Geospatiotemporal and causal inference study of cannabis and other drugs as risk factors for female breast cancer USA 2003–2017

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Abstract
Breast cancer (BC) is the commonest human cancer and its incidence (BC incidence, BCI) is rising worldwide. Whilst both tobacco and alcohol have been linked to BCI genotoxic cannabinoids have not been investigated. Age-adjusted state-based BCI 2003–2017 was taken from the Surveillance Epidemiology and End Results database of the Centers for Disease Control. Drug use from the National Survey of Drug Use and Health, response rate 74.1%. Median age, median household income and ethnicity were from US census. Inverse probability weighted (ipw) multivariable regression conducted in R. In bivariate analysis BCI was shown to be significantly linked with rising cannabis exposure [β-est. = 3.93 [95% confidence interval 2.99, 4.87], P = 1.10 × 10^-15]. At 8 years lag cigarettes:cannabis [β-est. = 2660 (2150.4, 3169.3), P = 4.60 × 10^-22] and cannabis:alcoholism [β-est. = 7010 (5461.6, 8558.4), P = 1.80 × 10^-17] were significant in ipw-panel regression. Terms including cannabidiol [CBD; β-est. = 16.16 (0.39, 31.93), P = 0.446] and cannabigerol [CBG; β-est. = 6.23 (2.06, 10.39), P = 0.0034] were significant in spatiotemporal models lagged 1:2 years, respectively. Cannabis-liberal paradigms had higher BCI [67.50 ± 0.26 v. 65.19 ± 0.21/100 000 (mean ± SEM), P = 1.87 × 10^-11]; β-est. = 2.31 (1.65, 2.96), P = 0.9.09 × 10^-17]. 55/58 expected values >1.25 and 13/58 >100. Abortion was independently and causally significant in space–time models. Data show that exposure to cannabis and the cannabinoid Δ9-tetrahydrocannabinol, CBD, CBG and alcoholism fulfil quantitative causal criteria for BCI across space and time. Findings are robust to adjustment for age and several known sociodemographic, socio-economic and hormonal risk factors and establish cannabinoids as an additional risk factor class for breast carcinogenesis. BCI is higher under cannabis-liberal legal paradigms.

Key words: cannabis; alcoholism; breast cancer; cannabidiol; THC; cannabigerol; breast carcinogenesis; abortion

Introduction
Globally 2.1 million women were diagnosed with breast cancer (BC) in 2018 including 626,679 deaths from this cause [1]. This equates to one case every 18 seconds. The BC incidence (BCI) is increasing worldwide. In the USA 279,100 cases are expected to occur in 2020 [2]. 276,480 of these tumours or 99.06% occur in females [2] and female BC will be the subject of analysis. Data from the Centers of Disease Control (CDC) Atlanta, Georgia, indicate that the BCI rose nationally from about 100 cases/100,000 to 127 cases/100,000 from 1980 to 1987, possibly related to the widespread introduction of mammographic screening but has been essentially unchanged since that time [2]. Happily the mortality rate has dropped progressively since 1990 due to various screening practices enabling earlier detection and therapeutic advances [2].

The aetiology of BC is usually understood to relate to a combination of factors including increased hormonal exposure so that factors such as early menarche, delayed menopause, reduced parity, advanced maternal age at first pregnancy, reduced breast-feeding, oral contraception and menopausal hormone replacement therapy are known to be linked with increased BCI [1, 3–6]. Obesity, central adiposity, lack of physical activity and alcohol use are also implicated [1]. The role of tobacco is controversial, although some data indicate it may increase severity of BC in those identified. The literature on the effects of elective termination of pregnancy on BC is controversial with meta-analyses reaching both positive [7] and negative conclusions [8, 9] being published. The main factors that influence risk include being a woman and getting older with most BC found in women who are 50 years old or older, with age also likely reflecting exposure to environmental factors. Significant ethnic differences are also described [10]. Mutations in the BRCA genes on Chromosomes 17 and 13 which
play critical roles in homologous DNA repair and are linked with BC. 
BRCA mutations occur with varying frequencies by ethnicity being 
0.5% amongst Asian populations and 10.2% amongst women of 
Ashkenazi Jewish descent [1]. Mutations in checkpoint 2 kinase 
(CHEK2), ataxia telangiectasia mutated (ATM), partner and local-
izer of BRCA2 (PALB2), tumour protein P53 (TP53), phosphatase 
and tensin homolog (PTEN) and serine threonine kinase 11 (STK11) 
are also implicated [1].

A recent PubMed literature search identified numerous papers 
discussing the putative potential of cannabinoid-derived thera-
petin in BC for various indications albeit in the absence of sup-
portive randomized clinical trials [11], however we were not able to 
identify any papers investigating the possibility that cannabinoids 
may impact the aetiological risk for BCI.

On the basis of several published series [12–16] it is often said 
that the cancer which is most closely linked with cannabis expo-
sure is testicular cancer [17–21]. Other studies link adult cannabis 
exposure with cancer of the head and neck, larynx, prostate, lung, 
brain and urethelium [12, 22–31] and for several tumours dose-
response relationships have been demonstrated [22, 24, 25, 32].

However it is important to appreciate that the evidence linking 
cannabis exposure with a paediatric cancer whose inci-
dence peaks in the first 5 years of life—acute myeloid leukaemia 
(AML) [33–35] is equally as strong as that for testicular cancer 
[33, 34, 36, 37]. Cannabis has also been linked with other 
paediatric tumours including neuroblastoma, rhabdomyoblast-
toma, acute lymphoid leukaemia (ALL) and total paediatric cancer 
[28, 33, 34, 36, 38–43]. It is widely understood that paediatric cancer 
largely results from inherited genotoxic or epigenotoxic car-
cinogenic insults [44–46]. Indeed, as was found by the California 
Environmental Protection Agency some years ago the evidence 
for paediatric cancerogenesis is more uniform than the evidence for 
adult oncogenesis [47].

Since BC (present report and [37]) is the commonest adult can-
cer and ALL, along with total paediatric cancer, is the commonest 
paediatric cancer these findings make cannabis a major player in the 
epidemiology of both adult and childhood oncogenesis and 
therefore across the whole span of life. Since cannabis has been 
shown to be driving ALL and total paediatric cancer rates [43, 48] 
transgenerational aspects of cannabinoid oncogenesis are clearly 
important. In that the breast is also part of the reproductive sys-

This study set out to investigate the potential involvement of 
cannabis, cannabinoids and other substances in patterns of BCI 
across space and time in the USA to assess if any epidemiological 
relationships could be identified, if any putative relationship 
was robust to multivariable adjustment and if the relationship fulfilled 
the formal criteria for causality.

Our intention prior to data analysis was to include substance 
exposure as an addition to known covariates which had previously 
been linked with BCI.

Methods

Data Cancer

National age-adjusted BCI rates including ethnic-specific inci-
dence rates were taken from the SEER*Explorer online web tool 
[10]. State-based age-adjusted BCI data were taken from the 
National Program of Cancer Registries (NPCR) and Surveillance, 
Epidemiology, and End Results (SEER) Incidence data set US Can-
cer Statistics Public Use database 2019 submission 2001–2017 for 
each US state using the SEER*Stat software rate sessions [49].

Drugs

Drug use data at the state level was taken from the state-
based datafiles of the National Survey of Drug Use and Health 
(NSDUH) Restricted Use Data Analysis System (RDAS) of the Sub-
stance Abuse and Mental Health Data Archive (SAMHDA) con-
ducted annually by the Substance Abuse and Mental Health Ser-
dices Administration (SAMHSA) [50]. The drugs of interest were 
tobacco (as last month cigarettes use, shown as “Cigarettes” in 
tables); alcohol use disorder (“AUD”, formerly known as 
alcohol dependence); last month cannabis use (“Cannabis”); 
last year non-medical use of analgesics (“Analgesics”) and last 
year use of cocaine (“Cocaine”). Cannabis use intensity by 
nativity at the national level was also sourced from the 
SAMHSA NSDUH RDAS data set using the RDAS variable “mrmj-
days”. The concentration of cannabinoids in federal seizures 
was taken from publications of the Drug Enforcement Agency 
[51–53].

Socio-Economic

Data on state-based ethnicity prevalence, median household 
income (“Income” in the tables) and median age was taken from 
the US Census Bureau via the tidycensus package in R [54]. The ethnicities of interest were Caucasian-American, 
African-American, Hispanic-American, American Indian/Alaska 
Native (AIAN) and Native Hawaiian/Pacific Islander (NHPI). 
Some of the CDC data refers to Non-Hispanic ethnicities (NH). 
This abbreviation appears in our tables where appropriate. In 
some cases there were minor disparities between the ethnic 
designations employed from the major data sets. Ethnicities 
were matched as closely as possible between the various data 
sets.

Reproductive Factors

Data on termination of pregnancy were sourced from the Annual 
CDC Abortion Surveillance Monitoring Reports and was recorded 
for abortions performed for intrastate residents only [55]. Data 
on menopausal hormone replacement therapy (HRT) was sourced 
by specific enquiry from CDC (Atlanta, Georgia). Following the 
Womens Health Initiative Study [3] a marked decline occurred 
in the rate of HRT prescribing nationally [56]. CDC was able 
to provide national-level data only for five years as discussed 
below [56]. Data were temporally kriged to provide estimates 
for the intervening years. As mentioned, only national-level 
data were available. Data on hormonal methods of contracep-
tion (hormonal contraception/combined oral contraceptive pill, 
COCP) were sourced from published reports directed by specific 
query from CDC [56–60]. Hormonal methods of contraception 
include the sum of oral contraception, injectable contraception 
and implant contraception. Data were only supplied for four years. 
The data set was completed for the intervening years by temporal 
kriging.

Cannabis Legal Status

Cannabis legal status was derived from an internet search [61].

Derived Data

State-Based Cannabinoid Exposure Estimates

State-based estimates of cannabinoid exposure were derived by 
multiplying the concentration of cannabinoids identified in fed-
eral seizures of cannabis as published by DEA laboratories [51–53] 
by the mean level of last month cannabis use in that state follow-

Accepted practices [16, 43, 62–69]. The cannabis use intensity 
in each category of use (1–3 days last month, 4–5 days, 6–19 days
and 20–30 days) was summed and averaged for each year of the NSDUH for each ethnicity to provide a cannabis use intensity score. This score was then multiplied by the prevalence of the relevant ethnicity in that state to derive a state-based estimate of monthly cannabis exposure. This measure was then multiplied by the ∆9-tetrahydrocannabinol (THC) and cannabidiol (CBD) concentrations, respectively, in federal seizures to derive estimates of ethic THC and CBD exposures at the state level.

**Substance Exposure Quintiles**

Substance exposure in each year was divided into quintiles for the substances cigarettes, AUD, cannabis, cocaine and analgesics.

**Dichotomization**

Substance exposure quintiles were dichotomized as the two highest quintiles versus the lower three quintiles. Similarly cannabis legal status was dichotomized as states where cannabis was illegal versus those where a more liberal policy was in place.

**Statistics**

Data were processed in R version 4.0.3 and R-Studio version 1.3.1093 from the R Foundation for Statistical Computing and the Comprehensive “R” Archive Network (CRAN) in November 2020. Numeric data are listed as mean ± SEM. Data were manipulated using dplyr and the tidyverse suite [70]. All data was log-transformed based on the results of the Shapiro test. The probability of Student’s t and Fisher’s F at extreme values was calculated using the functions pt and pf from the stats package. Graphs were drawn in ggplot2 [71]. Maps were drawn with ggplot2 and sf (“Simple Features”) [71, 72]. All maps have been originally drawn for this paper. Some maps use the “plasma” colour palette from R package viridis [73]. Other colour palettes were custom designed for this paper. Reduction of initial regression models was by serial deletion of the least significant term according to the classical method of model reduction. Only final reduced models are presented. Serial linear models were processed in broom, broom mixed and purrr [74–76].

Correlation matrices were constructed using the R-packages corrplot and corrgram [77–79]. Paired correlation plots were constructed with the gpairs function from GGally [80]. Graphs were assembled into four or six panels using the ggarrange function from ggpubr [81].

A variety of regression techniques were used for the following reasons. Linear regression was performed in R-Base. Mixed effects regression from package lme [82, 83] was performed as it is ideally suited to repeated measures of the same locations and it provides standard deviations from which to calculate expected values (e-values), and inverse probability weights can be employed. However, it does not allow lagging or the use of instrumental variables. Panel regression from package plm [84] was performed as the data are of the panel form and it allows the use of instrumental variables and lagging, although not together, and inverse probability weights can be employed. It also provides standard deviations from which e-values can be calculated. Robust generalized regression was performed from the survey package [81] as it allows inverse probability weights to be employed and provides robust regression estimates. It does not however allow lagging, instrumental variables or provide standard deviations for the calculation of e-values. Geospatiotemporal regression was performed using the spatial panel random error maximum likelihood (spreml) function from package splm (spatial panel linear models) [85–87] as the data are distributed across time and space, which are shown to be important environmental factors in these regression models, both spatial and temporal lagging can be performed, and standard deviations can be calculated to allow the derivation of e-values. However, models cannot be weighted using inverse probability weights and instrumental variables cannot be employed.

For both mixed effects and robust generalized regression the state was the level of the identifier.

For panel models the effects were two ways which relate to both space and time, model type was pooling relating to least squares algorithm, the random method was that of Swarny and the instrumental method that of Amemiya [84]. All panel models were inverse probability weighted.

Geospatial neighbourhood weights using the “queen” edge and corner relationships were calculated and edited using the spdep package in R [88]. All geospatial models used the spatial error with serial correlation and random effects with spatial lagging (“spreml+lag”) error structure which was confirmed in final models to be the appropriate model design specification as previously described [89]. Model coefficients are presented as phi for the random error component, psi for the serial correlation in the residual error, rho for the spatial error coefficient and lambda for the autocorrelation in the spatial error. The spreml constrained optimization method used was that of Baltagi, Pfaffermayr, Greene and Song (“BFGS”) [87, 89].

The use of inverse probability weights allows an observational study to be considered as a pseudo-randomized study from which causal conclusions can be drawn. Inverse probability weights were calculated using the R package ipw [90]. Cannabis exposure was adjusted across groups controlled for all other substance exposure. Inverse probability weighting was applied to all robust generalized regression models, mixed effects models and panel models. e-Values are a quantitative index of the required association between some hypothetical unmeasured confounding variable and both the dependent variable and the exposure of concern, measured on the risk ratio scale. e-Values were calculated from the R package EValue [91–93]. e-Values greater than 1.25 are considered in the literature to be indicative of presumptively causal relationships [94]. All t-tests were two tailed. P < 0.05 was considered significant throughout.

**Data Availability**

All data used during this study including datafiles, shapefiles, edited geospatial weights, inverse probability weights and programming code in “R” are included in this published article and its supplementary information files. Data have been made publicly available on the Mendeley Database Repository and can be accessed via: http://dx.doi.org/10.17632/yzjcvhphmc.1.

**Ethics**

The Human Research Ethics Committee of the University of Western Australia provided ethical approval for the study to be undertaken on 7 January 2020 (No. RA/4/20/4724). Consent to participate was not required as the data utilized were derived from publicly available anonymous data sets and no individually identifiable data were employed.

**Results**

The BC data set was the national BC state-based census data set [49]. The NSUDH is an annually conducted nationally representative data set which is representative of the non-institutionalized US population. It has a published 74.1% response rate [95].
Supplementary Figure S1 map-graphically presents the rates BCI across the USA over time.

As the leading risk factor for BC is chronological age it is important to take that into account. Supplementary Figure S2 map-graphically presents the relative median population ages across the USA over time.

Supplementary Figure S3 standardizes the BCI by age by dividing the BCI by chronological age. The results are presented map-graphically and considerable changes are noted from Supplementary Figure S1 with the hotspot in New England becoming more moderate and Utah emerging as a high corrected-incidence zone.

Supplementary Table S1A shows the raw data for menopausal HRT as derived from CDC data [56]. Supplementary Table S1B shows temporal kriging of these data to complete the missing years of the analysis. This is required as spatiotemporal analysis algorithms do not permit the presence of missing data. As no state-based data were available for this parameter the same values have been used for all states.

Supplementary Table S2 shows the data for the rates of hormonal contraception used in each US state as directed by CDC [57–60].

Supplementary Table S3 shows these data after temporal kriging for each of the years 2003–2017 and completion of the data set for each state.

Supplementary Table S4 shows the elective termination of pregnancy (abortion) data as derived from the annual CDC Abortion surveillance reports [55]. Supplementary Table S5 shows these data after temporal kriging.

Supplementary Table S6 shows the final bivariate linear regression results of the BCI against various groups of covariates. Significant relationships with cannabis use, cannabinoids and abortion rates are noted.

Supplementary Figure S4 shows the relationship of the (A) BCI to the abortion rate, (B) the log(BCI) to the standardized (z-transformed) abortion rate, (C) the log(BCI) to the log abortion rate and (D) the log(BCI) to the log (standardized abortion rate). The positive relationship between the BCI and abortion rate is noted to hold regardless of the transformation of both variables.

Supplementary Table S7 gives the final bivariate linear regression models for the BCI against the logarithm of the abortion rate. The relationship is noted to be highly significant.

Supplementary Table S6 lists the applicable linear regression results for the BCI by ethnicity for the state-level data. In the first model of the table the comparator group is African-Americans. In the model section of the table the comparator group is AIAN-Americans. In each case highly significant differences are noted.

Figure 1 shows the BCI as a function of exposure to various substances. Obviously positive relationships are shown with cannabis and cocaine.

Figure 2 shows the BCI as a function of various cannabinoid exposures. Positive relationships are noted in each case.

Supplementary Table S8 gives the line slopes of the regression lines for the various substances and the various cannabinoids. Since the rates of cigarette use, alcohol dependence, cocaine and analgesic use and CBD exposure are all falling it is of interest to consider quintile analyses of these exposures.
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Figure 2: Graphs of relationship of BCI to cannabinoid exposure

Figure 3: Graphs of relationship of BCI to substance exposure quintiles. (A) Scatterplot of BCI by cigarette use quintiles over time, (B) scatterplot of BCI by AUD quintiles over time, (C) scatterplot of BCI by cannabis use quintiles over time, (D) boxplot of BCI by cigarette use quintiles over aggregated time, (E) boxplot of BCI by AUD quintiles over aggregated time and (F) boxplot of BCI by cannabis use quintiles over aggregated time

the BCI as a function of the tobacco, AUD and cannabis quintiles as scatterplots and boxplots. Chi-squared test for trend for each of these three substances is: tobacco: Chi.Squ. = −892.39, df = 796, P = 0.0096; AUD: Chi.Squ. = 814.31, df = 796, P = 0.3184; cannabis: Chi.Squ. = 853.62, df = 796, P = 0.767.

Supplementary Table S9 illustrates the results of these regressions for four substances by quintile.

The applicable slopes, regression coefficients and significance values of the bivariate linear regressions for the cannabis quintiles are shown in Supplementary Table S10. The lower half of
the table lists the results for consideration of the dichotomized quintile comparisons. Highly significant results are shown.

The cannabis quintiles may be further aggregated into the lower three quintiles compared to the upper two quintiles. The time-based trends and boxplots for BCI are shown in Fig. 4. The differences between the BCIs of the higher and lower quintiles are significant (68.45 ± 0.36 v. 65.62 ± 0.18, t = 6.9603, df = 232.24 and P = 3.44 × 10^{-11}). The BCI of the fourth cannabis quintile is significantly lower than that of the fifth cannabis quintile (66.54 ± 0.45 v. 68.45 ± 0.36, t = 3.133, df = 279.96, P = 0.0010).

**Figure 5** is a compound correlogram prepared in the R package “corrplot”. It shows the correlations colour coded in the lower triangle and with the significance of the Pearson correlation coefficients shown in the upper triangle both by their P-value and as ellipses. The correlations are coded from purple to red in increasing order. Ellipses slope positively for positive correlations and negatively for negative correlations. The width of the ellipse also codes the strength of association with narrower ellipses indicating higher correlations. The diagonal is blank. The correlogram is ordered by hierarchical clustering according to the Ward 2 method. The BCI is denoted as "CancerRt" in this figure. Positive relationships amongst the cannabinoids and across ethnic THC exposure are noted in this correlogram. The BCI is noted to be positively related to cannabis, cannabinoids including CBD, abortions and cocaine exposure.

Supplementary Table S11 lists the results of mixed effects repeated measures regressions with state as the identifying variable from a series of successively more complex (mostly) additive models. The model series is of interest because in each model in which cannabis appears it is seen to be significant.

Supplementary Table S12 lists a series of successively more complex interactive mixed models. The first model is the full
interactive model and includes age, substances, ethnic prevalences, income and reproductive exposures. Five terms including cannabinoids are significant, and cannabis is noted to be independently and powerfully significant in this model \( (\beta \text{-est.} = 24.73 \text{ [95% confidence interval (CI) 14.98, 34.47], } P = 8.40 \times 10^{-7}) \). In place of the ethnic prevalence the second and third models list the ethnic THC and CBD exposure, respectively. In the second model Asian THC exposure is noted to be significant \( (\beta \text{-est.} = 3.53 \text{ (2.88, 4.18), } P = 1.10 \times 10^{-24}) \) and in the third model Caucasian CBD exposure is noted to be significant \( (\beta \text{-est.} = 65.45 \text{ (50.11, 80.79), } P = 3.00 \times 10^{-16}) \). The fourth model features the individual cannabinoids as main effects. CBD, cannabigerol (CBG) and THC are all independently significant of which the most positively significant one is CBD \( (\beta \text{-est.} = 3.00 \text{ (0.53, 5.47), } P = 0.0174) \). Terms including cannabinoids are significant \( (\beta \text{-est.} = 150.10 \text{ (74.14, 226.05), } P = 0.0001) \).

The intrastate elective pregnancy termination rate is also noted to be highly significant in all four models.

Supplementary Table S13 shows the final regression models from panel regression first including age and substances, then a full additive model and then a full interactive model. In each model cannabis is significant \( (\beta \text{-est.} = 26.87 \text{ (22.81, 30.94), } P = 1.06 \times 10^{-34}) \).

Supplementary Table S14 shows the results from final interactive panel models lagged to 2, 4, 6 and 8 years. In each case terms including cannabis are noted to be significant \( (\beta \text{-est.} = 1016.82 \text{ (822.42, 1211.21), } P = 1.30 \times 10^{-22} \text{ at 6 years lag}) \).

Supplementary Table S15 lists a series of final interactive panel models which include respectively cannabinoids, ethnic THC exposure and ethnic CBD exposure as instrumental variables. Interestingly in these models the significance of cannabis in the model covariates is greatly reduced. In the final model where ethnic CBD exposure is listed as the instrumental variable no terms including cannabis appear. These results confirm that the effect of cannabis as a covariate is partly accounted for by the listing of the various cannabinoids as instrumental variables.

Table 1 presents a series of geospatiotemporal models of increasing complexity. As shown in the first model when age and cannabis exposure are regressed interactively against the BCI together only cannabis use remains significant in the final model. The second model shows that when age and substances are regressed additively against BCI the only term remaining in the final model is cannabis exposure. The third model is an important additive model which lists all the non-ethnicity covariates. Only cannabis exposure \( (\beta \text{-est.} = 1.56 \text{ (0.69, 2.42), } P = 0.0004) \) and abortion \( (\beta \text{-est.} = 1.20 \text{ (0.54, 1.85), } P = 0.0003) \) remain as significant in the final model with positive coefficients. In a similar interactive model terms including cannabis are highly significant (fourth model). In a full interactive model including substance, age, income and ethnicity terms including cannabis do not appear in the final model (fifth model). In a full interactive model where an interactive term between THC:CBD:CBG replaces the term for cannabis an interactive term including the CBG:CBD interaction is significant in the final model (sixth model).

In an interactive model which replaces ethnicity with ethnic THC exposure Non-Hispanic African-American, Hispanic-American and Non-Hispanic Caucasian-American THC exposures are significant in the final model (seventh model). When the ethnic CBD exposure is used to replace the ethnic prevalences the CBD of the same three ethnic groups remains significant in the final model (eighth model).
Table 1: Introductory geospatiotemporal models

| Parameter | Estimate (CI) | P-value | SD | Log.Lik | Coefficient | Value | P-value |
|-----------|---------------|---------|----|---------|-------------|-------|---------|
| Cannabis alone | | | | | | | |
| spreml(Cancer_Rate ~ Age × Cannabis) | | | | | | | |
| Cannabis | 1.45 (0.61 2.29) | 0.0007 | 3.6514 | −1780.87 | phi | 1.5969 | 2.11E − 05 |
| | | | | | psi | 0.3437 | 1.46E − 15 |
| | | | | | rho | −0.4217 | 3.90E − 05 |
| | | | | | lambda | 0.4754 | 4.75E − 12 |
| Additive model | | | | | | | |
| spreml(Cancer_Rate ~ Age + Cigarettes + Cannabis + AUD + Analgesics + Cocaine) | | | | | | | |
| Cannabis | 1.45 (0.61 2.29) | 0.0007 | 3.6514 | −1780.87 | phi | 1.5969 | 2.11E − 05 |
| | | | | | psi | 0.3437 | 1.46E − 15 |
| | | | | | rho | −0.4217 | 3.90E − 05 |
| | | | | | lambda | 0.4754 | 4.75E − 12 |
| Additive model without ethnicity | | | | | | | |
| spreml(Cancer_Rate ~ Age + Cigarettes × Cannabis × AUD + Analgesics + Cocaine + Income + Abortion + HRT + COCP) | | | | | | | |
| Abortion | 1.2 (0.54, 1.85) | 0.0003 | 3.5943 | −1772.073 | phi | 1.575016 | 5.22E − 05 |
| | | | | | psi | 0.3144 | 3.41E − 13 |
| | | | | | rho | −0.4243 | 2.91E − 05 |
| | | | | | lambda | 0.4645 | 2.30E − 12 |
| Interactive model | | | | | | | |
| spreml(Cancer_Rate ~ Age + Cigarettes × Cannabis × AUD + Analgesics + Cocaine) | | | | | | | |
| Cigarettes × Cannabis | 3.59 (1.94 5.24) | 0.0010 | 1.90E − 05 | 3.6773 | phi | 1.6995 | 8.95E − 06 |
| | | | | | psi | 0.3144 | 3.41E − 13 |
| | | | | | rho | −0.4243 | 2.91E − 05 |
| | | | | | lambda | 0.4645 | 2.30E − 12 |
| Interactive full model | | | | | | | |
| spreml(Cancer_Rate ~ Age + Cigarettes × Cannabis × AUD + Analgesics + Cocaine + Income + Abortion + HRT + COCP + Caucasians + African + AIAN + Hispanic + Asian) | | | | | | | |
| Asian | 2 (1.08 2.92) | 0.0004 | 3.0967 | −1763.77 | phi | 1.2367 | 5.59E − 05 |
| | | | | | psi | 0.3152 | 3.41E − 13 |
| | | | | | rho | −0.4243 | 2.91E − 05 |
| | | | | | lambda | 0.4645 | 2.30E − 12 |
| Interactive full model—Cannabinoids as main effects | | | | | | | |
| spreml(Cancer_Rate ~ Age + Cigarettes × THC × CBG × CBD + AUD + Analgesics + Cocaine + Income + Abortion + HRT + COCP + Caucasians + African + Hispanic + Asian) | | | | | | | |
| Abortion | 1.21 (0.54 1.88) | 0.0004 | 0.3096 | −1763.67 | phi | 1.1775 | 4.41E − 05 |
| | | | | | psi | 0.3321 | 1.18E − 14 |
| | | | | | rho | −0.4176 | 3.99E − 05 |
| | | | | | lambda | 0.4478 | 5.27E − 11 |
| Interactive full model—Ethnic THC exposure as main effects | | | | | | | |
| spreml(Cancer_Rate ~ Age + Cigarettes + AUD + Analgesics + Cocaine + Income + Abortion + HRT + COCP + Caucasians + African + Hispanic + Asian) | | | | | | | |
| NHAfrican THC × Hispanic THC | 1.14 (0.48 1.81) | 0.0007 | 0.0279 | −1764.30 | phi | 1.5874 | 7.72E − 06 |
| | | | | | psi | 0.3168 | 2.17E − 13 |
| | | | | | rho | −0.4176 | 3.99E − 05 |
| | | | | | lambda | 0.4419 | 6.98E − 11 |
| Interactive full model—Ethnic CBD exposure as main effects | | | | | | | |
| spreml(Cancer_Rate ~ Age + Cigarettes + AUD + Analgesics + Cocaine + Income + Abortion + HRT + COCP + Caucasians + African + Hispanic + Asian) | | | | | | | |
| NHCaucas THC × Hispanic THC | 5.63 (2.85, 8.4) | 0.0001 | 3.5743 | −1759.431 | phi | 1.4579 | 9.55E − 05 |
| | | | | | psi | 0.3004 | 8.16E − 12 |
| | | | | | rho | −0.3859 | 3.00E − 04 |
| | | | | | lambda | 0.4104 | 2.94E − 08 |
Table 2: Lagged geospatiotemporal models

| Lagged models | Parameter | Estimate (CI) | P-value | SD | Log.Lik | Coefficient | Value | P-value |
|---------------|-----------|--------------|---------|----|---------|-------------|-------|---------|
| **Temporal models** | | | | | | | | |
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Table 2: (Continued)

| Lagged variables | Parameter | Estimate (CI) | P-value | SD | Log Lik | Coefficient | Value | P-value |
|------------------|-----------|---------------|---------|----|---------|-------------|-------|---------|
|                  | spremi(Cancer_Rate ~ Age + Cigarettes × THC × CBG × AUD + Analgesics + Cocaine + Income + Abortion + HRT + COCP + Caucas + African + Hispanic + Asian) |           |         |    |         |             |       |         |
| THC              | Abortion  | 1.31 (0.54 2.08) | 0.0009  | 3.7106 | −1635.79 | phi     | 1.9328 | 0.0000134 |
| CBG              | Cigarettes | 67.68 (3.55 131.82) | 0.0386 |      |         | psi      | 0.2759 | 0.055   |
| CBD              | Cigarettes:CBD | 16.16 (0.39 31.93) | 0.0446 |      |         | rho      | −0.4538 | 0.0365  |
| CBD              | CBD       | −3.87 (−7.42 −0.31) | 0.0329 |      |         | lambda   | 0.3150 | 0.0000134 |
| THC              | Cigarettes:THC | −79.49 (−133.54 −25.43) | 0.0039 |      |         | phi      | 1.9328 | 0.0000134 |
| THC              | Cigarettes:THC:CBG | −21.85 (−36.69 −7.02) | 0.0039 |      |         | phi      | 1.9328 | 0.0000134 |
| THC              | Cigarettes:THC:CBG:CBD | −294.66 (−492.99 −96.33) | 0.0036 |      |         | phi      | 1.9328 | 0.0000134 |
| THC              | Cigarettes:THC:CBG:CBD | −82.92 (−137.82 −28.01) | 0.0031 |      |         | phi      | 1.9328 | 0.0000134 |

Lagging cannabinoids—THC × CBG × CBD

1 Temporal lag

| THC              | Abortion  | 1.31 (0.54 2.08) | 0.0009  | 3.7106 | −1635.79 | phi     | 1.9328 | 0.0000134 |
| THC              | Cigarettes | 67.68 (3.55 131.82) | 0.0386 |      |         | psi      | 0.2759 | 0.055   |
| THC              | Cigarettes:CBD | 16.16 (0.39 31.93) | 0.0446 |      |         | rho      | −0.4538 | 0.0365  |
| THC              | CBD       | −3.87 (−7.42 −0.31) | 0.0329 |      |         | lambda   | 0.3150 | 0.0000134 |
| THC              | Cigarettes:THC | −79.49 (−133.54 −25.43) | 0.0039 |      |         | phi      | 1.9328 | 0.0000134 |
| THC              | Cigarettes:THC:CBG | −21.85 (−36.69 −7.02) | 0.0039 |      |         | phi      | 1.9328 | 0.0000134 |
| THC              | Cigarettes:THC:CBG:CBD | −294.66 (−492.99 −96.33) | 0.0036 |      |         | phi      | 1.9328 | 0.0000134 |
| THC              | Cigarettes:THC:CBG:CBD | −82.92 (−137.82 −28.01) | 0.0031 |      |         | phi      | 1.9328 | 0.0000134 |

Lagging cannabinoids—THC × CBG × CBD

2 Temporal lags

| THC              | Abortion  | 1.31 (0.54 2.08) | 0.0009  | 3.7106 | −1635.79 | phi     | 1.9328 | 0.0000134 |
| THC              | Cigarettes | 67.68 (3.55 131.82) | 0.0386 |      |         | psi      | 0.2759 | 0.055   |
| THC              | Cigarettes:CBD | 16.16 (0.39 31.93) | 0.0446 |      |         | rho      | −0.4538 | 0.0365  |
| THC              | CBD       | −3.87 (−7.42 −0.31) | 0.0329 |      |         | lambda   | 0.3150 | 0.0000134 |
| THC              | Cigarettes:THC | −79.49 (−133.54 −25.43) | 0.0039 |      |         | phi      | 1.9328 | 0.0000134 |
| THC              | Cigarettes:THC:CBG | −21.85 (−36.69 −7.02) | 0.0039 |      |         | phi      | 1.9328 | 0.0000134 |
| THC              | Cigarettes:THC:CBG:CBD | −294.66 (−492.99 −96.33) | 0.0036 |      |         | phi      | 1.9328 | 0.0000134 |
| THC              | Cigarettes:THC:CBG:CBD | −82.92 (−137.82 −28.01) | 0.0031 |      |         | phi      | 1.9328 | 0.0000134 |

One en passant notes that the intrastate abortion rate appears as an independently significant term in all four models in which it appears as an input term namely the last four of these models.

Table 2 presents a series of ten lagged geospatiotemporal models. Both spatially and temporally lagged models are presented. The lagged variables are indicated in the first column. At temporal lags 14 terms including cannabis are significant in final models and have positive regression coefficients (Models 1–5). Cannabis exposure is independently significant at one spatial lag in Models 1–5.

When an interactive term including the cannabinoids THC, CBD and CBG is used to replace cannabis at one temporal lag a term including CBD is significant [cigarettes:CBD interaction: β-est. = 16.16 (0.39, 31.93), P = 0.0446]. When the same procedure is repeated at two temporal lags terms including CBG and CBD are significant in final models.

The intrastate abortion rate is again included in all ten final models.

Table 3 lists selected e-values which issue from these models. Supplementary Table S16 is an ordered list of the minimal e-values. It is noted to range from 1.13 to 65.66 × 10−14. Many highly significant differences are seen between many of the lines in the scatter-plots and between the notches for the illegal—Decriminalized cannabis status and the illegal and liberal cannabis legislative paradigms.

The results of linear regressions as suggested by Fig. 6 are shown in Table 4. Many highly significant differences are documented. For example the decriminalized status is noted to have a significantly higher BCI [β-est. = 3.36 (2.51, 4.21), P = 2.60 × 10−14] as is the liberal status [β-est. = 2.31 (1.65, 2.96), P = 9.09 × 10−12]. The relevant e-values are shown in Table 3. For these two data the minimum e-values are 2.32 and 2.14.

For the BCI by dichotomized legal status the relevant BCIs for illegal versus liberal status are 65.19 ± 0.21 and 67.50 ± 0.27/100,000, respectively (t = 6.8354, df = 654.84, P = 1.87 × 10−11). The intrastate abortion rate has featured in many of the above regression tables in final models. Supplementary Table S17 summarizes the estimates and their CIs, relative risks (RRs) and e-values from 23 final models. As shown in Supplementary Table S18 21 of these 23 minimum e-values are greater than the critical 1.25 threshold [94].

**Discussion**

**Main Results**

Data demonstrate for the first time a strong relationship between cannabis exposure and BCI which is robust to adjustment for other age, sociodemographic and selected reproductive covariates in regression models of various forms, is applicable to all cannabisinoids investigated namely THC, CBG and CBD, is maintained across space and time, is observed across all six ethnicities studied, persists after spatial and temporal lagging to at least eight years, is evident after inverse probability weighting and is associated with high e-values and may thus be properly said to be causal in nature. BCI is significantly higher under medical and decriminalized cannabis legal paradigms and under cannabis-liberal paradigms generally. To the best of our knowledge this relationship has not been disclosed previously.
Table 3: e-Values for BCI

| Parameter                                           | Estimate (CI)       | RR (CI)          | e-Values          |
|-----------------------------------------------------|---------------------|------------------|-------------------|
| **LINEAR MODELS**                                   |                     |                  |                   |
| Cannabis_Use                                       | 3.93 (2.99, 4.87)   | 2.23 (1.84, 2.69)| 3.88, 3.09        |
| Cannabinoids                                        |                     |                  |                   |
| THC                                                 | 2.25 (1.61, 2.89)   | 1.57 (1.38, 1.79)| 2.53, 2.11        |
| Cannabichromene                                     | 3.68 (2.76, 4.6)    | 2.11 (1.75, 2.55)| 3.64, 2.90        |
| CBG                                                 | 3.23 (2.42, 4.04)   | 1.93 (1.64, 2.27)| 3.27, 2.66        |
| CBN                                                 | 1.96 (1.38, 2.54)   | 1.458 (1.32, 1.67)| 2.33, 1.97        |
| CBD                                                 | 1.15 (0.39, 1.9)    | 1.25 (1.08, 1.45)| 1.81, 1.37        |
| Legal status                                         |                     |                  |                   |
| Decriminalized                                      | 3.36 (2.51, 4.21)   | 1.98 (1.67, 2.35)| 3.37, 2.32        |
| Medical                                              | 1.63 (0.8, 2.46)    | 1.39 (1.17, 1.65)| 2.13, 1.64        |
| Time × Legal status                                  | 0.33 (0.13, 0.52)   | 1.06 (1.02, 1.10)| 1.32, 1.18        |
| Year × Medical                                       | 0.28 (0.08, 0.47)   | 1.05 (1.02, 1.09)| 1.28, 1.14        |
| Dichotomized legal status                           |                     |                  |                   |
| Liberal                                              | 2.31 (1.65, 2.96)   | 1.59 (1.39, 1.82)| 2.56, 2.14        |
| Year × Liberal                                       | 0.18 (0.07, 0.3)    | 1.03 (1.01, 1.06)| 1.24, 1.13        |
| **MIXED EFFECTS MODELS**                            |                     |                  |                   |
| Cannabis alone                                       | 3.06 (2.15, 3.97)   | 2.16 (1.72, 2.72)| 3.75, 2.83        |
| Age × cannabis interaction                          | 8.75 (3.55, 13.96)  | 9.42 (2.49, 35.59)| 18.33, 4.42       |
| Adding—Drugs                                        | 3.95 (2.81, 5.09)   | 2.89 (2.12, 3.91)| 5.21, 3.67        |
| Adding—Full model                                   | 3.08 (1.9, 4.26)    | 2.46 (1.75, 3.49)| 4.37, 2.89        |
| Interactive—Full model                              | 24.73 (14.98, 34.47)| 1.67E + 03 (90.37, 31.16E + 04)| 3.35E + 03, 180.25|
| Cigarettes × Cannabis:AUD                           | 1974.44 (1121.84, 2827.04) | 3.25E + 03 (3.33E + 04)+, Infinity)| Infinity, 6.66E + 146|
| Interactive with ethnic THC exposure                | 3.53 (2.88, 4.18)   | 3.31 (2.67, 4.15)| 6.12, 4.78        |
| Asian THC                                           | 27.9 (21.49, 34.32) | 1.35E + 04 (1.52E + 03, 1.19E + 05)| 2.70E + 04, 3.05E + 03|
| NHWhite THC                                         | 5.94 (4.41, 7.47)   | 7.57 (4.49, 12.74)| 14.61, 8.46       |
| NHWhite THC × Hispanic THC                          | 3.99 (2.77, 5.21)   | 3.89 (2.57, 5.90)| 7.26, 4.59        |
| Interactive with ethnic CBD exposure                | 65.45 (50.11, 80.79) | 9.23E + 09 (7.45E + 06, 1.14E + 11)| 1.85E + 09, 1.49E + 07|
| NHCaucas_CBD: NHAfrican_CBD                        | 7.87 (5.55, 10.18)  | 11.95 (5.78, 24.75)| 23.41, 11.03      |
| Asian CBD                                           | 1.32 (0.67, 1.98)   | 1.52 (1.58, 1.66)| 2.40, 1.77        |
| Interactive—Cannabinoids as main effects            | 150.1 (74.14, 226.05)| 2.14E + 21 (3.77E + 10, 1.21E + 32)| 4.28E + 21, 7.56E + 10|
| Cigarettes × CBG                                   | 25.77 (5.11, 46.44) | 4.59E + 03 (5.46, 3.87E + 06)| 9.19E + 03, 10.39|
| CBD                                                 | 3.00 (0.53, 5.47)   | 2.67 (1.19, 2.78)| 4.78, 1.67        |
| Cigarettes × CBD                                   | 80.19 (5.88, 154.5) | 2.49E + 11 (7.51, 8.25E + 21)| 4.97E + 11, 14.50|
| **PANEL REGRESSION**                                |                     |                  |                   |
| Additive model—Drugs only                           | 5.52 (4.18, 6.86)   | 1.27 (1.20, 1.36)| 1.87, 1.70        |
| Adding full model                                   | 8.226 (6.79, 9.66)  | 1.51 (1.41, 1.63)| 2.40, 2.17        |
| Interactive full model                              | 26.87 (22.81, 30.94)| 4.23 (3.40, 5.26)| 7.93, 6.26        |
| Cannabis                                             | 26.69 (19.39, 33.98)| 1.28 (1.18, 1.37)| 1.87, 1.66        |
| Interactive full model—2 Lags                       | 110.73 (53.78, 167.69)| 2.64E + 04 (232.51, 3.01E + 06)| 4.33E + 04, 464.53|
| Cannabis:AUD                                        | 1639.45 (1309.82, 1969.08)| 4.00E + 29 (8.99E + 23, 1.78E + 35)| 8.00E + 29, 1.79E + 24|
| Interactive full model—4 Lags                       | 116.37 (66.05, 166.7)| 2.90E + 03 (93.04, 9.07E + 03)| 5.81E + 03, 185.58|
| Cannabis:AUD                                        | 2190 (1656.88, 2723.12)| 3.59E + 63 (2.75E + 51, 4.69E + 75)| 7.19E + 63, 5.51E + 51|
| Cannabis:AUD                                        | 5240 (3640.64, 6859.36)| 1.92E + 167 (2.73E + 130, 1.34E + 204)| Infinity, 5.47E + 130|
apparently because it has not been investigated earlier and has also not been explored in a space–time context by prior researchers.

Cannabis genotoxicity has previously been demonstrated in relation to testicular and several paediatric cancers [12–15, 28, 33, 34, 36, 38–41], with genotoxicity expected to be reflected in birth defects and in tumourigenesis rates [96]. Transgenerationally transmissible cannabis genotoxicity has also been implied by previous studies linking prenatal cannabis exposure with congenital birth defects including anencephalus, diaphragmatic hernia, gastoschisis and oesophageal atresia [97–100], with ventricular septal defect and Ebstein anomaly [101] and more recently with atrial septal defect [65]. Prenatal paternal exposure has been linked with transposition of the great vessels [102]. Indeed a classical report from Hawaii linked prenatal cannabis exposure with 21 birth defects [103], in Canada total birth defects were recently linked with cannabis use [104], in Australia 18 defects were linked with cannabis exposure [105] and in Colorado a 29% rise in total congenital defects was noted across the period of legalization [106, 107].

One report has recently identified 42 birth defects as being significantly more common in the highest quintile of cannabis using US states compared to the others including arm reduction defects [64]. Reports from several areas in France where cannabinoids are allowed in the food chain and Germany show an unexplained spike in congenital limb defect anomalies [108–111]. However no such rise has been noted in nearby Switzerland where cannabinoids are not permitted to enter the food chain [108–110]. On the basis of this recent European experience one can only conclude in the broader genotoxic context that allowing cannabinoids to enter food chain can potentially lead to very serious public health consequences indeed.

The major question at issue appears to be therefore not “Is cannabis genotoxic?”—for that issue has clearly been settled in the affirmative beyond reasonable doubt—but “How genotoxic is cannabis?”—or more precisely “What are the limits of cannabis genotoxic?”—for that issue has clearly been settled in the affirmative beyond reasonable doubt.

As important as what has been shown, it seems that what has not been shown is even more intriguing. The striking finding that the commonest human cancer is causally related to cannabis consumption leaves open the question of which other cancers might also be similarly implicated. It raises the important issue that cannabis-related genotoxicity may have been seriously

| Parameter | Estimate (CI) | RR (CI) | e-Values |
|-----------|--------------|---------|----------|
| Interactive full model—Cannabis as instrumental variables | | | |
| Cigarettes:Cannabis | 20.44 (9.5, 31.38) | 281.71 (13.84, 5.73E + 03) | 562.93, 27.15 |
| Cannabis AUD | 196.03 (74.72, 317.34) | 3.14E + 23 (9.66E + 08, 1.02E + 38) | 6.28E + 23, 1.93E + 09 |

Interactive full model—Ethnic THC exposure as instrumental variables

| Parameter | Estimate (CI) | RR (CI) | e-Values |
|-----------|--------------|---------|----------|
| Cigarettes:Cannabis | 23.95 (8.92, 38.97) | 729.25 (11.75, 45.24E + 04) | 1.45E + 03, 22.99 |
| Cannabis AUD | 245.79 (56.05, 435.54) | 2.42E + 29 (5.58E + 06, 1.05E + 52) | 4.84E + 29, 1.11E + 07 |

Interactive full model—Cannabinoids as instrumental variables

| Parameter | Estimate (CI) | RR (CI) | e-Values |
|-----------|--------------|---------|----------|
| Cannabis | 1.45 (0.61, 2.29) | 1.43 (1.16, 1.77) | 2.22, 1.60 |
| Additive model | | | |
| Cannabis | 1.45 (0.61, 2.29) | 1.44 (1.16, 1.77) | 2.22, 1.60 |
| Additive model without ethnicity | | | |
| Cannabis | 1.56 (0.69, 2.42) | 1.47 (1.18, 1.83) | 2.31, 1.66 |
| Interactive model | | | |
| Cigarettes:Cannabis | 3.59 (1.94, 5.24) | 2.43 (1.62, 3.65) | 4.30, 2.62 |

Interactive full model—Ethnic THC exposure as main effects

| Parameter | Estimate (CI) | RR (CI) | e-Values |
|-----------|--------------|---------|----------|
| NHAfrican_THC:Hispanic_THC | 1.14 (0.48, 1.81) | 1.33 (1.13, 1.58) | 2.01, 1.51 |
| NHAfrican_THC | 1.8 (0.34, 3.25) | 1.18 (1.09, 1.26) | 2.53, 1.41 |

Interactive full model—Cannabinoids exposure as main effects

| Parameter | Estimate (CI) | RR (CI) | e-Values |
|-----------|--------------|---------|----------|
| NHCAucas_CBD | 5.63 (2.85, 8.4) | 4.39 (2.10, 8.90) | 8.13, 3.63 |

GEOSPATIAL MODELS

| Parameter | Estimate (CI) | RR (CI) | e-Values |
|-----------|--------------|---------|----------|
| Cannabis | 7.26 (0.83, 13.7) | 1.48 (1.19, 1.85) | 2.39, 1.67 |
| 1 Temporal lags | | | |
| Cigarettes:Cannabis:Analgesics | 313.25 (200.08, 426.42) | 7.19E + 03 (209.11, 2.47E + 05) | 1.44E + 04, 417.71 |
| 2 Temporal lags | | | |
| Cigarettes:Cannabis | 21.23 (3.72, 38.73) | 244.77 (2.64, 2.26E + 04) | 489.04, 4.72 |
| 3 Temporal lags | | | |
| Cigarettes:Cannabis:Analgesics | 20.15482 (1.77, 38.54) | 166.36 (1.58, 1.74E + 04) | 332.22, 2.54 |
| 4 Temporal lags | | | |
| Cigarettes:Cannabis | 20.84 (1.36, 40.31) | 185.30 (1.42, 2.42E + 04) | 370.10, 2.19 |
| 1 Spatial lag | | | |
| Cannabis | 20.69 (5.29, 36.09) | 273.37 (4.23, 1.76E + 04) | 546.24, 7.94 |
| Lagging cannabinoids—THC × CBG | | | |
| THC:AUD | 16.69 (11.04, 22.35) | 64.43 (15.75, 263.63) | 128.37, 30.98 |
| 1 Temporal lag cannabinoids—THC × CBG | 16.16 (0.39, 31.93) | 52.63 (1.11, 2.49E + 03) | 104.76, 1.46 |
| 2 Temporal lag cannabinoids—THC × CBG | | | |
| Cigarettes CBG | 6.23 (2.06, 10.39) | 4.55 (1.65, 12.52) | 8.57, 2.69 |
Cannabinoid and other drug risk factors for female breast cancer

Figure 6: Graphs of relationship of BCI to cannabis legal status. (A) Scatterplot of BCI by cannabis legal status, (B) boxplot of BCI by cannabis legal status, (C) scatterplot of BCI by cannabis legal status dichotomized as illegal versus liberal legal paradigms and (D) boxplot of BCI by dichotomized cannabis legal status

Table 4: Linear regression of the relationship of cannabis legal status to BCI

| Parameter | Estimate (CI) | P-value | Model        | SD | Adj. R-Squared | F   | Df | P-value |
|-----------|--------------|---------|--------------|----|---------------|-----|----|---------|
| Legal status |              |         |              |    |               |     |    |         |
| $\text{lm(Cancer\_Rate \sim Legal\_Status)}$ |              |         |              |    |               |     |    |         |
| Decriminalized | 3.36 (2.51, 4.21) | 2.60E − 14 |              | 4.4734 | 0.0757 | 21.44 | 3746 | 2.51E − 13 |
| Medical | 1.63 (0.8, 2.46) | 0.0001 |              |     |           |     |    |         |
| Time × Legal status | $\text{lm(Cancer\_Rate \sim Year \times Legal\_Status)}$ |              |              |    |               |     |    |         |
| Decriminalized | $-651.52 (-1050.31, -252.73)$ | 0.0014 |              | 4.4233 | 0.0962 | 12.39 | 7742 | 4.62E − 15 |
| Medical | $-555.49 (-947.68, -163.31)$ | 0.0056 |              |     |           |     |    |         |
| Year: Decriminalized | 0.33 (0.13, 0.52) | 0.0014 |              |     |           |     |    |         |
| Year: Medical | 0.28 (0.08, 0.47) | 0.0055 |              |     |           |     |    |         |
| Dichotomized legal status | $\text{lm(Cancer\_Rate \sim Dichotomized legal\_status)}$ |              |              |    |               |     |    |         |
| Liberal | 2.31 (1.65, 2.96) | 9.09E − 12 |              | 4.5133 | 0.0591 | 48.03 | 1748 | 9.09E − 12 |
| Time × Dichotomized legal status | $\text{lm(Cancer\_Rate \sim Year \times Dichotomized legal\_status)}$ |              |              |    |               |     |    |         |
| Liberal | $-436.94 (-746.96, -126.92)$ | 0.0059 |              | 4.4887 | 0.0693 | 19.6  | 3746 | 3.08E − 12 |
| Year: Liberal | 0.18 (0.07, 0.3) | 0.0018 |              |     |           |     |    |         |

underestimated in our culture generally in the consciousness of the public health community, the medical profession, government and health regulators and the general community alike. Indeed a recent analysis of European data confirms that cannabis exposure is similarly related to several common cancers when considered in a space–time paradigm and by applying the tools of causal inference (three manuscripts in press).

AUD (formerly known as alcohol dependence) is featured in some final geospatial models but it was not independently significant or prominent in the results in the same way as cannabis,
the cannabinoids or abortion. The index of alcohol consumption used in the present analysis was AUD which is a different metric to alcohol consumption per se. The AUD measure was used as we wished to look at the possibly genotoxic effects of alcohol which are likely more linked with individuals dosing at higher levels. Importantly it has been noted that foetal alcohol syndrome is mediated epigenomically via the cannabinoid type 1 receptor (CB1R) [112–119].

While there are many modes of consuming cannabis, some common ones involve mixing cannabis with tobacco, and consuming as either a self-rolled cigarette or cigar, or smoking in a pipe. Accordingly, this may cause confounding when assessing the association of cannabis use with selected morbidities. However, despite laboratory based mechanistic evidence that compounds found in tobacco may induce BC [120, 121], data from a number of systematic epidemiological reviews have identified no overall association [122, 123]. Notwithstanding controversy still continues with a number of recent cohort studies indicating an increased risk of BCI among women with a significant history of tobacco use, or who commenced use at a young age [124, 125]. Unequivocal results likely reflect tobacco’s negative or lesser role as a contributing antecedent to BC compared to other more robust known aetiological factors. It is therefore unlikely that co-use of tobacco with cannabis impacts largely on study findings.

Although the intrastate abortion rate was not a primary focus of the present analysis it was included as a covariate. It is noted that abortion persisted as an independently significant term in many final space–time models and so it appears to be an independent BCI covariate in this space–time and causal inference analysis. However since much of these data are temporally and spatially kriged, this conclusion should be regarded as provisional at this point.

Pathophysiological Mechanisms

Endocrine Disruption

Various cannabinoids have been shown to interact with the endocrine system and have been noted to act as endocrine disruptors in ovaries, testes and placenta [126–130], and cannabinoids are also involved in breast pathophysiology [11, 131] and are normally excreted in breast milk [132, 133]. Endocrine disruption has been noted to be a powerful negative impactor of human health [134, 135]. Agonists at the Type 1 and 2 cannabinoid receptors (CB1R and CB2R) are known to interfere with the hypothalamic-pituitary-gonadal axis in human females [11], hypothalamic-pituitary-adrenal axis [136–138], with insulin [139, 140] and other hormones and to stimulate human prolactin levels [141–143]. Various cannabinoid concentrations have been noted both to stimulate [131] and inhibit [144–146] the growth of BC cells in culture.

It was recently noted that many hormones cause rapid and widespread re-arrangement of the genome through epigenomic mechanisms [147]. This makes sense particularly for the many steroid and sex hormones which are lipophilic and directly engage nuclear hormone receptors [148].

Genotoxicity and Epigenotoxicity

Several cannabinoids also act at clinically relevant doses by multiple genotoxic mechanisms on genes, the bases of DNA, chromosomes and the epigenome [64, 149–158]. Cannabis tars contain most of the same carcinogens as tobacco tars [159–163]. For example the cannabinoid THC has long been known to test positive in the micronuclear assay and micronuclei are known to be a major engine for chromothriptic events [149, 164]; THC, CBD and cannabiol (CBN) have been implicated in chromosomal translocation events [165]; THC and CBN have been implicated in congenital heart defects incidence across USA [65, 101]; cannabidiavirin and CBD have been shown to test positive in the comet assay for DNA breaks and have been shown to cause the oxidation of all four DNA bases [166]; THC largely modulates DNA methylation at CpG islands of sperm DNA with neurological and functional impacts for subsequent generations [150, 151, 154–156, 158]; and cannabis use has been linked with the chromosomal trisomy Downs syndrome in Canada, Australia, Colorado, Hawaii and the USA [103–105, 167, 168]. Cannabinoids are also highly toxic to mitochondria [169–177] which impact genetic and epigenetic processes directly through ATP and epigenetic substrate supply [107, 178, 179] and also indirectly through mitonuclear balance pathways [178, 179]. Hence multiple pathways exist by which cannabis use could potentially impact BCI.

The subjects of cannabinoid genotoxicity and epigenotoxicity are large and complex and have been reviewed in detail elsewhere [40, 64, 65, 105, 107, 149–158, 166, 168, 180]. In this regard a recent single tumour cell DNA sequencing study showing that haematological malignancies can arise due to clonal sweeps in the setting of specific genotoxic stressors is of particular interest and may also apply to solid organ carcinogenesis [181].

Transgenerational Effects

Epimutations of the DNA methylome noted in the sperm after cannabis use in rats and humans include pathways in cancer, hippo pathways and mitogen-activated protein kinase pathways which are all involved in cancer [156, 182]. Significant overlap has also been found with autism genes, genes involved in neural, cerebral, cognitive and brain development and learning, glutamatergic synapse formation and cardiogenesis [156, 182]. This important finding implies transgenerational epigenetic inheritance in humans and confirmed the significance of such findings in rodents on reproductive outcomes.

Reproductive cancers identified as cannabis-associated by a recent review of European data include testicular cancers including both non-seminoma germ cell and seminoma and also its homologue in the female the dysgerminoma of the ovary together with breast, vulvar and vaginal cancers [183].

In a recent review of European congenital anomalies genital disorders including hypospadias and the genetic syndromes trisomies 21, 18 and 13 (Syndromes of Down, Edwards and Patau) along with chromosomal disorders, genetic and microdeletion syndromes, and Turner (female XO) and Klinefelter (male XXY) syndromes were found to be cannabis-related [183]. It is important to note that if one adds together the length of all the chromosomes implicated by these clinical syndromes (13, 18, 21, 22 and X) with those implicated from cannabis-related tumorigenesis (testicular cancer and ALL [43, 48]. Chromosomes 12 and 19) one arrives at a surprising 585 MB of the 3000 MB or 19.5%, of human genome directly impacted by cannabinoid genotoxicity.

Accelerated Ageing Including Potentially Gamete Ageing

It was shown several years ago that cannabis consumption is associated with an increase in cardiovascular age and therefore the biological age of the human organism [185].
It has also been shown that patients who consume tobacco, opioids and cannabis have a dramatic truncation of the female reproductive lifespan with a 58% reduction in their fertile period as measured by the key metric the Follicle Stimulating Hormone (FSH)/Luteinizing Hormone (LH) ratio which inverts pre-menopausally and is a sensitive biomarker of the perimenopause [185]. These investigators found a reduction in the age of ratio inversion from 46.2 years to 28.1 years. It was also recently demonstrated that smoking 20 cigarettes daily reduces the age of natural menopause by only one year [186]. Moreover, these investigators also found that ovarian ageing is invariably caused by activation of the DNA damage response (DDR). This further implies that the dramatic acceleration of premature ovarian failure by combined opioid–cannabinoid use is induced by a marked increase in ovarian DDR to damaged germline DNA.

Numerous deleterious effects of cannabinoids on sperm development have been described including DNA fragmentation, disruption of protamine–histone substitution and so DNA packing, DNA nicking by nuclear transition protein 2 (tnp2), protection of DNA and nuclear size and a reduced concentration of sperm in the seminiferous ducts [177, 187, 188]. Cannabinoids are also found in the midcycle oviduct fluid and in the fluid of the Graafian follicle [177, 187, 188].

Together with the finding that nuclear architecture is exquisitely sensitive to hormonal signals [147] this demonstrates that reproductive tissues can be powerfully impacted by environmental stimuli. A dramatic effect of cannabis on oocyte cell division was also shown by classical investigators including the documentation of a 20% cell loss with just a single oocyte cell division and severe derangement of nuclear architecture including nuclear blebs and bridges and chromosomal nondisjunctions [189]. The above noted parallelism between the well-established cannabis-testicular non-seminomatous germ cell tumours [12–15, 18–21] and the newly described link between cannabis consumption and the homologous female tumour the ovarian dysgerminoma is particularly germane in regard to gonadal and germ cell ageing (manuscript submitted).

These more recent findings collectively imply accelerated ageing of the germ cells themselves and thus the gametes derived from them as their downstream progeny. In terms of breast carcinogenesis one can conjecture that it may be shown in time that these factors may be relevant to either the oncogenic incubation phase in the adult or in pre-conceptual developmental influences.

It is important to observe that whilst malignant and congenital anomaly outcomes are relatively rare as cannabinoids increasingly enter the food chain [190], population-wide genomic and epigenomic ageing can be expected to become universal as implied by elegant, sophisticated and powerful research on epigenomic ageing from Harvard Medical School [191].

**Generalizability**

We feel that the present results are widely generalizable for several reasons. The present analysis is based on a large population-level data set and has many narrow CIs and highly significant P-values. This analysis takes into account many covariates which have been previously shown to be related to BCI. Many very high e-values imply that the inclusion of further covariates is unlikely to disturb the main conclusions. Moreover, the results explain various lifestyle factors which may be driving a global increase in the BCI beyond those which are have been identified to date. The strongly positive results from the causal inference analyses indicate that the relationship fulfills the criteria for causality and so is likely to apply in all nations where data of adequate quality exists.

**Strengths and Limitations**

This report has a number of strengths and weaknesses. Its strengths include the use of a national census database for BC and socio-economic and sociodemographic variables, the use of a nationally representative sample with high response rates for drug use data, the confirmation of the main results by a variety of regression techniques, the use of multivariable regression across both space and time simultaneously, the use of spatially and temporally lagged models, the use of additive and interactive models, the calculation of high precision P-values down to $P < 10^{-320}$, the use of multiple covariates across different domains, the use of multiple graphs and map-graphs to display the results and direct the analysis, the use of different forms of correlation, the use of the techniques of causal inference particularly inverse probability weighting and e-values and the use of robust regression techniques. Weaknesses include the unavailability of some component data sets for HRT, hormonal contraception and abortions, the unavailability of data relating to other reproductive factors such as age of first childbirth, age of menarche, age of menopause and duration of breastfeeding and the limitation of the present analysis to state-level data. However, the generally high e-values indicate that the inclusion of further covariates is unlikely to change the principal conclusions substantially. Clearly subsequent analyses in this field need to be performed by those who have access to more comprehensive data sets and can perform analyses at higher geospatial resolution.

A further extension of the present work is the combining of causal inference techniques into spatial models. In R-packages such as the complex survey package it is possible to assign the error term as a product of several lists of weights [81]. This facility is not presently implemented in geospatial modelling techniques in R. However such an implementation within geospatial methods would represent a major addition to the field by ushering in a first-in-class causal geospatial method which has not previously been deployed. Such an implementation would therefore powerfully enhance both formal quantitative causal inference as well as geospatial inferential techniques. The option of the use of instrumental variables within spatial methods would also be analytically and inferentially of both considerable interest and utility.

The implications of this finding are far reaching. As noted in the Background section of the present paper BC is the commonest cancer of all. Cannabis is presently enjoying widespread popularity deriving from its celebrated and indeed unique status in the popular culture and the common perception of its apparent safety as a “soft drug.” In many US states foods which are marketed as low in THC are represented as posing no threat to human health. The dramatic results presented above applying to CBG and CBD in particular demonstrate that in relation to BC this is quite untrue and indeed in terms of the downstream public health implications constitutes a very dangerous practice.

This is particularly applicable to “industrial hemp” which is said to be low in THC, but likely higher in other cannabinoids. The US Farm Act is believed to have allowed hemp products to be used as cattle fodder, implying that cannabinoids can now enter the food chain in meat, milk and dairy products. If used in chicken feed, this will extend also to eggs.
In states such as Colorado where cannabis is completely legalized, CBD cookies, sauces, jams and sweets are widely marketed apparently as they are non-psychoactive and said to be benign. Both claims are likely erroneous. CBD in fact does bind to CB1 receptors at high doses [192–196] which can presumably be achieved under high level dosing such as may commonly be seen under cannabis-legal paradigms, and CBD has mental and genotoxic effects which can be reversed by application of canonical CB1 antagonists [96].

**Conclusion**

The present analysis shows that BCI demonstrates a strong bivariate relationship to cannabis use and exposure to the cannabinoids THC, CBD and CBG across all ethnicities which is maintained after multivariable regression performed in a variety of model types, persists after space–time regression and is a causal relationship as demonstrated by the canonical accepted tools of epidemiological causal inferential reasoning. BCI was significantly higher under cannabis-liberal legal paradigms including medicalization and decriminalization. The kriged intrastate abortion rate was also shown to be an independent and robust BCI covariate in space–time analyses and was shown to be causally related to BCI. Due to the missing data fraction in this covariate field this conclusion is provisional at this point. This work therefore adds the cannabinoids as a previously unrecognized class of breast carcinogens which may explain some of the recent global rise in BCI. These robust and internally consistent findings involving on the one hand the commonest human cancer of all and on the other three major cannabinoids including CBD carry far-reaching implications and indicate that cannabinoid genotoxicity has been seriously underestimated broadly across western culture. Cannabinoid genotoxicity can be expected to manifest in public health in the clinical domains of congenital anomalies and cancer epidemiology. Combining recent multi-jurisdictional congenital anomaly data from Colorado, Hawaii, Canada, Australia and the USA [64, 103–105, 157, 167, 168] with the present report and previous testicular and paediatric cancer reports [12–15, 18, 21, 33, 34, 36, 38, 39], together with well-documented negative impacts on mental health [66] and paediatric autism rates [62, 63, 100], the conclusion that widespread cannabis genotoxicity and neurotoxicity as implicit in cannabis-liberal paradigms constitute an impending public health disaster of catastrophic proportions seems inescapable. Further historical and time-projected health econometric quantitative studies across these wide domains of clinical pathology are indicated.

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**Data availability**

All data generated or analysed during this study are included in this published article and its supplementary information files. Data have been made publicly available on the Mendeley Database Repository and can be accessed from this URL: http://dx.doi.org/10.17632/y2jcvphmc.1.

**Supplementary data**

Supplementary data is available at EnvEpig online.

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**Conflict of interest statement**

None declared.

**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 7 January 2020 (No. RA/4/20/4724). Consent to participate was not required as the data utilized were derived from publicly available anonymous data sets and no individual identifiable data were utilized. All methods were performed in accordance with the relevant guidelines and regulations.

**Consent for publication**

Not applicable.

**Author 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. All authors have read and approved the manuscript.

**Abbreviations**

| Acronym | Expanded meaning |
|---------|------------------|
| lambda  | Autocorrelation in the spatial error model term |
| LogLik  | Log Likelihood at Model Optimization |
| phi     | Random Effects model term |
| psi     | Serial error correlation model term |
| rho     | Spatial error model term |
| semsre  | Spatial error with serial correlation and random effects with spatial lagging |

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