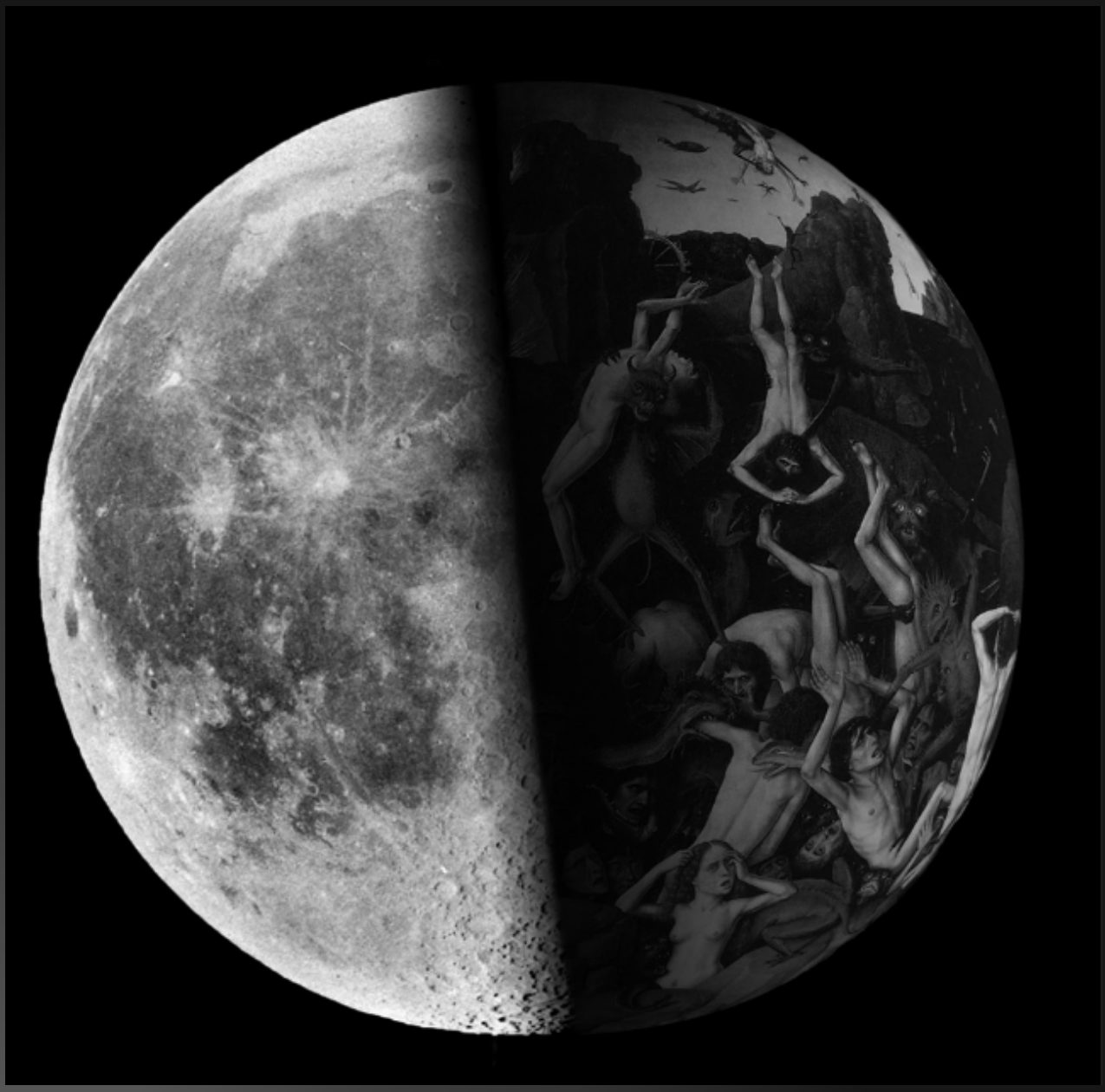
Re-Casting the Cannabis Debate :

Efficacy,

Genotoxicity and

Teratogenicity

Prof. Dr Stuart Reece
ECU: Joondalup, Western Australia
A/Prof: UWA: School of Psychiatry, Perth, Western Australia



Poison Glands in Hemp
Capitate-Sessile Glands

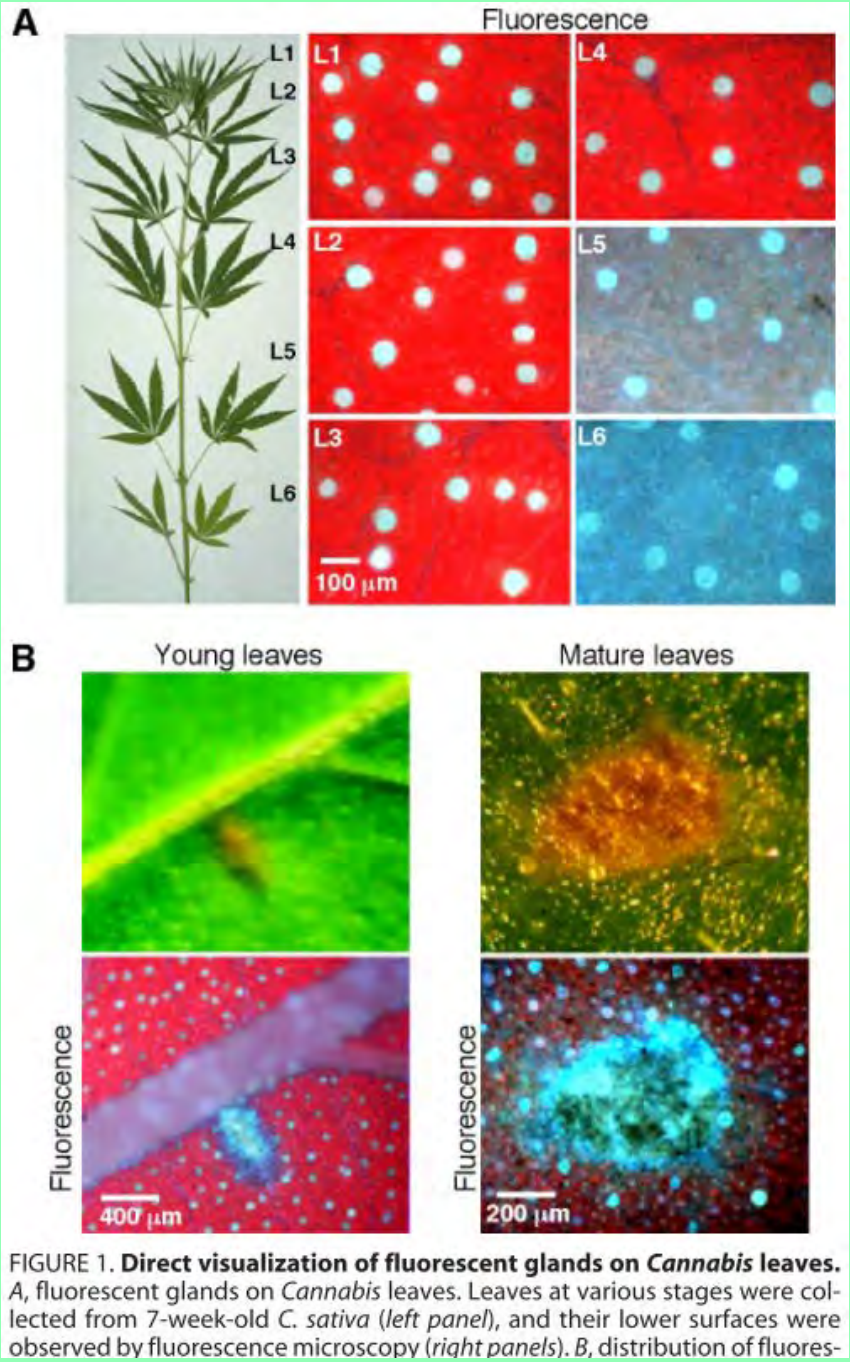
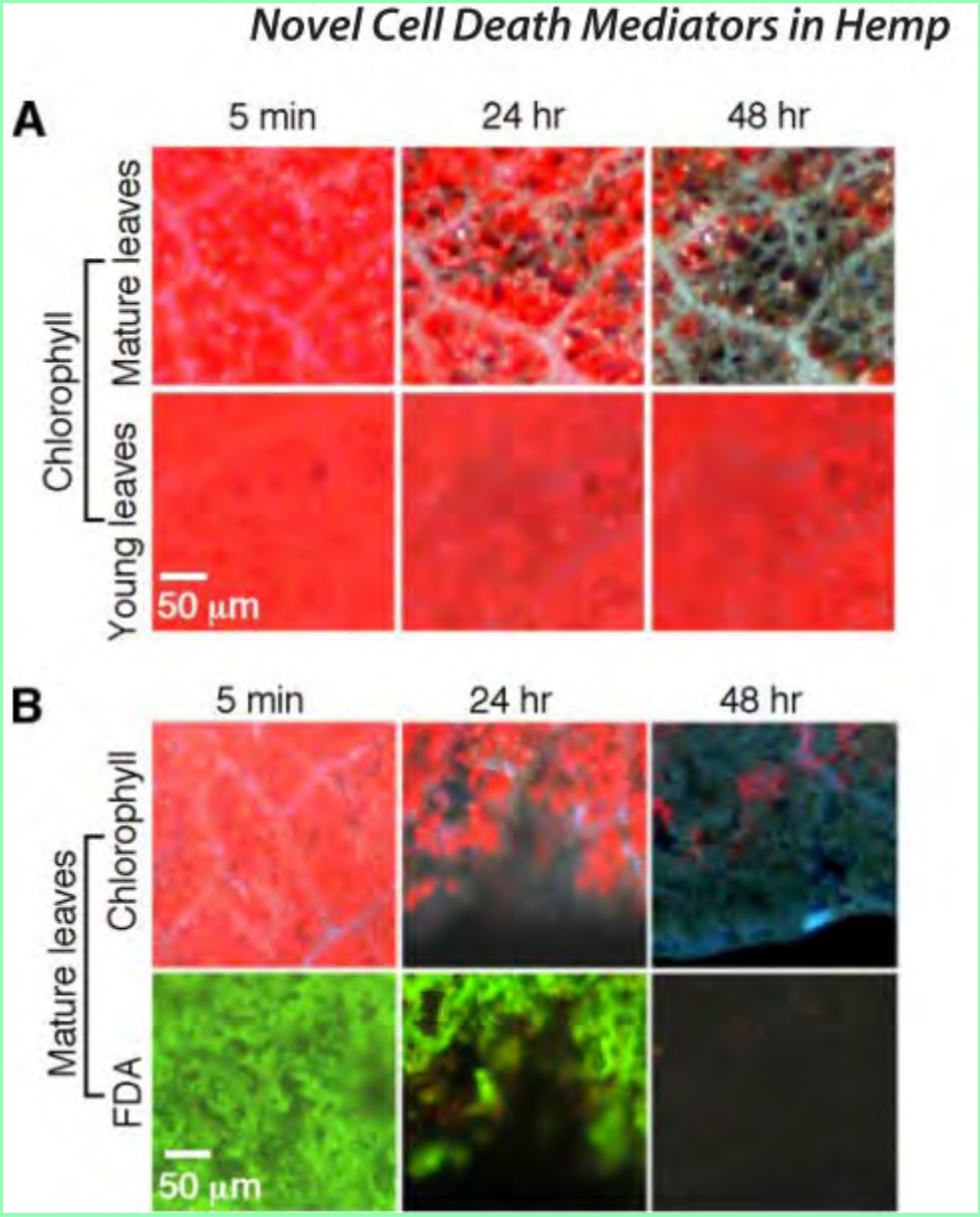


FIGURE 1. **Direct visualization of fluorescent glands on *Cannabis* leaves.** *A*, fluorescent glands on *Cannabis* leaves. Leaves at various stages were collected from 7-week-old *C. sativa* (*left panel*), and their lower surfaces were observed by fluorescence microscopy (*right panels*). *B*, distribution of fluores-

J Biol Chem. 2007 Jul 13;282(28):20739-51. Epub 2007 May 17.

Identification and characterization of cannabinoids that induce cell death through mitochondrial permeability transition in Cannabis leaf cells.

Poison Glands' Rapid Effects



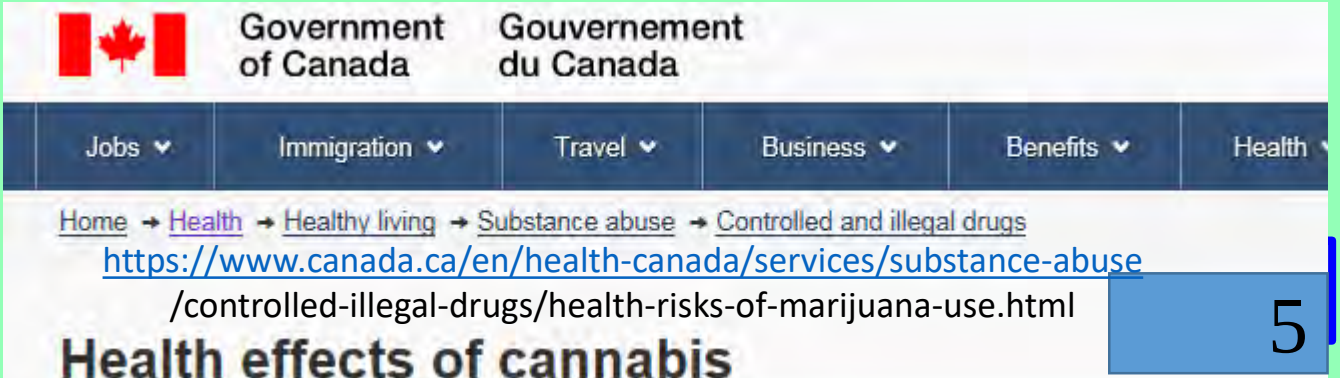
J Biol Chem. 2007 Jul 13;282(28):20739-51. Epub 2007 May 17.

Identification and characterization of cannabinoids that induce cell death through mitochondrial permeability transition in Cannabis leaf cells.

Morimoto S[1], Tanaka Y, Sasaki K, Tanaka H, Fukamizu T, Shoyama Y, Shoyama Y, Taura F.

Summary of Evidence

Syndrome	Dr. N. Volkow 2014-2017	Wayne Hall 2009-2016	Health Canada 2016-2017
Cannabis is Addictive	✓	✓	✓
Brain Development	✓	✓	✓
Gateway to Other Drug Use	✓	✓	
Psych.Disease - Depression, Anxiety, Psychosis	✓	✓	✓
Developmental Trajectory	✓	✓	✓
Driving / MVA	✓	✓	✓
Respiratory	✓		✓
Immunosuppression	✓	✓	
Heart Attack / Stroke / CVS Disease	✓	✓	✓
Cautions and Queries			
Cancer	?	✓	
Gestational Exposures	✓	✓	✓
Increased Potency	✓	✓	✓
ER Presentations	✓		✓



Cannabis Toxicity Effects: Generalized Systemic Toxicity

- Brain – Acute Intoxication
- Brain - Mental Illnesses
- Gateway Effect to Other Addictions
- Aborts Normal Lifetime Trajectory
- Respiratory System
- Aerodigestive Tract
- Bladder and Kidneys
- Congenital Abnormalities
- **** Reproductive Tract – Male & Female***
- **** Liver – Cirrhosis***
- **** Cancer – x10, 3 in Children***
- **** Arterial System –***
- **** Heart Attacks, Strokes***
- **** Immune System***
- **** Hormones***
- **** Genotoxicity***

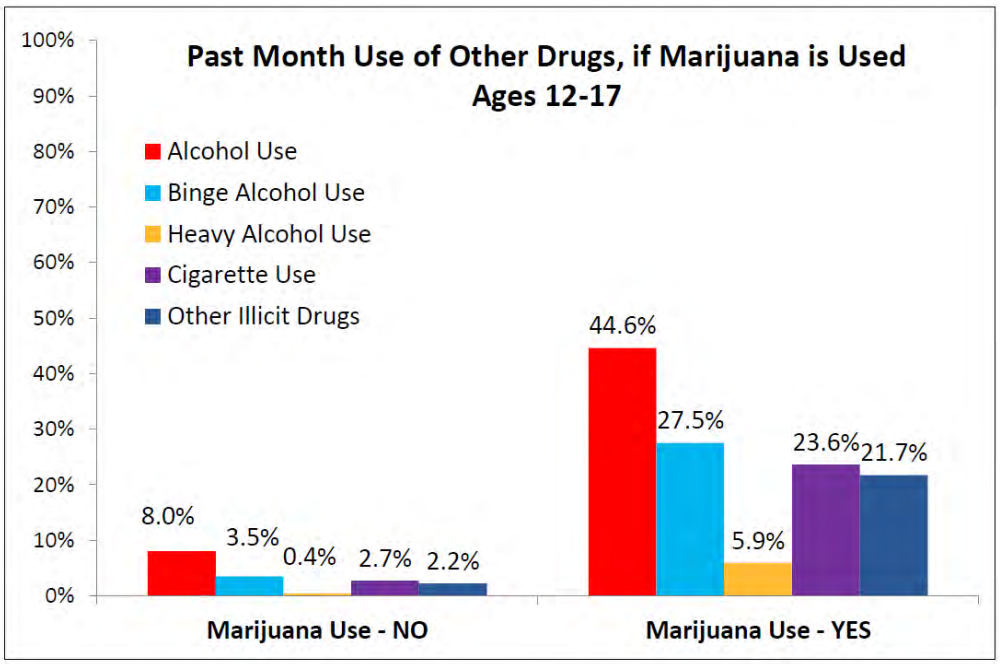
i.e. Cannabis Accelerates the Ageing Process

**** = Age Defining Illnesses***

Gateway Effect – USA 2017

www.OneChoicePrevention.org

Youth Marijuana Use Associated With Higher Use of Other Drugs



Data from DuPont, Han, Shea, Madras. Preventive Medicine 113: 68-73, 2018. [Graph prepared by BK Madras, C Shea]
Past month use of alcohol, tobacco and illicit drugs, among youth aged 12-17, by marijuana status (past month adjusted prevalence; n = 17,000; data from Table 1). Y-axis: past month prevalence in %)

Dr. Bob DuPont (Inaugural Director NIDA) & Prof Bertha Madras, Harvard University, Graphs 2018

Package leaflet: Information for the patient

Sativex® Oromucosal Spray

(delta-9-tetrahydrocannabinol and cannabidiol)

Warnings and precautions

Page 2

Talk to your doctor or pharmacist before using Sativex:

- If you are pregnant or plan to become pregnant.

Do not use Sativex:

- If you are allergic to cannabis extracts or any of the other ingredients of this medicine (listed in section 6).
- If you or anyone directly related to you has any mental health problems such as schizophrenia, psychosis or other significant psychiatric disorder. This does not include depression due to your multiple sclerosis.
- If you are breast-feeding.

Page 2

Pregnancy, breast-feeding and contraception (men and women)

Page 3

- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.
- Do not use Sativex during pregnancy, unless advised to by your doctor.
- Whether male or female you must use a reliable contraceptive method while using this medicine. Keep using it for at least 3 months after your treatment has stopped.
- Do not use Sativex while breast-feeding.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EPIDIOLEX® safely and effectively. See full prescribing information for EPIDIOLEX.

EPIDIOLEX® (cannabidiol) oral solution, CX [pending DEA scheduling action]

Initial U.S. Approval: XXXX [pending controlled substance scheduling]

----------INDICATIONS AND USAGE----------

EPIDIOLEX is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older (1)

----------ADVERSE REACTIONS----------

The most common adverse reactions (10% or more for EPIDIOLEX and greater than placebo) are: somnolence; decreased appetite; diarrhea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder, and poor quality sleep; and infections. (6.1).

8 USE IN SPECIFIC POPULATIONS

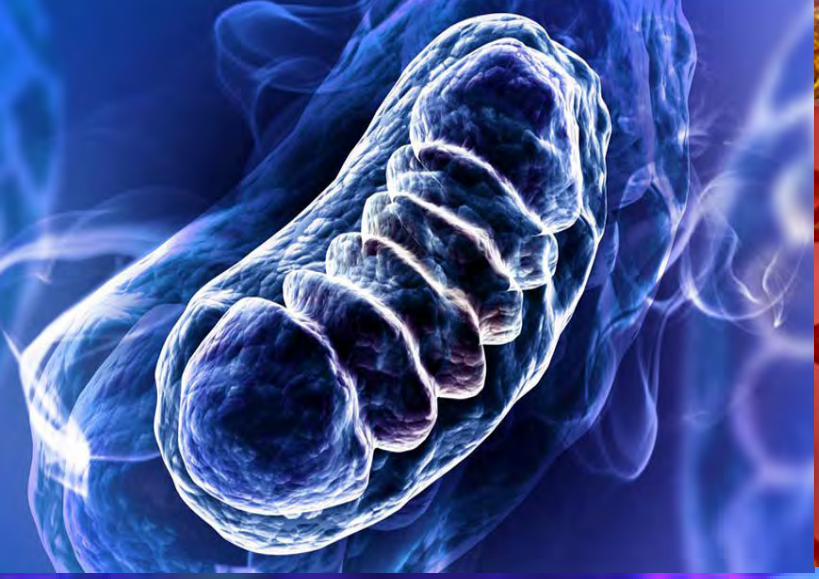
8.1 Pregnancy

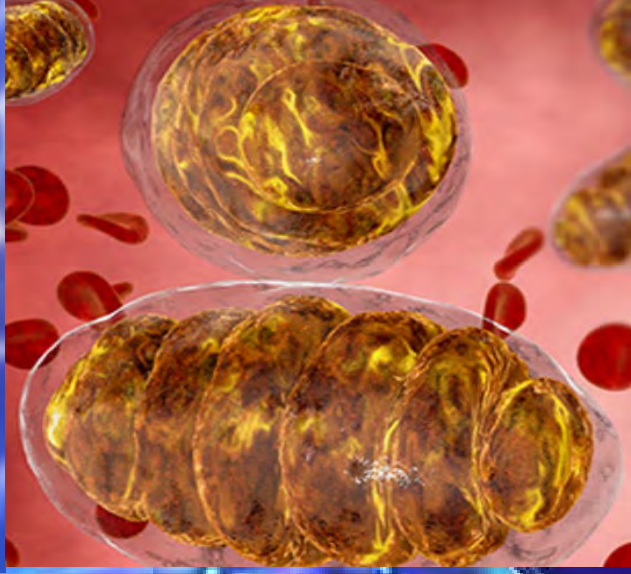
Risk Summary

There are no adequate data on the developmental risks associated with the use of EPIDIOLEX in pregnant women. Administration of cannabidiol to pregnant animals produced evidence of developmental toxicity (increased embryofetal mortality in rats and decreased fetal body weights in rabbits; decreased growth, delayed sexual maturation, long-term neurobehavioral changes, and adverse effects on the reproductive system in rat offspring) at maternal plasma exposures similar to (rabbit) or greater than (rat) that in humans at therapeutic doses *(see Animal Data)*. In the U.S. general population, the estimated background risk of

Oral administration of cannabidiol (0, 50, 80, or 125 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in decreased fetal body weights and increased fetal structural variations at the highest dose tested, which was also associated with maternal toxicity. Maternal plasma cannabidiol exposures at the no-effect level for embryofetal developmental toxicity in rabbits were less than that in humans at the RHD.

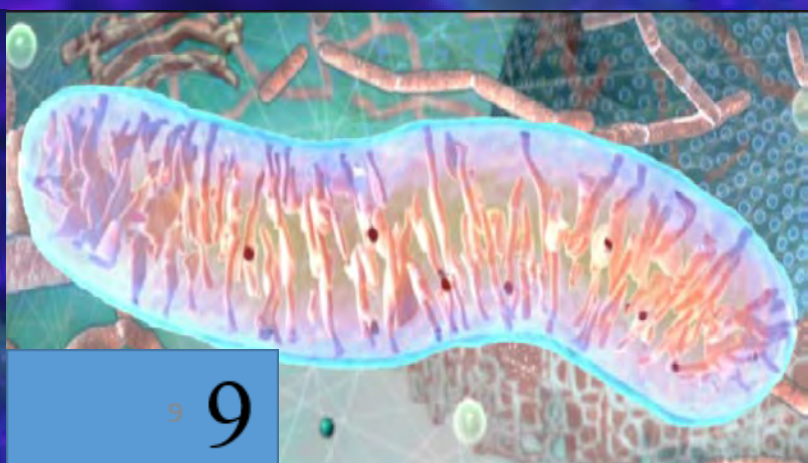
https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210365lbl.pdf



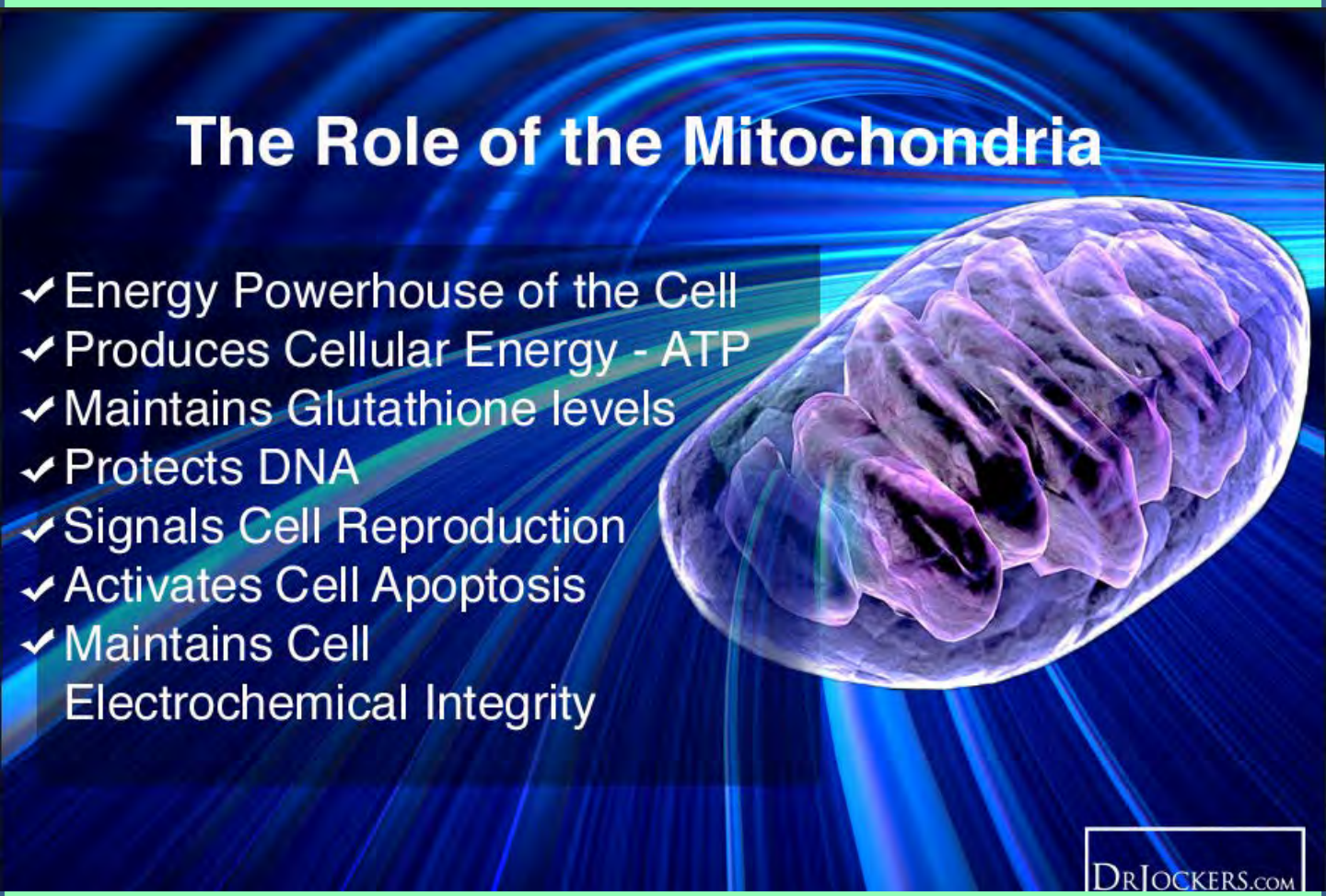


Mitochondrion POWERHOUSE of the Cell

Produces 90% of the ATP of the Cell



Selected Mitochondrial Functions



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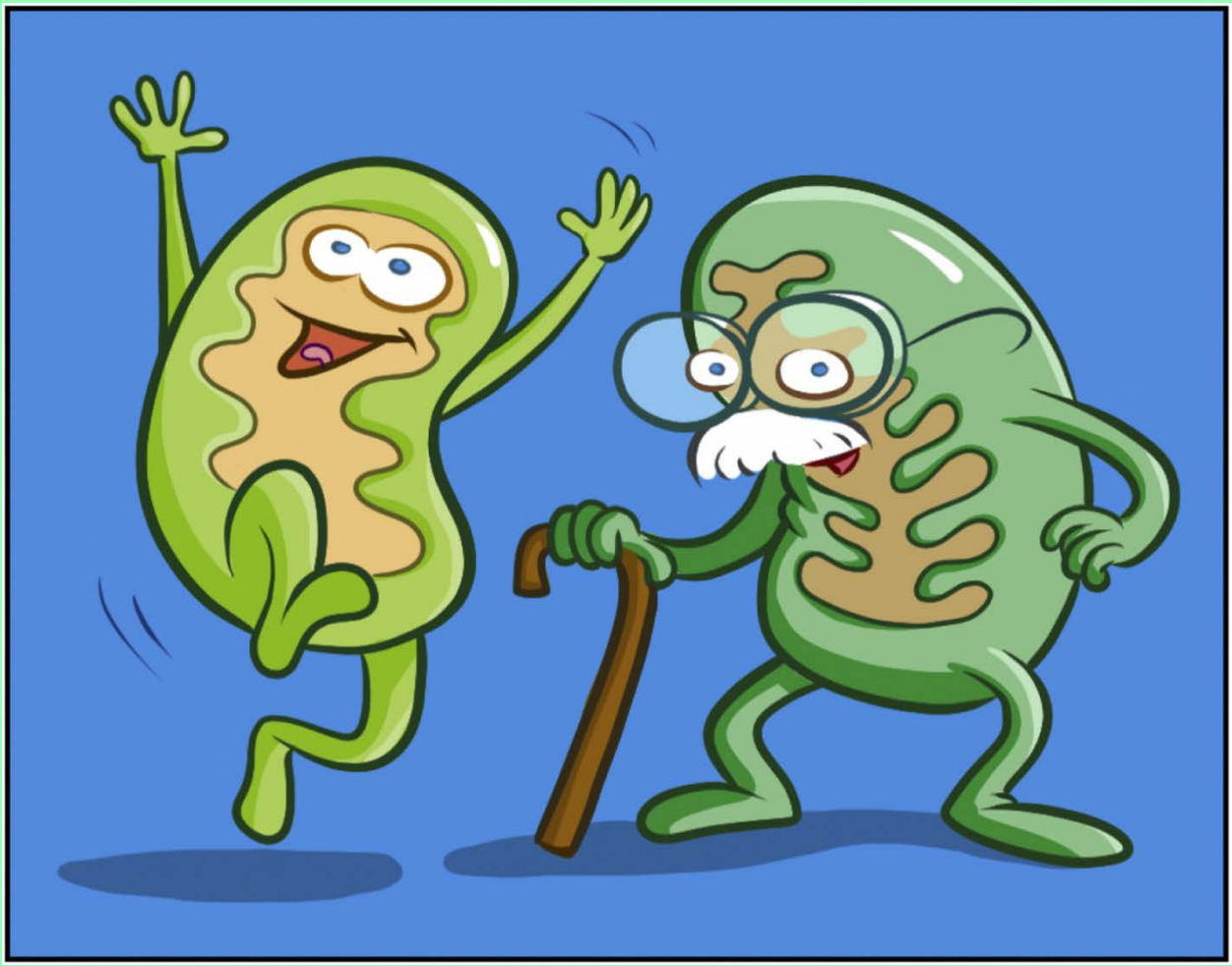
Mitochondria Rapidly Aged by Cannabinoids

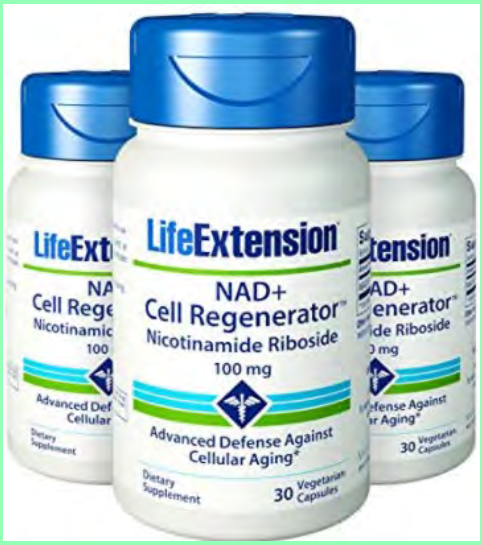


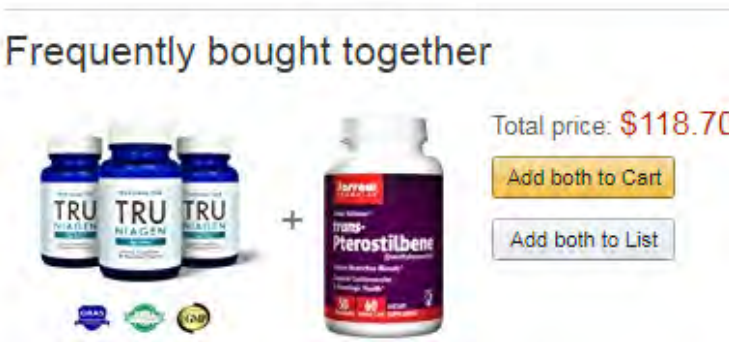
Secrets for Staying Young

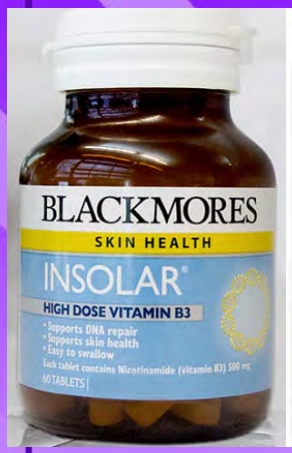
Cell *161*, June 4, 2015 ©2015 Elsevier Inc. 1235

Cindy Lu

NAD Precursors







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Implications for Ageing Medicine

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ALL ADDICTIVE DRUGS

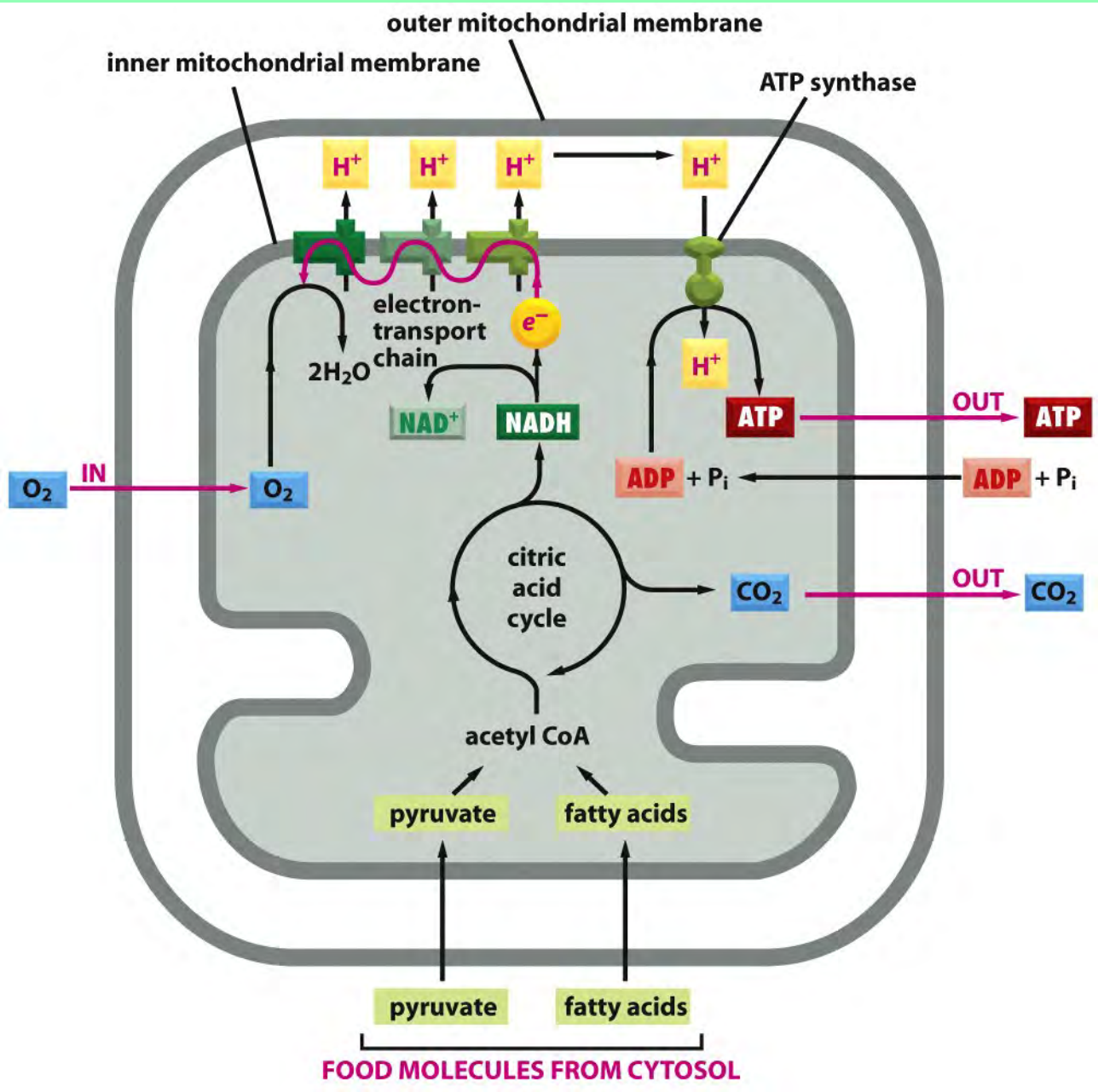
& Also:

BMJ Open. 2017 Jul 4;7(6):e015735. doi: 10.1136/bmjopen-2016-015735.

Risk of death among users of Proton Pump Inhibitors: a longitudinal observational cohort study of United States veterans.

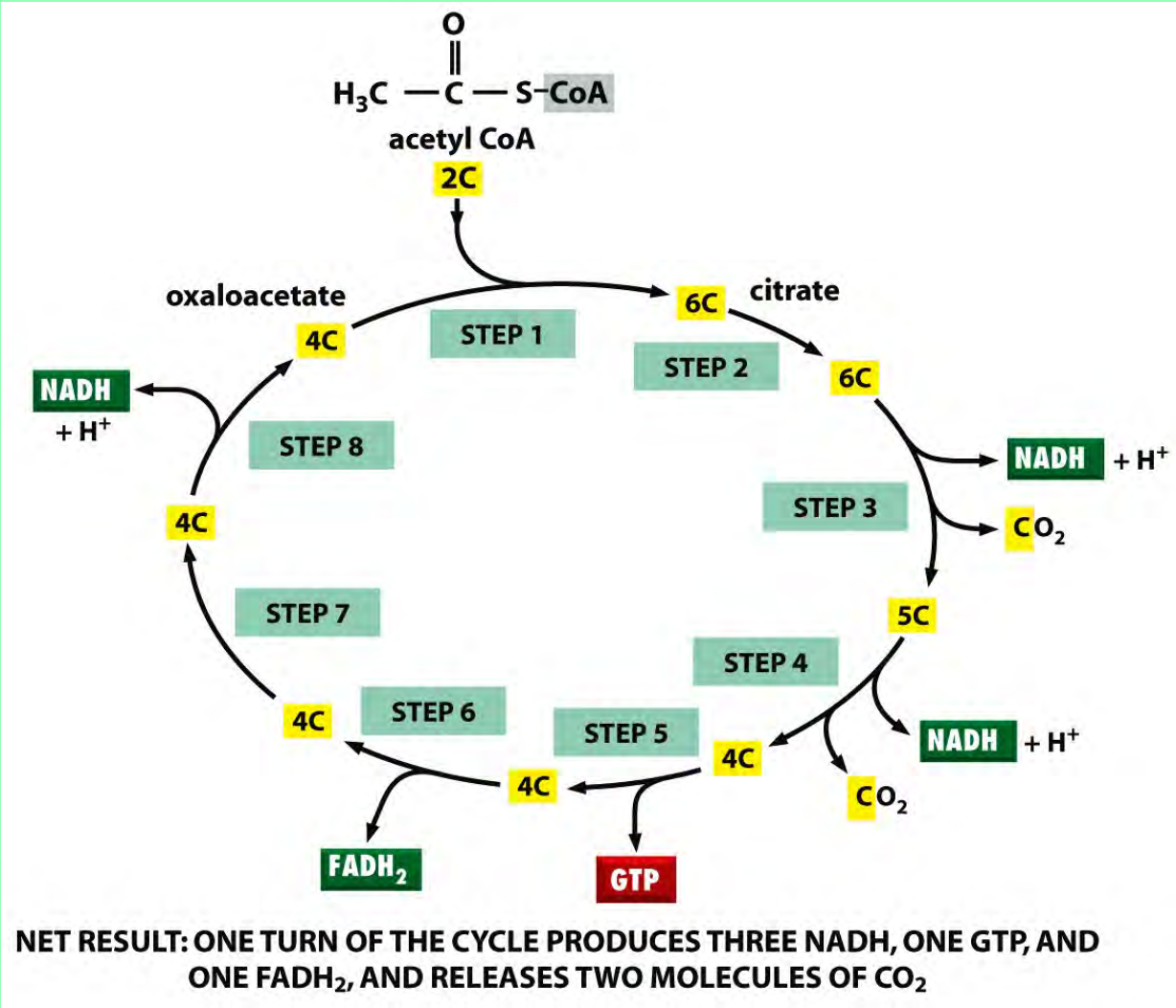
Xie Y[1], Bowe B[1], Li T[1,2], Xian H[1,3], Yan Y[1,4], Al-Aly Z[1,2,5,6].

Mitochondrial Schema



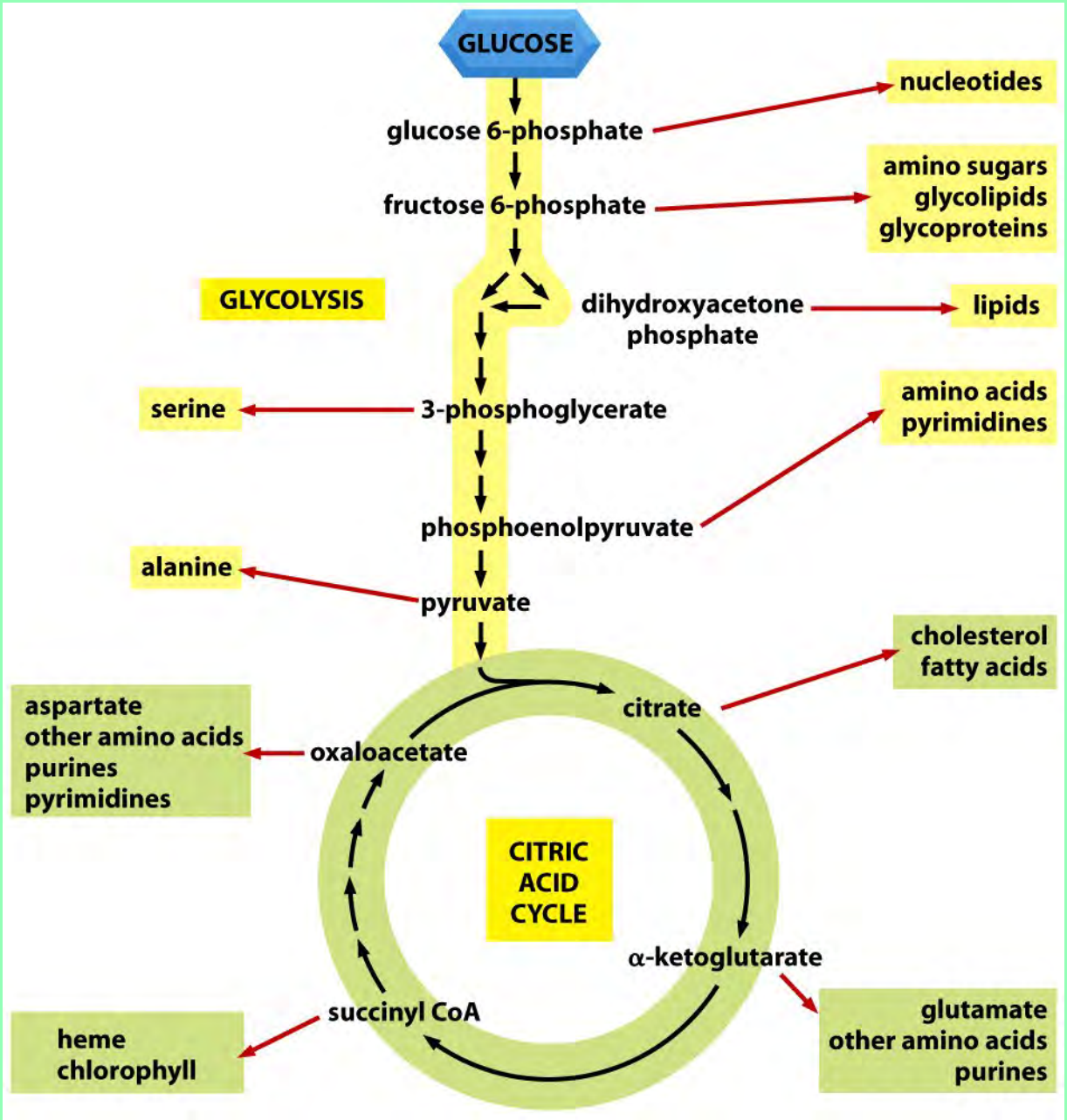
"Biology of the Cell", Alberts, Garland Science, 2008

Citric Acid
Tricarboxylic Acid Cycle



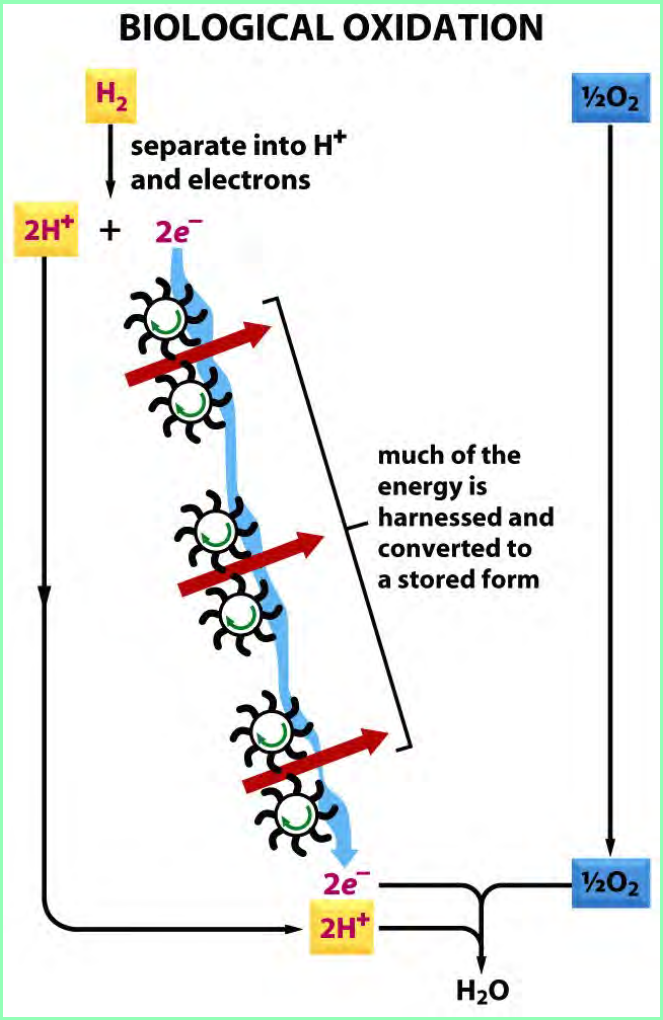
"Biology of the Cell", Alberts, Garland Science, 2008

Glycolysis & TCA



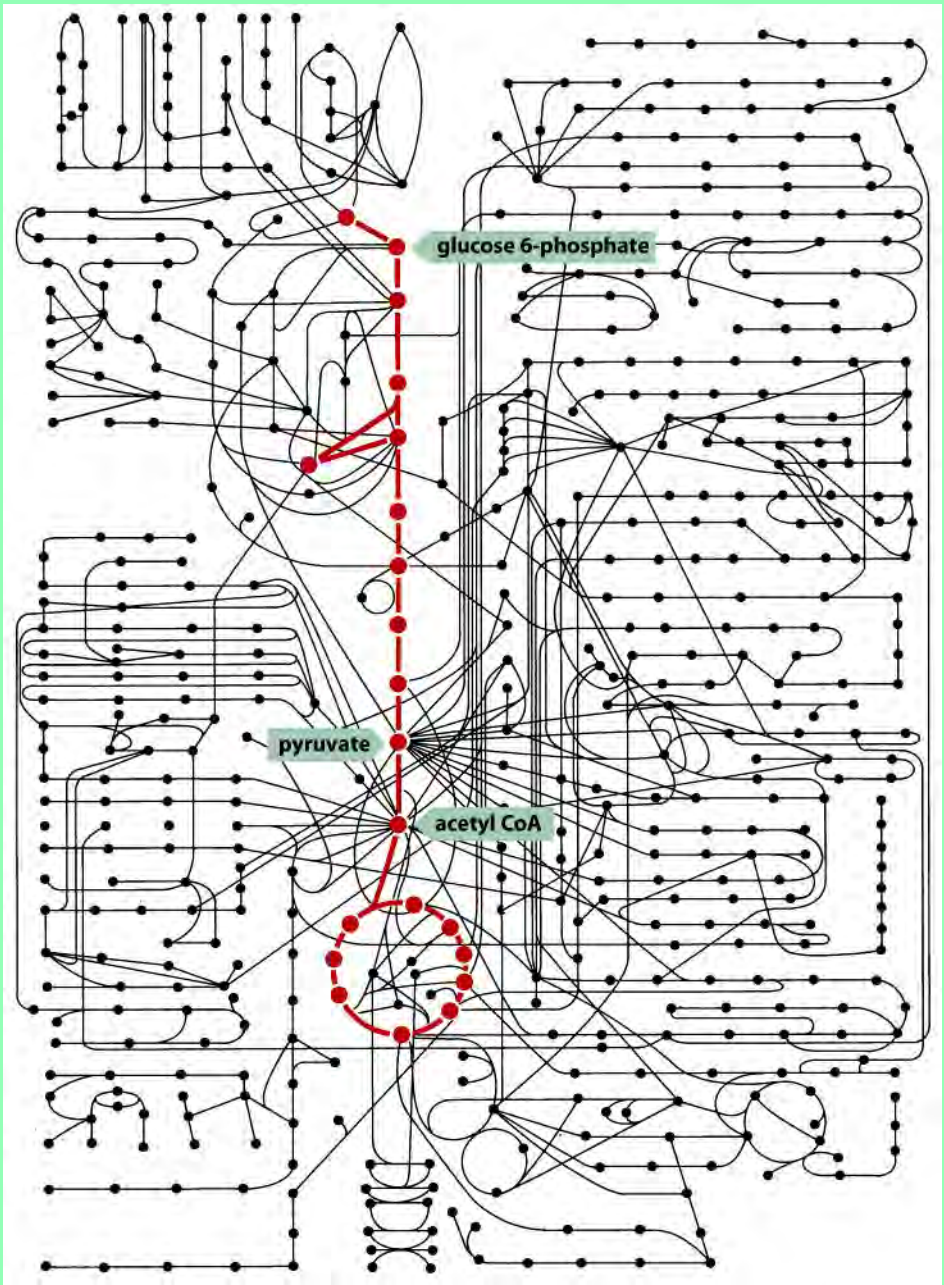
"Biology of the Cell", Alberts, Garland Science, 2008

Controlled Oxidation



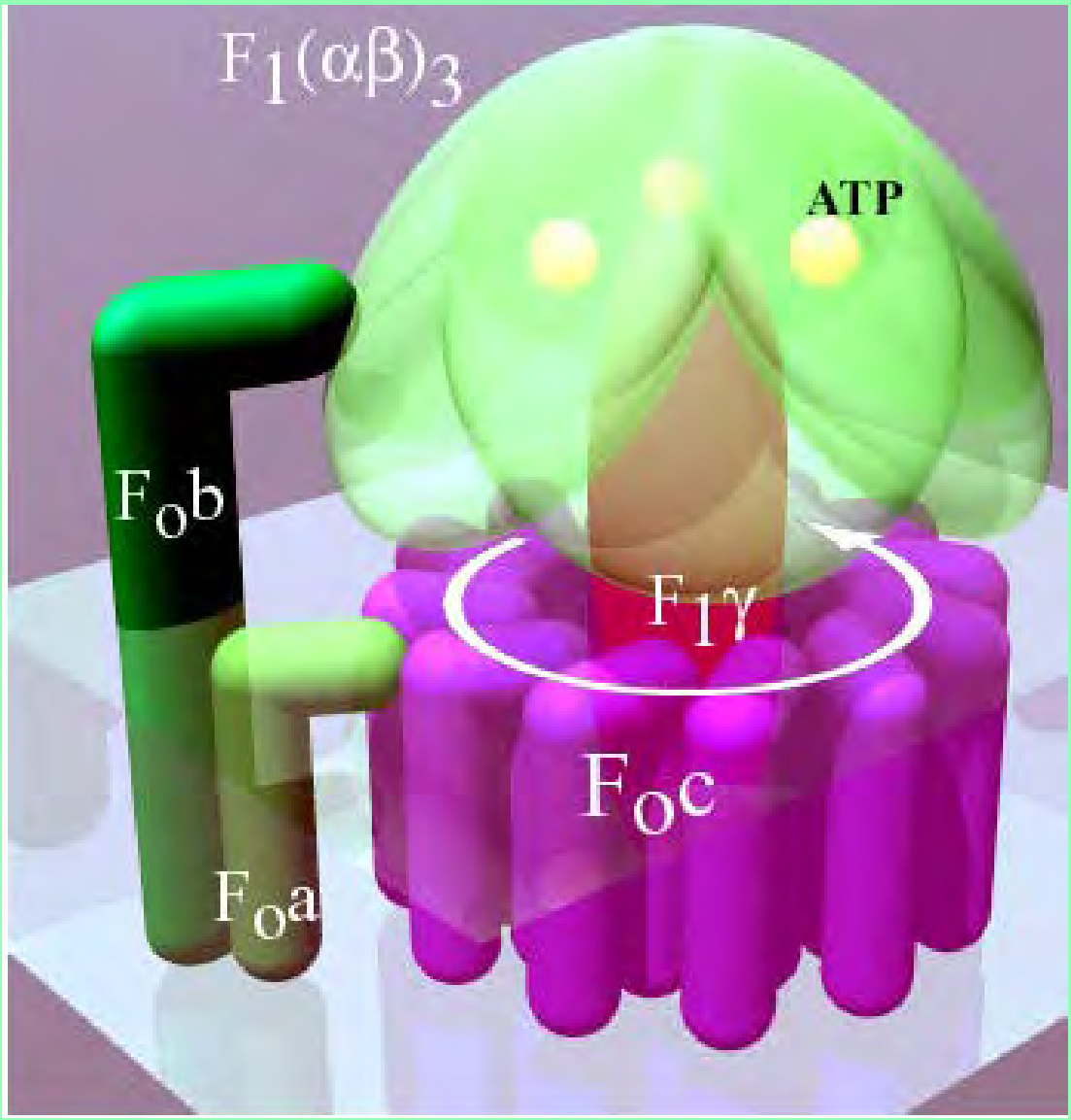
"Biology of the Cell", Alberts, Garland Science, 2008

Centrality of Glycolysis – TCA to Cellular Metabolic Pathways



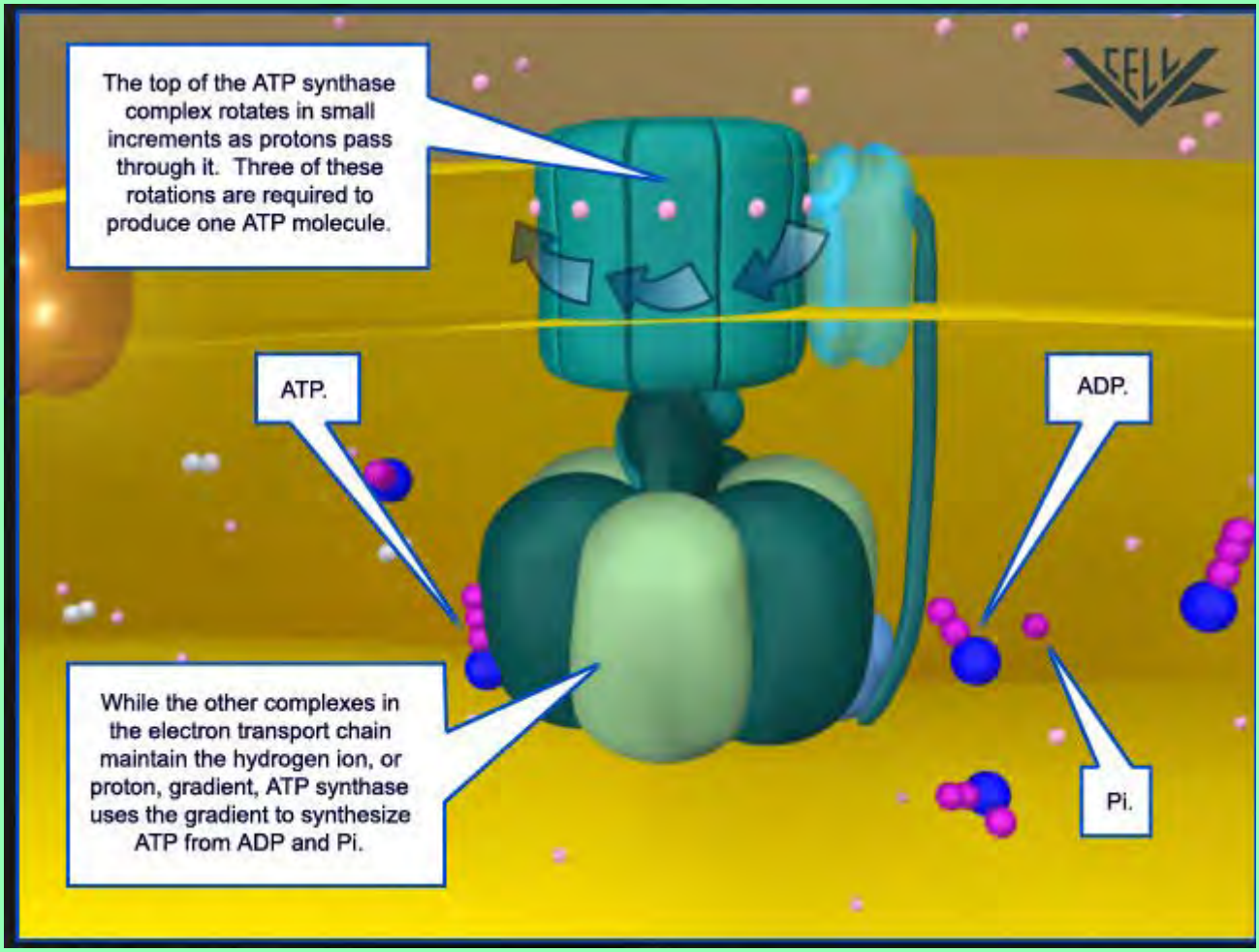
"Biology of the Cell", Alberts, Garland Science, 2008

ATP Synthase



https://en.wikipedia.org/wiki/File:Atpsynthase.jpg

ATP Synthase



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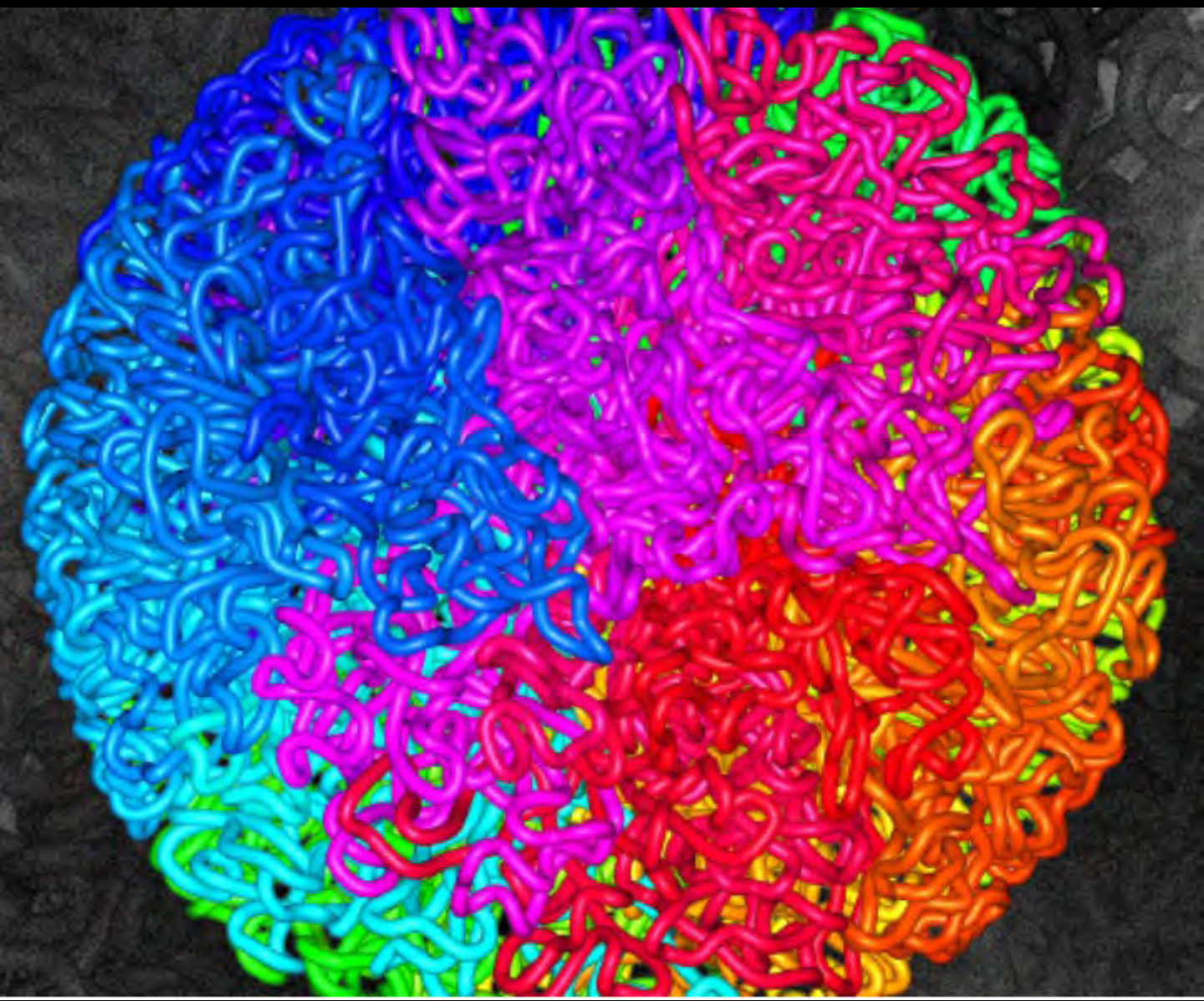
Cancer & Mitochondria

GENOTOXICITY

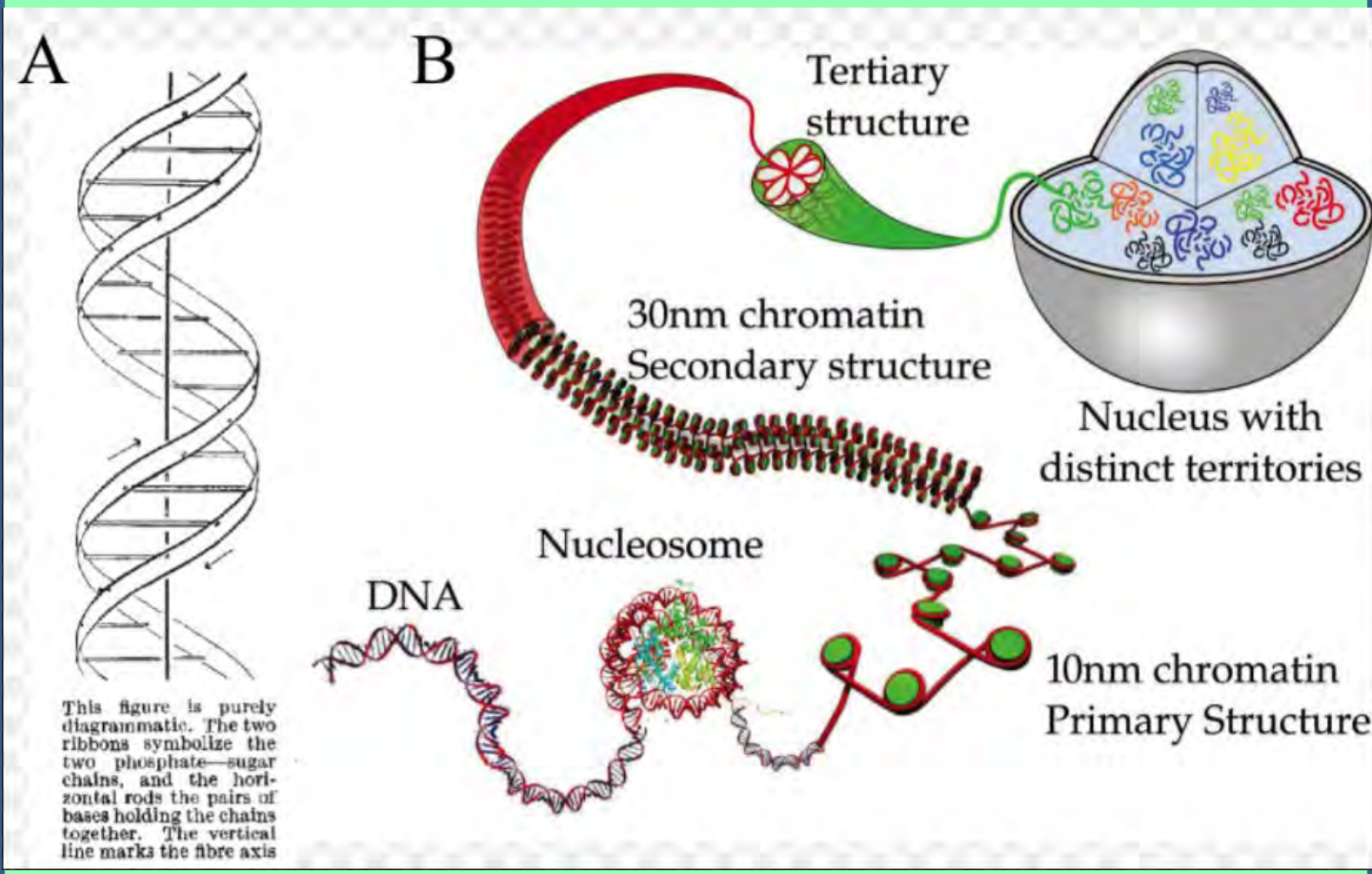
https://thetruthaboutcancer.com/mitochondria-function-reduce-cancer-risk/

Chromatin Loops



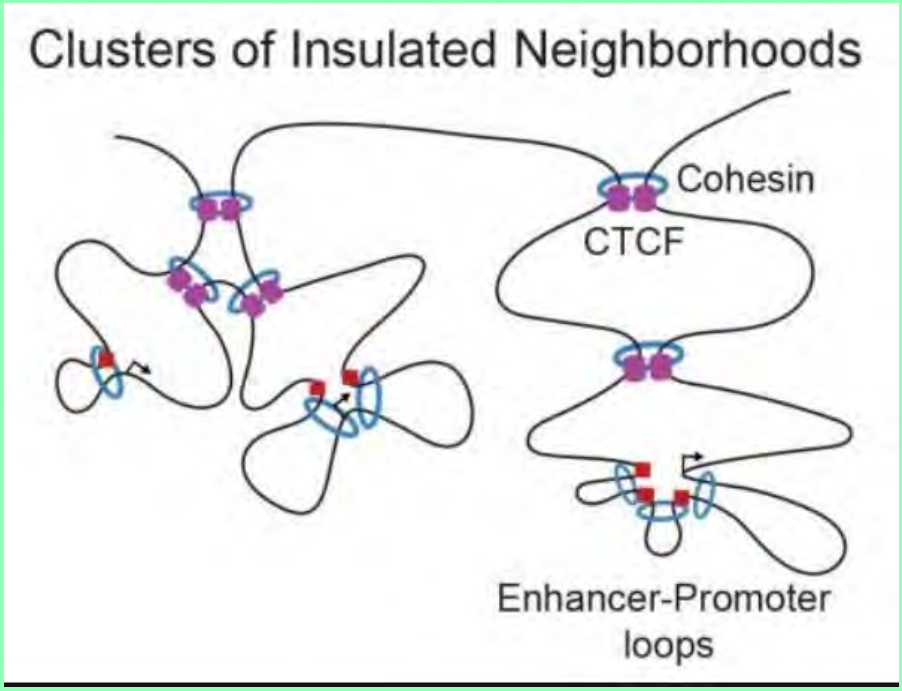
https://www.quantamagazine.org/genome-architecture-in-twists-of-dna-20150225/

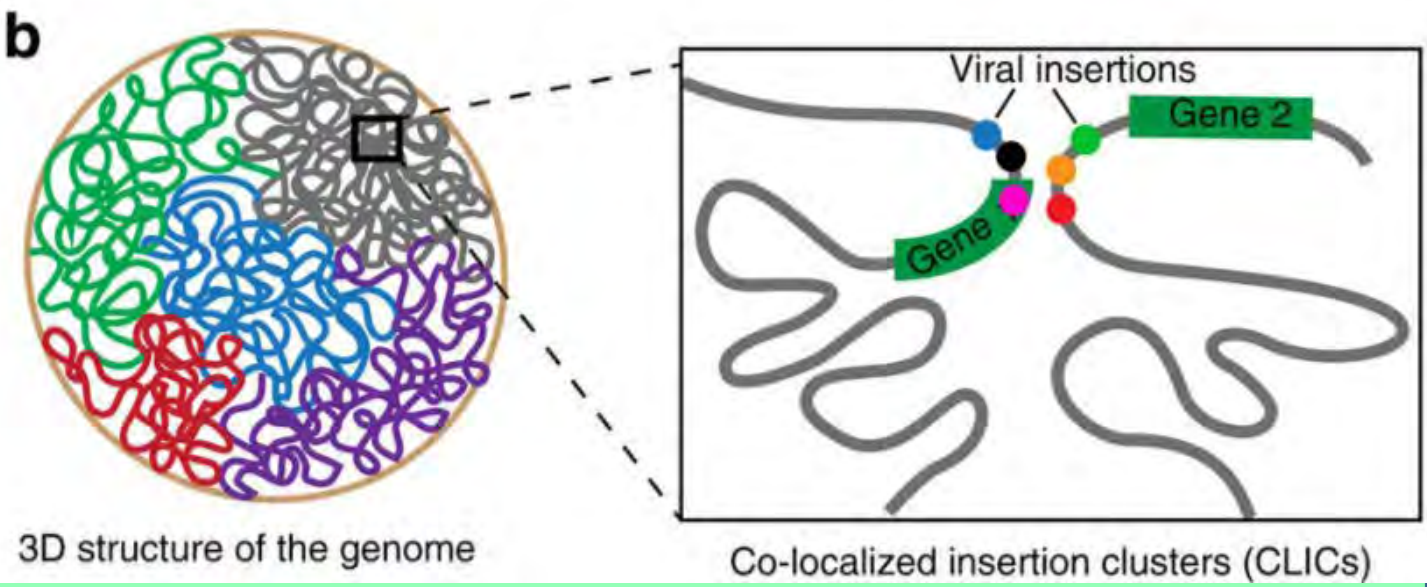
3D Nuclear Structure



https://www.google.com.au/search?q=3d+structure+of+the+genome&rlz=1C1CHBD_en-GBAU702AU702&tbm=isch&source=iu&ictx=1&fir=4tFcpM3JjNr-ZM%253A%252ClKGAXwdHFb8HBM%252C_&usg=__3iwU0sDoXZoSIrxaWjkshbh9Xds%3D&sa=X&ved=0ahUKEwjEnf6Ro-PZAhWHUbwKHRc-BIMQ9QEIKzAA#imgrc=4tFcpM3JjNr-ZM:

Transcription Factories – Promoter-Enhancer Loops





https://www.google.com.au/imgres?imgurl=https%3A%2F%2Fwww.sciencedaily.com%2Fimages%2F2015%2F12%2F151210130724_1_900x600.jpg&imgrefurl=https%3A%2F%2Fwww.sciencedaily.com%2Freleases%2F2015%2F12%2F151210130724.htm&docid=c5TcfnXA79k08M&tbnid=kPQQPP3qQ2s_SM%3A&vet=10ahUKEwiR0uWVo-PZAhUL57wKHYMHCiwQMwhKKAswCw..i&w=570&h=364&bih=900&biw=1920&q=3d%20structure%20of%20the%20genome&ved=0ahUKEwiR0uWVo-PZAhUL57wKHYMHCiwQMwhKKAswCw&iact=mrc&uact=8

https://www.nature.com/articles/ncomms7381/figures/1

Cannabinoids and Mitochondria

Early Studies

Abstract

Delta9-Tetrahydrocannabinol (delta9-THC), the active ingredient of marihuana was found to be a highly effective inhibitor in vitro of the NADH-oxidase activity of rat brain and heart mitochondria. The degree of inhibition of the enzyme system obtained from rat brain tissue varied with the region from which it was derived as follows, in the presence of 10(-5) M delta9-THC: hypothalamus plus thalamus plus midbrain, 73 +/- 4%; cerebellum, 66 +/- 4%; medulla oblongata plus pons, 63 +/- 6%; cerebral cortex, 50 +/- 8%. The same concentration inhibited rat heart NADH-oxidase activity 69 +/- 9%. Inhibition of NADH-oxidase activity by a corresponding concentration of deoxycorticosterone was significantly less in all tissue preparations tested, ranging from 11% to 26%. The inhibition of delta9-THC appeared to be competitive and near the amytal-sensitive site of the electron transport system. Suggestive evidence was also obtained for a second site of action, above the cytochrome c site.

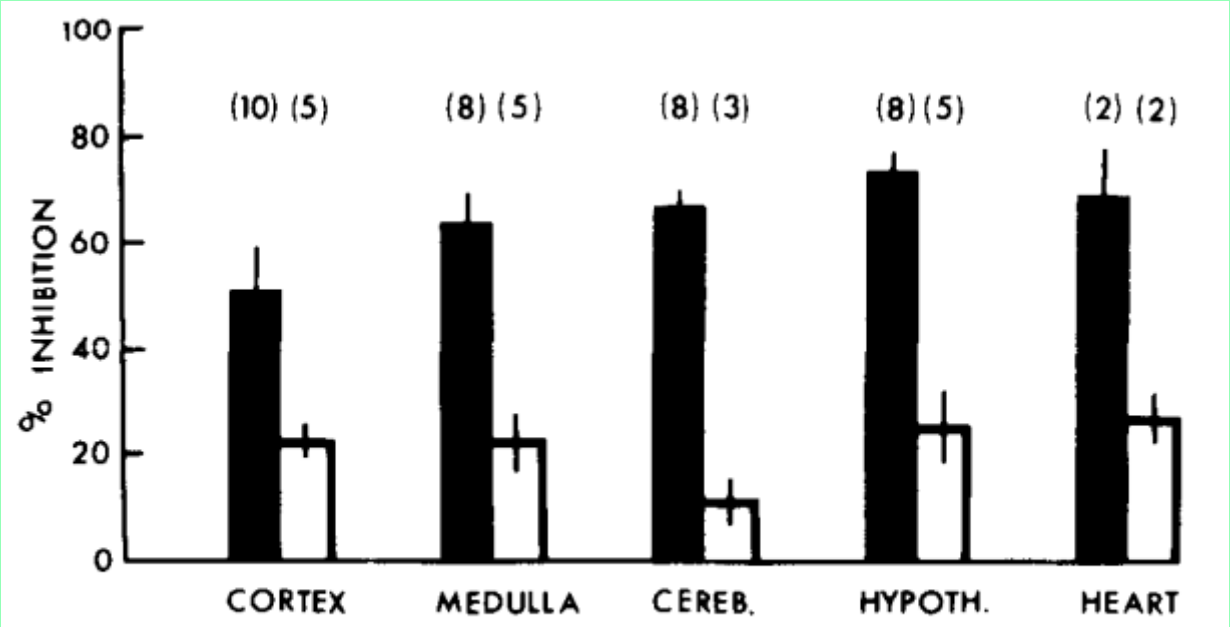


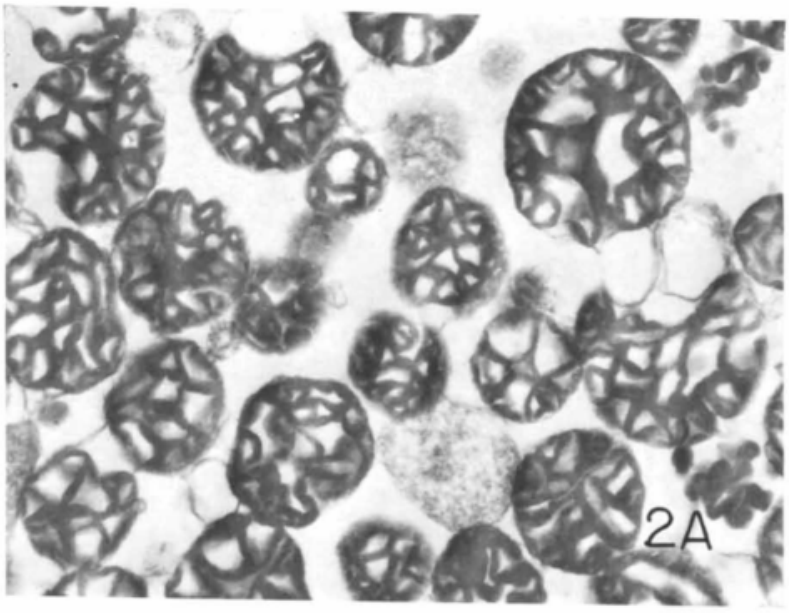
FIG. 1. Effects of Δ^9-THC and deoxycorticosterone on NADH-oxidase activity of rat brain and heart mitochondria. The enzyme

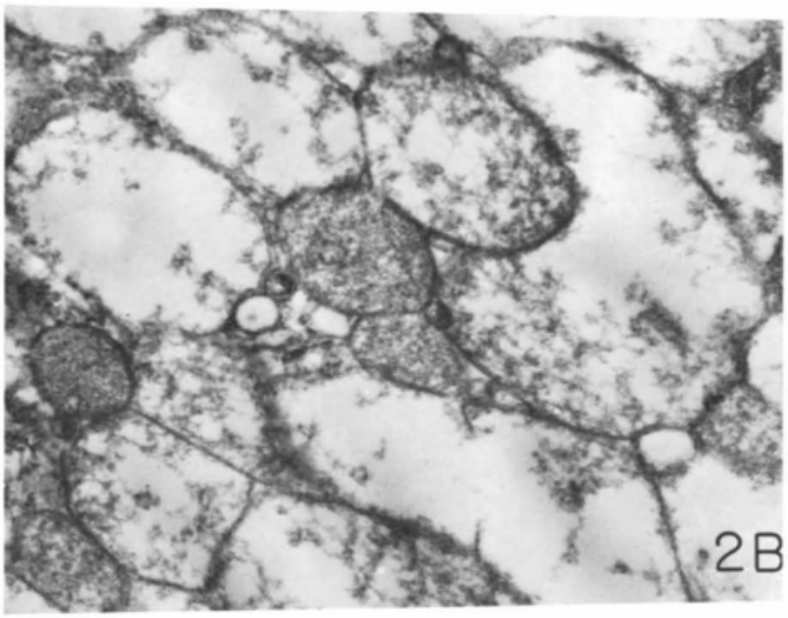
J Biol Chem. 1976 Aug 25;251(16):5002-6.

Effect of delta9-tetrahydrocannabinol on mitochondrial NADH-oxidase activity.

Bartova A, Birmingham MK.

Electron Microscopic Studies - Mitochondrial Swelling @ 50mcg/ml protein





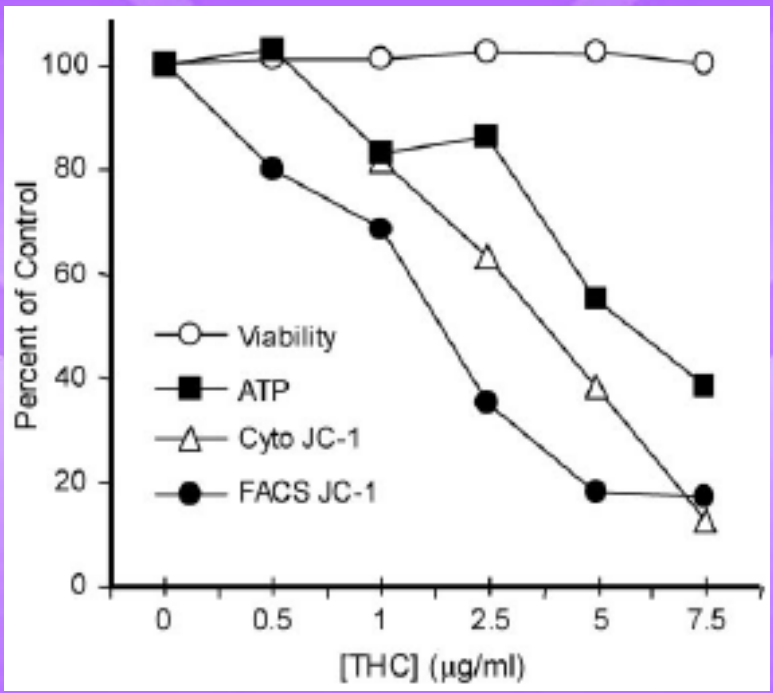
Biochim. Biophys. Acta, 288 (1972) 195–202

Biochim Biophys Acta. 1972 Oct 23;288(1):195-202.

Biochemical effects and morphological changes in rat liver mitochondria exposed to 1 -tetrahydrocannabinol.

Bino T, Chari-Bitron A, Shahar A.

Collapse of Mitochondrial Membrane Permeability and ATP Production



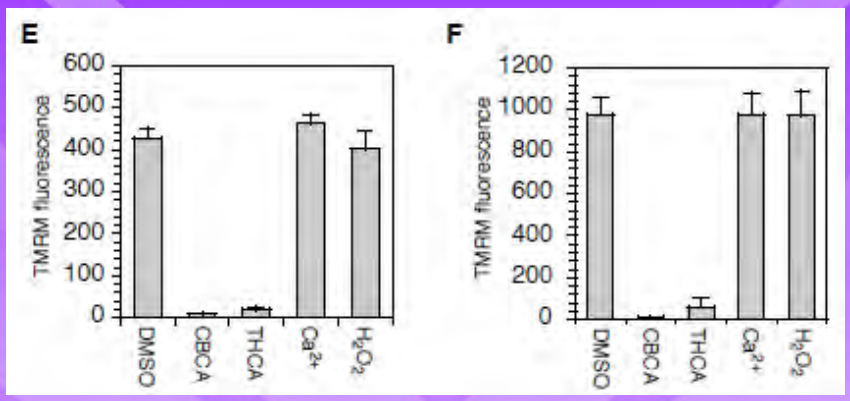
Delta 9-tetrahydrocannabinol disrupts **mitochondrial** function and cell energetics.

Sarafian TA, Kouyoumjian S, Khoshaghideh F, Tashkin DP, Roth MD.

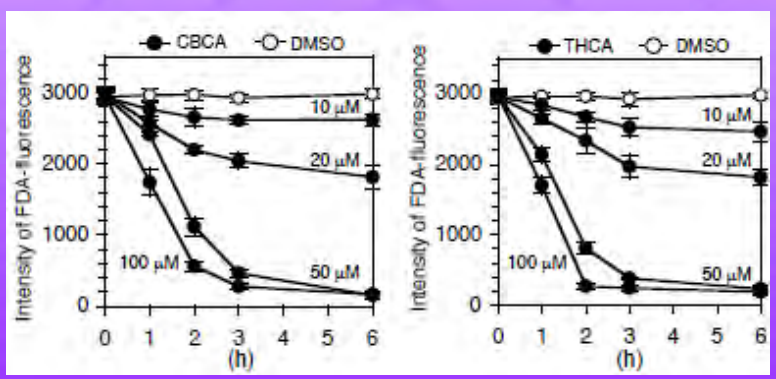
Am J Physiol Lung Cell Mol Physiol. 2003 Feb;284(2):L298-306. Epub 2002 Oct 25.

PMID: 12533310 **Free Article**

Collapse of Mitochondrial Potential with Cannabichromene or THC



Cell Death Rates with Cannabichromene or THC

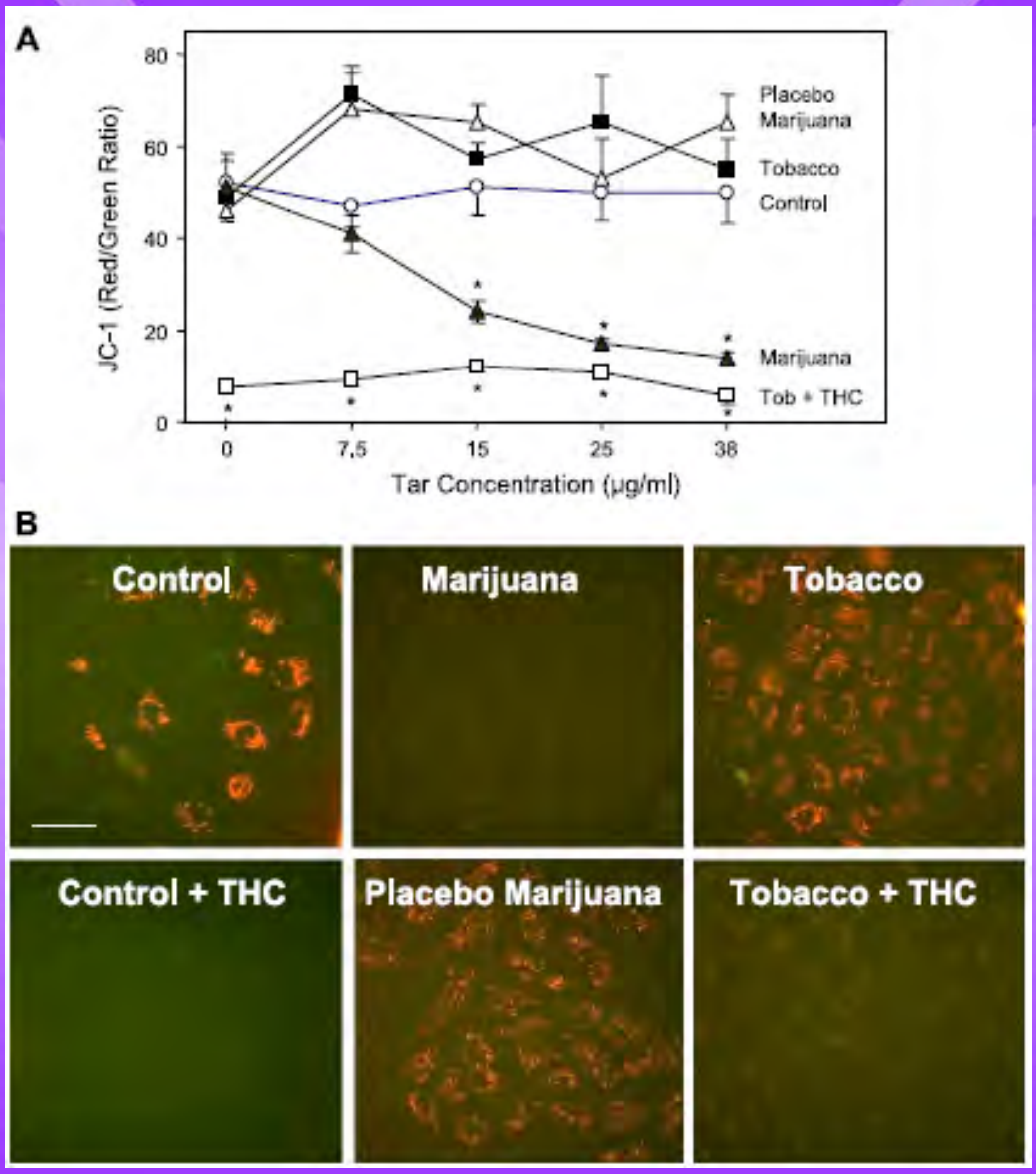


J Biol Chem. 2007 Jul 13;282(28):20739-51. Epub 2007 May 17.

Identification and characterization of cannabinoids that induce cell death through mitochondrial permeability transition in Cannabis leaf cells.

Morimoto S[1], Tanaka Y, Sasaki K, Tanaka H, Fukamizu T, Shoyama Y, Shoyama Y, Taura F.

Mitochondrial Membrane Potential



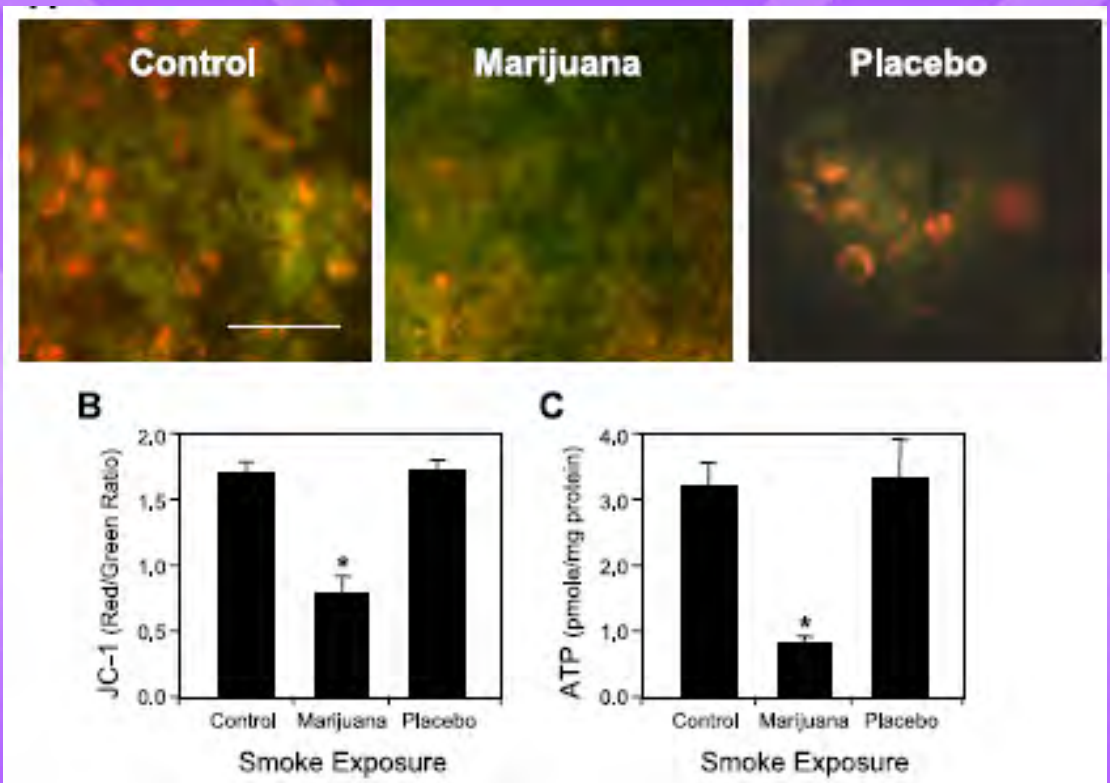
Inhaled marijuana smoke disrupts **mitochondrial** energetics in pulmonary epithelial cells in vivo.

Sarafian TA, Habib N, Oldham M, Seeram N, Lee RP, Lin L, Tashkin DP, Roth MD.

Am J Physiol Lung Cell Mol Physiol. 2006 Jun;290(6):L1202-9. Epub 2006 Jan 13.

PMID: 16414979 Free Article

Membrane Potential Collapse and ATP Collapse



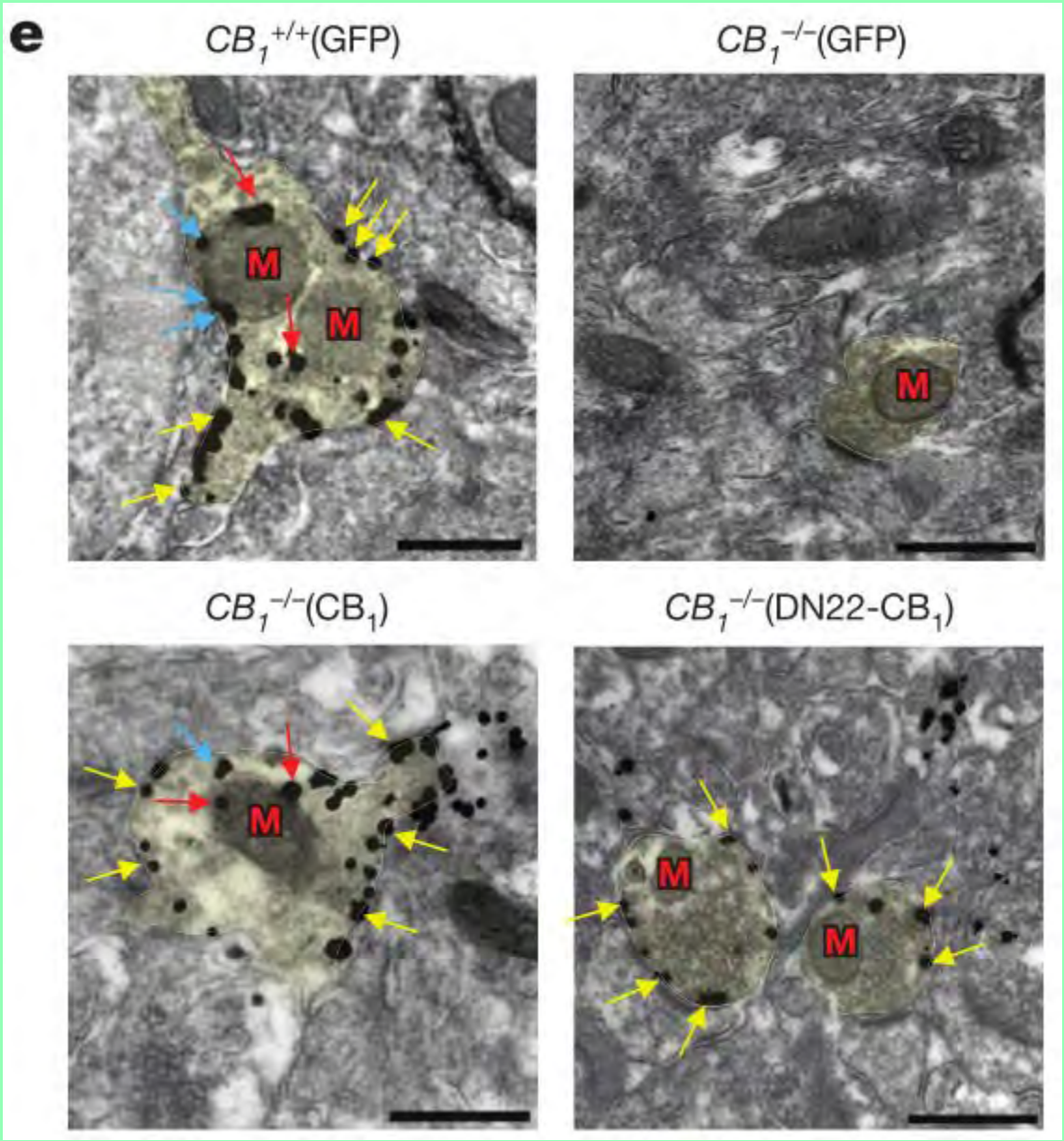
Inhaled marijuana smoke disrupts **mitochondrial** energetics in pulmonary epithelial cells in vivo.

Sarafian TA, Habib N, Oldham M, Seeram N, Lee RP, Lin L, Tashkin DP, Roth MD.

Am J Physiol Lung Cell Mol Physiol. 2006 Jun;290(6):L1202-9. Epub 2006 Jan 13.

PMID: 16414979 **Free Article**

CB1R in Mitochondria



Nature. 2016 Nov 24;539(7630):555-559. doi: 10.1038/nature20127. Epub 2016 Nov 9.

A cannabinoid link between mitochondria and memory.

Hebert-Chatelain E[1,2,3], Desprez T[1,2], Serrat R[1,2], Bellocchio L[1,2,4], Soria-Gomez E[1,2], Busquets-Garcia A[1,2], Pagano Zottola AC[1,2], Delamarre A[1,2], Cannich A[1,2], Vincent P[1,2], Varilh M[1,2], Robin LM[1,2], Terral G[1,2], García-Fernández MD[5,6], Colavita M[1,2,7], Mazier W[1,2], Drago F[7], Puente N[8,9], Reguero L[8,9], Elezgarai I[8,9], Dupuy JW[10], Cota D[1,2], Lopez-Rodriguez ML[11], Barreda-Gómez G[5], Massa F[1,2], Grandes P[8,9,12], Bénard G[1,2], Marsicano G[1,2].

CB1R's on Mitochondrial Membranes

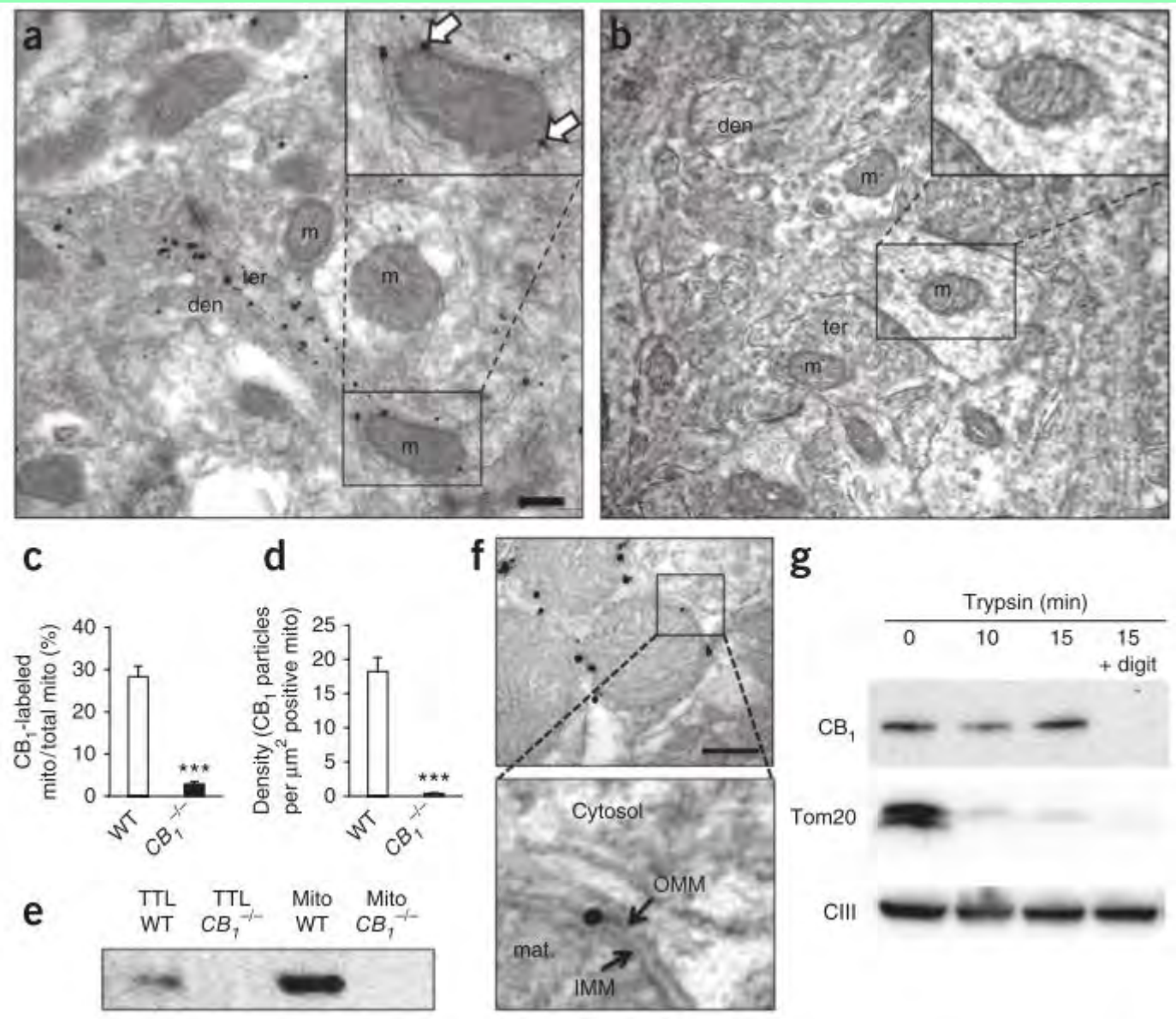


Figure 1 CB_1 receptors in neuronal mitochondria. (**a**,**b**) Electron immunogold detection of CB_1 receptors on mitochondrial membranes of neurons in the CA1 hippocampal region of wild-type (**a**) and $CB_1^{-/-}$ mice (**b**).

Nat Neurosci. 2012 Mar 4;15(4):558-64. doi: 10.1038/nn.3053.

Mitochondrial CB_1 receptors regulate neuronal energy metabolism.

Bénard G[1], Massa F, Puente N, Lourenço J, Bellocchio L, Soria-Gómez E, Matias I, Delamarre A, Metna-Laurent M, Cannich A, Hebert-Chatelain E, Mulle C, Ortega-Gutiérrez S, Martín-Fontecha M, Klugmann M, Guggenhuber S, Lutz B, Gertsch J, Chaouloff F, López-Rodríguez ML, Grandes P, Rossignol R, Marsicano G.

mt CB1R's on both Glutamate and GABA terminals

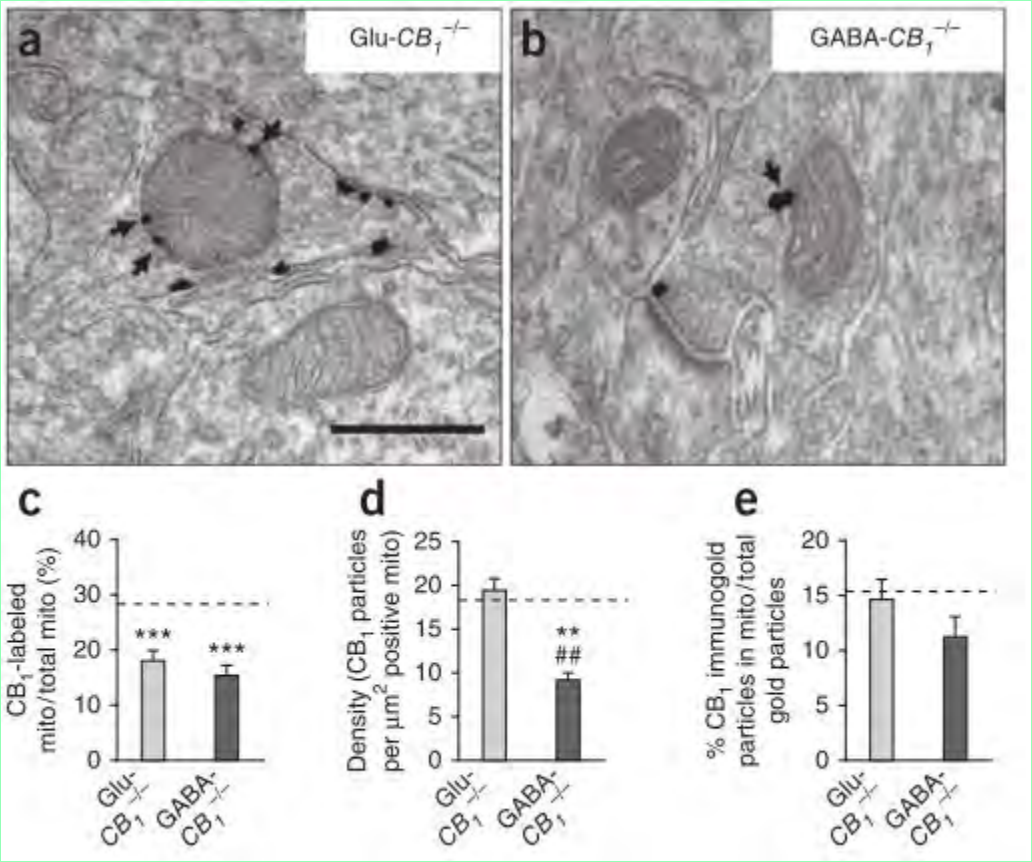


Figure 2 Mt-CB_1 is present in both GABAergic and glutamatergic CA1 hippocampal neurons. (**a**,**b**) Immunogold localization of mtCB_1 (arrows) in

Nat Neurosci. 2012 Mar 4;15(4):558-64. doi: 10.1038/nn.3053.

Mitochondrial CB_1 receptors regulate neuronal energy metabolism.

Bénard G[1], Massa F, Puente N, Lourenço J, Bellocchio L, Soria-Gómez E, Matias I, Delamarre A, Metna-Laurent M, Cannich A, Hebert-Chatelain E, Mulle C, Ortega-Gutiérrez S, Martín-Fontecha M, Klugmann M, Guggenhuber S, Lutz B, Gertsch J, Chaouloff F, López-Rodríguez ML, Grandes P, Rossignol R, Marsicano G.

Control of Mitochondrial Respiration by THC & 2-AG

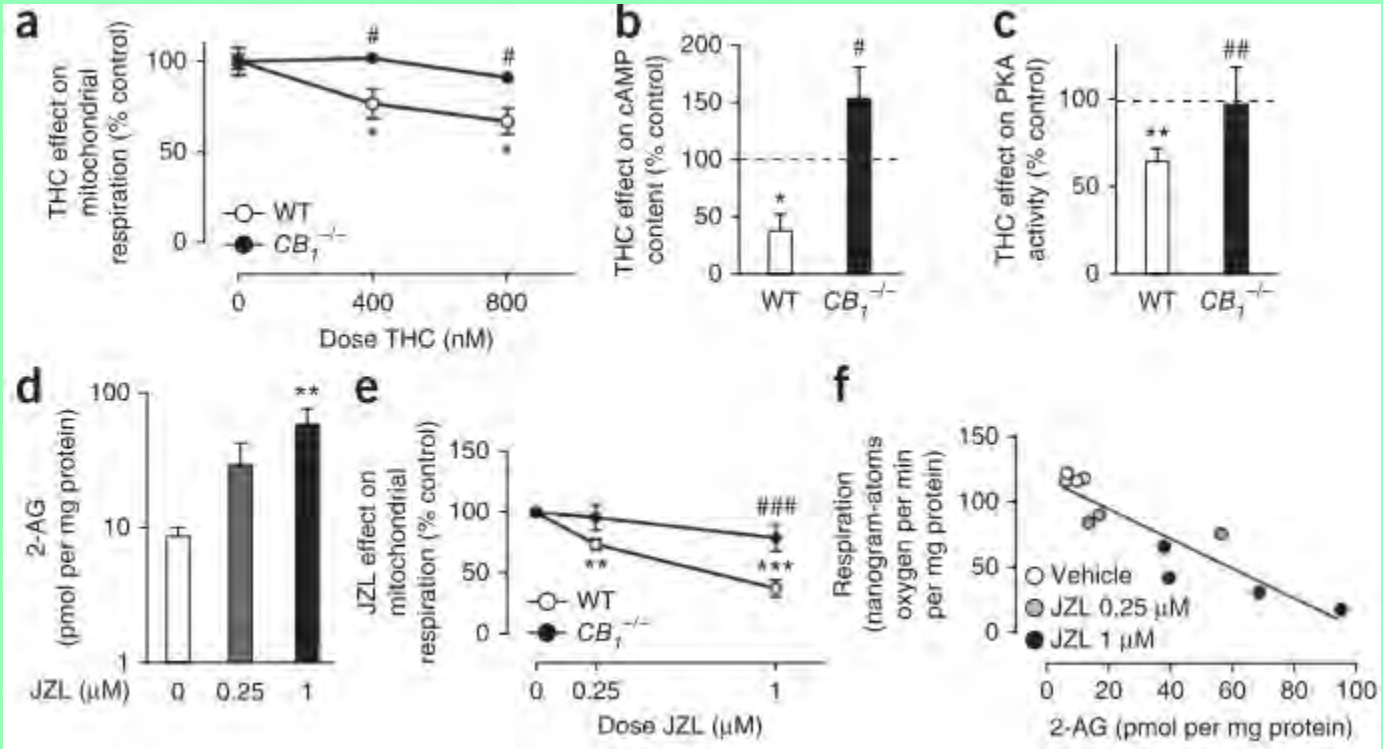


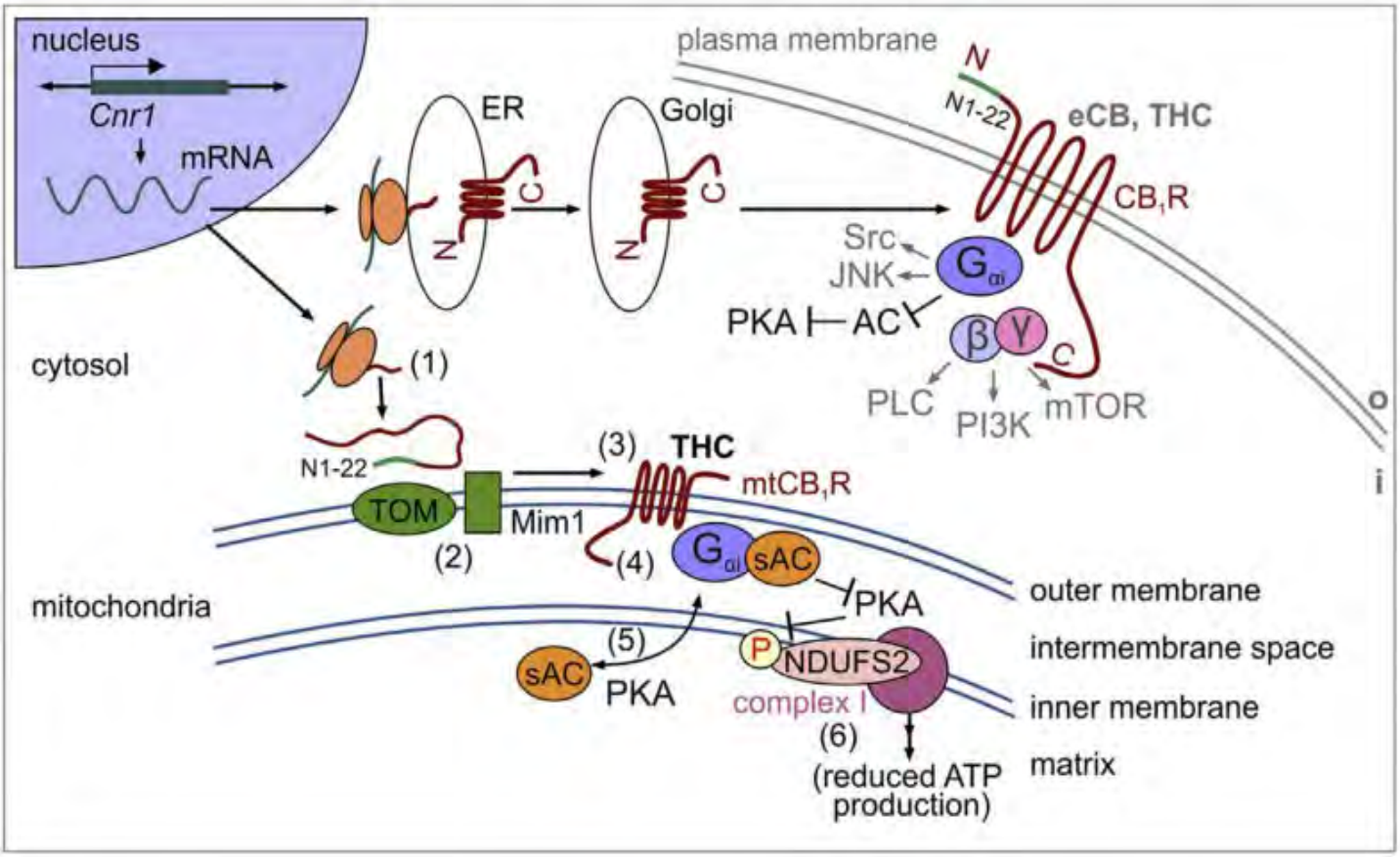
Figure 4 MtCB$_1$ receptors are activated by THC, and mitochondria contain biologically active endocannabinoids. (**a**) Dose–response

Nat Neurosci. 2012 Mar 4;15(4):558-64. doi: 10.1038/nn.3053.

Mitochondrial CB$_1$ receptors regulate neuronal energy metabolism.

Bénard G[1], Massa F, Puente N, Lourenço J, Bellocchio L, Soria-Gómez E, Matias I, Delamarre A, Metna-Laurent M, Cannich A, Hebert-Chatelain E, Mulle C, Ortega-Gutiérrez S, Martín-Fontecha M, Klugmann M, Guggenhuber S, Lutz B, Gertsch J, Chaouloff F, López-Rodríguez ML, Grandes P, Rossignol R, Marsicano G.

Amnesia
~ mtCB1R Inhibition

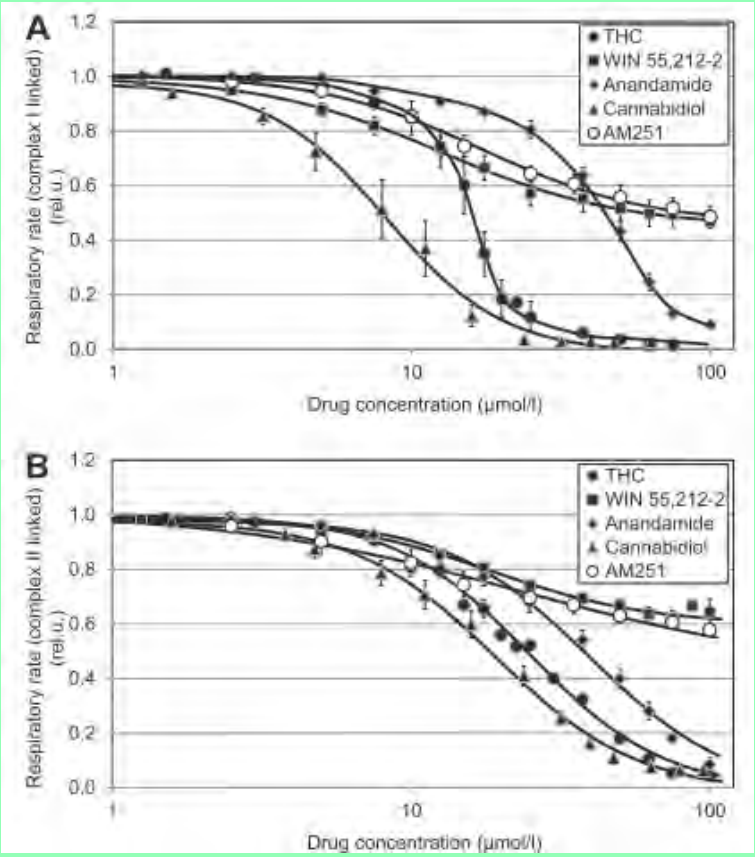


(S)Pot on Mitochondria: Cannabinoids Disrupt Cellular Respiration to Limit Neuronal Activity

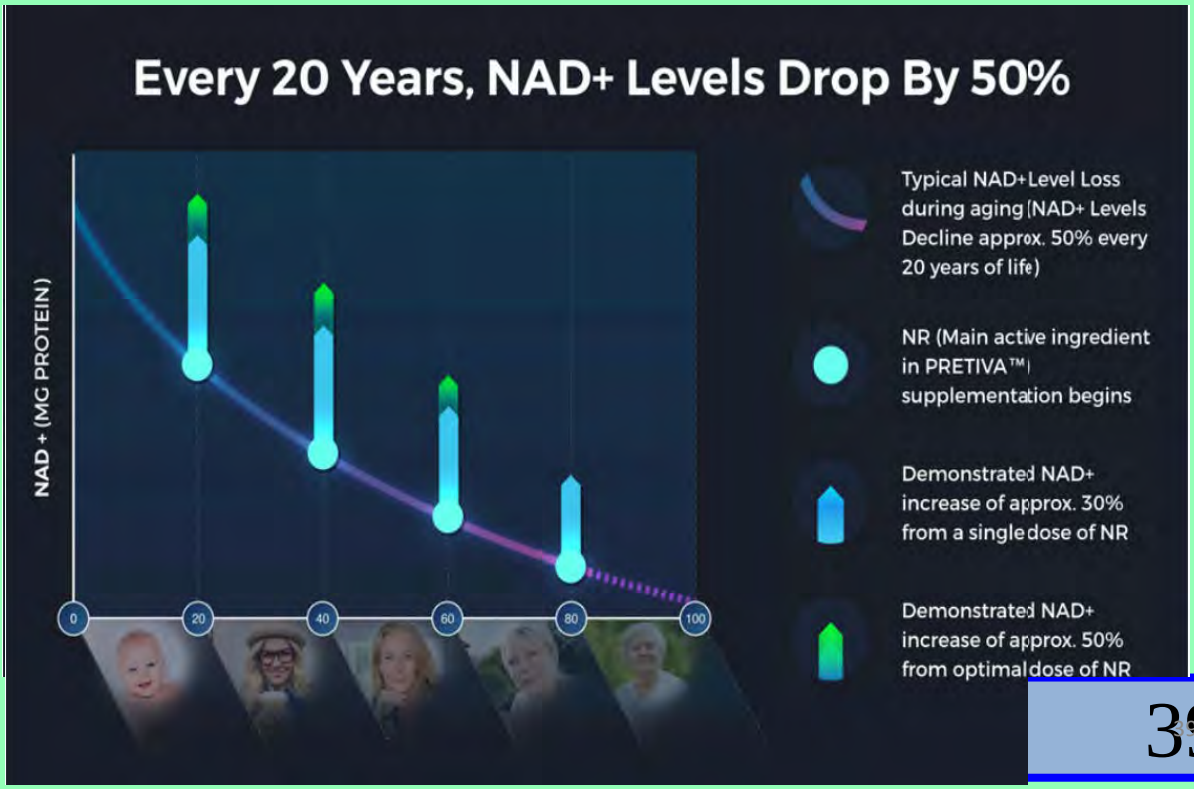
Tibor Harkany[1,2,*] and Tamas L. Horvath[3]
[1]Department of Molecular Neurosciences, Center for Brain Research, Medical University of Vienna, 1090 Vienna, Austria
[2]Department of Neuroscience, Karolinska Institutet, 17177 Stockholm, Sweden
[3]Program in Integrative Cell Signaling and Neurobiology of Metabolism, Section of Comparative Medicine, Yale University School of Medicine, New Haven, CT 06510, USA
*Correspondence: tibor.harkany@meduniwien.ac.at
http://dx.doi.org/10.1016/j.cmet.2016.12.020

Classical views posit G protein-coupled cannabinoid receptor 1s (CB1Rs) at the cell surface with cytosolic Giα-mediated signal transduction. Hebert-Chatelain et al. (2016) instead place CB_1Rs at mitochondria limiting neuronal respiration by soluble adenylyl cyclase-dependent modulation of complex I activity. Thus, neuronal bioenergetics link to synaptic plasticity and, globally, learning and memory

Cannabinoid Decline with age Mimics that Occurring with Age



Fisar Z., Singh N., Hroudova J. *"Cannabinoid-induced changes in respiration of brain mitochondria"* Toxicol. Lett., (2014); 23 (1) 62-71



More Brain Activation to Think

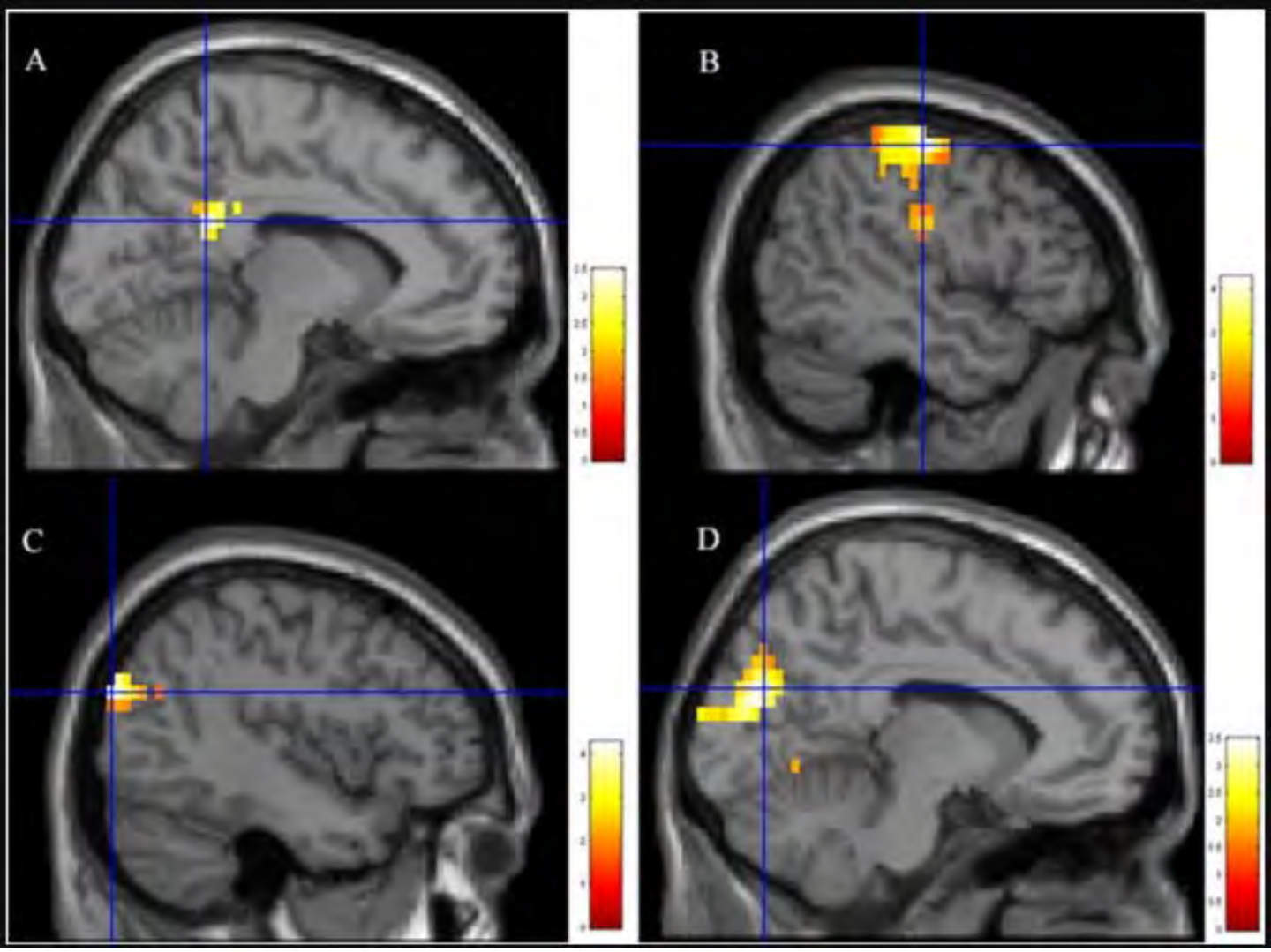


Fig. 1. Blue cross hairs represent the most significantly different voxel between groups for each task with the prenatally exposed group showing significantly more activity than the non-exposed group. A) Visuospatial 2-Back – left posterior cingulate gyrus, B) Go/NoGo task – left postcentral gyrus, C) Letter 2-Back – left middle occipital gyrus, D) Counting Stroop – left cuneus and lingual gyrus.

Prenatal marijuana exposure impacts executive functioning into young adulthood: An fMRI study.
Smith AM, Mioduszewski O, Hatchard T, Byron-Alhassan A, Fall C, **Fried PA**.
Neurotoxicol Teratol. 2016 Nov - Dec;58:53-59. doi: 10.1016/j.ntt.2016.05.010. Epub 2016 Jun 1. Review.
PMID: 27263090

Brain Cortex Changes

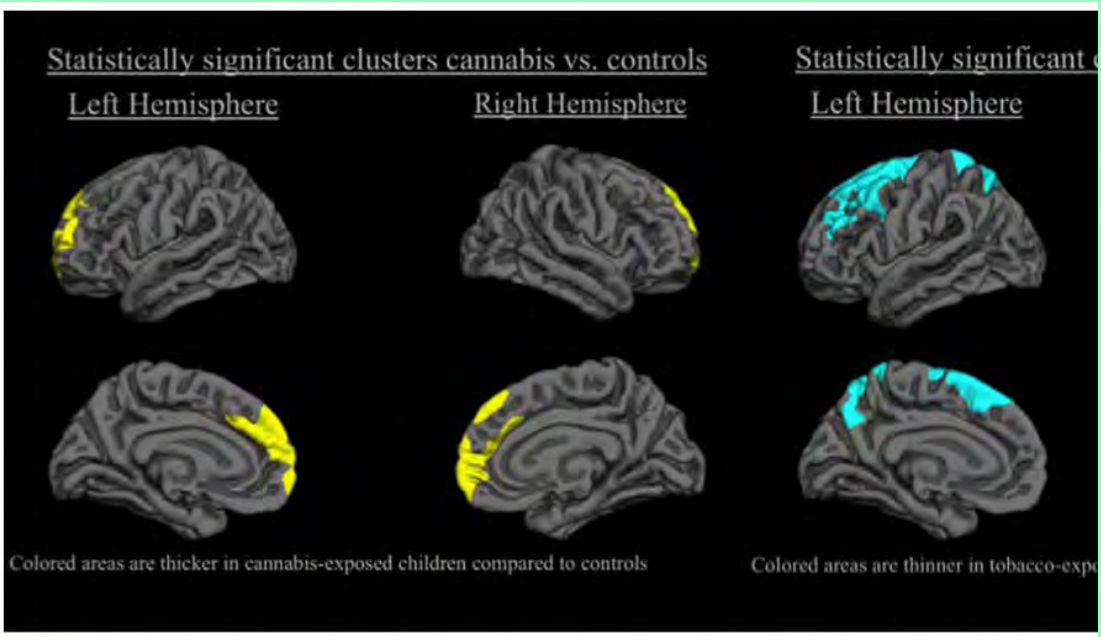
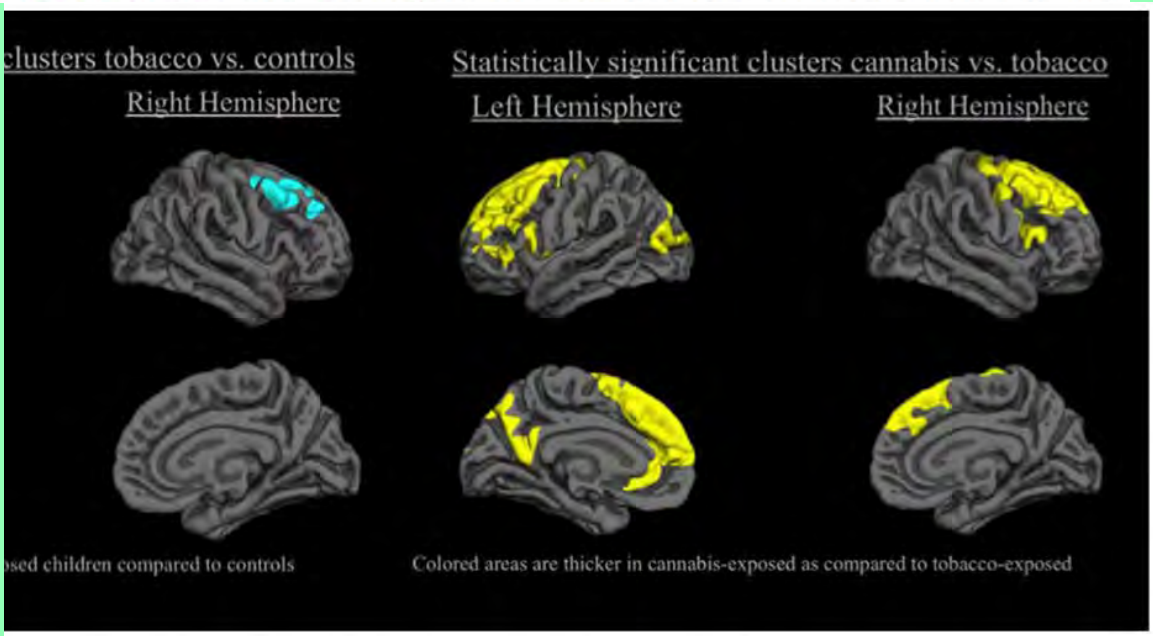


Figure 1. Vertexwise analysis: The association between prenatal cannabi



s and/or tobacco exposure and cortical thickness.

Biol Psychiatry. 2016 Jun 15;79(12):971-9. doi: 10.1016/j.biopsych.2015.08.024. Epub 2015 Sep 1.

Prenatal Cannabis and Tobacco Exposure in Relation to Brain Morphology: A Prospective Neuroimaging Study in Young Children.

El Marroun H[1], Tiemeier H[2], Franken IH[3], Jaddoe VW[4], van der Lugt A[5], Verhulst FC[6], Lahey BB[7], White T[8].

***Mortality* in 30 Year Study of Cannabis Users - Sweden**

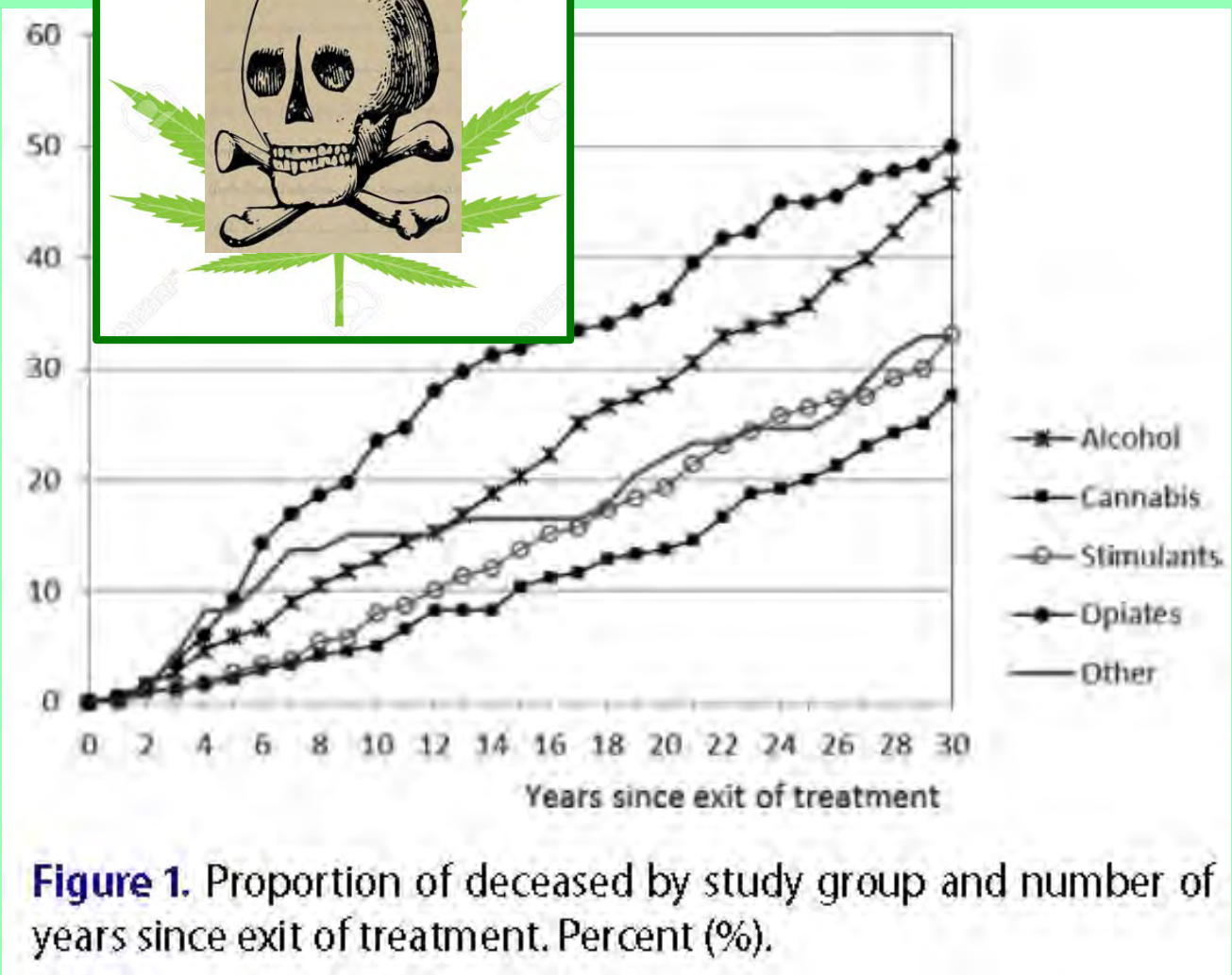


Figure 1. Proportion of deceased by study group and number of years since exit of treatment. Percent (%).

Subst Use Misuse. 2018 Mar 26:1-9. doi: 10.1080/10826084.2018.1452261. [Epub ahead of print]

Mortality and Cause of Death-A 30-Year Follow-Up of Substance Misusers in Sweden.

von Greiff N[1], Skogens L[1], Berlin M[2], Bergmark A[1].

Mortality in 30 Year Study of Cannabis Users - Sweden

Table 2. Age and gender standardised mortality ratio (SMR) for the period of 1984–2013.

	Age at end of 1984	No: in study population 1984-01-01	Observed number of deaths	Percent deceased (CDR)	Expected number of deaths	Standard mortality rate (SMR)	95% CI Lower	Higher
Women	17-24 yrs	140	23	16.4	1.6	14.3	8.4	20.1
	25-34 yrs	181	49	27.1	4.5	10.9	7.8	13.9
	35-43 yrs	32	13	40.6	2.2	6.0	2.8	9.3
	All	353	85	24.1	8.3	10.3	8.1	12.4
Men	17-24 yrs	206	66	32.0	4.1	16.3	12.4	20.2
	25-34 yrs	441	205	46.5	15.6	13.1	11.3	14.9
	35-43 yrs	136	84	61.8	10.8	7.8	6.1	9.5
	All	783	355	45.3	30.4	11.7	10.5	12.9
By study group:								
Alcohol	Women	65	23	35.4	1.6	14.4	8.5	20.2
	Men	180	91	50.6	7.1	12.8	10.2	15.5
	All	245	114	46.5	8.7	13.1	10.7	15.5
Cannabis	Women	51	4	7.8	0.9	4.3	0.1	8.4
	Men	187	64	34.2	6.4	9.9	7.5	12.4
	All	238	68	28.6	7.4	9.2	7.0	11.4
Stimulants	Women	134	27	20.1	3.1	8.6	5.4	11.9
	Men	269	114	42.4	11.6	9.8	8.0	11.6
	All	403	141	35.0	14.7	9.6	8.0	11.1
Opiates	Women	75	23	30.7	1.7	13.5	8.0	19.1
	Men	103	66	64.1	3.6	18.3	13.8	22.7
	All	178	89	50.0	5.3	16.7	13.3	20.2
Other	Women	28	8	28.6	0.9	8.8	2.7	14.9
	Men	44	20	45.5	1.7	11.9	6.7	17.1
	All	72	28	38.9	2.6	10.8	6.8	14.8

Note. Expected number of death were calculated based on the life tables by sex and age for the general population 1984 & 2014. Study groups are based on self-reported most dominant substance misuse.

Subst Use Misuse. 2018 Mar 26:1-9. doi: 10.1080/10826084.2018.1452261. [Epub ahead of print]

Mortality and Cause of Death-A 30-Year Follow-Up of Substance Misusers in Sweden.

von Greiff N[1], Skogens L[1], Berlin M[2], Bergmark A[1].

Mortality in Cannabis Users - 11 References

Title
Mortality and Cause of Death-A 30-Year Follow-Up of Substance Misusers in Sweden
Cocaine and Marijuana Use among Young Adults Presenting with Myocardial Infarction: The Partners YOUNG-MI Registry
Recreational Marijuana Use and Acute Myocardial Infarction: Insights from Nationwide Inpatient Sample in the United States
Marijuana use and long-term mortality among survivors of acute myocardial infarction
Mortality among substance-using mothers in California: a 10-year prospective study
All-cause mortality among individuals with disorders related to the use of methamphetamine: a comparative cohort study
Mortality risk in a cohort of subjects reported by authorities for cannabis possession for personal use. Results of a longitudin...
Mortality associated with illegal drug use among adults in the United States
Self-reported drug use and mortality among a nationwide sample of Swedish conscripts - a 35-year follow-up
Mortality among individuals with cannabis, cocaine, amphetamine, MDMA, and opioid use disorders: a nationwide follow-up ...
Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabi...

Author	Journal	Pages	Year
von Greiff, N.; Skogens, L.; Berlin, M.; Bergmark, A.	**Subst Use Misuse**	**1-9**	**2018**
DeFilippis E.M.,; Singh A.,; Divakaran S.,; Gupta A.,; Collins B.L....	**Journal of the American College o...**		**2018**
Desai, R.; Patel, U.; Sharma, S.; Amin, P.; Bhuva, R.; Patel, M. S...	**Cureus**	**e1816**	**2017**
Frost, L.; Mostofsky, E.; Rosenbloom, J. I.; Mukamal, K. J.; Mitt...	**Am Heart J**	**170-5**	**2013**
Hser, Y. I.; Kagihara, J.; Huang, D.; Evans, E.; Messina, N.	Addiction	215-22	2012
Callaghan, R. C.; Cunningham, J. K.; Verdichevski, M.; Sykes, J....	**Drug Alcohol Depend**	**290-4**	**2012**
Pavarin, R. M.; Berardi, D.	**Epidemiol Prev**	**89-93**	**2011**
Muhuri, P. K.; Gfroerer, J. C.	**Am J Drug Alcohol Abuse**	**155-64**	**2011**
Davstad, I.; Allebeck, P.; Leifman, A.; Stenbacka, M.; Romelsj...	**Drug Alcohol Depend**	**383-90**	**2011**
Arendt, M.; Munk-Jorgensen, P.; Sher, L.; Jensen, S. O.	**Drug Alcohol Depend**	**134-9**	**2011**
Calabria, B.; Degenhardt, L.; Hall, W.; Lynskey, M.	**Drug Alcohol Rev**	**318-30**	**2010**

Genetics & Epigenetics Overview

Epigenetics

Health

Memory

Addiction

Ageing

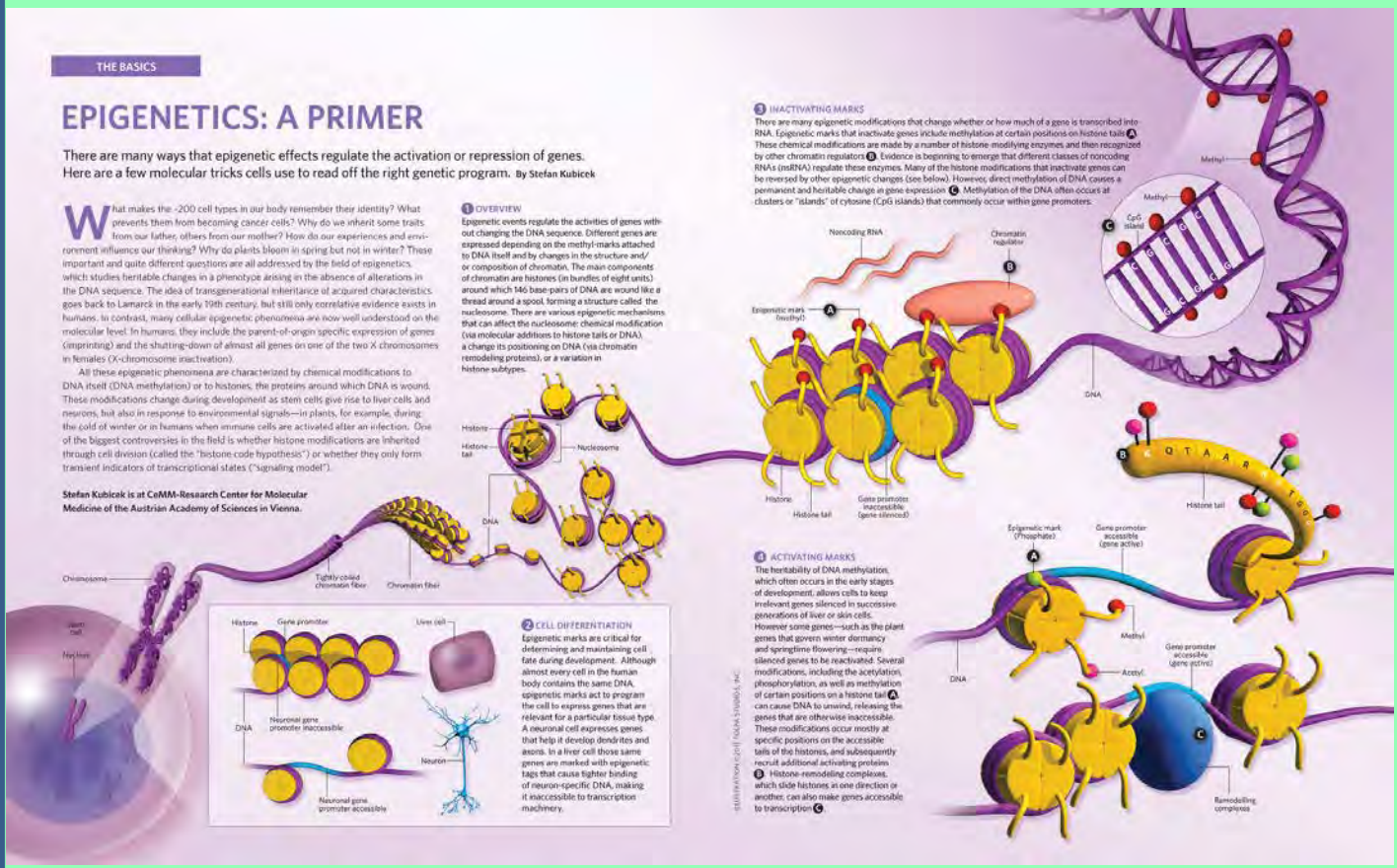
Diseases

Cancer

Foetal Malformations

~ EPI-MUTATIONS

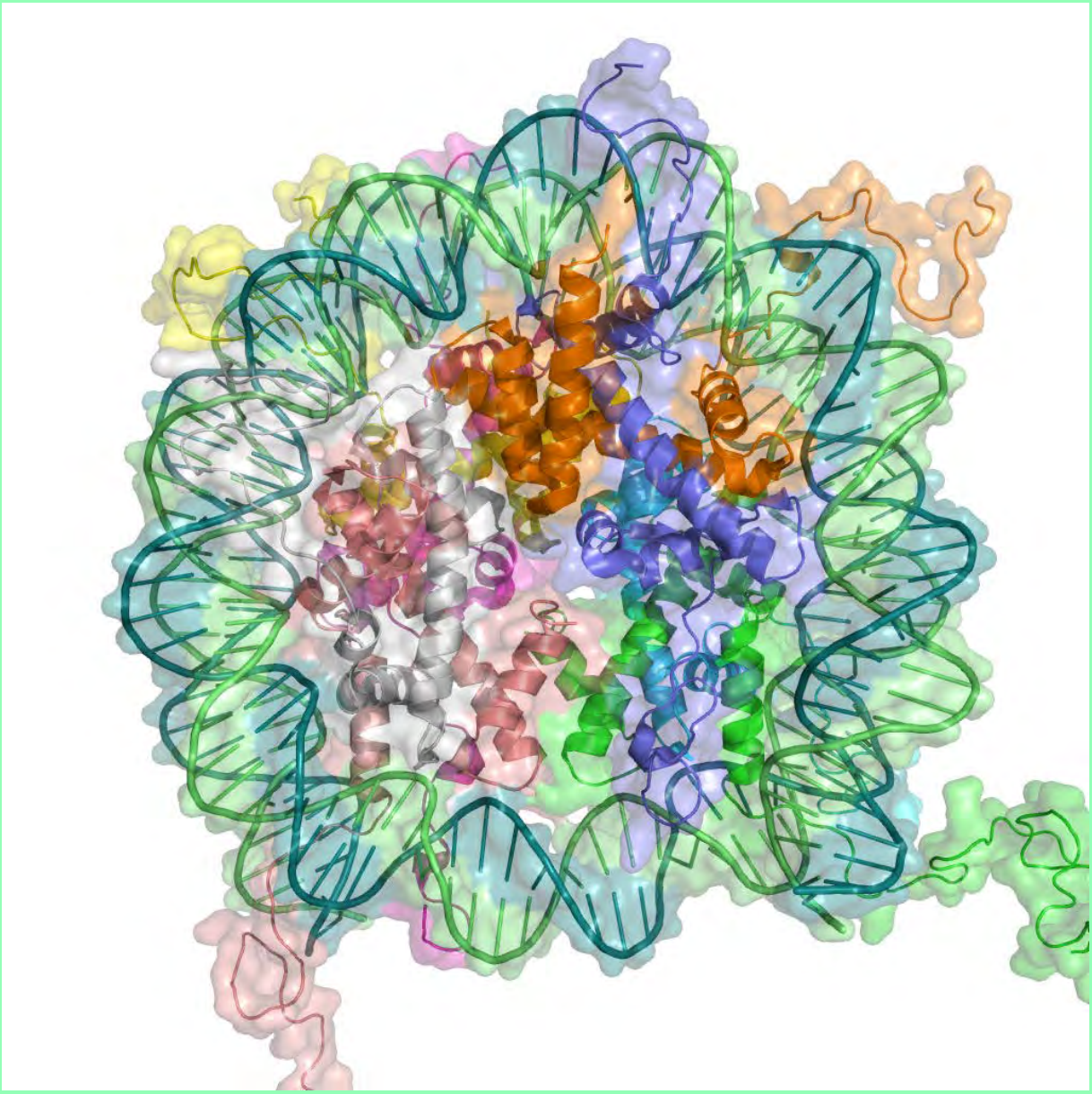
Overview of Epigenetics



PLoS Comput Biol. 2010 Jul 8;6(7):e1000834.
Learning a weighted sequence model of the nucleosome core and linker yields more accurate predictions in Saccharomyces cerevisiae and Homo sapiens.
Reynolds SM· et. al. Used by Permission.

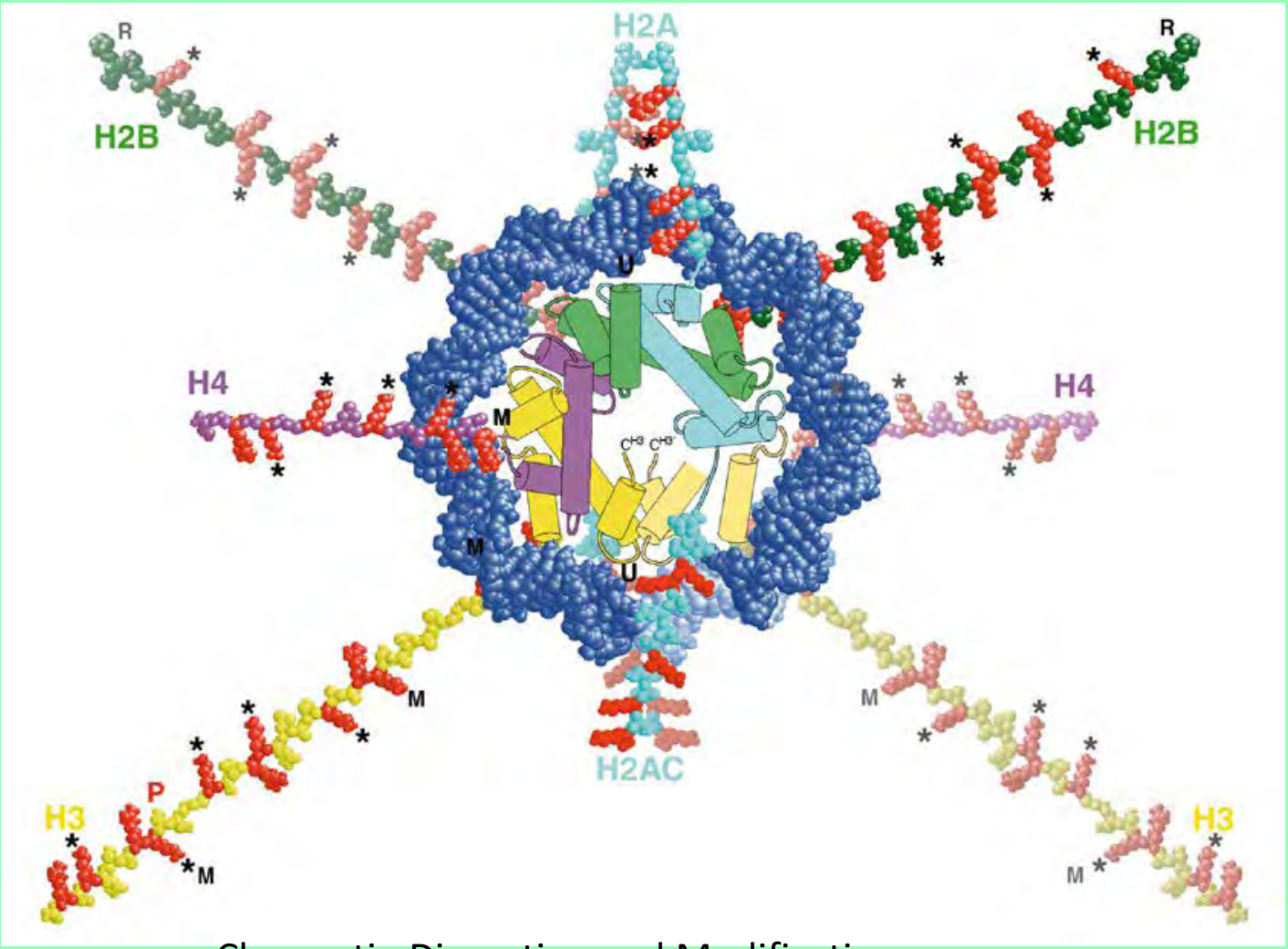
DNA Helix Around Histone Octamer Core

http://en.wikipedia.org/wiki/Epigenetics



PLoS Comput Biol. 2010 Jul 8;6(7):e1000834.
Learning a weighted sequence model of the nucleosome core and linker yields more accurate predictions in Saccharomyces cerevisiae and Homo sapiens.
Reynolds SM· et. al. Used by Permission.

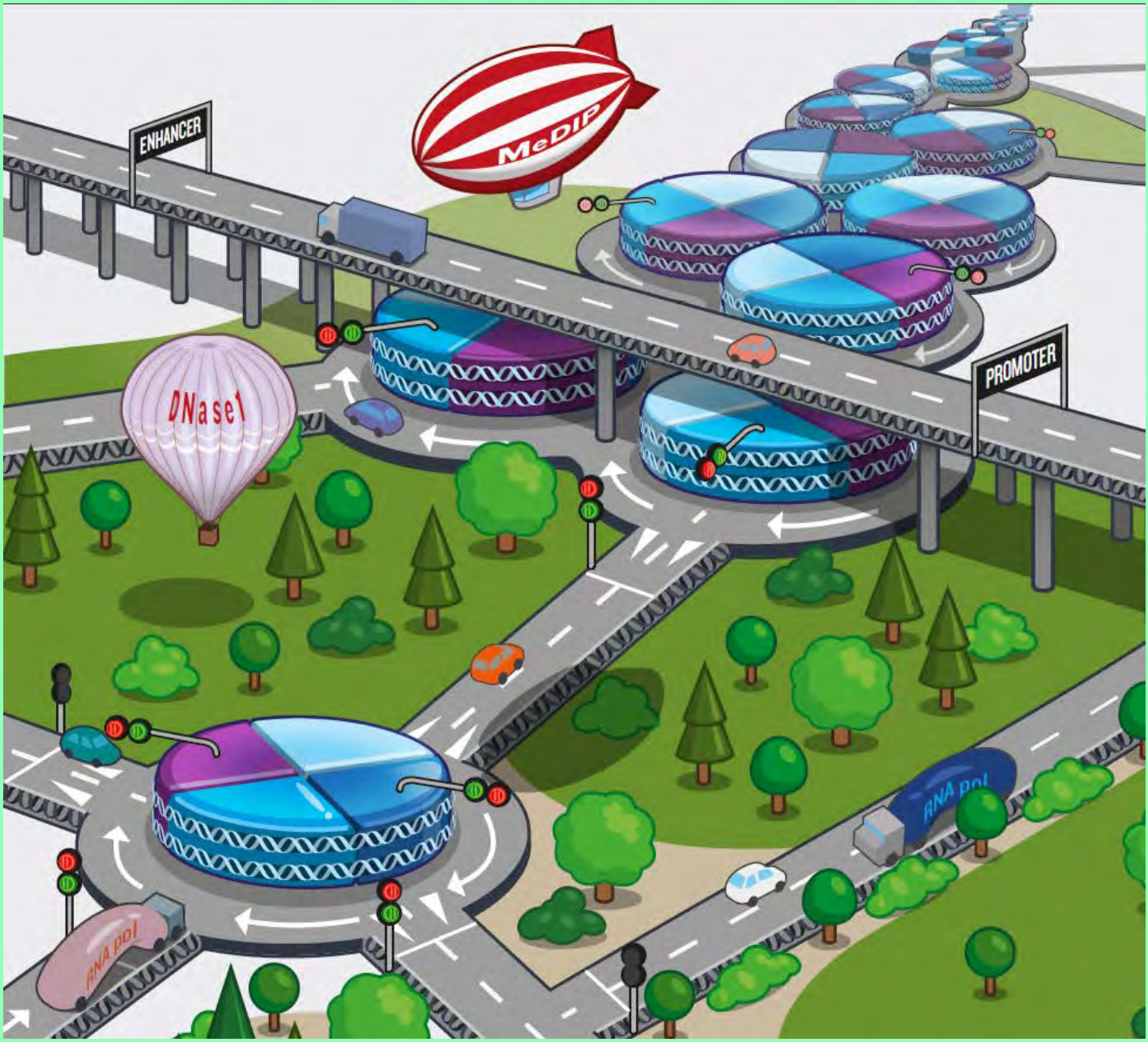
End View of DNA Helix Featuring Histone Tails



Chromatin Disruption and Modification
Wolffe A.P. and Hayes J.J., 1999; 27 (3): 711-720.
Figure 2, Used by Permission.

Nature 2015, Vol 518 No.7539

HISTONE CODE



Skipper M., Accleston A., Gray N., Heemels T., Le Bot N., Maerte B, Weiss U
Epigenome Roadmap Nature 2015, 518 (7539) p313, Figure 1,
Used by Permission

Note the RNA Polymerase II – the semitrailer travelling on the highways,
And the H3K4 and H3K27 "traffic lights" controlling gene transcription

Altered Dopamine Receptor Signaling NAcc MSN's

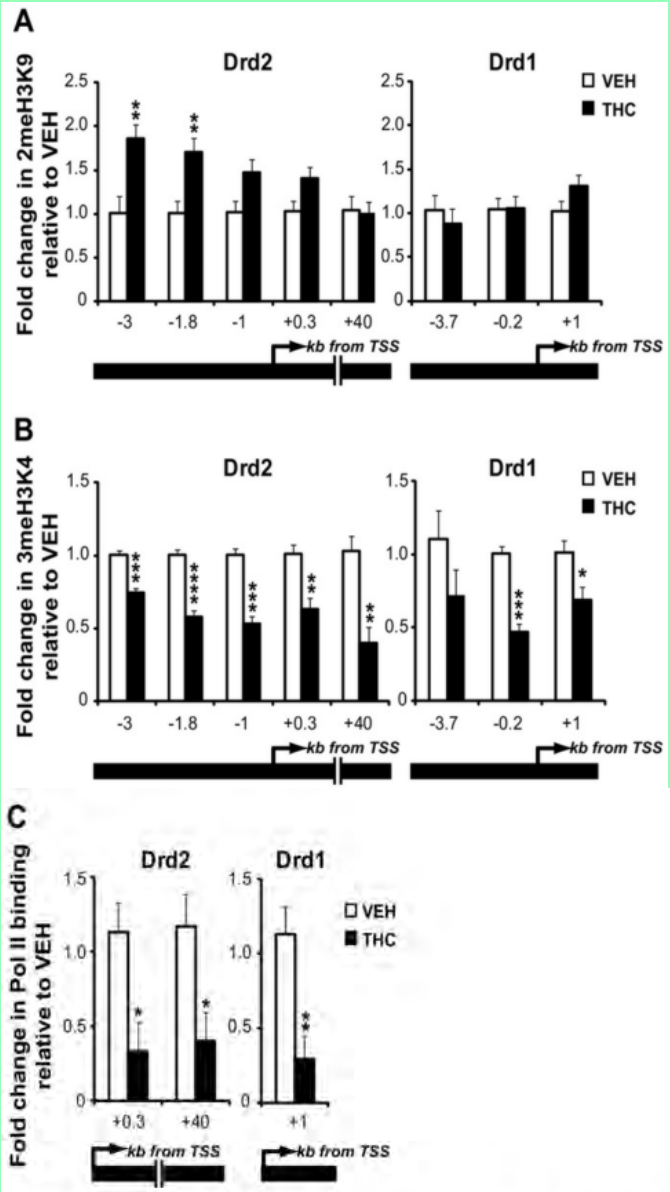


Figure 3. Dopamine receptor gene regulation in the NAc of adult rats with prenatal THC exposure. **(A)** Analysis of 2meH3K9 at the *Drd2* gene and *Drd1* gene. **(B)** Analysis of 3meH3K4 at the *Drd2* gene and *Drd1* gene. **(C)** Analysis of polymerase (Pol) II binding in *Drd2* and *Drd1* gene. Values are expressed as mean ± SEM. $^{*}p < .05$; $^{**}p < .01$; $^{***}p < .001$; $^{****}p < .0001$ vs. control subjects. $n = 5–6$ samples (bilateral pooled NAc from two rats in each sample)/group. kb, kilobases; TSS, transcription start site; other abbreviations as in Figures 1 and 2.

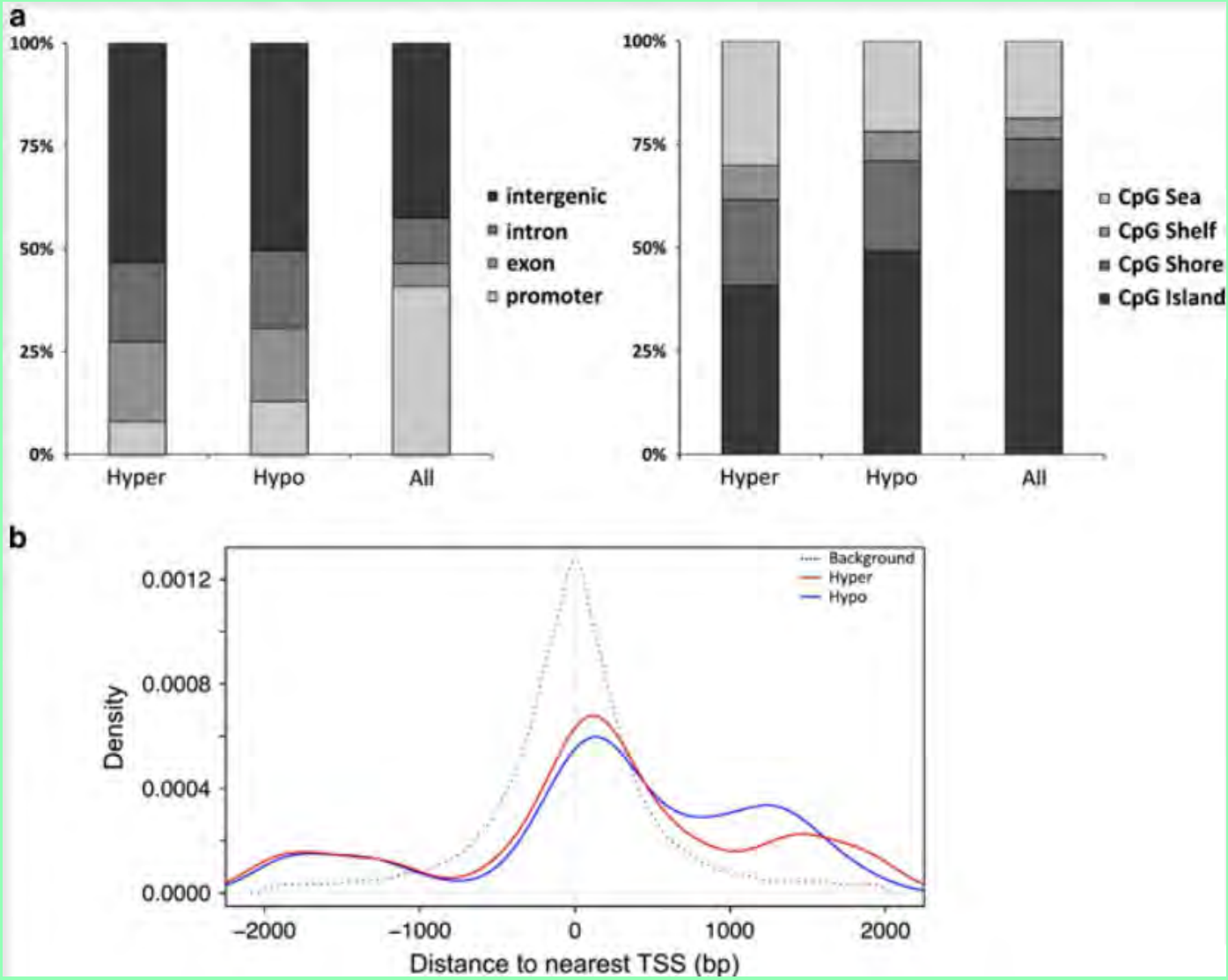
51

Biol Psychiatry. 2011 Oct 15;70(8):763-9. doi: 10.1016/j.biopsych.2011.06.027. Epub 2011 Aug 5.

Maternal cannabis use alters ventral striatal dopamine D2 gene regulation in the offspring

DiNieri JA[1], Wang X, Szutorisz H, Spano SM, Kaur J, Casaccia P, Dow-Edwards D, Hurd YL.

Cross-Generational Differential Gene Methylation

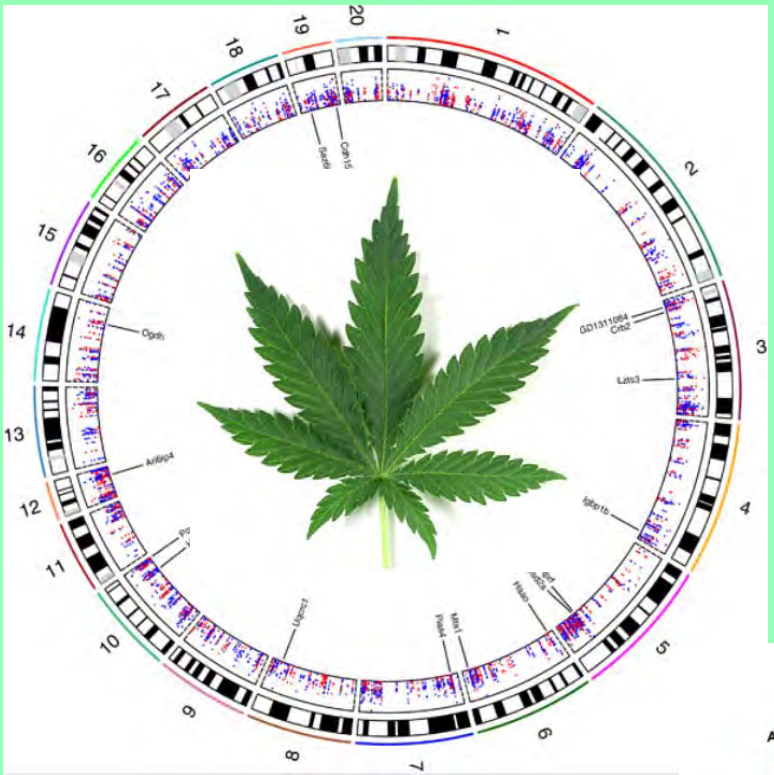


Neuropsychopharmacology. 2015 Jun 5. doi: 10.1038/npp.2015.155. [Epub ahead of print]

Genome-Wide DNA Methylation Profiling Reveals Epigenetic Changes in the Rat Nucleus Accumbens Associated With Cross-Generational Effects of Adolescent THC Exposure.

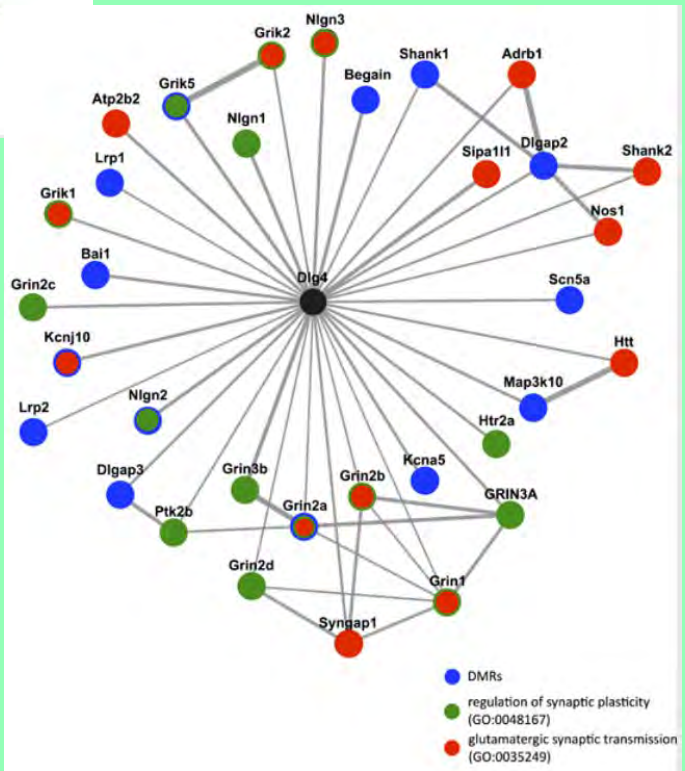
Watson CT[1], Szutorisz H[2], Garg P[3], Martin Q[3], Landry JA[3], Sharp AJ[3], Hurd YL[4].

Cross-Generational Epigenetic FX



(Illustrations Modified)

All Autosomes



Differential Methylation Key Neuronal Genes Synaptic Transmission

Neuropsychopharmacology. 2015 Jun 5. doi: 10.1038/npp.2015.155. [Epub ahead of print]

Genome-Wide DNA Methylation Profiling Reveals Epigenetic Changes in the Rat Nucleus Accumbens Associated With Cross-Generational Effects of Adolescent THC Exposure.

Watson CT[1], Szutorisz H[2], Garg P[3], Martin Q[3], Landry JA[3], Sharp AJ[3], Hurd YL[4].

Used I

Epigenetics - Dramatically Altered Immune Function

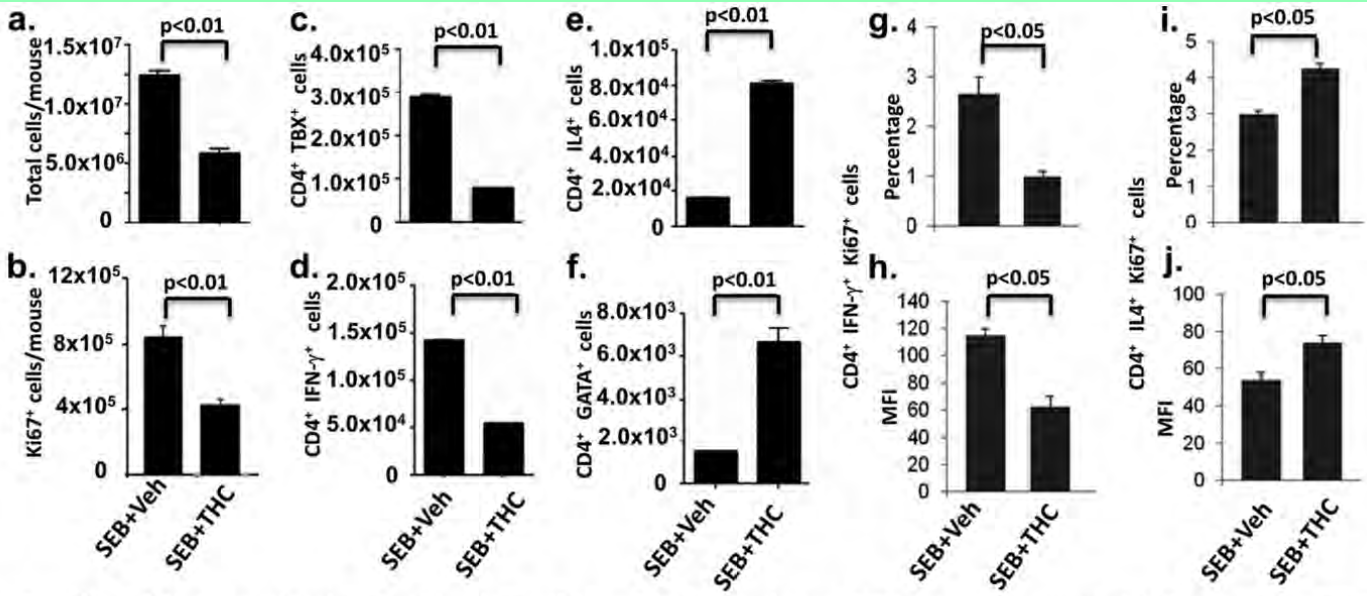


FIGURE 1. **Effect of THC on lymph node cell proliferation and Th1 and Th2 subpopulations.** C57BL/6J mice were treated with THC or vehicle as described under "Experimental Procedures" on days 0 and 1, and 2 h later, 10 μg of SEB was injected into each foot pad. Three days after SEB challenge, draining popliteal lymph nodes of SEB + vehicle- or SEB + THC-treated mice ($n = 3$) were harvested, and cells were analyzed. *a*, total cells in two popliteal lymph nodes in each mouse. *b*, cells were gated by $CD4^+$ and analyzed by FACS for the expression of Ki67. *c–f*, based on flow cytometric analysis as described under "Experimental Procedures," cell numbers of various $CD4^+$ T cell subpopulations expressing IFN-γ, TBX21, IL-4, or GATA3 were depicted. *g* and *h*, overall frequency and mean fluorescence intensity (*MFI*) of Ki67, CD4, and IFN-γ triple-positive cells. *i* and *j*, overall frequency and MFI of Ki67, CD4, and IL-4 triple-positive cells. *p* values were determined by Student's *t* test. *Error bars*, S.E.

J Biol Chem. 2014 Jul 4;289(27):18707-18. doi: 10.1074/jbc.M113.545210. Epub 2014 May 19.

Histone modifications are associated with Δ9-tetrahydrocannabinol-mediated alterations in antigen-specific T cell responses.

3rd Generational Epigenetic Inheritance!!!
F3 DNA Methylation Aberrations

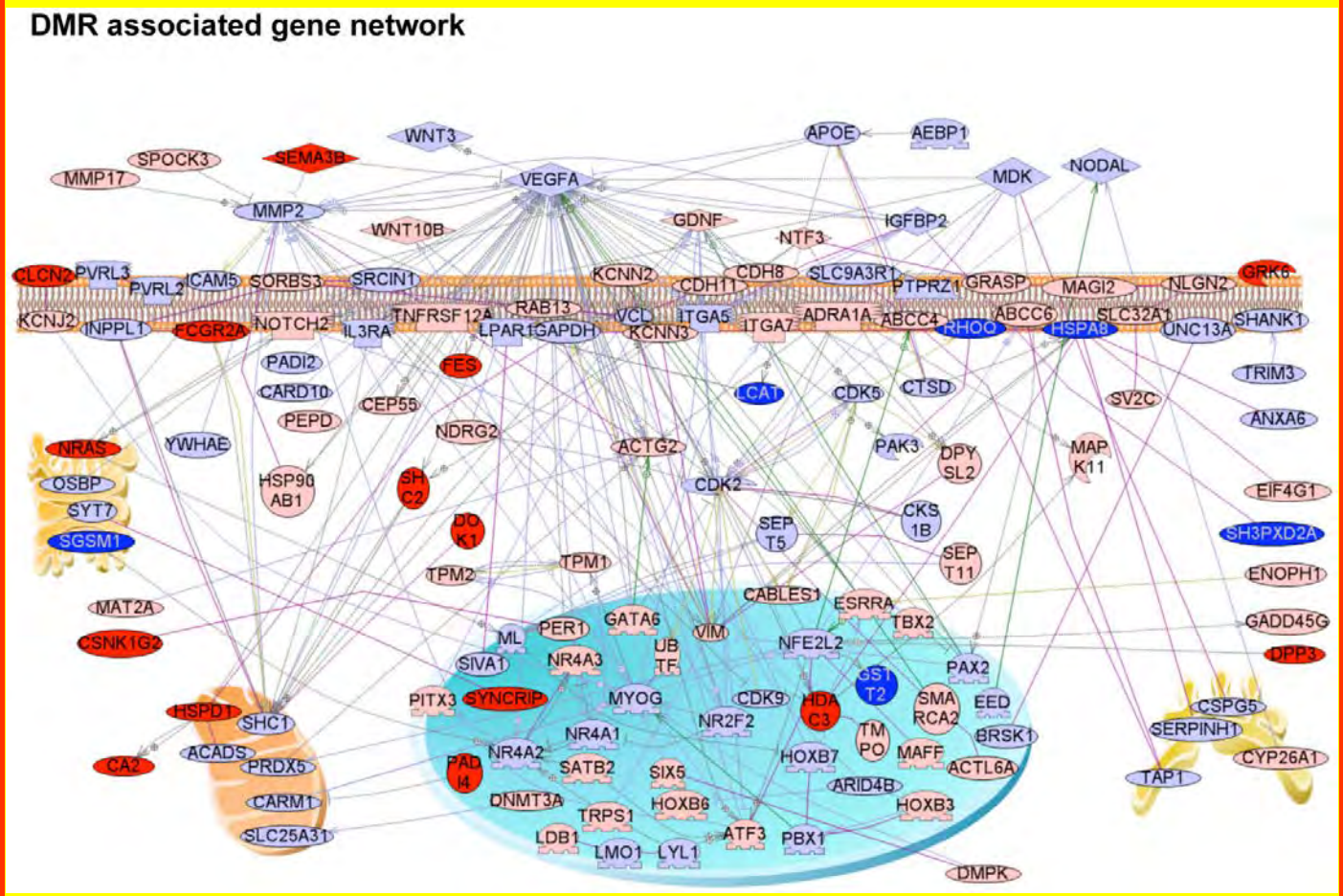


Figure shows only 140/500 Differentially Methylated Genes

PLoS One. 2012;7(2):e31901. doi: 10.1371/journal.pone.0031901. Epub 2012 Feb 28.

Transgenerational actions of environmental compounds on reproductive disease and identification of epigenetic biomarkers of ancestral exposures.

Manikkam M[1], Guerrero-Bosagna C, Tracey R, Haque MM, Skinner MK.

55

7x Cannabinoid Receptors!!!!
On Microglia!!!

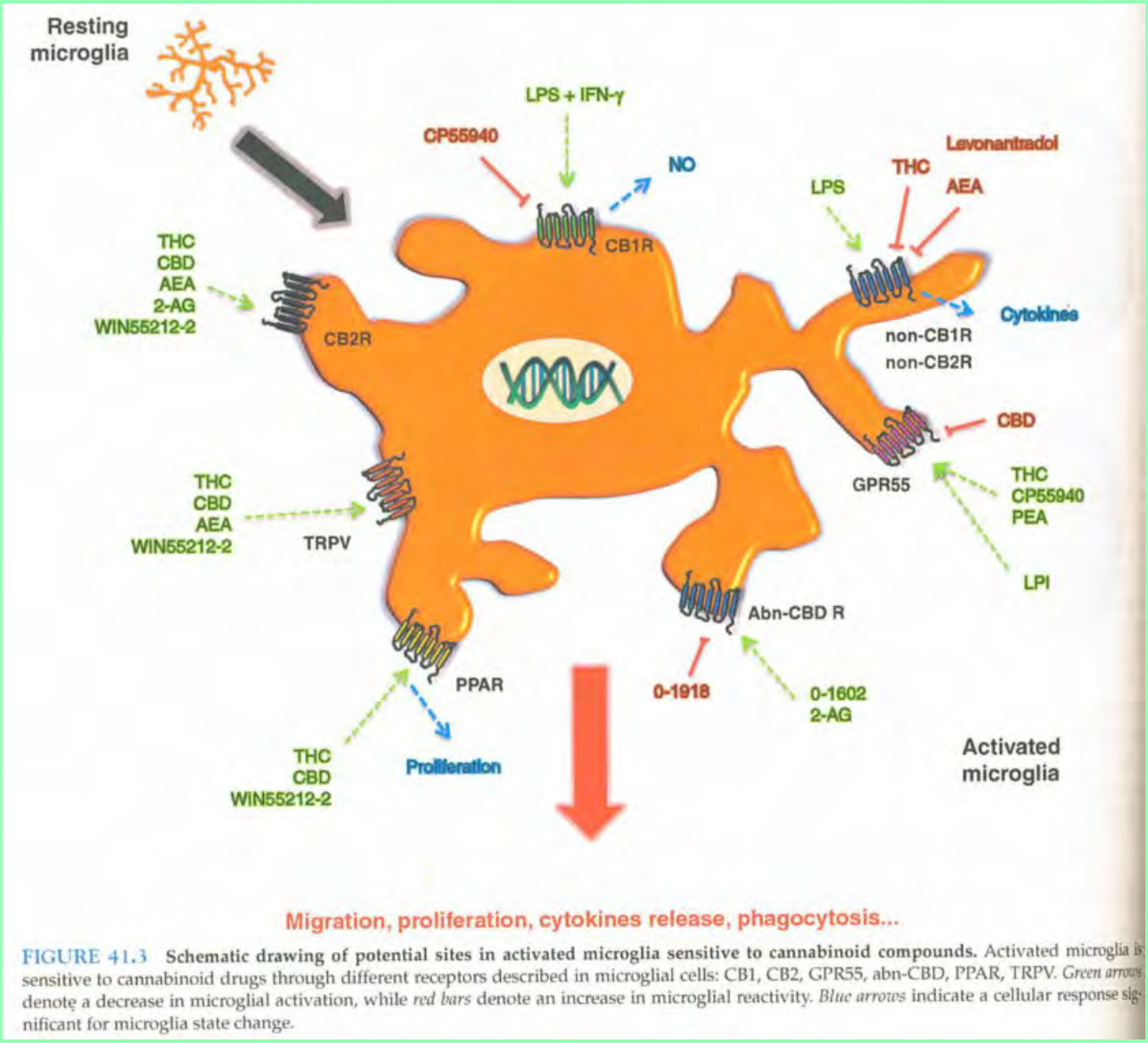


FIGURE 41.3 **Schematic drawing of potential sites in activated microglia sensitive to cannabinoid compounds.** Activated microglia is sensitive to cannabinoid drugs through different receptors described in microglial cells: CB1, CB2, GPR55, abn-CBD, PPAR, TRPV. *Green arrows* denote a decrease in microglial activation, while *red bars* denote an increase in microglial reactivity. *Blue arrows* indicate a cellular response significant for microglia state change.

Cutando L., Maldonado R., Ozaita A. "Microglial Activation and Cannabis Exposure" Figure 41.3 in Chapter 41 In Handbook of Cannabis and Related Pathologies: Biology, Pharmacology, Diagnosis and Treatment" Ed. Preedy V.R. Academic Press 2017.

Non-Linear Dose-Response Kinetics

Cell Growth

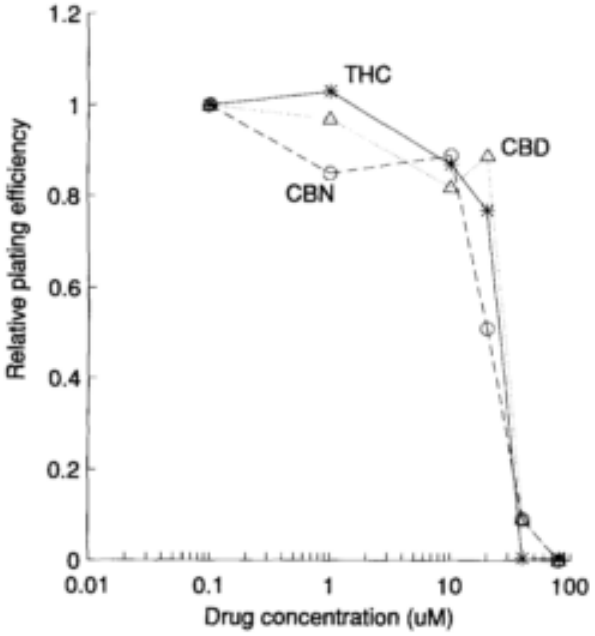


FIG. 1. The plating efficiency of CHO AuxB1 cells to THC, CBD and CBN. An equal number of cells were plated in triplicate onto 2.0 cm^2 wells and treated with cannabinoids for 2 h. Macroscopically visible colonies were counted 5–7 days after drug treatment. Plating efficiency for drug-treated cells was expressed relative to untreated controls. No difference in plating efficiency was observed between untreated and vehicle control cells.

Pharmacology Biochemistry & Behavior, Vol. 40, pp. 617–623. © Pergamon Press plc, 1991. Printed in the U.S.A. 0091-3057/91 $3.00 + .00

Influence of Marihuana on Cellular Structures and Biochemical Activities

STEPHEN K. TAHIR AND ARTHUR M. ZIMMERMAN

Cell Viability
Fresh and 2-Day Old Cells

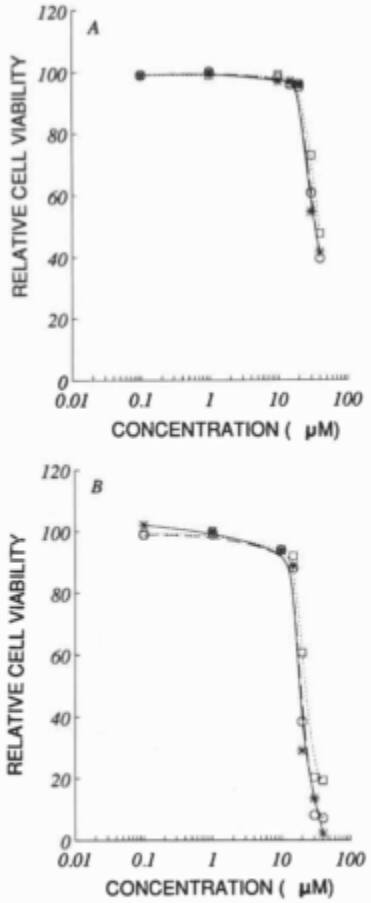


FIG. 1. The effect of varying concentrations of cannabinoids (0.1–40 μM) THC (★—★), CBD (□···□), and CBN (○- -○) on the viability of undifferentiated and 2-day differentiating PC12 cells following a 4-h treatment. Cell viability was assessed by trypan blue dye exclusion. The cells were incubated for 2–5 min with 0.4% trypan blue following drug treatment. The percentage of cells that did not take up the dye (viable cells) are plotted relative to untreated controls. Each value represents the mean of two independent experiments performed in triplicate. The viability of vehicle-treated cells was similar to untreated controls. (A) Undifferentiated cells; (B) 2-day differentiating cells.

Cytoskeletal organization following cannabinoid treatment in undifferentiated and differentiated PC12 cells

STEPHEN K. TAHIR[1]

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JUDY E. TROGADIS AND JOHN K. STEVENS

Playfair Neuroscience Unit, University of Toronto – Toronto Western Hospital, Toronto, Ont., Canada M5T 2S8

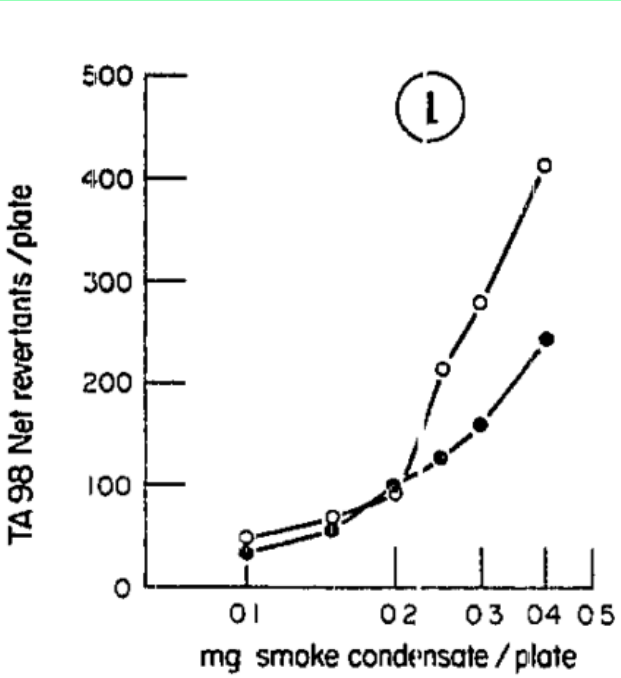
AND

ARTHUR M. ZIMMERMAN[2]

Department of Zoology, University of Toronto, 25 Harbord St., Toronto, Ont., Canada M5S 1A1

Received March 30, 1992

Mutagenesis



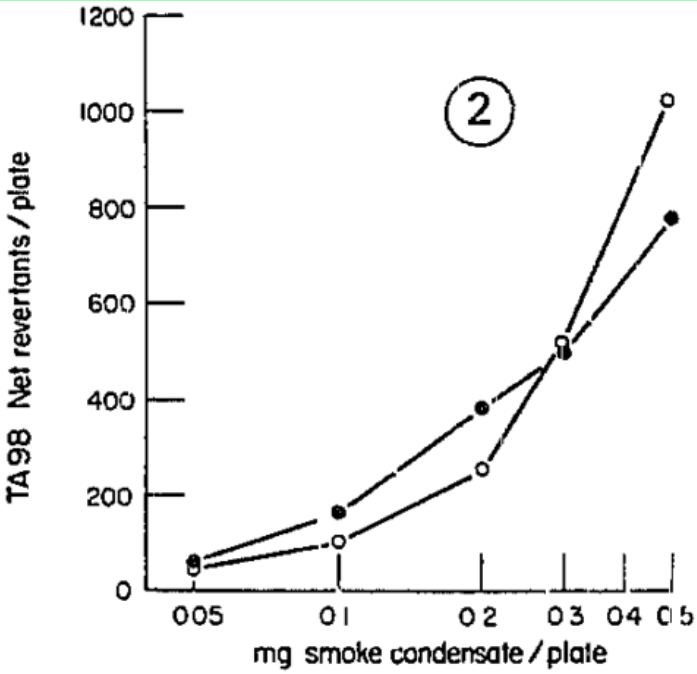


Fig 1. Mutagenic activities of smoke condensates with *S typhimurium* strain TA98 in the presence of liver 9000 × *g* supernatant. The open circles represent the mean values of experimental results for condensate obtained from Kentucky Reference Cigarettes (2R1) and the closed circles represent those for the marihuana condensate given to us from NIDA. The positive control used for this assay was 2-aminofluorene; the number of spontaneous revertants was 31 colonies/plate.

Fig. 2. Mutagenic activities of smoke condensates with *S. typhimurium* strain TA98 in the presence of liver 9000 × *g* supernatant. The condensates were prepared in our laboratory. The open circles represent the American brand of 100-mm filtered cigarettes, the closed circles represent the hand-rolled marihuana cigarettes

Cancer Letters, 6 (1979) 319—324

MUTAGENIC ACTIVITY OF MARIHUANA SMOKE CONDENSATES*

60

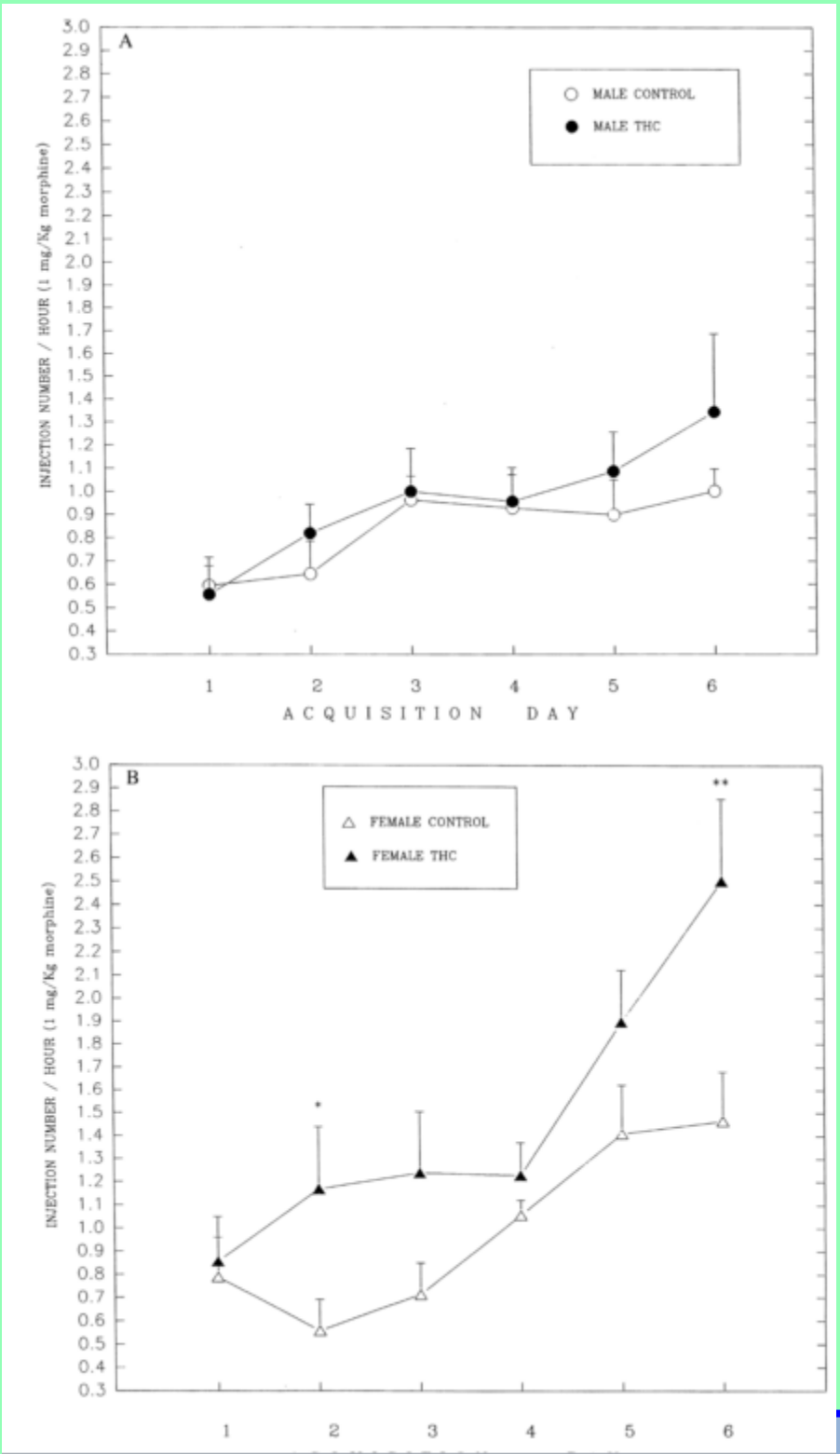
FRIEDRICH W. BUSCH, DONNA A. SEID and EDDIE T. WEI

School of Public Health, University of California, Berkeley, CA 94720 (U.S.A.)

Morphine Self-Administration after Pre-Natal Exposure to THC

Maternal exposure to Δ^9-tetrahydrocannabinol facilitates morphine self-administration behavior and changes regional binding to central μ opioid receptors in adult offspring female rats

Gema Vela [a], Sonsoles Martín [b], Lucía García-Gil [c], José Antonio Crespo [b], Mariano Ruiz-Gayo [a], José Javier Fernández-Ruiz [c], Carmen García-Lecumberri [d], Didier Pelaprat [c], José Angel Fuentes [a], José Antonio Ramos [c], Emilio Ambrosio [b,*]



Brain Research 807 (1998) 101±109

Tubulin, Actin, RNA

Tubulin

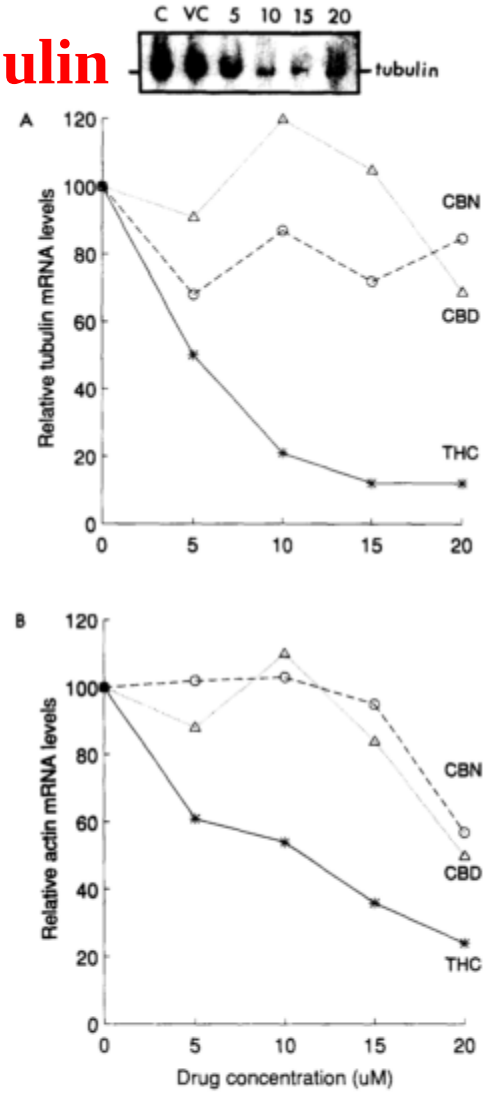


FIG. 3. Northern blot hybridization analysis of tubulin and actin mRNA levels in THC, CBD or CBN treated CHO cells for 2 h. Total RNA was phenol extracted from cells following treatment. A 10 μg aliquot of total RNA from each sample was fractionated by electrophoresis on a 1.5% agarose-6% formaldehyde gel, transferred to nitrocellulose and hybridized with a ^{32}P nick-translated tubulin (PT25) or actin (PA72) cDNA probe. Autoradiograms were analyzed by densitometry and the relative intensity of mRNA levels were determined and expressed relative to untreated controls. There was no difference in tubulin or actin mRNA levels between untreated and vehicle controls. The insert shows a representative autoradiogram of the region where the PT25 clone hybridized to the nitrocellulose filter. (A) Relative tubulin mRNA levels; (B) Relative actin mRNA levels.

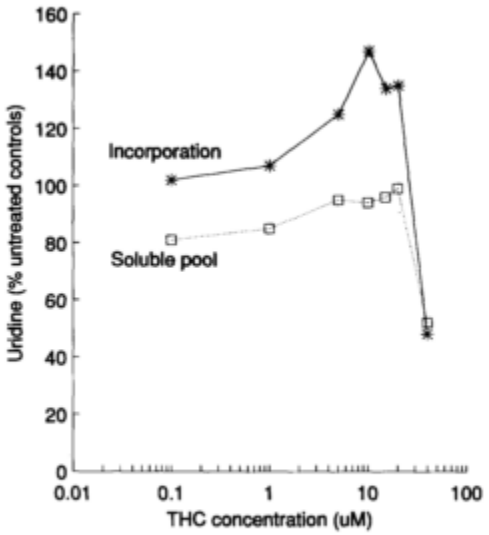


FIG. 4. Influence of THC on the incorporation of ^{3}H uridine into RNA. CHO cells grown in monolayer were pulsed during the last hour of drug treatment with 5 μCi/ml ^{3}H uridine. The incorporation of radioactivity into the acid-insoluble fraction was determined. The acid-soluble uridine fraction was estimated by subtracting the acid-insoluble fraction from the total cellular uptake of uridine for cells treated between 0.1 and 40 μM THC for 2 h. Data is expressed as a percentage of untreated controls. The vehicle had no effect on the incorporation of uridine as compared to untreated controls.

was a change in the cytoskeletal architecture and the mRNA levels of cytoskeletal proteins (tubulin and actin) in CHO cells following THC but not CBD or CBN treatment at concentrations which did not adversely affect cell proliferation. Stress fibers were reduced in number and length, and microtubules became fragmented in CHO cells treated with 10 μM THC for 2 h. Moreover, the levels of tubulin and actin mRNA transcripts were reduced.

The mechanism(s) by which THC alters the cytoskeletal architecture is unknown. THC may interact directly with the cytoskeletal elements or interfere with the process of assembly and disassembly. Preliminary reports have shown that THC influenced the in vitro assembly and disassembly of tubulin (40). THC may also affect the cytoskeleton indirectly by its effects on other cellular structures or other biochemical activities. Since the cytoskeleton is closely associated with cell membranes, THC interaction with the lipid bilayer or membrane bound enzyme systems, may adversely influence the cytoskeletal architecture. THC may also affect the permeability of the membrane to ions such as Ca^{2+}, an ion known to inhibit microtubule polymerization and disrupt actin microfilament assembly (37). THC may influence the organization of the cytoskeleton by affecting biochemical events involved in gene regulation. In our studies, the reduction in tubulin and actin mRNA levels may reflect cannabinoid-mediated effects on mRNA transcription, stability or processing of mRNA transcripts. Thus further studies on the cytoarchitecture and the expression of cytoskeletal proteins will be useful in assessing the effects of cannabinoids at the cellular and molecular levels.

Influence of Marihuana on Cellular Structures and Biochemical Activities

STEPHEN K. TAHIR AND ARTHUR M. ZIMMERMAN

Pharmacology Biochemistry & Behavior, Vol. 40, pp. 617–623. © Pergamon Press plc, 1991.

Micronucleus Formation

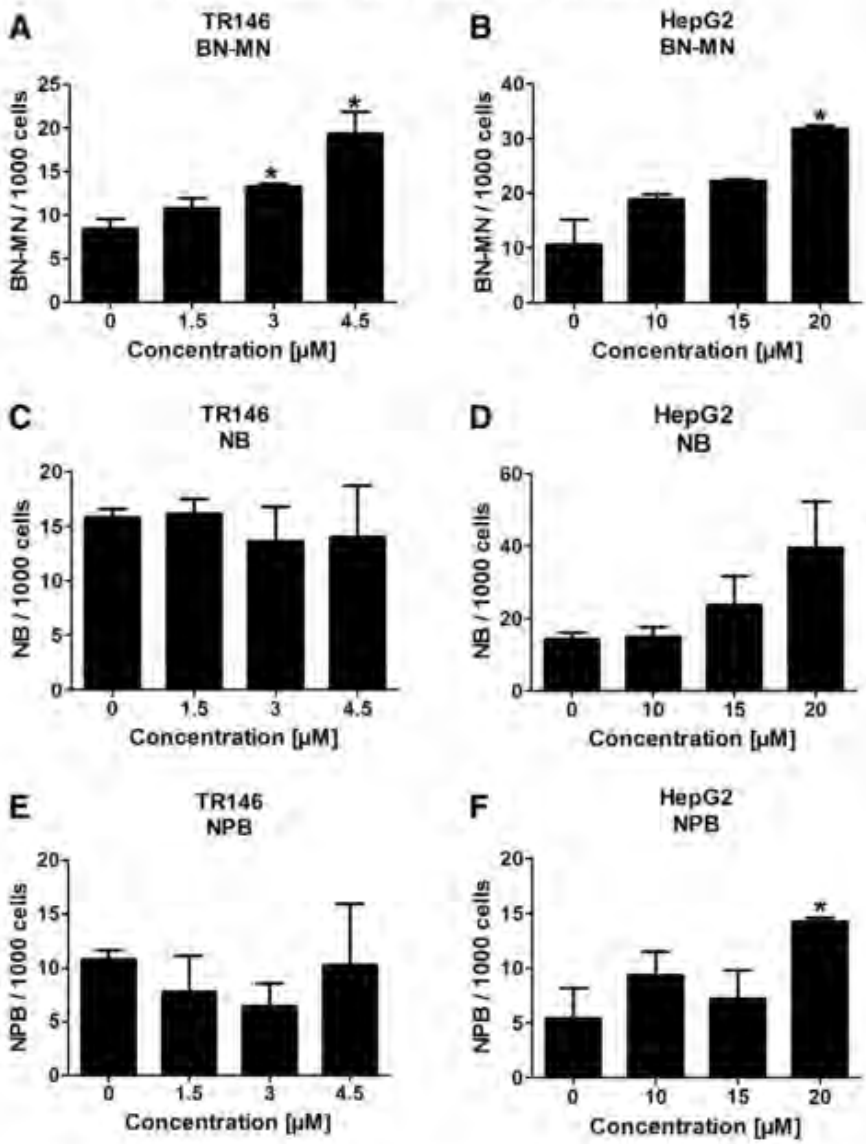


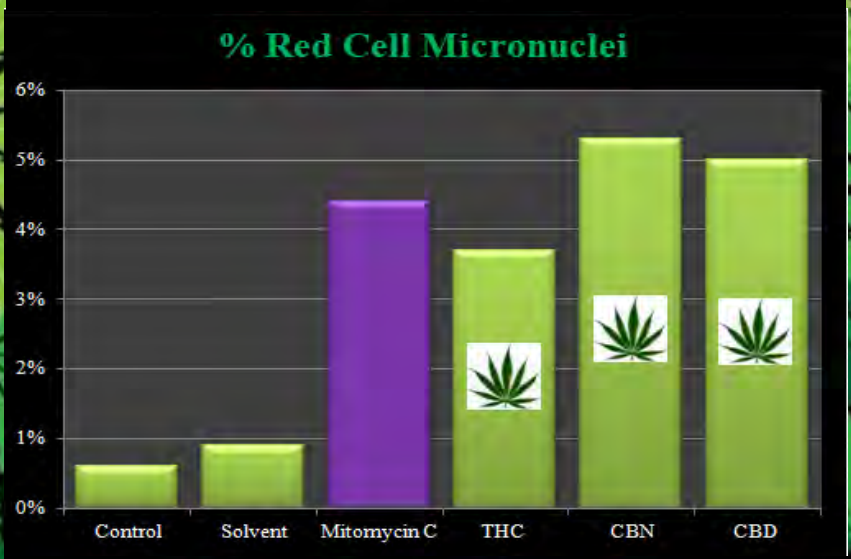
Fig. 4. Impact of the synthetic cannabinoid CP-47,497-C8 on the frequencies of BN-MN – micronuclei in binucleated cells (A–B), NB – nuclear buds (C–D) and NPB – nucleo-plasmatic bridges (E–F) in buccal TR146 and human liver HepG2 cells. The cells were treated with different concentrations of the test compound for 24 h. Subsequently, cytochalasin B (3.0 µg/ml) was added for either 48 h (TR146) or 28 h (HepG2). The different endpoints were determined as described by Fenech (2007). Bars represent the means ± SD of results obtained with two different cultures; from each culture ~1000 cells were evaluated. Asterisks indicate significant differences from control values (chi-square test with Yate's correction, *$p \leq 0.05$).

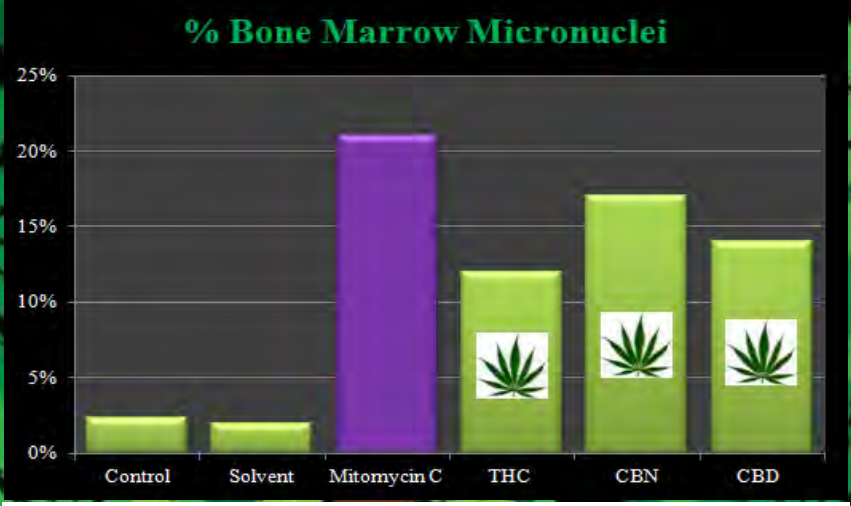
Investigation of the in vitro toxicological properties of the synthetic cannabimimetic drug CP-47,497-C8

Verena J. Koller [a], Volker Auwärter [b], Tamara Grummt [c], Bjoern Moosmann [b], Miroslav Mišík [a], Siegfried Knasmüller [a,*]

Toxicology and Applied Pharmacology 277 (2014) 164–171

Cannabis Micronuclei



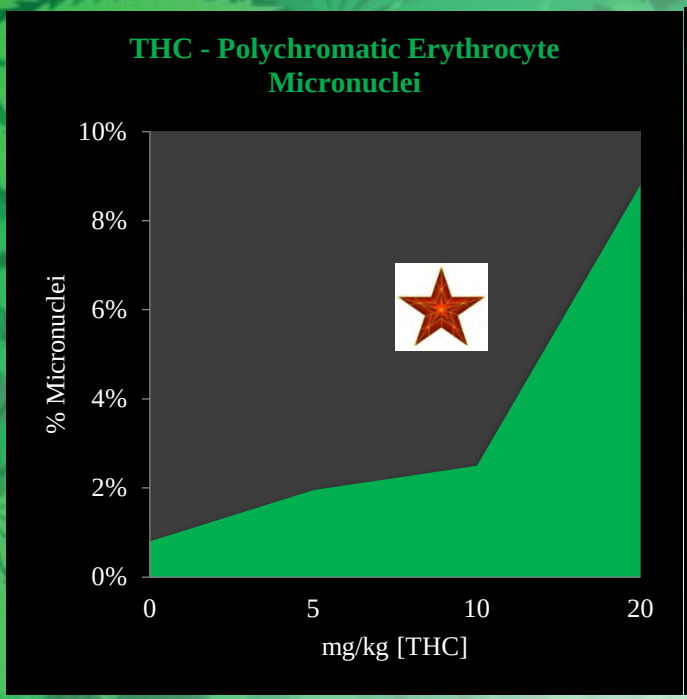


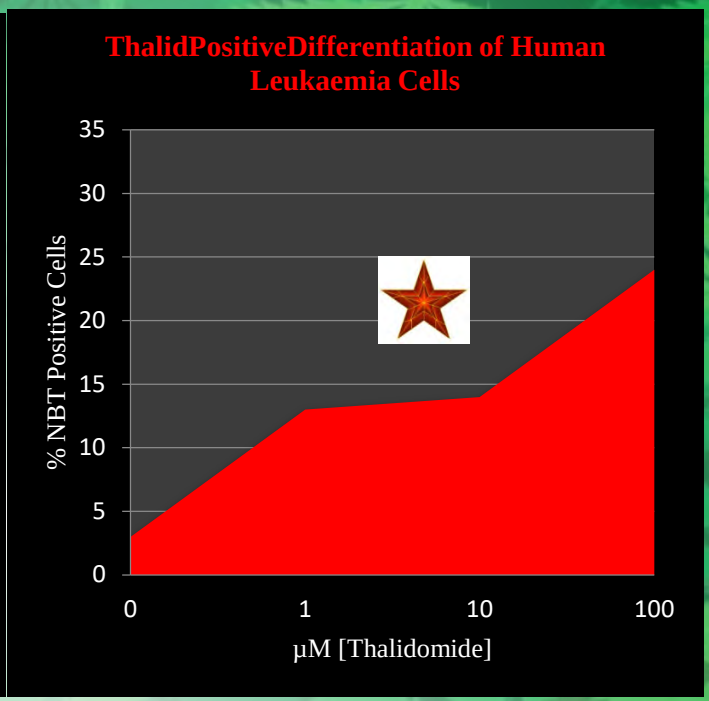
Pharmacology. 1980;21(4):277-87.

Influence of cannabinoids on somatic cells in vivo.

Zimmerman AM, Raj AY.

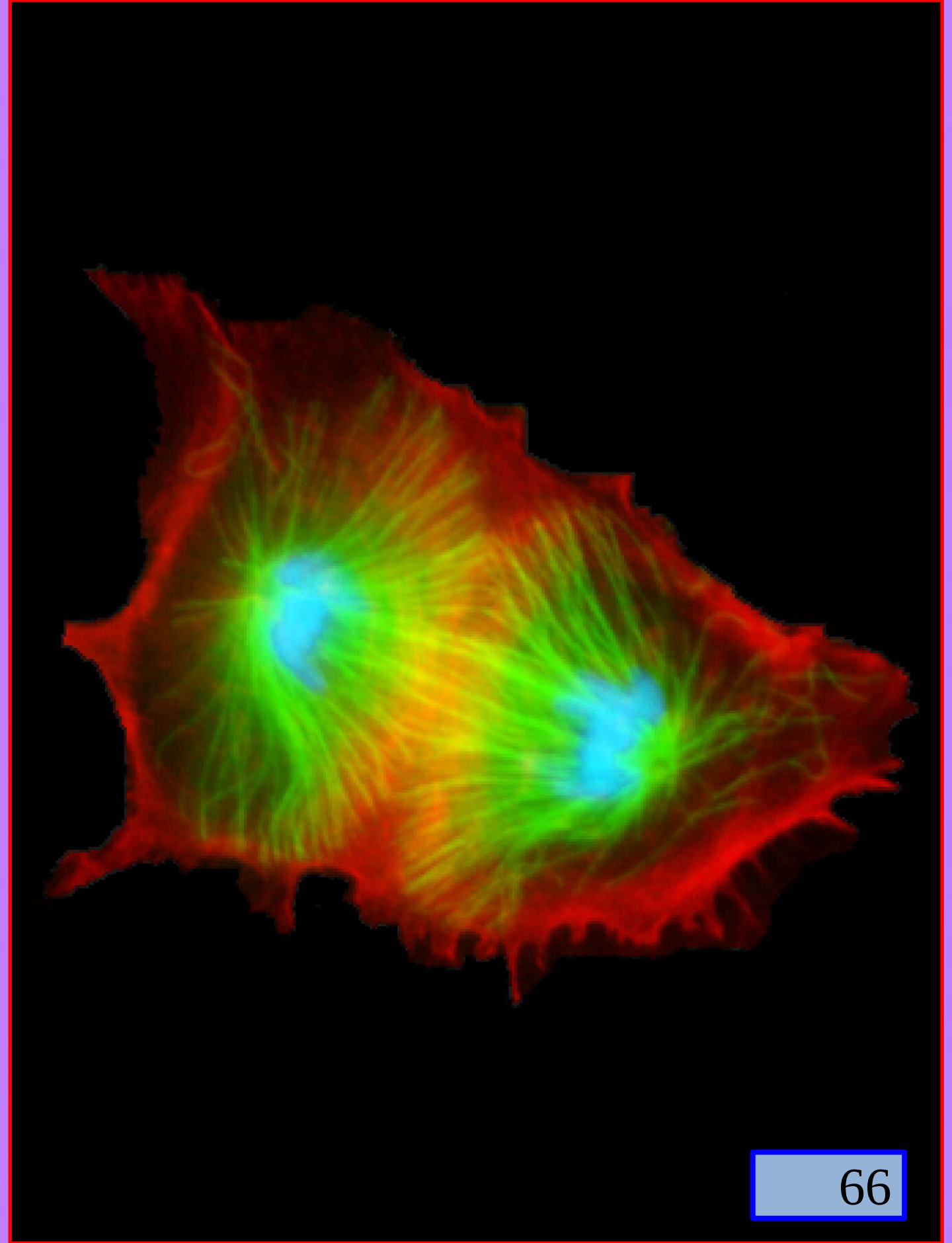
Comparative Non-Linear Dose-Response Kinetics of THC and Thalidomide

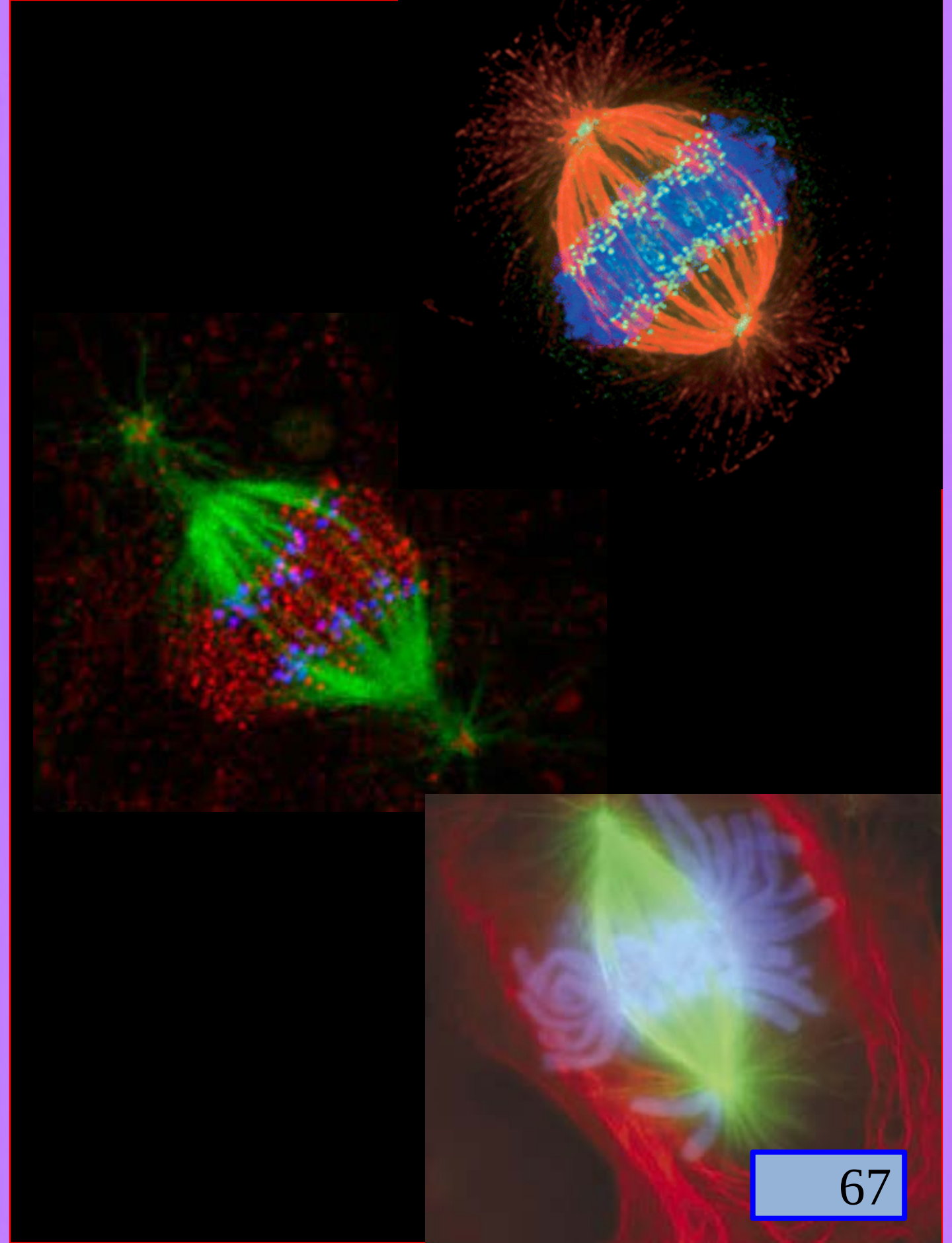




Data from Table 2, Single day exposure, Zimmerman A.M. and Raj Y. 1980, "Influence of Cannabinoids on Somatic Cells in vivo", Pharmacology 21 (4): 277-287. Permission Requested.

Data after Figure 2A, 2nM all-*trans* retinoic acid –induced Differentiation Assay Kizaki M & Hashimoto Y., 2008 "New Tubulin Polymerization Inhibitor Derived from Thalidomide: Implications for Anti-Myeloma Therapy" Current Medicinal Chemistry 15: 754-765. Re-used by Permission.





+End Force

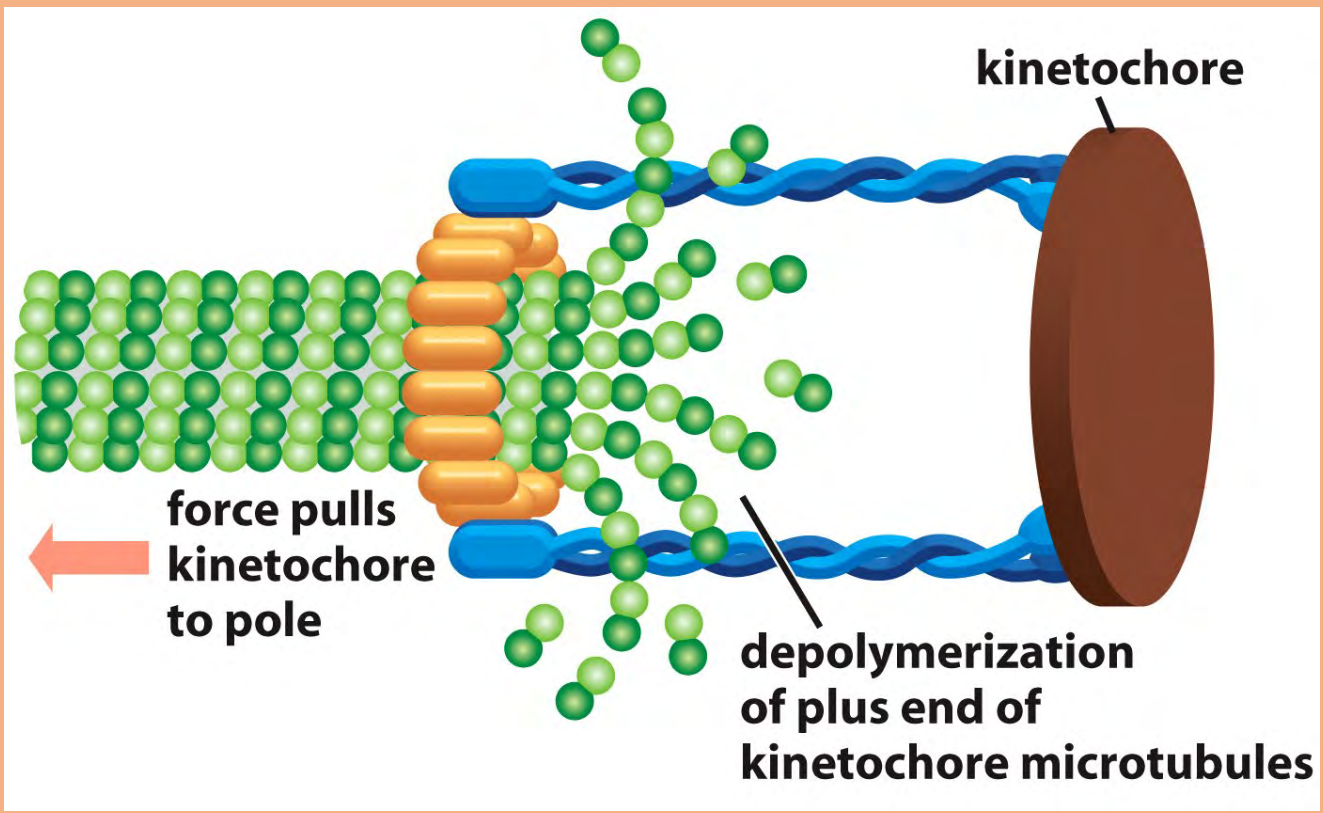
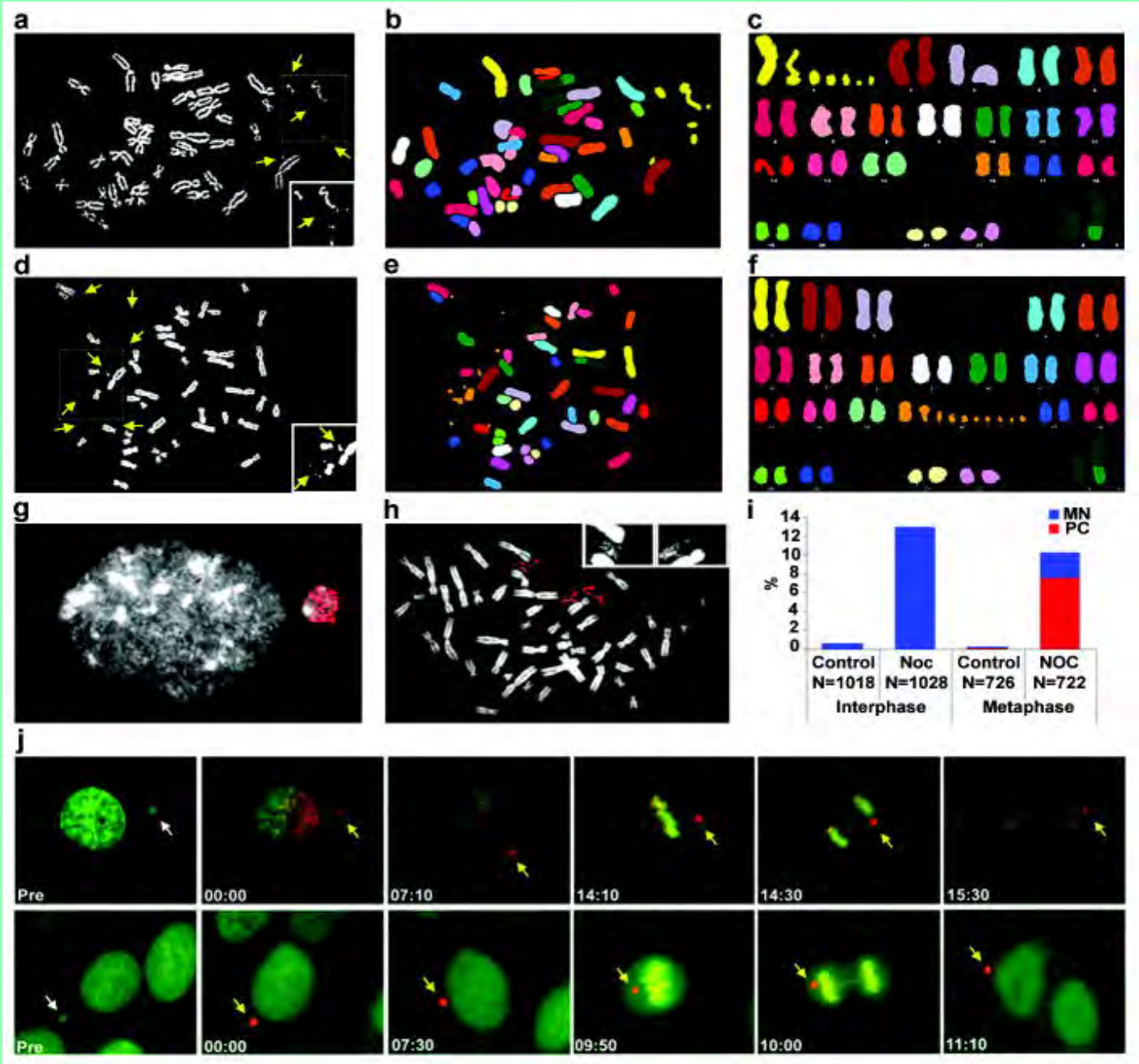


Figure 17-40 *Molecular Biology of the Cell* (© Garland Science 2008)

"Biology of the Cell", Alberts, Garland Science, 2008

Pulverization



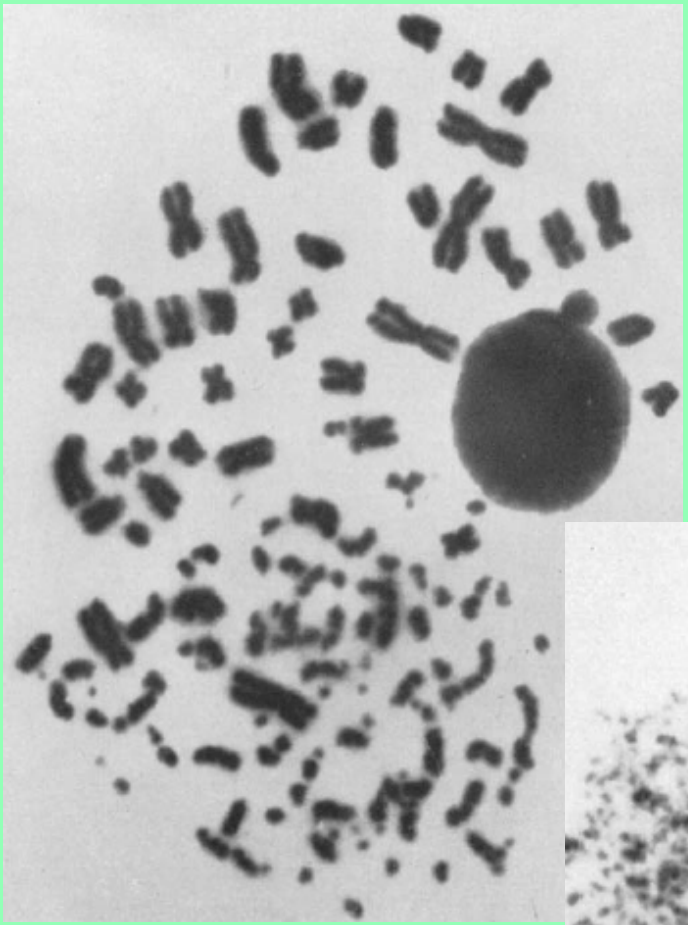
Nature. 2012 Jan 18;482(7383):53-8. doi: 10.1038/nature10802.

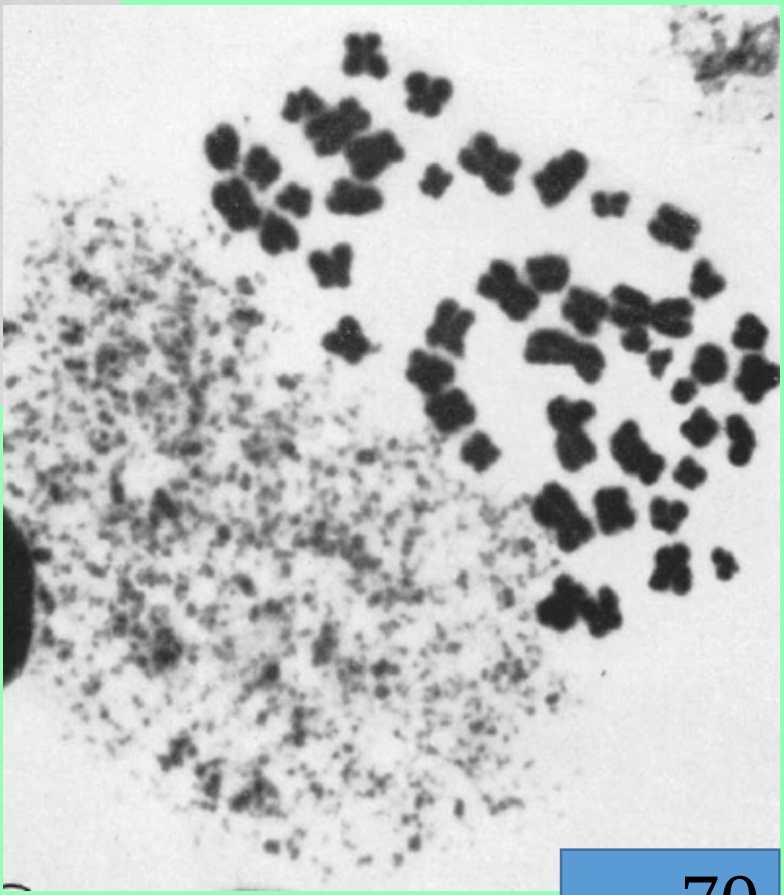
DNA breaks and chromosome pulverization from errors in mitosis.

Crasta K[1], Ganem NJ, Dagher R, Lantermann AB, Ivanova EV, Pan Y, Nezi L, Protopopov A, Chowdhury D, Pellman D.

69

Chromosomal Pulverization





70

J Cell Biol. 1967 Jul;34(1):35-45.

Chromosome pulverization in human binucleate cells following colcemid treatment.

Kato H, Sandberg AA.

THC – Microtubule Disruptor
- Stathmin/SCG10

Miswiring the brain: Δ^9-tetrahydrocannabinol disrupts cortical development by inducing an SCG10/stathmin-2 degradation pathway

Giuseppe Tortoriello[1], Claudia V Morris[2], Alan Alpar[1], Janos Fuzik[1,3], Sally L Shirran[4], Daniela Calvigioni[1], Erik Keimpema[1,3], Catherine H Botting[4], Kirstin Reinecke[5], Thomas Herdegen[5], Michael Courtney[6], Yasmin L Hurd[2] & Tibor Harkany[1,3,*]

Human Study

MICROTUBULE DISRUPTION

Abstract

Children exposed in utero to cannabis suffer perpetual neurobehavioral and cognitive impairments. Psychoactive constituents from *Cannabis* spp., particularly Δ^9-tetrahydrocannabinol (THC), bind to cannabinoid receptors in the fetal brain. However, it is unknown whether THC can trigger a cannabinoid receptor-driven molecular cascade to disrupt neurodevelopmental specification. Here, we show that repeated THC exposure dysregulates cannabinoid signaling, particularly the temporal dynamics of CB_1 cannabinoid receptor, to rewire the fetal cortical circuitry. By interrogating the THC-sensitive neuronal proteome we identify Superior Cervical Ganglion 10 (SCG10)/stathmin-2, a microtubule-binding protein in axons, as a substrate of altered neuronal connectivity. We find SCG10 mRNA and protein reduced in the hippocampus of midgestational human cannabis-exposed fetuses, defining SCG10 as the first cannabis-driven molecular effector in the developing cerebrum. CB_1 cannabinoid receptor activation recruits c-Jun N-terminal kinases to phosphorylate SCG10, promoting its rapid degradation *in situ* in motile axons and microtubule stabilization. Thus, THC enables ectopic formation of filopodia and alters axon morphology. These data highlight the maintenance of cytoskeletal dynamics as a molecular target for cannabis, whose imbalance can limit the computational power of neuronal circuitries in affected offspring.

Introduction

The recreational use of cannabis use continu with adolescents and young adults being prin (Substance Abuse & Mental Health Service Administ Cannabis exposure of infants *in utero* or cannabis us (pregnant 15-17 years of age) (Substance Abuse & Service Administration, 2013) can coincide with crit in the developing brain when neuronal connectivity is pre lished (Kostovic & Jovanov-Milosevic, 2006) or postn to increase modularity and integrative capacity (Denn Accordingly, prospective longitudinal assessments *et al*, 2004; Willford *et al*, 2010; Day *et al*, 2011) cannabis use during pregnancy can increase the behaviors (Goldschmidt *et al*, 2004; Day *et al*, 2011), c (Huizink & Mulder, 2006), drug seeking (Day *et al*, 20 deficit (Leech *et al*, 1999), and anxiety and depressio 2006) among affected neonatal or adolescent offsprin population analysis associates growth retardation cannabis use (El Marroun *et al*, 2009), particularly sin efficient cross-placental transfer of Δ^9-tetrahydrocann (Grotenhermen, 2003), the major psychoactive *Cannabis* spp. Nevertheless, a gap of knowledge ex the neuronal basis of cannabis-induced developmen the nervous system.

EMBO J. 2014 Apr 1;33(7):668-85. doi: 10.1002/embj.201386035. Epub 2014 Jan 27.

Miswiring the brain: Δ9-tetrahydrocannabinol disrupts cortical development by inducing an SCG10/stathmin-2 degradation pathway.

Tortoriello G[1], Morris CV, Alpar A, Fuzik J, Shirran SL, Calvigioni D, Keimpema E, Botting CH, Reine Courtney M, Hurd YL, Harkany T.

Cannabinoids &

CANCER

Cancer

Adult:

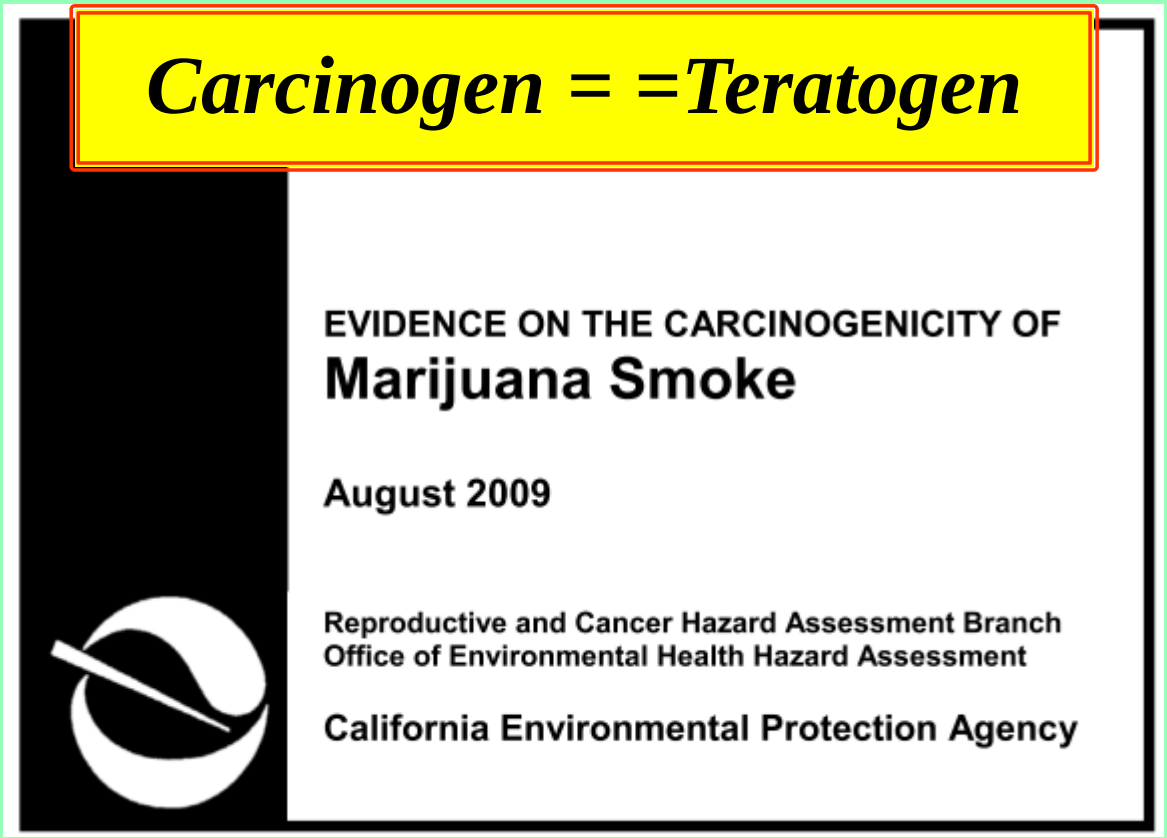
1) ***Head & Neck***
2) ***Larynx***
3) ***Lung***
4) ***Leukaemia***
5) ***Prostate***
6) ***Cervix***
7) ***Testes***
8) ***Bladder***

Childhood / Paediatric / Neonatal

1) ***Neuroblastoma***
2) ***Acute Lymphoblastic Leukaemia***
3) ***Acute Myeloid leukaemia***
4) ***Rhabdomyosarcoma***

Risk – 2-6 times;
Dose-Response Relationship Demonstrated x 4

Carcinogen = =Teratogen



The Office of Environmental Health Hazard Assessment's (OEHHA) Reproductive and Cancer Hazard Assessment Branch was responsible for the preparation of this document.

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150 Pages

https://oehha.ca.gov/media/downloads/proposition-65/chemicals/finalmjsmokehid.pdf

Cancer Rate in California EPA Review

6/11 Adult Studies
Positive for Cancer

Adult Cancers

Child Cancers

5/6 Gestational / Perinatal Exposure
Studies Positive for Cancer

Testicular Cancer

Cancer Epidemiol Biomarkers Prev. 2017 Nov;26(11):1644-1652. doi: 10.1158/1055-9965.EPI-17-0428.

Cannabis Use and Incidence of Testicular Cancer: A 42-Year Follow-up of Swedish Men between 1970 and 2011.

Callaghan RC[1], Allebeck P[2], Akre O[3], McGlynn KA[4], Sidorchuk A[2].

Cancer. 2009 Mar 15;115(6):1215-23. doi: 10.1002/cncr.24159.

Association of marijuana use and the incidence of testicular germ cell tumors.

Daling JR[1], Doody DR, Sun X, Trabert BL, Weiss NS, Chen C, Biggs ML, Starr JR, Dey SK, Schwartz SM.

Population-based case-control study of recreational drug use and testis cancer risk confirms an association between marijuana use and nonseminoma risk.

Lacson JC, Carroll JD, Tuazon E, Castelao EJ, Bernstein L, Cortessis VK.

Cancer. 2012 Nov 1;118(21):5374-83. doi: 10.1002/cncr.27554. Epub 2012 Sep 10.

PMID: 22965656 **Free PMC Article**

Marijuana use and testicular germ cell tumors.

Trabert B, Sigurdson AJ, Sweeney AM, Strom SS, McGlynn KA.

Cancer. 2011 Feb 15;117(4):848-53. doi: 10.1002/cncr.25499. Epub 2010 Oct 5.

PMID: 20925043 **Free PMC Article**

BMC Cancer. 2015 Nov 11;15:897. doi: 10.1186/s12885-015-1905-6.

Cannabis exposure and risk of testicular cancer: a systematic review and meta-analysis.

Gurney J[1], Shaw C[2], Stanley J[3], Signal V[4], Sarfati D[4].

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Making sperm count

Female sex hormone progesterone targets sperm-tail ion channel at conception PAGES 313, 382 & 387

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THE AFTERSHOCK

Nuclear safety shattered by natural disaster

PAGE 273 & NATURE.COM/NEWS

HISTORY

MAXWELL'S LEGACY

The man who invented modern physics

PAGES 286, 289 & 292

REVIEWS

SPRING BOOKS SPECIAL

Feynman to Flannery — the new titles reviewed

PAGE 294

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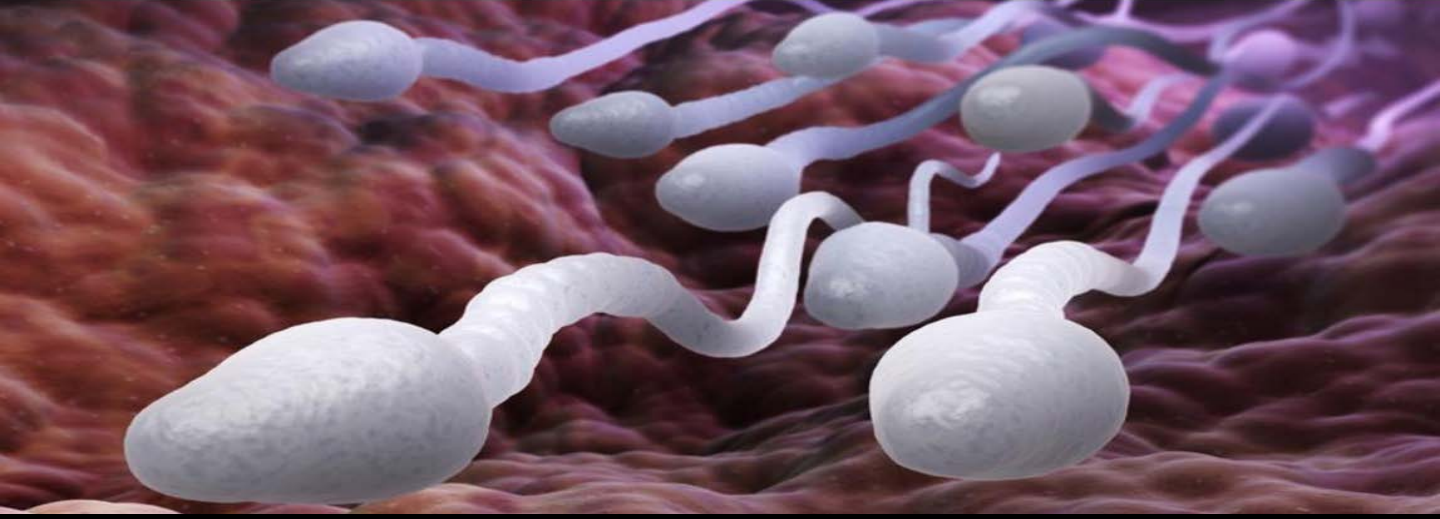
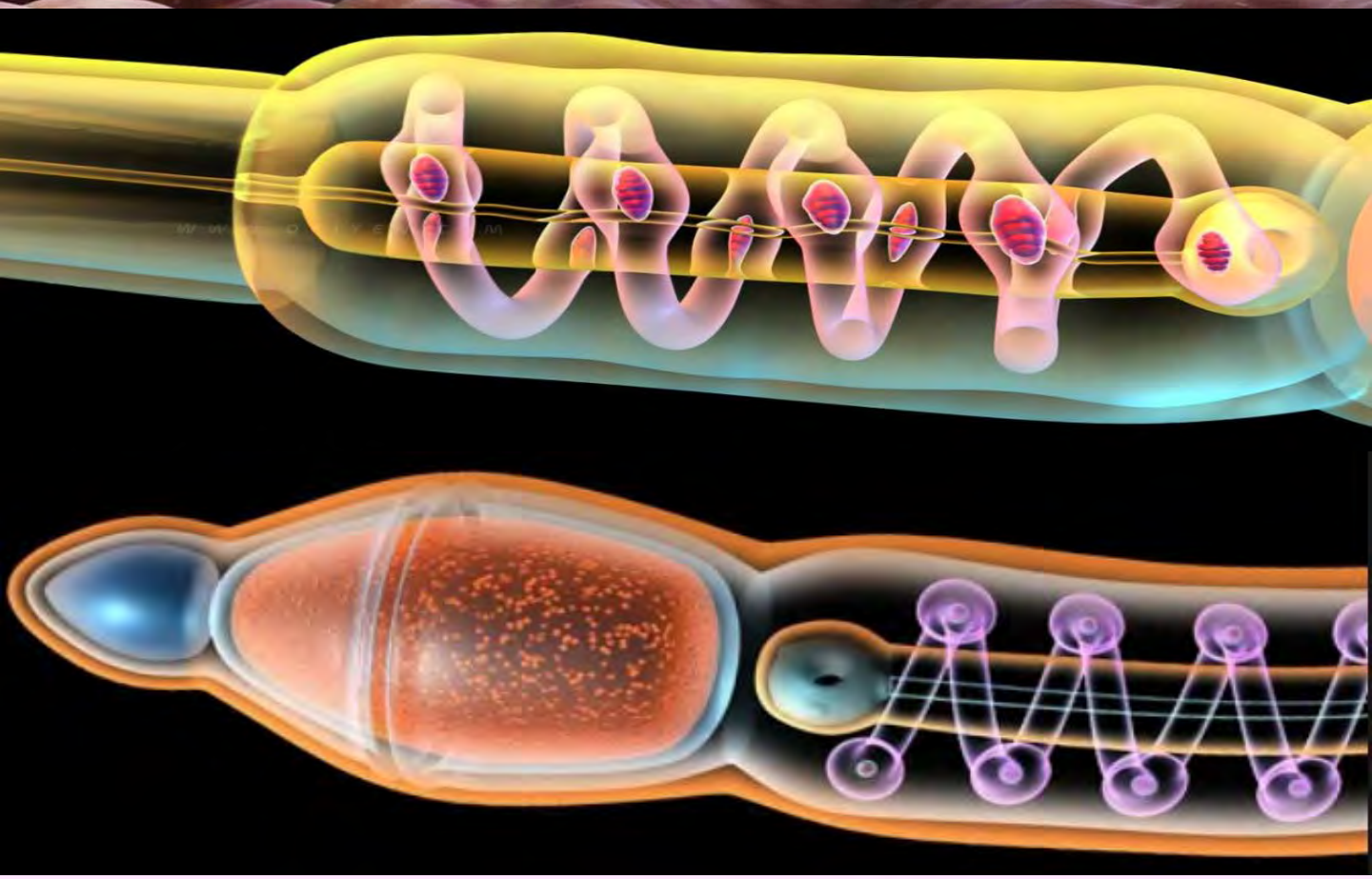
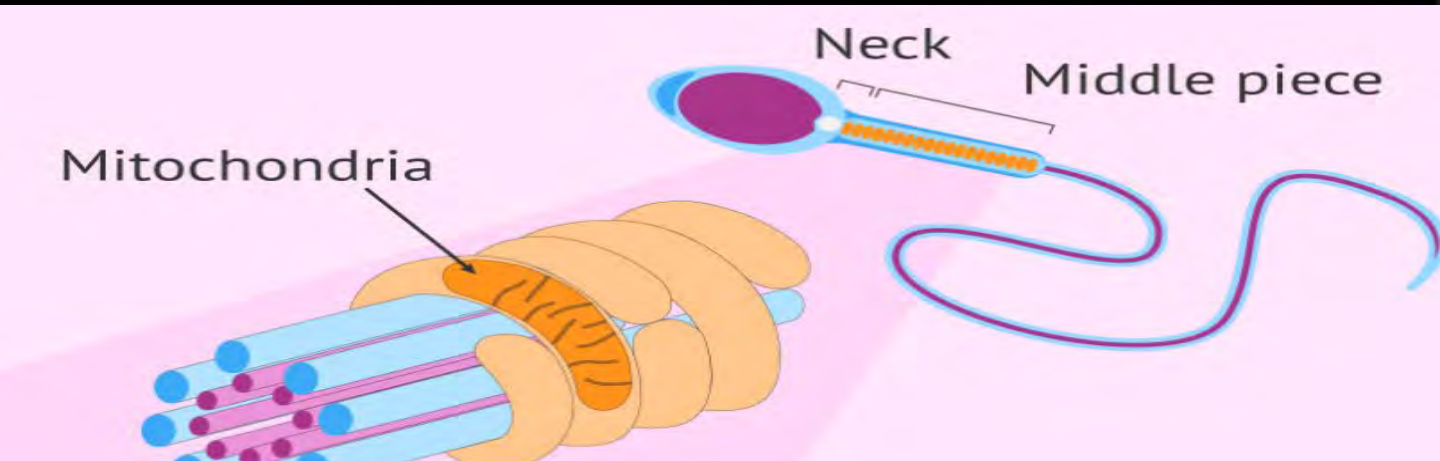
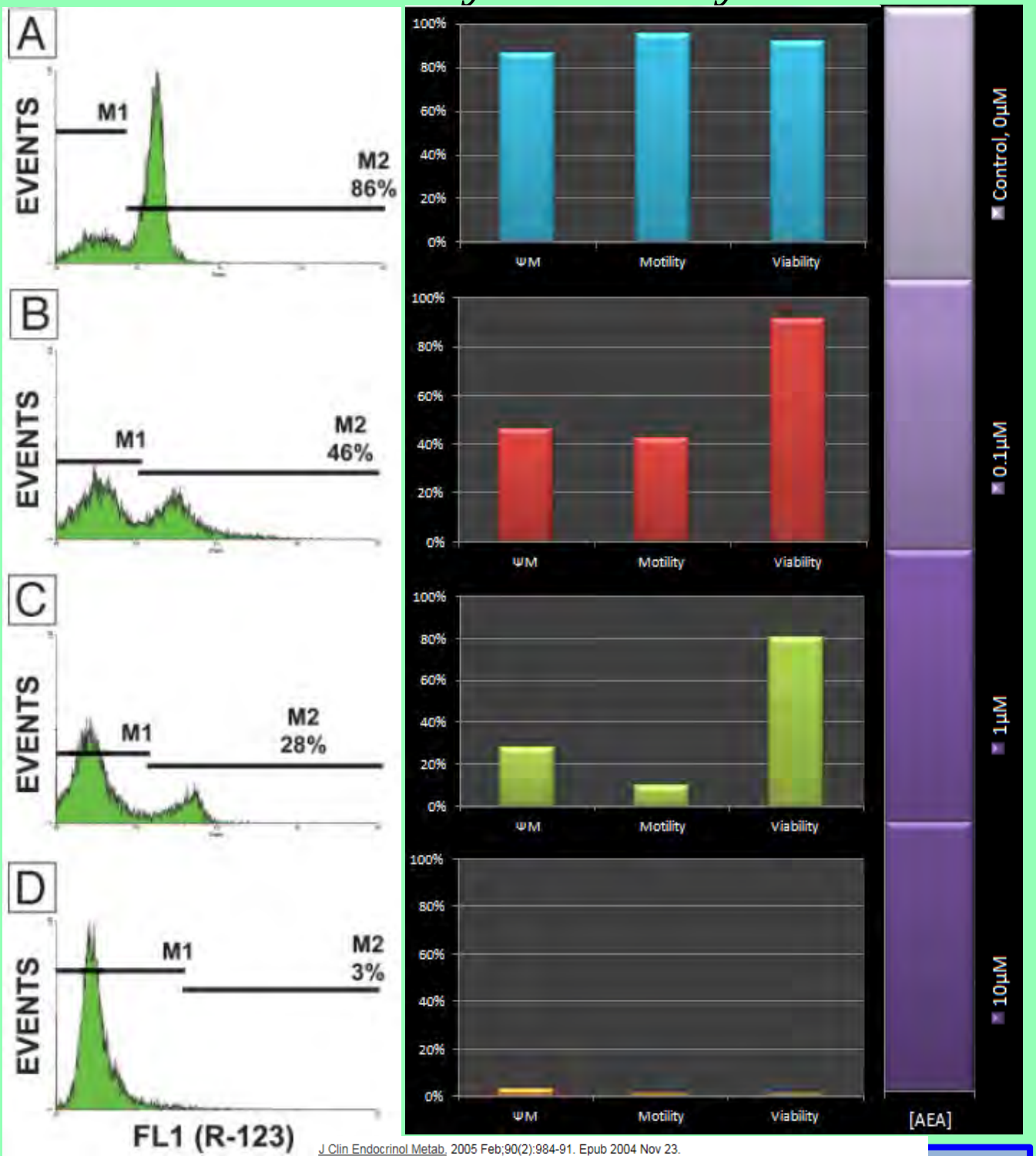





Neck
Middle piece
Mitochondria

Sperm Mitochondrial Membrane Potential, Motility & Viability



J Clin Endocrinol Metab. 2005 Feb;90(2):984-91. Epub 2004 Nov 23.

Human sperm express cannabinoid receptor Cb1, the activation of which inhibits motility, acrosome reaction, and mitochondrial function.

Rossato M[1], Ion Popa F, Ferigo M, Clari G, Foresta C.

Sperm Cannabinoids (CB1R) Control:

- Seminal Fluid, Falling concentration
- Midcycle Oviduct Fluid
- Graafian Follicular Fluid

- DNA Fragmentation
- Sperm Maturation
- DNA Packing and
- Repackaging
- Histone- Transitional Proteins – Protamine Transitions
- DNA Nicking involved in Sperm Packing by Tnp2
- DNA Repairs
- Protection of DNA
- Nuclear size
- Completeness of DNA Packing – Histone-Protamine Transition

Endocrinology. 2010 Oct;151(10):5017-29. doi: 10.1210/en.2010-0133. Epub 2010 Sep 1.

Cannabinoid receptor 1 influences chromatin remodeling in mouse spermatids by affecting content of transition protein 2 mRNA and histone displacement.

Chioccarelli T[1], Cacciola G, Altucci L, Lewis SE, Simon L, Ricci G, Ledent C, Meccariello R, Fasano S, Pierantoni R, Cobellis G.

J Clin Endocrinol Metab. 2005 Feb;90(2):984-91. Epub 2004 Nov 23.

Human sperm express cannabinoid receptor Cb1, the activation of which inhibits motility, acrosome reaction, and mitochondrial function.

Rossato M[1], Ion Popa F, Ferigo M, Clari G, Foresta C.

Human Sperm Head Assay

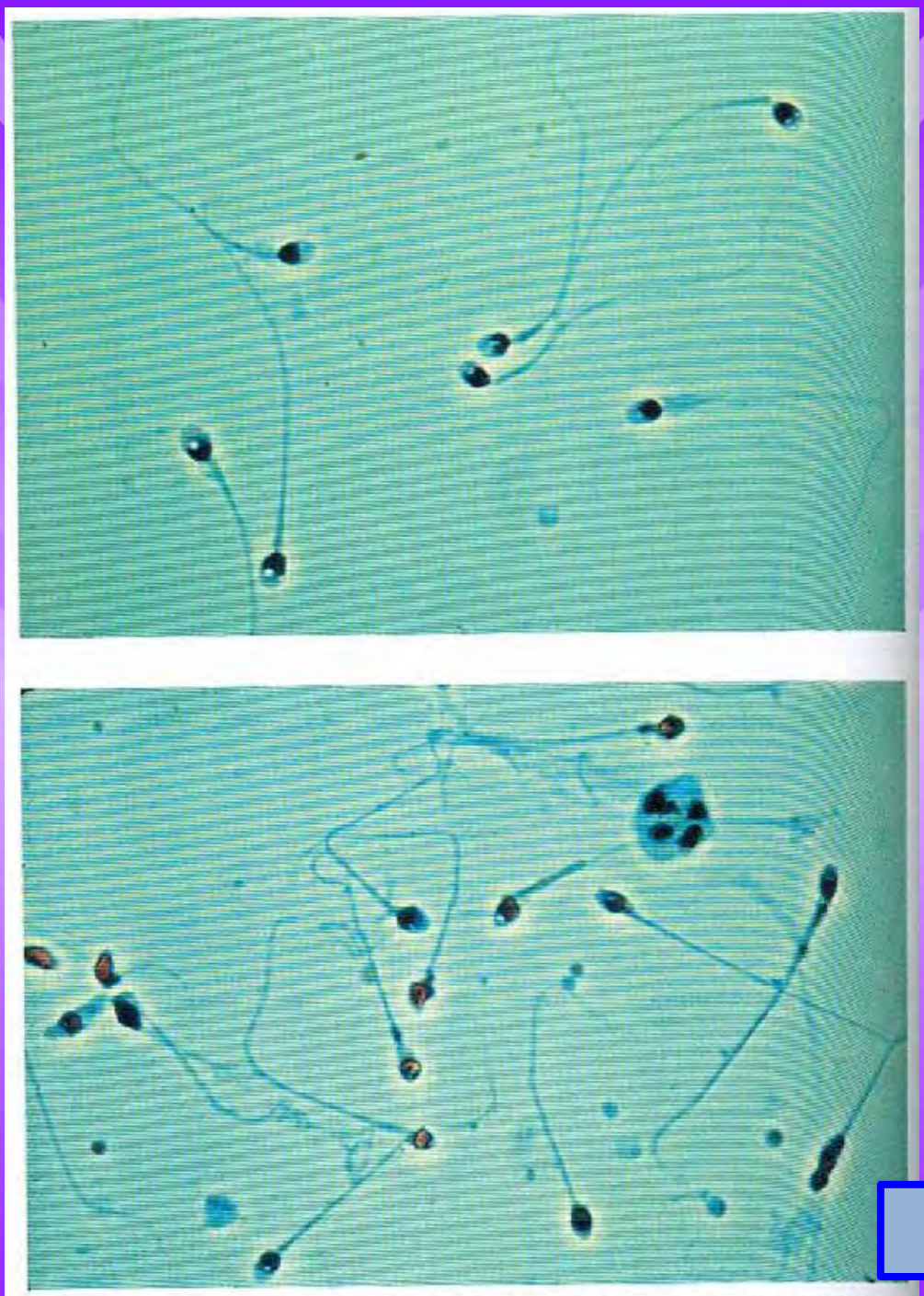


Fig. 8. *Top:* Normal ovoid shape human spermatazoa sampled from tobacco smoker and moderate alcohol drinker. *Bottom:* Nonovoid and immature form present among ovoid shape human spermatazoa sampled from daily marihuana smoker.

82

Hembree W.C. NGG, Zeidenberg P., Huang H.F.S. Changes in Human Spermatozoa Associated with High Dose Marihuana Smoking. In: Nahas G.G. SKM, Harvey D.J., Agurell S., ed. Marijuana and Medicine. Totowa, New Jersey: Humana Press; 1999:367-78

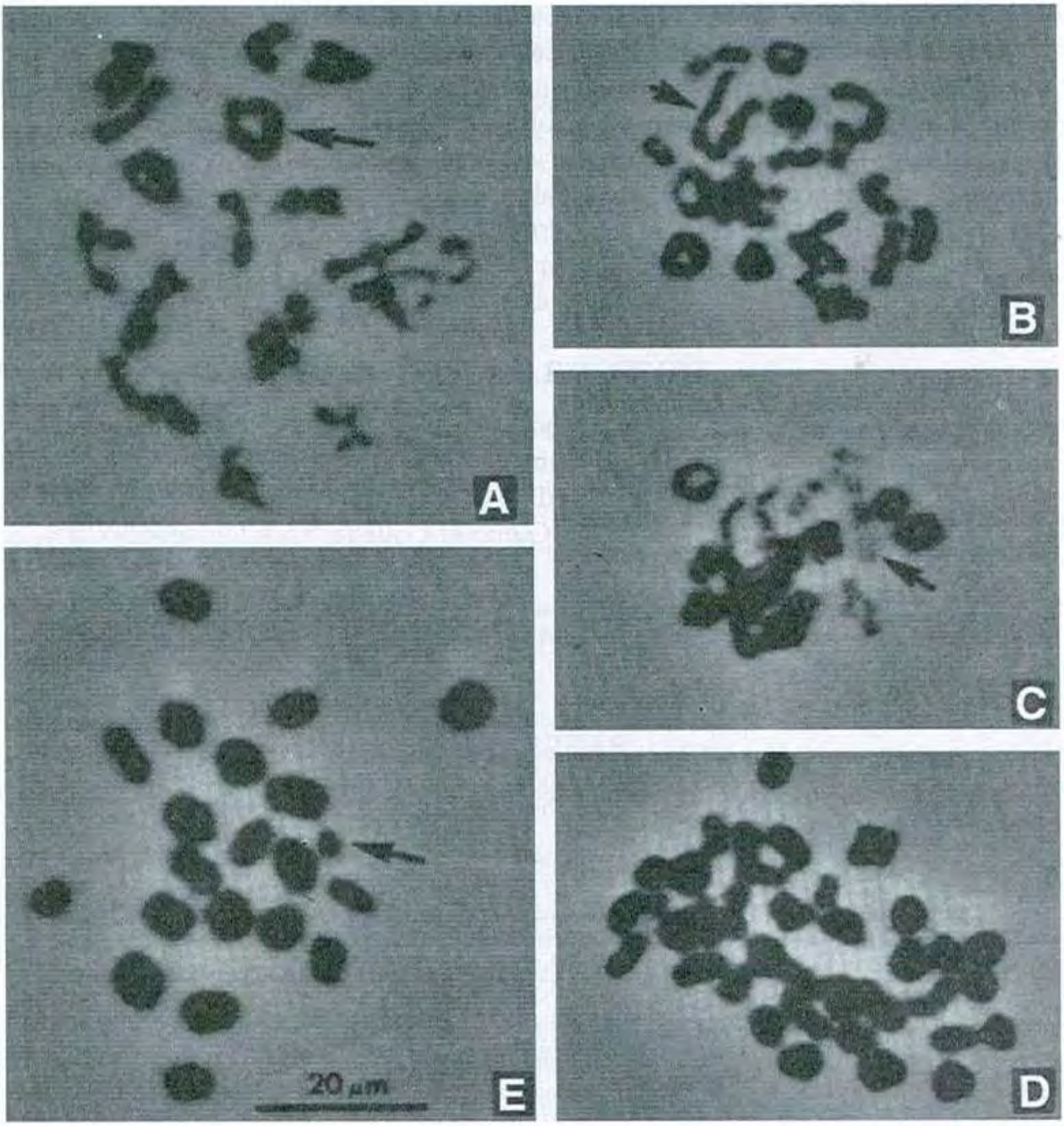
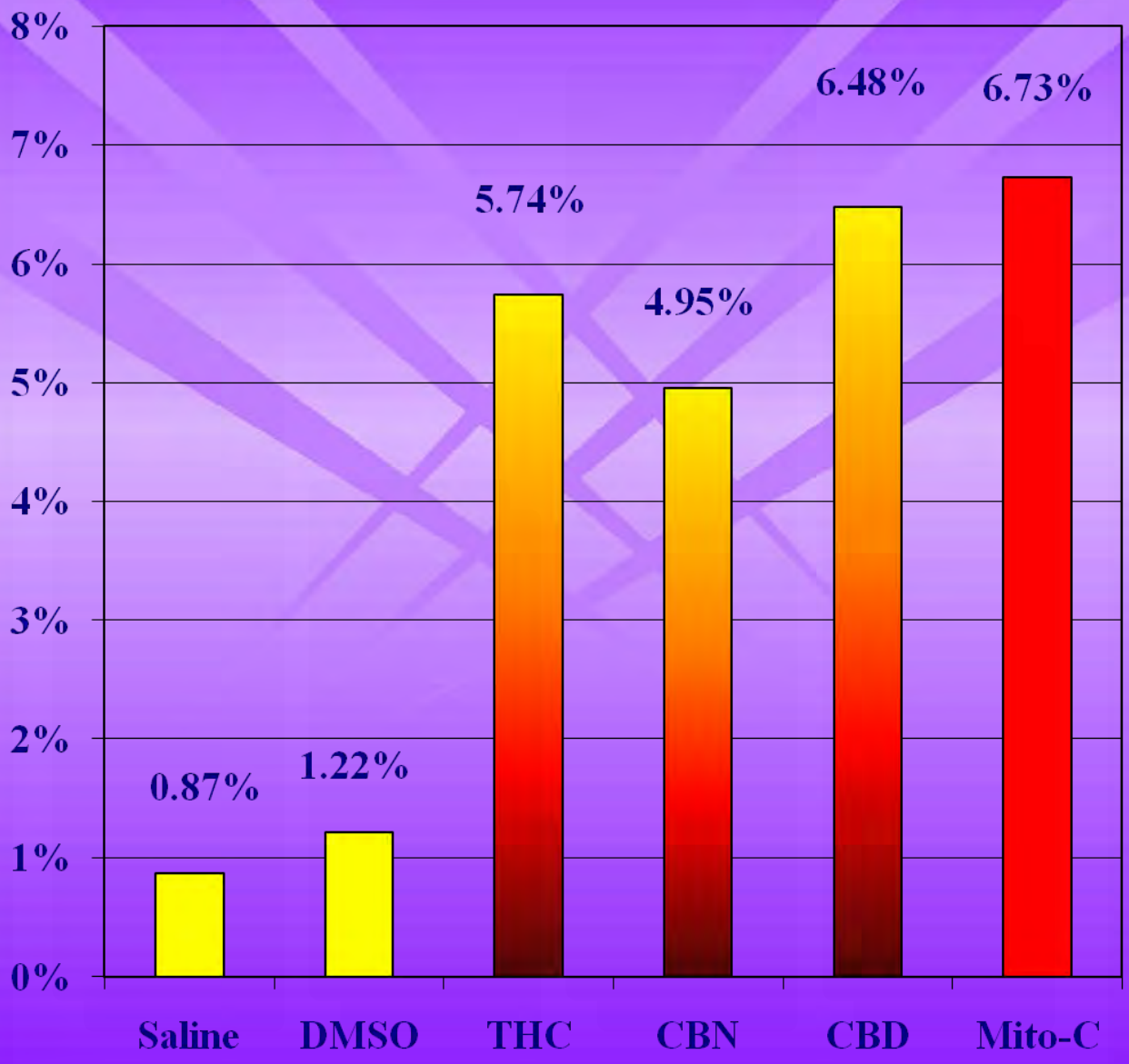


Fig. 3. Photomicrographs of primary spermatocyte at diakinesis illustrating ring and chain translocations and early metaphase chromosomes showing aneuploidy and broken segments induced by Δ^9-THC. Mice were treated for 5 days with 10 mg/kg of Δ^9-THC and the primary spermatocytes were assessed 16 days after the last treatment. (**A**) Translocation ring of four chromosomes and 18 bivalents. (**B**) Translocation chain of four chromosomes. (**C**) Translocation chain of three chromosomes. (**D**) Aneuploid cell showing 30 bivalents. (**E**) Broken chromosome segment and 20 bivalents.

Zimmerman AM, Zimmerman S, Raj AY "Effects of Cannabinoids on spermatogenesis in mice." Chapter 27 In: "Marijuana and Medicine" Humana Press Totowa, New Jersey, 1999, PP347-357. See Figure 3 page 355.

THC & Cannabinoids

% Chromosomal Translocations



Zimmerman AM, Zimmerman S, Raj AY "Effects of Cannabinoids on spermatogenesis in mice." Chapter 27 In: "Marijuana and Medicine" eds.: Nahas GG, Sutin KM, Harvey DJ, Agurell S. Humana Press Totowa, New Jersey, 1999, PP347-357. See Figure 3 page 355 and text P352-353

Normal Brain Development

Neural Migration

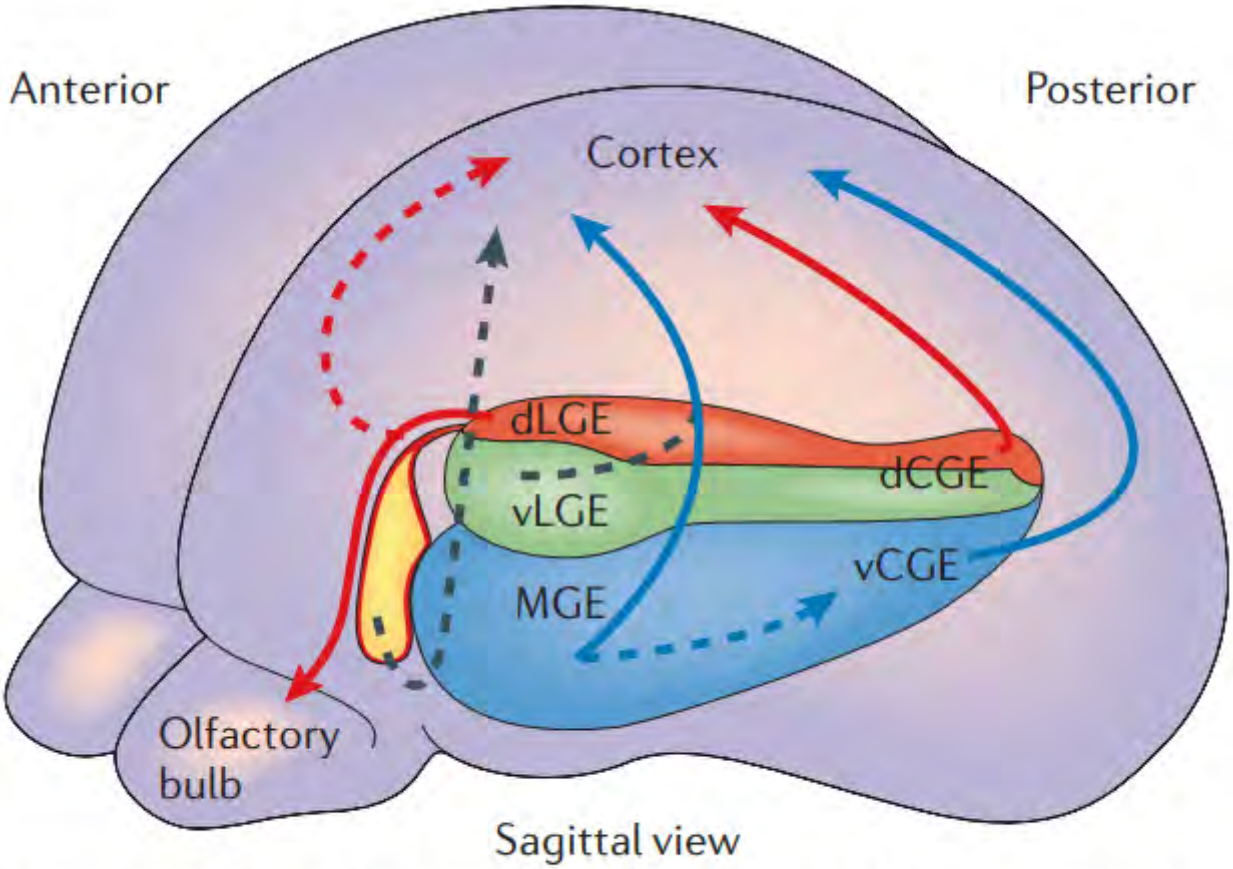


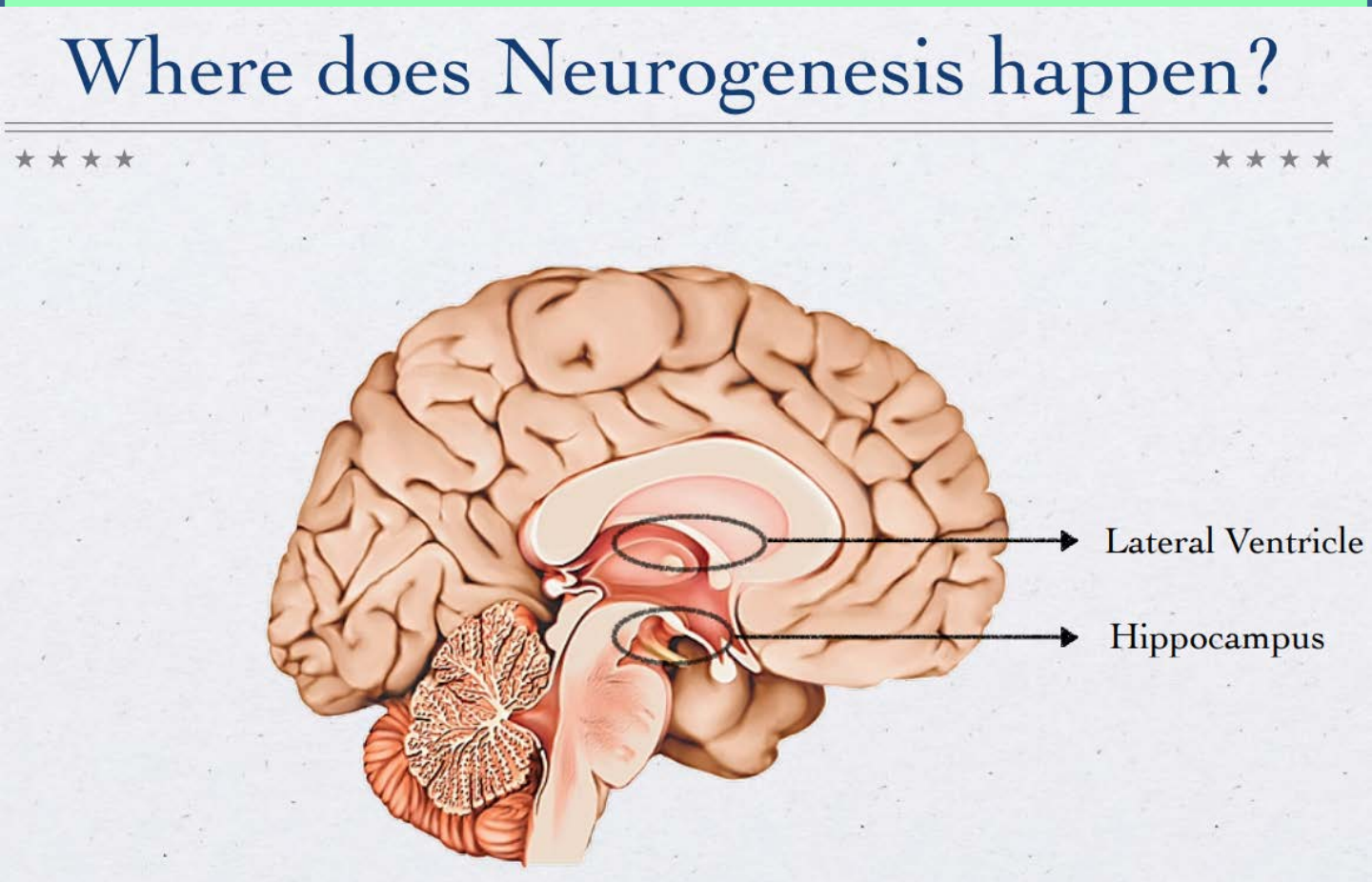
Figure 1 | **Migration pathways of cortical interneuron subgroups from the ventral telencephalon.** Schematic

Nat Rev Neurosci. 2006 Sep;7(9):687-96. Epub 2006 Aug 2.

The origin and specification of cortical interneurons

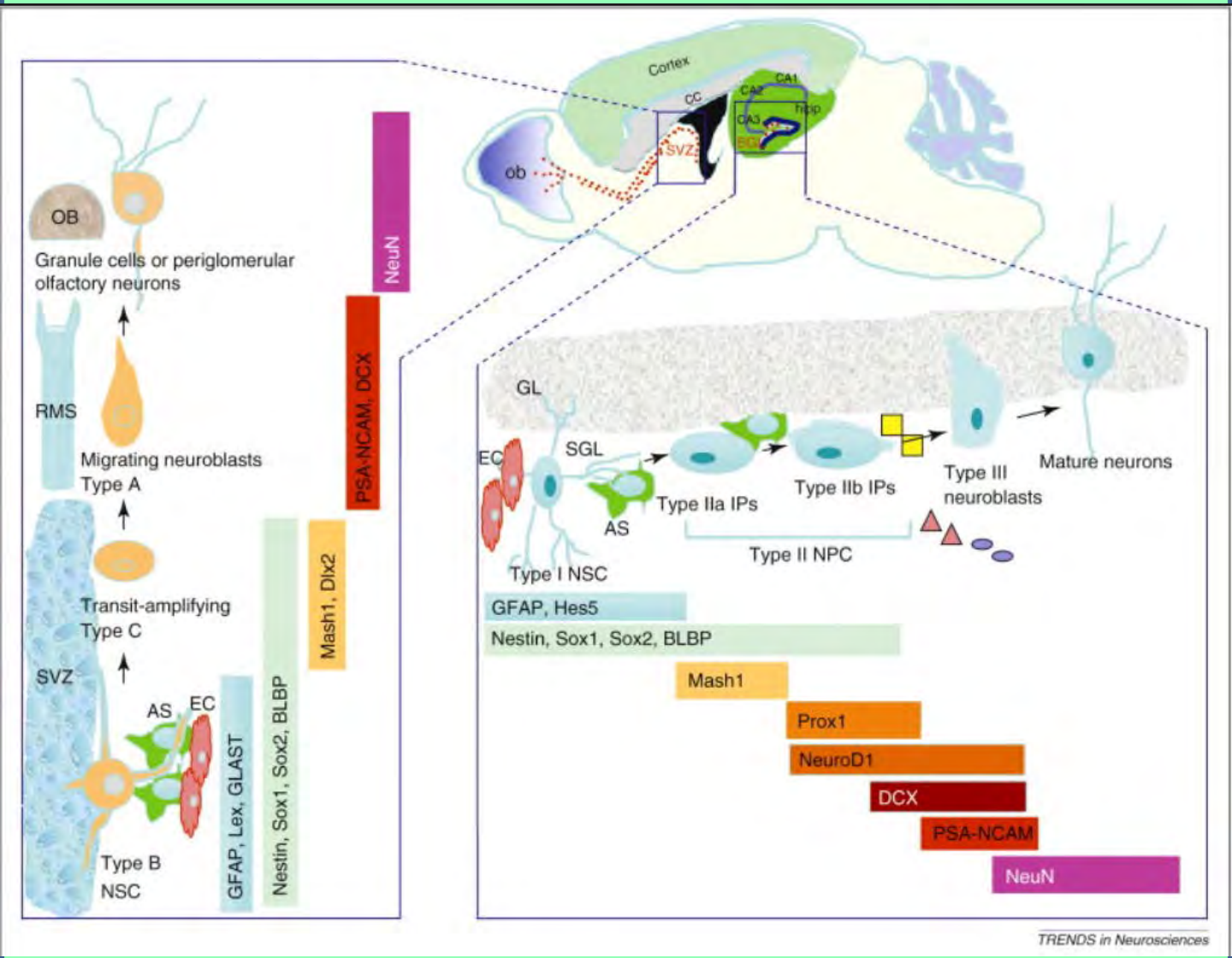
Wonders CP[1], Anderson SA.

Neurogenesis



https://www.slideshare.net/IngridNeuro/infant-and-adult-neurogenesis

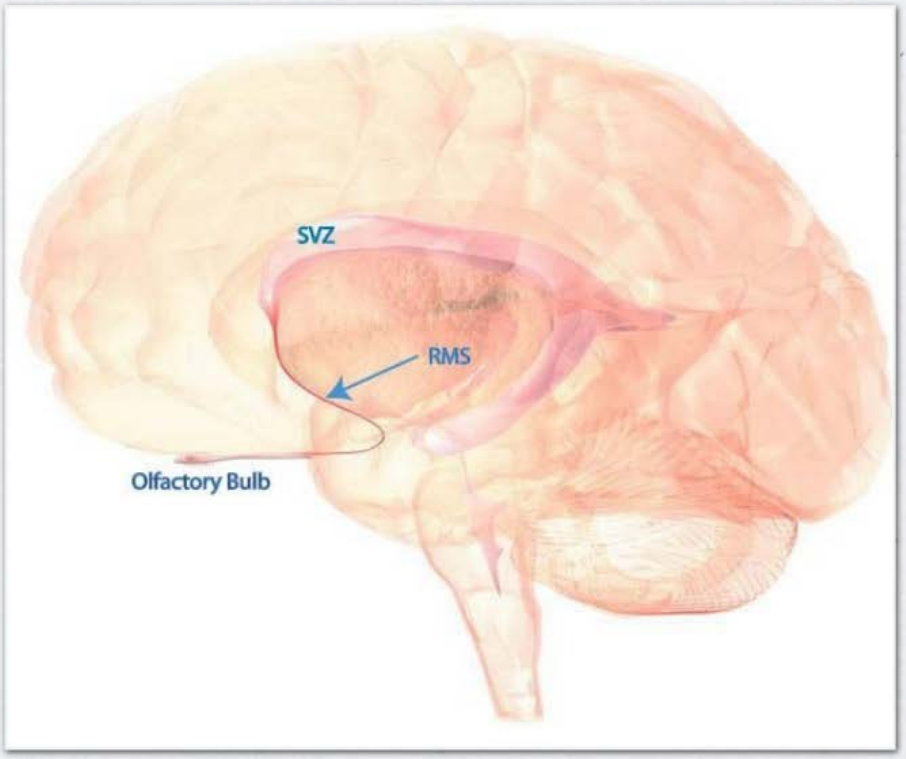
Bidirectional Migration



https://www.cell.com/trends/neurosciences/fulltext/S0166-2236(10)00134-7

Rostral Migratory Stream

The RMS : Rostral Migratory Stream



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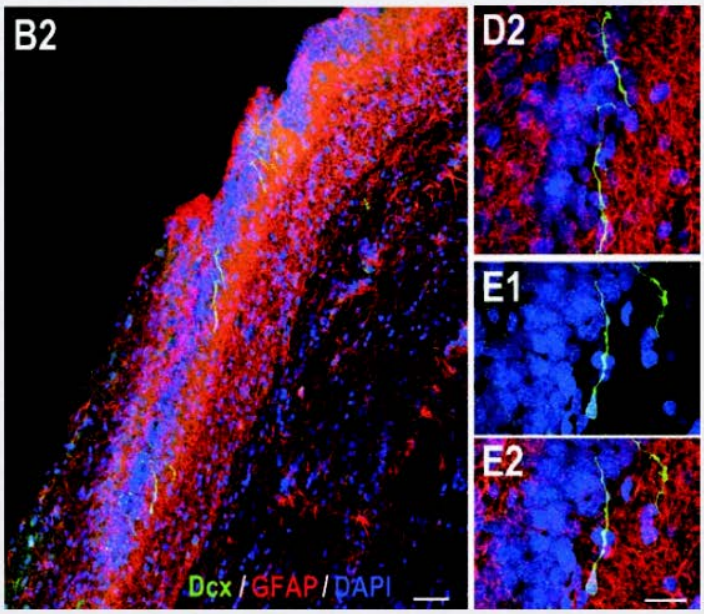
Human RMS

Horizontal Section of the Adult RMS

★ ★ ★ ★ ★ ★ ★ ★



Staining

- Glia
- Immature neuron
- Cells

The RMS-like pathway exists in the adult human forebrain

Zhengang Yang et al, *Cell Research (2011) 21:1534-1550*

https://www.slideshare.net/IngridNeuro/infant-and-adult-neurogenesis

Medial Migratory Stream to Human Infant Ventromedial Prefrontal Cortex

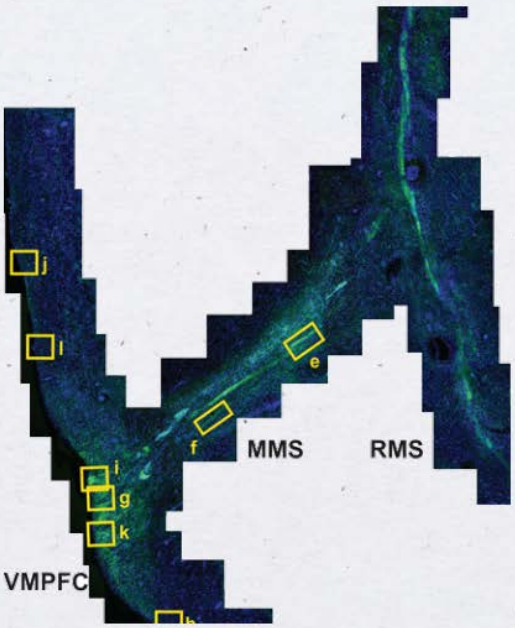
Hypothesis for decline in cell number

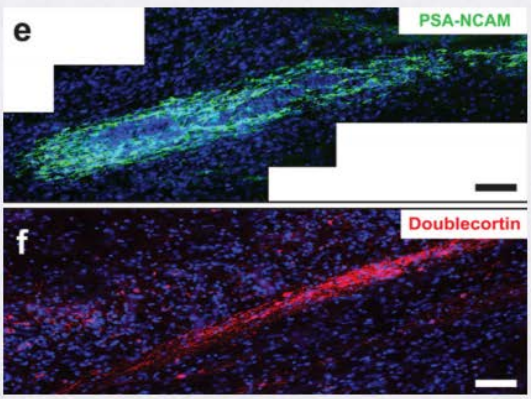
At 6 Months

Staining

Immature neuron

Migrating and immature neuron



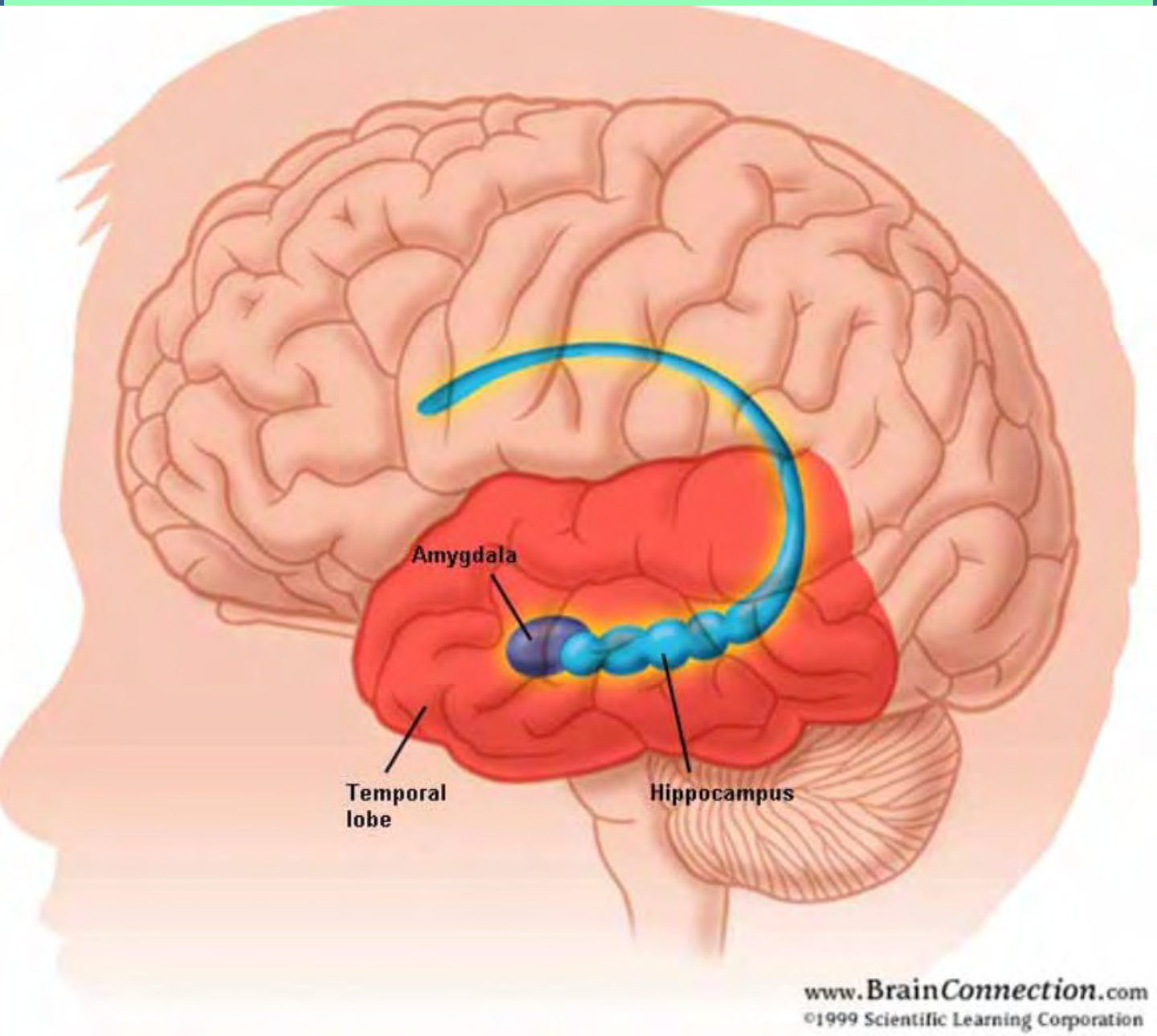


A medial migratory stream (MMS) of immature neurons branches from the proximal rostral migratory stream (RMS) in the infant human brain to supply the ventromedial prefrontal cortex (VMPFC)

Arturo Alvarez- Buylla et al, *Nature.* ; 478(7369): 382–386. doi:10.1038/nature10487

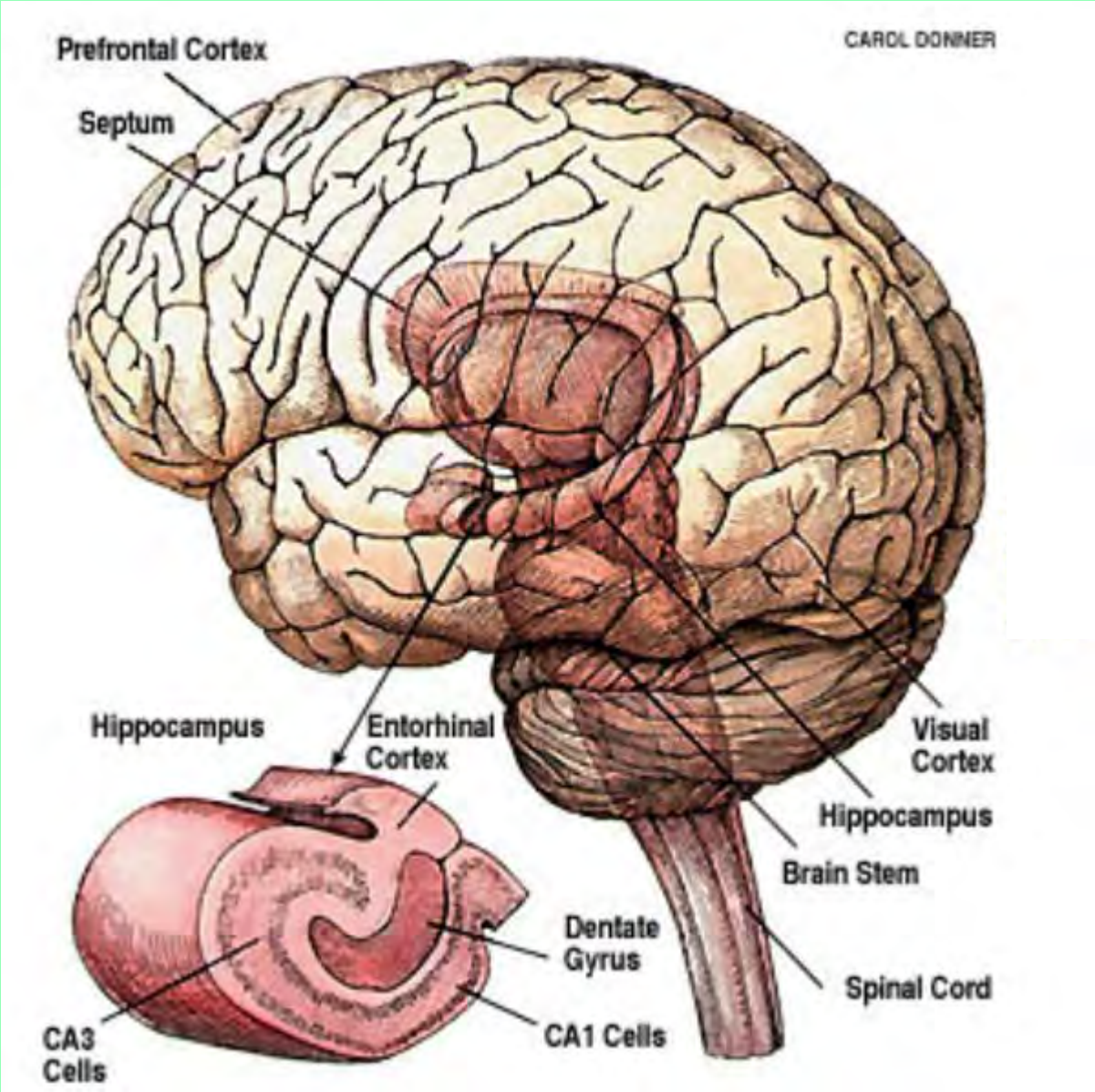
https://www.slideshare.net/IngridNeuro/infant-and-adult-neurogenesis

Hippocampus Anatomy



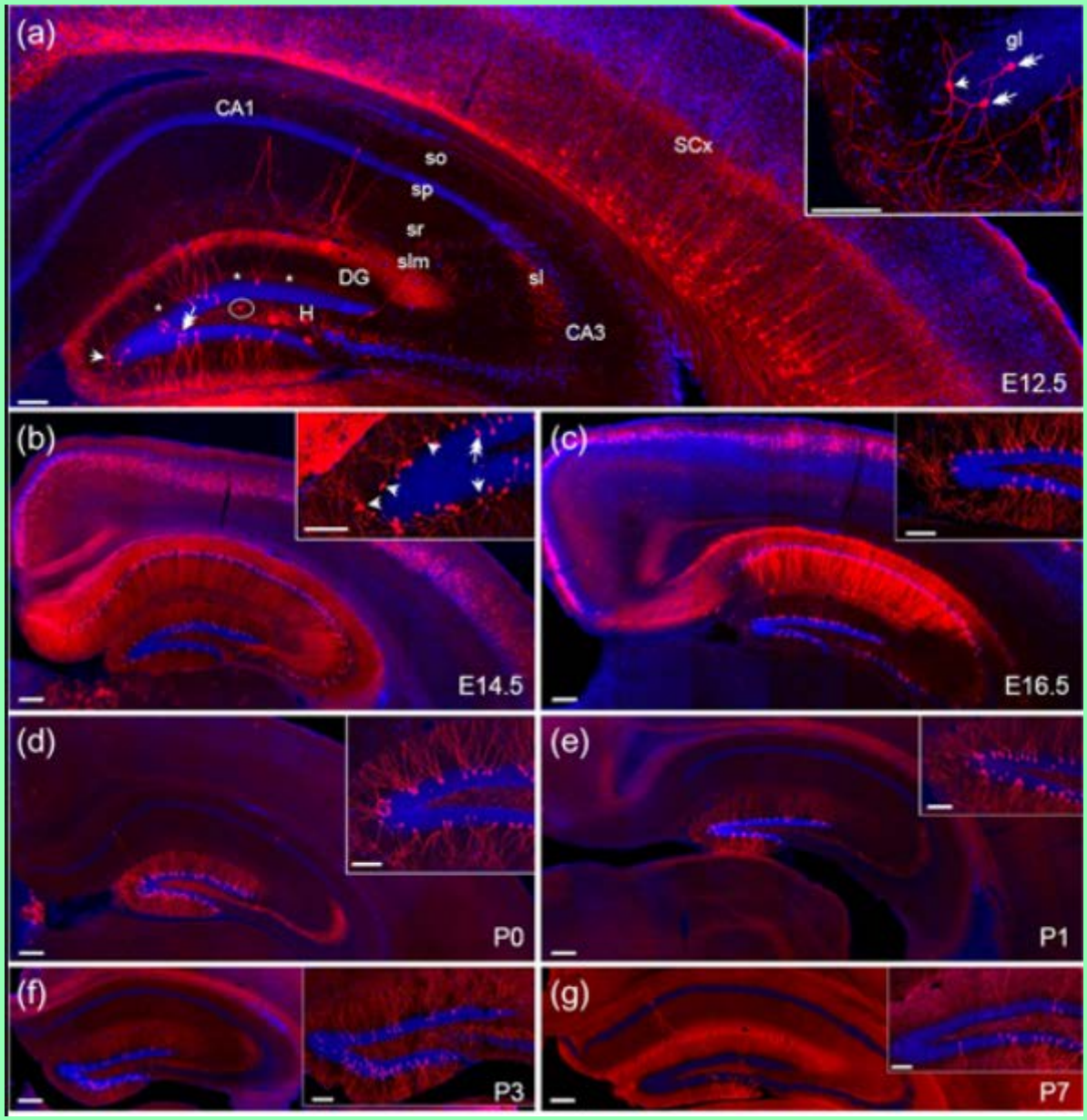
http://www.visembryo.com/story1044.html

Hippocampal Folds



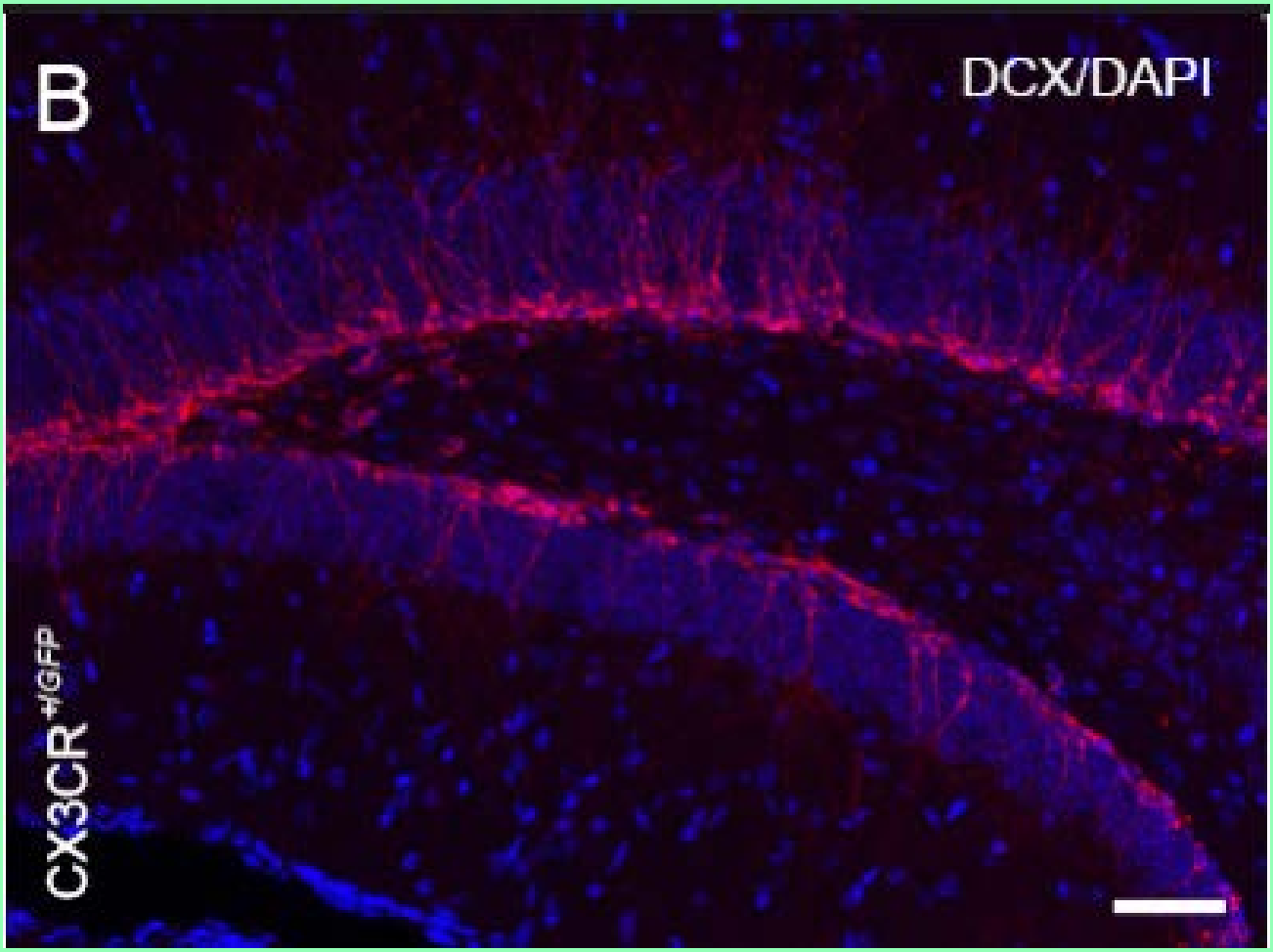
http://wps.prenhall.com/wps/media/objects/803/822654/psychplace/dreams/hippo.html

Hippocampal Wave



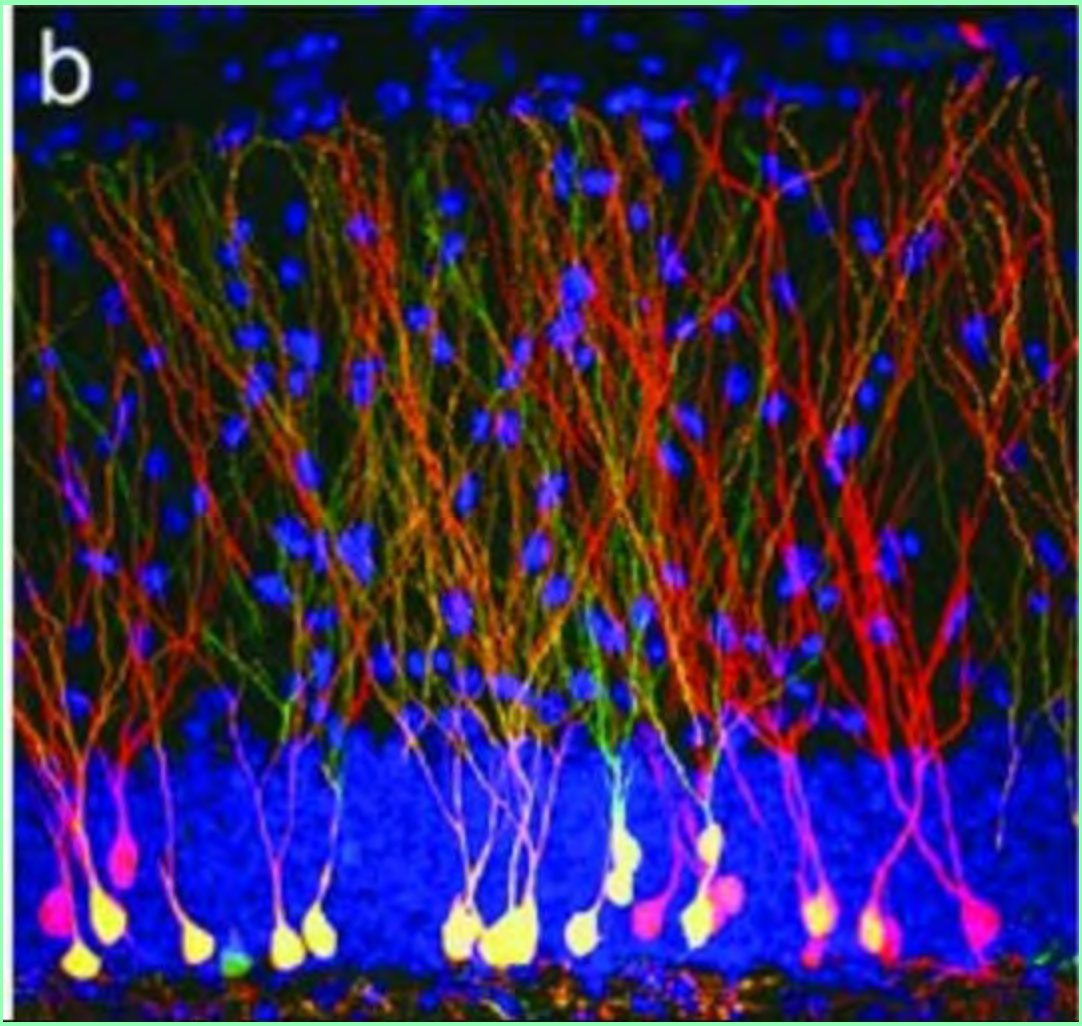
https://academic.oup.com/cercor/advance-article-abstract/doi/10.1093/cercor/bhy132/5033561?redirectedFrom=fulltext

Subdentate Gyrus Progenitor Zone

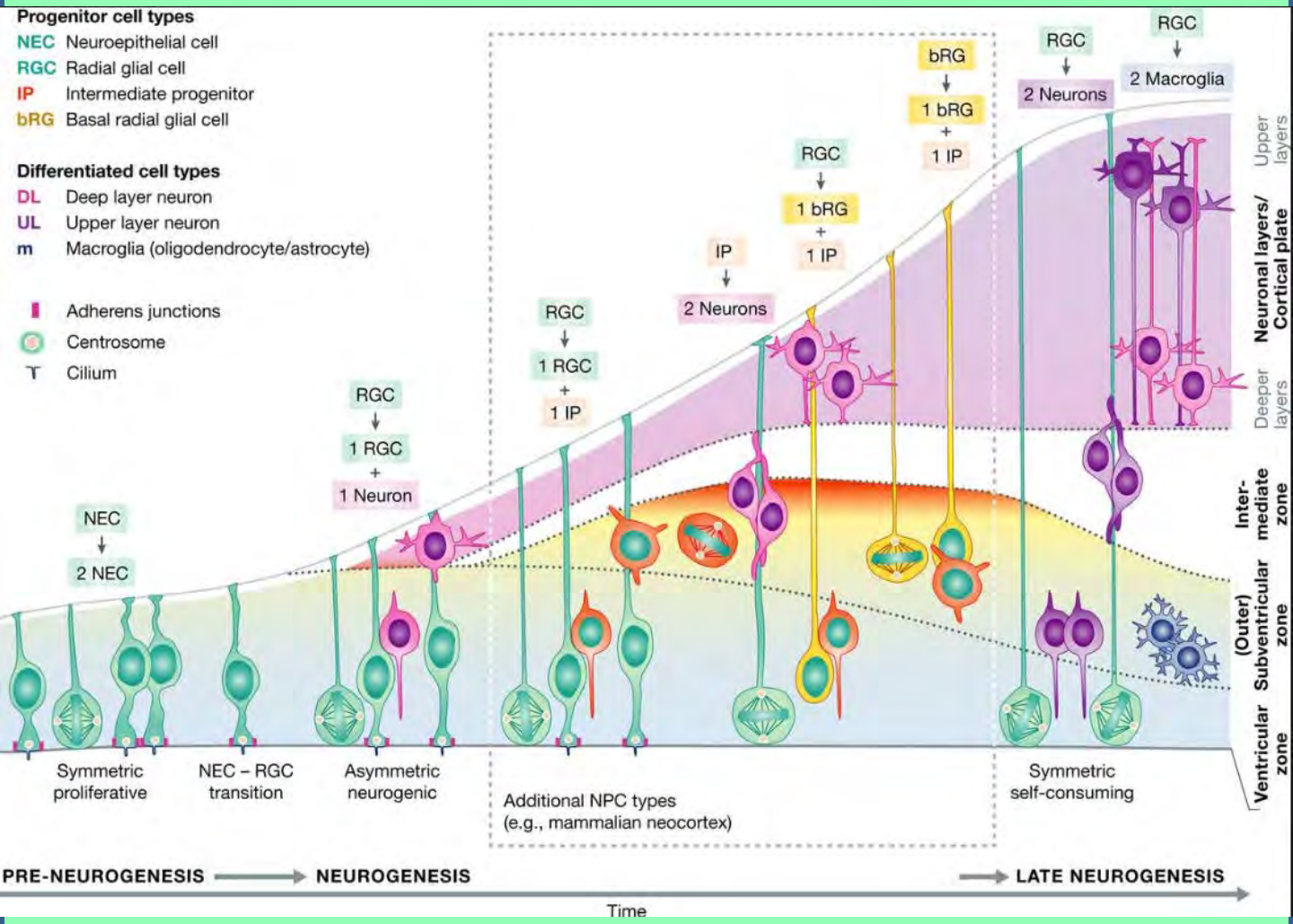


http://www.nrronline.org/article.asp?issn=1673-5374;year=2015;volume=10;issue=5;spage=772;epage=777;aulast=Xiao

Granule Cells of the Dentate Gyrus

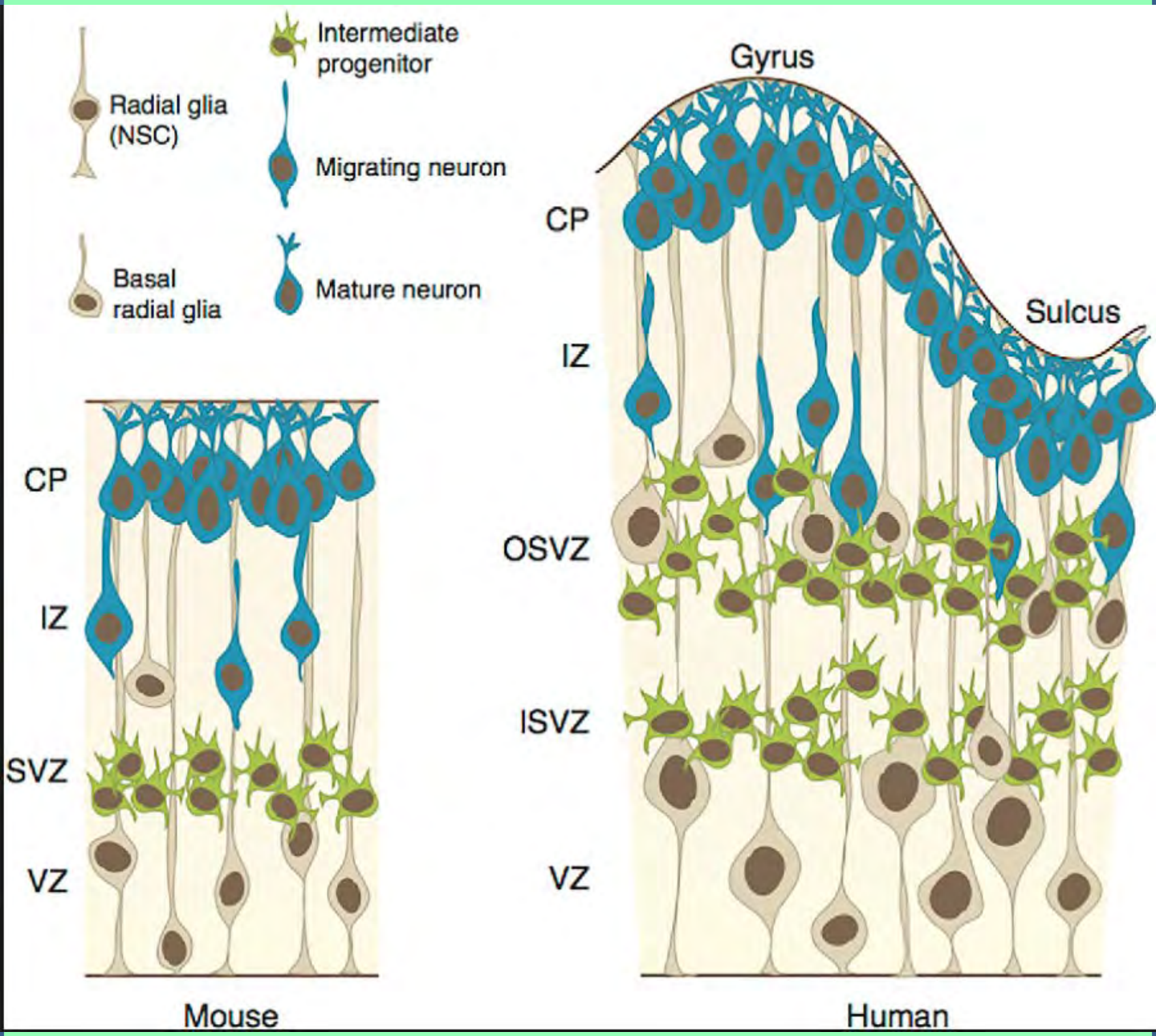


Corticogenesis



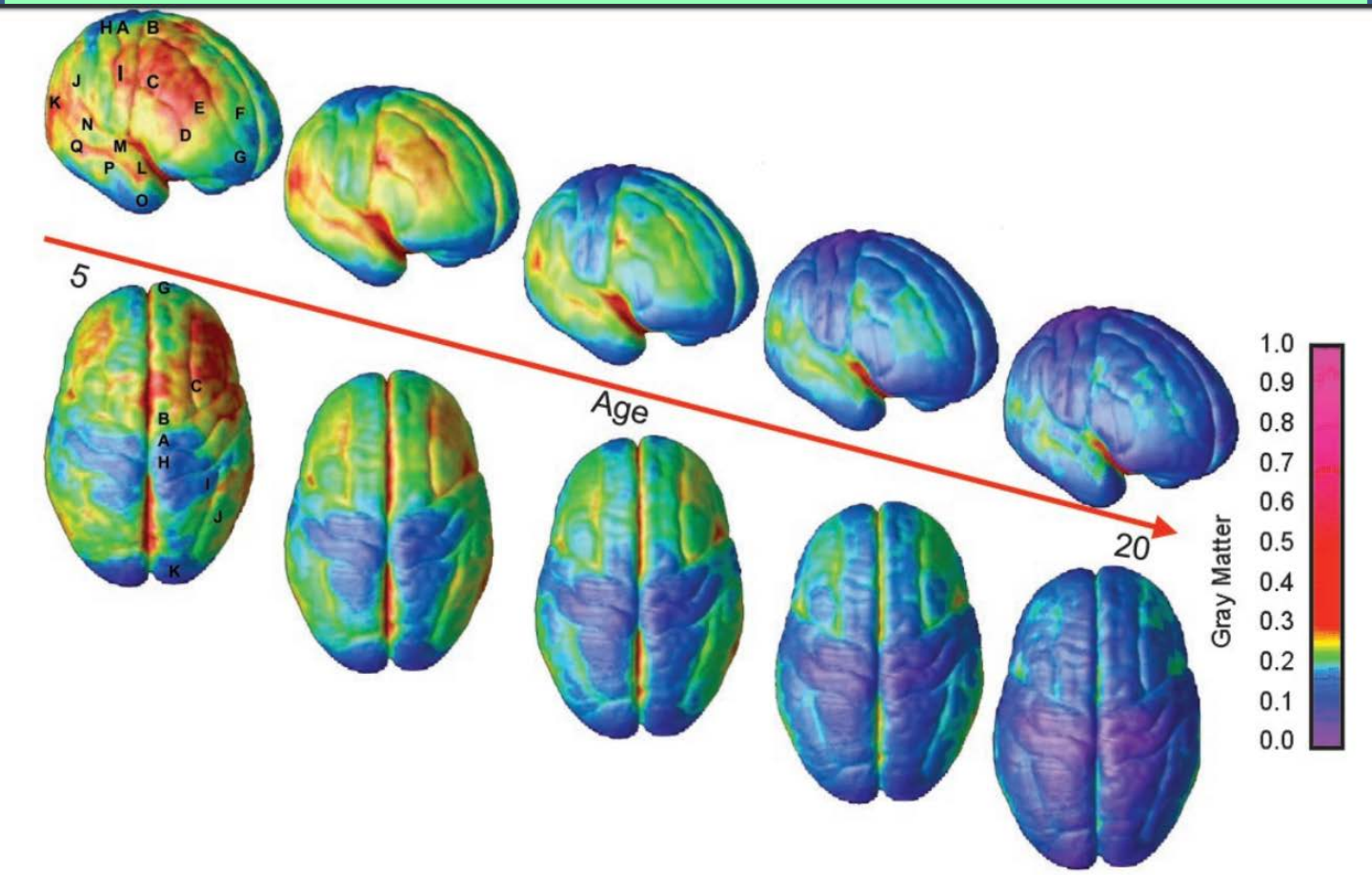
http://embor.embopress.org/content/15/4/351

Cortical Growth



https://www.semanticscholar.org/paper/Stem-Cell-Models-of-Human-Brain-Development.-Kelava-Lancaster/8faeba222db73de2bb769be5481d316d1ba29ccf/figure/0

Brain Maturation Through Adolescence



Proc Natl Acad Sci U S A. 2004 May 25;101(21):8174-9. Epub 2004 May 17.

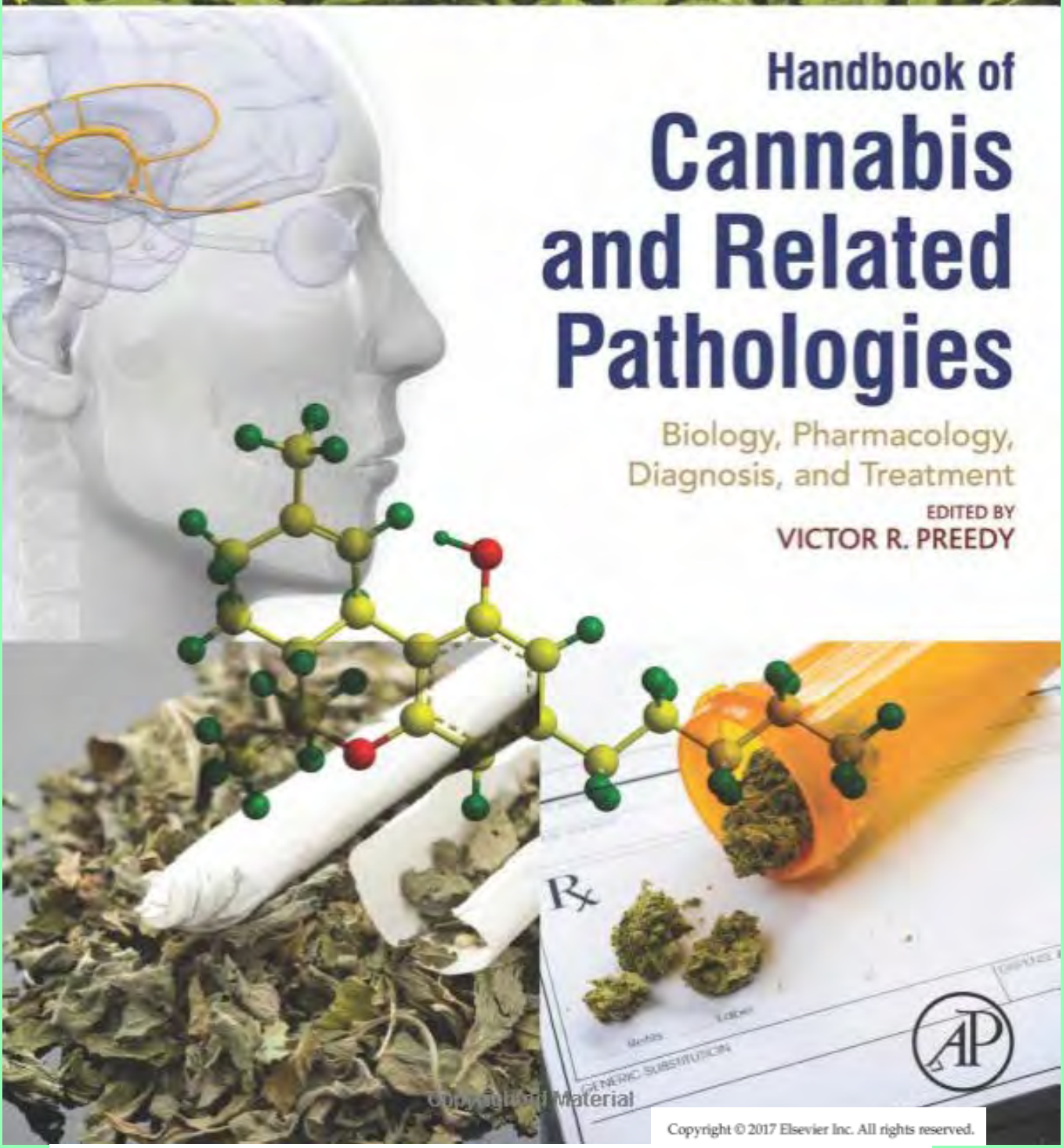
Dynamic mapping of human cortical development during childhood through early adulthood.

Gogtay N[1], Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, Nugent TF 3rd, Herman DH, Clasen LS, Toga AW, Rapoport JL, Thompson PM.

Impact of Cannabis

100

Birth Defects



Handbook of Cannabis and Related Pathologies

Biology, Pharmacology, Diagnosis, and Treatment

EDITED BY

VICTOR R. PREEDY

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Prenatal Cannabis Exposure (PCE) Is linked with:

- "Only a small minority of women (<35%) are forthcoming about their cannabis use
- Women who use cannabis during pregnancy are more likely to be younger, unmarried, of lower socioeconomic status (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 gestation
  - ***Neonatal neurological disturbances***
  - ***Reduced function in specific cognitive domains:***
  - ***In Grade school***
  - ***Increased impulsivity and***
  - ***Hyperactivity and***
  - ***Depression at age 10***
  - ***Poor school achievement***
  - ***Delinquency in adolescence***
  - ***Increase adolescent use of***
    - ***Tobacco and***
    - ***Cannabis***
  - ***Altered neural function for visuo-spatial memory and***
  - ***Motor impulse control in Early adulthood"***

Correlates and consequences of Prenatal Cannabis Exposure (PCE): Identifying and Characterizing Vulnerable Maternal Populations and Determining Outcomes in Exposed Offspring
Ed: Brents L.K. In: "Handbook of Cannabis and Related Pathologies: Biology, Pharmacology, Diagnosis and Treatment." Ed. Preedy V.R. 23017, Academic Press. London.

103

Anencephaly

https://www.cdc.gov/ncbddd/birthdefects/anencephaly.html

Increased Anencephaly

R.R. = 1.7
(95%C.I. 0.9-3.4)

R.R. = 1.9
(95%C.I. 1.1-3.2)

Epidemiology. 2009 Jan;20(1):60-6. doi: 10.1097/EDE.0b013e31818e5930.

Maternal periconceptional illicit drug use and the risk of congenital malformations.

van Gelder MM[1], Reefhuis J, Caton AR, Werler MM, Druschel CM, Roeleveld N; National Birth Defects Prevention Study.

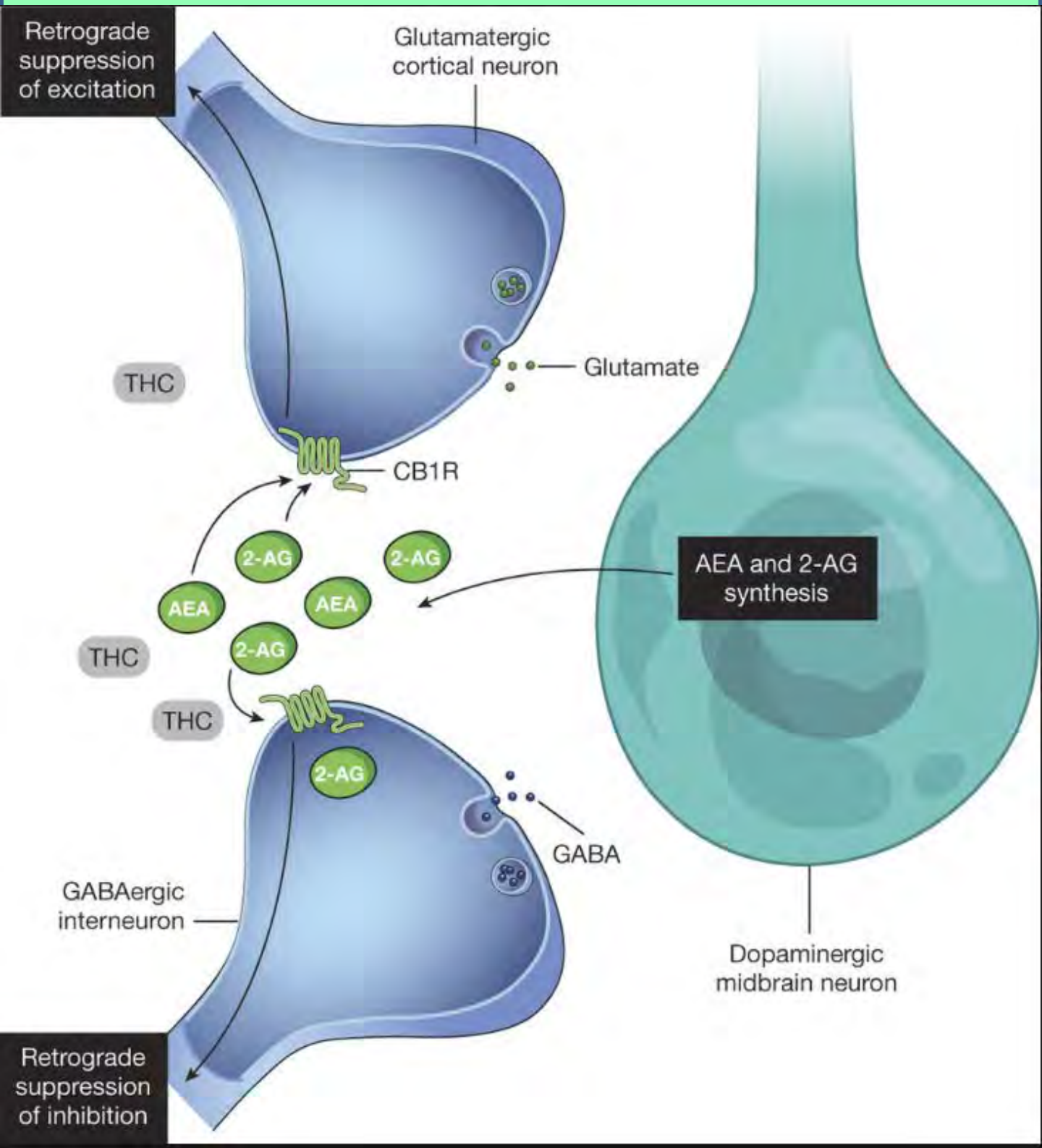
Author information

1 National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA 30333, USA.

Paediatr Perinat Epidemiol. 2014 Sep;28(5):424-33. doi: 10.1111/ppe.12140. Epub 2014 Aug 26.

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.

van Gelder MM[1], Donders AR, Devine O, Roeleveld N, Reefhuis J; National Birth Defects Prevention Study.

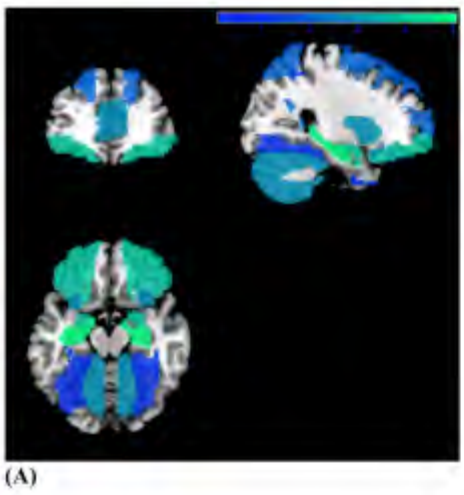


Nature. 2016 Nov 17;539(7629):369-377. doi: 10.1038/nature20153.

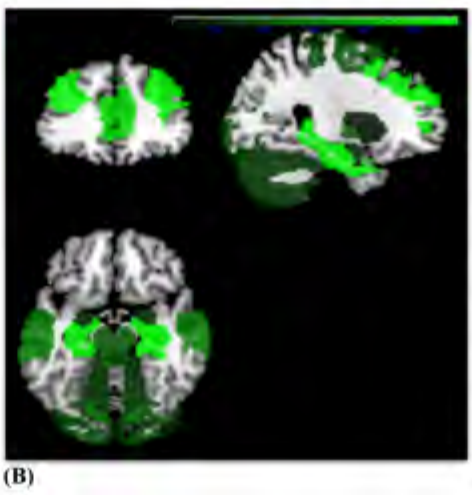
The effects of Δ^9-tetrahydrocannabinol on the dopamine system.

Bloomfield MA[1,2,3,4,5], Ashok AH[1,2,4], Volkow ND[6], Howes OD[1,2,4].

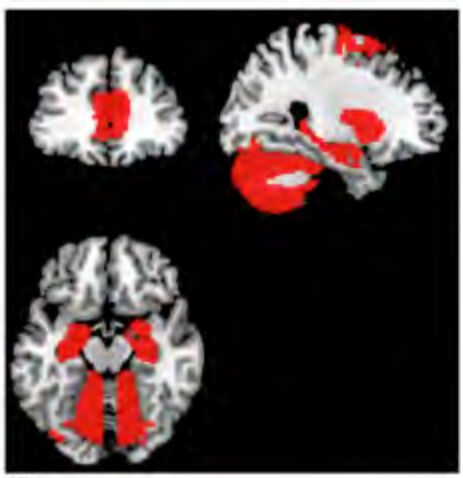
CB1R Distribution in Adult Brain



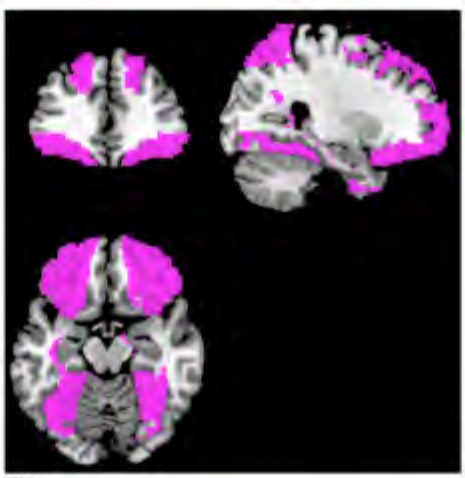
(A)



(B)



(C)



(D)

Figure 3. Weighted color maps. **(A)** Neuroanatomical alterations in cannabis users (blue-green), relative to control subjects (two to six studies). **(B)** Brain map with regional distribution of cannabinoid receptor density [dark-light green; range, 40–1680 density of receptor binding sites, measured via autoradiographic techniques (3)]. Lighter colors indicate evidence from more studies and greater density of receptors. **(C)** Binary map (red) illustrates overlap between **(A)** and **(B)**, including regions high in cannabinoid receptors that also show neuroanatomical alterations. **(D)** Binary map (violet) illustrates nonoverlap between **(A)** and **(B)**, including areas that showed neuroanatomic alterations and are low in cannabinoid receptors.

Biol Psychiatry. 2016 Apr 1;79(7):e17-31. doi: 10.1016/j.biopsych.2015.11.013. Epub 2015 Dec 4.

The Role of Cannabinoids in Neuroanatomic Alterations in Cannabis Users.

Lorenzetti V[1], Solowij N[2], Yücel M[3].

Adult - Hippocampus & Amygdala

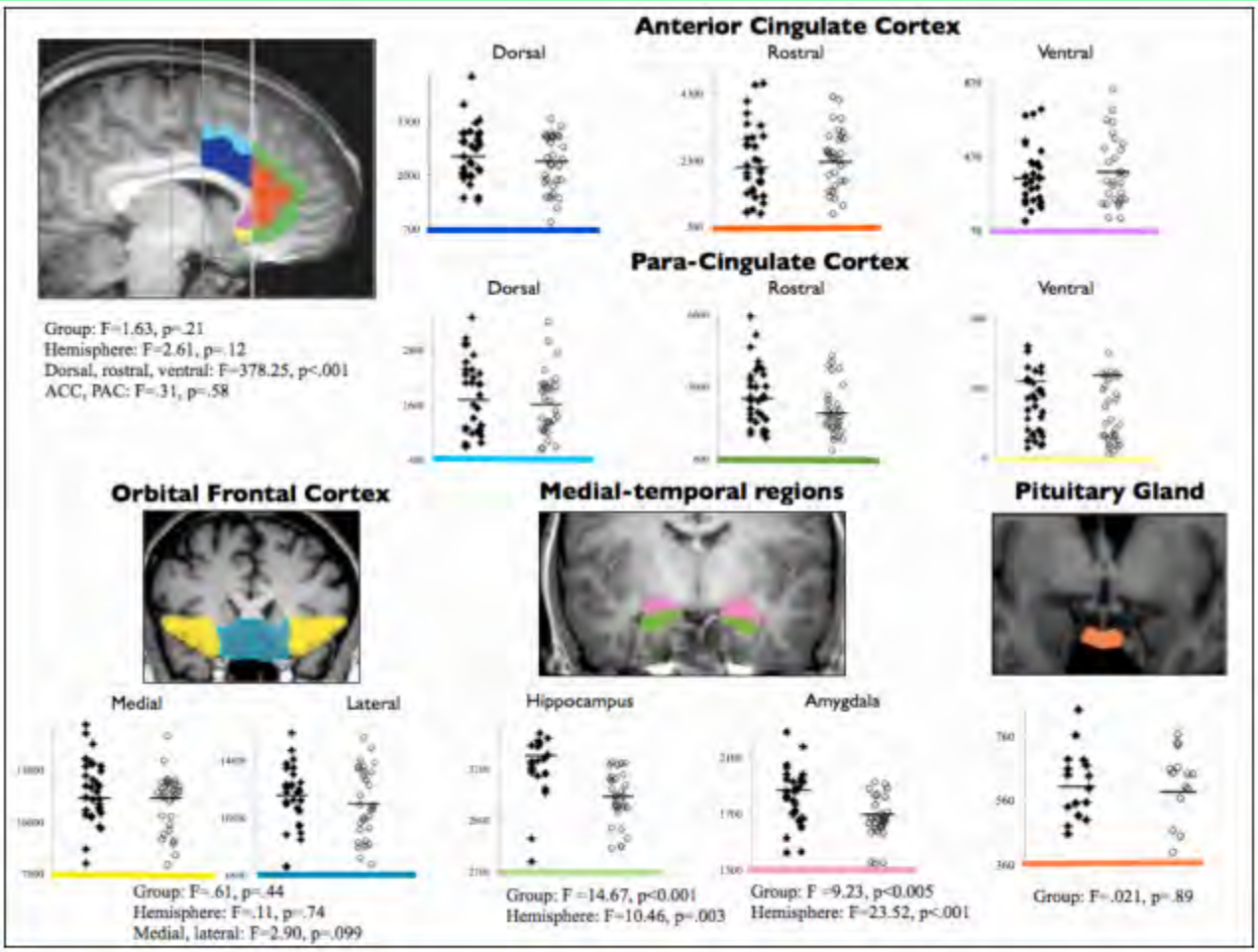


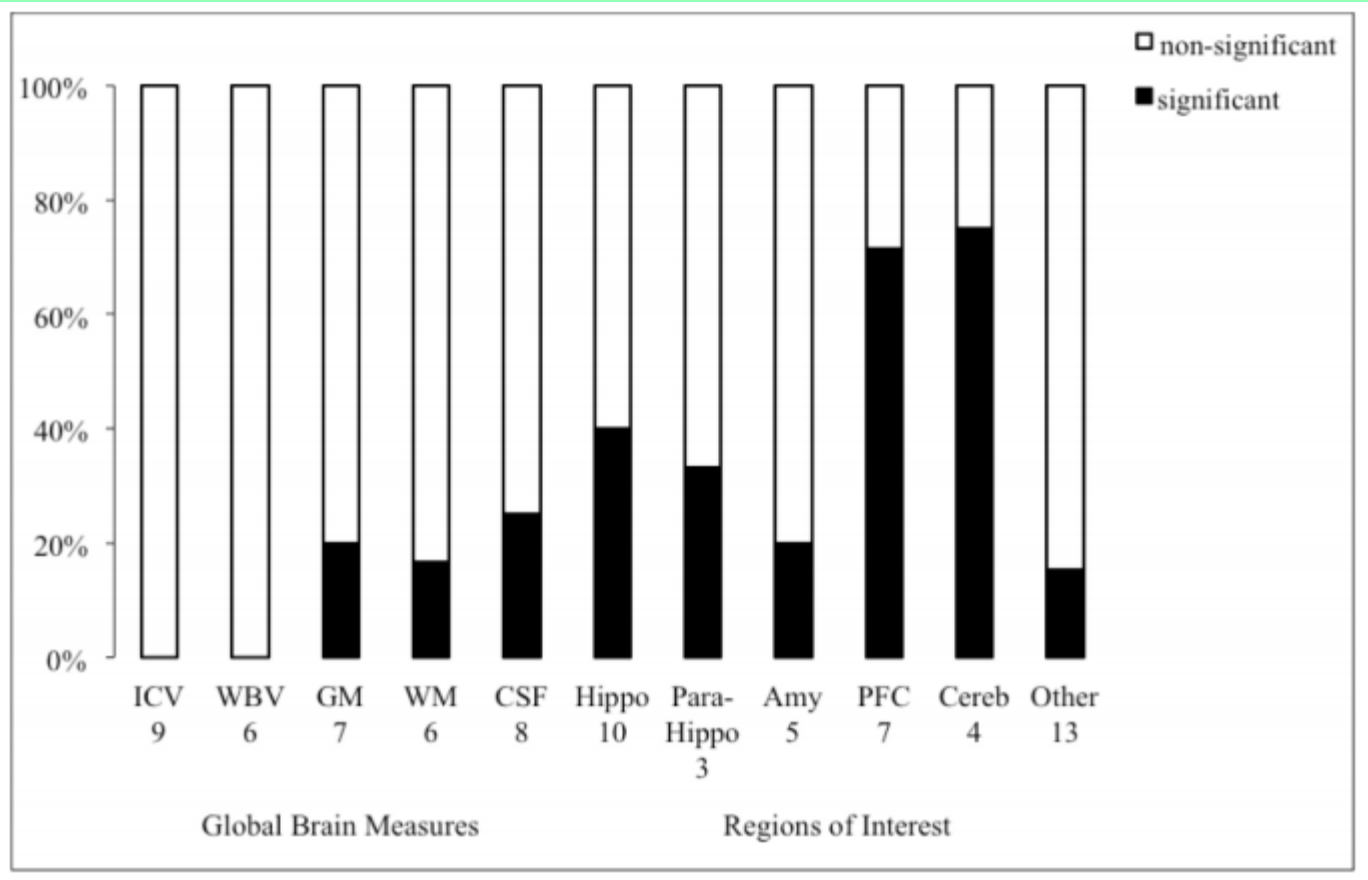
Fig. DS1 Regional brain volumes in chronic cannabis users (white) and non-cannabis-using controls (black). Horizontal lines represent group means for regional brain volumes. For all comparisons, d.f. = 1,29.

Br J Psychiatry. 2015 Jan;206(1):77-8. doi: 10.1192/bjp.bp.114.151407. Epub 2014 Nov 27.

Gross morphological brain changes with chronic, heavy cannabis use.

Lorenzetti V[1], Solowij N[1], Whittle S[1], Fornito A[1], Lubman DI[1], Pantelis C[1], Yücel M[1].

Changes to Brain Areas

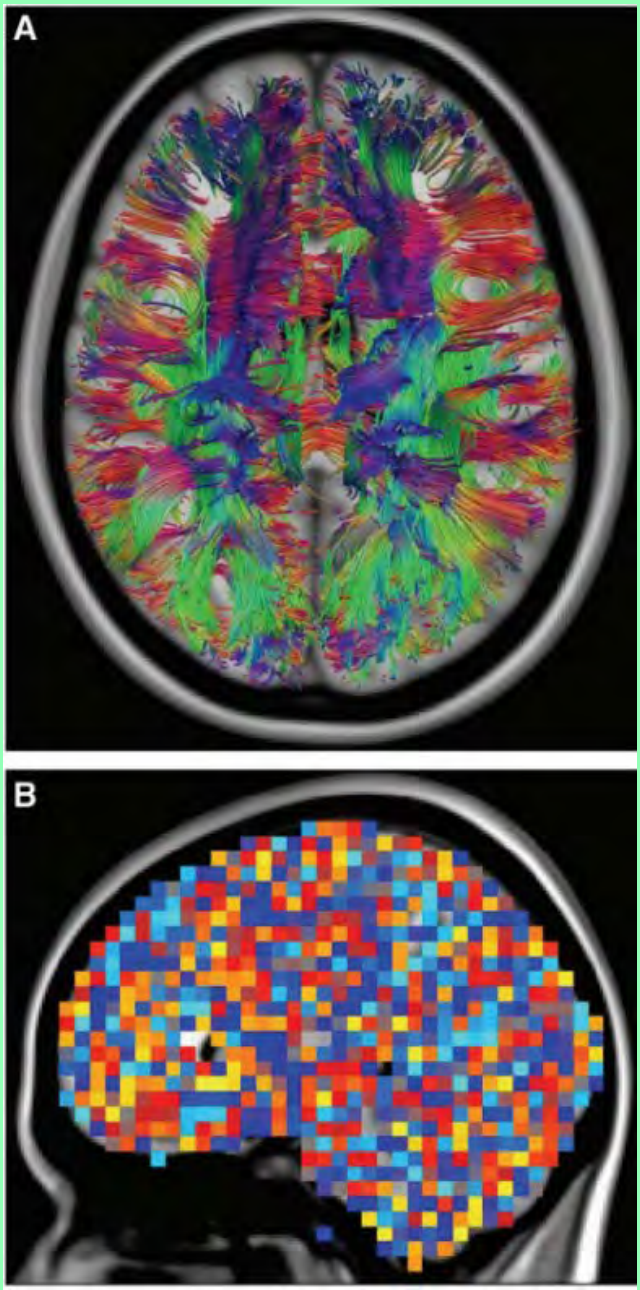


Curr Pharm Des. 2014;20(13):2138-67.

The association between regular cannabis exposure and alterations of human brain morphology: an updated review of the literature.

Lorenzetti V, Solowij N, Fornito A, Lubman DI, Yucel M[1].

White Matter Connectivity Deficits



Brain. 2012 Jul;135(Pt 7):2245-55. doi: 10.1093/brain/aws136. Epub 2012 Jun 4.

Effect of long-term cannabis use on axonal fibre connectivity.

Zalesky A[1], Solowij N, Yücel M, Lubman DI, Takagi M, Harding IH, Lorenzetti V, Wang R, Searle K, Pantelis C, Seal

84% Reduction!!!
Memory – Fimbria of Fornix

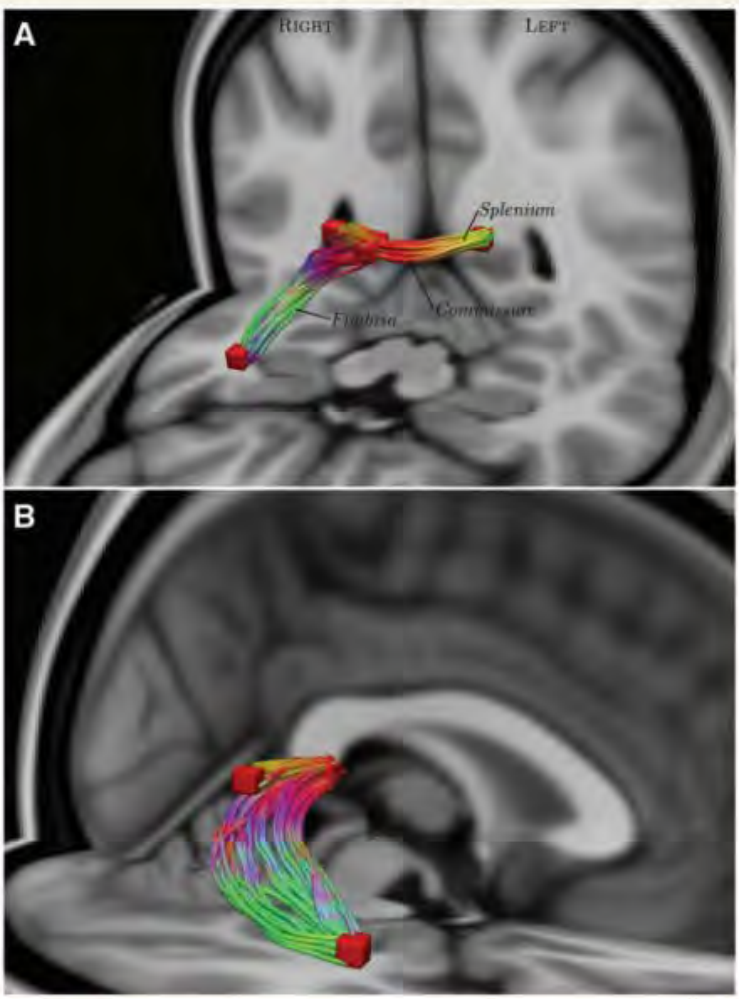


Figure 3 The right fimbria of the hippocampus, hippocampal commissure and splenium comprised fewer streamlines in cannabis users compared to non-users ($P < 0.05$, corrected). Voxels interconnected by fewer streamlines are coloured red and the corresponding streamlines via which they are interconnected are coloured such that: left–right is red, superior–inferior is blue and anterior–posterior is green. **A** and **B** show different oblique views. The splenium and hippocampal commissure are obscured in **B** by the sagittal slice of the underlay image.

Brain. 2012 Jul;135(Pt 7):2245-55. doi: 10.1093/brain/aws136. Epub 2012 Jun 4.

Effect of long-term cannabis use on axonal fibre connectivity.

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88% Reduction!!!!
Memory Splenium to Precuneus

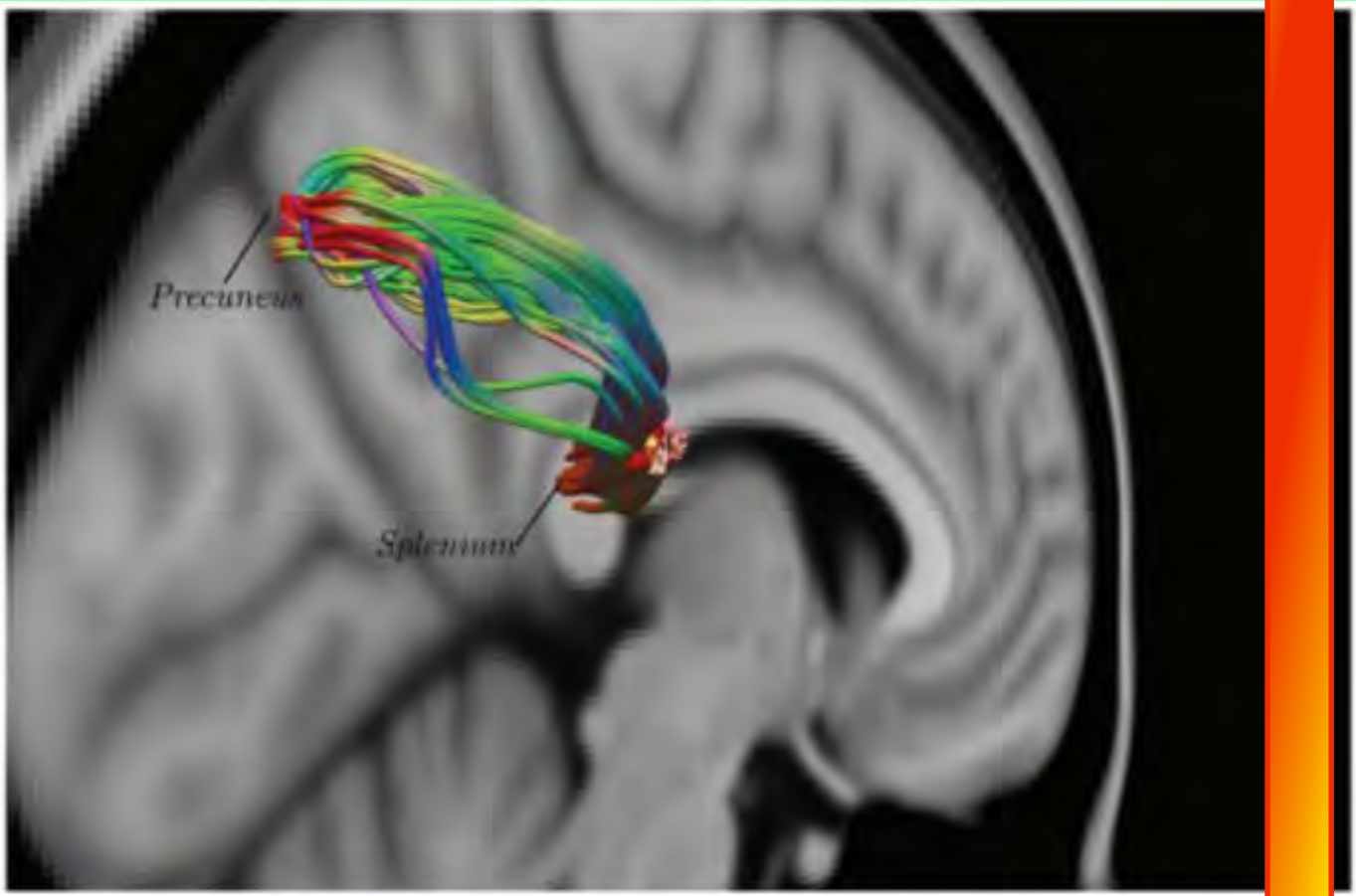

Figure 4 Fewer streamlines interconnected the right precu us with the splenium in cannabis users compared to non-user ($P < 0.05$, corrected). Voxels interconnected by fewer stre lines are coloured red and the corresponding streamlines v which they are interconnected are coloured such that: left- t is red, superior–inferior is blue and anterior–posterior is green.

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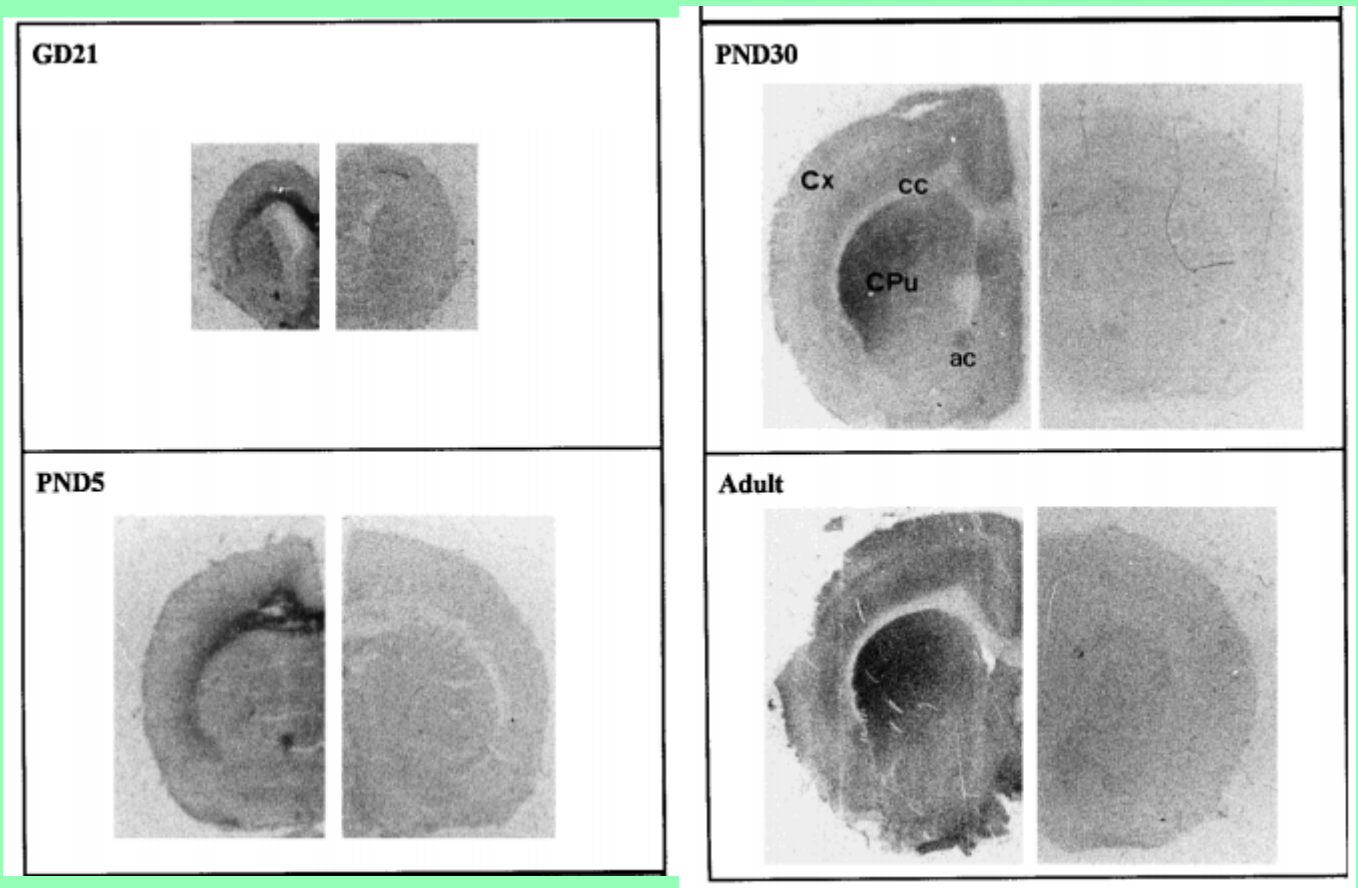
Zalesky A[1], Solowij N, Yücel M, Lubman DI, Takagi M, Harding IH, Lorenzetti V, Wang R, Searle K, Pantelis C, Seal M

High Concentration CB1R's on Developing Rat Brain



Synapse. 1997 Jul;26(3):317-23.

Atypical location of cannabinoid receptors in white matter areas during rat brain development.

Romero J[1], Garcia-Palomero E, Berrendero F, Garcia-Gil L, Hernandez ML, Ramos JA, Fernández-Ruiz JJ.

CB1R Changes with CB1R Stimulation

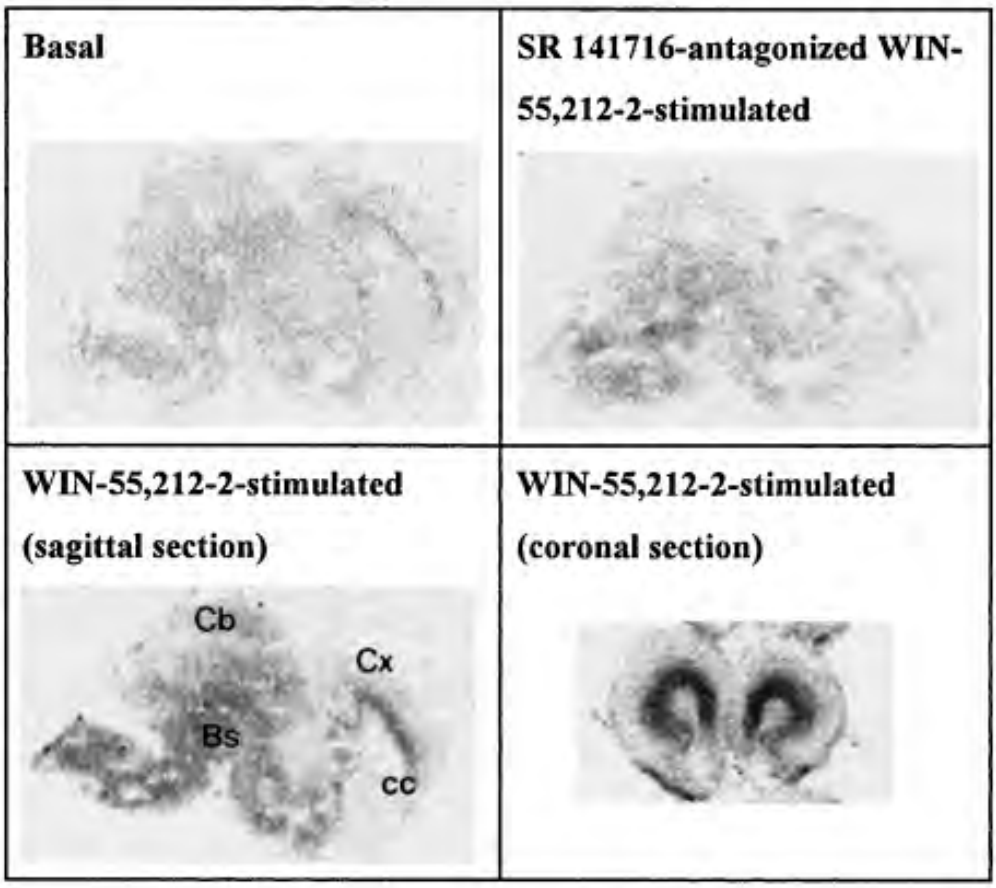


Fig. 2. Representative autoradiograms corresponding to basal (**left top**), WIN-55,212-2-stimulated (**bottom**) and SR141716-antagonized WIN-55,212-2-stimulated (**right top**) [^{35}S]-GTPγS binding in a brain section (5×) obtained from male rat brains at fetal age (GD21). Autoradiograms were processed according to the conditions described in Materials and Methods. (Cx, cortex; cc, corpus callosum; Cb, cerebellum; Bs, brainstem.)

Synapse. 1997 Jul;26(3):317-23.

Atypical location of cannabinoid receptors in white matter areas during rat brain development.

Romero J[1], Garcia-Palomero E, Berrendero F, Garcia-Gil L, Hernandez ML, Ramos JA, Fernández-Ruiz JJ.

CB1R Staining in Embryo & Brain

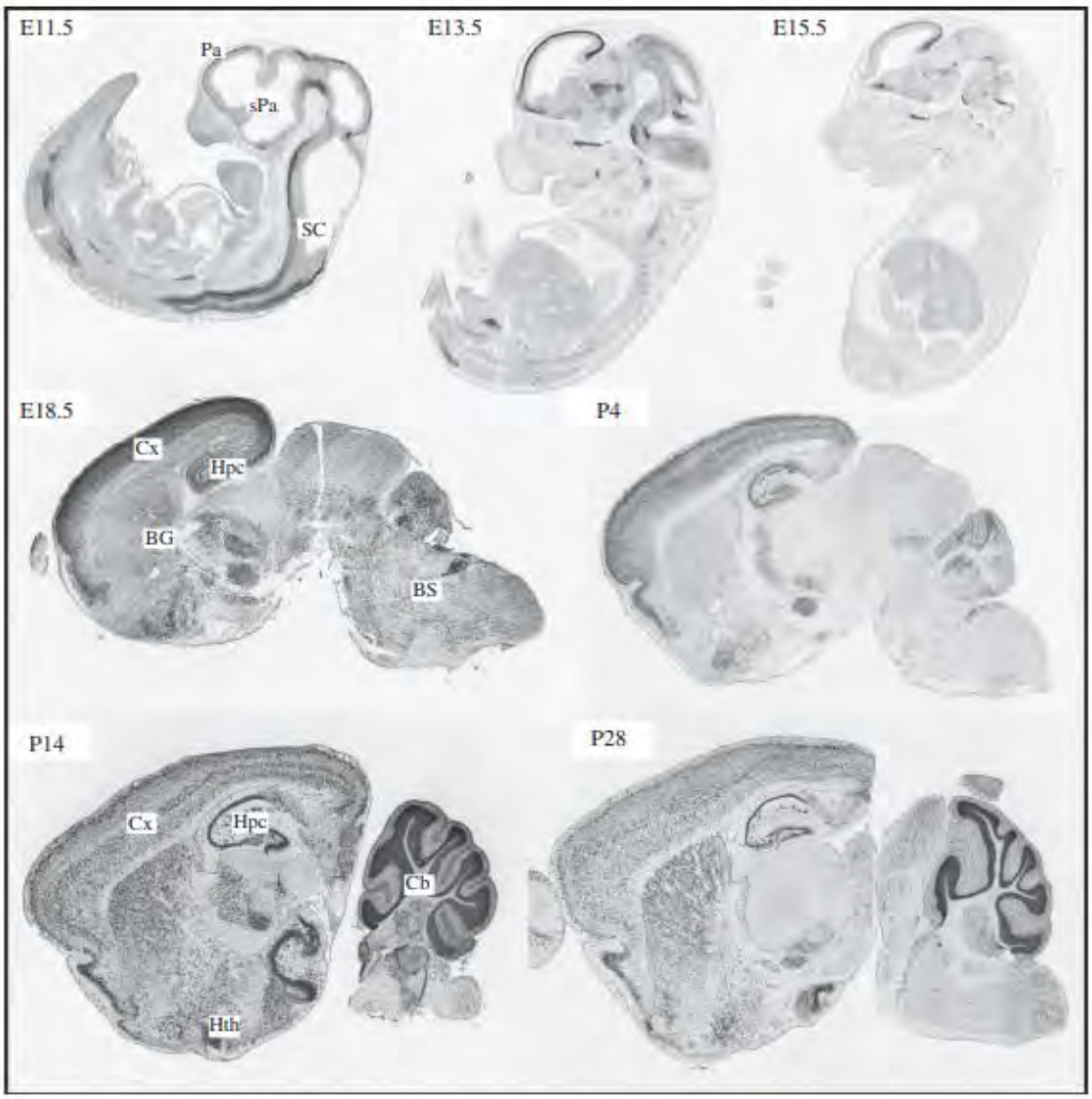


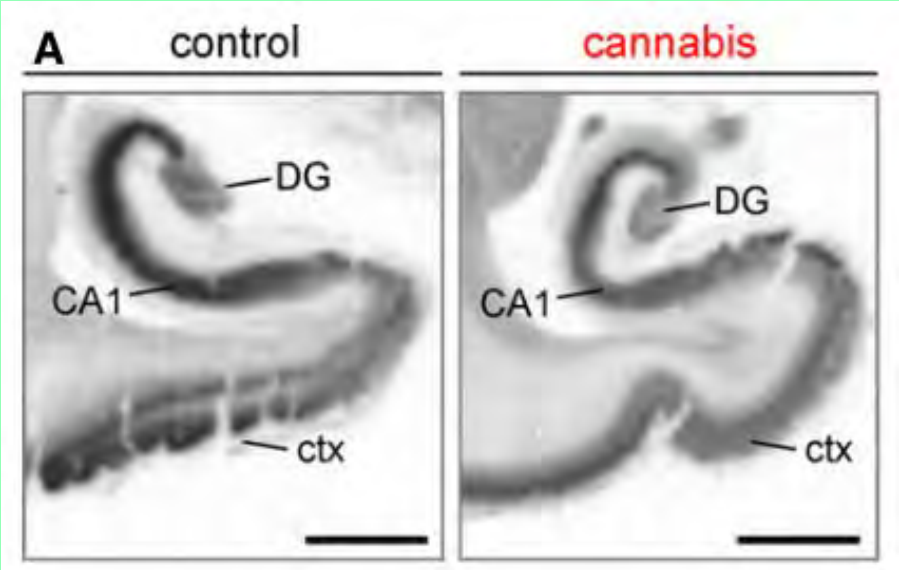
Figure 1. Expression pattern of the CB_1 cannabinoid receptor mRNA at different developmental stages. CB_1 mRNA *in situ* hybridization in the developing mouse nervous system is shown at the indicated stages. BG, basal ganglia; BS, brainstem; Cx, cortex; Hpc, hippocampus; Hth, hypothalamus; Pa, pallium; sPa, subpallium; SC, spinal cord. Published with permission of Allen Developing Mouse Brain Atlas, Seattle (WA), Allen Institute for Brain Science. Copyright ©2009. Available at: http://developingmouse.brain-map.org.

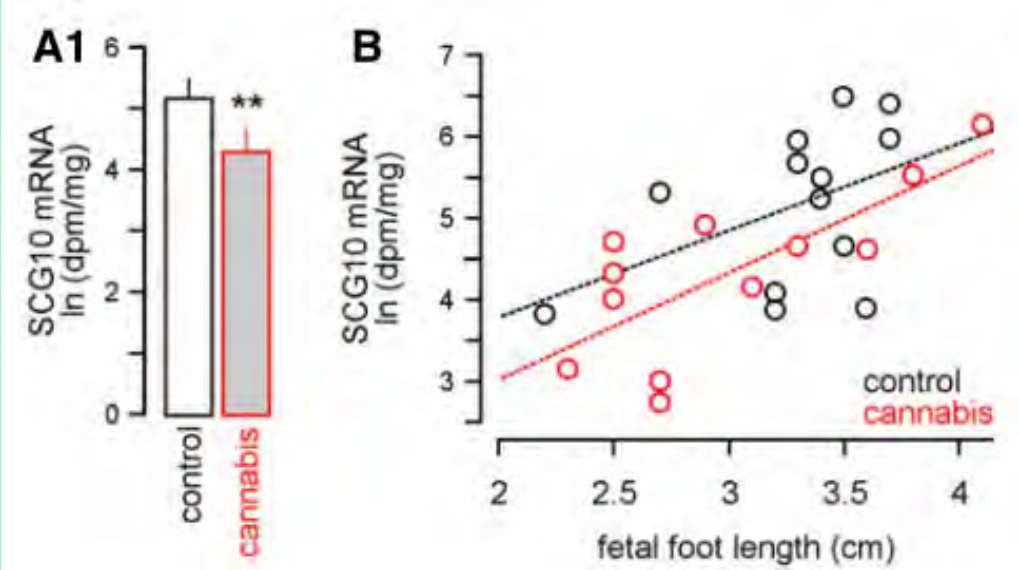
Philos Trans R Soc Lond B Biol Sci. 2012 Dec 5;367(1607):3229-41. doi: 10.1098/rstb.2011.0385.

Endocannabinoids via CB_1 receptors act as neurogenic niche cues during cortical development.

Díaz-Alonso J[1], Guzmán M, Galve-Roperh I.

Stathmin in the Hippocampus



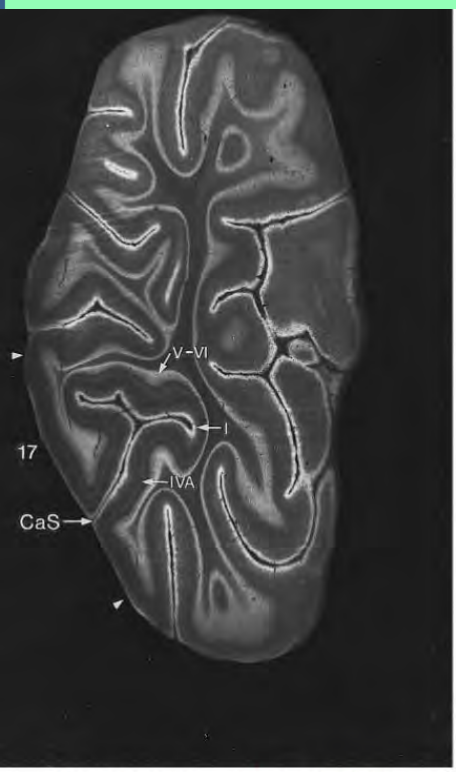


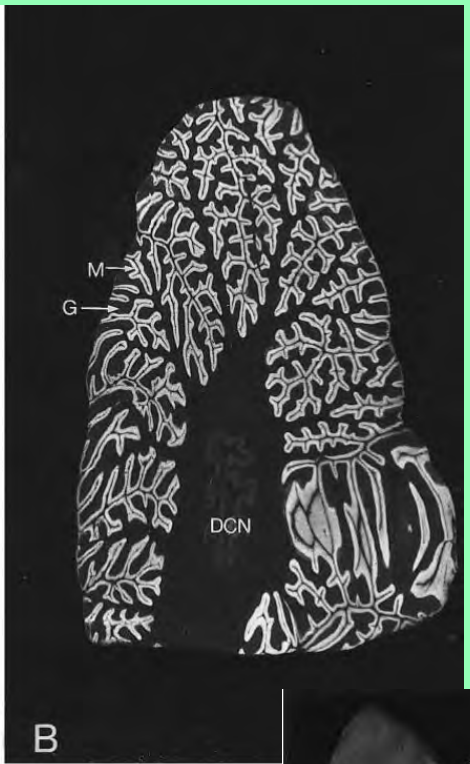
EMBO J. 2014 Apr 1;33(7):668-85. doi: 10.1002/embj.201386035. Epub 2014 Jan 27.

Miswiring the brain: Δ9-tetrahydrocannabinol disrupts cortical development by inducing an SCG10/stathmin-2 degradation pathway.

Tortoriello G[1], Morris CV, Alpar A, Fuzik J, Shirran SL, Calvigioni D, Keimpema E, Botting CH, Reinecke K, Herdegen T, Courtney M, Hurd YL, Harkany T.

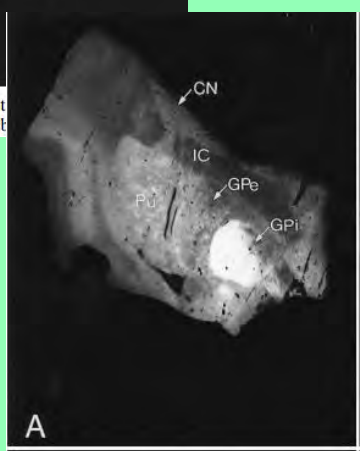
Human Neonatal Brain CB1R Staining 6 Months Gestational Age

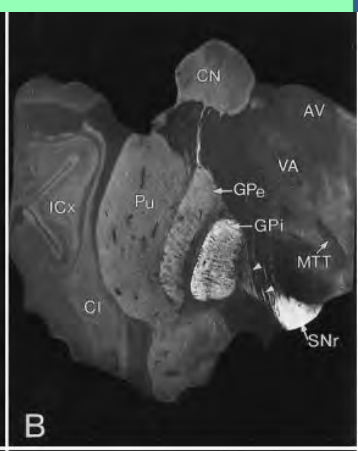




Cortex & Cerebellum

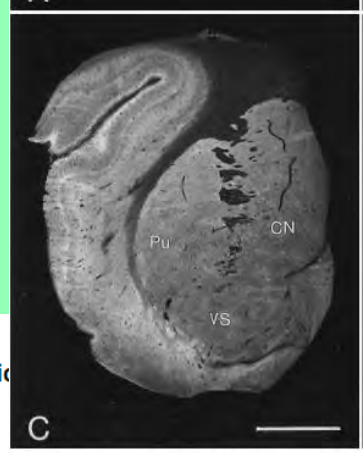
Fig. 6. Autoradiograms showing the distribution of cannabinoid receptors in the neonat
(case N2; six months of age). (A) The occipital cortex. (B) The cerebellum. Scale b





Limbic & Midbrain Structures

117



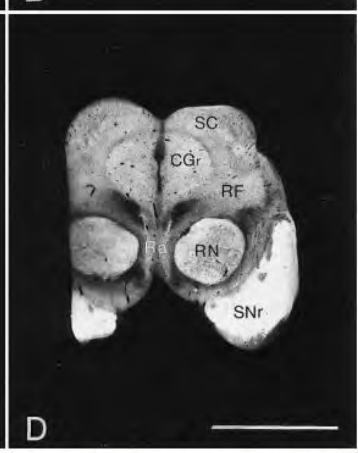


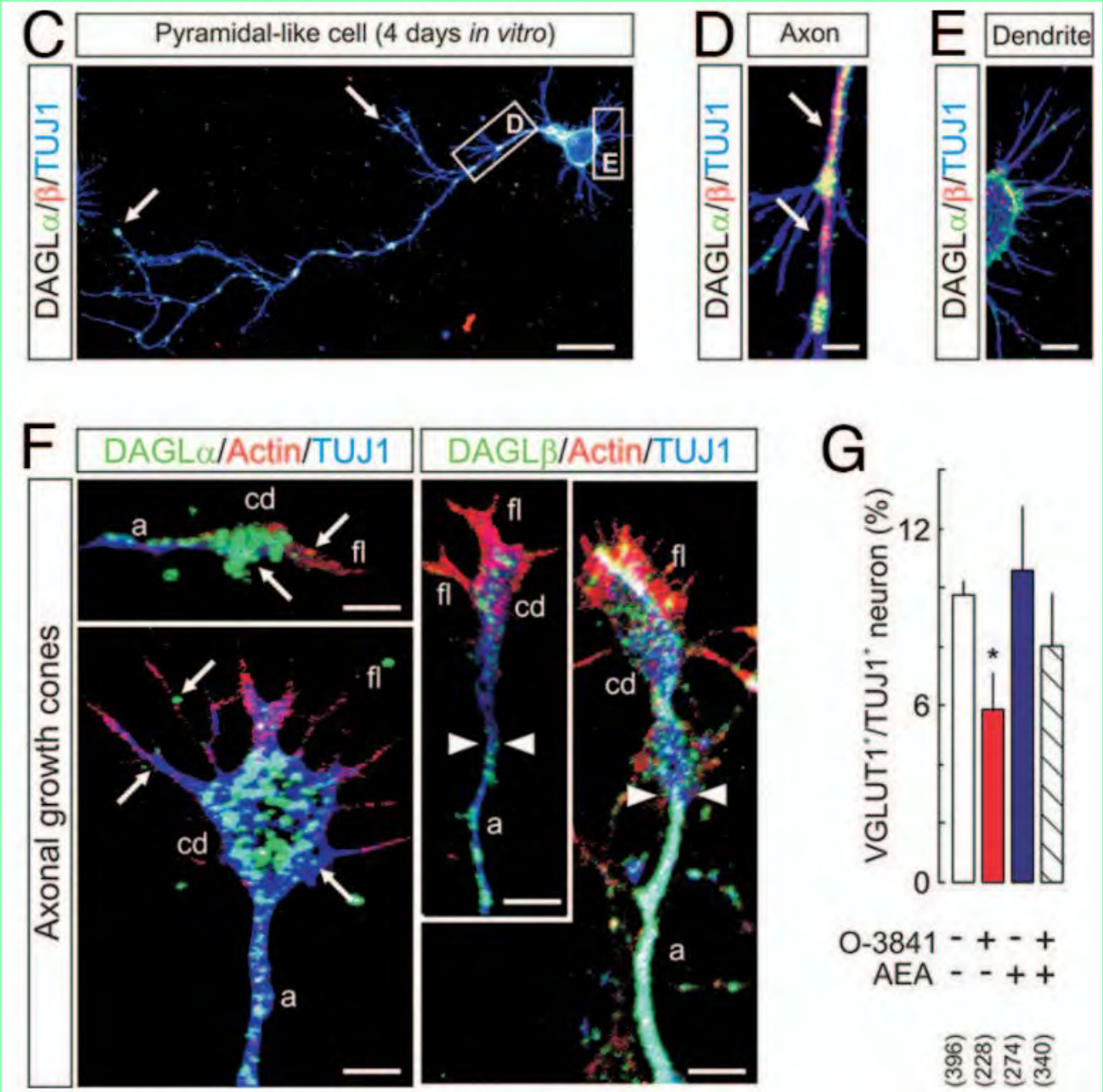
Fig. 7. Autoradiograms showing the distribution of cannabinoid receptors in the lenticular nucleus (A) of the fetal human brain (case FH1; 33 weeks of gestation), and in the lenticular nucleus (B), striatal complex (C) and midbrain (D) of the neonatal human brain (case N2; six months of age). The arrowheads in B indicate cannabinoid receptor binding sites in fibre bundles coursing from the level of the lenticular nucleus towards the substantia nigra in the midbrain. Scale bar=1 cm.

Neuroscience. 1997 Mar;77(2):299-318.

Cannabinoid receptors in the human brain: a detailed anatomic and quantitative autoradiographic study in the fetal, neonatal and adult human brain.

Glass M[1], Dragunow M, Faull RL.

CB1R's n Axonal Growth Cones - Connectivity Guidance Systems

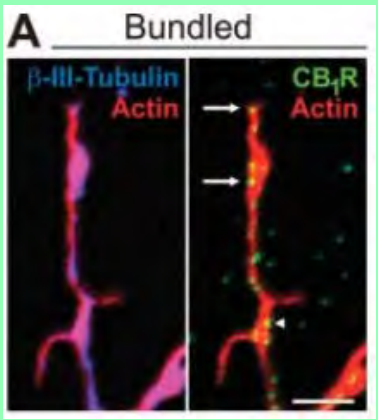


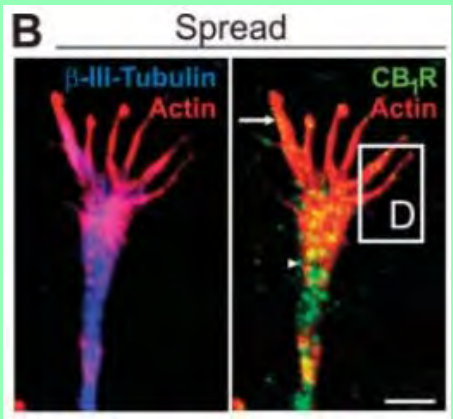
Proc Natl Acad Sci U S A. 2008 Jun 24;105(25):8760-5. doi: 10.1073/pnas.0803545105. Epub 2008 Jun 18.

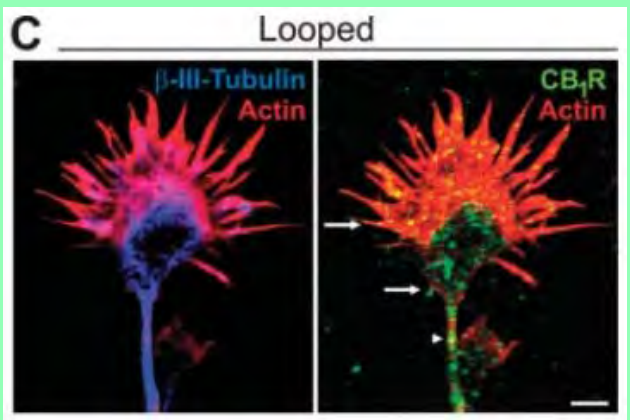
Endocannabinoid signaling controls pyramidal cell specification and long-range axon patterning.

Mulder J[1], Aguado T, Keimpema E, Barabás K, Ballester Rosado CJ, Nguyen L, Monory K, Marsicano G, Di Marzo V, Hurd YL, Guillemot F, Mackie K, Lutz B, Guzmán M, Lu HC, Galve-Roperh I, Harkany T.

CB1R's on Axonal Growth Cones





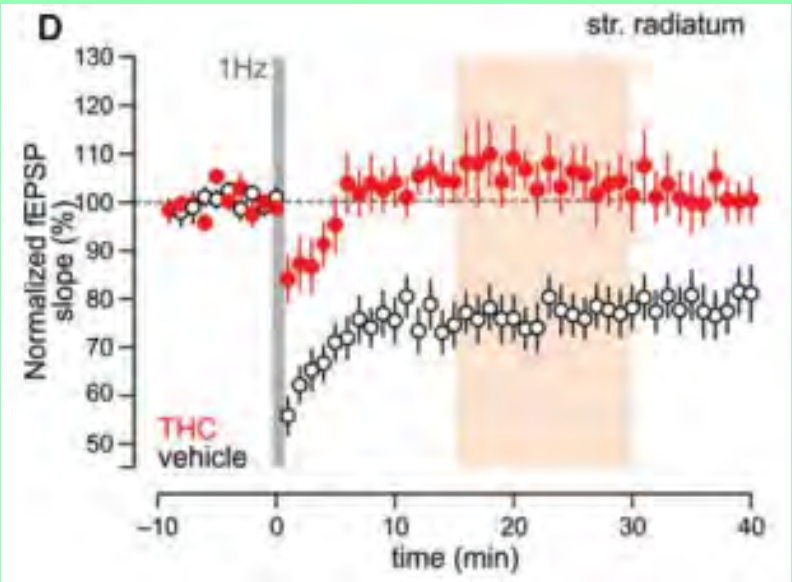


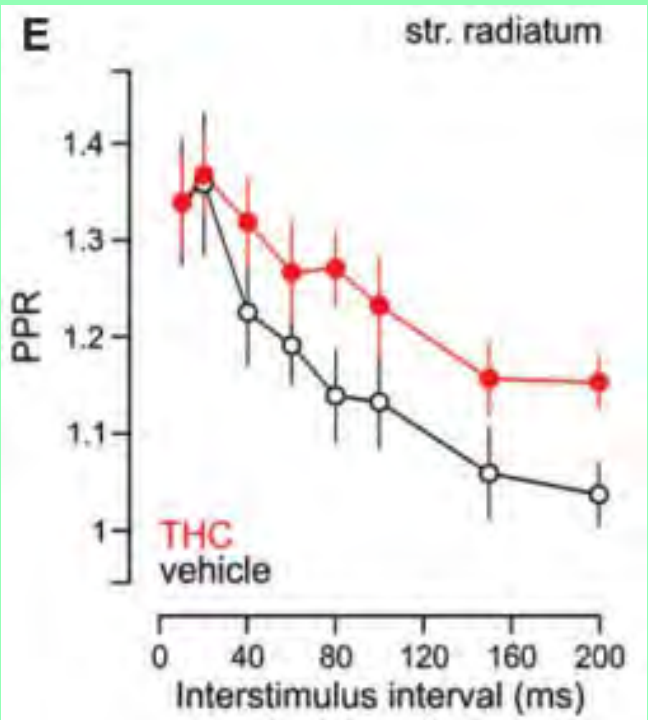
Science. 2007 May 25;316(5828):1212-6.

Hardwiring the brain: endocannabinoids shape neuronal connectivity.

Berghuis P[1], Rajnicek AM, Morozov YM, Ross RA, Mulder J, Urbán GM, Monory K, Marsicano G, Matteoli M, Canty A, Irving AJ, Katona I, Yanagawa Y, Rakic P, Lutz B, Mackie K, Harkany T.

Altered Excitation Following Cannabis



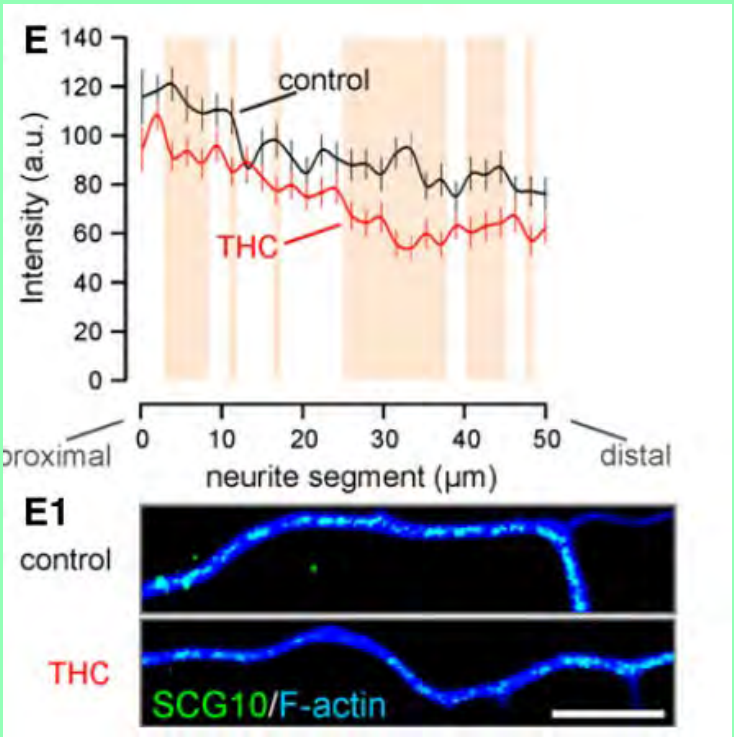


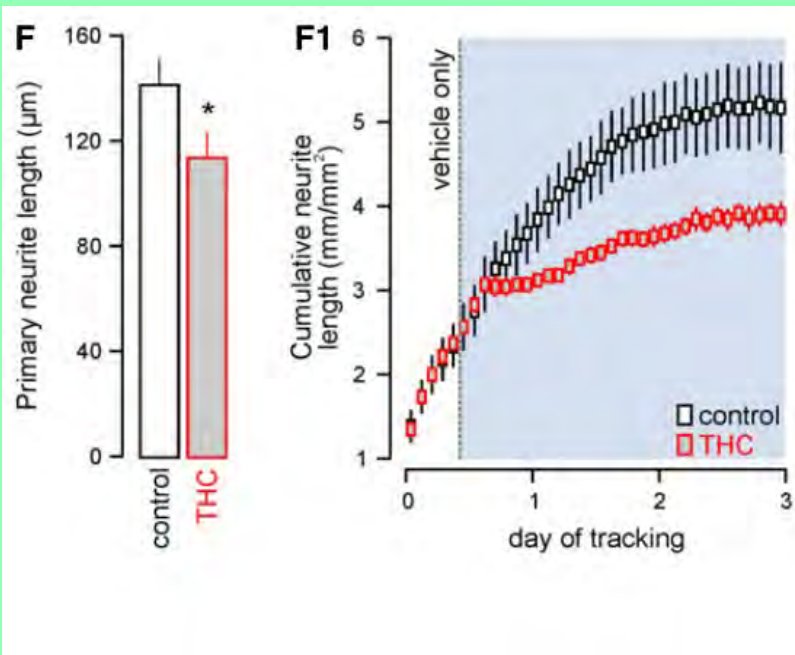
EMBO J. 2014 Apr 1;33(7):668-85. doi: 10.1002/embj.201386035. Epub 2014 Jan 27.

Miswiring the brain: Δ9-tetrahydrocannabinol disrupts cortical development by inducing an SCG10/stathmin-2 degradation pathway.

Tortoriello G[1], Morris CV, Alpar A, Fuzik J, Shirran SL, Calvigioni D, Keimpema E, Botting CH, Reinecke K, Herdegen T, Courtney M, Hurd YL, Harkany T.

Shorter Thinner Neurites





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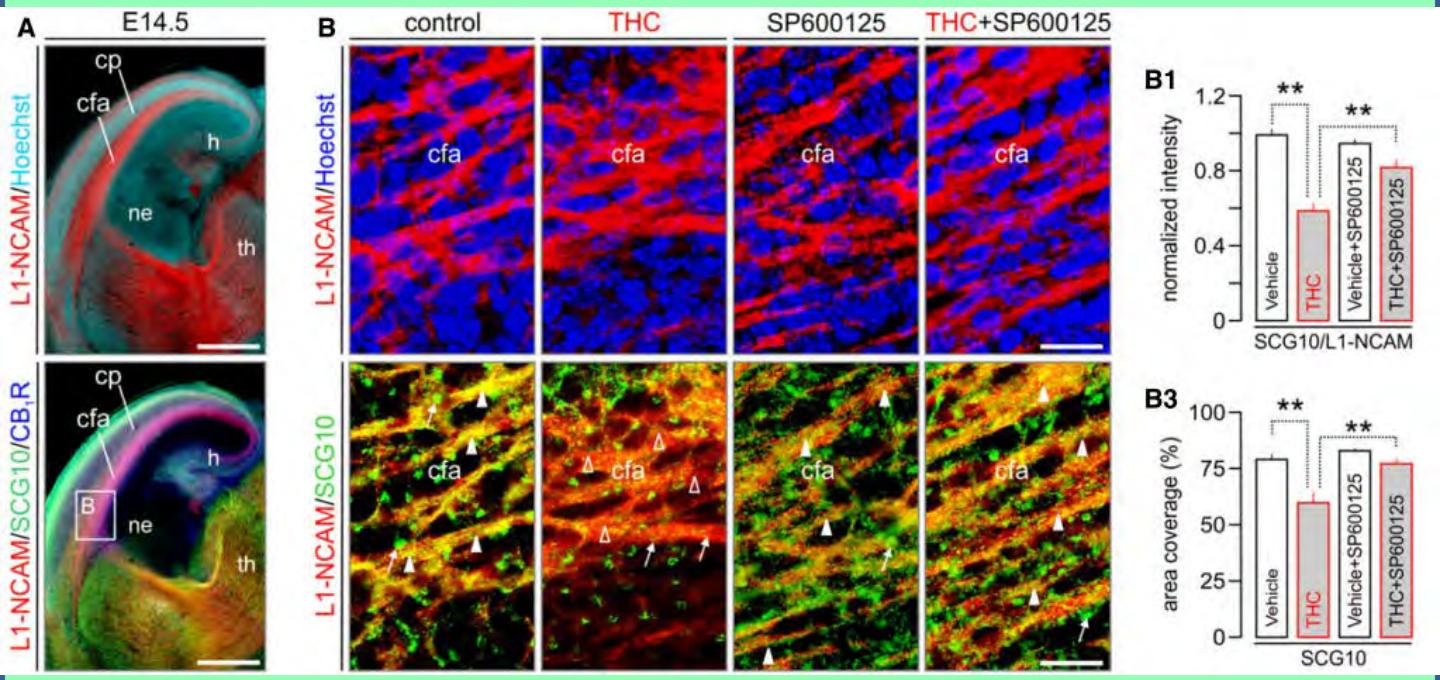
Reduced Nerve Cells



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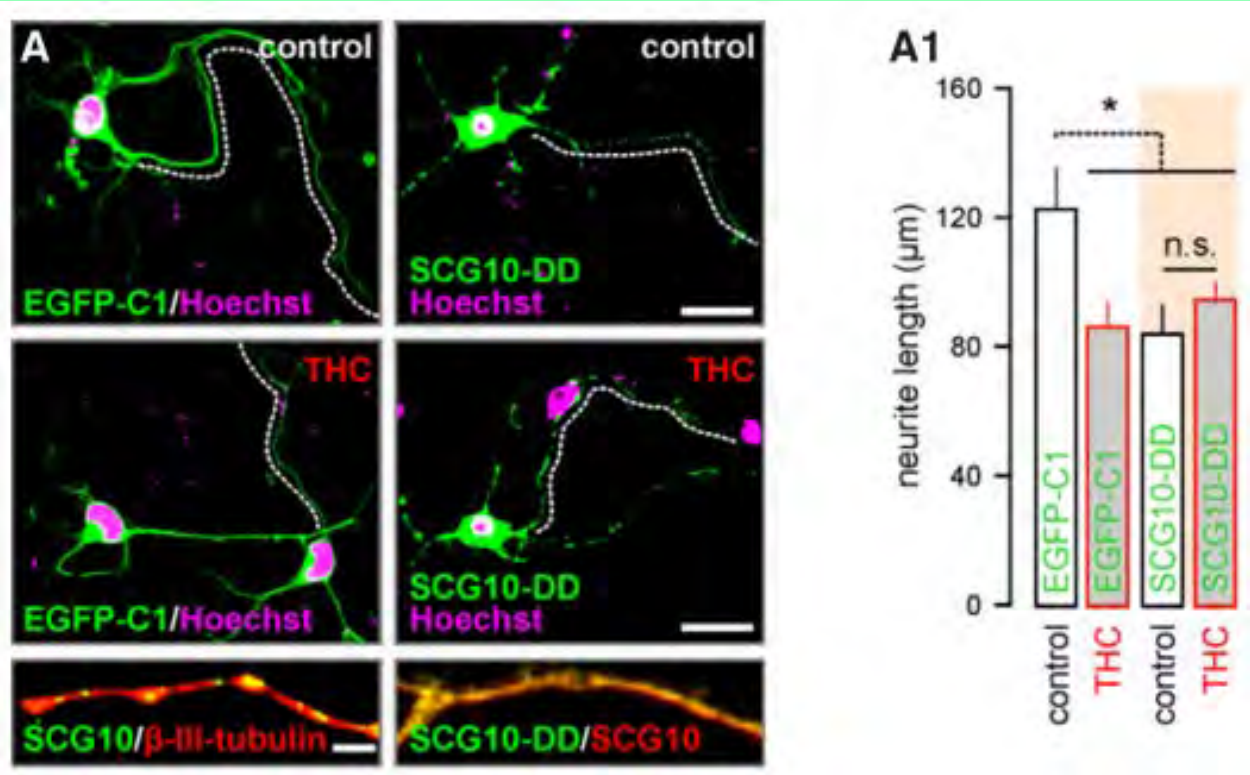
Reduced Neurite Length



EMBO J. 2014 Apr 1;33(7):668-85. doi: 10.1002/embj.201386035. Epub 2014 Jan 27.

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CB1R's in Neural and Cortex Development

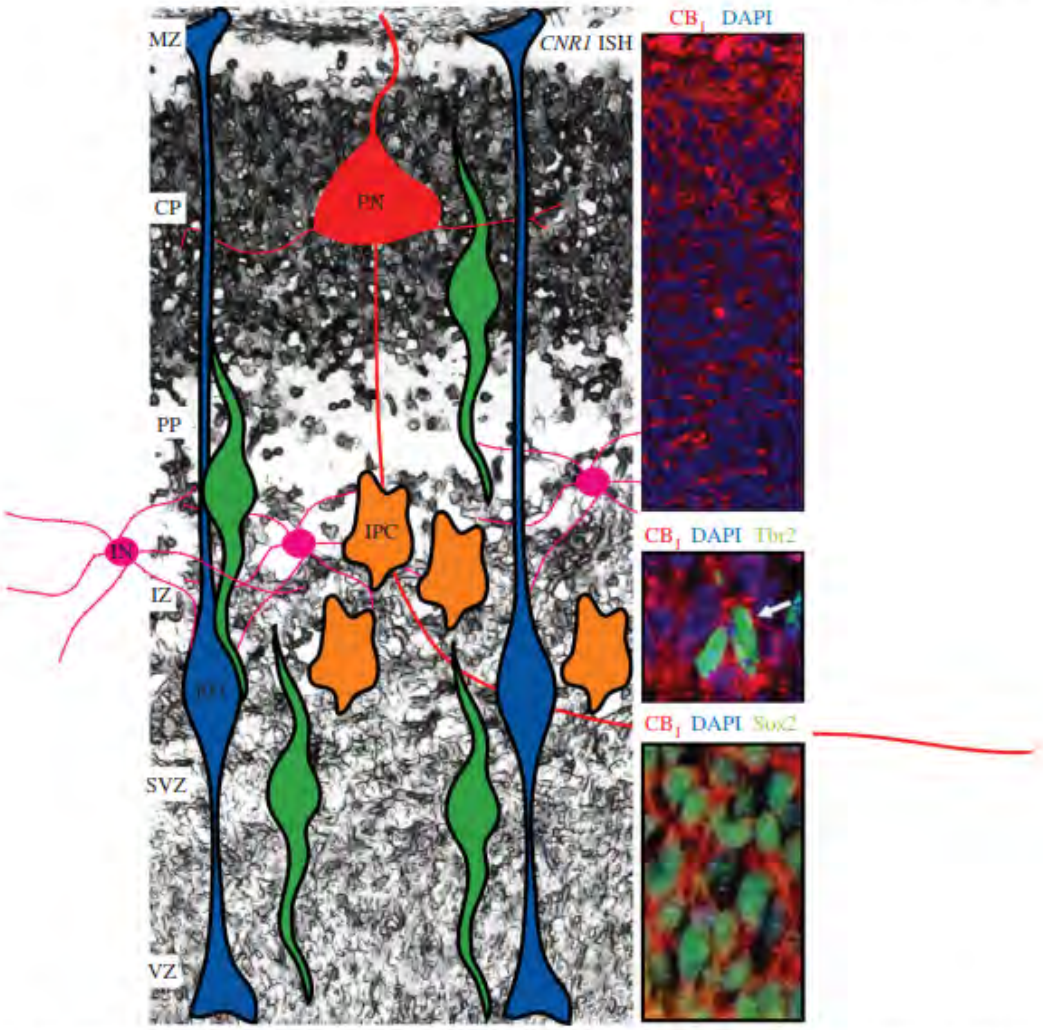

Figure 2. CB_1 cannabinoid receptor expression during cortical development. The CB_1 receptor is present in the developing cortex, showing increasing expression levels from undifferentiated to differentiated projection neurons (PNs). The CB_1 receptor is present in Cajal–Retzius cells of the marginal zone (MZ) and apical and basal progenitors in the ventricular and subventricular (VZ/SVZ) proliferative area. Representative immunofluorescence images showing the colocalization of the CB_1 receptor in radial glial (RG) progenitors and intermediate amplifying progenitor cells (IPCs) as identified with Sox2 and Tbr2 antibodies, respectively [13] (copyright National Academy of Sciences, USA 2009). Higher expression levels of the CB_1 receptor are evident in maturing neurons that have reached the CP, that correspond to locally generated PNs. CB_1 receptor is present in certain interneuron (IN) populations that reach the pallium upon tangential migration from the ganglionic eminences. Image background corresponds to a representative *in situ* hybridization of the *CNR1* mRNA at E.16.5 (by C. Hoffman and B. Lutz, Johannes Gutenberg University Mainz, Germany).

124

Philos Trans R Soc Lond B Biol Sci. 2012 Dec 5;367(1607):3229-41. doi: 10.1098/rstb.2011.0385.

Endocannabinoids via CB_1 receptors act as neurogenic niche cues during cortical development.

Díaz-Alonso J[1], Guzmán M, Galve-Roperh I.

eCB's in Cortex Development

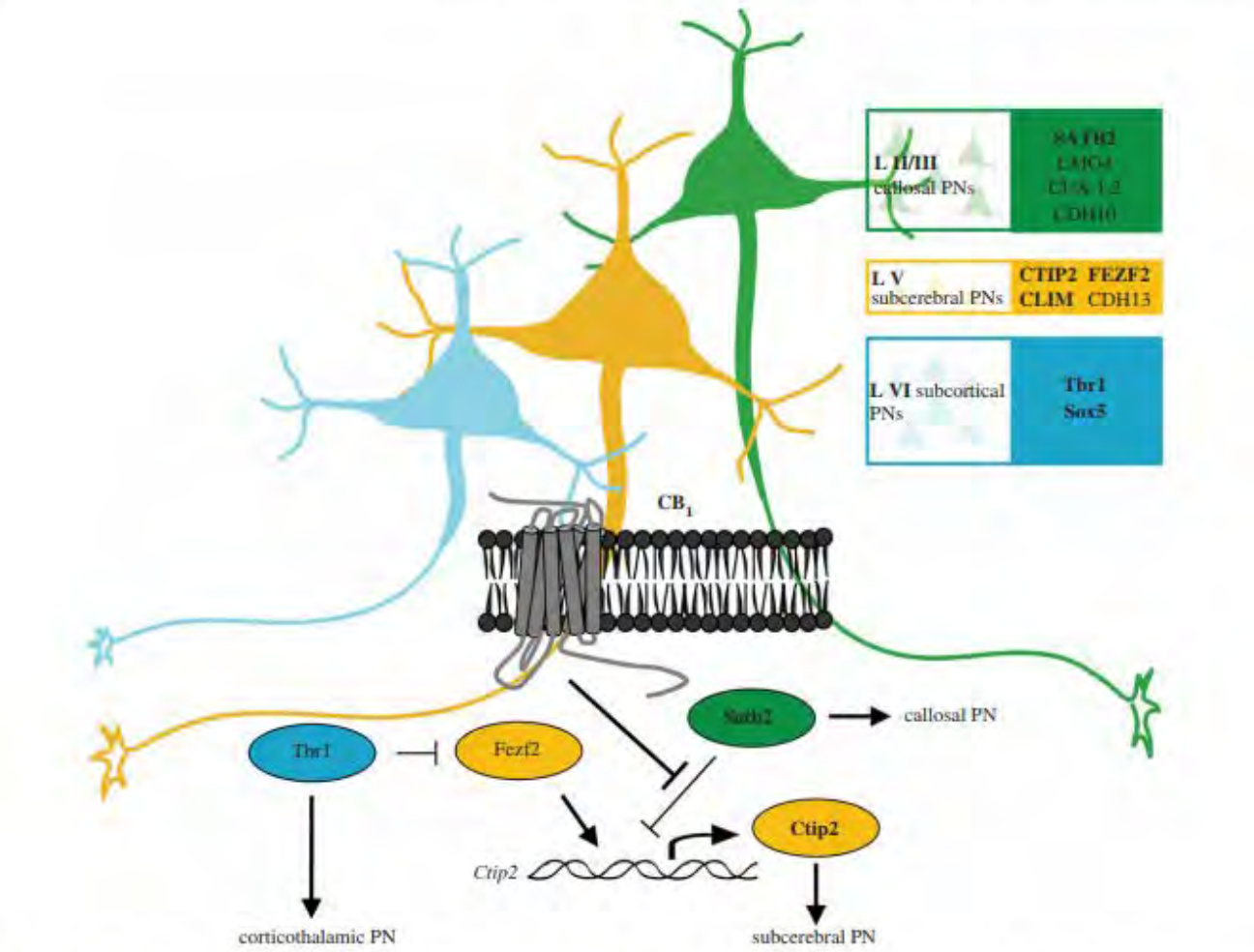

Figure 4. CB_1 cannabinoid receptor signalling and neuronal differentiation. CB_1 receptor activity in differentiating cortical neurons is coupled by as yet unknown mechanisms to the modulation of the neurogenic transcription factor code Ctip2-Satb2. CB_1 receptors are positively coupled to COUP-TF II interacting protein 2 (Ctip2) and negatively to Satb2-mediated repression of Ctip2. Thus, CB_1 receptor activity tunes the transcriptional neurogenic programme responsible for upper and lower cortical neuron differentiation. Transcription factors involved in cortical laminar specification regulated by CB_1 receptor are indicated in bold letters.

125

Philos Trans R Soc Lond B Biol Sci. 2012 Dec 5;367(1607):3229-41. doi: 10.1098/rstb.2011.0385.

Endocannabinoids via CB_1 receptors act as neurogenic niche cues during cortical development.

Díaz-Alonso J[1], Guzmán M, Galve-Roperh I.

CB1R's Preferentially Expressed in Human Cord Blood iPSC's

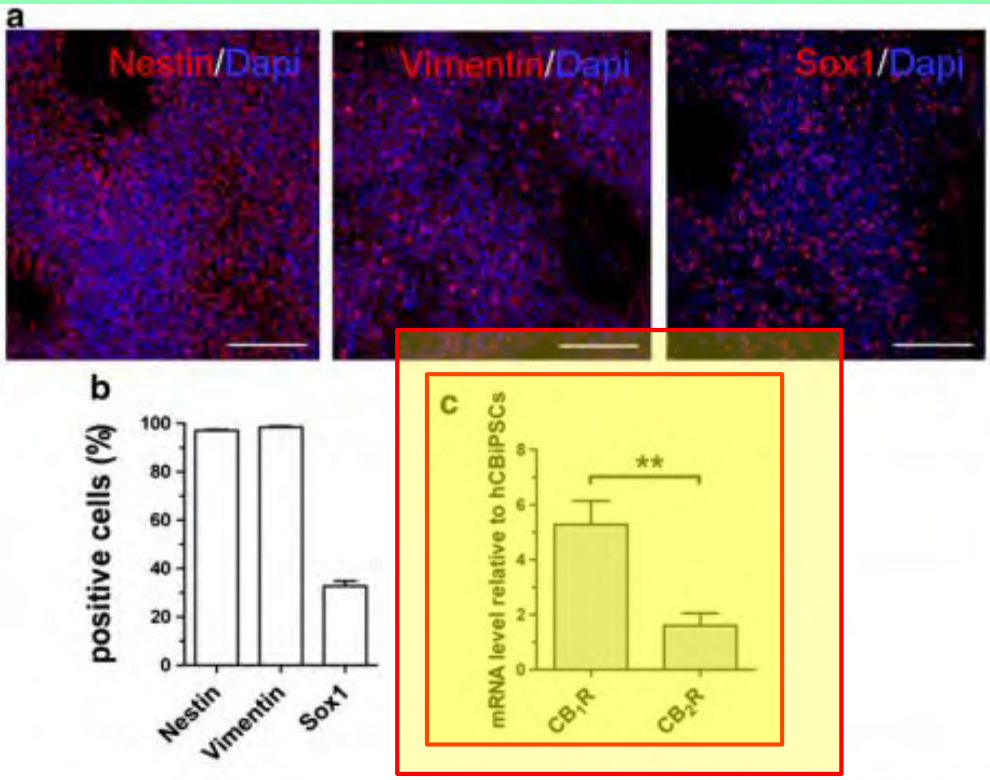

Figure 1 A homogeneous population of smNPCs derived from hCBiPSCs expressed CB_1R over CB_2R. (A + B) smNPCs uniformly expressed the neural progenitor markers nestin and vimentin and stained positive for Sox1 (33%). Nuclei were counterstained with Dapi. Bar graphs represent 50 µm. (C) qRT-PCR revealed significantly higher levels of the nervous system-specific CB_1R in smNPCs than CB_2R, which is more abundant in the immune system ($p = 0.0086$, Mann–Whitney test). Data are given relative to undifferentiated hCBiPSCs

126

Addict Biol. 2017 Sep;22(5):1329-1342. doi: 10.1111/adb.12394. Epub 2016 Mar 30.

Functional effects of cannabinoids during dopaminergic specification of human neural precursors derived from induced pluripotent stem cells.

Stanslowsky N[1], Jahn K[2], Venneri A[1], Naujock M[1,3], Haase A[4], Martin U[4,5], Frieling H[2,3], Wegner F[1,3].

Hi Dose CB's Reduce Brain Maturation iPSC NSC's Synaptic Currents

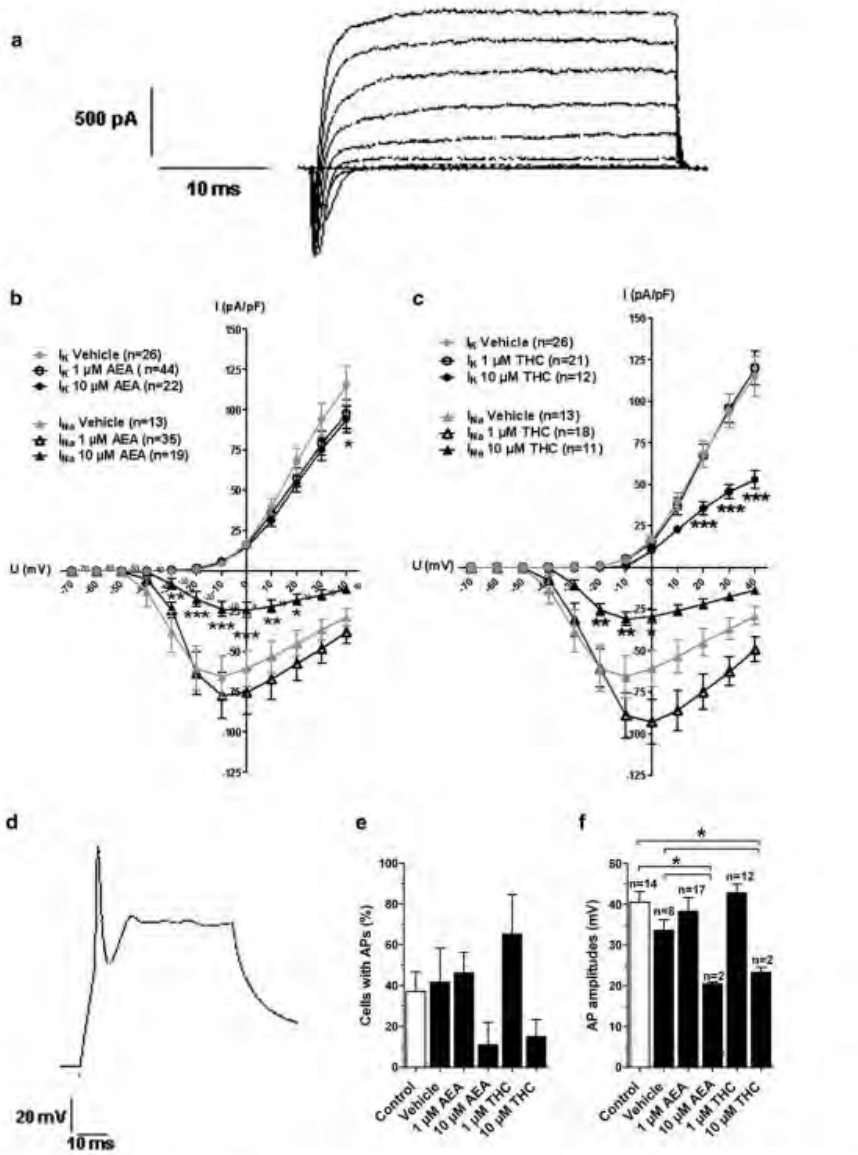

Figure 5 Treatment of differentiating smNPCs with higher dosages of CBs reduced voltage-gated ion currents and AP amplitudes. (A) Exemplary illustration of sodium inward (I_{Na}) and potassium outward currents (I_K) in smNPC-derived neurons after 21 days of differentiation. Current–voltage plots of neurons treated with 10-µM AEA (B) or 10-µM THC (C) showed significantly reduced I_{Na} and I_K compared to vehicle treated controls. Current amplitudes were normalized for cell capacitances and are plotted as means ± SEM. *P*-values were calculated using two-way ANOVA with Bonferroni post-test (***$p < 0.001$, **$p < 0.01$, *$p < 0.05$). (D) AP of a smNPC-derived neuron after 21 days of differentiation. (E) Under each condition a similar amount of around 40% of the cells fired APs. Only the cells that were incubated with 10-µM AEA or THC showed a tendency to lower percentages of cells with APs. (F) AP amplitudes were significantly reduced in cells co-incubated with 10-µM AEA or THC. Values were determined from three differentiation experiments as means ± SEM. *P*-values were determined using a Mann–Whitney test (*$p < 0.05$)

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Addict Biol. 2017 Sep;22(5):1329-1342. doi: 10.1111/adb.12394. Epub 2016 Mar 30.

Functional effects of cannabinoids during dopaminergic specification of human neural precursors derived from induced pluripotent stem cells.

Stanslowsky N[1], Jahn K[2], Venneri A[1], Naujock M[1,3], Haase A[4], Martin U[4,5], Frieling H[2,3], Wegner F[1,3].

Hi dose CB's Alters iPSC NSC Synaptic Activity

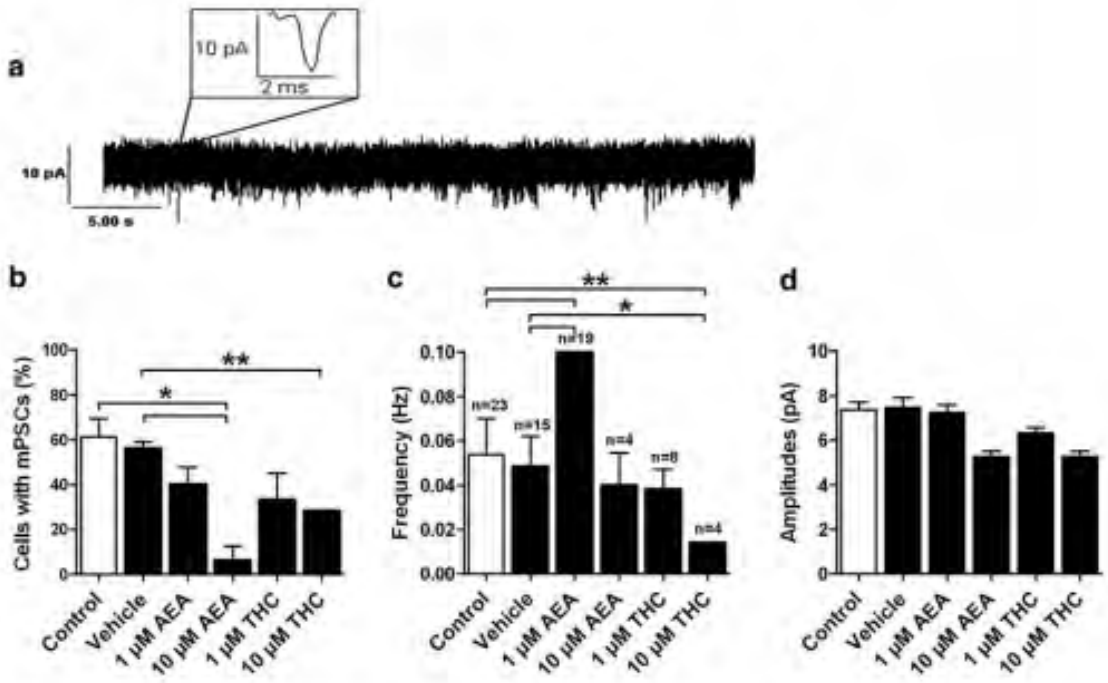


Figure 6 High concentrations of CBs reduced the percentage of smNPC-derived neurons with spontaneous synaptic activity while 1 µM AEA increased the frequency of synaptic currents. (A) Exemplary illustration of a current trace representing miniature spontaneous post-synaptic currents (mPSCs) recorded from a single cell after 21 days of differentiation. (B) The percentage of cells with mPSCs was significantly reduced by treatment with 10 µM AEA or THC. (C) Cells incubated with 1 µM AEA showed elevated current frequencies, while frequencies of cells differentiated in the presence of 10 µM THC were reduced. (D) No change in mPSC amplitudes was detected under the conditions tested. Data represent means ± SEM. *P*-values were calculated using a Mann–Whitney test (**$p < 0.01$, *$p < 0.05$)

128

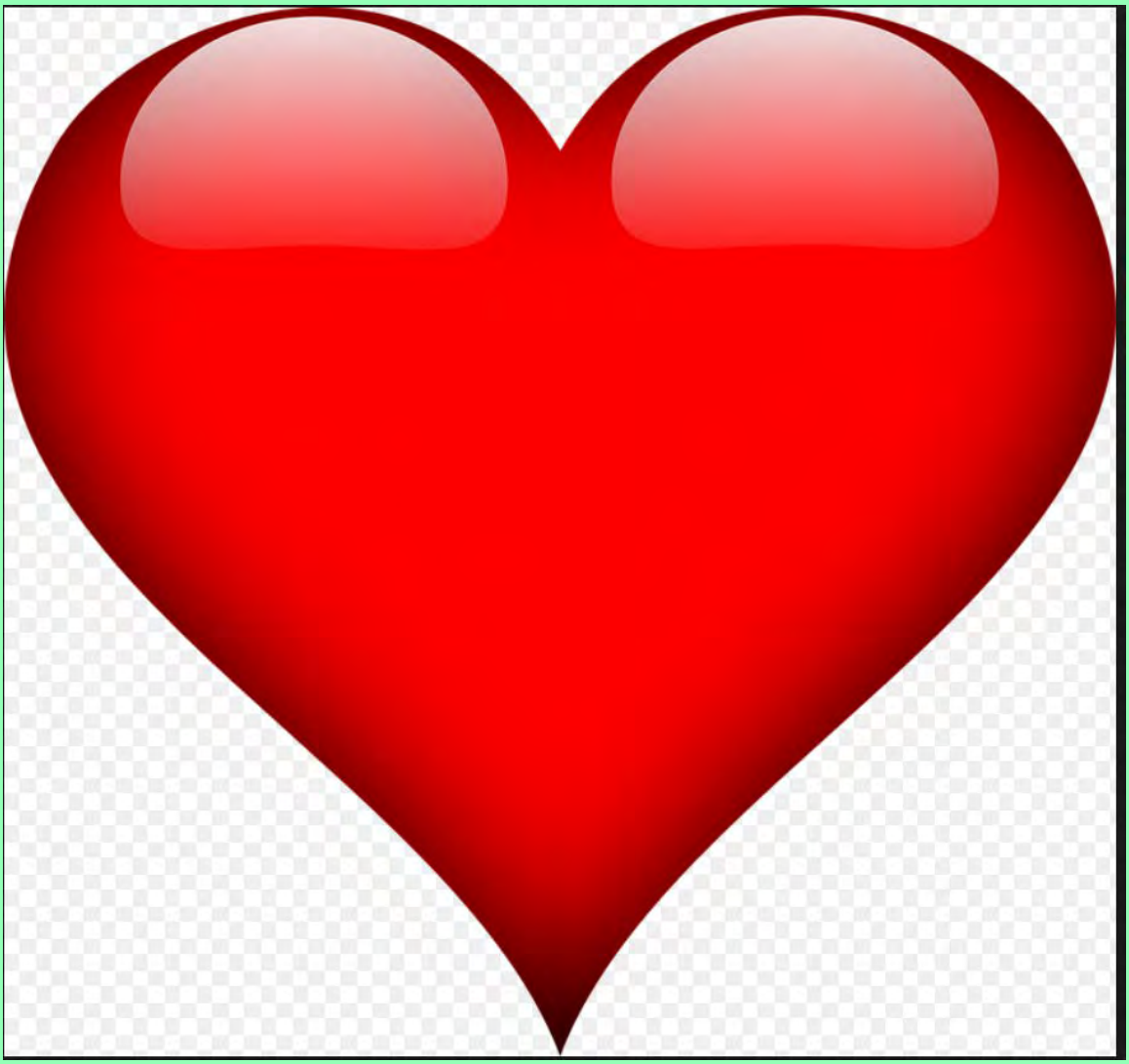
Addict Biol. 2017 Sep;22(5):1329-1342. doi: 10.1111/adb.12394. Epub 2016 Mar 30.

Functional effects of cannabinoids during dopaminergic specification of human neural precursors derived from induced pluripotent stem cells.

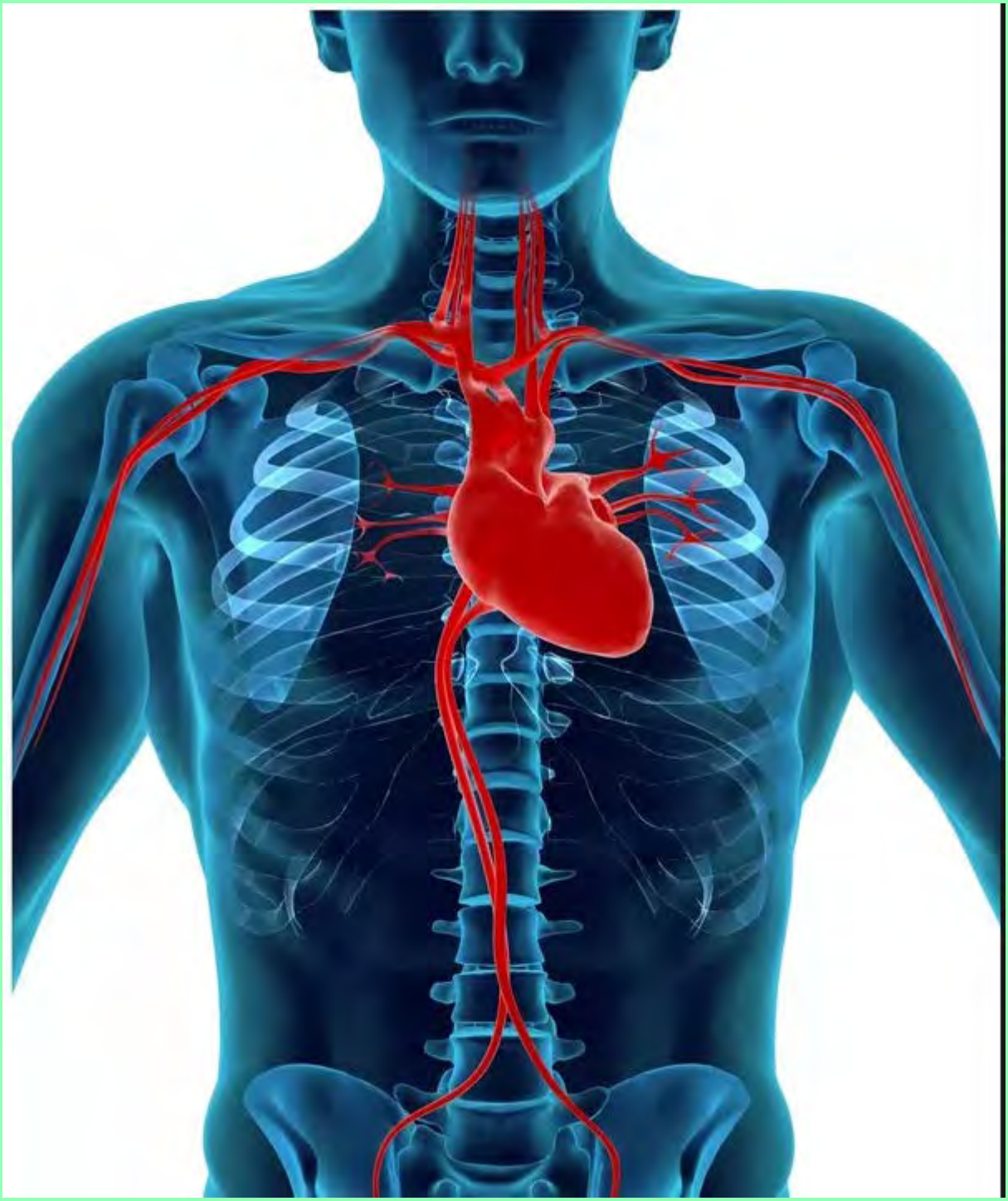
Stanslowsky N[1], Jahn K[2], Venneri A[1], Naujock M[1,3], Haase A[4], Martin U[4,5], Frieling H[2,3], Wegner F[1,3].

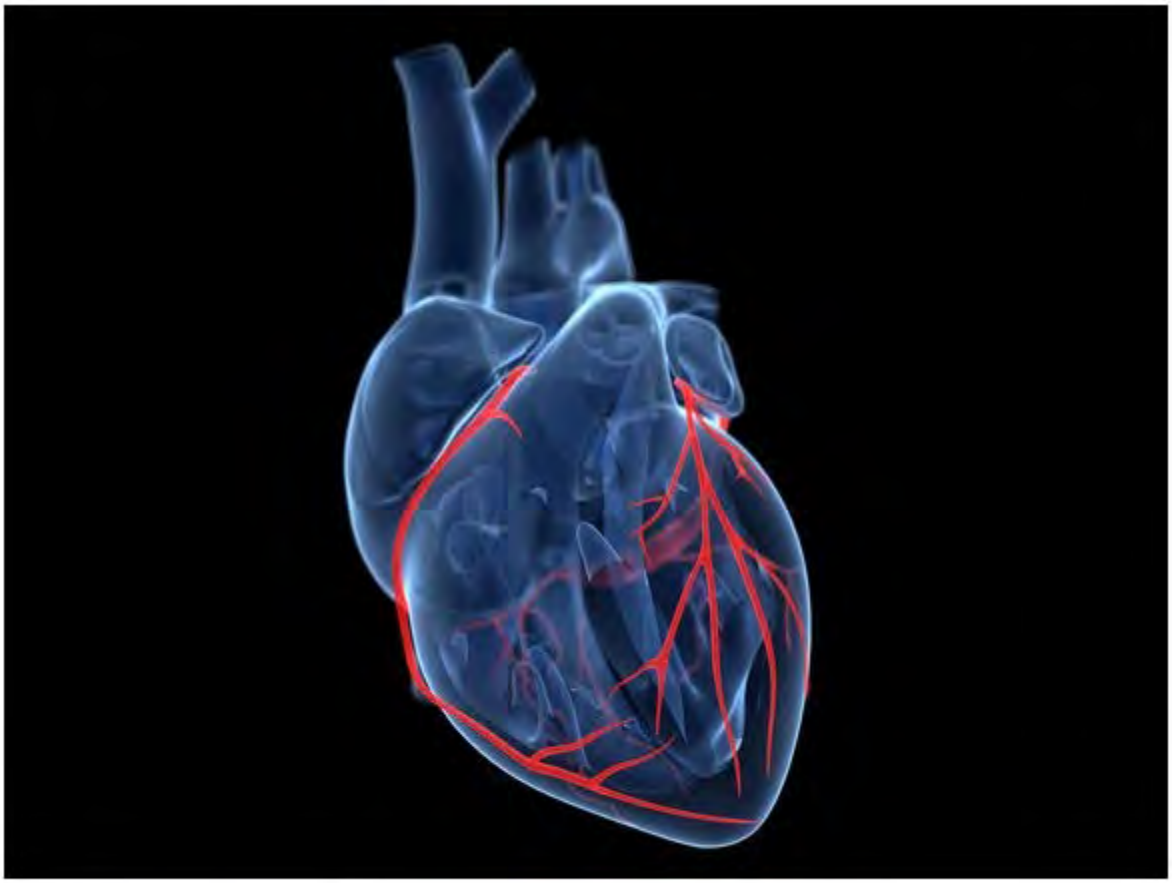
Heart Formation

Heart

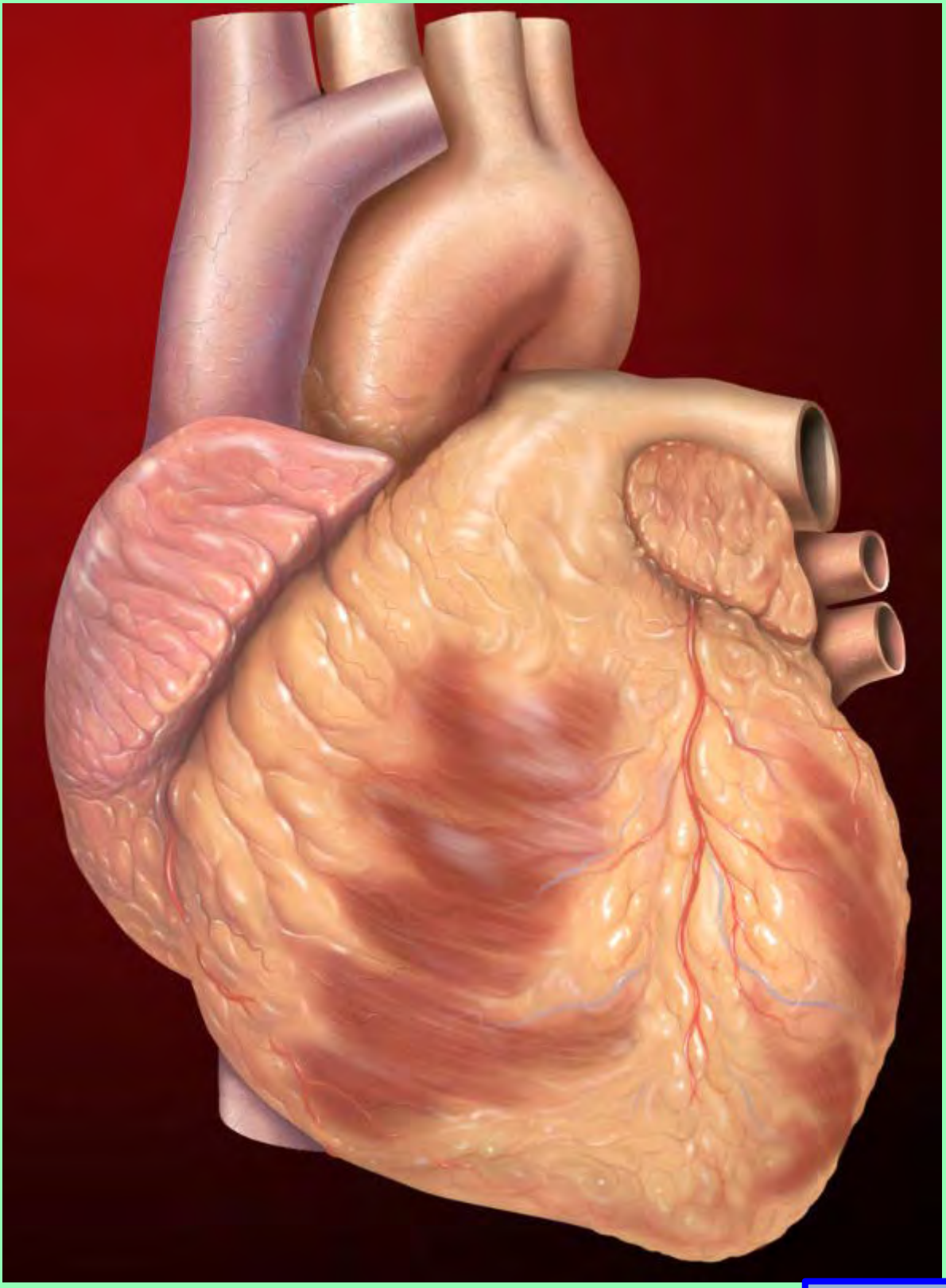


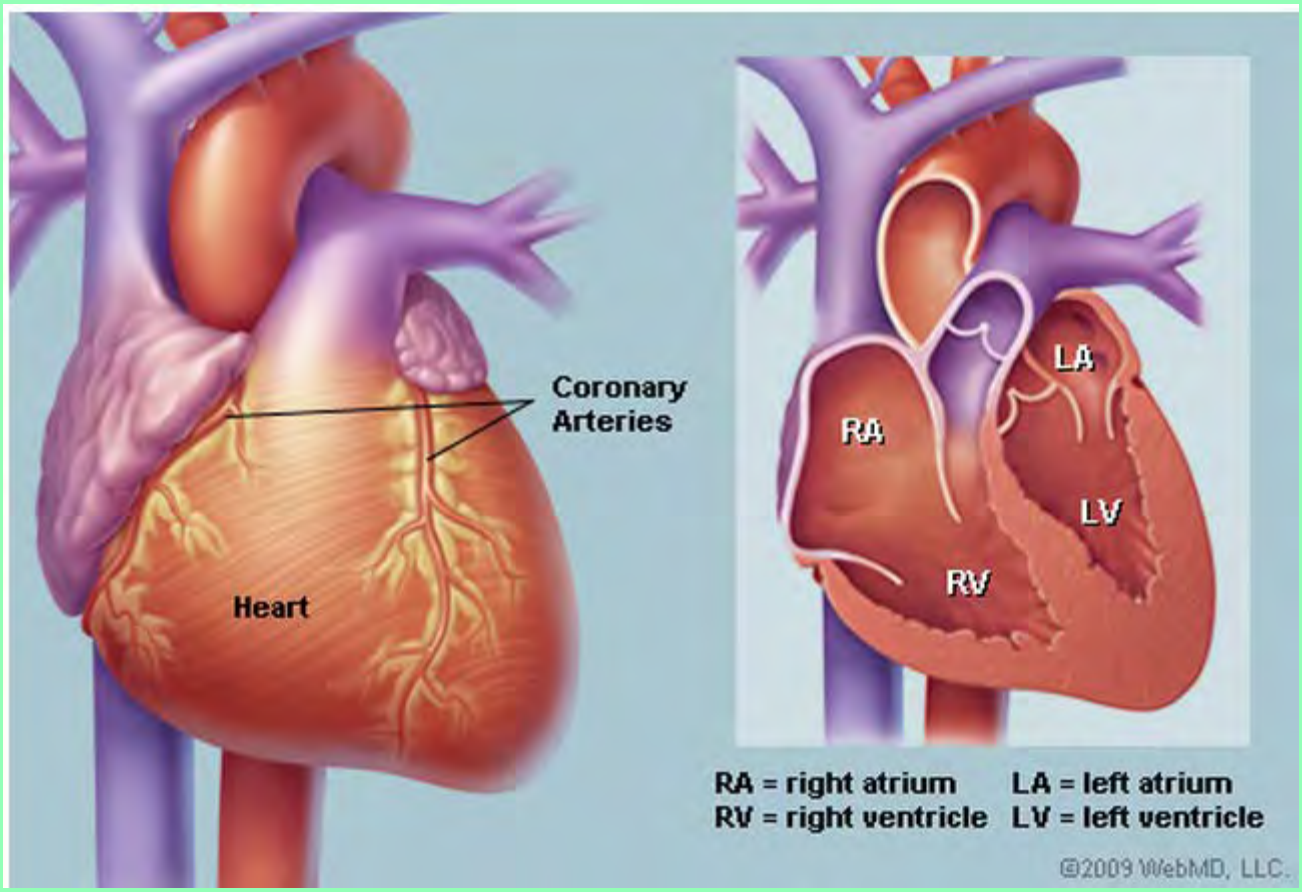
Structure

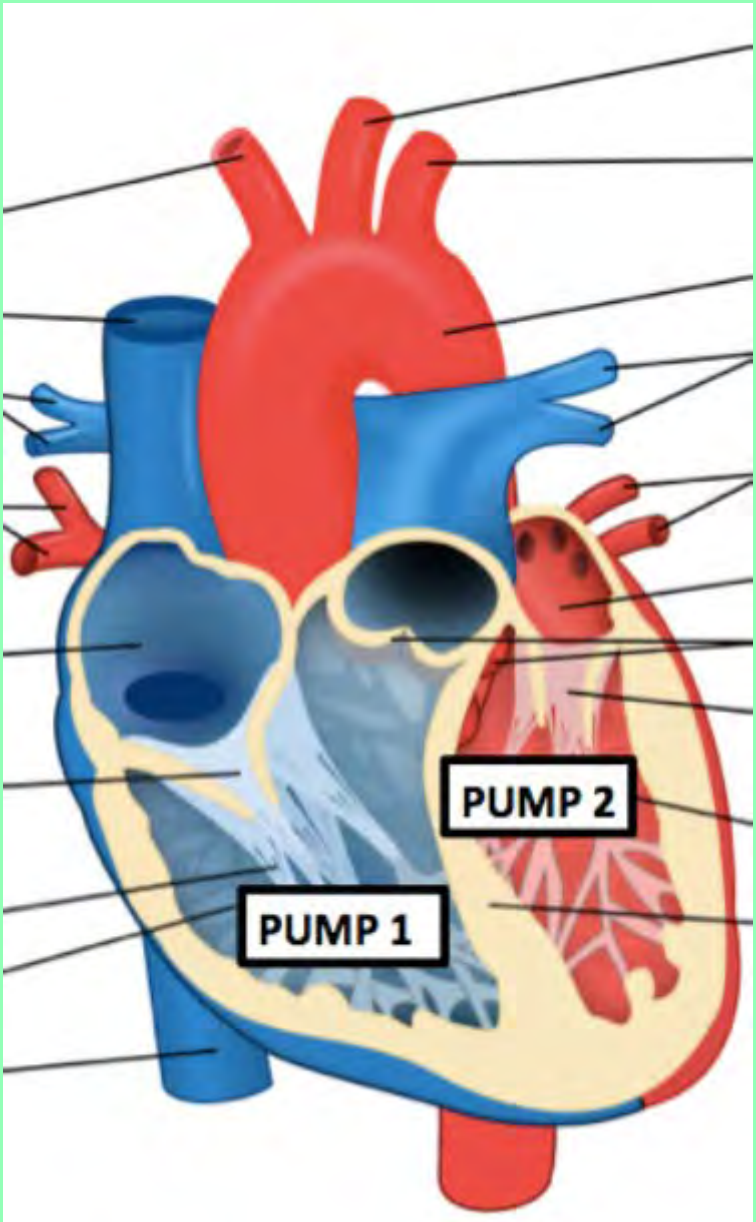




Coronary arteries, artwork GETTY IMAGES



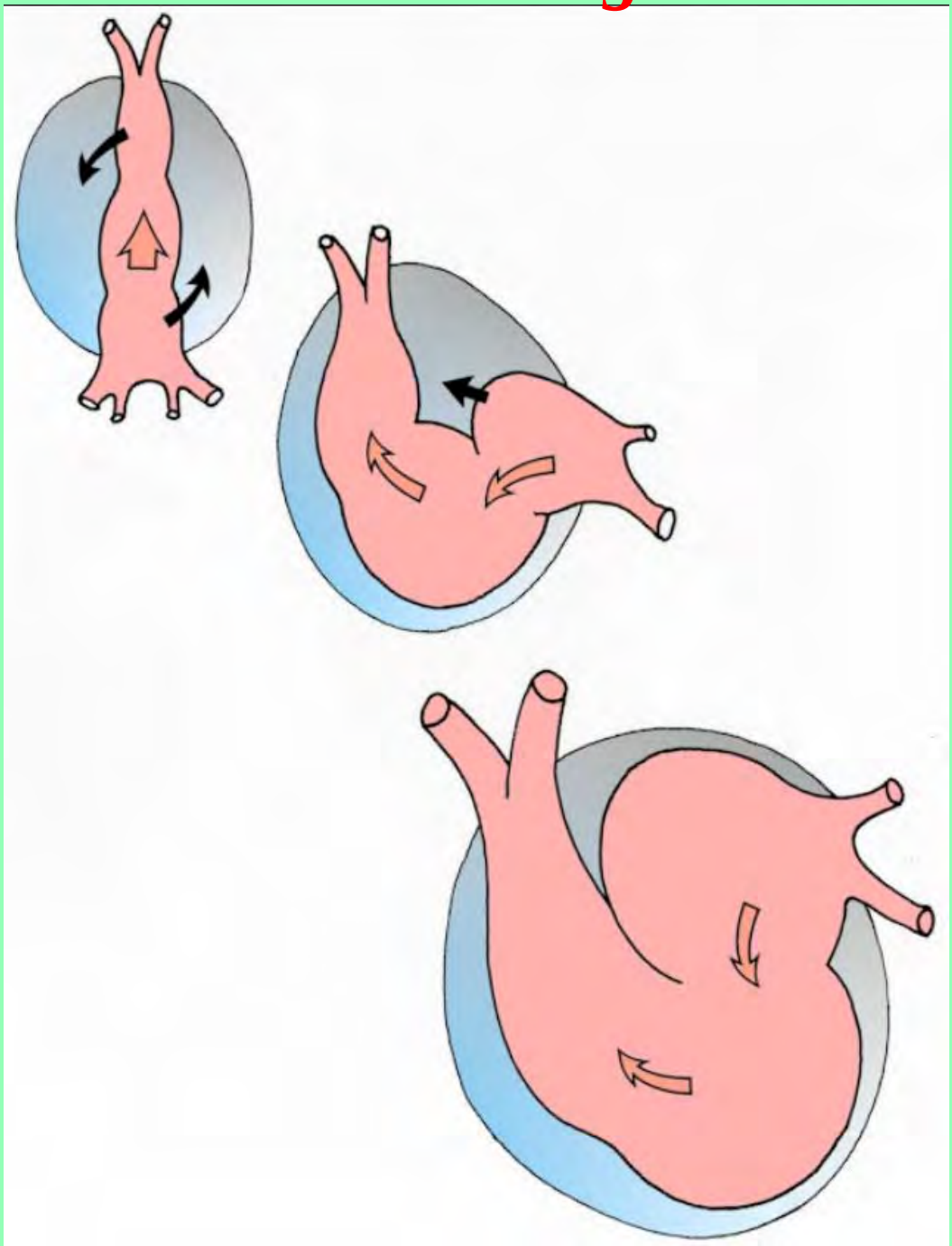

Coronary Arteries
Heart
LA
RA
LV
RV
RA = right atrium
RV = right ventricle
LA = left atrium
LV = left ventricle
©2009 WebMD, LLC.


PUMP 2
PUMP 1

Heart

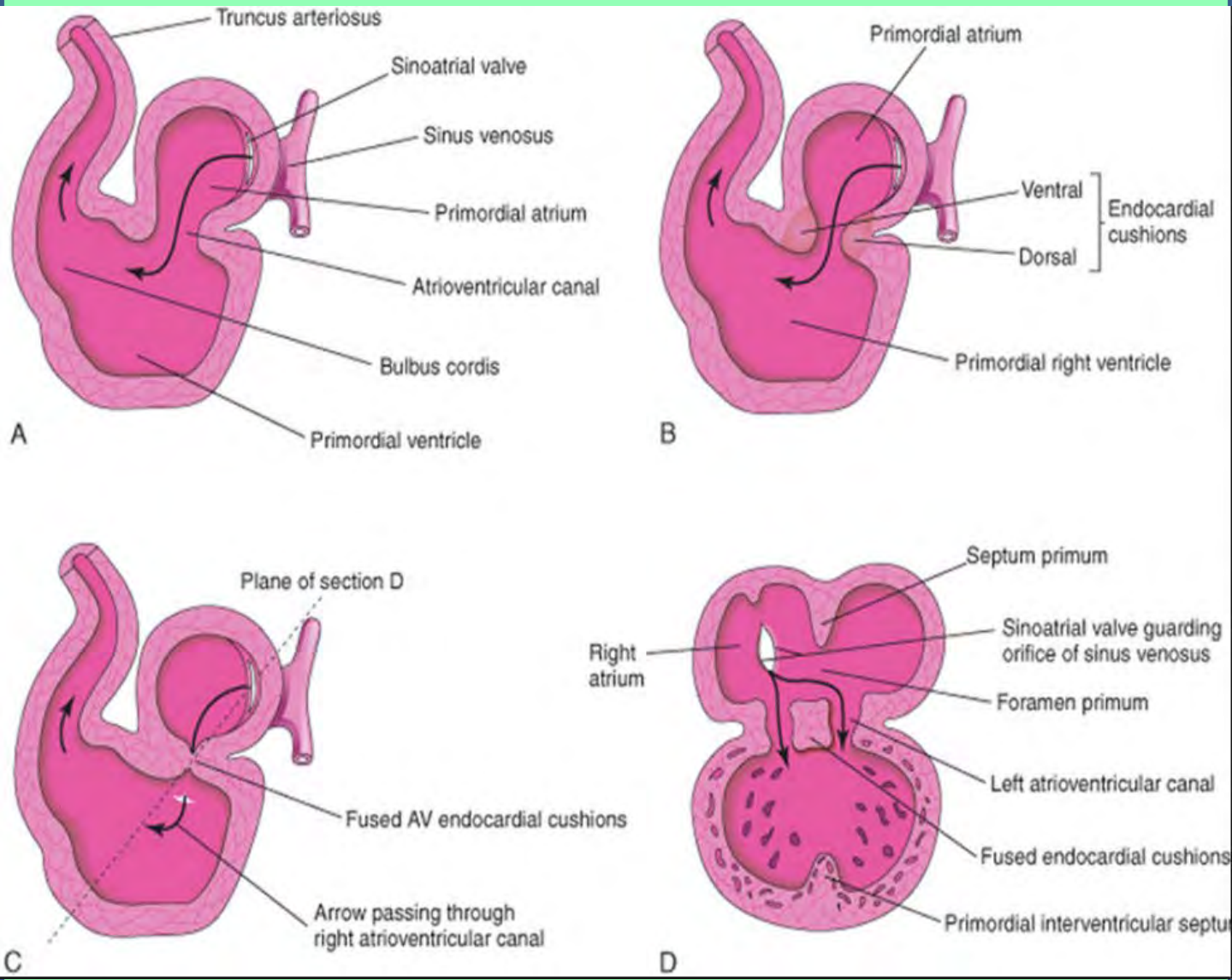
Formation

Two Arteries into One & Folding



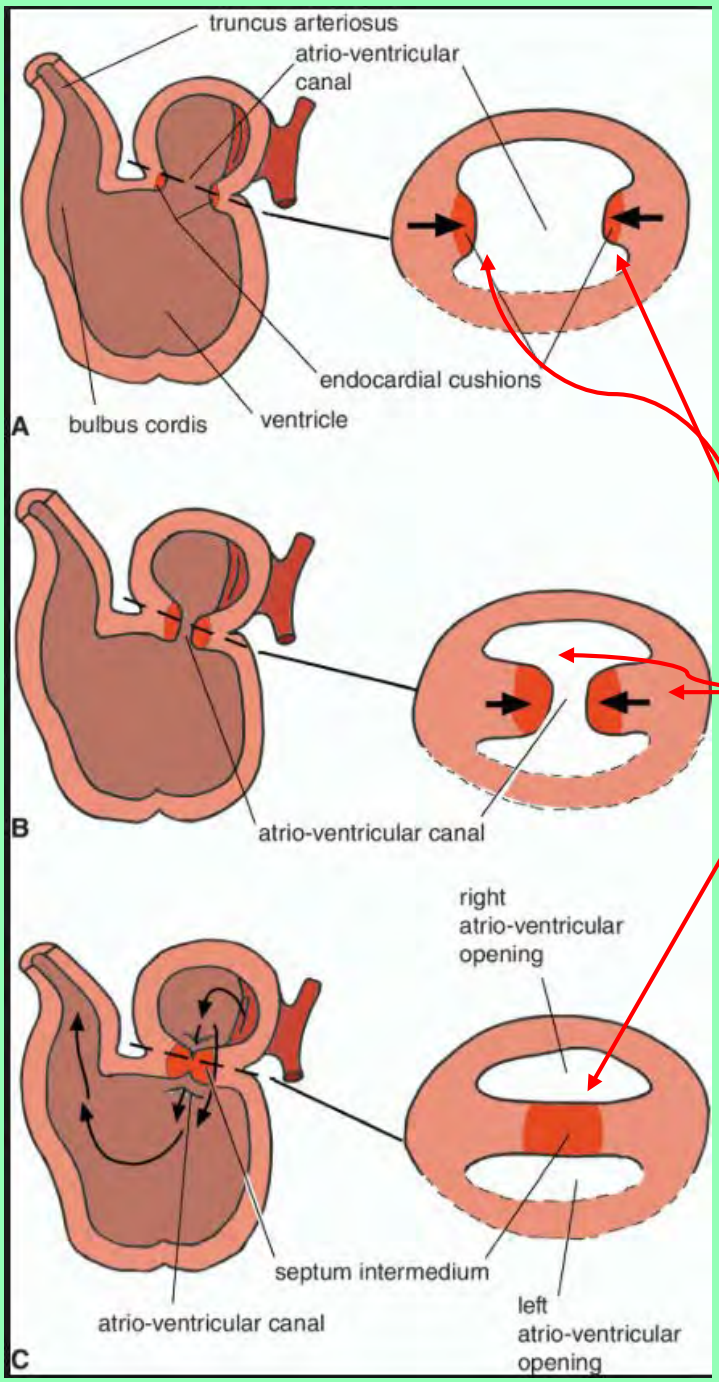
https://www.memorangapp.com/flashcards/71421/3.+Embryonic+Development+of+the+CV+System/

Folding



https://www.memorangapp.com/flashcards/71421/3.+Embryonic+Development+of+the+CV+System/

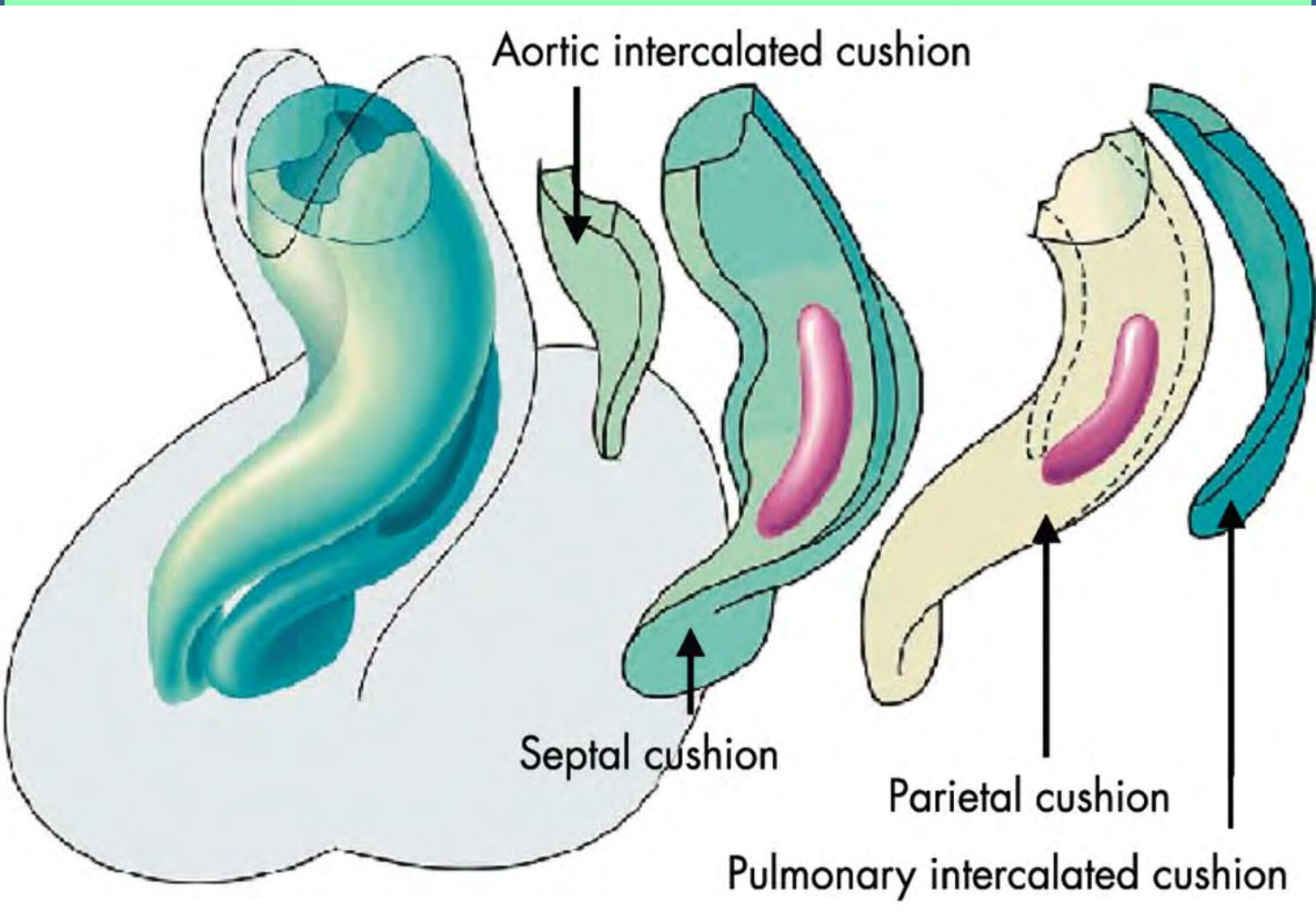
Endocardial Cushions



Endocardial Cushions High in CB1R's

https://www.memorangapp.com/flashcards/71421/3.+Embryonic+Development+of+the+CV+System/

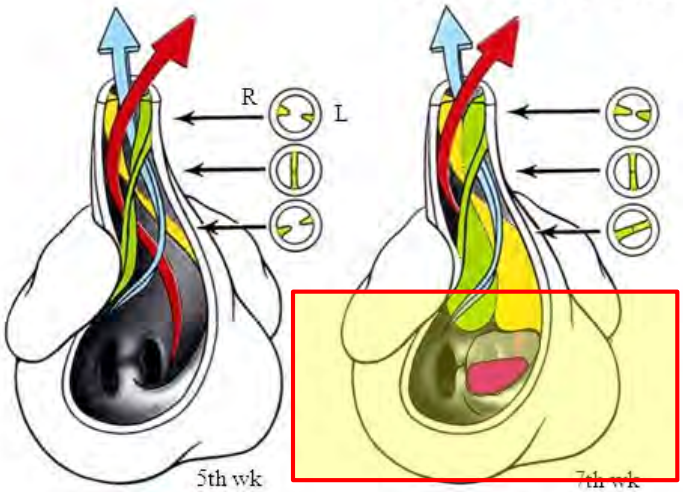
Twisting of the Ventricular Outflow Tract "The Conus"



https://www.memorangapp.com/flashcards/71421/3.+Embryonic+Development+of+the+CV+System/

Outflow Tract Partitioning
Cono-Ventricular Ridges

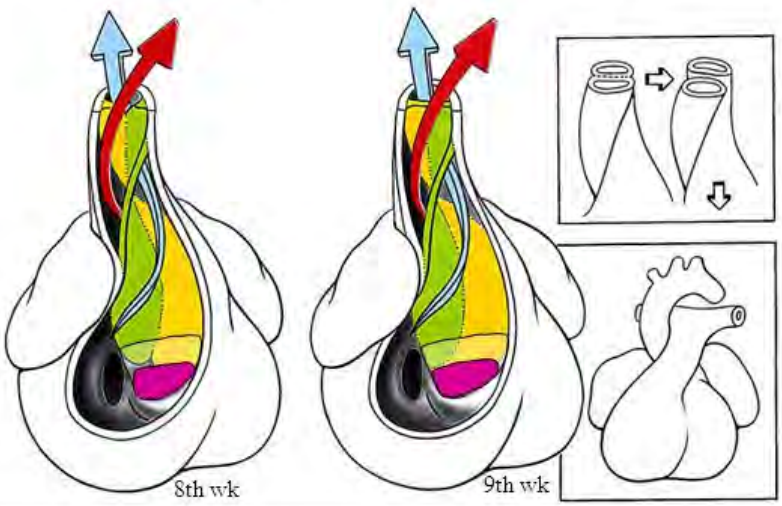
Outflow Tract Partitioning

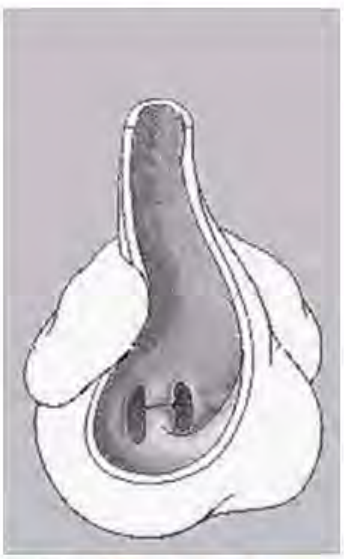


Truncoconal ridges

- Neural crest-derived endocardial cushions form in truncus arteriosis and conus (bulbus) cordis region
- Fuse at truncoconal transition and "zip" proximally and distally to form aorticopulmonary septum.

Membranous septum formed by contributions from AV cushions and truncoconal cushions.



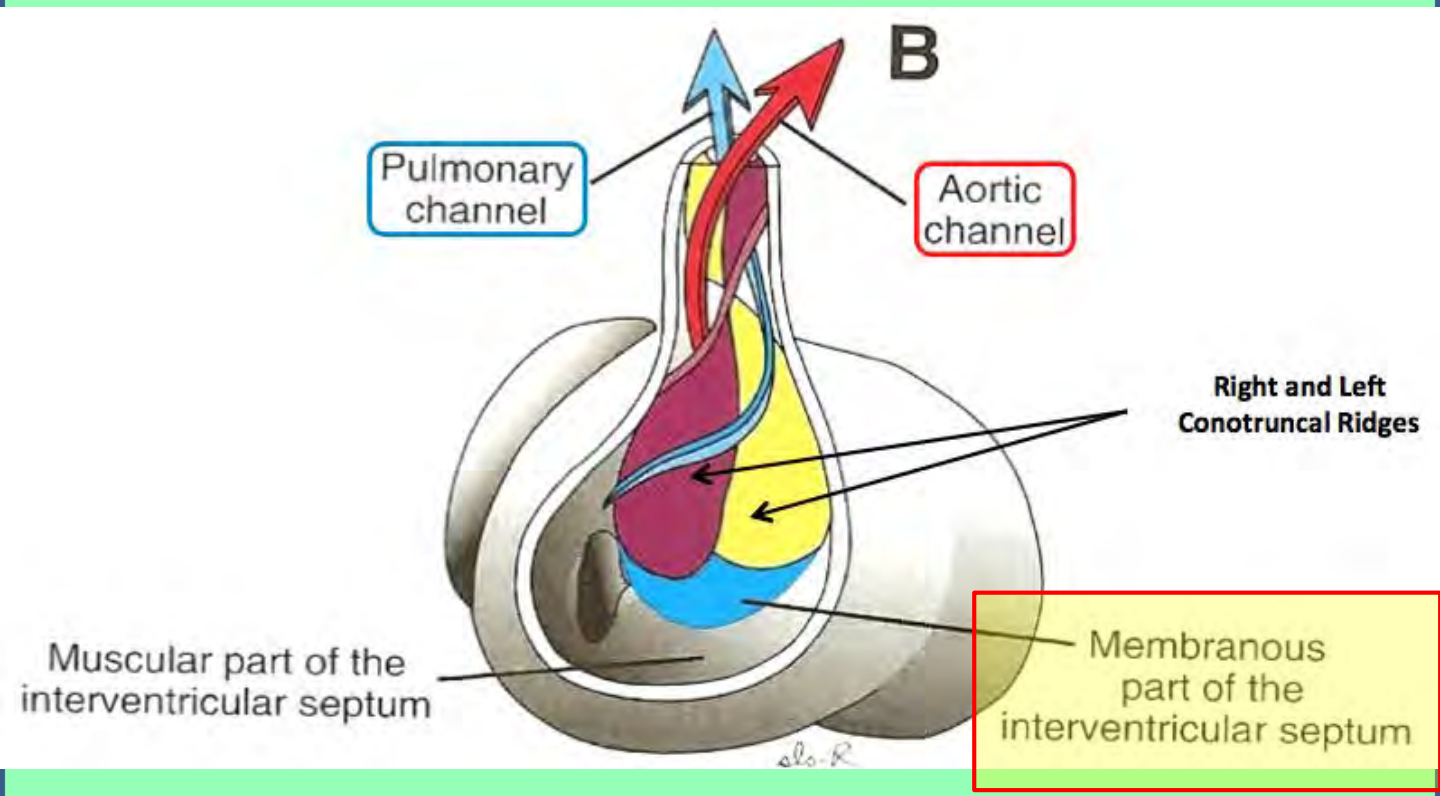


QuickTime version

Larsen's fig 12-33

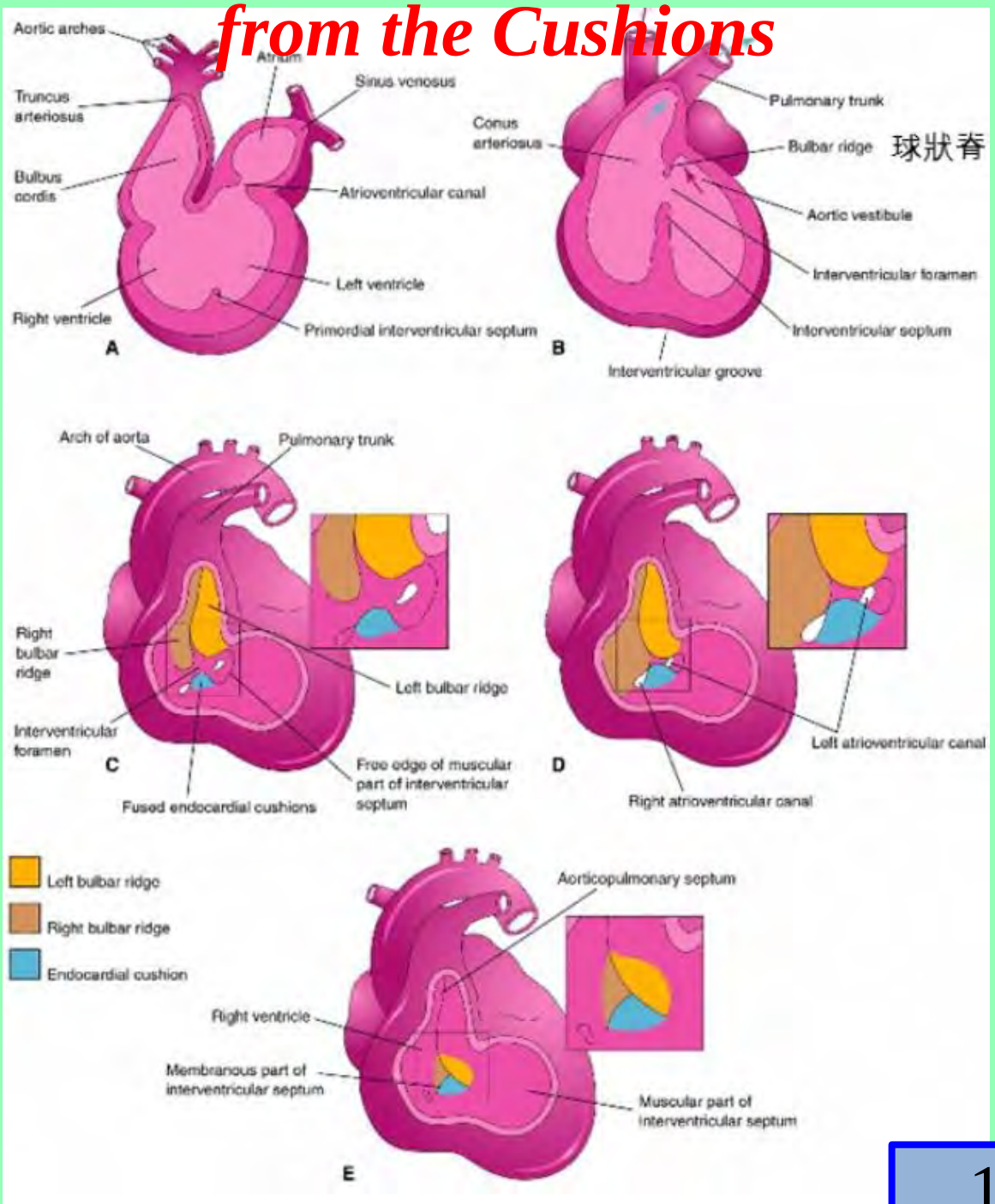
https://www.memorangapp.com/flashcards/71421/3.+Embryonic+Development+of+the+CV+System/

Twisting and Curling



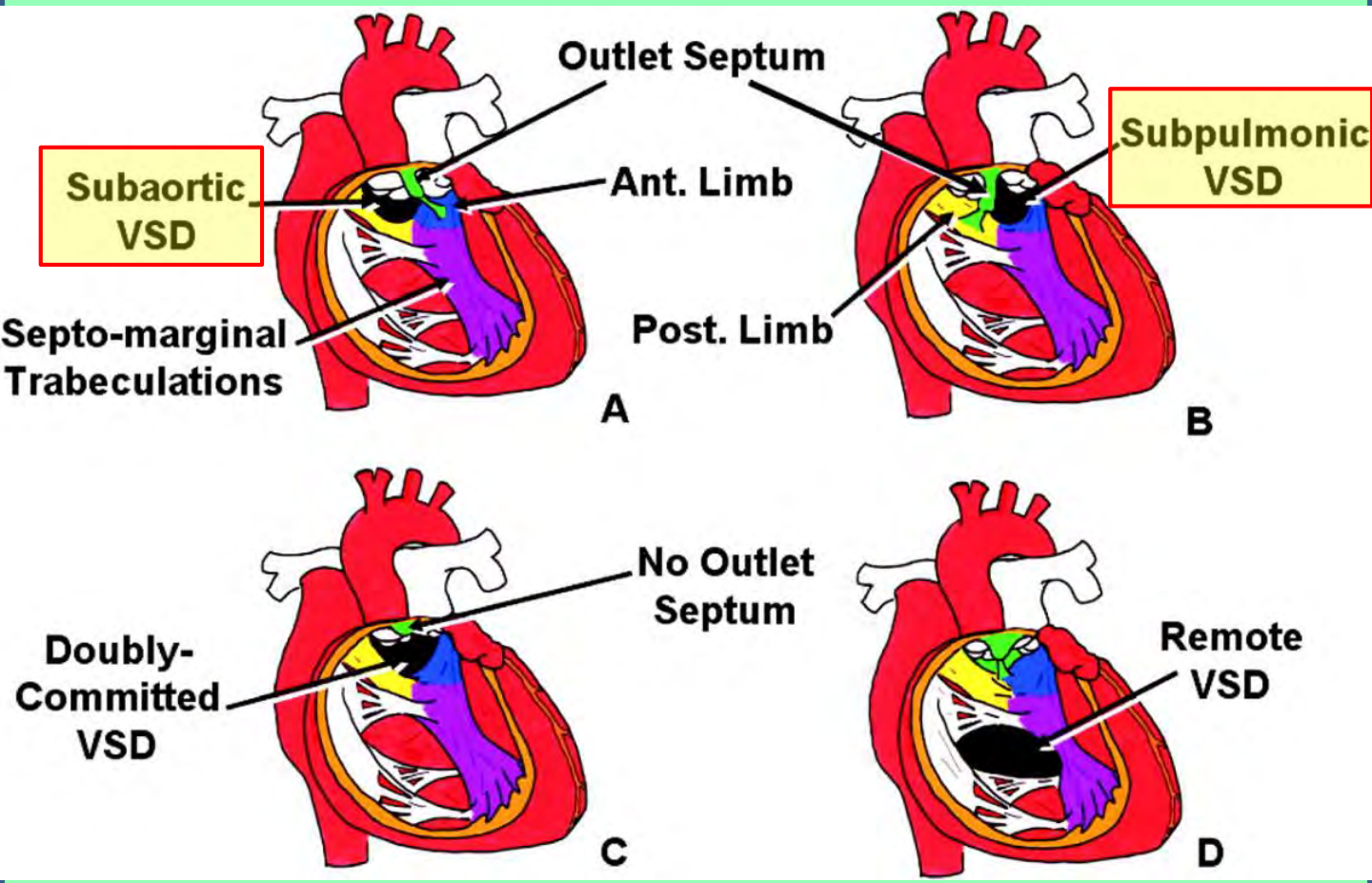
https://www.memorangapp.com/flashcards/71421/3.+Embryonic+Development+of+the+CV+System/

Combined Formation of the Inter-Atrial and Inter-Ventricular Septa from the Cushions



https://www.memorangapp.com/flashcards/71421/3.+Embryonic+Development+of+the+CV+System/

Central Cardiac Defects - VSD Types



https://www.memorangapp.com/flashcards/71421/3.+Embryonic+Development+of+the+CV+System/

Cannabis Effects

Combined
AHA / AAP Statement

American Heart Association and American Academy of Pediatrics

	Defect	RR	Reference(s)
Vitamin A congeners/retinoids	Any defects	†	85, 86
Maternal nontherapeutic drug exposure			
Marijuana	VSD	1.9	160
	Ebstein's	2.4	6

Circulation. 2007 Jun 12;115(23):2995-3014. Epub 2007 May 22.

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.

Jenkins KJ[1], Correa A, Feinstein JA, Botto L, Britt AE, Daniels SR, Elixson M, Warnes CA, Webb CL; American Heart Association Council on Cardiovascular Disease in the Young.

Author information

1 Boston Children's Hospital, USA.

Adverse FX CB1R's on Arterial Pathophysiology

1. J. Diaz-Alonso et. al. *Philos Trans R Soc Lond B Biol Sci* **367**, 3229-3241 (2012).
2. C. Mingorance et. al. *J Cardiovasc Pharmacol* **56**, 560-569 (2010).
3. F. Molica *et al. J Lipid Res* **54**, 1360-1368 (2013).
4. F. Molica *et al. Am J Physiol Heart Circ Physiol* **302**, H1064-1074 (2012).
5. D. H. O'Leary *et al. Heart* **97**, 1143-1150 (2011).
6. M. Rajesh *et. al. Biochem Biophys Res Commun* **377**, 1248-1252 (2008).
7. S. Slavic *et al. J Mol Med (Berl)* **91**, 811-823 (2013).
8. Y. Y. Yang *et al*. *Clin Sci (Lond)* **112**, 533-542 (2007).

1. J. Diaz-Alonso, M. Guzman, I. Galve-Roperh, Endocannabinoids via CB(1) receptors act as neurogenic niche cues during cortical development. *Philos Trans R Soc Lond B Biol Sci* **367**, 3229-3241 (2012).
2. C. Mingorance, M. A. de Sotomayor, E. Marhuenda, M. D. Herrera, Chronic treatment with the cannabinoid 1 antagonist rimonabant altered vasoactive cyclo-oxygenase-derived products on arteries from obese Zucker rats. *J Cardiovasc Pharmacol* **56**, 560-569 (2010).
3. F. Molica *et al.*, Endogenous cannabinoid receptor CB1 activation promotes vascular smooth-muscle cell proliferation and neointima formation. *J Lipid Res* **54**, 1360-1368 (2013).
4. F. Molica *et al.*, Cannabinoid receptor CB2 protects against balloon-induced neointima formation. *Am J Physiol Heart Circ Physiol* **302**, H1064-1074 (2012).
5. D. H. O'Leary *et al.*, Effect of rimonabant on carotid intima-media thickness (CIMT) progression in patients with abdominal obesity and metabolic syndrome: the AUDITOR Trial. *Heart* **97**, 1143-1150 (2011).
6. M. Rajesh, P. Mukhopadhyay, G. Hasko, P. Pacher, Cannabinoid CB1 receptor inhibition decreases vascular smooth muscle migration and proliferation. *Biochem Biophys Res Commun* **377**, 1248-1252 (2008).
7. S. Slavic *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 (2013).
8. Y. Y. Yang *et al.*, Effect of chronic CB1 cannabinoid receptor antagonism on livers of rats with biliary cirrhosis. *Clin Sci (Lond)* **112**, 533-542 (2007).

eCB in Arteries

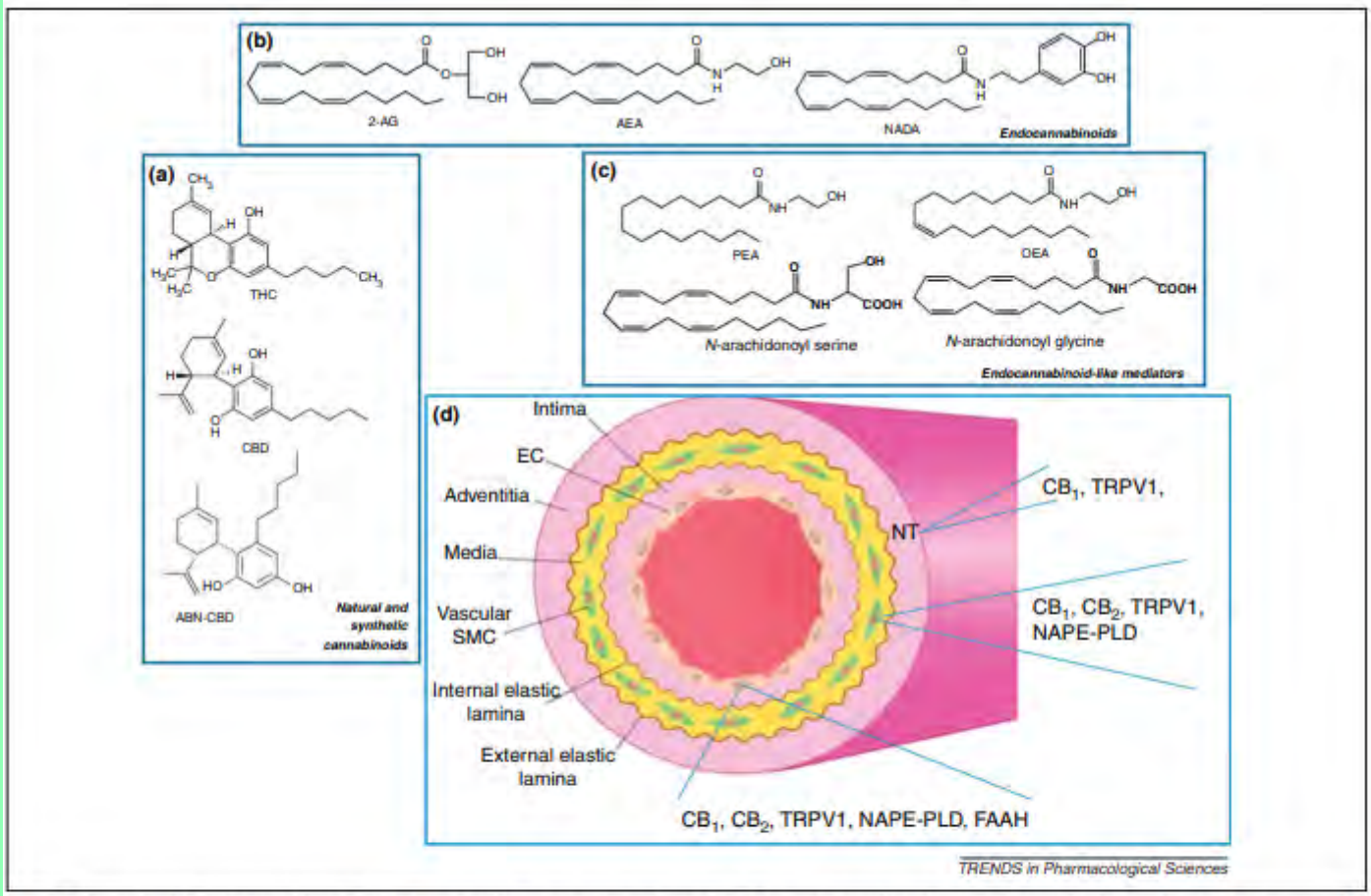


Figure 1. Cannabinoids, endocannabinoids, endocannabinoid-like molecules and proteins of the endocannabinoid system in vascular tissues. Chemical structures of **(a)** plant cannabinoids, **(b)** endocannabinoids and **(c)** endocannabinoid-like molecules that have been most thoroughly investigated for their cardiovascular actions. (a) Plant cannabinoids Δ^9-tetrahydrocannabinol (THC, which activates cannabinoid receptors CB_1 and CB_2) and cannabidiol (CBD), and the synthetic analog abnormal cannabidiol (ABN-CBD) (which, like CBD, has very low affinity for CB_1 and CB_2 receptors). (b) The three endocannabinoids 2-arachidonoyl glycerol (2-AG), anandamide (AEA) and *N*-arachidonoyl dopamine (NADA). (c) Some endocannabinoid-like molecules with low affinity for CB_1 and CB_2 receptors: *N*-palmitoyl ethanolamine (PEA), *N*-oleoyl ethanolamine (OEA), *N*-arachidonoyl serine and *N*-arachidonoyl glycine. **(d)** Current knowledge of the distribution of molecularly characterized targets for 2-AG (CB_1, CB_2), AEA (CB_1, CB_2, TRPV1) and NADA (CB_1, CB_2, TRPV1), and of biosynthesizing (*N*-arachidonoyl-phosphatidylethanolamine-selective phospholipase D, NAPE-PLD) and hydrolytic (fatty acid amide hydrolase-1, FAAH) enzymes for AEA in cells of vascular tissues, as demonstrated so far by immunohistochemistry or quantitative PCR. EC, endothelial cells; SMC, smooth muscle cells; NT, sensory or sympathetic neuron terminals.

Trends Pharmacol Sci. 2012 Jun;33(6):331-40. doi: 10.1016/j.tips.2012.03.002. Epub 2012 Apr 13.

At the heart of the matter: the endocannabinoid system in cardiovascular function and dysfunction.

Montecucco F , Di Marzo V.

Adverse FX Cannabis

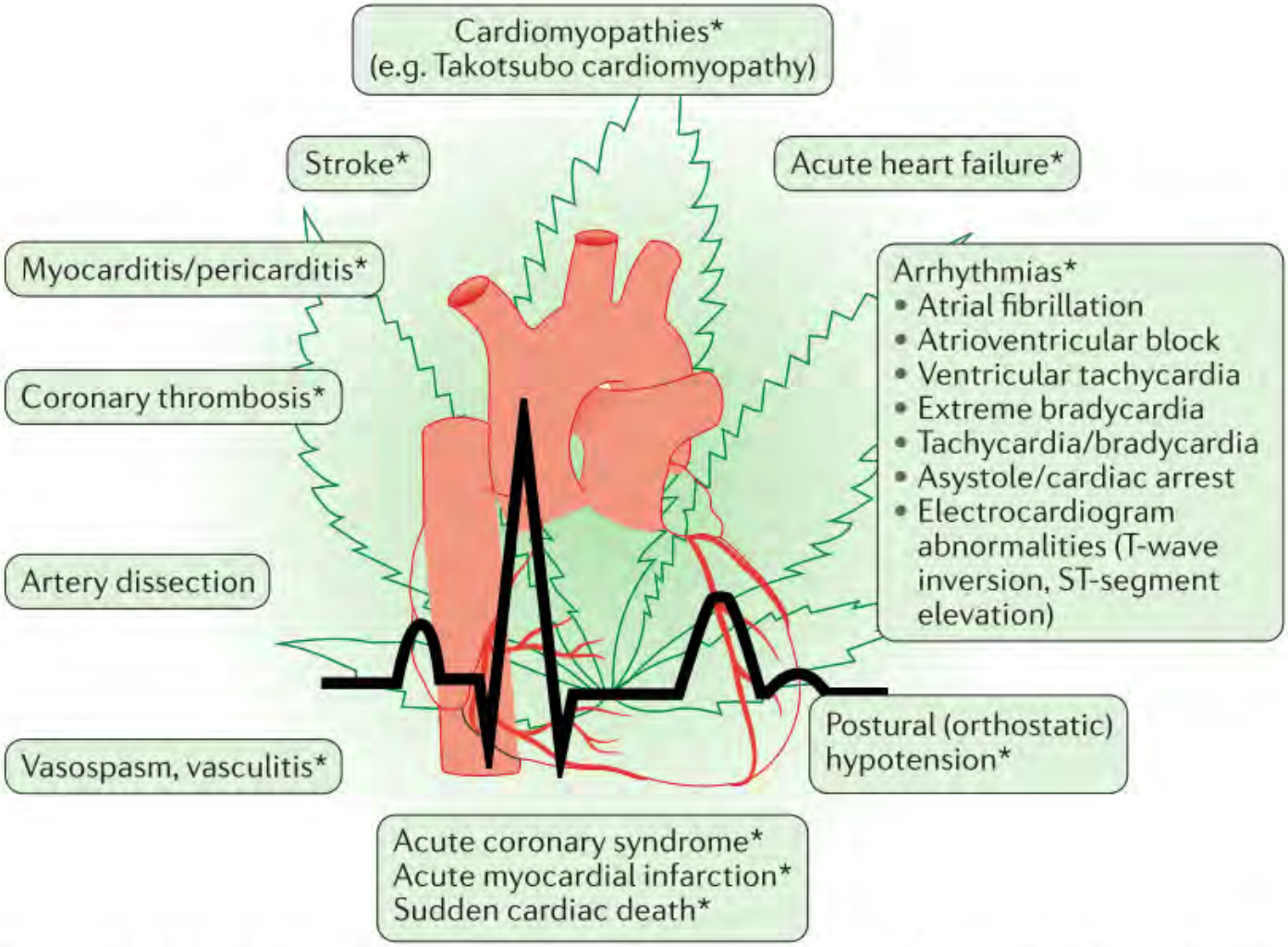


Figure 2 | **Reported cardiovascular adverse consequences of recreational marijuana and synthetic cannabinoid use.** *Adverse effects that were reported for synthetic cannabinoids; note almost complete overlap with the adverse effects of marijuana.

See 1 citation found using an alternative search:

Nat Rev Cardiol. 2018 Mar;15(3):151-166. doi: 10.1038/nrcardio.2017.130. Epub 2017 Sep 14.

Cardiovascular effects of marijuana and synthetic cannabinoids: the good, the bad, and the ugly.

Pacher P[1], Steffens S[2], Haskó G[3], Schindler TH[4], Kunos G[5].

Author information

1 Laboratory of Cardiovascular Physiology and Tissue Injury, National Institutes of Health/NIAAA, 5625 Fishers Lane, Bethesda, Maryland 20892, USA.

2 Institute for Cardiovascular Prevention, Ludwig-Maximilians-University and German Centre for Cardiovascular Research (DZHK), partner site Munich Heart Alliance, Pettenkoferstrasse 8a und 9b, Munich, D-80336, Germany.

3 Department of Surgery, Rutgers New Jersey Medical School, 185 South Orange Avenue, Newark, New Jersey 07103, USA.

4 Department of Radiology, Johns Hopkins University, 601 North Caroline Street, Baltimore, Maryland 21287, USA.

5 Laboratory of Physiological Studies, National Institutes of Health/NIAAA, 5625 Fishers Lane, Bethesda, Maryland 20892, USA.

5.8 Seconds Cardiac Arrest

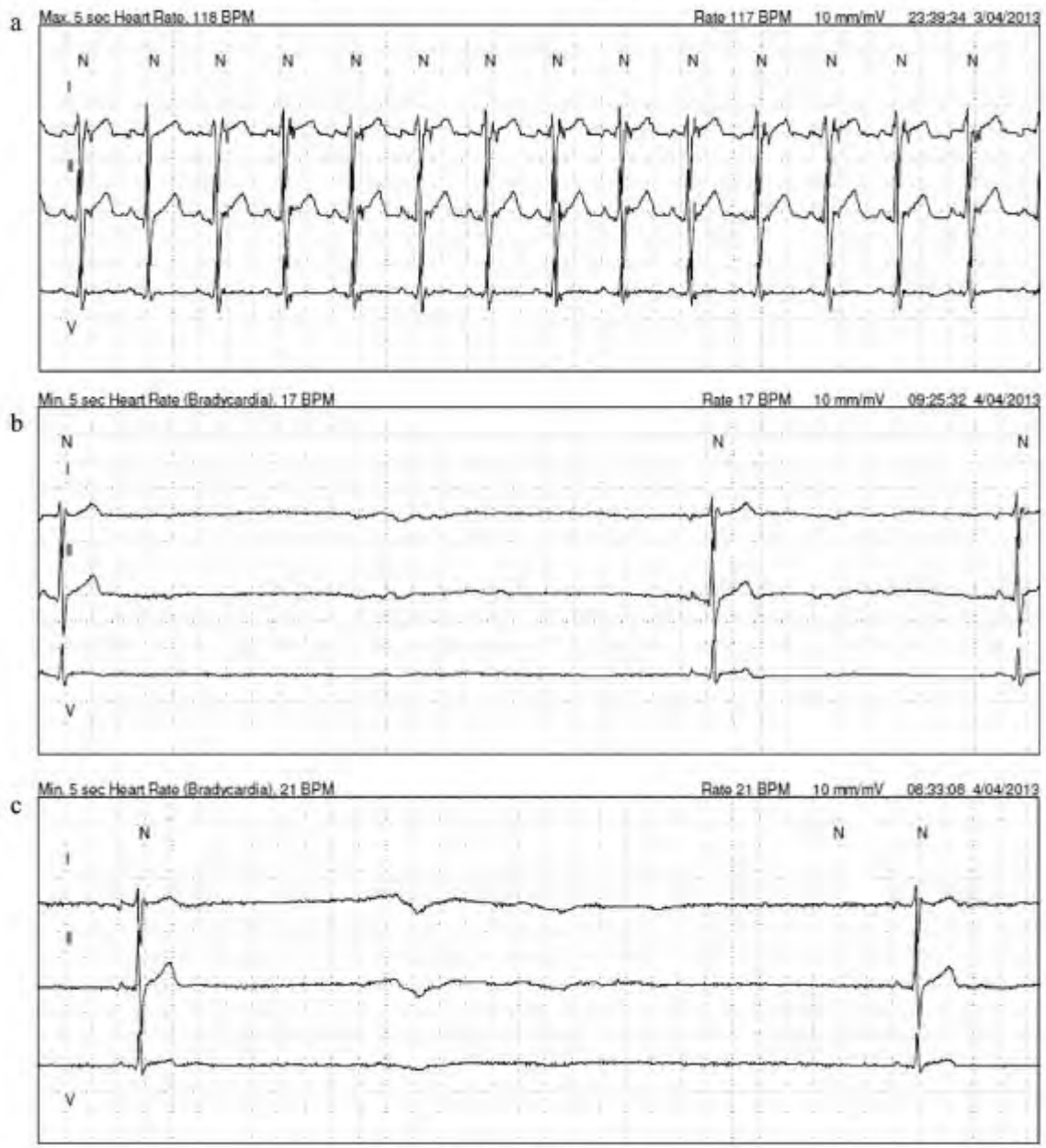


Fig. 1. Strips from a 24-h Holter showing (a) sinus rhythm/tachycardia and (b) repeated and prolonged pauses related to cardiac asystole associated in timing with marijuana usage. (c) Longest pause 5.8 s.

Forensic Sci Int. 2013 Dec 10;233(1-3):e3-5. doi: 10.1016/j.forsciint.2013.10.007. Epub 2013 Oct 14.

Cardiac asystole following cannabis (marijuana) usage--additional mechanism for sudden death?

Menahem S[1].

150

Sinus Arrest

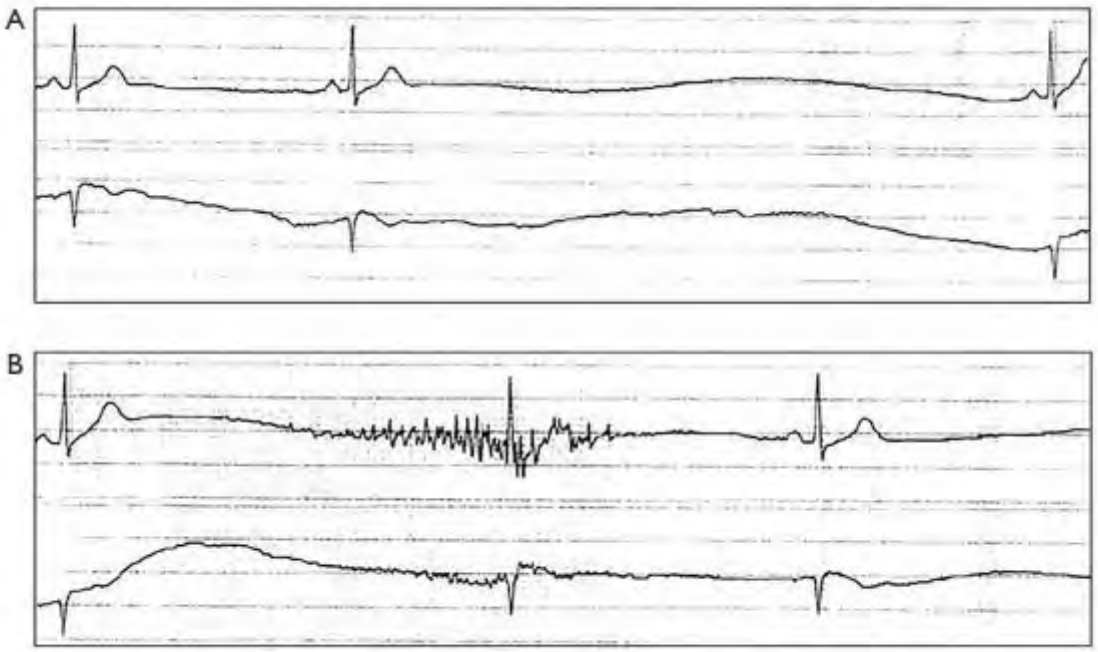


Figure 1 Rhythm strip. (A) A rhythm strip demonstrating an episode of sinus arrest after marijuana use; (B) another repeated episode of prolonged asystole after a few beats.

J Thorac Dis. 2018 Feb;10(2):1121-1123. doi: 10.21037/jtd.2018.01.139.

Symptomatic sinus arrest induced by acute marijuana use

Grieve-Eglin L[1], Haseeb S[2], Wamboldt R[2], Baranchuk A[2].

Heart Attack & Cardiac Arrest

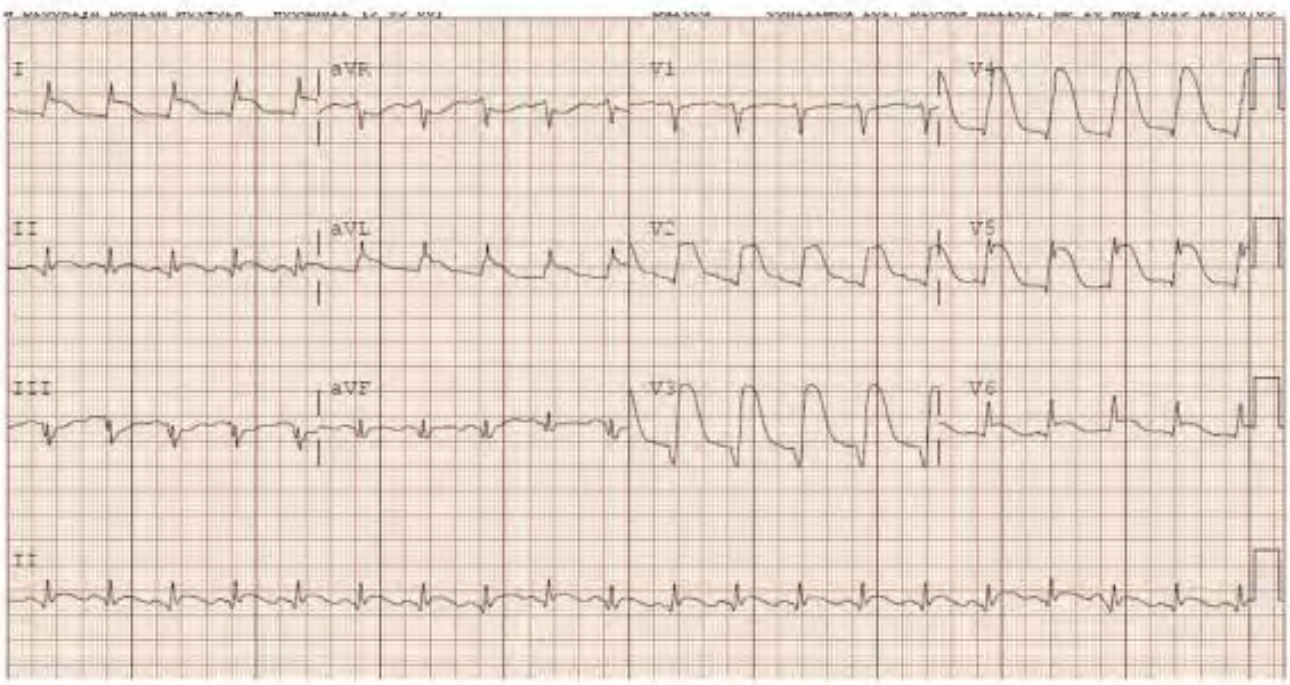


Fig. 2. Initial ECG demonstrating ST-segment elevation in multiple leads.

J Community Hosp Intern Med Perspect. 2016 Sep 7;6(4):31695. doi: 10.3402/jchimp.v6.31695. eCollection 2016.

Prolonged cardiac arrest complicating a massive ST-segment elevation myocardial infarction associated with marijuana consumption.

Orsini J[1], Blaak C[2], Rajayer S[2], Gurung V[2], Tam E[2], Morante J[2], Shamian B[2], Malik R[2].

Published Cases of Cannabis Induced Cardiac Arrest

Table 1. Summary of cases of cardiac arrest and sudden cardiac death associated with consumption of marijuana

Reference	Age, gender	Outcome
Lindsay et al. (8)	48, M	Survived
Casier et al. (16)	52, M	Dead
	23, M	Survived
	28, M	Dead
Hartung et al. (17)	23, M	Dead
	28, M	Dead
Menahem (18)	21, M	Survived
Bachs et al. (19)	39, M	Dead
	40, M	Dead
	43, M	Dead
	37, M	Dead
	17, M	Dead
	42, M	Dead
Tormey (20)[a]	17, F	Dead
	50, M	Dead
	19, M	Dead
	47, M	Dead
	28, M	Dead
	54, M	Dead
	47, M	Dead
	31, M	Dead
	61, M	Dead
	36, M	Dead
	20, F	Dead
	50, M	Dead
	59, M	Dead
Diffley et al. (22)	15, M	Survived
Daisley et al. (23)	18, M	Dead
Montisci et al. (24)	31, M	Dead
Sattout et al. (25)	15, M	Survived

F, Female; M, male.
[a]Autopsy cases.

J Community Hosp Intern Med Perspect. 2016 Sep 7;6(4):31695. doi: 10.3402/jchimp.v6.31695. eCollection 2016.

Prolonged cardiac arrest complicating a massive ST-segment elevation myocardial infarction associated with marijuana consumption.

Orsini J[1], Blaak C[2], Rajayer S[2], Gurung V[2], Tam E[2], Morante J[2], Shamian B[2], Malik R[2].

One Minute THC Smoke on Arterial Cells

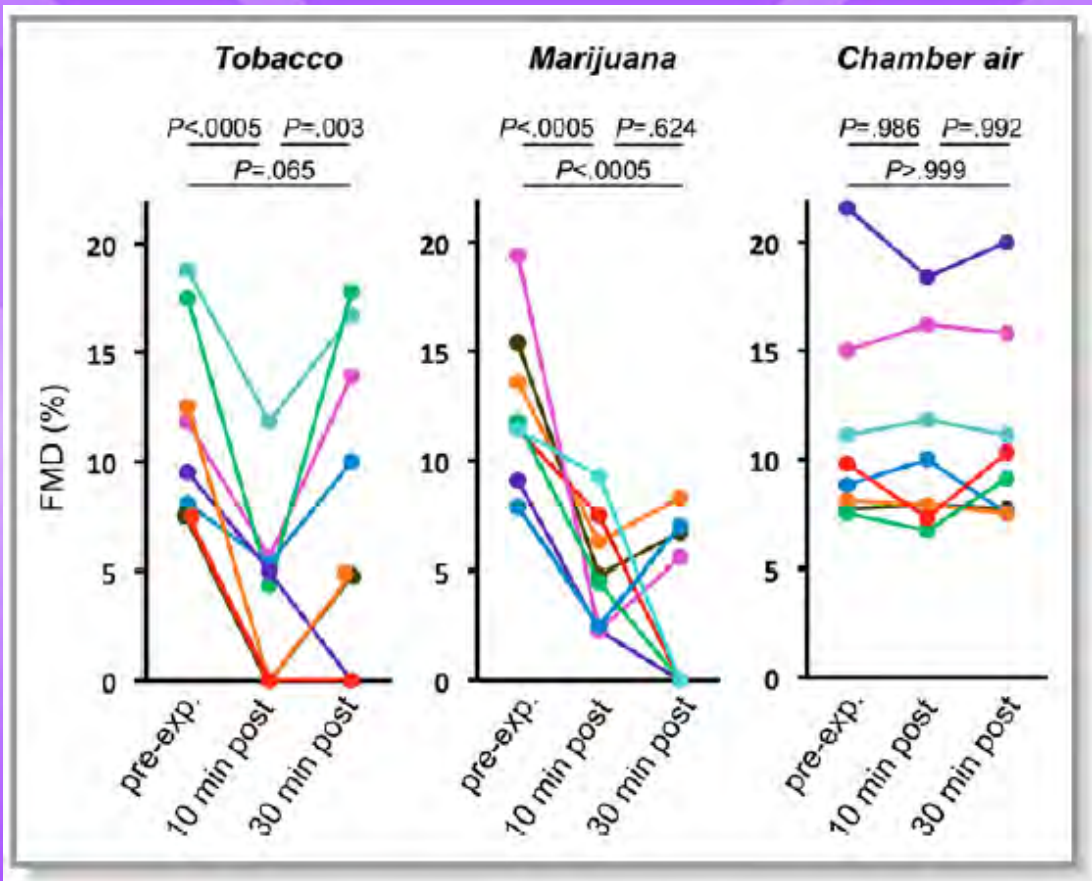


Figure 6. Impairment of FMD from 1 minute of marijuana SHS persists longer than impairment from tobacco SHS. Impairment of

One Minute of Marijuana Secondhand Smoke Exposure Substantially Impairs Vascular Endothelial Function.

Wang X, Derakhshandeh R, Liu J, Narayan S, Nabavizadeh P, Le S, Danforth OM, Pinnamaneni K, Rodriguez HJ, Luu E, Sievers RE, Schick SF, Glantz SA, Springer ML. J Am Heart Assoc. **2016** Jul 27;5(8). pii: e003858. doi: 10.1161/JAHA.116.003858. PMID: 27464788 **Free Article**

Arterial Stiffness
SphygmoCor System

Millar Microtonometer Indexes Arterial Stiffness Function {Vascular Age}, SphygmoCor Software Performs Dedifferentiation & Analyzes Output

155

THC log(RA/CA) - Mean Effect Size 25.1%

Cannabis :Age IR P* = 0.0014, Longitudinal Dataset

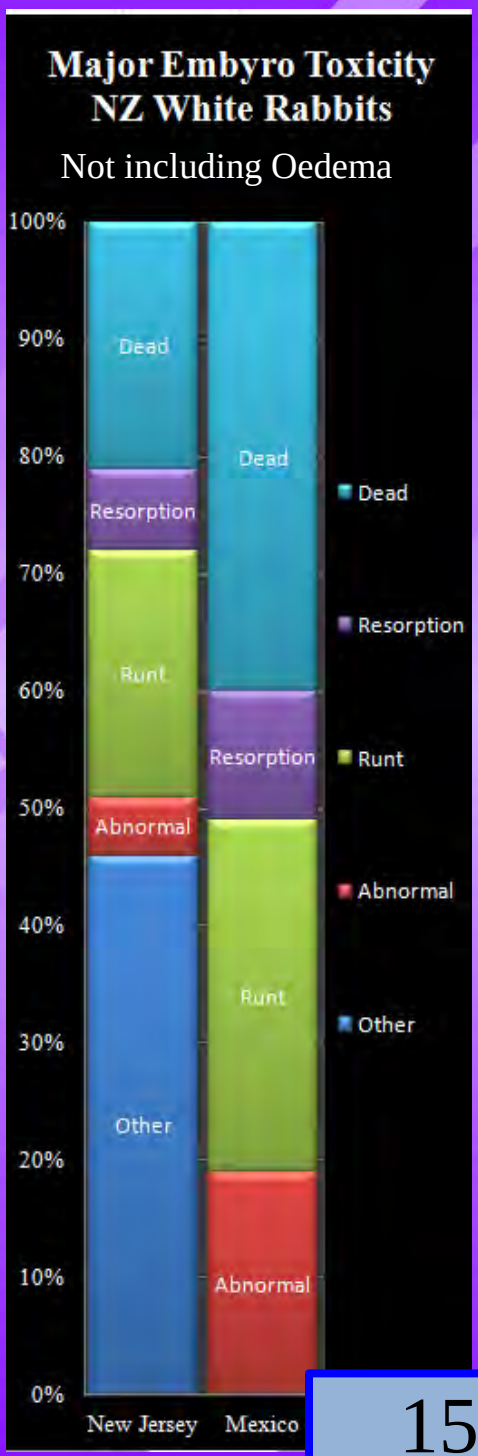
Parameter	Value	Std.Error	DF	t-value	p-value	
Age	-0.4700	0.0856	717	-5.4926	0.0000	***
Age : Tobacco	0.2078	0.0910	717	2.2841	0.0227	*
Age : Buprenorphine	0.1007	0.0461	717	2.1855	0.0292	*
Age : Cannabis	0.2178	0.1044	717	2.0858	0.0374	*
Age ^2 : Cannabis	0.3878	0.2210	717	1.7545	0.0798	.
Age^2 : Tobacco	0.2943	0.1711	717	1.7204	0.0858	.

Cannabis exposure as an interactive cardiovascular risk factor and accelerant ageing: a longitudinal study Reece AS[1], Norman A[1], Hulse GK[1]. BMJ Open. 2016 Nov 7;6(11):e011891. doi: 10.

CHILDREN

Embryotoxicity
Thalidomide Tests

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



158

Cannabis & Health, JDP Graham, Cannabis & Health, 1976 Academic Press, pp271-320.

Effect of marihuana extract on fetal hamsters and rabbits.
Geber WF, Schramm LC. 158
Toxicol Appl Pharmacol. **1969** Mar;14(2):276-82. No abstract available.
PMID: 5772851

Journal of Toxicology and Environmental Health, Part A, 70: 7–18, 2007

ISSN: 1528-7394 print/1087-2620 online
DOI: 10.1080/15287390600748799

Risk of Selected Birth Defects with Prenatal Illicit Drug Use, Hawaii, 1986–2002

Mathias B. Forrester and Ruth D. Merz
Hawaii Birth Defects Program, Honolulu, Hawaii, USA

The literature on the association between prenatal illicit drug use and birth defects is inconsistent. The objective of this study was to determine the risk of a variety of birth defects with prenatal illicit drug use. Data were derived from an active, population-based adverse pregnancy outcome registry. Cases were all infants and fetuses with any of 54 selected birth defects delivered during 1986–2002. The prenatal methamphetamine, cocaine, or marijuana use rates were calculated for each birth defect and compared to the prenatal use rates among all deliveries. Among all deliveries, the prenatal use rate was 0.52% for methamphetamine, 0.18% for cocaine, and 0.26% for marijuana. Methamphetamine rates were significantly higher than expected for 14 (26%) of the birth defects. Cocaine rates were significantly higher than expected for 13 (24%) of the birth defects. Marijuana rates were significantly higher than expected for 21 (39%) of the birth defects. Increased risk for the three drugs occurred predominantly among birth defects associated with the central nervous system, cardiovascular system, oral clefts, and limbs. There was also increased risk of marijuana use among a variety of birth defects associated with the gastrointestinal system. Prenatal uses of methamphetamine, cocaine, and marijuana are all associated with increased risk of a variety of birth defects. The affected birth defects are primarily associated with particular organ systems.

Journal of Toxicology and Environmental Health, Part A, 70: 7–18, 2007

ISSN: 1528-7394 print / 1087-2620 online
DOI: 10.1080/15287390600748799

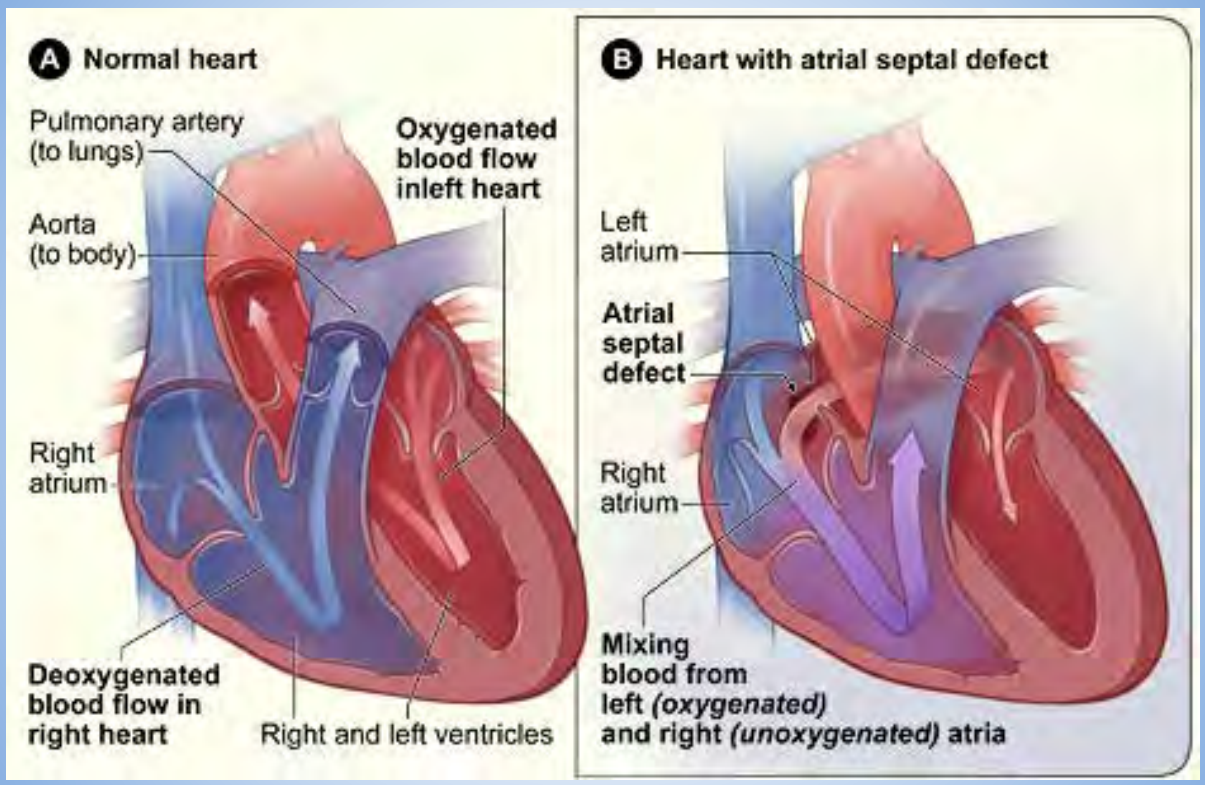
Risk of Selected Birth Defects with Prenatal Illicit Drug Use, Hawaii, 1986–2002

Mathias B. Forrester and Ruth D. Merz
Hawaii Birth Defects Program, Honolulu, Hawaii, USA

Deformity	*Rate Ratio*	*95%C.I.*
Encephalocoele	39.98	9.03-122.29
Hypoplastic Left Heart Syndrome	32.29	3.81-122.65
Syndactyly	24.33	10.40-48.63
Gastroschisis	23.11	4.69-69.34
Reduction Deformity Upper Limbs	21.90	4.45-65.63
Hydrocephly	16.65	6.65-34.66
Cleft Palate	14.73	3.98-38.23
Anotia / Microtia	13.99	1.68-51.66
Tetralogy of Fallot	13.65	1.64-50.37
Pyloric Stenosis	13.17	3.56-34.13
Microcephaly	12.80	4.13-30.17
Pulmonary Valve Atresia / Stenosis	11.46	3.10-29.66
Anal, Rectal, Large Bowel Atresia / Stenosis	10.36	1.25-38.05
Obstructive Genito-Urinary Defect	9.23	2.98-21.69
Polydactyly	8.87	3.24-19.42
Ventricular Septal Defect	8.83	4.82-14.87
Anopthalmia / Microphthalmia	8.31	0.21-47.38
Cleft Lip with / without Cleft Palate	8.19	2.22-21.13
Atrial Septal Defect	6.12	1.98-14.35
Trisomy 21	5.26	1.08-15.46

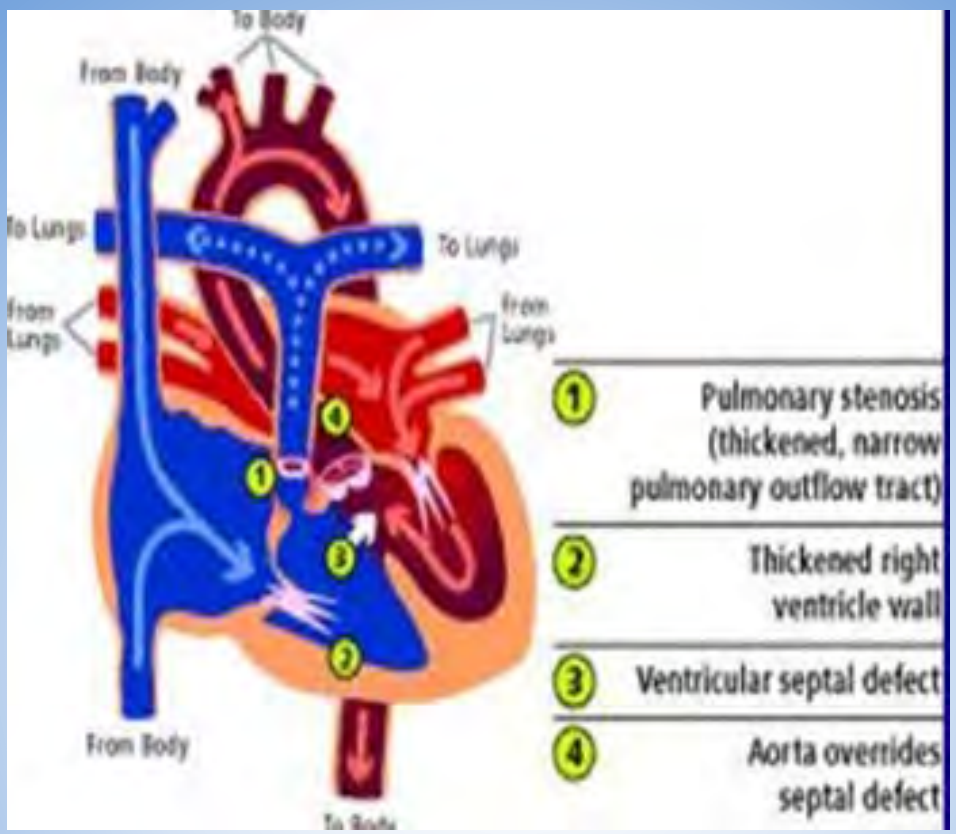
Data Taken from Table 3 – Re-formatted

Atrial Septal Defect



http://www.chd-uk.co.uk/wp-content/uploads/2012/04/atrialseptaldefect2.jpeg

Tetralogy of Fallot



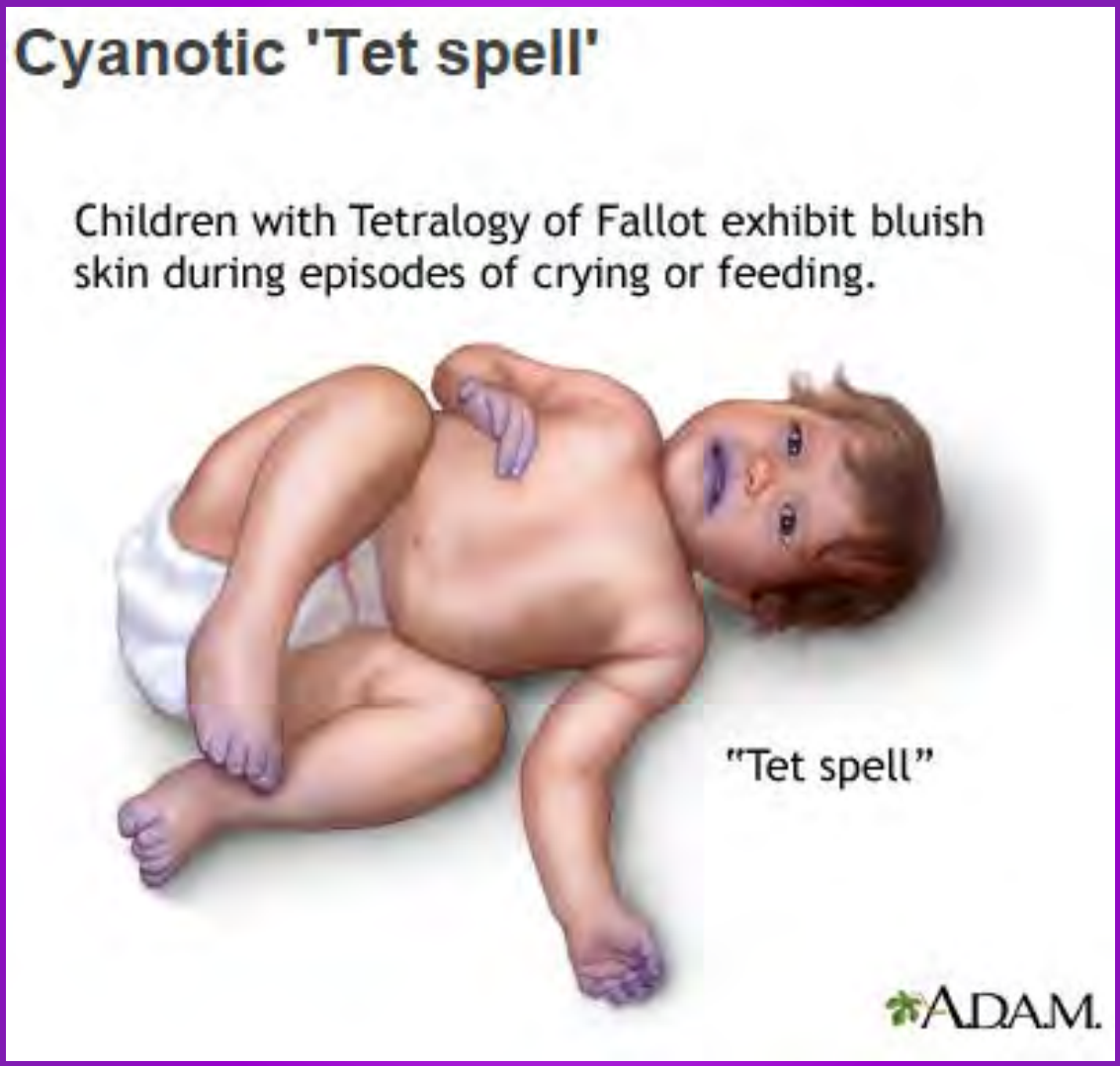
- Most common cyanotic heart defect
- Described in 1888

1. Infundibular Pulmonic Stenosis
2. Right ventricular hypertrophy
3. Conoventricular VSD
4. Dextroposition of the Aorta
   - Overrides VSD

http://www.bing.com/images/search?q=conoventricular+defect&view=detailv2&&id=48578A56799C197B441D491D00FEEB85A84D8148&selectedIndex=17&ccid=SNNO58pU&simid=608032834661977895&thid=OIP.M48d34ee7ca540a52e9ab9ae4cf86397bo0&ajaxhist=0

Cyanotic Congenital Heart Disease

~ Tetralogy of Fallot



https://medlineplus.gov/ency/imagepages/18134.htm

PATERNAL Cannabis Largest Contributor for one Congenital Heart Disease

American Journal of Epidemiology
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Printed in U.S.A.

ORIGINAL CONTRIBUTIONS

Attributable Fraction for Cardiac Malformations

P. David Wilson,[1] Christopher A. Loffredo,[1] Adolfo Correa-Villaseñor,[2] and Charlotte Ferencz[1]

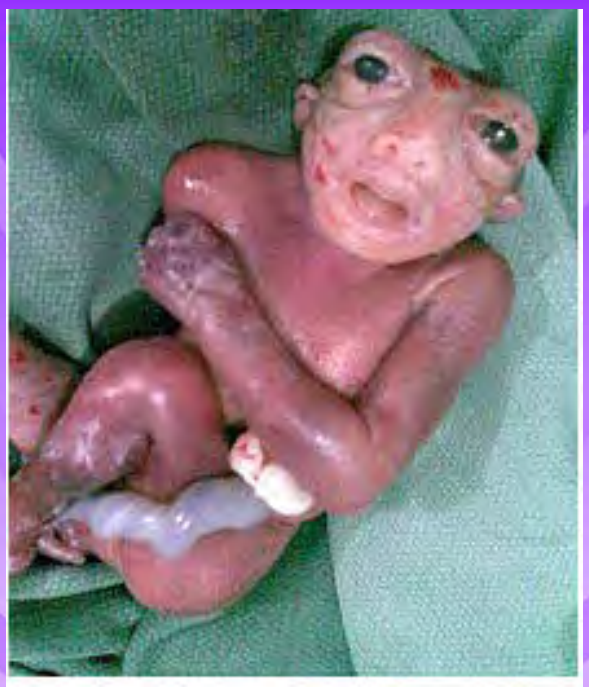
To the authors' knowledge, attributable fractions for cardiac malformations have not been reported before. The Baltimore-Washington Infant Study published factors associated with several major cardiac malformations in Maryland, the District of Columbia, and adjacent counties of northern Virginia in 1981–1989. For eight of these malformations, the authors provide attributable fractions of those factors that are potentially causal. Summary attributable fractions range from 13.6% (four factors) for hypoplastic left heart to 30.2% (seven factors) for transposition of great arteries with intact ventricular septum. Extra attributable fraction for factor *x*, defined as summary attributable fraction for all factors minus that for all but *x*, is largest for: 1) paternal marijuana use in transposition of great arteries with intact ventricular septum, 7.8%; 2) paternal anesthesia in tetralogy of Fallot, 3.6%; 3) painting in atrioventricular septal defect with Down syndrome, 5.1%; 4) solvent/degreasing agent exposure in hypoplastic left heart, 4.6%; 5) sympathomimetics in coarctation of aorta, 5.8%; 6) pesticide exposure in isolated membranous ventricular septal defect, 5.5%; 7) hair dye in multiple/multiplex membranous ventricular septal defect, 3.3%; and 8) urinary tract infection in atrial septal defect, 6.4%. Percent-of-cases-exposed dominates relative risk in attributable fraction. If these factors are causal, the larger extra attributable fractions suggest the potential for prevention by specific interventions before/during pregnancy. *Am J Epidemiol* 1998;148:414–23.

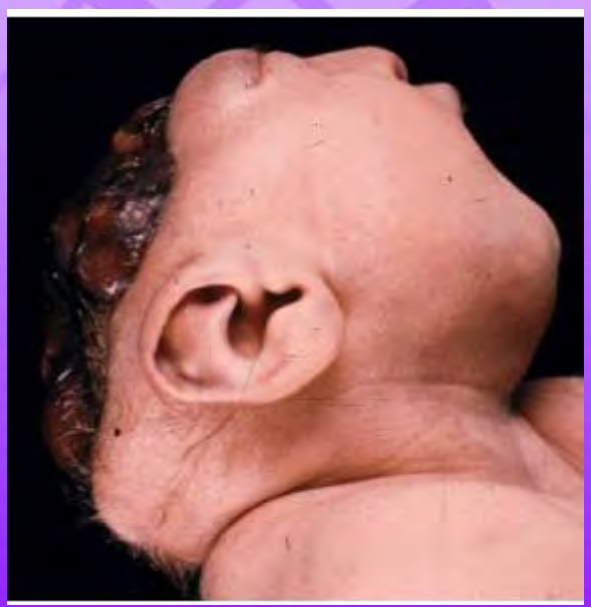
https://medlineplus.gov/ency/imagepages/18134.htm

Anencephaly

http://thegiftofrachelslife.blogspot.com/2012/07/the-truth-about-anencepahly.html

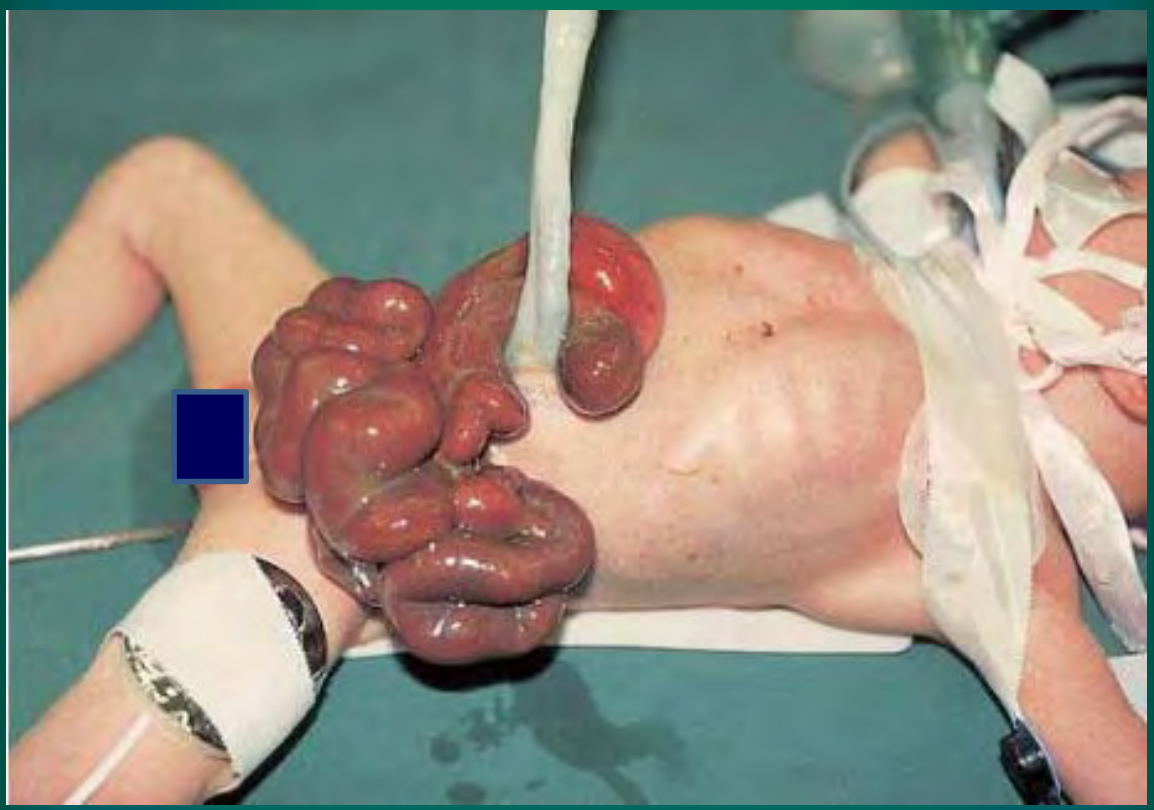
Anencephaly





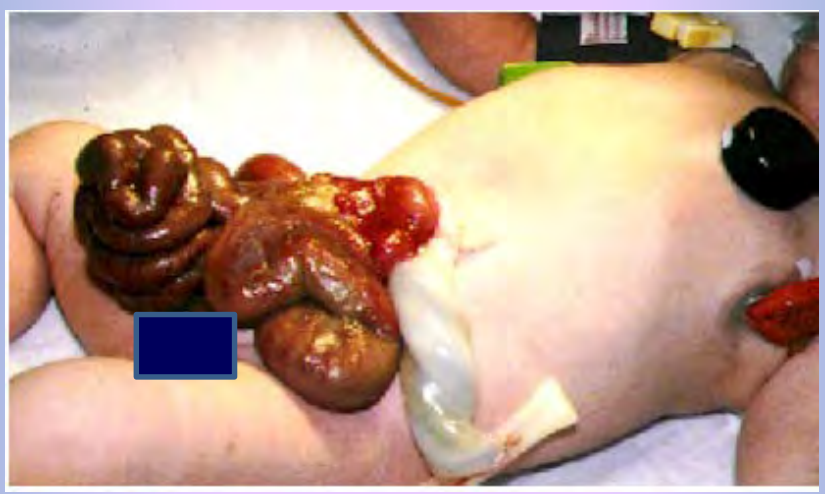
Gastroschisis

Gastroschisis - *Endangered Bowel*



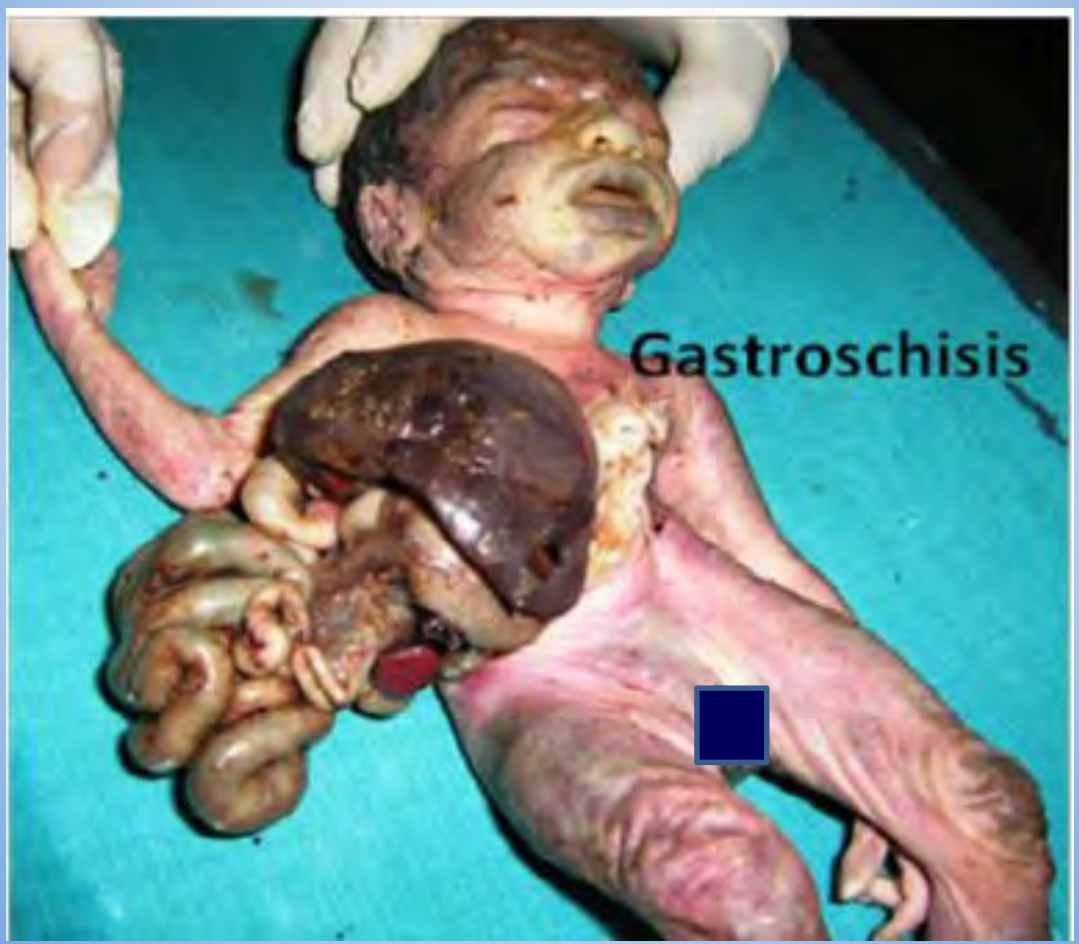
http://www.medicaldaily.com/rare-birth-defect-gastroschisis-rise-newborns-babies-external-organs-have-90-survival-rate-247799

Gastroschisis



Dead Bowel

Gastroschisis - *Dead Baby*



https://www.researchgate.net/publication/272171722_Gastroschisis_with_Skeletal_Deformities_A_Case_Report_with_Review_of_Literature/figures?lo=1

Queensland

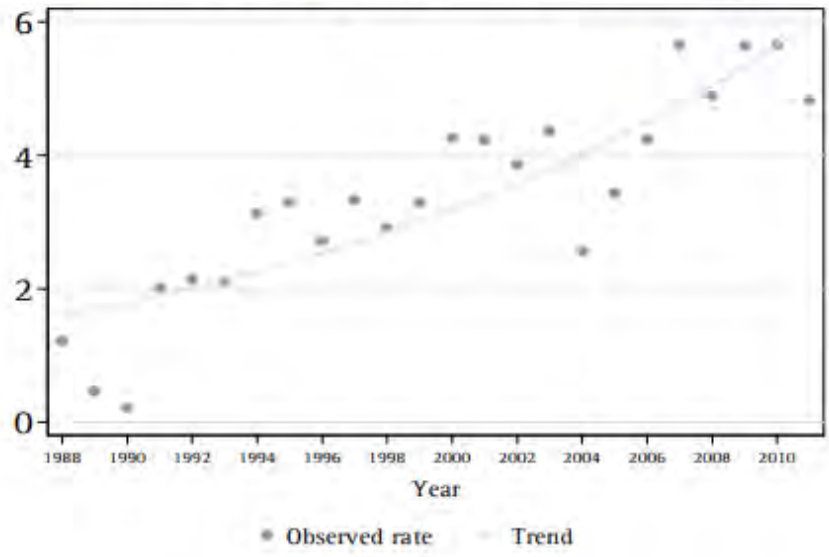
StatBite #57 October 2013

Gastroschisis in Queensland

Taku Endo[a], Trisha Johnston[a], Joanne Ellerington[a], Tim Donovan[b]
[a]Health Statistics Unit, Queensland Health
[b]Grantley Stable Neonatal Unit, Royal Brisbane and Women's Hospital

Gastroschisis is a form of congenital anomaly which is characterised by an uncovered visceral herniation through a (typically) right side abdominal wall defect with an intact umbilical cord[1-3]. While omphalocele, another common form of abdominal wall defect, is often associated with other structural or chromosomal

Figure 1. Gastroschisis rate per 10,000 births, Queensland, 1988–2011



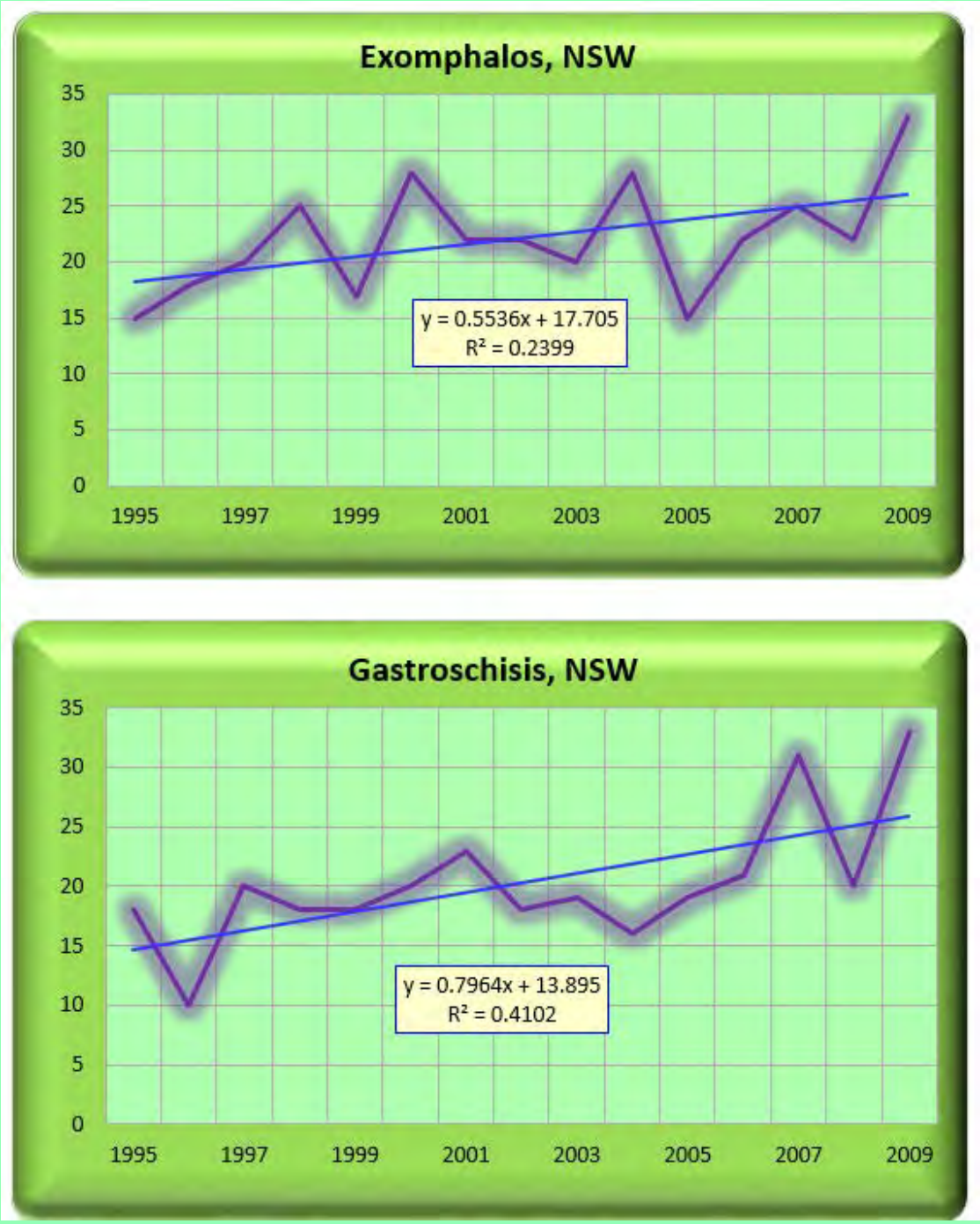
Source: Queensland Perinatal Data Collection

In Queensland it has increased by 500% over the past 20 years.

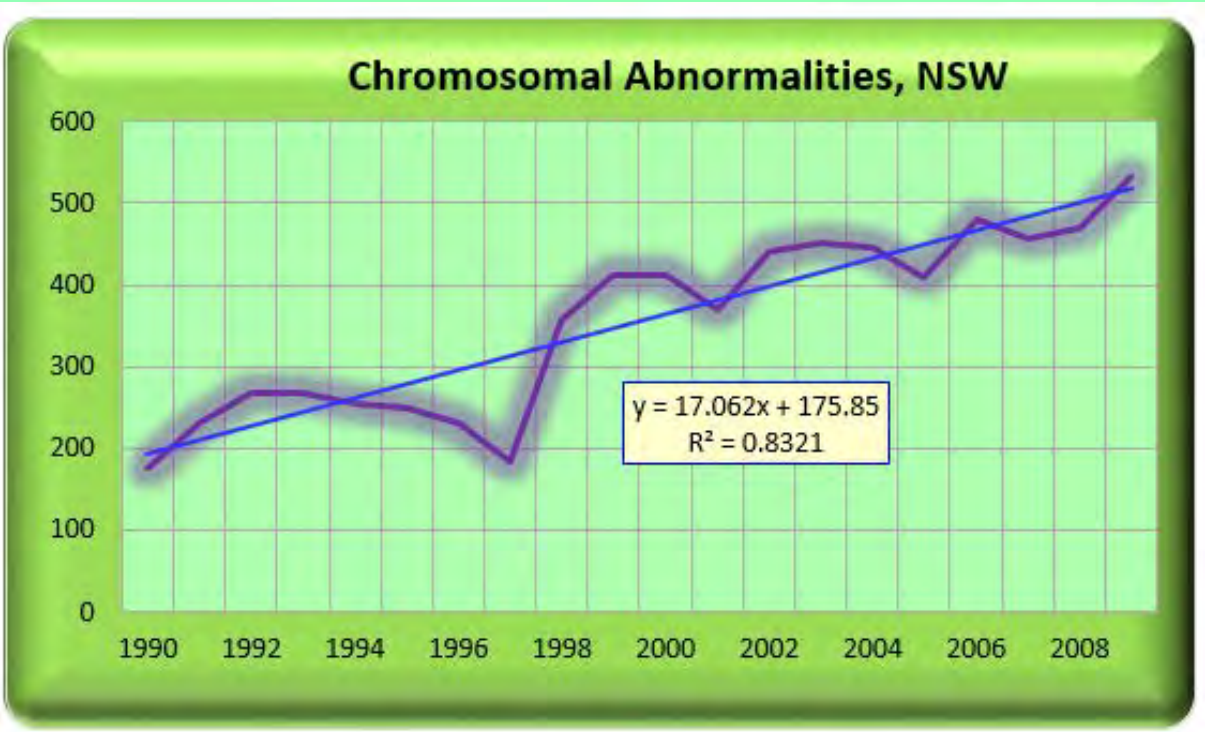
https://www.health.qld.gov.au/__data/assets/pdf_file/0026/361385/statbite57.pdf

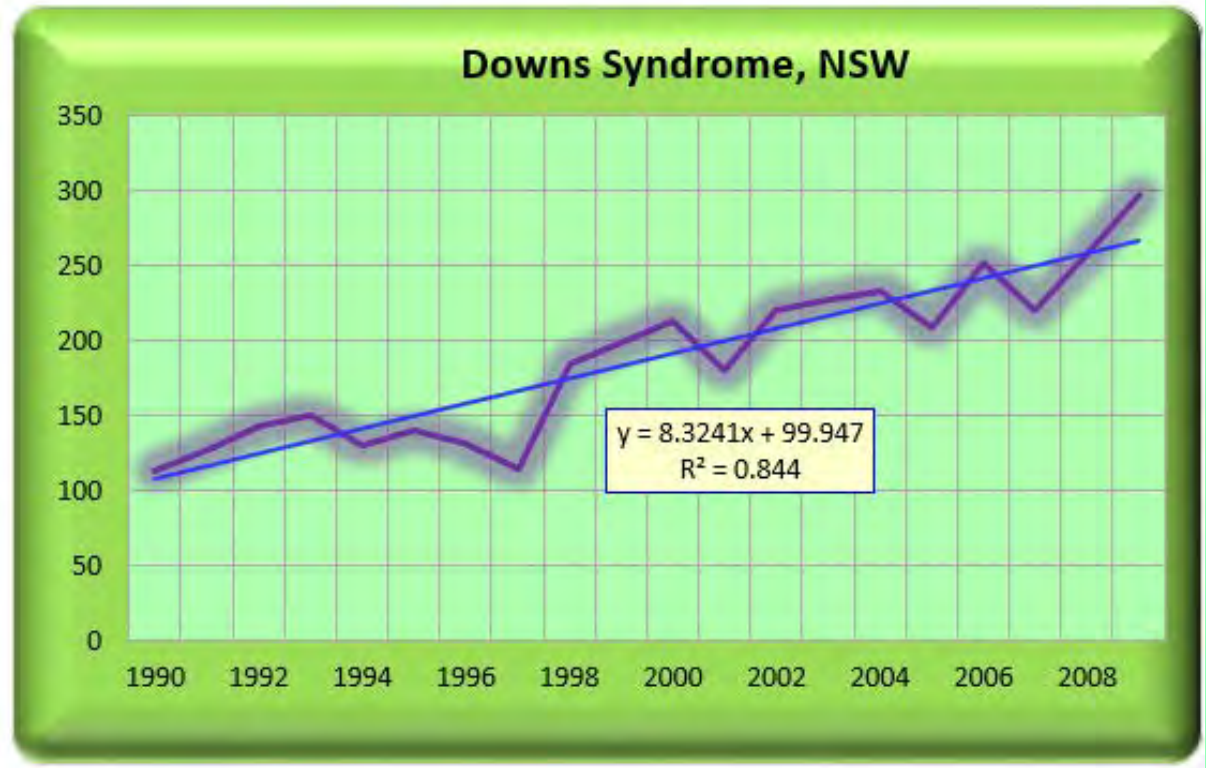
https://www.northernstar.com.au/news/cases-of-birth-defect-exceed-state-average/867706/

New South Wales



New South Wales





NSW

Birth defects exceed NSW average

ONE in every 422 Lismore babies born between 2008 and 2010 had the horrific birth defect gastroschisis, a NSW Health report released yesterday shows.

The birth defect, in which babies are born with their intestinal contents protruding through the abdominal wall, affects about one baby in every 5000 to 10,000 live births.

The final report into a Northern Rivers cluster of gastroschisis – a condition in which babies are born with their intestinal contents freely protruding through a hole in the abdomen – has also revealed there were 26 cases of the rare condition over the past decade within an area extending from the Tweed to Port Macquarie.

Only 11 of these cases had been reported to NSW Register of Congenital Conditions, with 15 babies' details going unrecorded due do a breakdown in communication between NSW health authorities and the Brisbane hospital where the babies were transferred prior to birth for specialist treatment.

https://www.northernstar.com.au/news/cases-of-birth-defect-exceed-state-average/867706/

What is Hanging Around Dad's Neck??

https://www.frasercoastchronicle.com.au/news/parents-dissatisfied-with-probe-birth-defects-nsw/863109/

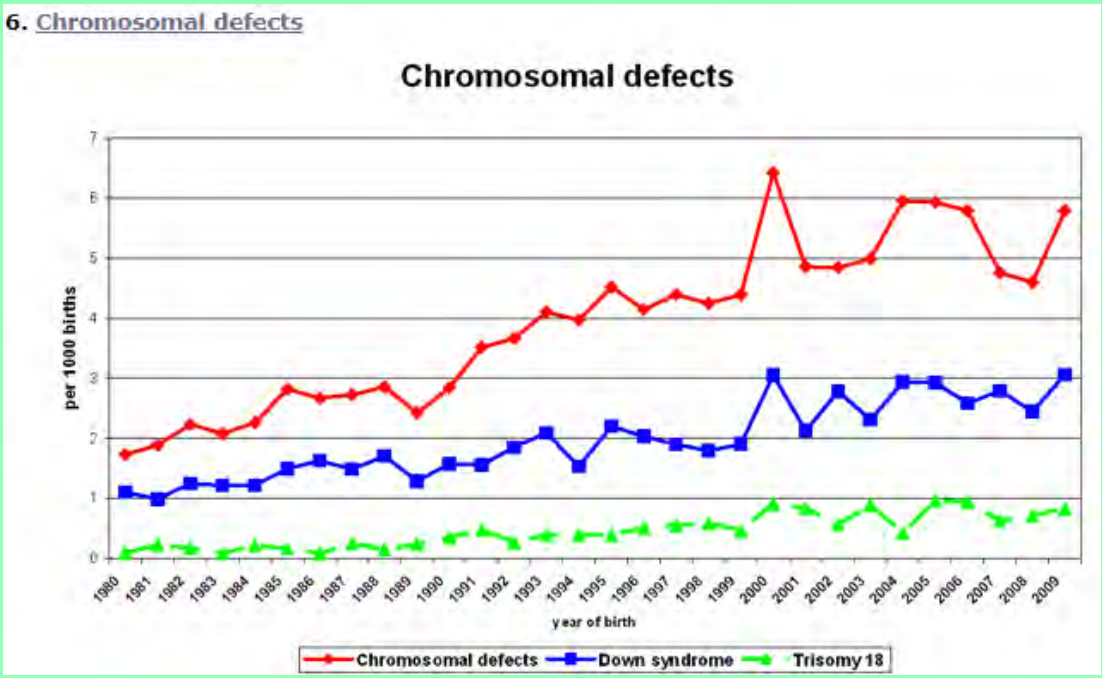
Eight-month-old baby Olive Ostila of Barkers Vale, pictured with parents Jacqui McSkimming and Matt Ostila, was born with gastroschisis. Picture: Cathy Adams

HEALTH

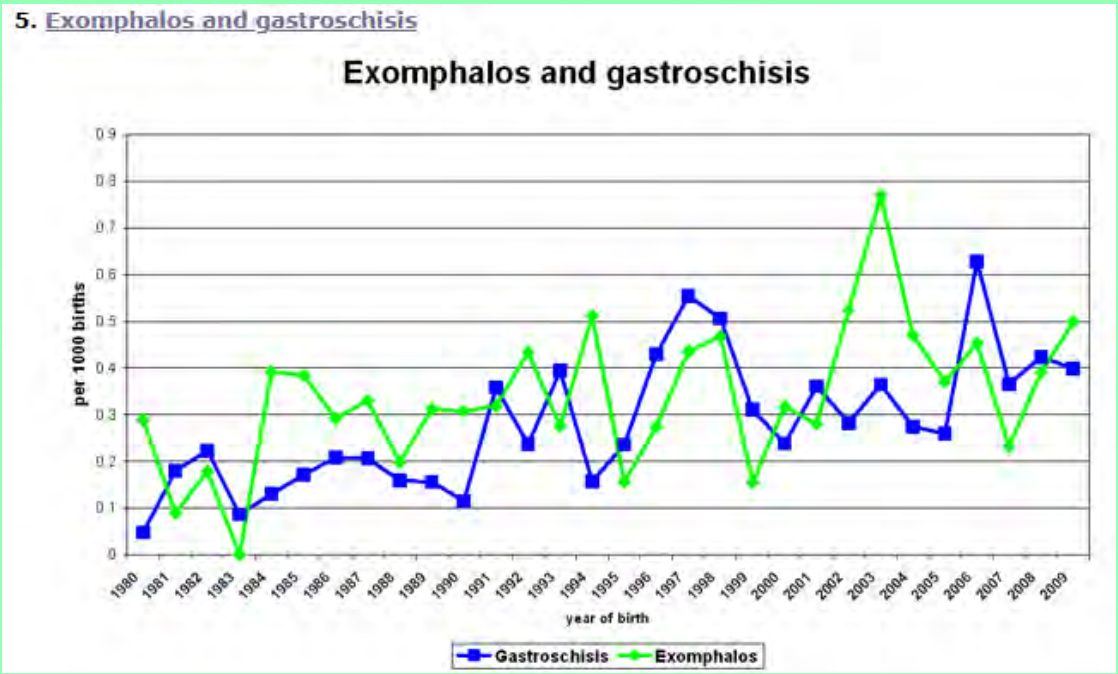
NSW Health to monitor birth defects

Western Australia

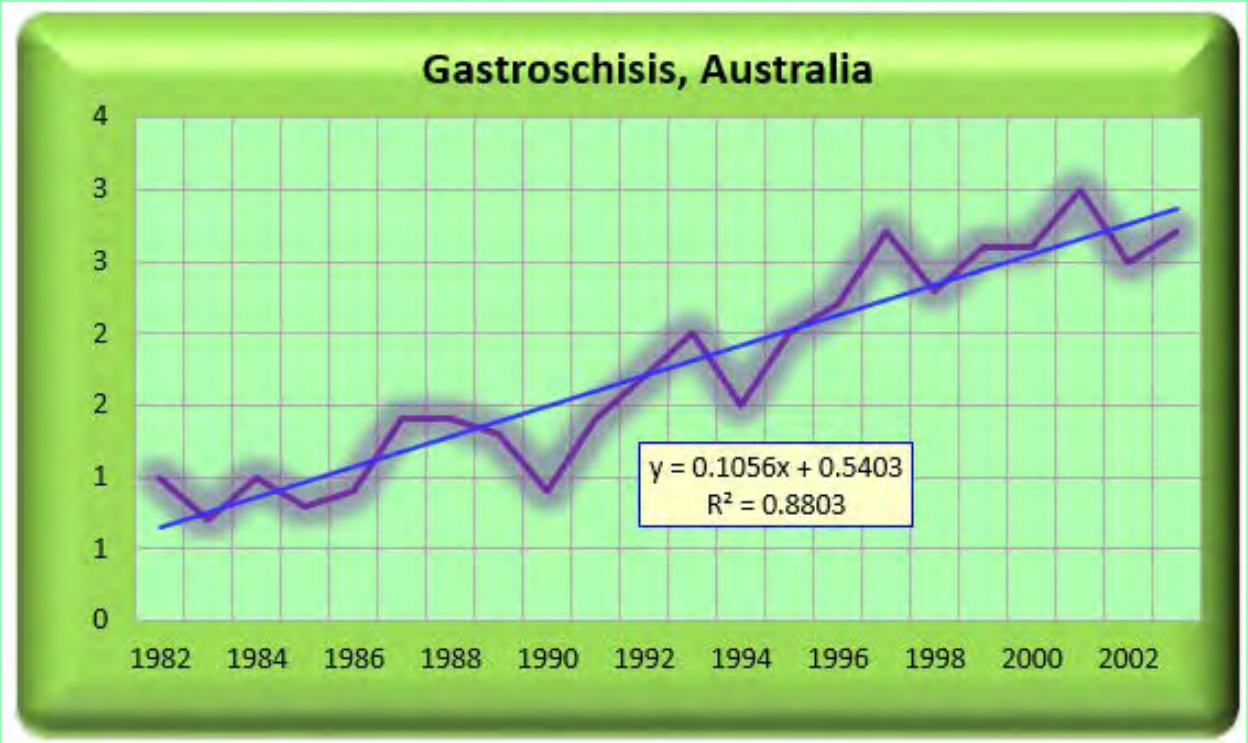
6. Chromosomal defects

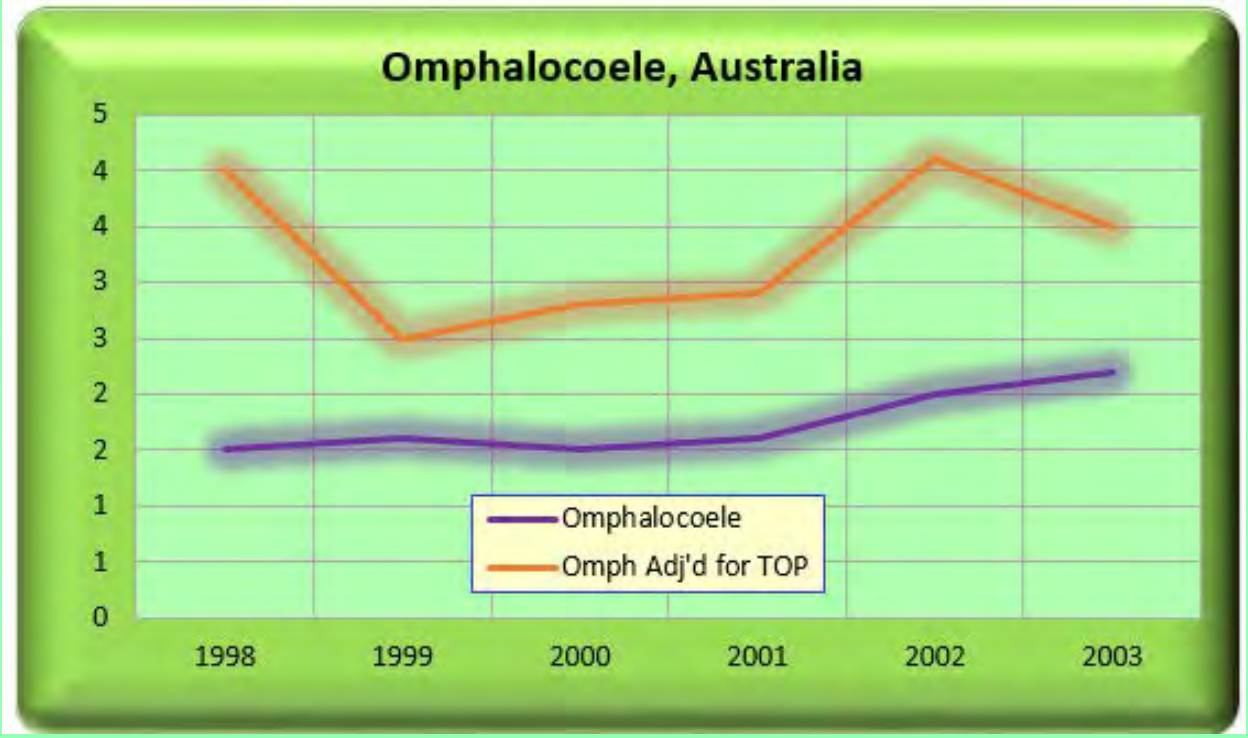


5. Exomphalos and gastroschisis

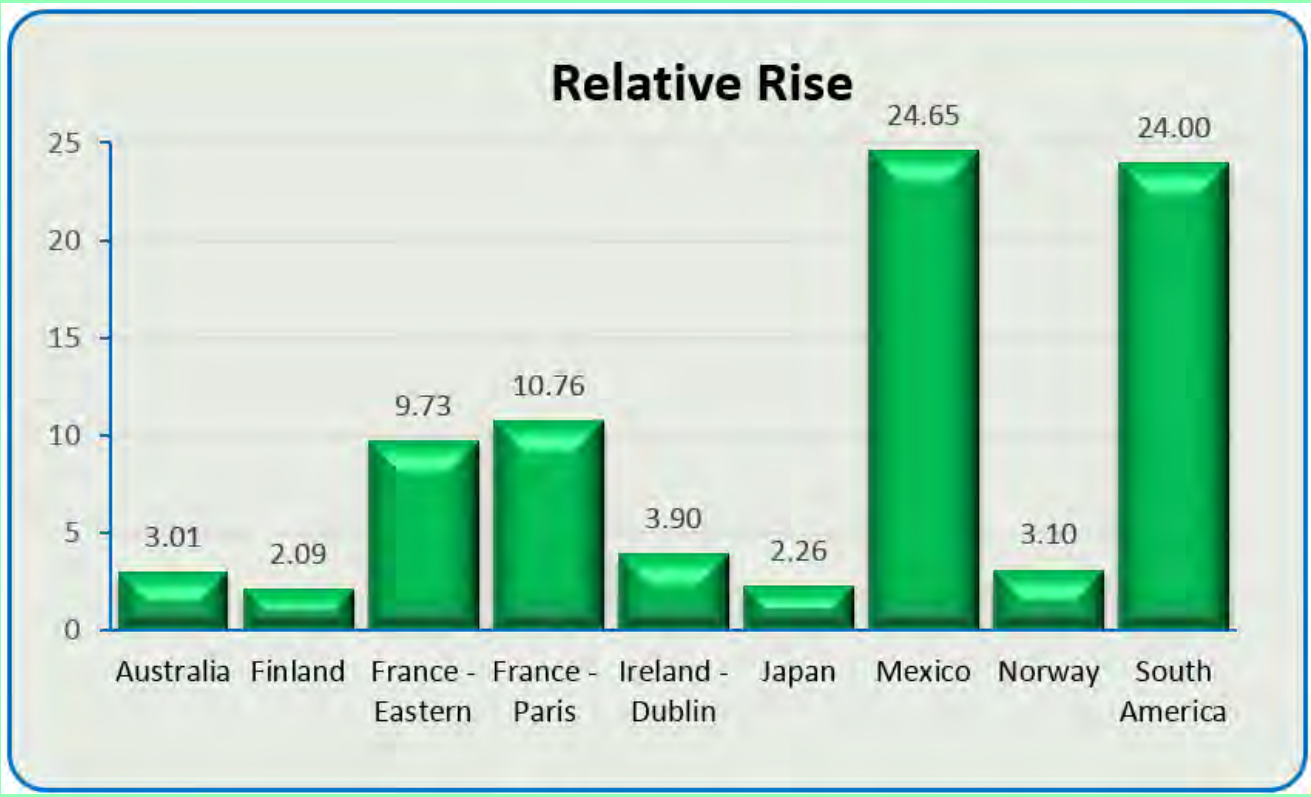


Australia


Gastroschisis, Australia
4
3
3
2
2
1
1
0
1982
1984
1986
1988
1990
1992
1994
1996
1998
2000
2002
y = 0.1056x + 0.5403
R² = 0.8803


Omphalocoele, Australia
5
4
4
3
3
2
2
1
1
0
1998
1999
2000
2001
2002
2003
Omphalocoele
Omph Adj'd for TOP

Gastroschisis Annual Incidence Tripled in 9/19 Nations in 24 Years Overall Rise 0.3 to 1.66 / 10,000 Births



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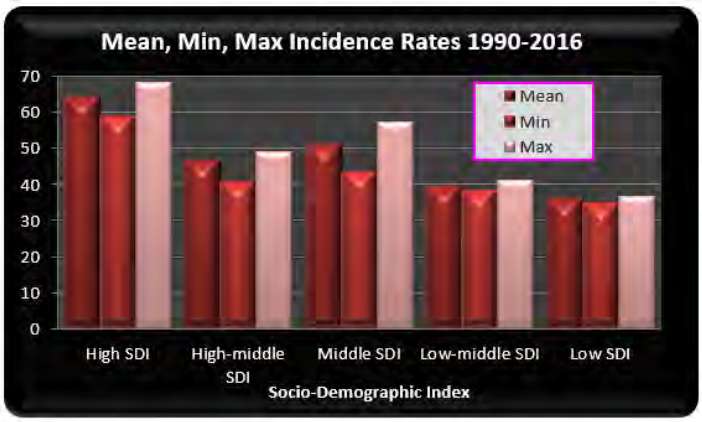
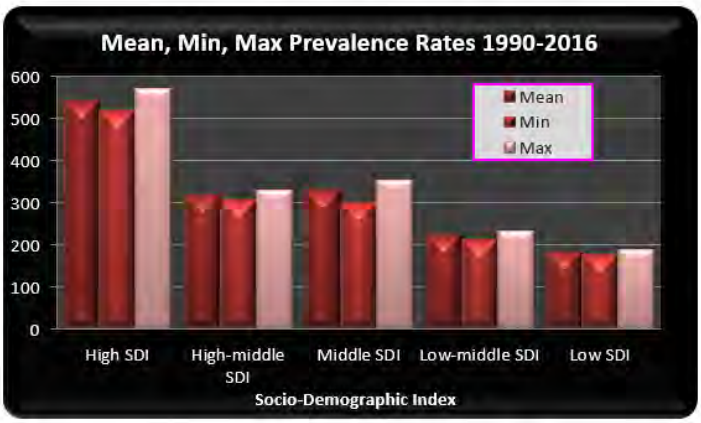
Prevalence of gastroschisis at birth: retrospective study

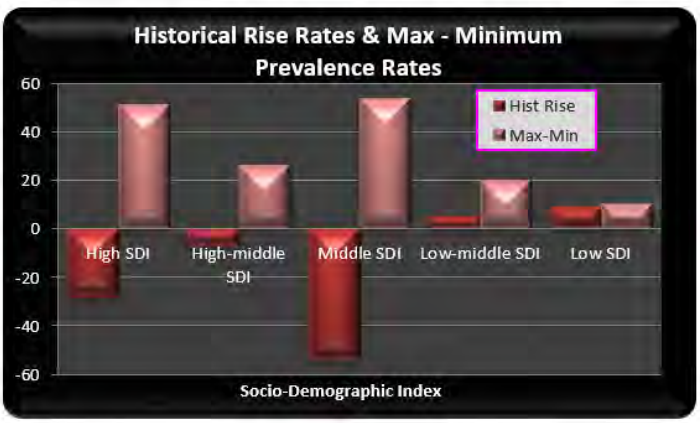
BMJ 2002 ; 325 doi: https://doi.org/10.1136/bmj.325.7377.1389 (Published 14 December 2002)
Cite this as: *BMJ* 2002;325:1389

Gian Luca Di Tanna, senior statistician [a], *Aldo Rosano, senior researcher* [b], *Pierpaolo Mastroiacovo, director* (icbd@icbd.org) a

Cannabis Use Incidence & Prevalence Global Patterns, Global Burden of Disease Data

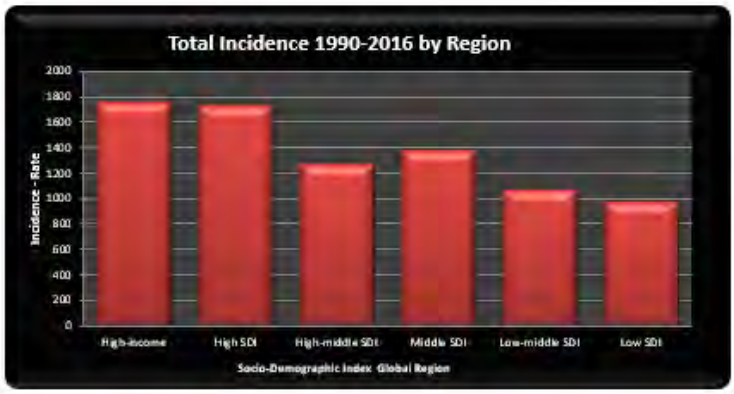


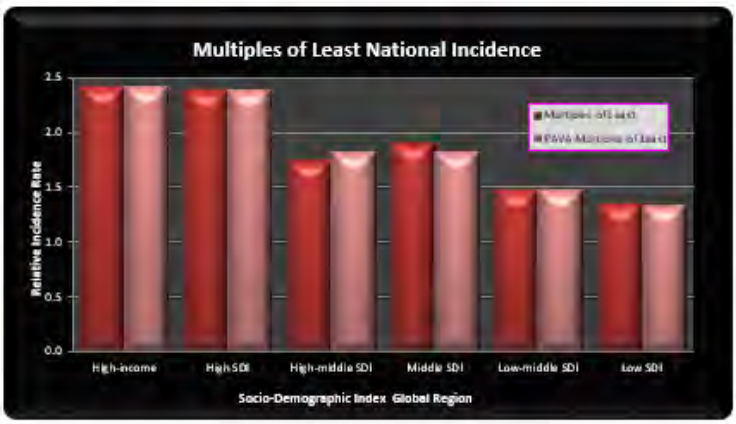


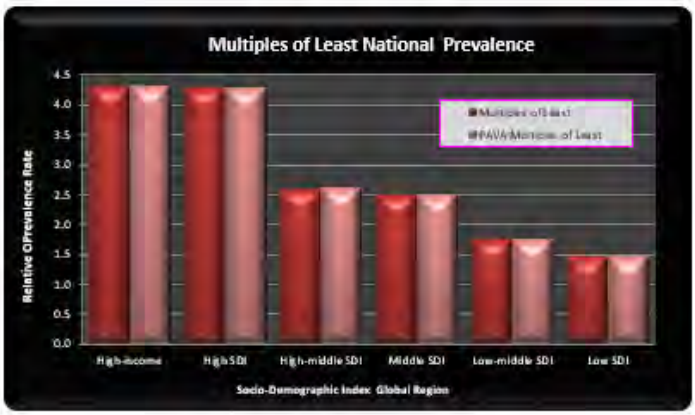


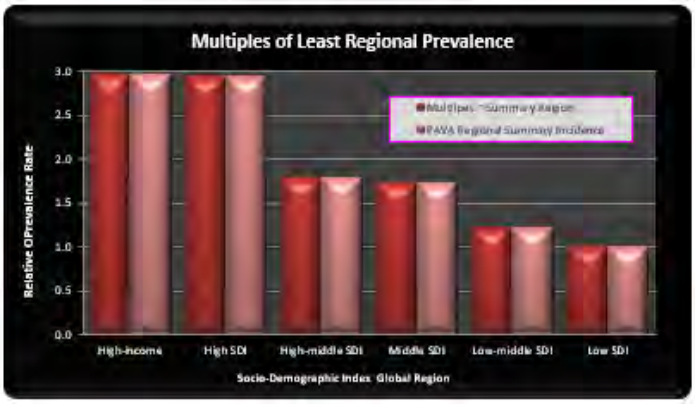
http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2016-permalink/8a96f2917cad95b4226c62037a530994

Cannabis Use
Incidence & Prevalence
Global Patterns,
Global Burden of Disease Data



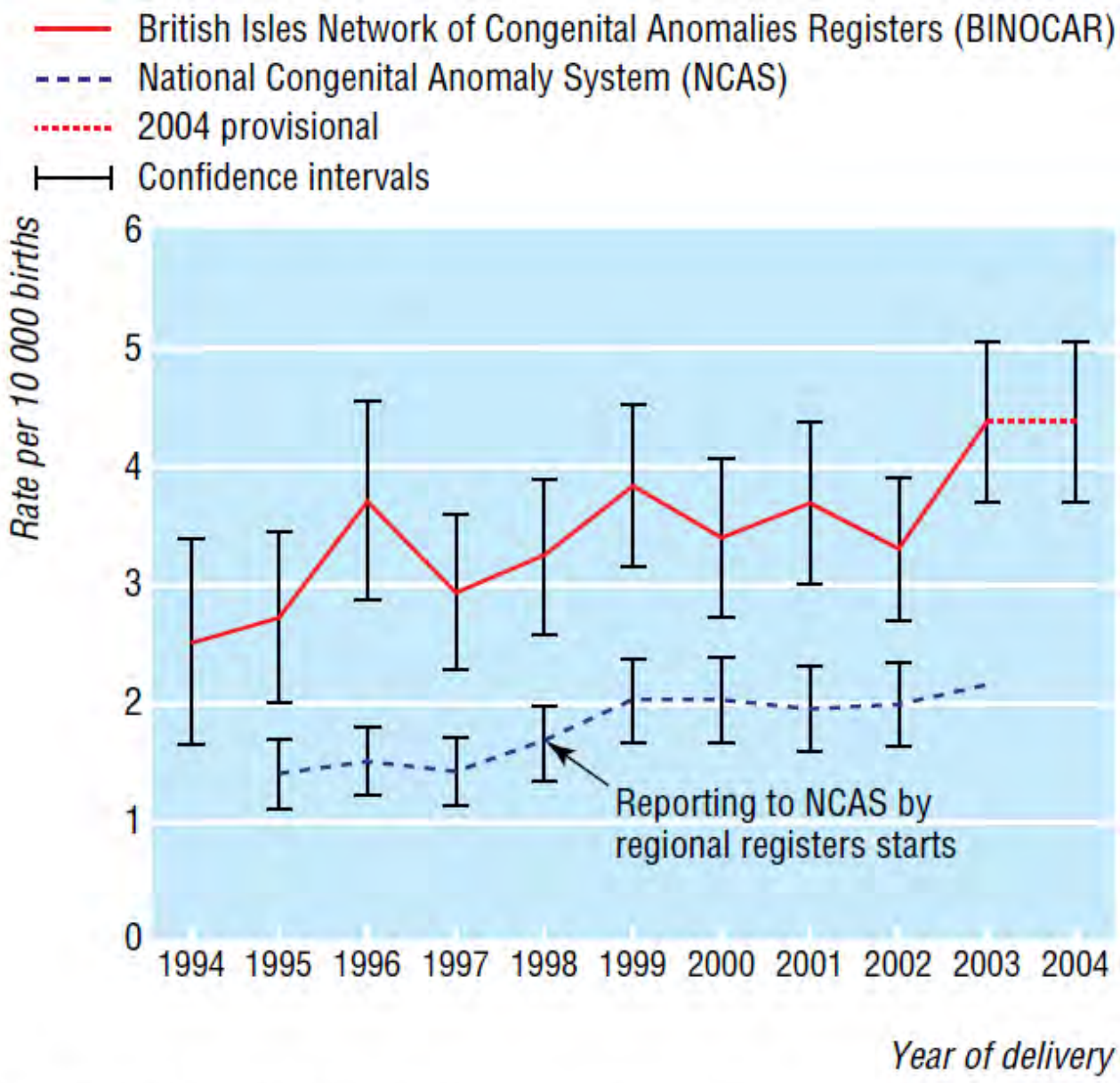






http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2016-permalink/d8c6859394af01664d6c9ab9ddcb1530

Gastroschisis in U.K.



Number of reported cases of gastroschisis between 1994 and 2004. Reproduced with permission from the Department of Health

The incidence of **gastroschisis**: Is increasing in the UK, particularly among babies of young mothers

Mark D Kilby

BMJ. 2006 February 4; 332(7536): 250–251. doi: 10.1136/bmj.332.7536.250

PUBLIC HEALTH AGENCY OF CANADA

CONGENITAL ANOMALIES IN CANADA 2013

A PERINATAL HEALTH SURVEILLANCE REPORT



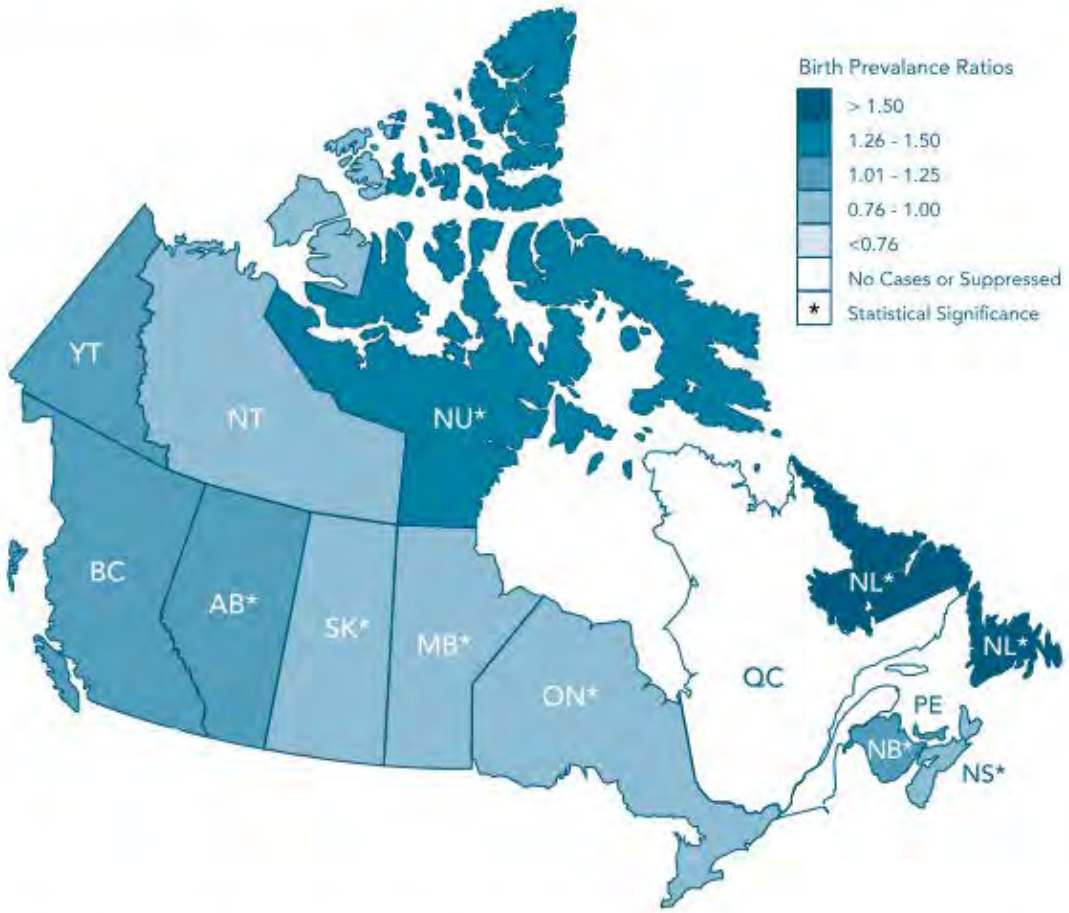
http://publications.gc.ca/collections/collection_2014/aspc-phac/HP35-40-2013-eng.pdf

PROTECTING CANADIANS FROM ILLNESS

Marked Variation ~ All Congenital Anomalies

FIGURE 1.5B

Ratio of provincial/territorial congenital anomaly rate to national rate,** *Canada, (excluding Québec) 2000–2009 combined*

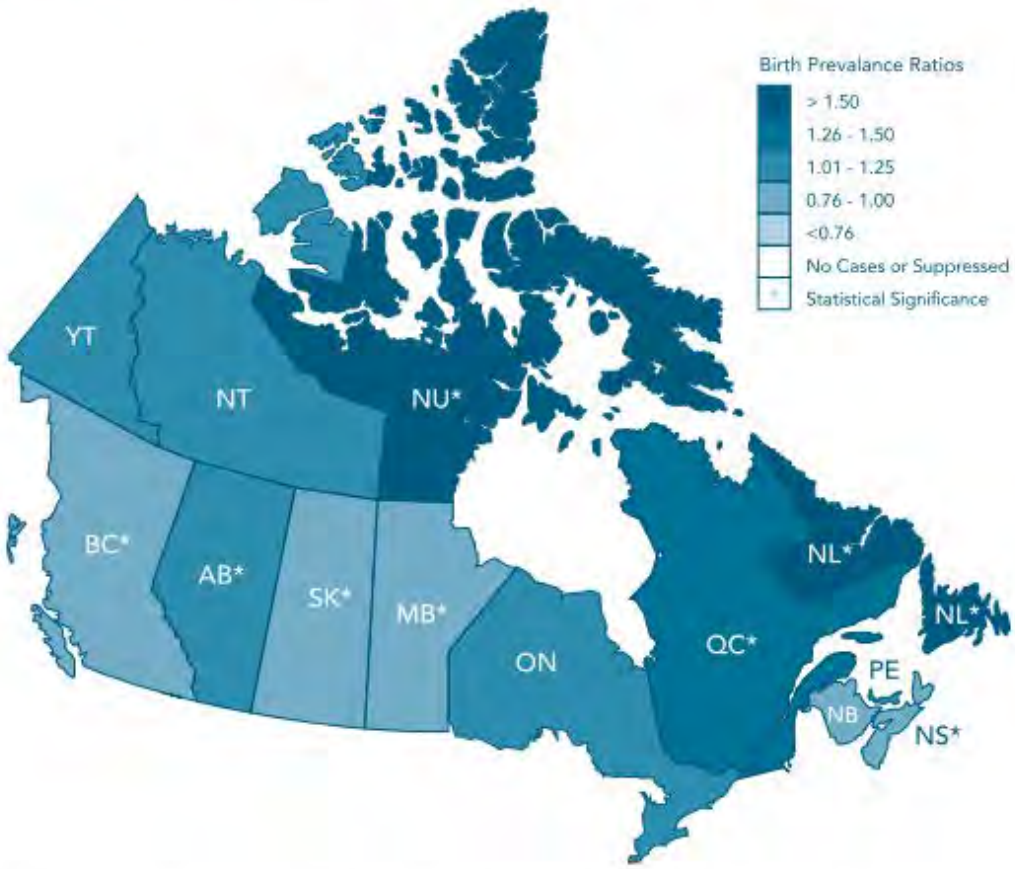


Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 2000–2009.
**This ratio calculates the birth prevalence rate per 10,000 total births of each individual province/territory to the birth prevalence rate for Canada during the specified time period. The birth prevalence for Canada includes cases for which province/territory is unknown.
***Québec was excluded because data were not available for all years.

Marked Variation
~ Cardiac Anomalies

FIGURE 4.3B

Ratio of provincial/territorial congenital heart defect rate to national rate,**
Canada, 2000–2009, (Québec 1998–2007) combined

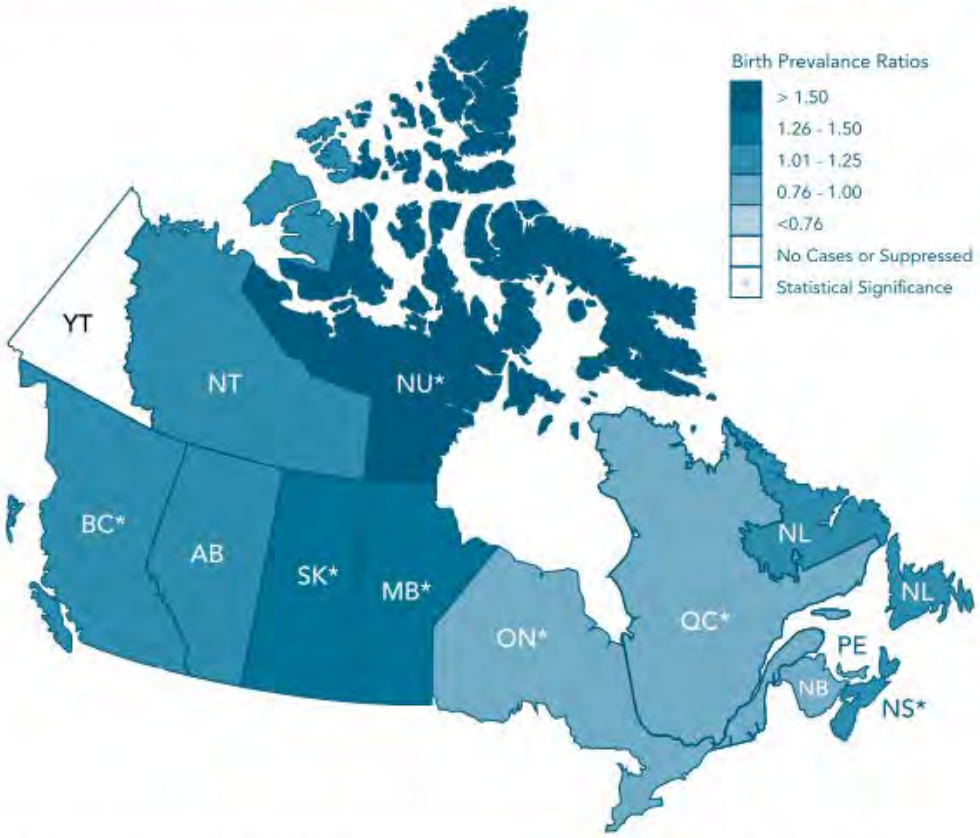


Source: Canadian Congenital Anomalies Surveillance System database, 1998–2009 (Québec 1998–2007).
**This ratio calculates the birth prevalence rate per 10,000 total births of each individual province/territory to the birth prevalence rate for Canada during the specified time period. The birth prevalence for Canada includes cases for which province/territory is unknown.

Marked Variation ~ Orofacial Clefts

FIGURE 5.2B

Ratio of provincial/territorial orofacial cleft rate to national rate,** *Canada, 1998–2007 combined*

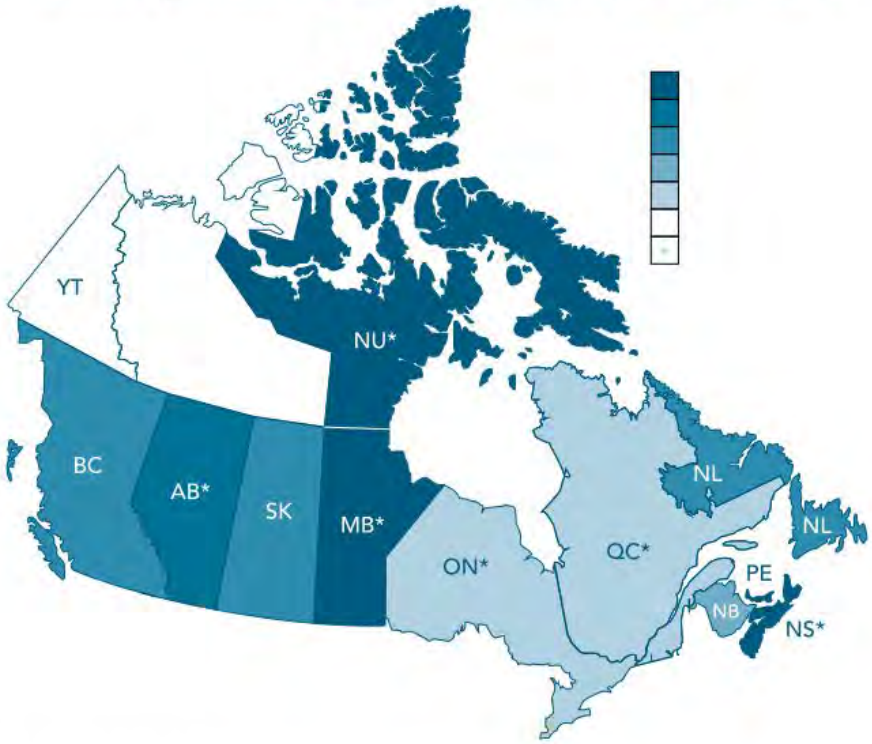


Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 1998–2007.
Source of Alberta data: Alberta Congenital Anomalies Surveillance System, 1998–2007.
**This ratio calculates the birth prevalence rate per 10,000 total births of each individual province/territory to the birth prevalence rate for Canada during the specified time period. The birth prevalence for Canada includes cases for which province/territory is unknown.

Marked Variation ~ Gastroschisis

FIGURE 7.2B

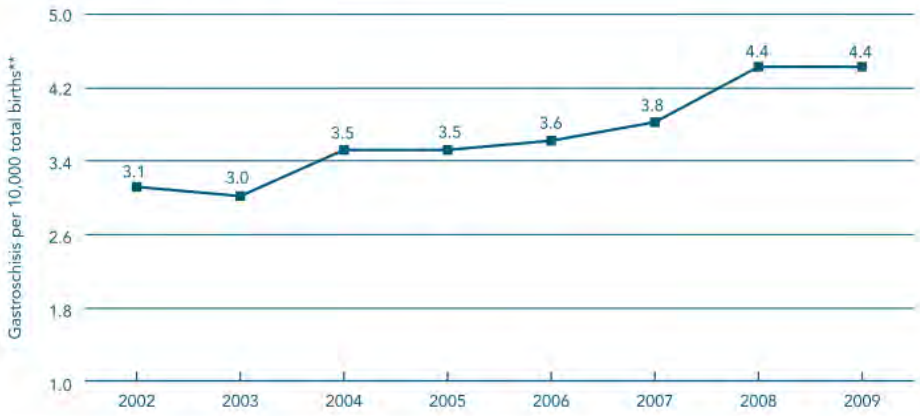
Ratio of provincial/territorial gastroschisis rate to national rate,** *Canada, 2000–2009 combined*



Source: Public Health Agency of Canada. Canadian Congenital Anomalies Surveillance System, 2000–2009.
**This ratio calculates the birth prevalence rate per 10,000 total births of each individual province/territory to the birth prevalence rate for Canada combined for the eight-year period 2002–2009, with the exception of New Brunswick 2004–2009, Manitoba 2005–2009 and Québec 2006–2007. The birth prevalence for Canada includes cases for which province/territory is unknown.

FIGURE 7.1

Gastroschisis rate, *Canada, 2002–2009**

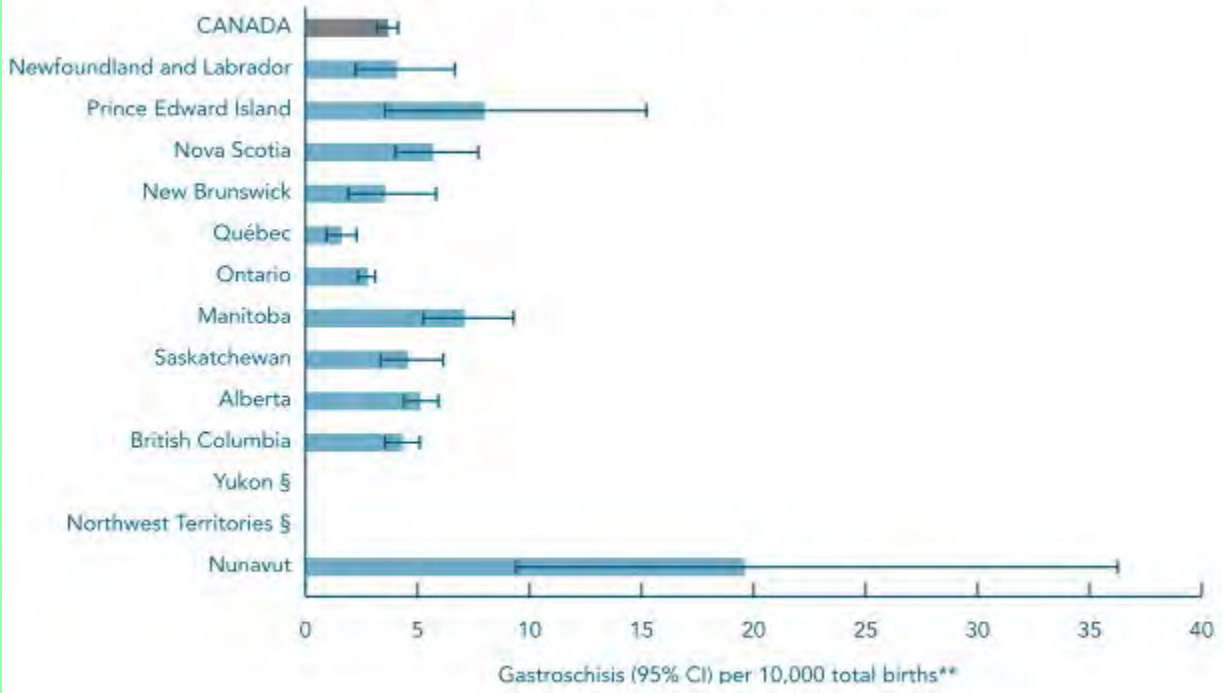


Source: Public Health Agency of Canada, Canadian Congenital Anomalies Surveillance System, 2002–2009.
*Some provincial data were only available for certain years: New Brunswick (2004–2009), Québec (2006–2007) and Manitoba All others were available for the full period (2002–2009). **Total births include live births and stillbirths.

Gastroschisis Rate ~ Province

FIGURE 7.2A

Gastroschisis rate, by province/territory, *Canada, 2002–2009* combined*



Source: Public Health Agency of Canada, Canadian Congenital Anomalies Surveillance System, 2002-2009.
*New Brunswick 2004-2009, Manitoba 2005-2009 and Québec 2006-2007. **Total births include live births and stillbirths.
§ Rate suppressed due to small cell numbers (<5). CI—Confidence Interval

10-Fold Variability in Gastroschisis Across Canada

Table 1. Rate of gastroschisis by province/territory, 2006–2011

Province/territory	Rate per 100,000 live births (95% CI)	Age-standardized rate* (95% CI)
Alberta	27 (21–34)	24 (19–31)
British Columbia	35 (28–43)	37 (30–45)
Manitoba	40 (28–55)	29 (19–41)
New Brunswick	46 (28–71)	34 (19–54)
Newfoundland and Labrador	56 (32–91)	51 (29–82)
Nova Scotia	45 (29–67)	40 (26–60)
Ontario	26 (23–30)	26 (22–29)
Prince Edward Island	82 (33–169)	68 (26–137)
Quebec	23 (19–27)	22 (19–27)
Saskatchewan	23 (14–36)	15 (8–25)
Yukon	90 (11–325)	89 (11–325)
Northwest Territories	118 (38–274)	68 (15–170)
Nunavut	123 (45–268)	36 (5–115)

* There were 42 infants with missing maternal age information that were not included in the age-standardized rate.

Spatial variability of gastroschisis in Canada, 2006–2011: An exploratory analysis

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Kate L. Bassil, PhD,[1] Junmin Yang, MSc,[2] Laura Arbour, MSc, MD,[3] Rahim Moineddin, PhD,[4] Mary E. Brindle, MD, MPH,[5] Emily Hazell, MSA,[6] Erik D. Skarsgard, MSc, MD[7]

Marked Gastroschisis Incidence Variability Across Canada

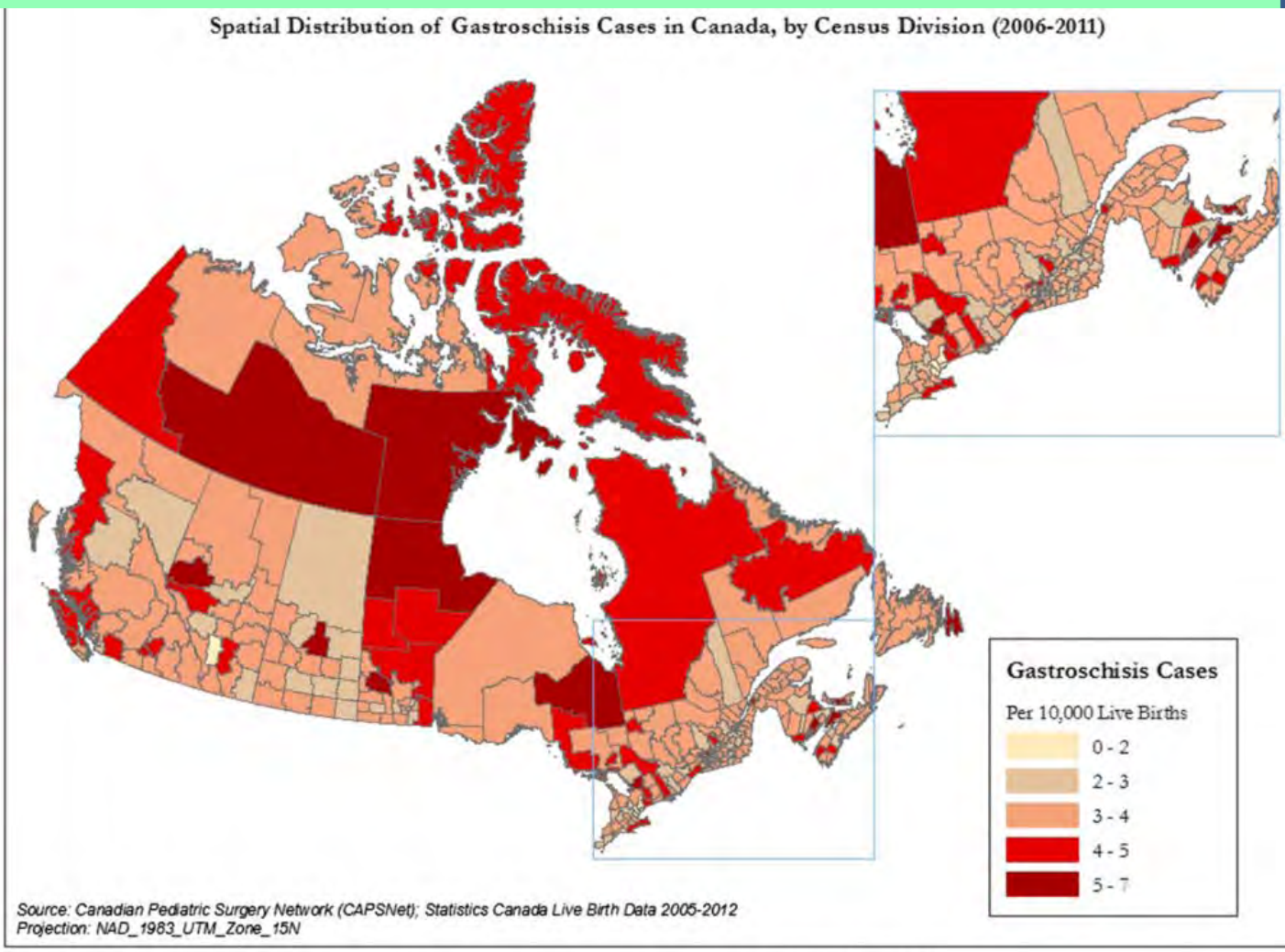

Figure 1. Spatial distribution of gastroschisis cases in Canada by census division, 2006–2011

Spatial variability of gastroschisis in Canada, 2006–2011: An exploratory analysis

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Gastroschisis Clusters - Canada

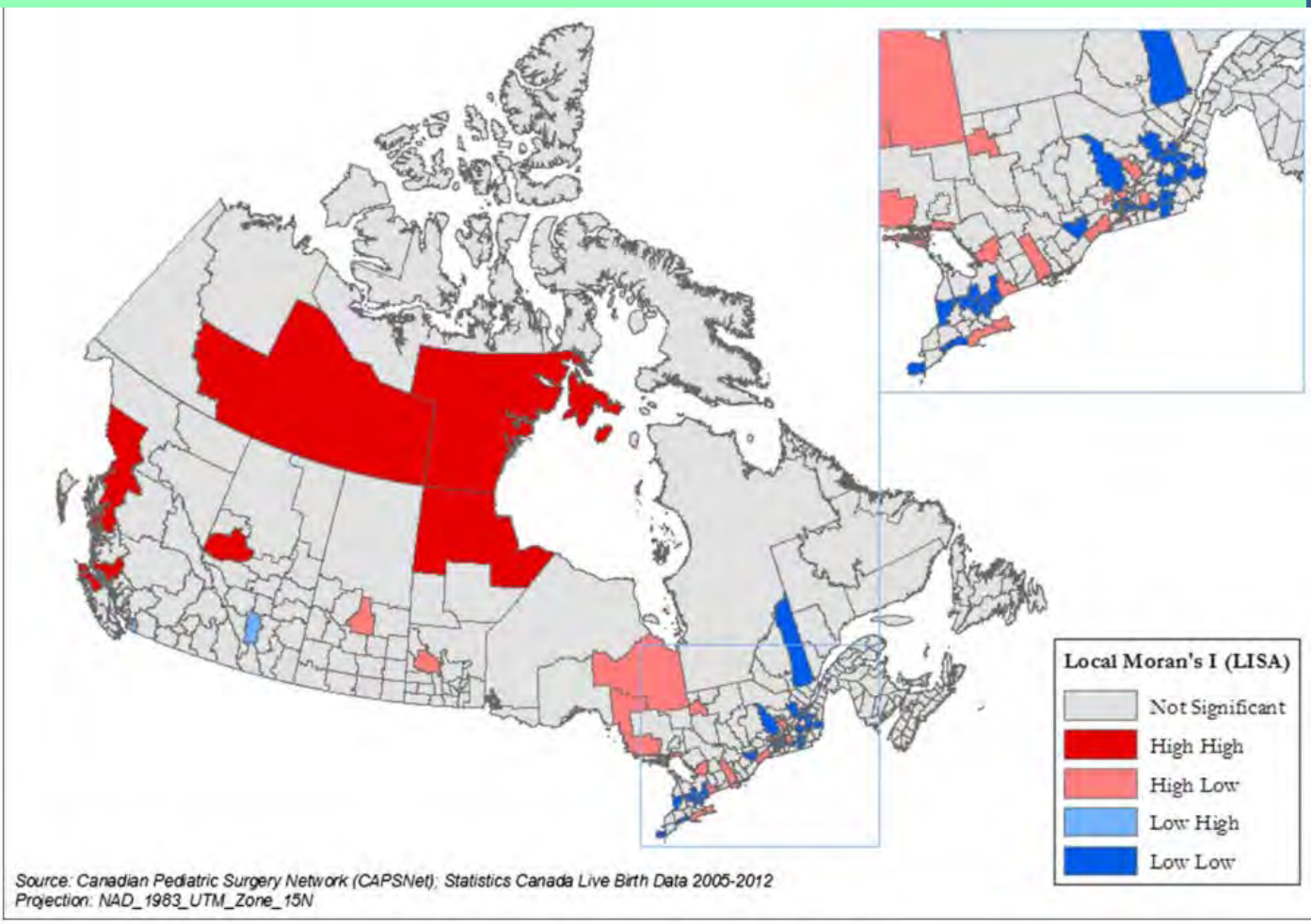

Figure 2. Cluster analysis of gastroschisis in Canada by census division, 2006–2011

http://journal.cpha.ca/index.php/cjph/article/view/5084/3354

Spatial variability of gastroschisis in Canada, 2006–2011: An exploratory analysis

Can J Public Health 2016;107(1):e62–e67
doi: 10.17269/CJPH.107.5084

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Kate L. Bassil, PhD,[1] Junmin Yang, MSc,[2] Laura Arbour, MSc, MD,[3] Rahim Moineddin, PhD,[4] Mary E. Brindle, MD, MPH,[5] Emily Hazell, MSA,[6] Erik D. Skarsgard, MSc, MD[7]

Gastroschisis:

Maternal Risk Factors for Gastroschisis in Canada

Erik D. Skarsgard*[1], Christopher Meaney[2], Kate Bassil[3], Mary Brindle[4], Laura Arbour[5], Rahim Moineddin[2], and the Canadian Pediatric Surgery Network (CAPSNet)

Background: Gastroschisis is a congenital abdominal wall defect that occurs in one per 2200 pregnancies. Birth defect surveillance in Canada has shown that the prevalence of gastroschisis has increased threefold over the past 10 years. The purpose of this study was to compare maternal exposures data from a national gastroschisis registry with pregnancy exposures from vital statistics to understand maternal risk factor associations with the occurrence of gastroschisis. **Methods:** Using common definitions, pregnancy cohorts were developed from two databases. The Canadian Pediatric Surgery Network database, a population-based dataset was used to record maternal exposures for women who experienced a gastroschisis pregnancy, while a contemporaneous, geographically cross-sectional "control" cohort of pregnant women and their exposures was developed from Canadian Community Health Survey data. Groups comparison of maternal risk factors was performed using univariate and multivariate logistic generalized estimating equation techniques. **Results:** A total of 692 gastroschisis pregnancies (from Canadian Pediatric Surgery Network) and 4708 pregnancies from Canadian Community Health Survey were compared. Younger maternal age (odds ratio, 0.85; 95% confidence interval, 0.83–0.87; $p < 0.0001$), smoking (odds ratio, 2.86; 95% confidence interval, 2.22–3.66; $p < 0.0001$), a history of pregestational or gestational diabetes (odds ratio, 2.81; 95% confidence interval, 1.42–5.5; $p = 0.0031$), and use of medication to treat depression (odds ratio, 4.4; 95% confidence interval, 1.38–11.8; $p = 0.011$) emerged as significant associations with gastroschisis pregnancies. **Conclusion:** Gastroschisis in Canada is associated with maternal risk factors, some of which are modifiable. Further studies into sociodemographic birth defect risk are necessary to allow targeted improvements in perinatal health service delivery and health policy.

Birth Defects Research (Part A) 103:111–118, 2015.

Key words: gastroschisis; population-based registry; maternal risk factors; maternal age; teratogenesis

- ***Young Age***
- ***Smoking***
- ***Gestational Diabetes***
- ***Depression Rx***

https://www.ctvnews.ca/polopoly_fs/1.3010179!/httpFile/file.pdf

Gastroschisis Epidemic !!!!

TABLE 2. *2 x 2 Contingency Tables with Odds Ratios, 95% Confidence Intervals, and p-Values Describing the Relationship between the Association between Maternal Risk Factors and the Occurrence of a Gastroschisis Pregnancy*

	GS (*N*, %)	Controls (*N*, %)	Odds ratio	95% CI	*p*-Value
Alcohol					
Yes	44 (7.02)	203 (4.36)	1.66	1.18, 2.32	0.0031
No	583 (92.98)	4454 (95.64)			
Tobacco					
Yes	231 (33.38)	610 (13.06)	3.34	2.79, 3.99	<0.0001
No	461 (66.62)	4061 (86.94)			
Marijuana					
Yes	78 (11.27)	55 (1.56)	8.03	5.63, 11.46	<0.0001
No	614 (88.73)	3477 (98.44)			
Any illicit drug					
Yes	92 (13.29)	57 (1.61)	9.35	6.64, 13.15	<0.0001
No	600 (86.71)	3475 (98.39)			
History diabetes					
Yes	19 (2.75)	56 (1.19)	2.34	1.39, 3.98	0.0011
No	672 (97.25)	4651 (98.81)			
Depression meds					
Yes	22 (3.18)	26 (0.70)	4.65	2.61, 8.30	<0.0001
No	670 (96.82)	3544 (99.30)			
Folic acid					
Yes	134 (19.36)	1289 (27.83)	0.62	0.51, 0.76	<0.0001
No	558 (80.64)	3342 (72.17)			

Empty cells, suppressed due to low counts.

Rate x 8-9 !!!!

Gastroschisis Epidemic !!!!

Multivariate Regression

TABLE 3. *Bivariate, Age-Adjusted, and Multivariate Logistic Regression Models Evaluating Risk Factor Prediction of a Gastroschisis Pregnancy*

	Bivariate logistic gee model			Age-adjusted logistic GEE model			Multivariate logistic GEE model		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Age (years)	0.84	0.83, 0.86	<0.0001	—	—	—	0.85	0.83, 0.87	<0.0001
Alcohol	1.65	1.20, 2.29	0.0023	1.67	1.22, 2.30	0.0016	0.82	0.57, 1.18	0.2885
Tobacco	3.32	2.77, 3.98	<0.0001	2.53	2.08, 3.06	<0.0001	2.86	2.22, 3.66	<0.0001
Marijuana	7.94	5.50, 11.48	<0.0001	4.58	3.05, 6.90	<0.0001	—	—	—
Cocaine	11.32	5.10, 25.13	<0.0001	8.02	3.41, 18.83	<0.0001	—	—	—
Methamphetamine	2.90	0.83, 10.15	0.0950	1.16	0.32, 4.21	0.8236	—	—	—
Heroin	10.05	1.88, 53.79	0.0070	5.39	0.73, 39.87	0.0990	—	—	—
Any illicit drug	9.24	6.47, 13.21	<0.0001	5.46	3.69, 8.07	<0.0001	3.54	2.22, 5.63	<0.0001
History diabetes	2.29	1.39, 3.78	0.0011	3.40	1.97, 5.88	<0.0001	2.81	1.42, 5.57	0.0031
Depression meds	4.69	2.60, 8.45	<0.0001	6.09	2.97, 12.49	<0.0001	4.04	1.38, 11.80	0.0108
Folic Acid	0.62	0.51, 0.76	<0.0001	0.95	0.77, 1.17	0.6448	0.88	0.69, 1.14	0.3514

—, not used in multivariate model, rather combined in composite "illicit drug" variable.
GEE, general estimating equation.

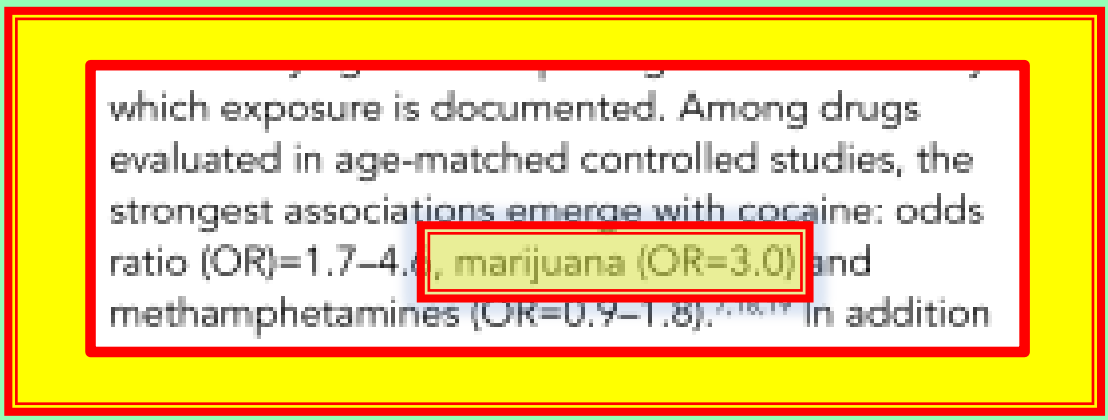
Rate x 3.54 after Adjustment !!!!

Gastroschisis Rate
*~ **TRIPLED** BY CANNABIS!!!!!*


CHAPTER 7

GASTROSCHISIS

Aideen Moore
Jocelyn Rouleau
Erik Skarsgard


which exposure is documented. Among drugs evaluated in age-matched controlled studies, the strongest associations emerge with cocaine: odds ratio (OR)=1.7–4.6, marijuana (OR=3.0) and methamphetamines (OR=0.9–1.8). In addition

Tobacco Use in Canada: Patterns and Trends

Special Supplement: Cannabis in Canada

https://uwaterloo.ca/tobacco-use-canada/sites/ca.tobacco-use-canada/files/uploads/files/cannabissupplement_2017_final_accessible.pdf

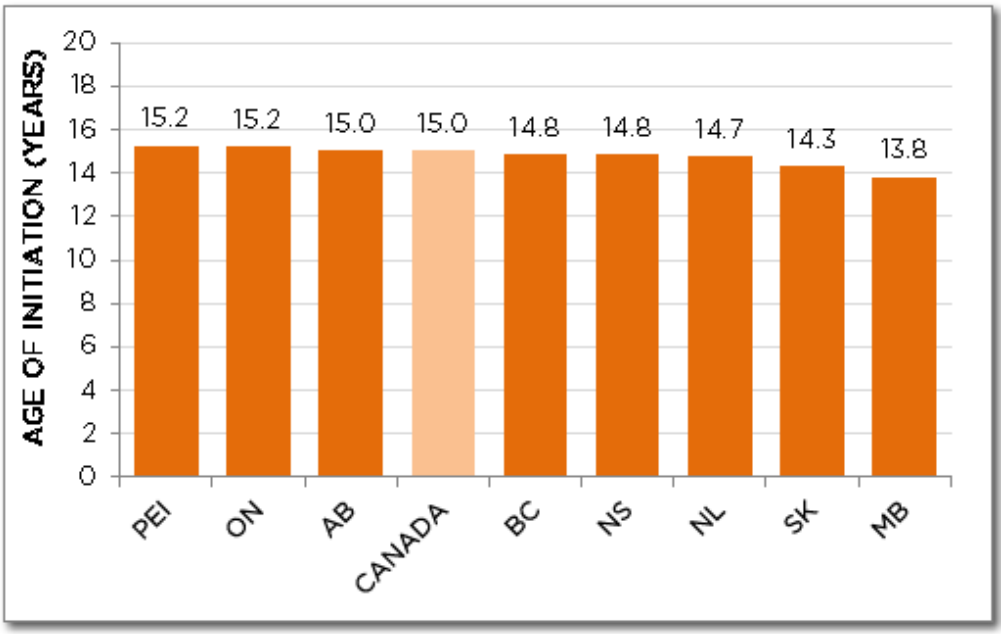
PROPEL
CENTRE FOR POPULATION HEALTH IMPACT

University of Waterloo | Waterloo, Ontario

Age of Initiation by Province

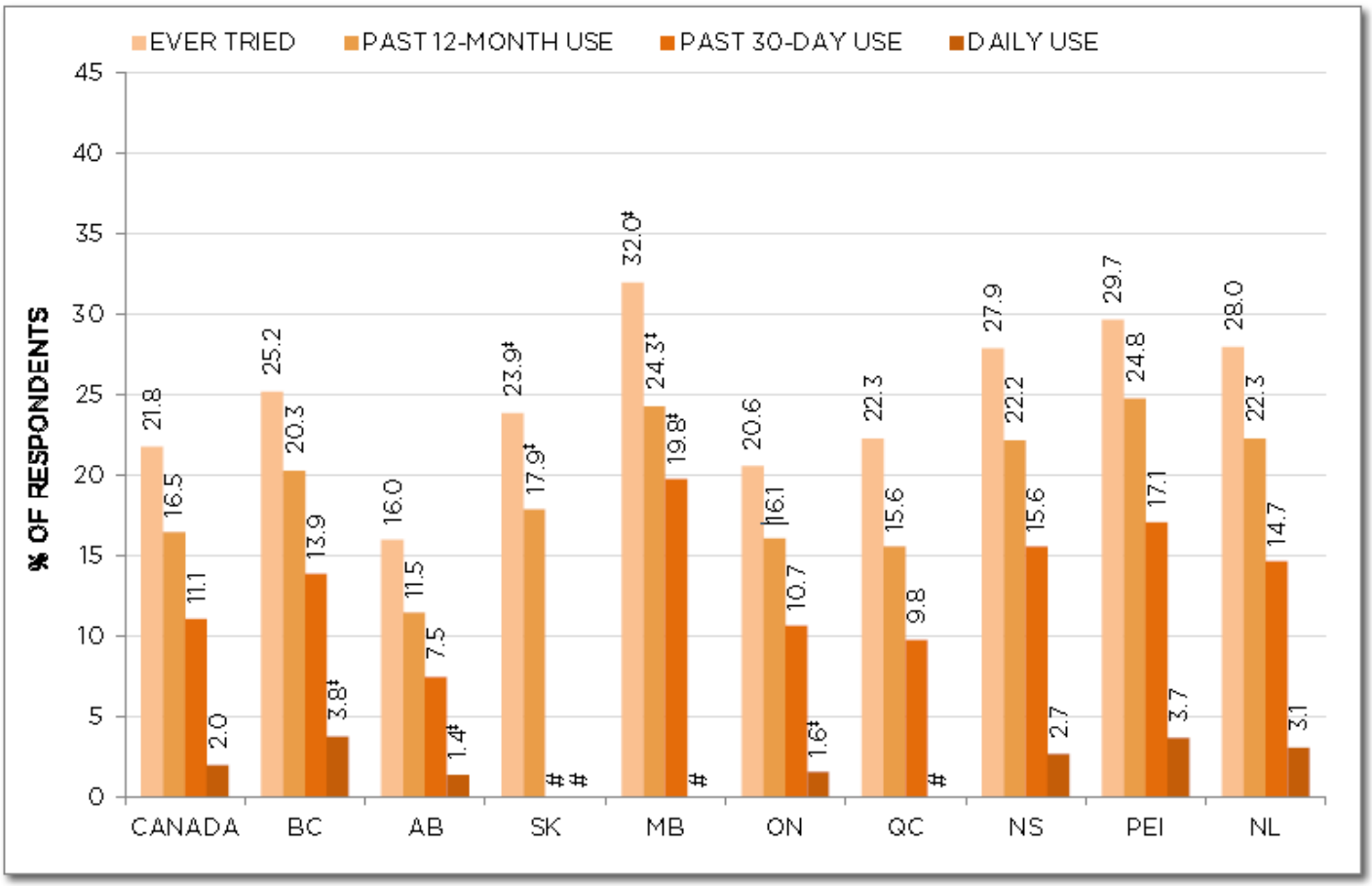
The mean age of initiation among cannabis users in grade 12 varied between provinces (p=0.04). Age of initiation ranged from 13.8 years of age in Manitoba to 15.2 years of age in Prince Edward Island and Ontario, as shown in Figure 23.

FIGURE 23: MEAN AGE OF INITIATION AMONG CANNABIS USERS IN GRADE 12, BY PROVINCE*, 2014-15



DATA SOURCE: CSTADS, 2014-15
NOTE: DATA FROM QUEBEC ARE NOT INCLUDED: QUEBEC SCHOOLS DID NOT INCLUDE GRADE 12.
*PROVINCIAL ESTIMATE FOR NEW BRUNSWICK NOT REPORTED BECAUSE CSTADS DID NOT ACHIEVE A GENERALIZABLE SAMPLE OF NB STUDENTS IN 2014-15.

FIGURE 21: PREVALENCE OF CANNABIS USE BY PROVINCE*, GRADES 7-12, 2014-15



DATA SOURCE: CSTADS, 2014-15
NOTE: DATA FROM QUEBEC ARE FOR SECONDARY I-V (IE., DO NOT INCLUDE GRADE 12).
*PROVINCIAL ESTIMATE FOR NEW BRUNSWICK NOT REPORTED BECAUSE CSTADS DID NOT ACHIEVE A GENERALIZABLE SAMPLE OF NB STUDENTS IN 2014-15
‡ MODERATE SAMPLING VARIABILITY, INTERPRET WITH CAUTION
# DATA ARE SUPPRESSED: UNRELEASABLE DUE TO HIGH SAMPLING VARIABILITY OR LOW SAMPLE SIZE

Cannabis in Nunavut

Nunavut Cannabis Seeds

Compare Our Cannabis Seed Strains

World Wide Shipping

We ship and deliver world wide via USPS and various couriers.

Data on availability and prevalence of drug use in Inuit communities is not readily available. On its Nunavut Web page, the Canadian Centre for Substance Abuse states that marijuana is often cheaper and easier to bring into the Territory than alcohol. Street drugs

http://www.naho.ca/documents/it/2007_Parliamentarian_Substance_Abuse.pdf

https://growerschoiceseeds.com/cannabis-seeds-delivery-areas/
cannabis-seeds-canada/nunavut-cannabis-seeds/

Nunavut Cannabis

In that region, 84.6 per cent of men in Nunavik aged 15 to 19 admitted they used illegal drugs, mostly cannabis, during the 12 months prior to the date of the survey. For adult men up to the age of 45, self-reported numbers were similar, but dropped to 43.5 per cent after age 45.

Among girls and women in Nunavik, self-reported drug use, mostly cannabis, was lower: 69.3 per cent for girls aged 15 to 19 and falling to 49.6 per cent for women aged 25 to 44.

NUNATSIAQ ONLINE

http://www.nunatsiaqonline.ca/stories/article/65674cannabis_regulation_nunavut_must_take_its_time/

EDITORIAL: **Around the Arctic** April 19, 2017 - 7:00 am

Cannabis regulation: Nunavut must take its time

"The GN must not feel bound by Ottawa's timetable"

NUNATSIAQ NEWS

Thanks to the two cannabis bills that Justin Trudeau's Liberal government unveiled this past April 13, the Government of Nunavut now faces some tough political choices.

That's because, if the Trudeau government's plan works out, Parliament will pass Bill C-45 and Bill C-46 in time for the new laws to take effect July 1, 2018, the date when Nunavut would be expected to do its part in carrying out Ottawa's agenda.

By then, territorial and provincial governments are supposed to decide, through regulations, how recreational cannabis products will be legally sold and distributed within their jurisdictions.

But July 2018, the Trudeau government wants to create a legalized cannabis system, subject to multiple restrictions, that r... territorial, provincial and municipal regulation. How sh... respond? (WIKIMEDIA FILE IMAGE)

Cannabis Co-Occurs

With Congenital Anomalies: Manitoba, Saskatchewan, Nunavut Judged by Area and Age of First Use

200

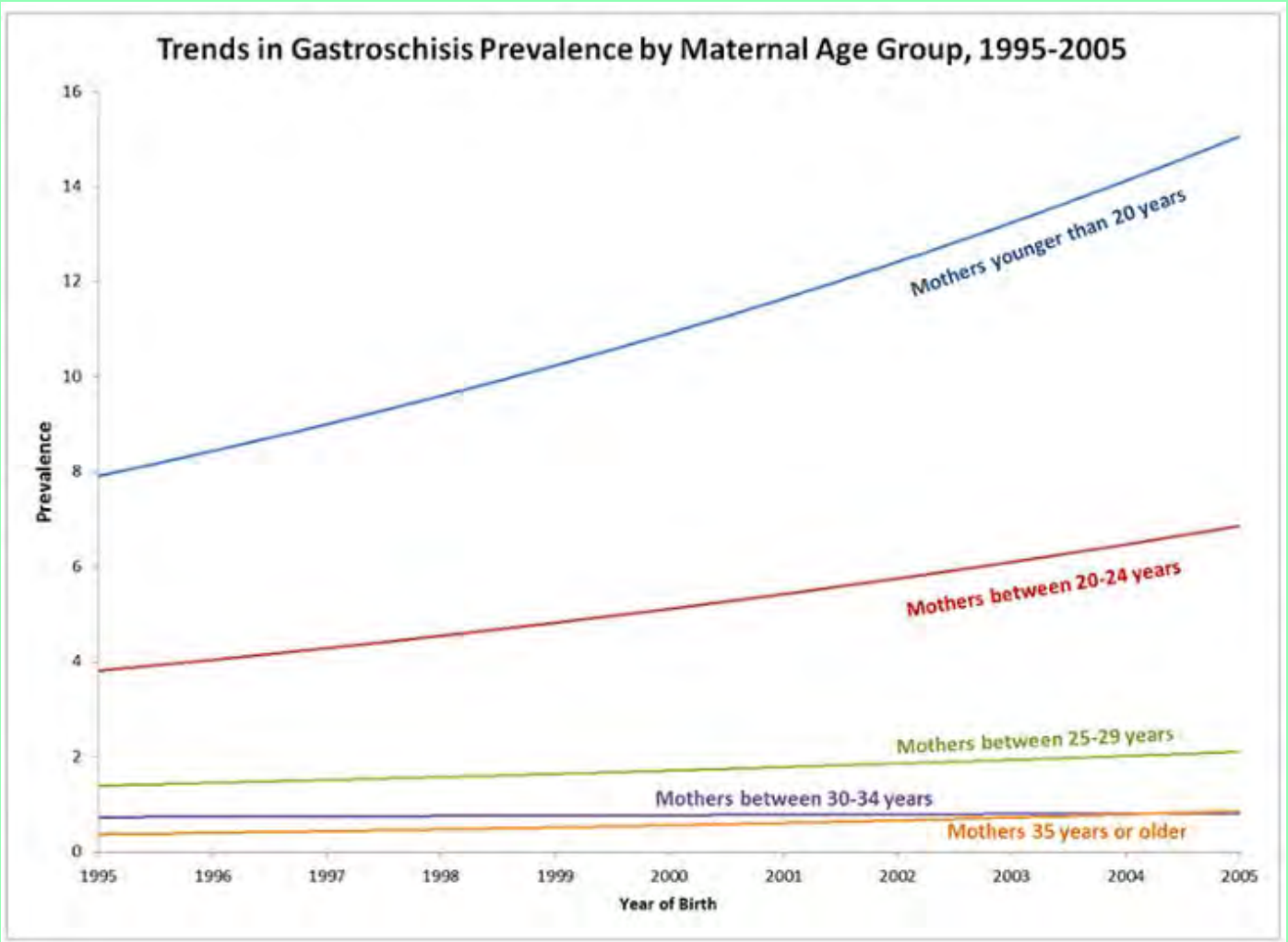
Major Causes of Infant Deaths
USA, 2015
C.D.C. Atlanta, Georgia

Rank	Disorder	No.	%
1	Congenital Abnormalities Inc. Chromsomal Anomalies	4746	20.4%
2	Short Gestation / Low Birth Weight	4173	18.0%
3	Maternal Complications of Pregnancy	1574	6.8%
4	SIDS	1545	6.7%
5	Accidental Injuries	1161	5.0%
6	Placental Diseases	965	4.2%
7	Infections	544	2.3%
8	Respiratory Distress	460	2.0%
9	Circulatory Disorders	444	1.9%
10	Haemorrhage	441	1.9%

CDC – National Vital Statistics 65(5) Deaths: Leading Causes for 2014.
Deaths: Leading Causes for 2014

http://www.cdc.gov/nchs/data/nvsr/nvsr65/nvsr65_05.pdf

Gastroschisis - U.S.A.

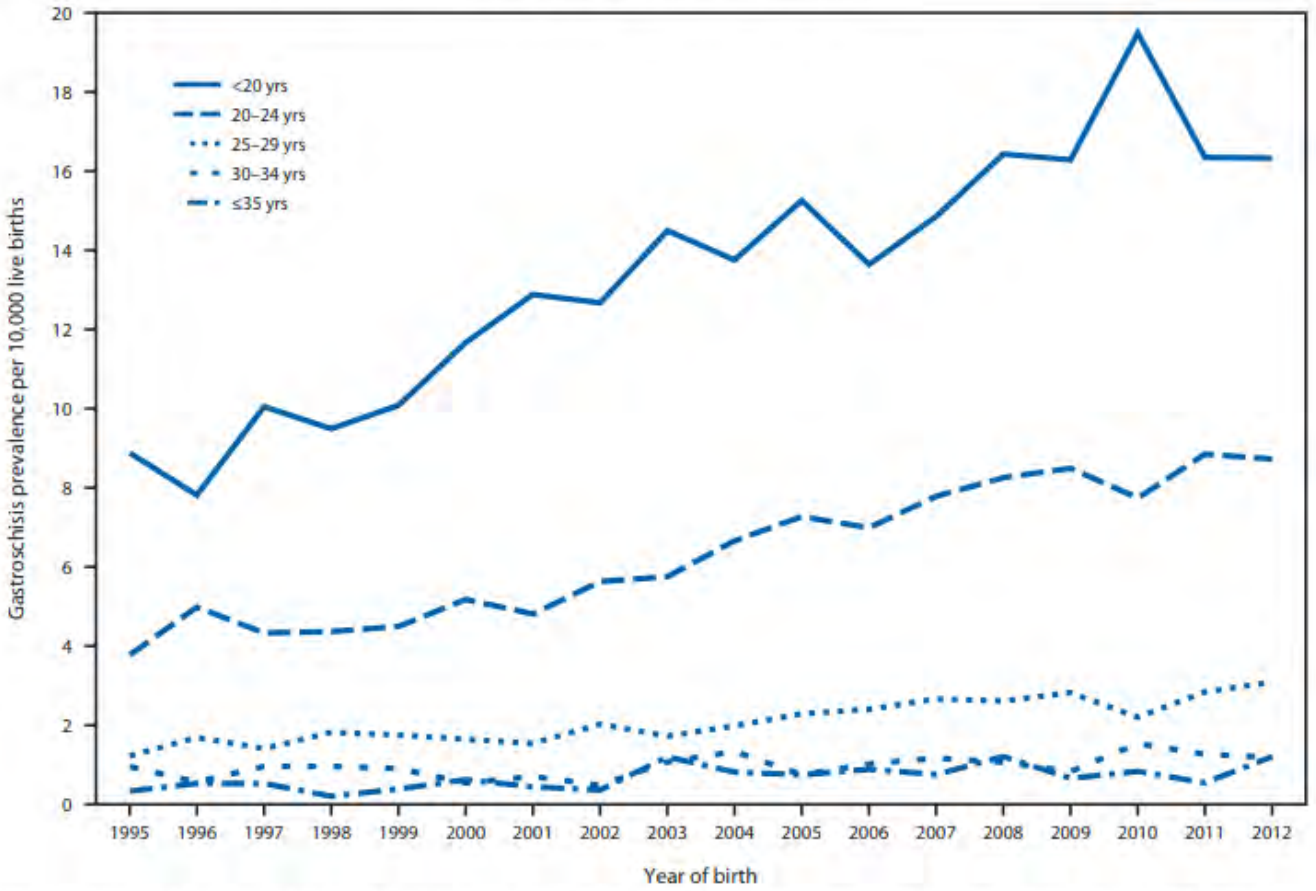


CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

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

Gastroschisis - U.S.A.
Continues to Rise!!!!

FIGURE. Trends in gastroschisis prevalence, by maternal age group — 14 states,* 1995–2012



* States contributing data and years for which data are provided: Arizona (1995–2012), Arkansas (1995–2012), California (1995–2012), Colorado (1997–2012), Georgia (1995–2012), Iowa (1995–2012), Kentucky (1998–2012), New Mexico (1998–2012), New York (1995–2012), North Carolina (1999–2012), Oklahoma (1995–2012), Rhode Island (2002–2012), Texas (1996–2012), Utah (1997–2012). Total live births = 21,278,784.

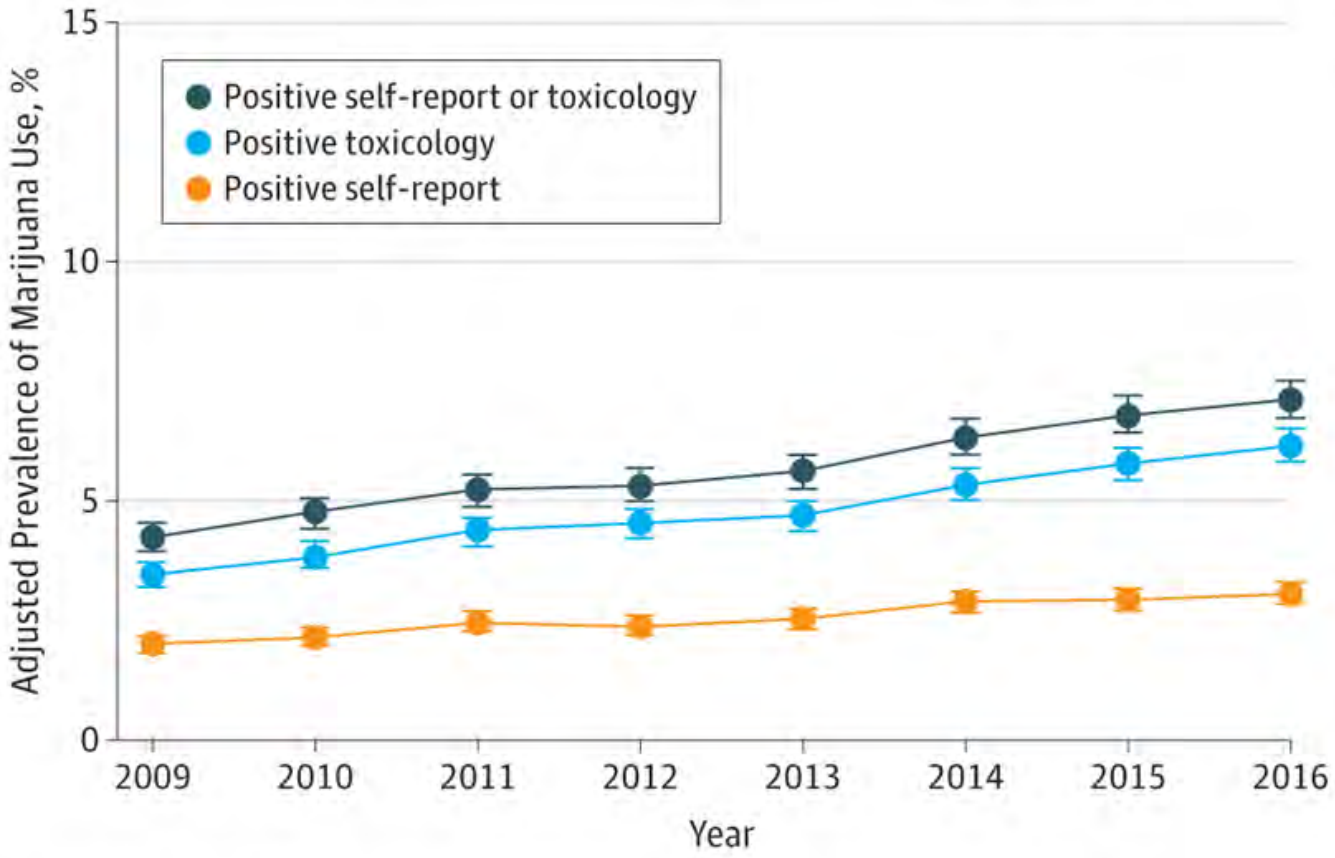
CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

https://www.cdc.gov/mmwr/volumes/65/wr/mm6502a2.htm?s_cid=mm6502a2_w

Cannabis Use Amongst 279,457 Pregnant Mothers in California

Figure 1.

View Large Download



Adjusted Prevalence of Marijuana Use Among 279 457 Pregnant Females in KPNC by Screening Type, 2009-2016

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[1]; Lue-Yen Tucker, BA[1]; Stacey Alexeeff, PhD[1]; Mary Anne Armstrong, MA[1]; Amy Conway, MPH[2]; Constance Weisner, DrPH[3]; Nancy Goler, MD[4]

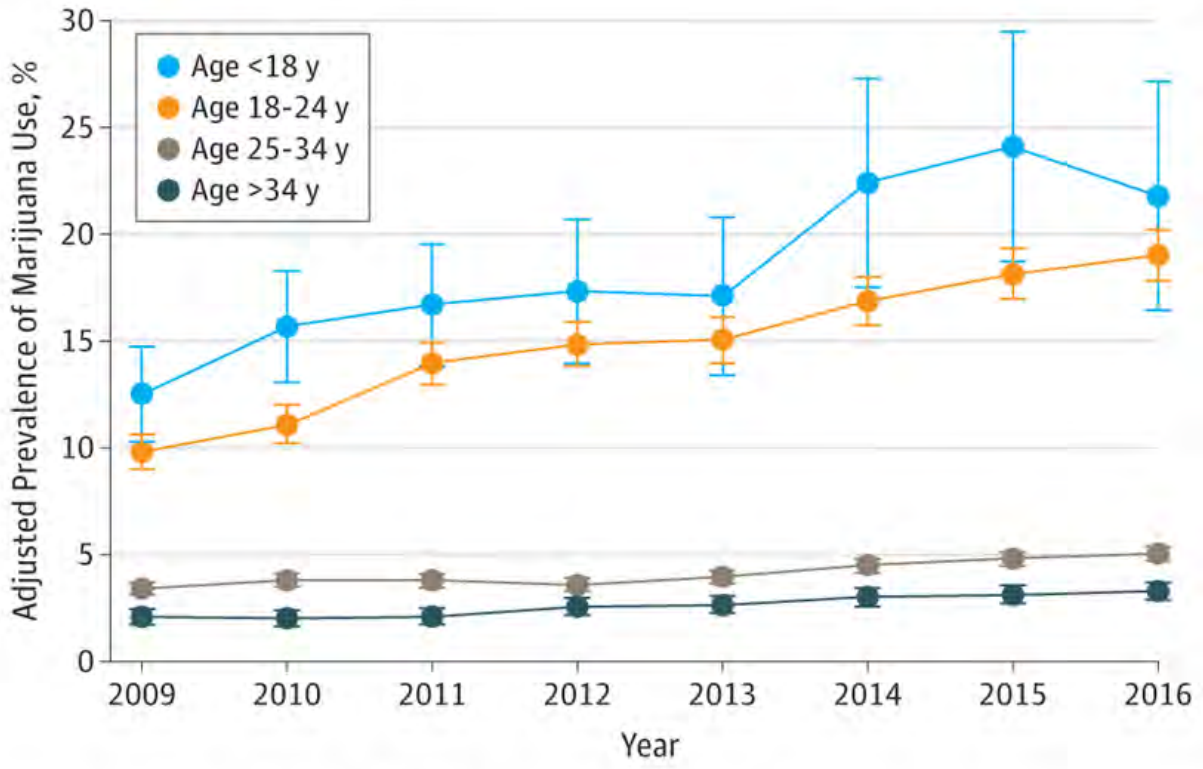
» Author Affiliations | Article Information

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

Cannabis Use Rates by Age, California

Figure 2.

View Large Download



Adjusted Prevalence of Marijuana Use Among 279 457 Pregnant Females in KPNC by Age, 2009-2016

December 26, 2017

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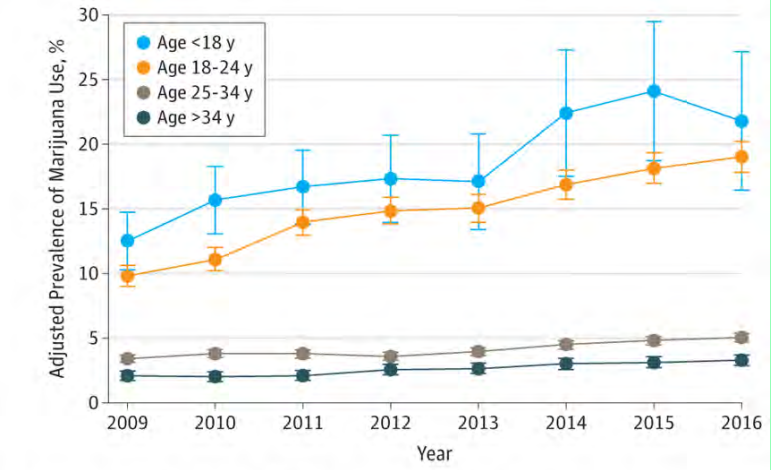
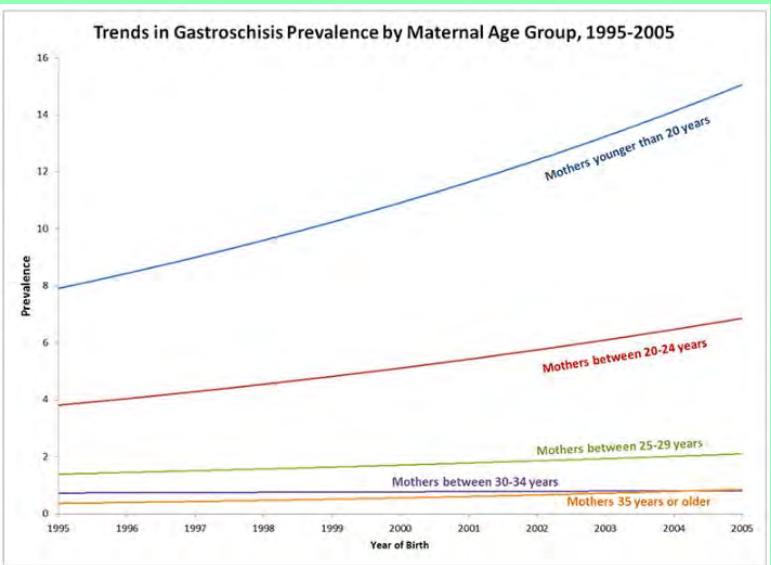
Cannabis Use California & Gastroschisis Rates USA by Age

Figure 2. View Large Download



Adjusted Prevalence of Marijuana Use Among 279 457 Pregnant Females in KPNC by Age, 2009-2016



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

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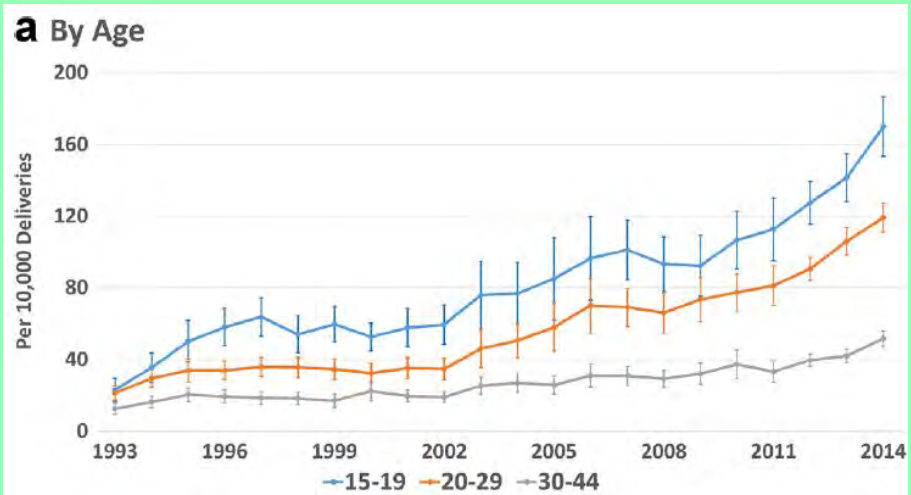
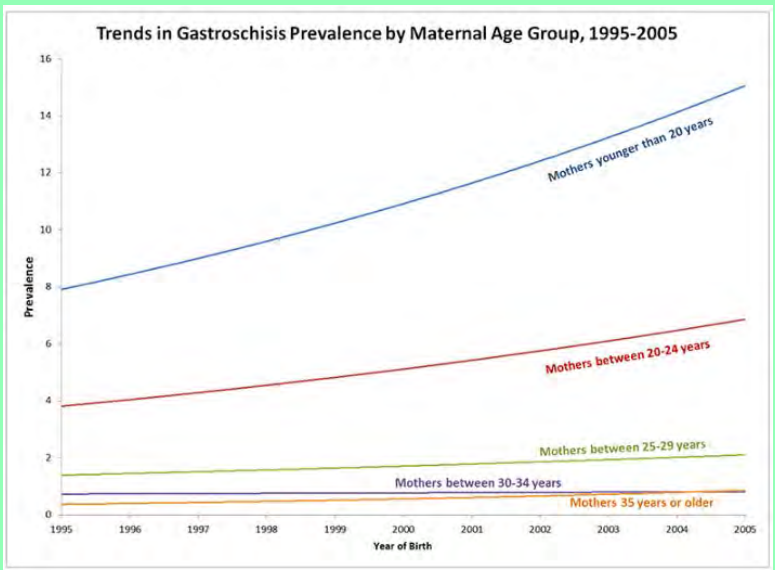
Cannabis Use California & Gastroschisis Rates USA by Age





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

J Gen Intern Med. 2018 Mar;33(3):245-246. doi: 10.1007/s11606-017-4201-0.

Trends in Cannabis Use Disorder among Pregnant Women in the U.S., 1993-2014.

Shi Y[1], Zhong S[2].

Gastroschisis - U.S.A.

15-Fold Variation 1.2 – 18.1 Prevalence!!!!

3-8% Annual % Rise!!!!

TABLE. Number of cases and gastroschisis prevalence, prevalence ratio, and average annual percent change, by maternal age group and race/ethnicity — 14 states,* 1995–2012

Maternal age group (yrs)†	Maternal race/ethnicity	1995–2005 No.	1995–2005 Prevalence§ (95% CI)	2006–2012 No.	2006–2012 Prevalence§ (95% CI)	PR¶ (95% CI)	Joinpoint analysis: Average annual percent change (95% CI**)	Joinpoint analysis: Overall percent change††
<20	Non-Hispanic white	816	15.4 (14.3–16.5)	574	18.1 (16.7–19.7)	1.2 (1.1–1.3)	3.1 (1.5–4.7)	68
	Non-Hispanic black	137	5.2 (4.3–6.1)	169	10.2 (8.7–11.9)	2.0 (1.6–2.5)	7.9 (5.7–10.1)	263
	Hispanic	698	11.6 (10.7–12.5)	710	16.1 (14.9–17.3)	1.4 (1.2–1.5)	4.4 (3.1–5.7)	108
	Total§§	**1,749**	**11.9 (11.3–12.4)**	**1,562**	**16.1 (15.3–16.9)**	**1.4 (1.3–1.5)**	**4.3 (3.3–5.3)**	**105**
20–24	Non-Hispanic white	846	6.0 (5.6–6.4)	889	8.8 (8.2–9.4)	1.5 (1.3–1.6)	4.6 (3.5–5.7)	115
	Non-Hispanic black	135	2.9 (2.4–3.4)	193	5.4 (4.7–6.2)	1.9 (1.5–2.3)	7.0 (3.7–10.4)	216
	Hispanic	601	5.5 (5.1–6.0)	706	8.3 (7.7–8.9)	1.5 (1.3–1.7)	5.6 (4.3–6.8)	151
	Total§§	**1,687**	**5.3 (5.1–5.6)**	**1,899**	**8.1 (7.7–8.4)**	**1.5 (1.4–1.6)**	**5.2 (4.4–6.0)**	**137**
≥25	Non-Hispanic white	501	1.2 (1.1–1.3)	541	1.7 (1.6–1.9)	1.4 (1.3–1.6)	4.1 (2.6–5.6)	99
	Non-Hispanic black	71	0.9 (0.7–1.1)	77	1.2 (1.0–1.5)	1.4 (1.0–1.9)	3.5 (0.4–6.8)	81
	Hispanic	213	1.2 (1.0–1.3)	314	1.9 (1.7–2.1)	1.6 (1.3–1.9)	4.7 (2.4–7.2)	120
	Total§§	**853**	**1.2 (1.1–1.2)**	**1,014**	**1.7 (1.6–1.8)**	**1.5 (1.3–1.6)**	**4.5 (3.5–5.4)**	**111**

Abbreviations: CI = confidence interval, PR = prevalence ratio.

* States contributing data and years for which data are provided: Arizona (1995–2012), Arkansas (1995–2012), California (1995–2012), Colorado (1997–2012), Georgia (1995–2012), Iowa (1995–2012), Kentucky (1998–2012), New Mexico (1998–2012), New York (1995–2012), North Carolina (1999–2012), Oklahoma (1995–2012), Rhode Island (2002–2012), Texas (1996–2012), Utah (1997–2012). Total live births = 21,278,784.

† Cases missing information on maternal age are not included in this table.

§ Prevalence per 10,000 live births.

¶ Prevalence during 2006–2012 divided by the prevalence during 1995–2005.

** Statistically significant differences from zero percent change.

†† Overall percent change is calculated using the average annual percent change and represents the estimated overall change in prevalence during 1995–2012.

§§ Total includes non-Hispanic white, non-Hispanic black, Hispanic, all other reported racial/ethnic groups and other/unknown maternal race/ethnicity.

Morbidity and Mortality Weekly Report

Increasing Prevalence of Gastroschisis — 14 States, 1995–2012

Abbey M. Jones, MPH[1]; Jennifer Isenburg, MSPH[1]; Jason L. Salemi, PhD[2]; Kathryn E. Arnold, MD[1]; Cara T. Mai, DrPH[1]; Deepa Aggarwal, PhD[3]; William Arias, MPH[4]; Gerard E. Carrino, PhD[5]; Emily Ferrell, MPH[6]; Olakunle Folorunso, MBBS[7]; Brendan Ibe, MD[8]; Russell S. Kirby, PhD[9]; Heidi R. Krapfl, MS[10]; Lisa K. Marengo, MS[11]; Bridget S. Mosley, MPH[12]; Amy E. Nance, MPH[13]; Paul A. Romitti, PhD[14]; Joseph Spadafino, MPH[15]; Jennifer Stock[16]; Margaret A. Honein, PhD[1]

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https://www.cdc.gov/mmwr/volumes/65/wr/mm6502a2.htm?s_cid=mm6502a2_w

Gastroschisis - U.S.A.

15-Fold Variation 1.2 – 18.1

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3-8% Annual % Rise!!!!

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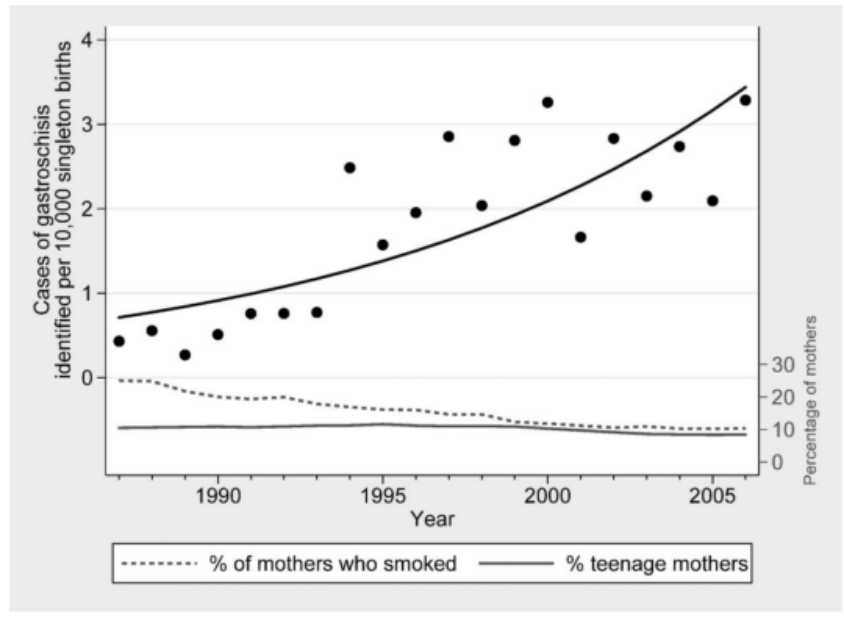
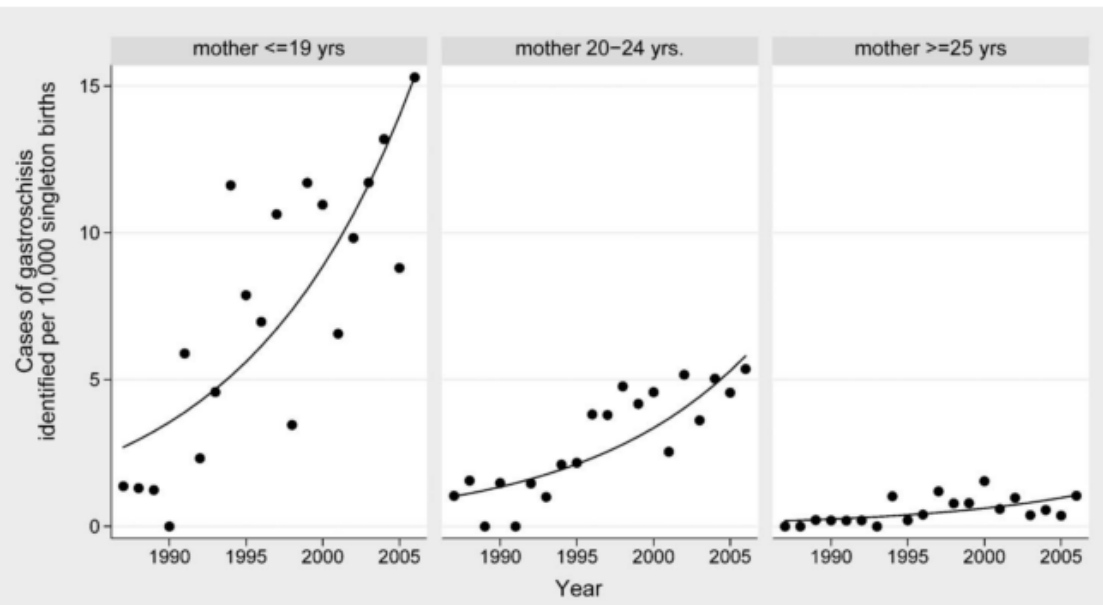
https://www.cdc.gov/mmwr/volumes/65/wr/mm6502a2.htm?s_cid=mm6502a2_w

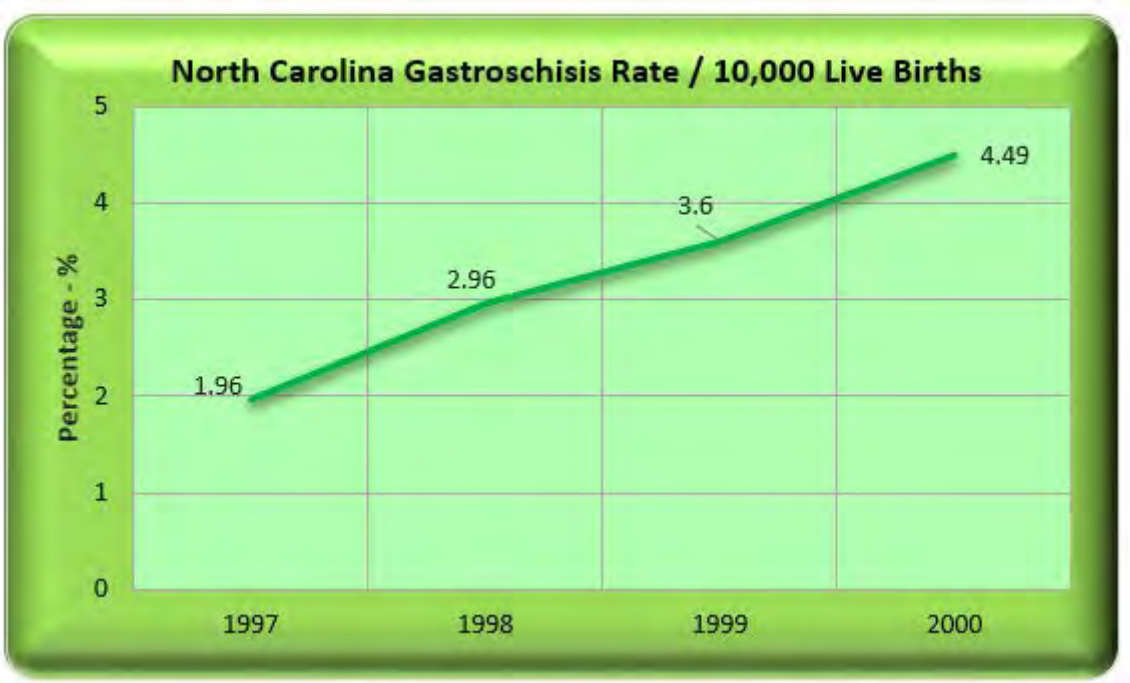
Washington State

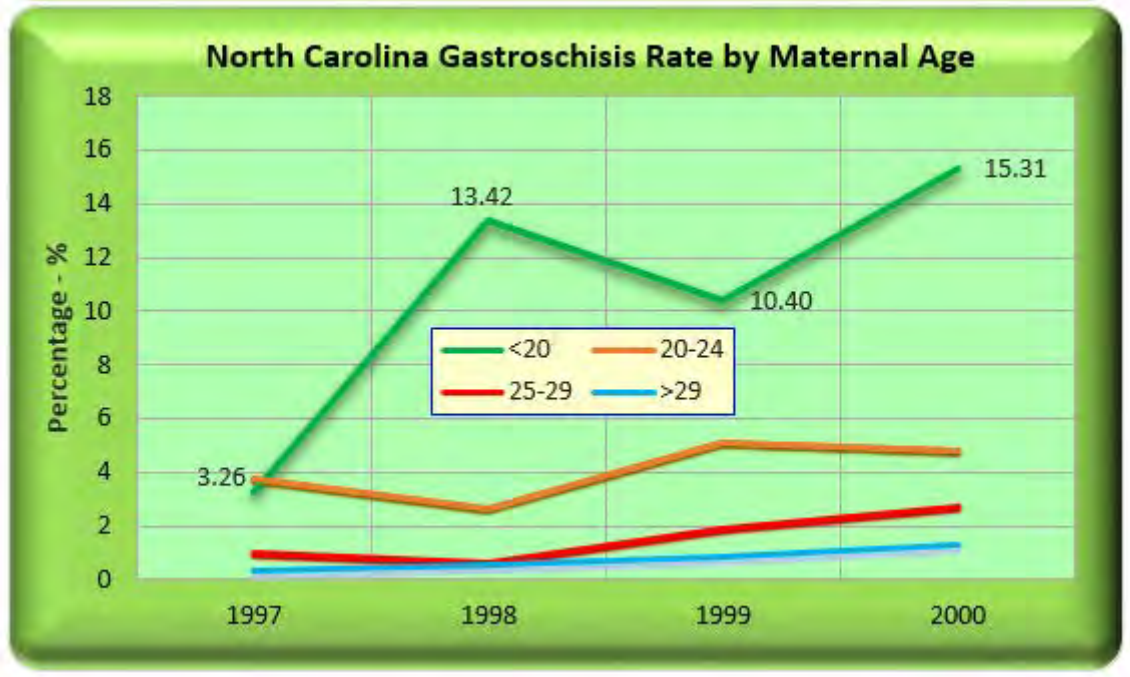




Rising Prevalence Gastroschisis Washington State
Chabra S., J Toxicology Env Health Part A, 74: 5 pp336-345

North Carolina 1997-2000





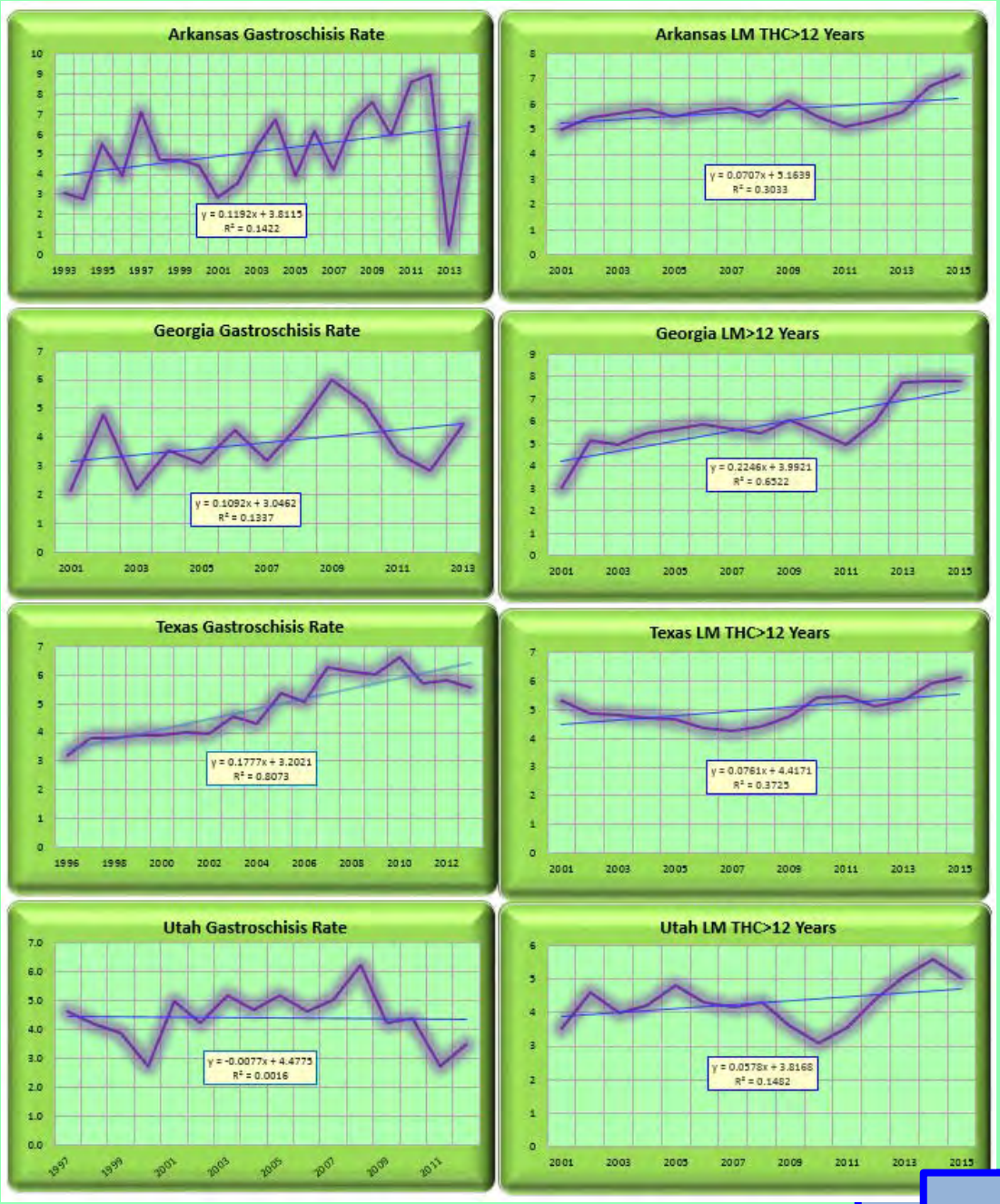
J Perinatol. 2003 Jun;23(4):291-3.

Rising birth prevalence of gastroschisis.

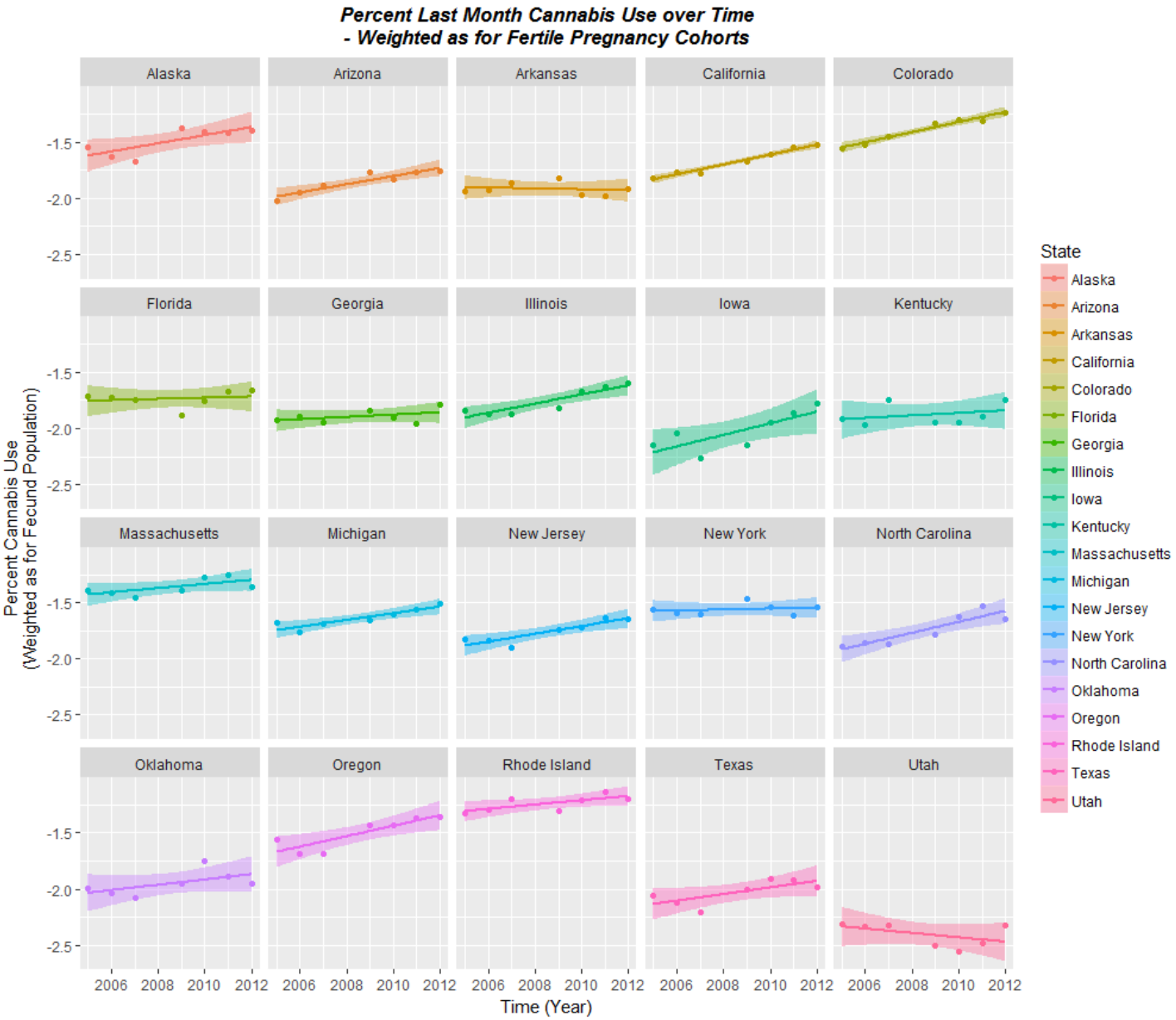
Laughon M[1], Meyer R, Bose C, Wall A, Otero E, Heerens A, Clark R.

Gastroschisis Rate – Last Month Cannabis Use Rates

Cannabis Use – P = 0.0368
Year: Cannabis Use – P = 0.0367

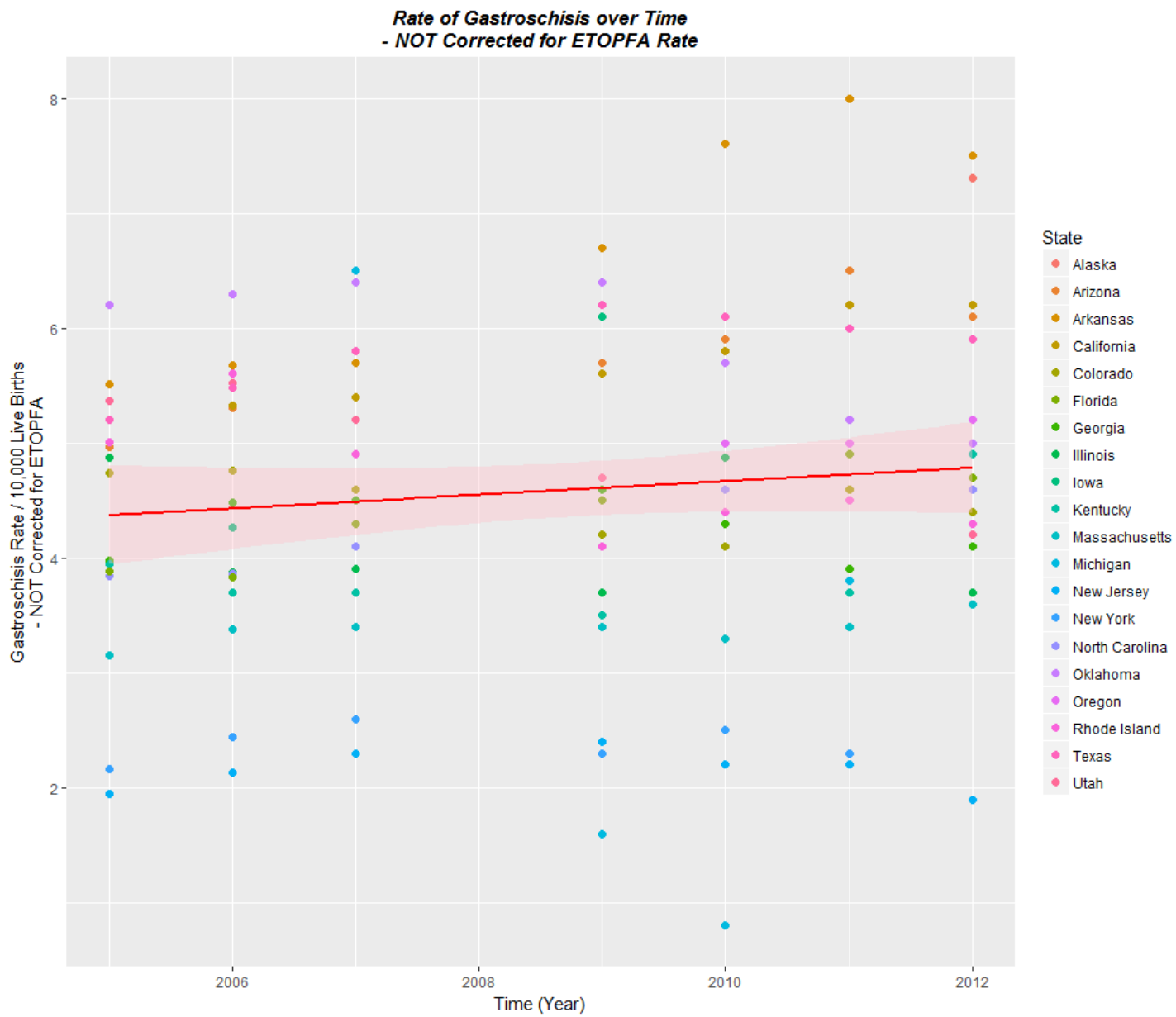


US Cannabis Use by State



Data from NSDUH, SAMHSA

Gastroschisis Rate Across USA
All States Combined



Data from NBDPN, US DHHS Public Reports

*Regression Model Gastroschisis Rate (Uncorrected) on State * Year * Cannabis Use*

Parameter	Estimate	Std. Error	t-value	P Value	
log(LMonth)	1.00E+00	2.37E-13	4.22E+12	2.00E-16	***
StateArkansas	4.02E-12	6.31E-13	6.365	3.00E-08	***
Year:StateArkansas	-1.63E-15	2.63E-16	-6.201	5.66E-08	***
Year:StateArkansas:log(LMonth)	-1.10E-15	1.80E-16	-6.079	9.06E-08	***
StateArkansas:log(LMonth)	2.20E-12	3.62E-13	6.079	9.08E-08	***
Year:Statelowa:log(LMonth)	-2.90E-16	1.22E-16	-2.371	0.0210	*
Statelowa:log(LMonth)	5.82E-13	2.46E-13	2.369	0.0211	*
Statelowa	8.53E-13	3.70E-13	2.307	0.0245	*
Year:StateNorth Carolina:Lmonth	-2.87E-16	1.29E-16	-2.223	0.0300	*
StateNorth Carolina:Lmonth	5.76E-13	2.59E-13	2.221	0.0301	*
Year:log(LMonth)	2.62E-16	1.18E-16	2.218	0.0304	*
Year:StateCalifornia:log(LMonth)	-2.84E-16	1.28E-16	-2.216	0.0305	*
StateCalifornia:log(LMonth)	5.70E-13	2.58E-13	2.214	0.0306	*
Year:StateKentucky:log(LMonth)	-2.72E-16	1.24E-16	-2.194	0.0322	*
StateKentucky:log(LMonth)	5.47E-13	2.49E-13	2.192	0.0323	*
Year:StateAlaska	3.70E-16	1.72E-16	2.151	0.0355	*
Year:StateRhode Island:Lmonth	-2.82E-16	1.33E-16	-2.114	0.0386	*
StateRhode Island	5.65E-13	2.68E-13	2.113	0.0388	*
StateCalifornia	8.38E-13	3.97E-13	2.110	0.0390	*
StateNorth Carolina	8.28E-13	3.96E-13	2.093	0.0406	*
StateRhode Island	7.92E-13	3.79E-13	2.092	0.0407	*
StateKentucky	7.79E-13	3.74E-13	2.081	0.0417	*
Year:StateOregon:log(LMonth)	-2.65E-16	1.30E-16	-2.039	0.0458	*
StateOregon:LMonth	5.32E-13	2.61E-13	2.038	0.0460	*
Year:StateMichigan:log(LMonth)	-2.61E-16	1.30E-16	-2.009	0.0490	*
StateMichigan:log(LMonth)	5.24E-13	2.61E-13	2.008	0.0492	*

```
Residual standard error: 2.081e-17 on 60 degrees of freedom
Multiple R-squared:      1,     Adjusted R-squared:      1
F-statistic: 3.305e+32 on 79 and 60 DF,  p-value: < 2.2e-16

Warning message:
In summary.lm(lm(log(value) ~ Year * State * log(LMonth) - Year,
  essentially perfect fit: summary may be unreliable
```

Cf. Alaska

Data from NBDPN, US DHHS and NSDUH, SAMHSA

*Regression Model Gastroschisis Rate (ETOPFA Corrected) on State * Year * Cannabis Use*

Parameter	Estimate	Std. Error	t-value	P Value	
log(LMonth)	**1.00E+00**	**2.37E-13**	**4.22E+12**	**<2.0E-16**	***
StateArkansas	4.02E-12	6.31E-13	6.365	3.00E-08	***
Year:StateArkansas	-1.63E-15	2.63E-16	-6.201	5.66E-08	***
Year:StateArkansas:log(LMonth)	-1.10E-15	1.80E-16	-6.079	9.06E-08	***
StateArkansas:log(LMonth)	2.20E-12	3.62E-13	6.079	9.08E-08	***
Year:StateIowa:log(LMonth)	-2.90E-16	1.22E-16	-2.371	0.021	*
StateIowa:log(LMonth)	5.82E-13	2.46E-13	2.369	0.0211	*
StateIowa	8.53E-13	3.70E-13	2.307	0.0245	*
Year:StateNorth Carolina	-2.87E-16	1.29E-16	-2.223	0.03	*
StateNorth Carolina:Lmonth	**5.76E-13**	**2.59E-13**	**2.221**	**0.0301**	*
Year:log(LMonth)	2.62E-16	1.18E-16	2.218	0.0304	*
Year:StateCalifornia:log(LMonth)	**-2.84E-16**	**1.28E-16**	**-2.216**	**0.0305**	*
StateCalifornia:log(LMonth)	**5.70E-13**	**2.58E-13**	**2.214**	**0.0306**	*
Year:StateKentucky:log(LMonth)	-2.72E-16	1.24E-16	-2.194	0.0322	*
StateKentucky:log(LMonth)	5.47E-13	2.49E-13	2.192	0.0323	*
Year:StateAlaska	3.70E-16	1.72E-16	2.151	0.0355	*
Year:StateRhode Island:log(LMonth)	**-2.82E-16**	**1.33E-16**	**-2.114**	**0.0386**	*
StateRhode Island:log(LMonth)	**5.65E-13**	**2.68E-13**	**2.113**	**0.0388**	*
StateCalifornia	8.38E-13	3.97E-13	2.110	0.039	*
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Year:StateOregon:log(LMonth)	**-2.65E-16**	**1.30E-16**	**-2.039**	**0.0458**	*
StateOregon:log(LMonth)	**5.32E-13**	**2.61E-13**	**2.038**	**0.046**	*
Year:StateMichigan:log(LMonth)	-2.61E-16	1.30E-16	-2.009	0.049	*
StateMichigan:log(LMonth)	5.24E-13	2.61E-13	2.008	0.0492	*

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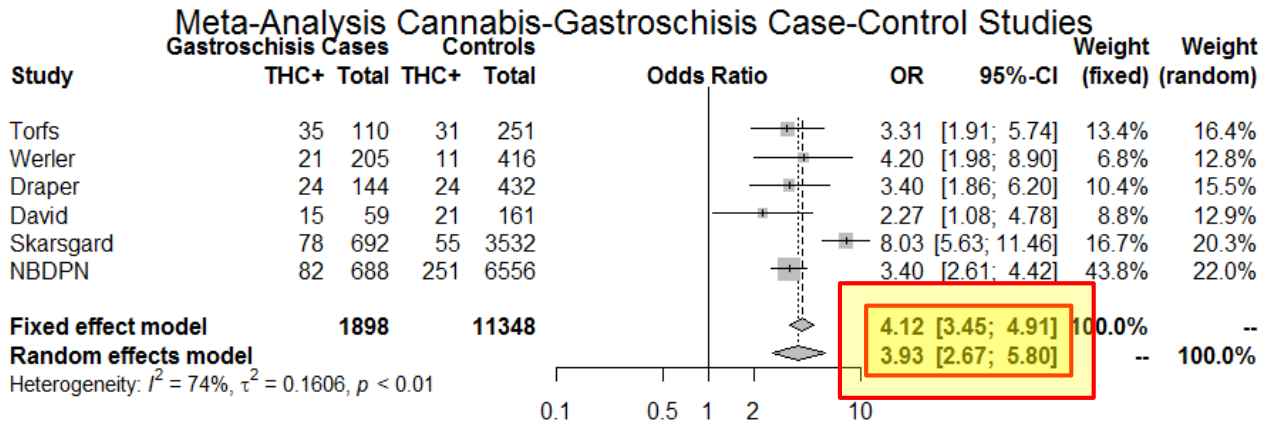
```

Cf. Alaska

Data from NBDPN, US DHHS and NSDUH, SAMHSA

Global Univariate Meta-Analysis Cannabis-Gastroschisis



1. A. L. David *et al. PLoS One* **9**, e111038 (2014).
2. E. S. Draper *et al. Am J Epidemiol* **167**, 485-491 (2008).
3. E. D. Skarsgard *et al. Birth Defects Res A Clin Mol Teratol* **103**, 111-118 (2015).
4. C. P. Torfs *Teratology* **50**, 44-53 (1994).
5. M. M. van Gelder *et al. Epidemiology* **20**, 60-66 (2009).
6. M. M. Werler *et. al. Epidemiology* **14**, 349-354 (2003).

Also, Not Included:

7. M. B. Forrester et. al. *J. Toxicol Environ. Health* **70**, 7-18 (2007).

NSW 2011 Report

30 May 2011

Review of gastroschisis on the NSW North Coast

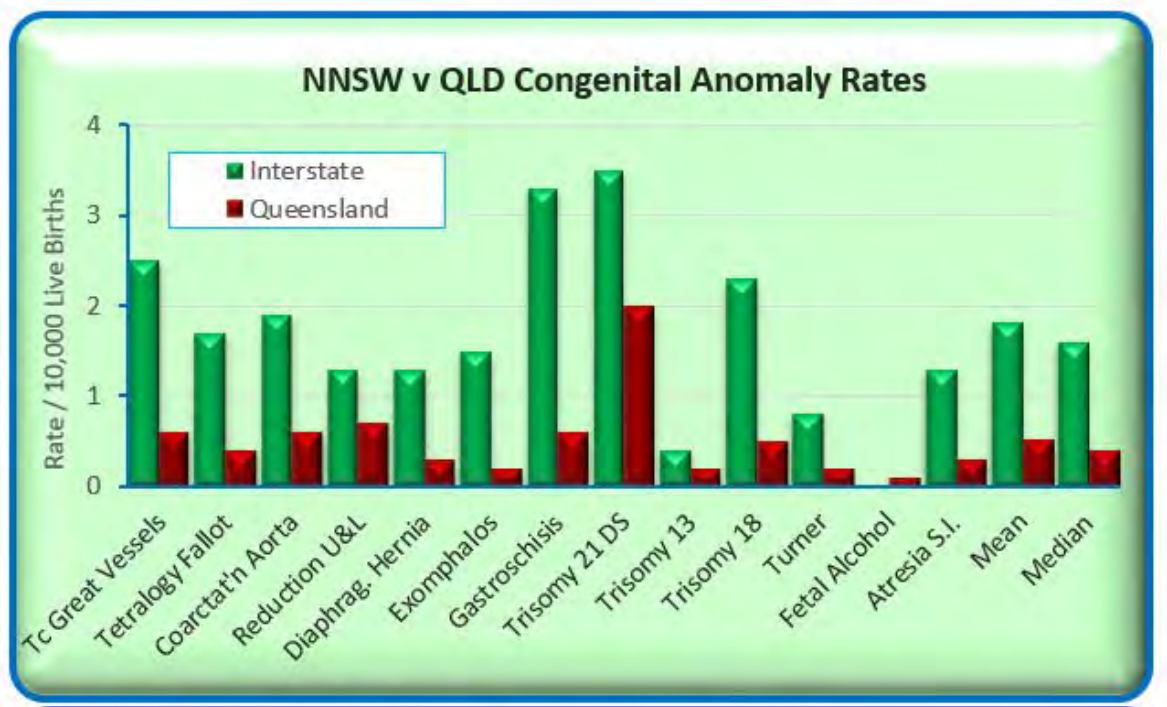
Table of Contents

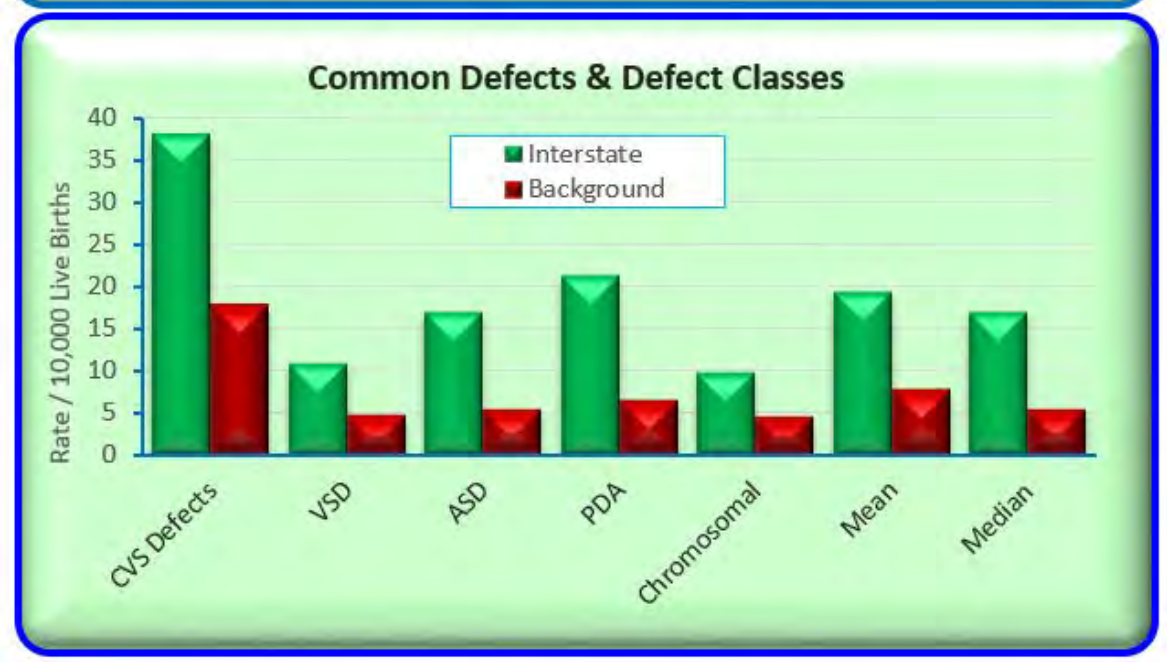
Erroneous NSW Report

- *Numerator* - 5 not 8 Cases reported in Press
- *Denominator* - Size of Area Boundaries
- *Correction Factor* - Over correction for multiple testing (Bonferroni)
- 150 areas used rather than 9 – three areas for three time periods

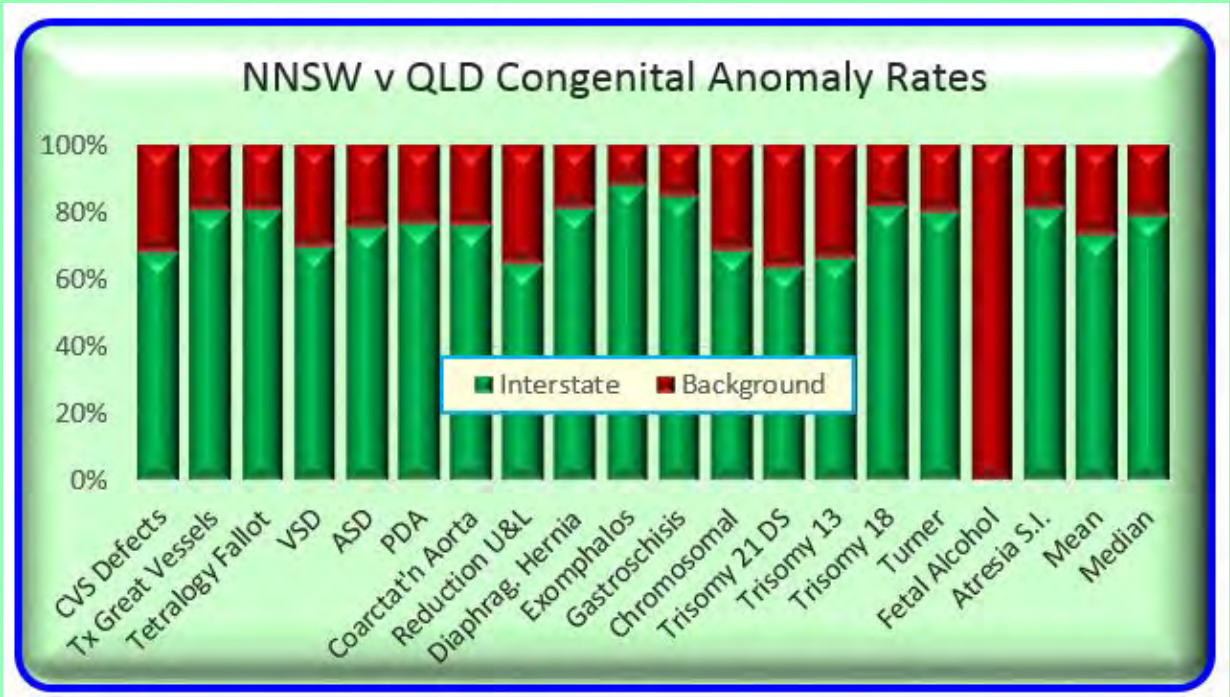
CASE SHIFTING TO QUEENSLAND

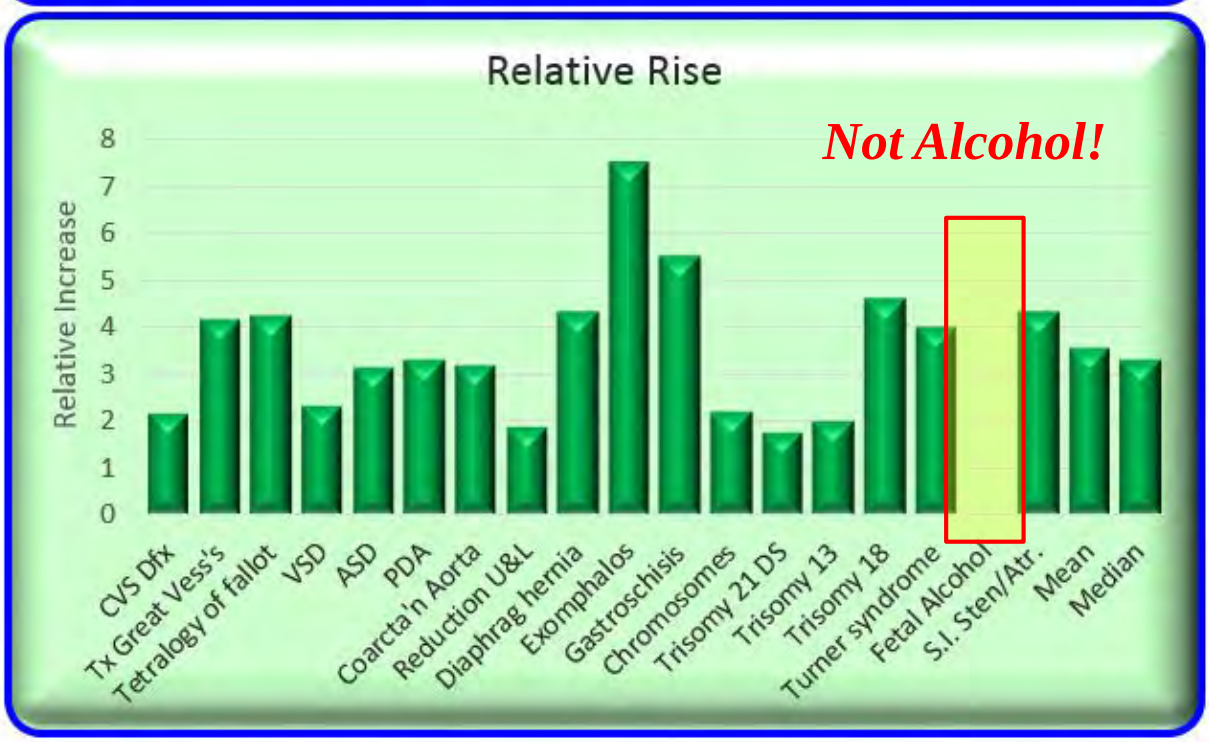
QLD v NNSW Major and Minor Congenital Anomaly Rates



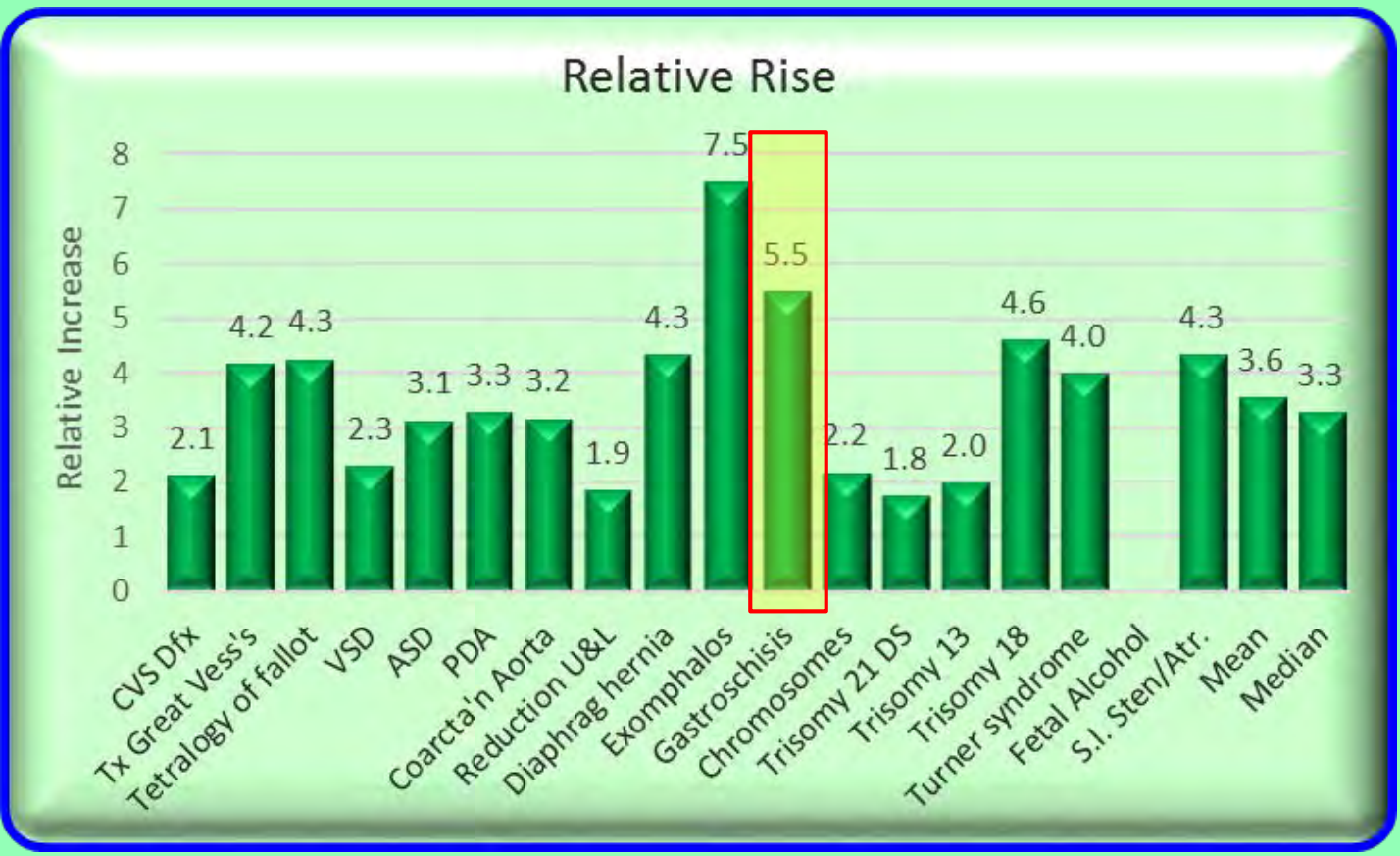


QLD v NNSW Major and Minor Relative Congenital Anomaly Rates





NNSW – QLD
Relative Rises – Exact Rates

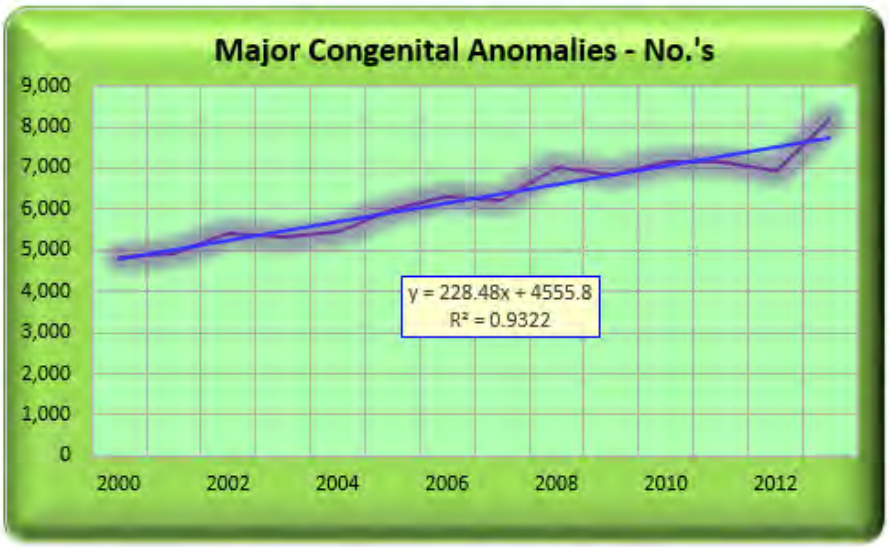


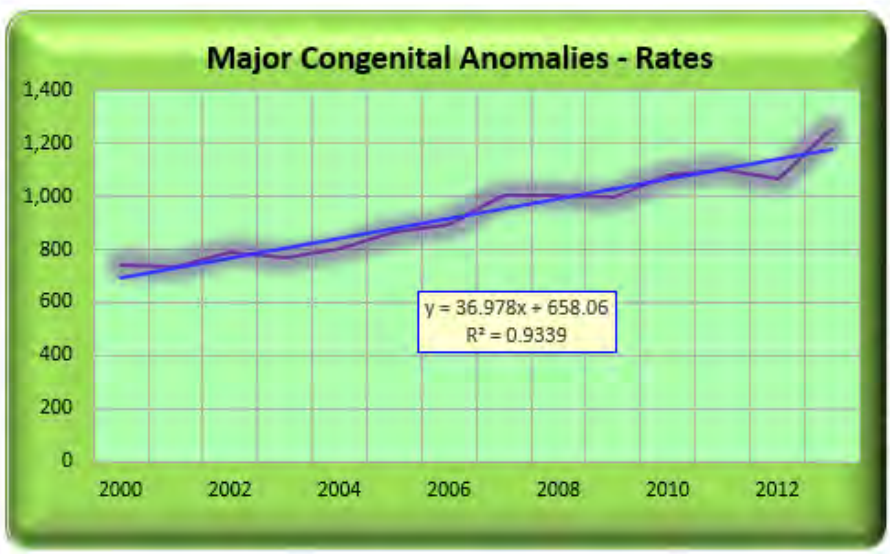
Congenital Anomalies Colorado

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





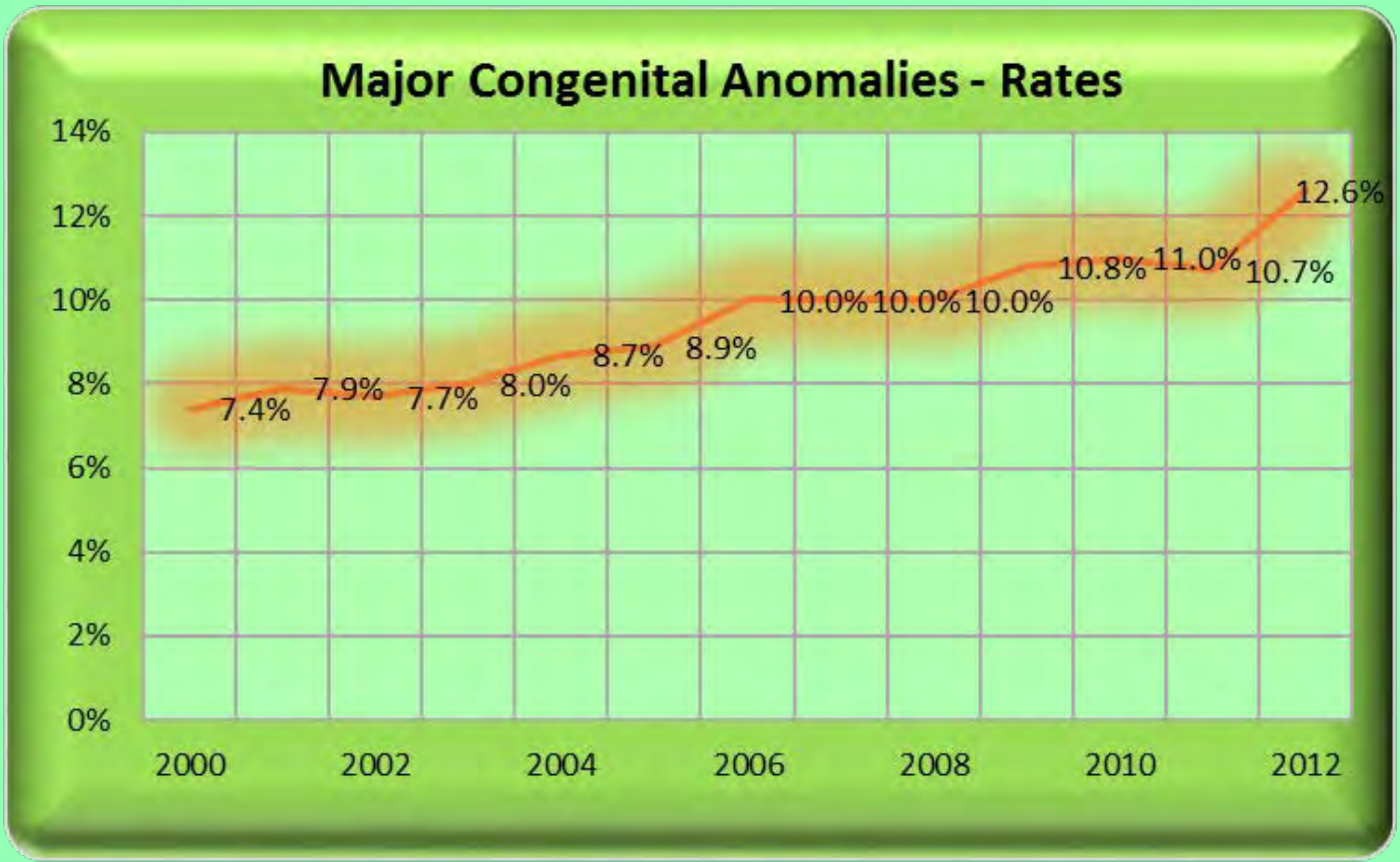
Major Congenital Anomalies

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%

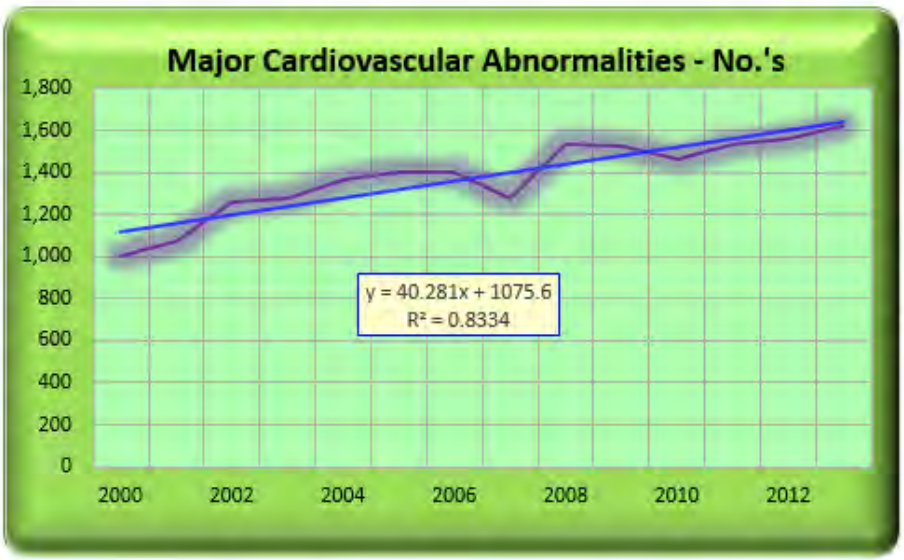
http://www.chd.dphe.state.co.us/cohid/
http://www.cohid.dphe.state.co.us/scripts/htmsql.exe/CrcsnPub.hsql

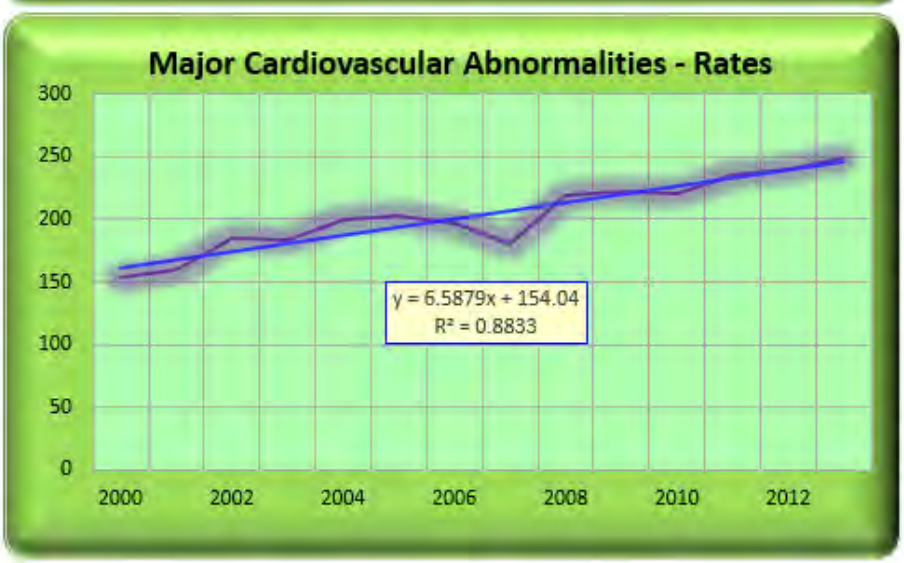
Major Congenital Anomalies as Percentage



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

Major Cardiovascular Anomalies





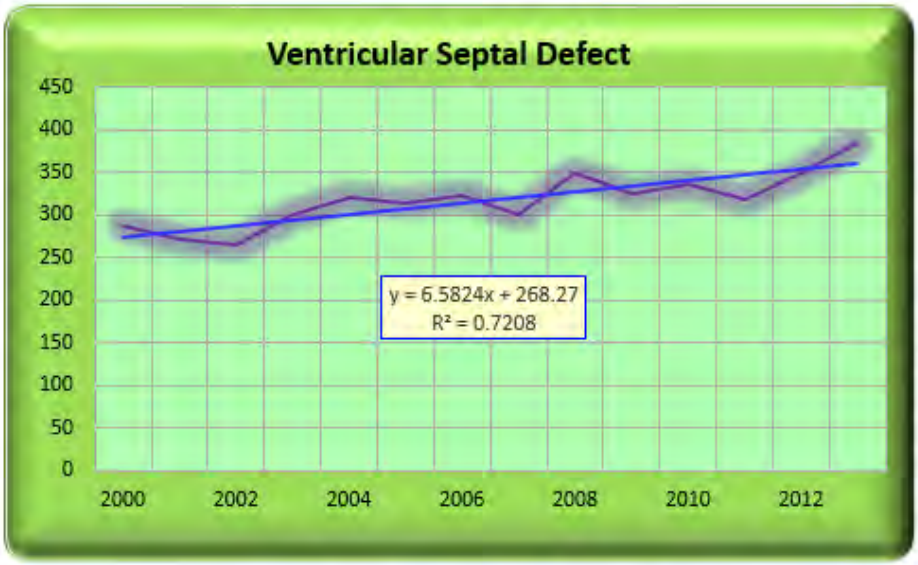
Major CVS Abnormalities

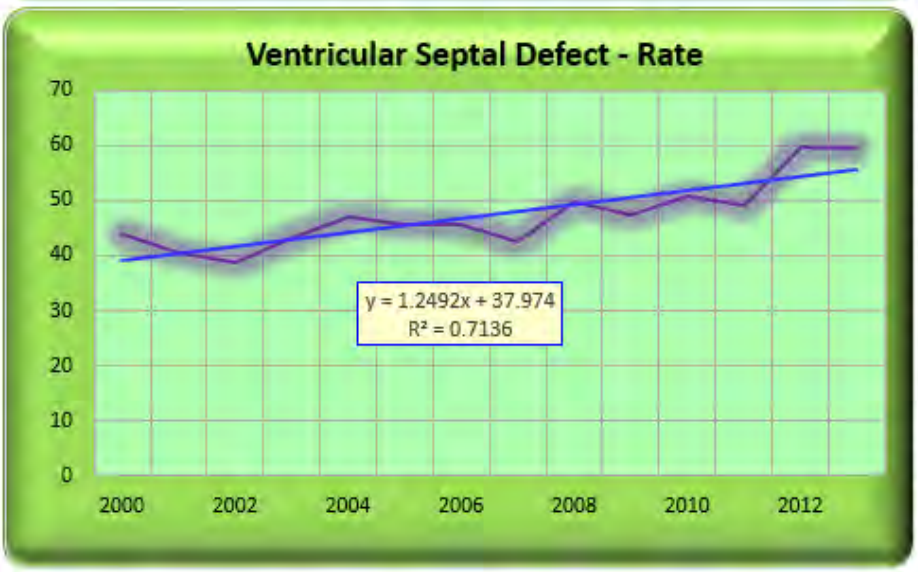
Rates/ 10,000 Live births
(Excluding Terminations)

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%

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

Ventricular Septal Defect





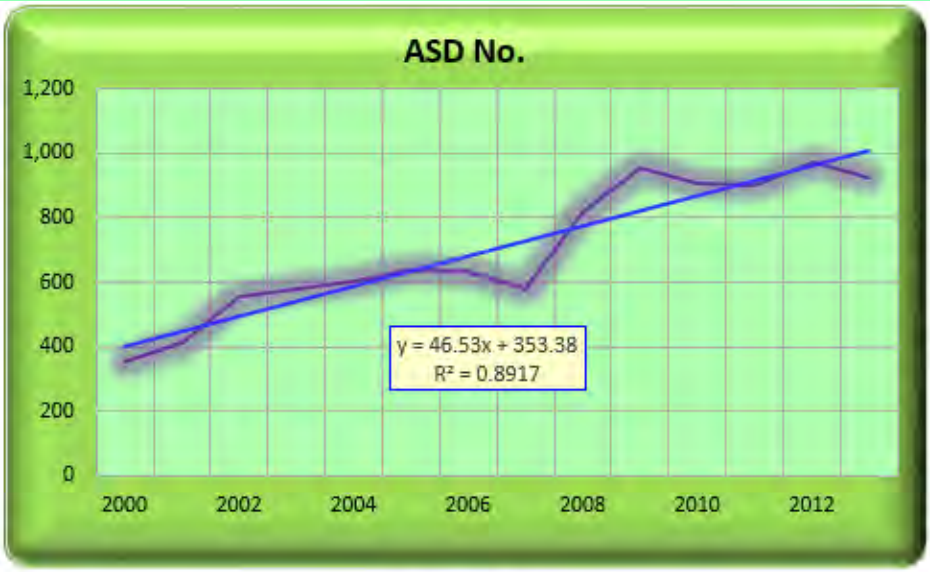
VSD

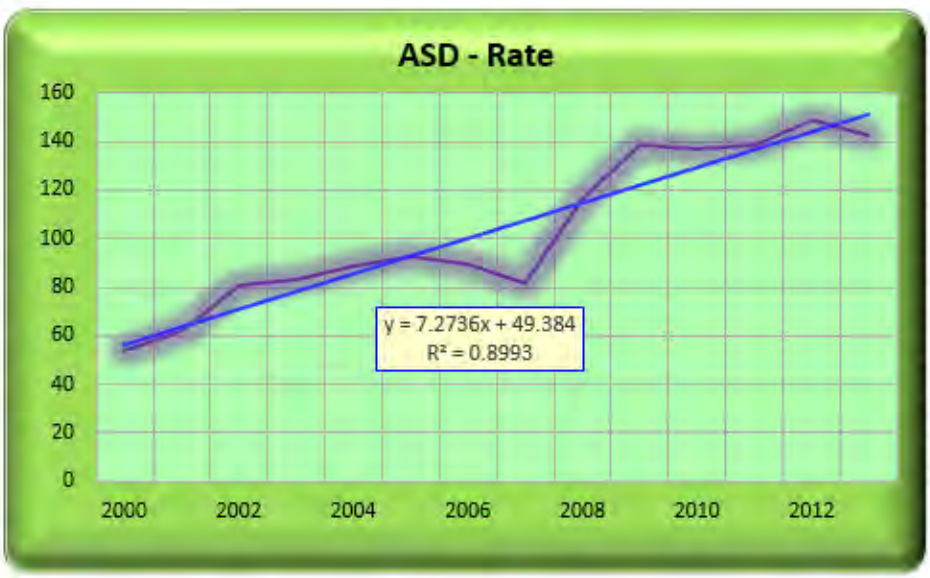
Rates/ 10,000 Live births
(Excluding Terminations)

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%

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

Atrial Septal Defects - Ostium Secundum





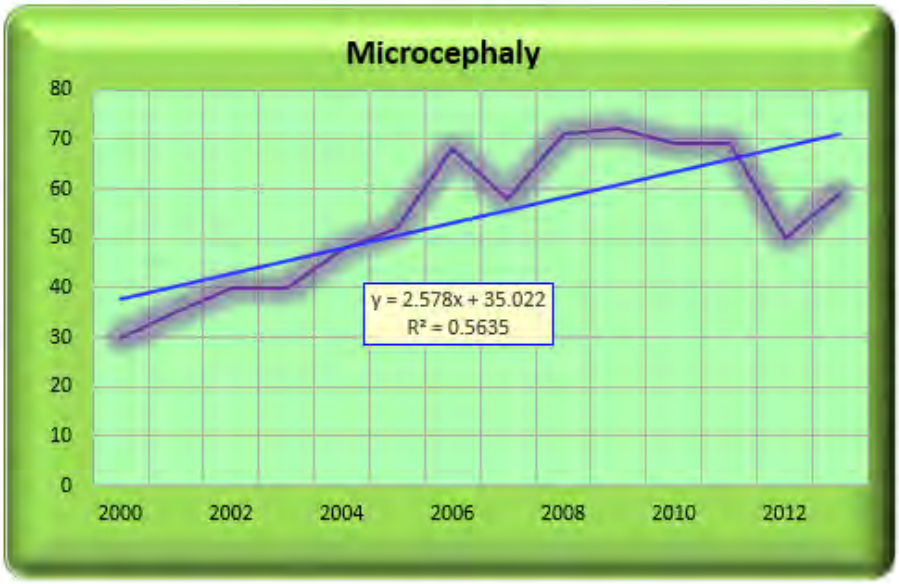
Ostium Secundum ASD's

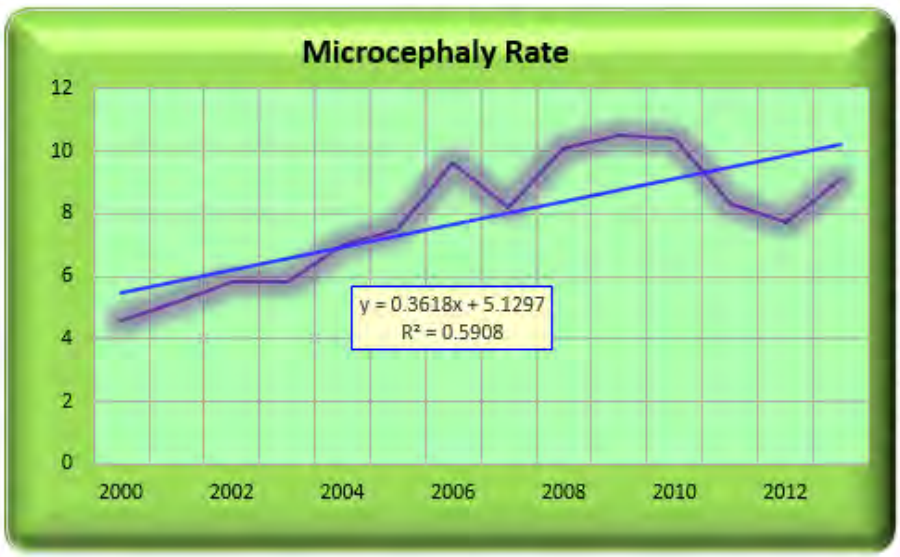
Rates/ 10,000 Live births
(Excluding Terminations)

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%

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

Microcephaly





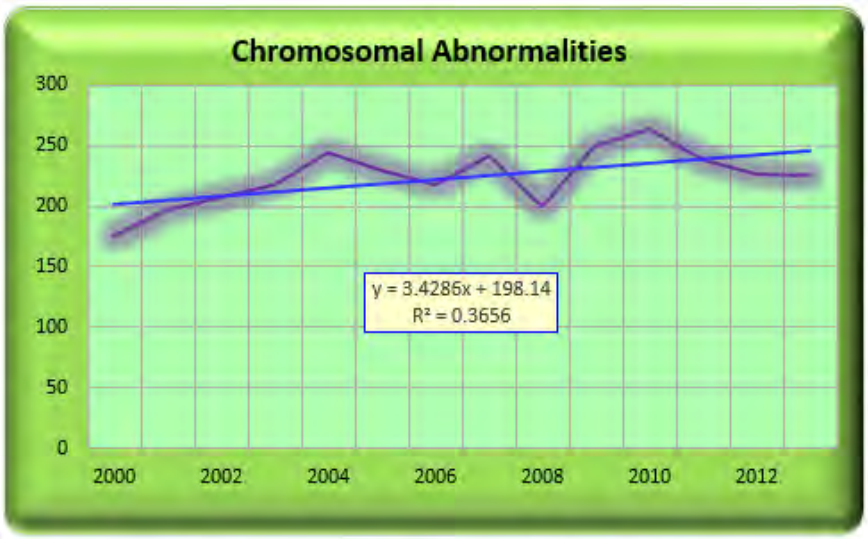
Microcephaly

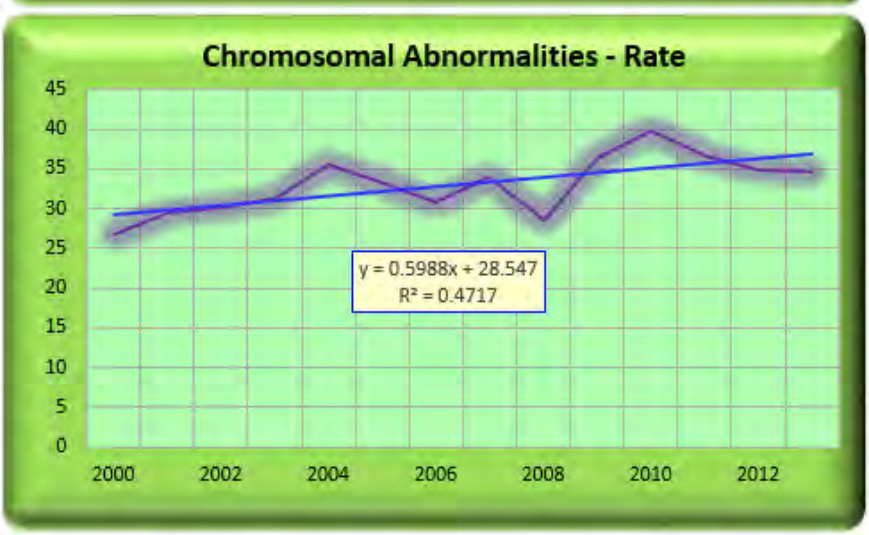
Rates/ 10,000 Live births
(Excluding Terminations)

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%**

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

Chromosomal Anomalies





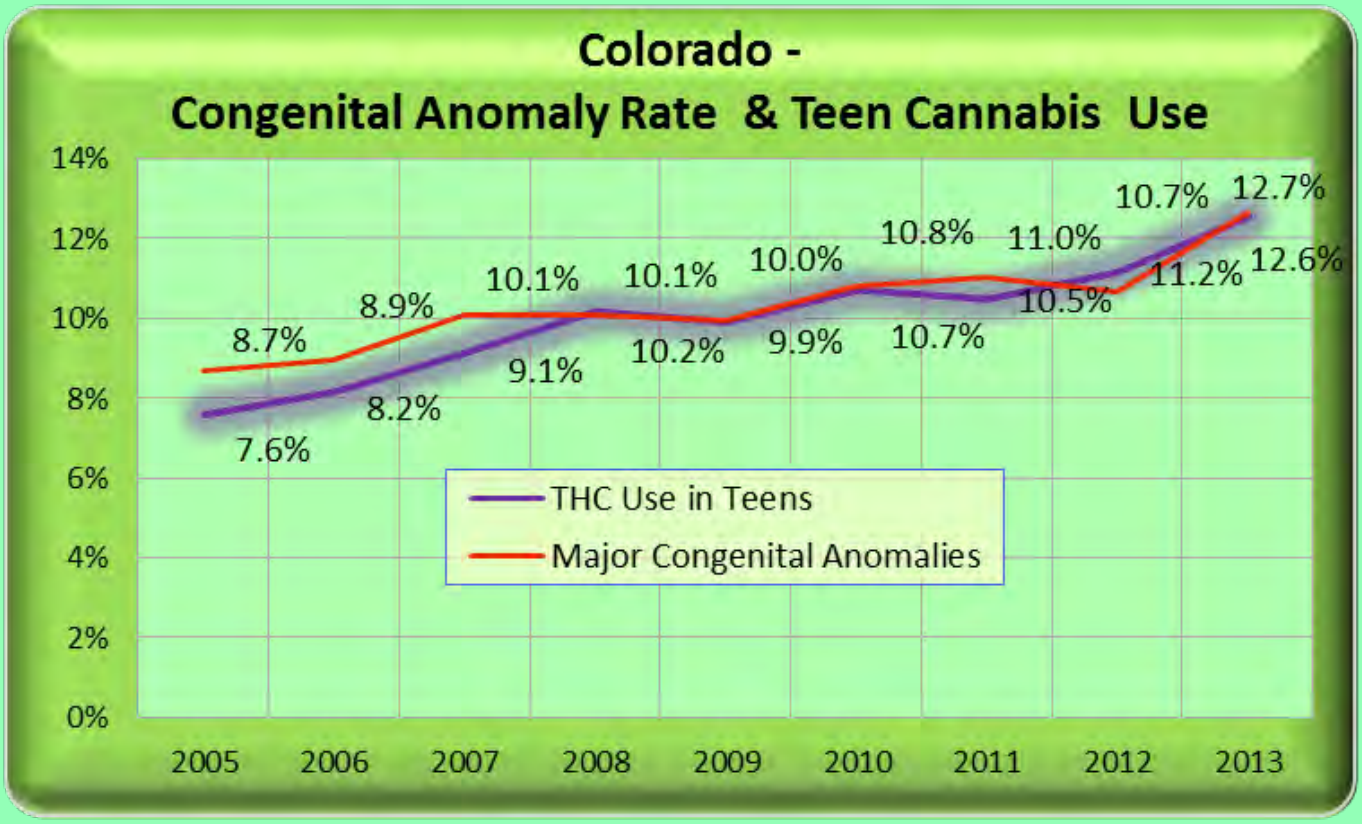
Chromosomal Abnormalities

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%

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

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
```

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

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

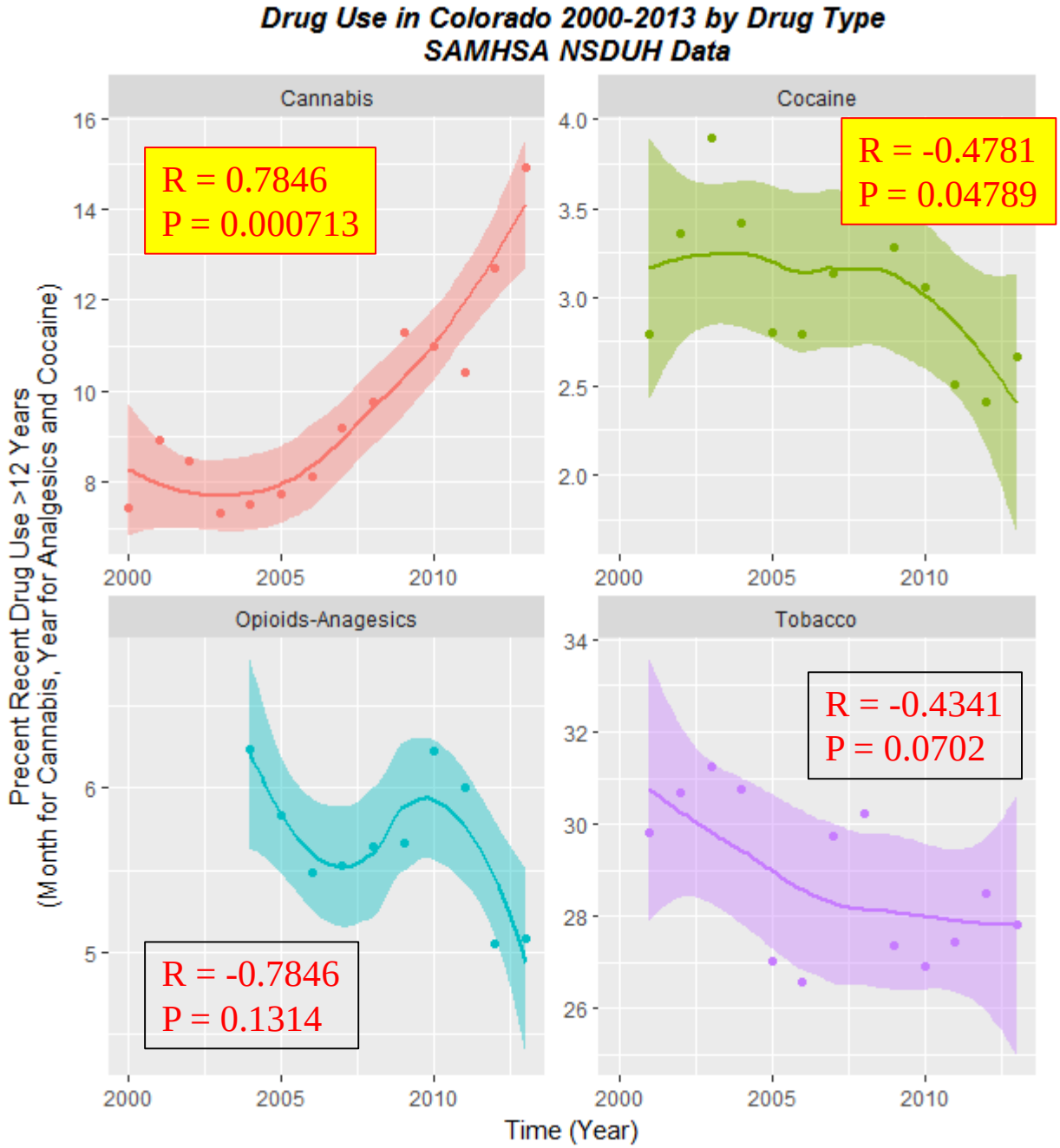
https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.pdf

Cumulative Overall Effects

Anomaly	Cumulative Total 2000-2013	Projected Total from Baseline	Excess Above Baseline	% Change 2000-2013	Increase Relative to Births
Births	949,317	916,006	33,311	3.6%	1.00
Major Congenital 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

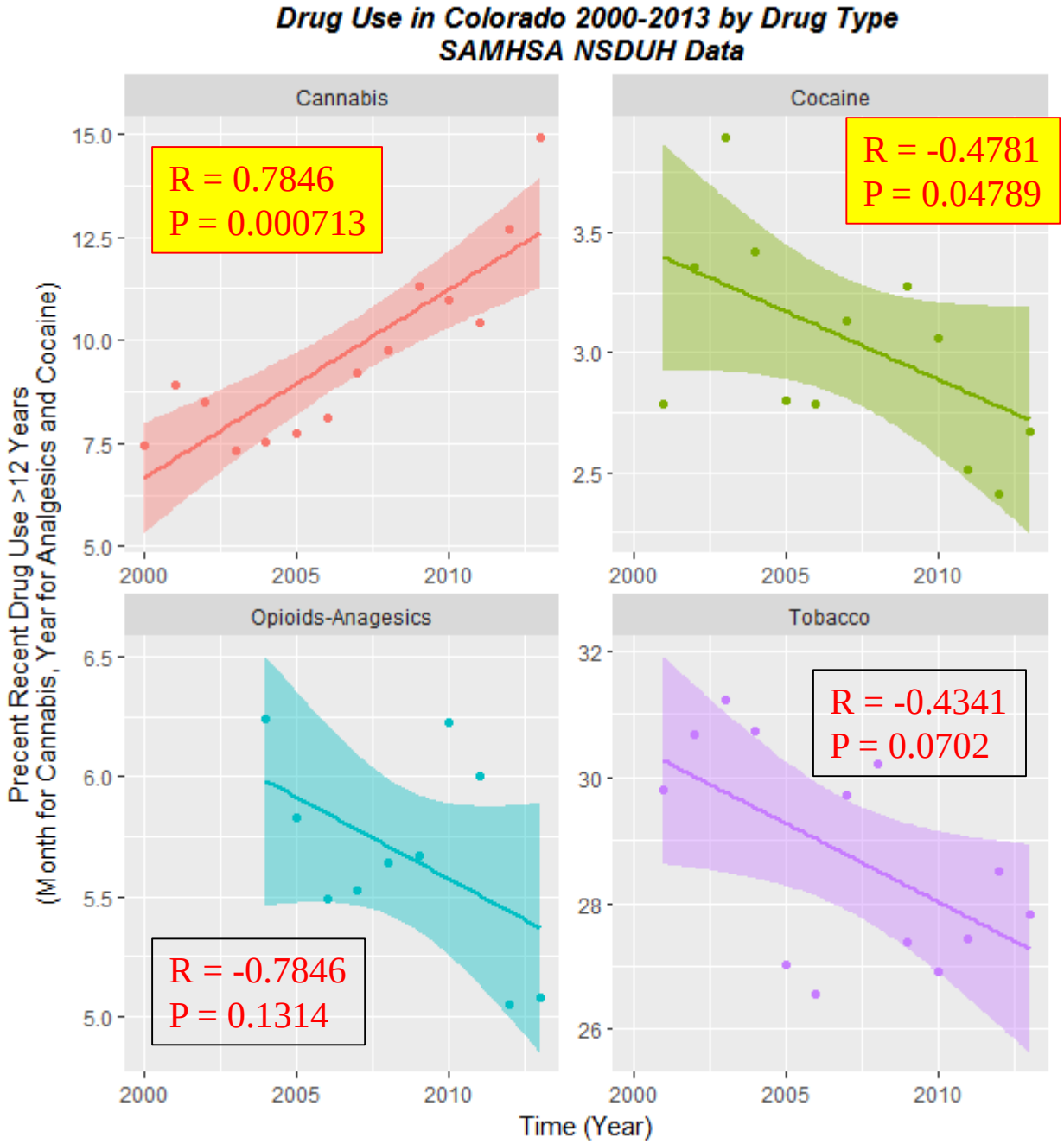
http://www.chd.dphe.state.co.us/cohid/
http://www.cohid.dphe.state.co.us/scripts/htmsql.exe/CrcsnPub.hsql

Coloradan Drug Use Trends - Loess



SAMHSA NSDUH Data

Coloradan Drug Use Trends - Linear



SAMHSA NSDUH Data

ASD ~ Drug Type
Colorado, 2000-2013
Only Cannabis is Significant!!

```
> summary(lm(log(ColDr$ASDSecundum) ~ log(ColDr$LMTHCGr12) + log(ColDr$Tobacco

Call:
lm(formula = log(ColDr$ASDSecundum) ~ log(ColDr$LMTHCGr12) +
    log(ColDr$Tobacco) + log(ColDr$Cocaine) + ColDr$OpPain +
    ColDr$Alcohol - ColDr$OpPain - log(ColDr$Tobacco) - log(ColDr$Cocaine) -
    ColDr$Alcohol, data = ColDr)

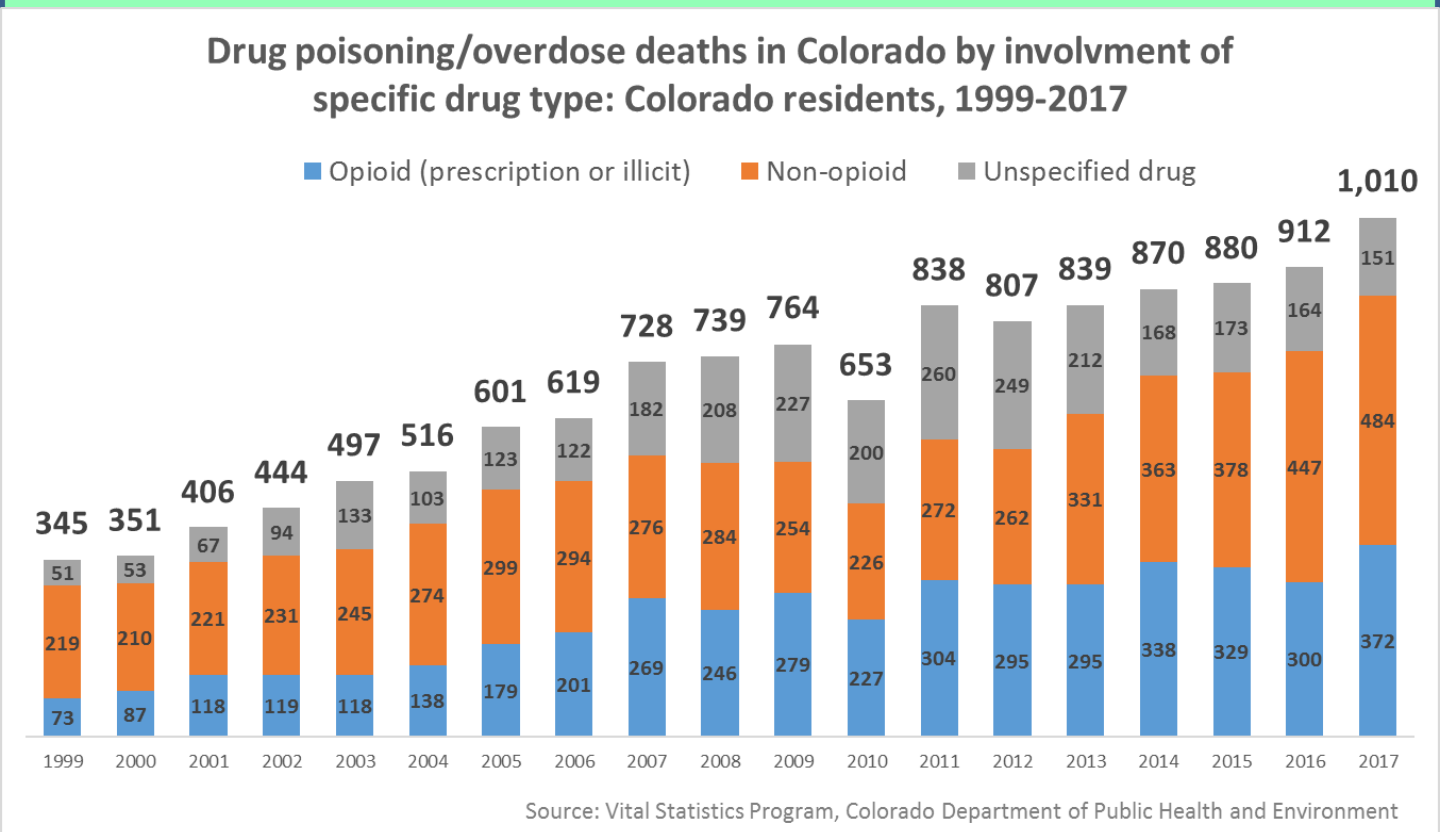
Residuals:
     Min       1Q   Median       3Q      Max
-0.22493 -0.02787  0.01960  0.08022  0.12040

Coefficients:
                      Estimate Std. Error t value Pr(>|t|)
(Intercept)             4.7899     0.4142  11.565 2.84e-06 ***
log(ColDr$LMTHCGr12)    0.8091     0.1788   4.525  0.00194 **
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

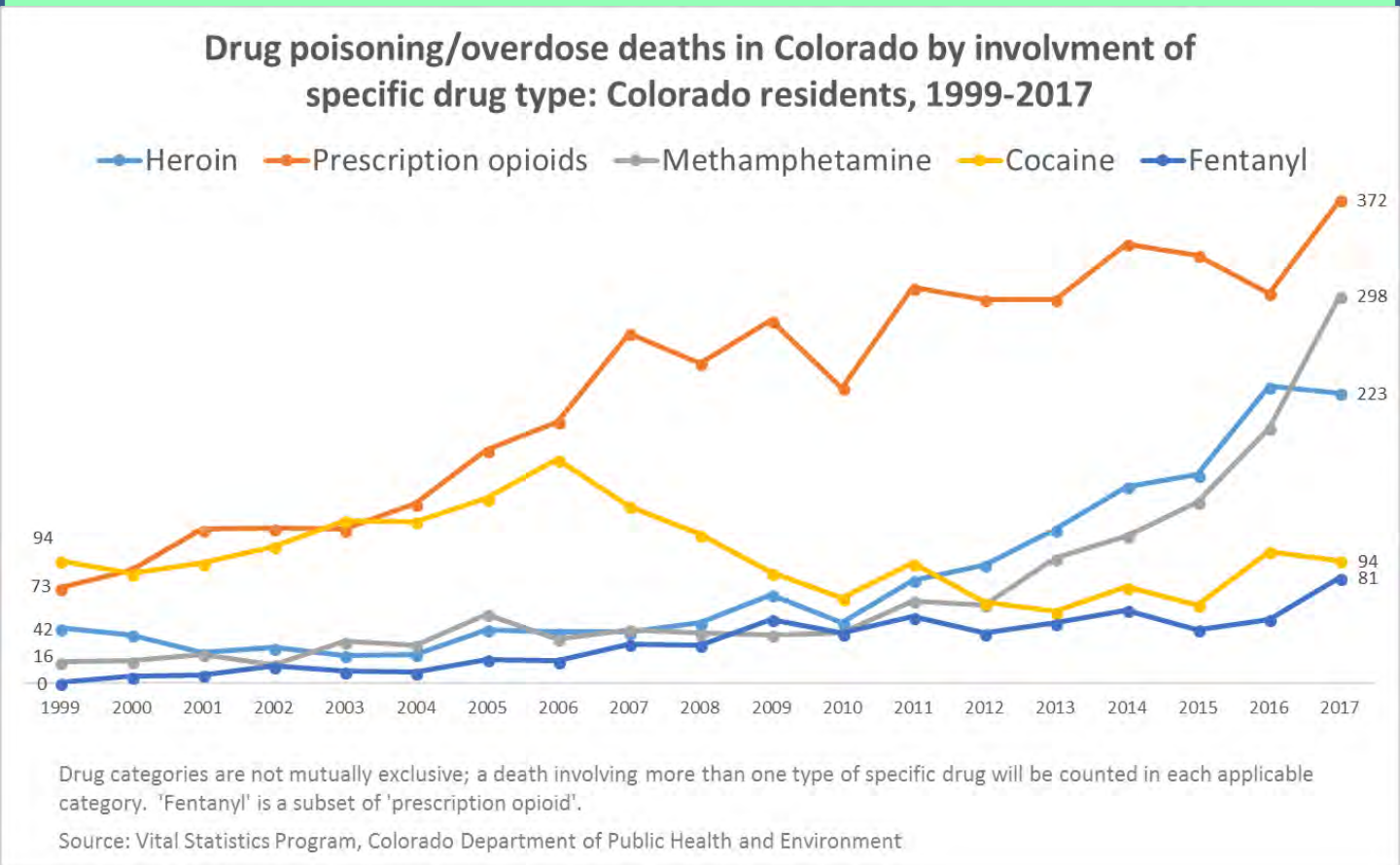
Residual standard error: 0.1183 on 8 degrees of freedom
  (4 observations deleted due to missingness)
Multiple R-squared:  0.7191,    Adjusted R-squared:  0.684
F-statistic: 20.48 on 1 and 8 DF,  p-value: 0.001936
```

SAMHSA NSDUH Data

Colorado Drug Deaths



Colorado Drug Deaths



Drug categories are not mutually exclusive; a death involving more than one type of specific drug will be counted in each applicable category. 'Fentanyl' is a subset of 'prescription opioid'.

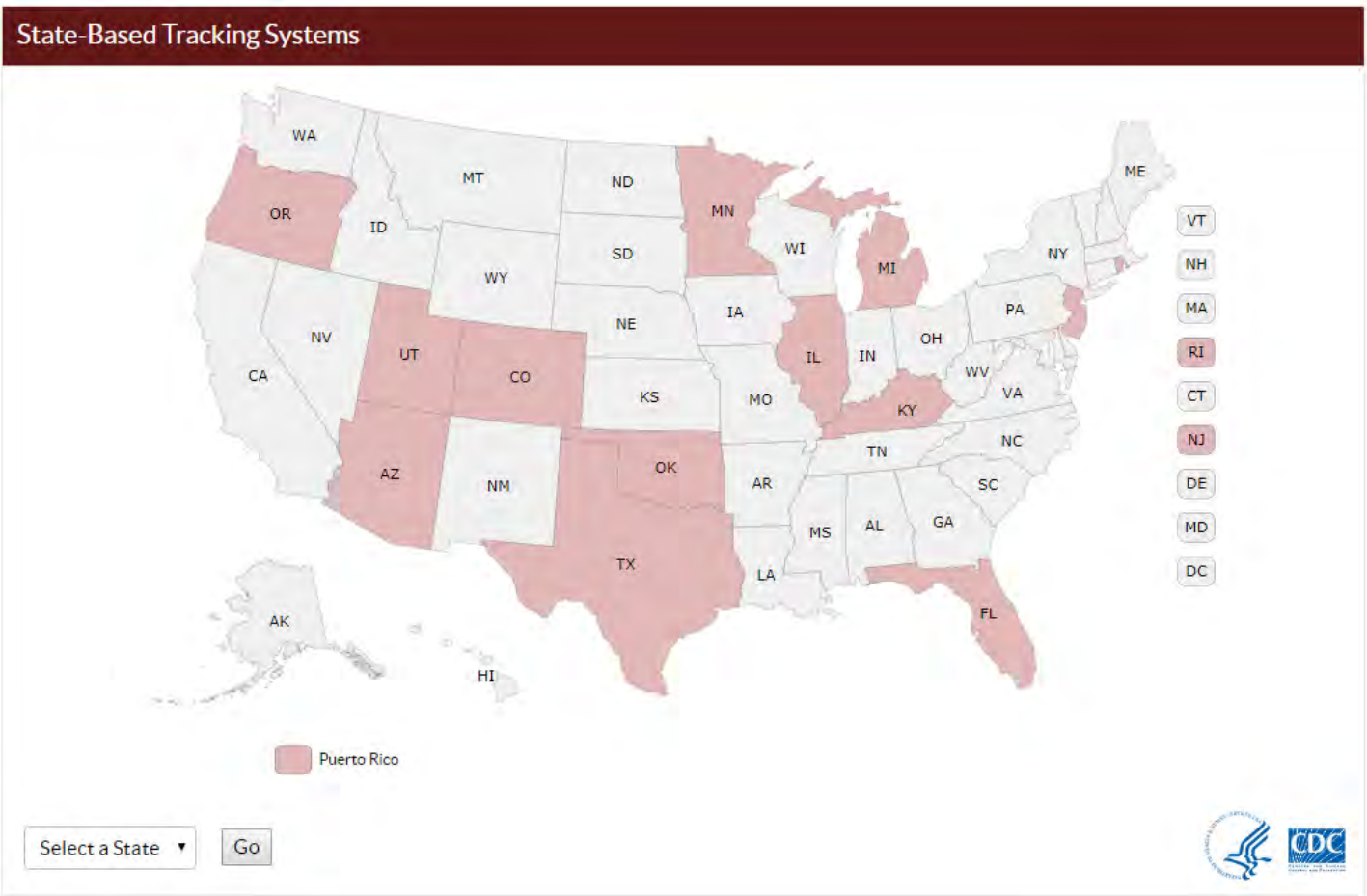
Source: Vital Statistics Program, Colorado Department of Public Health and Environment

USA Births
Defects Patterns
Analysis and Review

CDC USA
Centres for Births Defects Research and Prevention (CBDRP)

https://www.cdc.gov/ncbddd/birthdefects/cbdrp.html

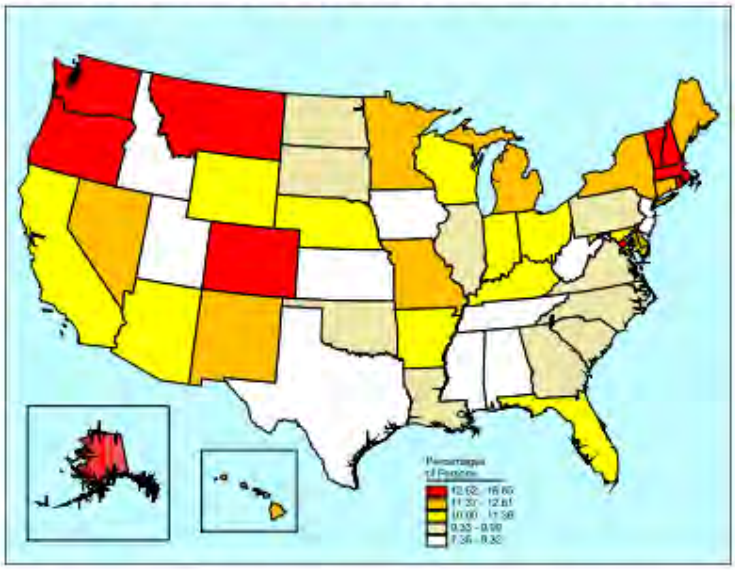
Births Defects Study to Evaluate Pregnancy Exposures (BD-STEPS)



https://www.cdc.gov/ncbddd/birthdefects/states/index.html

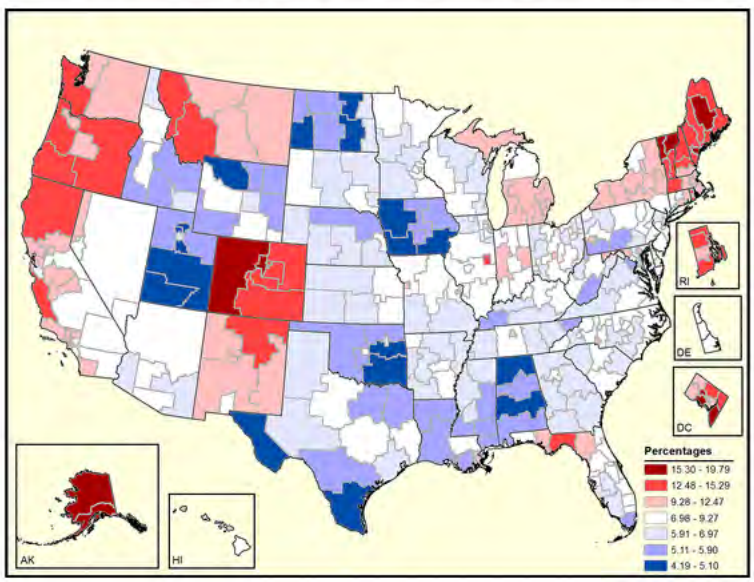
Growth - Monthly Cannabis Use

Figure 2.5 ***Marijuana Use in Past Year among Persons Aged 12 or Older,*** **by State: Percentages, Annual Averages Based on 2002 and 2003 NSDUHs**



Source: SAMHSA, Office of Applied Studies, National Survey on Drug Use and Health, 2002 and 2003.

Figure 2. Marijuana Use in the Past Month among Individuals Aged 12 or Older, by Substate Region: Percentages, Annual Averages Based on 2014, 2015, and 2016 NSDUHs

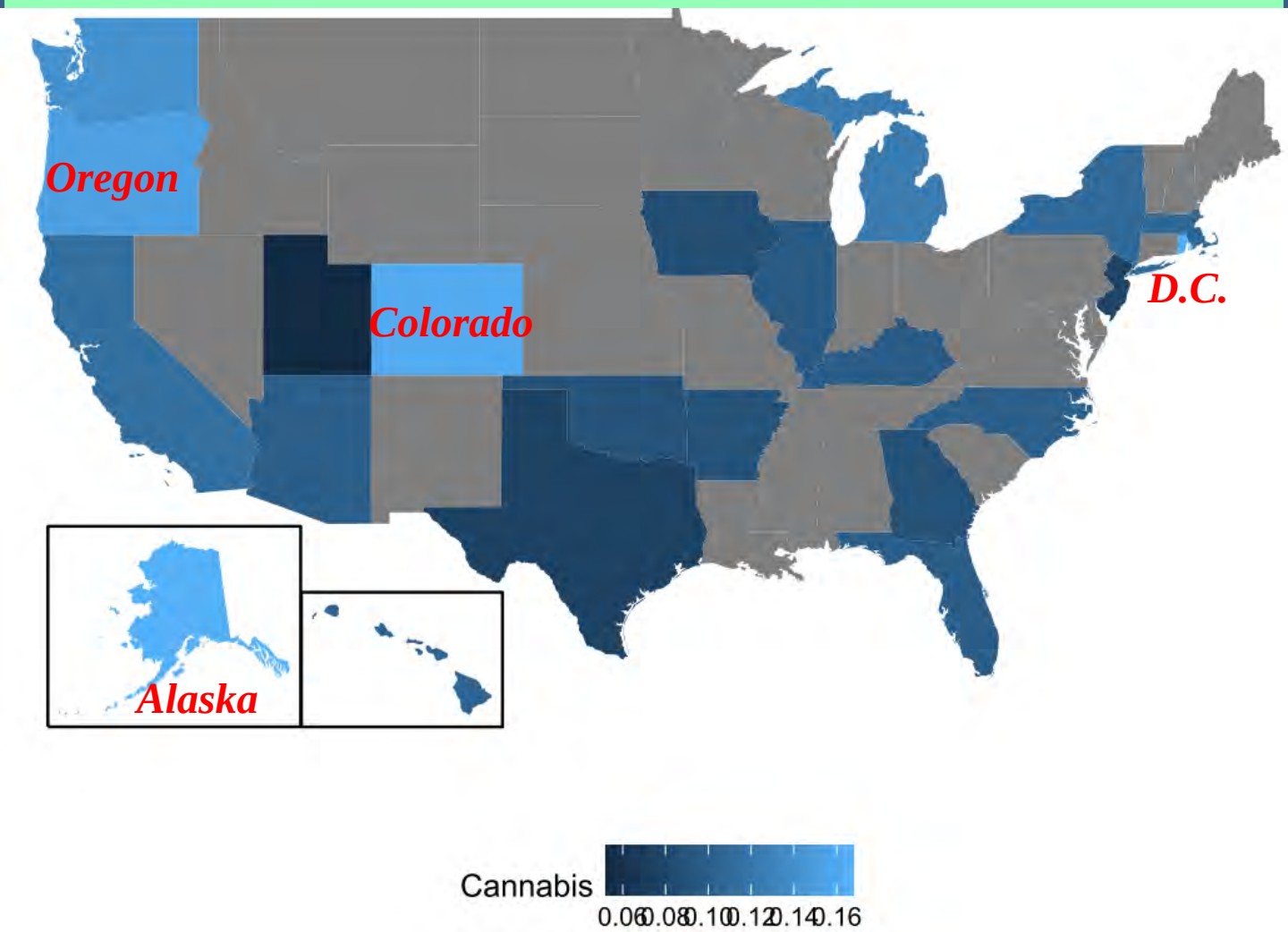


D

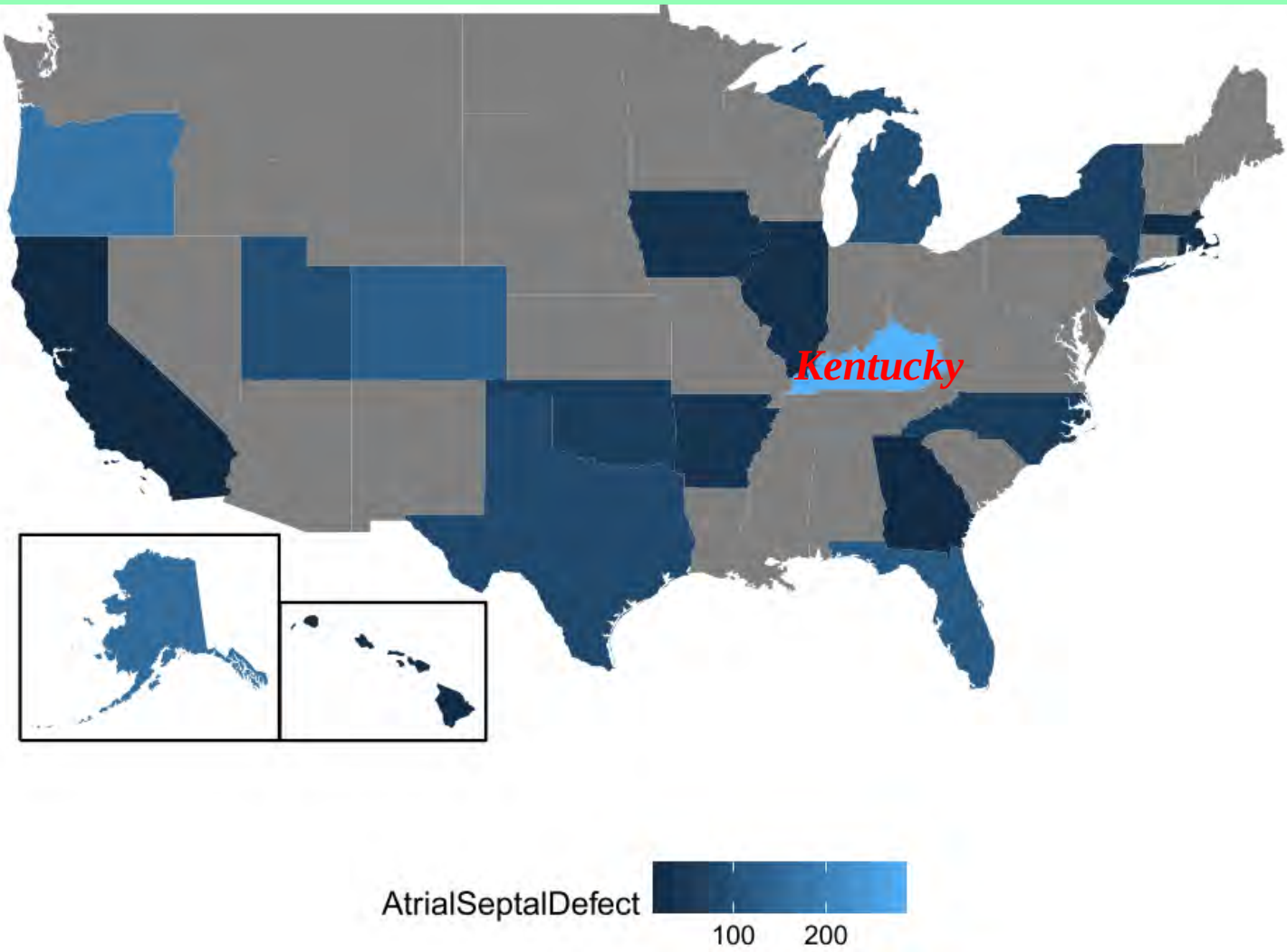
Click here for a larger image.

NOTE: For substate region definitions, see the "2014-2016 National Survey on Drug Use and Health Substate Region Definitions" at https://www.samhsa.gov/data/.
Source: SAMHSA, Center for Behavioral Health Statistics and Quality, National Survey on Drug Use and Health, 2014, 2015, and 2016.

Cannabis Use

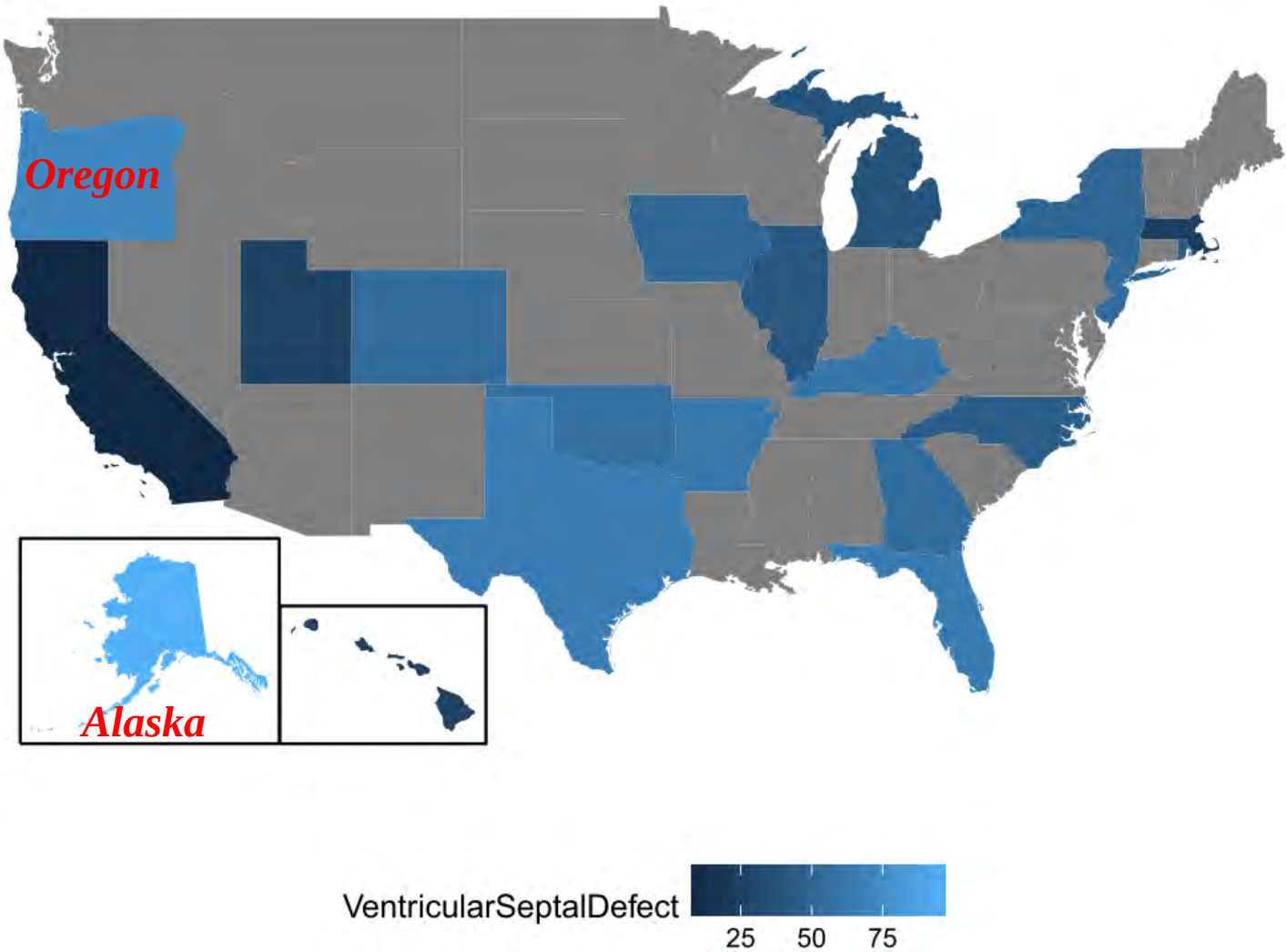


ASD
Atrial Septal Defect



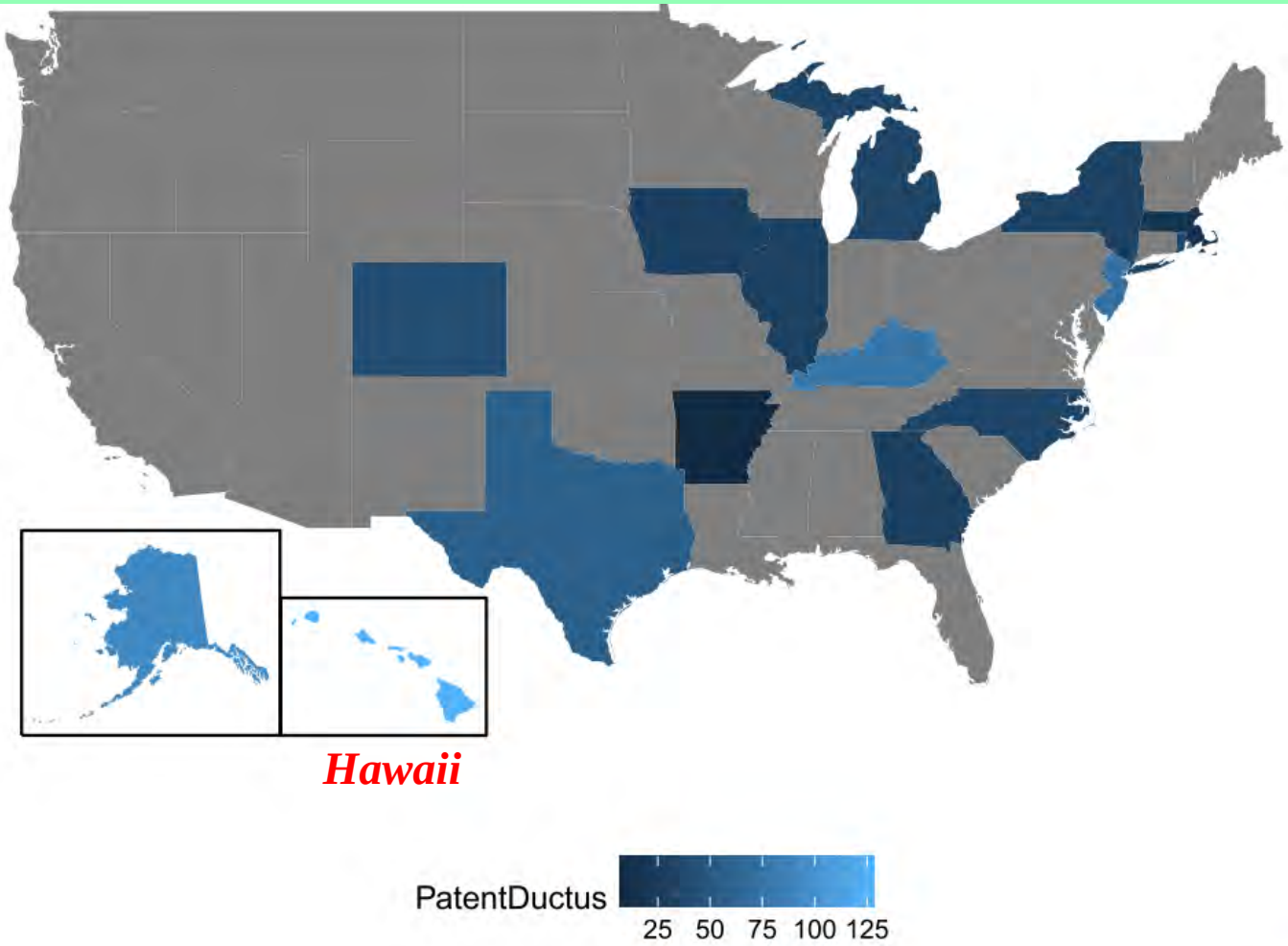
NBDPN & NSDUH Publicly Available Data

VSD
Ventricular Septal Defect



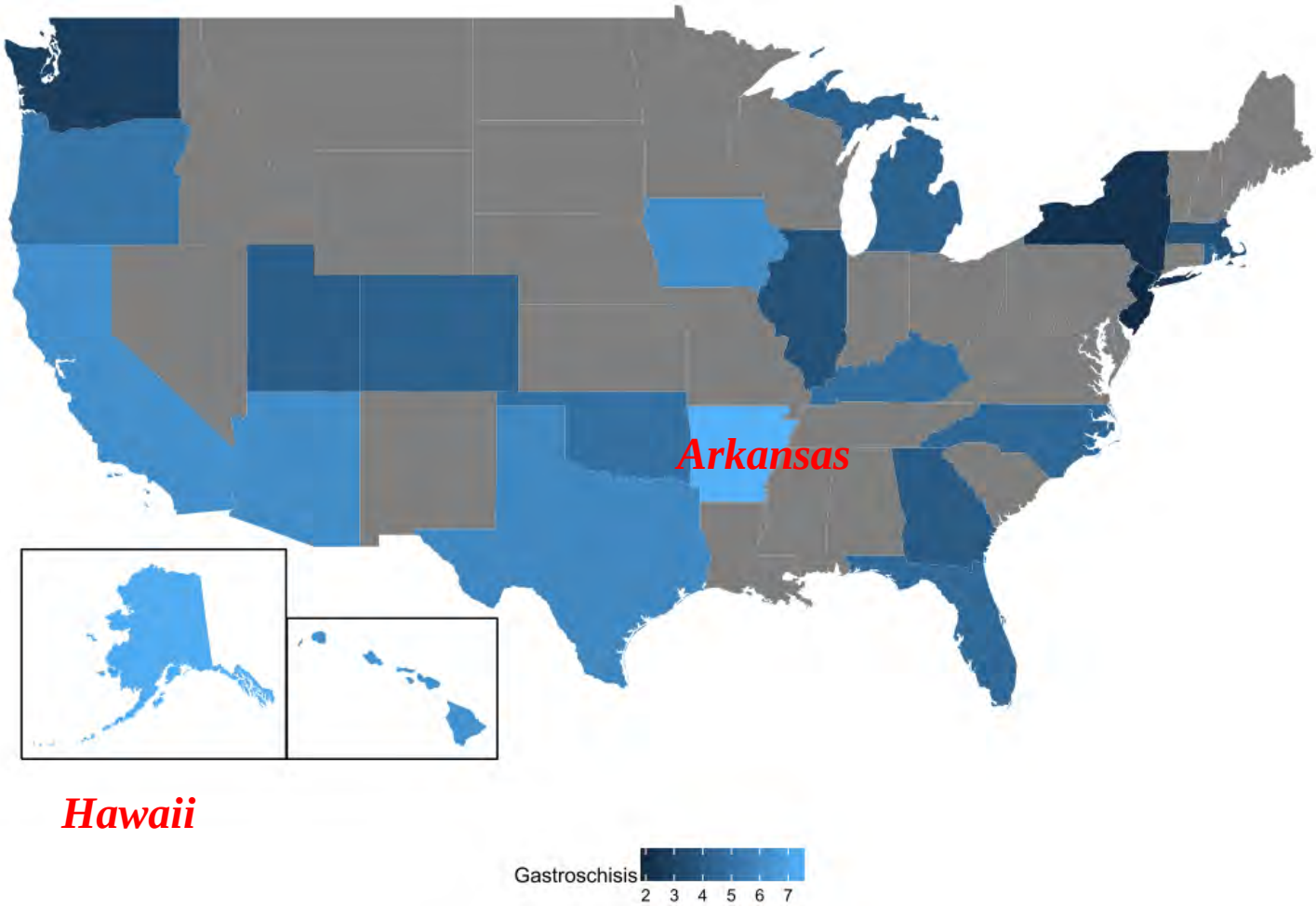
NBDPN & NSDUH Publicly Available Data

PDA
Patent Ductus Arteriosus



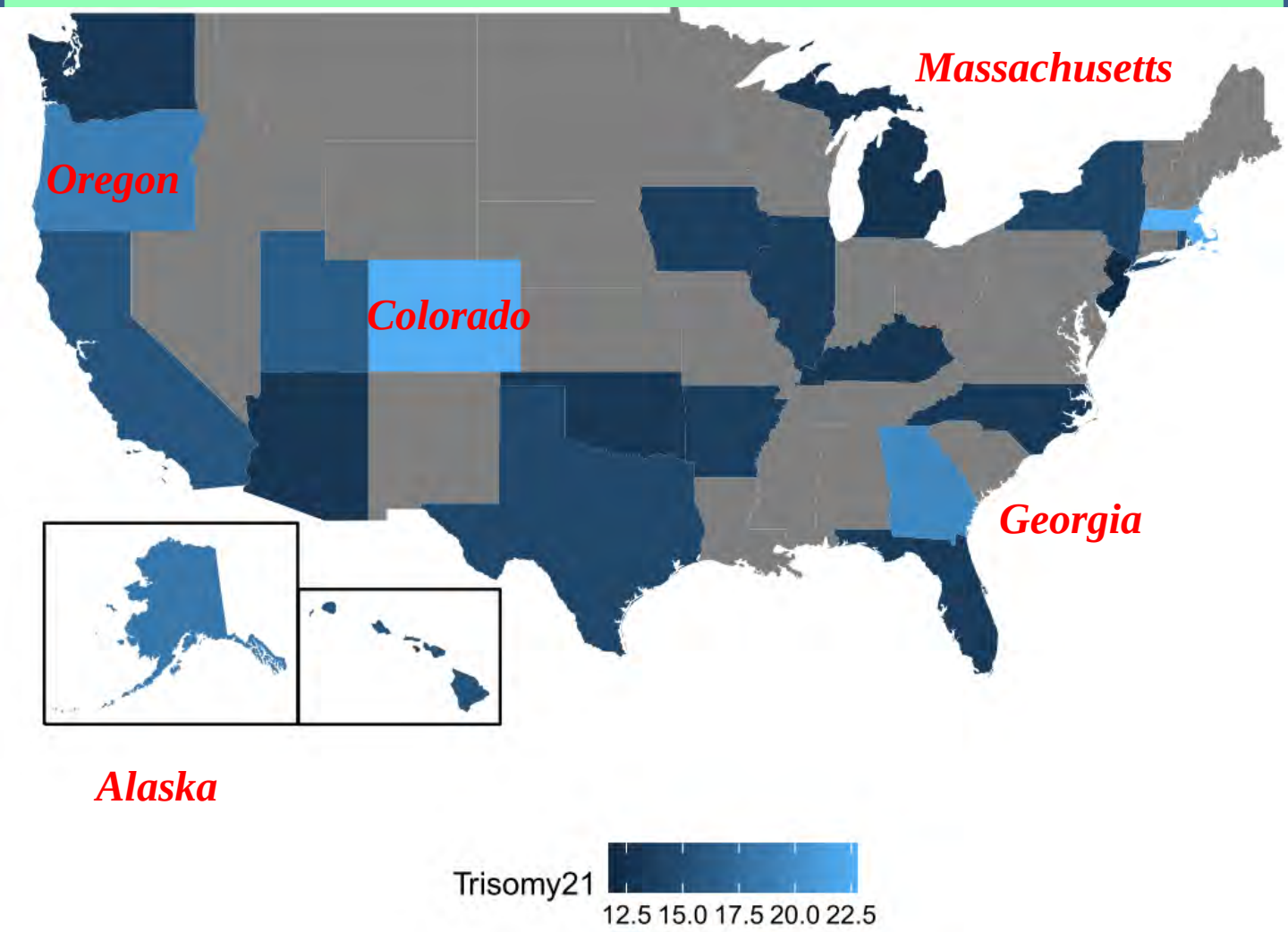
NBDPN & NSDUH Publicly Available Data

Gastroschisis



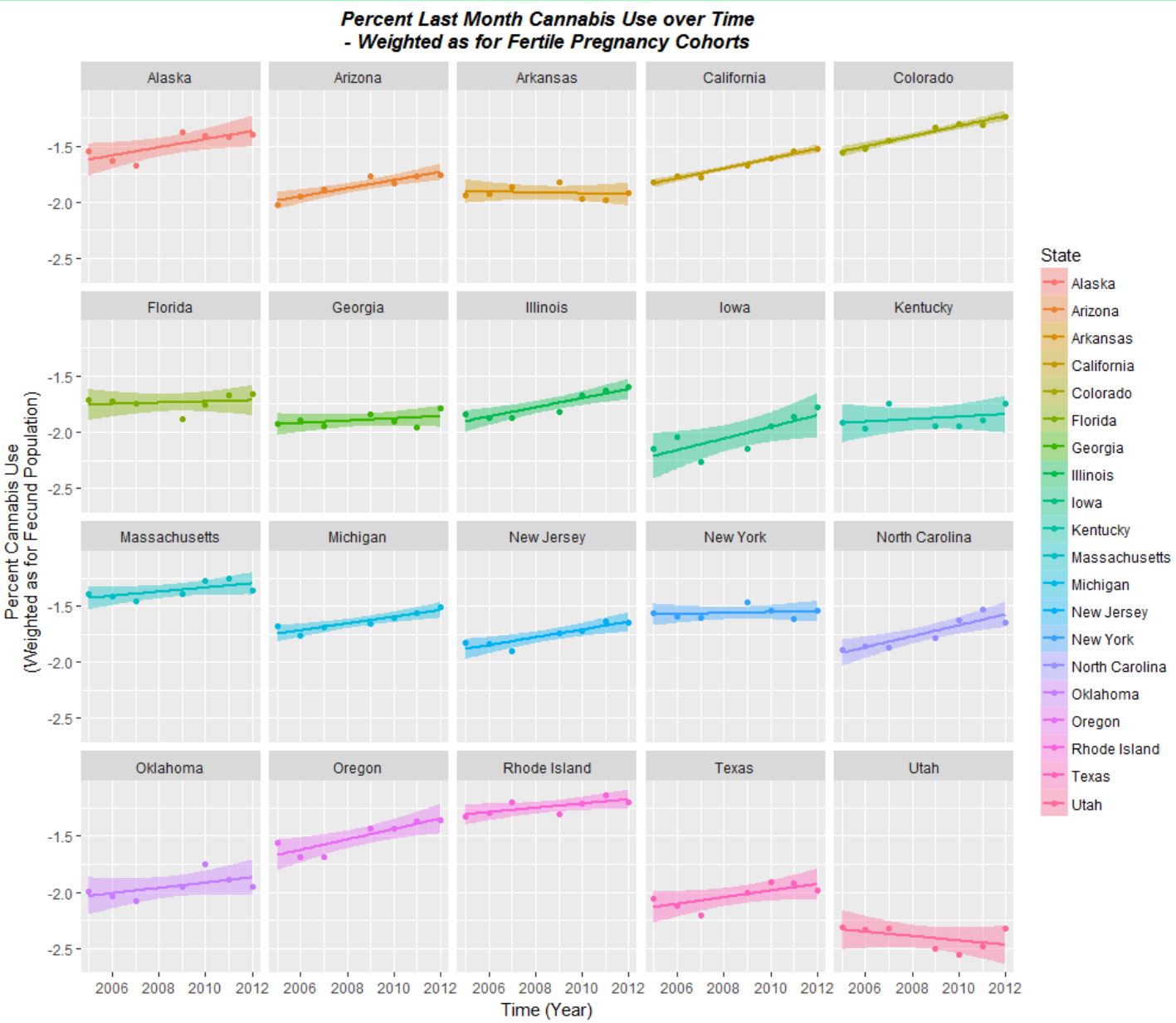
NBDPN & NSDUH Publicly Available Data

Downs Syndrome



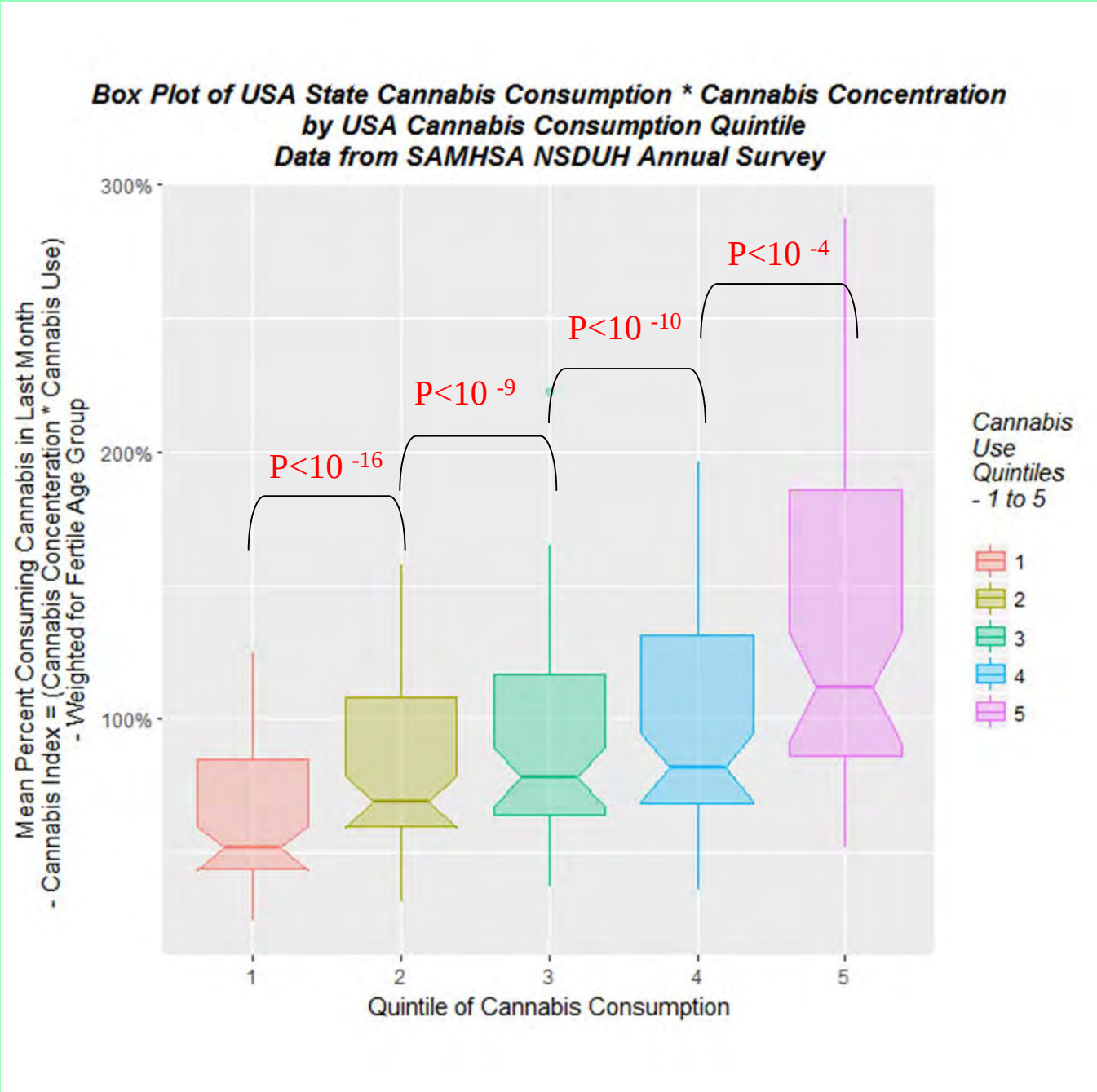
NBDPN & NSDUH Publicly Available Data

US Cannabis Use by State

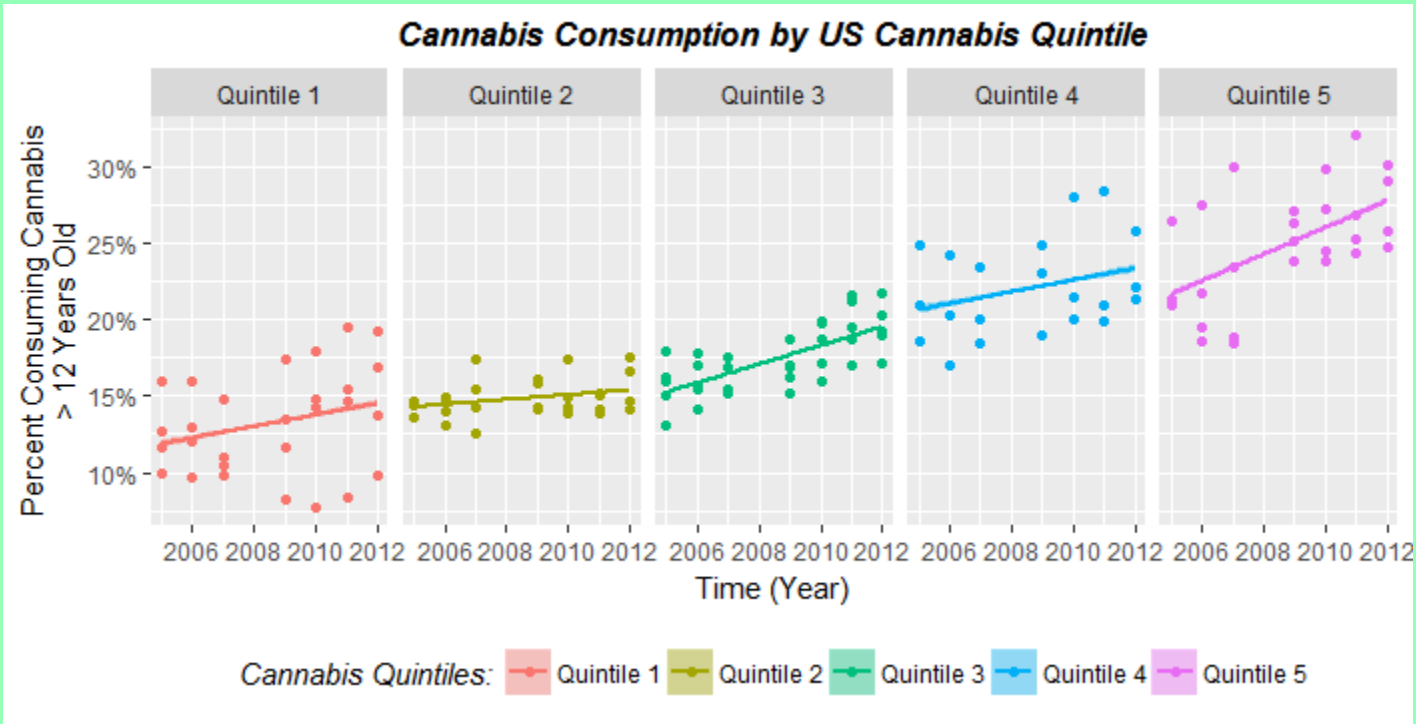


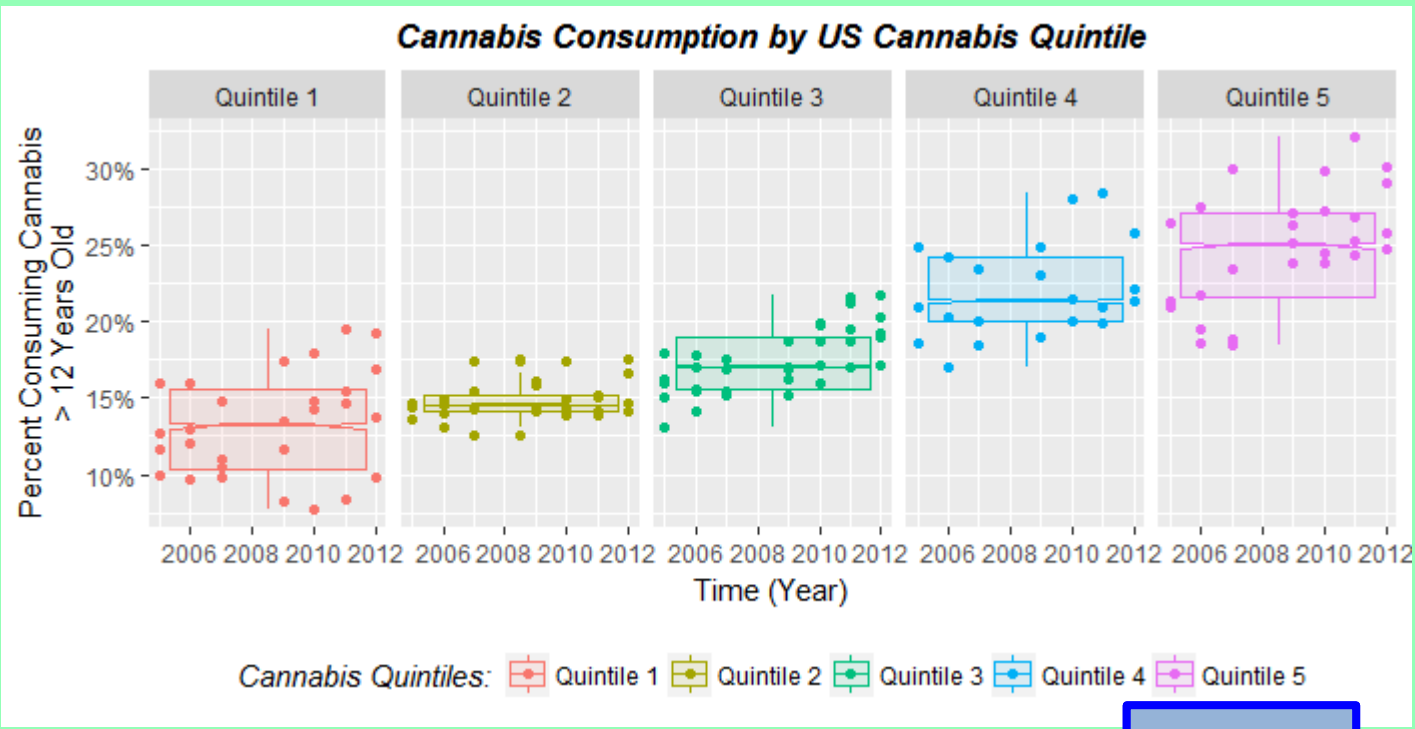
Data from NSDUH, SAMHSA

Cannabis Consumption Quintiles



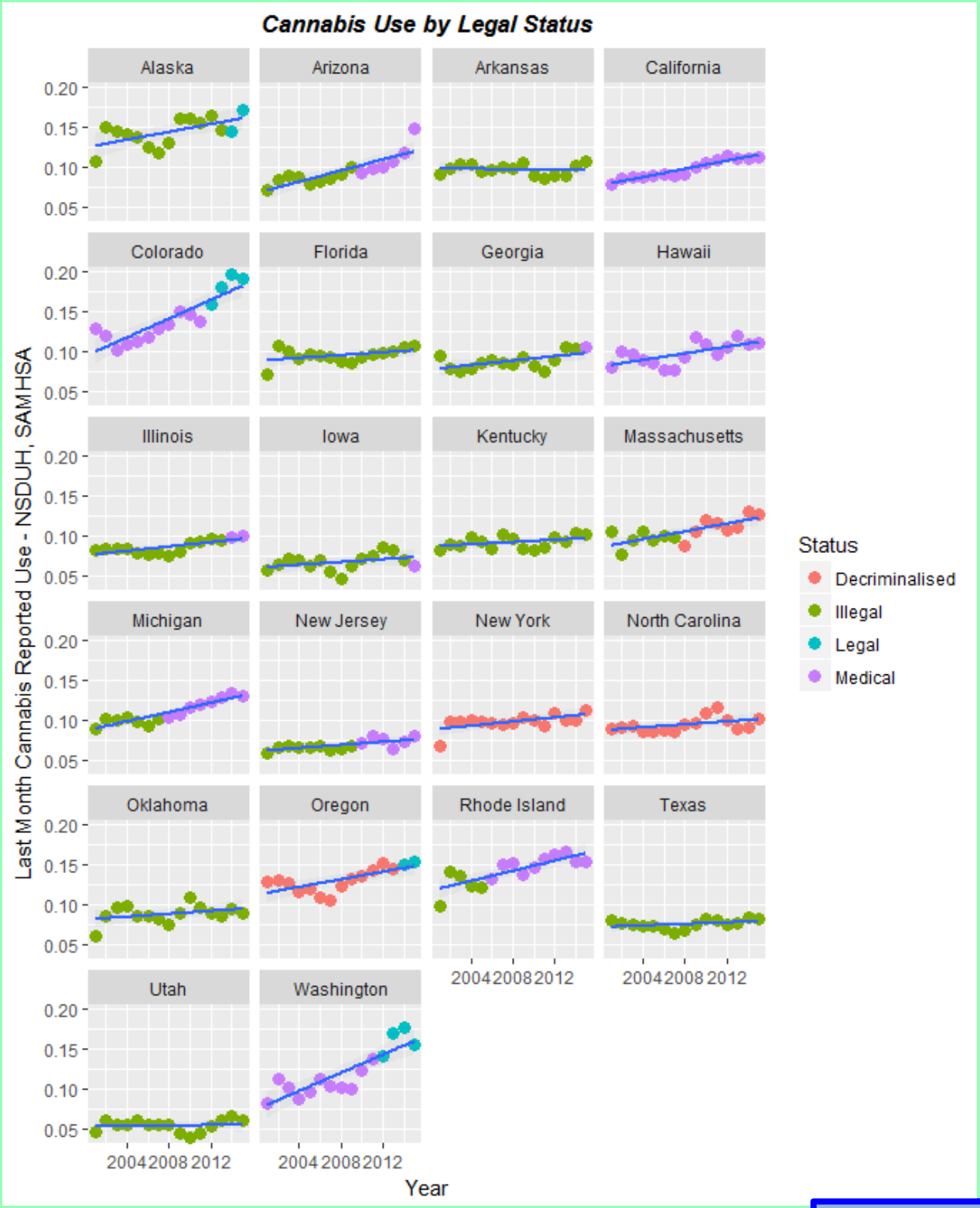
USA Cannabis Quintiles



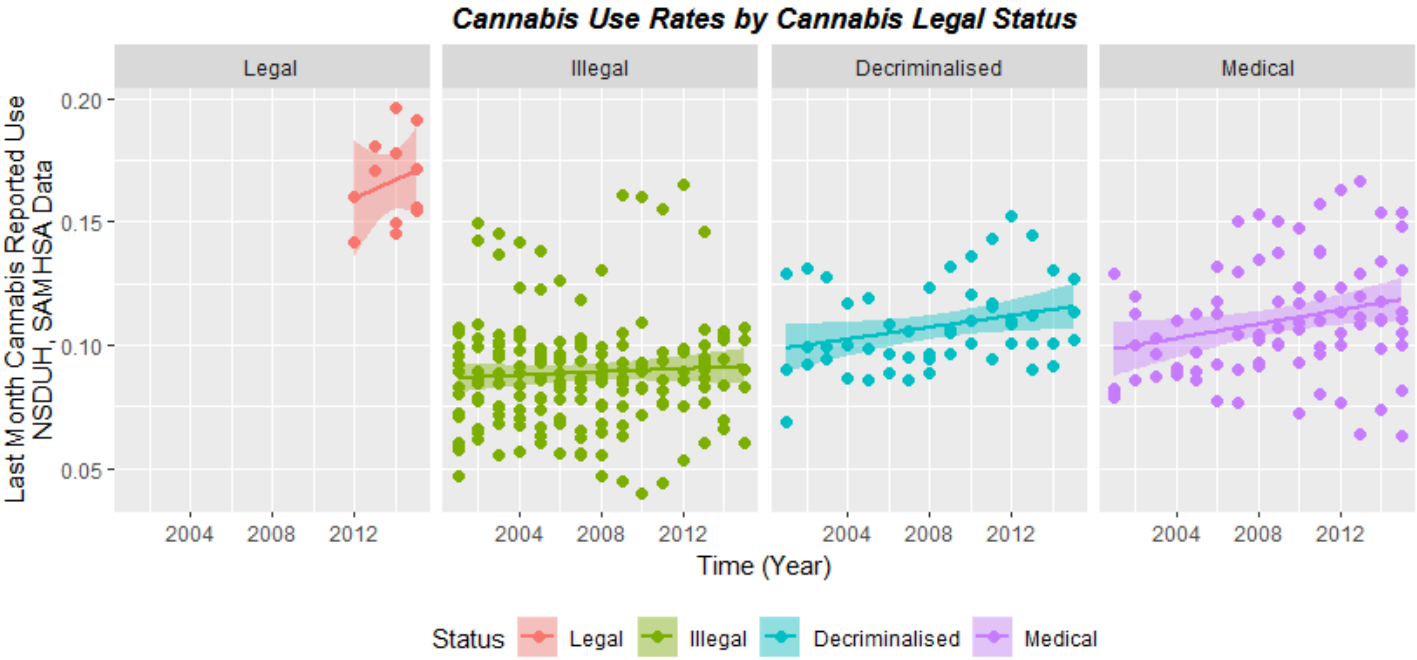


NSDUH Publicly Available Data

Cannabis Use by Legal Status



Cannabis Use Rates by Legal Status




```
> summary(lm(log(LMonth)~Year*Status-Status, data=THCS))

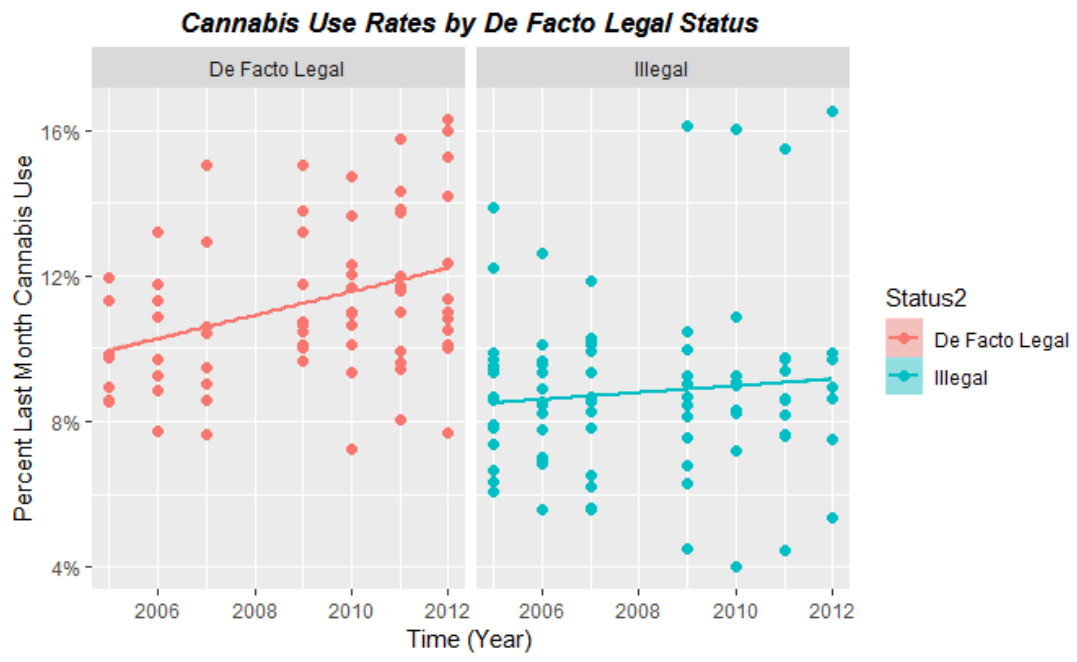
Call:
lm(formula = log(LMonth) ~ Year * Status - Status, data = THCS)

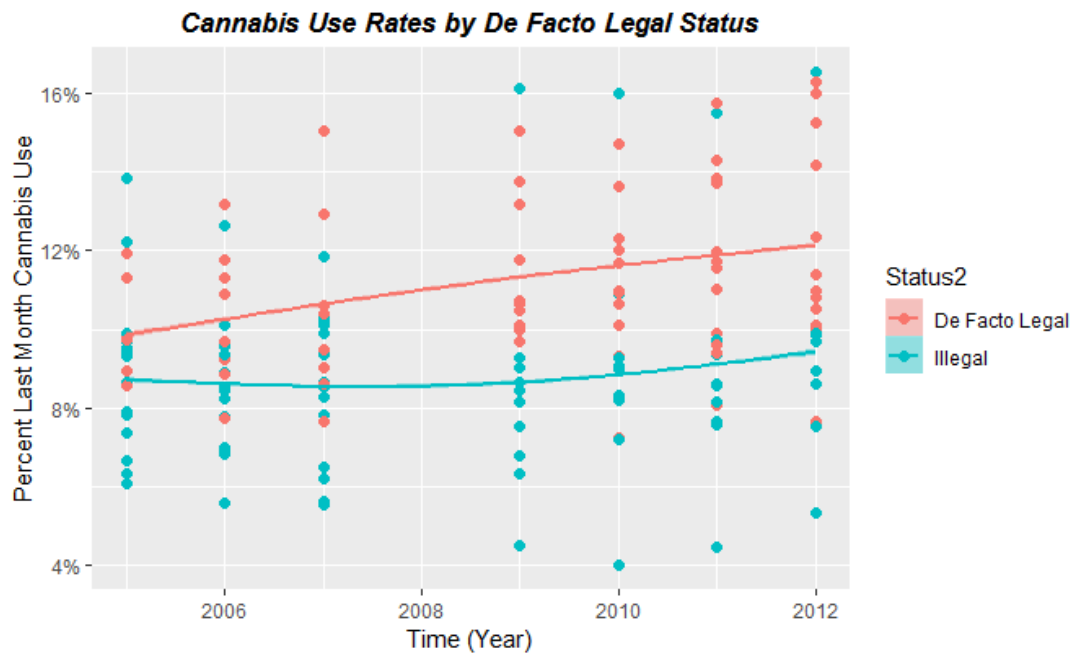
Residuals:
     Min       1Q   Median       3Q      Max
-0.78419 -0.12946  0.00341  0.13463  0.61815

Coefficients:
                           Estimate Std. Error t value Pr(>|t|)
(Intercept)               -1.705e+01  6.138e+00  -2.777   0.0058 **
Year                       7.271e-03  3.058e-03   2.378   0.0180 *
Year:StatusDecriminalised  1.007e-04  1.798e-05   5.605 4.46e-08 ***
Year:StatusLegal           3.006e-04  3.507e-05   8.572 4.19e-16 ***
Year:StatusMedical         1.037e-04  1.508e-05   6.880 3.08e-11 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Residual standard error: 0.2264 on 325 degrees of freedom
Multiple R-squared:  0.3151,    Adjusted R-squared:  0.3067
F-statistic: 37.38 on 4 and 325 DF,  p-value: < 2.2e-16
```

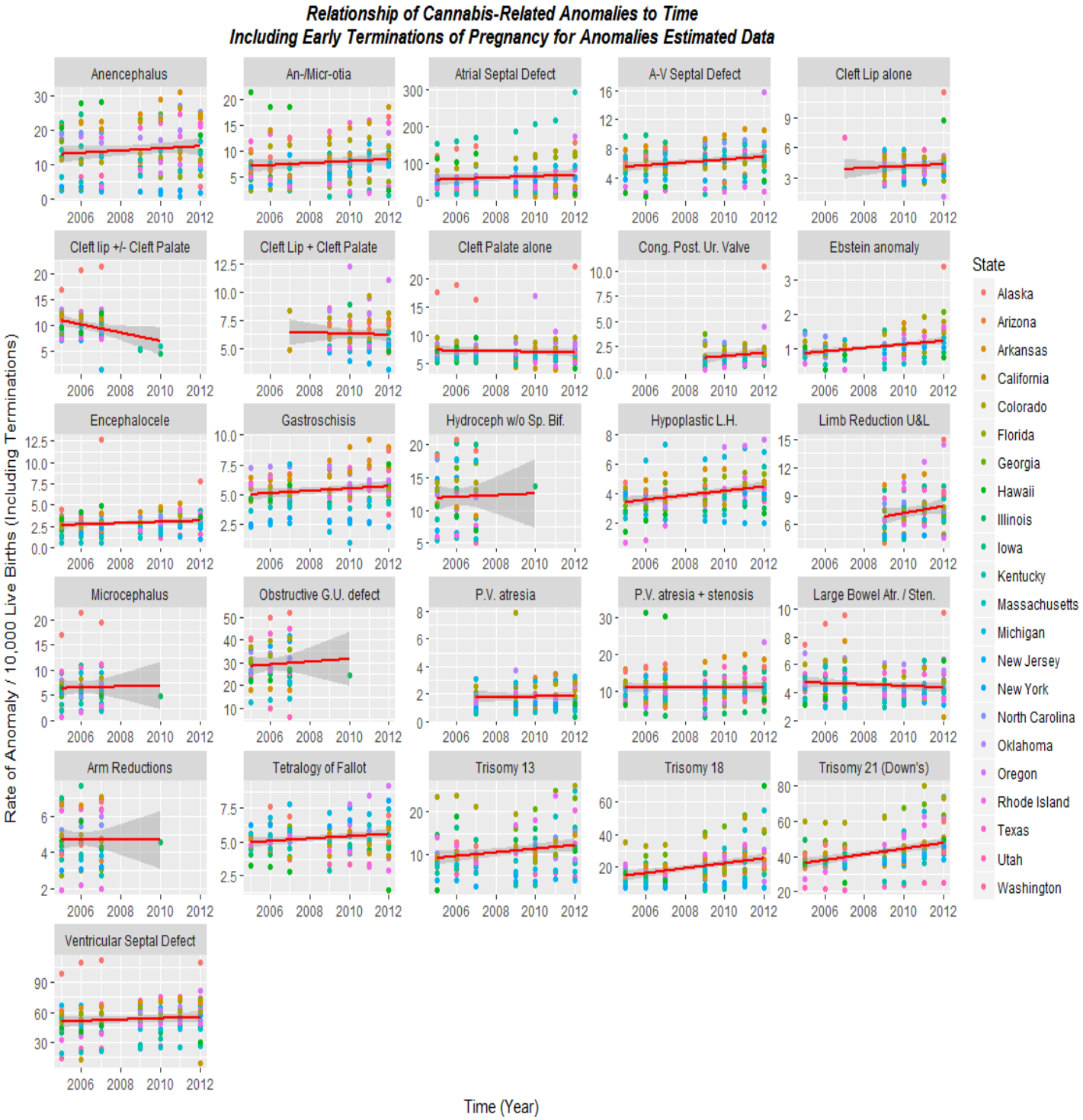
Cannabis Use Rates by De Facto Legal Status



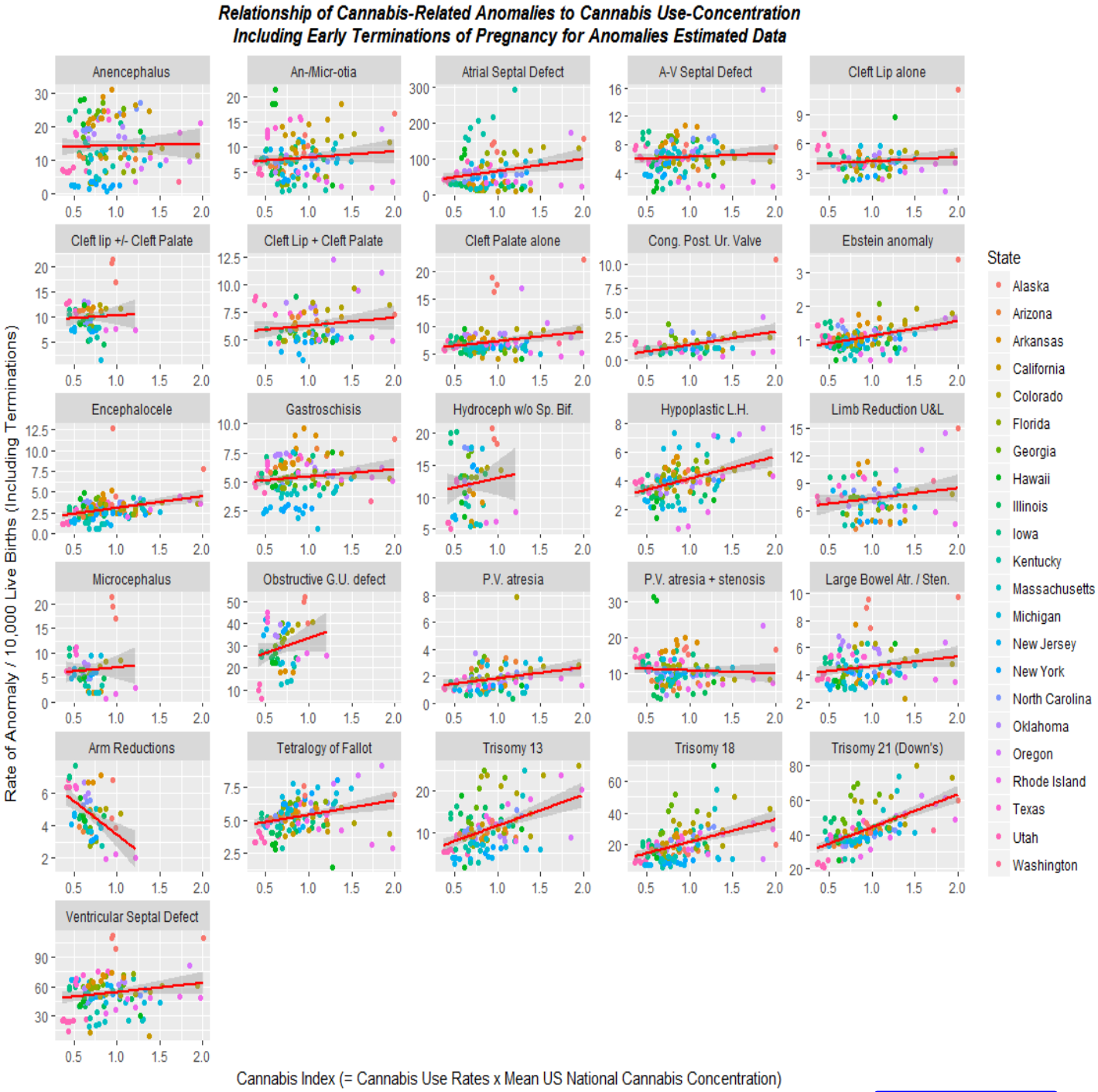


NBDPN & NSDUH Publicly Available Data

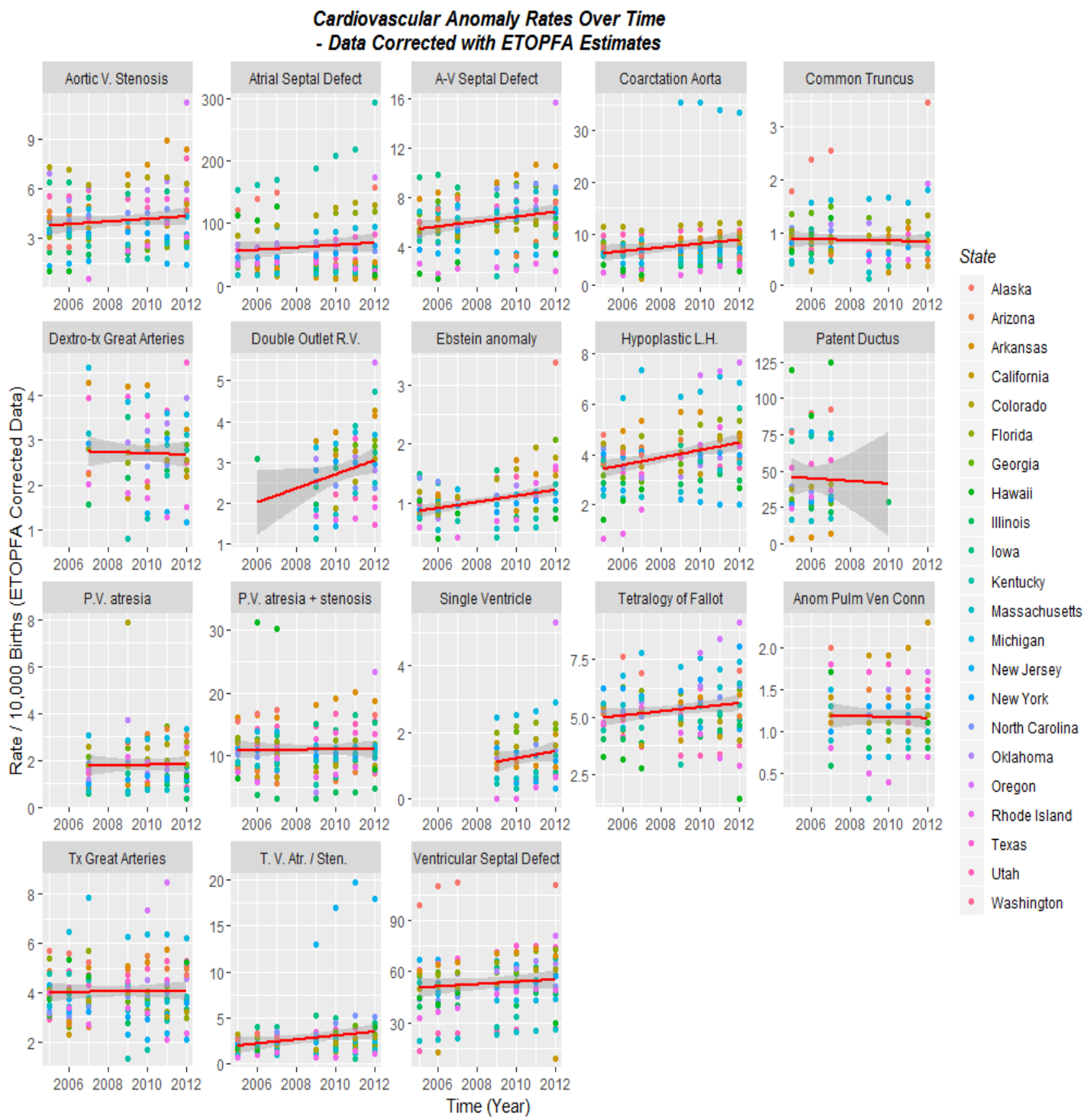
Cannabis Related Anomalies Over Time – ETOPFA Corrected



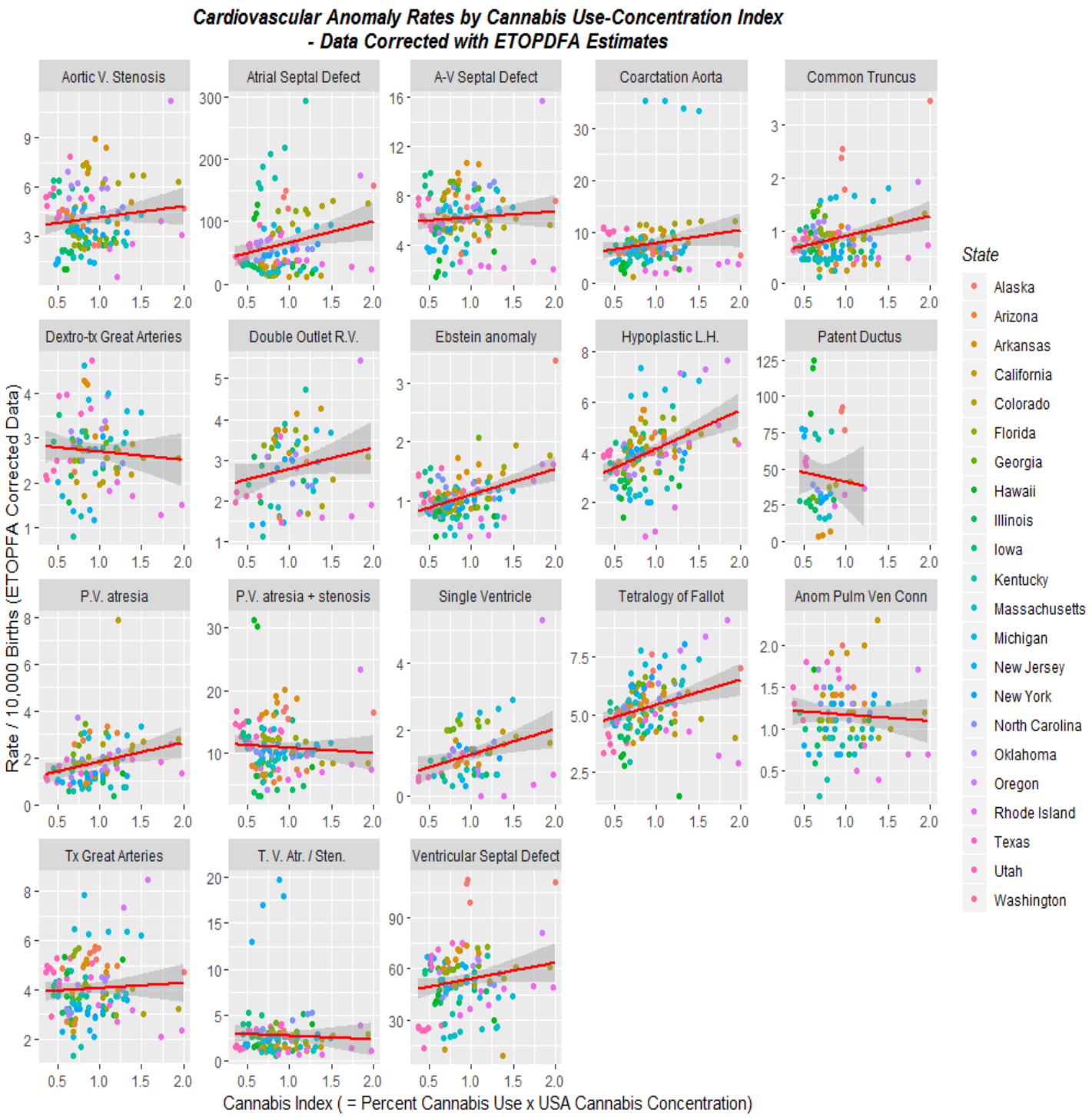
Cannabis Related Anomalies ~ Cannabis Use-Concentration – ETOPFA Corrected



Cardiovascular Anomalies Over Time - ETOPFA Corrected



Cardiovascular Anomalies ~ Cannabis Index - ETOPFA Corrected



Cardiovascular Defects

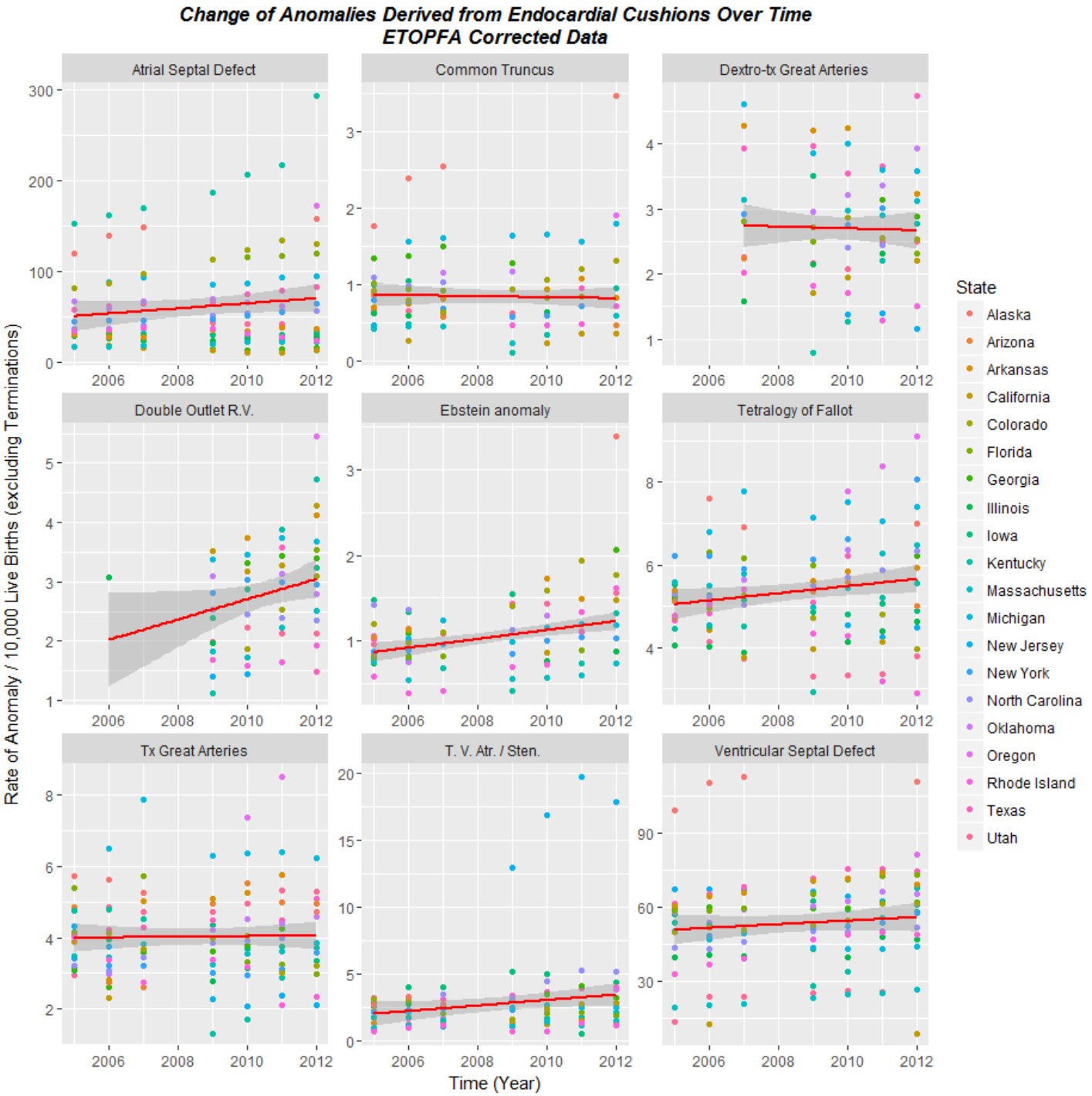
```
> Results <- runDefects(asinh(value)~State+Year+LLMPot2,longNBDxCVS,c('LLMPot2'))
> Results <- Results %>% arrange(pVal)
> Results$AdjpVal <- p.adjust(Results$pVal,method='BH')
> Results
```

	Defect	THC.Related	THCRel2	CVS	Endocardial		t	pVal	AdjpVal
1	P.V. atresia + stenosis	Related	Related	CVS	Not		10.6722743	0.000000e+00	0.000000e+00
2	P.V. atresia	Related	Related	CVS	Not		-6.6975507	5.569069e-09	5.012162e-08
3	Anom Pulm Ven Conn	NotRelated	NotRelated	CVS	Not		6.0423303	7.170391e-08	3.423507e-07
4	Tetralogy of Fallot	Related	Related	CVS			5.7795760	7.607793e-08	3.423507e-07
5	Hypoplastic L.H.	Related	Related	CVS	Not		5.5950170	1.684656e-07	6.064762e-07
6	Ebstein anomaly	Related	Related	CVS			4.9967385	2.366134e-06	7.098402e-06
7	A-V Septal Defect	Related	Related	CVS	Not		4.5039766	1.763874e-05	4.535675e-05
8	Double Outlet R.V.	NotRelated	NotRelated	CVS			4.5500355	3.781339e-05	8.508014e-05
9	Aortic V. Stenosis	NotRelated	NotRelated	CVS	Not		3.5467197	5.865056e-04	1.173011e-03
10	Common Truncus	NotRelated	NotRelated	CVS			3.0024251	3.361392e-03	6.050505e-03
11	Single Ventricle	NotRelated	NotRelated	CVS	Not		2.9886348	4.336216e-03	7.095627e-03
12	Patent Ductus	NotRelated	NotRelated	CVS	Not		2.9223055	7.101173e-03	1.065176e-02
13	Atrial Septal Defect	Related	Related	CVS			2.4309191	1.689730e-02	2.339626e-02
14	Coarctation Aorta	NotRelated	NotRelated	CVS	Not		2.2885760	2.408734e-02	3.096944e-02
15	T. V. Atr. / Sten.	NotRelated	NotRelated	CVS			-1.3041040	1.951050e-01	2.341260e-01
16	Ventricular Septal Defect	Related	Related	CVS			1.1226650	2.643510e-01	2.973948e-01
17	Tx Great Arteries	NotRelated	NotRelated	CVS			0.8901766	3.755292e-01	3.976192e-01
18	Dextro-tx Great Arteries	NotRelated	NotRelated	CVS			-0.0414693	9.670470e-01	9.670470e-01

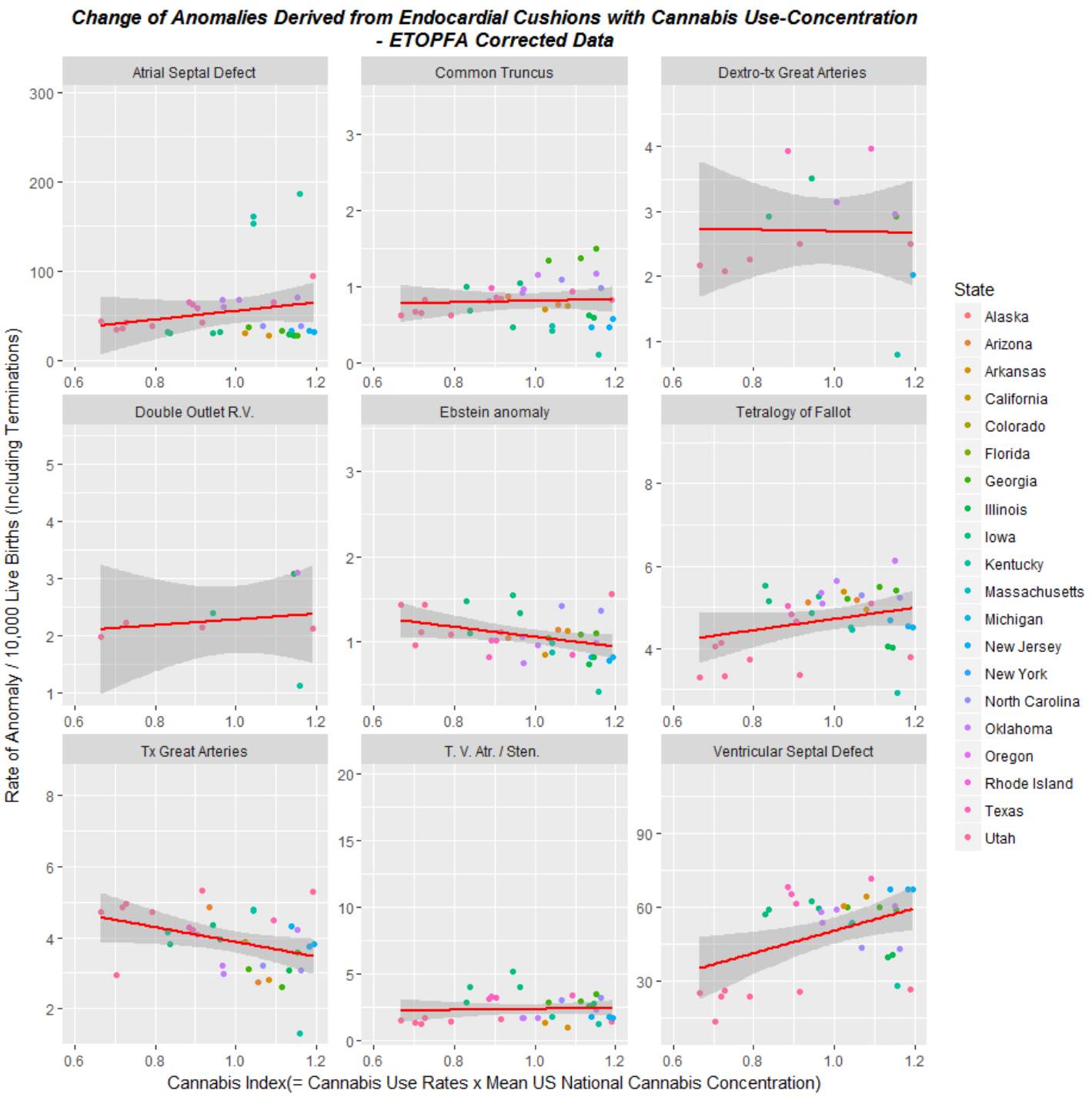
```
> Results <- runDefects(asinh(TrueRt2)~State+Year+LLMPot2,longNBDxCVS,c('LLMPot2'))
> Results <- Results %>% arrange(pVal)
> Results$AdjpVal <- p.adjust(Results$pVal,method='BH')
> Results
```

	Defect	THC.Related	THCRel2	CVS	Endocard	t	pVal	AdjpVal
1	P.V. atresia + stenosis	Related	Related	CVS		11.3262081	0.000000e+00	0.000000e+00
2	Tetralogy of Fallot	Related	Related	CVS		7.1304299	1.277656e-10	1.149890e-09
3	Hypoplastic L.H.	Related	Related	CVS		6.4572820	3.129970e-09	1.877982e-08
4	Ebstein anomaly	Related	Related	CVS		6.0747965	2.061998e-08	9.278991e-08
5	P.V. atresia	Related	Related	CVS		-6.2251420	3.764522e-08	1.355228e-07
6	Anom Pulm Ven Conn	NotRelated	NotRelated	CVS		6.0423303	7.170391e-08	2.151117e-07
7	A-V Septal Defect	Related	Related	CVS		5.7396550	9.622614e-08	2.474386e-07
8	Double Outlet R.V.	NotRelated	NotRelated	CVS		5.3284434	2.748639e-06	6.184439e-06
9	Aortic V. Stenosis	NotRelated	NotRelated	CVS		4.1691247	6.344488e-05	1.268898e-04
10	Single Ventricle	NotRelated	NotRelated	CVS		4.1779526	1.178448e-04	2.121206e-04
11	Common Truncus	NotRelated	NotRelated	CVS		3.5894626	5.092028e-04	8.332409e-04
12	Coarctation Aorta	NotRelated	NotRelated	CVS		2.8846601	4.747149e-03	7.120724e-03
13	Patent Ductus	NotRelated	NotRelated	CVS		2.9223055	7.101173e-03	9.832394e-03
14	Atrial Septal Defect	Related	Related	CVS		2.4309191	1.689730e-02	2.172510e-02
15	Ventricular Septal Defect	Related	Related	CVS		1.6357388	1.051352e-01	1.261623e-01
16	Tx Great Arteries	NotRelated	NotRelated	CVS		1.4778277	1.426283e-01	1.604568e-01
17	T. V. Atr. / Sten.	NotRelated	NotRelated	CVS		-0.7125269	4.777496e-01	5.058525e-01
18	Dextro-tx Great Arteries	NotRelated	NotRelated	CVS		0.4518318	6.528716e-01	6.528716e-01

ETOPFA-Corrected Rates of Endocardial Cushion Defects Trends Over Time



ETOPFA-Corrected Rates of Endocardial Cushion Defects ~ Cannabis Use-Concentration



Endocardial Cushion Derivatives – Holm Correction

```
Results <- runDefects(log(TrueRt2)~State+Year+LLMPot2,longNBDxEndoc,c('LLMPot2'
Results <- Results %>% arrange(pVal)
Results$AdjpVal <- p.adjust(Results$pVal,method='holm')
Results
```

	Defect	THC.Related	Tl	t	pVal	AdjpVal
	Tetralogy of Fallot	Related	R	7.1124633	1.395408e-10	1.255867e-09
	Common Truncus	NotRelated	NotR	6.3292787	6.497929e-09	5.198343e-08
	Ebstein anomaly	Related	R	5.8764813	5.098228e-08	3.568759e-07
	Double Outlet R.V.	NotRelated	NotR	5.2247232	3.919491e-06	2.351694e-05
	Atrial Septal Defect	Related	R	2.4291902	1.697332e-02	8.486662e-02
	Tx Great Arteries	NotRelated	NotR	1.6745237	9.710410e-02	3.887364e-01
	Ventricular Septal Defect	Related	R	1.6302815	1.062851e-01	3.887364e-01
	T. V. Atr. / Sten.	NotRelated	NotR	-0.8007544	4.251171e-01	8.502342e-01
	Dextro-tx Great Arteries	NotRelated	NotR	0.5678840	5.720407e-01	8.502342e-01

```
> Results <- runDefects(log(value)~State+Year+LLMPot2,longNBDxEndoc,c('LLMPot2'))
> Results <- Results %>% arrange(pVal)
> Results$AdjpVal <- p.adjust(Results$pVal,method='holm')
> Results
```

	Defect	THC.Related	Tl	t	pVal	AdjpVal
1	Common Truncus	NotRelated	NotR	5.942943	3.848948e-08	3.464053e-07
2	Tetralogy of Fallot	Related	R	5.737143	9.212171e-08	7.369737e-07
3	Ebstein anomaly	Related	R	5.057297	1.835737e-06	1.285016e-05
4	Double Outlet R.V.	NotRelated	NotR	4.427221	5.657183e-05	3.394310e-04
5	Atrial Septal Defect	Related	R	2.429190	1.697332e-02	8.486662e-02
6	T. V. Atr. / Sten.	NotRelated	NotR	-1.551939	1.237441e-01	4.949764e-01
7	Tx Great Arteries	NotRelated	NotR	1.176530	2.422045e-01	7.266134e-01
8	Ventricular Septal Defect	Related	R	1.117062	2.667270e-01	7.266134e-01
9	Dextro-tx Great Arteries	NotRelated	NotR	0.114427	9.092467e-01	9.092467e-01

Endocardial Cushion Derivatives
– Benjamin-Hochberg Correction

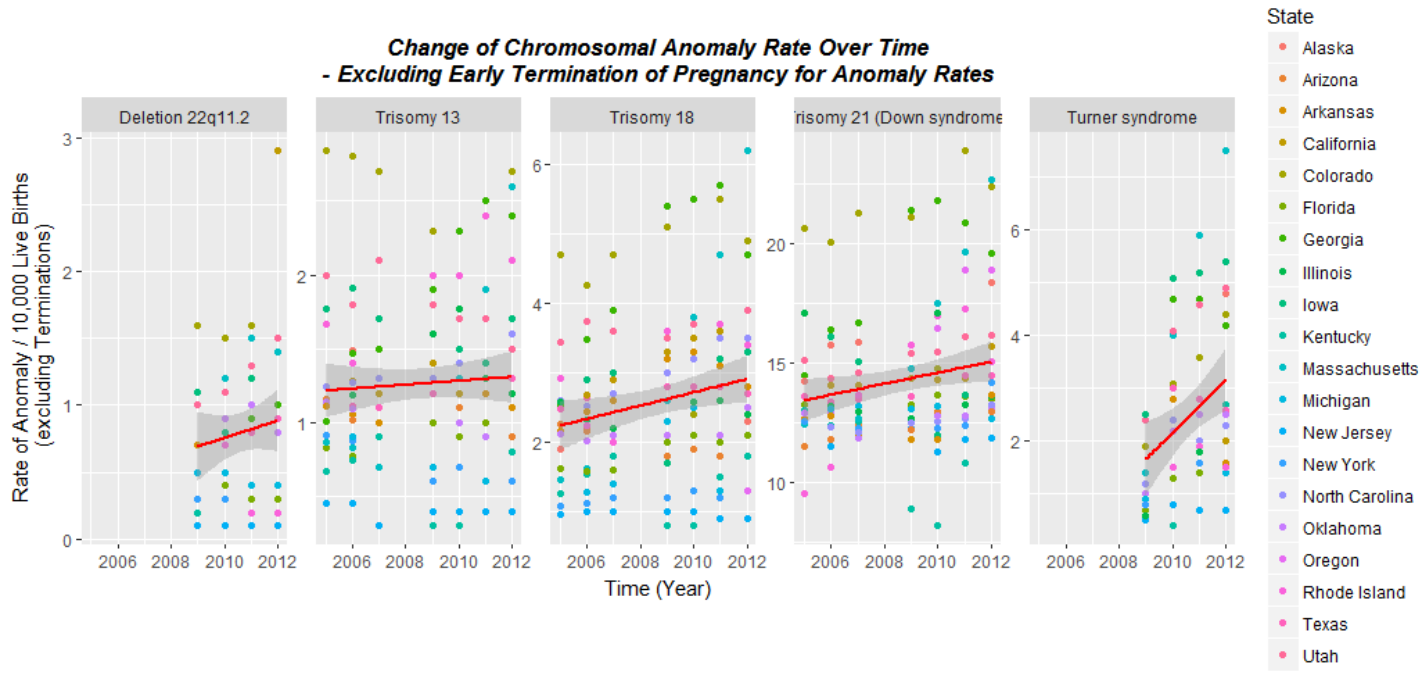
```
> Results <- runDefects(log(TrueRt2)~State+Year+LLMPot2,longNBDxEndoc,c('LLMPot2'))
> Results <- Results %>% arrange(pVal)
> Results$AdjpVal <- p.adjust(Results$pVal,method='BH')
> Results
```

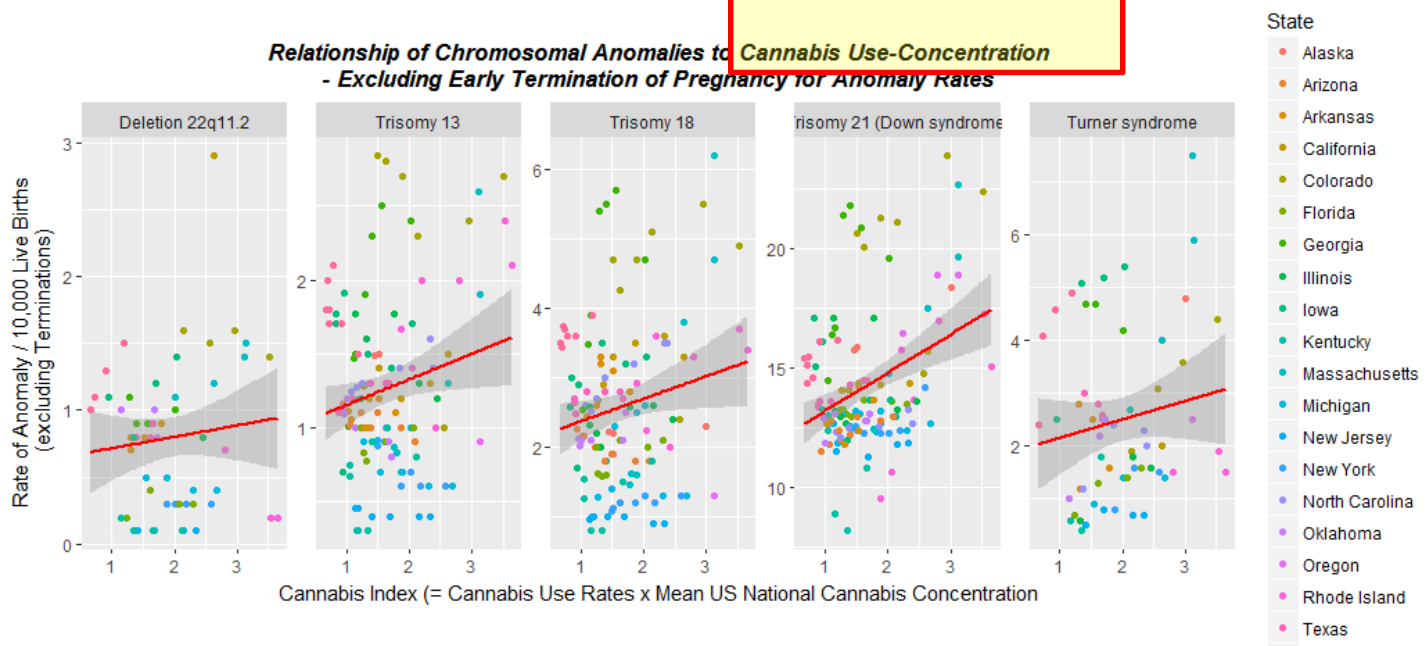
	Defect	THC.Related	THCR	t	pVal	AdjpVal
1	Tetralogy of Fallot	Related	Rela	7.1124633	1.395408e-10	1.255867e-09
2	Common Truncus	NotRelated	NotRela	6.3292787	6.497929e-09	2.924068e-08
3	Ebstein anomaly	Related	Rela	5.8764813	5.098228e-08	1.529468e-07
4	Double Outlet R.V.	NotRelated	NotRela	5.2247232	3.919491e-06	8.818854e-06
5	Atrial Septal Defect	Related	Rela	2.4291902	1.697332e-02	3.055198e-02
6	Tx Great Arteries	NotRelated	NotRela	1.6745237	9.718410e-02	1.366523e-01
7	Ventricular Septal Defect	Related	Rela	1.6302815	1.062851e-01	1.366523e-01
8	T. V. Atr. / Sten.	NotRelated	NotRela	-0.8007544	4.251171e-01	4.782567e-01
9	Dextro-tx Great Arteries	NotRelated	NotRela	0.5678840	5.720407e-01	5.720407e-01

```
> Results <- runDefects(log(value)~State+Year+LLMPot2,longNBDxEndoc,c('LLMPot2'))
> Results <- Results %>% arrange(pVal)
> Results$AdjpVal <- p.adjust(Results$pVal,method='BH')
> Results
```

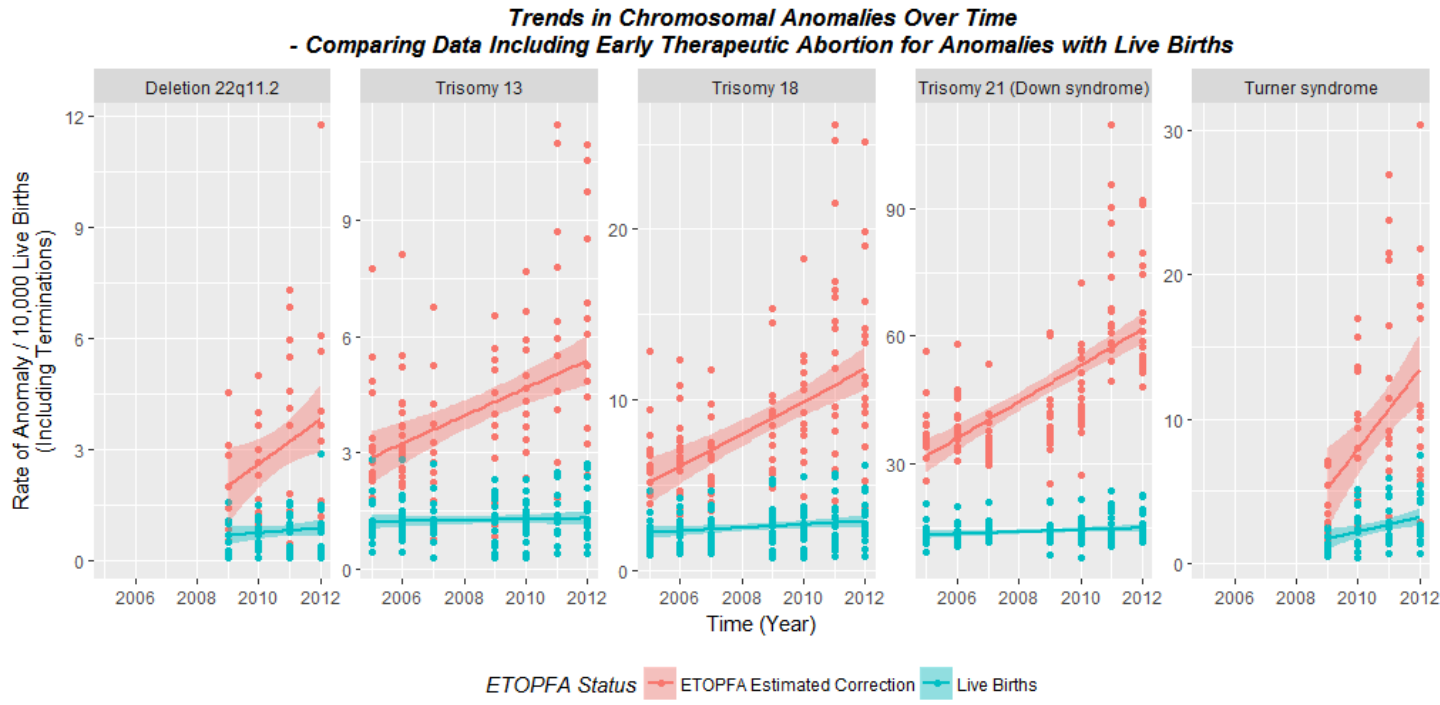
	Defect	THC.Related	THCR	t	pVal	AdjpVal
1	Common Truncus	NotRelated	NotRela	5.942943	3.848948e-08	3.464053e-07
2	Tetralogy of Fallot	Related	Rela	5.737143	9.212171e-08	4.145477e-07
3	Ebstein anomaly	Related	Rela	5.057297	1.835737e-06	5.507211e-06
4	Double Outlet R.V.	NotRelated	NotRela	4.427221	5.657183e-05	1.272866e-04
5	Atrial Septal Defect	Related	Rela	2.429190	1.697332e-02	3.055198e-02
6	T. V. Atr. / Sten.	NotRelated	NotRela	-1.551939	1.237441e-01	1.856161e-01
7	Tx Great Arteries	NotRelated	NotRela	1.176530	2.422045e-01	3.000678e-01
8	Ventricular Septal Defect	Related	Rela	1.117062	2.667270e-01	3.000678e-01
9	Dextro-tx Great Arteries	NotRelated	NotRela	0.114427	9.092467e-01	9.092467e-01

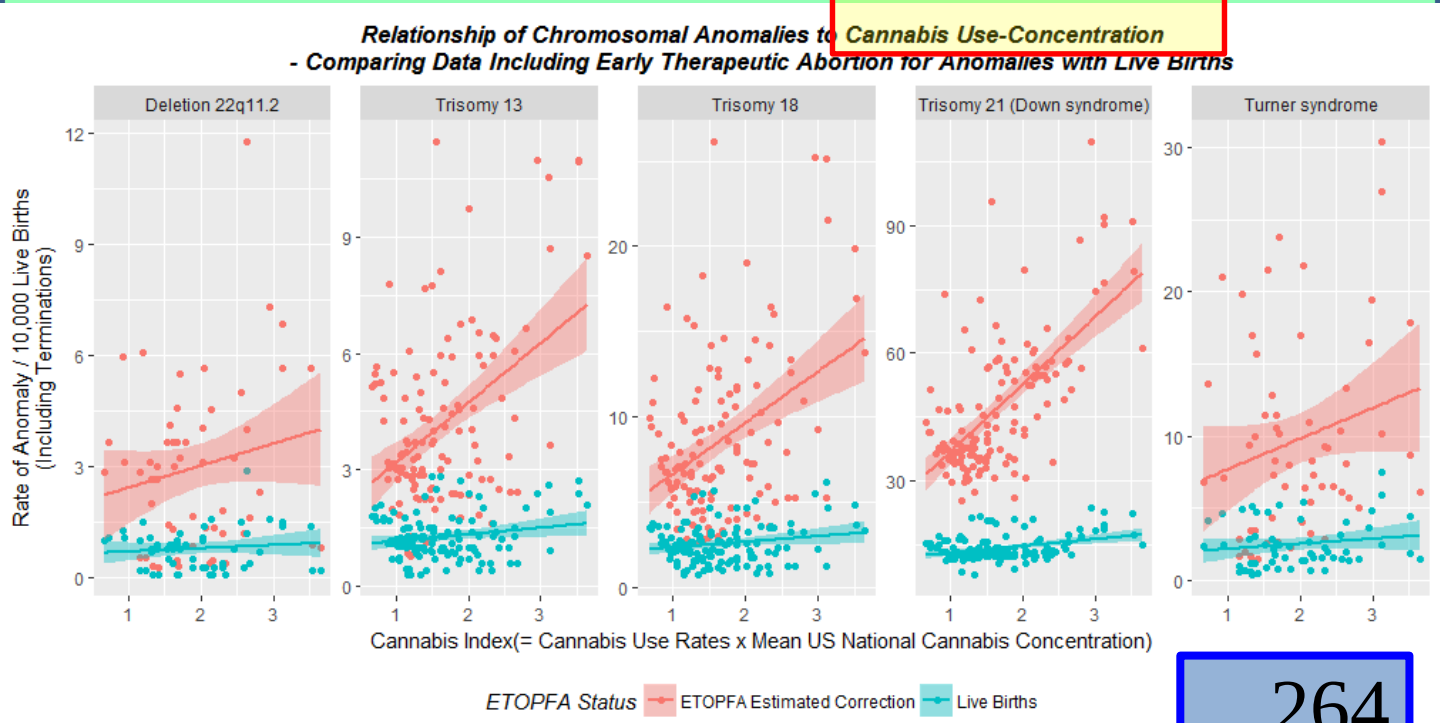
Chromosomal Anomalies , By Time & Cannabis Index





Chromosomal ETOPFA Corrections





Chromosomes

```
> Results <- runDefects(log(value)~State+Year+LLMPot2,longNBDxChr,c('LLMPot
> Results <- Results %>% arrange(pVal)
> Results$AdjpVal <- p.adjust(Results$pVal,method='holm')
> Results
```

	Defect	THC.Related	TH	t	pVal	AdjpVal
1	Trisomy 13	Related	Re	6.047895	2.333180e-08	9.332721e-08
2	Turners Syn.	NotRelated	NotRe	6.639353	6.726519e-08	2.017956e-07
3	Trisomy 21 (Down's)	Related	Re	5.446045	3.215610e-07	6.431220e-07
4	Trisomy 18	Related	Re	2.194681	3.034789e-02	3.034789e-02

```
> Results <- runDefects(log(TrueRt2)~State+Year+LLMPot2,longNBDxChr,c('LLMP
> Results <- Results %>% arrange(pVal)
> Results$AdjpVal <- p.adjust(Results$pVal,method='holm')
> Results
```

	Defect	THC.Related	TH	t	pVal	AdjpVal
1	Trisomy 21 (Down's)	Related	Re	8.593655	6.750156e-14	2.700062e-13
2	Trisomy 13	Related	Re	7.740289	6.761480e-12	2.028444e-11
3	Turners Syn.	NotRelated	NotRe	7.336757	7.423367e-09	1.484673e-08
4	Trisomy 18	Related	Re	4.313368	3.593718e-05	3.593718e-05

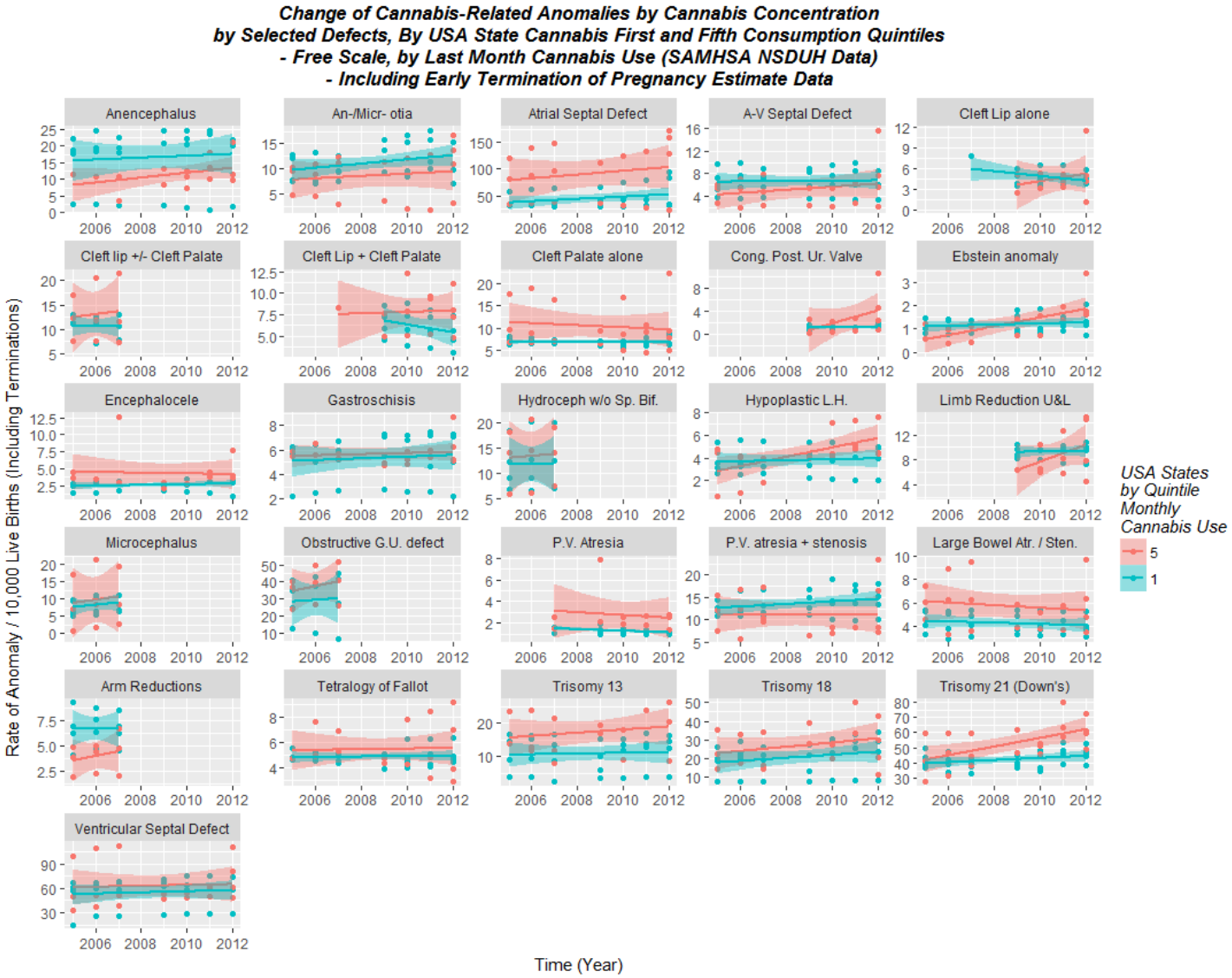
Gastroschisis Rates

```
> Results <- runDefects(log(value)~State+Year+LLMonth,longNBD
> Results <- Results %>% arrange(pVal)
> Results$AdjpVal <- p.adjust(Results$pVal,method='holm')
> Results
          Defect THC.Related TH          t      pVal    AdjpVal
1 Gastroschisis      Related Re 2.148028 0.03403333 0.03403333
```

```
> Results <- runDefects(log(TrueRt2)~State+Year+LLMonth,longNB
> Results <- Results %>% arrange(pVal)
> Results$AdjpVal <- p.adjust(Results$pVal,method='holm')
> Results
          Defect THC.Related TH(         t      pVal    AdjpVal
1 Gastroschisis      Related Re 2.381738 0.01904915 0.01904915
```

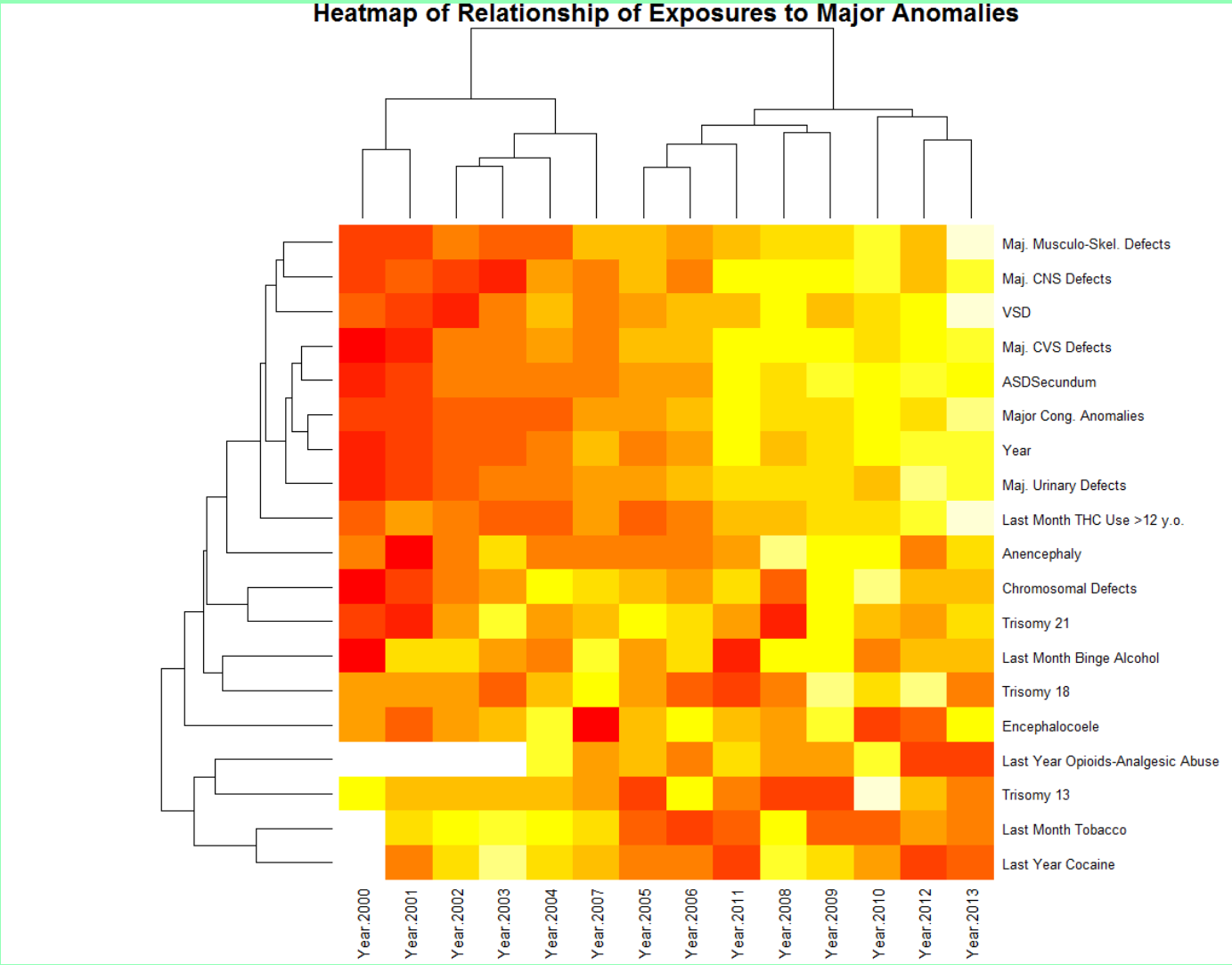
NBDPN & NSDUH Publicly Available Data

Defect Rates by Highest v Lowest Cannabis Use Quintiles



NBDPN & NSDUH Publicly Available Data

Heatmap – Selected Defect Clusters



CHILDREN

Congenital Defects Linked to Cannabis

- *Anencephaly – CDC / NBDPN, 2009, 2014*
- *Gastroschisis – CDC / NBDPN / Meta-analysis / Canada / NNSW – Frequency and Severity*
- *Diaphragmatic Hernia – CDC / NBDPN*
- *Oesophageal Stenosis ± Tracheal Fistula – CDC / NBDPN*
- *VSD – AHA / AAP / Colorado*
- *Ebsteins – AHA / AAP*
- *CVS Disorders – Colorado, AHA / AAP, Wilson 1998; Present*
- *ASD – Colorado Experience*
- *Chromosomal Defects – Forrest 2007 / Present USA analysis / Colorado / NNSW*
- *Brain Defects - Intelligence, Higher Cortical Functioning*
  - *First Principles – Stem Cells, Stem Cell Niche, NSC Wiring, Axon Guidance, Epigenetics, Immunity, Brain Inflammation*
  - *Vasculopathy – Large and small vessels*
  - *Longitudinal Studies OPPS, MHPCD, GenRStudy*
  - ***ANENCEPHALY***

Mechanisms of Cannabis Teratogenesis

- *Epigenetic*
- *Microtubule Disruption / Mitotic Spindle Toxicity / Indirect Genotoxin / Micronuclear formation / Chromosomal clastogens*
- *Mitonuclear Stress Signalling and Imbalance*
- *Secondary Effects of Low Cellular Energy Charge to DNA Maintenance*
- *Damage to Reproductive Tract*
- *Foetal Vasculopathy – CB1R / GPR55 / VR1 Mediated inflammation, vasospasm – Brain, Limbs, Abdomen*
- *Damage to VEGF / Stem Cell Niche*
- *Aging effect*
- *Mitochondrial Toxicity / Uncoupling / UCP2*
- *Carcinogenicity*
- *Non-linear kinetics*
- *Damage to Brain formation / Neuronal network formation to the point of Anencephaly*
- *Damage to Heart Formation – Endocardial Cushions – CB1R, GPR55*
- *Threshold Effect*

Clinical Trials

2,020 Clinical Trials!!!

www. clinicaltrials.gov
Accessed 1st July 2018

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

104 studies found for: cannabidiol
Modify this search | How to Use Search Results

162 studies found for: tetrahydrocannabinol
Modify this search | How to Use Search Results

GW Pharmaceuticals major clinical trial sponsor

Comments:

Pain – many negative studies, a few positive
Lennox-Gestaut Syndrome Treatment Refractory Epilepsy
- Some positive studies, some negative
Dravet Syndrome Epilepsy – Positive Studies
MS – Several negative studies
Cancer – several negative studies
Long term Safety – 2.5 years –
No cancer, no foetal safety data, no statistical tests
Adverse Events data – no statistics
Tiny Size - 6 or 8 in treatment groups

Overall

- ***MANY NEGATIVE STUDIES***
- Many studies small,
- Low powered,
- Inadequately documented,
- Major design issues,
- No statistical comparisons

Dravet – No results posted; 3 trials Incl. Dose ranging & PK
Lennox Gestaut Synd not recruiting

European Registry:
Dravet - 4 Trials – No results available
Lennox-Gestaut - 3 Trials – No results available

Clinicaltrials.gov

Overall RCT Study Description

Study No.	CT No.	Drug	Short Description	N
28	NCT01606189	Sativex (THC/CBD) & THC	Pain - Nerve Injury - Arm	48
32	NCT01604265	Sativex (THC/CBD)	Pain - Neuropathic | Multiple Sclerosis	66
26	NCT00674609	Sativex (THC/CBD) & THC	Pain | Advanced Cancer	177
15	NCT00530764	Sativex (THC/CBD)	Pain | Advanced Cancer	360
20	NCT01606176	Sativex (THC/CBD)	Pain | Multiple Sclerosis	70
31	NCT01606202	THC/CBD	Pain - Nerve Injury - Spinal Cord	116
27	NCT00681538	Sativex (THC/CBD)	Multiple Sclerosis | Spasticity - **Selected**	241
23	NCT00702468	Sativex (THC/CBD)	Multiple Sclerosis | Spasticity - **Selected**	36
16	NCT01610700	Sativex (THC/CBD)	Multiple Sclerosis	160
25	NCT01599234	Sativex (THC/CBD)	Multiple Sclerosis	337
24	NCT00391079	Sativex (THC/CBD)	Multiple Sclerosis	339
19	NCT00678795	Sativex (THC/CBD)	Detrusor Overactivity | Multiple Sclerosis	124
33	NCT01964547	Sativex (THC/CBD)	Multiple Sclerosis | Spasticity	127
1	NCT01217112	CBD	Fatty Liver	25
3	NCT01284634	CBD	Dyslipidemias|Diabetes Mellitus, Type 2	62

Clinicaltrials.gov

Primary End Points

12/15 Failed!!!!

Study No.	Trial	N	Met Primary	Primary Failed	Primary P
28	Pain	48	1		0.005, 0.002
32	Pain	66	1		0.005
26	Pain	177	1		0.014
15	Pain	360		1	0.33
20	Pain	70		1	0.33
31	Pain	116		1	0.7
27	M.S.	241	(1)		0.002
23	M.S.	36	(1)		0.013
16	M.S.	160		1	0.12
25	M.S.	337		1	0.22
24	M.S.	339		1	0.5
19	M.S.	124		1	0.57
33	M.S.	127		1	1
1	Fatty Liver	25		1	0.22
3	Lipids in DM	62		1	0.5

Clinicaltrials.gov

Secondary End Points

Many Major Failures

Study No.	Trial	N	Positive Secondaries	Failed Secondaries	Sec P's +
28	Pain	48	Pain, Sleep, McGill Pain Score, Disability Score		0.017-<0.001, 0.015-0.04,
15	Pain	360	Cum Pain Scores, Mean Daily Pain	Dose Relationship, Sleep, Depression	<0.001, <0.01
26	Pain	177	Pain score, Memory Deterioration, Appetite, Concentration Decline	Extra Medication, Sleep, Nausea, QoL Improvement, Brief Pain Inventory	0.045-0.056, 0.045-0.056, 0.021, 0.028
32	Pain	66	Pain, Sleep, Global Impression at Week 4, Memory	Depression, MS Functional Score	0.003, 0.005, 0.04, 0.009
20	Pain	70	Extra analgesia, Sleep	Sleep, Pain disability index, Pain inventory, QoL, Mean Pain Reduction	0.002
31	Pain	116	Pain inventory score at end	Extra Medication, Spasm,, Carer Strain, Sleep	0.032
27	M.S.	241	Mean spasticity scores, spasm frequency, Sleep, Global Improvement, Physician ratings	Spasticity scores, Spasticity Scale Ashworth, Motor function, motor improvement, walk time, QoL, Beck Depression Rating	0.0003, 0.0046, <0.0001, 0.023, 0.005, 0.0045
23	M.S.	36	Time to Treatment failure, Global Impression, Carer Impressions of change	Mean daily spasticity improvement, Functional Improvement, Improved motor function, Sleep, Carer Transfer Improvements	0.017, 0.001
16	M.S.	160	Tremor, Guy's Neuro Score	Secondary Spasticity, Spasms, Tremor, bladder Spasm, Global Rating, General Health, Sleep	0.047, 0.048
25	M.S.	337		Global Impression, Sleep	
24	M.S.	339		30% improvement daily, Pain improvement end of study, Extra analgesia	
19	M.S.	124	Nocturia, Overall bladder condition, Global Impression, Reduction in Voids	Urinary Frequency, Urges, Incontinence Pads, QoL	0.01, 0.001, 0.002, 0.007
33	M.S.	127	Spasticity, Physicians Impression of Improvement	Cognition and Mood, Depression, Carer's Impression of Improvement, Spasticity rating, Walk Time	0.0001, 0.002
1	Fatty Liver	25		Liver TG on MRI, Serum Cholesterol, LDL and HDL and Ration, Fasting Glucose, Albumin, Insulin	
3	Lipids in DM	62		HDL Declined, HDL Ratio over time, Ser Cholesterol, LDL, Lipo-protein A, NEFA, Apo-Lipoprotein B, Appetite, Fasting Glucose and Insulin, Insulin Resistance, HOMA, BMI, V % Liver fat on MRI	

Clinicaltrials.gov

Severe Side Effect Profile,

Readily Acknowledged by Company

Study No.	CT No.	Trial	N	Side FX %'s	Side FX - P
28	NCT01606189	Pain	48	79% v 41%	0.0005
15	NCT00530764	Pain	360	75%-90%	All Bad
26	NCT00674609	Pain	177	85% v 70%	0.3
32	NCT01604265	Pain	66	88% v 69%	0.07
20	NCT01606176	Pain	70	98% v 77%	0.032
31	NCT01606202	Pain	116	82% v 48%	0.0003
27	NCT00681538	M.S.	241	53% v 33%	0.0044
23	NCT00702468	M.S.	36	84% v 78%	1
16	NCT01610700	M.S.	160	84% v 77%	0.12
25	NCT01599234	M.S.	337	93% v 77%	0.00002
24	NCT00391079	M.S.	339	60% v 38%	0.0001
19	NCT00678795	M.S.	124	71% v 63%	0.44
33	NCT01964547	M.S.	127	63% v 32%	0.001
1	NCT01217112	Fatty Liver	25	85%-100%	All Bad
3	NCT01284634	Lipids in DM	62	60%-90%	All Bad

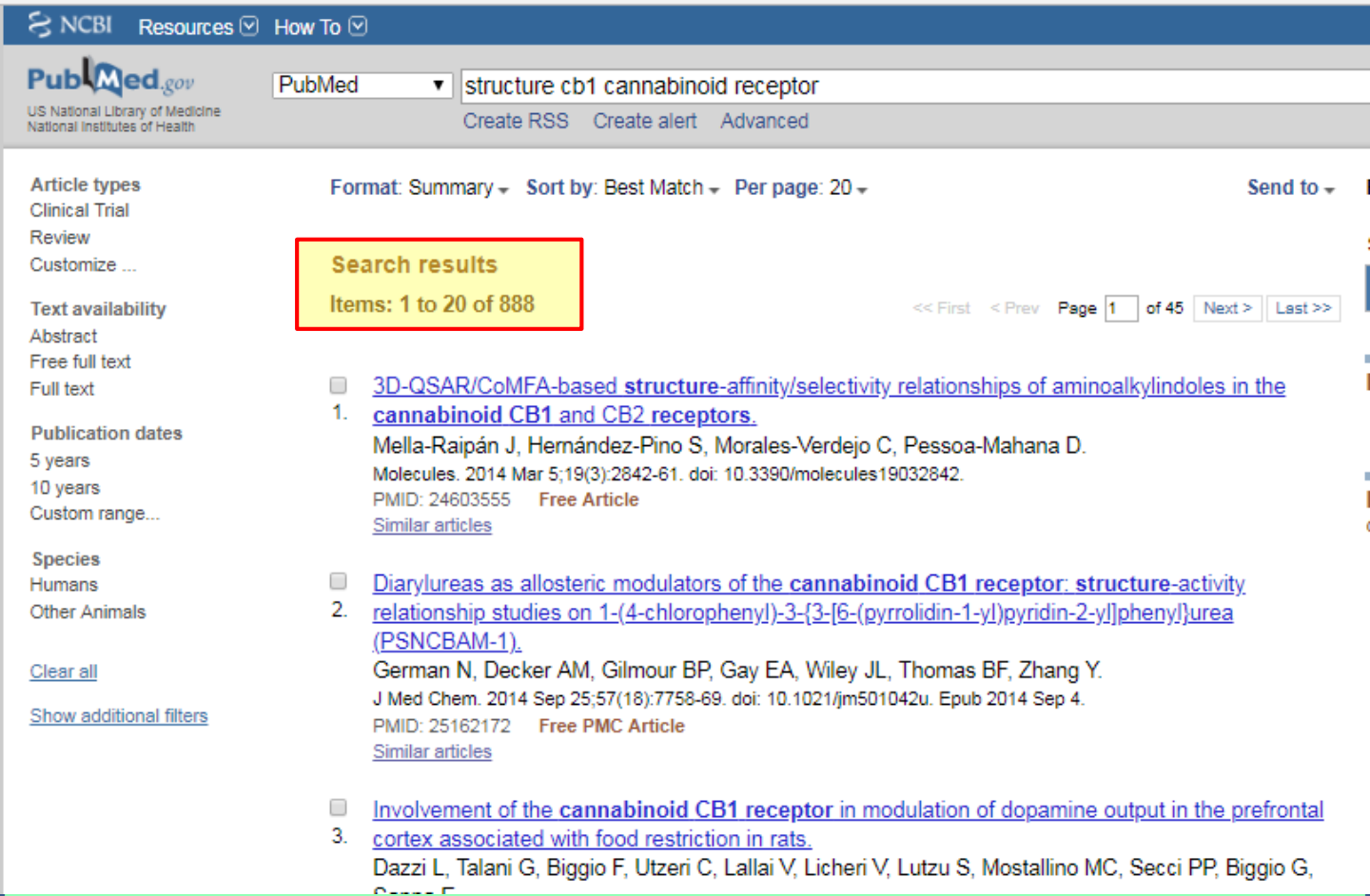
Medicinal Chemistry

CB1R
Cannabinoid Receptor Type 1

Receptor Structure –

Medicinal Chemistry
Studies!!!

888 Papers on PubMed Search!!!



PubMed Accessed 30.06.2018

CB1R Structure

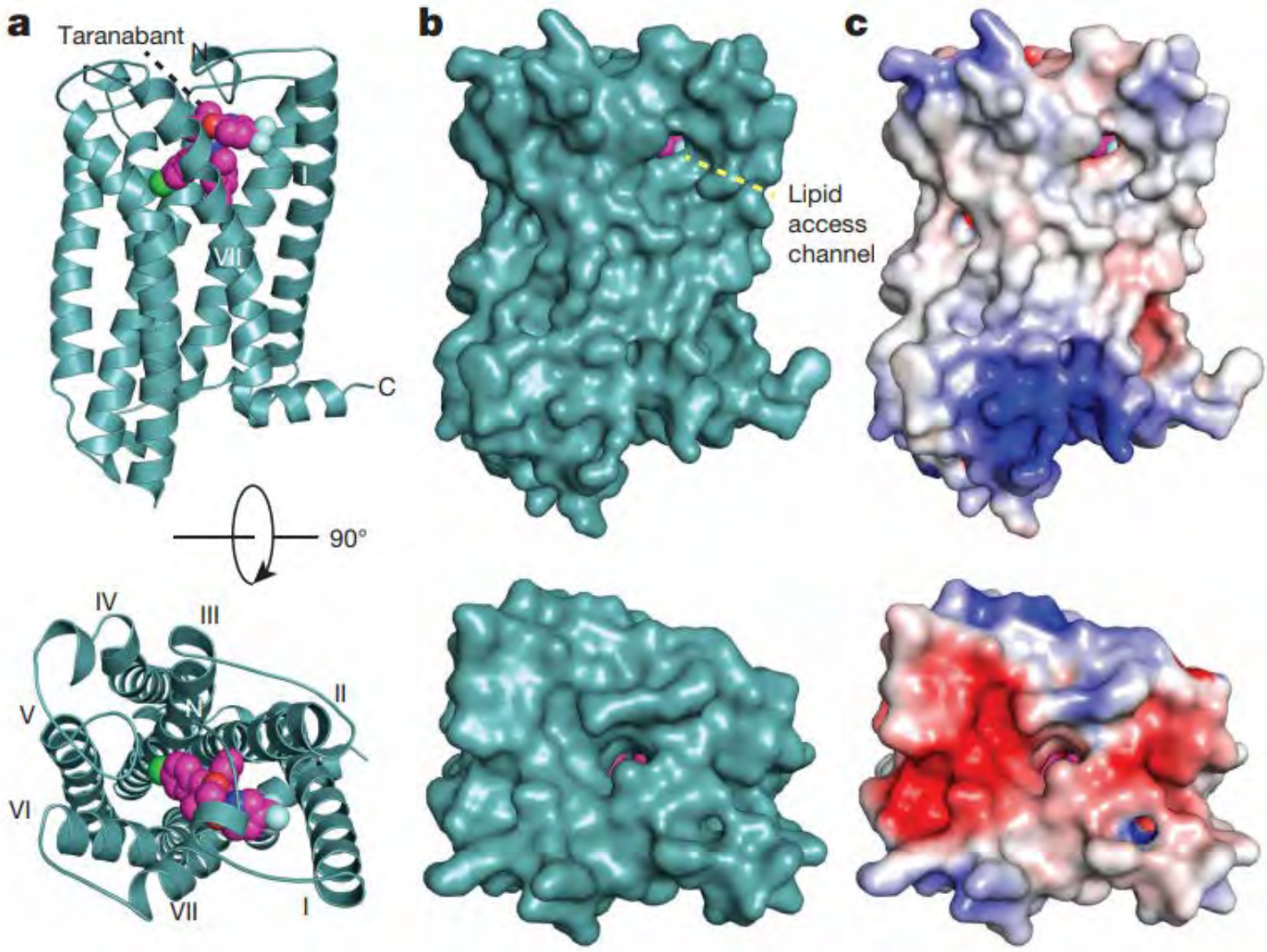


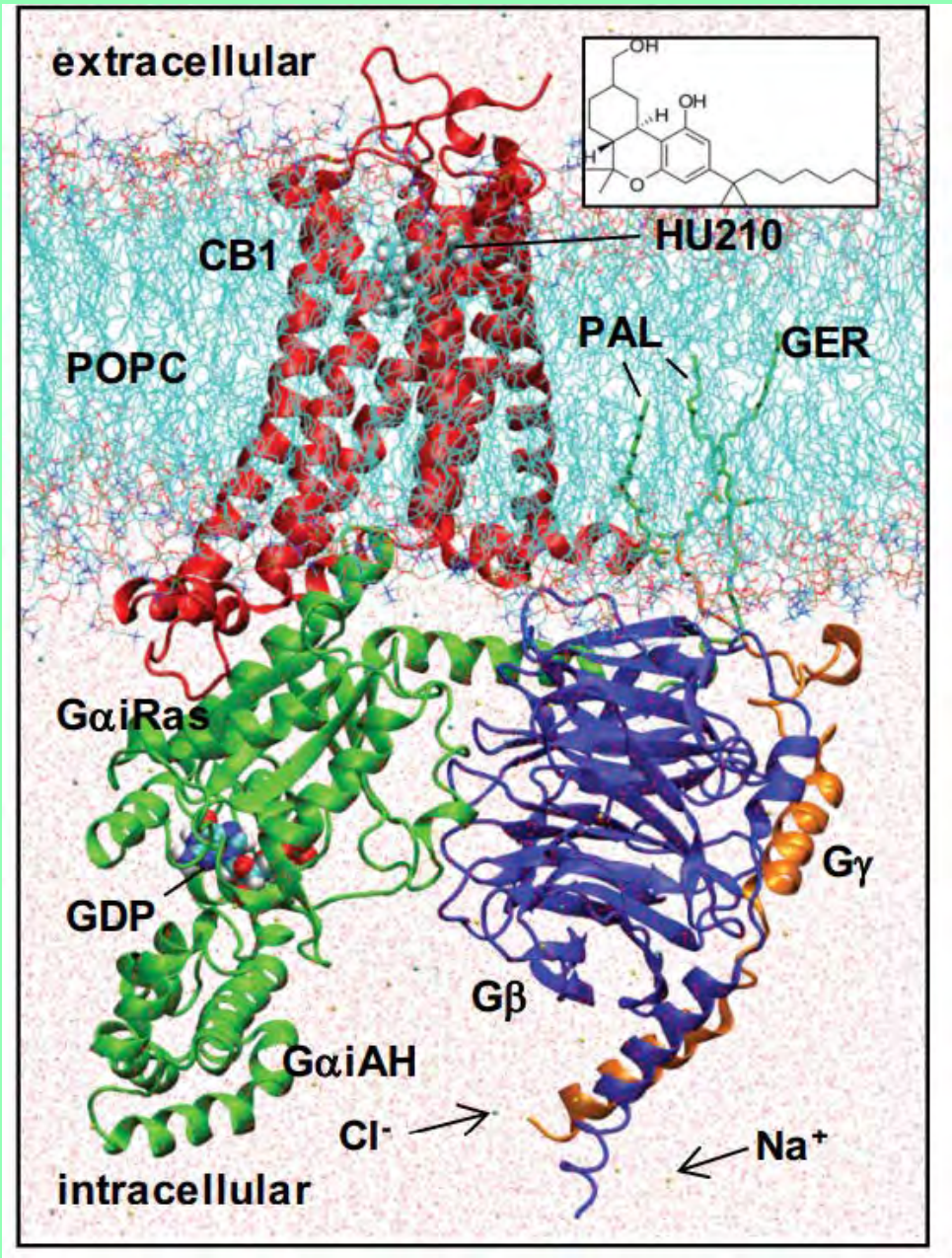
Figure 1 | Global structure of CB1 bound to taranabant. a, CB1 is

Nature. 2016 Nov 16. doi: 10.1038/nature20613. [Epub ahead of print]

High-resolution crystal structure of the human CB1 cannabinoid receptor.

Shao Z[1], Yin J[1], Chapman K[1], Grzemska M[1], Clark L[1], Wang J[2], Rosenbaum DM[1].

Key CB1 Contacts with the C-terminal Helix α_5 of $G\alpha_i$



J Biol Chem. 2013 Nov 8;288(45):32449-65. doi: 10.1074/jbc.M113.489153. Epub 2013 Oct 3.

Molecular basis of cannabinoid CB1 receptor coupling to the G protein heterotrimer Gαiβγ: identification of key CB1 contacts with the C-terminal helix α5 of Gαi.

Shim JY[1], Ahn KH, Kendall DA.

THC Docking

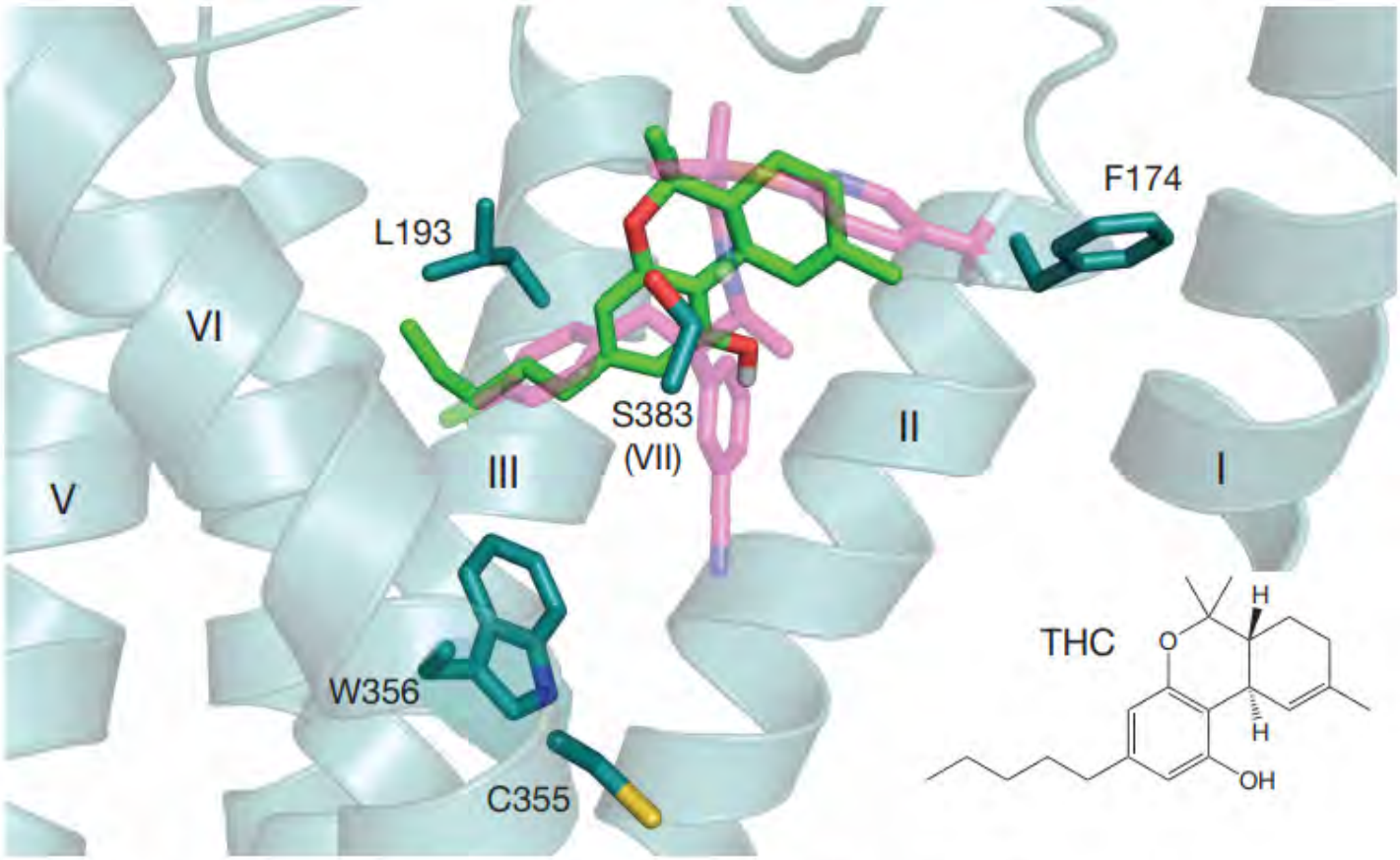


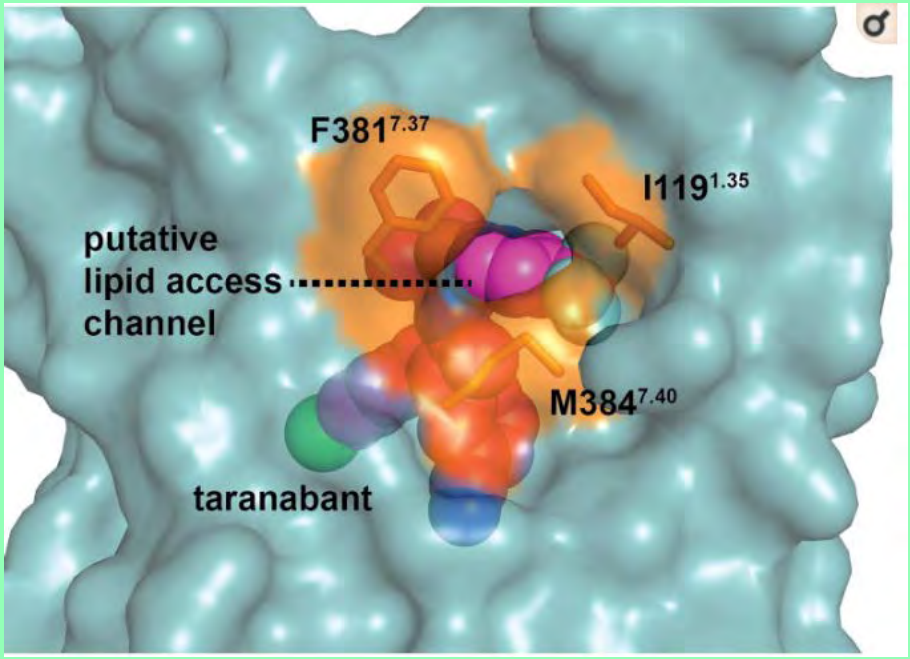
Figure 4 | Docking of rimonabant and THC to the CB1 receptor. **a**, Overlay of the crystal structure pose of taranabant (transparent magenta sticks) with the top-scoring docking pose of rimonabant shown using orange sticks (see Methods). The contact residues within 4 Å of taranabant are shown as transparent teal sticks. The 2D structure of rimonabant is shown at upper left. **b**, Top-scoring docking pose of THC is shown as light green sticks, along with taranabant (transparent magenta sticks). Selected residues important for the binding of THC and agonist activity are shown as teal sticks. TM7 cartoon is removed for clarity. The 2D structure of THC is shown on the bottom right.

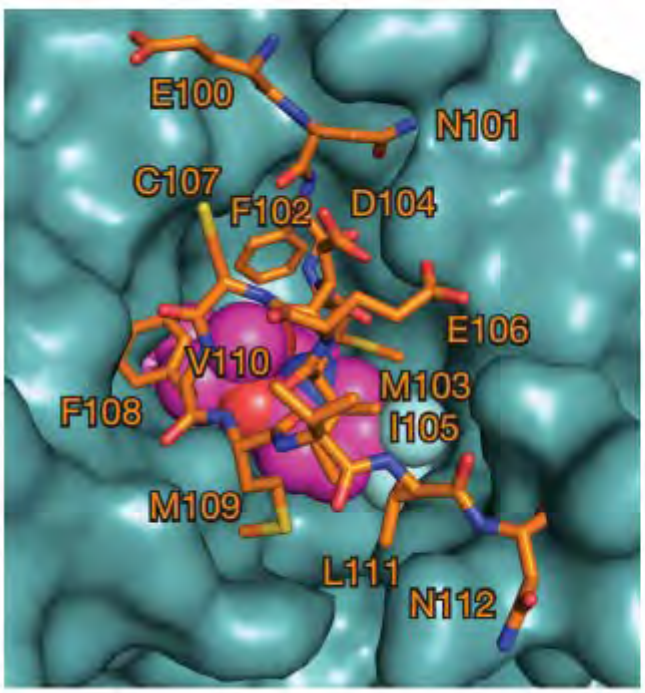
Nature. 2016 Nov 16. doi: 10.1038/nature20613. [Epub ahead of print]

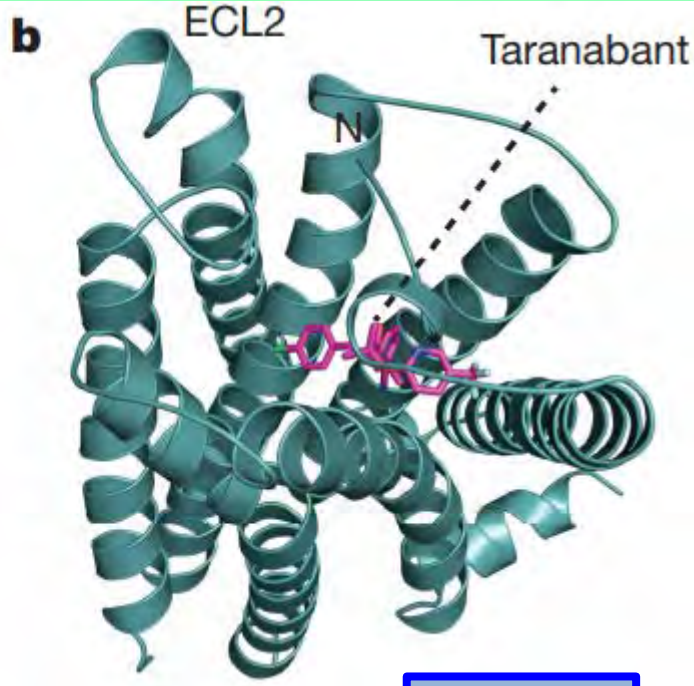
High-resolution crystal structure of the human CB1 cannabinoid receptor.

Shao Z[1], Yin J[1], Chapman K[1], Grzemska M[1], Clark L[1], Wang J[2], Rosenbaum DM[1].

Ligand Docking







284

Nature. 2016 Nov 16. doi: 10.1038/nature20613. [Epub ahead of print]

High-resolution crystal structure of the human CB1 cannabinoid receptor.

Shao Z[1], Yin J[1], Chapman K[1], Grzemska M[1], Clark L[1], Wang J[2], Rosenbaum DM[1].

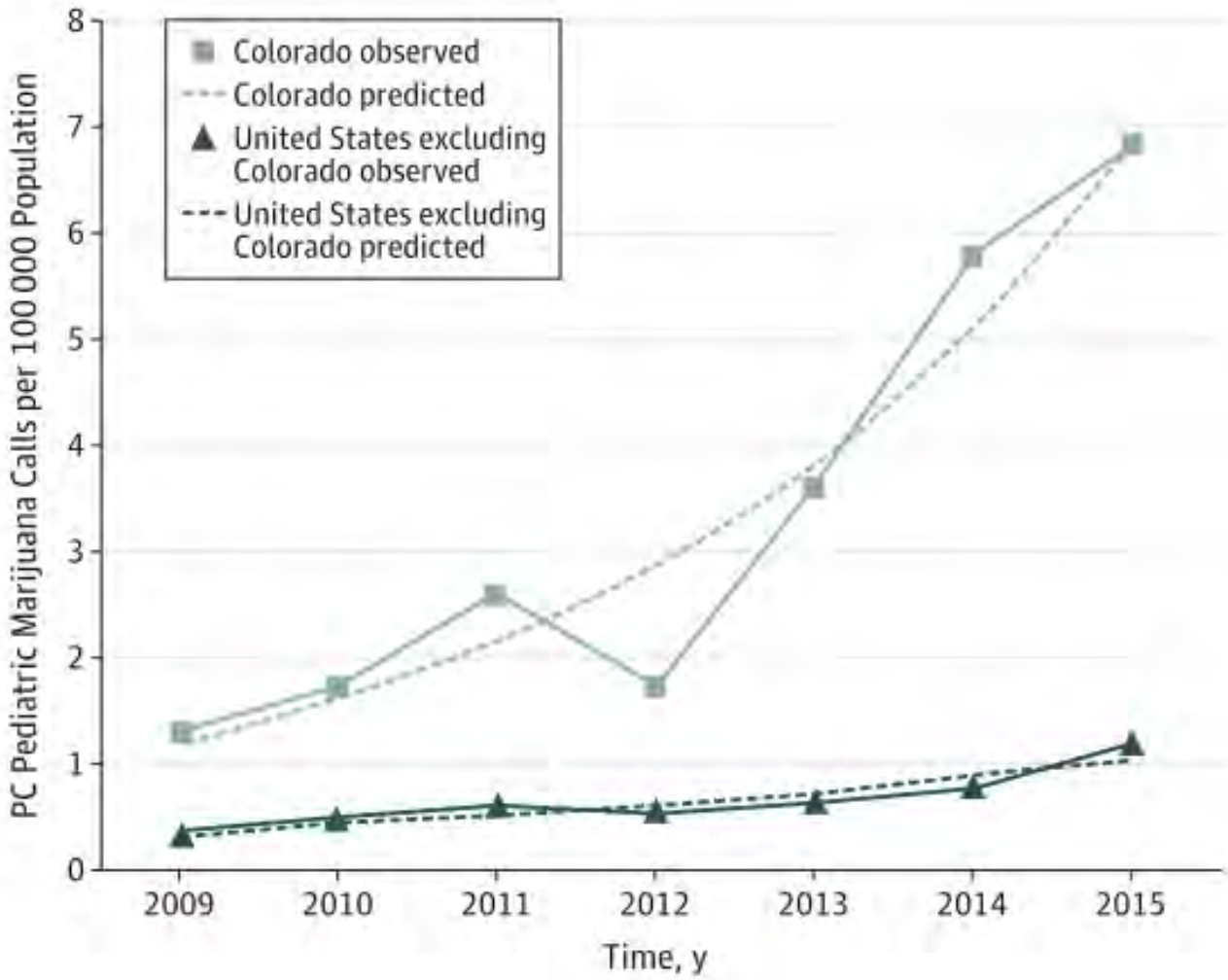
The Last Sorcerer

Echoes of the Rainforest

a novel by Ethan Russo, MD

Colorado

Figure 2. Colorado Pediatric Marijuana Exposures vs US Pediatric Exposures



287

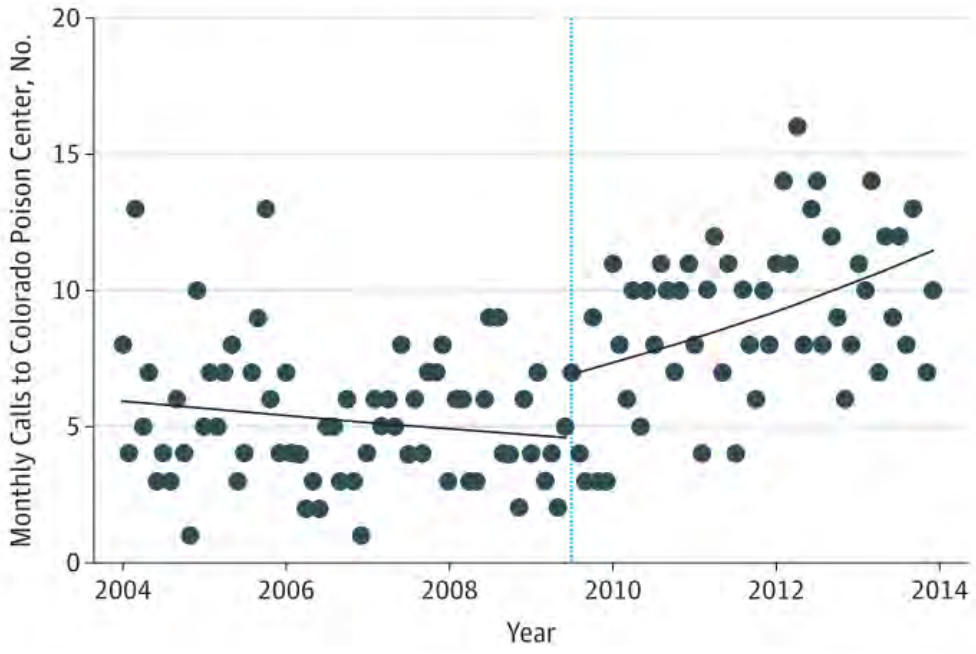
JAMA Pediatr. 2016 Sep 6;170(9):e160971. doi: 10.1001/jamapediatrics.2016.0971. Epub 2016 Sep 6.

Unintentional Pediatric Exposures to Marijuana in Colorado, 2009-2015

Wang GS[1], Le Lait MC[2], Deakyne SJ[3], Bronstein AC[2], Bajaj L[4], Roosevelt G[5].

Colorado

Figure. Calls to Colorado Poison Center

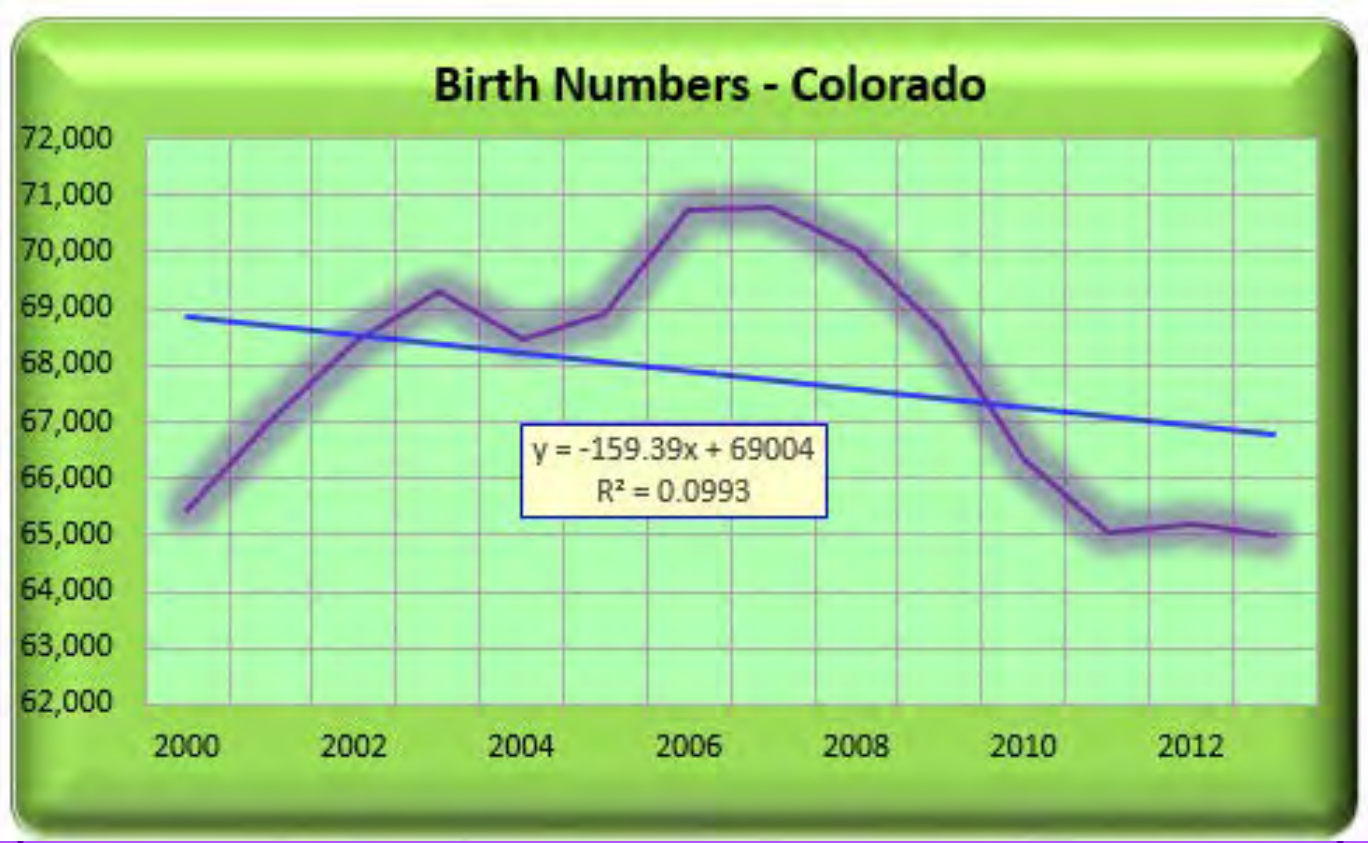


Monthly calls to the Rocky Mountain Poison and Drug Center regarding cannabis intoxication over time. The dots indicate the number of calls per month; the solid line, the best-fit trend line; the dotted line, July 2009, when the policy change was passed that allowed medical marijuana dispensaries. Adapted with permission from Davis et al.[7]

Medical Marijuana Laws and Cannabis Use
Intersections of Health and Policy

Wilson M. Compton, MD, MPE; Nora D. Volkow, MD; Marsha F. Lopez, PhD, MHS

Colorado Births



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

“Oregon Medical Marijuana”
2009

Pueblo County, Colorado

Pueblo County, Colorado

http://www.posadapueblo.org/images/PowerPointPresentations/Posada-MJ-Brief-September-28-2016-for-Print.pdf

Nimbin Cult Festival

International Church of Cannabis, Colorado

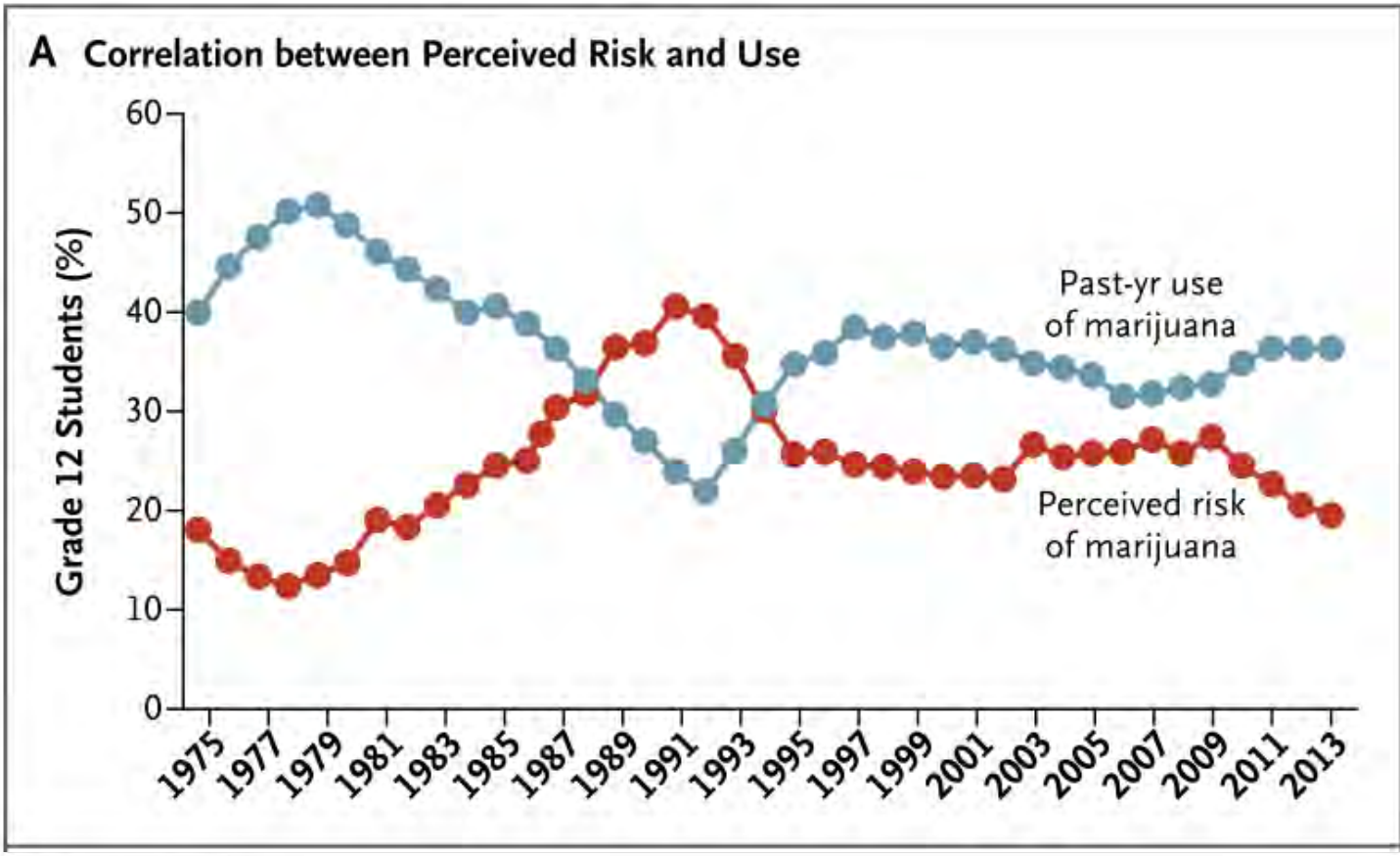
https://www.atlasobscura.com/places/international-church-of-cannabis

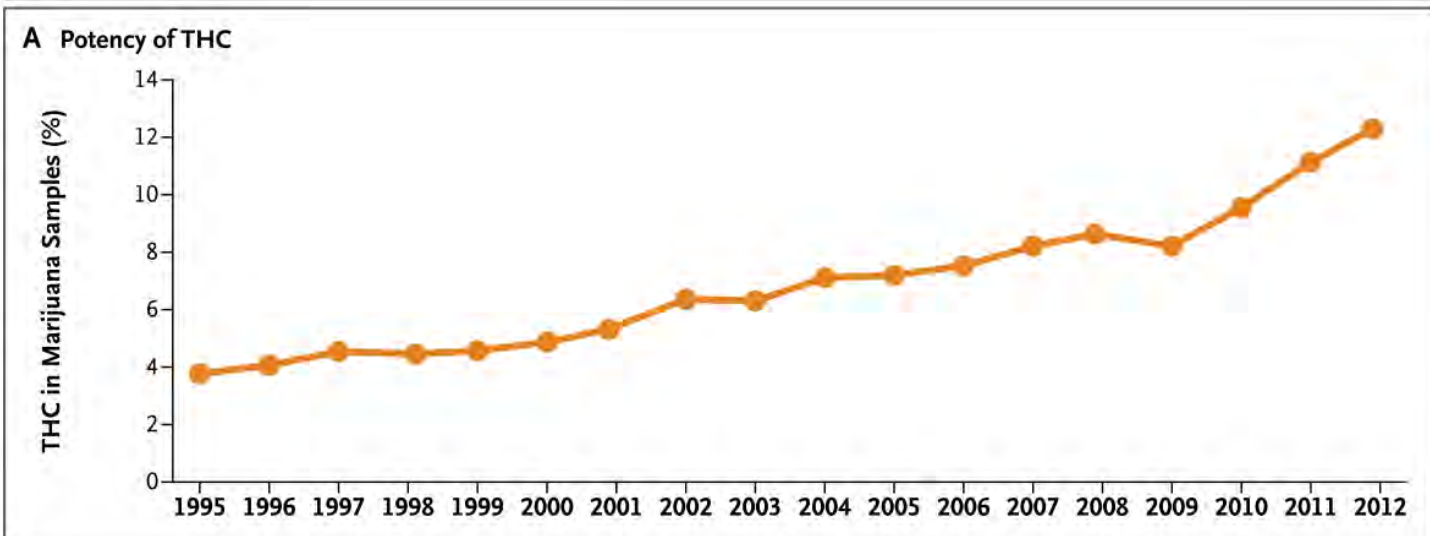

I Know Nothing


I Know Nothing


TEENAGE MUTANT
NINJA
TURTLES

Education





Adverse health effects of marijuana use.
Volkow ND, Compton WM, Weiss SR.
N Engl J Med. **2014** Aug 28;371(9):879. doi: 10.1056/NEJMc1407928.

Summary of Evidence

Syndrome	Dr. N. Volkow 2014-2017	Wayne Hall 2009-2016	Health Canada 2016-2017
Cannabis is Addictive	✓	✓	✓
Brain Development	✓	✓	✓
Gateway to Other Drug Use	✓	✓	
Psych.Disease - Depression, Anxiety, Psychosis	✓	✓	✓
Developmental Trajectory	✓	✓	✓
Driving / MVA	✓	✓	✓
Respiratory	✓		✓
Immunosuppression	✓	✓	
Heart Attack / Stroke / CVS Disease	✓	✓	✓
Cautions and Queries			
Cancer	?	✓	
Gestational Exposures	✓	✓	✓
Increased Potency	✓	✓	✓
ER Presentations	✓		✓

Cannabis Toxicity Effects: Generalized Systemic Toxicity

- Brain – Acute Intoxication
- Brain - Mental Illnesses
- Gateway Effect to Other Addictions
- Aborts Normal Lifetime Trajectory
- Respiratory System
- Aerodigestive Tract
- Bladder and Kidneys
- Congenital Abnormalities
- **** Reproductive Tract – Male & Female***
- **** Liver – Cirrhosis***
- **** Cancer – x10, 3 in Children***
- **** Arterial System –***
- **** Heart Attacks, Strokes***
- **** Immune System***
- **** Hormones***
- **** Genotoxicity***

i.e. Cannabis Accelerates the Ageing Process

**** = Age Defining Illnesses***

Summary

Cannabis Not Safe for:

BABIES

- Car Drivers
- Commercial Drivers - Taxis, Buses, Trains,
- Pilots of Aeroplanes
- Workers – Manual Tools, Construction, Concentration Jobs
- Children
- Adolescents
- Females of Reproductive age
- Males of Reproductive age
- Pregnancy
- Lactation
- Workers
- Older People – Mental Illness
- Immunosuppressed
- Asthmatics – 80% Population
- People with Personal History of Cancer
- People with Family History of Cancer
- People with Personal History of Mental Illness
- People with Family History of Mental Illness

- ***Accelerated Aging in Whole Population***

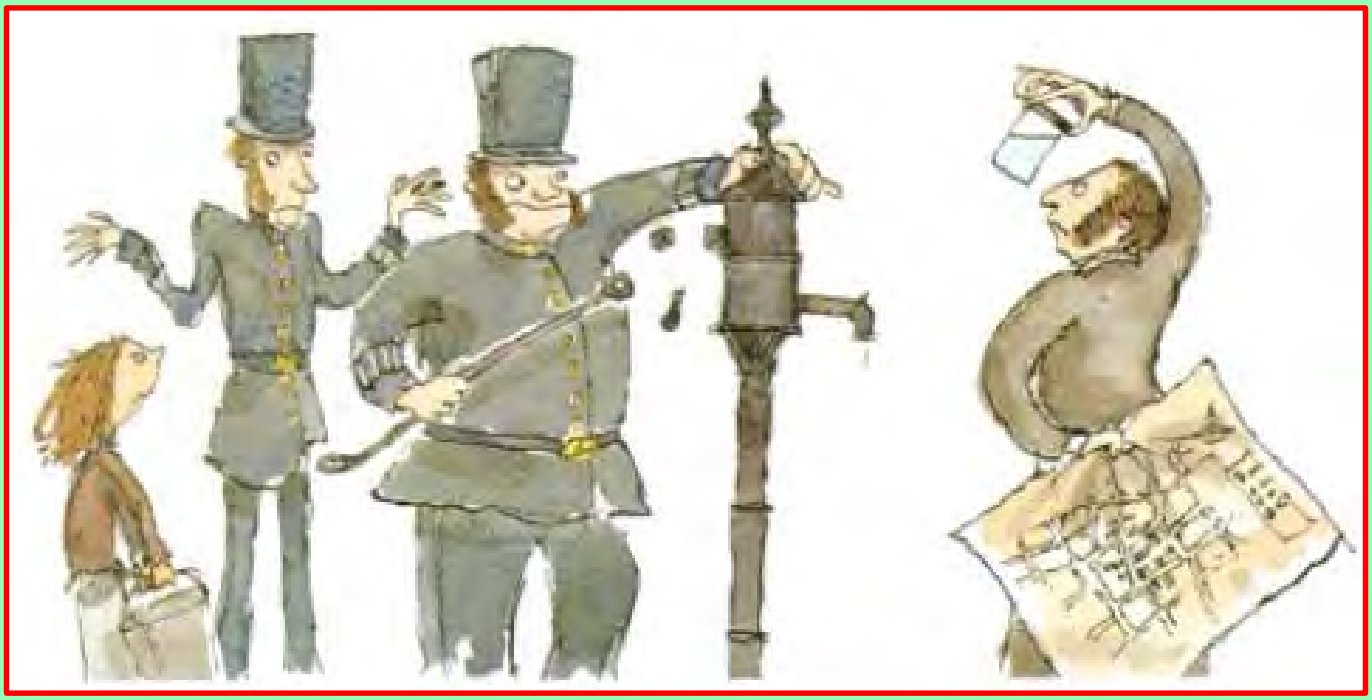
CAUSATION

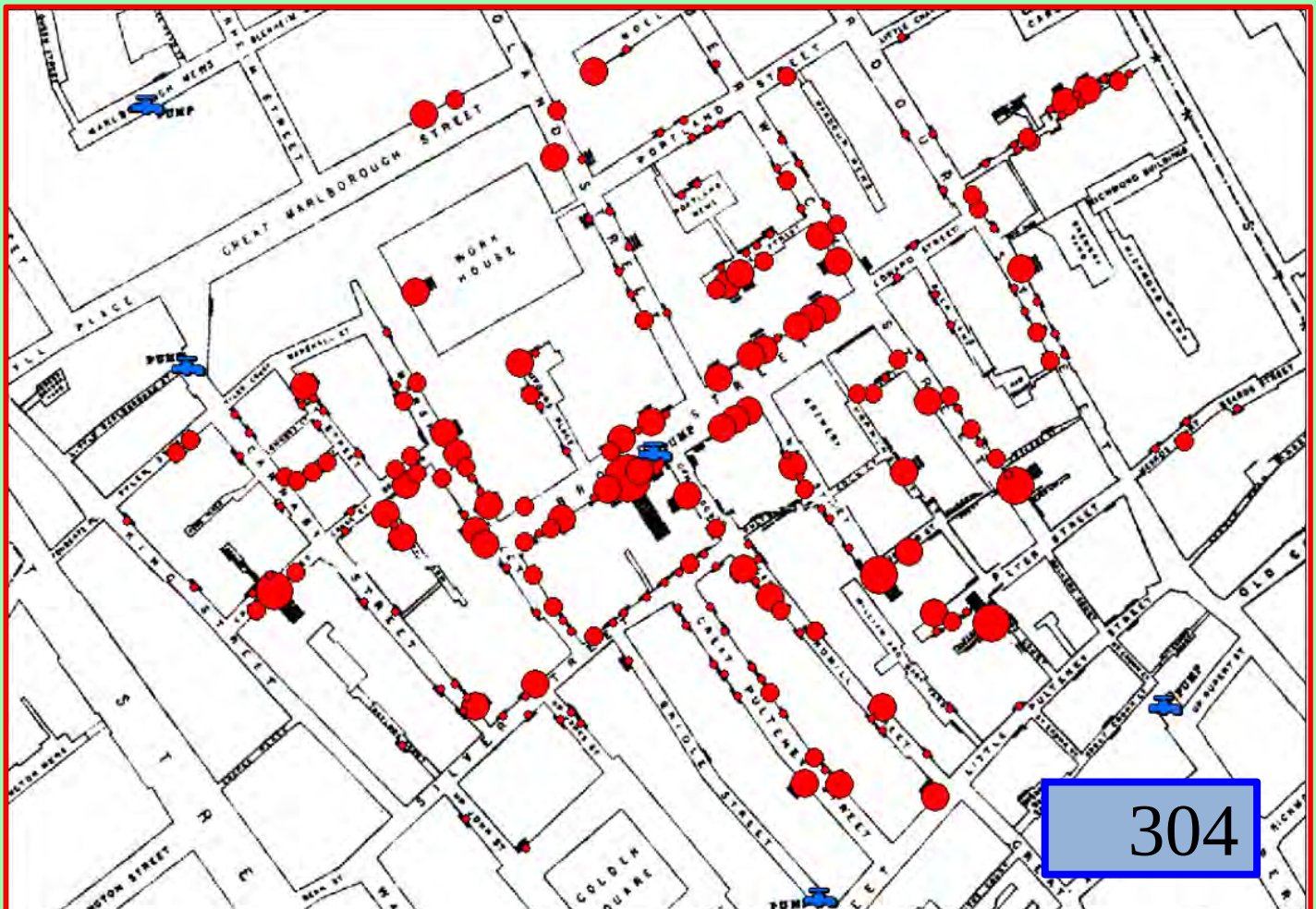
- *Far-Reaching*
- *Public Policy &*
- *Public Health Implications*

- *For Many Generations*

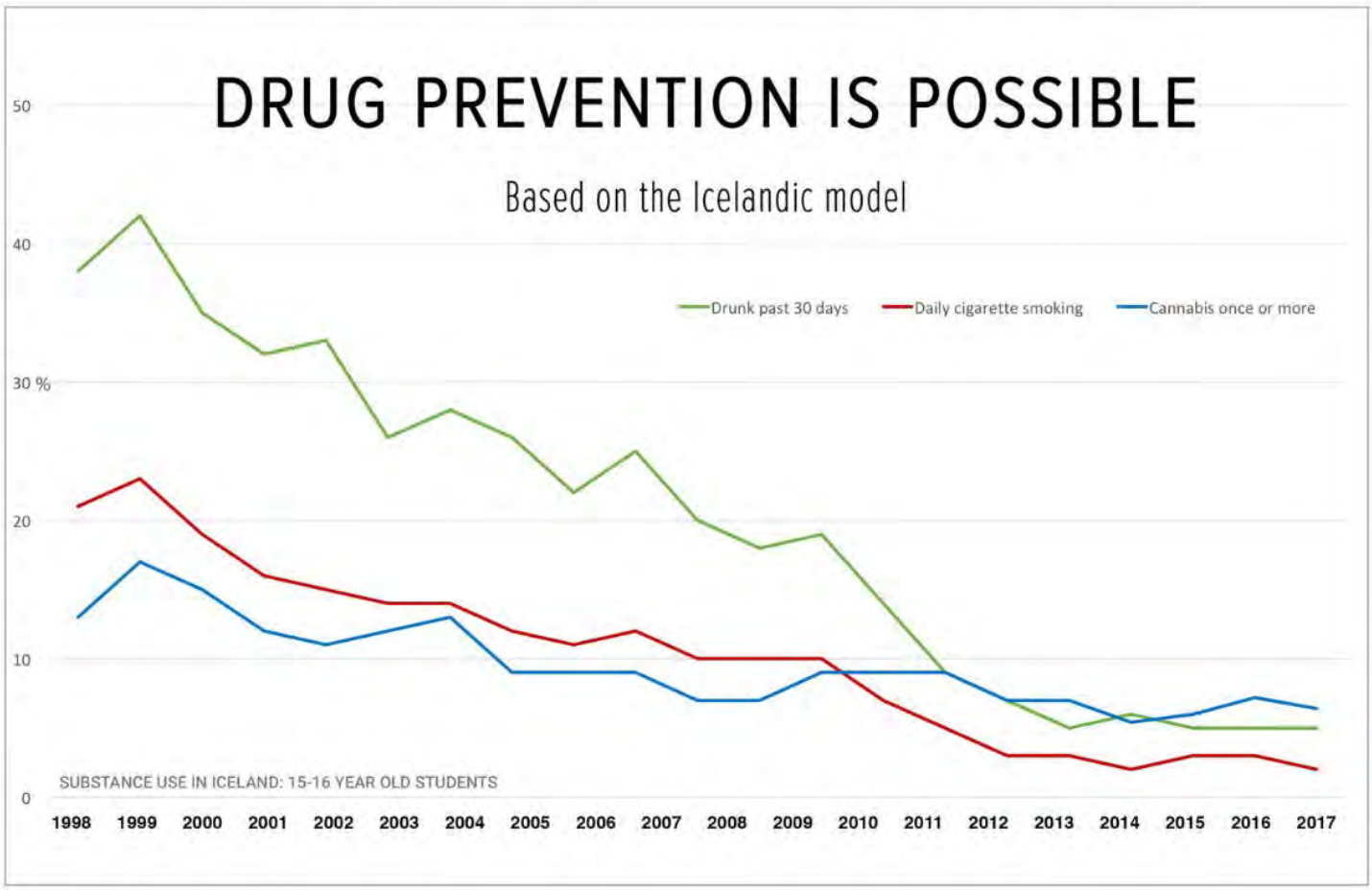

Legalization

Public Health Approach: John Snow & the Broad Street Pump



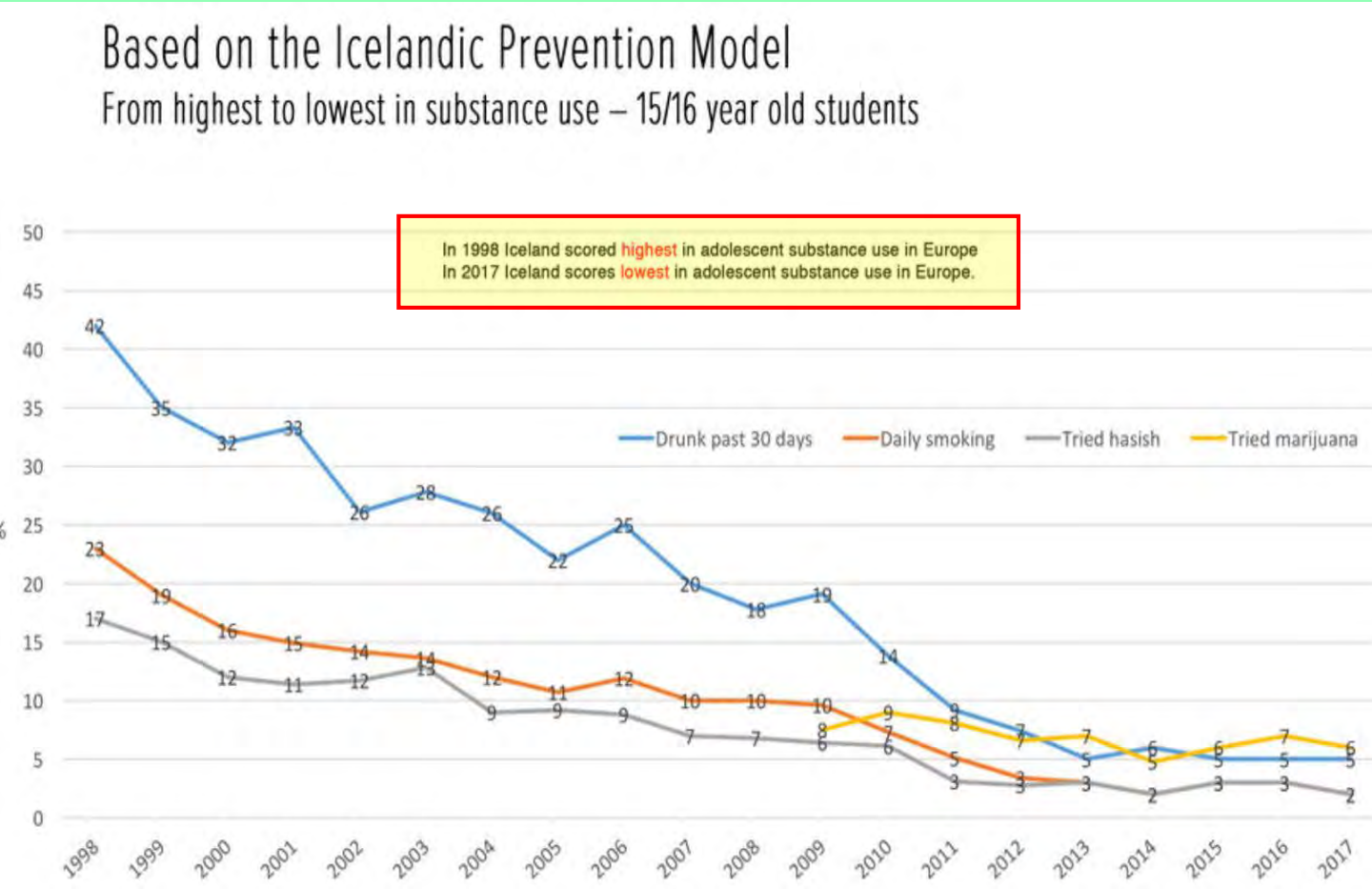


Iceland
Drug Prevention is Possible and Do-able Today!!!



https://planetyouth.community/

Iceland - Highest to Lowest in Just 19 Years!!!!



https://planetyouth.community/coremessage/

Re-Casting the Cannabis Debate :

Efficacy,

Genotoxicity and

Teratogenicity

Prof. Dr Stuart Reece
ECU: Joondalup, Western Australia
A/Prof: UWA: School of Psychiatry, Perth, Western Australia

http://www.momjunction.com/articles/adorable-mother-and-baby-images_00355204/