Hypothesis

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Hypothesis: Emerging Evidence Might Suggest That Increases in Cannabis Use Disorder Following Legalization of Recreational Cannabis Significantly Contribute to Socioeconomic-Dependent Increases in the Prevalence of Autism Spectrum Disorder

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Hypothesis: Emerging Evidence Might Suggest That Increases in Cannabis Use Disorder Following Legalization of Recreational Cannabis Significantly Contribute to Socioeconomic-Dependent Increases in the Prevalence of Autism Spectrum Disorder

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Abstract

A recent report on the prevalence of autism spectrum disorder (ASD) from California describes unprecedented levels of ASD in that population. The data indicate a transition or changepoint in 2015-2016 in which the prevalence of ASD began to accelerate more rapidly after almost a decade of relatively consistent yearly increases. The changepoint is associated strongly with socioeconomic status, being most readily observable in black children and in low-income counties. Herein we propose the hypothesis that legalization of recreational cannabis in late 2016 led to several cultural changes that in turn caused socioeconomic-dependent increases in very frequent cannabis use and/or cannabis use disorder (CUD). CUD is strongly associated with ASD and with socioeconomic status, and we hypothesize that an adverse drug-drug interaction between acetaminophen and a component or components of cannabis may be at play, resulting in an increased prevalence of ASD. It remains unknown whether prenatal or postnatal exposures may be more critical, and further work aimed at evaluating very frequent cannabis use and/or CUD and ASD rates in subsets of the population is strongly encouraged. Paradoxically, caution is urged so that work to decrease CUD does not impede ongoing and promising work using cannabis and cannabis-derived products for the treatment of patients with ASD.

Keywords: acetaminophen; autism; cannabis; CBD; drug-drug interaction; socioeconomic; THC

Introduction

The prevalence of autism spectrum disorder (ASD) has been increasing for more than 60 years, with increases noted in the early 1980s. Factors underlying the changing prevalence including changes in the number of individuals with ASD, changes in diagnostic practices, changing awareness, and a variety of other social factors, including financial resources to assist families who have children with ASD. The prevalence of ASD was relatively low prior to 1980, with some estimates as low as 1 in 2500. Most recently, the Autism and Developmental Disabilities Monitoring Network (ADDM) reported that ASD affects 1 in every 31 children born in 2014 [1]. However, the latest data from the California public school systems, which include children born as late as 2019, were recently made available in a report by Nevison and Zahorodny [2]. These data show unprecedented increases in the prevalence of ASD, and may provide insight into the etiology of the disorder.

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A Changepoint in Birth Years 2015-2016 Showing a Dramatic Uptick in ASD Prevalence

The data reported by Nevison and Zahorodny [2] were obtained from the California Department of Developmental Services (DDS). Data from DDS includes information from more severe ASD cases, and thus underestimates the total prevalence of ASD, perhaps by a factor of 2 [2]. Further, due to governmental data sharing policies, the DDS data do not include information at the county level where populations are sparse. For that reason, Nevison and Zahorodny evaluated data from the most populated 36 counties out of 58 total counties. Further, data demarcated by race/ethnic background were not available in many counties due to low population counts, especially for black children and to a lesser extent white and Asian children. Thus, the trends observed are not necessarily representative of the entire population, but rather provide a sampling of data demarcated by race/ethnicity that represent the most populated areas of California.

The DDS data reported by Nevison and Zahorodny [2] from public schools in California show that, in more than half of the counties evaluated, the changing prevalence of Autism underwent an upward shift affecting children born starting in 2015 or 2016, depending on the county. The first derivative plot reported by Nevison and Zahorodny clearly shows a switch point from a relatively low rate of increase, stable for almost a decade, followed by a discrete jump in the 2015-2016 time period to a new level. Based on that analysis, a steady increase (e.g., second order polynomial or exponential) does not fit the data, but rather a "hockey stick" model, with two discrete linear sections, is most appropriate. Of the 36 counties where data were available, significant changes in the increasing prevalence of ASD for children born during the 2015-2016 time period were noted in at least 20 (55.6%) of those counties. Three examples of the changepoint identified by Nevison and Zahorodny are shown in **Figure 1**. The 2015-2016 changepoint was quite striking in many counties, depending on race/ethnicity. Striking changepoints in the 2015-2016 time period, depending on race/ethnicity, were evident in Fresno, Kern, Kings, Los Angeles, Madera, Merced, Napa, San Joaquin, Santa Barbara, Shasta, Solano, Sonoma, Stanislaus, Tulare, and Ventura counties.

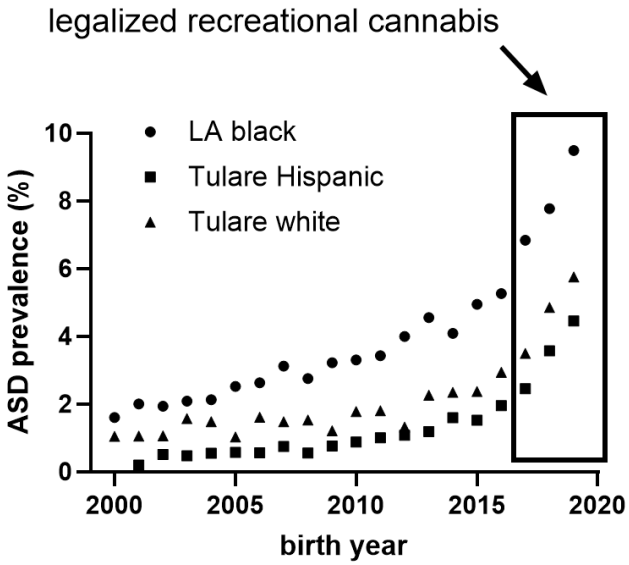

Figure 1. Changes in ASD prevalence as a function of time in black children from Los Angeles (LA) County, California and for Hispanic and white children in Tulare County, California. Recreational cannabis was legalized in California in November of 2016. However, changes in cannabis use in 2017 would have altered second-hand smoke exposure for children born in 2015 and 2016 at a stage of neurodevelopment when regression into ASD is most likely. Data are from Nevison and Zahorodny [2].

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The 2015-2016 change point was associated with socioeconomic status. The rate of change in the prevalence of ASD following the 2015-2016 changepoint was significantly and strongly correlated with the proportion of students on Medicaid ($r^2 = 0.46$, $p < 0.001$) and on median income ($r^2 = 0.42$, $p = 0.001$) within a given county. The rate of change before the 2015-2016 changepoint was less strongly associated with the proportion of students on Medicaid ($r^2 = 0.14$, $p < 0.04$) and on median income ($r^2 = 0.20$, $p = 0.009$) within a given county. Thus, economic/financial status was more strongly and negatively correlated with the prevalence of ASD after the 2015-2016 changepoint than before the 2015-2016 changepoint.

The rise in prevalence of ASD following the 2015-2016 changepoint was most striking among black children (**Figure 2**) when compared to Asians, Hispanics and whites. The mean increase in ASD prevalence for black children before and after the 2015-2016 changepoint was 0.155%/yr and 1.073%/yr, respectively. This 7.0-fold difference in yearly prevalence increase before and after the changepoint was less than that seen in Hispanics (4.8-fold change), Asians (4.3-fold change) and whites (5.7-fold change). However, the yearly change in ASD prevalence was already higher among blacks before the 2015-2016 change point (Figure 2A), suggesting the factors driving up the prevalence of ASD among black children were present in that population before the changepoint.

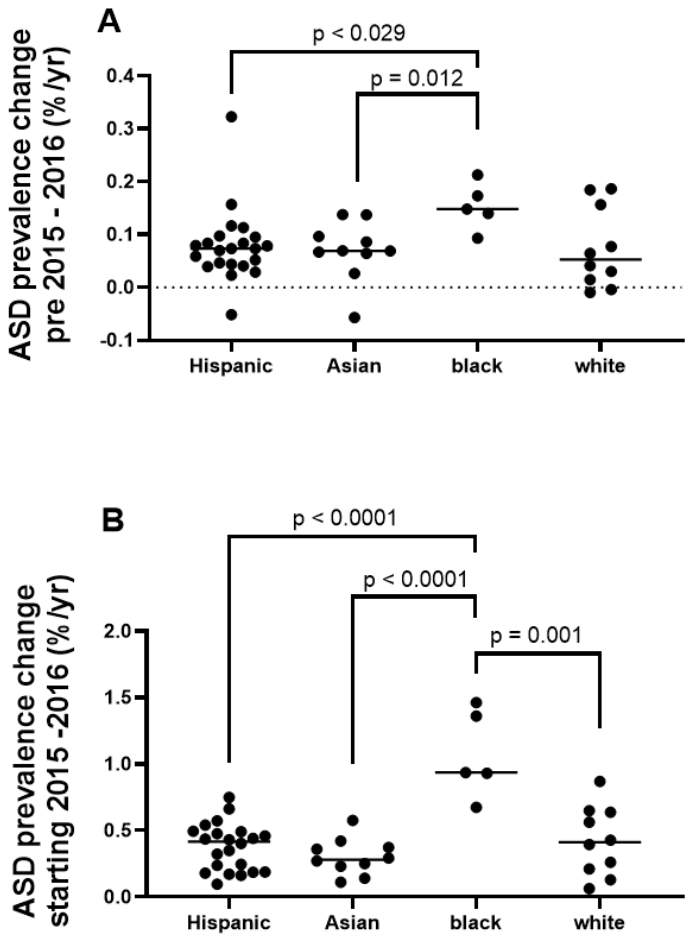

Figure 2. Change in prevalence of ASD prior to 2015 or 2016 (A) and starting in 2015-2016 (B). Data covered the years 2000 through 2019, as shown in Figure 1. The slope of the best fit line of the data was used as the change in prevalence. Data are derived from information published by Nevison and Zahorodny [2].

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Hypothesis Summary:

Several factors suggest the hypothesis that legalization of cannabis may have increased the prevalence of cannabis use disorder in a manner associated with socioeconomic status, which is turn may adversely interact with acetaminophen, a potent trigger for the induction of ASD in the presence of oxidative stress [3–5], thus increasing the prevalence of ASD (**Figure 3**). Considering the different elements of Figure 3, starting from the top, the evidence supporting the hypothesis that legalization of recreational cannabis is connected to the 2015-2016 changepoint in ASD prevalence can be enumerated as follows:

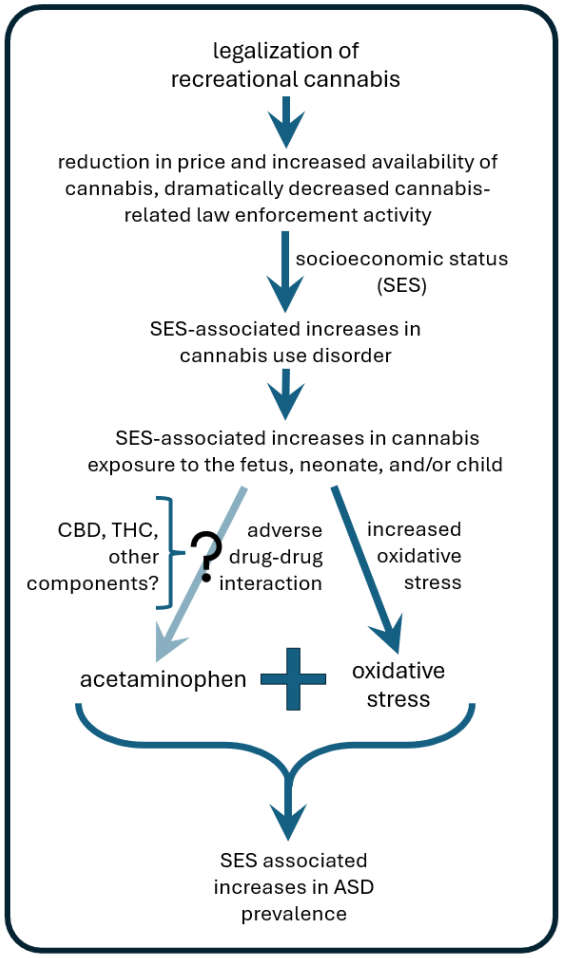

Figure 3. A hypothetical model that might potentially explain, perhaps in part, the socioeconomic status (SES)-associated uptick of ASD prevalence observed starting with children born in 2015-2016 in several counties throughout the state of California [2].

- Recreational cannabis was legalized in California in November of 2016. The price of cannabis in California decreased by about 33% starting in early 2015, reaching a low point toward the end of 2017 [6]. However, oversupply following legalization [7] and dramatically decreased law enforcement activity (**Figure 4**) has apparently driven a black market supply, which can be at a considerably lower cost [7].
- Evidence suggests that use of cannabis, in general, is not strongly associated with ASD. However, cannabis use disorder (CUD) is strongly associated with ASD, with one study showing odds ratios for ASD between 4 and 5 for mothers with CUD compared to mothers without CUD [8]. See discussion.
- Socioeconomic status profoundly interacts with cannabis use in terms of adverse outcomes. For example, as shown in **Figure 5**, the number of cannabis-associated emergency department visits

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is strongly associated with racial/ethnic factors, with blacks being most adversely impacted by the use of cannabis. In addition, minority populations are more likely to be exposed to unlicensed cannabis retailers [9], who are more likely to engage in business practices that lead to CUD, including allowing onsite consumption and selling high potency cannabis products, products designed to be attractive to children, and products without child-resistant packaging [10].

- Legalization of cannabis in California has resulted in a dramatic increase in secondhand exposure of children to cannabis.
- Cannabis may potentially have an adverse drug-drug interaction with acetaminophen, which is implicated in the induction of ASD [3–5]. Both drugs profoundly affect endocannabinoid signaling in the brain. A study from the University of Arkansas Children's hospital showed that, in laboratory mice, neither acetaminophen nor a CBD-high, THC-low cannabis extract were lethal, but the combination was lethal [11]. Further, cannabis use has complex effects on metabolism, creating potential for drug-drug interactions [12].
- Exposure to cannabis smoke profoundly increases oxidative stress [13], a cofactor in the acetaminophen-mediated induction of ASD [14].

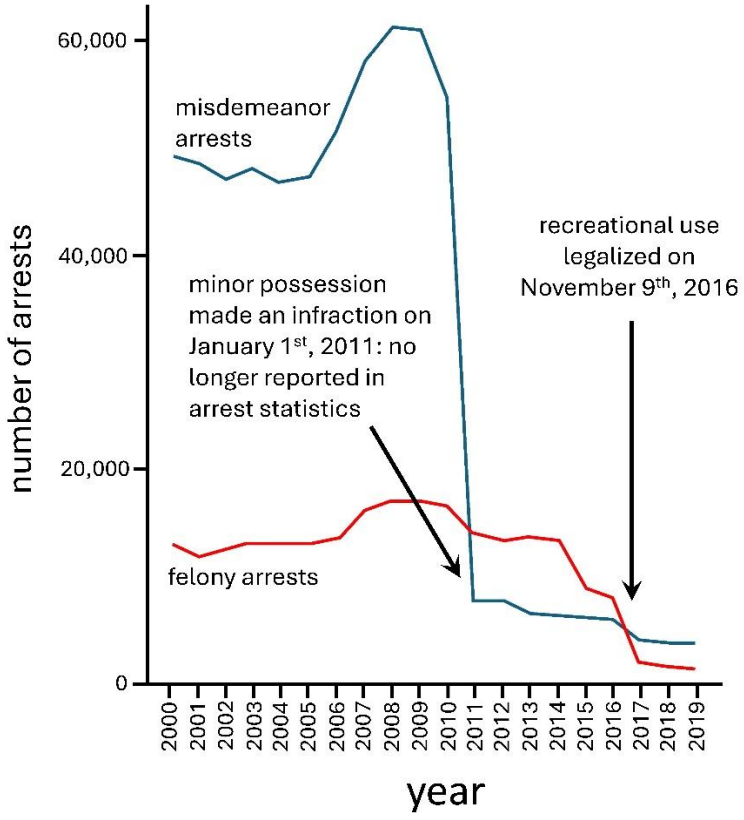

Figure 4. Number of cannabis-associated arrests and changes in California policy regarding cannabis possession and use. The graph is based on a report [42] by California NORML, the state chapter of the National Organization for the Reform of Marijuana Laws.

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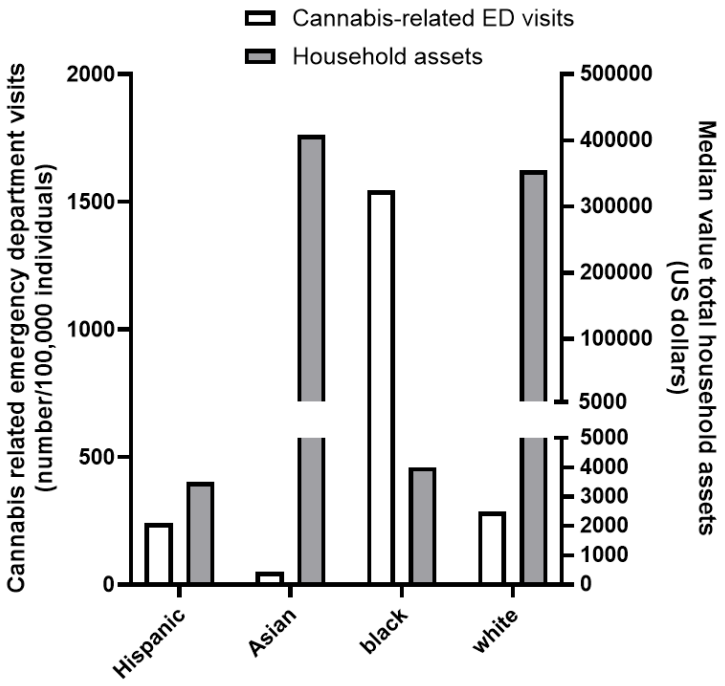

Figure 5. Cannabis-associated emergency department (ED) visits and wealth by race/ethnicity. Emergency department visits are from Los Angeles county in 2017 [10]. Median wealth (total household assets) was assessed in the National Asset Scorecard for Communities of Color (NASCC) telephone survey in approximately 2013-2014 [43]. The median wealth values shown are for the Los Angeles–Long Beach–Anaheim, CA Metropolitan Statistical Area (including Los Angeles and Orange counties). Wealth data were reported based on areas of origin, and data for most prevalent areas of origin are shown in the graph. For Hispanics and Asians, data are from individuals of Mexican and Chinese ancestry, respectively. For blacks, data are from African Americans.

Cannabis, Very Frequent Cannabis Use, Cannabis Use Disorder, and ASD

It is probably not reasonable to suggest that cannabis alone is sufficient to induce ASD. Cannabis has been used for psychoactive purposes and for traditional medicine for thousands of years [15] without being connected with ASD. Further, no associations have been observed between ASD and cultures/countercultures that were known for heavy cannabis use, such as the Haight-Ashbury area of San Francisco in the 1960s, which saw use of cannabis in as much as 95% of the population [16]. In addition, recent work indicates that use of cannabis, even during pregnancy, is not associated with ASD. For example, DiGuiseppi and colleagues [17], comparing 1428 children with ASD and 1628 neurotypical controls, found no significant associations between cannabis use during pregnancy and ASD (adjusted hazard ratio = 0.85; 95% CI 0.52 - 1.38). Similarly, Avalos and colleagues [18] examined cannabis use during pregnancy in 178948 pregnancies and found that cannabis use was not associated with ASD (adjusted hazard ratio = 1.05; 95% CI 0.84 - 1.32).

The California data recently reported by Nevison and Zahorodny [2] indicate that socioeconomic status profoundly influences the observed trends in increasing ASD prevalence (Figure 2). This observation is consistent with the hypothesis that *very frequent* use of cannabis, and/or perhaps cannabis use *disorder* could be associated with ASD, since a variety of low socioeconomic status indicators, especially low education level, are associated with cannabis use disorder [19]. For example, in a Swedish study, almost half of individuals, three times the national average, with cannabis use disorder had less than 9 years of primary education [19]. Further, as shown in Figure 5, race/ethnic factors can contribute to the prevalence of adverse effects of cannabis use. With this in mind, the demographics of study participants should be assessed when considering the connection between cannabis and ASD. One study in the US showed that low socioeconomic status is strongly

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associated (adjusted odds ratios between 2.38 and 2.64 for three different states in the USA) with cannabis use during pregnancy [20], but the extent of cannabis use disorder was not assessed in that study.

A survey study conducted in California in late 2022/early 2023 [21] found that about 14% of 15,208 survey responders were very frequent users (multiple times a day) of cannabis in late 2022/early 2023. Very frequent use of cannabis was associated with less education (OR = 1.7, $p < 0.001$) and with lower incomes (under \$50K vs \$100K, OR = 2.3, $p < 0.001$).

In the study by DiGuiseppi and colleagues cited above [17], only 5% of the mothers of children with ASD had not attained a high school education [22], suggesting a relatively high socioeconomic status in the sample population. Similarly, only 4.6% of the pregnancies assessed by Avelos and colleagues [18] were insured by Medicaid, which is less than a third of the number of individuals on Medicaid in even the richest counties in California assessed by Nevison and Zahorodny [2]. Thus, studies finding no association between cannabis use and ASD may be dominated by individuals with relatively high socioeconomic status, potentially obscuring associations that may exist in populations with lower socioeconomic status. Indeed, the loss of potentially important signals in healthcare data as a result of averaging data from different subgroups is expected [23].

Corsi and colleagues [24] found an association between cannabis use during pregnancy and ASD (adjusted hazard ratio = 1.51; 95% CI 1.17 - 1.96) in the entire birth cohort from Ontario, Canada between 2007 and 2012. However, the authors caution that interpretation of their finding should be considered in the light of likely "residual confounding". It is important to note that a hazard ratio of 1.5 for ASD can be considered "moderate" given the host of oxidative stress related factors associated with ASD, many of which carry a hazard ratio exceeding 2.0 [14].

One study from New South Wales has assessed the connection between cannabis use disorder and ASD. This study stands in contrast to the studies described above which examined cannabis use, but not cannabis use disorder. Tadesse and colleagues [8] found that, among individuals not using tobacco, prenatal cannabis use disorder was very strongly associated with ASD (crude relative risk 5.27; 95% CI 2.91 - 11.43; $p < 0.001$) (adjusted relative risk 4.55; CI 2.26 - 9.16; $p< 0.001$). The relative risk was substantially less when individuals that used tobacco during the pregnancy were evaluated (adjusted relative risk 1.87; CI 1.21 – 2.91; $p< 0.01$), suggesting that some interaction might occur between tobacco use and cannabis use. Both psychosocial and physiological interactions might be envisioned when considering potential interactions between tobacco and cannabis use. For example, individuals using tobacco might, on average, use less cannabis as a matter of practice. On the other hand, perhaps cannabis smoke may not induce oxidative stress in tobacco users to the extent that it does in non-tobacco users.

Very frequent cannabis use and/or cannabis use disorder may have been a contributor to the increasing pandemic of ASD for some time.

Cannabis use is not a new phenomenon that was facilitated by legalization. The relative number of cannabis-associated ED visits among blacks have been more than 5-fold greater than whites since at least 2013 [10]. Further, nation-wide, use of cannabis in pregnant women tripled between 2002-2003 and 2016-2017, with 3 to 4% of pregnant women reporting daily cannabis exposure by 2016-2017 [25]. In addition, during the 2012-2016 time period in San Diego county, CA, before recreational cannabis was legalized, 27.3% of 275 children (mean age 3.6 years) had detectable urinary cannabinoids [26]. Thus, although the 2015-2016 changepoint described by Nevison and Zahorodny [2] may provide some insight into factors that potentially affect the etiology of ASD, this is not to suggest that cannabis use disorder has not affected the prevalence of ASD in the past.

The yin and the yang of cannabis: Apparent medical benefits may be profound and should not be hampered in efforts to curb cannabis use disorder.

Cannabis and components of cannabis extracts, particularly cannabidiol (CBD) and tetrahydrocannabinol (THC), have long been known to have medicinal effects that benefit a variety of medical conditions [27]. The impact of cannabis or cannabis related extracts on patients with ASD is one of the many conditions for which the utility of cannabis or cannabis extracts has been evaluated.

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The results have been very encouraging. In a study of 20 children with ASD and treatment resistant behavioral symptoms, Fortini and colleagues reported that administration of CBD extracts was associated with improvement in 90% of cases, with an astounding 83.5% of all reported symptoms improving in the responders [28]. Psychotropic medication was reduced in 40% of the children following CBD treatment, and improvements in the quality of life of both the children and their families were reported [28]. A number of other studies have agreed. David and colleagues reported improvements in family life as a result of treating family members with ASD using CBD-rich products[29]. Hacohen and colleagues [30] concluded that "treatment with CBD-rich medicinal cannabis can lead to significant improvements in social communication skills of some ASD individuals, particularly those with more severe initial symptoms." The authors point out that the improvements were sufficiently large enough to be identified by relatively coarse evaluation tools [30]. In another study, Aran and colleagues found that disruptive behavior was either much or very much improved in 49% of children treated with a cannabinoid extract containing both CBD and THC ($n = 45$) versus 21% of children much improved or very much improved on placebo ($n = 47$; $p = 0.005$) [31]. Further, Barchel and colleagues [32] reported improvements in children with ASD following treatment with CBD, finding improvement in a variety of behaviors for most children in their study (n = 53), including rage attacks, self-injury, and sleep problems. Finally, physicians at the Tufts University School of Medicine reported that the large majority (20 out of 22, 92%) of their patients who self-treated with cannabis or cannabis extracts reported improvements in ASD related symptoms [33].

The above studies point toward the possibility that cannabis and/or cannabis extracts may be beneficial to individuals with ASD. Indeed, some studies suggest that the benefit may be very substantial. However, as pointed out by Pereira and colleagues [34], large-scale, controlled trials evaluating the potential benefits for cannabis have not been conducted, and the long-term potential impact of cannabis on the treatment of ASD remains unclear. Riera and colleagues also concluded that there was insufficient information from randomized controlled trials to draw any conclusions at the present time [35]. With that in mind, a primary concern of voicing this hypothesis connecting cannabis use disorder with the induction of ASD is that we do not wish to impede (a) ongoing research evaluating the beneficial effects of cannabis on the treatment of ASD, or (b) the medicinal use of cannabis already approved and in use for the treatment of ASD.

Thus, even if additional evidence emerges in the future which supports the hypothesis put forth in this paper, it is hoped that ongoing research evaluating the potential benefits of cannabis for ASD and ongoing treatment of individuals with ASD will not be impeded.

Unknowns

As with any hypothesis, the primary unknown is whether or not the hypothesis is correct. It seems highly unlikely that very frequent use of cannabis and/or cannabis use disorder do not result in at least some increased propensity for the induction of ASD. Indeed, most factors associated with inflammation and oxidative stress are associated with ASD [14], and likely play a role in the etiology of that disorder, contributing to a "total load" or burden, the cumulative weight of which predisposes individuals to ASD [3]. Given that cannabis smoke is a potent inducer of oxidative stress [13], it seems unlikely that cannabis would be an exception to the rule. However, it remains unknown whether cannabis use disorder might contribute significantly to the overall prevalence of ASD. Indeed, so many other factors induce oxidative stress and are associated with ASD [3] that it seems unlikely that any one factor along would contribute significantly enough to cause the 2015-2016 changepoint seen in the data reported by Nevison and Zahorodny [2]. On the other hand, the very high prevalence of very frequent cannabis use associated with socioeconomic status in California [21] coupled with extremely high associations of cannabis use disorder with ASD [8] indicate that very frequent cannabis use could account for dramatic socioeconomic-associated shifts in ASD prevalence within the population Further, acetaminophen is apparently a critical (necessary) trigger for the induction of many if not most cases of ASD [3–5,36–38]. Acetaminophen and cannabis both affect the brain

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through alteration of cannabinoid-mediated brain function. A bioactive metabolite of acetaminophen, AM404, blocks endocannabinoid reuptake and activates endocannabinoid receptors [39,40], placing the drug in the same area of neurobiology affected by both CBD and THC. Thus, an adverse drug-drug interaction between cannabis and acetaminophen, as potentially suggested by experiments at the University of Arkansas Children's hospital using a laboratory animal model [11], is not unthinkable. If such an adverse reaction exists, it is not unreasonable to hypothesize that it affects the induction of ASD mediated by the exposure of susceptible children to acetaminophen (Figure 3).

Insufficient evidence is available to refine some elements of the hypothesis. For example, it is unknown whether cannabis use disorder during the prenatal period or the postnatal period might be more important. Indeed, the induction of autism occurs over a broad time frame, possibly starting during conception, peaking in the peripartum period, and diminishing slowly until about 6 years of age [14]. Thus, it is difficult to hypothesize whether exposure of the mother to cannabis or cannabis-derived products during pregnancy is potentially more or less important than postpartum exposures. Post-partum exposures would presumably involve exposure during breastfeeding or second-hand exposure from one or more members of the household smoking cannabis. However, direct exposures to toddlers cannot be ruled out if caregivers believe that cannabis is safe and effective based on their own experience or on community beliefs (anecdote and consensus biases). Further, it is unknown whether CBD, THC, other cannabis related molecules, or some combination of the above, are more likely to mediate the induction of ASD. The study out of Arkansas Children's Hospital pointing toward a potential adverse drug-drug interaction in laboratory mice [11] used a CBD-rich mixture, but THC was still present, albeit to a lesser extent. Further, comprehensive assessment of commercially available cannabis products has identified mixtures of CBD and TCH in the average product, regardless of its intended use for medicine or for recreation [41]. Finally, another inflection point is observable when evaluating changes in the prevalence of black children born in 2011, with an uptick in the rate of increase in ASD that is less severe than the changepoint noted in 2015-2016. This 2011 uptick is evident when all of the California data for black children are combined and [2], separately, when all of the data from Asian children are combined [2]. Whether this earlier uptick is connected in a causal relationship with changes in laws that might encourage the use of cannabis in California in 2011 (Figure 4) is also an interesting question.

Suggested Course of Action

At the present time, we encourage the careful evaluation of ASD prevalence in a manner that carefully evaluates the impact of very frequent use of cannabis and cannabis use disorder for both the prenatal and the postnatal period. The use of aggregated data for this purpose is of some concern, as data aggregation may obscure important trends present in subsets of the population. Finally, it is hoped that ongoing research evaluating the potential benefits of cannabis and cannabis-derived products for individuals with ASD, and ongoing use of cannabis and cannabis-derived products for the treatment of individuals with ASD will not be impeded.

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Data Availability Statement: All data generated or analyzed during this study are included in the published article.

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Conflicts of Interest: The authors declare that they have no financial conflicts of interest to report. All authors have non-financial conflicts of interest arising from reputational risk, a conflict shared among most scientists and clinicians conducting work related to autism. Coauthors W.P. is a paid employees of WPLab. Coauthors M.H., J.P.J. III, Z.K. and S.M.-K. are non-paid collaborators working with WPLab. Coauthors W.P. and S.M.-K. are husband and wife.

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