Cannabis in Pregnancy – Rejoinder, Exposition and Cautionary Tales

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Relevant Topics
Cannabis use during pregnancy is associated with a host of negative outcomes.

The recent paper by Stanciu discussing cannabis use in pregnancy[1] makes several useful and highly salient points. With a more complete understanding of the published literature further important patterns in the data emerge. They aid our understanding of the pathobiology of *in utero* cannabis exposure and thereby powerfully inform the community on the most appropriate manner in which to regulate cannabis and cannabinoids from an improved evidence base.

It is well known that cannabis use has been liberalized across the United States as a result of well-financed and orchestrated campaigns.[2] Stanciu is correct that most epidemiological studies point towards harmful associations, that cannabis use in pregnancy is becoming more common, that it is widely recommended in pregnancy by cannabis dispensaries, and that increased rates of low birth weight, premature and stillbirths, and increased neonatal intensive care admission are well recognized associations. It is correct that all 4 longitudinal studies of children born after prenatal cannabis exposure (PCE) show increased adverse neurodevelopmental outcomes including impaired executive function, visuomotor processing deficits, heightened startle responses, impulse control, heightened susceptibility to addiction in later life, emotional behaviors, and motor defects.[3-5] Well-documented impacts on the glutamatergic, GABAergic and dopaminergic signaling in the brain are of concern as they represents major neurotransmitters in the central nervous system [CNS]. Well-established links between cannabis use and schizophrenia, bipolar disorder, anxiety, depression, and suicidal ideation are also correctly described. It is true that ACOG have made both historical and recent recommendations against its use in pregnancy, and these recommendations are relevant to practice in all medical specialties.

Conceptual and epidemiological extensions

While it is correct to observe that there is no described phenotype following PCE, it is also important to note that many of these neurodevelopmental deficits have been noted to overlap the ADHD and autism spectrum disorders. This is likely epidemiologically highly significant for the US, where autistic spectrum disorders have been shown to be growing exponentially.[6] Cannabis use across the US was shown to be independently associated with autism rates across both time and space, to be dose-related[6], and, based on conservative projections, has been predicted to be at least 60% higher in cannabis-legal states than in states where cannabis was illegal by 2030.[7]

A large Hawaiian study found an increased incidence of microcephaly (R.R. = 12.80, 95%C.I. 4.13-36.17)[8] and the CDC have twice reported elevated rates of anencephalus (adjusted O.R. 1.7, C.I. 0.9-3.4) and (posterior O.R. 1.9 (C.I. 1.1, 3.2).[9,10] This sets up a clear spectrum of severity from mild neurodevelopmental impairment, to microcephaly, to anencephalus and then fetal death. In the context of dose-response relationships and strong geotemporospatial associations issues of causality necessarily arise.

Stanciu's observation that preclinical studies in experimental animals are important to understand the likely effects of PCE in individuals, not least due to the problem of the frequent exposure to

multiple substances clinically, is also correct. This issue was studied in detail long ago in the 1960s and 1970s, and succinctly summarized by Graham's telling observation: "oedema, phocomelia, omphalocoele, spina bifida, exencephaly, multiple malformations including myelocoele. This is a formidable list."[11]

However, a reasonable question might be: "Why don't we see such a broad teratological spectrum clinically?"

Stanciu's remark that there are "no overt birth defects" is an oft-repeated myth and is in error, as well as obviously being at odds with several preclinical studies, especially in the most predictive species for human teratology (ie, hamsters and white rabbits).[12,13]

A recent paper from the Centers for Disease Control (CDC) noted that 4 defects, anencephalus, gastroschisis, diaphragmatic hernia and esophageal atresia were more common following PCE.[9] The American Academy of Pediatrics (AAP) and the American Heart Association (AHA) issued a joint position statement that both ventricular septal defect (VSD) and Ebsteins anomaly were also elevated by PCE.[14]

The review of 17 years of birth defects from Hawaii found 21 defects to be elevated after PCE and featured prominently cardiovascular defects (atrial septal defect (ASD), VSD, hypoplastic left heart syndrome, tetralogy of Fallot (ToF) and pulmonary valve atresia or stenosis), chromosomal defects such as Downs syndrome, body wall defects such as gastroschisis, limb defects including syndactyly and upper limb reduction defects, facial, bowel and genitourinary system defects with calculated rate ratios ranging from 5.26 (C.I. 1.08-15.46) to 39.98 (C.I. 9.03-122.29).[8]

In September and October 2018 Colorado released 2 datasets of congenital anomalies across the period of its cannabis legalization program from 2000 to 2013 and 2000 to 2014 and reported 87,772 and 64,463 major defects respectively (which are obviously contradictory).[15] Based on 4830 and 4026 major anomalies in the year 2000 this represents a case excess of 20,152 (29.80%) or 11,753 anomalies (22.30%) respectively. During this period the use of tobacco and alcohol was declining and other drug use was not rising. Only cannabis use rose. Importantly, models quartic in time indicated a non-linear response of total birth defects to rising cannabinoid exposure. Estimated exposure to several cannabinoids including cannabinol, THC, and tetrahydrocannabivarin was shown to be positively associated with major defect rates and to be robust to adjustment for other drug use. CNS defects (microcephalus, neural tube defects), cardiovascular defects (ASD, VSD, patent ductus arteriosus (PDA)), total chromosomal anomalies including Downs syndrome, musculoskeletal, respiratory and genitourinary anomalies all rose dramatically.

Defects described as being cannabis-related (by the Hawaiian, CDC, AAP and AHA investigators) rose more quickly than cannabis-unrelated defects ($P<0.003$). As fetal cardiac tissue and the central great vessels have high numbers of cannabinoid receptors from early in fetal life it is easy to understand why this pattern might emerge. Since ASD, VSD and PDA are the most common cardiovascular congenital anomalies it is understandable that total cardiovascular anomalies increased in Colorado.

A recent review of total congenital anomalies in Canada showed that they were 3 times more common in the northern territories which consume more cannabis, and that these effects were robust to adjustment for other drug exposure and for socioeconomic variables.[16] Total cardiovascular defects, Downs syndrome and gastroschisis were noted prominently in this series. Neural tube defects including anencephalus and spinal bifida and meningomyelocoele were falling across Canada from 1991 to 2007, although it was not clear whether the decline was due to dietary folate supplementation or increased antenatal early termination of pregnancy for anomalies

(ETOPFA).[17] Notwithstanding this it was recently shown that within each of 3 periods (the pre-folate period, the transitional period and the post-folate period) neural tube defects across Canada were becoming more common.[17]

An Australian dataset found greatly elevated relative rates of cardiovascular (PDA, ASD, VSD, ToF, transposition of great vessels), body wall (gastroschisis, exomphalos, diaphragmatic hernia), chromosomal (Downs syndrome, Turners syndrome, Edwards Syndrome (trisomy 18)), genitourinary, hydrocephalus, neural tube defects, and bowel defects with borderline results for anencephalus (ETOPFA data unavailable) in a high cannabis use area in Northern New South Wales compared to Queensland state-wide data.[18]

Transposition of the great vessels was previously linked with paternal cannabis exposure.[19]

The presence of Downs syndrome on the list of cannabis-associated anomalies in Hawaii, Colorado, Canada and Australia is important as it necessarily implies megabase-scale genetic damage.[8,15,16,18] Since cannabis interferes with tubulin metabolism and thus the separation of the chromosomes which occurs in mitotic anaphase it is easy to see how PCE-induced chromosomal mis-segregation errors might occur.[20] Studies of PCE in rodents show that cannabis induces major alterations of gene expression widely with 8% alteration in DNA sperm methylation patterns, changes which are transmissible to subsequent F1 generations.[21]

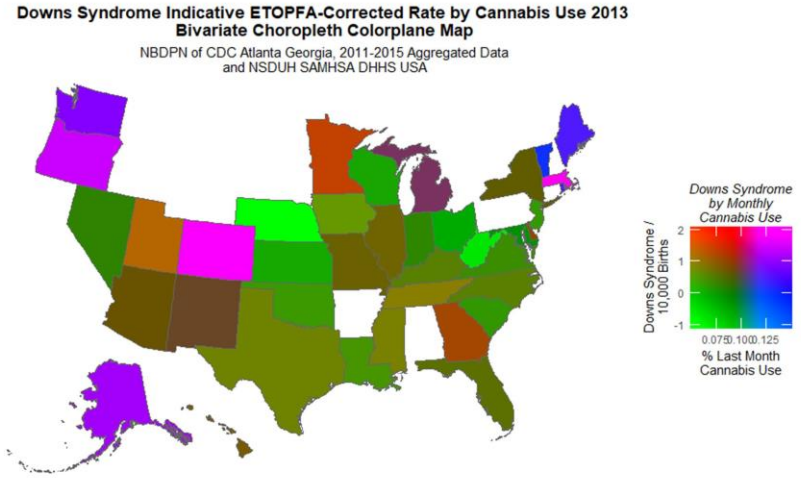
Stanciu's comment about a so-called "cannabis phenotype" is provocative. It is true that a "fetal cannabis syndrome" (FCS) has not been described in the way that a "fetal alcohol syndrome" (FAS) has. Fetal alcohol syndrome of course is a very diverse and pleomorphic group of clinical presentations and a wide spectrum of presentations is described. Importantly the fetal alcohol has been described as being mediated by the cannabinoid type 1 receptor (CB1R's) and is mediated epigenetically.[22-26] The suggestion that alcohol can work epigenetically via CB1Rs but cannabinoids cannot defies the bounds of credulity. Moreover, as noted above, there is as yet no objective marker of gestational cannabinoid exposure. Once such a biomarker has been derived (say epigenetically and / or glycomically[27]) then an objective measure will exist to allow genotype-epigenotype-phenotype correlative studies to be performed so that we can usefully investigate if a fetal cannabis syndrome phenotype spectrum might exist. However, if researchers do not believe it might exist then it is clear that one will not be described. It is our view that once an objective biomarker is established it will only be a matter of time before a diverse and highly variable FCS is also defined and enters the clinical diagnostic compendium.

Recent US data and analysis

CDC publish 5-year averaged birth defect data for many states as part of the National Birth Defects Prevention Network (NBDPN) annual reports which can be combined with Substance Abuse and Mental Health Services Administration (SAMHSA) state and substate data to examine nationwide drug-related trends. ETOPFA rates are taken from historical time series.

Figure 1A charts Downs syndrome rates corrected for estimated ETOPFA rates against cannabis exposure. Both rates are elevated (shown as pink and purple) in Colorado, Oregon, Washington, Alaska, Maine and Massachusetts.

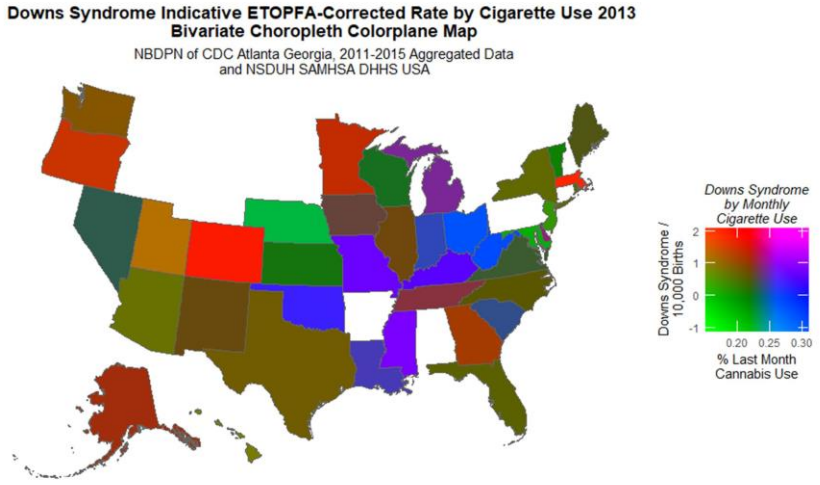
A



Downs Syndrome By Cannibus Use

Figure 1B shows the relationship of Downs syndrome to cigarette use for this year which is very different.

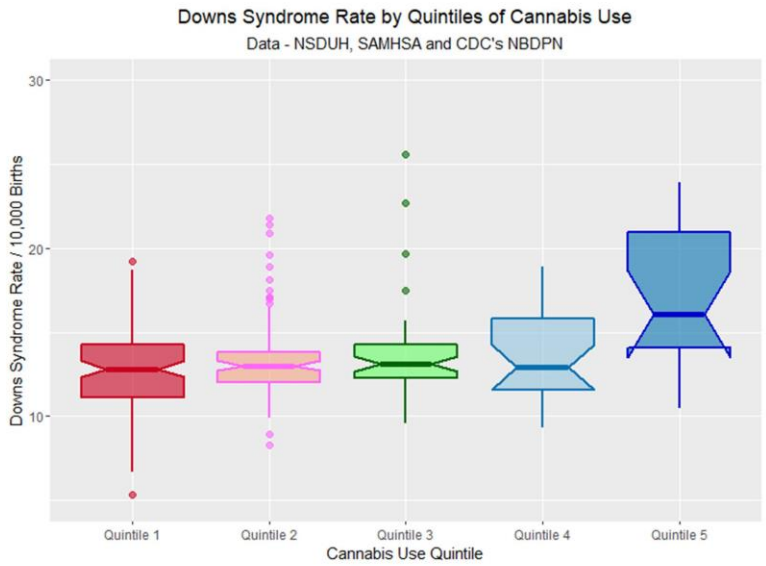
B



Downs Syndrome By Cigarette Use

The **Figure** also shows the Downs syndrome rates by cannabis use quintile for both the raw Downs syndrome rates (**Figure 1C**) and the ETOPFA-corrected data (**Figure 1D**). One notes not only a rising trend with cannabis use, but also an abrupt jump from the fourth to the fifth quintile.

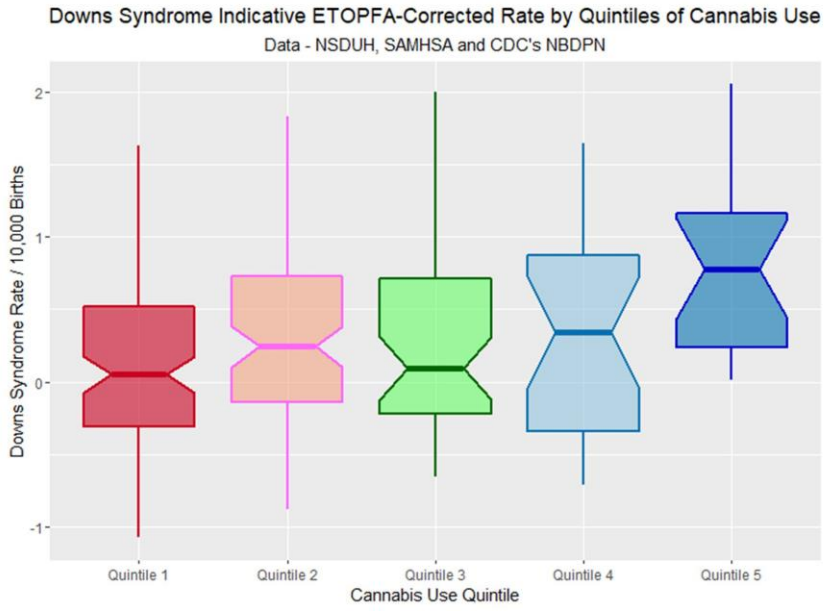
C



Downs Syndrome Rate by Quintiles of Cannabis Use

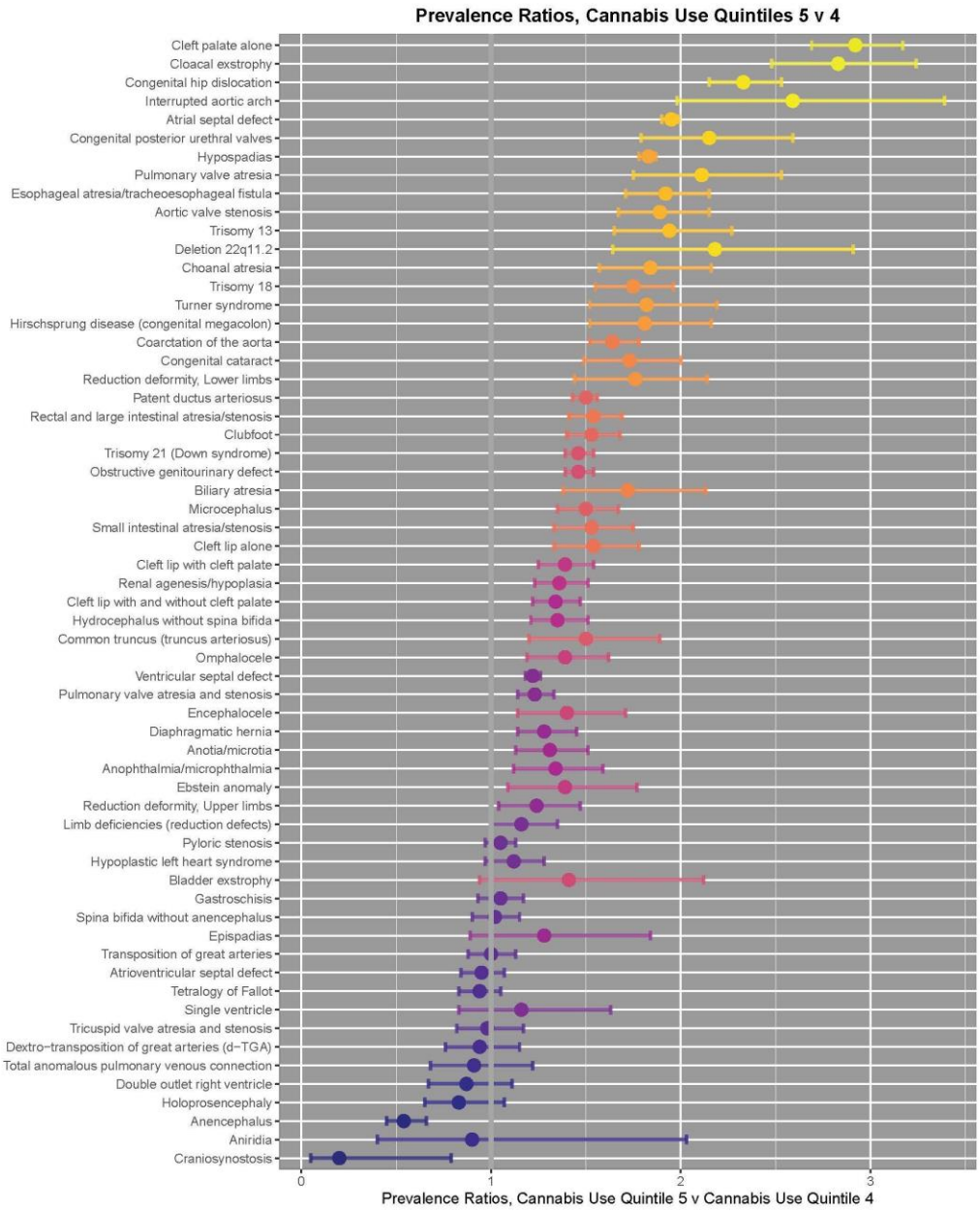
This jump is seen when many defects are analyzed in this manner. A list of defects would include, but would not be limited to: atrial septal defect, atrioventricular septal defect, cleft lip and / or palate (all forms combined), trisomy 21 (Downs syndrome), Turners syndrome and ventricular septal defect.

D



Downs Syndrome by Quintiles of Cannabis Use (ETOPFA-CORRECTED)

Figure 2 lists the prevalence ratio of 62 congenital anomalies tracked by the National Birth Defect Prevention Network (NBDPN) in quintile 5 versus lower quintiles and notes that 44 of them are significantly elevated in the highest quintile of cannabis using states.



Prevalence Ratios

Literature-wide limitations

It should be noted in passing that most of these studies suffer from several major common limitations. Many of the defects described are disorders for which ETOPFA is commonly practiced and frequently recommended to pregnant patients. ETOPFA data was generally not available to investigators. It is beyond question that were such data included the findings would be of greater magnitude and of even greater concern. Secondly many studies rely on self-report which is subject to recall-bias and may be misled. Patients who use cannabis early in pregnancy but stop after they are informed of their pregnant status might answer “no” to questions of PCE, but in fact their fetus is exposed prenatally due to the prolonged terminal half-life of excretion of cannabinoids from body fat stores. Hence a reliable biomarker is required to properly define the denominator in these

studies, but it is not thought to exist at present. It could however easily be derived from epigenomic and/or glycomic studies.[27]

Thirdly there are major analytical limitations of the described series. Advanced analytical methods that allow data analysis simultaneously across both space and time exist and are called geospatial or spatiotemporal techniques. The CDC has demonstrated ability to track congenital anomalies by county. Application of geospatial techniques to county data is therefore possible and would be well assisted by the provision of cannabis-exposure data from the SAMHSA 395 substate areas. Methods which allow the investigation of apparently causal relationships, including inverse probability weighting and the calculation of E-values to quantify unmeasured confounding have similarly not been deployed in this field.

These deficits in the literature represent major gaps in our knowledge which may readily be addressed by the application of available techniques to currently extant data and thus vastly augment the evidence base for well-informed policy formulation. Our group is presently addressing this major knowledge gap with a series of papers on these and related subjects utilizing geospatiotemporal regression, the formal techniques of causal inference, and multiple imputation of chained equations to complete CDC data for various congential anomalies and heritable childhood cancers where such data is missing or withheld for specific ethnic minorities.

Extensive presently unpublished analyses from our group extend the United States analyses presented in preliminary and embryonic form in **Figure 1** and **Figure 2** using geotemporospatial and causal inference techniques with strongly confirmatory results for both state-based spatiotemporal association and in several cases causal links.

Concluding thoughts

In broad overview the patterns which emerge from these major population-based studies of cannabis-related human teratology indicate several findings that are remarkable for their consistency across series originating from Hawaii, Colorado, Canada, and Australia and for their exact and precise concordance with very worrying data in experimental animals. Prominent amongst affected organ systems includes the CNS, CVS and chromosomal disorders. Body wall and limb defects also likely follow the endovascular cannabinoid receptor distribution pattern, and this is consistent with current understandings related to the pathogenesis of gastroschisis and limb embryogenesis which are both thought to be primarily vasculocentric. Similarly, in the genitourinary and gastrointestinal systems, peripheral cannabinoid receptors are widely distributed and appear from as early as 12 weeks of fetal life. Dose-response effects are seen in many of the above analyses which is one of the major criteria of Hill's causal algorithm. The sequence of severity of CNS defects (neurodevelopmental impairments/autism-microcephaly-anencephaly-foetal death) also implies a gradation of phenotypic effects of PCE.

The PCE literature has widespread limitations including its reliance on self-report data, the general non-availability of ETOPFA data, the lack of reliable biomarkers to define exposure, and the pointed absence of state-of-the-art analytical techniques including high-resolution geotemporospatial analysis and the formal techniques of causal inference assessment.

Given these limitations the concordance with preclinical and mechanistic data and the positive and highly consistent associations that have been demonstrated in several jurisdictions are particularly concerning. They carry far-reaching genotoxic and intergenerational implications and argue powerfully against cannabis legalization.

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