Autism and vitamin D

A look into the body of research that links vitamin D deficiency and autism

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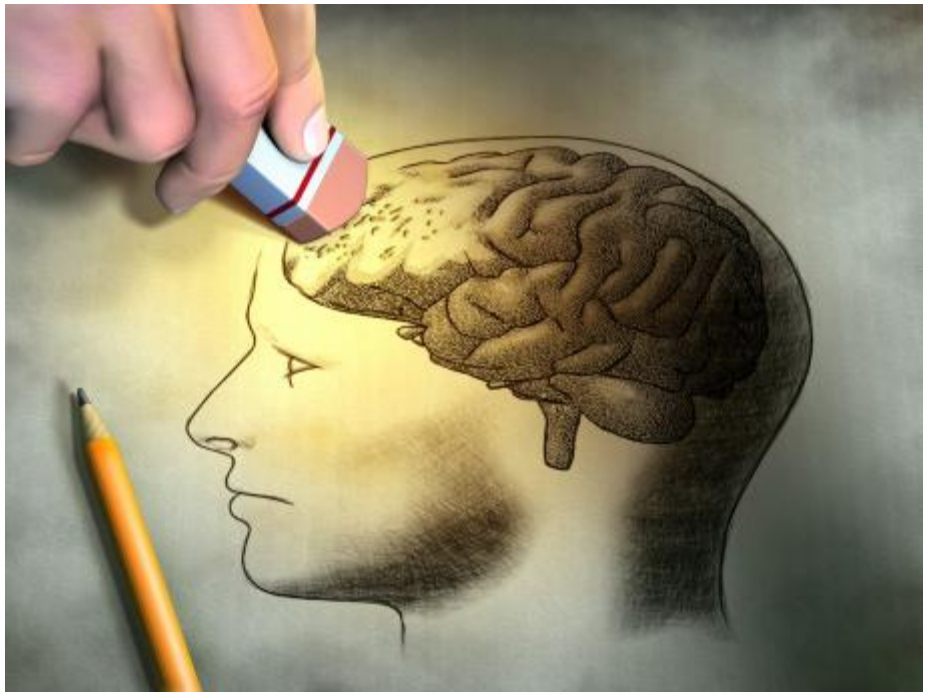
Autism and vitamin D

Disclaimers

- I receive royalties from Purity Products upon sale of their vitamin D
- I have an autism and vitamin D book to be published shortly
- I get paid for being ED of the Vitamin D Council (we're a nonprofit)
- For years we had no conflicts and no money
- I prefer having conflicts



Autism and vitamin D

In 2001, John McGrath theorized that D deficiency was a “candidate risk factor for the neurodevelopmental disorders.”

In 2006, Bill Grant and Connie Soles found that UVB correlated with autism rates before 1985 but not after.

In 2008, I wrote a paper in the journal of Medical Hypothesis about “Autism and vitamin D.”

McGrath J, Feron F, Eyles D, Mackay-Sim A. Vitamin D: the neglected neurosteroid? Trends Neurosci. 2001 Oct;24(10):570-2.

Grant WB, Soles CM. Epidemiologic evidence supporting the role of maternal vitamin D deficiency as a risk factor for the development of infantile autism. Dermatoendocrinol. 2009 Jul;1(4):223-8.

Cannell JJ. Autism and vitamin D. Med Hypotheses. 2008;70(4):750-9. Epub 2007 Oct 24.

Autism and vitamin D

In 2010, five Harvard researchers accepted and modified the vitamin D and autism theory. They said:

- Some of the genetic damage may be done before conception
- Vitamin D acts on the genome to reduce mutations from toxins (a repair and maintenance function of vitamin D)
- Authors issued a plea to immediately take steps to prevent vitamin D deficiency

Kinney DK, Barch DH, Chayka B, Napoleon S, Munir KM. Environmental risk factors for autism: do they help cause de novo genetic mutations that contribute to the disorder? Med Hypotheses 2010; 74: 102–6.

Autism and vitamin D

Professor Christopher Gillberg

In 2012, one of the best known autism researchers in the world called for “urgent research” into the vitamin D theory of autism.

Why did he do that?

Kočovská E, Fernell E, Billstedt E, Minnis H, Gillberg C. Vitamin D and autism: Clinical review. Res Dev Disabil. 2012 Sep;33(5):1541-50. Epub 2012 Apr 21.

Autism and vitamin D

Very recently, Irvine Gentile and colleagues have written the most current vitamin D theory of autism.

Vitamin D deficiency during gestation and/or toddlerhood damages the immune system. When a genetically predisposed fetus or toddler is confronted with an environmental injury (virus, toxin, Tylenol, etc.) that damaged immune system causes an autoimmune disorder in which the immune system attacks the child's own brain. The result is autism.

Gentile I, et al. Etiopathogenesis of autism spectrum disorders: Fitting the pieces of the puzzle together. Med Hypotheses. 2013 Jul;81(1):26-35.

Autism and vitamin D

- Hence, others have proposed several modifications of McGrath's original theory. I do not expect the revisions to prove invincible, nor do I delude myself that autism is now comprehensible. Rather, many may build on the theory so that it may be corroborated, corrected, or disproved.

Autism and vitamin D

- Parsimony or Occum's Razor

- The simplest theory that makes the fewest assumptions and that can explain the most facts is usually correct.

- "We are to admit no more causes of natural things than such as are both true and sufficient to explain their appearances. Therefore, to the same natural effects we must, so far as possible, assign the same causes." Sir Isaac Newton

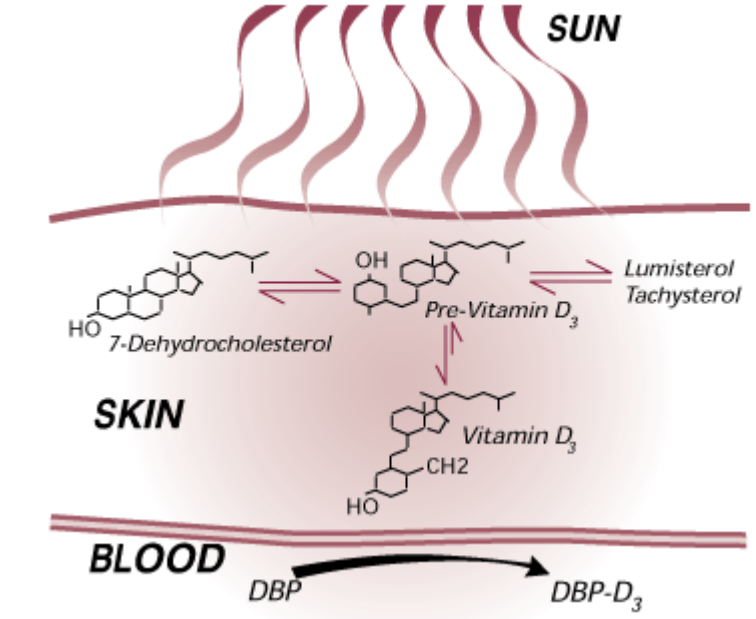
- So we are looking for a simple theory that can explain the most facts about autism without making any new assumptions.

Autism and vitamin D

Vitamin D is not a vitamin, it is a secosteroid prehormone.

How are we supposed to get vitamin D?

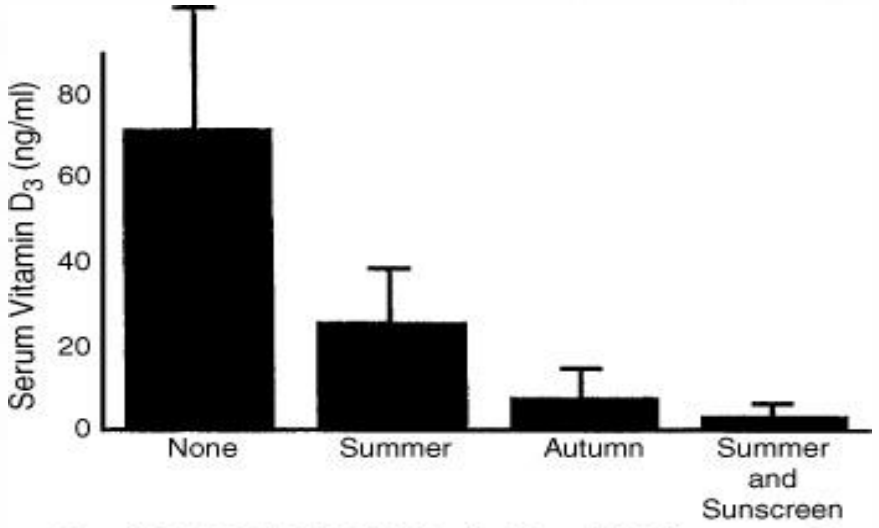
Manufactured in the skin, not put in the mouth.



Autism and vitamin D

Big problem:

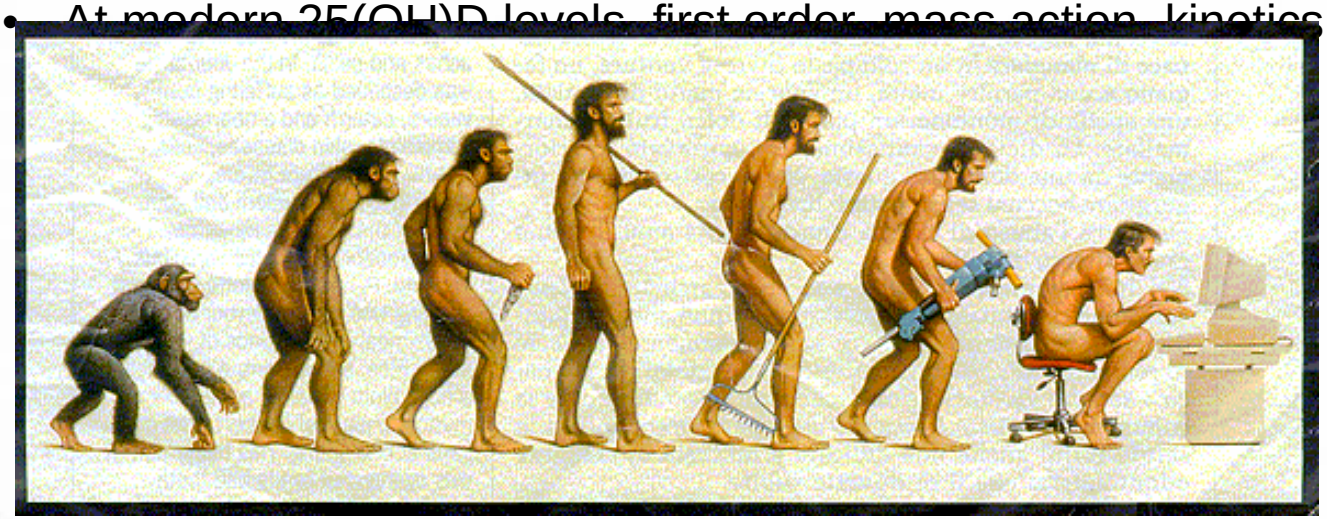
- We don't get unfiltered UVB exposure anymore.
- We don't make much vitamin D anymore.



Effect of clothing and sunscreen on vitamin D status.

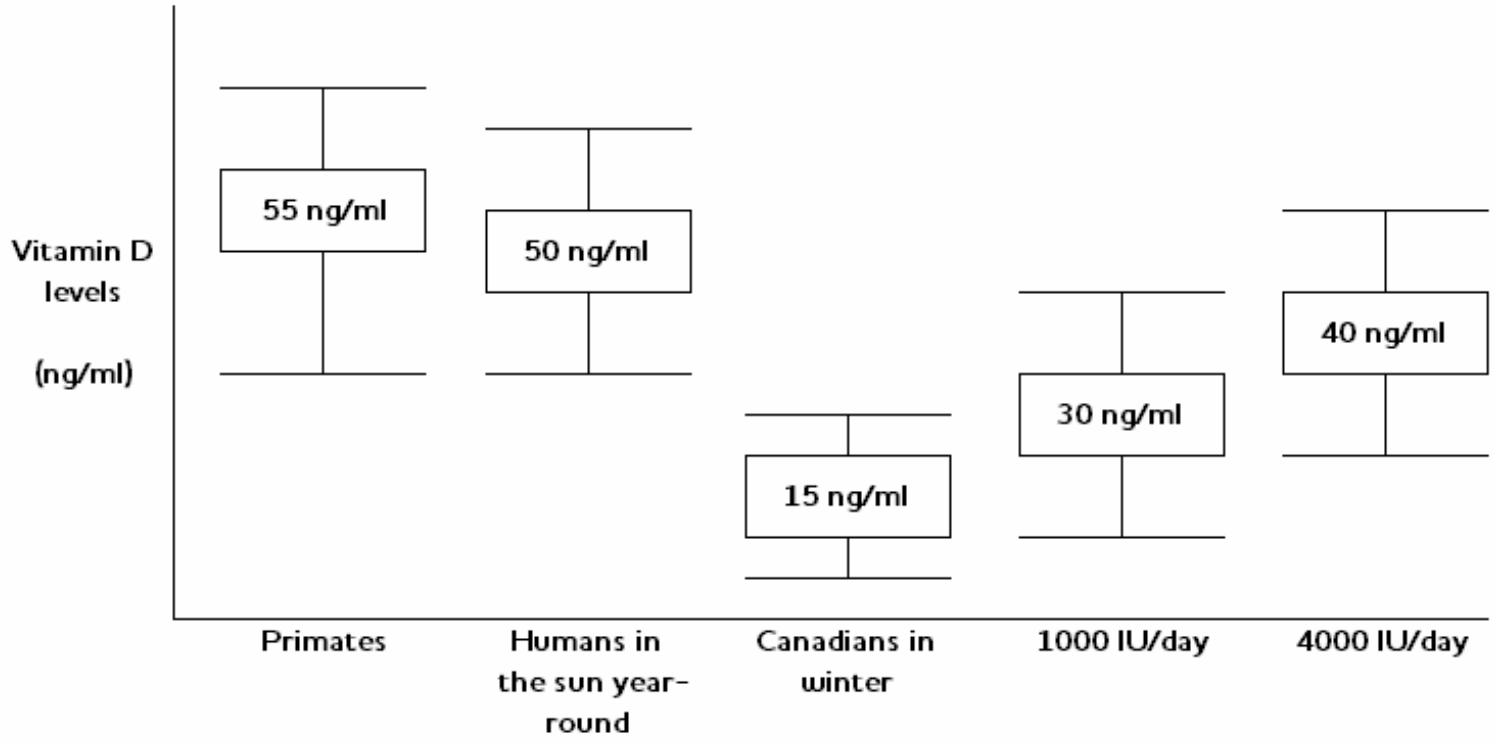
Relevant facts about vitamin D

- Traditionally, ninety percent of vitamin D stores come from sun, not oral intake
- One full-body summer sun exposure (one MED) delivers 20,000 IU to systemic circulation
- It takes 200 glasses of milk or 50 multivitamin tablets to do the same
- At modern 25(OH)D levels, first order, mass action, kinetics are the rule.



Autism and vitamin D

Vitamin D nutritional status through the ages



Autism and vitamin D

Ideal vitamin D levels?

- Ask your doctor for a 25 OH vitamin D blood test.
- Ideal 25(OH)D levels are unknown but they are probably close to levels the human genome evolved on.
- Natural levels, that is, levels found in humans who live or work in the sun, are around 50 ng/ml – levels obtained by a tiny fraction of modern humans.
- 25(OH)D levels of modern day hunter gatherers in Tanzania are 46 ng/ml.

Cannell JJ, Hollis B, Heaney RP. Diagnosis and treatment of vitamin D deficiency. Expert Opinions 2007.
Vieth R. What is the optimal vitamin D status for health? Prog Biophys Mol Biol 2006;92(1):26-32.
Luxwolda MF, et al. Traditionally living populations in East Africa have a mean serum 25-hydroxyvitamin D concentration of 115 nmol/l. Br J Nutr. 2012 Nov 14;108(9):1557-61.

Autism and vitamin D

This behavior is new to the human brain. It just started occurring in the last few decades.

Autism and vitamin D

This is new to human brain development.

Autism and vitamin D

Unplanned, gigantic “open study”

- It’s as if we started a giant scientific study in the 1980s:
  - Let’s dramatically reduce skin production of vitamin D by avoiding the sun and wearing sunblock and see what happens.
  - Let’s not give our children supplements to make up for what the skin is no longer producing, let’s just cut them off.
  - Then we can see if any epidemics occur among our children.
  - There are 3 childhood epidemics in few decades: autism, asthma and autoimmune disorders.

Autism and vitamin D

Sun-avoidance advice works

- In 1989, the first AMA warned about the dangers of sunlight, advising mothers to keep children out of the sun “as much as possible.”
- In 1999, the APA went further, advising mothers to always keep children out of direct sunlight, use sun-protective clothing, sunblock, and make sure children’s activities minimize sun-exposure.
- In 2001, the CDC said such measures were becoming effective, stating, “protection from sun exposure is reported for a high proportion of children.”

Council on Scientific Affairs. Harmful effects of ultraviolet radiation. JAMA. 1989 Jul 21;262(3):380-4.

American Academy of Pediatrics. Committee on Environmental Health. Ultraviolet light: a hazard to children. Pediatrics. 1999 Aug;104(2 Pt 1):328-33.

Hall HI, *et al.* Protection from sun exposure in US white children ages 6 months to 11 years. Public Health Rep. 2001 Jul-Aug;116(4):353-61.

IOM's recent 2010 advice failed to compensate for lack of sun

- During the three decades of sun-avoidance advice, vitamin D recommendations did not change for pregnant women or for children.
- There was no effort made to compensate for the vitamin D deficiency such advice would predictably induce.
- IOM recommendations stayed the same, that is, 400 IU per day for infants and children!
- In 2010, they increased to 600 IU/day for pregnant women

Autism and vitamin D

Now lets look at autism

Clinical signs of autism:

- Appears in early childhood
- Impaired social interaction
- Impaired communication skills
- Reciprocal interpersonal unresponsiveness
- Stereotyped behaviors and interests
- Phenotype (like all psychiatric conditions) is widely variable

Autism and vitamin D

DSM -IV

- Autistic Disorder
- Rett's Disorder
- Childhood Disintegrative Disorder
- Asperger's Disorder
- Pervasive Developmental Disorder NOS

•DSM –V

•will have only one, autism spectrum disorder with two categories of findings.

- Social communication deficits
- Repetitive interests and behavior

Autism and vitamin D

Common beliefs about autism

- Autism is a genetic disease so it cannot be dramatically increasing in incidence (better detection theory).
- Autism cannot be a genetic disease because it is dramatically increasing in incidence (environmental toxins only).
- Autism is caused by vaccinations (most experts think not).
- The 4:1 male to female ratio means the defect is on the sex chromosomes. (Geneticists cannot locate such a defect).
- There are probably many different environmental triggers for autism (many toxins seem to contribute a little).
- To my knowledge, no one has looked at the genetics of vitamin D in relation to autism.

Autism and vitamin D

- Vitamin D levels are relatively highly heritable. Is not intuitively obvious.
- It looks as if a few genes determine heritability (oligogenomic)
- Estimates of the heritability of 25(OH)D levels based on family and twin studies vary between a low of 43% to a high of 80%.

- Hiraki LT, et al. Exploring the genetic architecture of circulating 25-hydroxyvitamin D. Genet Epidemiol. 2013 Jan;37(1):92-8.
- Karohl C, Su S, Kumari M, Tangpricha V, Veledar E, Vaccarino V, Raggi P. Heritability and seasonal variability of vitamin D concentrations in male twins. Am J Clin Nutr. 2010

Autism and vitamin D

Epigenetics

- the study of heritable changes in phenotype (appearance) or gene expression caused by mechanisms other than changes in the underlying DNA sequence.
- Vitamin D has many epigenetic mechanisms of action.

- Hossein-nezhad A, Holick MF. Optimize dietary intake of vitamin D: an epigenetic perspective. Curr Opin Clin Nutr Metab Care. 2012 Nov;15(6):567-79.

Autism and vitamin D

Five Most Striking Epidemiological Features

1. monozygotic (50-90%) versus dizygotic (10%) twin concordance rates
2. widely varying clinical presentation of autism even among monozygotic twins
3. striking male: female ratio (4 or 5:1)
4. increased prevalence in dark skinned immigrants from sunny lands
5. apparent rapid increase in incidence over the last 30 years

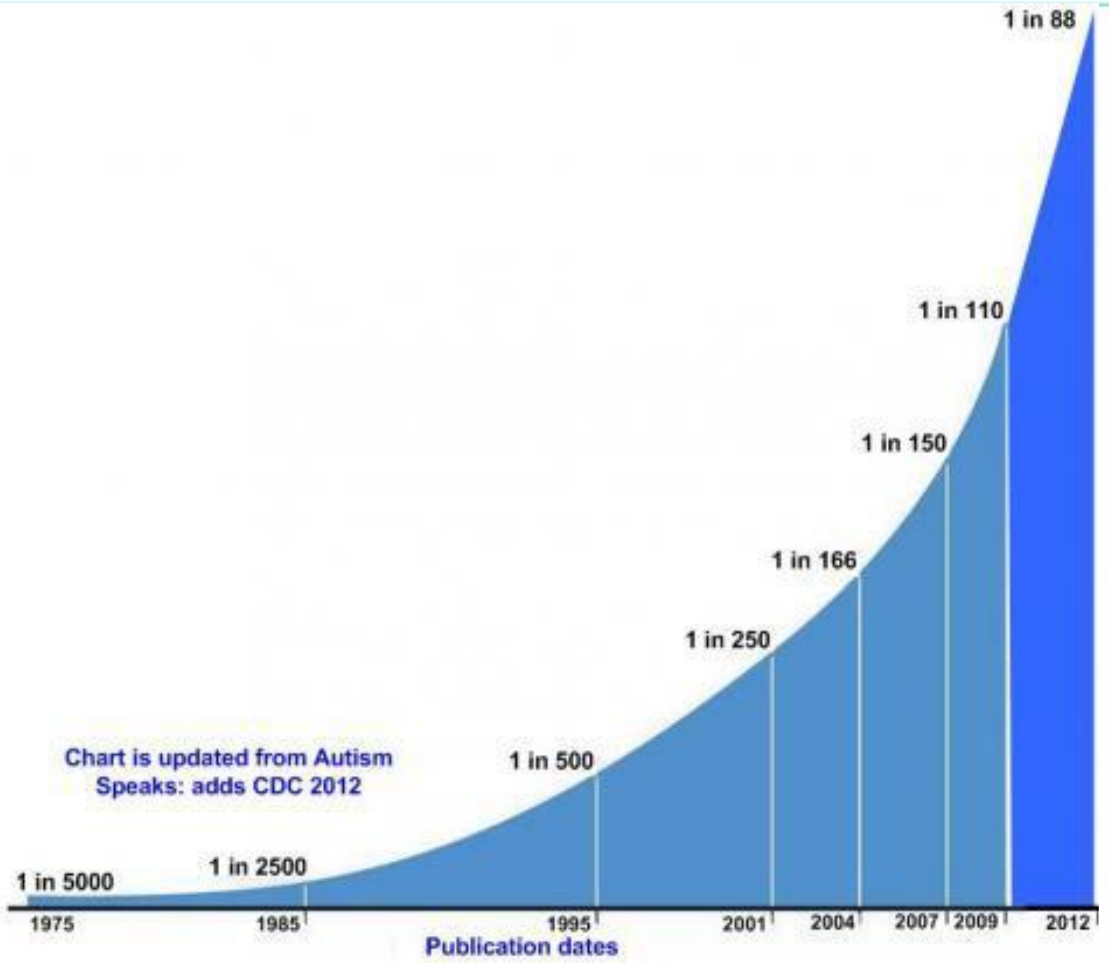
Autism and vitamin D

Remember Parsimony

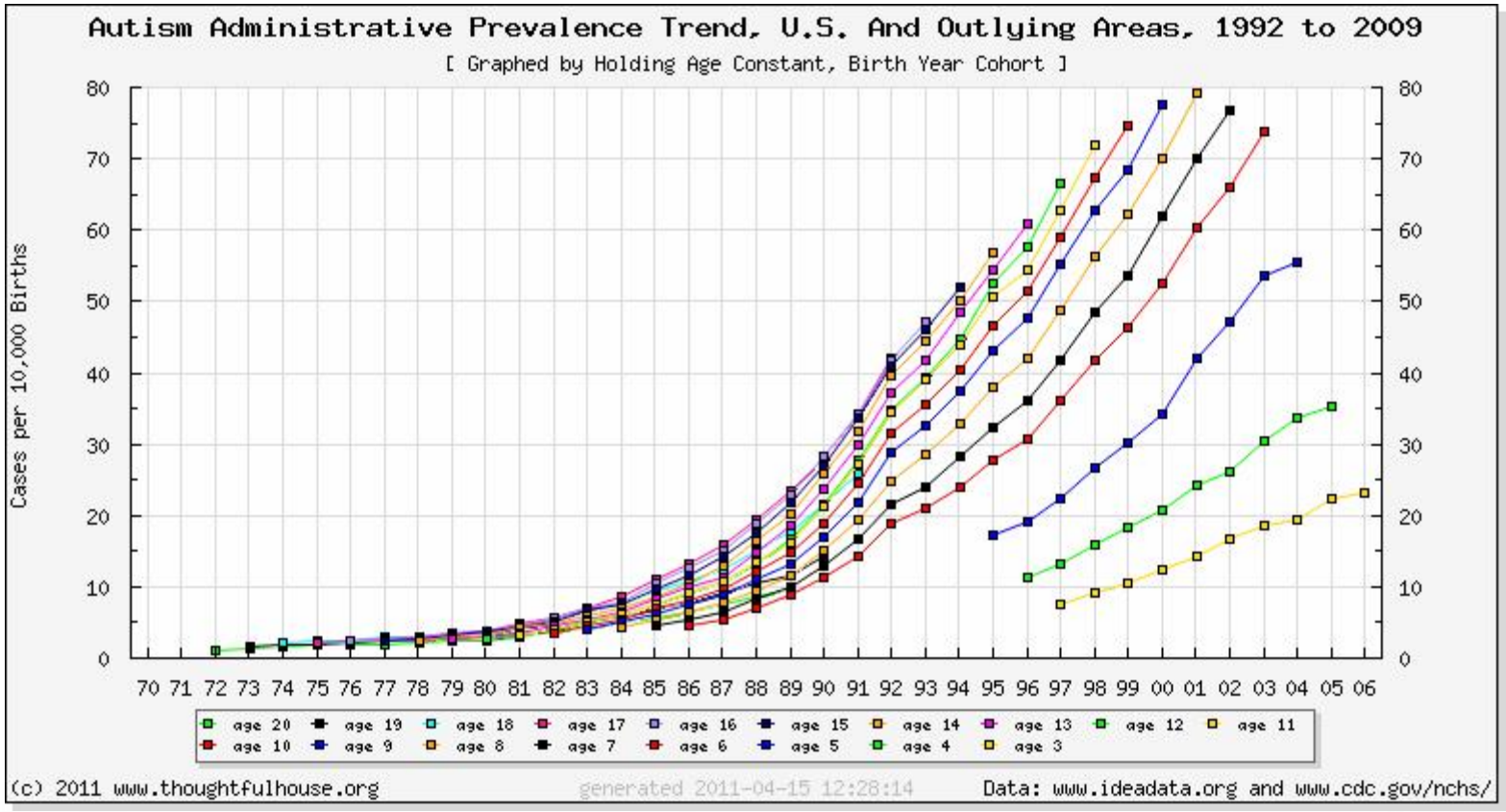
The theory must explain all five epidemiological features of autism without making any new assumptions.

- Very easy to come up with ten different theories to explain 10 different facts.
- We need one theory to explain all the facts
- What facts about autism does the vitamin D theory explain?

Autism and vitamin D



Autism and vitamin D



Autism and vitamin D

- Only one study which has shown that 25(OH)D levels fell dramatically from 1994 to 2004.
- No studies are able to look at changes in 25(OH)D from 1985 to present.
- More than 60 % of US children had insufficient 25(OH)D levels in the National Health and Nutrition Examination Survey of 2001-2004.

- Ginde AA, Liu MC, Camargo CA Jr. Demographic differences and trends of vitamin D insufficiency in the US population, 1988-2004. Arch Intern Med. 2009 Mar 23;169(6):626-32.
- Kumar J, Muntner P, Kaskel FJ, Hailpern SM, Melamed ML. Prevalence and associations of 25-hydroxyvitamin D deficiency in US children: NHANES 2001-2004. Pediatrics. 2009 Sep;124(3):e362-70.

Autism and vitamin D

- Some say the epidemic is due to better diagnosis now then earlier.
- Think of what the “better diagnosis” theory implies?
- Autism is not subtle, it is an obvious diagnosis; these kids are hard to miss. They often do not speak or speak strangely, they have no friends, they often stim (sometimes hitting themselves), they usually fly into rages if their routines are changed.
- The better diagnosis theory implies that parents, teachers and doctors in the 1950s, 60s and 70s all missed this nonsubtle diagnosis in obviously impaired children.
- Such a theory has no face validity. When you think about it is ludicrous.

Autism and vitamin D

Neurosteroids like vitamin D are good candidates

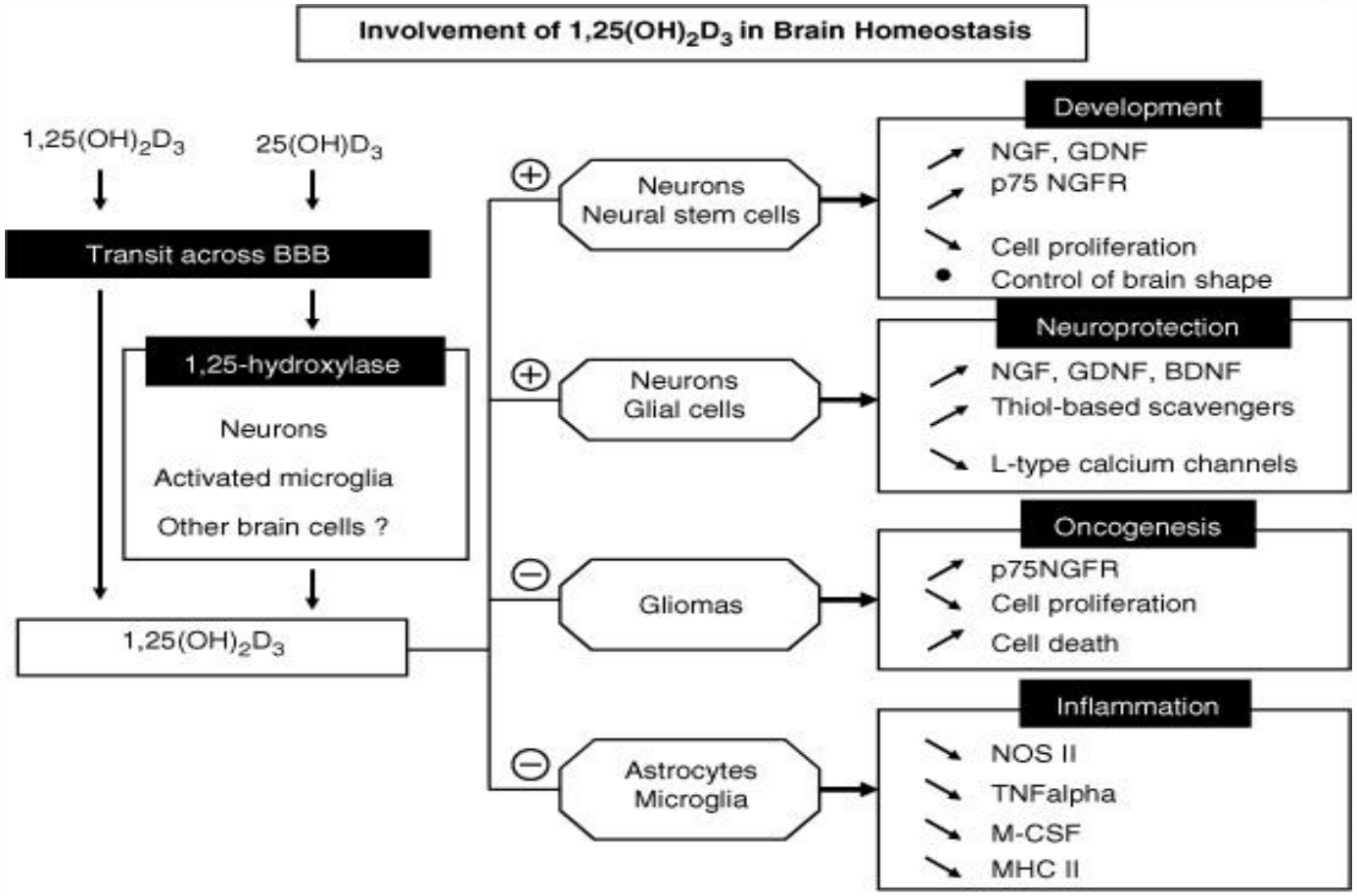
- Environmental genetic contributors
- Involved in brain development
- Under genetic organization
- Is affected by the environment.

Autism and vitamin D

Looking for a neurosteroid…

- that profoundly affects brain development
- whose levels have fallen over the last 30 years
- whose levels show racial variation
- whose levels are enhanced by estrogen but not by testosterone
- whose levels vary with human behavior
- Any such neurosteroid would explain all five of the striking epidemiological characteristics of autism

Autism and vitamin D



Autism and vitamin D

- Here what is known:
  - On brain development and function
    - Vitamin D is involved in numerous ways in brain development, including:
      - Synaptic development
      - Nerve migration and growth
      - Neurotransmission, both excitatory and inhibitory
      - Preventing excessive cell proliferation
      - Orchestrating signaling pathways in the brain
      - Cell differentiation
      - Nerve growth factor expression
      - Regulation of inflammatory cytokines
      - Neurotransmitter synthesis
      - Intra-neuronal calcium signaling
      - Anti-oxidant activity,
      - Control of the expression of genes involved in brain structure and metabolism
      - Regulation of glutathione, the master antioxidant and heavy metal remover
      - Protection from glutamate toxicity

Kočovská E, Fernell E, Billstedt E, Minnis H, Gillberg C. Vitamin D and autism: Clinical review. Res Dev Disabil. 2012 Sep;33(5):1541-50. Epub 2012 Apr 21.

Autism and vitamin D

Are Autistic Individuals Vitamin D Deficient?

- Five studies
- All show autistic individuals deficient but not always different from typically developing children.
- This is to be expected as we are only talking about children with a genetic load for autism.

Fernell E, *et al*. Serum levels of 25-hydroxyvitamin D in mothers of Swedish and of Somali origin who have children with and without autism. Acta Paediatr 2010; 99: 743–7.

Humble MB, Gustafsson S, Bejerot S. Low serum levels of 25- hydroxyvitamin D (25-OHD) among psychiatric outpatients in Sweden: relations with season, age, ethnic origin and psychiatric diagnosis. J Steroid Biochem Mol Biol 2010 Mar 7. [Epub ahead of print].

Meguid NA, *et al*. Reduced serum levels of 25-hydroxy and 1,25-dihydroxy vitamin D in Egyptian children with autism. J Altern Complement Med. 2010 Jun;16(6):641-5.
Meguid NA, Hashish AF, Anwar M, Sidhom G. Reduced serum levels of 25-hydroxy and 1,25-dihydroxy vitamin D in Egyptian children with autism. J Altern Complement Med. 2010 Jun;16(6):641-5.

Molloy CA, et al. Plasma 25(OH)D concentration in children with autism spectrum disorder. Dev Med Child Neurol. 2010 Oct;52(10):969-71

Neuropsychology of rickets

- Two old papers describe ‘weak mindedness,’ ‘feeble minds,’ ‘mental dullness,’ unresponsiveness and developmental delays.
- Even more intriguing, both papers report that the mental condition in rickets improved with vitamin D treatment.

Hallerhan MM. The effect of rickets on the mental development of young children. Arch Psychol 1938; 229: 1–67.

Gilmour A. The mental condition in rickets. School Hygiene 1912; 9: 6–16.

Autism and vitamin D

Experiment of Nature

- Even more interesting, children with Williams syndrome, have greatly elevated vitamin D levels during gestation and for several months in early infancy. They often have remarkable sociability, overfriendliness, empathy, and willingness to initiate social interaction
- Strikingly the opposite of autism.

Mervis CB, Klein-Tasman BP. Williams syndrome: cognition, personality, and adaptive behavior. Ment Retard Dev Disabil Res Rev 2000;6(2):148–58.

Autism and vitamin D

Vitamin D rich fish consumption by mothers reduces symptoms of autism

- Higher fish consumption during pregnancy was associated with belter infant cognition and that association was strengthened after adjustment for hair mercury levels.
- Lower consumption of vitamin D rich fish during pregnancy was associated with an increased risk of lower verbal IQs and suboptimal outcomes for pro-social behaviors, fine motor skill, communication, and social development, outcomes similar to autism.

Oken E, Wright RO, Kleinman KP,et al. Maternal fish consumption, hair mercury, and infant cognition in a U.S. Cohort. Environ Health Perspect 2005;113(10):1376-80.

Hibbeln JR, Davis JM, Steer C, et al. Maternal seafood consumption in pregnancy and neurodevelopmental outcomes in childhood (ALSPAC study): an observational cohort study. Lancet 2007;369(9561):578-85.

Abnormal bones in autism

- 75 boys, ages 4–8 years with autism or ASD
- Bone cortical thickness significantly decreased
- Bone cortical thickness on casein-free diets was lower than that of boys on unrestricted diets.
- However, children on milk still showed reductions in cortical thickness compared to typically developing children.
- Findings explained by vitamin D theory.

Hediger ML, *et al*. Reduced bone cortical thickness in boys with autism or autism spectrum disorder. J Autism Dev Disord 2008; 38: 848–56.

Autism and vitamin D

Why do autistic children fail to develop or lose developmental milestones in toddlerhood?

- A unique prospective longitudinal study of 87 infants, some at high risk for autism, and others not, found no statistically significant neurocognitive differences between the two groups at 6 months.
- However, around the age of weaning, 12 months, the babies separated significantly. Those who ended up developing autism first showed clinical signs, with rapid additional impairments occurring between 14 and 24 months.
- Same age many autistic children fail to develop or deteriorate
- Same age many children are weaned onto fruit juice instead of the vitamin D enriched cow's milk that was common before the autism epidemic

Landa R, Garrett-Mayer E. Development in infants with autism spectrum disorders: a prospective study. J Child Psychol Psychiatry 2006;47(6):629-38.

Northstone K, Rogers I, Emmett P; ALSPAC Team Study. Avon Longitudinal Study of Pregnancy and Childhood. Drinks consumed by 18-month-old children: are current recommendations being followed? Eur J Clin Nutr 2002;56(3):236-44.

Autism and vitamin D

- Eight anti-neural auto-antibodies have been detected so far in autism and at least two anti-neural auto-autoantibodies are directly and strongly associated with autism severity.

- Onore C, Careaga M, Ashwood P. The role of immune dysfunction in the pathophysiology of autism. Brain Behav Immun. 2012 Mar;26(3):383-92.
- Mostafa GA, Al-Ayadhi LY. The relationship between the increased frequency of serum antineuronal antibodies and the severity of autism in children. Eur J Paediatr Neurol. 2012 Sep;16(5):464-8.
- Mostafa GA, Al-Ayadhi LY. Reduced serum concentrations of 25-hydroxy vitamin D in children with autism: relation to autoimmunity. J Neuroinflammation. 2012 Aug 17;9:201.

Autism and vitamin D

Rich, well-educated parents are more likely to have autistic child

- Numerous studies linked higher social class with autism,
- Socioeconomic bias in case ascertainment confounds such associations.
- However, a recent large California study found significant positive associations between mother's education, family income, and autism and ascertainment bias could not explain the findings.
- Parents from higher socioeconomic strata with higher education are also more likely to apply sunscreen to their children.

Bhasin TK, Schendel D. Sociodemographic Risk Factors for Autism in a US Metropolitan Area. J Autism Dev Disord 2007;37(4):667-77.

Van Meter KC, Christiansen LE, Delwiche LD, Azari R, Carpenter TE, Hertz-Picciotto I. Geographic distribution of autism in California: a retrospective birth cohort analysis. Autism Res 2010; 3: 19–29.

Robinson JK, Rigel DS, Amonette RA. Summertime sun protection used by adults for their children. J Am Acad Dermatol 2000;42(5 Pt 1):746-53.

Hall HI, Jorgensen CM, McDavid K, Kraft JM, Breslow R. Protection from sun exposure in US white children ages 6 months to 11 years. Public Health Rep 2001;116(4):353-61.

Autism and vitamin D

Drugs that lower vitamin D levels will increase the risk of autism

- The vitamin D theory predicts medications that lower vitamin D levels, if taken during pregnancy, would increase the risk for autism.
- They do.

Nicolaidou P, Georgouli H, Kotsalis H, et al. Effects of anticonvulsant therapy on vitamin D status in children: prospective monitoring study. J Child Neurol 2006;21(3):205-9.

Rasalam AD, Hailey H, Williams JH, et al. Characteristics of fetal anticonvulsant syndrome associated autistic disorder. Dev Med Child Neurol 2005;47(8):551-5.

Evatt ML et al. Autism spectrum disorders following in utero exposure to antiepileptic drugs. Neurology. 2009 Sep 22;73(12):997.

Autism and vitamin D

Seizures more common in autism

- Seizures are common in autism
- Calcitriol (activated vitamin D) significantly increases the seizure threshold.
- Controlled study found vitamin D reduces the incidence of seizures.

Rossi PG, Parmeggiani A, Bach V, Santucci M, Visconti P. EEG features and epilepsy in patients with autism. Brain Dev 1995;17(3):169-74.

Siegel A, Malkowitz L, Moskovits MJ, Christakos S. Administration of 1,25-dihydroxyvitamin D3 results in the elevation of hippocampal seizure threshold levels in rats. Brain Res 1984;298(1):125-9.

Christiansen C, Rodbro P, Sjo O. "Anticonvulsant action" of vitamin D in epileptic patients? A controlled pilot study. Br Med J 1974;2(5913):258-9.

Seasonality of autism symptoms?

- If childhood vitamin D deficiency is involved in autism, symptoms should improve in the summer.
- A case study reported dramatic improvements in both sleep and behavioral problems in the summer.
- Significant improvements in autistic behaviors were reported after a summer camp program that included swimming, hiking, boating, and other outdoor activities.
- Parents of autistic children who let their child out in the summer, report to me a seasonality of symptoms.

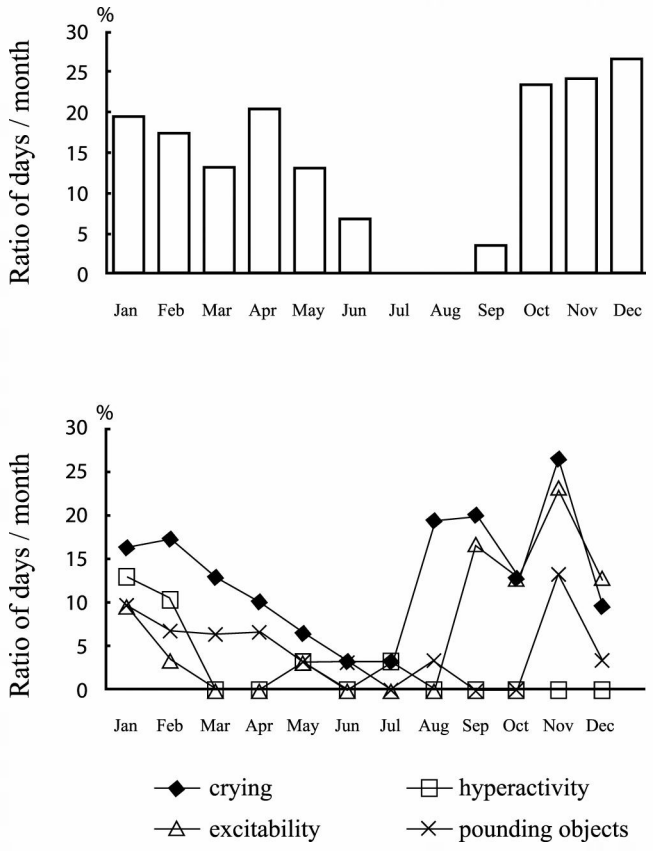
Hayashi E. Seasonal changes in sleep and behavioral problems in a pubescent case with autism. Psychiatry Clin Neurosci 2001;55(3):223-4.

Hung DW, Thelander MJ. Summer camp treatment program for autistic children. Except Child 1978;44(7):534-6.

Autism and vitamin D

Seasonal case report

- Ratio of days with sleep problems (top) and ratio of days with behavioral problems (bottom) in each month for a 15-year-old Japanese male with autism



Hayashi E. Seasonal changes in sleep and behavioral problems in a pubescent case with autism. Psychiatry Clin Neurosci 2001;55(3):223-4.

Latitude and autism

•Grant and Soles found a positive association between latitude and prevalence of autism in international cohorts born before 1985.

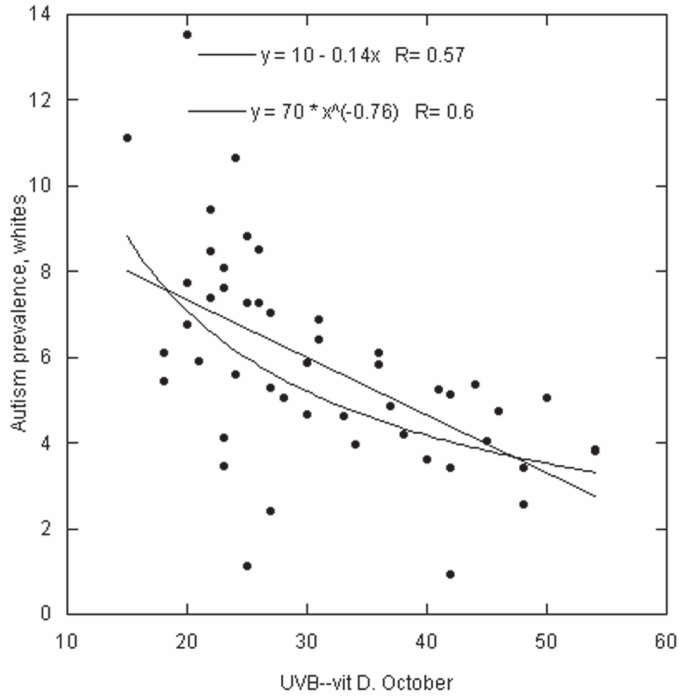
Grant WB, Soles CM. Epidemiological evidence for supporting the role of maternal vitamin D deficiency as a significant risk factor for the development of infantile autism in those born prior to 1985. Unpublished manuscript.

Grant WB, Soles CM. Epidemiologic evidence supporting the role of maternal vitamin D deficiency as a risk factor for the development of infantile autism. Dermatoendocrinol. 2009 Jul;1(4):223-8.

Autism and vitamin D

UVB radiation and autism

- Since then, Dr William Grant has found that the lower the UVB exposure, the higher the risk of autism.
  - Based on incidence of autism in each state
  - Figure shows amount of UVB a State gets in October and prevalence of autism.



Grant WB, Cannell JJ. Autism prevalence in the United States with respect to solar UV-B doses: An ecological study. Dermato-Endocrinology, 2012 Jan-Mar;5(1).

Autism and vitamin D

Season of birth

•Excessive autism births in the winter, especially March, when vitamin D levels are at their lowest.

Stevens MC, Fein DH, Waterhouse LH. Season of birth effects in autism. J Clin Exp Neuropsychol 2000;22(3):399-407.

Williams JG, Higgins JP, Brayne CE. Systematic review of prevalence studies of autism spectrum disorders. Arch Dis Child 2006;91(1):8-15.

Urban/rural gradient

- Autism's urban/rural gradient is about 2:1
- Less sun exposure in the city

Williams JG, Higgins JP, Brayne CE. Systematic review of prevalence studies of autism spectrum disorders. Arch Dis Child 2006; 91: 8–15.

Autism and vitamin D

Air pollution

- Air pollution dramatically lowers vitamin D levels
- Vitamin D theory predicts air pollution would increase risk of autism and it does.

Windham GC, Zhang L, Gunier R, Croen LA, Grether JK. Autism spectrum disorders in relation to distribution of hazardous air pollutants in the san francisco bay area. Environ Health Perspect 2006;114(9):1438-44.
Agarwal KS, Mughal MZ, Upadhyay P, Berry JL, Mawer EB, Puliyel JM. The impact of atmospheric pollution on vitamin D status of infants and toddlers in Delhi, India. Arch Dis Child 2002;87(2):111-3.

Autism and vitamin D

Clouds and rain associated with higher rates of autism

- Strong positive associations between precipitation rates and autism also support the vitamin D theory as clouds and rain impair UVB atmospheric penetration.

Waldman M, Nicholson S, Adilov N, Williams J. Autism prevalence and precipitation rates in California, Oregon, and Washington counties. Arch Pediatr Adolesc Med. 2008 Nov;162(11):1026-34.

Autism and vitamin D

Closely spaced pregnancies associated with increased autism

- Inter-pregnancy interval (IPI) of <12, 12 to 23, and 24 to 35 months were associated with odds ratios for autism of 3.39, 1.86, and 1.26 relative to IPIs of ≥ 36 months.
- Suggests a nutrient depleted in pregnancy involved in autism

Cheslack-Postava K, Liu K, Bearman PS. Closely spaced pregnancies are associated with increased odds of autism in California sibling births. *Pediatrics*. 2011;127:246 –253.

Autism and vitamin D

Abnormal immune response in autism similar to that in vitamin D deficiency

- Dysregulated immune responses are associated with both autism and vitamin D deficiency
- Autistic individuals have T cell abnormalities and cytokine excesses that show a striking similarity to the immune functions affected by vitamin D.

Ashwood P, Wills S, Van de Water J. The immune response in autism: a new frontier for autism research. J Leukoc Biol 2006;80(1):1-15.

Cantorna MT, Zhu Y, Froicu M, Wittke A. Vitamin D status, 1,25-dihydroxyvitamin D3, and the immune system. Am J Clin Nutr 2004;80(6 Suppl):1717S-20S.

Maternal vitamin D deficiency in animals alters brain function

- aberrant apoptosis
- abnormal cell proliferation
- abnormal genes involved in neuronal structure
- alterations in both learning and memory

Ko P, Burkert R, **McGrath** J, **Eyles D**. Maternal vitamin D3 deprivation and the regulation of apoptosis and cell cycle during rat brain development. Brain Res Dev Brain Res 2004;153(1):61-8.

Féron F, Burne TH, Féron F, Burne TH, Brown J, Smith E, **McGrath JJ**, Mackay-Sim A, **Eyles DW**.. Developmental Vitamin D3 deficiency alters the adult rat brain. Brain Res Bull 2005;65(2):141-8.

Burne TH, Becker A, Brown J, **Eyles DW,** Mackay-Sim A, **McGrath JJ**. Transient prenatal Vitamin D deficiency is associated with hyperlocomotion in adult rats. Behav Brain Res 2004;154(2):549-55.

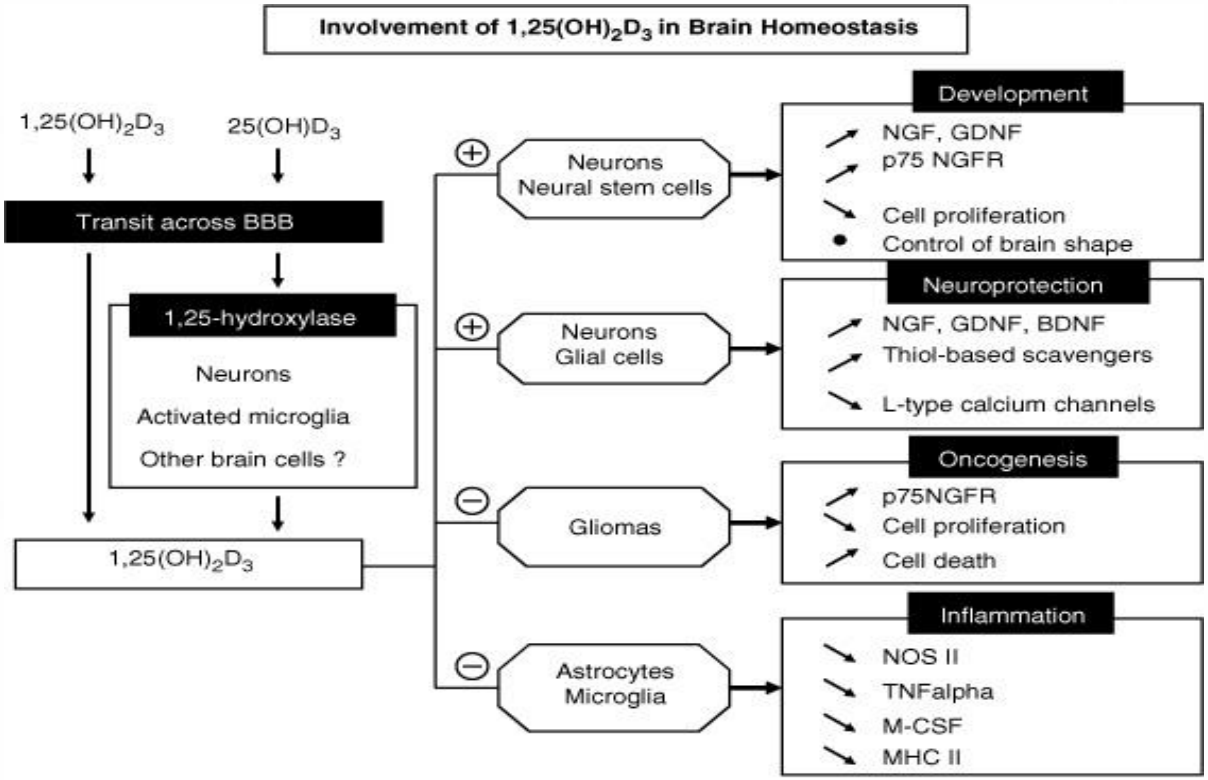
Becker A, **Eyles DW**, **McGrath JJ**, Grecksch G. Transient prenatal vitamin D deficiency is associated with subtle alterations in learning and memory functions in adult rats. Behav Brain Res 2005;161(2):306-12.

Maternal vitamin D deficiency and brain development

•36 proteins dysregulated involved in mammalian brain development, including biological pathways for oxidative phosphorylation, redox balance, cytoskeleton maintenance, calcium homeostasis, chaperoning, post-translational modification, synaptic plasticity, and neurotransmission.

Almeras L**, Eyles D**, Benech P, Laffite D, Villard C, Patatian A, Boucraut J, Mackay-Sim A, **McGrath J,** Féron F.. Developmental vitamin D deficiency alters brain protein expression in the adult rat: implications for neuropsychiatric disorders. Proteomics 2007;7(5):769-80.

Autism and vitamin D



Chapter 100, Vitamin D, Third Edition

Autism and vitamin D

Brain size and brain shape

•One cannot do brain biopsies so the lack of pathological specimens from infants with autism prohibits us from knowing how similar animal pathology is to human pathology, but severe gestational vitamin D deficiency in rats produces pups with increased brain size and enlarged ventricles, anatomical abnormalities similar to those found in autism.

Eyles D, Brown J, Mackay-Sim A, McGrath J, Feron F. Vitamin D3 and brain development. Neuroscience 2003;118(3):641-53.

Piven J, Arndt S, Bailey J, Havercamp S, Andreasen NC, Palmer P. An MRI study of brain size in autism. Am J Psychiatry 1995;152(8):1145-9.

Hardan AY, Minshew NJ, Mallikarjuhn M, Keshavan MS. Brain volume in autism. J Child Neurol 2001;16(6):421-4.

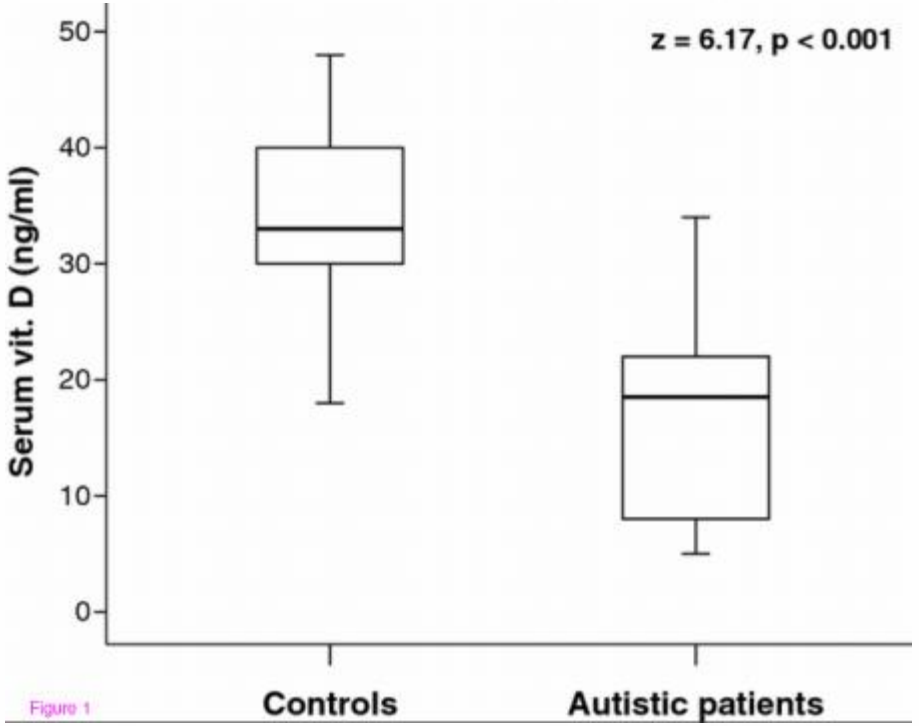
Vitamin D up-regulates glutathione

- Glutathione is the master antioxidant
- The primary route for the neurotoxicity of most heavy metals is through depletion of glutathione and subsequent generation of reactive oxygen and nitrogen species
- Glutathione also acts as a chelating agent to remove heavy metals

Garcion E, Wion-Barbot N, Montero-Menei CN, Berger F, Wion D. New clues about vitamin D functions in the nervous system. Trends Endocrinol Metab 2002;13(3):100-5.
Chen KB, Lin AM, Chiu TH. Systemic vitamin D3 attenuated oxidative injuries in the locus coeruleus of rat brain. Ann N Y Acad Sci 2003;993:313-24.
Lin AM, Chen KB, Chao PL. Antioxidative effect of vitamin D3 on zinc-induced oxidative stress in CNS. Ann N Y Acad Sci 2005;1053:319-29.
Valko M, Morris H, Cronin MT. Metals, toxicity and oxidative stress. Curr Med Chem 2005;12(10):1161-208.
Kern JK, Jones AM. Evidence of toxicity, oxidative stress, and neuronal insult in autism. J Toxicol Environ Health B Crit Rev 2006;9(6):485-99.

Autism and vitamin D

- Recently Dr. Mostafa and colleagues studied 50 autistic children.
- Compared to controls, autistic patients had much lower vitamin D levels despite reporting the same amount of sun exposure.



Gehan A Mostafa and Laila Y AL-Ayadhi Reduced serum concentrations of 25-hydroxy vitamin D in children with autism: Relation to autoimmunity. Journal of Neuroinflammation 2012, 9:201 doi:10.1186/1742-2094-9-201
Published: 17 August 2012

Autism and vitamin D

- Even more interestingly, they looked at anti-MAG levels and vitamin D levels.
- Anti-MAGs are antibodies associated with autism. Higher levels of anti-MAGs are associated with more severe autism.
- The higher your vitamin D level, the lower your anti-MAGs.

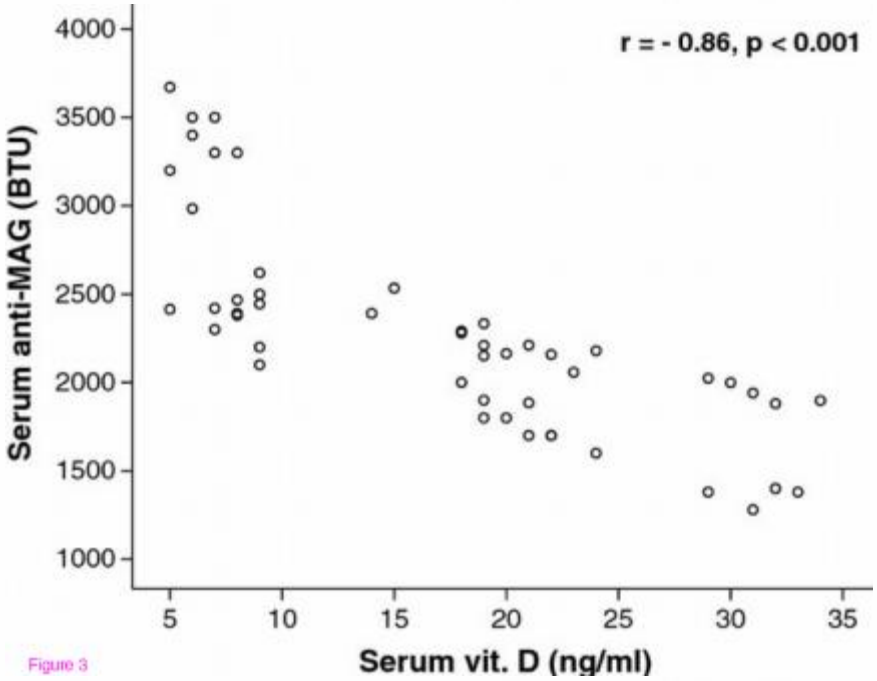


Figure 3

Gehan A Mostafa and Laila Y AL-Ayadhi Reduced serum concentrations of 25-hydroxy vitamin D in children with autism: Relation to autoimmunity. Journal of Neuroinflammation 2012, 9:201 doi:10.1186/1742-2094-9-201
Published: 17 August 2012

Autism and vitamin D

Autism and autoimmune diseases in mother

Table 4. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Autism Associated With Maternal Autoimmune Diseases, Asthma, and Allergies

Disorder	Crude OR (95% CI)	Adjusted OR (95% CI)*
Autoimmune diseases	1.3 (0.9-1.8)	1.2 (0.8-1.7)
Alopecia	1.4 (0.6-3.1)	1.4 (0.6-3.0)
Autoimmune thyroid disease	0.6 (0.3-1.3)	0.6 (0.3-1.2)
Psoriasis	2.9 (1.4-6.1)	2.7 (1.3-5.8)
Type 1 diabetes mellitus	2.9 (1.0-8.8)	2.6 (0.8-7.9)
Asthma	1.6 (1.2-2.1)	1.6 (1.2-2.2)
Allergies	1.5 (1.1-1.9)	1.5 (1.2-1.9)
Allergic rhinitis	1.6 (1.2-2.1)	1.6 (1.2-2.1)
Anaphylaxis	1.4 (0.7-2.9)	1.5 (0.7-3.1)
Atopic eczema	1.8 (1.0-3.3)	1.8 (1.0-3.4)
Conjunctivitis	1.2 (0.6-2.6)	1.2 (0.6-2.6)

*These ORs were adjusted for maternal age, maternal education, maternal race/ethnicity, and plurality.

Croen LA, et al. Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders: a case-control study. Arch Pediatr Adolesc Med. 2005 Feb;159(2):151-7.

Autism and vitamin D

Estrogen increases neural vitamin D but not so with testosterone

- Estrogen and testosterone appear to have strikingly different effects on vitamin D metabolism, which may explain the striking sex differences in autism.
- Estrogen increases neural calcitriol, but testosterone does not; such differences during brain development may mean that estrogen shields developing female brains from calcitriol deficiencies, while testosterone exposes male ones..

Epstein S, Schneider AE. Drug and hormone effects on vitamin D metabolism. In Feldman D., Pike JW, Glorieux FH, eds. Vitamin D. San Diego: Elsevier, 2005

Autism and vitamin D

CDC says autism is more common among African Americans

- Higher incidence rates among black children.
- CDC and others report black children have significantly higher rates of mild mental retardation (common in autism), socioeconomic factors could not explain the differences.
- Dealberto recently found Blacks with 2-3 fold increases

Yeargin-Allsopp M, Drews CD, Decoufle P, Murphy CC. Mild mental retardation in black and white children in metropolitan Atlanta: a case-control study. Am J Public Health 1995;85(3):324-8.
Dealberto MJ. Prevalence of autism according to maternal immigrant status and ethnic origin. Acta Psychiatr Scand. 2011 May;123(5):339-48.
Drews CD, Yeargin-Allsopp M, Decoufle P, Murphy CC. Variation in the influence of selected sociodemographic risk factors for mental retardation. Am J Public Health 1995;85(3):329-34.

Autism and vitamin D

Six studies found autism more common in Blacks

- The vitamin D theory predicts that autism would be more common in children born to darker-skinned mothers.
- Such studies are difficult as they raise sensitive social issues.
- At least six studies found a higher incidence of autism in black children, often appreciably higher.

Wing L. Childhood autism and social class: a question of selection? Br J Psychiatry. 1980 Nov;137:410-7.
Akinsola H Fryers T. A comparison of patterns of disability in severely mentally handicapped children of different ethnic origins. Psychol Med 1986;16(1):127-33
Gillberg C. et al. Infantile autism in children of immigrant parents. A population-based study from Göteborg, Sweden. Br J Psychiatry 1987;150():856-8
Goodman R, Richards H. Child and adolescent psychiatric presentations of second-generation Afro-Caribbeans in Britain. Br J Psychiatry. 1995 Sep;167(3):362-9.
Croen LA, Grether JK, Hoogstrate J, Selvin S. The changing prevalence of autism in California. J Autism Dev Disord 2002;32(3):207-15.
Hillman RE, Kanafani N, Takahashi TN, Miles JH. Prevalence of autism in Missouri: changing trends and the effect of a comprehensive state autism project. Mo Med 2000;97(5):159-63.

Autism and vitamin D

"A mysterious connection: autism and Minneapolis' Somali children" by Elizabeth Gorman, Minneapolis Post, Thursday, July 24, 2008

•"Short yellow school buses deliver children with special education needs to Minneapolis public schools every weekday morning. As students arrive at the elementary school where I work part time, I can't help but notice something about the autistic kids as they climb down the buses' steep steps: Almost all are Somali children."

Autism and vitamin D

- In Somalia (located right on the equator), autism has no name.
- However, Somali immigrants in Sweden call autism, the ‘Swedish disease’
- Somali immigrants in Minnesota call autism, the “American disease”

Autism and vitamin D

Dark-skinned immigrants in Europe have higher autism rates

- In Europe, autism rates are higher in children of dark-skinned immigrants.
- Gillberg et al reported that the incidence of autism in Goteborg, Sweden, for children born to the very dark-skinned women who emigrate from Uganda, was about 200 times higher than the general population.

Goodman R, Richards H. Child and adolescent psychiatric presentations of second-generation Afro-Caribbeans in Britain. Br J Psychiatry 1995;167(3):362-9.
Gillberg C, Schaumann H, Gillberg IC. Autism in immigrants: children born in Sweden to mothers born in Uganda. J Intellect Disabil Res 1995;39(Pt 2):141-4.

Autism and vitamin D

Black women severely deficient

- Recent studies of vitamin D deficiency during pregnancy showed striking racial inequities in maternal vitamin D levels.
- For example, Bodnar et al found that only 4% of black women and 37% of white women in the northern United States were vitamin D sufficient in early gestation (4-21 weeks).

Bodnar LM, Simhan HN, Powers RW, Frank MP, Cooperstein E, Roberts JM. High prevalence of vitamin D insufficiency in black and white pregnant women residing in the northern United States and their neonates. J Nutr 2007;137(2):447-52.

Autism and vitamin D

Prenatal vitamins do not prevent deficiency during pregnancy as prenatal vitamins have low amounts of D (400-600 IU).

- 45% of all pregnant black women, but only two percent of the pregnant white women, were severely deficient.
- Prenatal vitamins containing 400 IU of vitamin D (10 mcg) offered little protection for mother or infant, 90% of the women in the study reported taking them.

Bodnar LM, Simhan HN, Powers RW, Frank MP, Cooperstein E, Roberts JM. High prevalence of vitamin D insufficiency in black and white pregnant women residing in the northern United States and their neonates. J Nutr 2007;137(2):447-52.

Autism and vitamin D

Does vitamin D explain the five features of autism?

1.Predisposing genetic variations in some component of the vitamin D system may explain its high monozygotic twin concordance rates.

2.Environmentally determined variations in substrate levels during later life would explain its varying phenotype.

3.Low vitamin D levels would explain its increased prevalence in African Americans.

4.Falling vitamin D levels over the last 30 years explain its increasing incidence.

5.Discrepant effects of sex steroids on calcitriol metabolism would explain male preponderance.

Autism and vitamin D

The Vitamin D Theory

- of medical and social consequence
- parsimonious
- has a tenable mechanism of action
- subsumes numerous other theories
- implies simple prevention
- hints at a treatment effect
- is easily disprovable
- all components of a useful theory.

Prevalence continues to increase

- In 2006, Baird et al reported the prevalence of autism spectrum disorder in 56,000 British children was 1 in 86 children. CDC says 1 in 58. Recent South Korean study closer to one in 36.
- This is a calamitous epidemic

Baird G, Simonoff E, Pickles A, et al. Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). Lancet 2006;368(9531):210-5.

Expenses are immense

- Whatever its true incidence, the results are tragic and the cost immense.
- Families caring for autistic children are under more stress than those caring for a child with a fatal illness.
- The lifetime additive societal cost of autism is $3.2 million per case.

Bouma R, Schweitzer R. The impact of chronic childhood illness on family stress: a comparison between autism and cystic fibrosis. J Clin Psychol 1990;46(6):722-30.

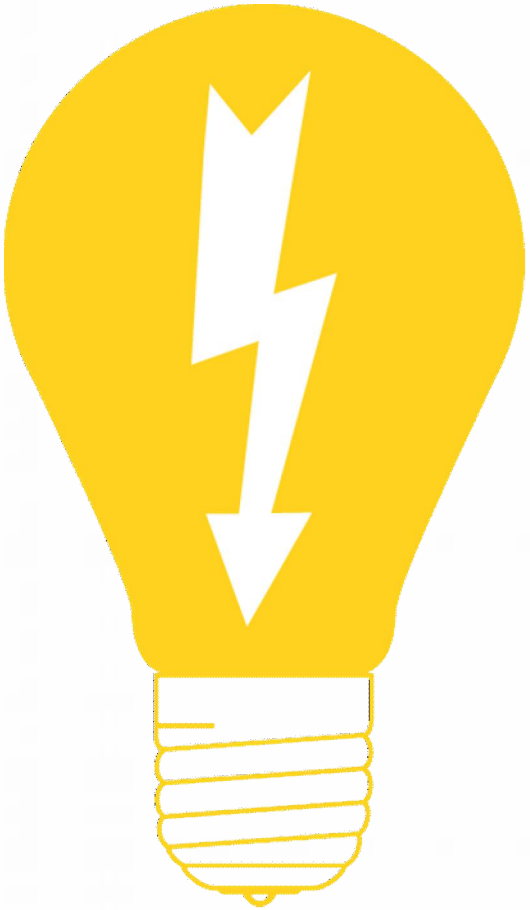
Ganz ML. The lifetime distribution of the incremental societal costs of autism. Arch Pediatr Adolesc Med 2007;161(4):343-9.

Autism and vitamin D

Iatrogenic epidemic

- Is epidemic caused by environmental trigger, such as virus or Tylenol?
- Is epidemic caused by impaired immune system secondary to uncompensated sun-avoidance advice?

Autism and vitamin D



Why has the theory not translated into action?

- Billions spent on autism research, money can't be wasted on vitamins.
- If it sounds too good to be true, it probably is? (too simple?)
- This is simply more "vitamin" nonsense?
- Iatrogenic implications are profound.

Autism and vitamin D

Vitamin D Council's action

- Funding UCSF study of high dose vitamin D in established autism (open pilot trial now; RCT if open trial positive).
- Vitamin D Council announced an autism clinic, beginning September 1st, 2011.
- Education to parent about vitamin D deficiency in autism
- Telephone calls, Skype sessions, severity rating scales, blood tests and vitamin D were all free
- So far about 30 children involved, all treated with 5,000 to 10,000 IU of D3/day
- Hopelessly subjective but my impressions are about 25% of children responded dramatically, about 50% responded significantly and 25% didn't respond.

Autism and vitamin D

- **My observations on predictors of response to vitamin D:**
  - Younger age
  - Distinct seasonality of symptoms (always respond)
  - Milder disease
  - Period of normal early infantile development
  - Did not have any of the known genetic causes of autism.

Check out our organization

Vitamin D Council
1241 Johnson Ave., #134
San Luis Obispo, CA 93401
805 439-1075

- Just Google “Vitamin D Council”
- Check out our new website at
- www.vitaminDcouncil.org