gastroenterology insights

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Sociodemographically Stratified Exploration of Pancreatic Cancer Incidence in Younger US Patients: Implication of Cannabis Exposure as a Risk Factor

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Abstract: Introduction. The aetiology for the recent increase in pancreatic cancer incidence (PCI) in the US is unknown. This paper provides an epidemiological investigation of the exponential increase in PCI in young people aged 15–34 years, particularly amongst females, with a focus on the exponential rise amongst African American females, and its relationship to substance use. Methods. National pancreatic cancer data from recent reports. Tobacco, alcohol and daily cannabis use data taken from the annual nationally representative National Survey of Drug Use and Health, response rate = 74%. Results. Amongst the 15–34-year-aged cohort, PCI was found to be significantly more common in females (females: β-est. = 0.1749 $p = 0.0005$). African American females are noted to have the highest rates of daily cannabis use amongst females in the 26–34 and 35–49-year groups. The relationship between PCI and daily cannabis use was strongly positive across all ethnicities and in both sexes. In African American females, the Pearson correlation between daily cannabis use and PCI was R = 0.8539, $p = 0.0051$. In an additive multivariable model for each sex and race, cannabis was the only significant term remaining in the final model in the 15–34-year-aged cohort and thus out-performed alcohol as a risk factor. The most significant term in multivariate models was the alcohol:cannabis interaction which was highly significant in all ethnicities from $p = 2.50 \times 10^{-7}$ for Caucasian American females and the highest E-value pair was for Hispanic American females (E-value estimate = 1.26×10^{102} and E-value lower bound 2.20×10^{74}). Conclusion. These data show that cannabis fulfills quantitative criteria of causality in all age, sex and ethnicity cohorts, and thus explains both the recent surge in PCI and its ethnocentric predominance. Cannabis interacts powerfully genotoxically and cancerogenically with alcohol, with increases in cannabis use driving the current PCI surge. These results raise the important question as to how much cannabis might be responsible for the modern renaissance in cancer rates amongst younger people.

Keywords: cannabis; cannabinoid; genotoxicity; epigenotoxicity; transgenerational inheritance

Citation: Reece, A.S.; Hulse, G.K. Sociodemographically Stratified Exploration of Pancreatic Cancer Incidence in Younger US Patients: Implication of Cannabis Exposure as a Risk Factor. *Gastroenterol. Insights* **2023**, *14*, 204–235. https://doi.org/10.3390/gastroent14020016

Academic Editor: Yasushi Sasaki

Received: 1 March 2023
Revised: 1 May 2023
Accepted: 7 May 2023
Published: 11 May 2023

1. Introduction

Pancreatic cancer is a common and serious condition with a five-year survival rate of only 12.5% in 2013–2019 [1]. Pancreatic cancer is becoming more common in many places [1] for reasons which are presently obscure. Indeed, the rising incidence of many different cancers occurring in younger people has been noted across many nations [2]. This phenomenon begins to challenge the medical dogma that cancer is primarily a disease of older age. A detailed review of the whole USA caseload of pancreatic cancer 2001–2018 was recently published numbering in total around 734,761 cases [3]. Very concerningly, it showed that the disease is growing quickly across the USA and is more common in females in many age cohorts. Indeed, in some groups, such as African American females aged 15–34 years and for localized disease, exponential effects were noted. Some of the curves drawn in that report suggest that a break point occurred in pancreatic incidence

around 2006–2009. The authors suggest that an environmental intoxicant may be acting whose effects were most marked amongst females [3] and it appears to have become more widespread about the time of the decadal change.

In this context, recent reports from the USA and Europe that cannabis is associated with pancreatic cancer [4–7] become both interesting and highly relevant. Moreover, as it is well known that cannabis use is being popularized in the USA and its daily use has doubled in that country in recent years [8,9], it is theoretically possible that the use of a known carcinogen is becoming widespread and commonplace and indeed normalized. Interestingly, the role of cannabis in hepatocarcinogenic changes is increasingly being realized and the American Association of Liver Diseases has recently released a statement to this effect [10]. This conclusion solidly implicates cannabinoids in gastrointestinal system oncogenic pathways.

Several powerful epigenomic studies of cannabis exposure in humans and rodents have recently appeared [11–16] which have greatly increased our understanding of cannabinoid pathophysiology. Global hypomethylation of DNA has been reported by many workers [15,17,18] and this is a change which is characteristic of aging [19–21] and also has the effect of removing the control of mobile elements from the genome which is an oncogenic and pro-aging change [22,23]. Many cannabinoids (including cannabidiol) cause single- and double-stranded DNA breaks [24–30] and this perturbation has been shown to cause aging [21] by re-arranging the epigenomic machinery and causing DNA hypomethylation [21]. Since epigenomic markers are concentrated at tissue defining superenhancers, and since superenhancers play a critical and irreplaceable role in cell lineage definition and control of differentiation state [31–35], this major change weakens cell identity and primes them towards de-differentiation and malignant transformation in the pancreas and also in many other tissues [36–42]. Moreover, cannabis exposure also weakens the CTCF boundary markers [17] including superanchors which control active gene transcription generally and superenhancer activation in particular, which further disrupts the normal control of gene expression. Many cancers are caused by superenhancers gaining aberrant access to the promoter regions of oncogenes such as KRAS, a process which is common in pancreatic neocarcinogenesis [43–45].

Modern multi-channel sequencing methods are increasingly being applied in order to advance our understanding of the pathogenesis of pancreatic cancer [45–48]. It has recently been shown that pancreatic acinar cells remember past episodes of inflammation epigenomically which is a change which both allows them to mobilize their genes more rapidly the next time they are required for a similar episode and moves them along the cancerogenic spectrum to the point where a widespread premalignant field change can be induced [45,48]. This disruption will be exacerbated by the known frequently pro-inflammatory [49–55] and generally pro-aging [56–58] effect of cannabinoids.

This is believed to be the underlying mechanism by which known predisposing factors such as gall stones and alcohol act to raise the risk of pancreatic tumours which is through chronic or recurrent inflammation in that organ [45,48].

It should be noted in passing that cancerogenesis is just one part of the broader subject of cannabinoid genotoxicity more generally. The use of significantly genotoxic compounds may be expected to be reflected in higher rates of cancer, congenital anomalies (birth defects) and aging. Increased evidence of such outcomes has appeared in the recent literature [7,59–82] which becomes important background information to the present study and is highly relevant to the consideration of causal issues. The rising rates of cannabis use have recently been shown to be driving breast cancer, acute lymphoid leukaemia, hepatocellular carcinoma, testicular cancer and total paediatric cancer in the USA [10,83–90].

Accordingly, this study tested the hypothesis that the rising rate of high intensity daily cannabis use in the USA may be an important driver of higher rates of pancreatic cancer. We particularly wanted to test this hypothesis in population subgroups defined by age, sex and ethnicity. The main focus of this study was on the pancreatic cancer incidence in younger patients of 15–34 years of age and in localized disease, which are the two groups shown in

the Abboud study where the disease appeared to be growing fastest and exponentially [3]. These dual hypotheses were formulated prior to the commencement of this study. This study also represents a quantitative follow-up of an epidemiological investigation which has recently been suggested [91].

2. Methods

2.1. Pancreatic Cancer Rates

Pancreatic cancer rates were taken from two of the graphs in the report of Abboud et. al. [6] which were Figure 4C for males and females aged 15–34 and Figure 6C for localized tumours presenting in males and females. The senior study author disclosed that data had been provided to them on a confidential basis only and they were not permitted to release it for secondary analysis (Gaddam S, personal communication). The data were taken from the graphs very carefully using highly exploded images of the graphs using WebDigitizer [92] which is a highly accurate platform for performing such tasks. These two sex-specific rates were log transformed in the interests of improving compliance with normality assumptions as indicated by the Shapiro–Wilks test.

2.2. Drug Use Rates

The data on national levels of drug use by age group, sex and ethnicity were derived from the Substance Abuse and Mental Health Services Administration (SAMHSA) 2020 National Survey of Drug Use and Health (NSDUH) [11]. This is a nationally representative study of the non-institutionalized US population conducted each year by SAMHSA. Consideration was restricted to the major ethnicities Caucasian American ("White"), African American ("Black") and Hispanic American ("Hispanic). The annual results of NSDUH appear as a Public Data Archive System (PDAS) on the Substance Abuse and Mental Health Data Archive (SAMHDA) and can be searched manually. The major terms of interest were for age (CATAG3), ethnicity and sex combined (SEXRACE) and then substance. The three substances of interest and their metrics were for tobacco, the percentage which reported tobacco consumption in the previous month (TOBMON); for alcohol, the percentage which reported alcohol consumption in the previous month (ALCMON); and for cannabis, the percentage reporting daily or near daily use for 20–30 days per month (MRJMDAYS). In each case, cross-tabulations were performed with the sex–race metric as the columns, substance exposure as the rows and the age category as the control variable. In the analysis, these three substance exposure rates were not log transformed as indicated by the Shapiro–Wilks test.

2.3. Data Analysis

The data analysis was performed in February 2023 in R Studio v 2002.12.0 Build 353 based on R version 4.2.2 (2002-10-31 ucrt)). Multiple regression and correlation matrices were constructed using the R Base and stats modules. Graphs were drawn in ggplot2 from the tidyverse [93]. Multiple graphs were arranged using the R packages ggpubr and patchwork [94,95]. Multiple regression models were reduced by the classical technique of removal of the least significant term. p-values were adjusted for multiple testing using the false discovery rate or adjustment method described by Holm. Multiple linear or exponential models were analysed simultaneously using the purrr-broom workflow described in the tidyverse [93,96,97]. E-Values were calculated using the package EValue in R [98–100]. Correlograms including correlograms of significance levels were drawn with the R Package corrplot [101]. p-values less than 0.05 were considered significant.

2.4. Data Extrapolation

Data on the rate of pancreas cancer incidence were available from the source paper by Abboud from 2001 to 2018 [3]. Drug use data from SAMHDA were available from 2002 to 2019. To match up this slight discrepancy in the time periods of the two datasets, an extra year was added in 2001 to the SAMSHA dataset and in 2019 for the pancreatic cancer

dataset. Extrapolation was performed with the predict function on the log model as detailed in the accompanying R Code. Each dataset was processed separately (pancreatic cancer 15–34 years, localized pancreatic disease, tobacco, alcohol and daily cannabis use rates).

3. Results

3.1. Input Data

Pancreatic cancer (PC) rates were taken from the figures in the paper by Abboud and colleagues as described [3]. Our main focus of interest was on the exponentially rising cancer rates in younger patients 15–34 years of age. The sex differential of this rise was first published in 2021 from the SEER dataset [102]. Abboud et.al. extended this finding by confirming the sex differential in the data of the US Cancer Statistics (USCS) dataset without the data from states contributing to the SEER data [3]. Whilst both the USCS and SEER data are available publicly, the data used by the Abboud group which omits data from the states contributing the SEER data are not publicly available. This is why the data employed had to be derived from the figures of the later publication [3]. The sex differential of the three datasets are compared directly in Supplementary Figure S1 (present publication) and are found to be qualitatively similar across all three datasets. Data on disease incidence by stage are not publicly available so this also had to be similarly derived from the published figures.

Drug use data were taken from online databases at NSDUH as discussed in the Methods section. This survey has a reported completion rate of 74% [103].

The rates of PC by sex in younger patients of 15–34-years-of-age are shown graphically in Figure 1 on linear and log scales with both quadratic and loess curves fitted. As suggested in these figures, the rates were significantly different between the two sexes when sex was considered in an additive exponential model with time (females: β-est. = 0.1749, t = 3.838, $p = 0.0005$; model Adj.R.Squ. = 0.90, F = 1598.1, df = 2.33, model $p < 2.2 \times 10^{-16}$). When sex was considered as an interactive term with time, both sex as a factor (females: β-est. = −35.99, t = −2.148, $p = 0.0394$; model Adj.R.Squ. = 0.9103, F = 119.4, df = 3.32, model $p < 2.2 \times 10^{-16}$) and in a sex:time interaction (Females: β-est. = 0.0180, t = 2.159, $p = 0.0385$) were significant.

Figure 2 shows the rates of tobacco consumption by the ethnicity, gender and age cohorts over time and a general decline is observed consistent with the overall trend to reduced tobacco consumption in the community.

Figure 3 is a similar representation of alcohol consumption. This pattern also shows an earlier rise followed by a later decline in all ethnicities and age cohorts.

Daily or near daily cannabis use trends are shown in Figure 4 by age, sex and ethnicity. Strong rises are noted in all sub-groups. African American females are noted to have the highest rates of daily cannabis use amongst females in the 26–34 year group and in the 35–49 year group. Indeed, amongst African American females in this age cohort, daily or near-daily use rose from 3.11% in 2002 to 9.59% in 2019 which represents more than a tripling in rate (308% rise). This compares to rises amongst Hispanic American females from 1.05% to 5.02% (334%) and in Caucasian American females from 3.19% to 7.72% (242%).

The rises in near daily cannabis use in males in this age cohort across this period for these three ethnicities were for African Americans 7.08% to 15.9% (224%), Caucasian Americans 7.51% to 12.8% (170%) and for Hispanic Americans 3.45% to 10.1% (292%).

In Figure 5, NSDUH respondents have been dichotomized into patients older than 50 years and those who are younger. There is a clear trend to increased substance use for all types in younger patients. This difference is particularly marked in the case of cannabis where monotonic rises are also observed (Figure 5E,F).

Figure 6 sets out the relationship of pancreatic cancer incidence (PCI) to the various substance exposures. The relationship of PCI with tobacco appears to be inverse (lower panels). The relationship with alcohol is apparently non-descript (upper panels). However, for all ethnicities and in both sexes the relationship with daily cannabis use is clearly strongly positively correlated (middle panels).

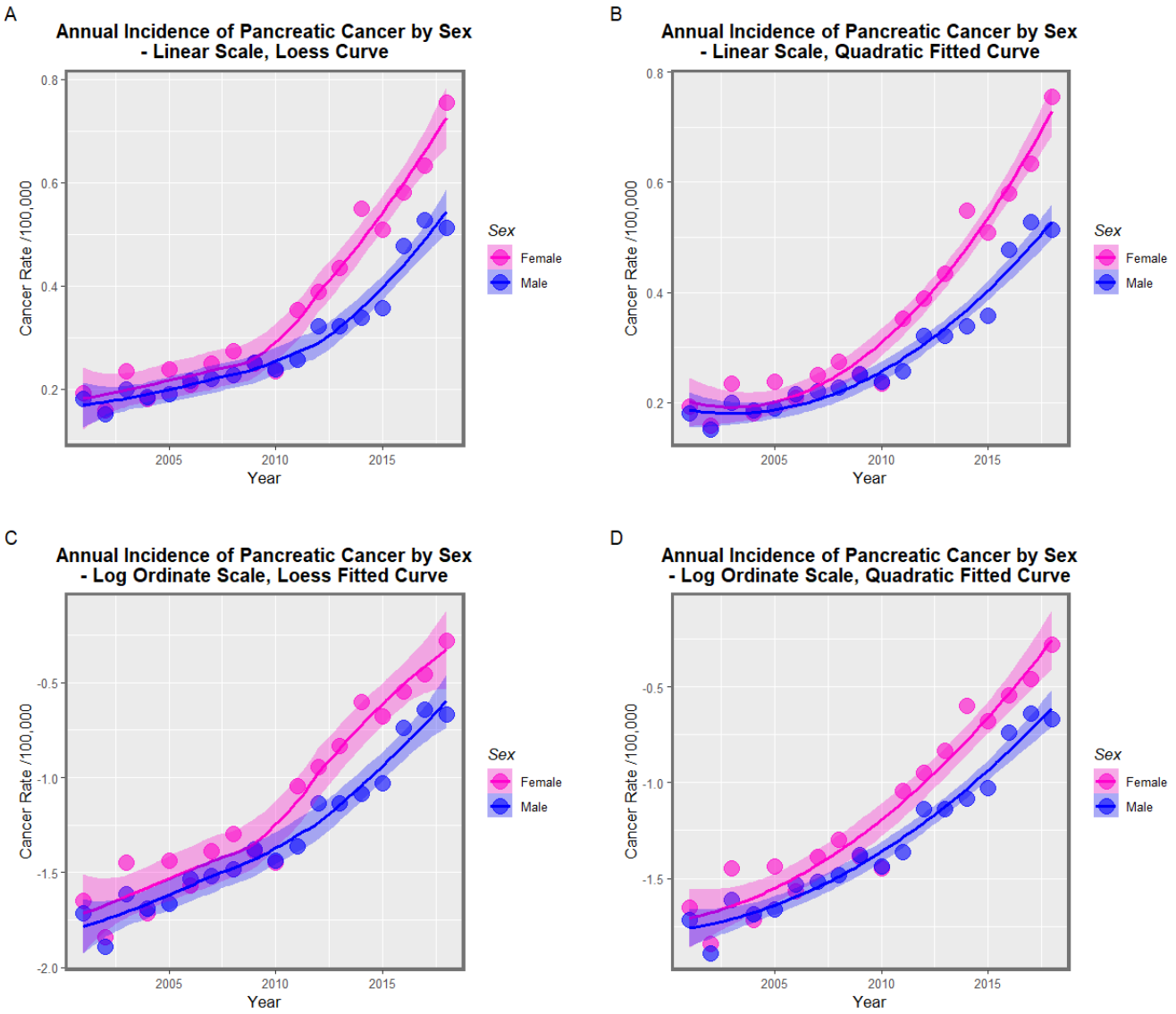

Figure 1. Annual incidence of pancreatic cancer with (**A**) linear scale and loess fitted curves, (**B**) linear scale and quadratic fitted curve, (**C**) log scale and loess fitted curve and (**D**) log scale and quadratic fitted curves.

3.2. Correlations

Figure 7 is a correlogram showing the correlation between the two different pancreatic cancer rates (15–34 years and localized disease (HOP) shown in third and fourth rows) and tobacco, alcohol and cannabis in males of a Caucasian background 18–34 years. The left-hand panel depicts the correlation coefficients and the panel on the right shows the statistical significance. The left-hand panel indicates the strong correlation of both pancreatic cancer and localized disease with cannabis exposure (Pearson R = 0.83, 0.70) which are both significant (p = 0.006 and 0.023), respectively. Negative correlations of pancreatic cancer with both alcohol and tobacco are observed. A weak and non-significant positive correlation between daily cannabis and alcohol use is noted here (R = 0.1657, p = 0.1369).

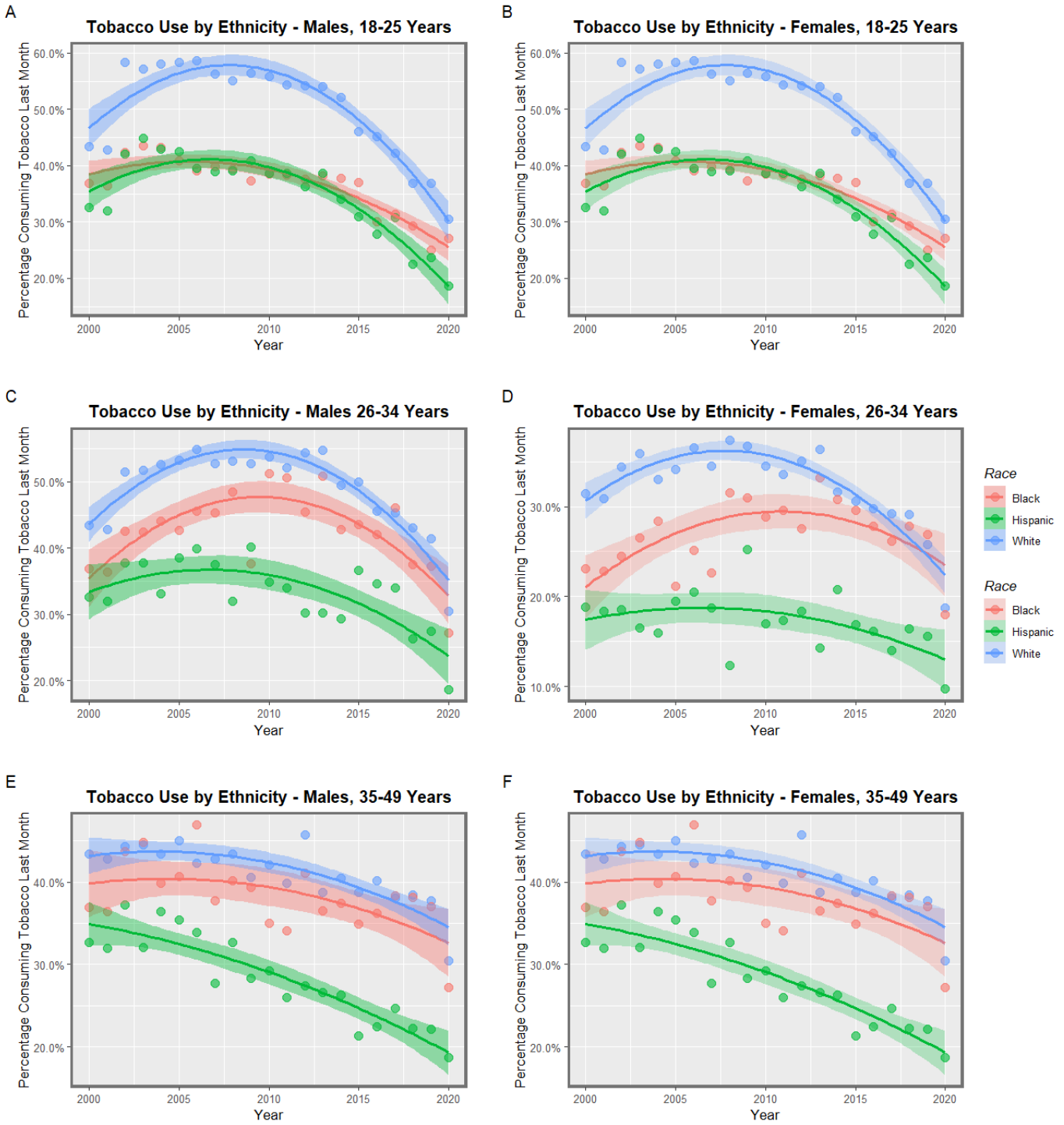

Figure 2. Tobacco Consumption by Sociodemographic Strata.

In African American males of 18–34 years, a similar pattern is observed (Figure 8). In this case, the Pearson correlation coefficients for pancreatic cancer and for localized disease are 0.83 and 0.64 which are again significant (0.007 and 0.038).

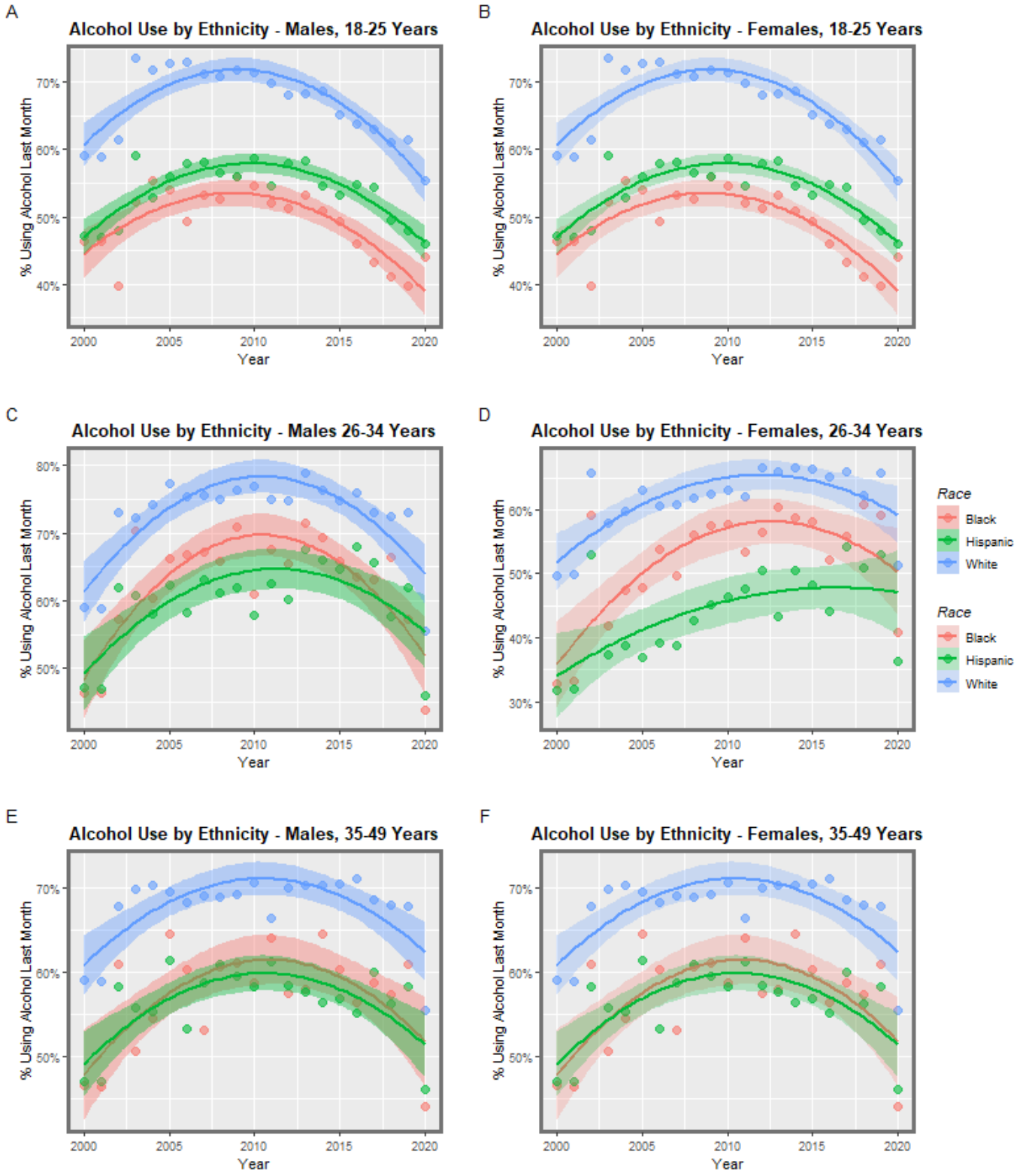

Figure 3. Alcohol Consumption by Sociodemographic Strata.

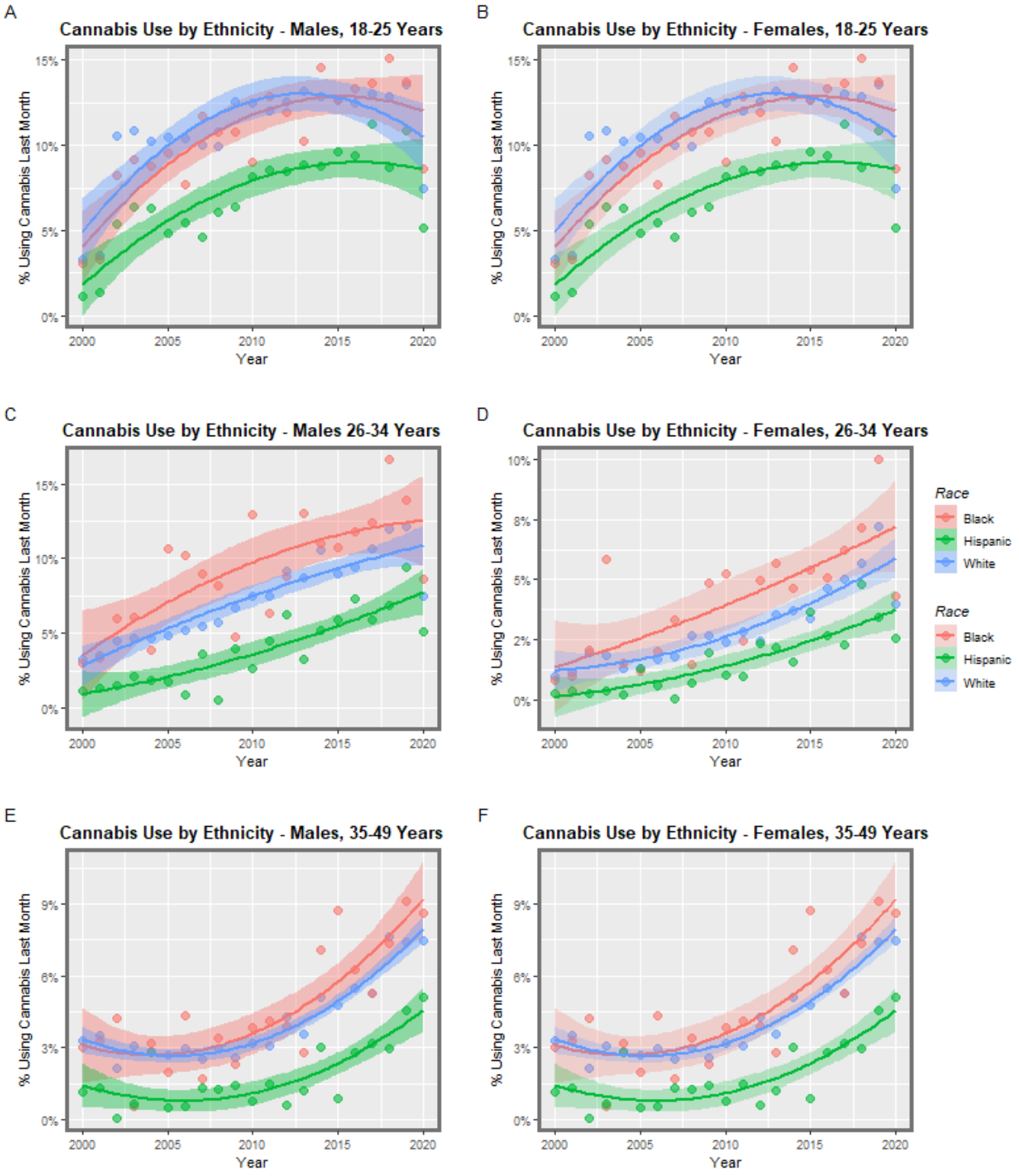

Figure 4. Near Daily Cannabis Use by Sociodemographic Strata.

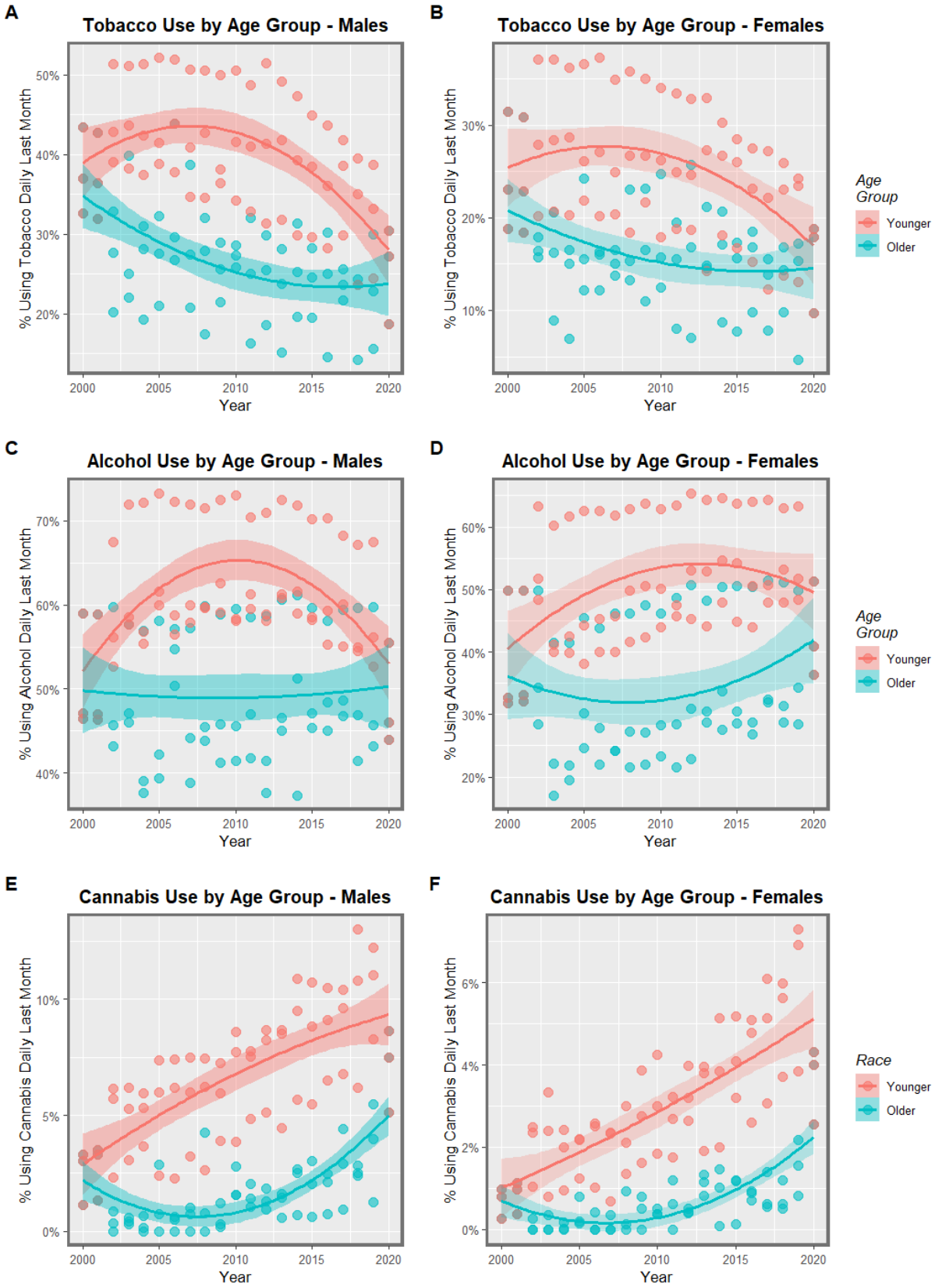

Figure 5. Substance Use by Age Group as younger or older than 50 years.

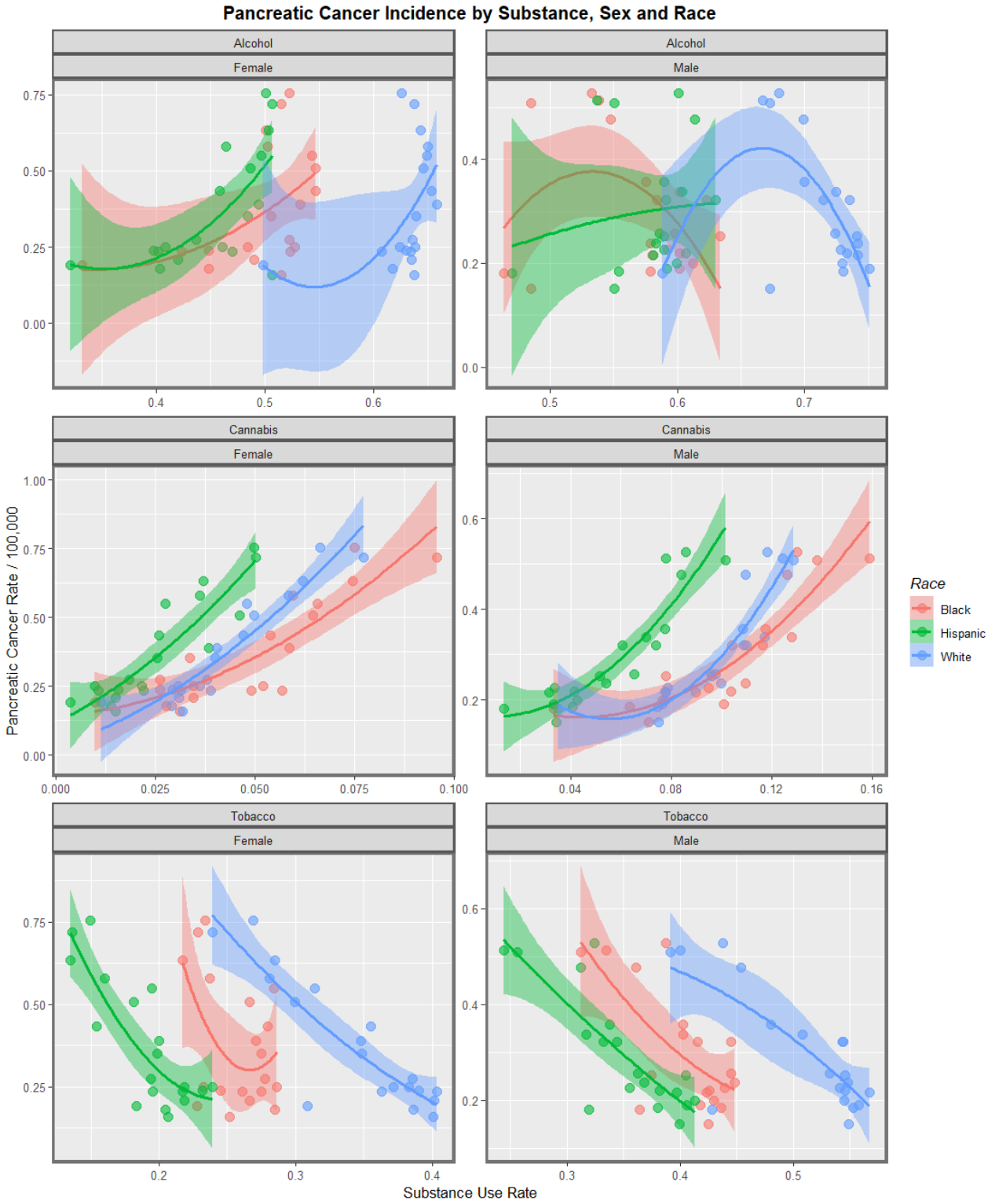

Figure 6. Substance Exposure by Sociodemographic Strata.

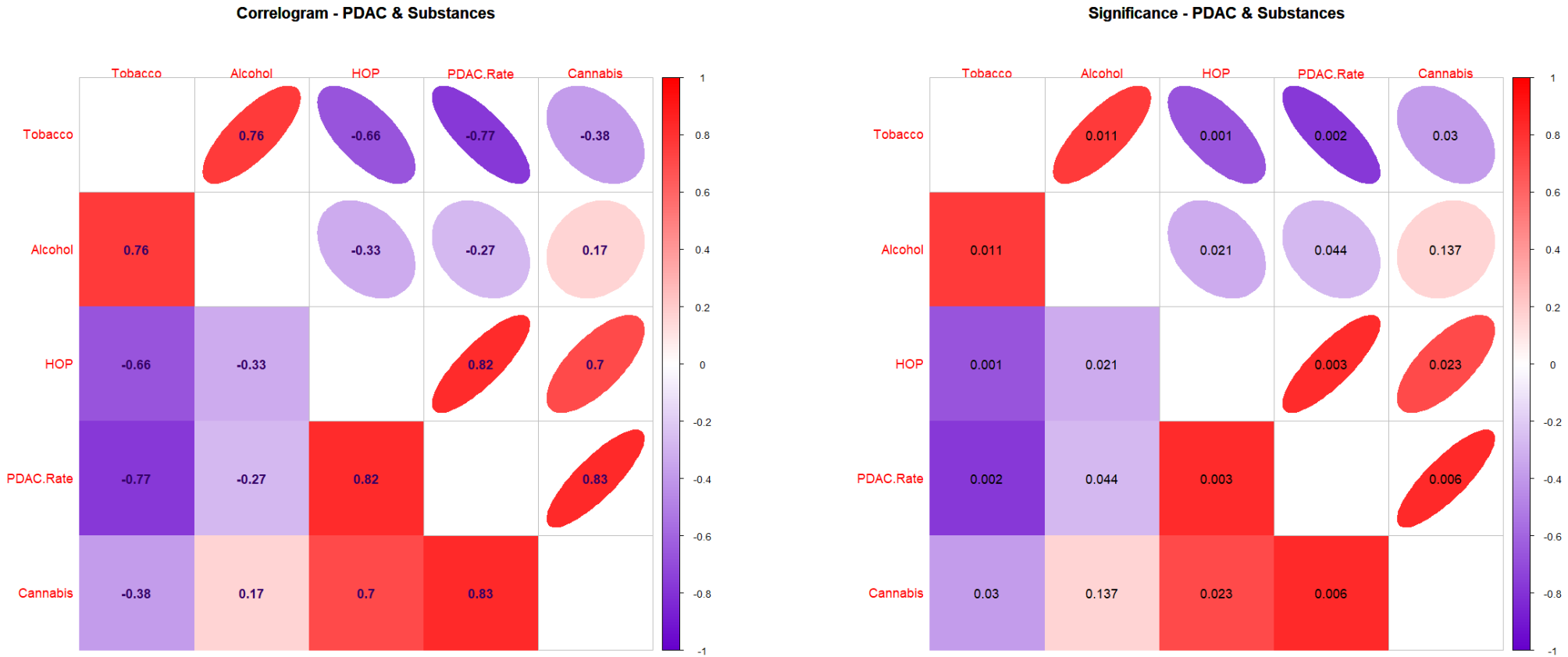

Figure 7. Correlogram for Caucasian American males 15–34 years (**left**) Pearson correlation coefficient and (**right**) significance levels.

In Hispanic American males, a very similar pattern is again observed (Supplementary Figure S2).

Figure 9 shows the situation in white females 15–34 years of age. There, the correlation between PCI and daily cannabis exposure is 0.9309 and between localized disease and cannabis is 0.9040. These correlations are significant at the $p = 0.0008$ and 0.0005 levels, respectively.

When African American females are considered, there is again a strong relationship (Figure 10). The Pearson correlation coefficients for PCI and localized disease are 0.8539 and 0.8421 which are significant at the $p = 0.0051$ and 0.0056 levels, respectively. In this figure, a weak correlation and non-significant correlation between daily cannabis use and alcohol use is noted (R = 0.59, $p = 0.68$). Similar patterns are observed when Hispanic American females are considered (Supplementary Figure S3). The correlation in this group with daily cannabis exposure is 0.8982 and 0.9133 which are significant at the 0.0008 and 0.0005 levels, respectively.

Thus, similar changes are observed in all age and ethnicity sub-groups.

The exact values of these various correlation coefficients are shown in tabular form in Table 1 and their corresponding significance levels are given in Table 2. If one compares these tables closely, it emerges that the only consistent positive correlations of interest are between cannabis and PCI and localized disease. Most of these correlations are 0.8–0.9 which indicate statistical significance mostly in the range 0.001–0.01.

Table 1. Stratified Correlation Matrix.

Covariate	PDAC.Rate	HOP	Tobacco	Alcohol	Cannabis
Males, White					
PDAC.Rate	1	0.8225	−0.7732	−0.2712	0.8308
HOP	0.8225	1	−0.6628	−0.3257	0.7015
Tobacco	−0.7732	−0.6628	1	0.7601	−0.3816
Alcohol	−0.2712	−0.3257	0.7601	1	0.1657
Cannabis	0.8308	0.7015	−0.3816	0.1657	1
Males, Black					
PDAC.Rate	1	0.8225	−0.6820	−0.2524	0.8312
HOP	0.8225	1	−0.4851	−0.2569	0.6359
Tobacco	−0.6820	−0.4851	1	0.5705	−0.3691
Alcohol	−0.2524	−0.2569	0.5705	1	0.0738
Cannabis	0.8312	0.6359	−0.3691	0.0738	1
Males, Hispanic					
PDAC.Rate	1	0.8225	−0.8191	0.1464	0.8980
HOP	0.8225	1	−0.7125	0.1052	0.7840
Tobacco	−0.8191	−0.7125	1	0.2834	−0.6757
Alcohol	0.1464	0.1052	0.2834	1	0.3221
Cannabis	0.8980	0.7840	−0.6757	0.3221	1
Females, White					
PDAC.Rate	1	0.9350	−0.8865	0.3475	0.9309
HOP	0.9350	1	−0.8052	0.4427	0.9040
Tobacco	−0.8865	−0.8052	1	0.0211	−0.7555
Alcohol	0.3475	0.4427	0.0211	1	0.5538
Cannabis	0.9309	0.9040	−0.7555	0.5538	1
Females, Black					
PDAC.Rate	1	0.9350	−0.3878	0.4460	0.8539
HOP	0.9350	1	−0.2896	0.5253	0.8421
Tobacco	−0.3878	−0.2896	1	0.3687	−0.1939
Alcohol	0.4460	0.5253	0.3687	1	0.5877
Cannabis	0.8539	0.8421	−0.1939	0.5877	1
Females, Hispanic					
PDAC.Rate	1	0.9350	−0.8151	0.6311	0.8982
HOP	0.9350	1	−0.7138	0.6912	0.9133
Tobacco	−0.8151	−0.7138	1	−0.4312	−0.6870
Alcohol	0.6311	0.6912	−0.4312	1	0.7699
Cannabis	0.8982	0.9133	−0.6870	0.7699	1

Figure 8. Correlogram for African American males 15–34 years (**left**) Pearson correlation coefficient and (**right**) significance levels.

Figure 9. Correlogram for Caucasian American females 15–34 years (**left**) Pearson correlation coefficient and (**right**) significance levels.

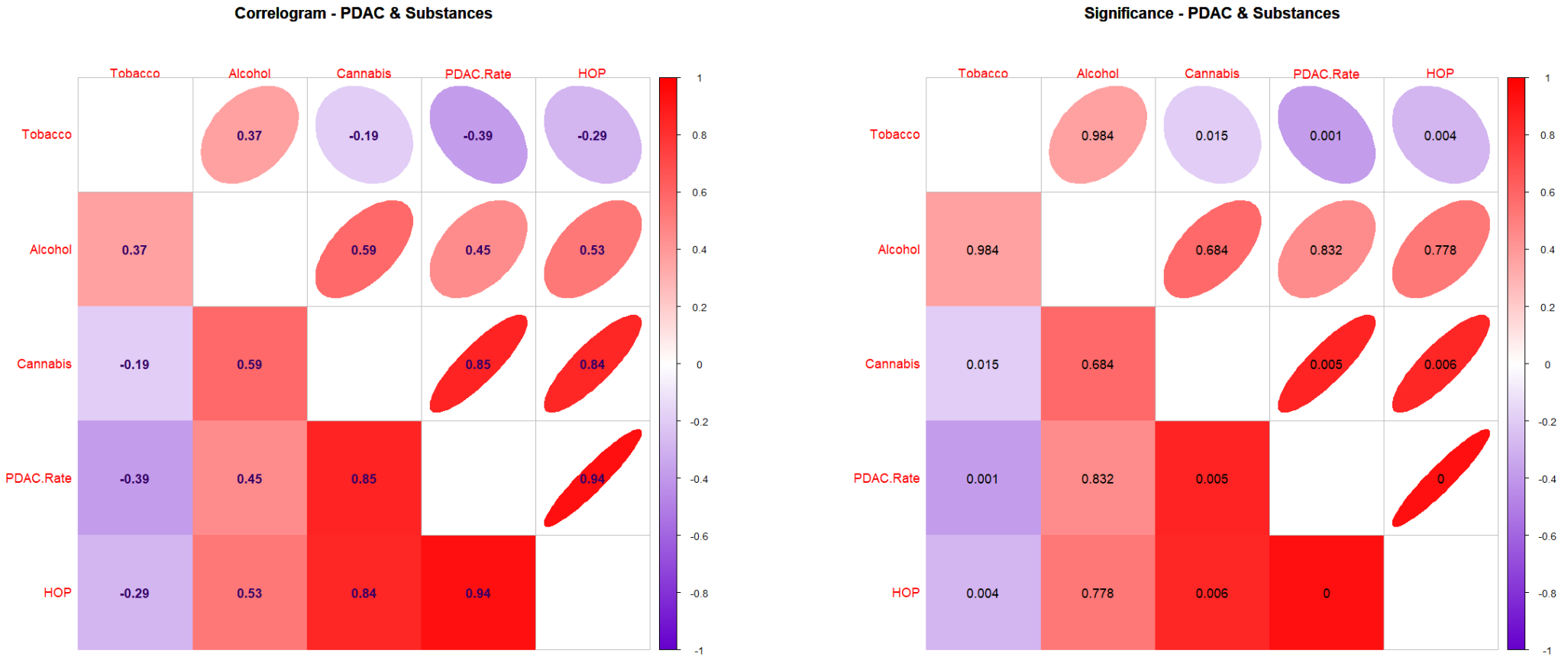

Figure 10. Correlogram for African American females 15–34 years (**left**) Pearson correlation coefficient and (**right**) significance levels.

Table 2. Significance Levels (*p*-Values) of Correlation Matrix.

Covariate	PDAC.Rate	HOP	Tobacco	Alcohol	Cannabis
Males, White					
PDAC.Rate	0	0.0029	0.0023	0.0439	0.0063
HOP	0.0029	0	0.0015	0.0210	0.0229
Tobacco	0.0023	0.0015	0	0.0115	0.0303
Alcohol	0.0439	0.0210	0.0115	0	0.1369
Cannabis	0.0063	0.0229	0.0303	0.1369	0
Males, Black					
PDAC.Rate	0	0.0052	0.0002	0.0607	0.0068
HOP	0.0052	0	0.0041	0.0304	0.0376
Tobacco	0.0002	0.0041	0	0.0553	0.0139
Alcohol	0.0607	0.0304	0.0553	0	0.1487
Cannabis	0.0068	0.0376	0.0139	0.1487	0
Males, Hispanic					
PDAC.Rate	0	0.0028	0.0014	0.6334	0.0009
HOP	0.0028	0	0.0021	0.5626	0.0068
Tobacco	0.0014	0.0021	0	0.4703	0.0073
Alcohol	0.6334	0.5626	0.4703	0	0.7493
Cannabis	0.0009	0.0068	0.0073	0.7493	0
Females, White					
PDAC.Rate	0	0.0002	0.0010	0.4540	0.0008
HOP	0.0002	0	0.0028	0.4089	0.0005
Tobacco	0.0010	0.0028	0	0.6000	0.0068
Alcohol	0.4540	0.4089	0.6000	0	0.3435
Cannabis	0.0008	0.0005	0.0068	0.3435	0
Females, Black					
PDAC.Rate	0	0.0003	0.0013	0.8324	0.0051
HOP	0.0003	0	0.0038	0.7778	0.0056
Tobacco	0.0013	0.0038	0	0.9841	0.0147
Alcohol	0.8324	0.7778	0.9841	0	0.6839
Cannabis	0.0051	0.0056	0.0147	0.6839	0
Females, Hispanic					
PDAC.Rate	0	0.0001	0.0000	0.0344	0.0008
HOP	0.0001	0	0.0002	0.0280	0.0005
Tobacco	0.0000	0.0002	0	0.0351	0.0010
Alcohol	0.0344	0.0280	0.0351	0	0.0166
Cannabis	0.0008	0.0005	0.0010	0.0166	0

3.3. Bivariate Regressions

Table 3 sets out the results of the regression studies for PCI against the three substances of interest considered separately. The rate of pancreatic cancer which was regressed as the dependent variable was the sex-specific rate taken from the Abboud paper [3]. The main positive and significant terms in this table relate to cannabis in both sexes and alcohol in females. If one compares the size of the β-estimates, they are clearly much greater for cannabis (19–32 in females) than alcohol (5–6 in females). Interestingly, the relationship between sex and alcohol seems to be somewhat different.

These various regression coefficients are associated with applicable E-Values as indicated in the Table. The E-Value estimates are very high for cannabis in females (2×10^{28} to 3.46×10^{53}) and also in males (3.74×10^{21} to 2.97×10^{38}). Whilst the E-Values for alcohol are also elevated, they are much less elevated than those for cannabis.

Indeed, considering the lower bounds of these E-Values, those for cannabis are all strongly positive and highly significant (6.88×10^{19} to 1.20×10^{42} in females and 2.53×10^{15} to 4.73×10^{30} in males). Two of the four lower E-Values for alcohol are significant in this table, and they are both for females.

Thus, the uniform finding from this table is that cannabis is a much more powerful covariate for pancreatic cancer incidence than alcohol.

Table 3. Bivariate Regression Results for 15–34-Year Cohort.

Subs	Race	Sex	β-Estimate (S.E.)	*p*-Value	P.Adj.Holm	P.Adj.FDR	E-Value Estimate	E-Value Lower Bound
Cannabis	White	Female	29.05 (22.7, 35.4)	7.00×10^{-8}	1.19×10^{-6}	6.30×10^{-7}	3.46×10^{53}	8.41×10^{41}
Cannabis	Hispanic	Female	32.1 (24.45, 39.75)	2.50×10^{-7}	4.00×10^{-6}	1.50×10^{-6}	1.32×10^{55}	1.20×10^{42}
Cannabis	Black	Female	19.67 (13.71, 25.63)	5.80×10^{-6}	6.96×10^{-5}	1.49×10^{-5}	2.04×10^{28}	6.88×10^{19}
Alcohol	Hispanic	Female	6.28 (2.62, 9.94)	0.0037	0.0296	0.0060	3.19×10^{6}	785.71
Alcohol	Black	Female	4.76 (0.84, 8.68)	0.0292	0.1750	0.0404	3.26×10^{4}	10.81
Alcohol	White	Female	6.01 (−0.36, 12.37)	0.0817	0.4087	0.1051	2.20×10^{5}	1.00
Tobacco	Black	Female	−6.67 (−16.72, 3.38)	0.2107	0.8428	0.2529	4.53×10^{5}	-
Tobacco	Hispanic	Female	−12.6 (−17.52, −7.69)	1.04×10^{-4}	1.04×10^{-3}	2.08×10^{-4}	3.27×10^{15}	-
Tobacco	White	Female	−8.37 (−10.83, −5.91)	3.97×10^{-6}	5.16×10^{-5}	1.19×10^{-5}	3.02×10^{12}	-
Cannabis	Hispanic	Male	15.44 (12.28, 18.6)	3.00×10^{-8}	5.40×10^{-7}	5.40×10^{-7}	2.97×10^{38}	4.73×10^{30}
Cannabis	White	Male	14.66 (10.68, 18.64)	1.43×10^{-6}	2.15×10^{-5}	6.44×10^{-6}	1.64×10^{29}	2.42×10^{21}
Cannabis	Black	Male	11.35 (8.05, 14.64)	3.43×10^{-6}	4.80×10^{-5}	1.19×10^{-5}	3.74×10^{21}	2.53×10^{15}
Alcohol	Hispanic	Male	2.57 (−2.55, 7.7)	0.3389	1.0000	0.3813	770.9897	1.00
Alcohol	Black	Male	−1.09 (−4.91, 2.73)	0.5838	1.0000	0.5838	23.24	-
Alcohol	White	Male	−1.82 (−6.48, 2.83)	0.4530	1.0000	0.4797	129.86	-
Tobacco	Black	Male	−6.21 (−9.93, −2.49)	0.0045	0.0315	0.0067	1.14×10^{8}	-
Tobacco	White	Male	−4.83 (−7.1, −2.56)	6.47×10^{-4}	0.0058	0.0012	1.02×10^{7}	-
Tobacco	Hispanic	Male	−6.51 (−8.83, −4.2)	3.72×10^{-5}	0.0004	8.36×10^{-5}	8.94×10^{10}	-

Table 4 sets out the findings for localized disease with again very similar findings.

Table 4. Bivariate Regression Results for Localized Disease.

Substance	Race	Sex	β-Estimate (S.E.)	*p*-Value	P.Adj.Holm	P.Adj.FDR	E-Value Estimate	E-Value Lower Bound
Cannabis	Hispanic	Female	24.47 (18.25, 30.69)	6.00×10^{-7}	1.08×10^{-5}	1.08×10^{-5}	5.10×10^{51}	4.63×10^{38}
Cannabis	White	Female	21.48 (15.68, 27.29)	1.34×10^{-6}	2.28×10^{-5}	1.21×10^{-5}	2.41×10^{43}	5.86×10^{31}
Cannabis	Black	Female	14.69 (9.72, 19.66)	2.15×10^{-5}	0.0003	0.0001	2.56×10^{25}	8.62×10^{16}
Alcohol	Hispanic	Female	5.16 (2.46, 7.86)	0.0016	0.0179	0.0037	1.59×10^{7}	3.91×10^{3}
Alcohol	Black	Female	4.23 (1.36, 7.09)	0.0101	0.0707	0.0152	2.61×10^{5}	90.28
Alcohol	White	Female	5.73 (1.07, 10.38)	0.0275	0.1648	0.0380	7.45×10^{6}	34.35
Tobacco	Black	Female	−3.32 (−11.31, 4.67)	0.4267	0.9056	0.4518	4.51×10^{3}	-
Tobacco	Hispanic	Female	−8.13 (−12.71, −3.56)	0.0028	0.0254	0.0051	7.14×10^{10}	-
Tobacco	White	Female	−5.64 (−8.06, −3.22)	2.76×10^{-4}	0.0039	0.0010	4.34×10^{8}	-
Cannabis	Hispanic	Male	7.06 (4.35, 9.77)	8.74×10^{-5}	0.0013	0.0004	4.62×10^{20}	7.36×10^{12}
Cannabis	White	Male	6.37 (3.28, 9.47)	8.60×10^{-4}	0.0103	0.0022	2.84×10^{16}	4.20×10^{8}
Cannabis	Black	Male	4.49 (1.84, 7.15)	0.0041	0.0330	0.0067	5.60×10^{10}	3.79×10^{4}
Alcohol	Hispanic	Male	0.56 (−2.27, 3.39)	0.7032	0.9056	0.7032	20.3545	1.00
Alcohol	Black	Male	−1.09 (−3.11, 0.92)	0.3019	0.9056	0.3396	223.3997	-
Alcohol	White	Male	−1.79 (−4.2, 0.62)	0.1645	0.6580	0.1974	5.40×10^{3}	-
Tobacco	Black	Male	−2.61 (−4.85, −0.36)	0.0361	0.1805	0.0464	4.95×10^{5}	-
Tobacco	White	Male	−2.42 (−3.73, −1.11)	0.0021	0.0211	0.0042	1.35×10^{6}	-
Tobacco	Hispanic	Male	−3.23 (−4.64, −1.82)	3.28×10^{-4}	0.0043	0.0010	8.74×10^{8}	-

3.4. Multivariable Regressions

A multivariable model with additive terms for the three substances of concern was tested during exploratory investigations. In each subgroup, only cannabis was left as the significant term in the final model. This is illustrated in Table 5 where the only significant terms in the table relate to cannabis exposure in all subgroups. As shown in this table, the levels of significance are high and the E-Values are also very elevated. This again shows that, statistically, cannabis is a more powerful covariate for pancreatic cancer incidence than alcohol and indeed cannabis terms would knock alcohol terms out of final regression models were model reduction to proceed by the classical method.

Table 5. Additive Multivariable Regression for Substances for 15–34-Year Age Group.

Race	Sex	Substance	β-Estimate (S.E.)	*p*-Value	P.Adj.Holm	P.Adj.FDR	E-Value Estimate	E-Value Lower Bound
Black	Female	Cannabis	18.17 (7.87, 28.46)	0.0038	0.0461	0.0099	5.59×10^{25}	2.27×10^{11}
Black	Female	Alcohol	1.36 (−2.59, 5.31)	0.5105	1	0.5743	1.60×10^{2}	1.00
Black	Female	Tobacco	−5.37 (−12.79, 2.04)	0.1775	0.8876	0.2282	6.77×10^{7}	-
Hispanic	Female	Cannabis	27.84 (13.14, 42.54)	0.0023	0.0325	0.0084	4.81×10^{50}	1.34×10^{24}
Hispanic	Female	Alcohol	−0.77 (−3.99, 2.44)	0.6443	1.0000	0.6822	4.99×10^{1}	-
Hispanic	Female	Tobacco	−4.95 (−9.64, −0.27)	0.0572	0.5147	0.1029	1.85×10^{9}	-
White	Female	Cannabis	14.28 (−1.19, 29.76)	0.0919	0.7350	0.1393	9.44×10^{37}	1.00
White	Female	Alcohol	2.71 (−1.74, 7.17)	0.2523	1	0.3028	2.88×10^{7}	1.00
White	Female	Tobacco	−5.99 (−9.58, −2.39)	0.0057	0.0624	0.0128	1.23×10^{16}	-
Black	Male	Cannabis	9.63 (6.34, 12.91)	5.14×10^{-5}	9.24×10^{-4}	4.63×10^{-4}	4.20×10^{21}	2.26×10^{14}
Black	Male	Alcohol	0.11 (−2.17, 2.39)	0.9284	1	0.9284	2.83×10^{0}	1.00
Black	Male	Tobacco	−3.96 (−7.09, −0.84)	0.0262	0.2617	0.0523	1.19×10^{9}	-
Hispanic	Male	Cannabis	8.97 (4.05, 13.89)	0.0031	0.0399	0.0092	1.33×10^{31}	1.75×10^{14}
Hispanic	Male	Alcohol	2.16 (−0.28, 4.6)	0.1047	0.7350	0.1449	5.25×10^{7}	1.00
Hispanic	Male	Tobacco	−4.38 (−6.53, −2.23)	0.0013	0.0202	0.0060	2.24×10^{15}	-
White	Male	Cannabis	9.9 (6.52, 13.29)	0.0001	0.0009	0.0005	2.84×10^{38}	2.80×10^{25}
White	Male	Alcohol	2.65 (−0.23, 5.53)	0.0929	0.73497576	0.1393	3.23×10^{10}	1.00
White	Male	Tobacco	−5.18 (−7.37, −2.99)	3.81×10^{-4}	0.0060976	0.0023	1.83×10^{20}	-

When a model which was interactive between the three substance exposure terms was tested during exploratory data mining, in each case the alcohol:cannabis interaction was the most significant and indeed only remaining term in the final model and excluded all other terms including daily cannabis use. For these reasons, this interaction was tested against PCI specifically across all combinations of race and sex in this 15–34-year cohort. As shown in Table 6, in every subgroup the alcohol:cannabis interaction was highly significant which in general terms was more marked amongst females. The lowest *p*-value shown in this table was for Caucasian American females ($p = 2.50 \times 10^{-7}$) and the highest E-Value pair was for Hispanic American females (E-Value estimate = 1.26×10^{102} and E-Value lower bound of 2.20×10^{74}).

Table 6. Multivariable Interactive Regression Results for 15–34-Year Age Group.

Race	Sex	ß-Estimate (S.E.)	*p*-Value	P.Adj.Holm	P.Adj.FDR	E-Value Estimate	E-Value Lower Bound
Black	Female	37.76 (25.24, 50.28)	2.19×10^{-5}	6.57×10^{-5}	3.29×10^{-5}	1.60×10^{54}	2.33×10^{36}
Hispanic	Female	61.97 (45.04, 78.9)	2.21×10^{-6}	8.84×10^{-6}	4.42×10^{-6}	1.26×10^{102}	2.20×10^{74}
White	Female	48.15 (37.05, 59.26)	2.50×10^{-7}	1.50×10^{-6}	1.41×10^{-6}	5.70×10^{90}	8.62×10^{69}
Black	Male	17.46 (10.63, 24.29)	1.28×10^{-4}	2.56×10^{-4}	1.38×10^{-4}	8.62×10^{28}	5.71178×10^{17}
Hispanic	Male	25.9 (19.63, 32.17)	4.70×10^{-7}	2.35×10^{-6}	1.41×10^{-6}	1.38×10^{60}	4.84×10^{45}
White	Male	18.26 (11.07, 25.46)	1.38×10^{-4}	2.56×10^{-4}	1.38×10^{-4}	1.32×10^{30}	2.48×10^{18}

When localized disease was considered, similar results were obtained (Table 7).

Table 7. Multivariable Interactive Regression Results for Localized Disease.

Race	Sex	ß-Estimate (S.E.)	*p*-Value	P.Adj.Holm	P.Adj.FDR	E-Value Estimate	E-Value Lower Bound
Black	Female	27.2 (18.43, 35.98)	1.24×10^{-5}	4.94×10^{-5}	2.47×10^{-5}	1.98×10^{48}	6.99×10^{32}
Hispanic	Female	46.53 (34.52, 58.54)	7.40×10^{-7}	4.44×10^{-6}	3.09×10^{-6}	7.76×10^{96}	1.02×10^{72}
White	Female	32.85 (24.15, 41.54)	1.03×10^{-6}	5.15×10^{-6}	3.09×10^{-6}	1.59×10^{67}	3.41×10^{49}
Black	Male	6.94 (1.77, 12.11)	0.0174	0.0174	0.0174	1.67×10^{15}	1.37×10^{4}
Hispanic	Male	11.95 (7.33, 16.57)	9.42×10^{-5}	2.83×10^{-4}	1.41×10^{-4}	4.26×10^{34}	2.46×10^{21}
White	Male	8.14 (3.28, 12.99)	0.0044	0.0087	0.0052	1.44×10^{19}	8.63×10^{7}

4. Discussion

4.1. Main Results

As the most detailed data to date on the relationship between cannabis and pancreatic cancer, this study explores the sociodemographic profiling of younger pancreatic cancer patients in greater detail than has appeared previously. Of the many striking results described herein, arguably the most impressive is the clear direct linear relationship between daily cannabis exposure and pancreatic cancer incidence across all sex and ethnic cohorts in the 15–34-year age group as shown unequivocally in Figure 6 and Tables 1–5. This high performance is reflected in the unexpected supersession of cannabis over alcohol as a risk factor for pancreatic disease of any type and pancreatic malignant disease in particular. The predominant picture which emerges from this study is that the heightened and exponentially rising rate of PCI in young African American females appears to relate largely to their tripled environmental exposure to cannabinoids. The determination of any genetic contribution to this predisposition conferred by ethnicity must await further research.

The effect of increased cannabis use was so strong that in an additive multivariable model, cannabis knocked out the other terms for tobacco and alcohol in all sociodemographic strata in this age cohort. Given that alcohol is a long-established risk factor for pancreatic disease of any type, this is a most remarkable finding; albeit, it could be predicted from the shape of the curves in Figure 6. At multivariable interactive modelling, the cannabis:alcohol interaction was shown to be the only thing more powerful than the effect of the cannabis variable itself. This was also predominant across all sociodemographic strata clearly demonstrating the co-carcinogenicity of these two agents and the importance that consideration of this co-genotoxicity should take in public health planning in this field.

Importantly, Figure 5 shows clearly that the level of cannabis use in populations aged older than 50 years is much less than younger groups. This has two implications. Firstly, it implies that since cannabis is a significant pancreatic carcinogen this effect will be less marked in older populations, which is indeed what is observed because the rise in pancreatic cancer seems to be disproportionate amongst younger patients. Secondly, many studies show that both cannabinoid genotoxicity [25,104–109] and cannabinoid metabolic toxicity [110–115] follow exponential dose-response curves. We note again that metabolomotoxicity and epigenotoxicity are closely and inherently interrelated in numerous ways. It is also clear that the rise in the prevalence of cannabis use, the intensity of people smoking cannabis daily and the THC concentration of cannabis herb and resin and the many other cannabinoid products widely available on the market are all occurring at the same time. From a public health perspective, this can be expected to launch the community relatively abruptly into the high cannabis use zones where genotoxic outcomes become much more commonplace. It seems clear from the evidence that this is exactly what is occurring in younger populations with cannabis use prevalence and the intensity of use such as in younger African American females in the USA over the past decade.

4.2. Interpretation

Our interpretation of these data is that in this younger patient cohort, cannabis is clearly linked with pancreatic carcinogenesis across all sex and ethnic cohorts considered in this younger patients age cohort. Given that younger patients are normally considered to be at a low risk for pancreatic carcinogenesis, this is a signal finding indeed. The findings from this and similar studies are consistent with those from Europe [4–7].

4.3. Causal Inference

4.3.1. Qualitative Causal Inference

In 1965, after his experience with the tobacco-induced lung cancer epidemic of the 1950s, renowned epidemiologist A.B. Hill laid out nine criteria which were required to be fulfilled to confidently denote any particular epidemiological relationship as being causal in nature. These criteria were: strength of association, consistency amongst studies, specificity, temporality, coherence with known data, biological plausibility, a dose-response

curve, similar analogies elsewhere and experimental confirmation. The current data clearly indicate that the cannabis–pancreatic cancer link fulfils the first eight of these criteria. Experimental confirmation is still lacking but only because laboratory studies have not yet been performed to the best of our knowledge at the time of writing. However, given the centrality of the biological pathways and mechanisms to supporting the causality of the cannabis–pancreatic cancerogenesis causal argument, discussion on this topic is expanded below.

4.3.2. Quantitative Causal Inference

One of the major limitations of observational studies is that they are subject to a failure to include the full universe of covariates in their analytical models. This error of uncontrolled confounding is known by several names. For an unknown covariate to disrupt a relationship which at first appears to be causal in nature, it must be correlated with both the exposure of interest and the outcome of concern. This co-correlation is quantified as the E-Value which is a mathematical re-formulation of the relative risk. As noted above, an E-Value greater than 1.25 generally denotes a causal relationship [100]. E-Values in excess of nine, such as those between lung cancer and tobacco smoking, are said to be high [116]. Studies of E-Values of 1.32×10^{55}, 3.46×10^{53} and 2.04×10^{28} for Hispanic American, Caucasian American and African American females, respectively (Table 3), are far in excess of these levels, and are observed in causal relationships [100]. Moreover, the E-Value has a 95% lower bound which signifies the bottom end of the applicable confidence interval. In Table 3, the lower bounds for these E-Values are given as 1.20×10^{42}, 8.41×10^{41} and 6.88×10^{19}. These are also far in excess of the typical cut-offs required to show causality and provide robust arithmetical support to the main conclusions of the study. For these reasons, the study data provide epidemiological evidence of causality; albeit, this is not the same thing as experimental evidence of causality.

4.4. Mechanisms

4.4.1. Epigenomics

Cannabis has been found to have a large epigenomic footprint and changes the methylation status of up to 9% of the whole genome [15]. This has far-reaching implications on virtually every cellular system including the epigenomic machinery for DNA methylation and demethylation, for histone methylation and acetylation and their reversal and for the active repositioning of the nucleosomes to allow new gene transcription to occur [17,77–79,117]. Cannabis causes DNA breaks [24–30] which ages the genome [21]. Cannabis interferes with actin and tubulin and thus the cytoskeleton and machinery of the mitotic spindle [21] and the kinetochore–centrosomal machinery of chromosomal segregation at mitotic and meiotic division [17,118]. This interference with mitotic and meiotic division sets up micronucleus formation and chromosomal shattering (chromothripsis) [73] which is a powerful engine for major and widespread genomic rearrangement and instability [73,119–130] and also powerfully stimulates innate immunity through cyclic AMP-GMP (cGAS)–STimulator of Interferon Gamma (STING) signalling [43,130–136]. cGAS-STING has been shown to be the prime driver of the senescence-associated secretory phenotype (SASP) [135,137] which both drives innate immunity with the release of TNFα (tumour necrosis factor α), and interferon IL1β and interleukin 6 (IL6) [132]. Together, this drives senescence induction in nearby cells systemically [135,138] and also induces the inflammaging which is known to drive DNA damage and further exacerbate cellular aging [128,130–133,136–147]. The growth factors and cytokines and chemokines of the SASP are also known to drive malignant transformation [137,138,140,141]. cGAS-STING activation both increases the degree of malignancy and drives metastasis [148] which also provides an explanation for the many reports of increased incidence of cancer in young patients and their rapid demise due to a widespread and aggressive disease at presentation [149–152].

The action of cannabinoids is often directly immunostimulatory especially when acting via the type 1 cannabinoid receptor (CB1R) [90,153–158]. Cannabis disrupts both

the tubulin code and the histone code [17,26,118,159–163]. By inhibiting mitochondrial metabolism [111,112,164–170], cannabinoids interfere with the supply of substrates to the epigenomic machinery and the supply of energy for both genomic and epigenomic maintenance. Due to mitochondrial inhibition, the cellular levels of lactate rises [171–175] which induces both passive and enzymically mediated lactylation of key metabolic enzymes [176,177]. This further reinforces the increase in cellular dependence on glycolysis and a stem-like cellular de-differentiated state and locks cells into a premalignant metabolomic–epigenomic state [176–179].

Low doses of cannabidiol have also been implicated directly in genotoxicity and have been shown to induce both DNA breaks and DNA base oxidation [25].

Since all of these changes are pro-carcinogenic, the link between cannabis and pancreatic cancer is not surprising from a mechanistic perspective.

4.4.2. Alcohol: Cannabis Interaction

As mentioned above, alcohol is a classical cause of acute pancreatitis and the mechanisms by which it predisposes to cancer has been shown several times to arise from the incomplete resolution of the inflammatory changes in the epigenome of the acinar stem cells [45,48]. Such epigenomic changes are an example of antagonistic pleiotropy in that they help the cells reactivate subsequent to another episode, but also reset the epigenome towards cancer and aging based on this alteration [45,48,180–182]. The fact that cannabis way outperformed the recognized pancreatic disease risk factor of alcohol in the study results presented above is one of the most remarkable findings to emerge from the present study.

As noted above, the effect of cannabinoids in tissues is often pro-inflammatory especially when acting through CB1R [90,153–158]. Cannabinoids interfere with the machinery of DNA methylation and the net effect of this is to cause DNA hypomethylation which is an aging change and also tends to weaken epigenomic cell linage specification and therefore the epigenomic hills between the "Waddington valleys" (to borrow Waddington's now famous analogy [183]) and thus drive the cells both towards aging and de-differentiation [21]. Cannabinoids (including cannabidiol) also cause DNA breakages [24–30] which attract the large multiprotein epigenomic complexes to the sites of DNA breakage and away from their usual stations on the genome which directly lead to DNA demethylation and cellular aging [21]. By inducing chromosomal mis-segregation, cannabis drives chromosomal shattering releasing fragments of double-stranded DNA into the cytoplasm where it is a powerful stimulus for cytosolic sensors and a driver of both intracellular and extracellular innate immune effectors including cGAS-STING, some of the toll-like receptors (TLRs 3, 7 and 8), the RIG1 sensors, the AIM1 (Absent in Melanoma 1) and ASC1 (Apoptosis-associated Speck-like protein containing a CARD (caspase activation and recruitment domain) inflammasomes, the SASP [128,131,132,136–139,184–186] and a long list of cytosolic sensors of DNA including RNA polymerase III, DAI (DNA-dependent activator of interferons or Z-DNA binding protein), IFI16 (interferon gamma inducible protein 16), DDX4 (DEAD-Box helicase 4), LSm14A (LSM14A MRNA Processing Body Assembly Factor), LRRFIP1 (LRR Binding FLII Interacting Protein 1), Sox2 (SRY-Box Transcription Factor 2), DHX9/36 (DExH-Box Helicase 9/36) and Ku70 (X-Ray Repair Cross Complementing 6) [187].

Therefore, it is not at all surprising that there should be a powerful carcinogenic synergism between the two genotoxins, cannabis and alcohol, as documented above in our multivariate regression models both for PCI and for localized disease. However, it was surprising to us that this interactive effect was so powerful statistically as to lead to the complete deletion of cannabis from the final interactive models across all sociodemographic categories.

4.5. Future Research Directions

As this study is the most detailed investigation of the cannabis–pancreatic cancer link to have been published, it raises many further research questions both epidemiological and mechanistic in nature. Epidemiologically, with a combined sample of 734,761 cancers

this dataset almost certainly lends itself to small area–space–time studies. Epidemiological studies would be facilitated by the availability from SAMHSA of NSDUH results in 405 small substate areas across the USA. Assuming that pancreatic cancer incidence could be similarly mapped at such fine spatial resolution across a series of aggregated years, this would lend itself to further space–time epidemiological models which is conceptually very powerful. Ideally such space–time modelling could also incorporate inverse probability weighting to allow causal geospatial models to be developed, although to our knowledge this methodology has not yet been invented.

From a mechanistic perspective, many studies in the basic sciences should be undertaken to explore cannabinoid-induced pancreatic tumourigenesis in molecular detail. The above-described convergence of pro-inflammatory, pro-aging, de-differentiating, direct genotoxic and various epigenotoxic pathways should all be dissected to define the route to carcinogenesis induced by cannabis. It needs to be resolved how many cannabinoids are implicated in pancreaticocarcinogenesis especially in the light of earlier demonstrations that the genotoxic moiety resides with the olivetol nucleus on the C-ring which is common to all cannabinoids [26]. It is common for the profusion of names for modern cannabinoids such as Δ8-, Δ0-, Δ10, Δ11-tetrahydrocannabinol etc. to confuse lay people. However, as these designations only refer to the carbon atom on the A ring which is hydroxylated and the genotoxic moiety is the olevitol nucleus of the C-ring, none of these modifications have been found to materially impact the genotoxic actions after extensive in vitro testing [26] and nor would they really be expected to do so (because it is the wrong benzene ring). Dose-response and timing studies need to be performed for cannabinoids in clinically relevant concentrations. It may be that as such processes are understood, agents acting either in the endocannabinoid system or perhaps in other pathways may be developed which will become lead candidates for further therapeutic development for this very serious disease.

Cannabinoids are known to negatively impact the mitochondria in many ways [111,112, 164–170]. This will induce genotoxic stress through mitonuclear signalling and also impede the genomic and epigenomic machinery which are both dependent on mitochondrially derived substrates and energy and homeostatic mechanisms to ensure genomic stability. Therefore, the cannabinoid-induced mitochondriopathy can reasonably be expected to interact powerfully and negatively with the cannabinoid-induced epigenotoxicity. Since as described the lactylation state is modified by cannabinoids and is involved in numerous cancerogenic pathways, it is likely that the impact of cannabinoids on the lactylation machinery and metabolome presents a key investigative window which will likely find downstream utility in areas such as stem cell and regenerative medicine and cancer biology. These mechanisms need to be investigated both in the mitochondria and in the epigenome and genome in a coordinated and comprehensive manner.

As described above, cannabinoids generally have a heavy epigenetic footprint. The general footprint of cannabinoids is DNA hypomethylation which is a classical age-related change. Thus, phytocannabinoids can be expected to relatively de-differentiate cells. This putative cannabinoid-induced de-differentiation needs to be compared with premalignant de-differentiation and also that occurring normally in inflammatory and post-inflammatory states to investigate how this might compare to these better characterized states. In addition, the epigenome is known to be further impacted by immune and metabolic processes, all of which are disrupted by cannabinoid exposure.

The deep learning algorithms of artificial intelligence may find a place in the epidemiological and other studies of pancreatic cancer in years to come. Some of these directions have been explored in a recent paper on the application of integrative medicine to the pathobiology of cancer of the pancreas [188].

Thus, the present study strongly suggests many lines for further research investigations both in epidemiology and in the basic sciences.

4.6. Generalizability

Given that the sample on which this study is based is the whole US population of pancreatic cancer from 2001 to 2018 combined with SAMHSA's highly reputable nationally representative annual NSDUH study including its high response rate, and given also that the present results are closely concordant with other published reports and with recent analyses from Europe, we are confident that these results are indeed generally applicable [4–7]. This view is reinforced by the very high E-Values reported throughout which exclude significant effects of unmeasured confounder covariates. The E-Values reported in the present study are far in excess of the threshold for causality which is usually said to be 1.25 [100] and also exceed the E-Value of the relationship of tobacco use with lung cancer incidence which is said to be nine and is typically regarded as being in the high range [116]. For these reasons, it is clear that the relationship between cannabis use and pancreatic cancer is much stronger than the tobacco–lung cancer relationship which is widely acknowledged to be causal. The present findings are also supported by the robust observation that the effects of cannabis interact with, and are exacerbated by, those of alcohol which is a known carcinogen in the pancreas [45,46,48].

4.7. Strengths and Limitations

This study has a number of strengths. Cancer incidence data were based on a national sample across the USA from 2001 to 2018. Drug use data were taken from the nationally representative survey with a high response rate which was SAMHSA's NSDUH. The analysis was stratified separately for each sex and major ethnic group with the single 15–34-year age group. Highly concordant and consistent results were obtained from bivariate, additive multivariable and interactive multivariable models. Furthermore, the findings for cannabis were noted to positively interact with alcohol which is a known pancreatic carcinogen. For these reasons, we regard the present analysis as being powerful in its elegant analytical simplicity. Importantly, the high incidence rate of pancreatic cancer in young African American females was found to be likely related mainly to their lifestyle exposures. Study shortcomings are that, in common with many other epidemiological studies, individual participant data were not available to the present investigators. Stratified data on income were not available to the present research team. Controlling for these and other covariates remains for future research projects. However, in view of the very high E-Values reported herein, its consistency with other studies both in the USA and Europe, its concordance with a variety of basic aetiological mechanisms from laboratory and cellular science, and of similar studies which do take income into account [4–6], and its relationship with the known carcinogen ethanol, we are confident that controlling for these external covariates will not materially impact the major study conclusions.

5. Conclusions

The main results from this study are to confirm the opening hypotheses that cannabis is involved causally in pancreatic carcinogenesis in all sex and ethnic cohorts in the 15–35-year age bracket and thus it appears to be at least one of the previously unknown principal driver/s of the present renaissance in PCI across the USA. The present results are supported by other studies from both the USA and Europe and by much experimental research [4–7]. Cannabis was observed to powerfully interact at the epidemiological level with alcohol exposure and clearly this cooperative carcinogenicity requires further basic science and epidemiological research. Importantly, this report adds cancer of the pancreas to the growing list of cancers which cannabis has been shown to be driving including testicular, liver and breast cancer, childhood leukaemia and total paediatric cancer. Clearly, further research is indicated of the pathways to cannabinoid-induced tumourigenesis particularly in the metabolomic, immunomic and epigenomic fields. However, in the light of now-robust epidemiological evidence implicating cannabis in yet another significant cancer renaissance nationwide across the USA [10,83–90], it becomes essential and imperative that communities take cannabinoid carcinogenesis seriously and restrict access of their

populations to cannabinoid genotoxicity just as it is for many other significantly genotoxic compounds. This is not only for cancer prevention and public health concerns in regard to extant populations, but also to protect the generations to come from the implicit and now well-defined multigenerational cannabinoid epigenotoxicity with which carcinogenicity is so often intricately and intimately involved [77–79,117,189–193].

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/gastroent14020016/s1. Supplementary Figures S1–S3 have been made available online together with this paper on the journal website.

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, 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. All authors have read and agreed to the published version of the manuscript.

Funding: No funding was provided for this study. No funding organization played any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Institutional Review Board Statement: The Human Research Ethics Committee of the University of Western Australia provided ethical approval for the study to be undertaken 24 September 2021 (No. RA/4/20/4724).

Informed Consent Statement: Not applicable.

Data Availability Statement: 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: **Raw Data:** https:/data.mendeley.com/datasets/wjb5f622n4 (accessed on 19 February 2023) https://doi.org/10.17632/wjb5f622n4.1. **Pre-processed Data:** https:/data.mendeley.com/datasets/4s87k4v5n7 (accessed on 19 February 2023) https://doi.org/10.17632/4s87k4v5n7.1. **Major datasets:** https:/data.mendeley.com/datasets/y32txvjhpf (accessed on 19 February 2023) https://doi.org/10.17632/y32txvjhpf.1. **Computational Code:** https:/data.mendeley.com/datasets/shcnmv5dhx (accessed on 19 February 2023) https://doi.org/10.17632/shcnmv5dhx.1.

Acknowledgments: 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.

Conflicts of Interest: The authors declare that they have no competing interest.

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