

**From:** Stuart Reece  
**To:** [Select Committee RAB](#)  
**Subject:** RE: Call for Submissions - Select Committee for Reducing Addictive Behaviours  
**Date:** Monday, 23 July 2018 11:45:59 PM  
**Attachments:** [Viewpoint to JAMA 2.pdf](#)  
[Perinatal Marijuana Use and the Developing Child. JAMA 2018.pdf](#)  
[Chapter 17 - Correlates and Consequences of Prenatal Cannabis Exposure \(PCE\) - Identifying and Characterizing Vulnerable Maternal Populations and Determining Outcomes for Exposed .pdf](#)  
[03 FDA Federal Register Submission for WHO Review and Consideration - Genotoxicity & Teratogenicity. Concise 2.pdf](#)  
[Single Page Lay Summary - Cannabis Genotoxicity and Teratogenicity.pdf](#)  
[01 FDA Federal Register Submission for WHO Review and Consideration - On Cannabis Genotoxicity. General.pdf](#)  
[02 FDA Federal Register Submission for WHO Review and Consideration - Colorado Teratogenicity Patterns 4. Illustrated.pdf](#)  
[Sydney Cannabis Teratology Discussion - Summary 2.pdf](#)  
[BMJ Opinion Piece No. 2. 2.pdf](#)  
[Case for Caution with Cannabis BMJ Opinion 3.pdf](#)  
**Importance:** High

---

Dear NT,

I am not in favour of increased drugs in the community.

The enclosed attachments set out this case.

I would be grateful if these documents could please be placed in evidence before the committee.

As cannabis and other drugs are all contraindicated in numerous patient groups in the community it is unwise and imprudent to legalize and increase access.

Thankyou,

Yours sincerely,

Prof. Stuart Reece,  
MBBS(Hons.), FRCS(Ed.), FRCS(Glas.), FRACGP, MD(UNSW).  
Edith Cowan University and  
University of Western Australia.

---



April 16<sup>th</sup> 2018

Dockets Management Staff (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

Re: Department of Health and Human Services, Food and Drug Administration [Docket No. FDA-2018-N-1072]: International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; Cannabis Plant and Resin; Extracts and Tinctures of Cannabis; Delta-9-Tetrahydrocannabinol; Stereoisomers of Tetrahydrocannabinol; Cannabidiol; **Request for Comments** (FR Doc. 2018-07225).

Re: *Re-Scheduling of Cannabinoids in USA*  
- *Tetrahydrocannabinol and Cannabidiol Related*  
*Arteriopathy, Genotoxicity and Teratogenesis*

I am very concerned about the potential for increased cannabis availability in USA implied by full drug legalization; however, a comprehensive and authoritative submission of the evidence would take weeks and months to prepare. Knowing what we know now and indeed, what has been available in the scientific literature for a growing number of years concerning a myriad of harmful effects of marijuana, marijuana containing THC should not be reclassified. These effects that are now well documented in the scientific literature include, alarmingly, harm involving reproductive function and birth anomalies as a result of exposure to or use of marijuana with THC.

In addition to all of the usual concerns which you will have heard from many sources including the following I have further particular concerns:

- 1) Effect on developing brains <sup>1-15</sup>
- 2) Effect on driving <sup>16-26</sup>
- 3) Effect as a Gateway drug to other drug use including the opioid epidemic <sup>27-30</sup>
- 4) Effect on developmental trajectory and failure to attain normal adult goals (stable relationship, work, education) <sup>17,31-43</sup>
- 5) Effect on IQ and IQ regression <sup>13,44-48</sup>
- 6) Effect to increase numerous psychiatric and psychological disorders <sup>49-62</sup>
- 7) Effect on respiratory system <sup>63-85</sup>
- 8) Effect on reproductive system <sup>7,86-91</sup>
- 9) Effect in relation to immunity and immunosuppression <sup>92-108</sup>
- 10) Effect of now very concentrated forms of cannabis, THC and CBD which are widely available <sup>109,110</sup>
- 11) Outdated epidemiological studies which apply only to the era before cannabis became so potent and so concentrated <sup>110</sup>.

These issues are all well covered by a rich recent literature including reviews from such major international authorities as Dr Nora Volkow Director of NIDA at NIH <sup>1,3,5,110-112</sup>, Professor Wayne Hall <sup>113-117</sup> and others <sup>118</sup>.

### **Cannabinoid Therapeutics**

In my view the therapeutic effects of cannabinoids have been wildly inflated by the press.

Moreover, with over 1,000 studies listed for cannabinoids on [clinicaltrials.gov](https://clinicaltrials.gov), the chance of a type I experimental error, or studies being falsely reported to be positive when in fact they are not, is at last 25/1,000 at the 0.05 level.

THC as dronabinol is actually a failed drug from USA which has such a high incidence of side effects that it was rarely used as superior agents are readily available for virtually all of its touted and alleged therapeutic applications. My American liaisons advise that dronabinol sales have climbed in recent times as patients use it as a ruse to avoid detection of cannabinoid use at work in states where it is not yet legal. So when I call it a failed therapeutic I mean in a traditional sense, not in the novel way it is now applied for flagrantly flouting the law.

In considering the alleged benefits of cannabis one has to be particularly mindful of cannabis addiction in which cannabinoids will alleviate the effect of drug withdrawal as they do in any other addiction. Moreover, the fact that cannabis itself is known to cause both pain and nausea, greatly complicates the interpretation of many studies.

I also have the following concerns which relate in sum to **the arteriopathy and vasculopathy and the genotoxicity of cannabis, tetrahydrocannabinol and likely including cannabidiol and various other cannabinoids:**

### **Cannabinoid Arteriopathy**

12) Cannabis is now known to have an important arteriopathic effect and cardiovascular toxic effect <sup>5,110,119-183</sup>. Particularly noteworthy amongst these various reports are two reports by Dr Nora Volkow in 2014, the Director of the National Institute of Drug Abuse at NIH to the New England Journal of Medicine which together document the adverse cardiovascular and cerebrovascular effects of cannabis at the epidemiological level <sup>5,110</sup>; a report from our own clinic in 2016 documenting the effect of cannabis to increase cardiovascular aging to BMJ Open <sup>183</sup>; a series of reports showing a fivefold increase in the rate of heart attack within one hour after cannabis smoking <sup>121-123</sup>; several reports of cannabis related arteritis <sup>162,163,168,170,171</sup>; other reports of the cerebrovascular actions of cannabis <sup>184-187</sup>; documentation that cannabis exposure increases arterial stiffness and cardiovascular and organismal aging <sup>183</sup>; and a recent report showing that human endothelial vascular function – vasodilation - is substantially inhibited within just one minute of cannabis exposure <sup>188</sup>.

13) It is also relevant that a synthetic cannabinoid was recently shown to directly induce both thromboxane synthase and lipoxygenase, and so be directly vasoconstrictive, prothrombotic and proinflammatory <sup>189</sup>.

14) Vascular aging, including both macrovascular and microvascular aging is a major pathological feature not only because most adults in western nations die from

myocardial infarction or cerebrovascular accidents, but also because local blood flow and microvascular function is a key determinant of stem cell niche activity in many stem cell beds. This has given rise to the vascular theory of aging which has been produced by some of the leading researchers at the National Health Lung and Blood Institute at NIH, amongst many others<sup>190-192</sup>. It can thus be said not only that “You are as old as your (macrovascular) arteries”, but also that “you are as old as your (microvascular) stem cells.” Hence the now compelling evidence for the little known arteriopathic complications of cannabis and cannabinoids, carry very far reaching implications indeed. This was confirmed directly in the clinical study of arterial stiffness from my clinic mentioned above<sup>119</sup>.

- 15) Whilst aging, myocardial infarction and cerebrovascular accidents are all highly significant outcomes and major public health endpoints, these effects assume added significance in the context of congenital anomalies. Some congenital defects, such as gastroschisis, are thought to be due to a failure of vascular supply of part of the anterior abdominal wall<sup>193-198</sup>. Hence in one recent study the unadjusted odds ratio of having a gastroschisis pregnancy amongst cannabis users (O.R.=8.03, 95%C.I. 5.63-11.46) was almost as high as that for heroin, cocaine and amphetamine users (O.R.= 9.35, 95%C.I. 6.64-13.15), and the adjusted odds ratio for any illicit drug use (of which was 84% cannabis) was O.R.=3.54 (95%C.I. 2.22-5.63)<sup>199</sup> and for cannabis alone was said by these Canadian authors to be O.R.=3.0<sup>200</sup>. Hence cannabis related vasculopathy - arteriopathy beyond its very serious implications in adults also carries implications for paediatric and congenital disorders and may also constitute a major teratogenic mechanism.

### **Cannabinoid Genotoxicity and Teratogenesis**

- 16) Cannabis is associated with 11 cancers (lung, throat, bladder, airways, testes, prostate, cervix, larynx) including<sup>201,202</sup>;
- 17) Four congenital and thus inherited cancers (rhabdomyosarcoma, neuroblastoma, ALL, AML and AMML)<sup>201,202</sup>;
- 18) Sativex product insert in many nations carries standard warning against its use by males or females who might be having a baby<sup>203</sup>.
- 19) Cannabis – and likely also CBD – is known to be associated with epigenetic changes<sup>30</sup> some of which are believed to be inheritable for at least four generations<sup>204</sup>;
- 20) Cannabis is known to interfere with tubulin synthesis<sup>205-209</sup> and binding and it also acts via Stathmin so that microtubule function is impeded<sup>210</sup>. This leads directly to micronucleus formation<sup>113,211,212</sup>. Cannabis has been known to test positive in the micronucleus assay for over fifty years<sup>113,117,211</sup>. This is a major and standard test for genotoxicity. Micronucleus formation is known to lead directly to major chromosomal toxicity including chromosomal shattering – so-called chromothripsis – and is known to be associated with cell death, cancerogenesis and major foetal abnormalities<sup>202,213-215</sup>.

- 21) Cannabis has also been linked definitively with congenital heart disease is a statement by the American Heart Association and the American Academy of Pediatrics in 2007<sup>216</sup>, on the basis of just three epidemiological studies, all done in the days before cannabis became so concentrated. Congenital heart defects have also been linked with the father's cannabis use<sup>217</sup>. Indeed, one study showed that paternal cannabis use was the strongest risk factor of all for preventable congenital cardiac defects<sup>218</sup>.
- 22) Cannabis has also been linked with gastroschisis in at least *seven cohort and case control studies*<sup>199,219-224</sup> some of which are summarized in a Canadian Government Report<sup>200</sup>. In that report the geographic incidence of most major congenital anomalies closely paralleled the use of cannabis as described in other major Canadian reports<sup>225</sup>. The overall adjusted odds ratio for cannabis induction of gastroschisis was quoted by these authors as 3.0<sup>200</sup>.
- 23) Moreover, outbreaks of both congenital heart disease<sup>226</sup> and gastroschisis in North Carolina also paralleled the local use of cannabis in that state as described by Department of Justice Reports<sup>227</sup>. The incidence of gastroschisis was noted to double in North Carolina 1999-2001 in the same period the cannabis trade there was rising<sup>228</sup>. Figures of cannabis use in pregnant women in California by age were also recently reported to JAMA<sup>229</sup>, age group trend lines by age group which closely approximate those reported by CDC for the age incidence of gastroschisis in the USA<sup>230</sup> (Figure 1). Importantly much of the cannabis coming into both North Carolina and Florida is said to originate in Mexico<sup>227,231</sup>. An eight-fold rise in the rate of gastroschisis has been reported from Mexico<sup>232</sup>. Gastroschisis has also risen in Washington state<sup>233</sup>.
- 24) Cannabis has also been associated with 17 other major congenital defects by major Hawaiian epidemiological study reported by Forrester in 2007 when it was used alone<sup>221</sup>. When considered in association with other drug use – which in many cases cannabis leads to – cannabis use was associated with a further 19 major congenital defects.
- 25) In addition to the effect of cannabinoids on the epigenome and microtubules, cannabinoids have been firmly linked to a reduction of the ability of the cell to produce energy from their mitochondria<sup>78,82,91,234-249</sup>. An extensive and robust evidence base<sup>244</sup> now links cellular energy generation to the maintenance and care of cellular DNA<sup>250-253</sup>. Moreover, as the cellular energy charge falls so too DNA maintenance collapses, and indeed, the cell can spiral where its remaining energy resources, particularly as NAD<sup>+</sup>, are routed into failing and futile DNA repair, the cell slips into pseudohypoxic metabolism like the Warburg effect well known in cancerogenesis<sup>254</sup>, NAD<sup>+</sup> falls below the level required for further energy generation and cellular metabolism collapses. Hence this well-established collapse of the mitochondrial energy charge and transmembrane potential forms a potent engine of continuing and accelerating genotoxicity<sup>255</sup>.

26) Moreover, the well documented decline in mitochondrial respiration induced by cannabinoids, including tetrahydrocannabinol, cannabidiol and anandamide <sup>78,82,91,234-242,244-248</sup> achieves particular significance in the light of the robustly documented decline in cellular energetics including NAD<sup>+</sup> which not only occurs with age <sup>251,256-268</sup> but indeed, ***has now been shown to be one of the primary drivers of cellular and whole organismal aging*** <sup>250-254,263,269-289</sup>. This close parallel is illustrated in Figure 2. It follows therefore that ***cannabinoid administration (including THC and CBD) necessarily phenocopies cellular aging***. This implies of course that cannabinoid dependent patients are old at the cellular level. Indeed, normal human aging is phenocopied in the clinical syndrome of cannabinoid dependence which includes (most references are provided above):

- 1) Neurological deficits in:
  - i) attention,
  - ii) learning and
  - iii) memory;
  - iv) social withdrawal and disengagement and
  - v) academic and
  - vi) occupational underachievement
- 2) Psychiatric disorders including
  - i) Anxiety,
  - ii) Depression,
  - iii) Mixed Psychosis
  - iv) Bipolar Affective disorder and
  - v) Schizophrenia,
- 3) Respiratory disorders including:
  - i) Asthma
  - ii) Chronic Bronchitis (increased sputum production)
  - iii) Emphysema (Increased residual volume)
  - iv) Probably increased carcinomas of the aerodigestive tract
- 4) Immune suppression which generally implies
  - i) segmental immunostimulation in some parts of the immune system since  
the innate and adaptive immune systems exert profound homeostatic mechanisms in response to suppression of one of its parts;  
A Substantial literature on immunostimulation
- 5) Reproductive effects generally characterized by reduced
  - i) Male and
  - ii) Female fertility
- 6) Cardiovascular toxicity with elevated rates of
  - i) Myocardial infarction
  - ii) Cerebrovascular accident
  - iii) Arteritis
  - iv) Vascular age – vascular stiffness <sup>119</sup>
- 7) Genotoxicity in
  - i) Respiratory epithelium and
  - ii) Gonadal tissues.
- 8) Osteoporosis <sup>290-300</sup>

- 9) Cancers of the
  - i) Head and neck
  - ii) Larynx
  - iii) Lung
  - iv) Leukaemia
  - v) Prostate
  - vi) Cervix
  - vii) Testes
  - viii) Bladder
  - ix) Childhood neuroblastoma
  - x) Childhood acute lymphoblastic leukaemia
  - xi) Childhood Acute Myeloid and myelomonocytic leukaemia
  - xii) Childhood rhabdomyosarcoma <sup>201,202</sup>.

**The issue here of course is that cannabinoid dependence therefore copies without exception all of the major disorders of old age, each of which is also faithfully phenocopied by cannabis dependence.**

**The most prominent disorders of older age include:**

- 1) Alzheimer's disease**
- 2) Cardiovascular and cerebrovascular disease**
- 3) Osteoporosis**
- 4) Systemic inflammatory syndrome**
- 5) Changes in lung volume and the mechanics of breathing**
- 6) Cancers**

Hence this provides one powerful pathway by which cannabinoid exposure can replicate and phenocopy the disorders of old age.

This is not of course to suggest that this is the only such pathway. Obviously changes of the general level of immune activity, or alterations of the level of DNA repair occurring directly or indirectly associated with cannabis use can form similar such pathways: both are well documented in cannabis use and also in the aging literature as major pathways implicated in systemic aging. Nevertheless, the decline in mitochondrial energetics together with its inherent genotoxic implications does seem to be a particularly well substantiated and robustly demonstrated pathway which must give serious pause to cannabinoid advocates if the sustainability of the health and welfare systems is to be factored in together with any consideration of individual patient, advocate and industrial-complex rights.

- 27) The genotoxicity of THC, CBD and CBN has been noted against sperm since at least 1999 (Zimmerman and Zimmerman in Nahas "Marijuana and Medicine" 1999, Springer). This is clearly highly significant as sperm go directly into the formation of the zygote and the new human individual.

- 28) CB1R receptors are known to exist intracellularly on both the membranes of endoplasmic reticulum and mitochondria. In both locations they can induce organellar stress and major cell toxicity including disruption of DNA maintenance. Interestingly mitochondrial outer membrane CB1R's signal via a complex signaling chain involving the G-protein transduction machinery, protein kinase A and cyclic-AMP across the intermembrane space to the inner membrane and cristae, in a fashion replicating much of the G-protein signaling occurring at the cell membrane. This machinery is also implicated in mitonuclear signaling, and the mitonuclear DNA balance between mitochondrial DNA and nuclear DNA transcriptional control, which has long been implicated in inducing the mitochondrial unfolded protein cellular stress response cell aging, stem cell behaviour and DNA genotoxic mechanisms<sup>248,301</sup>.
- 29) You are no doubt aware that human sperm are structured like express outboard motors behind DNA packets with layers of mitochondria densely coiled around the rotating flagellum which powers their progress in the female reproductive tract (Figure 3). These mitochondria also carry CB1R's and are significantly inhibited even at 100 nanomolar THC. The acrosome reaction is also inhibited<sup>239</sup>.
- 30) A similar arrangement is shown in Figure 4, where mitochondria are shown in green surrounding the mitotic spindle (pink, with the chromosomes shown in blue), which is the cellular machinery and apparatus of cell division. Mitosis and meiosis, the classical processes of cell division, are highly energy dependent and mitochondria are clearly positioned strategically to supply the required energy for this process, just as they are positioned in proximity to the root of the sperm flagellum rotor in that situation.
- 31) Cannabidiol is known to act via the PPAR $\gamma$  system<sup>101,302-308</sup>. PPAR $\gamma$  is known to have a major effect on gene expression, reproductive and embryonic and zygote function during development<sup>309-332</sup> so that significant genotoxic and / or teratogenic effects seem inevitable via this route. Drugs which act in this class, known as the thiazolidinediones, are classed as category B3 in pregnancy and caution is indicated in their use in pregnancy and lactation.
- 32) The Report of the Reproductive and Cancer Hazard Assessment Branch of the Office of Environmental Health Hazard Assessment of the Health Department of California was mentioned above in connection with the carcinogenicity of marijuana smoke<sup>333</sup>. ***Since virtually all mutagens are also teratogens*** it follows therefore from the basic tenets of mutagenesis that if cannabis is unsafe as a known carcinogen it must also be at the very least a putative teratogen.
- 33) CBD has also been noted to be a genotoxic in other studies<sup>334-336</sup>.
- 34) All of which points to major teratogenic activity for both THC and CBD.

Some of the quotations from Professor James Graham's classical book on the effects of THC in hamsters and white rabbits, the best animal models for human genotoxicity, bear repeating <sup>337</sup> :

- a) "The concentration of THC was relatively low and the **malignancy severe.**"
- b) "40-100µg resin/ml there occurred **marked inhibition of cell division.**
- c) "large total dose, Hamsters, 25-300mg/kg ... "oedema, **phocomelia, omphalocoele, spina bifida, exencephaly,** multiple malformations and **myelocoele.** **This is a formidable list.**"
- d) "It is to this **anti-mitotic action** that the authors attribute the **embryotoxic** action of cannabis."
- e) "By such criteria resin or extract of cannabis would be **forbidden to women** during the first three months of **pregnancy.**" <sup>337</sup>

Indeed, even from the other side of the world I have heard many exceedingly adverse reports from US states in which cannabis has been legalized including Colorado, Washington, Oregon, Florida and California <sup>231,233,338-342</sup>. Taken together the above evidence suggests that these negative reports stem directly from the now known actions of cannabis and cannabinoids, and are by no means incidental epiphenomena somehow related to social constructs surrounding cannabis use or the product forms, dosages, or routes of administration involved <sup>343</sup>.

**Cannabis that contains increasingly high levels of THC is now widely available, particularly in the jurisdictions where the use of cannabis has been legalized. This means that another major genotoxin, akin to Thalidomide, is being unleashed on the USA and the world. This is clearly a very grave, and, indeed, an entirely preventable occurrence.**

Dr Frances Kelsey of FDA is said to have the public servant based at FDA who saved American from the thalidomide scandal which devastated so many other English-speaking nations including my own <sup>344</sup>. This occurred because the genotoxicity section of the file application with FDA was blank. It was blank because thalidomide tested positive in various white rabbit and guinea pig assays. **It is these same tests which cannabis is known to have failed** <sup>88,337,345,346</sup>. Dr Kelsey's photograph has been published in the medical press with President Kennedy for her service to the nation (Figure 5) <sup>344</sup>. The challenge to FDA at this time seems whether Science can triumph over agenda driven populism, its primary vehicle, the mass media, and its primary proximate driver the burgeoning cannabis industry. Since FDA is the Federal agency par excellence where Health Science is weighed, commissioned and thoughtfully considered the challenge in our time would appear to be no less.

Evidence to date does not suggest that major congenital malformations are as common after prenatal cannabis exposure as they are after prenatal thalidomide exposure. Nevertheless the qualitative similarities remain and indeed are prominent. It is yet to be seen whether the rate of congenital anomalies after cannabis are quantitatively as common: epidemiological studies in a high potency era have not been undertaken; and even the birth defects rates from most birth defects registers in western nations including that held by CDC, Atlanta appear to be seriously out of date at the time of writing. Moreover the non-linear dose response curve in

many cannabis genotoxicity studies which includes a sharp knee bend upwards beyond a certain threshold level which suggests that we could well be in for a very unpleasant quantitative surprise. At the time of writing this remains to be formally determined.

Dr Bertha Madras, Professor of Addiction Psychiatry at Harvard Medical School has recently argued against re-scheduling of cannabis. Her comments include the following:

*“Why do nations schedule drugs? ..... Nations schedule psychoactive drugs because we revere this three-pound organ (of our brain) differently than any other part of our body. It is the repository of our humanity. It is the place that enables us to write poetry and to do theater, to conjure up calculus and send rockets to Pluto three billion miles away, and to create I Phones and 3 D computer printing. And that is the magnificence of the human brain. Drugs can influence (the brain) adversely. So, this is not a war on drugs. This is a defense of our brains, the ultimate source of our humanity”<sup>347</sup>.*

I look forward to seeing the comments that you post concerning the reasons why the classification for marijuana should not be changed and that, indeed, the public should be alerted to the very harmful effects of marijuana with THC, especially in light of the wide range of marijuana’s harmful effects and the high potency of THC in today’s marijuana and in light of the idiosyncratic effects of marijuana of even low doses of THC and owing to the certain risk of harm to progeny and babies born to users of marijuana.

Please feel free to call on me if you would like further information concerning the research to which I have referred herein.

Yours sincerely,



Professor Dr. Stuart Reece,  
Edith Cowan University and  
University of Western Australia,  
Perth,  
Western Australia,  
Australia, 6009.

## References

- 1 Bloomfield, M. A., Ashok, A. H., Volkow, N. D. & Howes, O. D. The effects of Delta9-tetrahydrocannabinol on the dopamine system. *Nature* **539**, 369-377, doi:10.1038/nature20153 (2016).
- 2 DuPont, R. L. & Lieberman, J. A. Young Brains on Drugs. *Science* **344**, 557, doi:10.1126/science.1254989 (2014).
- 3 Nora Volkow (Director, NIDA), George Koob (Director, NIAAA), Alan Guttmacher (Director, NICHD), and Bob Croyle (Director, Division of Cancer Control and Population Sciences, NCI). *National Longitudinal Study of the Neurodevelopmental Consequences of Substance Use*, <<http://www.niaaa.nih.gov/news-events/news-noteworthy/national-longitudinal-study-neurodevelopmental-consequences-substance>> (2014).
- 4 Volkow, N. D., Compton, W. M. & Wargo, E. M. The Risks of Marijuana Use During Pregnancy. *JAMA* **317**, 129-130, doi:10.1001/jama.2016.18612 (2017).
- 5 Volkow, N. D., Compton, W. M. & Weiss, S. R. Adverse health effects of marijuana use. *N Engl J Med* **371**, 879, doi:10.1056/NEJMc1407928 (2014).
- 6 Volkow, N. D., Han, B., Compton, W. M. & Blanco, C. Marijuana Use During Stages of Pregnancy in the United States. *Ann Intern Med* **166**, 763-764, doi:10.7326/L17-0067 (2017).
- 7 Goldschmidt, L., Richardson, G. A., Willford, J. & Day, N. L. Prenatal marijuana exposure and intelligence test performance at age 6. *J Am Acad Child Adolesc Psychiatry* **47**, 254-263, doi:10.1097/chi.0b013e318160b3f0 (2008).
- 8 Penke, L. *et al.* Brain-wide white matter tract integrity is associated with information processing speed and general intelligence. *Mol Psychiatry* **17**, 955-955 (2012).
- 9 Wu, C. S., Jew, C. P. & Lu, H. C. Lasting impacts of prenatal cannabis exposure and the role of endogenous cannabinoids in the developing brain. *Future Neurol* **6**, 459-480 (2011).
- 10 DeRosse, P. *et al.* Adding insult to injury: childhood and adolescent risk factors for psychosis predict lower fractional anisotropy in the superior longitudinal fasciculus in healthy adults. *Psychiatry Res* **224**, 296-302, doi:10.1016/j.psychres.2014.09.001 (2014).
- 11 Madabhushi, R., Pan, L. & Tsai, L. H. DNA damage and its links to neurodegeneration. *Neuron* **83**, 266-282, doi:10.1016/j.neuron.2014.06.034 (2014).
- 12 Navakkode, S. & Korte, M. Pharmacological activation of CB1 receptor modulates long term potentiation by interfering with protein synthesis. *Neuropharmacology* **79**, 525-533, doi:10.1016/j.neuropharm.2013.11.018 (2014).
- 13 Becker, M. P., Collins, P. F., Lim, K. O., Muetzel, R. L. & Luciana, M. Longitudinal changes in white matter microstructure after heavy cannabis use. *Developmental cognitive neuroscience* **16**, 23-35, doi:10.1016/j.dcn.2015.10.004 (2015).
- 14 Lorenzetti, V. *et al.* Gross morphological brain changes with chronic, heavy cannabis use. *Br J Psychiatry* **206**, 77-78, doi:10.1192/bjp.bp.114.151407 (2015).
- 15 Vargish, G. A. *et al.* Persistent inhibitory circuit defects and disrupted social behaviour following in utero exogenous cannabinoid exposure. *Mol Psychiatry* **22**, 56-67, doi:10.1038/mp.2016.17 (2017).
- 16 Alvarez, F. J., Fierro, I. & Del Rio, M. C. Cannabis and driving: results from a general population survey. *Forensic science international* **170**, 111-116 (2007).
- 17 Fergusson, D. M., Horwood, L. J. & Boden, J. M. Is driving under the influence of cannabis becoming a greater risk to driver safety than drink driving? Findings from a longitudinal study. *Accident; analysis and prevention* **40**, 1345-1350, doi:S0001-4575(08)00026-2 [pii] 10.1016/j.aap.2008.02.005 (2008).
- 18 Grotenhermen, F. *et al.* Developing limits for driving under cannabis. *Addiction* **102**, 1910-1917 (2007).
- 19 Jones, C., Donnelly, N., Swift, W. & Weatherburn, D. Preventing cannabis users from driving under the influence of cannabis. *Accident; analysis and prevention* **38**, 854-861 (2006).
- 20 Jones, C. G., Swift, W., Donnelly, N. J. & Weatherburn, D. J. Correlates of driving under the influence of cannabis. *Drug Alcohol Depend* **88**, 83-86 (2007).
- 21 Kelly, E., Darke, S. & Ross, J. A review of drug use and driving: epidemiology, impairment, risk factors and risk perceptions. *Drug and alcohol review* **23**, 319-344 (2004).
- 22 McCarthy, D. M., Lynch, A. M. & Pederson, S. L. Driving after use of alcohol and marijuana in college students. *Psychol Addict Behav* **21**, 425-430 (2007).

- 23 McIntosh, J., O'Brien, T. & McKeganey, N. Drug driving and the management of risk: the perspectives and practices of a sample of problem drug users. *Int J Drug Policy* **19**, 248-254, doi:S0955-3959(06)00248-9 [pii] 10.1016/j.drugpo.2006.12.003 (2008).
- 24 Walsh, G. W. & Mann, R. E. On the high road: driving under the influence of cannabis in Ontario. *Canadian journal of public health* **90**, 260-263 (1999).
- 25 Wilson, D. Experience with drugs and driving in Queensland, Australia. *Medicine, science, and the law* **25**, 2-10 (1985).
- 26 Fergusson, D. M. & Horwood, L. J. Cannabis use and traffic accidents in a birth cohort of young adults. *Accident; analysis and prevention* **33**, 703-711, doi:S0001-4575(00)00082-8 [pii] (2001).
- 27 Gurman S. Legal pot in Colorado hasn't stopped black market. *Associated Press*, 1-2 (October 2014).
- 28 Wang, X., Dow-Edwards, D., Anderson, V., Minkoff, H. & Hurd, Y. L. Discrete opioid gene expression impairment in the human fetal brain associated with maternal marijuana use. *Pharmacogenomics J* **6**, 255-264, doi:10.1038/sj.tpj.6500375 (2006).
- 29 Cadoni, C., Pisanu, A., Solinas, M., Acquas, E. & Di Chiara, G. Behavioural sensitization after repeated exposure to Delta 9-tetrahydrocannabinol and cross-sensitization with morphine. *Psychopharmacology (Berl)* **158**, 259-266, doi:10.1007/s002130100875 (2001).
- 30 DiNieri, J. A. *et al.* Maternal cannabis use alters ventral striatal dopamine D2 gene regulation in the offspring. *Biol Psychiatry* **70**, 763-769, doi:10.1016/j.biopsych.2011.06.027 (2011).
- 31 Fergusson, D. M., Lynskey, M. T. & Horwood, L. J. The short-term consequences of early onset cannabis use. *Journal of abnormal child psychology* **24**, 499-512 (1996).
- 32 Fergusson, D. M. & Horwood, L. J. Early onset cannabis use and psychosocial adjustment in young adults. *Addiction* **92**, 279-296 (1997).
- 33 Fergusson, D. M. & Horwood, L. J. Does cannabis use encourage other forms of illicit drug use? *Addiction* **95**, 505-520 (2000).
- 34 Fergusson, D. M. & Horwood, L. J. Cannabis use and dependence in a New Zealand birth cohort. *The New Zealand medical journal* **113**, 156-158 (2000).
- 35 Fergusson, D. M., Horwood, L. J. & Swain-Campbell, N. Cannabis use and psychosocial adjustment in adolescence and young adulthood. *Addiction* **97**, 1123-1135 (2002).
- 36 Taylor, D. R. *et al.* A longitudinal study of the effects of tobacco and cannabis exposure on lung function in young adults. *Addiction* **97**, 1055-1061 (2002).
- 37 Fergusson, D. M., Horwood, L. J. & Beaudrais, A. L. Cannabis and educational achievement. *Addiction* **98**, 1681-1692, doi:573 [pii] (2003).
- 38 Fergusson, D. M., Poulton, R., Smith, P. F. & Boden, J. M. Cannabis and psychosis. *BMJ (Clinical research ed)* **332**, 172-175, doi:332/7534/172 [pii] 10.1136/bmj.332.7534.172 (2006).
- 39 Fergusson, D. M. & Boden, J. M. Cannabis use and adult ADHD symptoms. *Drug Alcohol Depend* **95**, 90-96, doi:S0376-8716(07)00512-1 [pii] 10.1016/j.drugalcdep.2007.12.012 (2008).
- 40 Horwood, L. J. *et al.* Cannabis use and educational achievement: findings from three Australasian cohort studies. *Drug Alcohol Depend* **110**, 247-253, doi:S0376-8716(10)00109-2 [pii] 10.1016/j.drugalcdep.2010.03.008 (2010).
- 41 Meier, M. H. *et al.* Associations Between Cannabis Use and Physical Health Problems in Early Midlife: A Longitudinal Comparison of Persistent Cannabis vs Tobacco Users. *JAMA Psychiatry* **73**, 731-740, doi:10.1001/jamapsychiatry.2016.0637 (2016).
- 42 Fergusson, D. M. & Boden, J. M. Cannabis use and later life outcomes. *Addiction* **103**, 969-976; discussion 977-968, doi:ADD2221 [pii] 10.1111/j.1360-0443.2008.02221.x (2008).
- 43 Swain, N. R., Gibb, S. J., Horwood, L. J. & Fergusson, D. M. Alcohol and cannabis abuse/dependence symptoms and life satisfaction in young adulthood. *Drug and alcohol review* **31**, 327-333, doi:10.1111/j.1465-3362.2011.00339.x (2012).
- 44 Meier, M. H. *et al.* Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proc Natl Acad Sci US A* **109**, E2657-2664, doi:10.1073/pnas.1206820109 (2012).
- 45 Thames, A. D., Arbid, N. & Sayegh, P. Cannabis use and neurocognitive functioning in a non-clinical sample of users. *Addictive behaviors* **39**, 994-999, doi:10.1016/j.addbeh.2014.01.019 (2014).

- 46 Buchy, L. *et al.* Evaluating the relationship between cannabis use and IQ in youth and young adults at clinical high risk of psychosis. *Psychiatry Res* **230**, 878-884, doi:10.1016/j.psychres.2015.11.033 (2015).
- 47 Castellanos-Ryan, N. *et al.* Adolescent cannabis use, change in neurocognitive function, and high-school graduation: A longitudinal study from early adolescence to young adulthood. *Dev Psychopathol* **29**, 1253-1266, doi:10.1017/S0954579416001280 (2017).
- 48 Bogaty, S. E. R., Lee, R. S. C., Hickie, I. B. & Hermens, D. F. Meta-analysis of neurocognition in young psychosis patients with current cannabis use. *J Psychiatr Res* **99**, 22-32, doi:10.1016/j.jpsychires.2018.01.010 (2018).
- 49 Grech, A., Van Os, J., Jones, P. B., Lewis, S. W. & Murray, R. M. Cannabis use and outcome of recent onset psychosis. *Eur Psychiatry* **20**, 349-353, doi:S0924-9338(04)00227-5 [pii] 10.1016/j.eurpsy.2004.09.013 (2005).
- 50 Henquet, C. *et al.* Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. *BMJ (Clinical research ed)* **330**, 11, doi:bmj.38267.664086.63 [pii] 10.1136/bmj.38267.664086.63 (2005).
- 51 Henquet, C., Murray, R., Linszen, D. & van Os, J. The environment and schizophrenia: the role of cannabis use. *Schizophr Bull* **31**, 608-612, doi:sbi027 [pii] 10.1093/schbul/sbi027 (2005).
- 52 Monshouwer, K., Smit, F., de Graaf, R., van Os, J. & Vollebergh, W. First cannabis use: does onset shift to younger ages? Findings from 1988 to 2003 from the Dutch National School Survey on Substance Use. *Addiction* **100**, 963-970, doi:ADD1088 [pii] 10.1111/j.1360-0443.2005.01088.x (2005).
- 53 van Os, J., Henquet, C. & Stefanis, N. Cannabis-related psychosis and the gene-environment interaction: comments on Ferdinand *et al.* 2005. *Addiction* **100**, 874-875, doi:ADD1083 [pii] 10.1111/j.1360-0443.2005.01083.x (2005).
- 54 Henquet, C. & Van Os, J. The coherence of the evidence linking cannabis with psychosis. *Psychological medicine* **38**, 461-462; author reply 462-464, doi:S0033291707002279 [pii] 10.1017/S0033291707002279 (2008).
- 55 Konings, M., Henquet, C., Maharajh, H. D., Hutchinson, G. & Van Os, J. Early exposure to cannabis and risk for psychosis in young adolescents in Trinidad. *Acta psychiatrica Scandinavica* **118**, 209-213, doi:ACP1202 [pii] 10.1111/j.1600-0447.2008.01202.x (2008).
- 56 Luzi, S., Morrison, P. D., Powell, J., di Forti, M. & Murray, R. M. What is the mechanism whereby cannabis use increases risk of psychosis? *Neurotox Res* **14**, 105-112, doi:10.1007/BF03033802 (2008).
- 57 Veling, W., Mackenbach, J. P., van Os, J. & Hoek, H. W. Cannabis use and genetic predisposition for schizophrenia: a case-control study. *Psychological medicine* **38**, 1251-1256, doi:S0033291708003474 [pii] 10.1017/S0033291708003474 (2008).
- 58 Hall, W. The adverse health effects of cannabis use: What are they, and what are their implications for policy? *Int J Drug Policy*, doi:S0955-3959(09)00050-4 [pii] 10.1016/j.drugpo.2009.02.013 (2009).
- 59 Hall, W. & Lynskey, M. The challenges in developing a rational cannabis policy. *Current opinion in psychiatry* **22**, 258-262, doi:10.1097/YCO.0b013e3283298f36 (2009).
- 60 Hall, W. D. Challenges in reducing cannabis-related harm in Australia. *Drug and alcohol review* **28**, 110-116, doi:DAR039 [pii] 10.1111/j.1465-3362.2008.00039.x (2009).
- 61 Henquet, C. *et al.* COMT ValMet moderation of cannabis-induced psychosis: a momentary assessment study of 'switching on' hallucinations in the flow of daily life. *Acta psychiatrica Scandinavica* **119**, 156-160, doi:ACP1265 [pii] 10.1111/j.1600-0447.2008.01265.x (2009).
- 62 Spechler, P. A. *et al.* Cannabis use in early adolescence: Evidence of amygdala hypersensitivity to signals of threat. *Developmental cognitive neuroscience* **16**, 63-70, doi:10.1016/j.dcn.2015.08.007 (2015).
- 63 Wu, T. C., Tashkin, D. P., Djahed, B. & Rose, J. E. Pulmonary hazards of smoking marijuana as compared with tobacco. *N Engl J Med* **318**, 347-351 (1988).
- 64 Wu, T. C., Tashkin, D. P., Rose, J. E. & Djahed, B. Influence of marijuana potency and amount of cigarette consumed on marijuana smoking pattern. *Journal of psychoactive drugs* **20**, 43-46 (1988).

- 65 Fligiel, S. E. *et al.* Marijuana exposure and pulmonary alterations in primates. *Pharmacology, biochemistry, and behavior* **40**, 637-642 (1991).
- 66 Sherman, M. P., Roth, M. D., Gong, H., Jr. & Tashkin, D. P. Marijuana smoking, pulmonary function, and lung macrophage oxidant release. *Pharmacology, biochemistry, and behavior* **40**, 663-669 (1991).
- 67 Wu, H. D., Wright, R. S., Sassoon, C. S. & Tashkin, D. P. Effects of smoked marijuana of varying potency on ventilatory drive and metabolic rate. *The American review of respiratory disease* **146**, 716-721 (1992).
- 68 Tashkin, D. P. Is frequent marijuana smoking harmful to health? *The Western journal of medicine* **158**, 635-637 (1993).
- 69 Simmons, M. S. & Tashkin, D. P. The relationship of tobacco and marijuana smoking characteristics. *Life Sci* **56**, 2185-2191 (1995).
- 70 Baldwin, G. C. *et al.* Marijuana and cocaine impair alveolar macrophage function and cytokine production. *American journal of respiratory and critical care medicine* **156**, 1606-1613 (1997).
- 71 Barsky, S. H., Roth, M. D., Kleerup, E. C., Simmons, M. & Tashkin, D. P. Histopathologic and molecular alterations in bronchial epithelium in habitual smokers of marijuana, cocaine, and/or tobacco. *Journal of the National Cancer Institute* **90**, 1198-1205 (1998).
- 72 Sarafian, T. A., Magallanes, J. A., Shau, H., Tashkin, D. & Roth, M. D. Oxidative stress produced by marijuana smoke. An adverse effect enhanced by cannabinoids. *American journal of respiratory cell and molecular biology* **20**, 1286-1293 (1999).
- 73 Zhang, Z. F. *et al.* Marijuana use and increased risk of squamous cell carcinoma of the head and neck. *Cancer Epidemiol Biomarkers Prev* **8**, 1071-1078 (1999).
- 74 Zhu, L. X. *et al.* Delta-9-tetrahydrocannabinol inhibits antitumor immunity by a CB2 receptor-mediated, cytokine-dependent pathway. *J Immunol* **165**, 373-380, doi:10.1152/ajplung.00157.2002 [pii] (2000).
- 75 Roth, M. D. *et al.* Induction and regulation of the carcinogen-metabolizing enzyme CYP1A1 by marijuana smoke and delta (9)-tetrahydrocannabinol. *American journal of respiratory cell and molecular biology* **24**, 339-344 (2001).
- 76 Tashkin, D. P. Airway effects of marijuana, cocaine, and other inhaled illicit agents. *Current opinion in pulmonary medicine* **7**, 43-61 (2001).
- 77 Tashkin, D. P., Baldwin, G. C., Sarafian, T., Dubinett, S. & Roth, M. D. Respiratory and immunologic consequences of marijuana smoking. *Journal of clinical pharmacology* **42**, 71S-81S (2002).
- 78 Sarafian, T. A., Kouyoumjian, S., Khoshaghideh, F., Tashkin, D. P. & Roth, M. D. Delta 9-tetrahydrocannabinol disrupts mitochondrial function and cell energetics. *American journal of physiology* **284**, L298-306, doi:10.1152/ajplung.00157.2002 (2003).
- 79 Roth, M. D., Whittaker, K., Salehi, K., Tashkin, D. P. & Baldwin, G. C. Mechanisms for impaired effector function in alveolar macrophages from marijuana and cocaine smokers. *J Neuroimmunol* **147**, 82-86 (2004).
- 80 Tashkin, D. P. Smoked marijuana as a cause of lung injury. *Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace / Fondazione clinica del lavoro, IRCCS [and] Istituto di clinica fisiologica e malattie apparato respiratorio, Universita di Napoli, Secondo ateneo* **63**, 93-100 (2005).
- 81 Copersino, M. L. *et al.* Cannabis withdrawal among non-treatment-seeking adult cannabis users. *Am J Addict* **15**, 8-14 (2006).
- 82 Sarafian, T. A. *et al.* Inhaled marijuana smoke disrupts mitochondrial energetics in pulmonary epithelial cells in vivo. *American journal of physiology* **290**, L1202-1209 (2006).
- 83 Alibhai, I. N., Green, T. A., Potashkin, J. A. & Nestler, E. J. Regulation of fosB and DeltafosB mRNA expression: in vivo and in vitro studies. *Brain Res* **1143**, 22-33, doi:S0006-8993(07)00139-4 [pii] 10.1016/j.brainres.2007.01.069 (2007).
- 84 Gong, H., Jr., Fligiel, S., Tashkin, D. P. & Barbers, R. G. Tracheobronchial changes in habitual, heavy smokers of marijuana with and without tobacco. *The American review of respiratory disease* **136**, 142-149 (1987).
- 85 British Lung Foundation. (London, 2005).
- 86 Wright, P. L., Smith, S. H., Keplinger, M. L., Calandra, J. C. & Braude, M. C. Reproductive and teratologic studies with  $\Delta$ 9-tetrahydrocannabinol and crude marijuana extract. *Toxicology and applied pharmacology* **38**, 223-235, doi:10.1016/0041-008X(76)90131-9 (1976).
- 87 Hatoum, N. S., Davis, W. M., Elsohly, M. A. & Turner, C. E. Perinatal exposure to cannabichromene and  $\Delta$ 9-tetrahydrocannabinol: Separate and combined effects on viability of pups and

- on male reproductive system at maturity. *Toxicology letters* **8**, 141-146, doi:10.1016/0378-4274(81)90042-4 (1981).
- 88 Braude, M. C. Marijuana effects on the endocrine and reproductive systems. Discussion and recommendations. *NIDA Res Monogr* **44**, 124-129 (1984).
  - 89 Dalterio S., Steger R.W. & Bartke A. in *Marijuana in Medicine* Vol. 1 (eds G. G. Nahas, Sutin K.M., Harvey D.J., & Agurell S.) Ch. 35, 441-448 (Humana Press, 1999).
  - 90 Smith C.G., Almirez R.G., Sher P.M. & Asch R.H. in *Marijuana and Medicine* Vol. 1 (eds G. G. Nahas, Sutin K.M., Harvey D.J., & Agurell S.) Ch. 30, 379-384 (Humana Press, 1999).
  - 91 Rossato, M., Pagano, C. & Vettor, R. The cannabinoid system and male reproductive functions. *Journal of neuroendocrinology* **20 Suppl 1**, 90-93 (2008).
  - 92 Galiegue, S. *et al.* Expression of central and peripheral cannabinoid receptors in human immune tissues and leukocyte subpopulations. *Eur J Biochem* **232**, 54-61 (1995).
  - 93 Salzet, M., Breton, C., Bisogno, T. & Di Marzo, V. Comparative biology of the endocannabinoid system possible role in the immune response. *Eur J Biochem* **267**, 4917-4927 (2000).
  - 94 Klein, T. W. *et al.* The cannabinoid system and immune modulation. *Journal of leukocyte biology* **74**, 486-496 (2003).
  - 95 El-Gohary, M. & Eid, M. A. Effect of cannabinoid ingestion (in the form of bhang) on the immune system of high school and university students. *Human & experimental toxicology* **23**, 149-156 (2004).
  - 96 McKallip, R. J., Nagarkatti, M. & Nagarkatti, P. S. Delta-9-tetrahydrocannabinol enhances breast cancer growth and metastasis by suppression of the antitumor immune response. *J Immunol* **174**, 3281-3289, doi:174/6/3281 [pii] (2005).
  - 97 Klein, T. W. & Cabral, G. A. Cannabinoid-induced immune suppression and modulation of antigen-presenting cells. *J Neuroimmune Pharmacol* **1**, 50-64 (2006).
  - 98 Eisenstein, T. K., Meissler, J. J., Wilson, Q., Gaughan, J. P. & Adler, M. W. Anandamide and Delta9-tetrahydrocannabinol directly inhibit cells of the immune system via CB2 receptors. *J Neuroimmunol* **189**, 17-22, doi:S0165-5728(07)00185-3 [pii] 10.1016/j.jneuroim.2007.06.001 (2007).
  - 99 Xu, H. *et al.* Anti-inflammatory property of the cannabinoid receptor-2-selective agonist JWH-133 in a rodent model of autoimmune uveoretinitis. *Journal of leukocyte biology* **82**, 532-541, doi:jl.b.0307159 [pii] 10.1189/jlb.0307159 (2007).
  - 100 Rodgers, K. M. *et al.* The cortical innate immune response increases local neuronal excitability leading to seizures. *Brain* **132**, 2478-2486, doi:awp177 [pii] 10.1093/brain/awp177 (2009).
  - 101 De Filippis, D. *et al.* Cannabidiol reduces intestinal inflammation through the control of neuroimmune axis. *PLoS One* **6**, e28159, doi:10.1371/journal.pone.0028159 (2011).
  - 102 Giacoppo, S. *et al.* A new formulation of cannabidiol in cream shows therapeutic effects in a mouse model of experimental autoimmune encephalomyelitis. *Daru* **23**, 48, doi:10.1186/s40199-015-0131-8 (2015).
  - 103 Kozela, E. *et al.* Pathways and gene networks mediating the regulatory effects of cannabidiol, a nonpsychoactive cannabinoid, in autoimmune T cells. *J Neuroinflammation* **13**, 136, doi:10.1186/s12974-016-0603-x (2016).
  - 104 Gonzalez-Garcia, C. *et al.* Mechanisms of action of cannabidiol in adoptively transferred experimental autoimmune encephalomyelitis. *Experimental neurology* **298**, 57-67, doi:10.1016/j.expneurol.2017.08.017 (2017).
  - 105 Stenchever, M. A. & Allen, M. The effect of delta-9-tetrahydrocannabinol on the chromosomes of human lymphocytes in vitro. *Am J Obstet Gynecol* **114**, 819-821, doi:0002-9378(72)90908-8 [pii] (1972).
  - 106 Henrich, R. T., Nogawa, T. & Morishima, A. In vitro induction of segregational errors of chromosomes by natural cannabinoids in normal human lymphocytes. *Environ Mutagen* **2**, 139-147 (1980).
  - 107 Wallace, J. M., Tashkin, D. P., Oishi, J. S. & Barbers, R. G. Peripheral blood lymphocyte subpopulations and mitogen responsiveness in tobacco and marijuana smokers. *Journal of psychoactive drugs* **20**, 9-14 (1988).
  - 108 Sherman, M. P. *et al.* Effects of smoking marijuana, tobacco or cocaine alone or in combination on DNA damage in human alveolar macrophages. *Life Sci* **56**, 2201-2207 (1995).
  - 109 McLaren, J., Swift, W., Dillon, P. & Allsop, S. Cannabis potency and contamination: a review of the literature. *Addiction* **103**, 1100-1109 (2008).

- 110 Volkow, N. D., Baler, R. D., Compton, W. M. & Weiss, S. R. B. Adverse Health Effects of Marijuana Use. *New England Journal of Medicine* **370**, 2219-2227, doi:doi:10.1056/NEJMra1402309 (2014).
- 111 Compton, W. M., Volkow, N. D. & Lopez, M. F. Medical Marijuana Laws and Cannabis Use: Intersections of Health and Policy. *JAMA Psychiatry* **74**, 559-560, doi:10.1001/jamapsychiatry.2017.0723 (2017).
- 112 Volkow, N. D. *et al.* Decreased dopamine brain reactivity in marijuana abusers is associated with negative emotionality and addiction severity. *Proc Natl Acad Sci U S A* **111**, E3149-3156, doi:10.1073/pnas.1411228111 (2014).
- 113 Hall, W. & Degenhardt, L. Adverse health effects of non-medical cannabis use. *Lancet* **374**, 1383-1391, doi:10.1016/S0140-6736(09)61037-0 (2009).
- 114 Degenhardt, L. *et al.* The persistence of the association between adolescent cannabis use and common mental disorders into young adulthood. *Addiction* **108**, 124-133, doi:10.1111/j.1360-0443.2012.04015.x (2013).
- 115 Hall, W. What has research over the past two decades revealed about the adverse health effects of recreational cannabis use? *Addiction* **110**, 19-35, doi:10.1111/add.12703 (2015).
- 116 Hall, W. & Degenhardt, L. High potency cannabis: a risk factor for dependence, poor psychosocial outcomes, and psychosis. *BMJ (Clinical research ed)* **350**, h1205, doi:10.1136/bmj.h1205 (2015).
- 117 Hall, W. & Solowij, N. Adverse effects of cannabis. *Lancet* **352**, 1611-1616 (1998).
- 118 Reece, A. S. Chronic toxicology of cannabis. *Clinical Toxicology* **47**, 517-524, doi:10.1080/15563650903074507 (2009).
- 119 Reece A.S., Norman, A. & Hulse G.K. Cannabis Exposure as an Interactive Cardiovascular Risk Factor and Accelerant of Organismal Ageing – A Longitudinal Study. *BMJ - Open* **In Press**, doi: <http://dx.doi.org/10.1136/bmjopen-2016-011891> (2016).
- 120 Blazquez, C. *et al.* Cannabinoids inhibit the vascular endothelial growth factor pathway in gliomas. *Cancer Res* **64**, 5617-5623, doi:10.1158/0008-5472.CAN-03-3927 (2004).
- 121 DeFilippis, E. M. *et al.* Cocaine and Marijuana Use among Young Adults Presenting with Myocardial Infarction: The Partners YOUNG-MI Registry. *Journal of the American College of Cardiology*, doi:10.1016/j.jacc.2018.02.047 (2018).
- 122 Desai, R. *et al.* Recreational Marijuana Use and Acute Myocardial Infarction: Insights from Nationwide Inpatient Sample in the United States. *Cureus* **9**, e1816, doi:10.7759/cureus.1816 (2017).
- 123 Frost, L., Mostofsky, E., Rosenbloom, J. I., Mukamal, K. J. & Mittleman, M. A. Marijuana use and long-term mortality among survivors of acute myocardial infarction. *Am Heart J* **165**, 170-175, doi:10.1016/j.ahj.2012.11.007 (2013).
- 124 Miller, W. E., Spiekerman, R. E. & Hepper, N. G. Pneumomediastinum resulting from performing Valsalva maneuvers during marihuana smoking. *Chest* **62**, 233-234 (1972).
- 125 Zagon, I. S., McLaughlin, P. J., Goodman, S. R. & Rhodes, R. E. Opioid receptors and endogenous opioids in diverse human and animal cancers. *Journal of the National Cancer Institute* **79**, 1059-1065 (1987).
- 126 Hess, G. D. & Zagon, I. S. Endogenous opioid systems and neural development: ultrastructural studies in the cerebellar cortex of infant and weanling rats. *Brain research bulletin* **20**, 473-478 (1988).
- 127 Barbers, R. G., Evans, M. J., Gong, H., Jr. & Tashkin, D. P. Enhanced alveolar monocytic phagocyte (macrophage) proliferation in tobacco and marijuana smokers. *The American review of respiratory disease* **143**, 1092-1095 (1991).
- 128 Bourque, L. B., Tashkin, D. P., Clark, V. A. & Schuler, R. Demographic and health characteristics of heavy marijuana smokers in Los Angeles County. *The International journal of the addictions* **26**, 739-755 (1991).
- 129 Isayama, T., McLaughlin, P. J. & Zagon, I. S. Endogenous opioids regulate cell proliferation in the retina of developing rat. *Brain Res* **544**, 79-85 (1991).
- 130 Kay, M. M., Hughes, J., Zagon, I. & Lin, F. B. Brain membrane protein band 3 performs the same functions as erythrocyte band 3. *Proc Natl Acad Sci U S A* **88**, 2778-2782 (1991).
- 131 Lambrecht, G. L., Malbrain, M. L., Coremans, P., Verbist, L. & Verhaegen, H. Acute renal infarction and heavy marijuana smoking. *Nephron* **70**, 494-496 (1995).
- 132 Chen, H., Campisi, J. & Padmanabhan, R. SV40 large T antigen transactivates the human cdc2 promoter by inducing a CCAAT box binding factor. *J Biol Chem* **271**, 13959-13967 (1996).
- 133 Fowler, J. S. *et al.* Comparison of Brain Glucose Metabolism and Monoamine Oxidase B (MAO B) in Traumatic Brain Injury. *Clin Positron Imaging* **2**, 71-79 (1999).

- 134 Okereke, U. N., Weber, B. E. & Israel, R. H. Spontaneous pneumomediastinum in an 18-year-old black Sudanese high school student. *Journal of the National Medical Association* **91**, 357-359 (1999).
- 135 Grella, C. E., Joshi, V. & Hser, Y. I. Program variation in treatment outcomes among women in residential drug treatment. *Evaluation review* **24**, 364-383 (2000).
- 136 Hser, Y. I., Hoffman, V., Grella, C. E. & Anglin, M. D. A 33-year follow-up of narcotics addicts. *Arch Gen Psychiatry* **58**, 503-508 (2001).
- 137 Blasco, M. Profile. Maria Blasco. Interview by Laura Spinney. *Trends Cell Biol* **12**, 489 (2002).
- 138 Hosokawa, M. A higher oxidative status accelerates senescence and aggravates age-dependent disorders in SAMP strains of mice. *Mech Ageing Dev* **123**, 1553-1561 (2002).
- 139 Jones, R. T. Cardiovascular system effects of marijuana. *Journal of clinical pharmacology* **42**, 58S-63S (2002).
- 140 Klatsky, A. L., Armstrong, M. A., Friedman, G. D. & Sidney, S. Alcohol drinking and risk of hemorrhagic stroke. *Neuroepidemiology* **21**, 115-122 (2002).
- 141 Melbourne Division of General Practice. *Relationships between Mental Health, personal circumstances and drug use in young Victorian Australians*. (AGPS, 2002).
- 142 Sidney, S. Cardiovascular consequences of marijuana use. *Journal of clinical pharmacology* **42**, 64S-70S (2002).
- 143 Blasco, M., Losada, J., Fernandez Val, J. F. & Sarria, R. [Transitional bladder carcinoma TaG1: role of the EGFr tyrosin kinase activation in the cellular proliferation]. *Med Clin (Barc)* **121**, 641-644 (2003).
- 144 Grella, C. E., Hser, Y. I. & Hsieh, S. C. Predictors of drug treatment re-entry following relapse to cocaine use in DATOS. *J Subst Abuse Treat* **25**, 145-154 (2003).
- 145 Ruiz Villaverde, R., Blasco Melguizo, J., Linares Solano, J. & Serrano Ortega, S. Lichen planus-like eruption due to enalapril. *J Eur Acad Dermatol Venereol* **17**, 612-614 (2003).
- 146 Gonzalez, S. *et al.* Behavioral and molecular changes elicited by acute administration of SR141716 to Delta9-tetrahydrocannabinol-tolerant rats: an experimental model of cannabinoid abstinence. *Drug Alcohol Depend* **74**, 159-170 (2004).
- 147 Harrist, A. *et al.* Alteration of hippocampal cell proliferation in mice lacking the beta 2 subunit of the neuronal nicotinic acetylcholine receptor. *Synapse* **54**, 200-206 (2004).
- 148 Beck, J. D. *et al.* Periodontal disease and coronary heart disease: a reappraisal of the exposure. *Circulation* **112**, 19-24 (2005).
- 149 Desvarieux, M. *et al.* Periodontal microbiota and carotid intima-media thickness: the Oral Infections and Vascular Disease Epidemiology Study (INVEST). *Circulation* **111**, 576-582 (2005).
- 150 Gatley, S. J. *et al.* PET imaging in clinical drug abuse research. *Curr Pharm Des* **11**, 3203-3219 (2005).
- 151 Kalivas, P. W., Volkow, N. & Seamans, J. Unmanageable motivation in addiction: a pathology in prefrontal-accumbens glutamate transmission. *Neuron* **45**, 647-650 (2005).
- 152 Steingrimsson, E., Copeland, N. G. & Jenkins, N. A. Melanocyte stem cell maintenance and hair graying. *Cell* **121**, 9-12 (2005).
- 153 Beyond Blue. *Beyond Blue*, <<http://www.beyondblue.org.au/>> (2006).
- 154 Volkow, N. D. Hispanic drug abuse research: challenges and opportunities. *Drug Alcohol Depend* **84 Suppl 1**, S4-7 (2006).
- 155 Alia-Klein, N. *et al.* What is in a word? No versus Yes differentially engage the lateral orbitofrontal cortex. *Emotion* **7**, 649-659 (2007).
- 156 Ch'ng, C. W. *et al.* Drug use in motor vehicle drivers presenting to an Australian, adult major trauma centre. *Emerg Med Australas* **19**, 359-365 (2007).
- 157 Fosados, R., Evans, E. & Hser, Y. I. Ethnic differences in utilization of drug treatment services and outcomes among Proposition 36 offenders in California. *J Subst Abuse Treat* (2007).
- 158 Niv, N., Wong, E. C. & Hser, Y. I. Asian Americans in community-based substance abuse treatment: Service needs, utilization, and outcomes. *J Subst Abuse Treat* **33**, 313-319 (2007).
- 159 Ortar, G. *et al.* Carbamoyl tetrazoles as inhibitors of endocannabinoid inactivation: A critical revisitation. *Eur J Med Chem* (2007).
- 160 Rock, R. B. *et al.* WIN55,212-2-mediated inhibition of HIV-1 expression in microglial cells: involvement of cannabinoid receptors. *J Neuroimmune Pharmacol* **2**, 178-183 (2007).
- 161 Starowicz, K. *et al.* Tonic endovanilloid facilitation of glutamate release in brainstem descending antinociceptive pathways. *J Neurosci* **27**, 13739-13749 (2007).
- 162 Schneider, H. J., Jha, S. & Burnand, K. G. Progressive arteritis associated with cannabis use. *Eur J Vasc Endovasc Surg* **18**, 366-367, doi:10.1053/ejvs.1999.0859 (1999).

- 163 Disdier, P. *et al.* Cannabis arteritis revisited--ten new case reports. *Angiology* **52**, 1-5 (2001).
- 164 Ducasse, E. *et al.* Popliteal artery entrapment associated with cannabis arteritis. *Eur J Vasc Endovasc Surg* **27**, 327-332, doi:10.1016/S1533 (2004).
- 165 Kogan, N. M. *et al.* A cannabinoid quinone inhibits angiogenesis by targeting vascular endothelial cells. *Mol Pharmacol* **70**, 51-59, doi:10.1124/mol.105.021089 (2006).
- 166 Netherland, C. D., Pickle, T. G., Bales, A. & Thewke, D. P. Cannabinoid receptor type 2 (CB2) deficiency alters atherosclerotic lesion formation in hyperlipidemic Ldlr-null mice. *Atherosclerosis* **213**, 102-108, doi:10.1016/j.atherosclerosis.2010.07.060 (2010).
- 167 Steffens, S. & Pacher, P. Targeting cannabinoid receptor CB(2) in cardiovascular disorders: promises and controversies. *Br J Pharmacol* **167**, 313-323, doi:10.1111/j.1476-5381.2012.02042.x (2012).
- 168 Molica, F. *et al.* Endogenous cannabinoid receptor CB1 activation promotes vascular smooth-muscle cell proliferation and neointima formation. *J Lipid Res* **54**, 1360-1368, doi:10.1194/jlr.M035147(2013).
- 169 Slavic, S. *et al.* Cannabinoid receptor 1 inhibition improves cardiac function and remodelling after myocardial infarction and in experimental metabolic syndrome. *J Mol Med (Berl)* **91**, 811-823, doi:10.1007/s00109-013-1034-0 (2013).
- 170 Jouanjus, E., Lapeyre-Mestre, M., Micallef, J., French Association of the Regional, A. & Dependence Monitoring Centres Working Group on Cannabis, C. Cannabis use: signal of increasing risk of serious cardiovascular disorders. *J Am Heart Assoc* **3**, e000638, doi:10.1161/JAHA.113.000638 (2014).
- 171 Stanley, C. & O'Sullivan, S. E. Vascular targets for cannabinoids: animal and human studies. *Br J Pharmacol* **171**, 1361-1378, doi:10.1111/bph.12560 (2014).
- 172 Kosior, D. A., Filipiak, K. J., Stolarz, P. & Opolski, G. Paroxysmal atrial fibrillation in a young female patient following marijuana intoxication--a case report of possible association. *Med Sci Monit* **6**, 386-389 (2000).
- 173 Rezkalla, S. H., Sharma, P. & Kloner, R. A. Coronary no-flow and ventricular tachycardia associated with habitual marijuana use. *Annals of emergency medicine* **42**, 365-369, doi:10.1067/mem.2003.297 (2003).
- 174 Fisher, B. A., Ghuran, A., Vadamalai, V. & Antonios, T. F. Cardiovascular complications induced by cannabis smoking: a case report and review of the literature. *Emerg Med J* **22**, 679-680, doi:10.1136/emj.2004.014969 (2005).
- 175 Baranchuk, A., Johri, A. M., Simpson, C. S., Methot, M. & Redfearn, D. P. Ventricular fibrillation triggered by marijuana use in a patient with ischemic cardiomyopathy: a case report. *Cases J* **1**, 373, doi:10.1186/1757-1626-1-373 (2008).
- 176 Korantzopoulos, P., Liu, T., Papaioannides, D., Li, G. & Goudevenos, J. A. Atrial fibrillation and marijuana smoking. *International journal of clinical practice* **62**, 308-313, doi:10.1111/j.1742-1241.2007.01505.x (2008).
- 177 Diffley, M., Armenian, P., Gerona, R., Reinhartz, O. & Avasarala, K. Catecholaminergic polymorphic ventricular tachycardia found in an adolescent after a methylenedioxymethamphetamine and marijuana-induced cardiac arrest. *Crit Care Med* **40**, 2223-2226, doi:10.1097/CCM.0b013e318250a870 (2012).
- 178 Heath, T. S., Burroughs, Z., Thompson, A. J. & Tecklenburg, F. W. Acute intoxication caused by a synthetic cannabinoid in two adolescents. *J Pediatr Pharmacol Ther* **17**, 177-181, doi:10.5863/1551-6776-17.2.177 (2012).
- 179 Menahem, S. Cardiac asystole following cannabis (marijuana) usage--additional mechanism for sudden death? *Forensic science international* **233**, e3-5, doi:10.1016/j.forsciint.2013.10.007 (2013).
- 180 Casier, I., Vanduyhoven, P., Haine, S., Vrints, C. & Jorens, P. G. Is recent cannabis use associated with acute coronary syndromes? An illustrative case series. *Acta Cardiol* **69**, 131-136, doi:10.2143/AC.69.2.3017293 (2014).
- 181 Korantzopoulos, P. Marijuana smoking is associated with atrial fibrillation. *The American journal of cardiology* **113**, 1085-1086, doi:10.1016/j.amjcard.2014.01.001 (2014).
- 182 Wolff, V. *et al.* Cannabis-related stroke: myth or reality? *Stroke; a journal of cerebral circulation* **44**, 558-563, doi:10.1161/STROKEAHA.112.671347 (2013).
- 183 Reece, A. S., Norman, A. & Hulse, G. K. Cannabis exposure as an interactive cardiovascular risk factor and accelerant of organismal ageing: a longitudinal study. *BMJ Open* **6**, e011891, doi:10.1136/bmjopen-2016-011891 (2016).

- 184 Herning, R. I., Better, W. & Cadet, J. L. EEG of chronic marijuana users during abstinence: relationship to years of marijuana use, cerebral blood flow and thyroid function. *Clin Neurophysiol* **119**, 321-331, doi:10.1016/j.clinph.2007.09.140 (2008).
- 185 Mathew, R. J., Wilson, W. H., Humphreys, D., Lowe, J. V. & Wiethe, K. E. Middle cerebral artery velocity during upright posture after marijuana smoking. *Acta psychiatrica Scandinavica* **86**, 173-178 (1992).
- 186 Wagner, J. A., Jarai, Z., Batkai, S. & Kunos, G. Hemodynamic effects of cannabinoids: coronary and cerebral vasodilation mediated by cannabinoid CB(1) receptors. *European journal of pharmacology* **423**, 203-210 (2001).
- 187 Wolff, V. *et al.* High frequency of intracranial arterial stenosis and cannabis use in ischaemic stroke in the young. *Cerebrovascular diseases (Basel, Switzerland)* **37**, 438-443, doi:10.1159/000363618 (2014).
- 188 Wang, X. *et al.* One Minute of Marijuana Secondhand Smoke Exposure Substantially Impairs Vascular Endothelial Function. *J Am Heart Assoc* **5**, doi:10.1161/JAHA.116.003858 (2016).
- 189 Bileck, A. *et al.* Impact of a synthetic cannabinoid (CP-47,497-C8) on protein expression in human cells: evidence for induction of inflammation and DNA damage. *Archives of toxicology* **90**, 1369-1382, doi:10.1007/s00204-015-1569-7 (2016).
- 190 Strait, J. B. & Lakatta, E. G. Aging-associated cardiovascular changes and their relationship to heart failure. *Heart Fail Clin* **8**, 143-164, doi:S1551-7136(11)00101-2 [pii]; 10.1016/j.hfc.2011.08.011 (2012).
- 191 Le Couteur, D. G. & Lakatta, E. G. A vascular theory of aging. *J Gerontol A Biol Sci Med Sci* **65**, 1025-1027, doi:glq135 [pii]; 10.1093/gerona/glq135 (2010).
- 192 Sutton-Tyrrell, K. *et al.* Elevated aortic pulse wave velocity, a marker of arterial stiffness, predicts cardiovascular events in well-functioning older adults. *Circulation* **111**, 3384-3390, doi:CIRCULATIONAHA.104.483628 [pii]; 10.1161/CIRCULATIONAHA.104.483628 (2005).
- 193 Lubinsky, M. A vascular and thrombotic model of gastroschisis. *Am J Med Genet A* **164A**, 915-917, doi:10.1002/ajmg.a.36370 (2014).
- 194 Folkerth, R. D. *et al.* Gastroschisis, destructive brain lesions, and placental infarction in the second trimester suggest a vascular pathogenesis. *Pediatr Dev Pathol* **16**, 391-396, doi:10.2350/13-03-1316-CR.1 (2013).
- 195 Werler, M. M., Mitchell, A. A., Moore, C. A., Honein, M. A. & National Birth Defects Prevention, S. Is there epidemiologic evidence to support vascular disruption as a pathogenesis of gastroschisis? *Am J Med Genet A* **149A**, 1399-1406, doi:10.1002/ajmg.a.32897 (2009).
- 196 Van Allen, M. I. & Smith, D. W. Vascular pathogenesis of gastroschisis. *J Pediatr* **98**, 662-663 (1981).
- 197 Hoyme, H. E., Higginbottom, M. C. & Jones, K. L. The vascular pathogenesis of gastroschisis: intrauterine interruption of the omphalomesenteric artery. *J Pediatr* **98**, 228-231 (1981).
- 198 Pistor, G., Marzheuser-Brands, S., Weber, G. & Streich, R. Intraoperative vascular assessment for estimation of risk in primary closure of omphalocele and gastroschisis. *Pediatr Surg Int* **11**, 86-90, doi:10.1007/BF00183732 (1996).
- 199 Skarsgard, E. D. *et al.* Maternal risk factors for gastroschisis in Canada. *Birth Defects Res A Clin Mol Teratol* **103**, 111-118, doi:10.1002/bdra.23349 (2015).
- 200 Moore A., Roulean J. & Skarsgard E. Vol. 1 (ed Health Canada Public Health Agency of Canada) 57-63 (Health Canada, Ottawa, 2013).
- 201 Reece, A. S. Chronic toxicology of cannabis. *Clin Toxicol (Phila)* **47**, 517-524, doi:10.1080/15563650903074507 (2009).
- 202 Reece, A. S. & Hulse, G. K. Chromothripsis and epigenomics complete causality criteria for cannabis- and addiction-connected carcinogenicity, congenital toxicity and heritable genotoxicity. *Mutat Res* **789**, 15-25, doi:10.1016/j.mrfmmm.2016.05.002 (2016).
- 203 GW Pharmaceuticals. *Package Leaflet: Information for the Patient Sativex Oromucosal spray*, <<http://www.medicines.org.uk/emc/PIL.23228.latest.pdf>> (2016).
- 204 Manikkam, M., Guerrero-Bosagna, C., Tracey, R., Haque, M. M. & Skinner, M. K. Transgenerational actions of environmental compounds on reproductive disease and identification of epigenetic biomarkers of ancestral exposures. *PLoS One* **7**, e31901, doi:10.1371/journal.pone.0031901 (2012).
- 205 Wang, J., Yuan, W. & Li, M. D. Genes and pathways co-associated with the exposure to multiple drugs of abuse, including alcohol, amphetamine/methamphetamine, cocaine, marijuana, morphine, and/or

- nicotine: a review of proteomics analyses. *Molecular neurobiology* **44**, 269-286, doi:10.1007/s12035-011-8202-4 (2011).
- 206 Zhuo, H. Q., Huang, L., Huang, H. Q. & Cai, Z. Effects of chronic tramadol exposure on the zebrafish brain: a proteomic study. *J Proteomics* **75**, 3351-3364, doi:10.1016/j.jprot.2012.03.038 (2012).
- 207 Tahir, S. K., Trogadis, J. E., Stevens, J. K. & Zimmerman, A. M. Cytoskeletal organization following cannabinoid treatment in undifferentiated and differentiated PC12 cells. *Biochem Cell Biol* **70**, 1159-1173 (1992).
- 208 Tahir, S. K. & Zimmerman, A. M. Influence of marihuana on cellular structures and biochemical activities. *Pharmacology, biochemistry, and behavior* **40**, 617-623 (1991).
- 209 Wilson, R. G., Jr., Tahir, S. K., Mechoulam, R., Zimmerman, S. & Zimmerman, A. M. Cannabinoid enantiomer action on the cytoarchitecture. *Cell Biol Int* **20**, 147-157 (1996).
- 210 Tortoriello, G. *et al.* Miswiring the brain: Delta9-tetrahydrocannabinol disrupts cortical development by inducing an SCG10/stathmin-2 degradation pathway. *EMBO J* **33**, 668-685, doi:10.1002/embj.201386035 (2014).
- 211 Hall, W. & Degenhardt, L. The adverse health effects of chronic cannabis use. *Drug Test Anal* **6**, 39-45, doi:10.1002/dta.1506 (2014).
- 212 Zimmerman, A. M. & Raj, A. Y. Influence of Cannabinoids on Somatic Cells in vivo. *Pharmacology* **21**, 277-287 (1980).
- 213 Zhang, C. Z. *et al.* Chromothripsis from DNA damage in micronuclei. *Nature* **522**, 179-184, doi:10.1038/nature14493 (2015).
- 214 Kloosterman, W. P. *et al.* Chromothripsis is a common mechanism driving genomic rearrangements in primary and metastatic colorectal cancer. *Genome Biol* **12**, R103, doi:10.1186/gb-2011-12-10-r103 (2011).
- 215 de Pagter, M. S. *et al.* Chromothripsis in healthy individuals affects multiple protein-coding genes and can result in severe congenital abnormalities in offspring. *Am J Hum Genet* **96**, 651-656, doi:10.1016/j.ajhg.2015.02.005 (2015).
- 216 Jenkins, K. J. *et al.* Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. *Circulation* **115**, 2995-3014, doi:10.1161/CIRCULATIONAHA.106.183216 (2007).
- 217 Ewing, C. K., Loffredo, C. A. & Beaty, T. H. Paternal risk factors for isolated membranous ventricular septal defects. *Am J Med Genet* **71**, 42-46 (1997).
- 218 Wilson, P. D., Loffredo, C. A., Correa-Villasenor, A. & Ferencz, C. Attributable fraction for cardiac malformations. *Am J Epidemiol* **148**, 414-423 (1998).
- 219 David, A. L. *et al.* A case-control study of maternal periconceptual and pregnancy recreational drug use and fetal malformation using hair analysis. *PLoS One* **9**, e111038, doi:10.1371/journal.pone.0111038 (2014).
- 220 Draper, E. S. *et al.* Recreational drug use: a major risk factor for gastroschisis? *Am J Epidemiol* **167**, 485-491, doi:10.1093/aje/kwm335 (2008).
- 221 Forrester, M. B. & Merz, R. D. Risk of selected birth defects with prenatal illicit drug use, Hawaii, 1986-2002. *Journal of toxicology and environmental health* **70**, 7-18 (2007).
- 222 Torfs, C. P., Velie, E. M., Oechsli, F. W., Bateson, T. F. & Curry, C. J. A population-based study of gastroschisis: demographic, pregnancy, and lifestyle risk factors. *Teratology* **50**, 44-53, doi:10.1002/tera.1420500107 (1994).
- 223 van Gelder, M. M. *et al.* Maternal periconceptual illicit drug use and the risk of congenital malformations. *Epidemiology* **20**, 60-66, doi:10.1097/EDE.0b013e31818e5930 (2009).
- 224 Werler, M. M., Sheehan, J. E. & Mitchell, A. A. Association of vasoconstrictive exposures with risks of gastroschisis and small intestinal atresia. *Epidemiology* **14**, 349-354 (2003).
- 225 Leos-Toro C. *et al.* in *Cannabis in Canada: Patterns and Trends, 2017* Vol. 1 (eds PROPEL, Centre for Population Health Impact, & University of Waterloo) 1-23 (University of Waterloo, Waterloo, Ontario, 2017).
- 226 Nelson, J. S., Stebbins, R. C., Strassle, P. D. & Meyer, R. E. Geographic distribution of live births with tetralogy of Fallot in North Carolina 2003 to 2012. *Birth Defects Res A Clin Mol Teratol* **106**, 881-887, doi:10.1002/bdra.23566 (2016).
- 227 Centre, N. D. i. *North Carolina Drug Threat Assessment, April 2003: Marijuana*, <  
<https://www.justice.gov/archive/ndic/pubs3/3690/marijuan.htm>> (2003).

- 228 Root, E. D., Meyer, R. E. & Emch, M. E. Evidence of localized clustering of gastroschisis births in North Carolina, 1999-2004. *Social science & medicine (1982)* **68**, 1361-1367, doi:10.1016/j.socscimed.2009.01.034 (2009).
- 229 Young-Wolff, K. C. *et al.* Trends in Self-reported and Biochemically Tested Marijuana Use Among Pregnant Females in California From 2009-2016. *JAMA* **318**, 2490-2491, doi:10.1001/jama.2017.17225 (2017).
- 230 Prevention, C. f. D. C. a. *Key Findings: Gastroschisis Increased from 1995-2005*, <<http://www.cdc.gov/ncbddd/birthdefects/features/gastroschisis-key-findings.html>> (2014).
- 231 Florida High Intensity Drug Trafficking Area. Vol. 1 (ed Funded by the Office of Drug Control Policy from the White House) 1-50; [https://www.cannabisskunksense.co.uk/uploads/site-files/USA\\_Florida\\_2018-2003-2002\\_Florida\\_Medical\\_Marijuana\\_Impact\\_Report\\_data\\_\(2011\).pdf](https://www.cannabisskunksense.co.uk/uploads/site-files/USA_Florida_2018-2003-2002_Florida_Medical_Marijuana_Impact_Report_data_(2011).pdf) (Florida High Intensity Drug Trafficking Area, Florida, USA, 2018).
- 232 Mutrchinick O.M., Luna L., Aerteaga J. & Ryvemce Collaborative Group. Increasing at Birth Prevalence of Isolated Gastroschisis and Associated Risk Factors. *Birth Defects Research (Part A)* **91**, 354: P358 (2011).
- 233 Chabra, S., Gleason, C. A., Seidel, K. & Williams, M. A. Rising prevalence of gastroschisis in Washington State. *Journal of toxicology and environmental health* **74**, 336-345, doi:10.1080/15287394.2011.534424 (2011).
- 234 Bino, T., Chari-Bitron, A. & Shahar, A. Biochemical effects and morphological changes in rat liver mitochondria exposed to 1 -tetrahydrocannabinol. *Biochem Biophys Acta* **288**, 195-202 (1972).
- 235 Mahoney, J. M. & Harris, R. A. Effect of 9 -tetrahydrocannabinol on mitochondrial processes. *Biochemical pharmacology* **21**, 1217-1226 (1972).
- 236 Chari-Briton, A. Proceedings: Swelling of rat liver mitochondria induced by delta1-tetrahydrocannabinol. *Isr J Med Sci* **11**, 1189 (1975).
- 237 Chiu, P., Karler, R., Craven, C., Olsen, D. M. & Turkanis, S. A. The influence of delta9-tetrahydrocannabinol, cannabinol and cannabidiol on tissue oxygen consumption. *Research communications in chemical pathology and pharmacology* **12**, 267-286 (1975).
- 238 Bartova, A. & Birmingham, M. K. Effect of delta9-tetrahydrocannabinol on mitochondrial NADH-oxidase activity. *J Biol Chem* **251**, 5002-5006 (1976).
- 239 Rossato, M., Ion Popa, F., Ferigo, M., Clari, G. & Foresta, C. Human sperm express cannabinoid receptor Cb1, the activation of which inhibits motility, acrosome reaction, and mitochondrial function. *The Journal of clinical endocrinology and metabolism* **90**, 984-991, doi:10.1210/jc.2004-1287 (2005).
- 240 Morimoto, S. *et al.* Identification and characterization of cannabinoids that induce cell death through mitochondrial permeability transition in Cannabis leaf cells. *J Biol Chem* **282**, 20739-20751, doi:10.1074/jbc.M700133200 (2007).
- 241 Shrivastava, A., Kuzontkoski, P. M., Groopman, J. E. & Prasad, A. Cannabidiol induces programmed cell death in breast cancer cells by coordinating the cross-talk between apoptosis and autophagy. *Mol Cancer Ther* **10**, 1161-1172, doi:10.1158/1535-7163.MCT-10-1100 (2011).
- 242 Benard, G. *et al.* Mitochondrial CB(1) receptors regulate neuronal energy metabolism. *Nat Neurosci* **15**, 558-564, doi:10.1038/nn.3053 (2012).
- 243 Zaccagnino, P. *et al.* The endocannabinoid 2-arachidonoylglycerol decreases calcium induced cytochrome c release from liver mitochondria. *J Bioenerg Biomembr* **44**, 273-280, doi:10.1007/s10863-012-9431-6 (2012).
- 244 Fisar, Z., Singh, N. & Hroudova, J. Cannabinoid-induced changes in respiration of brain mitochondria. *Toxicology letters* **231**, 62-71, doi:10.1016/j.toxlet.2014.09.002 (2014).
- 245 Hebert-Chatelain, E. *et al.* Cannabinoid control of brain bioenergetics: Exploring the subcellular localization of the CB1 receptor. *Mol Metab* **3**, 495-504, doi:10.1016/j.molmet.2014.03.007 (2014).
- 246 Laprairie, R. B., Bagher, A. M., Kelly, M. E., Dupre, D. J. & Denovan-Wright, E. M. Type 1 cannabinoid receptor ligands display functional selectivity in a cell culture model of striatal medium spiny projection neurons. *J Biol Chem* **289**, 24845-24862, doi:10.1074/jbc.M114.557025 (2014).
- 247 Wolff, V. *et al.* Tetrahydrocannabinol induces brain mitochondrial respiratory chain dysfunction and increases oxidative stress: a potential mechanism involved in cannabis-related stroke. *Biomed Res Int* **2015**, 323706, doi:10.1155/2015/323706 (2015).
- 248 Hebert-Chatelain, E. *et al.* A cannabinoid link between mitochondria and memory. *Nature* **539**, 555-559, doi:10.1038/nature20127 (2016).
- 249 Young-Wolff, K. C., Tucker, L., Alexeeff, S. & *et al.* Trends in self-reported and biochemically tested marijuana use among pregnant females in California from 2009-2016. *JAMA* **318**, 2490-2491, doi:10.1001/jama.2017.17225 (2017).

- 250 Gage, F. H., Guarente, L. P. & Wagers, A. J. Aging and Rejuvenation: Insights from Rusty Gage, Leonard Guarente, and Amy Wagers. *Trends Mol Med* **22**, 633-634, doi:10.1016/j.molmed.2016.06.011 (2016).
- 251 Guarente, L. Linking DNA damage, NAD(+)/SIRT1, and aging. *Cell Metab* **20**, 706-707, doi:10.1016/j.cmet.2014.10.015 (2014).
- 252 Satoh, A., Imai, S. I. & Guarente, L. The brain, sirtuins, and ageing. *Nat Rev Neurosci* **18**, 362-374, doi:10.1038/nrn.2017.42 (2017).
- 253 Zhang, H. *et al.* NAD(+) repletion improves mitochondrial and stem cell function and enhances life span in mice. *Science* **352**, 1436-1443, doi:10.1126/science.aaf2693 (2016).
- 254 Gomes, A. P. *et al.* Declining NAD(+) induces a pseudohypoxic state disrupting nuclear-mitochondrial communication during aging. *Cell* **155**, 1624-1638, doi:10.1016/j.cell.2013.11.037 (2013).
- 255 Canto, C., Menzies, K. J. & Auwerx, J. NAD(+) Metabolism and the Control of Energy Homeostasis: A Balancing Act between Mitochondria and the Nucleus. *Cell Metab* **22**, 31-53, doi:10.1016/j.cmet.2015.05.023 (2015).
- 256 Aksoy, P., White, T. A., Thompson, M. & Chini, E. N. Regulation of intracellular levels of NAD: a novel role for CD38. *Biochem Biophys Res Commun* **345**, 1386-1392, doi:10.1016/j.bbrc.2006.05.042 (2006).
- 257 Braidy, N. *et al.* Age related changes in NAD<sup>+</sup> metabolism oxidative stress and Sirt1 activity in wistar rats. *PLoS One* **6**, e19194, doi:10.1371/journal.pone.0019194 (2011).
- 258 Camacho-Pereira, J. *et al.* CD38 Dictates Age-Related NAD Decline and Mitochondrial Dysfunction through an SIRT3-Dependent Mechanism. *Cell Metab* **23**, 1127-1139, doi:10.1016/j.cmet.2016.05.006 (2016).
- 259 Canto, C. *et al.* The NAD(+) precursor nicotinamide riboside enhances oxidative metabolism and protects against high-fat diet-induced obesity. *Cell Metab* **15**, 838-847, doi:10.1016/j.cmet.2012.04.022 (2012).
- 260 Chini, C. C. S., Tarrago, M. G. & Chini, E. N. NAD and the aging process: Role in life, death and everything in between. *Molecular and cellular endocrinology* **455**, 62-74, doi:10.1016/j.mce.2016.11.003 (2017).
- 261 Chini, E. N. CD38 as a regulator of cellular NAD: a novel potential pharmacological target for metabolic conditions. *Curr Pharm Des* **15**, 57-63 (2009).
- 262 Christian, B. E. & Shadel, G. S. Aging: it's SIRTainly possible to restore mitochondrial dysfunction. *Curr Biol* **24**, R206-208, doi:10.1016/j.cub.2014.01.027 (2014).
- 263 Imai, S. & Guarente, L. NAD<sup>+</sup> and sirtuins in aging and disease. *Trends Cell Biol* **24**, 464-471, doi:10.1016/j.tcb.2014.04.002 (2014).
- 264 Massudi, H. *et al.* Age-associated changes in oxidative stress and NAD<sup>+</sup> metabolism in human tissue. *PLoS One* **7**, e42357, doi:10.1371/journal.pone.0042357 (2012).
- 265 Matalonga, J. *et al.* The Nuclear Receptor LXR Limits Bacterial Infection of Host Macrophages through a Mechanism that Impacts Cellular NAD Metabolism. *Cell Rep* **18**, 1241-1255, doi:10.1016/j.celrep.2017.01.007 (2017).
- 266 Schultz, M. B. & Sinclair, D. A. Why NAD(+) Declines during Aging: It's Destroyed. *Cell Metab* **23**, 965-966, doi:10.1016/j.cmet.2016.05.022 (2016).
- 267 Son, M. J. *et al.* Upregulation of mitochondrial NAD(+) levels impairs the clonogenicity of SSEA1(+) glioblastoma tumor-initiating cells. *Exp Mol Med* **49**, e344, doi:10.1038/emmm.2017.74 (2017).
- 268 Verdin, E. NAD(+) in aging, metabolism, and neurodegeneration. *Science* **350**, 1208-1213, doi:10.1126/science.aac4854 (2015).
- 269 Alger, B. E. & Tang, A. H. Do cannabinoids reduce brain power? *Nat Neurosci* **15**, 499-501, doi:10.1038/nn.3072 (2012).
- 270 Brown, K. D. *et al.* Activation of SIRT3 by the NAD(+) precursor nicotinamide riboside protects from noise-induced hearing loss. *Cell Metab* **20**, 1059-1068, doi:10.1016/j.cmet.2014.11.003 (2014).
- 271 Cha, Y. *et al.* Metabolic control of primed human pluripotent stem cell fate and function by the miR-200c-SIRT2 axis. *Nat Cell Biol* **19**, 445-456, doi:10.1038/ncb3517 (2017).
- 272 Chalkiadaki, A. & Guarente, L. The multifaceted functions of sirtuins in cancer. *Nat Rev Cancer* **15**, 608-624, doi:10.1038/nrc3985 (2015).
- 273 Chen, H. *et al.* DEPTOR Suppresses Lipogenesis and Ameliorates Hepatic Steatosis and Acute-on-Chronic Liver Injury in Alcoholic Liver Disease. *Hepatology*, doi:10.1002/hep.29849 (2018).
- 274 Dellinger, R. W. *et al.* Repeat dose NRPT (nicotinamide riboside and pterostilbene) increases NAD(+) levels in humans safely and sustainably: a randomized, double-blind, placebo-controlled study. *NPJ Aging Mech Dis* **3**, 17, doi:10.1038/s41514-017-0016-9 (2017).

- 275 Elhassan, Y. S., Philp, A. A. & Lavery, G. G. Targeting NAD<sup>+</sup> in Metabolic Disease: New Insights Into an Old Molecule. *Journal of the Endocrine Society* **1**, 816-835, doi:10.1210/js.2017-00092 (2017).
- 276 Guarente, L. Overcoming ATM Deficiency by Activating the NAD(+)/SIRT1 Axis. *Cell Metab* **24**, 526-528, doi:10.1016/j.cmet.2016.09.019 (2016).
- 277 Guarente, L. CELL METABOLISM. The resurgence of NAD(+). *Science* **352**, 1396-1397, doi:10.1126/science.aag1718 (2016).
- 278 Igarashi, M. & Guarente, L. mTORC1 and SIRT1 Cooperate to Foster Expansion of Gut Adult Stem Cells during Calorie Restriction. *Cell* **166**, 436-450, doi:10.1016/j.cell.2016.05.044 (2016).
- 279 Igarashi, M. & Guarente, L. The unexpected role of mTORC1 in intestinal stem cells during calorie restriction. *Cell Cycle* **16**, 1-2, doi:10.1080/15384101.2016.1221210 (2017).
- 280 Imai, S. I. & Guarente, L. It takes two to tango: NAD(+) and sirtuins in aging/longevity control. *NPJ Aging Mech Dis* **2**, 16017, doi:10.1038/npjamd.2016.17 (2016).
- 281 Ma, Z. *et al.* Resveratrol improves alcoholic fatty liver disease by downregulating HIF-1alpha expression and mitochondrial ROS production. *PLoS One* **12**, e0183426, doi:10.1371/journal.pone.0183426 (2017).
- 282 Mohrin, M. *et al.* Stem cell aging. A mitochondrial UPR-mediated metabolic checkpoint regulates hematopoietic stem cell aging. *Science* **347**, 1374-1377, doi:10.1126/science.aaa2361 (2015).
- 283 Mohs, M. E., Watson, R. R. & Leonard-Green, T. Nutritional effects of marijuana, heroin, cocaine, and nicotine. *J Am Diet Assoc* **90**, 1261-1267 (1990).
- 284 Ondracek, C. R., Frappier, V., Ringel, A. E., Wolberger, C. & Guarente, L. Mutations that Allow SIR2 Orthologs to Function in a NAD(+)-Depleted Environment. *Cell Rep* **18**, 2310-2319, doi:10.1016/j.celrep.2017.02.031 (2017).
- 285 Raval, A. P., Borges-Garcia, R., Diaz, F., Sick, T. J. & Bramlett, H. Oral contraceptives and nicotine synergistically exacerbate cerebral ischemic injury in the female brain. *Transl Stroke Res* **4**, 402-412, doi:10.1007/s12975-013-0253-6 (2013).
- 286 Sifferlin A. You Asked: Is an Anti-Aging Pill on the Horizon? *Time Magazine - Australian Edition*, 26th February 2018, 64 (2018).
- 287 Wakley, A. A. & Craft, R. M. THC-methadone and THC-naltrexone interactions on discrimination, antinociception, and locomotion in rats. *Behavioural pharmacology* **22**, 489-497, doi:10.1097/FBP.0b013e328348ed22 (2011).
- 288 Wellman, A. S. *et al.* Intestinal Epithelial Sirtuin 1 Regulates Intestinal Inflammation During Aging in Mice by Altering the Intestinal Microbiota. *Gastroenterology* **153**, 772-786, doi:10.1053/j.gastro.2017.05.022 (2017).
- 289 Williams, E. O. *et al.* Sirtuin 1 Promotes Deacetylation of Oct4 and Maintenance of Naive Pluripotency. *Cell Rep* **17**, 809-820, doi:10.1016/j.celrep.2016.09.046 (2016).
- 290 Bab, I., Ofek, O., Tam, J., Rehnelt, J. & Zimmer, A. Endocannabinoids and the regulation of bone metabolism. *Journal of neuroendocrinology* **20 Suppl 1**, 69-74, doi:JNE1675 [pii] 10.1111/j.1365-2826.2008.01675.x (2008).
- 291 Bab, I. & Zimmer, A. Cannabinoid receptors and the regulation of bone mass. *Br J Pharmacol* **153**, 182-188, doi:0707593 [pii] 10.1038/sj.bjp.0707593 (2008).
- 292 Bab, I. A. Regulation of skeletal remodeling by the endocannabinoid system. *Ann N Y Acad Sci* **1116**, 414-422, doi:annals.1402.014 [pii] 10.1196/annals.1402.014 (2007).
- 293 Idris, A. I., Sophocleous, A., Landao-Bassonga, E., van't Hof, R. J. & Ralston, S. H. Regulation of bone mass, osteoclast function, and ovariectomy-induced bone loss by the type 2 cannabinoid receptor. *Endocrinology* **149**, 5619-5626, doi:en.2008-0150 [pii] 10.1210/en.2008-0150 (2008).
- 294 Johnson, D. R., Stebulis, J. A., Rossetti, R. G., Burstein, S. H. & Zurier, R. B. Suppression of fibroblast metalloproteinases by ajulemic acid, a nonpsychoactive cannabinoid acid. *J Cell Biochem* **100**, 184-190, doi:10.1002/jcb.21046 (2007).
- 295 Lunn, C. A. *et al.* Biology and therapeutic potential of cannabinoid CB2 receptor inverse agonists. *Br J Pharmacol* **153**, 226-239, doi:0707480 [pii] 10.1038/sj.bjp.0707480 (2008).
- 296 Ofek, O. *et al.* Peripheral cannabinoid receptor, CB2, regulates bone mass. *Proc Natl Acad Sci U S A* **103**, 696-701, doi:0504187103 [pii] 10.1073/pnas.0504187103 (2006).

- 297 Patinkin, D., Milman, G., Breuer, A., Fride, E. & Mechoulam, R. Endocannabinoids as positive or negative factors in hematopoietic cell migration and differentiation. *European journal of pharmacology* **595**, 1-6, doi:S0014-2999(08)00510-4 [pii] 10.1016/j.ejphar.2008.05.002 (2008).
- 298 Rossi, F. *et al.* The endovanilloid/endocannabinoid system in human osteoclasts: Possible involvement in bone formation and resorption. *Bone* **44**, 476-484, doi:S8756-3282(08)00866-1 [pii] 10.1016/j.bone.2008.10.056 (2008).
- 299 Tam, J. *et al.* Involvement of neuronal cannabinoid receptor CB1 in regulation of bone mass and bone remodeling. *Mol Pharmacol* **70**, 786-792 (2006).
- 300 Tam, J. *et al.* The cannabinoid CB1 receptor regulates bone formation by modulating adrenergic signaling. *FASEB J* **22**, 285-294, doi:fj.06-7957com [pii] 10.1096/fj.06-7957com (2008).
- 301 Jovaisaite, V., Mouchiroud, L. & Auwerx, J. The mitochondrial unfolded protein response, a conserved stress response pathway with implications in health and disease. *J Exp Biol* **217**, 137-143, doi:10.1242/jeb.090738 (2014).
- 302 Esposito, G. *et al.* Cannabidiol reduces Abeta-induced neuroinflammation and promotes hippocampal neurogenesis through PPARgamma involvement. *PLoS One* **6**, e28668, doi:10.1371/journal.pone.0028668 (2011).
- 303 Hegde, V. L., Singh, U. P., Nagarkatti, P. S. & Nagarkatti, M. Critical Role of Mast Cells and Peroxisome Proliferator-Activated Receptor gamma in the Induction of Myeloid-Derived Suppressor Cells by Marijuana Cannabidiol In Vivo. *J Immunol* **194**, 5211-5222, doi:10.4049/jimmunol.1401844 (2015).
- 304 Hind, W. H., England, T. J. & O'Sullivan, S. E. Cannabidiol protects an in vitro model of the blood-brain barrier from oxygen-glucose deprivation via PPARgamma and 5-HT1A receptors. *Br J Pharmacol* **173**, 815-825, doi:10.1111/bph.13368 (2016).
- 305 O'Sullivan, S. E. & Kendall, D. A. Cannabinoid activation of peroxisome proliferator-activated receptors: potential for modulation of inflammatory disease. *Immunobiology* **215**, 611-616, doi:10.1016/j.imbio.2009.09.007 (2010).
- 306 O'Sullivan, S. E., Sun, Y., Bennett, A. J., Randall, M. D. & Kendall, D. A. Time-dependent vascular actions of cannabidiol in the rat aorta. *European journal of pharmacology* **612**, 61-68, doi:10.1016/j.ejphar.2009.03.010 (2009).
- 307 Ramer, R. *et al.* COX-2 and PPAR-gamma confer cannabidiol-induced apoptosis of human lung cancer cells. *Mol Cancer Ther* **12**, 69-82, doi:10.1158/1535-7163.MCT-12-0335 (2013).
- 308 Scuderi, C., Steardo, L. & Esposito, G. Cannabidiol promotes amyloid precursor protein ubiquitination and reduction of beta amyloid expression in SHSY5YAPP+ cells through PPARgamma involvement. *Phytother Res* **28**, 1007-1013, doi:10.1002/ptr.5095 (2014).
- 309 Adaikalakoteswari, A. *et al.* Low Vitamin B12 in Pregnancy Is Associated With Adipose-Derived Circulating miRs Targeting PPARgamma and Insulin Resistance. *The Journal of clinical endocrinology and metabolism* **102**, 4200-4209, doi:10.1210/jc.2017-01155 (2017).
- 310 Anghebem-Oliveira, M. I. *et al.* Type 2 diabetes-associated genetic variants of FTO, LEPR, PPARg, and TCF7L2 in gestational diabetes in a Brazilian population. *Arch Endocrinol Metab* **61**, 238-248, doi:10.1590/2359-3997000000258 (2017).
- 311 Casamadrid, V., Amaya, C. A. & Mendieta, Z. H. Body Mass Index in Pregnancy Does Not Affect Peroxisome Proliferator-activated Receptor Gamma Promoter Region (-359 to -260) Methylation in the Neonate. *Ann Med Health Sci Res* **6**, 38-43, doi:10.4103/2141-9248.180272 (2016).
- 312 Cawyer, C. *et al.* Attenuation of hyperglycemia-induced apoptotic signaling and anti-angiogenic milieu in cultured cytotrophoblast cells. *Hypertens Pregnancy* **35**, 159-169, doi:10.3109/10641955.2015.1122035 (2016).
- 313 Drew, P. D. & Kane, C. J. Peroxisome Proliferator-Activated Receptor-gamma Agonists: Potential Therapeutics for Neuropathology Associated with Fetal Alcohol Spectrum Disorders. *J Clin Cell Immunol* **7**, doi:10.4172/2155-9899.1000469 (2016).
- 314 Gao, F., Hu, W., Li, Y., Shen, H. & Hu, J. Mono-2-ethylhexyl phthalate inhibits human extravillous trophoblast invasion via the PPARgamma pathway. *Toxicology and applied pharmacology* **327**, 23-29, doi:10.1016/j.taap.2017.04.014 (2017).
- 315 Hasby Saad, M., El-Anwar, N., Lotfy, S., Fouda, M. & Hasby, E. Human placental PPAR-gamma & SOX2 expression in serologically proved toxoplasmosis. *Parasite Immunol*, e12529, doi:10.1111/pim.12529 (2018).

- 316 Hu, W. *et al.* Activation of Peroxisome Proliferator-Activated Receptor Gamma and Disruption of Progesterone Synthesis of 2-Ethylhexyl Diphenyl Phosphate in Human Placental Choriocarcinoma Cells: Comparison with Triphenyl Phosphate. *Environ Sci Technol* **51**, 4061-4068, doi:10.1021/acs.est.7b00872 (2017).
- 317 Kurzynska, A., Chojnowska, K., Bogacki, M. & Bogacka, I. PPAR ligand association with prostaglandin F2alpha and E2 synthesis in the pig corpus luteum-An in vitro study. *Anim Reprod Sci* **172**, 157-163, doi:10.1016/j.anireprosci.2016.07.014 (2016).
- 318 Lecoutre, S. *et al.* Depot- and sex-specific effects of maternal obesity in offspring's adipose tissue. *The Journal of endocrinology* **230**, 39-53, doi:10.1530/JOE-16-0037 (2016).
- 319 Lendvai, A., Deutsch, M. J., Plosch, T. & Ensenauer, R. The peroxisome proliferator-activated receptors under epigenetic control in placental metabolism and fetal development. *Am J Physiol Endocrinol Metab* **310**, E797-810, doi:10.1152/ajpendo.00372.2015 (2016).
- 320 Lin, Y., Bircsak, K. M., Gorczyca, L., Wen, X. & Aleksunes, L. M. Regulation of the placental BCRP transporter by PPAR gamma. *J Biochem Mol Toxicol* **31**, doi:10.1002/jbt.21880 (2017).
- 321 Maekawa, M. *et al.* Polyunsaturated fatty acid deficiency during neurodevelopment in mice models the prodromal state of schizophrenia through epigenetic changes in nuclear receptor genes. *Transl Psychiatry* **7**, e1229, doi:10.1038/tp.2017.182 (2017).
- 322 Mahendra, J. *et al.* Evidence Linking the Role of Placental Expressions of Peroxisome Proliferator-Activated Receptor-gamma and Nuclear Factor-Kappa B in the Pathogenesis of Preeclampsia Associated With Periodontitis. *J Periodontol* **87**, 962-970, doi:10.1902/jop.2016.150677 (2016).
- 323 Marginean, C. *et al.* The role of TGF-beta1 869 T > C and PPAR gamma2 34 C > G polymorphisms, fat mass, and anthropometric characteristics in predicting childhood obesity at birth: A cross-sectional study according the parental characteristics and newborn's risk for child obesity (the newborns obesity's risk) NOR study. *Medicine (Baltimore)* **95**, e4265, doi:10.1097/MD.00000000000004265 (2016).
- 324 Meher, A. P. *et al.* Placental DHA and mRNA levels of PPARgamma and LXRalpha and their relationship to birth weight. *J Clin Lipidol* **10**, 767-774, doi:10.1016/j.jacl.2016.02.004 (2016).
- 325 Papamitsou, T., Toskas, A., Papadopoulou, K., Economou, Z. & Sioga, A. Expression of peroxisome proliferator activation receptors (PPARs) and TNFalpha in placenta tissues in unexplained recurrent pregnancy loss: an immunohistochemical study. *Histology and histopathology* **31**, 1029-1036, doi:10.14670/HH-11-734 (2016).
- 326 Roberti, S. L. *et al.* Critical role of mTOR, PPARgamma and PPARdelta signaling in regulating early pregnancy decidual function, embryo viability and fetoplacental growth. *Molecular human reproduction*, doi:10.1093/molehr/gay013 (2018).
- 327 Shapiro, A. L. *et al.* Nicotinamide Promotes Adipogenesis in Umbilical Cord-Derived Mesenchymal Stem Cells and Is Associated with Neonatal Adiposity: The Healthy Start BabyBUMP Project. *PLoS One* **11**, e0159575, doi:10.1371/journal.pone.0159575 (2016).
- 328 Singh, S. P. *et al.* Gestational Exposure to Sidestream (Secondhand) Cigarette Smoke Promotes Transgenerational Epigenetic Transmission of Exacerbated Allergic Asthma and Bronchopulmonary Dysplasia. *J Immunol* **198**, 3815-3822, doi:10.4049/jimmunol.1700014 (2017).
- 329 Sonanez-Organis, J. G. *et al.* HIF-1alpha and PPARgamma during physiological cardiac hypertrophy induced by pregnancy: Transcriptional activities and effects on target genes. *Gene* **591**, 376-381, doi:10.1016/j.gene.2016.06.025 (2016).
- 330 Wang, L. L., Yu, Y., Guan, H. B. & Qiao, C. Effect of Human Umbilical Cord Mesenchymal Stem Cell Transplantation in a Rat Model of Preeclampsia. *Reprod Sci* **23**, 1058-1070, doi:10.1177/1933719116630417 (2016).
- 331 Wu, Y., Ruan, Y., Shen, L. & Gong, Q. Protective effects of PPAR-gamma against pregnancy-induced hypertension by differential ETR expression in rat models. *J Cell Biochem* **119**, 3118-3128, doi:10.1002/jcb.26454 (2018).
- 332 Xu, Y. *et al.* An M1-like Macrophage Polarization in Decidual Tissue during Spontaneous Preterm Labor That Is Attenuated by Rosiglitazone Treatment. *J Immunol* **196**, 2476-2491, doi:10.4049/jimmunol.1502055 (2016).
- 333 Tomar R.S. *et al.* Evidence on the Carcinogenicity of Marijuana Smoke. *California Health Department* **1**, 1-150 (August 2009).
- 334 Maor, Y. *et al.* Cannabidiol inhibits growth and induces programmed cell death in kaposi sarcoma-associated herpesvirus-infected endothelium. *Genes Cancer* **3**, 512-520, doi:10.1177/1947601912466556 (2012).

- 335 Pucci, M. *et al.* Epigenetic control of skin differentiation genes by phytocannabinoids. *Br J Pharmacol* **170**, 581-591, doi:10.1111/bph.12309 (2013).
- 336 Karmaus, P. W., Wagner, J. G., Harkema, J. R., Kaminski, N. E. & Kaplan, B. L. Cannabidiol (CBD) enhances lipopolysaccharide (LPS)-induced pulmonary inflammation in C57BL/6 mice. *J Immunotoxicol* **10**, 321-328, doi:10.3109/1547691X.2012.741628 (2013).
- 337 Graham, J. D. P. in *Cannabis and Health* Vol. 1 (ed J.D.P. Graham) Ch. 8, 271-320 (Academic Press, 1976).
- 338 Rocky Mountain High Drug Trafficking Area. The Legalization of Marijuana in Colorado: The Impact. **1**, 1-168 (October 2017).
- 339 Oregon State Police. Vol. 1 *I* (ed Police Department) 1-32, Slide 29 (Oregon Police Department, Oregon, 2009).
- 340 Oregon - Idaho High Intensity Drug Trafficking Area Program. Vol. 1 (ed Oregon - Idaho High Intensity Drug Trafficking Area Program) 1-75 (Oregon - Idaho High Intensity Drug Trafficking Area Program, Oregon, 2018).
- 341 Mills D. & The Communications Institute. Cultivating Disaster: the Effect of Cannabis Cultivation on the Environment of Calaveras County. **1**, 1-61 (2017).
- 342 Posada Pueblo. Posada - Bringing Pueblo Home. **1**, 1-35 (2016).
- 343 McCance-Katz E.F. in *SAMSHA's 14th Annual Prevention Day* (ed Health and Human Services) (US Department of Health and Human Services, Washington DC, 2018).
- 344 Rehman, W., Arfons, L. M. & Lazarus, H. M. The rise, fall and subsequent triumph of thalidomide: lessons learned in drug development. *Ther Adv Hematol* **2**, 291-308, doi:10.1177/2040620711413165 (2011).
- 345 Geber, W. F. & Schramm, L. C. Effect of marihuana extract on fetal hamsters and rabbits. *Toxicology and applied pharmacology* **14**, 276-282 (1969).
- 346 Geber, W. F. & Schramm, L. C. Teratogenicity of marihuana extract as influenced by plant origin and seasonal variation. *Arch Int Pharmacodyn Ther* **177**, 224-230 (1969).
- 347 Brookings Institute. *Brookings Debate: Should the federal government remove marijuana from its list of Schedule I drugs?*, <<https://www.brookings.edu/events/brookings-debate-should-the-federal-government-remove-marijuana-from-its-list-of-schedule-i-drugs/>> (2016).

### **Figure Captions**

Figure 1: Cannabis Use Rates in Pregnancy in California and Gastroschisis Rates USA, by Age Groups

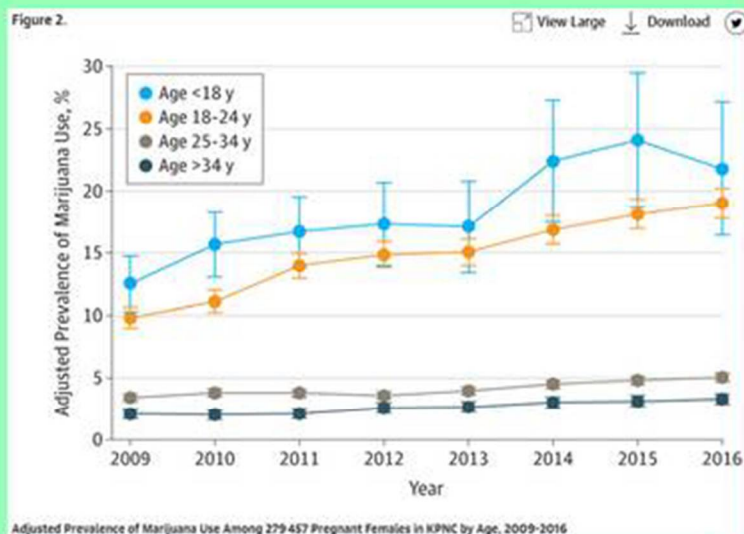
Figure 2: Close Parallel between the Collapse of Mitochondrial NAD<sup>+</sup> Dependent Respiration in Complexes I, II and IV and the Decline of NAD<sup>+</sup> with Physiological Aging.

Figure 3: Sperm swimming demonstrating how mitochondria are wrapped around the central axel of the flagellum to provide local energy where it is needed.

Figure 4: Mitochondria (green) surrounding the mitotic spindle (made of microtubules shown in pink) which carry the chromosomes (blue) at the time of cell division. Photo taken from NIH laboratories (<http://https://visualsonline.cancer.gov/details.cfm?imageid=10708>).

Figure 5: Presentation of Dr Frances Kelsey of FDA to President John F Kennedy.

## Cannabis Use in Pregnancy, California & Gastroschisis Rates, USA by Age Groups



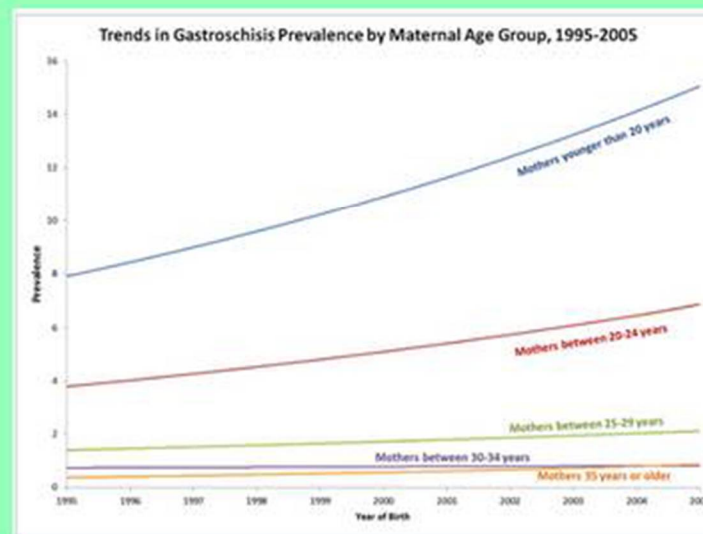
December 26, 2017

### Trends in Self-reported and Biochemically Tested Marijuana Use Among Pregnant Females in California From 2009-2016

Kelly C. Young-Wolff, PhD, MPH<sup>1</sup>; Lue-Yen Tucker, BA<sup>1</sup>; Stacey Alexseff, PhD<sup>2</sup>; Mary Anne Armstrong, MA<sup>1</sup>; Amy Conway, MPH<sup>3</sup>; Constance Weisner, DrPH<sup>3</sup>; Nancy Goler, MD<sup>4</sup>

> Author Affiliations | Article Information

JAMA. 2017;318(24):2490-2491. doi:10.1001/jama.2017.17225




**Centers for Disease Control and Prevention**  
 CDC 24/7: Saving Lives. Protecting People™

<http://www.cdc.gov/ncbddd/birthdefects/features/gastroschisis-key-findings.html>

## Decline in NAD<sup>+</sup> from Cannabinoids Mimics those Occurring with Age

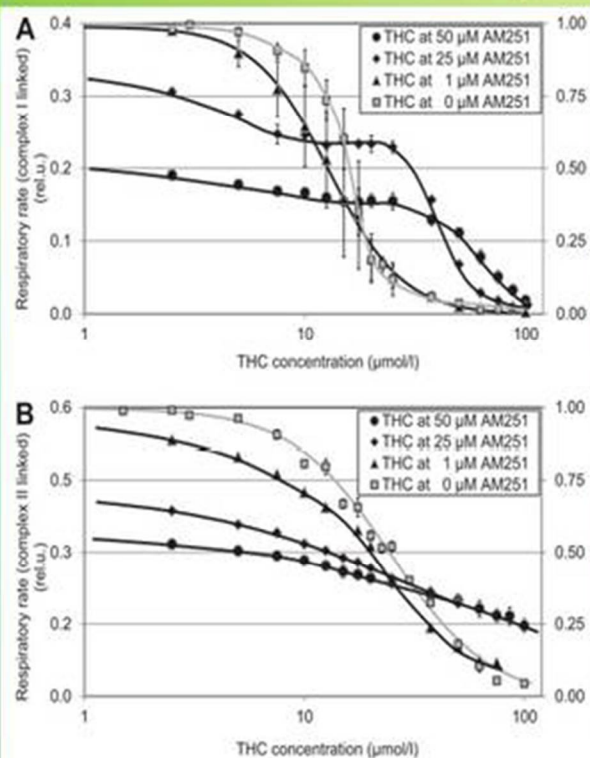


**Fig. 3.** THC-induced inhibition of the respiratory rate in pig brain mitochondria incubated in substrates of electron supply through (A) complex I or (B) complex II.

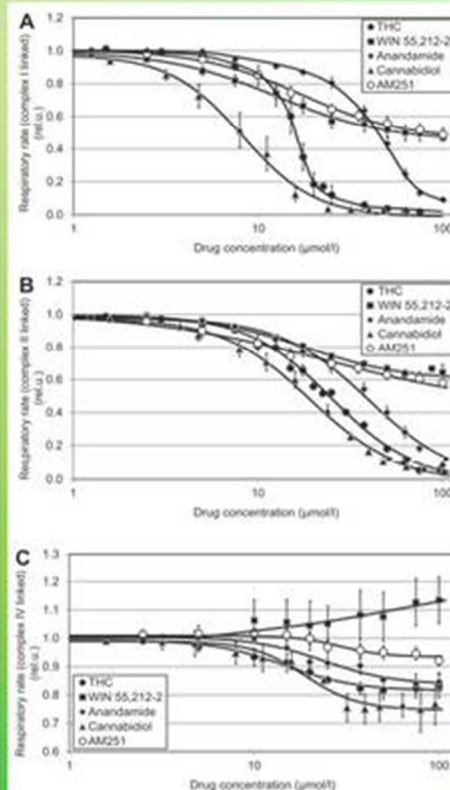


**Fig. 2.** Cannabinoid-induced inhibition of the respiratory rate in pig brain mitochondria incubated in substrates of electron supply through (A) complex I, (B) complex II, and (C) complex IV. Dose-response curves are displayed as plots of

Toxicol Lett. 2014 Nov 18;231(1):62-71. doi: 10.1016/j.toxlet.2014.09.002. Epub 2014 Sep 6.

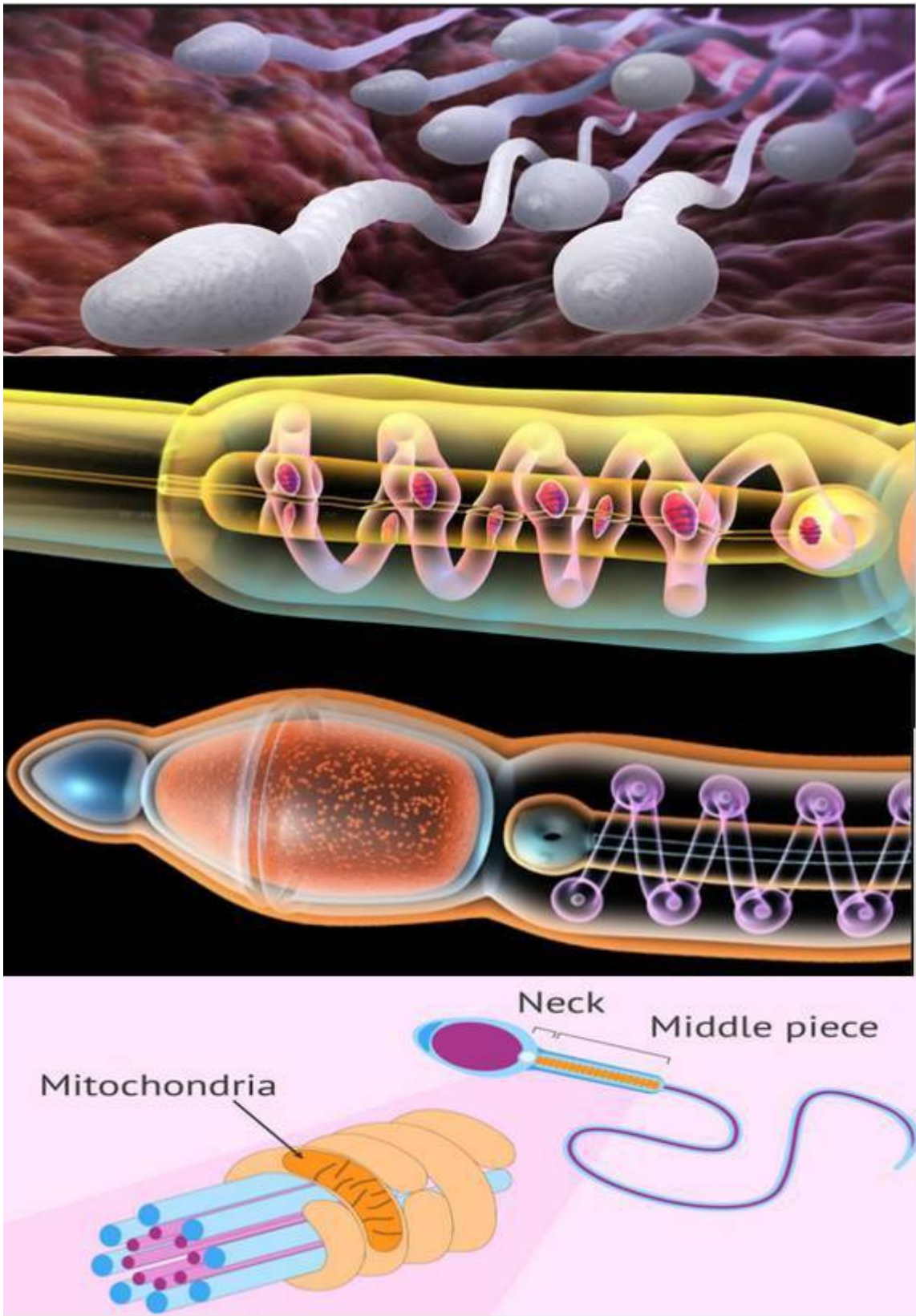
### Cannabinoid-induced changes in respiration of brain mitochondria.

Fišar Z<sup>1</sup>, Singh N<sup>2</sup>, Hroudová J<sup>3</sup>.

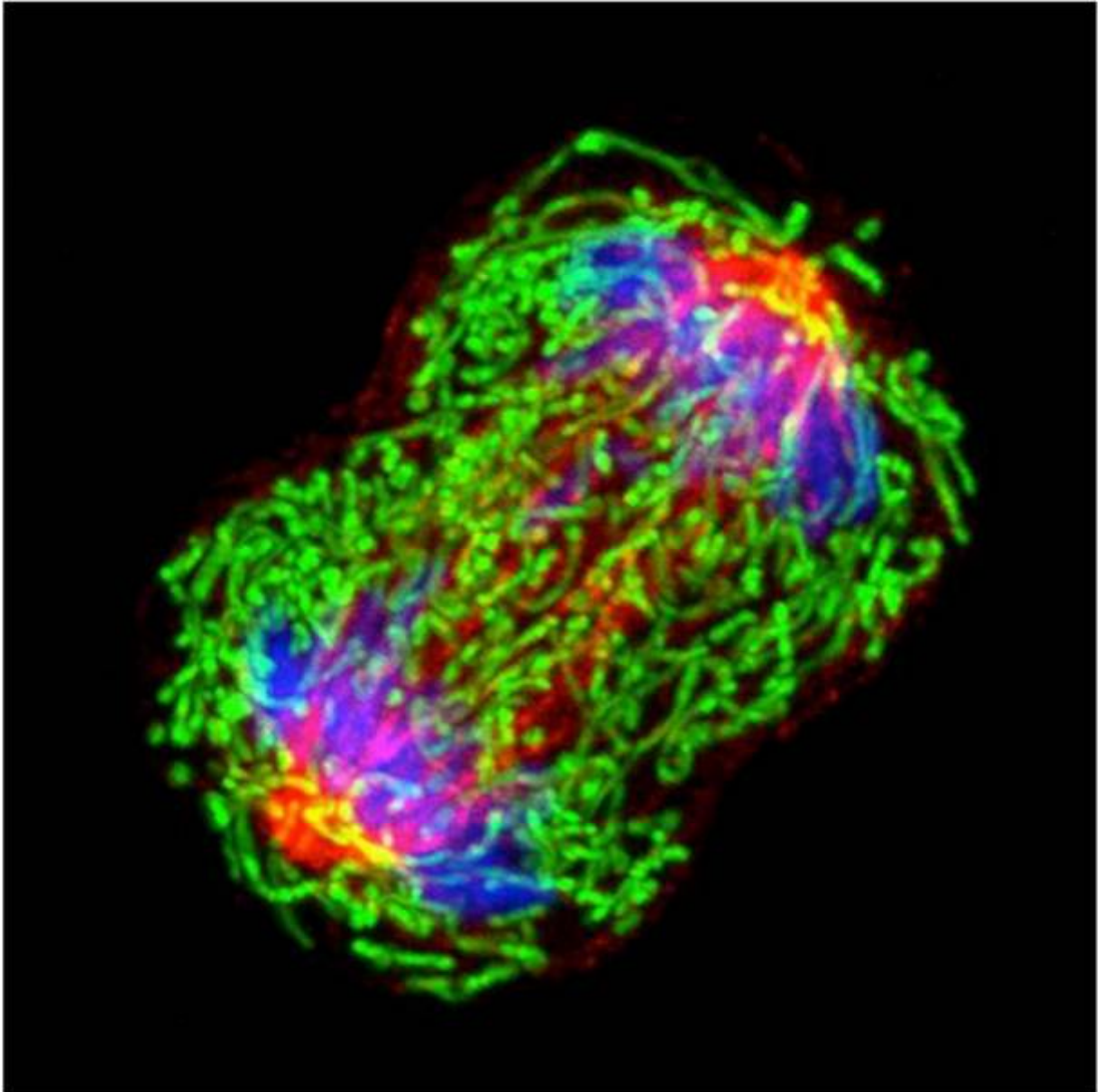
## Every 20 Years, NAD<sup>+</sup> Levels Drop By 50%



<http://dailytrendsetter.com/health/pretiva-a-pill-to-slow-the-aging-process-would-you-take-it/>



## Cell Dividing



<http://https://visualsonline.cancer.gov/details.cfm?imageid=10708>

## *Dr Frances Kelsey* @ FDA Saved USA from Thalidomide



**Figure 2.** Dr Frances Kelsey is awarded the President's Award for Distinguished Federal Civilian Service from President John F. Kennedy in 1962.





15<sup>th</sup> April 2018

Dockets Management Staff (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

Re: Department of Health and Human Services, Food and Drug Administration [Docket No. FDA-2018-N-1072]: International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; Cannabis Plant and Resin; Extracts and Tinctures of Cannabis; Delta-9-Tetrahydrocannabinol; Stereoisomers of Tetrahydrocannabinol; Cannabidiol; **Request for Comments** (FR Doc. 2018-07225).

### **Federal Register Submission**

#### ***Re: Re-Scheduling of Cannabinoids in USA Pattern of Colorado Birth Defects 2000-2013***

As a researcher I am concerned about the public health impacts of the known genotoxic effects of cannabis at the population health level.

One of the more obvious places to look to pick up clues that this might be acting is in the Registers of Birth Defects. Unfortunately it appears that extracting quantitative data on birth defects is very difficult as very few make their data publicly available. I have written to Hawaii, Colorado, California, CDC Atlanta, Georgia and MACDP Atlanta, Georgia but as at the time of writing have not had meaningful responses.

Naturally your office is in a much better position to request data urgently from your counterparts in other branches of the American Government and I would strongly urge you to do so.

However a friend was able to send me a link to a registry in Colorado which is of some use and more than a little interest. The data is so concerning that I wished to bring it to your attention. The following notes are written as a commentary on the attached short slide series. Note that the data from the Colorado Registry is supplied only by a single abnormality one at a time, and only for a single year, one at a time. Hence actually downloading the data is very time consuming and more than a little laborious. The two URL's concerned to the Colorado Health Information Dataset are <http://www.chd.dphe.state.co.us/cohid/> and <http://www.cohid.dphe.state.co.us/scripts/htmsql.exe/CrcsnPub.hsqli>. Colorado legalized cannabis for recreational use in 2012 and then again fully for recreational use in 2014. Hence the 2014 births defects data is of particular interest. I am told that this data was to be released four months ago, but at the time of writing it is not available.

The data series achieves particular significance in the light of a previously cited teratological literature linking cannabis to various major congenital malformations.

It should be noted that a major factor in interpreting these curves is the termination rate. Since therapeutic termination is a major management option chosen by many parents for the more severe defects, and widely recommended by many obstetricians, one cannot really form a comprehensive understanding of the applicable trends without knowledge of and due consideration to, the associated antenatal termination rate for the applicable defect.

Both for this reason, and because the data only goes to 2013 it is considered that this data is only reflecting the lower bound of the effects in question. That is to say that these estimates form a lower estimate of the putative cannabis -related teratogenic effect.

### **Slide Series**

Slide 1 (S1) introduces a title slide for this slide series.

S2 shows the overall pattern of births in Colorado which is drawn on two scales for clarity. The equation given for the top line shows that whilst the birth rate in Colorado fluctuates somewhat over the study period there is an overall decline of 159 births per years over the study period, albeit the detailed pattern is somewhat irregular. It is important to bear this in mind in considering the following graphs showing numbers of defects and rates.

S3 shows Down's syndrome data from Western Australia. This slide makes it very clear that whilst the rate of Downs syndrome born as live births is declining somewhat, the termination rate for this anomaly has risen markedly, so that their sum shows a clear upward trend. This important graph clearly underscores the critical role played by the applicable termination data in interpreting the trend lines under consideration. One notes that the termination data for Colorado for the present defects is believed not to be available at the time of writing.

On the basis of this graph it may be that the effects described below are as much as one half to one third of their total level net of the effect of therapeutic termination – although the level of this is obviously highly defect specific.

S4 introduces a title slide for this section.

S5 shows a very important slide which graphs the numbers and rates for all major congenital anomalies. It shows a clear upward trend for both numbers and rates. The raw data is given in the table to the right hand side. The numbers show a 69% rise across this fourteen year period, whilst the rates show a 70% rise. This annualizes to approximately 4.93% annual rate of rise for numbers and a 5.01% annual rate of rise for rates. Maintained over a 14 year period this is a not insignificant increase in the health burden to both individuals and the health system which treats these significant inborn defects.

There is also a rich literature linking antenatal cannabis use with cardiovascular defects <sup>1-6</sup>, and a statement from the combined American Heart Association and American Academy of Pediatrics acknowledging that there is a causal link between cannabis and congenital heart disease <sup>7</sup>.

S6 shows these rates as a percentage including the data on the graph.

The graphs in S7 show a significant rise in the rate of congenital heart disease. The equation on the upper graph shows an additional 40 cases per year (line slope). Both the numbers and rates of congenital heart disease are rising by about 4.5% annually, and about 61% over the whole period.

Ventricular Septal Defect (VSD) is also linked with cannabis use <sup>1,6,7</sup>. S8 shows that this is rising by about 6 cases annually, 35% overall, and about 2.5% annually.

S9 illustrates trends in the ostium secundum Artrial Septal Defect (ASD) which has previously been linked with cannabis exposure <sup>6,7</sup>. This is noted to be rising by about 46 cases annually; to have increased 260% over the whole period and to be rising at 18% annually. Indeed one also notes that the linear regression line accounts for 89% of the variance of the data. This implies that the rising trend is a strong and dominant factor in this trend line.

S10 shows data for microcephaly. One notes and average of 2 extra cases annually, a 96% rise over the 14 year period, and an annual rate of rise of 7%.

Chromosomal abnormalities have been reported as being associated with antenatal cannabis use. The data in S11 shows a increase of 3 cases per year, of 28% over the whole period and of 2% annually.

S12 introduces a summary slide for some of the selected stationary trends.

Many of the trends for congenital defects in Colorado are essentially stationary. Such data is shown for Cleft lip with or without cleft palette in S13, and for combined abdominal wall defects in S14. Several of the other defects which were inspected also appeared to be showing no real time dependent change or to occur at such low level that their trends are not stable. One notes in particular that gastroschisis, a defect which has been strongly linked with cannabis use in many studies <sup>6,8-14</sup> does not have data presented separately for it on the Colorado Health Information Dataset site at this time.

S15 presents a title slide for the cumulative and summative effect.

S16 shows a simple method, carry-forward projection for analyzing historcial trends. This is done first for births. The birth rate in the first 1-2 years (whichever is the lower) is simply carried forwards as if it had not changed in any of the subsequent years. The actual birth rate is listed in the second column. The difference appears in the fourth column and is the difference from the expected rate had the historical trends been simply continued along.

These various columns are then summed at their base as shown. One notes that an extra 33,311 births occurred than would have been expected, representing a 3.6% increase in births over this historical period, which annualizes to a 0.26% increase per year.

S17 shows the trend for all major congenital birth defects. This slide shows that whereas 67,620 would have been expected based on the historical trend, in fact 87,772 were observed, an excess of 20,152 cases or 29.8%.

S18 performs a similar calculation for all major cardiovascular defects and finds a 37% excess caseload.

S19 performs a similar function and finds a 17% excess for VSD.

S20 does the same function for ostium secundum ASD and finds a 98% excess caseload.

S21 shows a 30% excess for Microcephaly. The significance of this finding in a Zika virus era will I am sure not be lost on you.

S22 shows the data for the combined chromosomal anomalies and finds a 28% excess caseload.

S23 introduces a title slide for the final Summary section.

S24 shows the apparently very close correlation between all major congenital anomalies and cannabis use by various age groups in Colorado, as taken from the SAMHSA NSDUH survey at <https://www.samhsa.gov/data/population-data-nsduh/reports?tab=38>.

S25 Shows the key graph again with its data included.

S26 presents the output of the R statistical analytical software showing the correlation coefficient,  $R=0.953852$  and  $P = 0.00006594$ .

S27 presents another correlation calculation this time with the young adult rate of cannabis use again from the NSDUH SAMHSA survey (Data given in S24). In this study  $R=0.9254789$  and  $P = 0.00003457$ .

S28 shows similar data with the major anomaly rate compared to the cannabis use rate in all Colorado dwellers over the age of 12 years.  $R=0.8825038$  and  $P = 0.00002936$ .

S29 again shows this key graph.

S30 shows a final slide which summarizes all of the above information in a single table. The first column lists the various rising defects which have been considered. The second column shows the numbers of actual cases observed over the study period. The third column shows the number which would have been expected had the baseline trend been simply projected forwards. The fourth column gives the observed excess of cases for these defects. The fifth column shows the percentage rise over the entire period. The first line shows the numbers of births which forms the baseline trend against which the other categories are compared. The numbers of births rose 3.6% in the period 2000-2013. The other anomalies are compared with the rise in births to calculate the final column as a multiplicand of the baseline increase in birth numbers.

As noted above, this factor is believed to be a lower bound baseline since it is expected that for many of these defects foetal wastage would have occurred either by natural spontaneous miscarriage or by induced therapeutic termination of pregnancy, as indicated in Slide 3.

## **Conclusion**

Hence these data indicate a significant rise in the official numbers of major congenital anomalies in Colorado over the period when cannabis was gaining in popularity and into the very start of its medical legalization. Hence the figures are believed to be an underestimate of the cannabis related effect. They would almost certainly be substantially increased were data on therapeutic and other termination of pregnancy to become available. Hence these estimates included in the final table on S23 can only be seen as estimating the lower bound of the cannabis effect. Since the net effect shows an increase of 30% of all major defects, this can only be interpreted as a finding generating significant concern.

Matters of attributable risk effect arise in terms of interpreting how much of the increase might properly be attributed to cannabis itself and how much to various other extraneous and unknown confounding causes. Given that there is a published literature relating cannabis to all of these identified anomalies it seems likely that some significant fraction of the 20,152 excess cases can well be laid at the feet of cannabinoids. One notes also that these patients are exposed to mixed cannabinoids as occur in natural and cultured cannabis, including tetrahydrocannabinol, cannabidiol, cannabinol, cannabichromene, cannabiverin and many others so that all of them are potentially implicated on epidemiological grounds. Moreover many studies implicate multiple cannabinoids including cannabidiol in both genotoxic<sup>15-24</sup> and arteriopathic and / or arteritic<sup>25-65</sup> pathways.

The above cited literature links both maternal and paternal cannabis exposure<sup>4</sup> to teratological outcomes particularly congenital heart disease which is also the commonest of the major foetal malformations. The above citations also demonstrate significant multiple and complex interactions between cannabinoids and the cardiovascular system. Thus there are multiple potential mechanistic pathways from cannabis exposure to foetal pathology.

It was considered at the present time that it was important to bring these data to your attention as they are likely of significant public health import, particularly when amplified up to the national level. This is particularly so if, as is now a matter of record, cannabis use is becoming more common<sup>64,66</sup>, if cannabis itself is becoming more concentrated as has also been amply documented<sup>64</sup> and if the major effect of therapeutic abortion is also included as seems only proper<sup>67</sup>.

Please feel free to call on me if you would like further information concerning the research to which I have referred.

Yours sincerely,

A handwritten signature in black ink, appearing to read 'S Reece', with a stylized flourish at the end.

Assoc. Prof. Dr. Stuart Reece.  
University of Western Australia and  
Edith Cowan University,  
Perth,  
Australia.

## References

1. 1 Feng, Y. *et al.* Maternal lifestyle factors in pregnancy and congenital heart defects in offspring: review of the current evidence. *Ital J Pediatr* **40**, 85, doi:10.1186/s13052-014-0085-3 (2014).
2. 2 Simeone, R. M. *et al.* Proportion of selected congenital heart defects attributable to recognized risk factors. *Annals of epidemiology* **26**, 838-845, doi:10.1016/j.annepidem.2016.10.003 (2016).
3. 3 Williams, L. J., Correa, A. & Rasmussen, S. Maternal lifestyle factors and risk for ventricular septal defects. *Birth Defects Res A Clin Mol Teratol* **70**, 59-64, doi:10.1002/bdra.10145 (2004).
4. 4 Wilson, P. D., Loffredo, C. A., Correa-Villasenor, A. & Ferencz, C. Attributable fraction for cardiac malformations. *Am J Epidemiol* **148**, 414-423 (1998).
5. 5 Ferencz C., Correa-Villasenor A. & Lofredo C.A. *Genetic and Environmental Risk Factors of Major Cardiovascular Malformations: The Baltimore-Washington Study: 1981-1989*. Vol. 1 (Futura Publishing, 1997).
6. 6 Forrester, M. B. & Merz, R. D. Risk of selected birth defects with prenatal illicit drug use, Hawaii, 1986-2002. *Journal of toxicology and environmental health* **70**, 7-18 (2007).
7. 7 Jenkins, K. J. *et al.* Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. *Circulation* **115**, 2995-3014, doi:10.1161/CIRCULATIONAHA.106.183216 (2007).
8. 8 David, A. L. *et al.* A case-control study of maternal periconceptual and pregnancy recreational drug use and fetal malformation using hair analysis. *PLoS One* **9**, e111038, doi:10.1371/journal.pone.0111038 (2014).
9. 9 Draper, E. S. *et al.* Recreational drug use: a major risk factor for gastroschisis? *Am J Epidemiol* **167**, 485-491, doi:10.1093/aje/kwm335 (2008).
10. 10 Skarsgard, E. D. *et al.* Maternal risk factors for gastroschisis in Canada. *Birth Defects Res A Clin Mol Teratol* **103**, 111-118, doi:10.1002/bdra.23349 (2015).
11. 11 Torfs, C. P., Velie, E. M., Oechsli, F. W., Bateson, T. F. & Curry, C. J. A population-based study of gastroschisis: demographic, pregnancy, and lifestyle risk factors. *Teratology* **50**, 44-53, doi:10.1002/tera.1420500107 (1994).
12. 12 van Gelder, M. M. *et al.* Maternal periconceptional illicit drug use and the risk of congenital malformations. *Epidemiology* **20**, 60-66, doi:10.1097/EDE.0b013e31818e5930 (2009).
13. 13 Werler, M. M., Sheehan, J. E. & Mitchell, A. A. Association of vasoconstrictive exposures with risks of gastroschisis and small intestinal atresia. *Epidemiology* **14**, 349-354 (2003).
14. 14 Moore A., Roulean J. & Skarsgard E. Vol. 1 (ed Health Canada Public Health Agency of Canada) 57-63 (Health Canada, Ottawa, 2013).
15. 15 Zimmerman A.M., Zimmerman S. & Raj A.Y. in *Marijuana and Medicine* Vol. 1 (eds G. G. Nahas, Sutin K.M., Harvey D.J., & Agurell S.) Ch. 27, 347-358 (Humana Press, 1999).
16. 16 Busch, F. W., Seid, D. A. & Wei, E. T. Mutagenic activity of marihuana smoke condensates. *Cancer Lett* **6**, 319-324 (1979).
17. 17 Mon, M. J., Haas, A. E., Stein, J. L. & Stein, G. S. Influence of psychoactive and nonpsychoactive cannabinoids on chromatin structure and function in human cells. *Biochemical pharmacology* **30**, 45-58 (1981).
18. 18 Stein, G. S. & Stein, J. L. Effects of cannabinoids on gene expression. *NIDA Res Monogr* **44**, 5-24 (1984).
19. 19 Zimmerman, S. & Zimmerman, A. M. Genetic effects of marijuana. *The International journal of the addictions* **25**, 19-33 (1990).
20. 20 Karmaus, P. W., Wagner, J. G., Harkema, J. R., Kaminski, N. E. & Kaplan, B. L. Cannabidiol (CBD) enhances lipopolysaccharide (LPS)-induced pulmonary inflammation in C57BL/6 mice. *J Immunotoxicol* **10**, 321-328, doi:10.3109/1547691X.2012.741628 (2013).
21. 21 Maor, Y. *et al.* Cannabidiol inhibits growth and induces programmed cell death in kaposi sarcoma-associated herpesvirus-infected endothelium. *Genes Cancer* **3**, 512-520, doi:10.1177/1947601912466556 (2012).
22. 22 Pucci, M. *et al.* Epigenetic control of skin differentiation genes by phytocannabinoids. *Br J Pharmacol* **170**, 581-591, doi:10.1111/bph.12309 (2013).
23. 23 Hegde, V. L., Singh, U. P., Nagarkatti, P. S. & Nagarkatti, M. Critical Role of Mast Cells and Peroxisome Proliferator-Activated Receptor gamma in the Induction of Myeloid-Derived Suppressor Cells by Marijuana Cannabidiol In Vivo. *J Immunol* **194**, 5211-5222, doi:10.4049/jimmunol.1401844 (2015).

24. 24 Scuderi, C., Steardo, L. & Esposito, G. Cannabidiol promotes amyloid precursor protein ubiquitination and reduction of beta amyloid expression in SHSY5YAPP+ cells through PPARGgamma involvement. *Phytother Res* **28**, 1007-1013, doi:10.1002/ptr.5095 (2014).
25. 25 Jones, R. T. Cardiovascular system effects of marijuana. *Journal of clinical pharmacology* **42**, 58S-63S (2002).
26. 26 Klatsky, A. L., Armstrong, M. A., Friedman, G. D. & Sidney, S. Alcohol drinking and risk of hemorrhagic stroke. *Neuroepidemiology* **21**, 115-122 (2002).
27. 27 Lambrecht, G. L., Malbrain, M. L., Coremans, P., Verbist, L. & Verhaegen, H. Acute renal infarction and heavy marijuana smoking. *Nephron* **70**, 494-496 (1995).
28. 28 O'Sullivan, S. E., Sun, Y., Bennett, A. J., Randall, M. D. & Kendall, D. A. Time-dependent vascular actions of cannabidiol in the rat aorta. *European journal of pharmacology* **612**, 61-68, doi:10.1016/j.ejphar.2009.03.010 (2009).
29. 29 Sidney, S. Cardiovascular consequences of marijuana use. *Journal of clinical pharmacology* **42**, 64S-70S (2002).
30. 30 Wang, X. *et al.* One Minute of Marijuana Secondhand Smoke Exposure Substantially Impairs Vascular Endothelial Function. *J Am Heart Assoc* **5**, doi:10.1161/JAHA.116.003858 (2016).
31. 31 Wolff, V. *et al.* Cannabis-related stroke: myth or reality? *Stroke; a journal of cerebral circulation* **44**, 558-563, doi:10.1161/STROKEAHA.112.671347 (2013).
32. 32 Freeman, M. J. *et al.* Ischemic stroke after use of the synthetic marijuana "spice". *Neurology* **81**, 2090-2093, doi:10.1212/01.wnl.0000437297.05570.a2 (2013).
33. 33 Parakh, P. Letter by Parakh regarding article, "cannabis-related stroke: myth or reality?". *Stroke; a journal of cerebral circulation* **44**, e56, doi:10.1161/STROKEAHA.113.001092 (2013).
34. 34 Phillips, M. C. *et al.* Ischaemic stroke among young people aged 15 to 50 years in Adelaide, South Australia. *Med J Aust* **195**, 610-614 (2011).
35. 35 Wolff, V., Rouyer, O. & Geny, B. Response to letter regarding article, "cannabis-related stroke: myth or reality?". *Stroke; a journal of cerebral circulation* **44**, e57 (2013).
36. 36 Wolff, V. *et al.* Tetrahydrocannabinol induces brain mitochondrial respiratory chain dysfunction and increases oxidative stress: a potential mechanism involved in cannabis-related stroke. *Biomed Res Int* **2015**, 323706, doi:10.1155/2015/323706 (2015).
37. 37 Disdier, P. *et al.* Cannabis arteritis revisited--ten new case reports. *Angiology* **52**, 1-5 (2001).
38. 38 Ducasse, E. *et al.* Popliteal artery entrapment associated with cannabis arteritis. *Eur J Vasc Endovasc Surg* **27**, 327-332, doi:10.1016/S1533 (2004).
39. 39 Jouanjus, E., Lapeyre-Mestre, M., Micallef, J., French Association of the Regional, A. & Dependence Monitoring Centres Working Group on Cannabis, C. Cannabis use: signal of increasing risk of serious cardiovascular disorders. *J Am Heart Assoc* **3**, e000638, doi:10.1161/JAHA.113.000638 (2014).
40. 40 Kogan, N. M. *et al.* A cannabinoid quinone inhibits angiogenesis by targeting vascular endothelial cells. *Mol Pharmacol* **70**, 51-59, doi:10.1124/mol.105.021089 (2006).
41. 41 Molica, F. *et al.* Endogenous cannabinoid receptor CB1 activation promotes vascular smooth-muscle cell proliferation and neointima formation. *J Lipid Res* **54**, 1360-1368, doi:10.1194/jlr.M035147 (2013).
42. 42 Netherland, C. D., Pickle, T. G., Bales, A. & Thewke, D. P. Cannabinoid receptor type 2 (CB2) deficiency alters atherosclerotic lesion formation in hyperlipidemic Ldlr-null mice. *Atherosclerosis* **213**, 102-108, doi:10.1016/j.atherosclerosis.2010.07.060 (2010).
43. 43 Schneider, H. J., Jha, S. & Burnand, K. G. Progressive arteritis associated with cannabis use. *Eur J Vasc Endovasc Surg* **18**, 366-367, doi:10.1053/ejvs.1999.0859 (1999).
44. 44 Slavic, S. *et al.* Cannabinoid receptor 1 inhibition improves cardiac function and remodelling after myocardial infarction and in experimental metabolic syndrome. *J Mol Med (Berl)* **91**, 811-823, doi:10.1007/s00109-013-1034-0 (2013).
45. 45 Stanley, C. & O'Sullivan, S. E. Vascular targets for cannabinoids: animal and human studies. *Br J Pharmacol* **171**, 1361-1378, doi:10.1111/bph.12560 (2014).
46. 46 Steffens, S. & Pacher, P. Targeting cannabinoid receptor CB(2) in cardiovascular disorders: promises and controversies. *Br J Pharmacol* **167**, 313-323, doi:10.1111/j.1476-5381.2012.02042.x (2012).
47. 47 Batkai, S. *et al.* Endocannabinoids acting at cannabinoid-1 receptors regulate cardiovascular function in hypertension. *Circulation* **110**, 1996-2002, doi:10.1161/01.CIR.0000143230.23252.D2 (2004).
48. 48 Bedi, G., Cooper, Z. D. & Haney, M. Subjective, cognitive and cardiovascular dose-effect profile of nabilone and dronabinol in marijuana smokers. *Addict Biol* **18**, 872-881, doi:10.1111/j.1369-1600.2011.00427.x (2013).

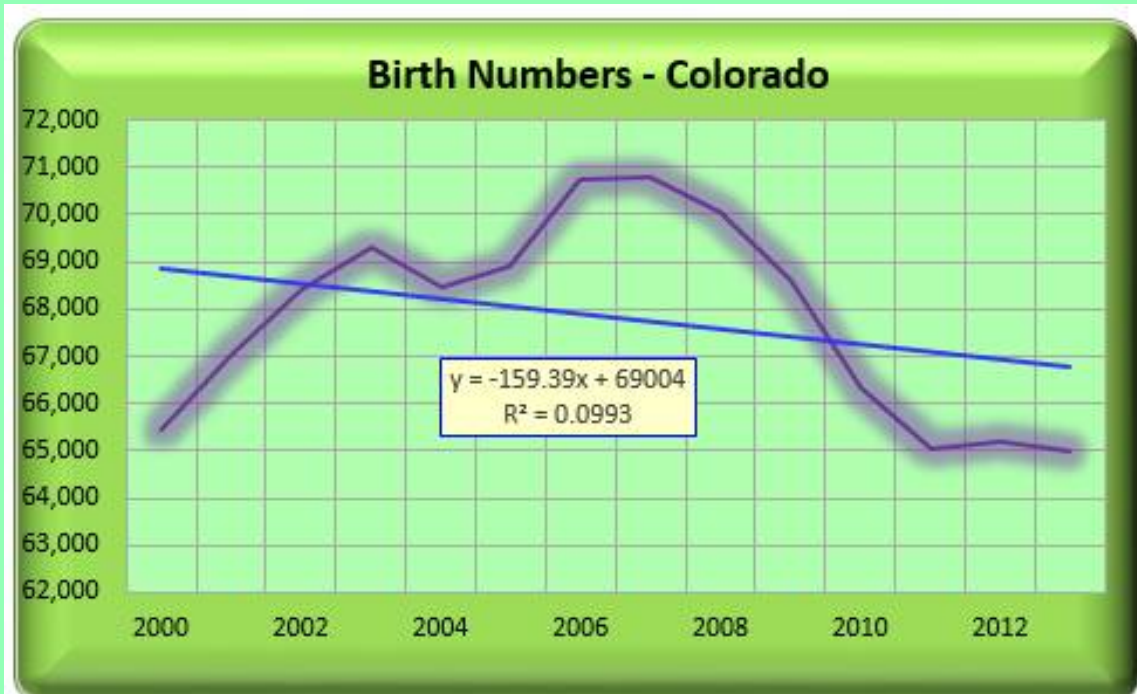
49. 49 Benowitz, N. L. & Jones, R. T. Cardiovascular and metabolic considerations in prolonged cannabinoid administration in man. *Journal of clinical pharmacology* **21**, 214S-223S (1981).
50. 50 Foltin, R. W. & Fischman, M. W. The effects of combinations of intranasal cocaine, smoked marijuana, and task performance on heart rate and blood pressure. *Pharmacology, biochemistry, and behavior* **36**, 311-315 (1990).
51. 51 Gottschalk, L. A., Aronow, W. S. & Prakash, R. Effect of marijuana and placebo-marijuana smoking on psychological state and on psychophysiological cardiovascular functioning in anginal patients. *Biol Psychiatry* **12**, 255-266 (1977).
52. 52 Graham, J. D. & Li, D. M. Cardiovascular and respiratory effects of cannabis in cat and rat. *Br J Pharmacol* **49**, 1-10 (1973).
53. 53 Lamontagne, D., Lepicier, P., Lagneux, C. & Bouchard, J. F. The endogenous cardiac cannabinoid system: a new protective mechanism against myocardial ischemia. *Arch Mal Coeur Vaiss* **99**, 242-246 (2006).
54. 54 Li, D. M. Cardiovascular and respiratory effects of cannabis extracts and 1-tetra-hydrocannabinol (1-THC). *Br J Pharmacol* **47**, 627P (1973).
55. 55 Liu, J. *et al.* Functional CB1 cannabinoid receptors in human vascular endothelial cells. *Biochem J* **346 Pt 3**, 835-840 (2000).
56. 56 Malinowska, B., Kwolek, G. & Gothert, M. Anandamide and methanandamide induce both vanilloid VR1- and cannabinoid CB1 receptor-mediated changes in heart rate and blood pressure in anaesthetized rats. *Naunyn Schmiedeberg's Arch Pharmacol* **364**, 562-569 (2001).
57. 57 Mathew, R. J., Wilson, W. H., Humphreys, D., Lowe, J. V. & Wiethe, K. E. Middle cerebral artery velocity during upright posture after marijuana smoking. *Acta psychiatrica Scandinavica* **86**, 173-178 (1992).
58. 58 Wagner, J. A., Jarai, Z., Batkai, S. & Kunos, G. Hemodynamic effects of cannabinoids: coronary and cerebral vasodilation mediated by cannabinoid CB(1) receptors. *European journal of pharmacology* **423**, 203-210 (2001).
59. 59 Barana, A. *et al.* Endocannabinoids and cannabinoid analogues block cardiac hKv1.5 channels in a cannabinoid receptor-independent manner. *Cardiovasc Res* **85**, 56-67, doi:10.1093/cvr/cvp284 (2010).
60. 60 Finsterer, J., Christian, P. & Wolfgang, K. Occipital stroke shortly after cannabis consumption. *Clin Neurol Neurosurg* **106**, 305-308, doi:10.1016/j.clineuro.2004.02.001 (2004).
61. 61 Herning, R. I., Better, W. & Cadet, J. L. EEG of chronic marijuana users during abstinence: relationship to years of marijuana use, cerebral blood flow and thyroid function. *Clin Neurophysiol* **119**, 321-331, doi:10.1016/j.clinph.2007.09.140 (2008).
62. 62 Inal, T. *et al.* Acute temporal lobe infarction in a young patient associated with marijuana abuse: An unusual cause of stroke. *World J Emerg Med* **5**, 72-74, doi:10.5847/wjem.j.1920-8642.2014.01.013 (2014).
63. 63 Wolff, V. *et al.* High frequency of intracranial arterial stenosis and cannabis use in ischaemic stroke in the young. *Cerebrovascular diseases (Basel, Switzerland)* **37**, 438-443, doi:10.1159/000363618 (2014).
64. 64 Volkow, N. D., Baler, R. D., Compton, W. M. & Weiss, S. R. B. Adverse Health Effects of Marijuana Use. *New England Journal of Medicine* **370**, 2219-2227, doi:doi:10.1056/NEJMr1402309 (2014).
65. 65 Volkow, N. D., Compton, W. M. & Weiss, S. R. Adverse health effects of marijuana use. *N Engl J Med* **371**, 879, doi:10.1056/NEJMc1407928 (2014).
66. 66 Cerda, M., Wall, M., Keyes, K. M., Galea, S. & Hasin, D. Medical marijuana laws in 50 states: investigating the relationship between state legalization of medical marijuana and marijuana use, abuse and dependence. *Drug Alcohol Depend* **120**, 22-27, doi:S0376-8716(11)00274-2 [pii] 10.1016/j.drugalcdep.2011.06.011 (2012).
67. 67 Western Australian Department of Health. *Western Australian Register of Developmental Anomalies: Monitoring Trends in Western Australia*, <[http://www.kemh.health.wa.gov.au/services/register\\_developmental\\_anomalies/monitoring\\_trends.htm](http://www.kemh.health.wa.gov.au/services/register_developmental_anomalies/monitoring_trends.htm)> (2018).

# ***Congenital Anomalies Colorado***

## ***2000-2013***

<http://www.chd.dphe.state.co.us/cohid/>  
<http://www.cohid.dphe.state.co.us/scripts/htmsql.exe/CrcsnPub.hsrl>

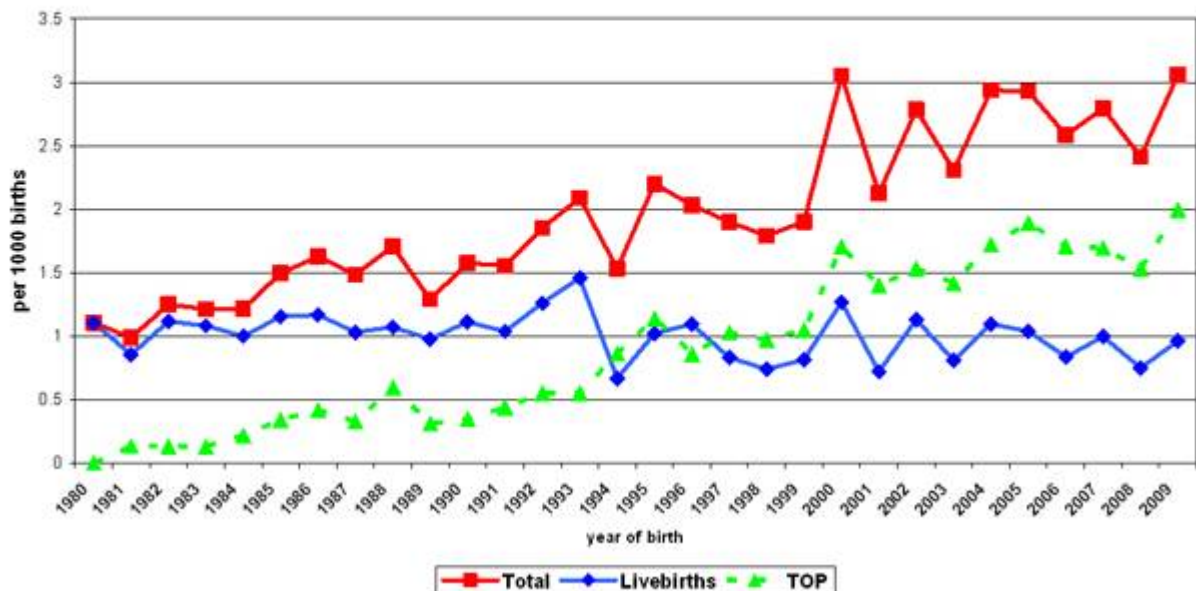
# *Births*



# *Down's Syndrome in Western Australia*

## 8. Down Syndrome: total, live births and terminations of pregnancy

**Down syndrome: total, livebirths and terminations of pregnancy**



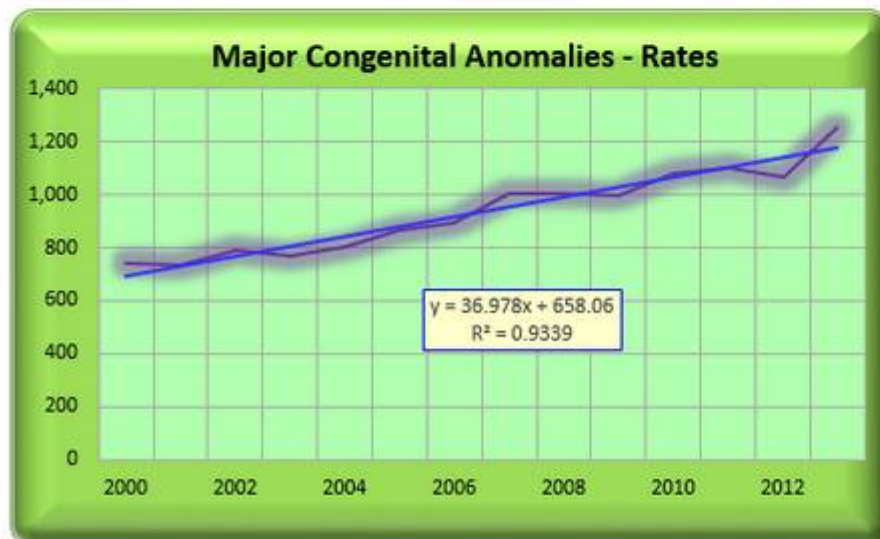
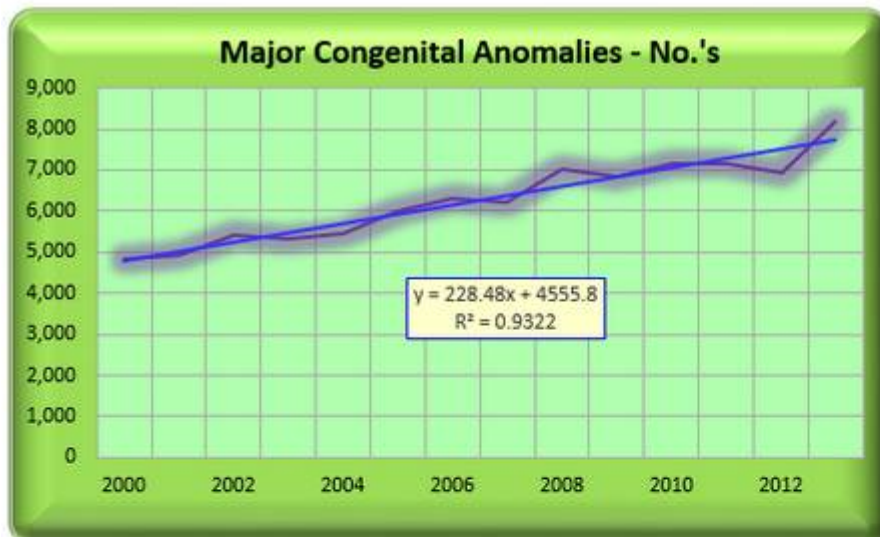
[http://www.kemh.health.wa.gov.au/services/register\\_developmental\\_anomalies/monitoring\\_trends.htm](http://www.kemh.health.wa.gov.au/services/register_developmental_anomalies/monitoring_trends.htm)

# ***Rising Trends***

## ***Colorado 2000-2013***

<http://www.chd.dphe.state.co.us/cohid/>  
<http://www.cohid.dphe.state.co.us/scripts/htmsql.exe/CrcsnPub.hsql>

# Major Congenital Anomalies



## Major Congenital Anomalies

Rates/ 10,000 Live births  
(Excluding Terminations)

| Year       | Majors | Majors Rate |
|------------|--------|-------------|
| 2000       | 4830   | 738.2       |
| 2001       | 4942   | 737.5       |
| 2002       | 5406   | 790.1       |
| 2003       | 5311   | 766.3       |
| 2004       | 5482   | 800.6       |
| 2005       | 5978   | 867.4       |
| 2006       | 6325   | 894.2       |
| 2007       | 6213   | 1001.0      |
| 2008       | 7010   | 1001.0      |
| 2009       | 6826   | 995.0       |
| 2010       | 7171   | 1080.8      |
| 2011       | 7174   | 1102.8      |
| 2012       | 6939   | 1064.5      |
| 2013       | 8165   | 1256.1      |
| Rise %     | 69.04% | 70.16%      |
| Annualized | 4.93%  | 5.01%       |

# *Major Congenital Anomalies as Percentage*



# Major Cardiovascular Anomalies

**Major Cardiovascular Abnormalities - No.'s**



**Major Cardiovascular Abnormalities - Rates**

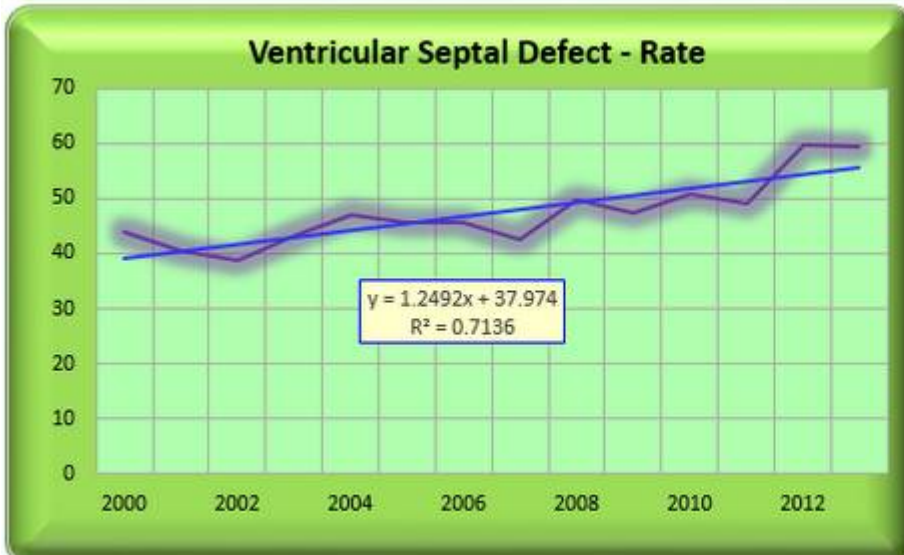
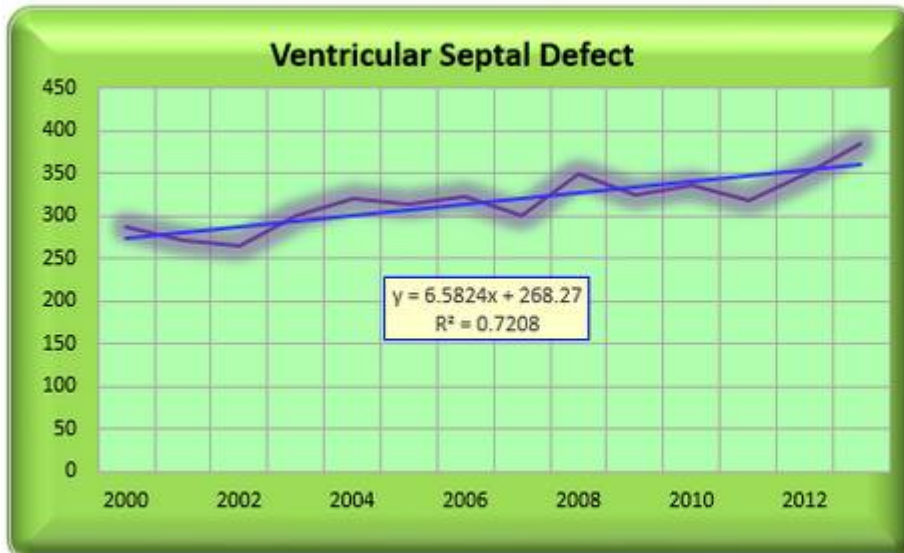


## Major CVS Abnormalities

Rates/ 10,000 Live births  
(Excluding Terminations)

| Year       | CVS    | CVS Rate |
|------------|--------|----------|
| 2000       | 1002   | 153.1    |
| 2001       | 1071   | 159.8    |
| 2002       | 1263   | 184.6    |
| 2003       | 1273   | 183.7    |
| 2004       | 1368   | 199.8    |
| 2005       | 1398   | 202.8    |
| 2006       | 1397   | 197.5    |
| 2007       | 1274   | 179.9    |
| 2008       | 1530   | 218.5    |
| 2009       | 1528   | 222.7    |
| 2010       | 1464   | 220.7    |
| 2011       | 1536   | 236.1    |
| 2012       | 1562   | 239.6    |
| 2013       | 1622   | 249.5    |
| Rise %     | 61.88% | 62.97%   |
| Annualized | 4.42%  | 4.50%    |

# Ventricular Septal Defect

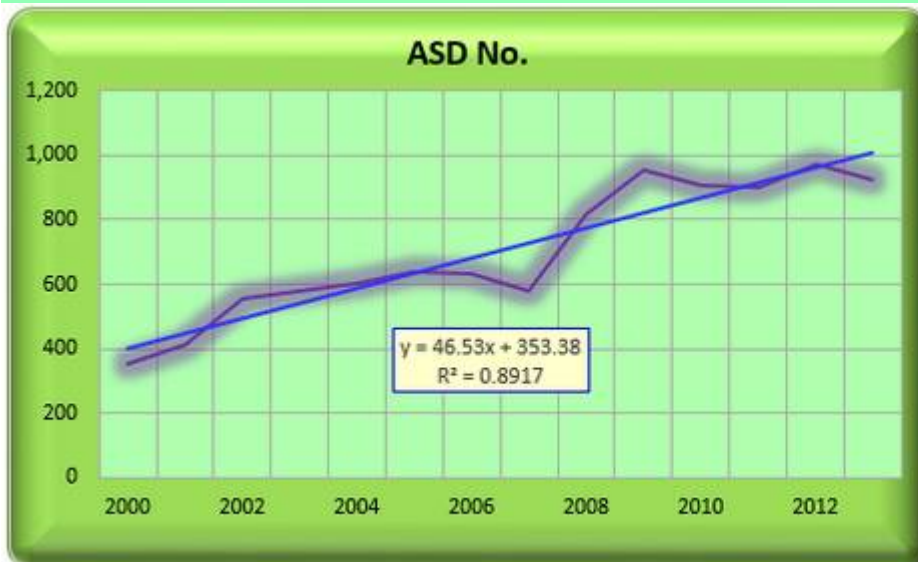


## VSD

Rates/ 10,000 Live births  
(Excluding Terminations)

| Year       | VSD    | VSD Rate |
|------------|--------|----------|
| 2000       | 287    | 43.9     |
| 2001       | 271    | 40.4     |
| 2002       | 265    | 38.7     |
| 2003       | 300    | 43.3     |
| 2004       | 321    | 46.9     |
| 2005       | 315    | 45.7     |
| 2006       | 323    | 45.7     |
| 2007       | 300    | 42.4     |
| 2008       | 349    | 49.8     |
| 2009       | 324    | 47.2     |
| 2010       | 337    | 50.8     |
| 2011       | 319    | 49.0     |
| 2012       | 350    | 59.6     |
| 2013       | 386    | 59.4     |
|            |        |          |
| Rise %     | 34.49% | 35.31%   |
| Annualized | 2.46%  | 2.52%    |

# *Atrial Septal Defects - Ostium Secundum*



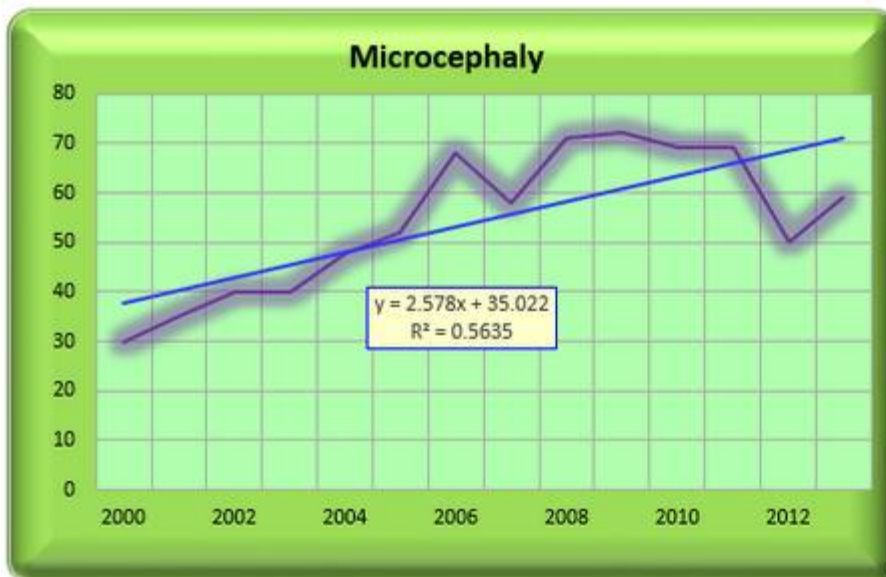
## Ostium Secundum ASD's

Rates/ 10,000 Live births  
(Excluding Terminations)

| Year       | ASD No. | ASD - Rate |
|------------|---------|------------|
| 2000       | 355     | 54.3       |
| 2001       | 415     | 61.9       |
| 2002       | 554     | 81         |
| 2003       | 579     | 83.5       |
| 2004       | 606     | 88.5       |
| 2005       | 637     | 92.4       |
| 2006       | 635     | 89.8       |
| 2007       | 579     | 81.8       |
| 2008       | 815     | 116.4      |
| 2009       | 951     | 138.6      |
| 2010       | 909     | 137        |
| 2011       | 903     | 138.8      |
| 2012       | 969     | 148.6      |
| 2013       | 926     | 142.5      |
| Rise %     | 260.85% | 262.43%    |
| Annualized | 18.63%  | 18.75%     |



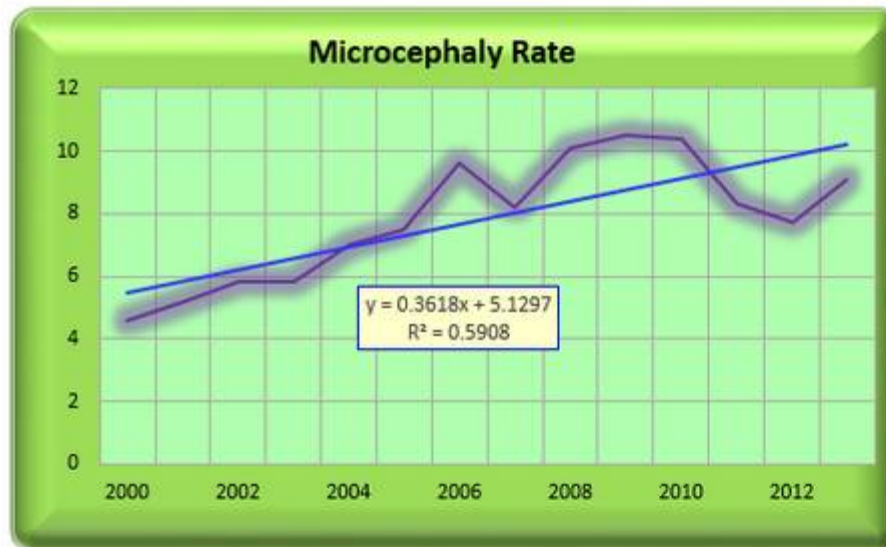
# Microcephaly



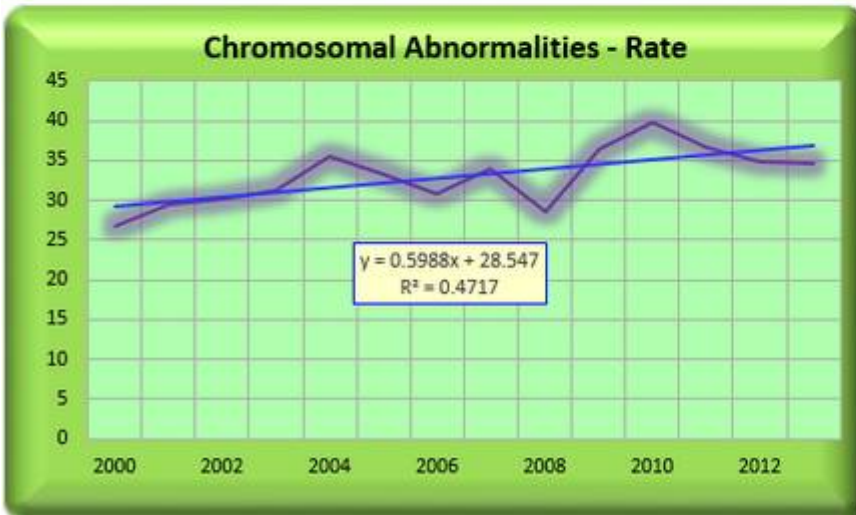
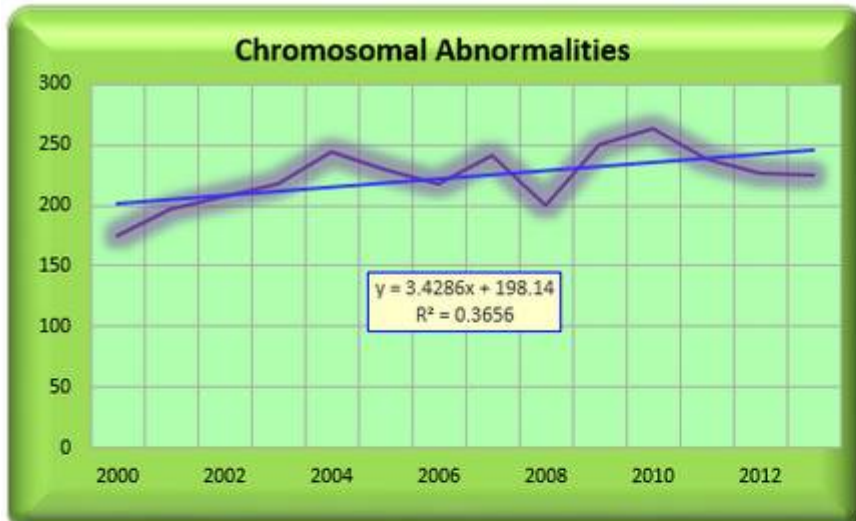
## Microcephaly

Rates/ 10,000 Live births  
(Excluding Terminations)

| Year       | Microcephaly No. | Microcephaly Rate |
|------------|------------------|-------------------|
| 2000       | 30               | 4.6               |
| 2001       | 35               | 5.2               |
| 2002       | 40               | 5.8               |
| 2003       | 40               | 5.8               |
| 2004       | 48               | 7                 |
| 2005       | 52               | 7.5               |
| 2006       | 68               | 9.6               |
| 2007       | 58               | 8.2               |
| 2008       | 71               | 10.1              |
| 2009       | 72               | 10.5              |
| 2010       | 69               | 10.4              |
| 2011       | 69               | 8.3               |
| 2012       | 50               | 7.7               |
| 2013       | 59               | 9.1               |
| Rise %     | 96.67%           | 97.83%            |
| Annualized | 6.90%            | 6.99%             |



# Chromosomal Anomalies



## Chromosomal Abnormalities

Rates/ 10,000 Live births  
(Excluding Terminations)

| Year       | Chromosomal Abnormalities Number | Chromosomal Abnormalities Rate |
|------------|----------------------------------|--------------------------------|
| 2000       | 175                              | 26.7                           |
| 2001       | 197                              | 29.4                           |
| 2002       | 207                              | 30.3                           |
| 2003       | 217                              | 31.3                           |
| 2004       | 244                              | 35.6                           |
| 2005       | 230                              | 33.4                           |
| 2006       | 218                              | 30.8                           |
| 2007       | 241                              | 34.0                           |
| 2008       | 200                              | 28.6                           |
| 2009       | 250                              | 36.4                           |
| 2010       | 264                              | 39.8                           |
| 2011       | 239                              | 36.7                           |
| 2012       | 227                              | 34.8                           |
| 2013       | 225                              | 34.6                           |
|            |                                  |                                |
| Rise %     | 28.57%                           | 29.41%                         |
| Annualized | 2.04%                            | 2.10%                          |

# *Stationary Time Trends*

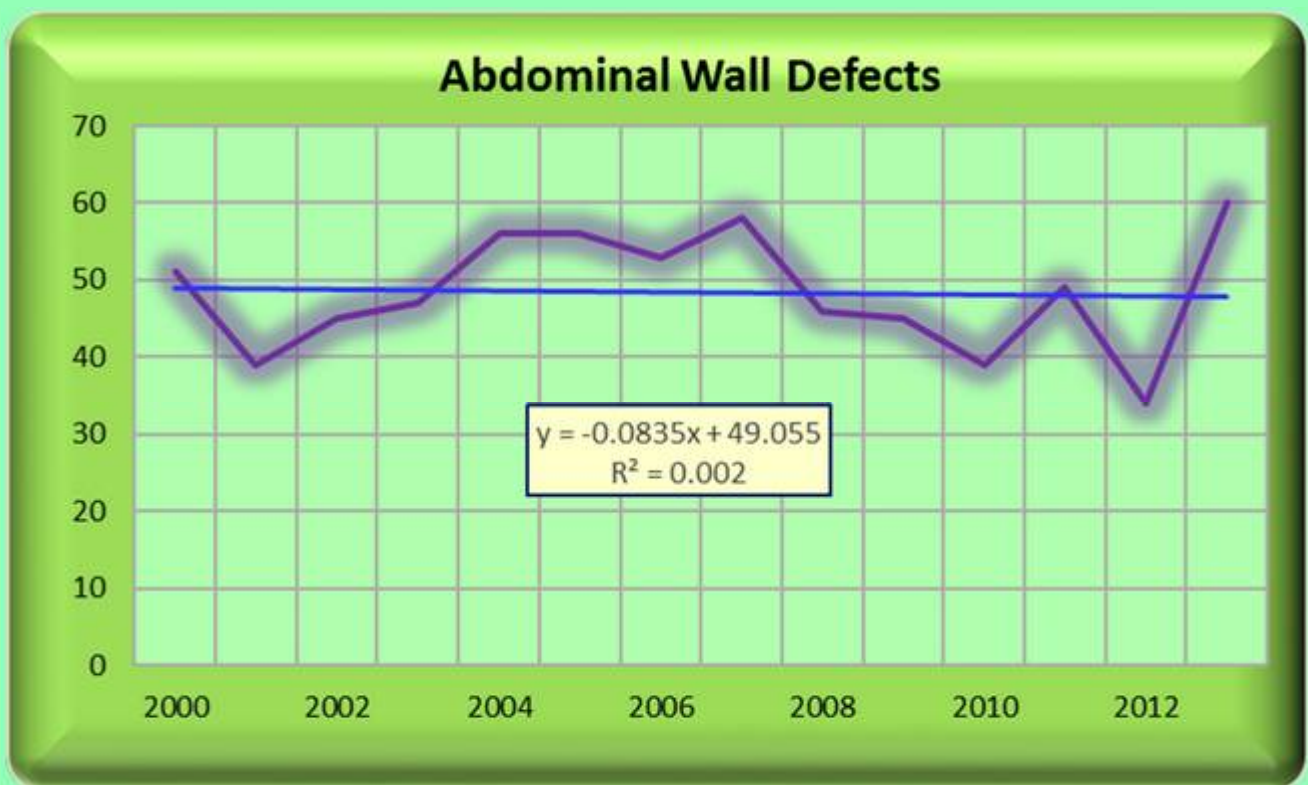
*Colorado  
2000-2013*

<http://www.chd.dphe.state.co.us/cohid/>  
<http://www.cohid.dphe.state.co.us/scripts/htmsql.exe/CrcsnPub.hsql>

# Cleft Lip +/- Palate



# Abdominal Wall Defects

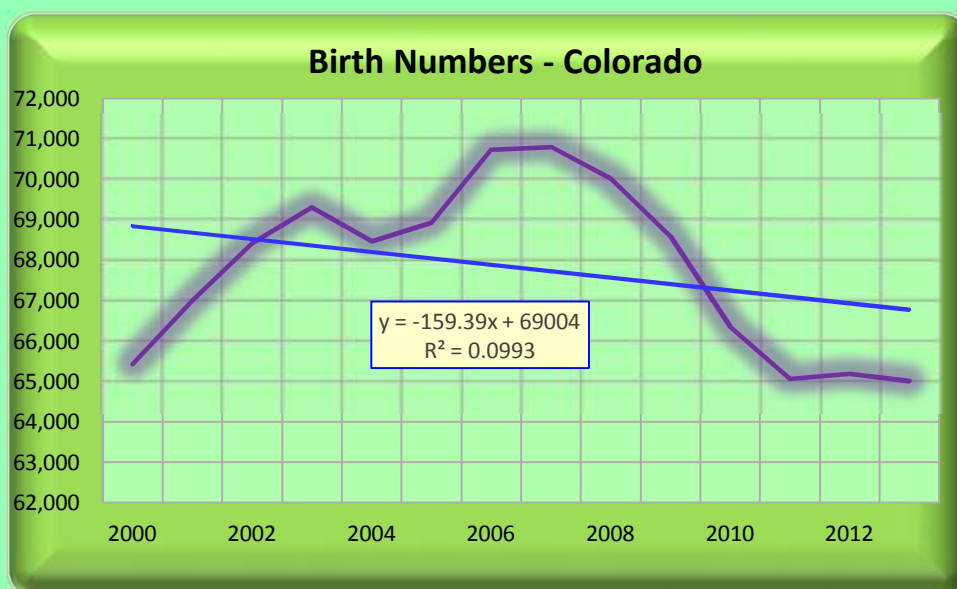


# *Cumulative Effects*

*Colorado*  
*2000-2013*

<http://www.chd.dphe.state.co.us/cohid/>  
<http://www.cohid.dphe.state.co.us/scripts/htmsql.exe/CrcsnPub.hsrl>

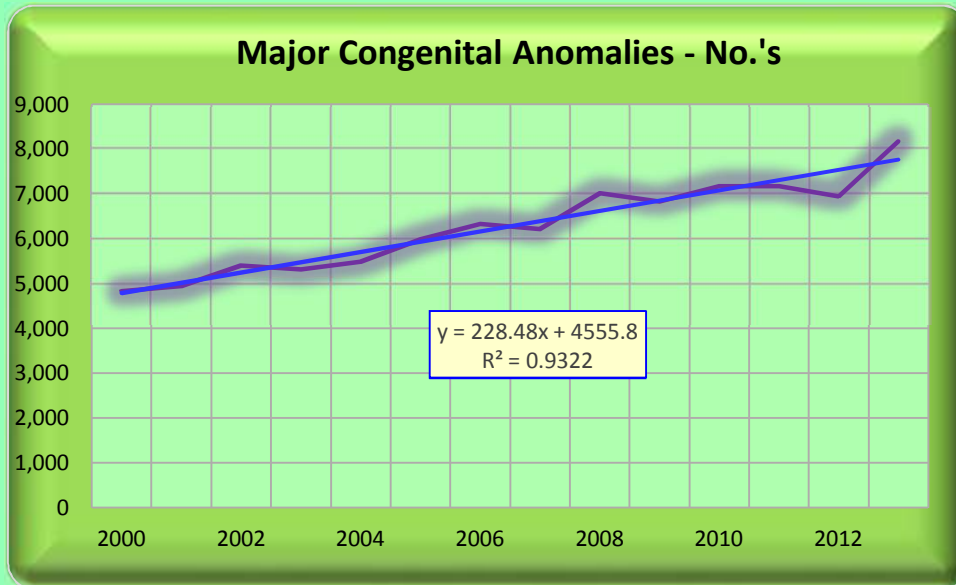
# Cumulative Effects - Births



| Year              | Births        | Projected     | Difference   |
|-------------------|---------------|---------------|--------------|
| 2000              | 65429         | 65429         | 0            |
| 2001              | 67006         | 65429         | 1577         |
| 2002              | 68420         | 65429         | 2991         |
| 2003              | 69304         | 65429         | 3875         |
| 2004              | 68475         | 65429         | 3046         |
| 2005              | 68922         | 65429         | 3493         |
| 2006              | 70737         | 65429         | 5308         |
| 2007              | 70804         | 65429         | 5375         |
| 2008              | 70028         | 65429         | 4599         |
| 2009              | 68602         | 65429         | 3173         |
| 2010              | 66346         | 65429         | 917          |
| 2011              | 65052         | 65429         | -377         |
| 2012              | 65188         | 65429         | -241         |
| 2013              | 65004         | 65429         | -425         |
|                   |               |               |              |
| <b>Cumulative</b> | <b>949317</b> | <b>916006</b> | <b>33311</b> |
| <b>% Change</b>   |               |               | <b>3.6%</b>  |
| <b>Annualized</b> |               |               | <b>0.26%</b> |

<http://www.chd.dphe.state.co.us/cohid/>  
<http://www.cohid.dphe.state.co.us/scripts/htmsql.exe/CrcsnPub.hsql>

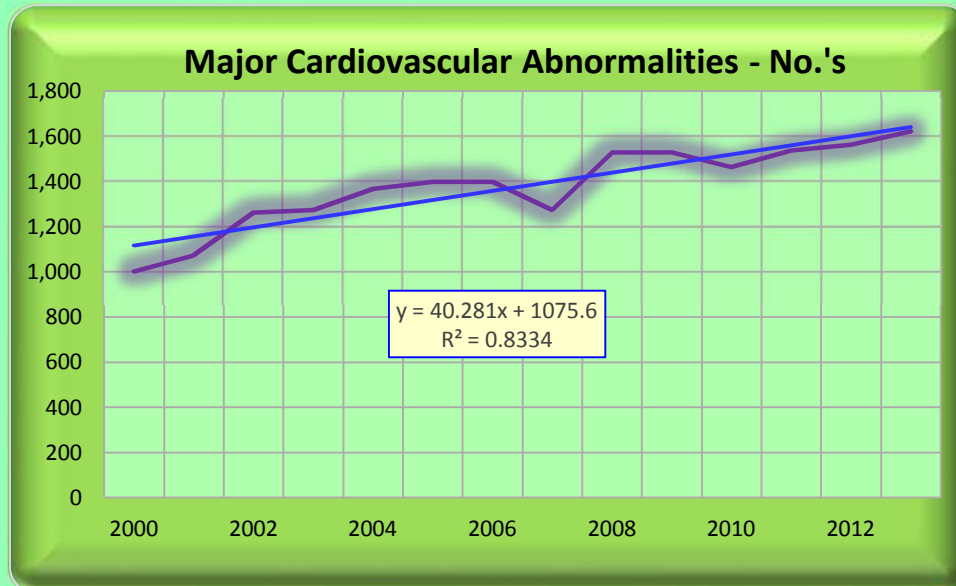
# *Cumulative Effects - All Major Defects*



| Year       | Majors | Projection | Difference |
|------------|--------|------------|------------|
| 2000       | 4830   | 4830       | 0          |
| 2001       | 4942   | 4830       | 112        |
| 2002       | 5406   | 4830       | 576        |
| 2003       | 5311   | 4830       | 481        |
| 2004       | 5482   | 4830       | 652        |
| 2005       | 5978   | 4830       | 1148       |
| 2006       | 6325   | 4830       | 1495       |
| 2007       | 6213   | 4830       | 1383       |
| 2008       | 7010   | 4830       | 2180       |
| 2009       | 6826   | 4830       | 1996       |
| 2010       | 7171   | 4830       | 2341       |
| 2011       | 7174   | 4830       | 2344       |
| 2012       | 6939   | 4830       | 2109       |
| 2013       | 8165   | 4830       | 3335       |
|            |        |            |            |
| Cumulative | 87772  | 67620      | 20152      |
| % Change   |        |            | 29.8%      |

<http://www.chd.dphe.state.co.us/cohid/>  
<http://www.cohid.dphe.state.co.us/scripts/htmsql.exe/CrcsnPub.hsql>

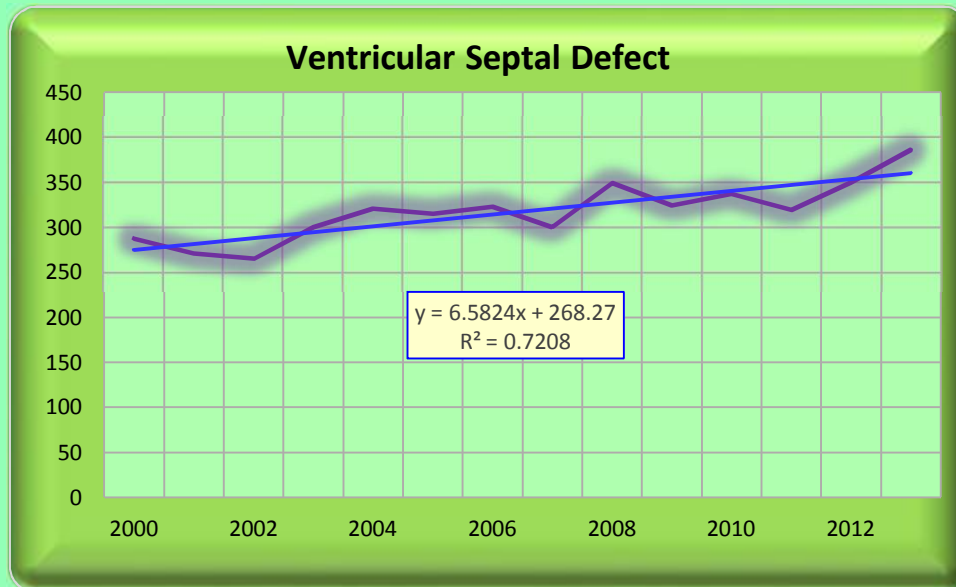
# *Cumulative Effects - All CVS Anomalies*



| Year       | CVS   | Projected | Difference |
|------------|-------|-----------|------------|
| 2000       | 1002  | 1002      | 0          |
| 2001       | 1071  | 1002      | 69         |
| 2002       | 1263  | 1002      | 261        |
| 2003       | 1273  | 1002      | 271        |
| 2004       | 1368  | 1002      | 366        |
| 2005       | 1398  | 1002      | 396        |
| 2006       | 1397  | 1002      | 395        |
| 2007       | 1274  | 1002      | 272        |
| 2008       | 1530  | 1002      | 528        |
| 2009       | 1528  | 1002      | 526        |
| 2010       | 1464  | 1002      | 462        |
| 2011       | 1536  | 1002      | 534        |
| 2012       | 1562  | 1002      | 560        |
| 2013       | 1622  | 1002      | 620        |
|            |       |           |            |
| Cumulative | 19288 | 14028     | 5260       |
| % Change   |       |           | 37.5%      |

<http://www.chd.dphe.state.co.us/cohid/>  
<http://www.cohid.dphe.state.co.us/scripts/htmsql.exe/CrcsnPub.hsql>

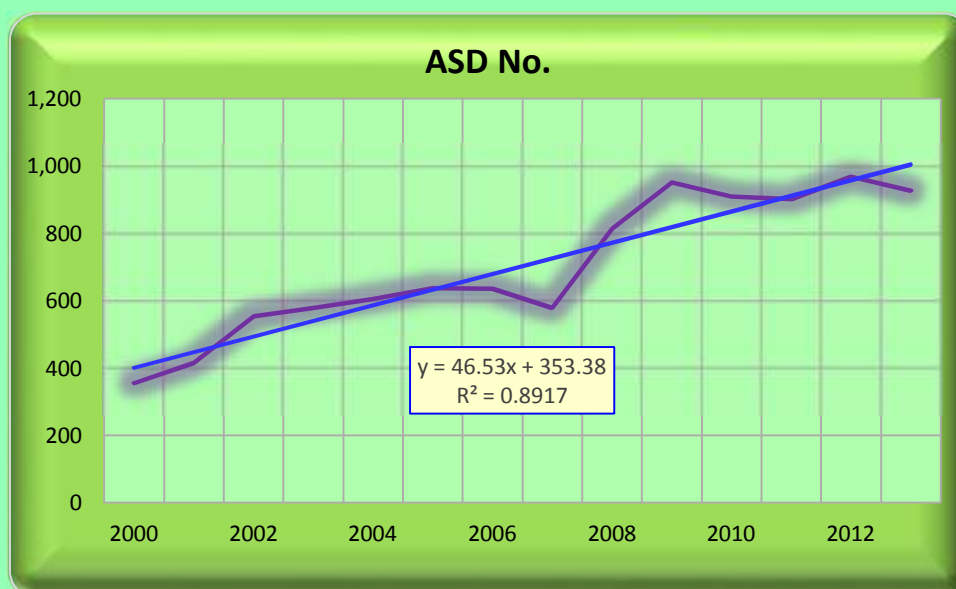
# Cumulative Effects - VSD



| Year              | VSD         | Projected   | Difference   |
|-------------------|-------------|-------------|--------------|
| 2000              | 287         | 271         | 16           |
| 2001              | 271         | 271         | 0            |
| 2002              | 265         | 271         | -6           |
| 2003              | 300         | 271         | 29           |
| 2004              | 321         | 271         | 50           |
| 2005              | 315         | 271         | 44           |
| 2006              | 323         | 271         | 52           |
| 2007              | 300         | 271         | 29           |
| 2008              | 349         | 271         | 78           |
| 2009              | 324         | 271         | 53           |
| 2010              | 337         | 271         | 66           |
| 2011              | 319         | 271         | 48           |
| 2012              | 350         | 271         | 79           |
| 2013              | 386         | 271         | 115          |
|                   |             |             |              |
| <b>Cumulative</b> | <b>4447</b> | <b>3794</b> | <b>653</b>   |
| <b>% Change</b>   |             |             | <b>17.2%</b> |

<http://www.chd.dphe.state.co.us/cohid/>  
<http://www.cohid.dphe.state.co.us/scripts/htmsql.exe/CrcsnPub.hsql>

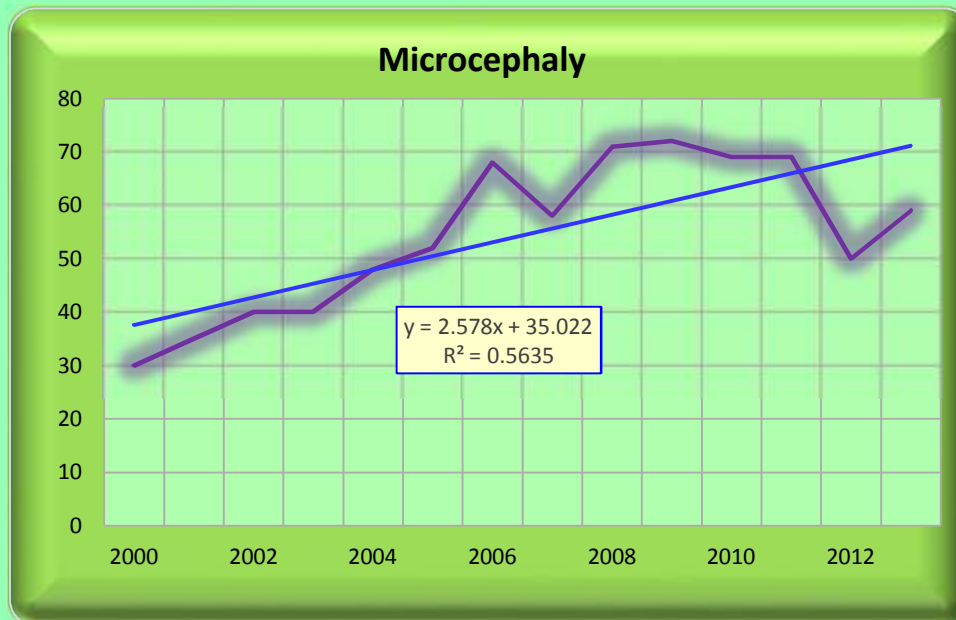
# Cumulative Effects - ASD - Secundum



| Year       | ASD No. | Projection | Difference |
|------------|---------|------------|------------|
| 2000       | 355     | 355        | 0          |
| 2001       | 415     | 355        | 60         |
| 2002       | 554     | 355        | 199        |
| 2003       | 579     | 355        | 224        |
| 2004       | 606     | 355        | 251        |
| 2005       | 637     | 355        | 282        |
| 2006       | 635     | 355        | 280        |
| 2007       | 579     | 355        | 224        |
| 2008       | 815     | 355        | 460        |
| 2009       | 951     | 355        | 596        |
| 2010       | 909     | 355        | 554        |
| 2011       | 903     | 355        | 548        |
| 2012       | 969     | 355        | 614        |
| 2013       | 926     | 355        | 571        |
|            |         |            |            |
| Cumulative | 9833    | 4970       | 4863       |
| % Change   |         |            | 97.8%      |

<http://www.chd.dphe.state.co.us/cohid/>  
<http://www.cohid.dphe.state.co.us/scripts/htmsql.exe/CrcsnPub.hsql>

# Cumulative Effects - Microcephaly

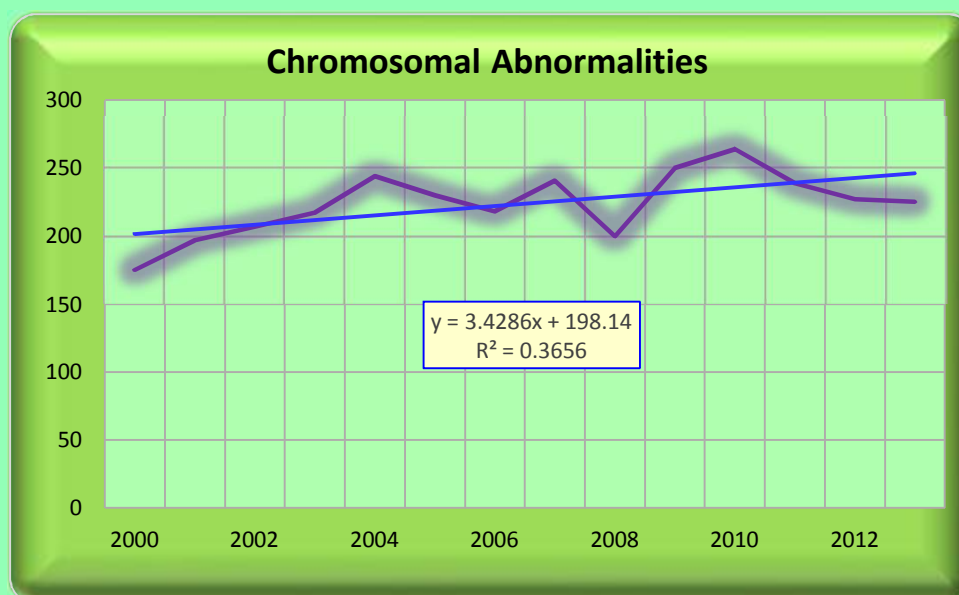


| Year       | Majors | Projection | Difference |
|------------|--------|------------|------------|
| 2000       | 4830   | 4830       | 0          |
| 2001       | 4942   | 4830       | 112        |
| 2002       | 5406   | 4830       | 576        |
| 2003       | 5311   | 4830       | 481        |
| 2004       | 5482   | 4830       | 652        |
| 2005       | 5978   | 4830       | 1148       |
| 2006       | 6325   | 4830       | 1495       |
| 2007       | 6213   | 4830       | 1383       |
| 2008       | 7010   | 4830       | 2180       |
| 2009       | 6826   | 4830       | 1996       |
| 2010       | 7171   | 4830       | 2341       |
| 2011       | 7174   | 4830       | 2344       |
| 2012       | 6939   | 4830       | 2109       |
| 2013       | 8165   | 4830       | 3335       |
|            |        |            |            |
| Cumulative | 87772  | 67620      | 20152      |
| % Change   |        |            | 29.8%      |

<http://www.chd.dphe.state.co.us/cohid/>  
<http://www.cohid.dphe.state.co.us/scripts/htmsql.exe/CrcsnPub.hsql>

# *Cumulative Effects*

## *- Chromosomal Abnormalities*



| Year              | Chromosomal Abnormalities Number | Projection  | Difference   |
|-------------------|----------------------------------|-------------|--------------|
| 2000              | 175                              | 175         | 0            |
| 2001              | 197                              | 175         | 22           |
| 2002              | 207                              | 175         | 32           |
| 2003              | 217                              | 175         | 42           |
| 2004              | 244                              | 175         | 69           |
| 2005              | 230                              | 175         | 55           |
| 2006              | 218                              | 175         | 43           |
| 2007              | 241                              | 175         | 66           |
| 2008              | 200                              | 175         | 25           |
| 2009              | 250                              | 175         | 75           |
| 2010              | 264                              | 175         | 89           |
| 2011              | 239                              | 175         | 64           |
| 2012              | 227                              | 175         | 52           |
| 2013              | 225                              | 175         | 50           |
|                   |                                  |             |              |
| <b>Cumulative</b> | <b>3134</b>                      | <b>2450</b> | <b>684</b>   |
| <b>% Change</b>   |                                  |             | <b>27.9%</b> |

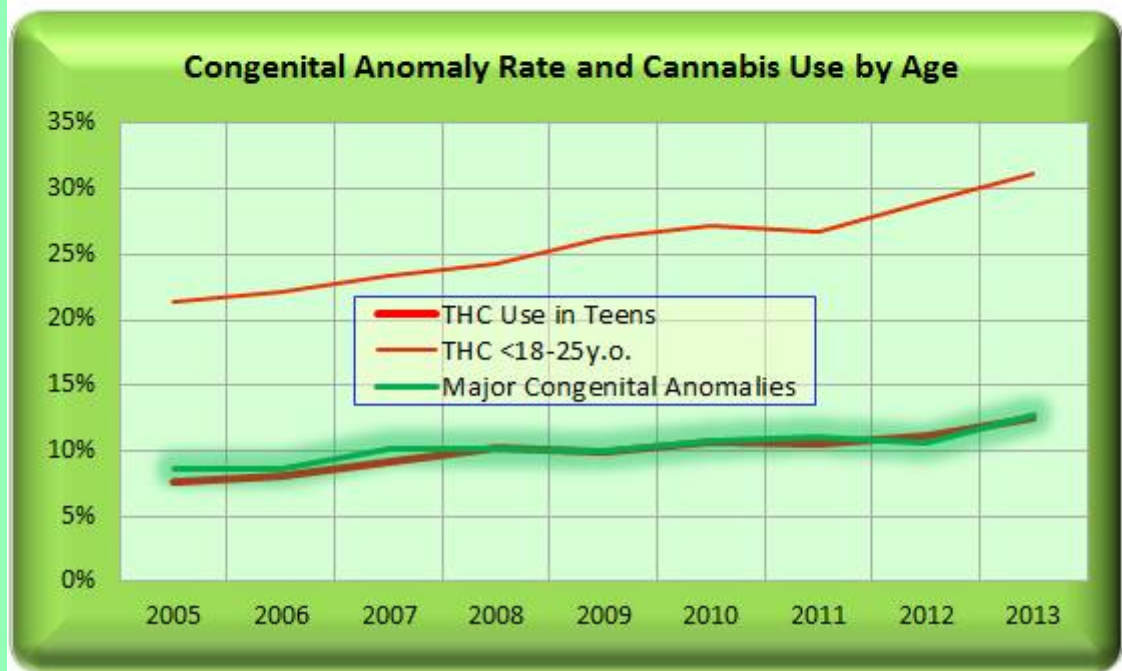
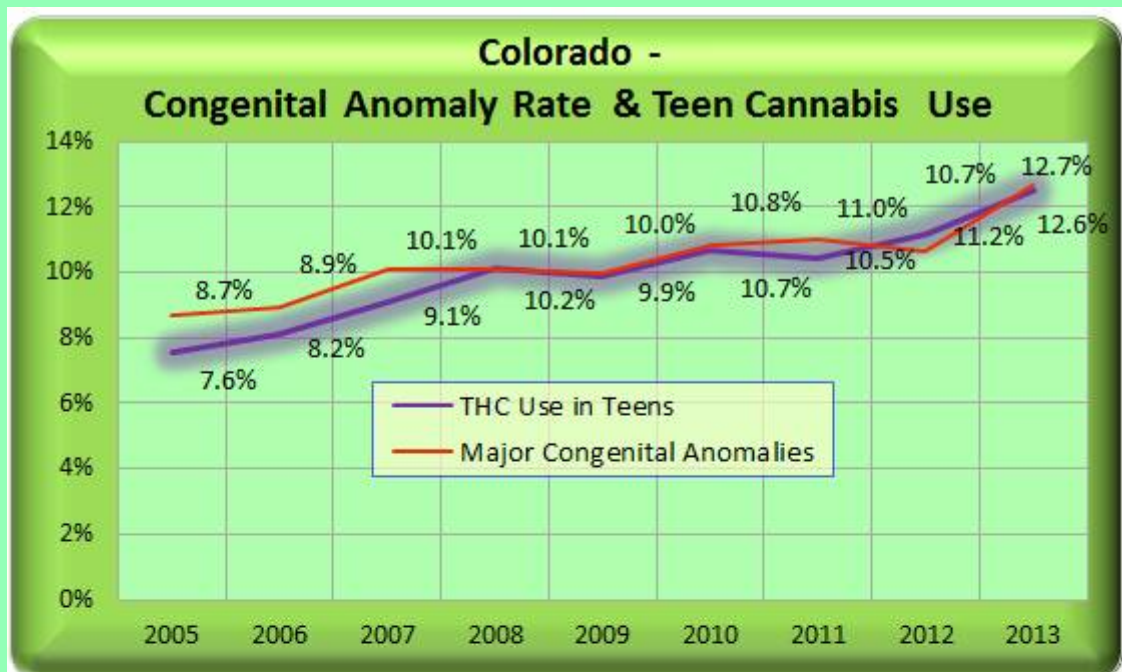
<http://www.chd.dphe.state.co.us/cohid/>  
<http://www.cohid.dphe.state.co.us/scripts/htmsql.exe/CrcsnPub.hsql>

# *Overall Cumulative Summary*

*Colorado  
2000-2013*

<http://www.chd.dphe.state.co.us/cohid/>  
<http://www.cohid.dphe.state.co.us/scripts/htmsql.exe/CrcsnPub.hspl>

## *Close Correlation between Cannabis Consumption and Congenital Anomalies Rates*

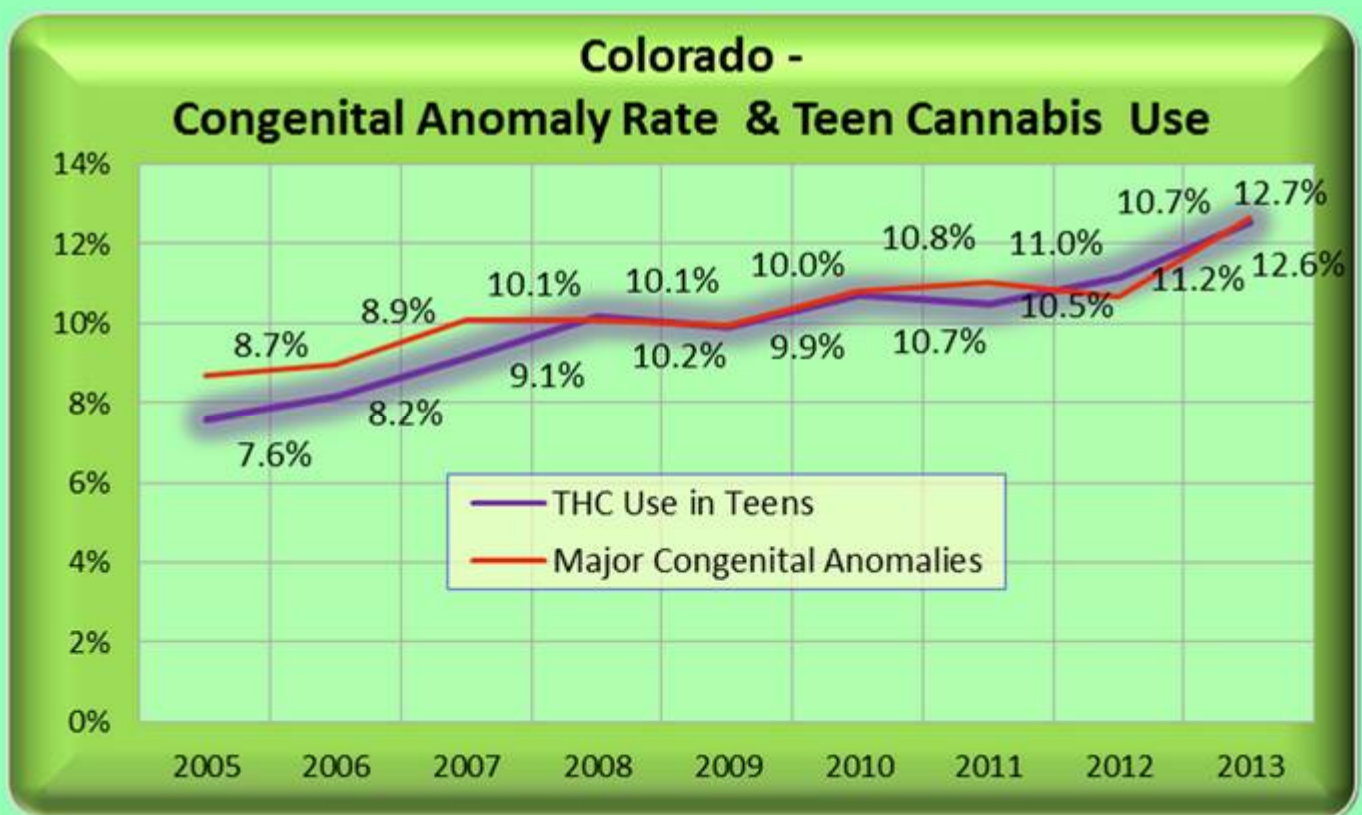


<http://www.chd.dphe.state.co.us/cohid/>

<http://www.cohid.dphe.state.co.us/scripts/htmsql.exe/CrcsnPub.hsql>

<https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.pdf>

## *Close Correlation between Cannabis Consumption and Congenital Anomalies Rates*



<http://www.chd.dphe.state.co.us/cohid/>

<http://www.cohid.dphe.state.co.us/scripts/htmsql.exe/CrcsnPub.hsql>

<https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.pdf>

***Correlation == 0.9539***  
***P == 0.00006594***

```
> cor.test (a,x, alternative="two.sided",  
+          method="pearson", exact=TRUE, conf.level = 0.95)  
  
Pearson's product-moment correlation  
  
data:  a and x  
t = 8.4142, df = 7, p-value = 6.594e-05  
alternative hypothesis: true correlation is not equal to 0  
95 percent confidence interval:  
 0.7908924 0.9905319  
sample estimates:  
      cor  
0.953952
```

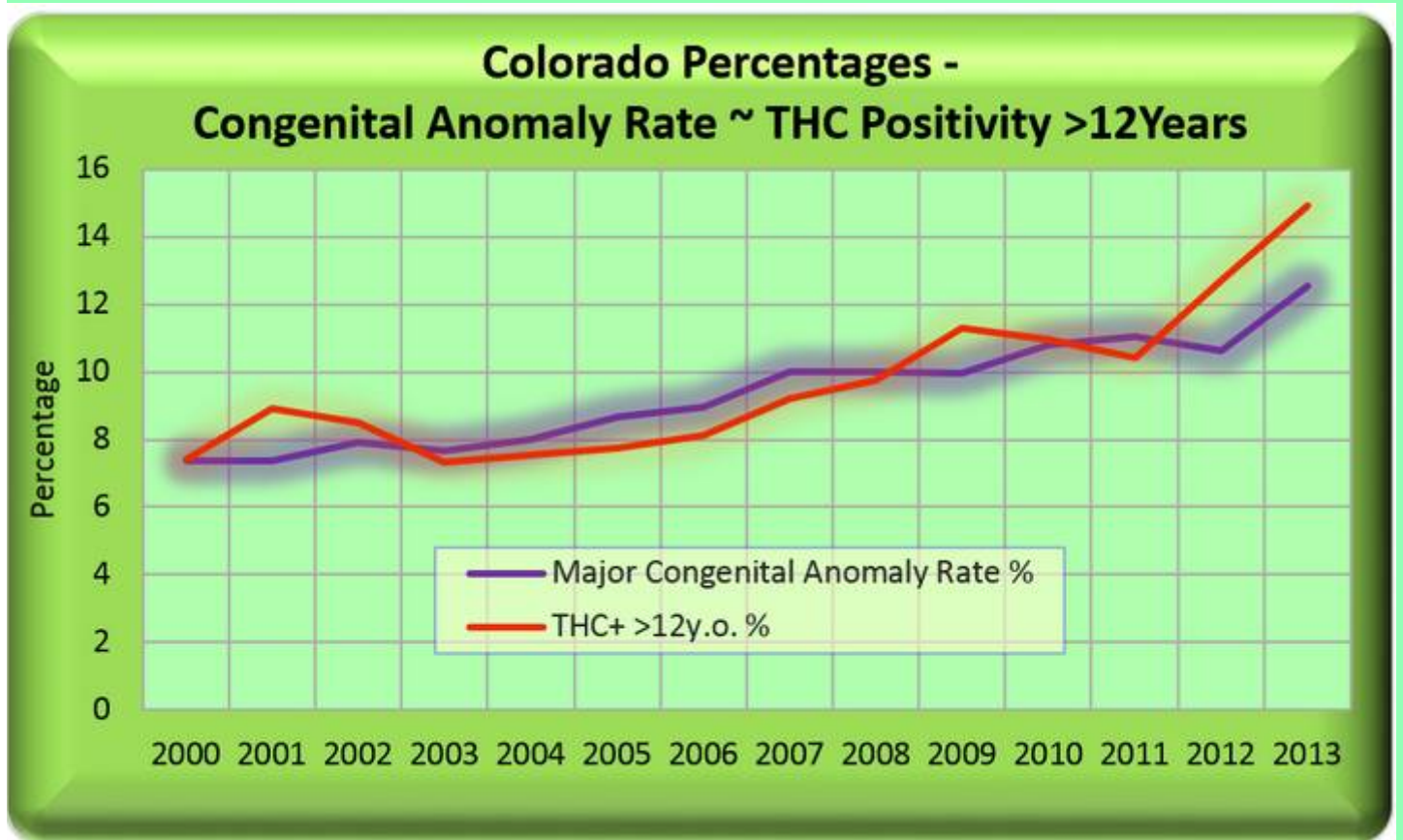
***Young Adult Correlation == 0.9258***  
***P == 0.0003457***

```
> CTD
  Year THCTeens THC18.25 MeanUse Majors
1 2005   0.0760   0.2143   0.1452 0.0867
2 2006   0.0815   0.2221   0.1518 0.0894
3 2007   0.0913   0.2344   0.1629 0.1001
4 2008   0.1017   0.2428   0.1723 0.1001
5 2009   0.0991   0.2635   0.1813 0.0995
6 2010   0.1072   0.2726   0.1899 0.1081
7 2011   0.1047   0.2681   0.1864 0.1103
8 2012   0.1116   0.2905   0.2011 0.1065
9 2013   0.1256   0.3124   0.2190 0.1265
>
> x <- CTD$THCTeens
> y <- CTD$THC18.25
> z <- CTD$MEanUse
> a <- CTD$Majors
>
> cor.test (a,y, alternative="two.sided",
+           method="pearson", exact=TRUE, conf.level = 0.95)

Pearson's product-moment correlation

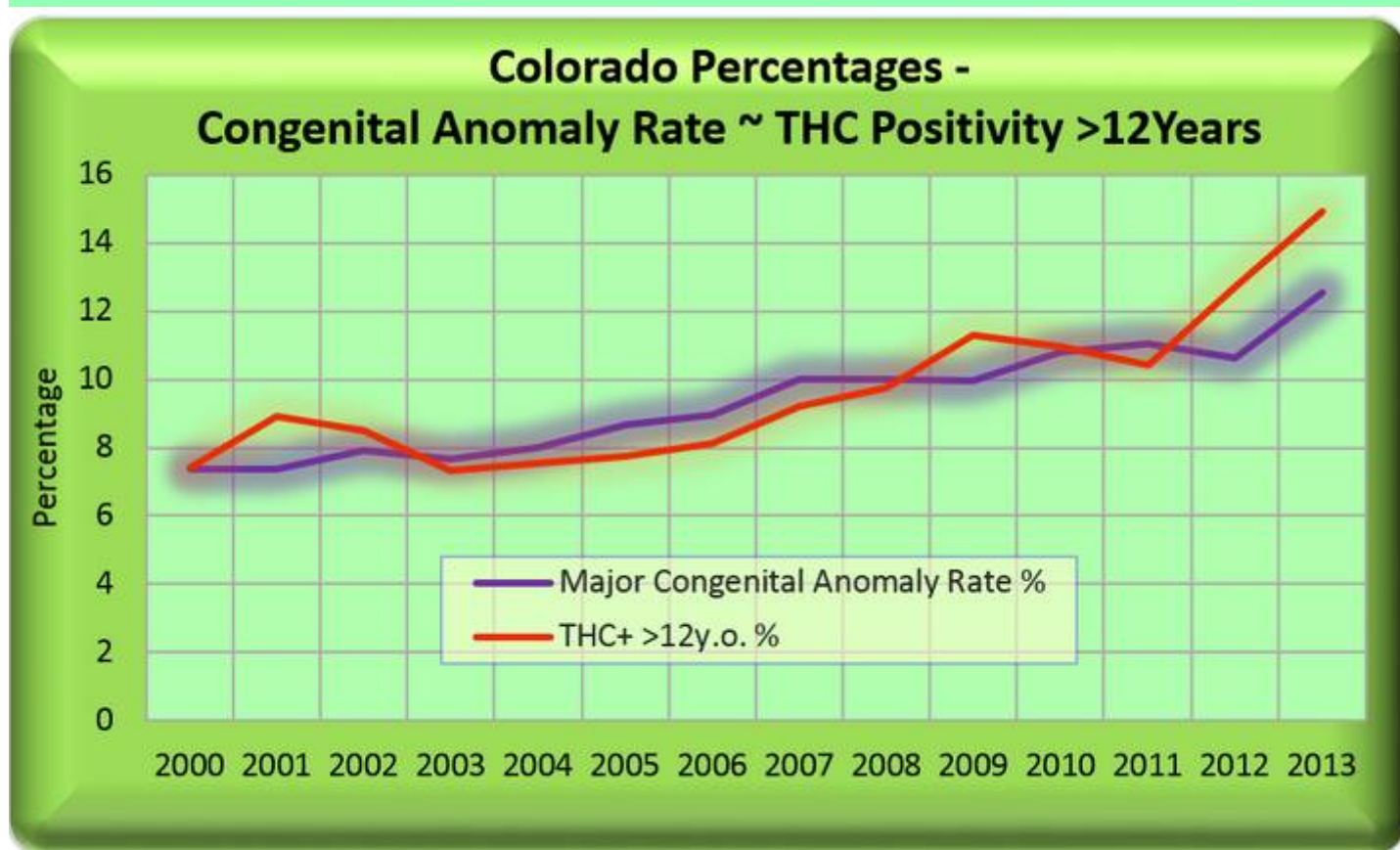
data:  a and y
t = 6.4639, df = 7, p-value = 0.0003457
alternative hypothesis: true correlation is not equal to 0
95 percent confidence interval:
 0.6781881 0.9844974
sample estimates:
      cor
0.9254759
```

## *Close Correlation between Cannabis Consumption and Congenital Anomalies Rates*



```
> cor.test (x,y, alternative="two.sided",  
+          method="pearson", exact=TRUE, conf.level = 0.95)  
  
Pearson's product-moment correlation  
  
data:  x and y  
t = 6.5002, df = 12, p-value = 2.936e-05  
alternative hypothesis: true correlation is not equal to 0  
95 percent confidence interval:  
 0.6618084 0.9624345  
sample estimates:  
      cor  
0.8825038
```

## *Colorado Percentages - Congenital Anomalies Rates & Cannabis Consumption Rates >12 Years*



[www.samhsa.gov](http://www.samhsa.gov)

<http://www.chd.dphe.state.co.us/cohid/>

<http://www.cohid.dphe.state.co.us/scripts/htmsql.exe/CrcsnPub.hsrl>

<https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.pdf>

# *Cumulative Overall Effects*

| Anomaly                        | Cumulative<br>Total<br>2000-2013 | Projected<br>Total from<br>Baseline | Excess<br>Above<br>Baseline | % Change<br>2000-2013 | Increase<br>Relative to<br>Births |
|--------------------------------|----------------------------------|-------------------------------------|-----------------------------|-----------------------|-----------------------------------|
| Births                         | 949,317                          | 916,006                             | 33,311                      | 3.6%                  | 1.00                              |
| Major<br>Congenital<br>Defects | 87,772                           | 67,620                              | 20,152                      | 29.8%                 | 8.20                              |
| Major CVS                      | 19,288                           | 14,028                              | 5,260                       | 37.5%                 | 10.31                             |
| VSD                            | 4,447                            | 3,794                               | 653                         | 17.2%                 | 4.73                              |
| ASD-Secundum                   | 9,833                            | 4,970                               | 4,863                       | 97.8%                 | 26.91                             |
| Microcephaly                   | 761                              | 420                                 | 341                         | 81.2%                 | 22.33                             |
| Chromosomal                    | 3,134                            | 2,450                               | 684                         | 27.9%                 | 7.68                              |

22<sup>nd</sup> April 2018

Dockets Management Staff (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Rm. 1061  
Rockville, MD 20852

Re: Department of Health and Human Services, Food and Drug Administration [Docket No. FDA-2018-N-1072]: International Drug Scheduling; Convention on Psychotropic Substances; Single Convention on Narcotic Drugs; Cannabis Plant and Resin; Extracts and Tinctures of Cannabis; Delta-9-Tetrahydrocannabinol; Stereoisomers of Tetrahydrocannabinol; Cannabidiol; **Request for Comments** (FR Doc. 2018-07225).

Re: *Novel Considerations for the FDA Evaluation of Re-scheduling  
Cannabinoids in United States:  
Cannabinoid Genotoxicity and  
Structural and Neurobehavioral Teratogenicity*

There exists sufficient empirical data from cellular to epidemiological studies to warrant caution in the use cannabinoids including cannabidiol as recreational and therapeutic agents.

Cannabinoids bind to CB1R receptors on neuronal mitochondrial membranes<sup>1-7</sup> where they can directly disrupt key functions<sup>8-12</sup> including cellular energy generation, DNA maintenance and repair, memory and learning<sup>1-7,9,10,13-24</sup>.

Empirical literature associates cannabinoid use with CB1R-mediated vasospastic and vasothrombotic strokes, myocardial infarcts, arrhythmias<sup>25-98</sup> and arteritis<sup>25,77,78,99-106</sup>. Cannabis has been associated with increased cardiovascular stiffness and vascular aging, a major surrogate for organismal aging<sup>107</sup>. In the pediatric-congenital context CB1R-mediated cannabis vasculopathy forms a major pathway to teratogenesis including VSD, ASD, endocardial cushion defects, several other cardiovascular anomalies<sup>75,108</sup> and, via the omphalo-vitelline arterial CB1R's<sup>25</sup>, gastroschisis<sup>108-114</sup>. Cannabis has been linked with several other malformations including hydrocephaly<sup>108</sup>. Cannabinoids also induce epigenetic perturbations<sup>115-123</sup>; and, like thalidomide<sup>124-126</sup>, interfere with tubulin polymerization<sup>127-132</sup> and the stability of the mitotic spindle precipitating micronucleus formation<sup>129,133-142</sup>, chromosomal shattering (chromothripsis)<sup>129,143-157</sup> providing further major pathways to genotoxicity.

Assuming validity of the above data, increased levels of both adult and neonatal morbidity should accompany increased cannabis use. The "Colorado Responds to Children with Special Needs" (CRCSN) program tracked congenital anomalies 2000-2013<sup>158</sup>. Importantly this data monitors the teratological history of Colorado since 2001 when the state was first advised that intrastate cannabis would not be prosecuted by the Federal Government. In 2012 medical cannabis was legalized and in 2014 cannabis was completely legalized.

Over the period 2000-2013 Colorado almost doubled its already high congenital anomaly rate rising from 4,830 anomalies / 65,429 births (7.4%) to 8,165 / 65,004 (12.6%; Figure 1); the US mean is 3.1%. Major cardiovascular defects rose 61% (number and rate); microcephaly rose 96% (from 30 to 60 cases peaking at 72 in 2009); and chromosomal anomalies rose 28% (from 175 to 225, peaking at 264 in 2010; Figure 2-7). Over the whole period this totals to 87,772 major congenital anomalies from 949,317 live births (9.25%).

The use of cannabis in Colorado can be determined from the SAMHSA National Survey on Drug Use and Health. A close correlation is noted between major congenital anomaly rates and rates of cannabis use in Coloradans >12 years ( $R=0.8825$ ;  $P=0.000029$ ; Figure 8). Although data is not strictly comparable across U.S. registries, the Colorado registry is a passive rather than active case-finding registry and so might be expected to underestimate anomaly rates. Given the Colorado birth rate remained almost constant over the period 2000-2013, rising only 3.6%, a simple way to quantitate historical trends is to simply project forwards the historical anomaly rate and compare it to the rise in birth numbers. However rather than remaining relatively stable in line with population births, selected defects (left hand column Table 1) have risen several times more than the birth rate (right hand column).

Colorado had an average of 67,808 births over the period 2000-2013 and experienced a total of 87,772 birth defects, 20,152 more than would have been predicted using 2000 rates. Given the association between cannabis use and birth defects and the plausible biological mechanisms, cannabis may be a major factor contributing to birth congenital morbidity in Colorado. If we accept this and apply the “Colorado effect” to the over 3,945,875 births in USA in 2016 we calculate an excess of 83,762 major congenital anomalies annually nationwide if cannabis use rises in the US to the level that it was in Colorado in 2013.

In reality both cannabis use and cannabis concentration is rising across USA following legalization which further implies that the above calculations represent significant underestimations<sup>159,160</sup>. This CRCSN data series terminates in 2013 prior to full legalization in 2014. Moreover parents of children harbouring severe anomalies may frequently elect for termination, which will again underestimate numbers of abnormal live births.

In California 7% of all pregnant mothers were recently shown to test positive for cannabis exposure, including almost 25% of teenage mothers in 2015 so cannabinoids clearly constitute a significant population-wide teratological exposure<sup>161</sup>. This is particularly relevant to cannabis genotoxicity as many studies show a dramatic up-tick in genotoxic effect in the dose-response curve for both tetrahydrocannabinol and cannabidiol above a certain threshold dose as higher, sedating levels are reached<sup>132,136,162-166</sup>. Cannabis is usually used amongst humans for its sedative effects.

Other examples of high congenital anomaly rates accompanying increased cannabis use include North Carolina<sup>167-169</sup>, Mexico<sup>170-175</sup>, Northern Canada<sup>111,176-178</sup>, New Zealand and the Nimbin area in Australia<sup>179-182</sup>.

The above data leave open the distinct possibility that the rate of congenital anomalies from significant prenatal paternal or maternal cannabis exposure may become substantial.

With over 1,000 trials listed on [clinicaltrials.gov](http://clinicaltrials.gov) the chance of a type I experimental error for cannabinoid therapeutics and a falsely positive trial finding is at least 25/1,000 trials at the 5% level.

The major anomaly rate is just the “tip of the iceberg” of the often subtle neurobehavioral teratology of Foetal Cannabinoid Syndrome (FCS) following antenatal cannabinoid exposure characterized by attention, learning, behavioral and social deficits which in the longer term impose significant educational, other addiction and welfare costs - and is clearly more common<sup>121,183-225</sup>. Foetal Alcohol Syndrome (FAS) is known to be epigenetically mediated<sup>226-251</sup> and foetal alcohol is known to act via CB1R's<sup>186,203,206-208,210,216,252-259</sup>. Cannabis has significant and heritable epigenetic imprints in neural, immune and germ cell (sperm) tissues<sup>20,117,119,120,122,260-262</sup>, and epigenomic disruption has been implicated in FCS<sup>241</sup>. CB1R-mediated disruption by disinhibition of the normal gamma and theta oscillatory rhythms of the forebrain which underpin thinking, learning and sanity have been implicated both in adult psychiatric disease and the neurodevelopmental aspects of FCS<sup>211</sup>.

All of this implies that in addition to usually short-term therapy-oriented clinical trials, longer term studies and careful twenty-first century next generation studies will be required to carefully review inter-related genotoxic, teratologic, epigenetic, transcriptomic, metabolomic, epitranscriptomic and long term cardiovascular outcomes which appears to have been largely overlooked in extant studies – effects which would appear rather to have taken Coloradans by surprise. Congenital registry data also needs to be open and transparent which it presently is not. We note that cannabidiol is now solidly implicated in genotoxicity<sup>134,263-269</sup>. Governments are duty-bound to carefully weigh and balance the implications of their social policies; lest like Colorado, we too unwittingly create a “Children with Special Needs Program”<sup>158</sup>.

These data also directly imply that young adults, as the very group which most consumes cannabis<sup>160,161,270-273</sup> is the very group which most requires protection from its reproductive, genotoxic and teratogenic effects.

Yours sincerely,



Assoc. Prof. Dr. Stuart Reece.  
University of Western Australia and  
Edith Cowan University,  
Perth,  
Australia.

**Table 1.:**  
**Cumulative Data for Colorado**  
**Birth Defects 2000-2013** \*

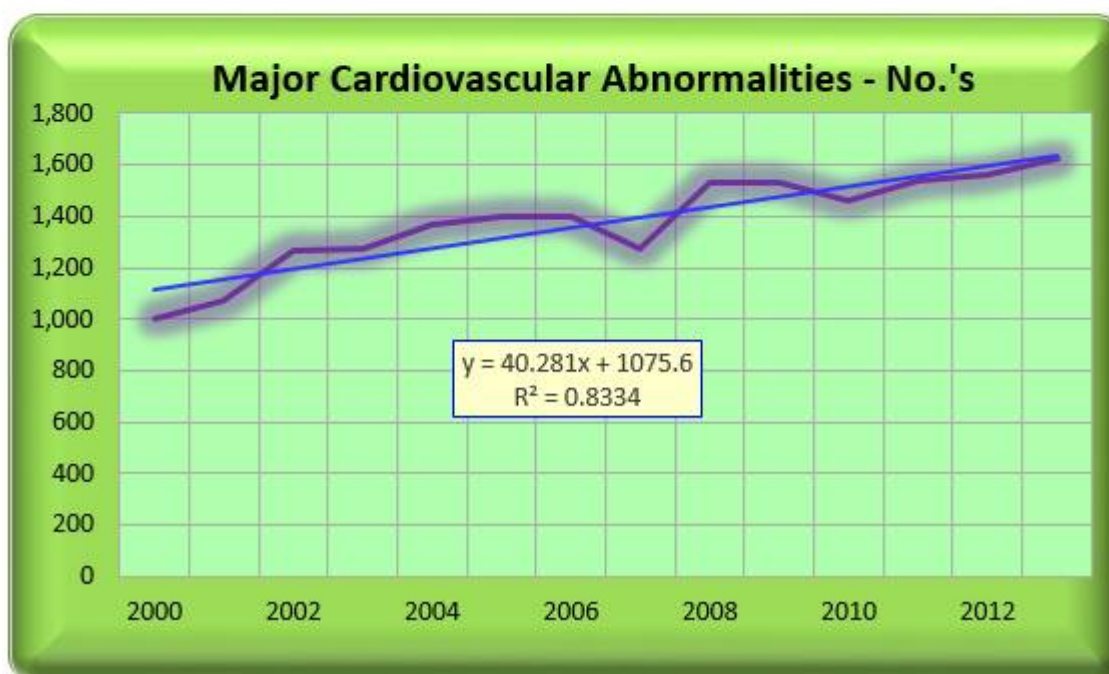
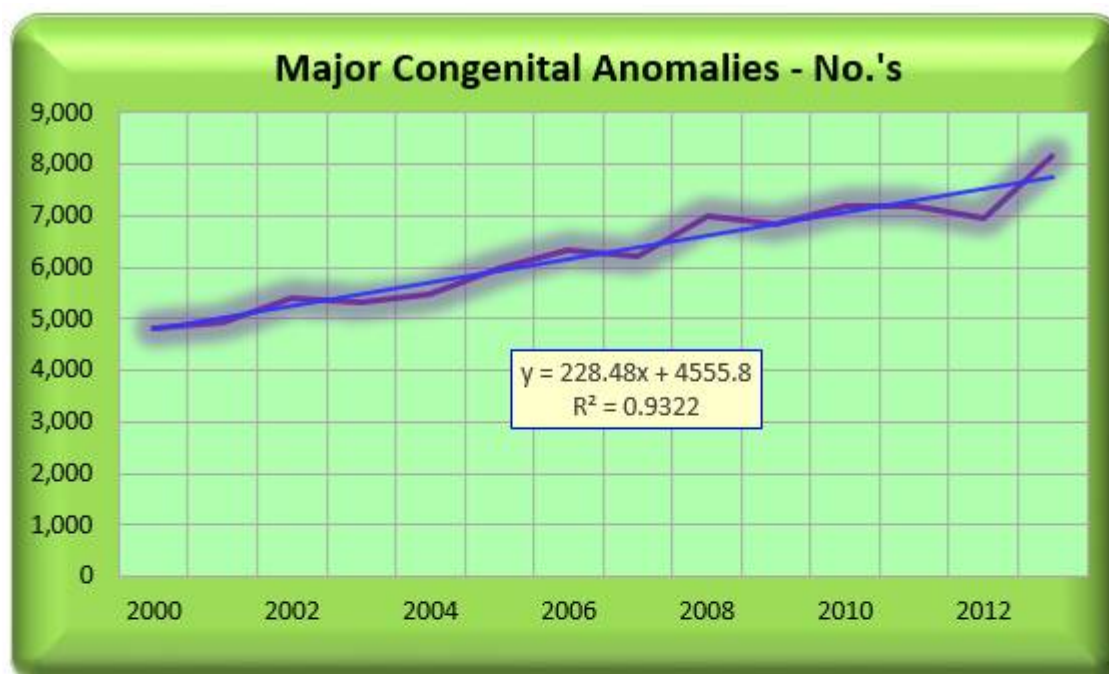
| Anomaly                     | Cumulative<br>Total<br>2000-2013 | Projected<br>Total from<br>Baseline | Excess Above<br>Baseline | % Change<br>2000-2013 | Times (x)<br>Increase<br>Relative to<br>Births |
|-----------------------------|----------------------------------|-------------------------------------|--------------------------|-----------------------|------------------------------------------------|
|                             |                                  |                                     |                          |                       |                                                |
|                             |                                  |                                     |                          |                       |                                                |
| Births                      | 949,317                          | 916,006                             | 33,311                   | 3.6%                  | 1.00                                           |
|                             |                                  |                                     |                          |                       |                                                |
| Major Congenital<br>Defects | 87,772                           | 67,620                              | 20,152                   | 29.8%                 | 8.20                                           |
| Major CVS                   | 19,288                           | 14,028                              | 5,260                    | 37.5%                 | 10.31                                          |
| VSD                         | 4,447                            | 3,794                               | 653                      | 17.2%                 | 4.73                                           |
| ASD-Secundum                | 9,833                            | 4,970                               | 4,863                    | 97.8%                 | 26.91                                          |
| Microcephaly                | 761                              | 420                                 | 341                      | 81.2%                 | 22.33                                          |
| Chromosomal                 | 3,134                            | 2,450                               | 684                      | 27.9%                 | 7.68                                           |

\* - From Reference (4)

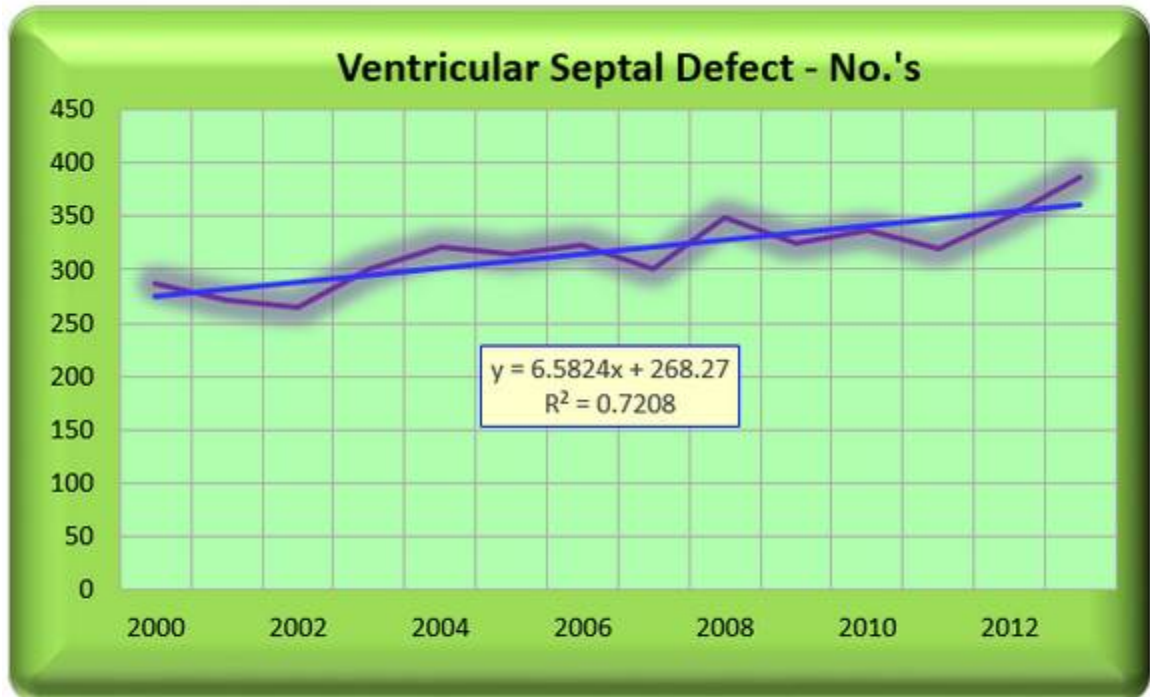
**Figure 1.**



**Figures 2, 3.**



**Figures 4, 5.**



**Figures 6. 7.**

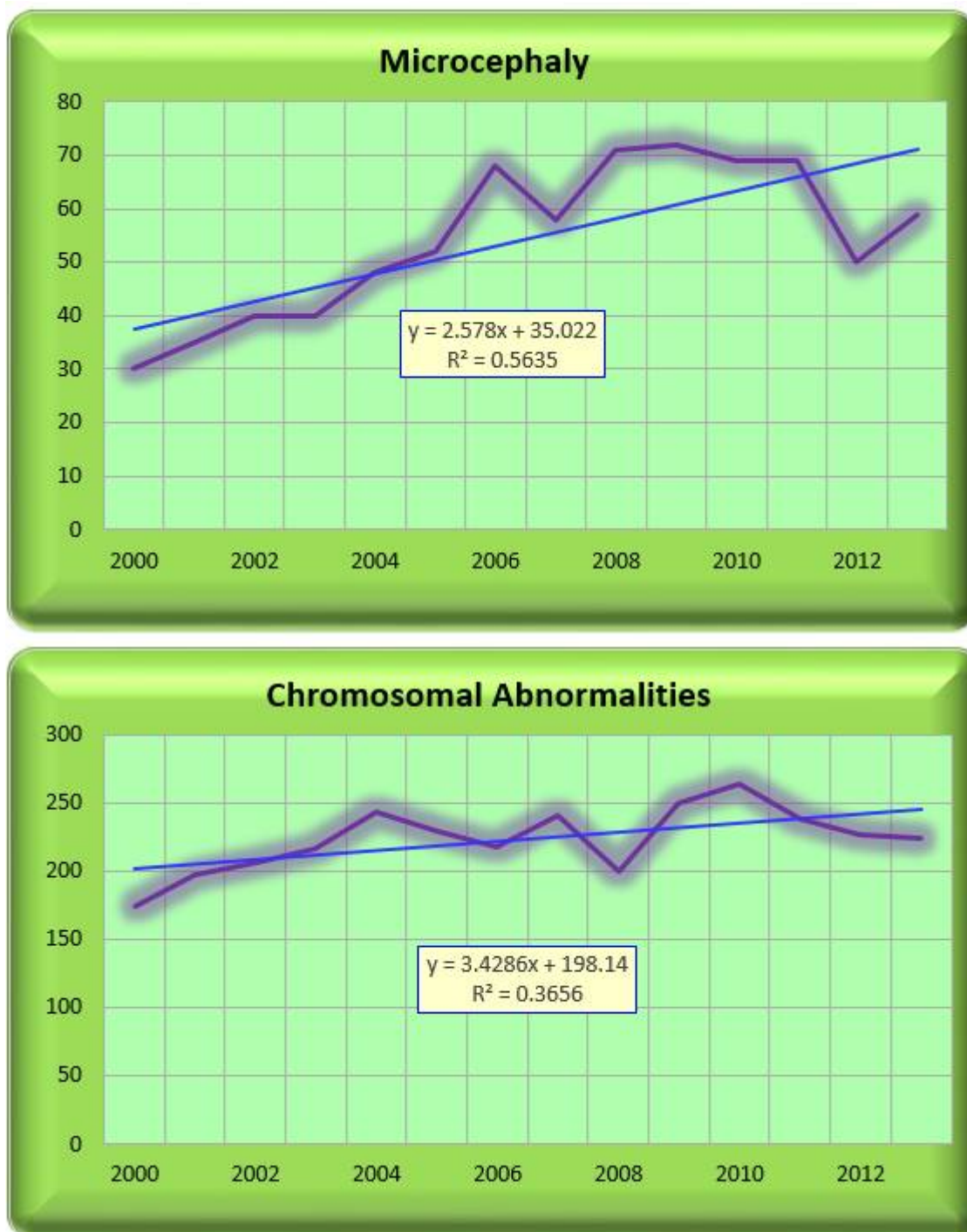
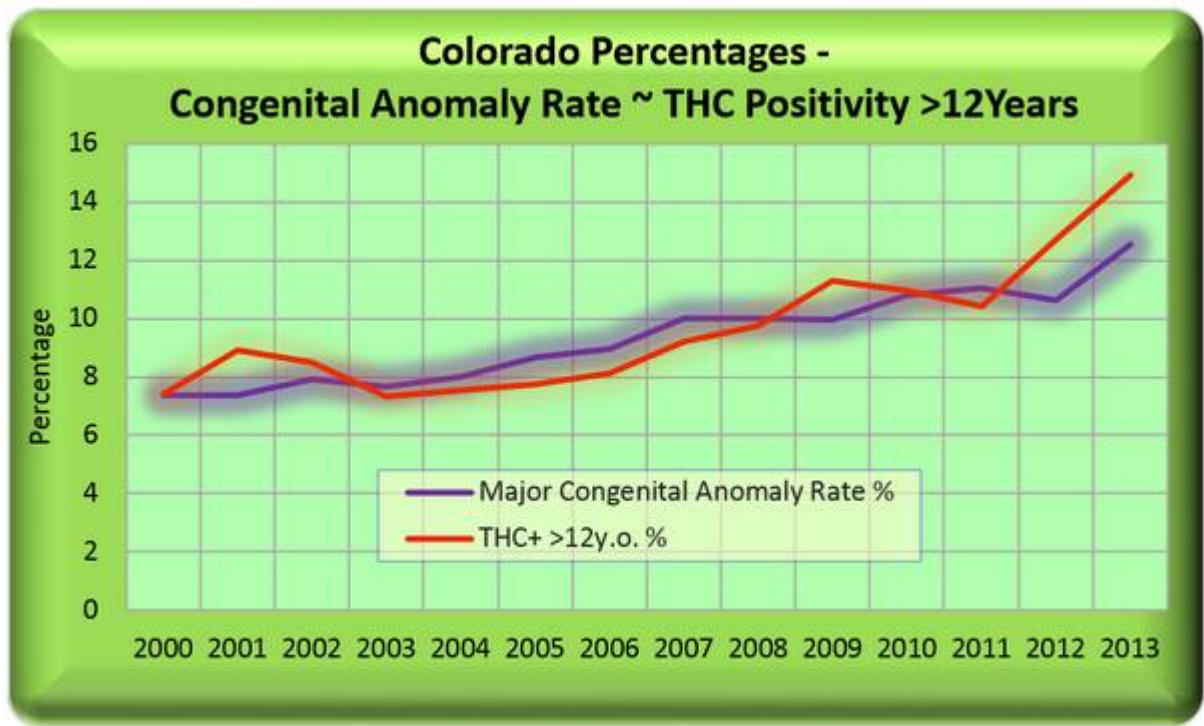


**Figure 8**



## References

1. 1 Bartova, A. & Birmingham, M. K. Effect of delta9-tetrahydrocannabinol on mitochondrial NADH-oxidase activity. *J Biol Chem* **251**, 5002-5006 (1976).
2. 2 Benard, G. *et al.* Mitochondrial CB(1) receptors regulate neuronal energy metabolism. *Nat Neurosci* **15**, 558-564, doi:10.1038/nn.3053 (2012).
3. 3 Hebert-Chatelain, E. *et al.* A cannabinoid link between mitochondria and memory. *Nature* **539**, 555-559, doi:10.1038/nature20127 (2016).
4. 4 Hebert-Chatelain, E. *et al.* Cannabinoid control of brain bioenergetics: Exploring the subcellular localization of the CB1 receptor. *Mol Metab* **3**, 495-504, doi:10.1016/j.molmet.2014.03.007 (2014).
5. 5 Koch, M. *et al.* Hypothalamic POMC neurons promote cannabinoid-induced feeding. *Nature* **519**, 45-50, doi:10.1038/nature14260 (2015).
6. 6 Mahoney, J. M. & Harris, R. A. Effect of 9 -tetrahydrocannabinol on mitochondrial precesses. *Biochemical pharmacology* **21**, 1217-1226 (1972).
7. 7 Wolff, V. *et al.* Tetrahydrocannabinol induces brain mitochondrial respiratory chain dysfunction and increases oxidative stress: a potential mechanism involved in cannabis-related stroke. *Biomed Res Int* **2015**, 323706, doi:10.1155/2015/323706 (2015).
8. 8 Costa, B. & Colleoni, M. Changes in rat brain energetic metabolism after exposure to anandamide or Delta(9)-tetrahydrocannabinol. *European journal of pharmacology* **395**, 1-7 (2000).
9. 9 Sarafian, T. A. *et al.* Inhaled marijuana smoke disrupts mitochondrial energetics in pulmonary epithelial cells in vivo. *American journal of physiology* **290**, L1202-1209 (2006).
10. 10 Sarafian, T. A., Kouyoumjian, S., Khoshaghideh, F., Tashkin, D. P. & Roth, M. D. Delta 9-tetrahydrocannabinol disrupts mitochondrial function and cell energetics. *American journal of physiology* **284**, L298-306, doi:10.1152/ajplung.00157.2002 (2003).
11. 11 Sarafian, T. A., Magallanes, J. A., Shau, H., Tashkin, D. & Roth, M. D. Oxidative stress produced by marijuana smoke. An adverse effect enhanced by cannabinoids. *American journal of respiratory cell and molecular biology* **20**, 1286-1293 (1999).
12. 12 Tashkin, D. P., Baldwin, G. C., Sarafian, T., Dubinett, S. & Roth, M. D. Respiratory and immunologic consequences of marijuana smoking. *Journal of clinical pharmacology* **42**, 71S-81S (2002).
13. 13 Chiu, P., Karler, R., Craven, C., Olsen, D. M. & Turkanis, S. A. The influence of delta9-tetrahydrocannabinol, cannabiniol and cannabidiol on tissue oxygen consumption. *Research communications in chemical pathology and pharmacology* **12**, 267-286 (1975).
14. 14 Harkany, T. & Horvath, T. L. (S)Pot on Mitochondria: Cannabinoids Disrupt Cellular Respiration to Limit Neuronal Activity. *Cell Metab* **25**, 8-10, doi:10.1016/j.cmet.2016.12.020 (2017).
15. 15 Bino, T., Chari-Bitron, A. & Shahar, A. Biochemical effects and morphological changes in rat liver mitochondria exposed to 1 -tetrahydrocannabinol. *Biochim Biophys Acta* **288**, 195-202 (1972).
16. 16 Chari-Briton, A. Proceedings: Swelling of rat liver mitochondria induced by delta1-tetrahydrocannabinol. *Isr J Med Sci* **11**, 1189 (1975).
17. 17 Fisar, Z., Singh, N. & Hroudova, J. Cannabinoid-induced changes in respiration of brain mitochondria. *Toxicology letters* **231**, 62-71, doi:10.1016/j.toxlet.2014.09.002 (2014).
18. 18 Laprairie, R. B., Bagher, A. M., Kelly, M. E., Dupre, D. J. & Denovan-Wright, E. M. Type 1 cannabinoid receptor ligands display functional selectivity in a cell culture model of striatal medium spiny projection neurons. *J Biol Chem* **289**, 24845-24862, doi:10.1074/jbc.M114.557025 (2014).
19. 19 Morimoto, S. *et al.* Identification and characterization of cannabinoids that induce cell death through mitochondrial permeability transition in Cannabis leaf cells. *J Biol Chem* **282**, 20739-20751, doi:10.1074/jbc.M700133200 (2007).
20. 20 Rossato, M., Ion Popa, F., Ferigo, M., Clari, G. & Foresta, C. Human sperm express cannabinoid receptor Cbl, the activation of which inhibits motility, acrosome reaction, and mitochondrial function. *The Journal of clinical endocrinology and metabolism* **90**, 984-991, doi:10.1210/jc.2004-1287 (2005).
21. 21 Rossato, M., Pagano, C. & Vettor, R. The cannabinoid system and male reproductive functions. *Journal of neuroendocrinology* **20 Suppl 1**, 90-93 (2008).
22. 22 Shrivastava, A., Kuzontkoski, P. M., Groopman, J. E. & Prasad, A. Cannabidiol induces programmed cell death in breast cancer cells by coordinating the cross-talk between apoptosis and autophagy. *Mol Cancer Ther* **10**, 1161-1172, doi:10.1158/1535-7163.MCT-10-1100 (2011).
23. 23 Young-Wolff, K. C., Tucker, L., Alexeeff, S. & et al. Trends in self-reported and biochemically tested marijuana use among pregnant females in california from 2009-2016. *JAMA* **318**, 2490-2491, doi:10.1001/jama.2017.17225 (2017).

24. 24 Zaccagnino, P. *et al.* The endocannabinoid 2-arachidonoylglycerol decreases calcium induced cytochrome c release from liver mitochondria. *J Bioenerg Biomembr* **44**, 273-280, doi:10.1007/s10863-012-9431-6 (2012).
25. 25 Pacher, P., Steffens, S., Hasko, G., Schindler, T. H. & Kunos, G. Cardiovascular effects of marijuana and synthetic cannabinoids: the good, the bad, and the ugly. *Nat Rev Cardiol* **15**, 151-166, doi:10.1038/nrcardio.2017.130 (2018).
26. 26 DeFilippis, E. M. *et al.* Cocaine and Marijuana Use among Young Adults Presenting with Myocardial Infarction: The Partners YOUNG-MI Registry. *Journal of the American College of Cardiology*, doi:10.1016/j.jacc.2018.02.047 (2018).
27. 27 Desai, R. *et al.* Recreational Marijuana Use and Acute Myocardial Infarction: Insights from Nationwide Inpatient Sample in the United States. *Cureus* **9**, e1816, doi:10.7759/cureus.1816 (2017).
28. 28 Frost, L., Mostofsky, E., Rosenbloom, J. I., Mukamal, K. J. & Mittleman, M. A. Marijuana use and long-term mortality among survivors of acute myocardial infarction. *Am Heart J* **165**, 170-175, doi:10.1016/j.ahj.2012.11.007 (2013).
29. 29 Gunawardena, M. D., Rajapakse, S., Herath, J. & Amarasekera, N. Myocardial infarction following cannabis induced coronary vasospasm. *BMJ Case Rep* **2014**, doi:10.1136/bcr-2014-207020 (2014).
30. 30 Alia-Klein, N. *et al.* What is in a word? No versus Yes differentially engage the lateral orbitofrontal cortex. *Emotion* **7**, 649-659 (2007).
31. 31 Barbers, R. G., Evans, M. J., Gong, H., Jr. & Tashkin, D. P. Enhanced alveolar monocyte phagocyte (macrophage) proliferation in tobacco and marijuana smokers. *The American review of respiratory disease* **143**, 1092-1095 (1991).
32. 32 Beck, J. D. *et al.* Periodontal disease and coronary heart disease: a reappraisal of the exposure. *Circulation* **112**, 19-24 (2005).
33. 33 Beyond Blue. *Beyond Blue*, <<http://www.beyondblue.org.au/>> (2006).
34. 34 Blasco, M. Profile. Maria Blasco. Interview by Laura Spinney. *Trends Cell Biol* **12**, 489 (2002).
35. 35 Blasco, M., Losada, J., Fernandez Val, J. F. & Sarria, R. [Transitional bladder carcinoma TaG1: role of the EGFr tyrosin kinase activation in the cellular proliferation]. *Med Clin (Barc)* **121**, 641-644 (2003).
36. 36 Bourque, L. B., Tashkin, D. P., Clark, V. A. & Schuler, R. Demographic and health characteristics of heavy marijuana smokers in Los Angeles County. *The International journal of the addictions* **26**, 739-755 (1991).
37. 37 Chen, H., Campisi, J. & Padmanabhan, R. SV40 large T antigen transactivates the human cdc2 promoter by inducing a CCAAT box binding factor. *J Biol Chem* **271**, 13959-13967 (1996).
38. 38 Ch'ng, C. W. *et al.* Drug use in motor vehicle drivers presenting to an Australian, adult major trauma centre. *Emerg Med Australas* **19**, 359-365 (2007).
39. 39 Desvarieux, M. *et al.* Periodontal microbiota and carotid intima-media thickness: the Oral Infections and Vascular Disease Epidemiology Study (INVEST). *Circulation* **111**, 576-582 (2005).
40. 40 Fosados, R., Evans, E. & Hser, Y. I. Ethnic differences in utilization of drug treatment services and outcomes among Proposition 36 offenders in California. *J Subst Abuse Treat* (2007).
41. 41 Fowler, J. S. *et al.* Comparison of Brain Glucose Metabolism and Monoamine Oxidase B (MAO B) in Traumatic Brain Injury. *Clin Positron Imaging* **2**, 71-79 (1999).
42. 42 Gatley, S. J. *et al.* PET imaging in clinical drug abuse research. *Curr Pharm Des* **11**, 3203-3219 (2005).
43. 43 Gonzalez, S. *et al.* Behavioral and molecular changes elicited by acute administration of SR141716 to Delta9-tetrahydrocannabinol-tolerant rats: an experimental model of cannabinoid abstinence. *Drug Alcohol Depend* **74**, 159-170 (2004).
44. 44 Grella, C. E., Hser, Y. I. & Hsieh, S. C. Predictors of drug treatment re-entry following relapse to cocaine use in DATOS. *J Subst Abuse Treat* **25**, 145-154 (2003).
45. 45 Grella, C. E., Joshi, V. & Hser, Y. I. Program variation in treatment outcomes among women in residential drug treatment. *Evaluation review* **24**, 364-383 (2000).
46. 46 Harriest, A. *et al.* Alteration of hippocampal cell proliferation in mice lacking the beta 2 subunit of the neuronal nicotinic acetylcholine receptor. *Synapse* **54**, 200-206 (2004).
47. 47 Hess, G. D. & Zagon, I. S. Endogenous opioid systems and neural development: ultrastructural studies in the cerebellar cortex of infant and weanling rats. *Brain research bulletin* **20**, 473-478 (1988).
48. 48 Hosokawa, M. A higher oxidative status accelerates senescence and aggravates age-dependent disorders in SAMP strains of mice. *Mech Ageing Dev* **123**, 1553-1561 (2002).
49. 49 Hser, Y. I., Hoffman, V., Grella, C. E. & Anglin, M. D. A 33-year follow-up of narcotics addicts. *Arch Gen Psychiatry* **58**, 503-508 (2001).
50. 50 Isayama, T., McLaughlin, P. J. & Zagon, I. S. Endogenous opioids regulate cell proliferation in the retina of developing rat. *Brain Res* **544**, 79-85 (1991).

51. 51 Jones, R. T. Cardiovascular system effects of marijuana. *Journal of clinical pharmacology* **42**, 58S-63S (2002).
52. 52 Kalivas, P. W., Volkow, N. & Seamans, J. Unmanageable motivation in addiction: a pathology in prefrontal-accumbens glutamate transmission. *Neuron* **45**, 647-650 (2005).
53. 53 Kay, M. M., Hughes, J., Zagon, I. & Lin, F. B. Brain membrane protein band 3 performs the same functions as erythrocyte band 3. *Proc Natl Acad Sci U S A* **88**, 2778-2782 (1991).
54. 54 Klatsky, A. L., Armstrong, M. A., Friedman, G. D. & Sidney, S. Alcohol drinking and risk of hemorrhagic stroke. *Neuroepidemiology* **21**, 115-122 (2002).
55. 55 Lambrecht, G. L., Malbrain, M. L., Coremans, P., Verbist, L. & Verhaegen, H. Acute renal infarction and heavy marijuana smoking. *Nephron* **70**, 494-496 (1995).
56. 56 Melbourne Division of General Practice. *Relationships between Mental Health, personal circumstances and drug use in young Victorian Australians*. (AGPS, 2002).
57. 57 Miller, W. E., Spiekerman, R. E. & Hepper, N. G. Pneumomediastinum resulting from performing Valsalva maneuvers during marihuana smoking. *Chest* **62**, 233-234 (1972).
58. 58 Niv, N., Wong, E. C. & Hser, Y. I. Asian Americans in community-based substance abuse treatment: Service needs, utilization, and outcomes. *J Subst Abuse Treat* **33**, 313-319 (2007).
59. 59 Okereke, U. N., Weber, B. E. & Israel, R. H. Spontaneous pneumomediastinum in an 18-year-old black Sudanese high school student. *Journal of the National Medical Association* **91**, 357-359 (1999).
60. 60 Ortar, G. *et al.* Carbamoyl tetrazoles as inhibitors of endocannabinoid inactivation: A critical revisitation. *Eur J Med Chem* (2007).
61. 61 O'Sullivan, S. E., Sun, Y., Bennett, A. J., Randall, M. D. & Kendall, D. A. Time-dependent vascular actions of cannabidiol in the rat aorta. *European journal of pharmacology* **612**, 61-68, doi:10.1016/j.ejphar.2009.03.010 (2009).
62. 62 Rock, R. B. *et al.* WIN55,212-2-mediated inhibition of HIV-1 expression in microglial cells: involvement of cannabinoid receptors. *J Neuroimmune Pharmacol* **2**, 178-183 (2007).
63. 63 Ruiz Villaverde, R., Blasco Melguizo, J., Linares Solano, J. & Serrano Ortega, S. Lichen planus-like eruption due to enalapril. *J Eur Acad Dermatol Venereol* **17**, 612-614 (2003).
64. 64 Sidney, S. Cardiovascular consequences of marijuana use. *Journal of clinical pharmacology* **42**, 64S-70S (2002).
65. 65 Starowicz, K. *et al.* Tonic endovanilloid facilitation of glutamate release in brainstem descending antinociceptive pathways. *J Neurosci* **27**, 13739-13749 (2007).
66. 66 Steingrimsdottir, E., Copeland, N. G. & Jenkins, N. A. Melanocyte stem cell maintenance and hair graying. *Cell* **121**, 9-12 (2005).
67. 67 Volkow, N. D. Hispanic drug abuse research: challenges and opportunities. *Drug Alcohol Depend* **84 Suppl 1**, S4-7 (2006).
68. 68 Wang, X. *et al.* One Minute of Marijuana Secondhand Smoke Exposure Substantially Impairs Vascular Endothelial Function. *J Am Heart Assoc* **5**, doi:10.1161/JAHA.116.003858 (2016).
69. 69 Wolff, V. *et al.* Cannabis-related stroke: myth or reality? *Stroke; a journal of cerebral circulation* **44**, 558-563, doi:10.1161/STROKEAHA.112.671347 (2013).
70. 70 Zagon, I. S., McLaughlin, P. J., Goodman, S. R. & Rhodes, R. E. Opioid receptors and endogenous opioids in diverse human and animal cancers. *Journal of the National Cancer Institute* **79**, 1059-1065 (1987).
71. 71 Duerr, G. D. *et al.* Impaired border zone formation and adverse remodeling after reperfused myocardial infarction in cannabinoid CB2 receptor deficient mice. *Life Sci* **138**, 8-17, doi:10.1016/j.lfs.2014.11.005 (2015).
72. 72 Ewing, C. K., Loffredo, C. A. & Beaty, T. H. Paternal risk factors for isolated membranous ventricular septal defects. *Am J Med Genet* **71**, 42-46 (1997).
73. 73 Florida High Intensity Drug Trafficking Area. Vol. 1 (ed Funded by the Office of Drug Control Policy from the White House) 1-50; [https://www.cannabisskunksense.co.uk/uploads/site-files/USA\\_Florida\\_2018-2003-2002\\_Florida\\_Medical\\_Marijuana\\_Impact\\_Report\\_data\\_\(2011\).pdf](https://www.cannabisskunksense.co.uk/uploads/site-files/USA_Florida_2018-2003-2002_Florida_Medical_Marijuana_Impact_Report_data_(2011).pdf) (Florida High Intensity Drug Trafficking Area, Florida, USA, 2018).
74. 74 Gonzalez, C. *et al.* Cannabinoid/agonist WIN 55,212-2 reduces cardiac ischaemia-reperfusion injury in Zucker diabetic fatty rats: role of CB2 receptors and iNOS/eNOS. *Diabetes Metab Res Rev* **27**, 331-340, doi:10.1002/dmrr.1176 (2011).
75. 75 Jenkins, K. J. *et al.* Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. *Circulation* **115**, 2995-3014, doi:10.1161/CIRCULATIONAHA.106.183216 (2007).

76. 76 Oregon - Idaho High Intensity Drug Trafficking Area Program. Vol. 1 (ed Oregon - Idaho High Intensity Drug Trafficking Area Program) 1-75 (Oregon - Idaho High Intensity Drug Trafficking Area Program, Oregon, 2018).
77. 77 Slavic, S. *et al.* Cannabinoid receptor 1 inhibition improves cardiac function and remodelling after myocardial infarction and in experimental metabolic syndrome. *J Mol Med (Berl)* **91**, 811-823, doi:10.1007/s00109-013-1034-0 (2013).
78. 78 Steffens, S. & Pacher, P. Targeting cannabinoid receptor CB(2) in cardiovascular disorders: promises and controversies. *Br J Pharmacol* **167**, 313-323, doi:10.1111/j.1476-5381.2012.02042.x (2012).
79. 79 Ugdyzhekova, D. S. *et al.* Activation of cannabinoid receptors decreases the area of ischemic myocardial necrosis. *Bull Exp Biol Med* **133**, 125-126 (2002).
80. 80 Wang, Y. *et al.* Effects of cannabinoid receptor type 2 on endogenous myocardial regeneration by activating cardiac progenitor cells in mouse infarcted heart. *Sci China Life Sci* **57**, 201-208, doi:10.1007/s11427-013-4604-z (2014).
81. 81 Wilson, P. D., Loffredo, C. A., Correa-Villasenor, A. & Ferencz, C. Attributable fraction for cardiac malformations. *Am J Epidemiol* **148**, 414-423 (1998).
82. 82 Baranchuk, A., Johri, A. M., Simpson, C. S., Methot, M. & Redfearn, D. P. Ventricular fibrillation triggered by marijuana use in a patient with ischemic cardiomyopathy: a case report. *Cases J* **1**, 373, doi:10.1186/1757-1626-1-373 (2008).
83. 83 Casier, I., Vanduyhoven, P., Haine, S., Vrints, C. & Jorens, P. G. Is recent cannabis use associated with acute coronary syndromes? An illustrative case series. *Acta Cardiol* **69**, 131-136, doi:10.2143/AC.69.2.3017293 (2014).
84. 84 Diffley, M., Armenian, P., Gerona, R., Reinhartz, O. & Avasarala, K. Catecholaminergic polymorphic ventricular tachycardia found in an adolescent after a methylenedioxymethamphetamine and marijuana-induced cardiac arrest. *Crit Care Med* **40**, 2223-2226, doi:10.1097/CCM.0b013e318250a870 (2012).
85. 85 Fisher, B. A., Ghuran, A., Vadamalai, V. & Antonios, T. F. Cardiovascular complications induced by cannabis smoking: a case report and review of the literature. *Emerg Med J* **22**, 679-680, doi:10.1136/emj.2004.014969 (2005).
86. 86 Heath, T. S., Burroughs, Z., Thompson, A. J. & Tecklenburg, F. W. Acute intoxication caused by a synthetic cannabinoid in two adolescents. *J Pediatr Pharmacol Ther* **17**, 177-181, doi:10.5863/1551-6776-17.2.177 (2012).
87. 87 Korantzopoulos, P. Marijuana smoking is associated with atrial fibrillation. *The American journal of cardiology* **113**, 1085-1086, doi:10.1016/j.amjcard.2014.01.001 (2014).
88. 88 Korantzopoulos, P., Liu, T., Papaioannides, D., Li, G. & Goudevenos, J. A. Atrial fibrillation and marijuana smoking. *International journal of clinical practice* **62**, 308-313, doi:10.1111/j.1742-1241.2007.01505.x (2008).
89. 89 Kosior, D. A., Filipiak, K. J., Stolarz, P. & Opolski, G. Paroxysmal atrial fibrillation in a young female patient following marijuana intoxication--a case report of possible association. *Med Sci Monit* **6**, 386-389 (2000).
90. 90 Menahem, S. Cardiac asystole following cannabis (marijuana) usage--additional mechanism for sudden death? *Forensic science international* **233**, e3-5, doi:10.1016/j.forsciint.2013.10.007 (2013).
91. 91 Rezkalla, S. H., Sharma, P. & Kloner, R. A. Coronary no-flow and ventricular tachycardia associated with habitual marijuana use. *Annals of emergency medicine* **42**, 365-369, doi:10.1067/mem.2003.297 (2003).
92. 92 Barana, A. *et al.* Endocannabinoids and cannabinoid analogues block cardiac hKv1.5 channels in a cannabinoid receptor-independent manner. *Cardiovasc Res* **85**, 56-67, doi:10.1093/cvr/cvp284 (2010).
93. 93 Finsterer, J., Christian, P. & Wolfgang, K. Occipital stroke shortly after cannabis consumption. *Clin Neurol Neurosurg* **106**, 305-308, doi:10.1016/j.clineuro.2004.02.001 (2004).
94. 94 Herning, R. I., Better, W. & Cadet, J. L. EEG of chronic marijuana users during abstinence: relationship to years of marijuana use, cerebral blood flow and thyroid function. *Clin Neurophysiol* **119**, 321-331, doi:10.1016/j.clinph.2007.09.140 (2008).
95. 95 Inal, T. *et al.* Acute temporal lobe infarction in a young patient associated with marijuana abuse: An unusual cause of stroke. *World J Emerg Med* **5**, 72-74, doi:10.5847/wjem.j.1920-8642.2014.01.013 (2014).
96. 96 Mathew, R. J., Wilson, W. H., Humphreys, D., Lowe, J. V. & Wiethe, K. E. Middle cerebral artery velocity during upright posture after marijuana smoking. *Acta psychiatrica Scandinavica* **86**, 173-178 (1992).

97. 97 Wagner, J. A., Jarai, Z., Batkai, S. & Kunos, G. Hemodynamic effects of cannabinoids: coronary and cerebral vasodilation mediated by cannabinoid CB(1) receptors. *European journal of pharmacology* **423**, 203-210 (2001).
98. 98 Wolff, V. *et al.* High frequency of intracranial arterial stenosis and cannabis use in ischaemic stroke in the young. *Cerebrovascular diseases (Basel, Switzerland)* **37**, 438-443, doi:10.1159/000363618 (2014).
99. 99 Disdier, P. *et al.* Cannabis arteritis revisited--ten new case reports. *Angiology* **52**, 1-5 (2001).
100. 100 Ducasse, E. *et al.* Popliteal artery entrapment associated with cannabis arteritis. *Eur J Vasc Endovasc Surg* **27**, 327-332, doi:10.1016/S1533 (2004).
101. 101 Jouanous, E., Lapeyre-Mestre, M., Micallef, J., French Association of the Regional, A. & Dependence Monitoring Centres Working Group on Cannabis, C. Cannabis use: signal of increasing risk of serious cardiovascular disorders. *J Am Heart Assoc* **3**, e000638, doi:10.1161/JAHA.113.000638 (2014).
102. 102 Kogan, N. M. *et al.* A cannabinoid quinone inhibits angiogenesis by targeting vascular endothelial cells. *Mol Pharmacol* **70**, 51-59, doi:10.1124/mol.105.021089 (2006).
103. 103 Molica, F. *et al.* Endogenous cannabinoid receptor CB1 activation promotes vascular smooth-muscle cell proliferation and neointima formation. *J Lipid Res* **54**, 1360-1368, doi:10.1194/jlr.M035147 (2013).
104. 104 Netherland, C. D., Pickle, T. G., Bales, A. & Thewke, D. P. Cannabinoid receptor type 2 (CB2) deficiency alters atherosclerotic lesion formation in hyperlipidemic Ldlr-null mice. *Atherosclerosis* **213**, 102-108, doi:10.1016/j.atherosclerosis.2010.07.060 (2010).
105. 105 Schneider, H. J., Jha, S. & Burnand, K. G. Progressive arteritis associated with cannabis use. *Eur J Vasc Endovasc Surg* **18**, 366-367, doi:10.1053/ejvs.1999.0859 (1999).
106. 106 Stanley, C. & O'Sullivan, S. E. Vascular targets for cannabinoids: animal and human studies. *Br J Pharmacol* **171**, 1361-1378, doi:10.1111/bph.12560 (2014).
107. 107 Reece A.S., Norman, A. & Hulse G.K. Cannabis Exposure as an Interactive Cardiovascular Risk Factor and Accelerant of Organismal Ageing – A Longitudinal Study. *BMJ - Open In Press*, doi: <http://dx.doi.org/10.1136/bmjopen-2016-011891> (2016).
108. 108 Forrester, M. B. & Merz, R. D. Risk of selected birth defects with prenatal illicit drug use, Hawaii, 1986-2002. *Journal of toxicology and environmental health* **70**, 7-18 (2007).
109. 109 David, A. L. *et al.* A case-control study of maternal periconceptual and pregnancy recreational drug use and fetal malformation using hair analysis. *PLoS One* **9**, e111038, doi:10.1371/journal.pone.0111038 (2014).
110. 110 Draper, E. S. *et al.* Recreational drug use: a major risk factor for gastroschisis? *Am J Epidemiol* **167**, 485-491, doi:10.1093/aje/kwm335 (2008).
111. 111 Skarsgard, E. D. *et al.* Maternal risk factors for gastroschisis in Canada. *Birth Defects Res A Clin Mol Teratol* **103**, 111-118, doi:10.1002/bdra.23349 (2015).
112. 112 Torfs, C. P., Velie, E. M., Oechsli, F. W., Bateson, T. F. & Curry, C. J. A population-based study of gastroschisis: demographic, pregnancy, and lifestyle risk factors. *Teratology* **50**, 44-53, doi:10.1002/tera.1420500107 (1994).
113. 113 van Gelder, M. M. *et al.* Maternal periconceptual illicit drug use and the risk of congenital malformations. *Epidemiology* **20**, 60-66, doi:10.1097/EDE.0b013e31818e5930 (2009).
114. 114 Werler, M. M., Sheehan, J. E. & Mitchell, A. A. Association of vasoconstrictive exposures with risks of gastroschisis and small intestinal atresia. *Epidemiology* **14**, 349-354 (2003).
115. 115 Bonawitz, N. D., Clayton, D. A. & Shadel, G. S. Initiation and beyond: multiple functions of the human mitochondrial transcription machinery. *Molecular cell* **24**, 813-825, doi:10.1016/j.molcel.2006.11.024 (2006).
116. 116 Dellinger, R. W. *et al.* Repeat dose NRPT (nicotinamide riboside and pterostilbene) increases NAD(+) levels in humans safely and sustainably: a randomized, double-blind, placebo-controlled study. *NPJ Aging Mech Dis* **3**, 17, doi:10.1038/s41514-017-0016-9 (2017).
117. 117 DiNieri, J. A. *et al.* Maternal cannabis use alters ventral striatal dopamine D2 gene regulation in the offspring. *Biol Psychiatry* **70**, 763-769, doi:10.1016/j.biopsych.2011.06.027 (2011).
118. 118 Li, J. *et al.* A conserved NAD(+) binding pocket that regulates protein-protein interactions during aging. *Science* **355**, 1312-1317, doi:10.1126/science.aad8242 (2017).
119. 119 Mohnle, P. *et al.* MicroRNA-665 is involved in the regulation of the expression of the cardioprotective cannabinoid receptor CB2 in patients with severe heart failure. *Biochem Biophys Res Commun* **451**, 516-521, doi:10.1016/j.bbrc.2014.08.008 (2014).
120. 120 Szutorisz, H. *et al.* Parental THC exposure leads to compulsive heroin-seeking and altered striatal synaptic plasticity in the subsequent generation. *Neuropsychopharmacology* **39**, 1315-1323, doi:10.1038/npp.2013.352 (2014).

121. 121 Vargish, G. A. *et al.* Persistent inhibitory circuit defects and disrupted social behaviour following in utero exogenous cannabinoid exposure. *Mol Psychiatry* **22**, 56-67, doi:10.1038/mp.2016.17 (2017).
122. 122 Watson, C. T. *et al.* Genome-Wide DNA Methylation Profiling Reveals Epigenetic Changes in the Rat Nucleus Accumbens Associated With Cross-Generational Effects of Adolescent THC Exposure. *Neuropsychopharmacology*, doi:10.1038/npp.2015.155 (2015).
123. 123 Zumbun, E. E., Sido, J. M., Nagarkatti, P. S. & Nagarkatti, M. Epigenetic Regulation of Immunological Alterations Following Prenatal Exposure to Marijuana Cannabinoids and its Long Term Consequences in Offspring. *J Neuroimmune Pharmacol* **10**, 245-254, doi:10.1007/s11481-015-9586-0 (2015).
124. 124 Aoyama, H. *et al.* Development of tubulin-polymerization inhibitors based on the thalidomide skeleton. *Chem Pharm Bull (Tokyo)* **55**, 944-949 (2007).
125. 125 Iguchi, T. *et al.* Novel tubulin-polymerization inhibitor derived from thalidomide directly induces apoptosis in human multiple myeloma cells: possible anti-myeloma mechanism of thalidomide. *Int J Mol Med* **21**, 163-168 (2008).
126. 126 Kizaki, M. & Hashimoto, Y. New tubulin polymerization inhibitor derived from thalidomide: implications for anti-myeloma therapy. *Current medicinal chemistry* **15**, 754-765 (2008).
127. 127 Bindukumar, B. *et al.* Genomic and proteomic analysis of the effects of cannabinoids on normal human astrocytes. *Brain Res* **1191**, 1-11, doi:10.1016/j.brainres.2007.10.062 (2008).
128. 128 Quinn, H. R. *et al.* Adolescent rats find repeated Delta(9)-THC less aversive than adult rats but display greater residual cognitive deficits and changes in hippocampal protein expression following exposure. *Neuropsychopharmacology* **33**, 1113-1126, doi:10.1038/sj.npp.1301475 (2008).
129. 129 Reece, A. S. & Hulse, G. K. Chromothripsis and epigenomics complete causality criteria for cannabis- and addiction-connected carcinogenicity, congenital toxicity and heritable genotoxicity. *Mutat Res* **789**, 15-25, doi:10.1016/j.mrfmmm.2016.05.002 (2016).
130. 130 Rubino, T. *et al.* The depressive phenotype induced in adult female rats by adolescent exposure to THC is associated with cognitive impairment and altered neuroplasticity in the prefrontal cortex. *Neurotox Res* **15**, 291-302, doi:10.1007/s12640-009-9031-3 (2009).
131. 131 Wang, J., Yuan, W. & Li, M. D. Genes and pathways co-associated with the exposure to multiple drugs of abuse, including alcohol, amphetamine/methamphetamine, cocaine, marijuana, morphine, and/or nicotine: a review of proteomics analyses. *Molecular neurobiology* **44**, 269-286, doi:10.1007/s12035-011-8202-4 (2011).
132. 132 Vela, G. *et al.* Maternal exposure to delta9-tetrahydrocannabinol facilitates morphine self-administration behavior and changes regional binding to central mu opioid receptors in adult offspring female rats. *Brain Res* **807**, 101-109 (1998).
133. 133 Bakhoun, S. F. *et al.* Chromosomal instability drives metastasis through a cytosolic DNA response. *Nature* **553**, 467-472, doi:10.1038/nature25432 (2018).
134. 134 Bileck, A. *et al.* Impact of a synthetic cannabinoid (CP-47,497-C8) on protein expression in human cells: evidence for induction of inflammation and DNA damage. *Archives of toxicology* **90**, 1369-1382, doi:10.1007/s00204-015-1569-7 (2016).
135. 135 Ferk, F. *et al.* Genotoxic properties of XLR-11, a widely consumed synthetic cannabinoid, and of the benzoyl indole RCS-4. *Archives of toxicology* **90**, 3111-3123, doi:10.1007/s00204-016-1664-4 (2016).
136. 136 Koller, V. J. *et al.* Investigation of the in vitro toxicological properties of the synthetic cannabimimetic drug CP-47,497-C8. *Toxicology and applied pharmacology* **277**, 164-171, doi:10.1016/j.taap.2014.03.014 (2014).
137. 137 Koller, V. J. *et al.* Genotoxic properties of representatives of alkylindazoles and aminoalkyl-indoles which are consumed as synthetic cannabinoids. *Food Chem Toxicol* **80**, 130-136, doi:10.1016/j.fct.2015.03.004 (2015).
138. 138 Mukudai, Y. *et al.* Tumor protein D54 is a negative regulator of extracellular matrix-dependent migration and attachment in oral squamous cell carcinoma-derived cell lines. *Cell Oncol (Dordr)* **36**, 233-245, doi:10.1007/s13402-013-0131-y (2013).
139. 139 Parolini, M. & Binelli, A. Oxidative and genetic responses induced by Delta-9-tetrahydrocannabinol (Delta-9-THC) to Dreissena polymorpha. *Sci Total Environ* **468-469**, 68-76, doi:10.1016/j.scitotenv.2013.08.024 (2014).
140. 140 Parolini, M., Castiglioni, S., Magni, S., Della Torre, C. & Binelli, A. Increase in cannabis use may indirectly affect the health status of a freshwater species. *Environ Toxicol Chem* **36**, 472-479, doi:10.1002/etc.3575 (2017).
141. 141 Piatti, E., Rizzi, R., Re, F. & Chiesara, E. Genotoxicity of heroin and cannabinoids in humans. *Pharmacol Res* **21 Suppl 1**, 59-60 (1989).

142. 142 Van Went, G. F. Mutagenicity testing of 3 hallucinogens: LSD, psilocybin and delta 9-THC, using the micronucleus test. *Experientia* **34**, 324-325 (1978).
143. 143 Gamba, B. F., Richieri-Costa, A., Costa, S., Rosenberg, C. & Ribeiro-Bicudo, L. A. Chromothripsis with at least 12 breaks at 1p36.33-p35.3 in a boy with multiple congenital anomalies. *Mol Genet Genomics*, doi:10.1007/s00438-015-1072-0 (2015).
144. 144 Ivkov, R. & Bunz, F. Pathways to chromothripsis. *Cell Cycle*, 0, doi:10.1080/15384101.2015.1068483 (2015).
145. 145 Jones, M. J. & Jallepalli, P. V. Chromothripsis: chromosomes in crisis. *Developmental cell* **23**, 908-917, doi:10.1016/j.devcel.2012.10.010 (2012).
146. 146 Kinsella, M., Patel, A. & Bafna, V. The elusive evidence for chromothripsis. *Nucleic Acids Res* **42**, 8231-8242, doi:10.1093/nar/gku525 (2014).
147. 147 Kloosterman, W. P. & Cuppen, E. Chromothripsis in congenital disorders and cancer: similarities and differences. *Curr Opin Cell Biol* **25**, 341-348, doi:10.1016/j.ceb.2013.02.008 (2013).
148. 148 Kloosterman, W. P. *et al.* Chromothripsis as a mechanism driving complex de novo structural rearrangements in the germline. *Hum Mol Genet* **20**, 1916-1924, doi:10.1093/hmg/ddr073 (2011).
149. 149 Magrangeas, F., Avet-Loiseau, H., Munshi, N. C. & Minvielle, S. Chromothripsis identifies a rare and aggressive entity among newly diagnosed multiple myeloma patients. *Blood* **118**, 675-678, doi:10.1182/blood-2011-03-344069 (2011).
150. 150 Molenaar, J. J. *et al.* Sequencing of neuroblastoma identifies chromothripsis and defects in neuritogenesis genes. *Nature* **483**, 589-593, doi:10.1038/nature10910 (2012).
151. 151 Nagel, S. *et al.* Chromothripsis in Hodgkin lymphoma. *Genes Chromosomes Cancer* **52**, 741-747, doi:10.1002/gcc.22069 (2013).
152. 152 Pei, J., Jhanwar, S. C. & Testa, J. R. Chromothripsis in a Case of -Deficient Chronic Lymphocytic Leukemia. *Leuk Res Rep* **1**, 4-6, doi:10.1016/j.lrr.2012.09.001 (2012).
153. 153 Pellestor, F. Chromothripsis: how does such a catastrophic event impact human reproduction? *Hum Reprod* **29**, 388-393, doi:10.1093/humrep/deu003 (2014).
154. 154 Pellestor, F., Gatinois, V., Puechberty, J., Genevieve, D. & Lefort, G. Chromothripsis: potential origin in gametogenesis and preimplantation cell divisions. A review. *Fertil Steril* **102**, 1785-1796, doi:10.1016/j.fertnstert.2014.09.006 (2014).
155. 155 Przybytkowski, E. *et al.* Chromosome-breakage genomic instability and chromothripsis in breast cancer. *BMC Genomics* **15**, 579, doi:10.1186/1471-2164-15-579 (2014).
156. 156 Zhang, C. Z., Leibowitz, M. L. & Pellman, D. Chromothripsis and beyond: rapid genome evolution from complex chromosomal rearrangements. *Genes Dev* **27**, 2513-2530, doi:10.1101/gad.229559.113 (2013).
157. 157 Zhang, C. Z. *et al.* Chromothripsis from DNA damage in micronuclei. *Nature* **522**, 179-184, doi:10.1038/nature14493 (2015).
158. 158 Colorado: Department of Public Health and the Environment. Vol. 1 Birth Defect Data - Colorado Register of Congenital Surveillance Network 1 (ed Colorado: Department of Public Health and the Environment) <http://www.chd.dphe.state.co.us/cohid/> (Colorado: Department of Public Health and the Environment, Denver Colorado, USA, 2018).
159. 159 Volkow, N. D., Baler, R. D., Compton, W. M. & Weiss, S. R. B. Adverse Health Effects of Marijuana Use. *New England Journal of Medicine* **370**, 2219-2227, doi:doi:10.1056/NEJMra1402309 (2014).
160. 160 Cerda, M., Wall, M., Keyes, K. M., Galea, S. & Hasin, D. Medical marijuana laws in 50 states: investigating the relationship between state legalization of medical marijuana and marijuana use, abuse and dependence. *Drug Alcohol Depend* **120**, 22-27, doi:S0376-8716(11)00274-2 [pii] 10.1016/j.drugalcdep.2011.06.011 (2012).
161. 161 Young-Wolff, K. C. *et al.* Trends in Self-reported and Biochemically Tested Marijuana Use Among Pregnant Females in California From 2009-2016. *JAMA* **318**, 2490-2491, doi:10.1001/jama.2017.17225 (2017).
162. 162 Mon, M. J., Jansing, R. L., Doggett, S., Stein, J. L. & Stein, G. S. Influence of delta9-tetrahydrocannabinol on cell proliferation and macromolecular biosynthesis in human cells. *Biochemical pharmacology* **27**, 1759-1765 (1978).
163. 163 Tahir, S. K. & Zimmerman, A. M. Influence of marihuana on cellular structures and biochemical activities. *Pharmacology, biochemistry, and behavior* **40**, 617-623 (1991).
164. 164 Tahir, S. K., Trogadis, J. E., Stevens, J. K. & Zimmerman, A. M. Cytoskeletal organization following cannabinoid treatment in undifferentiated and differentiated PC12 cells. *Biochem Cell Biol* **70**, 1159-1173 (1992).
165. 165 Busch, F. W., Seid, D. A. & Wei, E. T. Mutagenic activity of marihuana smoke condensates. *Cancer Lett* **6**, 319-324 (1979).

167. 166 Zimmerman, A. M. & Raj, A. Y. Influence of cannabinoids on somatic cells in vivo. *Pharmacology* **21**, 277-287 (1980).
168. 167 Centre, N. D. i. *North Carolina Drug Threat Assessment, April 2003: Marijuana*, <<https://www.justice.gov/archive/ndic/pubs3/3690/marijuan.htm>> (2003).
169. 168 Nelson, J. S., Stebbins, R. C., Strassle, P. D. & Meyer, R. E. Geographic distribution of live births with tetralogy of Fallot in North Carolina 2003 to 2012. *Birth Defects Res A Clin Mol Teratol* **106**, 881-887, doi:10.1002/bdra.23566 (2016).
170. 169 Root, E. D., Meyer, R. E. & Emch, M. E. Evidence of localized clustering of gastroschisis births in North Carolina, 1999-2004. *Social science & medicine* (1982) **68**, 1361-1367, doi:10.1016/j.socscimed.2009.01.034 (2009).
171. 170 Campollo, O. *et al.* Factors associated with tobacco, alcohol, and other drug use among youth living in West Central Mexico. *World J Psychiatry* **8**, 33-42, doi:10.5498/wjp.v8.i1.33 (2018).
172. 171 Encuesta Nacional, De Consumo de Drogas & Alcohol y Tabaco 2016-2017. Vol. 1 / (ed Secretaria de Salud) 1-3 (Secretaria de Salud, Government of Mexico, Mexico City, 2017).
173. 172 Medina-Mora, M. E. *et al.* Prevalence and correlates of drug use disorders in Mexico, . *Rev Panam Salud Publica* **19**, 265-276 (2006).
174. 173 Secretaria de Salud, Gobierno Federal & Government of Mexico. Vol. 1 / (ed Secretaria de Salud Government of Mexico) 1-100 (Secretaria de Salud Government of Mexico, Mexico City, 2011).
175. 174 Secretaria de Salud & Government of Mexico. Vol. 1 (ed Secretaria de Salud) 1-173 (Secretaria de Salud, Government of Mexico,, Mexico City, 2008).
176. 175 Mutchinick O.M. *et al.* Increasing at Birth Prevalence of Isolated Gastrsochisis and Associated Risk Factors 1978-2009. *Birth Defects Research (Part A)* **91**, P8, Page 354 (2011).
177. 176 Bassil, K. L. *et al.* Spatial variability of gastroschisis in Canada, 2006-2011: An exploratory analysis. *Canadian journal of public health* **107**, e62-67, doi:10.17269/cjph.107.5084 (2016).
178. 177 Fischer, B., Rehm, J. & Hall, W. Cannabis use in Canada: the need for a 'public health' approach. *Canadian journal of public health* **100**, 101-103 (2009).
179. 178 Public Health Agency of Canada. Vol. 1 (ed Health Canada Public Health Agency of Canada) 1-115 (Health Canada, Ottawa, 2013).
180. 179 Caro Meldrum-Hanna, A. N. *Birth Defects Cluster Sparks Investigation*, <<http://www.abc.net.au/news/2011-05-14/birth-defect-cluster-sparks-investigation/2715546>> (2011).
181. 180 Expert Review Panel Appointed to New South Wales Health. Vol. 1 / (ed Data Custodian From New South Wales Health Department Center for Record Linkage, Dr Lee Taylor, ltayl@doh.health.nsw.gov.au ,) 1-11 (New South Wales Health Department, , Sydney, 2011).
182. 181 McMillan M. in *Northern Star Newspaper, 3rd June 2011*. (Northern Star, Lismore, 2011).
184. 182 Mel McMillan. *Birth Defects Exceed NSW Average*, <<https://www.northernstar.com.au/news/cases-of-birth-defect-exceed-state-average/867706/>> (2011).
185. 183 Smith, A. M. *et al.* Prenatal marijuana exposure impacts executive functioning into young adulthood: An fMRI study. *Neurotoxicol Teratol* **58**, 53-59, doi:10.1016/j.ntt.2016.05.010 (2016).
186. 184 Abel, E. L. Effects of prenatal exposure to cannabinoids. *NIDA Res Monogr* **59**, 20-35 (1985).
187. 185 El Marroun, H. *et al.* Prenatal Cannabis and Tobacco Exposure in Relation to Brain Morphology: A Prospective Neuroimaging Study in Young Children. *Biol Psychiatry* **79**, 971-979, doi:10.1016/j.biopsych.2015.08.024 (2016).
188. 186 Faden, V. B. & Graubard, B. I. Maternal substance use during pregnancy and developmental outcome at age three. *J Subst Abuse* **12**, 329-340 (2000).
189. 187 Fried, P., Watkinson, B., James, D. & Gray, R. Current and former marijuana use: preliminary findings of a longitudinal study of effects on IQ in young adults. *CMAJ* **166**, 887-891 (2002).
190. 188 Fried, P. A. Behavioral and electroencephalographic correlates of the chronic use of marijuana--a review. *Behav Biol* **21**, 163-196 (1977).
191. 189 Fried, P. A. Postnatal consequences of maternal marijuana use. *NIDA Res Monogr* **59**, 61-72 (1985).
192. 190 Fried, P. A. Postnatal consequences of maternal marijuana use in humans. *Ann N Y Acad Sci* **562**, 123-132 (1989).
193. 191 Fried, P. A. Cigarettes and marijuana: are there measurable long-term neurobehavioral teratogenic effects? *Neurotoxicology* **10**, 577-583 (1989).
194. 192 Fried, P. A. Marijuana use during pregnancy: consequences for the offspring. *Semin Perinatol* **15**, 280-287 (1991).
195. 193 Fried, P. A. Prenatal exposure to tobacco and marijuana: effects during pregnancy, infancy, and early childhood. *Clin Obstet Gynecol* **36**, 319-337 (1993).

196. 194 Fried, P. A. Behavioral outcomes in preschool and school-age children exposed prenatally to marijuana: a review and speculative interpretation. *NIDA Res Monogr* **164**, 242-260 (1996).
197. 195 Fried, P. A. Adolescents prenatally exposed to marijuana: examination of facets of complex behaviors and comparisons with the influence of in utero cigarettes. *Journal of clinical pharmacology* **42**, 97S-102S (2002).
198. 196 Fried, P. A., Buckingham, M. & Von Kulmiz, P. Marijuana use during pregnancy and perinatal risk factors. *Am J Obstet Gynecol* **146**, 992-994 (1983).
199. 197 Fried, P. A., O'Connell, C. M. & Watkinson, B. 60- and 72-month follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol: cognitive and language assessment. *J Dev Behav Pediatr* **13**, 383-391 (1992).
200. 198 Fried, P. A. & Watkinson, B. 36- and 48-month neurobehavioral follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol. *J Dev Behav Pediatr* **11**, 49-58 (1990).
201. 199 Fried, P. A., Watkinson, B., Dillon, R. F. & Dulberg, C. S. Neonatal neurological status in a low-risk population after prenatal exposure to cigarettes, marijuana, and alcohol. *J Dev Behav Pediatr* **8**, 318-326 (1987).
202. 200 Fried, P. A., Watkinson, B. & Gray, R. Growth from birth to early adolescence in offspring prenatally exposed to cigarettes and marijuana. *Neurotoxicol Teratol* **21**, 513-525 (1999).
203. 201 Fried, P. A., Watkinson, B. & Siegel, L. S. Reading and language in 9- to 12-year olds prenatally exposed to cigarettes and marijuana. *Neurotoxicol Teratol* **19**, 171-183 (1997).
204. 202 Fried, P. A., Watkinson, B. & Willan, A. Marijuana use during pregnancy and decreased length of gestation. *Am J Obstet Gynecol* **150**, 23-27 (1984).
205. 203 Gal, P. & Sharpless, M. K. Fetal drug exposure-behavioral teratogenesis. *Drug Intell Clin Pharm* **18**, 186-201 (1984).
206. 204 Hans, S. L. Prenatal drug exposure: behavioral functioning in late childhood and adolescence. *NIDA Res Monogr* **164**, 261-276 (1996).
207. 205 Hutchings, D. E., Brake, S., Morgan, B., Lasalle, E. & Shi, T. M. Developmental toxicity of prenatal delta-9-tetrahydrocannabinol: effects of maternal nutrition, offspring growth, and behavior. *NIDA Res Monogr* **76**, 363-369 (1987).
208. 206 Kulaga, V., Shor, S. & Koren, G. Correlation between drugs of abuse and alcohol by hair analysis: parents at risk for having children with fetal alcohol spectrum disorder. *Alcohol (Fayetteville, N.Y)* **44**, 615-621, doi:10.1016/j.alcohol.2010.04.001 (2010).
209. 207 McCance-Katz, E. F. The consequences of maternal substance abuse for the child exposed in utero. *Psychosomatics* **32**, 268-274, doi:10.1016/S0033-3182(91)72064-1 (1991).
210. 208 Milman, D. H. Developmental outcome, at age 3 and 4 years, of children exposed in utero to alcohol, tobacco, and marijuana. *J Dev Behav Pediatr* **11**, 228 (1990).
211. 209 Porath, A. J. & Fried, P. A. Effects of prenatal cigarette and marijuana exposure on drug use among offspring. *Neurotoxicol Teratol* **27**, 267-277, doi:10.1016/j.ntt.2004.12.003 (2005).
212. 210 Psychoyos, D., Hungund, B., Cooper, T. & Finnell, R. H. A cannabinoid analogue of Delta9-tetrahydrocannabinol disrupts neural development in chick. *Birth Defects Res B Dev Reprod Toxicol* **83**, 477-488, doi:10.1002/bdrb.20166 (2008).
213. 211 Skosnik, P. D., Cortes-Briones, J. A. & Hajos, M. It's All in the Rhythm: The Role of Cannabinoids in Neural Oscillations and Psychosis. *Biol Psychiatry* **79**, 568-577, doi:10.1016/j.biopsych.2015.12.011 (2016).
214. 212 Smith, A., Fried, P., Hogan, M. & Cameron, I. The effects of prenatal and current marijuana exposure on response inhibition: a functional magnetic resonance imaging study. *Brain Cogn* **54**, 147-149 (2004).
215. 213 Smith, A. M., Fried, P. A., Hogan, M. J. & Cameron, I. Effects of prenatal marijuana on response inhibition: an fMRI study of young adults. *Neurotoxicol Teratol* **26**, 533-542, doi:10.1016/j.ntt.2004.04.004 (2004).
216. 214 Smith, A. M., Fried, P. A., Hogan, M. J. & Cameron, I. Effects of prenatal marijuana on visuospatial working memory: an fMRI study in young adults. *Neurotoxicol Teratol* **28**, 286-295, doi:10.1016/j.ntt.2005.12.008 (2006).
217. 215 Smith, A. M., Longo, C. A., Fried, P. A., Hogan, M. J. & Cameron, I. Effects of marijuana on visuospatial working memory: an fMRI study in young adults. *Psychopharmacology (Berl)* **210**, 429-438, doi:10.1007/s00213-010-1841-8 (2010).
218. 216 Subbanna, S., Psychoyos, D., Xie, S. & Basavarajappa, B. S. Postnatal ethanol exposure alters levels of 2-arachidonylglycerol-metabolizing enzymes and pharmacological inhibition of monoacylglycerol lipase does not cause neurodegeneration in neonatal mice. *J Neurochem* **134**, 276-287, doi:10.1111/jnc.13120 (2015).

219. 217 Tennes, K. *et al.* Marijuana: prenatal and postnatal exposure in the human. *NIDA Res Monogr* **59**, 48-60 (1985).
220. 218 Becker, M. P., Collins, P. F., Lim, K. O., Muetzel, R. L. & Luciana, M. Longitudinal changes in white matter microstructure after heavy cannabis use. *Developmental cognitive neuroscience* **16**, 23-35, doi:10.1016/j.dcn.2015.10.004 (2015).
221. 219 DeRosse, P. *et al.* Adding insult to injury: childhood and adolescent risk factors for psychosis predict lower fractional anisotropy in the superior longitudinal fasciculus in healthy adults. *Psychiatry Res* **224**, 296-302, doi:10.1016/j.psychres.2014.09.001 (2014).
222. 220 Lorenzetti, V. *et al.* Gross morphological brain changes with chronic, heavy cannabis use. *Br J Psychiatry* **206**, 77-78, doi:10.1192/bjp.bp.114.151407 (2015).
223. 221 Luby, J. L. *et al.* Developmental Trajectories of the Orbitofrontal Cortex and Anhedonia in Middle Childhood and Risk for Substance Use in Adolescence in a Longitudinal Sample of Depressed and Healthy Preschoolers. *Am J Psychiatry*, appiajp201817070777, doi:10.1176/appi.ajp.2018.17070777 (2018).
224. 222 Madabhushi, R., Pan, L. & Tsai, L. H. DNA damage and its links to neurodegeneration. *Neuron* **83**, 266-282, doi:10.1016/j.neuron.2014.06.034 (2014).
225. 223 Navakkode, S. & Korte, M. Pharmacological activation of CB1 receptor modulates long term potentiation by interfering with protein synthesis. *Neuropharmacology* **79**, 525-533, doi:10.1016/j.neuropharm.2013.11.018 (2014).
226. 224 Wu, C. S., Jew, C. P. & Lu, H. C. Lasting impacts of prenatal cannabis exposure and the role of endogenous cannabinoids in the developing brain. *Future Neurol* **6**, 459-480 (2011).
227. 225 Fried, P. A. Postnatal consequences of maternal marijuana use. *NIDA Research Monograph* **59**, 61-72 (1998).
228. 226 Sarman, I. Review shows that early foetal alcohol exposure may cause adverse effects even when the mother consumes low levels. *Acta Paediatr*, doi:10.1111/apa.14221 (2018).
229. 227 Lussier, A. A. *et al.* DNA methylation as a predictor of fetal alcohol spectrum disorder. *Clin Epigenetics* **10**, 5, doi:10.1186/s13148-018-0439-6 (2018).
230. 228 Blum, K. *et al.* The Food and Drug Addiction Epidemic: Targeting Dopamine Homeostasis. *Curr Pharm Des* **23**, 6050-6061, doi:10.2174/1381612823666170823101713 (2018).
231. 229 Veazey, K. J. *et al.* Disconnect between alcohol-induced alterations in chromatin structure and gene transcription in a mouse embryonic stem cell model of exposure. *Alcohol (Fayetteville, N.Y)* **60**, 121-133, doi:10.1016/j.alcohol.2017.01.007 (2017).
232. 230 Rachdaoui, N. *et al.* Turnover of histones and histone variants in postnatal rat brain: effects of alcohol exposure. *Clin Epigenetics* **9**, 117, doi:10.1186/s13148-017-0416-5 (2017).
233. 231 Ozturk, N. C., Resendiz, M., Ozturk, H. & Zhou, F. C. DNA Methylation program in normal and alcohol-induced thinning cortex. *Alcohol (Fayetteville, N.Y)* **60**, 135-147, doi:10.1016/j.alcohol.2017.01.006 (2017).
234. 232 Lussier, A. A., Weinberg, J. & Kobor, M. S. Epigenetics studies of fetal alcohol spectrum disorder: where are we now? *Epigenomics* **9**, 291-311, doi:10.2217/epi-2016-0163 (2017).
235. 233 Laufer, B. I., Chater-Diehl, E. J., Kapalanga, J. & Singh, S. M. Long-term alterations to DNA methylation as a biomarker of prenatal alcohol exposure: From mouse models to human children with fetal alcohol spectrum disorders. *Alcohol (Fayetteville, N.Y)* **60**, 67-75, doi:10.1016/j.alcohol.2016.11.009 (2017).
236. 234 Kitsiou-Tzeli, S. & Tzetis, M. Maternal epigenetics and fetal and neonatal growth. *Curr Opin Endocrinol Diabetes Obes* **24**, 43-46, doi:10.1097/MED.0000000000000305 (2017).
237. 235 Gavin, D. P., Grayson, D. R., Varghese, S. P. & Guizzetti, M. Chromatin Switches during Neural Cell Differentiation and Their Dysregulation by Prenatal Alcohol Exposure. *Genes (Basel)* **8**, doi:10.3390/genes8050137 (2017).
238. 236 Dasmahapatra, A. K., Carty, D. R. & Khan, I. A. Developmental ethanol exposure impairs locomotor movement in Japanese medaka (*Oryzias latipes*) larvae targeting epigenome. *Chemosphere* **186**, 901-910, doi:10.1016/j.chemosphere.2017.08.048 (2017).
239. 237 Chater-Diehl, E. J., Laufer, B. I. & Singh, S. M. Changes to histone modifications following prenatal alcohol exposure: An emerging picture. *Alcohol (Fayetteville, N.Y)* **60**, 41-52, doi:10.1016/j.alcohol.2017.01.005 (2017).
240. 238 Chang, R. C. *et al.* DNA methylation-independent growth restriction and altered developmental programming in a mouse model of preconception male alcohol exposure. *Epigenetics* **12**, 841-853, doi:10.1080/15592294.2017.1363952 (2017).
241. 239 Banik, A. *et al.* Maternal Factors that Induce Epigenetic Changes Contribute to Neurological Disorders in Offspring. *Genes (Basel)* **8**, doi:10.3390/genes8060150 (2017).

242. 240 Abbott, C. W., Rohac, D. J., Bottom, R. T., Patadia, S. & Huffman, K. J. Prenatal Ethanol Exposure and Neocortical Development: A Transgenerational Model of FASD. *Cereb Cortex*, 1-14, doi:10.1093/cercor/bhx168 (2017).
243. 241 Richardson, K. A., Hester, A. K. & McLemore, G. L. Prenatal cannabis exposure - The "first hit" to the endocannabinoid system. *Neurotoxicol Teratol* **58**, 5-14, doi:10.1016/j.ntt.2016.08.003 (2016).
244. 242 Portales-Casamar, E. *et al.* DNA methylation signature of human fetal alcohol spectrum disorder. *Epigenetics Chromatin* **9**, 25, doi:10.1186/s13072-016-0074-4 (2016).
245. 243 Lunde, E. R. *et al.* Alcohol-Induced Developmental Origins of Adult-Onset Diseases. *Alcohol Clin Exp Res* **40**, 1403-1414, doi:10.1111/acer.13114 (2016).
246. 244 Hoang, M. *et al.* Alcohol-induced suppression of KDM6B dysregulates the mineralization potential in dental pulp stem cells. *Stem Cell Res* **17**, 111-121, doi:10.1016/j.scr.2016.05.021 (2016).
247. 245 Gavin, D. P., Kusumo, H., Sharma, R. P. & Guizzetti, M. Ethanol-induced changes in poly (ADP ribose) polymerase and neuronal developmental gene expression. *Neuropharmacology* **110**, 287-296, doi:10.1016/j.neuropharm.2016.08.001 (2016).
248. 246 Veazey, K. J., Parnell, S. E., Miranda, R. C. & Golding, M. C. Dose-dependent alcohol-induced alterations in chromatin structure persist beyond the window of exposure and correlate with fetal alcohol syndrome birth defects. *Epigenetics Chromatin* **8**, 39, doi:10.1186/s13072-015-0031-7 (2015).
249. 247 Varadinova, M. & Boyadjieva, N. Epigenetic mechanisms: A possible link between autism spectrum disorders and fetal alcohol spectrum disorders. *Pharmacol Res* **102**, 71-80, doi:10.1016/j.phrs.2015.09.011 (2015).
250. 248 Mason, S. & Zhou, F. C. Editorial: Genetics and epigenetics of fetal alcohol spectrum disorders. *Front Genet* **6**, 146, doi:10.3389/fgene.2015.00146 (2015).
251. 249 Masemola, M. L., van der Merwe, L., Lombard, Z., Viljoen, D. & Ramsay, M. Reduced DNA methylation at the PEG3 DMR and KvDMR1 loci in children exposed to alcohol in utero: a South African Fetal Alcohol Syndrome cohort study. *Front Genet* **6**, 85, doi:10.3389/fgene.2015.00085 (2015).
252. 250 Laufer, B. I. *et al.* Associative DNA methylation changes in children with prenatal alcohol exposure. *Epigenomics* **7**, 1259-1274, doi:10.2217/epi.15.60 (2015).
253. 251 Dasmahapatra, A. K. & Khan, I. A. DNA methyltransferase expressions in Japanese rice fish (*Oryzias latipes*) embryogenesis is developmentally regulated and modulated by ethanol and 5-azacytidine. *Comp Biochem Physiol C Toxicol Pharmacol* **176-177**, 1-9, doi:10.1016/j.cbpc.2015.07.002 (2015).
254. 252 Subbanna, S. *et al.* CB1R-Mediated Activation of Caspase-3 Causes Epigenetic and Neurobehavioral Abnormalities in Postnatal Ethanol-Exposed Mice. *Front Mol Neurosci* **11**, 45, doi:10.3389/fnmol.2018.00045 (2018).
255. 253 Subbanna, S., Nagre, N. N., Umapathy, N. S., Pace, B. S. & Basavarajappa, B. S. Ethanol exposure induces neonatal neurodegeneration by enhancing CB1R Exon1 histone H4K8 acetylation and up-regulating CB1R function causing neurobehavioral abnormalities in adult mice. *Int J Neuropsychopharmacol* **18**, doi:10.1093/ijnp/pyu028 (2014).
256. 254 Subbanna, S., Shivakumar, M., Psychoyos, D., Xie, S. & Basavarajappa, B. S. Anandamide-CB1 receptor signaling contributes to postnatal ethanol-induced neonatal neurodegeneration, adult synaptic, and memory deficits. *J Neurosci* **33**, 6350-6366, doi:10.1523/JNEUROSCI.3786-12.2013 (2013).
257. 255 Buchi, K. F., Suarez, C. & Varner, M. W. The prevalence of prenatal opioid and other drug use in Utah. *Am J Perinatol* **30**, 241-244, doi:10.1055/s-0032-1323586 (2013).
258. 256 Shor, S., Nulman, I., Kulaga, V. & Koren, G. Heavy in utero ethanol exposure is associated with the use of other drugs of abuse in a high-risk population. *Alcohol (Fayetteville, N.Y)* **44**, 623-627, doi:10.1016/j.alcohol.2009.08.008 (2010).
259. 257 Giardina, S. & Becca, B. Drug abuse and reproduction. *Ann Ist Super Sanita* **29**, 121-129 (1993).
260. 258 Hutchings, D. E. & Dow-Edwards, D. Animal models of opiate, cocaine, and cannabis use. *Clin Perinatol* **18**, 1-22 (1991).
261. 259 Piccirillo, P., Belnome, G. & Serpico, R. [Oromaxillofacial teratogenic effects of heavy and light drugs]. *Arch Stomatol (Napoli)* **31**, 461-467 (1990).
262. 260 Wang, X., Dow-Edwards, D., Anderson, V., Minkoff, H. & Hurd, Y. L. Discrete opioid gene expression impairment in the human fetal brain associated with maternal marijuana use. *Pharmacogenomics J* **6**, 255-264, doi:10.1038/sj.tpj.6500375 (2006).
263. 261 Yang, X. *et al.* Histone modifications are associated with Delta9-tetrahydrocannabinol-mediated alterations in antigen-specific T cell responses. *J Biol Chem* **289**, 18707-18718, doi:10.1074/jbc.M113.545210 (2014).

264. 262 Chioccarelli, T. *et al.* Cannabinoid receptor 1 influences chromatin remodeling in mouse spermatids by affecting content of transition protein 2 mRNA and histone displacement. *Endocrinology* **151**, 5017-5029, doi:10.1210/en.2010-0133 (2010).
265. 263 Carty, D. R., Thornton, C., Gledhill, J. & Willett, K. L. Developmental effects of cannabidiol and Delta9-tetrahydrocannabinol in zebrafish. *Toxicol Sci*, doi:10.1093/toxsci/kfx232 (2017).
266. 264 Hwang, Y. S. *et al.* Cannabidiol upregulates melanogenesis through CB1 dependent pathway by activating p38 MAPK and p42/44 MAPK. *Chem Biol Interact* **273**, 107-114, doi:10.1016/j.cbi.2017.06.005 (2017).
267. 265 Simard, O., Niavarani, S. R., Gaudreault, V. & Boissonneault, G. Torsional stress promotes trinucleotide expansion in spermatids. *Mutat Res* **800-802**, 1-7, doi:10.1016/j.mrfmmm.2017.04.001 (2017).
268. 266 Karmaus, P. W., Wagner, J. G., Harkema, J. R., Kaminski, N. E. & Kaplan, B. L. Cannabidiol (CBD) enhances lipopolysaccharide (LPS)-induced pulmonary inflammation in C57BL/6 mice. *J Immunotoxicol* **10**, 321-328, doi:10.3109/1547691X.2012.741628 (2013).
269. 267 Maor, Y. *et al.* Cannabidiol inhibits growth and induces programmed cell death in kaposi sarcoma-associated herpesvirus-infected endothelium. *Genes Cancer* **3**, 512-520, doi:10.1177/1947601912466556 (2012).
270. 268 Pucci, M. *et al.* Epigenetic control of skin differentiation genes by phytocannabinoids. *Br J Pharmacol* **170**, 581-591, doi:10.1111/bph.12309 (2013).
271. 269 Zimmerman, A. M., Zimmerman S., Raj A.Y. in *Marihuana and medicine* (eds Nahas G.G., Sutin K.M., Harvey D.J., & Agurell S.) Ch. 27, 347-358 (Humana Press, 1999).
272. 270 Brown, Q. L. *et al.* Trends in marijuana use among pregnant and nonpregnant reproductive-aged women, 2002-2014. *JAMA* **317**, 207-209, doi:10.1001/jama.2016.17383 (2017).
273. 271 Shi, Y. & Zhong, S. Trends in Cannabis Use Disorder among Pregnant Women in the U.S., 1993-2014. *J Gen Intern Med* **33**, 245-246, doi:10.1007/s11606-017-4201-0 (2018).
274. 272 Han, B., Compton, W. M., Blanco, C. & Jones, C. M. Trends in and correlates of medical marijuana use among adults in the United States. *Drug Alcohol Depend* **186**, 120-129, doi:10.1016/j.drugalcdep.2018.01.022 (2018).
275. 273 Kerr, W. C., Lui, C. & Ye, Y. Trends and age, period and cohort effects for marijuana use prevalence in the 1984-2015 US National Alcohol Surveys. *Addiction* **113**, 473-481, doi:10.1111/add.14031 (2018).

# Cannabis Teratogenesis, a Missing Common Factor in the Cannabis Legalization Debates: Thalidomide Revisited

Short Title:

Case for Caution with Cannabis

Albert Stuart Reece <sup>1,2</sup>

1 - Division of Psychiatry,  
University of Western Australia,  
Crawley, Western Australia 6009, Australia.

2 – School of Medical and Health Sciences,  
Edith Cowan University,  
Joondalup, Western Australia, 6027, Australia.

**\* Correspondence to:**

Albert Stuart Reece  
39 Gladstone Rd.,  
Highgate Hill,  
Brisbane, Queensland, Australia.

Ph: (617) 3844-4000

FAX: (617) 3844-4015

Email: [stuart.reece@bigpond.com](mailto:stuart.reece@bigpond.com)

Word Count – 600.

Paradoxically, in the midst of a cacophony of cries for cannabis legalization there is a distinct but deafening silence in relation to its known teratogenic effects. Given the adverse experience of many nations with thalidomide within living memory in the 1950's–1960's this merits comment.

Nor is such teratogenesis controversial. A long running and spectacularly thorough suite of studies from Ottawa looking at the effects of antenatal cannabis exposure on brain development commenced in the 1970's and has now shown not only thinning of the brain's frontal cortex in preteen, teenage and young adult years, but also identifiable neuropsychological deficits of executive and higher cortical functioning including memory, visuospatial memory and counting Stroop tasks <sup>1</sup>. When tasks are observed by fMRI often much greater areas of cortex have to be activated to perform a function. All of this makes sense given what we know of the central role played by endocannabinoid system in retrograde inhibition – the “off” signal – at both stimulatory and inhibitory synapses in the CNS and hence its ability to halt both neurotransmission and the brain waves to which underlying neural activity gives rise <sup>2</sup>. Both of these are key to the guidance of migrating neurons into the developing cortex and the wiring in of those cells to the neuronal network. It seems self-evident that these effects would be greatly magnified by the stronger cannabis available today – about 30% in Colorado - than the 1-2% concentration material of the 1960's. Indeed it is not going too far to suggest that a majority of pregnancies with significant *in utero* exposure to high concentration cannabis are likely to show some evidence of such neurobehavioural teratogenesis in later years. This is certainly consistent with our clinical experience after several decades working with cannabis exposed offspring in an addiction medicine clinic.

In 2007 the American Heart Foundation and the American Academy of Pediatrics issued a joint statement noting that cannabis was a known teratogenic factor for congenital heart defects including atrial and ventricular septal defects and Epstein's valvular anomaly <sup>3</sup>. It is also known that the endocardial cushions inside the heart from which the valves and interventricular septum develop carry high concentrations of type 1 cannabinoid receptors (CB1R's) <sup>4</sup> which have a strongly inhibitory action on developing stem cells <sup>5</sup>, so that such endocardial teratological pathways seem direct and straightforward. This is also supported by the experience of Colorado which has seen a 70% rise in all major congenital

abnormalities including a 70% rise in congenital cardiac malformations 2000-2013 <sup>6</sup> in association with a 100% rise in cannabis use in Coloradans aged over 12 <sup>7</sup>.

Gastroschisis refers to an anomaly in newborns where the bowels lie outside the abdominal cavity. Ten studies looking at the link between cannabis use and gastroschisis have shown a positive relationship not only with incidence <sup>8</sup> but also with severity <sup>9</sup>. One of the causes of this is thought to be impaired blood flow to the muscles of the abdominal wall. The presence of high concentration CB1R's on the umbilical artery presents a clear biological pathway to account for this finding <sup>4</sup>.

And four studies show increased rates of cancer in exposed babies after congenital exposure – to what has historically been mild levels of THC concentration <sup>10</sup>.

Given that all four of the above major findings are beyond controversy their absence from the popular debate is particularly striking. The near doubling of congenital anomalies in Colorado is especially concerning, and has likely further increased since legalization in 2014. And the near ubiquity of neurobehavioral teratogenesis implies an impending tsunami of cannabis-related neuroteratogenesis dwarfing anything produced by thalidomide.

Conflict of Interest:

I have read and understood the BMJ Group policy on declaration of interests and declare the following interests: None.

Role of the Funding Source.

As no funding was provided to this study this is not applicable.

Authors Contribution.

ASR wrote and researched this paper.

Ethics Approval.

This analysis mentioned in this study was approved by the Southcity Medical Centre Human Ethics Research Committee.

## **References**

1. Smith AM, Mioduszeewski O, Hatchard T, et al. Prenatal marijuana exposure impacts executive functioning into young adulthood: An fMRI study. *Neurotoxicol Teratol* 2016;58:53-59. doi: 10.1016/j.ntt.2016.05.010
2. Bloomfield MA, Ashok AH, Volkow ND, et al. The effects of Delta9-tetrahydrocannabinol on the dopamine system. *Nature* 2016;539(7629):369-77. doi: 10.1038/nature20153
3. Jenkins KJ, Correa A, Feinstein JA, et al. Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. *Circulation* 2007;115(23):2995-3014. doi: 10.1161/CIRCULATIONAHA.106.183216
4. Pacher P, Steffens S, Hasko G, et al. Cardiovascular effects of marijuana and synthetic cannabinoids: the good, the bad, and the ugly. *Nat Rev Cardiol* 2018;15(3):151-66. doi: 10.1038/nrcardio.2017.130
5. Noonan M.A., A.J. E. Regulation of Adult Neurogenesis by Cannabinoids. *Chemistry Today* 2006;24(5):84-88.
6. Colorado: Department of Public Health and the Environment. Colorado Responds to Children with Special Needs - Birth Defect Data, Colorado. In: Environment CDoPHat, ed. 1 ed. Denver Colorado, USA: Colorado: Department of Public Health and the Environment, 2018:<http://www.chd.dphe.state.co.us/cohid/>.
7. Substance Abuse and Mental Health Administration, Department of Health and Human Services, United States Government. National Survey of Drug Use and Health 2018 Bethesda, Maryland: Substance Abuse and Mental Health Administration, Department of Health and Human Services, United States Government,; 2018 [cited 2018 June 2nd, 2018]. Available from: <https://www.samhsa.gov/data/all-reports> accessed June 2nd, 2018 2018.
8. Moore A., Roulean J., Skarsgard E. Congenital Anomalies in Canada, 2013. A Perinatal Health Surveillance Report. Chapter 7. Gastroschisis. In: Public Health Agency of Canada HC, ed. Ottawa: Health Canada, 2013:57-63.
9. Weinsheimer RL, Yanchar NL, Canadian Pediatric Surgical N. Impact of maternal substance abuse and smoking on children with gastroschisis. *J Pediatr Surg* 2008;43(5):879-83. doi: 10.1016/j.jpedsurg.2007.12.032
10. Reece AS. Chronic toxicology of cannabis. *Clin Toxicol (Phila)* 2009;47(6):517-24. doi: 10.1080/15563650903074507 [published Online First: 2009/07/10]

# Case for Caution with Cannabis in Colorado: Considerations of Genotoxicity and Teratogenicity

Short Title:

Case for Caution with Cannabis

Albert Stuart Reece <sup>1,2</sup>

1 - Division of Psychiatry,  
University of Western Australia,  
Crawley, Western Australia 6009, Australia.

2 – School of Medical and Health Sciences,  
Edith Cowan University,  
Joondalup, Western Australia, 6027, Australia.

**\* Correspondence to:**

Albert Stuart Reece  
39 Gladstone Rd.,  
Highgate Hill,  
Brisbane, Queensland, Australia.

Ph: (617) 3844-4000

FAX: (617) 3844-4015

Email: [stuart.reece@bigpond.com](mailto:stuart.reece@bigpond.com)

Word Count: 789.

There exists sufficient empirical data from cellular to epidemiological studies to warrant caution in the use cannabinoids including cannabidiol as recreational and therapeutic agents.

Cannabinoids bind to CB1R receptors on neuronal mitochondrial membranes where they can directly disrupt key functions including cellular energy generation, [DNA maintenance and repair, memory and learning](#).

Empirical literature associates cannabinoid use with CB1R-mediated vasospastic and vasothrombotic strokes, [myocardial infarcts and arrhythmias](#). Cannabis is associated with increased vascular aging, a major surrogate for organismal aging. In the pediatric-congenital context CB1R-mediated cannabis vasculopathy forms a major pathway to teratogenesis including [VSD and ASD amongst others](#) and, via the omphalo-vitelline arterial CB1R's, gastroschisis. Cannabinoids also induce epigenetic perturbations; and, like thalidomide, interfere with tubulin polymerization and the stability of the mitotic spindle providing further major pathways to genotoxicity.

The "[Colorado Responds to Children with Special Needs](#)" program tracked congenital anomalies 2000-2013 when Colorado was first advised that intrastate cannabis would not be prosecuted Federally.

Over the period 2000-2013 Colorado almost doubled its already high congenital anomaly rate rising from 4,830 anomalies / 65,429 births (7.4%) to 8,165 / 65,004 (12.6%); the US mean is 3.1%. Major cardiovascular defects rose 61% (number and rate); microcephaly rose 96% (from 30 to 60 cases peaking at 72 in 2009); and chromosomal anomalies rose 28% (from 175 to 225, peaking at 264 in 2010). Over the whole period this totals to 87,772 major congenital anomalies from 949,317 live births (9.25%).

The use of cannabis in Colorado can be determined from [the SAMHSA National Survey on Drug Use and Health](#). A close correlation is noted between major congenital anomaly rates and rates of cannabis use in Coloradans >12 years ( $R=0.8825$ ;  $P=0.000029$ ; Figure 1). Given the Colorado birth rate remained almost constant over the period 2000-2013, rising only 3.6%, a simple way to quantitate historical trends is to simply project forwards the historical anomaly rate and compare it to the rise in birth numbers (Table 1).

Colorado had an average of 67,808 births over the period 2000-2013 and experienced a total of 87,772 birth defects, 20,152 more than would have been predicted using 2000 rates. If we amplify this to the scale of the [3,945,875 births annually in USA](#) this implies an extra 83,762 major congenital anomalies nationwide at 2013 use rates.

In reality both cannabis use and cannabis concentration is rising across USA following legalization which further suggests that the above indicates underestimates. Moreover this series terminates in 2013 prior to full legalization in 2014. Parents of children harbouring severe anomalies may frequently elect termination which will again underestimate numbers of abnormal live births.

In California 7% of all pregnant mothers were recently shown to test positive for cannabis exposure, including almost [25% of teenage mothers in 2015](#) so cannabinoids clearly constitute a significant population-wide teratological exposure. This is particularly relevant to cannabis genotoxicity as many studies show a dramatic up-tick in genotoxic effect in the dose-response curve for both tetrahydrocannabinol and cannabidiol above a certain threshold.

Other examples of high congenital anomaly rates accompanying increased cannabis use include North Carolina, Mexico, Northern Canada, New Zealand and the Nimbin area in Australia.

The above data leave open the distinct possibility that the rate of congenital anomalies from significant prenatal paternal or maternal cannabis exposure may become substantial.

With over 1,000 trials listed on [clinicaltrials.gov](https://clinicaltrials.gov) the chance of a type I experimental error for cannabinoid therapeutics and a falsely positive trial finding is at least 25/1,000 trials at the 5% level.

The major anomaly rate is just the “tip of the iceberg” of the often subtle neurobehavioral teratology of Foetal Cannabinoid Syndrome (FCS) following antenatal cannabinoid exposure characterized by attention, learning, behavioral and social deficits which in the longer term impose [significant educational, other addiction and welfare costs](#) - and is clearly more common. Foetal Alcohol Syndrome (FAS) is known to be [epigenetically mediated](#) and foetal alcohol is known to act via CB1R's. Cannabis has significant and heritable epigenetic imprints in neural, immune and germ cell (sperm) tissues, and epigenomic disruption has been implicated in FCS. CB1R-mediated disruption by disinhibition of the normal gamma and theta oscillatory rhythms of the forebrain which [underpin thinking, learning and sanity](#) have been implicated both in adult psychiatric disease and the neurodevelopmental aspects of FCS.

All of this implies that in addition to usually short-term therapy-oriented clinical trials, longer term studies and careful twenty-first century next generation studies will be required to carefully review inter-related genotoxic, teratologic, epigenetic, and long term cardiovascular outcomes which appears to have been largely overlooked in extant studies – effects which would appear rather to have taken Coloradans by surprise. We also note that cannabidiol is now solidly implicated in genotoxicity.

Caution is warranted lest we repeat the costly genotoxicity-teratogenicity mistakes of thalidomide.

Conflict of Interest:

I have read and understood the BMJ Group policy on declaration of interests and declare the following interests: None.

Role of the Funding Source.

As no funding was provided to this study this is not applicable.

Authors Contribution.

ASR wrote and researched this paper.

Ethics Approval.

This was not obtained as it was not considered applicable to this comment.

**Table 1.:**  
**Cumulative Data for Colorado**  
**Birth Defects 2000-2013** \*

| <b>Anomaly</b>              | <b>Cumulative<br/>Total<br/>2000-2013</b> | <b>Projected<br/>Total from<br/>Baseline</b> | <b>Excess Above<br/>Baseline</b> | <b>% Change<br/>2000-2013</b> | <b>Times (x)<br/>Increase<br/>Relative to<br/>Births</b> |
|-----------------------------|-------------------------------------------|----------------------------------------------|----------------------------------|-------------------------------|----------------------------------------------------------|
|                             |                                           |                                              |                                  |                               |                                                          |
| Births                      | 949,317                                   | 916,006                                      | 33,311                           | 3.6%                          | 1.00                                                     |
|                             |                                           |                                              |                                  |                               |                                                          |
| Major Congenital<br>Defects | 87,772                                    | 67,620                                       | 20,152                           | 29.8%                         | 8.20                                                     |
| Major CVS                   | 19,288                                    | 14,028                                       | 5,260                            | 37.5%                         | 10.31                                                    |
| VSD                         | 4,447                                     | 3,794                                        | 653                              | 17.2%                         | 4.73                                                     |
| ASD-Secundum                | 9,833                                     | 4,970                                        | 4,863                            | 97.8%                         | 26.91                                                    |
| Microcephaly                | 761                                       | 420                                          | 341                              | 81.2%                         | 22.33                                                    |
| Chromosomal                 | 3,134                                     | 2,450                                        | 684                              | 27.9%                         | 7.68                                                     |

\* - From Reference (4)

Figure Caption.

Close parallel between combined adolescent and adult cannabis use rates and major congenital anomaly rates, Colorado, 2000-2013.

## VIEWPOINT

**Lauren M. Jansson, MD**

Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland.

**Chloe J. Jordan, PhD**

National Institute on Drug Abuse Intramural Research Program, Molecular Targets and Medications Discovery Branch, Baltimore, Maryland.

**Martha L. Velez, MD**

Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland.

# Perinatal Marijuana Use and the Developing Child

**Increasing public attention** has recently been paid to the opioid epidemic and attendant effects on prenatally exposed infants and children.<sup>1</sup> Current literature has emerged proposing marijuana as a safe alternative to opioids in addressing pain<sup>2</sup> and cannabis legalization as a way to decrease opioid fatalities.<sup>3</sup> As a result, perceptions of cannabis safety have increased, and the prevalence of marijuana use among pregnant women has expanded; past-month cannabis use among pregnant US women increased from 2.4% to 3.9% between 2002 and 2014.<sup>4</sup> Further, cannabis potency has been substantially increasing over the past 4 decades in the United States, and will likely continue to do so as extraction procedures of active components improve.

Although cannabis does have known medical utility for some conditions, its associated acute and long-term psychoactive effects on brain function are also known. Expanding use of cannabis among pregnant and lactating women (as likely will occur with legalization) may lead to increased risk from fetal and child exposures if the teratogenic potential of cannabis remains underappreciated.

Delta-9-tetrahydrocannabinol (THC), the major psychoactive component of marijuana (1 of more than 500 components, 104 of which are cannabinoids), crosses the placental barrier readily. Accumulating evidence in animals and humans indicates that prenatal

related regions of the brain (eg, the nucleus accumbens, amygdala, and cortical areas), potentially altering their functioning in postnatal life and introducing epigenetic alterations with consequences for transgenerational offspring. Because endocannabinoids dynamically regulate fetal development, the timing and duration of prenatal exposure (eg, first or second vs third trimester) may have differential effects and long-term consequences. Studies are needed to characterize common patterns of cannabis use during stages of pregnancy and their subsequent effects on fetal neural development.

Prenatal THC exposure has been documented to adversely affect infant neurobehavior and child development up through the teen years,<sup>5</sup> and postnatal exposures may compound prenatally acquired deficits. Neurobehavioral effects associated with prenatal THC exposure range from dysregulated arousal and motor difficulties at birth to disturbed sleep, memory impairment, aggression, and other developmental and behavioral concerns in childhood.<sup>5</sup>

As cannabis potency and maternal use continue to increase, it will be critical to systematically evaluate the long-term outcomes of THC-exposed individuals, inform breastfeeding guidelines, and identify interventions to manage resultant developmental, psychiatric, and behavioral effects at different developmental stages among THC-exposed individuals.

The influence of perinatal THC exposure on the developing fetus and infant can be amplified among mothers with cannabis use disorder (CUD). The *DSM-5* characterizes CUD as significant impairment due to the inability to control cannabis use despite negative consequences, spending inordinate amounts of time using or procuring can-

nabis, tolerance (such that increasing amounts of drug are required to achieve intoxication), and withdrawal symptoms during cessation of use. All of these symptoms can adversely affect a mother's ability to care for a child. Short-term effects of CUD, such as impairments in attention, judgment, and coordination, can affect child development and safety. Longer-term effects of maternal THC use, such as depression, high-risk behaviors, impaired executive functioning, and an increased risk of psychiatric comorbidity, could further adversely affect the well-being and development of children. Efforts to reduce and discourage cannabis use during pregnancy and breastfeeding are further complicated by cannabis withdrawal symptoms (including irritability, anxiety, insomnia, appetite loss, and depressed mood), which can be major deterrents to abstinence and relapse prevention.

The extent to which cannabis-using mothers also engage in additional substance use (eg, opioids,

## Advice from medical professionals should be consistent: pregnant and lactating women should be advised to avoid cannabis use...

exposure may be related to harm for the developing fetus and child.<sup>5</sup> THC exposure can adversely affect the developing fetal endocannabinoid system. Endocannabinoid receptors form very early in fetal life (ie, at 14 weeks' gestation) and have critical functions in fetal and postnatal brain development, neuronal connectivity, and glial cell differentiation. Endocannabinoids are important neuromodulators of multiple central neurotransmitter systems that are essential for fetal brain development, and optimal outcomes rely on normal physiologic activity at cannabinoid receptors. The exogenous supply of cannabinoids resulting from THC exposure can adversely affect fetal growth as well as structural and functional neurodevelopment.<sup>6</sup>

Prenatal THC exposure can modify not only the endocannabinoid system, but also can affect the maturation of dopamine, opioid, glutamate, and GABAergic neurotransmitter systems in key reward- and stress-

### Corresponding

**Author:** Lauren M. Jansson, MD, Department of Pediatrics, Johns Hopkins University School of Medicine, 4940 Eastern Ave, D4E, Baltimore, MD 21224 (ljansson@jhmi.edu).

nicotine, alcohol) remains unknown. It is imperative to characterize the prevalence of prenatal CUD and CUD/polysubstance use among pregnant and lactating women to better predict fetal/child outcomes and inform intervention efforts for both the mother and child.

Despite these risks, it appears that clinicians are not addressing cannabis use during pregnancy or lactation; in one study of 74 lactation professionals, 85% encouraged breastfeeding among marijuana-using mothers.<sup>7</sup> Most national breastfeeding guidelines (eg, the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists) have remained steadfast in recommending against cannabis use during lactation. However, the Academy of Breastfeeding Medicine has changed guidelines (2009 and 2015) to allow the potential use of cannabis during lactation, citing "data...not strong enough to recommend not breastfeeding with any marijuana use" despite urging caution due to "possible long-term neurobehavioral effects."<sup>8</sup>

The medical community should advise pregnant women to avoid perinatal THC exposure and intervene for women needing treatment, for children at risk for neurobiological and developmental problems, or for dyads at risk for negative outcomes associated with an untreated substance use disorder. Advice from medical professionals should be consistent: pregnant and lactating women should be advised to avoid cannabis use, and women (and men) caring for developing children also should be advised to maintain abstinence. Treatment programs for women with CUD should be available and accessible, and gender and culturally specific, particularly during pregnancy and postpartum periods. Converging, systematic research is necessary at both the preclinical and clinical levels to address insufficient evidence regarding maternal cannabis use<sup>9</sup> and to fully understand the short- and long-term effects of perinatal THC exposure, the effects of maternal cannabis use on fetal outcomes, and the consequences of polysubstance use in treatment and intervention efforts.

#### ARTICLE INFORMATION

**Published Online:** July 16, 2018.  
doi:10.1001/jama.2018.8401

**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

#### REFERENCES

1. Wachman EM, Schiff DM, Silverstein M. Neonatal abstinence syndrome: advances in diagnosis and treatment. *JAMA*. 2018;319(13):1362-1374. doi:10.1001/jama.2018.2640
2. Grover N. High hopes ride on marijuana amid opioid crisis: medical weed is a popular way to manage chronic pain. <https://www.scientificamerican.com/article/high-hopes-ride-on-marijuana-amid-opioid-crisis/>. Accessed April 20, 2018.
3. Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010. *JAMA Intern Med*. 2014;174(10):1668-1673. doi:10.1001/jamainternmed.2014.4005
4. Brown QL, Sarvet AL, Shmulewitz D, Martins SS, Wall MM, Hasin DS. Trends in marijuana use among pregnant and non-pregnant reproductive-aged women, 2002-2014. *JAMA*. 2017;317(2):207-209. doi:10.1001/jama.2016.17383
5. Huizink AC. Prenatal cannabis exposure and infant outcomes: overview of studies. *Prog Neuropsychopharmacol Biol Psychiatry*. 2014;52:45-52. doi:10.1016/j.pnpbp.2013.09.014
6. Jaques SC, Kingsbury A, Henshcke P, et al. Cannabis, the pregnant woman and her child: weeding out the myths. *J Perinatol*. 2014;34(6):417-424. doi:10.1038/jp.2013.180
7. Bergeria CL, Heil SH. Surveying lactation professionals regarding marijuana use and breastfeeding. *Breastfeed Med*. 2015;10(7):377-380. doi:10.1089/bfm.2015.0051
8. Reece-Stremtan S, Marinelli KA. ABM clinical protocol #21: guidelines for breastfeeding and substance use or substance use disorder, revised 2015. *Breastfeed Med*. 2015;10(3):135-141. doi:10.1089/bfm.2015.9992
9. National Academies of Sciences, Engineering, and Medicine. Prenatal, perinatal and neonatal exposure to cannabis. In: *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. Washington, DC: National Academies Press; 2017.

## Summary of Cannabis Genotoxicity Papers

There are several principal pathways to inheritable genotoxicity, mutagenicity and teratogenesis induced by cannabis which are known and well established at this time including the following. These three papers discuss different aspects of these effects.

- 1) **Stops Brain Waves and Thinking** The brain has both stimulatory and inhibitory pathways. GABA is the main brain inhibitory pathway. Brain centres talk to each other on gamma (about 40 cycles/sec) and theta frequencies (about 5 cycles/sec), where the theta waves are used as the carrier waves for the gamma wave which then interacts like harmonics in music. The degree to which the waves are in and out of phase carries information which can be monitored externally. GABA ( $\gamma$ -aminobutyric acid) inhibition is key to the generation of the synchronized firing which underpins these various brain oscillations. These GABA transmissions are controlled presynaptically by type 1 cannabinoid receptors (CB1R's) and CB1R stimulation shuts them down. This is why cannabis users forget and fall asleep.
- 2) **Blocks GABA Pathway and Brain Formation** GABA is also a key neurotransmitter in brain formation in that it guides and direct neural stem cell formation and transmission and development and growth of the cerebral cortex and other major brain areas. Gamma and theta brain waves also direct neural stem cell formation, sculpting and connectivity. Derangements then of GABA physiology imply that the brain will not form properly. Thin frontal cortical plate measurements have been shown in humans prenatally exposed to cannabis by fMRI. This implies that their brains can never be structurally normal which then explains the long lasting and persistent defects identified into adulthood.
- 3) **Epigenetic Damage** DNA not only carries the genetic hardware of our genetic code but it also carries the software of the code which works like traffic lights along the sequence of DNA bases to direct when to switch the genes on and off. This is known as the "epigenetic code". Fetal alcohol syndrome is believed to be due to damage to the software epigenetic code. The long lasting intellectual, mood regulation, attention and concentration defects which have been described after in utero cannabis exposure in the primary, middle and high schools and as college age young adults are likely due to these defects. Epigenetics "sets in stone" the errors of brain structure made in (2) above.
- 4) **Arterial Damage.** Cannabis has a well described effect to damage arteries through (CB1R's) (American Heart Association 2007) which they carry in high concentration (Nature Reviews Cardiology 2018). In adults this causes heart attack (500% elevation in the first hour after smoking), stroke, severe cardiac arrhythmias including sudden cardiac death; but in developing babies CB1R's acting on the developing heart tissues can lead to at least six major cardiac defects (Atrial- ventricular- and mixed atrio-ventricular and septal defects, Tetralogy of Fallot, Epstein's deformity amongst others), whilst constriction of various babies' arteries can lead to serious side effects such as gastroschisis (bowels hanging out) and possibly absent limbs (in at least one series).
- 5) **Disruption of Mitotic Spindle.** When cells divide the separating chromosomes actually slide along "train tracks" which are long chains made of tubulin. The tubulin chains are called "microtubules" and the whole football-shaped structure is called a "mitotic spindle". Cannabis inhibits tubulin formation, disrupting microtubules and the mitotic spindle causing the separating chromosomes to become cut off in tiny micronuclei, where they eventually become smashed up and pulverized into "genetic junk", which leads to foetal malformations, cancer and cell death. High rates of Down's syndrome, chromosomal anomalies and cancers in cannabis exposed babies provide clinical evidence of this.
- 6) **Defective Energy Generation & Downstream DNA Damage** DNA is the crown jewel of the cell and its most complex molecule. Maintaining it in good repair is a very energy

intensive process. Without energy DNA cannot be properly maintained. Cannabis has been known to reduce cellular energy production by the cell's power plants, mitochondria, for many decades now. This has now been firmly linked with increased DNA damage, cancer formation and aging of the cells and indeed the whole organism. As it is known to occur in eggs and sperm, this will also damage the quality of the germ cells which go into forming the baby and lead directly to damaged babies and babies lost and wasted through spontaneous miscarriage and therapeutic termination for severe deformities.

- 7) **Cancer induction** Cannabis causes 12 cancers and has been identified as a carcinogen by the California Environmental Protection agency (2009). This makes it also a mutagen. 4 of these cancers are inheritable to children; i.e. inheritable carcinogenicity and mutagenicity. All four studies in testicular cancer are strongly positive (elevation by three fold). Carcinogen = mutagen = teratogen.
- 8) **Colorado's Teratology Profile**. From the above described teratological profile we would expect exactly the profile of congenital defects which have been identified in Colorado (higher total defects and heart defects, and chromosomal defects) and Ottawa in Canada (long lasting and persistent brain damage seen on both functional testing and fMRI brain scans in children exposed in utero) where cannabis use has become common. Gastroschisis was shown to be higher in all seven studies looking at this; and including in Canada, carefully controlled studies. Moreover in Australia, Canada, North Carolina, Colorado, Mexico and New Zealand, gastroschisis and sometimes other major congenital defects cluster where cannabis use is highest. Colorado 2000-2013 has experienced an extra 20,152 severely abnormal births above the rates prior to cannabis liberalization which if applied to the whole USA would equate to more than 83,000 abnormal babies live born annually (and probably about that number again therapeutically aborted); actually much more since both the number of users and concentration of cannabis have risen sharply since 2013, and cannabis has been well proven to be much more severely genotoxic at higher doses.
- 9) **Cannabidiol is also Genotoxic** and tests positive in many genotoxicity assays, just as tetrahydrocannabinol does.
- 10) **Births defects registry data needs to be open and transparent and public.** At present it is not. This looks too much like a cover up.

## **Summary of Address to Australia as a Christian Nation Association**

**Sydney Parliament House, 09.07.2018**

Cannabis has been greatly oversold by a left leaning press controlled by globalist and centralist forces while its real and known dangers have not been given appropriate weight in the popular press. In particular its genotoxic and teratogenic potential on an unborn generation for the next hundred years has not been aired or properly weighed in popular forums. These weighty considerations clearly take cannabis out of the realm of personal choice or individual freedoms and place it squarely in the realm of the public good and a matter with which the whole community is rightly concerned and properly involved.

Cannabinoids are a group of 400 substances which occur only in the leaves of the Cannabis sativa plant where they are used by the plants as toxins and poisons in natural defence against other plants and against herbivores. Major leading world experts such as Dr Nora Volkow, Director of the National Institute of Drug Abuse at NIH <sup>1</sup>, Professor Wayne Hall, Previous Director of the Sydney Based National Drug and Alcohol Research Centre at UNSW <sup>2</sup>, and Health Canada <sup>3</sup> – amongst many others - are agreed that cannabis is linked with the following impressive lists of toxicities:

- 1) Cannabis is addictive, particularly when used by teenagers
- 2) Cannabis affects brain development
- 3) Cannabis is a gateway to other harder drug use
- 4) Cannabis is linked with many mental health disorders including anxiety, depression, psychosis, schizophrenia and bipolar disorder
- 5) Cannabis alters and greatly impairs the normal developmental trajectory – getting a job, finishing a course and forming a long term stable relationship <sup>4-11</sup>
- 6) Cannabis impairs driving ability <sup>12</sup>
- 7) Cannabis damages the lungs
- 8) Cannabis is immunosuppressive
- 9) Cannabis is linked with heart attack, stroke and cardiovascular disease
- 10) Cannabis is commonly more potent in recent years, with forms up to 30% being widely available in many parts of USA, and oils up to 100% THC also widely available.

Serious questions have also been raised about its involvement in 12 different cancers, increased Emergency Room presentations and exposures of developing babies during pregnancy. It is with this latter group that the present address is mainly concerned.

### **Basic Physiology and Embryology**

Cells make energy in dedicated organelles called mitochondria. Mitochondrial energy, in the form of ATP, is known to be involved in both DNA protection and control of the immune system. This means that when the cell's ATP is high DNA maintenance is good and the genome is intact. When cellular ATP drops DNA maintenance is impaired, DNA breaks remain unsealed, and cancers can form. Also immunity is triggered by low ATP. As organisms age ATP falls by half each 20 years after the age of 20. Mitochondria signal and

shuttle to the cell nucleus via several pathways. Not only do cells carry cannabinoid receptors on their surface, but they also exist, along with their signalling machinery, at high density on mitochondria themselves<sup>13-19</sup>. Cannabis, and indeed all addictive drugs, are known to impair this cellular energy generation and thus promote the biochemical aging process<sup>14-16,19,20</sup>. Most addictions are associated with increased cancers, increased infections and increased clinical signs of ageing<sup>21-34</sup>.

The foetal heart forms very early inside the mother with a heartbeat present from day 21 of human gestation. The heart forms by complicated pathways, and arises from more than six groups of cells inside the embryo<sup>35,36</sup>. First two arteries come together, they fold, then flex and twist to give the final shape of the adult heart. Structures in the centre of the heart mass called endocardial cushions grow out to form the heart valves between the atria and ventricles and parts of the septum which grows between the two atria and ventricles. These cardiac cushions, and their associated conoventricular ridges which grow into and divide the cardiac outflow tract into left and right halves, all carry high density cannabinoid type 1 receptors (CB1R's) and cannabis is known to be able to interfere with their growth and development. CB1R's appear on foetal arteries from week nine of human gestation<sup>37</sup>.

The developing brain grows out in a complex way in the head section<sup>35,36</sup>. Newborn brain cells are born centrally in the area adjacent to the central ventricles of the brain and then migrate along pathways into the remainder of the brain, and grow to populate the cortex, parietal lobes, olfactory lobes, limbic system, hypothalamus and hippocampus which is an important area deep in the centre of the temporal lobes where memories first form. Developing bipolar neuroblasts migrate along pathways and then climb out along 200 million guide cells, called radial glia cells, to the cortex of the brain where they sprout dendrites and a major central axon which are then wired in to the electrical network in a "use it or lose it", "cells that fire together wire together" manner. The brain continues to grow and mature into the 20's as new neurons are born and surplus dendrites are pruned by the immune system. Cannabinoids interfere with cellular migration, cellular division, the generation of newborn neurons and all the classes of glia, axonal pathfinding, dendrite sprouting, myelin formation around axons and axon tracts and the firing of both inhibitory and stimulatory synapses<sup>14-16,19,20,38-40</sup>. Cannabinoids interfere with gene expression directly, via numerous epigenetic means, and via immune perturbation.

Cannabinoids also disrupt the mechanics of cell division by disrupting the mitotic spindle on which chromosomal separation occurs, causing severe genetic damage and frank chromosomal mis-segregation, disruption, rupture and pulverization<sup>41-43</sup>.

Cannabis was found to be a human carcinogen by the California Environmental Protection agency in 2009<sup>44</sup>. This makes it a likely human teratogen (deforms babies). Importantly, while discussion continues over some cancers, it bears repeating that a positive association between cannabis and testicular cancer was found in all four studies which investigated this question<sup>45-49</sup>.

## Cannabis Teratogenesis

The best animal models for human malformations are hamsters and rabbits. In rabbits cannabis exhibits a severe spectrum of foetal abnormalities when applied at high dose including shortened limbs, bowels hanging out, spina bifida and exencephaly (brain hanging out). There is also impaired foetal growth and increased foetal loss and resorption <sup>50,51</sup>.

Many of these features have been noted in human studies <sup>52</sup>. In 2014 Centres for Disease Control Atlanta Georgia reported increased rates of anencephaly (no brain, usually rapid death) gastroschisis (bowels hanging out), diaphragmatic hernia, and oesophageal narrowing <sup>53,54</sup>. The American Heart Association and the American Academy of Pediatrics reported in 2007 an increased rate of ventricular septal defect and an abnormality of the tricuspid valve (Ebstein's anomaly) <sup>55</sup>. Strikingly, a number of studies have shown that cannabis exposure of the father is worse than that of the mother <sup>56</sup>. In Colorado atrial septal defect is noted to have risen by over 260% from 2000-2013 (see Figure 1; note close correlation (correlation coefficient  $R = 0.95$ ,  $P \text{ value} = 0.000066$ ) between teenage cannabis use and rising rate of major congenital anomalies in Colorado to 12.7%, or 1 in 8 live births, a rate four times higher than the USA national average !) <sup>57</sup>. And three longitudinal studies following children exposed to cannabis in utero have consistently noted abnormalities of brain growth with smaller brains and heads – persisting into adult life - and deficits of cortical and executive functioning persistent throughout primary, middle and high schools and into young adult life in the early 20's <sup>58-63</sup>. An Australian MRI neuroimaging study noted 88% disconnection of cortical wiring from the splenium to precuneus which are key integrating and computing centres in the cerebral cortex <sup>38,39,64</sup>. Chromosomal defects were also found to be elevated in Colorado (rose 30%) <sup>57</sup>, in Hawaii <sup>52</sup> in our recent analysis of cannabis use and congenital anomalies across USA, and in infants presenting from Northern New South Wales to Queensland hospitals <sup>65</sup>. And gastroschisis shows a uniform pattern of elevation in all recent studies which have examined it (our univariate meta-analysis) <sup>52,54,66-71</sup>. Interestingly the gastroschisis rate doubled in North Carolina in just three years 1997-2001 <sup>72</sup>, but rose 24 times in Mexico <sup>73</sup> which for a long time formed a principal supply source for Southern USA <sup>74</sup>. Within North Carolina gastroschisis and congenital heart defects closely followed cannabis distribution routes <sup>74-76</sup>. In Canada a remarkable geographical analysis by the Canadian Government has shown repeatedly that the highest incidence of all anomalies – including chromosomal anomalies - occurs in those northern parts where most cannabis is smoked <sup>77,78</sup>.

Congenital anomalies forms the largest cause of death of babies in the first year of life. The biggest group of them is cardiovascular defects. Since cannabis affects several major classes of congenital defects it is obviously a major human teratogen. Its heavy epigenetic footprint, by which it controls gene expression by controlling DNA methylation and histone modifications <sup>79-81</sup>, imply that its effects will be felt for the next three to four generations – that is the next 100 years <sup>82,83</sup>.

Equally obviously it is presently being marketed globally as a major commodity apparently for commercial – or ideological - reasons. Since cannabis is clearly contraindicated in several groups of people including:

- 1) Babies
- 2) Children
- 3) Adolescents
- 4) Car drivers

- 5) Commercial Drivers - Taxis, Buses, Trains,
- 6) Pilots of Aeroplanes
- 7) Workers – Manual Tools, Construction, Concentration Jobs
- 8) Children
- 9) Adolescents
- 10) Males of Reproductive age
- 11) Females of Reproductive age
- 12) Pregnancy
- 13) Lactation
- 14) Workers
- 15) Older People – Mental Illness
- 16) Immunosuppressed
- 17) Asthmatics – 80% Population after severe chest infection
- 18) People with Personal History of Cancer
- 19) People with Family History of Cancer
- 20) People with Personal History of Mental Illness
- 21) People with Family History of Mental Illness
- 22) Anyone or any population concerned about ageing effects <sup>34</sup>

... cannabis legalization is not likely to be in the best interests of public health.

### **Concluding Remarks**

In 1854 Dr John Snow achieved lasting public health fame by taking the handle off the Broad Street pump and saving east London from its cholera epidemic, based upon the maps he drew of where the cholera cases were occurring – in the local vicinity of the Broad Street pump.

**Looking across the broad spectrum of the above evidence one notices a truly remarkable concordance of the evidence between:**

- 1) Preclinical studies in
  - i) Rabbits and
  - ii) Hamsters
- 2) Cellular and biological mechanisms, particularly relating to:
  - i) Brain development
  - ii) Heart development
  - iii) Blood vessel development
  - iv) Genetic development
  - v) Abnormalities of chromosomal segregation
    - i. Downs syndrome
    - ii. Turners syndrome
    - iii. Trisomy 18
    - iv. Trisomy 13
  - vi) Cell division / mitotic poison / micronucleus formation
  - vii) Epigenetic change
  - viii) Growth inhibition
- 3) <sup>84</sup>Cross-sectional Epidemiological studies, especially from:
  - i) Canada <sup>77,85</sup>
  - ii) USA <sup>86,87</sup>

- iii) Northern New South Wales <sup>65,88</sup>
  - 4) Longitudinal studies from <sup>58</sup>:
    - i) Ottawa <sup>59-63</sup>
    - ii) Pittsburgh
    - iii) Netherlands

Our studies of congenital defects in USA have also shown a close concordance of congenital anomaly rates for 23 defects with the cannabis use rate indexed for the rising cannabis concentration in USA, and mostly in the three major classes of brain defects, cardiovascular defects and chromosomal defects, just as found by previous investigators in Hawaii <sup>52</sup>.

Of no other toxin to our knowledge can it be said that ***it interferes with brain growth and development to the point where the brain is permanently shrunk in size or does not form at all.*** The demonstration by CDC twice that the incidence of anencephaly (no brain) is doubled by cannabis <sup>53,54</sup> implies that ***anencephaly is the most severe end of the neurobehavioural teratogenicity of cannabis and forms one end of a continuum with all the other impairments*** which are implied by the above commentary. (Actually when blighted ova, foetal resorptions and spontaneous abortion are included in the teratological profile anencephaly is not the most severe end of the teratological spectrum – that is foetal death). It is our view that with the recent advent of high dose potent forms of cannabis reaching the foetus through both maternal and paternal lines ***major and clinically significant neurobehavioural teratological presentations will become commonplace, and might well become all but universal in infants experiencing significant gestational exposure.*** One can only wonder if the community has been prepared for such a holocaust and tsunami amongst its children??

It is the view of myself and my collaborators that these matters are significant and salient and should be achieving greater airplay in the public discussion proceeding around the world at this time on this subject. Whilst cannabis legalization may line the pockets of the few it will clearly not be in the public interest in any sense; and indeed the public will be picking up the bill for this unpremeditated move for generations to come. Oddly - financial gain seems to be one of the primary drivers of the present transnational push. When the above described public health message gets out amongst ambitious legal fraternities, financial gain and the threat of major medico-legal settlements for congenital defects - will quickly become be the ***worst*** reason for cannabis legalization.

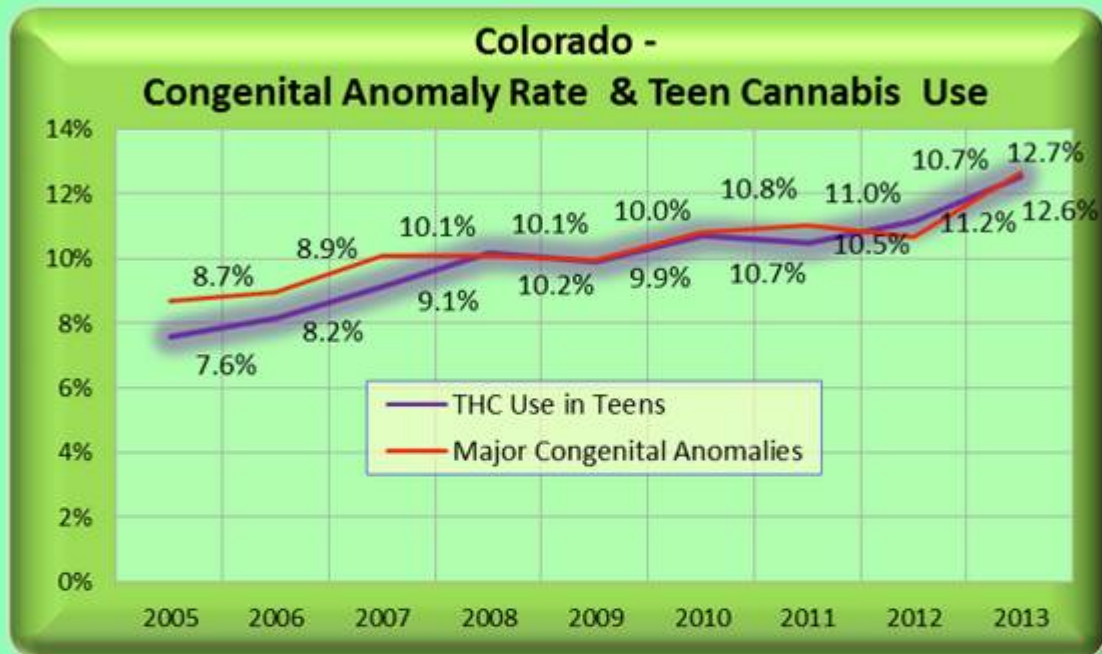
Indeed it can be argued that the legalization lobby is well aware of all of the above concerns – and their controlled media pretend debate does not allow such issues to air in the public forum. The awareness of these concerns is then the likely direct reason that cannabis requires its own legislation. As noted in the patient information leaflet for the recently approved Epidiolex (cannabidiol oil for pediatric fits) the US Food and Drug Administration (FDA) is well aware of the genotoxicity of cannabinoids.

The only possible conclusion therefore is that the public is deliberately being duped.

To which our only defence will be to publicize the truth.

Will we??

***Close Correlation between Cannabis  
Consumption and Congenital Anomalies Rates***  
 ***$R = 0.95, P = 0.00006594$***



```
> cor.test(a,x, alternative="two.sided",
+          method="pearson", exact=TRUE, conf.level = 0.95)

Pearson's product-moment correlation

data:  a and x
t = 8.4142, df = 7, p-value = 6.594e-05
alternative hypothesis: true correlation is not equal to 0
95 percent confidence interval:
 0.7908924 0.9905319
sample estimates:
cor
0.953952
```

## **References**

- 1 Volkow, N. D., Baler, R. D., Compton, W. M. & Weiss, S. R. B. Adverse Health Effects of Marijuana Use. *New England Journal of Medicine* **370**, 2219-2227, doi:doi:10.1056/NEJMra1402309 (2014).
- 2 Hall, W. & Degenhardt, L. Adverse health effects of non-medical cannabis use. *Lancet* **374**, 1383-1391, doi:10.1016/S0140-6736(09)61037-0 (2009).
- 3 Heath Canada. *Health Effects of Cannabis*, <<https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/health-effects/effects.html>> (2018).
- 4 Meier, M. H. *et al.* Associations Between Cannabis Use and Physical Health Problems in Early Midlife: A Longitudinal Comparison of Persistent Cannabis vs Tobacco Users. *JAMA Psychiatry* **73**, 731-740, doi:10.1001/jamapsychiatry.2016.0637 (2016).
- 5 Fergusson, D. M., Boden, J. M. & Horwood, L. J. Cannabis use and other illicit drug use: testing the cannabis gateway hypothesis. *Addiction* **101**, 556-569, doi:ADD1322 [pii] 10.1111/j.1360-0443.2005.01322.x (2006).
- 6 Fergusson, D. M. & Horwood, L. J. Early onset cannabis use and psychosocial adjustment in young adults. *Addiction* **92**, 279-296 (1997).
- 7 Fergusson, D. M., Horwood, L. J. & Beaudrais, A. L. Cannabis and educational achievement. *Addiction* **98**, 1681-1692, doi:573 [pii] (2003).
- 8 Fergusson, D. M., Horwood, L. J. & Swain-Campbell, N. Cannabis use and psychosocial adjustment in adolescence and young adulthood. *Addiction* **97**, 1123-1135, doi:103 [pii] (2002).
- 9 Fergusson, D. M., Lynskey, M. T. & Horwood, L. J. Conduct problems and attention deficit behaviour in middle childhood and cannabis use by age 15. *The Australian and New Zealand journal of psychiatry* **27**, 673-682 (1993).
- 10 Lynskey, M. T., Fergusson, D. M. & Horwood, L. J. The origins of the correlations between tobacco, alcohol, and cannabis use during adolescence. *Journal of child psychology and psychiatry, and allied disciplines* **39**, 995-1005 (1998).
- 11 Marie, D., Fergusson, D. M. & Boden, J. M. Links between ethnic identification, cannabis use and dependence, and life outcomes in a New Zealand birth cohort. *The Australian and New Zealand journal of psychiatry* **42**, 780-788, doi:901464301 [pii] 10.1080/00048670802277289 (2008).
- 12 Fergusson, D. M., Horwood, L. J. & Boden, J. M. Is driving under the influence of cannabis becoming a greater risk to driver safety than drink driving? Findings from a longitudinal study. *Accident; analysis and prevention* **40**, 1345-1350, doi:S0001-4575(08)00026-2 [pii] 10.1016/j.aap.2008.02.005 (2008).

- 13 Bartova, A. & Birmingham, M. K. Effect of delta9-tetrahydrocannabinol on mitochondrial NADH-oxidase activity. *J Biol Chem* **251**, 5002-5006 (1976).
- 14 Benard, G. *et al.* Mitochondrial CB(1) receptors regulate neuronal energy metabolism. *Nat Neurosci* **15**, 558-564, doi:10.1038/nn.3053 (2012).
- 15 Hebert-Chatelain, E. *et al.* A cannabinoid link between mitochondria and memory. *Nature* **539**, 555-559, doi:10.1038/nature20127 (2016).
- 16 Hebert-Chatelain, E. *et al.* Cannabinoid control of brain bioenergetics: Exploring the subcellular localization of the CB1 receptor. *Mol Metab* **3**, 495-504, doi:10.1016/j.molmet.2014.03.007 (2014).
- 17 Koch, M. *et al.* Hypothalamic POMC neurons promote cannabinoid-induced feeding. *Nature* **519**, 45-50, doi:10.1038/nature14260 (2015).
- 18 Mahoney, J. M. & Harris, R. A. Effect of 9 -tetrahydrocannabinol on mitochondrial precesses. *Biochemical pharmacology* **21**, 1217-1226 (1972).
- 19 Wolff, V. *et al.* Tetrahydrocannabinol induces brain mitochondrial respiratory chain dysfunction and increases oxidative stress: a potential mechanism involved in cannabis-related stroke. *Biomed Res Int* **2015**, 323706, doi:10.1155/2015/323706 (2015).
- 20 Chari-Briton, A. Proceedings: Swelling of rat liver mitochondria induced by delta1-tetrahydrocannabinol. *Isr J Med Sci* **11**, 1189 (1975).
- 21 Reece, A. S. Chronic toxicology of cannabis. *Clin Toxicol (Phila)* **47**, 517-524, doi:10.1080/15563650903074507 (2009).
- 22 Reece, A. S. Clinical implications of addiction related immunosuppression. *J Infect* **56**, 437-445, doi:S0163-4453(08)00123-0 [pii] 10.1016/j.jinf.2008.03.003 (2008).
- 23 Reece A. S., Norman, A. & Hulse G.K. Acceleration of Cardiovascular - Biological Age by Amphetamine Exposure is a Power Function of Chronological Age. *British Medical Journal Open* (2017).
- 24 Reece A.S., Norman, A. & Hulse G.K. Cannabis Exposure as an Interactive Cardiovascular Risk Factor and Accelerant of Organismal Ageing – A Longitudinal Study. *BMJ - Open* **6**(11) :e077891; doi:<http://dx.doi.org/10.1136/bmjopen-2016-011891> (2016).
- 25 Reece A.S. & G.K., H. Impact of Lifetime Opioid Exposure on Arterial Stiffness and Vascular Age: Cross-sectional and Longitudinal Studies in Men and Women. *BMJ Open* **4**, 1-19, doi:10.1136/bmjopen-2013-004521 (2014).
- 26 Reece A.S. & Hulse G.K. Impact of Opioid Pharmacotherapy on Arterial stiffness and Vascular Ageing: Cross-sectional and Longitudinal Studies. *Cardiovascular Toxicology* **13**, 254-266, doi:10.1007/s12012-013-9204-4 (2013).

- 27     Reece A. S. Relative and Age Dependent Stimulation of Soluble and Cellular Immunity in Opiate Dependence. *Journal of Addiction Medicine* **6**, 10-17, doi:10.1097/ADM.0b013e31822c3bf4 (2012).
- 28     Reece A. S. Chronic Immune Stimulation as a Contributing Cause of Chronic Disease in Opiate Addiction Including Multi-System Ageing *Medical hypotheses* **75**, 613-619, doi:10.1016/j.mehy.2010.07.047. Epub 2010 Aug 25. (2010).
- 29     Reece A.S. Improved Parameters of Metabolic Glycaemic and Immune Function and Arterial Stiffness with Naltrexone Implant Therapy. *British Medical Journal, Case Reports* (2008 ).
- 30     Reece A.S. & Hulse G. K.. Hypothalamic Pathophysiology in the Neuroimmune, Dysmetabolic and Longevity Complications of Chronic Opiate Dependency. *J. Forensic Toxicology and Pharmacology* **3**, 3-46, doi:10.4172/2325-9841.1000126 (2014).
- 31     Reece, A. S. Evidence of Accelerated Ageing in Clinical Drug Addiction from Immune, Hepatic and Metabolic Biomarkers. *Immun Ageing* **4**, 6-15, doi:10.1186/1742-4933-4-6. (2007).
- 32     Reece, A. S. Improved parameters of metabolic glycaemic and immune function and arterial stiffness with naltrexone implant therapy. *BMJ Case Rep* **2009**, bcr0820080799, doi:10.1136/bcr.08.2008.0799 bcr08.2008.0799 [pii] (2009).
- 33     Reece, A. S. & Hulse, G. K. Elevation of the ACTH/cortisol ratio in female opioid dependent patients: A biomarker of aging and correlate of metabolic and immune activation. *Neuro Endocrinol Lett* **37**, 325-336 (2016).
- 34     Reece A.S., Norman, A. & Hulse G.K. Cannabis Exposure as an Interactive Cardiovascular Risk Factor and Accelerant of Organismal Ageing – A Longitudinal Study. *BMJ - Open* **6**, e011891-e011900, doi:<http://dx.doi.org/10.1136/bmjopen-2016-011891> (2016).
- 35     Sadler, T. W. *Medical Embryology*. 13th Edition edn, Vol. 1 1-406 (Wolters Kluwer, 2015).
- 36     Carlson, B. M. *Human Embryology and Developmental Biology*. Vol. 1 1-506 (Elsevier, 2014).
- 37     Pacher, P., Steffens, S., Hasko, G., Schindler, T. H. & Kunos, G. Cardiovascular effects of marijuana and synthetic cannabinoids: the good, the bad, and the ugly. *Nat Rev Cardiol* **15**, 151-166, doi:10.1038/nrcardio.2017.130 (2018).
- 38     Lorenzetti, V. *et al.* Gross morphological brain changes with chronic, heavy cannabis use. *Br J Psychiatry* **206**, 77-78, doi:10.1192/bjp.bp.114.151407 (2015).
- 39     Solowij, N. *et al.* Alteration to hippocampal shape in cannabis users with and without schizophrenia. *Schizophrenia research* **143**, 179-184, doi:S0920-9964(12)00614-7 [pii] 10.1016/j.schres.2012.10.040 (2013).

- 40 Yates, D. Learning and memory: The cannabinoid connection. *Nat Rev Neurosci* **18**, 4, doi:10.1038/nrn.2016.171 (2016).
- 41 Reece, A. S. & Hulse, G. K. Chromothripsis and epigenomics complete causality criteria for cannabis- and addiction-connected carcinogenicity, congenital toxicity and heritable genotoxicity. *Mutat Res* **789**, 15-25, doi:10.1016/j.mrfmmm.2016.05.002 (2016).
- 42 Van Went, G. F. Mutagenicity testing of 3 hallucinogens: LSD, psilocybin and delta 9-THC, using the micronucleus test. *Experientia* **34**, 324-325 (1978).
- 43 Zhang, C. Z. *et al.* Chromothripsis from DNA damage in micronuclei. *Nature* **522**, 179-184, doi:10.1038/nature14493 (2015).
- 44 Tomar R.S. *et al.* Evidence on the Carcinogenicity of Marijuana Smoke. *California Health Department* **1**, 1-150 (August 2009).
- 45 Callaghan, R. C., Allebeck, P., Akre, O., McGlynn, K. A. & Sidorchuk, A. Cannabis Use and Incidence of Testicular Cancer: A 42-Year Follow-up of Swedish Men between 1970 and 2011. *Cancer Epidemiol Biomarkers Prev* **26**, 1644-1652, doi:10.1158/1055-9965.EPI-17-0428 (2017).
- 46 Daling, J. R. *et al.* Association of marijuana use and the incidence of testicular germ cell tumors. *Cancer* **115**, 1215-1223, doi:10.1002/cncr.24159 (2009).
- 47 Gurney, J., Shaw, C., Stanley, J., Signal, V. & Sarfati, D. Cannabis exposure and risk of testicular cancer: a systematic review and meta-analysis. *BMC Cancer* **15**, 897, doi:10.1186/s12885-015-1905-6 (2015).
- 48 Lacson, J. C. *et al.* Population-based case-control study of recreational drug use and testis cancer risk confirms an association between marijuana use and nonseminoma risk. *Cancer* **118**, 5374-5383, doi:10.1002/cncr.27554 (2012).
- 49 Trabert, B., Sigurdson, A. J., Sweeney, A. M., Strom, S. S. & McGlynn, K. A. Marijuana use and testicular germ cell tumors. *Cancer* **117**, 848-853, doi:10.1002/cncr.25499 (2011).
- 50 Graham, J. D. P. in *Cannabis and Health* Vol. 1 (ed J.D.P. Graham) Ch. 8, 271-320 (Academic Press, 1976).
- 51 Geber, W. F. & Schramm, L. C. Effect of marihuana extract on fetal hamsters and rabbits. *Toxicology and applied pharmacology* **14**, 276-282 (1969).
- 52 Forrester, M. B. & Merz, R. D. Risk of selected birth defects with prenatal illicit drug use, Hawaii, 1986-2002. *Journal of toxicology and environmental health* **70**, 7-18 (2007).
- 53 van Gelder, M. M. *et al.* Maternal periconceptional illicit drug use and the risk of congenital malformations. *Epidemiology* **20**, 60-66, doi:10.1097/EDE.0b013e31818e5930 (2009).

- 54 Van Gelder, M. M. H. J., Donders, A. R. T., Devine, O., Roeleveld, N. & Reefhuis, J. Using bayesian models to assess the effects of under-reporting of cannabis use on the association with birth defects, national birth defects prevention study, 1997-2005. *Paediatric and perinatal epidemiology* **28**, 424-433, doi:10.1111/ppe.12140 (2014).
- 55 Jenkins, K. J. *et al.* Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. *Circulation* **115**, 2995-3014, doi:10.1161/CIRCULATIONAHA.106.183216 (2007).
- 56 Wilson, P. D., Loffredo, C. A., Correa-Villasenor, A. & Ferencz, C. Attributable fraction for cardiac malformations. *Am J Epidemiol* **148**, 414-423 (1998).
- 57 Colorado: Department of Public Health and the Environment. Vol. 1 Birth Defect Data - Colorado Register of Congenital Surveillance Network 1 (ed Colorado: Department of Public Health and the Environment) <http://www.chd.dphe.state.co.us/cohid/> (Colorado: Department of Public Health and the Environment, Denver Colorado, USA, 2018).
- 58 Brents L. in *Handbook of Cannabis and Related Pathologies: Biology, Pharmacology, Diagnosis and Treatment* Vol. 1 (ed Preedy V.R.) Ch. 17, 160-170 (Academic Press, 2017).
- 59 Fried, P. A. & Smith, A. M. A literature review of the consequences of prenatal marihuana exposure. An emerging theme of a deficiency in aspects of executive function. *Neurotoxicol Teratol* **23**, 1-11 (2001).
- 60 Smith, A., Fried, P., Hogan, M. & Cameron, I. The effects of prenatal and current marijuana exposure on response inhibition: a functional magnetic resonance imaging study. *Brain Cogn* **54**, 147-149 (2004).
- 61 Smith, A. M., Fried, P. A., Hogan, M. J. & Cameron, I. Effects of prenatal marijuana on response inhibition: an fMRI study of young adults. *Neurotoxicol Teratol* **26**, 533-542, doi:10.1016/j.ntt.2004.04.004 (2004).
- 62 Smith, A. M., Longo, C. A., Fried, P. A., Hogan, M. J. & Cameron, I. Effects of marijuana on visuospatial working memory: an fMRI study in young adults. *Psychopharmacology (Berl)* **210**, 429-438, doi:10.1007/s00213-010-1841-8 (2010).
- 63 Smith, A. M. *et al.* Prenatal marijuana exposure impacts executive functioning into young adulthood: An fMRI study. *Neurotoxicol Teratol* **58**, 53-59, doi:10.1016/j.ntt.2016.05.010 (2016).
- 64 Zalesky, A. *et al.* Effect of long-term cannabis use on axonal fibre connectivity. *Brain* **135**, 2245-2255, doi:aws136 [pii] 10.1093/brain/aws136 (2012).
- 65 Report of the Queensland Perinatal Maternal and Perinatal Quality Council & Queensland Health. Vol. 1 (ed Queensland Health) 5 (Queensland Health, Brisbane, 2018).

- 66 Werler, M. M., Sheehan, J. E. & Mitchell, A. A. Association of vasoconstrictive exposures with risks of gastroschisis and small intestinal atresia. *Epidemiology* **14**, 349-354 (2003).
- 67 David, A. L. *et al.* A case-control study of maternal periconceptual and pregnancy recreational drug use and fetal malformation using hair analysis. *PLoS One* **9**, e111038, doi:10.1371/journal.pone.0111038 (2014).
- 68 van Gelder, M. M. *et al.* Maternal periconceptual illicit drug use and the risk of congenital malformations. *Epidemiology* **20**, 60-66, doi:10.1097/EDE.0b013e31818e5930 (2009).
- 69 Skarsgard, E. D. *et al.* Maternal risk factors for gastroschisis in Canada. *Birth Defects Res A Clin Mol Teratol* **103**, 111-118, doi:10.1002/bdra.23349 (2015).
- 70 Torfs, C. P., Velie, E. M., Oechsli, F. W., Bateson, T. F. & Curry, C. J. A population-based study of gastroschisis: demographic, pregnancy, and lifestyle risk factors. *Teratology* **50**, 44-53, doi:10.1002/tera.1420500107 (1994).
- 71 Draper, E. S. *et al.* Recreational drug use: a major risk factor for gastroschisis? *Am J Epidemiol* **167**, 485-491, doi:10.1093/aje/kwm335 (2008).
- 72 Laughon, M. *et al.* Rising birth prevalence of gastroschisis. *J Perinatol* **23**, 291-293, doi:10.1038/sj.jp.7210896 (2003).
- 73 Di Tanna, G. L., Rosano, A. & Mastroiacovo, P. Prevalence of gastroschisis at birth: retrospective study. *BMJ (Clinical research ed)* **325**, 1389-1390 (2002).
- 74 Centre, N. D. i. *North Carolina Drug Threat Assessment, April 2003: Marijuana*, < <https://www.justice.gov/archive/ndic/pubs3/3690/marijuan.htm> > (2003).
- 75 Nelson, J. S., Stebbins, R. C., Strassle, P. D. & Meyer, R. E. Geographic distribution of live births with tetralogy of Fallot in North Carolina 2003 to 2012. *Birth Defects Res A Clin Mol Teratol* **106**, 881-887, doi:10.1002/bdra.23566 (2016).
- 76 Root, E. D., Meyer, R. E. & Emch, M. E. Evidence of localized clustering of gastroschisis births in North Carolina, 1999-2004. *Social science & medicine (1982)* **68**, 1361-1367, doi:10.1016/j.socscimed.2009.01.034 (2009).
- 77 Leos-Toro C. *et al.* in *Cannabis in Canada: Patterns and Trends, 2017* Vol. 1 (eds PROPEL, Centre for Population Health Impact, & University of Waterloo) 1-23 (University of Waterloo, Waterloo, Ontario, 2017).
- 78 Moore A., Roulean J. & Skarsgard E. Vol. 1 (ed Health Canada Public Health Agency of Canada) 57-63 (Health Canada, Ottawa, 2013).
- 79 DiNieri, J. A. *et al.* Maternal cannabis use alters ventral striatal dopamine D2 gene regulation in the offspring. *Biol Psychiatry* **70**, 763-769, doi:10.1016/j.biopsych.2011.06.027 (2011).

- 80 Szutorisz, H. *et al.* Parental THC exposure leads to compulsive heroin-seeking and altered striatal synaptic plasticity in the subsequent generation. *Neuropsychopharmacology* **39**, 1315-1323, doi:10.1038/npp.2013.352 (2014).
- 81 Watson, C. T. *et al.* Genome-Wide DNA Methylation Profiling Reveals Epigenetic Changes in the Rat Nucleus Accumbens Associated With Cross-Generational Effects of Adolescent THC Exposure. *Neuropsychopharmacology*, doi:10.1038/npp.2015.155 (2015).
- 82 Manikkam, M., Guerrero-Bosagna, C., Tracey, R., Haque, M. M. & Skinner, M. K. Transgenerational actions of environmental compounds on reproductive disease and identification of epigenetic biomarkers of ancestral exposures. *PLoS One* **7**, e31901, doi:10.1371/journal.pone.0031901 (2012).
- 83 Manikkam, M., Tracey, R., Guerrero-Bosagna, C. & Skinner, M. K. Dioxin (TCDD) induces epigenetic transgenerational inheritance of adult onset disease and sperm epimutations. *PLoS One* **7**, e46249, doi:10.1371/journal.pone.0046249 (2012).
- 84 Yang, X. *et al.* Histone modifications are associated with Delta9-tetrahydrocannabinol-mediated alterations in antigen-specific T cell responses. *J Biol Chem* **289**, 18707-18718, doi:10.1074/jbc.M113.545210 (2014).
- 85 Public Health Agency of Canada. Vol. 1 (ed Health Canada Public Health Agency of Canada) 1-115 (Health Canada, Ottawa, 2013).
- 86 Substance Abuse and Mental Health Services Administration (SAMHSA), Department of Health and Human Services (HHS) & United States of America. *National Survey on Drug Use and Health*, <<https://www.samhsa.gov/data/data-we-collect/nsduh-national-survey-drug-use-and-health>> (2018).
- 87 National Birth Defects Prevention Network. *National Birth Defects Prevention Network*, <<https://www.nbdpn.org/ar.php>> (2018).
- 88 Queensland Maternal and Perinatal Quality Council 2017. Vol. 1 I (ed Queensland Health) 1-70 (Queensland Health, Brisbane, 2018).

## **Explaining Modern Patterns of Cannabis Teratology**

Short Title:

CB1R Expression Key to Understanding Cannabis Teratology

Albert Stuart Reece <sup>1,2</sup>

Moirira Sim <sup>2</sup>

Gary Kenneth Hulse <sup>1,2</sup>

1 - Division of Psychiatry,  
University of Western Australia,  
Crawley, Western Australia 6009, Australia.

2 – School of Medical and Health Sciences,  
Edith Cowan University,  
Joondalup, Western Australia, 6027, Australia.

### **\* Correspondence to:**

Albert Stuart Reece  
39 Gladstone Rd.,  
Highgate Hill,  
Brisbane, Queensland, Australia.

Ph: (617) 3844-4000

FAX: (617) 3844-4015

Email: [sreece@bigpond.net.au](mailto:sreece@bigpond.net.au)

Word Count: 1,000.

In an era when 24% of teenage Californian mothers test cannabis-positive it is unfortunate that the vast and conflicting literature on cannabis teratology has created professional confusion on the important subject of cannabis teratology. An appreciation of overarching patterns can contribute to clarity in this field.

There is considerable agreement in the literature that cannabis interferes with foetal development including earlier birth, higher rates of prematurity, and lifelong smaller heads – which obviously necessarily implies lifelong smaller brains as well <sup>1</sup>. Moreover the National Birth Defects Prevention Network coordinated by CDC have issued two papers documenting increased rates of anencephaly with R.R. = 1.7 (95% C.I. 0.9-3.4) and RR=1.9 (95% C.I. 1.1-3.2) respectively <sup>2</sup>. And there is very close agreement from the three major longitudinal studies from Ottawa, Pittsburgh and Netherlands of brain growth and intellectual development in children after prenatal cannabis exposure (PCE) which clearly document impaired executive functioning, poorer attention, difficulty in school work increased rates of addiction, persisting through all grades of school and into young adult life as long as the early 20's <sup>3</sup>. Other studies have shown reduced frontal cortical thickness and increased white matter tract disconnections approaching 90% in key executive and computational cortical areas. It is known that the foetal brain stem is low in cannabinoid type 1 receptors (CB1R's) but many parts of the rest of the brain, including cerebral, hippocampal, orbitofrontal and cerebellar cortices, the limbic system and parts of the midbrain have moderate to high density CB1R's.

This pattern of CB1R distribution forms both the greatest strength of cannabis and also its greatest weakness. It is often – although clearly wrongly - said that cannabis cannot kill patients because the brain stem is low in CB1R's so direct respiratory depression cannot occur as occurs from opioids. The tag line about cannabis not causing death, though thoroughly deserving of “urban myth” status is demonstrably erroneous as cannabis is now well linked with cardiac arrest, psychosis, testicular cancer, chronic lung disease and unemployment – amongst many others - all of which are greatly elevate mortality. As in adult life, so in foetal life the largely supratentorial distribution of CB1R's implies that perturbation of the endogenous endocannabinoid system could conceivably interfere with the development of the supratentorial brain. This pattern is well displayed by anencephaly in which the brain stem is often more or less intact. It can be argued that the remainder of the neuroteratological manifestations of PCE reflect the pattern of distribution and expression of

CB1R's which occur with development. This implies that cannabis neuroteratology actually reflects a continuum with subtle forms of neurobehavioral teratology at one end of the spectrum, microcephaly and smaller heads in an intermediate position and anencephaly at the most severe end. This continuum can be further extended to include neurologically induced foetal loss and spontaneous and therapeutically induced terminations.

Moreover high density CB1R's have been demonstrated on brain mitochondria where they subserve numerous key brain functions including thinking, attention, memory and wakefulness<sup>4</sup>. Their inhibition is directly linked with stimulating aging processes via mitonuclear crosstalk, induction of the mitochondrial stress response and impaired DNA repair. The implications of accelerated molecular and neuronal *aging* at the *foetal* stage have not been properly considered.

The American Heart Association and the American Academy of Pediatrics issued a statement as long ago as 2007 that found two heart defects, ventricular septal defect (VSD) and Ebsteins anomaly, were known to be related to cannabis use on the basis of two studies<sup>5</sup>. Importantly both the atrioventricular valves and parts of the membranous interventricular septum are derived from the endocardial cushions which are known to be high in CB1R's from as early as 9 weeks of gestation. The Colorado experience also fits here with a 35% increase in VSD rates and a 262% increase in atrial septal defect rates 2000-2013 (Figure 1). This early appearance of cardiovascular CB1R's is important as many women are unsure of their pregnancy at this time; and given the very long half-life of cannabis in fat stores of several months immediate cessation would not protect a developing foetus during critical periods of organogenesis. Studies show that *paternal* exposure is more significant than maternal exposure for several defects including transposition of the great arteries. CB1R is a key regulator of the neurovascular *neural stem cell niche*.

Gastroschisis incidence has also risen, and reflects vasoactive drug exposure. High density CB1R's on foetal arteries, CB1R-mediated vasospasm and cannabis arteritis imply that the demonstrated vasoactive properties of cannabis have been largely overlooked<sup>6</sup>. Seven studies uniformly document on univariate testing increased incidence of gastroschisis after cannabis exposure and a further two studies show increased severity. Carefully adjusted Canadian studies show a threefold elevation of gastroschisis risk.

$\Delta^9$ -Tetrahydrocannabinol also interferes with nuclear actin and tubulin polymerization directly interfering with the processes of DNA repair and cell division respectively <sup>7</sup>. Hence Down's syndrome, which is one of the chromosomal mis-segregation disorders has been linked with PCE.

Government reports from Canada show a clear association of high congenital anomaly rates for total defects, cardiovascular defects, orofacial clefts and gastroschisis with areas of high cannabis consumption. Similar evidence is also available for high cannabis use areas in Northern New South Wales in Australia. USA state level epidemiology replicates these same patterns.

As the second most common cannabinoid present in cannabis it is important to appreciate that the above-cited neonatal epidemiology also implicates cannabidiol which also binds to CB1R's at high doses and has demonstrated genotoxicity, epigenotoxicity and mitochondrial toxicity.

These observations show that the CB1R, the dominant cannabinoid endoreceptor, well explains much of the neurobehavioural and cardiovascular teratology which is now relatively well described.

Importantly such an understanding, together with the non-linear asymptotic cannabinoid-genotoxic dose-response curve, predicts that increased community exposure to cannabis both by prevalence and by the high concentrations widely available will necessarily imply severe brain damage which can safely be said to approach 100% for significant in utero or *paternal* exposure, a congenital defect from which recovery is not possible as brain growth is permanently compromised.

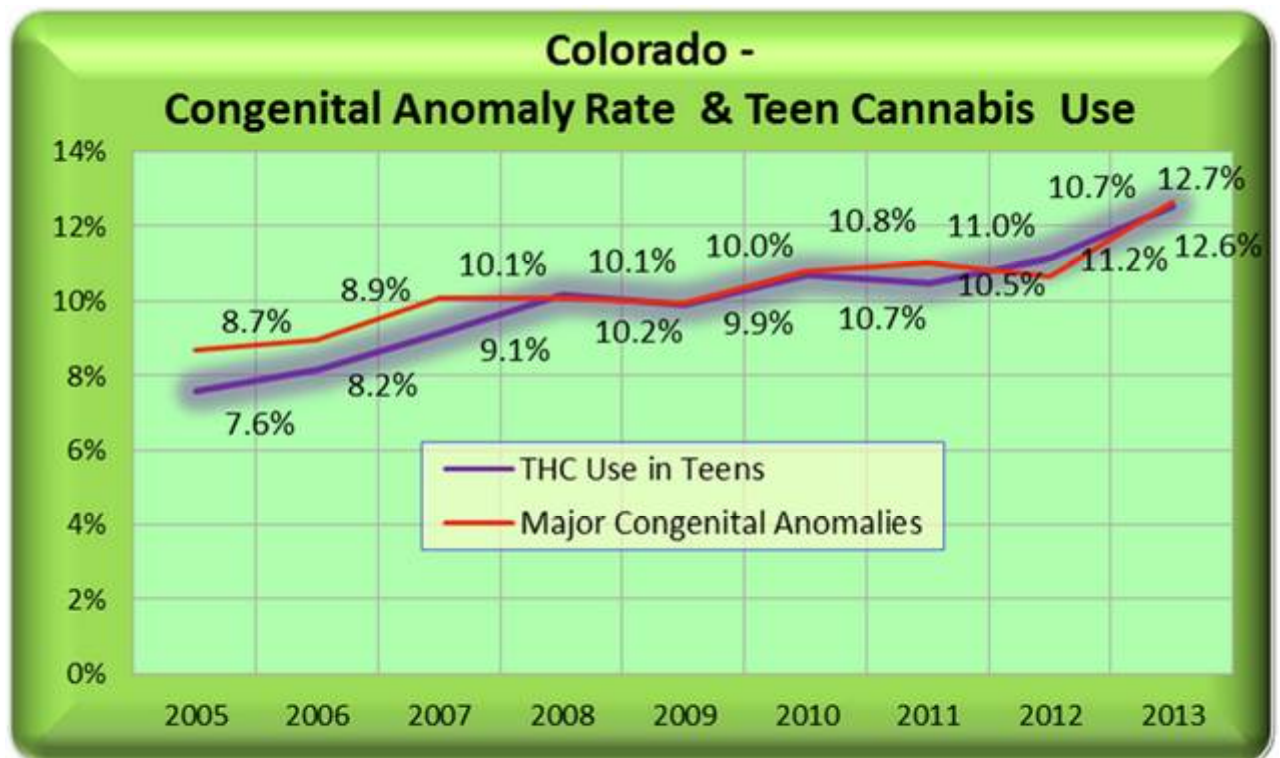
## **References**

1. Volkow ND, Compton WM, Wargo EM. The Risks of Marijuana Use During Pregnancy. *JAMA*. 2017;317(2):129-130.
2. Van Gelder MMHJ, Donders ART, Devine O, Roeleveld N, Reefhuis J. Using bayesian models to assess the effects of under-reporting of cannabis use on the association with birth defects, national birth defects prevention study, 1997-2005. *Paediatric and perinatal epidemiology*. 2014;28(5):424-433.
3. Brents L. Correlates and consequences of Prenatal Cannabis Exposure (PCE): Identifying and Characterizing Vulnerable Maternal Populations and Determining Outcomes in Exposed Offspring In: Preedy V.R., ed. *Handbook of Cannabis and Related Pathologies: Biology, Pharmacology, Diagnosis and Treatment*. Vol 1. London: Academic Press; 2017:160-170.
4. Hebert-Chatelain E, Desprez T, Serrat R, et al. A cannabinoid link between mitochondria and memory. *Nature*. 2016;539(7630):555-559.
5. Jenkins KJ, Correa A, Feinstein JA, et al. Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. *Circulation*. 2007;115(23):2995-3014.
6. Pacher P, Steffens S, Hasko G, Schindler TH, Kunos G. Cardiovascular effects of marijuana and synthetic cannabinoids: the good, the bad, and the ugly. *Nat Rev Cardiol*. 2018;15(3):151-166.
7. Reece AS, Hulse GK. Chromothripsis and epigenomics complete causality criteria for cannabis- and addiction-connected carcinogenicity, congenital toxicity and heritable genotoxicity. *Mutat Res*. 2016;789:15-25.

Captions:

Figure 1.: Colorado – Close Correlation between cannabis consumption and total congenital anomalies rates.  $R = 0.95$ ,  $P = 0.00006594$ .

**Figure 1.**



# Correlates and Consequences of Prenatal Cannabis Exposure (PCE): Identifying and Characterizing Vulnerable Maternal Populations and Determining Outcomes for Exposed Offspring

*L.K. Brents*

Brain Imaging Research Center, Psychiatric Research Institute, University of Arkansas for Medical Sciences, Little Rock, AR, United States

## SUMMARY POINTS

- Between 5% and 15% of pregnant women abuse illicit drugs.
- Of these women, 65–75% use cannabis during pregnancy, meaning that an estimated 5–10% of neonates are exposed to cannabis in utero.
- Prevalence estimates rely on a combination of self-report and analysis of biological samples (ie, maternal hair, urine, oral fluids, and neonatal meconium), which indicate that a small minority (<35%) of women are forthcoming about their cannabis use during pregnancy.
- Women who use cannabis during pregnancy are more likely to be younger, unmarried, of lower socioeconomic status (ie, lower education and income), and to have had unplanned pregnancies, compared to pregnant women who don't use cannabis.
- Effects of PCE are dose-dependent, with more severe negative effects occurring with heavier prenatal exposure.
- PCE is associated with lower birth weight, shorter birth length, lifelong smaller head circumference,

reduced length of gestation, neonatal neurological disturbances, reduced function in specific cognitive domains (memory, verbal, and abstract/visual reasoning), but not overall intelligence, during grade school, increased impulsivity and hyperactivity, depression at age 10, poor school achievement and delinquency in adolescence, increased use of tobacco and marijuana in adolescence, and altered neural function for visuospatial working memory and motor impulse control, in early adulthood.

## KEY FACTS OF CANNABIS EXPOSURE

- *Cannabis* is a plant that contains over 400 chemicals.
- The psychoactive effects of cannabis are caused by the cannabinoid  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC).
- The effects of  $\Delta^9$ -THC and other pharmacologically active cannabinoids are mediated by the endocannabinoid system (ECS); specifically,  $\Delta^9$ -THC activates at least two G-protein coupled receptors: the Cannabinoid 1 Receptor (CB1R) and the Cannabinoid 2 Receptor (CB2R).

- The ECS is integrally involved in a variety of biological processes that are vulnerable to disruption by exogenous cannabinoid exposure: mood, cognition, appetite, energy storage and metabolism, bone formation, reproduction, and embryonic and fetal neural development.
- Acute exposure to cannabis distorts spatial and temporal perception, elevates mood, increases appetite, impairs memory and cognition, and has a suspected link to adverse cardiovascular episodes.
- Cannabis with high  $\Delta^9$ -THC content can cause anxiety and/or lead to psychosis and schizophrenia onset in susceptible individuals.
- Chronic cannabinoid exposure can lead to cognition and memory problems, disrupt the function of the male and female reproductive systems, and lead to cannabis use disorder, which is characterized by dependence and withdrawal symptoms upon cessation.
- Younger individuals (adolescents) are more susceptible than adults to the adverse effects of marijuana, especially dependence and psychosis.

## LIST OF ABBREVIATIONS

|                                  |                                                           |
|----------------------------------|-----------------------------------------------------------|
| <b>CB1R, CB2R</b>                | Cannabinoid Receptors 1 and 2                             |
| <b><math>\Delta^9</math>-THC</b> | $\Delta^9$ -Tetrahydrocannabinol                          |
| <b>ECS</b>                       | Endocannabinoid system                                    |
| <b>fMRI</b>                      | Functional magnetic resonance imaging                     |
| <b>MHPCD</b>                     | Maternal Health Practices and Child Development           |
| <b>OPPS</b>                      | Ottawa Prenatal Prospective Study                         |
| <b>PCE</b>                       | Prenatal cannabis exposure                                |
| <b>SAMHSA</b>                    | Substance Abuse and Mental Health Services Administration |
| <b>SIDS</b>                      | Sudden Infant Death Syndrome                              |
| <b>UDS</b>                       | Urine drug screening                                      |

## INTRODUCTION

Cannabis is the most abused illicit drug worldwide (WHO, 2014) and has been used for millennia across diverse cultures for recreational, medicinal, religious, and industrial purposes (Zuardi, 2006). Because cannabis has never been documented as the primary cause of even a single death (Sidney, 2003), its use is regarded as safe by many in the public, leading to several strong movements throughout the world to legalize marijuana use for medicinal and recreational purposes (Johnson, 2014). Considering the widespread use of cannabis in the general

population, it is not surprising that cannabis is used by women immediately before, during, and after pregnancy. Despite the perceived safety of cannabis throughout the general public, unnecessary use of pharmacologically active substances during pregnancy is widely discouraged, especially when their effects on the mother–fetus dyad are unknown, or suspected to potentially cause harm. The issue of marijuana’s harm versus benefit in the general population is a controversial subject; similarly, reports on many of the suspected effects of prenatal cannabis exposure (PCE) are conflicted, or nuanced, and require careful consideration. This chapter aims to explore the correlates and consequences of PCE by examining the characteristics of women who use cannabis during pregnancy, and summarizing the scientific literature that describes the lifelong consequences of PCE on offspring.

## PREVALENCE OF PCE AND BEHAVIORAL PATTERNS OF CANNABIS USE ACROSS PREGNANCY

With few exceptions, the possession, sale, and transport of cannabis is illegal throughout the world. Nevertheless, cannabis use is highly prevalent. In a 2013 Pew Research Center poll in the United States, 48% of respondents reported ever using marijuana, with 12% of respondents reporting use in the past year (Desilver, 2013). An estimated 17.4% of past-year cannabis users were also daily or near-daily users (SAMHSA, 2014). Consistent with these data, 51.4% of young adults in an Australian sample reported ever using cannabis; importantly, more than 21% of individuals in this sample were diagnosed as ever having a cannabis use disorder by age 21 (Hayatbakhsh, Najman, Bor, O’Callaghan, & Williams, 2009).

To determine the prevalence and impact of PCE, one should focus on drug use by women. According to the US Substance Abuse and Mental Health Services Administration (SAMHSA), 11.4% of all women and 5.4% of pregnant women between ages of 15 and 44 were current illicit drug users in 2012–13, with rates as high as 14.6% for pregnant teenagers aged 15–17 (SAMHSA, 2014). In close agreement with the US SAMHSA data, a large Australian study ( $n = 25,049$ ) from 2000 to 2006 determined that 9.3% of nonpregnant women of childbearing age self-reported regular cannabis use (Hayatbakhsh et al., 2011), suggesting that a significant proportion of women use drugs during the periconceptual period. Investigators in a London study screened 807 consecutive positive urine pregnancy tests for licit and illicit drugs, and determined that 14.5% tested positive for cannabis, confirming that there is a high prevalence of early PCE (Sherwood, Keating, Kavvadia, Greenough, & Peters, 1999).

Most women abstain from drug use during pregnancy. Upon recognition of the pregnancy, at least half of women who use illicit drugs remit at some point in their pregnancy (SAMHSA, 2014). Such women are able to progressively reduce drug consumption, and even achieve complete abstinence by the third trimester (Ebrahim & Gfroerer, 2003; Gray et al., 2010). Remission of drug use during pregnancy is associated with baseline severity of drug use, psychosocial stressors, and initiation of prenatal care (Corse & Smith, 1998). Postpartum relapse is highly prevalent, with cannabis consumption returning to prepregnancy levels within a year of birth (Fried, Barnes, & Drake, 1985).

Marijuana is, by far, the most commonly abused illicit drug during pregnancy. Of pregnant and postpartum women who use illicit drugs, an overwhelming proportion—between 64% and 75%—use marijuana (Ebrahim & Gfroerer, 2003; Falcon et al., 2012). Furthermore, prenatal marijuana consumption is reduced much less than prenatal alcohol and nicotine consumption (Fried et al., 1985). Although many women achieve abstinence during pregnancy, a significant proportion of the population is being exposed to cannabis at one or more points during early development, potentially resulting in peripartum complications, and long-term alterations in development.

### **PCE DETECTION METHODS AND ACCURACY OF PREVALENCE ESTIMATES**

Many women are hesitant to report their drug use to health care providers, possibly due to the intense stigma of prenatal drug abuse, and to a fear of losing parental rights to their children. Estimates of prenatal drug use were derived from a combination of self-report and chemical analysis of urine, hair and oral fluids from pregnant and peripartum women, and meconium from neonates (Gray & Huestis, 2007). The prevalence of analysis-confirmed cannabis use in pregnancy can depend on participant sampling, the types of biological tissues that are analyzed, and the temporal relationship of drug use to biological sampling. Analytical results often conflict with self-report, due to underreporting or inadvertent sampling of prepregnancy biological specimens (eg, hair). One small, single site study ( $n = 107$ ) in Spain detected drugs of abuse in 15.9% of the maternal hair samples obtained, with cannabis being the most prevalent (detected in 10.3% of the total sample), although less than 1% reported cannabis use during pregnancy (Friguls et al., 2012). Another study in Spain detected metabolites of cannabis in 5.3% of meconium samples, although only 1.7% of mothers disclosed cannabis use in the pregnancy (Lozano et al., 2007). These two studies suggest that less than 35% of women who use cannabis

during pregnancy will disclose their drug use. The window of detection in meconium samples is restricted to the third trimester of pregnancy; therefore, a cannabis-positive meconium sample is indicative of third trimester PCE. Considering that most women who abuse drugs taper their use during pregnancy (Ebrahim & Gfroerer, 2003), third trimester use indicates that a drug was likely used throughout pregnancy, resulting in a greater overall burden of in utero exposure that occurs across most or all prenatal developmental stages. Detection of drug exposure in fetal and placental tissues is inconsistent with detection in the respective maternal hair. Less than 17% of placental and fetal tissues (gestational age 17–22 weeks) from women with a cannabis-positive hair test also tested positive for cannabis. Possible explanations of this phenomenon are that undetectable amounts of cannabis byproducts accumulate in fetal and placental tissues due to pharmacokinetic activity (ie, reduced fetal distribution, rapid metabolism, and complete excretion of cannabis from the placenta and fetus) and/or hair testing detects previous cannabis use that may have occurred only before pregnancy (Falcon et al., 2012). In contrast to hair, urine drug screening (UDS), which is the most common screening method, has a much shorter window of detection for cannabis. In a large study in the Netherlands ( $n = 3997$ ), 71 pregnant women had positive cannabis UDS, even though 92 women reported use during pregnancy (El Marroun et al., 2011a). Additionally, several of these positive screens were from women who self-reported only prepregnancy cannabis use, further increasing the disparity between self-reports of drug use and UDS. Despite the advances in analytical screening, it is clear that limitations exist in determining accurate, valid information on PCE. Clinicians must rely on a combination of self-report, family report, and multiple analytical screenings across pregnancy and the postpartum period to accurately confirm maternal drug abuse.

### **CHARACTERISTICS OF WOMEN WHO USE CANNABIS DURING PREGNANCY**

Women who abuse drugs during pregnancy tend to be younger, less educated, unemployed, and unmarried, with a history of childhood trauma, delinquency, and unplanned pregnancy (SAMHSA, 2014; Correia, Oliveria, Almeida, Sing, & Nobrega, 1995; Ebrahim & Gfroerer, 2003; El Marroun et al., 2008). Cannabis use by the biological father of the baby robustly increases the odds of a pregnant woman using cannabis (odds ratio = 38; El Marroun et al., 2008). One subgroup of prenatal drug users are women who decrease alcohol use and abstain from using some recreational drugs, specifically cocaine and ecstasy, but continue to use tobacco and cannabis at prepregnancy levels (Moore et al., 2010),

even though all of these substances are considered detrimental to the offspring. It is possible that this pattern of polydrug use is due to a misconception that tobacco and cannabis use is safer than other drugs, or to the highly rewarding or addictive properties of tobacco and cannabis. While it is presumed that most pregnant women who use cannabis do so for recreational purposes, a subset of this population reported using cannabis medicinally to treat severe morning sickness, and over 92% rated it as effective for this indication (Westfall, Janssen, Lucas, & Capler, 2006). Understanding who uses cannabis during pregnancy and their motivation for doing so is important to identifying such patients, and educating them about the potential harm of their drug use on their offspring.

## THE EFFECTS OF PCE ON OFFSPRING

Drug use during pregnancy is associated with complications of childbirth (Saleh Gargari et al., 2012) and negative physical, behavioral, and cognitive effects on the offspring (Steinhausen, Blattmann, & Pfund, 2007; Day, Richardson, Goldschmidt, & Cornelius, 2000; Conradt et al., 2013), but causal relationships between specific prenatal exposures and these negative outcomes can be difficult to establish. Potentially confounding variables that often correlate with PCE, such as, socioeconomic status, age, and coexposures to tobacco products, alcohol, and other illicit drugs complicate the identification of PCE-induced effects. Another challenge is determining the dosage of maternal cannabis use during pregnancy, and the relative in utero exposures of the offspring. To circumvent these issues, three large-scale prospective longitudinal studies that are examining offspring outcomes with an emphasis on PCE have been undertaken: the Ottawa Prenatal Prospective Study (OPPS; Fried, 1995), the Maternal Health Practices and Child Development (MHPCD) study (Day & Richardson, 1991), and the Generation R study (Jaddoe et al., 2006). The populations recruited into each study differ in demographics, and thus help to discern effects that may be due to variables other

than cannabis exposure; that is, consistent results across the cohorts strengthens the case that PCE plays a causal role. The OPPS cohort consists of a “low-risk,” racially homogenous middle class sample of pregnant women in Ottawa, Ontario in Canada who were recruited between 1978 and 1983. The MHPCD study recruited “high-risk” urban, racially and ethnically heterogeneous pregnant women of lower socioeconomic status in the Pittsburgh, Pennsylvania area in the United States, between May 1983 and Jan. 1986. The Generation R study, which began in 2001, recruited an ethnically diverse sample of slightly higher socioeconomic status in Rotterdam, the Netherlands. Much of what is known about the effects of in utero cannabis exposure comes from these studies.

In utero cannabinoid exposure has a suspected association with minor physical abnormalities, including facial-visual system anomalies, such as, ocular hypertelorism and severe epicanthus (Fried & Smith, 2001), particularly in children who had heavy PCE. Third trimester exposure to marijuana predicted a greater risk of chest and head shape abnormalities, after controlling for covariates in one study of 6-year-olds with prenatal exposure to cocaine and marijuana (Minnes et al., 2006). As shown in Table 17.1, there are also associated cardiovascular abnormalities of the PCE offspring, including isolated simple ventricular septal defect (Williams, Correa, & Rasmussen, 2004), and smaller fetal aortic diameter. Alterations in fetal blood supply that are associated with cannabis exposure include increased pulsatility and resistance indices of the uterine artery, indicating an increase in placental vascular resistance (El Marroun et al., 2010). Interestingly, decreased uterine artery pulsatility and resistance was observed when cannabis exposure was restricted to early pregnancy (El Marroun et al., 2010), suggesting that the developmental stage at which exposure occurs is critical in determining the ultimate effects on the fetal-placental complex.

Reports on how PCE affects offspring growth are conflicted (Table 17.2). While several report no effect on birth weight (English, Hulse, Milne, Holman, & Bower, 1997), a surprisingly positive relationship between PCE and

**TABLE 17.1** Cardiovascular Changes Associated With PCE

| Age group | Prenatal exposure    | Effects                                                     | References               |
|-----------|----------------------|-------------------------------------------------------------|--------------------------|
| All       |                      |                                                             |                          |
|           | Regular              | Increased risk of isolated simple ventricular septal defect | Williams et al. (2004)   |
| Prenatal  |                      |                                                             |                          |
|           | Regular              | Decreased fetal aortic diameter                             | El Marroun et al. (2010) |
|           | Regular              | Increased uterine artery pulsatility and resistance         | El Marroun et al. (2010) |
|           | Early pregnancy only | Decreased uterine artery pulsatility and resistance         | El Marroun et al. (2010) |

PCE offspring has an increased risk of a cardiac defect and greater fetal-placental cardiovascular alterations.

TABLE 17.2 Size Effects Associated With PCE

| Age group             | Prenatal exposure                                  | Effects                    | References                                                                  |
|-----------------------|----------------------------------------------------|----------------------------|-----------------------------------------------------------------------------|
| All                   |                                                    |                            |                                                                             |
|                       | Heavy                                              | Smaller head circumference | Fried et al. (1999), Gray et al. (2010)                                     |
| Prenatal and neonatal |                                                    |                            |                                                                             |
|                       | a                                                  | Small for gestational age  | Hayatbakhsh et al. (2012), Hurd et al. (2005)                               |
|                       | a                                                  | Reduced fetal foot length  | Hurd et al. (2005)                                                          |
|                       | a                                                  | No effect on birth weight  | English et al. (1997), meta-analysis                                        |
|                       | Infrequent                                         | Elevated birth weight      | Day and Richardson (1991), Fried and O'Connell (1987)                       |
|                       | More closely associated with regular, moderate use | Low birth weight           | Hayatbakhsh et al. (2012), Sherwood et al. (1999), El Marroun et al. (2009) |
|                       | a                                                  | Decreased length           | Gray et al. (2010)                                                          |
| Infant                |                                                    |                            |                                                                             |
|                       | a                                                  | Decreased body length      | Barr et al. (1984)                                                          |
| Toddler               |                                                    |                            |                                                                             |
|                       | Continuous                                         | Increased weight           | Fried and O'Connell (1987)                                                  |
| Adolescent            |                                                    |                            |                                                                             |
|                       | a                                                  | No effect on height        | Fried et al. (1999)                                                         |

Overall associates of PCE with offspring size are conflicted. Conflicts may be due to differences in prenatal cannabis exposure (ie, low exposures are associated with increased size, and larger exposures with decreased size, resulting in no net effect when data are unstratified by exposure levels). PCE, prenatal cannabis exposure.

<sup>a</sup>Unspecified.

birth weight was measured in the OPPS and the MHPCD study, with exposed babies being heavier than nonexposed (Day & Richardson, 1991), and remaining heavier up to 24 months of age (Fried & O'Connell, 1987). Heavier, more frequent use of cannabis during pregnancy was associated with low birth weight in several studies (Sherwood et al., 1999; Fried & Smith, 2001), including the Generation R cohort (El Marroun et al., 2009; Huizink, 2014). Conflicting results between the older OPPS and MHPCD study and the more recent Generation R study may be due, in part, to differences in the content of the psychoactive chemical of marijuana,  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC), during the two time periods. Over time, marijuana has been selectively bred to produce a higher concentration of  $\Delta^9$ -THC (Cascini, Aiello, & Di Tanna, 2012), potentially resulting in greater maternal intake and in utero exposure to  $\Delta^9$ -THC, in more recent studies. The size of cannabis-exposed fetuses was measured for the first time in the Generation R study. This study found that cannabis-exposed 17–22 week fetuses possessed slightly reduced foot length and body weight, with foot length decreasing in a dose-dependent manner (Hurd et al., 2005). In the OPPS cohort, PCE was negatively associated with birth length, but this relationship was not significant at 8 months, 1 year, 6 years or adolescence (Fried, Watkinson, & Gray, 1999; Fried

& Smith, 2001). In contrast, prenatally exposed infants in a different cohort were still significantly shorter at 8 months (Barr, Streissguth, Martin, & Herman, 1984). Children with heavy PCE had statistically smaller head circumferences at all ages, from early infancy to early adolescence (Fried et al., 1999). As shown in Table 17.3, gestation was reduced by almost a week in heavy users in the OPPS cohort (Fried, Watkinson, & Willan, 1984), and other studies reported an association of shortened gestation and increased risk of prematurity, as well (Sherwood et al., 1999). Reports on the effects of PCE on neonate size and gestation length are conflicting, but seem to suggest a dose-dependent, negative association between PCE and two pregnancy outcomes: birth size, and length of gestation.

There is an apparent association between neonatal and infant mortality and in utero cannabis exposure (Table 17.3). A large five-site study of stillbirth determined that the presence of cannabis in umbilical cord homogenate was associated with more than a twofold increased odds of stillbirth (Varner et al., 2014), a result that may be partially confounded by concurrent tobacco use. An Australian sample of PCE offspring also had a 2.23-fold increased risk of suffering from Sudden Infant Death Syndrome (SIDS; Scragg et al., 2001); in contrast, another large study ( $n = 2964$ ) found no association

**TABLE 17.3** Associations of PCE With Gestation and Infant Mortality

| Age group             | Prenatal exposure                                     | Effects                                          | References                                                             |
|-----------------------|-------------------------------------------------------|--------------------------------------------------|------------------------------------------------------------------------|
| Prenatal and neonatal | a                                                     | Increased preterm labor or birth                 | Hayatbakhsh et al. (2012), Fried et al. (1984), Sherwood et al. (1999) |
|                       | a                                                     | No effect on preterm birth                       | Fried and Smith (2001)                                                 |
|                       | a                                                     | Increased risk of stillbirth                     | Varner et al. (2014)                                                   |
|                       | a                                                     | Increased NICU admissions                        | Hayatbakhsh et al. (2012)                                              |
| Infant                | a                                                     | Increased risk of Sudden Infant Death Syndrome   | Scragg et al. (2001)                                                   |
|                       |                                                       |                                                  |                                                                        |
| Toddler               | Cannabis-positive meconium (third trimester exposure) | No increased risk of death before 2 years of age | Ostrea et al. (1997)                                                   |

Reports on the association PCE with preterm labor, stillbirth, and infant mortality are conflicted. Disagreements in the literature may be due to methodological differences between studies. *PCE*, prenatal cannabis exposure.

<sup>a</sup>Unspecified.

between having cannabis-positive meconium samples and risk of infant death within the first 2 years of life (Ostrea, Ostrea, & Simpson, 1997).

There are apparent long-term effects of PCE on offspring neurological and cognitive development (Table 17.4). Markers of altered neurological function in neonates and infants prenatally exposed to cannabis include increased risk of tremors, an exaggerated and prolonged startle response, altered autonomic arousal, a high-pitched cry, less time in quiet sleep, and poorer habituation to visual, but not auditory, stimuli (Fried & Smith, 2001). There is consistently no effect of PCE on the Bayley Scales of Infant Development, except for in children of exceptionally heavy users (one or more joints per day during the third trimester). These children had reduced mental scores on the Bayley Scales at 9 months, but not at 18 months (Richardson, Day, & Goldschmidt, 1995). After the age of 3, there were distinguishable dose-dependent effects of PCE on specific cognitive domains, including short-term memory, verbal, and abstract/visual reasoning, while composite intelligence scores were not affected (Fried & Smith, 2001; Day et al., 1994; Griffith, Azuma, & Chasnoff, 1994). Although there was no association of PCE with cognitive and receptive language development in 5- and 6-year-olds that were followed by the OPPS (Fried, O'Connell, & Watkinson, 1992a), high-risk 6-year-olds in the MHPCD who were heavily exposed during the first trimester of pregnancy had significantly lower verbal reasoning scores on the Stanford-Binet Intelligence Scale than nonexposed children (Goldschmidt, Richardson, Willford, & Day, 2008). Similarly, prenatally exposed school-aged children (ages 9–12) showed deficits in specific Wechsler Intelligence Scale for Children subtests of

visuospatial/visuomotor intelligence and planning, the Block Design and the Picture Completion subtests, but were equal to nonexposed children in global IQ measures (Fried, Watkinson, & Gray, 1998), and there was no effect of PCE on reading or language outcomes in this cohort (Fried, Watkinson, & Siegel, 1997). Prenatally exposed 9–12 year olds also showed poorer impulse control, and impaired hypothesis testing (Fried et al., 1998). In sum, PCE is associated with abnormal behavior in neonates, and deficits in multiple cognitive domains in preschool and school-aged children, including verbal reasoning, perceptual reasoning, memory, planning, and attentional processes, without affecting overall intelligence.

Neuroimaging studies have provided insights on the neural mechanisms underlying cognitive processing (Table 17.4). Visuospatial working memory was examined at age 18–22, in the OPPS cohort, using functional magnetic resonance imaging (fMRI) to measure neural activity while participants performed the two-back working memory task. Although behavioral performance did not differ between the prenatally exposed versus unexposed participants, there was a positive, dose-dependent relationship between PCE and neural activity in the left inferior and middle frontal gyri, left parahippocampal gyrus, left middle occipital gyrus and left cerebellum, and a negative relationship between exposure and activity in the right inferior and middle frontal gyri, during the task (Smith, Fried, Hogan, & Cameron, 2006). Similarly, a task of response inhibition that measures motor impulse, and is a correlate of drug use disorders, was measured in the 18–22 year old OPPS offspring cohort. After controlling for possible confounders, the prenatally exposed group exhibited more commission errors than the unexposed group, but both groups had similar reaction times. Brain

**TABLE 17.4** Associations of PCE on Neurocognitive Development

| Age group             | Prenatal exposure     | Effects                                                                                       | References                                      |
|-----------------------|-----------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------|
| Prenatal and neonatal | a                     | Increased tremors                                                                             | Fried and Smith (2001)                          |
|                       | a                     | Reduced habituation to visual stimuli                                                         | Fried and Smith (2001)                          |
|                       | a                     | Prolonged and exaggerated startle                                                             | Fried and Smith (2001)                          |
|                       | a                     | Sleep disturbances                                                                            | Fried and Smith (2001)                          |
| Toddler               | Heavy                 | Reduced mental scores on Bayley Scales of Infant Development (9, but not 18, months)          | Richardson et al. (1995)                        |
|                       | Mild-moderate         | No effect on Bayley Scales of Infant Development (9 and 18 months)                            | Richardson et al. (1995)                        |
| School-aged           | a                     | No effect on cognitive development (5 and 6 years)                                            | Fried et al. (1992a)                            |
|                       | a                     | No effect on receptive language development                                                   | Fried et al. (1992a)                            |
|                       | Heavy first trimester | Reduced verbal reasoning (6 years)                                                            | Goldschmidt et al. (2008)                       |
|                       | a                     | Deficits in WISC Block Design Task (spatial analysis, abstract visual reasoning) (9–12 years) | Fried et al. (1992b)                            |
|                       | a                     | Deficits in Picture Completion task (alertness to detail, visual discrimination) (9–12 years) | Fried et al. (1992b)                            |
|                       | a                     | Reduced planning (9–12 years)                                                                 | Fried et al. (1992b)                            |
|                       | a                     | Impaired hypothesis testing (9–12 years)                                                      | Fried et al. (1992b)                            |
|                       | a                     | No effect on global and composite intelligence (6, 9–12 years)                                | Fried et al. (1992b), Goldschmidt et al. (2008) |
|                       | a                     | No effect on verbal fluency (9–12 years)                                                      | Fried et al. (1997)                             |
|                       | a                     | No effect on reading (9–12 years)                                                             | Fried et al. (1997)                             |
| Young adult           | a                     | No effect on two-back performance (visual-spatial working memory task) (18–22 years)          | Smith et al. (2006)                             |
|                       | Dose-dependent effect | Altered neural activity during two-back task (18–22 years)                                    | Smith et al. (2006)                             |
|                       | a                     | Greater errors in response inhibition (18–22 years)                                           | Smith et al. (2004)                             |
|                       | Dose-dependent effect | Altered neural activity during response inhibition task (18–22 years)                         | Smith et al. (2004)                             |

Offspring with PCE show deficits and alterations in selective measures of neurocognitive development. PCE, prenatal cannabis exposure.

<sup>a</sup>Unspecified.

activity measured with fMRI during the task showed a positive dose-dependent relationship between PCE and activity in the bilateral prefrontal cortex and right premotor cortex, during response inhibition (Smith, Fried, Hogan, & Cameron, 2004). These functional neuroimaging studies indicate that PCE alters the neural strategy used in completing tasks of cognition.

PCE is also associated with alterations in emotional and behavioral development that are highly consistent between the “low risk” OPPS cohort and the “high

risk” MHPCD cohort (Table 17.5). A sex-specific effect of PCE was identified in 18-month old girls in the Generation R cohort, who exhibited notably greater aggressive and inattentive behavior, but this effect was not significant at 36 months (El Marroun et al., 2011b). Depression and anxiety at 10 was predicted by PCE that was specific to exposure during the first and third trimesters (Gray, Day, Leech, & Richardson, 2005). Prenatally exposed 10-year-olds in the MHPCD cohort had higher ratings of hyperactivity, inattention,

**TABLE 17.5** Behavioral Alterations in Children Prenatally Exposed to Cannabis

| Age group   | Prenatal exposure                  | Effects                                                                     | References                                                  |
|-------------|------------------------------------|-----------------------------------------------------------------------------|-------------------------------------------------------------|
| Toddler     |                                    |                                                                             |                                                             |
|             | a                                  | Aggressive, inattentive behavior (girls only, 18 months, but not 36 months) | El Marroun et al. (2011b), Generation R Study               |
| School-aged |                                    |                                                                             |                                                             |
|             | a                                  | Reduced impulse control (9–12 years)                                        | Fried et al. (1992b), OPPS                                  |
|             | Dose-dependent effect              | Increased externalizing behavior and delinquency (10 and 14 years)          | Goldschmidt et al. (2000), Day et al. (2011), MHPCD         |
|             | a                                  | Increased hyperactivity, inattention, impulsivity (10 years)                | Goldschmidt et al. (2000), MHPCD                            |
|             | First and third trimester exposure | Increased depression and anxiety (age 10)                                   | Gray et al. (2005), Leech, Larkby, Day, & Day (2006), MHPCD |
| Adolescent  |                                    |                                                                             |                                                             |
|             | a                                  | Reduced academic achievement (14 years)                                     | Goldschmidt et al. (2012), MHPCD                            |
| Young adult |                                    |                                                                             |                                                             |
|             | a                                  | Increased risk of marijuana and daily cigarette use (16–21 years)           | Porath and Fried (2005), MHPCD                              |
|             | a                                  | Predictive of marijuana use (22 years)                                      | Sonon et al. (2015), OPPS                                   |

Offspring with PCE exhibit greater behavioral and academic problems than nonexposed cohorts. PCE, prenatal cannabis exposure.

<sup>a</sup>Unspecified.

impulsivity, externalizing problems, and delinquency, with inattention mediating the effect between exposure and delinquency (Goldschmidt, Day, & Richardson, 2000). Heavier PCE increased odds of delinquency at the age of 14, mediated by depression at the age of 10 (Day, Leech, & Goldschmidt, 2011). Porath and Fried (2005) reported that adolescents and young adults (16–21 years) with PCE had greater than twofold increased odds of initiating marijuana and daily cigarette use. Similarly, prenatally exposed participants in the MHPCD cohort had higher rates of marijuana use at the age of 22 than nonexposed controls, even after controlling for maternal and offspring sociodemographic and psychiatric variables, as well as maternal history of drug abuse or disorder (Sonon, Richardson, Cornelius, Kim, & Day, 2015). The MHPCD study also revealed that school achievement at the age of 14 suffered in those with PCE (Goldschmidt, Richardson, Willford, Severtson, & Day, 2012). The Wechsler Individual Achievement Test Screener composite and reading scores were lower in adolescents with PCE (Table 17.4). These reduced scores were mediated by age performance at the age of 6, attention problems, depression symptoms at the age of 10, and early initiation of marijuana use (Goldschmidt et al., 2012). These results indicate that PCE is associated with adverse cognitive and behavioral outcomes that compromise offspring mental, emotional, and social development.

## CONCLUSIONS

Cannabis is the most prevalent illicit drug used by pregnant women. Although most women abstain from use while pregnant, a surprisingly large proportion of women continue to use cannabis throughout pregnancy. These women tend to be younger, single, less educated, and have lower income. Definitive “diagnosis” of PCE by health-care professions relies primarily on patient self-report, and analytical detection methods, such as urine drug screening or hair analysis, which each have their own limitation, and are not always sufficiently sensitive or accurate for the time period of interest.

Long-term effects of PCE on offspring are controversial, but become more robust at higher levels of exposure, even after controlling for confounders. Although small, infrequent exposures seem to have little effect on offspring outcomes, heavier, more frequent PCE is clearly associated with negative effects. Where the line between “no effect” and “adverse effect” doses lies is unknown; therefore, pregnant women should be encouraged to quit their use of cannabis (Fig. 17.1).

## MINI-DICTIONARY

**Bayley Scales of Infant Development** A norm-referenced assessment of early childhood development. The original version (1969) measured mental and motor development in infants aged

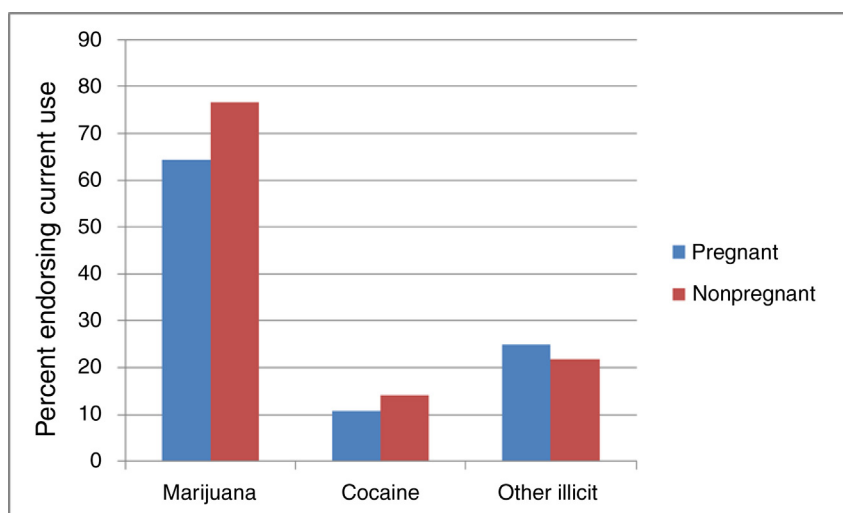


**FIGURE 17.1** Drugs used by pregnant and nonpregnant women who use any illicit drug. This figure shows the choice of drug(s) used by women who use illicit drugs, indicating that cannabis use is highly prevalent in pregnant women in this population. Source: (1996–1998) *National Household Survey on Drug Abuse*. Reproduced with permission from Ebrahim, S.H., and Gfroerer, J., 2003.

3–28 months. The second edition (1993) extended the age range to 1–42 months, and added a behavioral rating scale. The third edition (2005) is composed of a core battery of five scales: child cognitive, motor and language interaction, and parental report of the child's social–emotional and adaptive behavior.

**Cannabinoids** A class of chemicals that bind to one or both known cannabinoid receptors: Cannabinoid 1 Receptor (CB1R) and the Cannabinoid 2 Receptor (CB2R). These chemicals may be isolated from the *Cannabis* plant (phytocannabinoids, eg,  $\Delta^9$ -THC, the psychoactive component of cannabis), produced endogenously by a diverse array of Animalian species (endocannabinoids, eg, anandamide and 2-arachidonoylglycerol), or synthesized in laboratory conditions (synthetic cannabinoids, eg, JWH-018, WIN55, 212-2).

**Cannabis** A genus composed of three species of flowering plants (*C. sativa*, *C. indica* and *C. ruderalis*) that are best known for producing the psychoactive phytocannabinoid  $\Delta^9$ -THC. Consumption by smoking, vaporizing or eating the  $\Delta^9$ -THC-rich trichomes on the flowers of the plant results in alterations in mood, perception, and appetite. Resin extractions of the trichomes, such as, hashish and hash oil, contain high concentrations of  $\Delta^9$ -THC, and are also consumed for their psychoactive effects. In addition to recreational purposes, *Cannabis* is also cultivated for industrial (eg, hemp made from the fibrous stalk of the plant), medicinal, and religious uses.

**Hypertelorism** A congenital facial malformation in which the eyes are abnormally spaced apart.

**Meconium** The earliest stools of the neonate that are composed solely of materials consumed in utero.

**Pulsatility index** The variability of flow velocity in a blood vessel measured by Doppler ultrasound, and calculated by subtracting the minimum diastolic velocity from the maximum systolic velocity, and dividing the difference by the mean flow velocity.

**Resistance index** A measure of flow in a blood vessel that is calculated by subtracting the end diastolic velocity from the peak systolic velocity, and dividing the difference by the peak systolic velocity. Abnormal umbilical or uterine artery resistance may indicate compromised fetal–placental circulation associated with adverse maternal–fetal conditions, such as, intrauterine growth restriction, or preeclampsia.

**Severe epicanthus** Overgrowth of the skin in the corners of the eyelids (ie, epicanthic folds).

**Stanford-Binet Intelligence Scales** An assessment that measures five domains of cognition in people aged 2 and older: fluid reasoning, knowledge, quantitative reasoning, visual-spatial processing, and working memory.

**Wechsler Individual Achievement Test Screener** An assessment of academic strengths and weaknesses in the areas of reading, math, written language, and oral language in people aged 4–85.

**Wechsler Intelligence Scale for Children** An assessment of cognitive abilities in children aged 6–16 that measures overall intellect ability, verbal comprehension, perceptual reasoning, processing speed, and working memory.

## References

- Barr, H. M., Streissguth, A. P., Martin, D. C., & Herman, C. S. (1984). Infant size at 8 months of age: relationship to maternal use of alcohol, nicotine, and caffeine during pregnancy. *Pediatrics*, 74(3), 336–341.
- Cascini, F., Aiello, C., & Di Tanna, G. (2012). Increasing delta-9-tetrahydrocannabinol (Delta-9-Thc) content in herbal cannabis over time: systematic review and meta-analysis. *Current Drug Abuse Reviews*, 5(1), 32–40.
- Conradt, E., Sheinkopf, S. J., Lester, B. M., Tronick, E., Lagasse, L. L., Shankaran, S., Bada, H., Bauer, C. R., Whitaker, T. M. Hammond, J. A., & Maternal Lifestyle Study. (2013). Prenatal substance exposure: neurobiologic organization at 1 month. *Journal of Pediatrics*, 163(4), 989–94.e1.
- Correia, M. A., Oliveria, A. P., Almeida, J. P., Sing, C. K., & Nobrega, J. D. (1995). Drug-addicted mothers. *Acta Medica Portuguesa*, 8(1), 5–10.
- Corse, S. J., & Smith, M. (1998). Reducing substance abuse during pregnancy. Discriminating among levels of response in a prenatal setting. *Journal of Substance Abuse Treatment*, 15(5), 457–467.
- Day, N. L., & Richardson, G. A. (1991). Prenatal marijuana use: epidemiology, methodologic issues, and infant outcome. *Clinics in Perinatology*, 18(1), 77–91.
- Day, N. L., Richardson, G. A., Goldschmidt, L., Robles, N., Taylor, P. M., Stoffer, D. S., Cornelius, M. D., & Geva, D. (1994). Effect of prenatal

- marijuana exposure on the cognitive development of offspring at age three. *Neurotoxicology and Teratology*, 16(2), 169–175.
- Day, N. L., Richardson, G. A., Goldschmidt, L., & Cornelius, M. D. (2000). Effects of prenatal tobacco exposure on preschoolers' behavior. *Journal of Developmental and Behavioral Pediatrics*, 21(3), 180–188.
- Day, N. L., Leech, S. L., & Goldschmidt, L. (2011). The effects of prenatal marijuana exposure on delinquent behaviors are mediated by measures of neurocognitive functioning. *Neurotoxicology and Teratology*, 33(1), 129–136.
- Desilver, D. (2013). Nearly half of adults say they've tried marijuana, but not recently. Available from <http://www.pewresearch.org/fact-tank/2013/06/03/more-than-a-third-of-adults-say-theyve-tried-pot-but-not-recently/>
- Ebrahim, S. H., & Gfroerer, J. (2003). Pregnancy-related substance use in the United States during 1996–1998. *Obstetrics and Gynecology*, 101(2), 374–379.
- El Marroun, H., Tiemeier, H., Jaddoe, V. W., Hofman, A., Mackenbach, J. P., Steegers, E. A., Verhulst, F. C., Van Den Brink, W., & Huizink, A. C. (2008). Demographic, emotional and social determinants of cannabis use in early pregnancy: the Generation R study. *Drug and Alcohol Dependence*, 98(3), 218–226.
- El Marroun, H., Tiemeier, H., Steegers, E. A., Jaddoe, V. W., Hofman, A., Verhulst, F. C., Van Den Brink, W., & Huizink, A. C. (2009). Intrauterine cannabis exposure affects fetal growth trajectories: the Generation R Study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 48(12), 1173–1181.
- El Marroun, H., Tiemeier, H., Steegers, E. A., Roos-Hesselink, J. W., Jaddoe, V. W., Hofman, A., Verhulst, F. C., Van Den Brink, W., & Huizink, A. C. (2010). A prospective study on intrauterine cannabis exposure and fetal blood flow. *Early Human Development*, 86(4), 231–236.
- El Marroun, H., Hudziak, J. J., Tiemeier, H., Creemers, H., Steegers, E. A., Jaddoe, V. W., Hofman, A., Verhulst, F. C., Van Den Brink, W., & Huizink, A. C. (2011a). Intrauterine cannabis exposure leads to more aggressive behavior and attention problems in 18-month-old girls. *Drug and Alcohol Dependence*, 118(2–3), 470–474.
- El Marroun, H., Tiemeier, H., Jaddoe, V. W., Hofman, A., Verhulst, F. C., Van Den Brink, W., & Huizink, A. C. (2011b). Agreement between maternal cannabis use during pregnancy according to self-report and urinalysis in a population-based cohort: the Generation R Study. *European Addiction Research*, 17(1), 37–43.
- English, D. R., Hulse, G. K., Milne, E., Holman, C. D., & Bower, C. I. (1997). Maternal cannabis use and birth weight: a meta-analysis. *Addiction*, 92(11), 1553–1560.
- Falcon, M., Pichini, S., Joya, J., Pujadas, M., Sanchez, A., Vall, O., Garcia Algar, O., Luna, A., De La Torre, R., Rotolo, M. C., & Pellegrini, M. (2012). Maternal hair testing for the assessment of fetal exposure to drug of abuse during early pregnancy: Comparison with testing in placental and fetal remains. *Forensic Science International*, 218(1–3), 92–96.
- Fried, P. A. (1995). The Ottawa Prenatal Prospective Study (Opps): methodological issues and findings—it's easy to throw the baby out with the bath water. *Life Sciences*, 56(23–24), 2159–2168.
- Fried, P. A., & O'Connell, C. M. (1987). A comparison of the effects of prenatal exposure to tobacco, alcohol, cannabis and caffeine on birth size and subsequent growth. *Neurotoxicology and Teratology*, 9(2), 79–85.
- Fried, P. A., & Smith, A. M. (2001). A literature review of the consequences of prenatal marihuana exposure. An emerging theme of a deficiency in aspects of executive function. *Neurotoxicology and Teratology*, 23(1), 1–11.
- Fried, P. A., Watkinson, B., & Willan, A. (1984). Marijuana use during pregnancy and decreased length of gestation. *American Journal of Obstetrics and Gynecology*, 150(1), 23–27.
- Fried, P. A., Barnes, M. V., & Drake, E. R. (1985). Soft drug use after pregnancy compared to use before and during pregnancy. *American Journal of Obstetrics and Gynecology*, 151(6), 787–792.
- Fried, P. A., O'Connell, C. M., & Watkinson, B. (1992a). 60- and 72-month follow-up of children prenatally exposed to marijuana, cigarettes, and alcohol: cognitive and language assessment. *Journal of Developmental and Behavioral Pediatrics*, 13(6), 383–391.
- Fried, P. A., Watkinson, B., & Gray, R. (1992b). A follow-up study of attentional behavior in 6-year-old children exposed prenatally to marihuana, cigarettes, and alcohol. *Neurotoxicology and Teratology*, 14(5), 299–311.
- Fried, P. A., Watkinson, B., & Siegel, L. S. (1997). Reading and language in 9- to 12-year olds prenatally exposed to cigarettes and marijuana. *Neurotoxicology and Teratology*, 19(3), 171–183.
- Fried, P. A., Watkinson, B., & Gray, R. (1998). Differential effects on cognitive functioning in 9- to 12-year olds prenatally exposed to cigarettes and marihuana. *Neurotoxicology and Teratology*, 20(3), 293–306.
- Fried, P. A., Watkinson, B., & Gray, R. (1999). Growth from birth to early adolescence in offspring prenatally exposed to cigarettes and marijuana. *Neurotoxicology and Teratology*, 21(5), 513–525.
- Friguls, B., Joya, X., Garcia-Serra, J., Gomez-Culebras, M., Pichini, S., Martinez, S., Vall, O., & Garcia-Algar, O. (2012). Assessment of exposure to drugs of abuse during pregnancy by hair analysis in a Mediterranean island. *Addiction*, 107(8), 1471–1479.
- Goldschmidt, L., Day, N. L., & Richardson, G. A. (2000). Effects of prenatal marijuana exposure on child behavior problems at age 10. *Neurotoxicology and Teratology*, 22(3), 325–336.
- Goldschmidt, L., Richardson, G. A., Willford, J., & Day, N. L. (2008). Prenatal marijuana exposure and intelligence test performance at age 6. *Journal of the American Academy of Child and Adolescent Psychiatry*, 47(3), 254–263.
- Goldschmidt, L., Richardson, G. A., Willford, J. A., Severtson, S. G., & Day, N. L. (2012). School achievement in 14-year-old youths prenatally exposed to marijuana. *Neurotoxicology and Teratology*, 34(1), 161–167.
- Gray, T., & Huestis, M. (2007). Bioanalytical procedures for monitoring in utero drug exposure. *Analytical and Bioanalytical Chemistry*, 388(7), 1455–1465.
- Gray, K. A., Day, N. L., Leech, S., & Richardson, G. A. (2005). Prenatal marijuana exposure: effect on child depressive symptoms at ten years of age. *Neurotoxicology and Teratology*, 27(3), 439–448.
- Gray, T. R., Eiden, R. D., Leonard, K. E., Connors, G. J., Shisler, S., & Huestis, M. A. (2010). Identifying prenatal cannabis exposure and effects of concurrent tobacco exposure on neonatal growth. *Clinical Chemistry*, 56(9), 1442–1450.
- Griffith, D. R., Azuma, S. D., & Chasnoff, I. J. (1994). Three-year outcome of children exposed prenatally to drugs. *Journal of the American Academy of Child and Adolescent Psychiatry*, 33(1), 20–27.
- Hayatbakhsh, M. R., Najman, J. M., Bor, W., O'Callaghan, M. J., & Williams, G. M. (2009). Multiple risk factor model predicting cannabis use and use disorders: a longitudinal study. *The American Journal of Drug and Alcohol Abuse*, 35(6), 399–407.
- Hayatbakhsh, M. R., Kingsbury, A. M., Flenady, V., Gilshenan, K. S., Hutchinson, D. M., & Najman, J. M. (2011). Illicit drug use before and during pregnancy at a tertiary maternity hospital 2000–2006. *Drug and Alcohol Review*, 30(2), 181–187.
- Hayatbakhsh, M. R., Flenady, V. J., Gibbons, K. S., Kingsbury, A. M., Hurron, E., Mamun, A. A., & Najman, J. M. (2012). Birth outcomes associated with cannabis use before and during pregnancy. *Pediatric Research*, 71(2), 215–219.
- Huizink, A. C. (2014). Prenatal cannabis exposure and infant outcomes: overview of studies. *Progress in Neuro-psychopharmacology & Biological Psychiatry*, 52, 45–52.
- Hurd, Y. L., Wang, X., Anderson, V., Beck, O., Minkoff, H., & Dow-Edwards, D. (2005). Marijuana impairs growth in mid-gestation fetuses. *Neurotoxicology and Teratology*, 27(2), 221–229.
- Jaddoe, V. W., Mackenbach, J. P., Moll, H. A., Steegers, E. A., Tiemeier, H., Verhulst, F. C., Witteman, J. C., & Hofman, A. (2006). The Generation R study: design and cohort profile. *European Journal of Epidemiology*, 21(6), 475–484.

- Johnson, G. (2014). U.S. drug policies fueling global push to legalize marijuana. *The Seattle Times*, February 16. Available from [http://seattletimes.com/html/nationworld/2022928337\\_globalpotxml.html](http://seattletimes.com/html/nationworld/2022928337_globalpotxml.html)
- Leech, S. L., Larkby, C. A., Day, R., & Day, N. L. (2006). Predictors and correlates of high levels of depression and anxiety symptoms among children at age 10. *Journal of the American Academy of Child and Adolescent Psychiatry*, 45(2), 223–230.
- Lozano, J., Garcia-Algar, O., Marchei, E., Vall, O., Monleon, T., Giovannandrea, R. D., & Pichini, S. (2007). Prevalence of gestational exposure to cannabis in a Mediterranean city by meconium analysis. *Acta Paediatrica*, 96(12), 1734–1737.
- Minnes, S., Robin, N. H., Alt, A. A., Kirchner, H. L., Satayathum, S., Salbert, B. A., Ellison, L., & Singer, L. T. (2006). Dysmorphic and anthropometric outcomes in 6-year-old prenatally cocaine-exposed children. *Neurotoxicology and Teratology*, 28(1), 28–38.
- Moore, D. G., Turner, J. D., Parrott, A. C., Goodwin, J. E., Fulton, S. E., Min, M. O., Fox, H. C., Braddick, F. M., Axelsson, E. L., Lynch, S., Ribeiro, H., Frostick, C. J., & Singer, L. T. (2010). During pregnancy, recreational drug-using women stop taking ecstasy (3,4-methylenedioxymethylamphetamine) and reduce alcohol consumption, but continue to smoke tobacco and cannabis: initial findings from the Development and Infancy Study. *Journal of Psychopharmacology*, 24(9), 1403–1410.
- Ostrea, E. M., Jr, Ostrea, A. R., & Simpson, P. M. (1997). Mortality within the first 2 years in infants exposed to cocaine, opiate, or cannabinoid during gestation. *Pediatrics*, 100(1), 79–83.
- Porath, A. J., & Fried, P. A. (2005). Effects of prenatal cigarette and marijuana exposure on drug use among offspring. *Neurotoxicology and Teratology*, 27(2), 267–277.
- Richardson, G. A., Day, N. L., & Goldschmidt, L. (1995). Prenatal alcohol, marijuana, and tobacco use: infant mental and motor development. *Neurotoxicology and Teratology*, 17(4), 479–487.
- Saleh Gargari, S., Fallahian, M., Haghighi, L., Hosseinneshad-Yazdi, M., Dashti, E., & Dolan, K. (2012). Maternal and neonatal complications of substance abuse in Iranian pregnant women. *Acta Medica Iranica*, 50(6), 411–416.
- SAMHSA. (2014). Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings. NSDUH Series H-48, Hhs, Publication No.(SMA)14-4863. Rockville, Md: Substance Abuse and Mental Health Services Administration.
- Scragg, R. K., Mitchell, E. A., Ford, R. P., Thompson, J. M., Taylor, B. J., & Stewart, A. W. (2001). Maternal cannabis use in the sudden death syndrome. *Acta Paediatrica*, 90(1), 57–60.
- Sherwood, R. A., Keating, J., Kavvadia, V., Greenough, A., & Peters, T. J. (1999). Substance misuse in early pregnancy and relationship to fetal outcome. *European Journal of Pediatrics*, 158(6), 488–492.
- Sidney, S. (2003). Comparing cannabis with tobacco—again. *British Medical Journal*, 327(7416), 635–636.
- Smith, A. M., Fried, P. A., Hogan, M. J., & Cameron, I. (2004). Effects of prenatal marijuana on response inhibition: an fMRI study of young adults. *Neurotoxicology and Teratology*, 26(4), 533–542.
- Smith, A. M., Fried, P. A., Hogan, M. J., & Cameron, I. (2006). Effects of prenatal marijuana on visuospatial working memory: an fMRI study in young adults. *Neurotoxicology and Teratology*, 28(2), 286–295.
- Sonon, K. E., Richardson, G. A., Cornelius, J. R., Kim, K. H., & Day, N. L. (2015). Prenatal marijuana exposure predicts marijuana use in young adulthood. *Neurotoxicology and Teratology*, 47, 10.
- Steinhausen, H. C., Blattmann, B., & Pfund, F. (2007). Developmental outcome in children with intrauterine exposure to substances. *European Addiction Research*, 13(2), 94–100.
- Varner, M. W., Silver, R. M., Rowland Hogue, C. J., Willinger, M., Parker, C. B., Thorsten, V. R., Goldenberg, R. L., Saade, G. R., Dudley, D. J., Coustan, D., Stoll, B., Bukowski, R., Koch, M. A., Conway, D., Pinar, H., & Reddy, U. M., Eunice Kennedy Shriver National Institute of Child Health and Human Development Stillbirth Collaborative Research Network. (2014). Association between stillbirth and illicit drug use and smoking during pregnancy. *Obstetrics and Gynecology*, 123(1), 113–125.
- Westfall, R. E., Janssen, P. A., Lucas, P., & Capler, R. (2006). Survey of medicinal cannabis use among childbearing women: patterns of its use in pregnancy and retrospective self-assessment of its efficacy against ‘morning sickness’. *Complementary Therapies in Clinical Practice*, 12(1), 27–33.
- WHO. (2014). World Health Organization substance abuse facts—cannabis. Available from [http://www.who.int/substance\\_abuse/facts/cannabis/en/](http://www.who.int/substance_abuse/facts/cannabis/en/)
- Williams, L. J., Correa, A., & Rasmussen, S. (2004). Maternal lifestyle factors and risk for ventricular septal defects. *Birth defects Research Part A*, 70(2), 59–64.
- Zuardi, A. W. (2006). History of cannabis as a medicine: a review. *Revista Brasileira de Psiquiatria*, 28(2), 153–157.