcomes summarized in [Table 20](#) are seen. These values are again listed in descending order of median mEV. The value for daily use interpolated is noted to be much greater than that for the herb and cannabis resin THC concentrations.

These comparisons are formalized in [Table 21](#) where the various groups are compared for the E-value estimates and mEVs using the Wilcoxon test. In this case for both the E-value estimate and the mEV, the daily to resin and herb to resin comparisons are significant, but the comparisons between daily use interpolated and herb THC concentration are not significant ([Table 21](#)).

Main Results in Detail

At bivariate analysis the effects of tobacco and alcohol were weak or negative across all CCA's, while daily cannabis use interpolated was much stronger and more positive ([Figs 1–3](#)). While daily cannabis use was the most significant covariate on bivariate analyses ([Table 1](#)), resin and herb THC concentrations were also strongly related to CCA's ([Figs 4–6](#)).

Table 17: E-values by anomaly

No.	Regression	Anomaly	Model_Type	Term	Group	P-Value	E-Value Estimate	Lower Bound E-Value
1	Spatial	ASD	2 Lags	Daily.Interpol.	Daily	0.0215	1.54E + 139	1.07E + 21
2	Panel	ASD	Interactive	Herb	Herb	2.32E-12	3.59E + 05	1.76E + 04
3	Panel	ASD	Additive	Herb	Herb	0.0013	1.79E + 04	81.68
4	Panel	ASD	2 Lags	LM.Cannabis_x_Herb.THC	Herb	<2.2E-16	9.01E + 15	2.54E + 13
5	Panel	ASD	1 Lag	LM.Cannabis_x_Herb.THC	Herb	8.72E-15	7.28E + 09	6.31E + 07
6	Panel	ASD	4 Lags	LM.Cannabis_x_Herb.THC	Herb	0.0168	2.51E + 08	90.06
7	Panel	ASD	Additive	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Resin	0.0133	4.91	1.81
8	Spatial	ASD	1 Lag	Tobacco: Daily.Interpol.	Daily	0.0210	4.41E + 07	25.77
9	Spatial	AVSD	Additive	Herb	Herb	0.0014	5.88E + 03	43.32
10	Panel	AVSD	Interactive	LM.Cannabis_x_Resin.THC	Resin	8.05E-07	1.67E + 24	1.86E + 15
11	Panel	AVSD	1 Lag	LM.Cannabis_x_Resin.THC	Resin	0.0042	4.17E + 08	1.18E + 03
12	Panel	AVSD	Additive	Resin	Resin	4.05E-10	897.5	155.66
13	Spatial	AVSD	Additive	Resin	Resin	0.0296	33.65	1.99
14	Spatial	AVSD	Interactive	Tobacco: Resin	Resin	1.23E-05	4.06	2.56
15	Spatial	AVSD	2 Lags	Tobacco: Resin	Resin	0.0289	2.37	1.26
16	Panel	AVSD	1 Lag	Tobacco: Resin	Resin	1.11E-07	5.64	3.62
17	Panel	AVSD	Interactive	Tobacco: Resin	Resin	4.26E-07	5.56	3.48
18	Panel	AVSD	2 Lags	Tobacco: Resin	Resin	1.58E-12	1.54	1.44
19	Panel	AVSD	Interactive	Tobacco: Resin: LM.Cannabis_x_Resin.THC	Resin	0.0026	263.77	11.38
20	Panel	Cong. heart disease	1 Lag	Herb.THC	Herb	1.75E-19	8.06E + 19	3.88E + 16
21	Panel	Cong. heart disease	Interactive	Herb.THC	Herb	9.29E-10	3.95E + 14	2.95E + 10
22	Panel	Cong. heart disease	Additive	Herb.THC	Herb	1.93E-16	3.38E + 12	1.26E + 10

(continued)

Table 17: (Continued)

No.	Regression	Anomaly	Model_Type	Term	Group	P-Value	E-Value Estimate	Lower Bound E-Value
23	Panel	Cong. heart disease	2 Lags	Herb.THC	Herb	1.15E-05	6.66E + 08	1.86E + 05
24	Spatial	Cong. heart disease	Additive	Herb.THC	Herb	0.0038	1.20E + 05	70.68
25	Spatial	Cong. heart disease	Interactive	Herb.THC	Herb	0.0038	1.20E + 05	70.68
26	Spatial	Cong. heart disease	2 Lags	Herb.THC	Herb	0.0238	144.6	2.95
27	Spatial	Cong. heart disease	1 Lag	Herb.THC	Herb	0.0401	801.09	1.98
28	Panel	Cong. heart disease	2 Lags	Herb.THC:	Herb	4.14E-11	4.37E + 59	3.41E + 44
29	Panel	Cong. heart disease	Interactive	LM.Cannabis_x_Herb.THC	Herb	6.23E-03	5.19E + 13	2.14E + 04
30	Panel	Cong. heart disease	Interactive	LM.Cannabis_x_Herb.THC_x_Daily.Interpol.: LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Daily	1.91E-02	5.56E + 20	9.39E + 03
31	Panel	Double outlet right ventricle	Interactive	Herb	Herb	6.33E-05	1.34E + 05	740.60
32	Panel	Double outlet right ventricle	2 Lags	Herb: Resin	Herb	0.0138	5.10E + 24	5.89E + 05
33	Spatial	Double outlet right ventricle	2 Lags	LM.Cannabis_x_Herb.THC	Herb	9.11E-06	2.54E + 12	1.18E + 07
34	Panel	Double outlet right ventricle	2 Lags	LM.Cannabis_x_Herb.THC	Herb	0.0030	9.24E + 13	1.74E + 05
35	Spatial	Double outlet right ventricle	Interactive	LM.Cannabis_x_Herb.THC	Herb	0.0208	1.63E + 27	2.73E + 04
36	Spatial	Double outlet right ventricle	Additive	LM.Cannabis_x_Herb.THC	Herb	0.0099	7.76E + 04	25.13
37	Panel	Double outlet right ventricle	Interactive	LM.Cannabis_x_Herb.THC:	Daily	9.88E-05	2.08E + 32	7.82E + 16
38	Panel	Double outlet right ventricle	Interactive	LM.Cannabis_x_Resin.THC	Resin	0.0005	3.52E + 08	1.08E + 04
39	Panel	Double outlet right ventricle	2 Lags	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Resin	0.0052	3.92E + 03	22.14
40	Panel	Double outlet right ventricle	Interactive	Tobacco: LM.Cannabis_x_Resin.THC_x_Daily.Interpol.: LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	Daily	5.35E-12	4.53E + 04	3.72E + 03
41	Spatial	Hypoplastic right heart	2 Lags	Daily.Interpol.	Daily	5.10E-05	2.22E + 05	2.10E + 03
42	Spatial	Hypoplastic right heart	1 Lag	Daily.Interpol.	Daily	0.0079	901.95	32.41
43	Spatial	Hypoplastic right heart	2 Lags	LM.Cannabis_x_Herb.THC	Herb	0.0035	1.17E + 95	2.06E + 49
44	Spatial	Hypoplastic right heart	1 Lag	LM.Cannabis_x_Herb.THC	Herb	0.0333	5.17E + 33	1.34E + 09
45	Panel	Hypoplastic right heart	Additive	LM.Cannabis_x_Herb.THC	Herb	0.0265	5.02E + 07	17.69
46	Panel	Hypoplastic right heart	Interactive	LM.Cannabis_x_Resin.THC	Resin	0.0052	9.24	2.67
47	Spatial	Hypoplastic right heart	2 Lags	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Resin	1.09E-06	2.21E + 13	4.19E + 04
48	Spatial	Hypoplastic right heart	Interactive	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Resin	3.10E-07	1.48E + 03	118.27
49	Spatial	Hypoplastic right heart	Additive	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Resin	5.22E-06	960.35	67.27

(continued)

Table 17: (Continued)

No.	Regression	Anomaly	Model_Type	Term	Group	P-Value	E-Value Estimate	Lower Bound E-Value
50	Spatial	Hypoplastic right heart	1 Lag	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Resin	0.0003	6.18E + 07	7.55
51	Panel	Hypoplastic right heart	Additive	Resin	Resin	0.0050	1.11E + 03	14.31
52	Panel	Hypoplastic right heart	1 Lag	Resin	Resin	5.65E-05	25.73	7.38
53	Panel	Hypoplastic right heart	2 Lags	Resin	Resin	0.0009	25.49	5.44
54	Panel	Mitral valve anomalies	Additive	Daily.Interpol.	Daily	6.06E-10	6.92E + 21	4.76E + 15
55	Panel	Mitral valve anomalies	Interactive	Daily.Interpol.	Daily	7.46E-09	2.31E + 18	5.81E + 12
56	Panel	Mitral valve anomalies	2 Lags	Herb	Herb	0.0155	8.04E + 03	10.85
57	Panel	Mitral valve anomalies	Interactive	LM.Cannabis_x_Herb.THC	Herb	0.0189	6.44E + 05	19.02
58	Spatial	Mitral valve anomalies	1 Lag	LM.Cannabis_x_Herb.THC: LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Daily	0.0038	3.71E + 28	2.81E + 09
59	Spatial	Mitral valve anomalies	2 Lags	LM.Cannabis_x_Herb.THC: LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Daily	0.0115	5.36E + 35	2.03E + 08
60	Spatial	Mitral valve anomalies	Interactive	Tobacco: Daily.Interpol.	Daily	2.17E-07	9.91E + 05	7.03E + 03
61	Spatial	Mitral valve anomalies	1 Lag	Tobacco: Daily.Interpol.	Daily	4.14E-06	1.58E + 06	4.93E + 03
62	Spatial	Mitral valve anomalies	2 Lags	Tobacco: Daily.Interpol.	Daily	0.0038	3.97E + 04	49.19
63	Panel	Mitral valve anomalies	1 Lag	Tobacco: Daily.Interpol.	Daily	1.27E-13	9.27	6.31
64	Panel	PDA	Additive	Daily.Interpol.	Daily	4.3E-09	5.07E + 49	3.15E + 34
65	Panel	PDA	1 Lag	LM.Cannabis_x_Herb.THC	Herb	7.29E-14	8.51E + 14	4.28E + 11
66	Panel	PDA	2 Lags	LM.Cannabis_x_Herb.THC	Herb	2.33E-07	7.34E + 11	6.85E + 07
67	Panel	PDA	Interactive	LM.Cannabis_x_Herb.THC	Herb	3.27E-05	3.64E + 05	1.52E + 03
68	Spatial	PDA	2 Lags	LM.Cannabis_x_Herb.THC	Herb	0.0107	66.55	8.12
69	Panel	PDA	Additive	LM.Cannabis_x_Herb.THC	Herb	0.0158	2.80E + 03	8.07
70	Spatial	PDA	1 Lag	LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	Daily	0.0026	1.37E + 16	3.82E + 08
71	Spatial	PDA	Interactive	LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	Daily	2.50E-05	3.21E + 05	1.23E + 03
72	Spatial	PDA	Additive	LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	Daily	0.0011	4.73E + 03	44.81
73	Panel	PDA	Interactive	LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	Daily	0.0449	1.48	1.07
74	Spatial	PDA	1 Lag	Tobacco: Daily.Interpol.	Daily	4.13E-05	1.11E + 13	5.74E + 05
75	Spatial	PDA	Interactive	Tobacco: Daily.Interpol.	Daily	0.0015	5.09E + 06	576.84
76	Spatial	PDA	2 Lags	Tobacco: Daily.Interpol.	Daily	0.0008	7.25E + 09	344.71
77	Panel	PDA	1 Lag	Tobacco: Daily.Interpol.	Daily	1.39E-08	2.93E + 08	7.61E + 05
78	Panel	PDA	2 Lags	Tobacco: Daily.Interpol.	Daily	0.0042	3.30E + 05	111.26
79	Panel	PDA	Interactive	Tobacco: Daily.Interpol.	Daily	8.61E-10	243.5	59.42
80	Spatial	Severe cong. heart disease	Interactive	Herb	Herb	1.05E-10	1.19E + 13	1.61E + 09
81	Spatial	Severe Cong. heart disease	Additive	Herb	Herb	8.22E-07	8.11E + 07	7.77E + 04
82	Spatial	Severe cong. heart disease	1 Lag	Herb	Herb	0.0391	1.20E + 11	3.67E + 03
83	Spatial	Severe cong. heart disease	2 Lags	Herb	Herb	0.0221	6.71E + 03	5.99
84	Panel	Severe cong. heart disease	Interactive	Herb.THC	Herb	1.31E-05	3.89E + 07	2.94E + 05

(continued)

Table 17: (Continued)

No.	Regression	Anomaly	Model_Type	Term	Group	P-Value	E-Value Estimate	Lower Bound E-Value
85	Panel	Severe cong. heart disease	1 Lag	Herb.THC	Herb	0.0078	6.74E + 03	18.81
86	Panel	Severe cong. heart disease	2 Lags	Herb.THC	Herb	4.41E-02	3.46E + 03	2.10
87	Spatial	Severe cong. heart disease	Interactive	LM.Cannabis_x_Resin.THC	Resin	2.35E-05	2.21E + 05	1.03E + 03
88	Spatial	Severe cong. heart disease	Additive	LM.Cannabis_x_Resin.THC	Resin	0.0002	281.87	20.47
89	Spatial	Severe cong. heart disease	1 Lag	LM.Cannabis_x_Resin.THC: LM.Cannabis_x_Herb.THC_x_ Daily.Interpol.	Resin	0.0050	2.18E + 05	3.06
90	Spatial	Severe cong. heart disease	2 Lags	LM.Cannabis_x_Resin.THC_x_ Daily.Interpol.	Resin	0.0026	2.74E + 11	1.60E + 04
91	Panel	Severe cong. heart disease	Additive	LM.Herb.Daily.Intpltd	Daily	4.74E-02	5.25E + 13	3.67
92	Panel	Severe cong. heart disease	Additive	LM.Herb.THC	Herb	1.48E-03	7.57E + 06	850.24
93	Panel	Severe cong. heart disease	Additive	LM.Herb.THC.Daily.Interpol	Herb	4.43E-02	4.92E + 00	1.24
94	Panel	Severe cong. heart disease	Interactive	LM.Resin	Resin	9.62E-07	2.33E + 04	686.08
95	Panel	Severe cong. heart disease	2 Lags	LM.Resin	Resin	7.23E-06	1.31E + 03	91.92
96	Panel	Severe cong. heart disease	1 Lag	LM.Resin	Resin	0.0003	616.49	29.73
97	Panel	Severe cong. heart disease	Interactive	LM.Resin.Daily.Interpol	Daily	4.20E-11	4.84E + 13	1.30E + 10
98	Panel	Severe cong. heart disease	Interactive	LM.Resin.Daily.Interpol: LM.Herb.THC.Daily.Interpol	Daily	1.22E-13	108.11	42.72
99	Panel	Severe cong. heart disease	2 Lags	LM.Resin.Daily.Interpol: LM.Resin	Daily	4.42E-02	4.08E + 05	2.76
100	Panel	Severe cong. heart disease	1 Lag	LM.Resin: LM.Herb.THC.Daily.Interpol	Daily	0.0005	1.80E + 06	1.03E + 03
101	Panel	Severe cong. heart disease	Interactive	Tobacco: LM.Herb.THC.Daily.Interpol	Daily	3.85E-08	2.49	2.03
102	Panel	Tetralogy of Fallot	Interactive	Daily.Interpol.	Daily	2.1E-09	1.10E + 307	4.28E + 135
103	Panel	Tetralogy of Fallot	Additive	Daily.Interpol.	Daily	5.96E-09	3.79E + 19	3.72E + 13
104	Spatial	Tetralogy of Fallot	Additive	Herb	Herb	0.0033	2.95E + 07	503.90
105	Panel	Tetralogy of Fallot	2 Lags	LM.Cannabis_x_Herb.THC	Herb	3.86E-08	1.04E + 25	1.04E + 17
106	Panel	Tetralogy of Fallot	Interactive	LM.Cannabis_x_Herb.THC	Herb	0.0159	1.19E + 05	17.74
107	Panel	Tetralogy of Fallot	1 Lag	LM.Cannabis_x_Herb.THC: LM.Cannabis_x_Resin.THC_x_ Daily.Interpol.	Daily	2.59E-10	1.24E + 04	1.08E + 03
108	Panel	Tetralogy of Fallot	Interactive	LM.Cannabis_x_Herb.THC_x_ Daily.Interpol.	Daily	4.68E-07	36.96	12.31
109	Panel	Tetralogy of Fallot	2 Lags	LM.Cannabis_x_Resin.THC_x_ Daily.Interpol.	Resin	4.36E-16	3.78E + 03	868.53
110	Panel	Tetralogy of Fallot	2 Lags	Resin	Resin	0.0460	474.56	1.71
111	Spatial	Tetralogy of Fallot	1 Lag	Tobacco: Herb	Herb	5.26E-05	13.11	4.83
112	Spatial	Tetralogy of Fallot	2 Lags	Tobacco: LM.Cannabis_x_Herb.THC	Herb	1.07E-06	62.87	15.34
113	Spatial	Tetralogy of Fallot	Interactive	Tobacco: Resin	Resin	1.44E-05	26.76	7.86
114	Panel	Transposition great vessels	1 Lag	Herb	Herb	<2.2E-16	3.11E + 06	2.02E + 05

(continued)

Table 17: (Continued)

No.	Regression	Anomaly	Model_Type	Term	Group	P-Value	E-Value Estimate	Lower Bound E-Value
115	Panel	Transposition great vessels	2 Lags	Herb	Herb	0.0056	4.74E + 09	1.68E + 03
116	Panel	Transposition great vessels	Interactive	Herb	Herb	0.0013	5.06E + 04	121.42
117	Spatial	Transposition great vessels	Interactive	Herb	Herb	0.0005	4.95E + 03	61.38
118	Panel	Transposition great vessels	Additive	Herb	Herb	0.0003	9.44E + 07	8.52
119	Spatial	Transposition great vessels	Additive	LM.Cannabis_x_Herb.THC	Herb	0.0099	7.77E + 04	25.13
120	Panel	Transposition great vessels	Additive	LM.Cannabis_x_Resin.THC	Resin	0.0002	1.61E + 03	50.46
121	Panel	Transposition great vessels	2 Lags	LM.Cannabis_x_Resin.THC	Resin	0.0034	1.41E + 03	19.41
122	Spatial	Transposition great vessels	2 Lags	LM.Cannabis_x_Resin.THC	Resin	0.0001	12.51	4.51
123	Panel	Transposition great vessels	Interactive	LM.Cannabis_x_Resin.THC: Resin	Resin	8.46E-05	7.77E + 39	7.81E + 20
124	Panel	Transposition great vessels	2 Lags	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Resin	0.0437	54.68	1.59
125	Spatial	Transposition great vessels	1 Lag	Resin	Resin	0.0370	15.34	1.53
126	Panel	Transposition great vessels	Interactive	Tobacco: Resin	Resin	0.0002	3.72	2.28
127	Panel	Vascular disruptions	1 Lag	LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	Daily	6.72E-04	1.09E + 05	255.77
128	Panel	Vascular disruptions	2 Lags	LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	Daily	1.76E-04	1.48E + 03	55.25
129	Panel	Vascular disruptions	Interactive	LM.Cannabis_x_Herb.THC_x_Daily.Interpol.: LM.Cannabis_x_Resin.THC_x_Daily.Interpol.: Resin	Daily	1.27E-05	4.00E + 17	1.77E + 10
130	Panel	Vascular disruptions	1 Lag	LM.Cannabis_x_Resin.THC	Resin	9.61E-04	4.79E + 03	54.91
131	Panel	Vascular disruptions	Interactive	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Resin	1.56E-06	3.81E + 03	212.19
132	Spatial	Vascular disruptions	Additive	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Resin	8.77E-05	293.63	23.91
133	Spatial	Vascular disruptions	Interactive	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Resin	8.77E-05	293.63	23.91
134	Panel	Vascular disruptions	Additive	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Resin	4.85E-05	52.93	11.26
135	Spatial	Vascular disruptions	2 Lags	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Resin	0.0008	24.97	5.19
136	Spatial	Vascular disruptions	1 Lag	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Resin	0.0284	6.95	1.58
137	Panel	Vascular disruptions	2 Lags	Resin	Resin	3.50E-08	6.79E + 04	2.43E + 03
138	Panel	Vascular disruptions	Interactive	Resin	Resin	0.0038	62.36	5.91
139	Panel	Vascular disruptions	Additive	Resin	Resin	9.68E-03	44.48	3.89
140	Spatial	VSD	2 Lags	Daily.Interpol.	Daily	0.0137	3.41E + 57	1.44E + 12
141	Spatial	VSD	Additive	Herb	Herb	0.0014	33.67	1.99
142	Panel	VSD	2 Lags	LM.Cannabis_x_Herb.THC	Herb	2.7E-14	1.60E + 21	4.97E + 16
143	Spatial	VSD	2 Lags	LM.Cannabis_x_Herb.THC	Herb	2.15E-05	4.45E + 23	8.06E + 12
144	Spatial	VSD	Interactive	LM.Cannabis_x_Herb.THC	Herb	8.94E-06	1.16E + 17	4.81E + 09
145	Spatial	VSD	1 Lag	LM.Cannabis_x_Herb.THC	Herb	0.0003	9.50E + 09	4.91E + 05
146	Panel	VSD	1 Lag	LM.Cannabis_x_Herb.THC	Herb	<2.2E-16	3.04E + 06	2.58E + 05
147	Panel	VSD	Additive	LM.Cannabis_x_Herb.THC	Herb	<2.2E-16	2.38E + 06	1.96E + 05
148	Panel	VSD	Interactive	LM.Cannabis_x_Herb.THC	Herb	<2.2E-16	2.38E + 06	1.96E + 05
149	Spatial	VSD	Additive	Resin	Resin	0.0296	5.88E + 03	43.32

Table 18: Summary of E-values by anomaly

Anomaly	Number	Mean mEV	Median mEV	Minimum mEV	Maximum mEV	Mean E-Value Estimate	Median E-Value Estimate	mEV Estimate	Maximum E-Value Estimate
VSD	10	4.97E + 15	374 500.00	1.99	4.97E + 16	3.41E + 56	4.75E + 09	33.67	3.41E + 57
Cong. heart disease	11	3.10E + 43	21 400.00	1.98	3.41E + 44	3.97E + 58	3.38E + 12	144.6	4.37E + 59
Double outlet right ventricle	10	7.82E + 15	19 050.00	22.14	7.82E + 16	2.08E + 31	1.27E + 12	3920	2.08E + 32
ASD	8	1.34E + 20	8845.03	1.81	1.07E + 21	1.93E + 138	1.48E + 08	4.91	1.54E + 139
Mitral valve anomalies	10	4.77E + 14	5980.00	6.31	4.76E + 15	5.36E + 34	1 285 500	9.27	5.36E + 35
PDA	16	1.97E + 33	903.42	1.07	3.15E + 34	3.17E + 48	2 727 000	1.48	5.07E + 49
Tetralogy of Fallot	12	3.57E + 134	260.82	1.71	4.28E + 135	9.17E + 305	8090	13.11	1.10E + 307
Severe cong. heart disease	22	6.64E + 08	67.32	1.24	1.30E + 10	5.15E + 12	219 500	2.49	5.25E + 13
Hypoplastic right heart	13	1.58E + 48	32.41	2.67	2.06E + 49	9.00E + 93	1480	9.24	1.17E + 95
Transposition great vessels	13	6.01E + 19	25.13	1.53	7.81E + 20	5.98E + 38	4950	3.72	7.77E + 39
Vascular disruptions	13	1.36E + 09	23.91	1.58	1.77E + 10	3.08E + 16	293.63	6.95	4.00E + 17
AVSD	11	1.69E + 14	3.62	1.26	1.86E + 15	1.52E + 23	33.65	1.54	1.67E + 24

On bivariate map plots it was clear that CHD and severe CHD plotted against cannabis herb concentrations was rising simultaneously in countries with increasing cannabis use, such as Spain, France, Belgium, Netherlands, Croatia, Norway, Italy, Germany & Bulgaria indicated by all turning pink/purple (Figs 16–17). Trends for AVSD plotted against resin THC concentration were also moving together in Germany, France, Bulgaria, Norway, Netherlands all turned (Fig. 19). Trends for transposition of the great vessels plotted against cannabis resin THC concentration were moving together in Norway, Belgium, Italy, Spain, France, Bulgaria indicated by all turning pink/purple (Fig. 20).

Countries with rising daily cannabis use had in general higher CAR's over time than those without (time: status interaction: β -Est. = 0.0267, t = 2.7563, P = 0.0059; Fig. 21).

At inverse probability weighted panel regression cannabis terms were positive and significant for CHD, severe CHD, ASD, VSD, AVSD, PDA, tetralogy of Fallot, vascular disruptions, double outlet right ventricle, transposition of the great vessels, hypoplastic right heart and mitral valve anomalies from: 1.75×10^{-19} , 4.20×10^{-11} , $< 2.2 \times 10^{-16}$, $< 2.2 \times 10^{-16}$, 1.58×10^{-12} , 4.30×10^{-9} , 4.36×10^{-16} , 3.50×10^{-8} , 5.35×10^{-12} , $< 2.2 \times 10^{-16}$, 5.65×10^{-5} , 6.06×10^{-10} (Supplementary Tables S17–S28).

At spatial regression terms including cannabis were positive and significant for this same list of anomalies from: 0.0038, 1.05×10^{-10} , 0.0215, 8.94×10^{-6} , 1.23×10^{-5} , 2.05×10^{-5} , 1.07×10^{-6} , 8.77×10^{-5} , 9.11×10^{-6} , 0.0001, 3.10×10^{-7} , 2.17×10^{-7} (Tables 2–13).

92.6% and 75.2% of 149 E-value estimates and mEVs exceeded nine and 100.0% and 98.7% exceeded 1.25 (Table 16).

The order of relationship to cannabis judged by median mEV's was VSD > CHD > double outlet right ventricle > ASD > mitral valve abnormalities > PDA > tetralogy of Fallot > severe CHD > hypoplastic right heart syndrome > transposition great vessels > vascular disruptions > AVSD (Table 18).

The order of covariates judged by the median mEV was daily cannabis use interpolated > herb THC concentration > resin THC concentration (Table 20).

A detailed categorical quintile analysis of this data was presented previously [9]. The reader who is interested in precise

results from such analyses including risk ratios, attributable fractions in the exposed and population attributable fractions is cordially invited to peruse this important resource.

We note that in the present study were tobacco and alcohol use were unrelated or were negatively related to CAR's. This findings is at variance with other results such as those previously reported from North America [8, 74]. Such differing results will require further research.

Mechanisms Genotoxicity

Cannabinoids have been note to induce genotoxicity my many routes including severe morphological damage to sperm [75, 76], inducing high rates of failed oocyte division [77], induction of single- and double- stranded DNA breaks [78–80], formation of end-to-end chromosomal fusions and translocations [76, 81, 82], involvement in testicular cancer where whole genome doubling or quadrupling are known oncogenic events [81], disruption of telomerase [12, 83], interference with key epigenotoxic machinery (KMT2A [84]), induction of DNA bridges [77, 85, 86], alterations of DNA methylation which are heritable for the following generations [12, 84, 87–94], failure of histone-protamine substitution in sperm [95], and also alterations of histone proteins including acetylated- and phosphorylated- histones [96–99] which have also been shown to be heritable [99].

Epigenomics

Interpretation of current CCA cannabis related findings is assisted by comparing the list of genes in the core cardiogenic complex to those identified in the recently published whole genome epigenomic screen of cannabis dependence and withdrawal [12]. When this is done there are four hits identified for MEF2, 249 hits for NKX2, 127 hits for GATA and 15 hits for Tbx. No hits could be identified for Hand –1 or –2. In considering the list of genes identified as crucial in vasculogenesis there were five hits for VEGF, 6 for notch and 427 for Eph (and none for the Ephrins or COUP-TFII).

Table 19: E-values by the major covariate group

No.	Regression	Anomaly	Model_Type	Term	Group	P-Value	E-Value Estimate	Lower Bound E-Value
1	Spatial	ASD	2 Lags	Daily.Interpol.	Daily	0.0215	1.54E + 139	1.07E + 21
2	Panel	ASD	Interactive	Herb	Herb	2.32E-12	3.59E + 05	1.76E + 04
3	Panel	ASD	Additive	Herb	Herb	0.0013	1.79E + 04	81.68
4	Panel	ASD	2 Lags	LM.Cannabis_x_Herb.THC	Herb	<2.2E-16	9.01E + 15	2.54E + 13
5	Panel	ASD	1 Lag	LM.Cannabis_x_Herb.THC	Herb	8.72E-15	7.28E + 09	6.31E + 07
6	Panel	ASD	4 Lags	LM.Cannabis_x_Herb.THC	Herb	0.0168	2.51E + 08	90.06
7	Panel	ASD	Additive	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Resin	0.0133	4.91	1.81
8	Spatial	ASD	1 Lag	Tobacco: Daily.Interpol.	Daily	0.0210	4.41E + 07	25.77
9	Spatial	AVSD	Additive	Herb	Herb	0.0014	5.88E + 03	43.32
10	Panel	AVSD	Interactive	LM.Cannabis_x_Resin.THC	Resin	8.05E-07	1.67E + 24	1.86E + 15
11	Panel	AVSD	1 Lag	LM.Cannabis_x_Resin.THC	Resin	0.0042	4.17E + 08	1.18E + 03
12	Panel	AVSD	Additive	Resin	Resin	4.05E-10	897.5	155.66
13	Spatial	AVSD	Additive	Resin	Resin	0.0296	33.65	1.99
14	Spatial	AVSD	Interactive	Tobacco: Resin	Resin	1.23E-05	4.06	2.56
15	Spatial	AVSD	2 Lags	Tobacco: Resin	Resin	0.0289	2.37	1.26
16	Panel	AVSD	1 Lag	Tobacco: Resin	Resin	1.11E-07	5.64	3.62
17	Panel	AVSD	Interactive	Tobacco: Resin	Resin	4.26E-07	5.56	3.48
18	Panel	AVSD	2 Lags	Tobacco: Resin	Resin	1.58E-12	1.54	1.44
19	Panel	AVSD	Interactive	Tobacco: Resin: LM.Cannabis_x_Resin.THC	Resin	0.0026	263.77	11.38
20	Panel	Cong. heart disease	1 Lag	Herb.THC	Herb	1.75E-19	8.06E + 19	3.88E + 16
21	Panel	Cong. heart disease	Interactive	Herb.THC	Herb	9.29E-10	3.95E + 14	2.95E + 10
22	Panel	Cong. heart disease	Additive	Herb.THC	Herb	1.93E-16	3.38E + 12	1.26E + 10
23	Panel	Cong. heart disease	2 Lags	Herb.THC	Herb	1.15E-05	6.66E + 08	1.86E + 05
24	Spatial	Cong. heart disease	Additive	Herb.THC	Herb	0.0038	1.20E + 05	70.68
25	Spatial	Cong. heart disease	Interactive	Herb.THC	Herb	0.0038	1.20E + 05	70.68
26	Spatial	Cong. heart disease	2 Lags	Herb.THC	Herb	0.0238	144.6	2.95
27	Spatial	Cong. heart disease	1 Lag	Herb.THC	Herb	0.0401	801.09	1.98
28	Panel	Cong. heart disease	2 Lags	Herb.THC: LM.Cannabis_x_Herb.THC	Herb	4.14E-11	4.37E + 59	3.41E + 44
29	Panel	Cong. heart disease	Interactive	LM.Cannabis_x_Herb.THC	Herb	6.23E-03	5.19E + 13	2.14E + 04
30	Panel	Cong. heart disease	Interactive	LM.Cannabis_x_Herb.THC_x_Daily.Interpol.: LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Daily	1.91E-02	5.56E + 20	9.39E + 03
31	Panel	Double outlet right ventricle	Interactive	Herb	Herb	6.33E-05	1.34E + 05	740.60
32	Panel	Double outlet right ventricle	2 Lags	Herb: Resin	Herb	0.0138	5.10E + 24	5.89E + 05
33	Spatial	Double outlet right ventricle	2 Lags	LM.Cannabis_x_Herb.THC	Herb	9.11E-06	2.54E + 12	1.18E + 07
34	Panel	Double outlet right ventricle	2 Lags	LM.Cannabis_x_Herb.THC	Herb	0.0030	9.24E + 13	1.74E + 05
35	Spatial	Double outlet right ventricle	Interactive	LM.Cannabis_x_Herb.THC	Herb	0.0208	1.63E + 27	2.73E + 04
36	Spatial	Double outlet right ventricle	Additive	LM.Cannabis_x_Herb.THC	Herb	0.0099	7.76E + 04	25.13
37	Panel	Double outlet right ventricle	Interactive	LM.Cannabis_x_Herb.THC: LM.Cannabis_x_Resin.THC	Daily	9.88E-05	2.08E + 32	7.82E + 16
38	Panel	Double outlet right ventricle	Interactive	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Resin	0.0005	3.52E + 08	1.08E + 04
39	Panel	Double outlet right ventricle	2 Lags	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Resin	0.0052	3.92E + 03	22.14
40	Panel	Double outlet right ventricle	Interactive	Tobacco: LM.Cannabis_x_Resin.THC_x_Daily.Interpol.: LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	Daily	5.35E-12	4.53E + 04	3.72E + 03
41	Spatial	Hypoplastic right heart	2 Lags	Daily.Interpol.	Daily	5.10E-05	2.22E + 05	2.10E + 03
42	Spatial	Hypoplastic right heart	1 Lag	Daily.Interpol.	Daily	0.0079	901.95	32.41
43	Spatial	Hypoplastic right heart	2 Lags	LM.Cannabis_x_Herb.THC	Herb	0.0035	1.17E + 95	2.06E + 49
44	Spatial	Hypoplastic right heart	1 Lag	LM.Cannabis_x_Herb.THC	Herb	0.0333	5.17E + 33	1.34E + 09
45	Panel	Hypoplastic right heart	Additive	LM.Cannabis_x_Herb.THC	Herb	0.0265	5.02E + 07	17.69
46	Panel	Hypoplastic right heart	Interactive	LM.Cannabis_x_Resin.THC	Resin	0.0052	9.24	2.67
47	Spatial	Hypoplastic right heart	2 Lags	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Resin	1.09E-06	2.21E + 13	4.19E + 04
48	Spatial	Hypoplastic right heart	Interactive	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Resin	3.10E-07	1.48E + 03	118.27

(continued)

Table 19: (Continued)

No.	Regression	Anomaly	Model_Type	Term	Group	P-Value	E-Value Estimate	Lower Bound E-Value
49	Spatial	Hypoplastic right heart	Additive	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Resin	5.22E-06	960.35	67.27
50	Spatial	Hypoplastic right heart	1 Lag	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Resin	0.0003	6.18E + 07	7.55
51	Panel	Hypoplastic right heart	Additive	Resin	Resin	0.0050	1.11E + 03	14.31
52	Panel	Hypoplastic right heart	1 Lag	Resin	Resin	5.65E-05	25.73	7.38
53	Panel	Hypoplastic right heart	2 Lags	Resin	Resin	0.0009	25.49	5.44
54	Panel	Mitral valve anomalies	Additive	Daily.Interpol.	Daily	6.06E-10	6.92E + 21	4.76E + 15
55	Panel	Mitral valve anomalies	Interactive	Daily.Interpol.	Daily	7.46E-09	2.31E + 18	5.81E + 12
56	Panel	Mitral valve anomalies	2 Lags	Herb	Herb	0.0155	8.04E + 03	10.85
57	Panel	Mitral valve anomalies	Interactive	LM.Cannabis_x_Herb.THC	Herb	0.0189	6.44E + 05	19.02
58	Spatial	Mitral valve anomalies	1 Lag	LM.Cannabis_x_Herb.THC: LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Daily	0.0038	3.71E + 28	2.81E + 09
59	Spatial	Mitral valve anomalies	2 Lags	LM.Cannabis_x_Herb.THC: LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Daily	0.0115	5.36E + 35	2.03E + 08
60	Spatial	Mitral valve anomalies	Interactive	Tobacco: Daily.Interpol.	Daily	2.17E-07	9.91E + 05	7.03E + 03
61	Spatial	Mitral valve anomalies	1 Lag	Tobacco: Daily.Interpol.	Daily	4.14E-06	1.58E + 06	4.93E + 03
62	Spatial	Mitral valve anomalies	2 Lags	Tobacco: Daily.Interpol.	Daily	0.0038	3.97E + 04	49.19
63	Panel	Mitral valve anomalies	1 Lag	Tobacco: Daily.Interpol.	Daily	1.27E-13	9.27	6.31
64	Panel	PDA	Additive	Daily.Interpol.	Daily	4.3E-09	5.07E + 49	3.15E + 34
65	Panel	PDA	1 Lag	LM.Cannabis_x_Herb.THC	Herb	7.29E-14	8.51E + 14	4.28E + 11
66	Panel	PDA	2 Lags	LM.Cannabis_x_Herb.THC	Herb	2.33E-07	7.34E + 11	6.85E + 07
67	Panel	PDA	Interactive	LM.Cannabis_x_Herb.THC	Herb	3.27E-05	3.64E + 05	1.52E + 03
68	Spatial	PDA	2 Lags	LM.Cannabis_x_Herb.THC	Herb	0.0107	66.55	8.12
69	Panel	PDA	Additive	LM.Cannabis_x_Herb.THC	Herb	0.0158	2.80E + 03	8.07
70	Spatial	PDA	1 Lag	LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	Daily	0.0026	1.37E + 16	3.82E + 08
71	Spatial	PDA	Interactive	LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	Daily	2.50E-05	3.21E + 05	1.23E + 03
72	Spatial	PDA	Additive	LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	Daily	0.0011	4.73E + 03	44.81
73	Panel	PDA	Interactive	LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	Daily	0.0449	1.48	1.07
74	Spatial	PDA	1 Lag	Tobacco: Daily.Interpol.	Daily	4.13E-05	1.11E + 13	5.74E + 05
75	Spatial	PDA	Interactive	Tobacco: Daily.Interpol.	Daily	0.0015	5.09E + 06	576.84
76	Spatial	PDA	2 Lags	Tobacco: Daily.Interpol.	Daily	0.0008	7.25E + 09	344.71
77	Panel	PDA	1 Lag	Tobacco: Daily.Interpol.	Daily	1.39E-08	2.93E + 08	7.61E + 05
78	Panel	PDA	2 Lags	Tobacco: Daily.Interpol.	Daily	0.0042	3.30E + 05	111.26
79	Panel	PDA	Interactive	Tobacco: Daily.Interpol.	Daily	8.61E-10	243.5	59.42
80	Spatial	Severe cong. heart disease	Interactive	Herb	Herb	1.05E-10	1.19E + 13	1.61E + 09
81	Spatial	Severe cong. heart disease	Additive	Herb	Herb	8.22E-07	8.11E + 07	7.77E + 04
82	Spatial	Severe cong. heart disease	1 Lag	Herb	Herb	0.0391	1.20E + 11	3.67E + 03
83	Spatial	Severe cong. heart disease	2 Lags	Herb	Herb	0.0221	6.71E + 03	5.99
84	Panel	Severe cong. heart disease	Interactive	Herb.THC	Herb	1.31E-05	3.89E + 07	2.94E + 05
85	Panel	Severe cong. heart disease	1 Lag	Herb.THC	Herb	0.0078	6.74E + 03	18.81
86	Panel	Severe cong. heart disease	2 Lags	Herb.THC	Herb	4.41E-02	3.46E + 03	2.10
87	Spatial	Severe cong. heart disease	Interactive	LM.Cannabis_x_Resin.THC	Resin	2.35E-05	2.21E + 05	1.03E + 03
88	Spatial	Severe cong. heart disease	Additive	LM.Cannabis_x_Resin.THC	Resin	0.0002	281.87	20.47
89	Spatial	Severe cong. heart disease	1 Lag	LM.Cannabis_x_Resin.THC: LM.Cannabis_x_Herb.THC_x_Daily.Interpol.	Resin	0.0050	2.18E + 05	3.06
90	Spatial	Severe cong. heart disease	2 Lags	LM.Cannabis_x_Resin.THC_x_Daily.Interpol.	Resin	0.0026	2.74E + 11	1.60E + 04
91	Panel	Severe cong. heart disease	Additive	LM.Herb.Daily.Intpltd	Daily	4.74E-02	5.25E + 13	3.67
92	Panel	Severe cong. heart disease	Additive	LM.Herb.THC	Herb	1.48E-03	7.57E + 06	850.24
93	Panel	Severe cong. heart disease	Additive	LM.Herb.THC.Daily.Interpol	Herb	4.43E-02	4.92E + 00	1.24
94	Panel	Severe cong. heart disease	Interactive	LM.Resin	Resin	9.62E-07	2.33E + 04	686.08
95	Panel	Severe cong. heart disease	2 Lags	LM.Resin	Resin	7.23E-06	1.31E + 03	91.92
96	Panel	Severe cong. heart disease	1 Lag	LM.Resin	Resin	0.0003	616.49	29.73
97	Panel	Severe cong. heart disease	Interactive	LM.Resin.Daily.Interpol	Daily	4.20E-11	4.84E + 13	1.30E + 10
98	Panel	Severe cong. heart disease	Interactive	LM.Resin.Daily.Interpol: LM.Herb.THC.Daily.Interpol	Daily	1.22E-13	108.11	42.72

(continued)

Table 19: (Continued)

No.	Regression	Anomaly	Model_Type	Term	Group	P-Value	E-Value Estimate	Lower Bound E-Value
99	Panel	Severe cong. heart disease	2 Lags	LM.Resin.Daily.Interpol:	Daily	4.42E-02	4.08E + 05	2.76
				LM.Resin				
100	Panel	Severe cong. heart disease	1 Lag	LM.Resin:	Daily	0.0005	1.80E + 06	1.03E + 03
				LM.Herb.THC.Daily.Interpol				
101	Panel	Severe cong. heart disease	Interactive	Tobacco:	Daily	3.85E-08	2.49	2.03
				LM.Herb.THC.Daily.Interpol				
102	Panel	Tetralogy of Fallot	Interactive	Daily.Interpol.	Daily	2.1E-09	1.10E + 307	4.28E + 135
103	Panel	Tetralogy of Fallot	Additive	Daily.Interpol.	Daily	5.96E-09	3.79E + 19	3.72E + 13
104	Spatial	Tetralogy of Fallot	Additive	Herb	Herb	0.0033	2.95E + 07	503.90
105	Panel	Tetralogy of Fallot	2 Lags	LM.Cannabis_x_Herb.THC	Herb	3.86E-08	1.04E + 25	1.04E + 17
106	Panel	Tetralogy of Fallot	Interactive	LM.Cannabis_x_Herb.THC	Herb	0.0159	1.19E + 05	17.74
107	Panel	Tetralogy of Fallot	1 Lag	LM.Cannabis_x_Herb.THC:	Daily	2.59E-10	1.24E + 04	1.08E + 03
				LM.Cannabis_x_Resin.THC_x_				
				Daily.Interpol.				
108	Panel	Tetralogy of Fallot	Interactive	LM.Cannabis_x_Herb.THC_x_	Daily	4.68E-07	36.96	12.31
				Daily.Interpol.				
109	Panel	Tetralogy of Fallot	2 Lags	LM.Cannabis_x_Resin.THC_x_	Resin	4.36E-16	3.78E + 03	868.53
				Daily.Interpol.				
110	Panel	Tetralogy of Fallot	2 Lags	Resin	Resin	0.0460	474.56	1.71
111	Spatial	Tetralogy of Fallot	1 Lag	Tobacco: Herb	Herb	5.26E-05	13.11	4.83
112	Spatial	Tetralogy of Fallot	2 Lags	Tobacco:	Herb	1.07E-06	62.87	15.34
				LM.Cannabis_x_Herb.THC				
113	Spatial	Tetralogy of Fallot	Interactive	Tobacco: Resin	Resin	1.44E-05	26.76	7.86
114	Panel	Transposition great vessels	1 Lag	Herb	Herb	<2.2E-16	3.11E + 06	2.02E + 05
115	Panel	Transposition great vessels	2 Lags	Herb	Herb	0.0056	4.74E + 09	1.68E + 03
116	Panel	Transposition great vessels	Interactive	Herb	Herb	0.0013	5.06E + 04	121.42
117	Spatial	Transposition great vessels	Interactive	Herb	Herb	0.0005	4.95E + 03	61.38
118	Panel	Transposition great vessels	Additive	Herb	Herb	0.0003	9.44E + 07	8.52
119	Spatial	Transposition great vessels	Additive	LM.Cannabis_x_Herb.THC	Herb	0.0099	7.77E + 04	25.13
120	Panel	Transposition great vessels	Additive	LM.Cannabis_x_Resin.THC	Resin	0.0002	1.61E + 03	50.46
121	Panel	Transposition great vessels	2 Lags	LM.Cannabis_x_Resin.THC	Resin	0.0034	1.41E + 03	19.41
122	Spatial	Transposition great vessels	2 Lags	LM.Cannabis_x_Resin.THC	Resin	0.0001	12.51	4.51
123	Panel	Transposition Great Vessels	Interactive	LM.Cannabis_x_Resin.THC:	Resin	8.46E-05	7.77E + 39	7.81E + 20
				Resin				
124	Panel	Transposition great vessels	2 Lags	LM.Cannabis_x_Resin.THC_x_	Resin	0.0437	54.68	1.59
				Daily.Interpol.				
125	Spatial	Transposition great vessels	1 Lag	Resin	Resin	0.0370	15.34	1.53
126	Panel	Transposition great vessels	Interactive	Tobacco: Resin	Resin	0.0002	3.72	2.28
127	Panel	Vascular disruptions	1 Lag	LM.Cannabis_x_Herb.THC_x_	Daily	6.72E-04	1.09E + 05	255.77
				Daily.Interpol.				
128	Panel	Vascular disruptions	2 Lags	LM.Cannabis_x_Herb.THC_x_	Daily	1.76E-04	1.48E + 03	55.25
				Daily.Interpol.				
129	Panel	Vascular disruptions	Interactive	LM.Cannabis_x_Herb.THC_x_	Daily	1.27E-05	4.00E + 17	1.77E + 10
				Daily.Interpol.:				
				LM.Cannabis_x_Resin.THC_x_				
				Daily.Interpol.: Resin				
130	Panel	Vascular disruptions	1 Lag	LM.Cannabis_x_Resin.THC	Resin	9.61E-04	4.79E + 03	54.91
131	Panel	Vascular disruptions	Interactive	LM.Cannabis_x_Resin.THC_x_	Resin	1.56E-06	3.81E + 03	212.19
				Daily.Interpol.				
132	Spatial	Vascular disruptions	Additive	LM.Cannabis_x_Resin.THC_x_	Resin	8.77E-05	293.63	23.91
				Daily.Interpol.				
133	Spatial	Vascular disruptions	Interactive	LM.Cannabis_x_Resin.THC_x_	Resin	8.77E-05	293.63	23.91
				Daily.Interpol.				
134	Panel	Vascular disruptions	Additive	LM.Cannabis_x_Resin.THC_x_	Resin	4.85E-05	52.93	11.26
				Daily.Interpol.				
135	Spatial	Vascular disruptions	2 Lags	LM.Cannabis_x_Resin.THC_x_	Resin	0.0008	24.97	5.19
				Daily.Interpol.				
136	Spatial	Vascular disruptions	1 Lag	LM.Cannabis_x_Resin.THC_x_	Resin	0.0284	6.95	1.58
				Daily.Interpol.				
137	Panel	Vascular disruptions	2 Lags	Resin	Resin	3.50E-08	6.79E + 04	2.43E + 03
138	Panel	Vascular disruptions	Interactive	Resin	Resin	0.0038	62.36	5.91
139	Panel	Vascular disruptions	Additive	Resin	Resin	9.68E-03	44.48	3.89
140	Spatial	VSD	2 Lags	Daily.Interpol.	Daily	0.0137	3.41E + 57	1.44E + 12
141	Spatial	VSD	Additive	Herb	Herb	0.0014	33.67	1.99
142	Panel	VSD	2 Lags	LM.Cannabis_x_Herb.THC	Herb	2.7E-14	1.60E + 21	4.97E + 16

(continued)

Table 19: (Continued)

No.	Regression	Anomaly	Model_Type	Term	Group	P-Value	E-Value Estimate	Lower Bound E-Value
143	Spatial	VSD	2 Lags	LM.Cannabis_x_Herb.THC	Herb	2.15E-05	4.45E + 23	8.06E + 12
144	Spatial	VSD	Interactive	LM.Cannabis_x_Herb.THC	Herb	8.94E-06	1.16E + 17	4.81E + 09
145	Spatial	VSD	1 Lag	LM.Cannabis_x_Herb.THC	Herb	0.0003	9.50E + 09	4.91E + 05
146	Panel	VSD	1 Lag	LM.Cannabis_x_Herb.THC	Herb	<2.2E-16	3.04E + 06	2.58E + 05
147	Panel	VSD	Additive	LM.Cannabis_x_Herb.THC	Herb	<2.2E-16	2.38E + 06	1.96E + 05
148	Panel	VSD	Interactive	LM.Cannabis_x_Herb.THC	Herb	<2.2E-16	2.38E + 06	1.96E + 05
149	Spatial	VSD	Additive	Resin	Resin	0.0296	5.88E + 03	43.32

Table 20: Summary of E-values by the major covariate group

Group	Number	Mean mEV	Median mEV	Minimum mEV	Maximum mEV	Mean E-value estimate	Median E-value estimate	mEV estimate	Maximum E-value estimate
Daily	20	2.14E + 134	5980	6.31	4.28E + 135	5.50E + 305	1.69E + 08	9.27	1.10E + 307
Herb	75	2.75E + 47	1520	1.07	2.06E + 49	1.56E + 93	7.57E + 06	1.48	1.17E + 95
Resin	54	1.45E + 19	19.94	1.26	7.81E + 20	1.44E + 38	756.995	1.54	7.77E + 39

Table 21: Wilcoxon tests for inter-group comparisons for the major covariate group

Comparison	W-Statistic	Alternative	P-Value
Lower E-Value, Daily_v_Herb	917	two.sided	0.1285
Lower E-Value, Daily_v_Resin	888	two.sided	2.34E-05
Lower E-Value, Herb_v_Resin	2924	two.sided	1.79E-05
E-Value Estimate, Daily_v_Herb	872	two.sided	0.2674
E-Value Estimate, Daily_v_Resin	886	two.sided	2.61E-05
E-Value Estimate, Herb_v_Resin	3167	two.sided	5.05E-08

It was curious that there were initially no hits for the sonic hedgehog gene. However it is noted that for four of the key genes involved in the sonic hedgehog pathway or for its key interacting partners some hits were identified. Hence for GLI3 (Gli family zinc finger 3) there were 183 hits; for MEGF8 (multiple EGF-like domains 8) there were 105 hits, for TMEM107 (transmembrane protein 107) there were 22 hits and for BMP4 (bone morphogenetic protein 4) there were 166 hits. Since sonic hedgehog is a key morphogen controlling not only heart and arterial morphogenesis but the formation of many organs and structures this finding is potentially very important indeed.

Importantly there were 151 hits for KMT (histone lysine methyltransferase) in the epigenome-wide cannabinoid effects screen described [12]. This is important as this enzyme forms a key component of the epigenomic machinery.

Epigenomic Implication of Cardiovascular-Relevant Pathways

The report from Schrott and colleagues described several pathways that were prominently identified amongst the epigenome-wide screen conducted in rats and humans of cannabis dependence and withdrawal [12]. These included cardiogenesis, agenesis of the organism and growth of the organism. During cannabis withdrawal these workers reported that the area of the blood vessel component and organismal death were of concern [12].

There were nine hits on the cardiovascular system (CVS) including morphology of the CVS (39 genes, page 321; 35 genes, page 324), quantity of cardiomyocytes (4 genes, page 321) and hypoplasia of the heart chamber (7 genes, page 299).

Under heart there were three hits. Hypoplasia of the heart (10 genes, page 288; 7 genes, page 299; 6 genes, page 306), and hypoplasia of the trabeculae carnae (4 genes page 321). There were 26 genes noted on page 318 related to cardiogenesis.

These findings achieve particular significance in terms of our positive identification of hypoplastic right heart as a cannabis related anomaly (present report).

Atrial development occurred in several places including morphogenesis of the atrium (4 genes, page 314), morphogenesis of the atrial septum (3 genes page 318), atrial hypoplasia (2 genes page 319) and abnormal atrial morphology (6 genes, page 322).

In relation to the atrioventricular valves which are derived from the endocardial cushions abnormal morphology of the atrioventricular cushions (6 genes, page 296), lack of atrioventricular canal cushions (4 genes, page 300) and morphogenesis of the atrioventricular valve (3 genes, page 321).

Concerning the ventricle it was noted that formation of the ventricular septum (7 genes, page 315), VSDs type 3 (3 genes, page 301), hypoplasia of the cardiac ventricle (6 genes, page 306) and formation of the ventricular septum (7 genes, page 315).

In relation to blood vessel formation there angiogenesis was noted (54 genes, page 289), vascular development (56 genes, page 294), vasculogenesis (42 genes, page 302), sprouting angiogenesis (7 genes, page 324), movement of vascular endothelial cells (13 genes page 316), migration of endothelial cells (19 genes, page 317), migration of vascular endothelial cells (12 genes, page 317), angiogenesis of pulmonary vein (1 gene, page 357) and breakdown of blood vessel (1 gene, page 357).

These results are detailed in Table 22. Overall it is noted that this spectrum of epigenomic perturbations accounts for the epidemiologically observed pattern of teratological defects very well indeed.

Qualitative Causal Inference

In 1965 A.B. Hill, a famous epidemiologist investigating the link between tobacco and lung cancer, set out his now well-known criteria to determine if a reported association might be causal [100]. His criteria included strength of association, consistency amongst different studies, specificity, temporality, coherence with known data, biological plausibility, dose-response curve, analogy with similar situations elsewhere and experimental confirmation.

Table 22: EWAS annotations in epigenomic data of Schrott et.al [15]

Nearest Gene Name	Page	Dependence Status	Number Genes Identified	P-Value
Cardiovasculature				
Abnormal CVS	324	Withdrawal	35	0.002740
CVS Development	321	Withdrawal	39	0.001920
Heart				
Hypoplasia of heart	288	Withdrawal	10	8.83E-08
Cardiogenesis	318	Withdrawal	26	0.001640
Hypoplasia trabeculae carnae	321	Withdrawal	4	0.001960
Quantity cardiomyocytes	321	Withdrawal	4	0.001960
Hypoplasia heart chamber	299	Withdrawal	7	0.000021
Atrium				
Atrial morphogenesis	314	Withdrawal	4	0.000855
Atrial septal morphogenesis	318	Withdrawal	3	0.001650
Atrial hypoplasia	319	Withdrawal	2	0.001770
Abnormal atrial morphology	322	Withdrawal	6	0.002100
Atrioventricular valves				
Abnormal morphology AV cushions	296	Withdrawal	6	9.04E-06
Lack of AV canal cushions	300	Withdrawal	4	0.000040
AV valve morphogenesis	321	Withdrawal	3	0.002040
Ventricle				
VSD type 3	301	Withdrawal	3	0.000051
Hypoplasia heart ventricle	306	Withdrawal	6	0.000157
Formation ventricular septum	315	Withdrawal	7	0.001060
Vessels				
Angiogenesis	289	Withdrawal	54	1.73E-06
CVS development	294	Withdrawal	56	7.32E-06
Vasculogenesis	302	Withdrawal	42	6.65E-05
Sprouting angiogenesis	324	Withdrawal	7	0.002690
Vascular endothelial cell movement	316	Withdrawal	13	0.001210
Endothelial cell migration	317	Withdrawal	19	0.001450
Vascular endothelial cell migration	317	Withdrawal	12	0.001530
Early onset hypertension	357	Withdrawal	1	0.007010
Blood vessel breakdown	357	Withdrawal	1	0.007010
Pulmonary vein angiogenesis	357	Withdrawal	1	0.007010

All of these criteria are fulfilled for congenital heart disorders as described above.

Quantitative Causal Inference

One of the main limitations of observational studies is the non-comparability of study groups, so-called ‘comparing apples with oranges’. This issue is addressed in the present multivariable panel regression modelling by the use of ipw which is the technique of choice in causal inference to circumvent this issue.

One of the main limitations of observational studies is the non-comparability of study groups, so-called ‘comparing apples with oranges’. This issue is addressed in the present multivariable panel regression modelling by the use of ipw which is the technique of choice in causal inference to circumvent this issue.

The other major issue with observational studies is the so-called concern of uncontrolled confounding. The E-values (or expected value) quantifies and constrains the degree of association demanded of some external unknown covariate with both the exposure of concern and the outcome of interest in order to explain away some apparently causal relationship. E-values >9 are said to be unusually high and assign causality [68]; however, an E-value greater than only 1.25 is generally required to assign causality [67]. E-values also have a 95% confidence interval. The lower bound is the one quoted in this report which identifies that 97.5% of the estimates will lie above that position. As noted the very high lower E-values in this report give the reader confidence in the outcomes described.

Generalizability

This is the largest dataset of CAs in the world and the present results necessarily carry great weight based on that alone. Results are further strengthened by their clear concordance with many datasets external to the present study [4–9, 70]. The results seen in bivariate analysis were confirmed in multiple regression modelling with two different regression techniques. Importantly the major techniques for causal inference have been employed namely ipw and E-values which transforms the analysis from a purely observational dataset into a pseudorandomized paradigm from which causal inferences may properly be drawn. In that our work demonstrates causality in this context, given the sophisticated form of modelling and the large size of the database we are happy that our results are widely generalizable.

Strengths and Limitations

The strengths of our study are that it is based on one of the largest datasets in the world and uses sophisticated forms of analysis in multivariable adjustment. We have also widely deployed the key tools of causal inference to allow pseudorandomization of our analysis and causal inferential modelling. The E-values which have been calculated are generally in the higher range which further adds robustness to the results. The present results are also consistent with results from several other recent reports. Moreover univariate and bivariate maps have been liberally supplied to allow the reader to actually visualize the datasets being

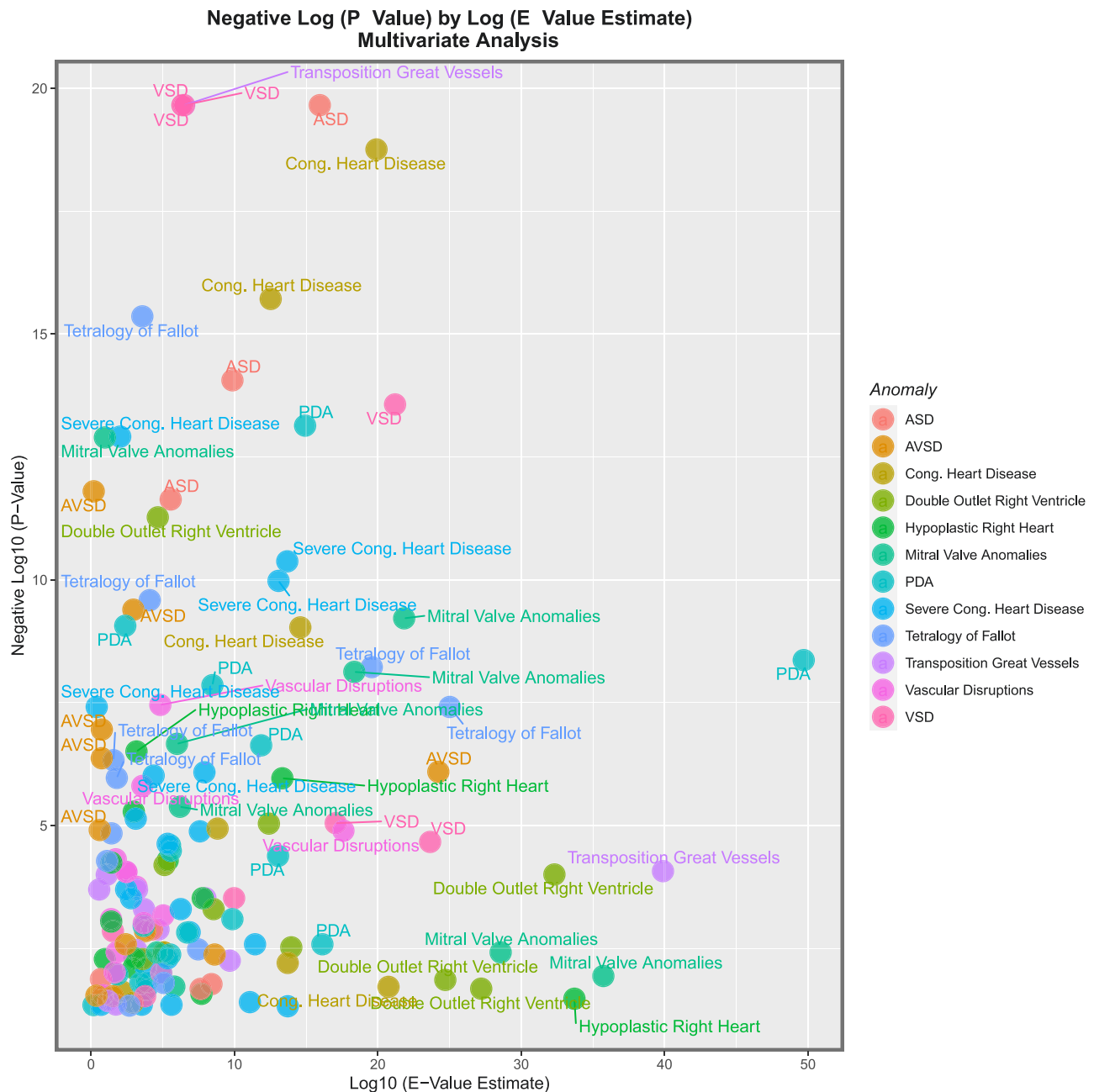


Figure 24: Magnified volcano plot of negative log of P-values against log of E-value estimates for multivariate regressions

described. Ranger regression was used for formal variable selection. Limitations of the study would include that, in common with many other epidemiological studies, individual cannabis exposure data was not available to the present investigators. Also some of the data had to be interpolated as in some datasets the degree of missing data was significant. This needs to be born in mind particularly when interpreting the data for daily cannabis use. Moreover the strong background of a genetic and biologically plausible explanatory frameworks, assisted greatly by the epigenetic work of Schrott and colleagues, makes findings mechanistically reasonable, further strengthening our confidence in both findings and generalizability. It is also observed that men and women who use cannabis may also differ in important respects from those who do not, albeit it can be argued that differences in long term relationship stability, rates of employment, and income are caused

by and deeply confounded with cannabis use in that there is an evident two-way relationship between common sociodemographic covariates and drug use. In this sense it is possible that multivariable studies could over-control for such variables. While multivariable modelling can adjust to some extent for some of these covariates further large detailed subgroup investigations are indicated.

Conclusion

In conclusion we note that 17 congenital cardiac anomalies were positively related to metrics of cannabis exposure at bivariate analysis. When 12 of these CCA's were studied in detail by inverse probability weighted panel regression and geospatial

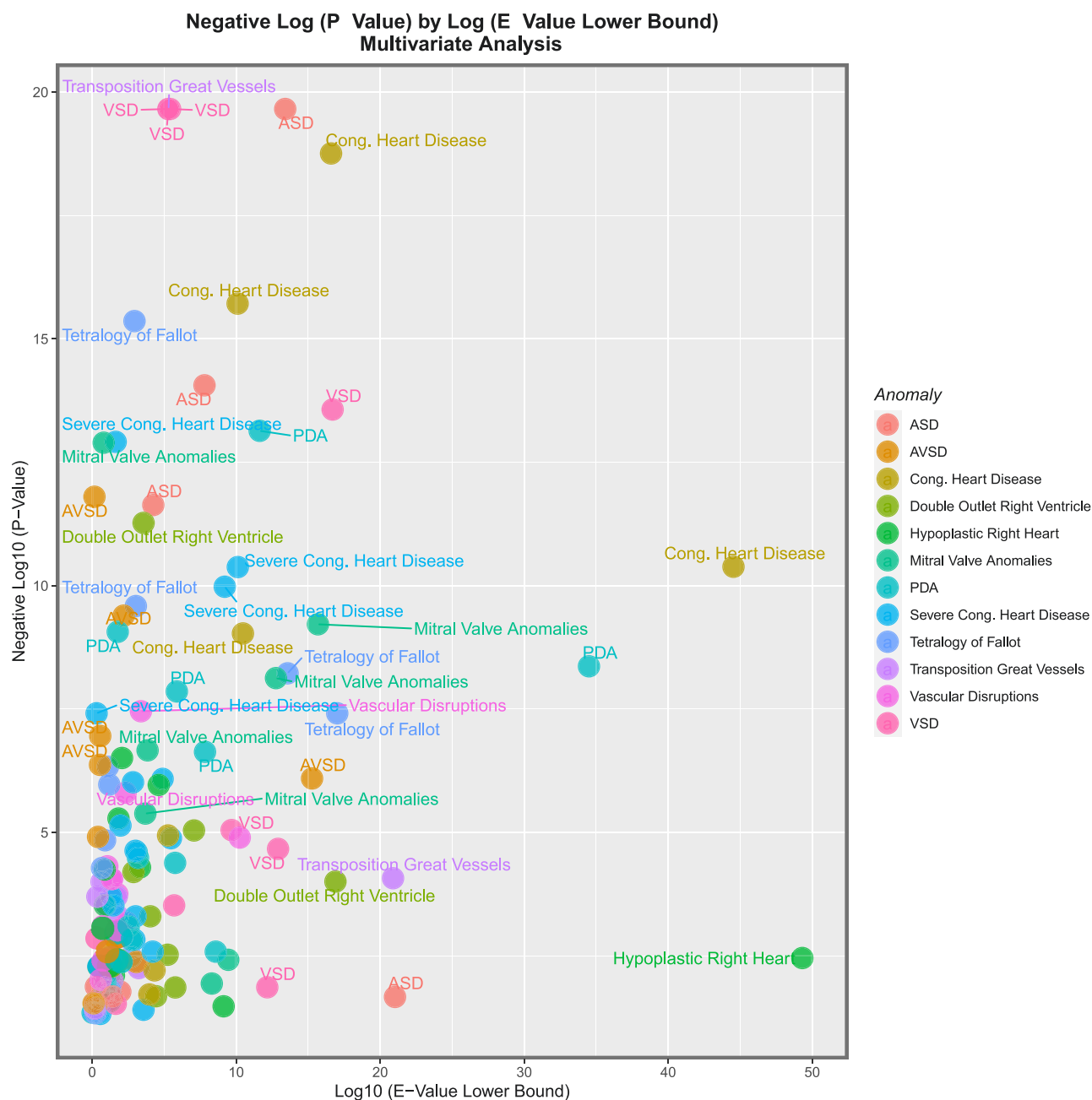


Figure 25: Magnified volcano plot of negative log of P-values against log of mEV for multivariate regressions

regression robust relationships to cannabis were confirmed which persisted after adjustment and fulfilled quantitative epidemiological criteria for causal relationships. Pathophysiologically the inhibition by cannabis through epigenomic pathways with the cardiac core regulatory gene complex and particularly the sonic hedgehog pathway by epigenomic mechanisms via heritable changes in DNA methylation is impressive and worthy of further study. The findings that 12–17 CCA's could be related to metrics of cannabis exposure and most powerfully daily cannabis use in the largest CA dataset in the world is very concerning indeed particularly

in the context of rapidly rising prevalence and daily intensity of cannabis use and cannabinoid potency and most especially in the context of the exponential genotoxic dose-response curve which has been demonstrated for cannabis genotoxicity both in the laboratory and epidemiologically. From this impressive dataset it can only be concluded that rational drug policy would require careful control of the penetration of powerful genotoxic compounds such as cannabinoids into the community in order to protect and preserve the genome and epigenome of the coming several generations.

Supplementary Data

Supplementary data is available at *EnvEpiG* online.

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All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of interest statement. The authors declare that they have no competing interests.

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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 on 24 September 2021 (No. RA/4/20/4724).

Data Availability

All data generated or analysed during this study are included in this published article and its supplementary information files. Data along with the relevant R code have been made publicly available on the Mendeley Database Repository and can be accessed from these URLs: 10.17632/vsmmmkncsd.1 and 10.17632/tysn37t426.1

Authors' Contributions

A.S.R. assembled the data, designed and conducted the analyses and wrote the first manuscript draft. G.K.H. provided technical and logistic support, co-wrote the paper, assisted with gaining ethical approval and provided advice on manuscript preparation and general guidance to study conduct. A.S.R. had the idea for the article, performed the literature search, wrote the first draft and is the guarantor for the article.

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