

REVIEW ARTICLE

Autism and Vitamin D

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SUMMARY

“I observe the physician with the same diligence as he the disease.”

John Donne
(1623)

Any theory of autism's etiology must take into account its strong genetic basis, but also explain how genetics interacts with the environment to produce autism's unusual epidemiology. Activated vitamin D, calcitriol, is a potent pleiotropic neurosteroid hormone with critical roles in mammalian brain development. Severe vitamin D deficiency during gestation severely impairs that development. Calcitriol's physiology is unique among the steroid hormones because normal steroid feedback inhibition does not regulate neural levels of calcitriol; instead, first-order mass action kinetics does so. The apparent dramatic increase in the prevalence of autism over the last 20 years corresponds with increasing medical advice to avoid the sun, advice that may have dramatically lowered brain calcitriol levels. Severe maternal vitamin D deficiency leads to rat pups with increased brain size and enlarged ventricles, abnormalities similar to those found in autistic children. Children with the Williams Syndrome, who can have greatly elevated calcitriol levels in early infancy, usually have phenotypes that are the opposite of autism. Estrogen and testosterone have very different effects on calcitriol's metabolism, differences that may explain the striking male/female sex ratios in autism. Calcitriol down-regulates production of inflammatory cytokines in the brain, which have been associated with autism. Vitamin D deficiency impairs glutathione metabolism, which may explain the link between autism and oxidative stress, as well as autism and mercury accumulation. Consumption of vitamin D containing fish during pregnancy reduces autistic symptoms in children. From the limited data available, it appears autism is more common in poleward latitudes. Autism is more common in dark-skinned persons and severe maternal vitamin D deficiency is exceptionally common, especially among African Americans, regardless of prenatal vitamin use. Conclusion: The recent increases in the incidence of autism may be iatrogenic, brought on by widespread medical advice to avoid sunshine. Several types of studies could easily test the theory.

INTRODUCTION

Pervasive developmental disorders like autism encompass a spectrum of complex neurodevelopmental abnormalities that appear in early childhood, impairing social interaction and communication skills. Individuals with autism typically show poor verbal and non-verbal communication, reciprocal interpersonal unresponsiveness, and exhibit stereotyped behaviors and interests. Autism affects afflicted individuals differently and to varying degrees.

Arguably, the five most striking epidemiological aspects of autism are its monozygotic (40%-90%) versus dizygotic (0% -10%) twin concordance rates,¹ widely varying phenotypic expression even among monozygotic twins,² striking male: female ratio (~4:1), increased prevalence in African Americans (see below), and apparent rapid increase in incidence rates over the last 20 years (see below). Whatever its genetic roots, and they are strong, autism hardly follows classic Mendelian inheritance.

When a disease with strong genetic roots displays such peculiar epidemiology, it is reasonable to seek an explanation among environmental genetic contributors. While the predisposing autistic lesion is genetic, the above epidemiological observations indicate the genotype is predispositional, not predestinational. Something in the environment, prenatally or postnatally, is affecting expression of the genotype, probably through gene-environment interactions.

The environment directly influences environmental genetic contributors and they, in turn, directly influence the genome, the neurosteroid hormones are a good example. That is, something in the environment may be altering concentrations of a neurosteroid, which, in turn, signals, or fails to signal, expression of the neural proteins that steroid regulates.

Furthermore, if current claims of increasing prevalence over the last twenty years (**Figure 1**)³ are due to actual increases in incidence and not just diagnostic substitution⁴ or increased diagnostic sensitivity⁵—and this seems increasingly likely^{6,7}—then it is reasonable to search for neurosteroids that may have changed over the same time autism has increased. Furthermore, if a neurosteroid exists that significantly affects brain development, whose levels have decreased during the same time that autism has increased, whose levels vary with human behavior, that are increased by estrogen but not testosterone, and that are much lower

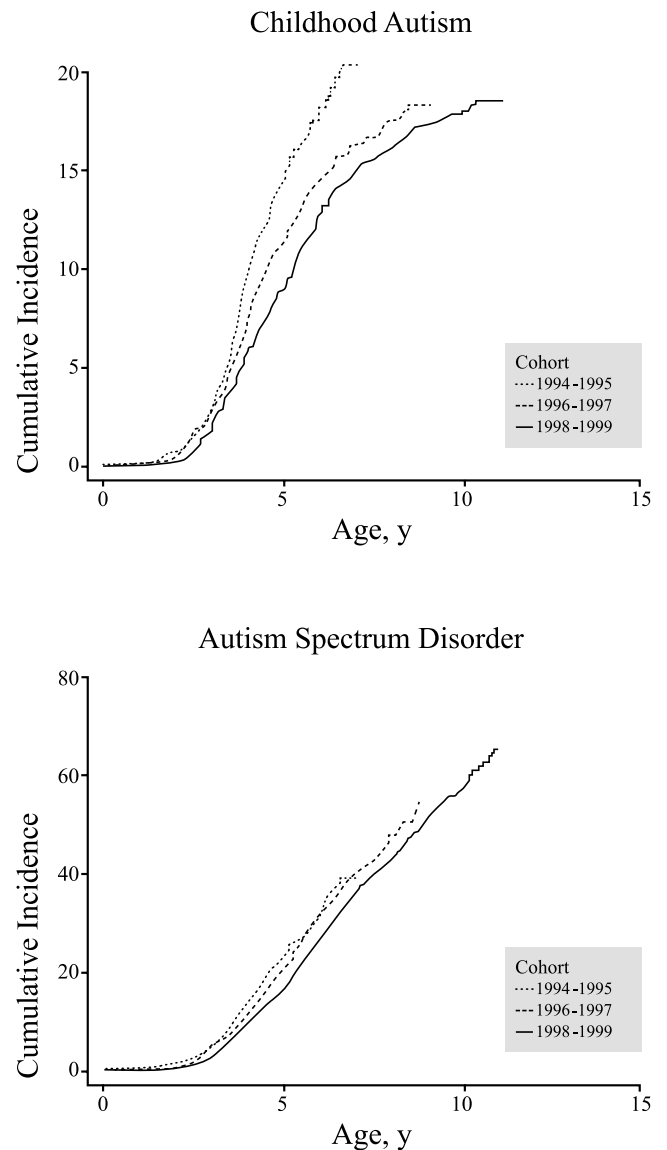


Figure 1. Time trend of autism spectrum disorder and childhood autism among children born in Denmark, 1990 to 1999, and reported 1995 to 2004: cumulative incidence proportion (per 10,000) for each 2-year analytic birth cohort for each disorder. (Reproduced with permission of American Medical Association, Atladottir *et al*, 2007)

in African Americans than in Whites, then surely that neurosteroid may be autism's environmental genetic contributor.

In a recent article discussing autism and genetics, Herbert *et al* warned that “‘environmentally responsive genes,’ not specifically associated with the nervous system, but potentially associated with systemic changes in autism, have not hitherto received sufficient attention in autism genetics investigations.”⁸ (p. 671) Although not among their final candidate genes, they could not have described any better the genes that

code for components of the steroid hormone system whose product is the systemic pleiotropic seco-steroid, calcitriol,⁹ or activated vitamin D.

Of the neurosteroids involved in brain development, calcitriol is unique, the least understood, but, arguably, one of the most profound. McGrath *et al* alerted us to this fact in 2001, pointing out that vitamin D is “the neglected neurosteroid.”¹⁰ In the same paper, they pointed out that calcitriol is a potent up-regulator of nerve growth factor and that the vitamin D receptor (VDR) is found in a wide variety of brain tissue very early in embryogenesis. These two facts alone led them to conclude “hypovitaminosis D should be examined in more detail as a candidate risk factor for neurodevelopmental ... disorders.” (p. 571)

In 2006, Kalueff *et al* went further, suggesting vitamin D offers “neuroprotection, antiepileptic effects, immunomodulation, possible interplay with several brain neurotransmitter system and hormones, as well as regulation of behaviors.”¹¹ (p. 363) In 2007, Kalueff and Tuohimaa reviewed the pleiotropic and nootropic properties of vitamin D in even more detail and concluded the data “stress the importance of prenatal, neonatal, and postnatal vitamin D supplementation for normal brain functioning.”¹² (p. 16)

Candidate Genes

If true, then candidate genes for autism should include all those that code for the various proteins involved in the metabolism, catabolism, transport, or binding of calcitriol. For example, expression and nuclear activation of the VDR is necessary for calcitriol’s effects. Several DNA sequence variations, VDR polymorphisms, occur frequently in the population.¹³ The high frequency with which VDR polymorphisms occur in humans make them candidates to explain variation in autism’s risk, but such research is inconclusive because it is not known how such polymorphisms vary in their functionality.¹⁴

A pilot study of VDR receptor mutations using a robotically enhanced multiplexed scanning method did not detect mutational VDR abnormalities in 24 autistic individuals but they did not assess for VDR polymorphisms.¹⁵ VDR polymorphisms are not associated with schizophrenia, but a highly significant association ($P = 0.002$) exists between one VDR polymorphism and larger head size.¹⁶ Furthermore,

mean head circumference is larger,¹⁷ and rates of macrocephaly higher¹⁸, in autism.

Children with pseudo-vitamin D deficiency rickets, an inborn error of metabolism involving the defective manufacture of calcitriol, have low levels of calcitriol. The disease is, nevertheless, responsive to massive doses of calcitriol’s precursor, vitamin D.¹⁹ That is, despite the genetic lesion, vitamin D overcomes the defect, probably via mass action (see below), and treats the rickets. The disorder has never been specifically studied in relationship to autism, but afflicted children have hypotonia, decreased activity, developmental motor delay, listlessness, failure to thrive, and other autistic markers similar to common vitamin D deficient rickets (see below). Another genetic lesion in the vitamin D system, hereditary calcitriol-resistant rickets, caused by mutations in the VDR, presents with similar autistic markers and occasionally responds to massive doses of vitamin D.²⁰

Even more interesting, children with the Williams syndrome,²¹ some of whom have greatly elevated calcitriol levels for several months in early infancy,^{22,23} often present in later life with remarkable sociability, overfriendliness, empathy, and willingness to initiate social interaction,²⁴ strikingly the opposite phenotype of autism.

Vitamin D

Perhaps because the term, vitamin D, contains the word “vitamin,” many people wrongly assume it is a vitamin. Instead, vitamin D is the only known substrate for a steroid hormone system that—until recent sun-avoidance campaigns—always began in the skin, not in the mouth. Ninety percent of human vitamin D stores come from skin production, not oral intake.^{25,26} Large populations of pregnant women putting small amounts in their mouths, instead of generating large amounts in their skins, is novel to human brain development.

Obviously, for such a change to be compensatory, oral intake must be adequate to make up for diminished skin production. But the skin’s production of vitamin D is rapid and robust, easily exceeding recognized dietary sources by an order of magnitude.²⁷ For example, when fair-skinned adults sunbathe in the summer (one, full-body, minimal erythral dose of ultraviolet light), for 20 minutes, they deliver about 20,000 units (0.5 mg) of vitamin D to their systemic circulation within 24 hours.²⁸ A pregnant woman would have to

drink two hundred glasses of milk or take 50 prenatal multivitamins to do the same.

Equally novel to human experience is recent advice that humans should avoid the sun, advice widely and successfully promulgated by medical and governmental bodies since the late 1980s. The increase in autism appears to have begun at the same time.²⁹ Indeed, most of the graphs showing rising prevalence rates of autism over the last 20 years (**Figure 2** next page) would be strikingly similar to graphs showing the rising rates of programs promulgating sun-avoidance.

No longitudinal studies of vitamin D levels exist, that is, we do not know how effective sun-avoidance campaigns have been in lowering vitamin D levels. However, if one assumes that at least some Americans follow their government's and their physician's advice, then a subgroup must have had declining vitamin D levels over time—unless they took enough supplemental vitamin D to make up for lack of sun-exposure, but few people take the thousands of daily units needed to do that.

Certainly, there is evidence prominent medical organizations targeted sun-avoidance campaigns to include infants, children, and young women.³⁰ For example, in 1989, around the time autism rates began to rise, the American Medical Association's (AMA) Council on Scientific Affairs warned about the dangers of sun-exposure and advised mothers to, "keep infants out of the sun as much as possible." (p. 383).³¹ In 1999, the American Academy of Pediatrics went further, advising mothers to always keep infants out of direct sunlight, use sun-protective clothes, sunblock, and make sure children's activities in general minimize sunlight exposure.³² Furthermore, quite inexplicably, they reported there was "no evidence" that "rigorous sun protection" would affect vitamin D levels. (p. 330) By 2002, the Centers for Disease Control (CDC) reported this medical advice was successful: "protection from sun exposure is reported for a high proportion of children."³³ (p. 360)

Apparently, no effort was made to counteract the vitamin D deficiency such sun-protection would predictably induce. For example, when the AMA's Council on Scientific Affairs—cited above—warned about the dangers of sunlight, they did not even mention that sunlight triggers the formation of vitamin D. Furthermore, the Food and Nutrition Board's (FNB) vitamin D recommendations for young women, pregnant women, infants, and children did not change during the decades of sun-avoidance advice,

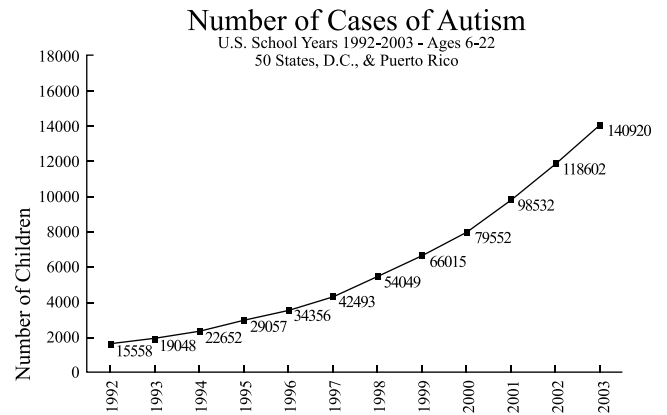


Figure 2. Time trend of autism prevalence for the 50 states and Puerto Rico. (Reproduced with permission, Fighting Autism, <http://www.fightingautism.org/idea/autism.php>, accessed 5/8/07)

200 units (5 mcg) per day for all infants, children, pregnant women, and young adults—regardless of weight.³⁴ That is, they did and do recommend the same daily 200 units for 5 pound infants as they do for 250 pound pregnant women! Unfortunately, in 2003, the American Academy of Pediatrics cut their longstanding 400 units per day recommendation for children in half,³⁵ apparently simply to comply with FNB recommendations, despite their earlier advice that children should assiduously avoid sunlight.

The unique steroid

Among the body's steroid hormone systems, the vitamin D system is unique. Unlike other steroids, the body cannot make calcitriol *de novo* from cholesterol to meet its needs. All of the body's calcitriol must come from vitamin D, either made in the skin or ingested orally. During skin production, UVB radiation photo-isomerizes a 7-dehydro-cholesterol molecule in the skin to produce pre-vitamin D and eventually the prehormone, vitamin D. Oral ingestion completely bypasses steroidogenesis in the skin, presenting the identical prehormone to the liver for an initial hydroxylation to produce 25-hydroxy-vitamin D [25(OH)D]. An additional hydroxylation in the kidneys generates 1,25(OH)₂D (calcitriol) for its endocrine function in maintaining the calcium economy. However, an identical hydroxylation of 25(OH)D in the tissues bypasses the kidneys and produces autonomous calcitriol for the cell's autocrine needs. In its autocrine, and perhaps paracrine, role, calcitriol discharges pleiotropic steroid functions

in multiple tissues, if—and only if—enough of its 25(OH)D substrate is available.³⁶

Most importantly, and totally unlike any other steroid hormone, substrate concentrations are absolutely rate limiting for calcitriol production.³⁷ The enzyme that first hydroxylates vitamin D in the liver and the enzyme in tissue that subsequently hydroxylates 25(OH)D to form calcitriol, both operate below their respective Michaelis-Menten constants throughout the full range of their normal substrate concentrations, i.e. the reactions follow first-order mass action kinetics. That means tissue levels of calcitriol during brain development directly depend on maternal 25(OH)D blood levels, which, in turn, directly depend on the amount of vitamin D the mother makes in her skin or puts in her mouth. That is, the rate-limiting step for the production of this neurosteroid is unique; concentrations of brain calcitriol literally depend on human behavior, be it the step into the sun, the step to the supplements, the step into the shade, or the step to the sunscreen. This is not only unique for a steroid hormone, it is fundamental to understanding vitamin D's pharmacology.

Calcitriol and the Developing Brain

Like all steroid hormones, calcitriol binds to a member of the nuclear hormone receptor superfamily where the complex then acts as a molecular switch to signal its target genes; about 0.5% of the human genome (200 genes) are primary targets of calcitriol and the list is steadily growing. (Kalueff *et al*, 2006) If and only if adequate substrate is available, most organs in the human body produce their own calcitriol, have a VDR, regulate their own needs in an autocrine manner, and thus do not depend on hematogenous endocrine supply of calcitriol from the kidney.³⁸ The brain is such an organ and the developing brain is heavily invested in calcitriol from very early gestation.³⁹ Both the VDR and the enzyme necessary to make calcitriol are present in a wide-variety of human brain tissues.⁴⁰

Serum calcitriol levels increase by 50-100% by the second trimester and by 100% during the third trimester, probably of placental origin.⁴¹ The enzyme necessary to make calcitriol in human placenta and decidua increases by several orders of magnitude starting in very early gestation.⁴² Expression of the VDR in the developing mammalian brain rises steadily beginning several weeks after conception where calcitriol induces

the expression of nerve growth factor and stimulates neuronal cell growth.⁴³ For a review of vitamin D's multiple effects on brain development and function, see Brachet *et al*.⁴⁴

In a series of recent animal experiments, an Australian group found severe maternal vitamin D deficiency in rats produce offspring with aberrant apoptosis and abnormal cell proliferation,⁴⁵ reduced expression of a number of genes involved in neuronal structure,⁴⁶ hyperlocomotion,⁴⁷ and subtle alterations in both learning and memory.⁴⁸ When vitamin D deficiency is restricted to late gestation only, such deficiencies are sufficient to disrupt adult brain functioning.⁴⁹

Recently, a French group found developmental vitamin D deficiency dysregulates 36 proteins 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.⁵⁰ 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 (Eyles *et al*, 2005), anatomical abnormalities similar to those found in autistic children.^{51,52}

Dysregulated immune responses are associated with both autism and vitamin D deficiency. For example, autistic individuals have T cell abnormalities and cytokine excesses⁵³ that show a striking similarity to the immune functions affected by vitamin D.⁵⁴ Animal evidence indicates some vitamin D deficiency induced brain damage may be malleable, that is, vitamin D may partially reverse the brain damage, if given early enough.⁵⁵ These studies offer hope that sunlight or exogenous vitamin D, especially in young autistic children, may have a treatment effect.

Both the brain and the blood of autistic individuals show evidence of ongoing chronic inflammation and oxidative stress.(Herbert *et al*.) That is, the disease process is probably increasingly destructive. Further hope for a nootropic effect rests in calcitriol's powerful anti-inflammatory properties. Its administration down-regulates production of inflammatory cytokines in the brain, which have consistently been associated with cognitive impairment.⁵⁶ Furthermore, calcitriol is remarkably neuroprotective by stimulating neurotrophin release, reducing toxic calcium levels in the brain, inhibiting the production of nitrous oxide,

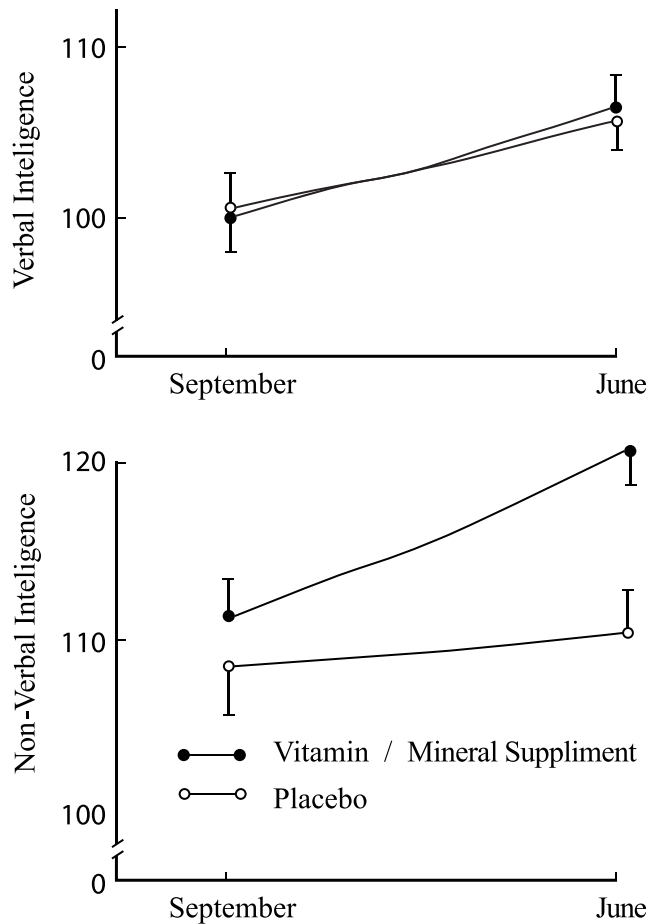


Figure 3. Influence of vitamin/mineral supplementation versus placebo on verbal and non-verbal intelligence of 60 English schoolchildren, $p < 0.01$. (Reprinted with permission from Elsevier, Benton and Roberts, 1988)

and by its immunomodulating properties—especially in reducing inflammatory cytokines⁵⁷—and by increasing brain glutathione.⁵⁸

This last function of vitamin D, increasing cellular levels of glutathione,⁵⁹ may explain the purported link between heavy metals, oxidative stress, and autism. For example, calcitriol attenuates iron-induced⁶⁰ and zinc-induced⁶¹ oxidative injuries in rat brain. The primary route for the neurotoxicity of most heavy metals is through depletion of glutathione and subsequent generation of reactive oxygen and nitrogen species.⁶² Besides its function as a master antioxidant, glutathione acts as a chelating agent to remove heavy metals.⁶³

Kern and Jones review several studies indicating autistic individuals have difficulty excreting heavy metals, especially mercury. If calcitriol deficient brains are unable to utilize glutathione properly, and thus unable to remove heavy metals, they may be

oxidatively damaged by heavy metal loads normal children easily excrete. That is, the mercury in Thiomerosol vaccines may have injured vitamin D deficient brains while vitamin D sufficient children would have easily chelated and excreted it. It bears repeating that the amount of calcitriol in the brain directly depends on how much vitamin D is made in the skin or put in the mouth.

Vitamin D and Autism

Many autistic children are also intellectually impaired. Although no studies associating vitamin D levels with cognitive abilities exist for children, several studies have found significant associations in adults.^{64,65,66} Another group found a high incidence of vitamin D deficiency among 337 individuals with intellectual disabilities in residential care.⁶⁷ The obvious explanation for these findings is that cognitively impaired individuals do not go outdoors as often as higher functioning individuals and thus have lower vitamin D levels. However, two groups found the association in adults after controlling for outdoor activities,^{68,69} making it possible that vitamin D deficiency *per se* impairs cognition.

Further evidence that vitamin D may favorably affect mentation comes from a series of randomized controlled interventional studies evaluating the effect of vitamin D containing multivitamins on childhood cognition. (For a review, see Schoenthaler *et al.*⁷⁰) All 14 studies they reference, including their own, reported small (1-2%) to modest (5-6%) improvements, most of them significant, usually in nonverbal IQ; the first study was reported in the *Lancet* in 1988 (**Figure 3**).⁷¹ More interestingly, most studies showed no effect on the majority of children but very significant effects (15% gains) in about 20% of the children, perhaps the vitamin D deficient subgroup.

Although no birth cohort studies exist that examined vitamin D supplementation during pregnancy or childhood and later development of autism, 2,000 units a day during the first year of life was associated with a four-fold reduction in the later development of schizophrenia in males (Risk ratio=0.23), but not in females.⁷² This is even more interesting when one remembers that males are four times more likely to develop autism than females.

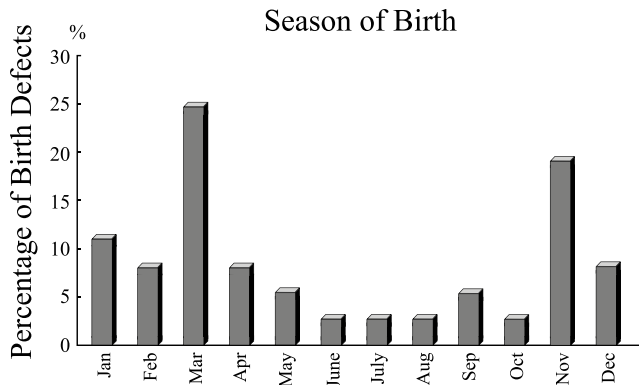


Figure 4. Proportion of birth dates per month of the passive subgroup of 131 children with autism using Wing’s Autistic Disorder Interview Checklist, social functioning classification (Reprinted with permission, Taylor and Francis, Stevens *et al*, 2000.)

In fact, estrogen and testosterone appear to have quite different effects on vitamin D metabolism, which may explain the striking sex differences in autism. For example, Epstein and Schneider report, “the majority of studies have found a positive effect of estrogen on calcitriol levels.”⁷³ However, after reviewing similar studies on testosterone, they say, “it is unlikely that testosterone is a major controlling factor in vitamin D metabolism.” (p. 1261) If 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.

A placebo controlled three-month study of 20 autistic children found multivitamins with even low doses of vitamin D (150 units or 3.75 mcg) significantly improved sleep and gastrointestinal problems.⁷⁴ Furthermore, a recent small controlled trial reported substantial benefits for omega-3 fatty acids in autism.⁷⁵ Such long chain fatty acids dissociate calcitriol from the vitamin D binding protein, do so well within the physiological concentrations of these fats, and should increase the amount free brain calcitriol.⁷⁶

The vitamin D theory of autism predicts that consumption of vitamin D-rich fish during pregnancy would favorably affect fetal development and improve the offspring’s mentation although several factors confound such studies. Some ocean going fatty fish, such as salmon, herring, and sardines, are rich sources of vitamin D but other fish are not. Furthermore, some fish contain mercury, which may impair mentation. Fatty fish, fish liver oils, and fish body oils also all contain omega-3 fats, which favorably affect mentation.

As mentioned above, fish oils dissociate vitamin D from its binding protein, raising free calcitriol levels. Finally, fish liver oils such as cod liver oil—but not fish or fish body oils—contains substantial, variable, but potentially toxic amounts of vitamin A, which antagonizes the action of vitamin D.^{77,78}

Consistent with the vitamin D theory of autism, higher fish consumption during pregnancy was associated with better infant cognition with the greatest effect for infants whose mothers consumed the most fish.⁷⁹ Very recently, low maternal seafood consumption was associated with infants who had an increased risk of lower verbal IQs and suboptimal outcomes for prosocial behaviors, fine motor, communication, and social development,⁸⁰ outcomes eerily similar to autism.

Furthermore, the group of women who received advice to consume sea fish during pregnancy produced infants with higher birth weights, and had fewer preterm births.⁸¹ Small for gestational age pregnancies and preterm births are associated with autism (see below). In reviewing studies of fish and fish oil on pregnancy outcomes, Rogers *et al* found fish consumption has a positive effect on fetal growth but fish oil consumption has little or no effect on fetal growth.⁸² The authors concluded, “It may be that some constituent of fish other than omega-3 fatty acids is responsible for the association of fish intake with birth weight.” (p. 490). Consistent with that constituent being vitamin D, are studies finding low maternal vitamin D intakes are associated with low birth weights and intrauterine growth retardation.^{83,84}

If vitamin D played a role in autism, the disorder should be less common at more sunny equatorial latitudes, at least before modern sun-avoidance. In an unpublished manuscript, Grant and Soles found a strong positive association between latitude and prevalence of autism in international cohorts born before 1985, but not after.⁸⁵ Recent CDC prevalence data from 14 states showed the state with the highest prevalence, New Jersey, was the second most northern; Alabama, with the lowest prevalence, was the most southern of the 14 states surveyed.⁸⁶ Studies on season-of-birth and autism are contradictory, as would be expected if calcitriol deficiencies can impair brain development during either gestation or in early childhood. However, at least seven studies found excessive autism births in the winter, especially March, (**Figure 4**) when vitamin D levels are at their lowest.⁸⁷ (See Stevens *et al* for a review)

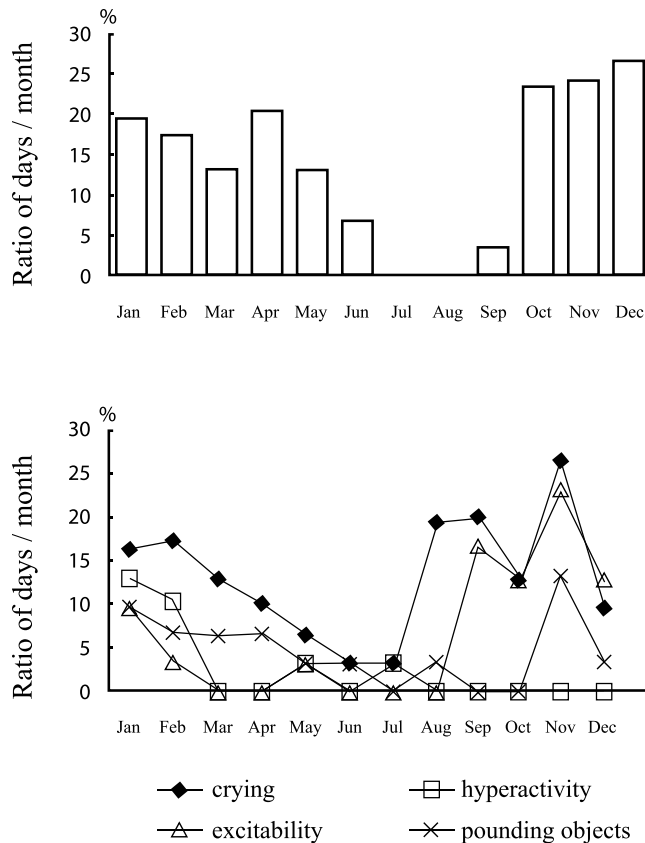


Figure 5. Ratio of days with sleep problems (top) and ratio of days with behavioral problems (bottom) in each month for a 15-year-old Japanese male with autism (Reprinted with permission, Blackwell Publishing, Hayashi, 2001)

If vitamin D has any treatment effect, autistic children may improve if they move to latitudes that are more equatorial, increase their sun-exposure, or change to vitamin D-rich diets. Consistent with the theory, not all children diagnosed with autism retain that diagnosis in adulthood and a few improve, either spontaneously, or after the myriad of various treatment programs available. (Herbert *et al.*) Naturally, the abundant anecdotal reports of improvement generate skepticism that the initial diagnosis was correct, an obvious possibility. However, if vitamin D was involved in autism, then symptoms might improve in the summer, when vitamin D levels are the highest. A case study reported dramatic improvements in both sleep and behavioral problems in the summer (**Figure 5**).⁸⁸ Furthermore, significant improvements in autistic behaviors occurred after a summer camp program that included swimming, hiking, boating, and other outdoor activities that would increase brain levels of calcitriol.⁸⁹

If maternal or postnatal vitamin D deficiency caused autism, then parents who rigorously complied with medical sun-avoidance advice would be more likely to have children with autism. Parents from higher socioeconomic strata are more likely to apply sunscreen to their children,⁹⁰ as are parents with a higher education.⁹¹ Although numerous studies, especially early ones, linked higher social class with autism, socioeconomic bias in case ascertainment confounds such associations. However, a recent study found significant positive associations between mother's education, family income, and autism and it was not clear that ascertainment bias could explain all the findings.⁹²

If postnatal vitamin D deficiency caused autism, then rachitic children would be at greater risk for the disease. To the best of my knowledge, no studies have looked at the neuropsychological profiles of children with vitamin D deficient rickets, although such children are more likely to be hypotonic, display decreased activity, and have developmental motor delay.⁹³ Hypotonia is common in children with autism,⁹⁴ as is decreased activity,⁹⁵ and developmental motor delays are the rule.⁹⁶

Vitamin D deficiency in childhood is associated with an increased risk of respiratory infections.⁹⁷ The vitamin D theory of autism predicts autistic children would be more prone to respiratory infections. A recent study found that children who went on to develop autism were not prone to increased infection in the first two years of life, before the children were diagnosed with autism.⁹⁸ Other studies have found an increased incidence of ear and other infections in children with autism.^{99,100,101} Furthermore, a Japanese study found a strong positive correlation ($r=0.92$) between the prevalence of infantile autism in one-year birth cohorts and the total number of children hospitalized for pneumonia and bronchiolitis during that cohort's birth year.¹⁰²

The vitamin D theory predicts medications that lower vitamin D levels, if taken during pregnancy, would increase the risk for autism. While little is known about the drugs that interfere with vitamin D metabolism, sodium valproate lowers vitamin D levels¹⁰³ and the drug has been associated with autism.¹⁰⁴ Furthermore, seizures are common in autism¹⁰⁵ and calcitriol decreases the seizure threshold.¹⁰⁶ Furthermore, a controlled pilot study found vitamin D reduced the incidence of seizures in intractable epileptic patients.¹⁰⁷

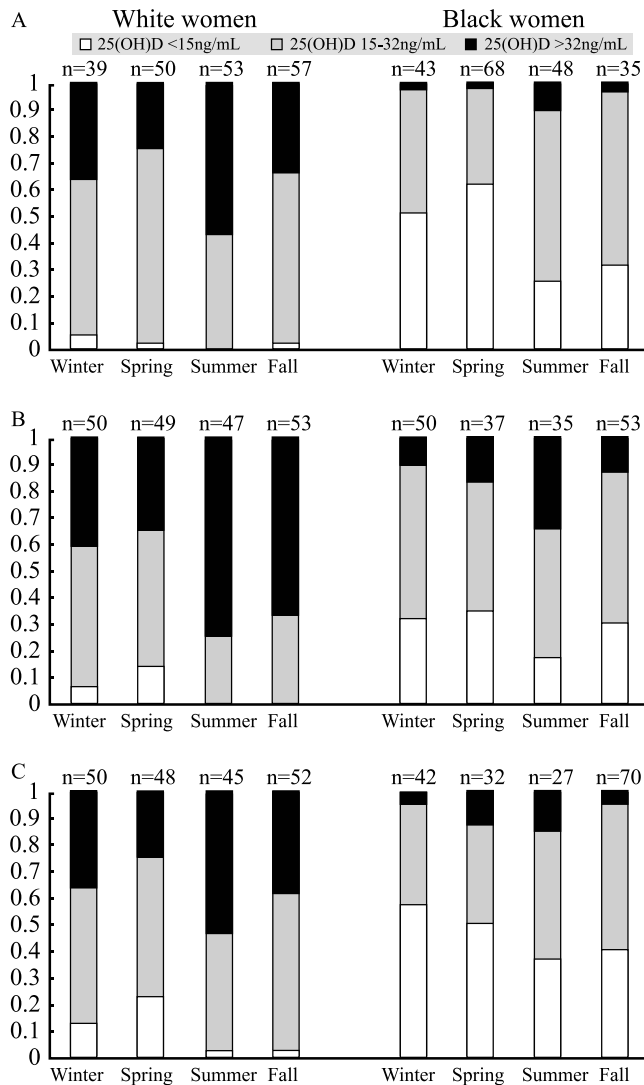


Figure 6. Prevalence of vitamin D deficiency [25(OH)D <15 ng/ml], insufficiency [25(OH)D 15–32 ng/ml], and sufficiency [25(OH)D >32 ng/ml] among 200 white and 200 black women at 4–21 wk gestation (A), at term (B), and in their neonates (C). (Reproduced with permission, American Society of Nutrition, Bodnar *et al*, 2007)

Finally, if postnatal—and not just prenatal—vitamin D deficiency causes autism, then it should be rare before weaning in formula fed babies (infant formula contains significant amounts of vitamin D when calculated on a per pound basis), and rare in breast-fed babies supplemented with vitamin D. However, it should rapidly progress after weaning, unless the child takes vitamin D supplements or drinks significant amounts of vitamin D fortified milk. Although, to the best of my knowledge, such infant dietary studies do not exist, a recent prospective longitudinal study of 87 infants, some at high risk for autism and others not, could not find any statistically significant

neurocognitive differences between the two groups at 6 months.¹⁰⁸ That is, the children who later developed autism appeared normal at 6 months. However, around the age of weaning, the babies who developed autism first showed signs, with rapid additional impairments occurring between 14 and 24 months, the age many children begin drinking sodas and juice instead of vitamin D enriched formula or milk.¹⁰⁹

Vitamin D and Skin Color

Vitamin D deficiency discriminates based on skin color, or more precisely, on the amount of melanin in the skin, which is an effective and ever-present sunscreen. The vitamin D theory predicts that neurodevelopmental disorders would be more common in children born to darker-skinned mothers. Such studies are difficult as they raise sensitive social issues although three of four recent U.S. studies found a higher incidence of autism in black children, sometimes appreciably higher. (Bhasin and Schendel)^{110,111,112} Furthermore, in Europe, autism rates are higher in children of dark-skinned immigrants.¹¹³ Gillberg *et al* reported that the incidence of autism in Goteborg, Sweden, for children born to mothers who emigrated from Uganda, was 15%, about 200 times higher than in the general population.¹¹⁴ (See Newschaffer *et al*¹¹⁵ for a review of autism's epidemiology.)

Several studies indicate black mothers are more likely to give birth to infants who weigh less and die shortly after birth^{116,117,118} and low birth weight is a clear risk factor for autism.¹¹⁹ Black babies also have lower Apgar scores.¹²⁰ Low Apgar scores are associated with both autism¹²¹ and poor prenatal vitamin D intake.¹²² The CDC and others report black children have significantly higher rates of mild mental retardation than white children do and socioeconomic factors could not explain all the differences.^{123,124} (For a review of such studies, see Yeargin-Allsopp *et al*, 1995.)

The incidence of preeclampsia significantly decreased in white women during the summer months, but not in black women, suggesting vitamin D has an effect in such disorders, as long as skin color is light enough to rapidly generate vitamin D from incidental sun-exposure.¹²⁵ Furthermore, multivitamins containing vitamin D reduced the risk of preterm and low birth weight infants.^{126,127} Twelve hundred units (30 mcg) per day of vitamin D in the third trimester significantly increased birth weights while 600,000

units (15 mg) given in both the 7th and 8th month of pregnancy increased birth weights even more.¹²⁸

Recent studies of vitamin D deficiency during pregnancy showed striking racial inequities in maternal vitamin D levels. 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).¹²⁹ (**Figure 6** previous page) That is, 96% of pregnant black women and 63% of pregnant white women did not have adequate 25(OH)D blood levels. Their infants fared little better and showed the same racial inequity. Furthermore, 45% of the pregnant black women, but only two percent of the pregnant white women, were severely deficient. Prenatal vitamins containing vitamin D (400 units or 10 mcg) offered little protection for mother or infant, 90% of the women in the study reported taking them.

Unless infants receive direct supplementation or drink vitamin D enriched formula, infant vitamin D levels are remarkably low with African American infants at highest risk; 78% of unsupplemented breastfed Iowa infants had levels less than 11 ng/ml during winter.¹³⁰ [For those who wonder how vitamin D could be important for brain development, given its very low levels in breast milk, Hollis and Wagner discovered that breast milk is always a rich source of vitamin D—enough to maintain healthy levels in infants—as long as the lactating mothers took 4,000 units (100 mcg) per day.¹³¹]

In 2002, Nesby-O'Dell *et al* found almost 50% of young black women of childbearing age had vitamin D levels lower than 15 ng/ml and 12 percent had levels less than 10 ng/ml, compared to ½ of 1 percent of white women.¹³² While it is unknown how those levels compare to levels obtained in the animal studies reviewed above, it may be that white children have a huge developmental advantage over black children, an advantage that begins immediately after conception—one that has nothing to do with innate ability and everything to do with environment.

DISCUSSION

The theory that vitamin D deficiency contributes to autism is of medical and social consequence, has a tenable mechanism of action, subsumes several other theories, implies simple prevention, and is easily disprovable—all components of a useful theory. A predisposing genetic lesion in some component of

the vitamin D system, a genetic predisposition the first-order mass action kinetics of calcitriol might be able to salvage, would explain its high monozygotic twin concordance rates and varying neural levels of calcitriol during later life would explain its varying phenotype. Low vitamin D levels may explain its increased prevalence in African Americans, and falling levels over the last 20 years explain its exploding incidence. Discrepant effects of sex steroids on calcitriol metabolism may explain its male preponderance. Several types of studies could easily address the theory.

For example, is there is an association between sun-exposure during pregnancy or childhood, and autism? Are parents of autistic children more likely to practice sun-avoidance for their children than controls? Is dietary vitamin D intake associated with autism? Does rickets predispose children to develop autism? Do autistic symptoms improve in the summer? Are 25(OH)D levels of mothers who had autistic children—available from stored sera—different from controls? Are there current latitudinal variations in autism? (Latitudinal studies would require similar and strict diagnostic criteria be used at all sites, an effort currently under way by the CDC)

Does ultraviolet irradiation, either natural or artificial, improve autistic symptoms? Is the severity of autistic symptoms associated with 25(OH)D levels? Do adequate doses of vitamin D reduce markers of oxidative stress? Do they affect immunological markers? Do they restore normal glutathione metabolism. Do they promote heavy metal excretion? Do autistic symptoms improve when vitamin D deficiency is treated? What 25(OH)D levels, if any, are associated with maximal mental functioning?

The critical question is “What is an ideal 25-hydroxy-vitamin D level?” The answer must be, “In regard to what?” Levels needed to prevent rickets and osteomalacia (10-20 ng/ml) are lower than those that dramatically suppress parathyroid hormone levels (20-30 ng/ml)¹³³ In turn, those levels are lower than levels needed to optimize intestinal calcium absorption (34 ng/ml).¹³⁴ In turn, Lappe *et al* recently found levels of around 40 ng/ml was associated with a significant reduction in the incidence of internal cancers.¹³⁵ Finally, neuromuscular performance in 4100 older patients steadily improved as 25(OH)D levels increased and maximum performance was associated with levels around 50 ng/ml.¹³⁶ Levels for optimal brain development and function are unknown.

Given what we do know, adequate 25(OH)D levels are now thought to be somewhere above 40 and probably closer 50 ng/ml.¹³⁷ 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 50-70 ng/ml—levels obtained by only a small fraction of modern humans.¹³⁸

Dr. Cannell heads the non-profit educational group,

CONCLUSION

Baird *et al* recently reported the prevalence of autism spectrum disorder in 56,000 British children was 1 in 88 children, numbers suggesting a calamitous epidemic.¹³⁹ It seems less and less likely that this entirely represents a change in diagnostic sensitivity or diagnostic substitution, but a real and dramatic increase in incidence. 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 cystic fibrosis, a fatal illness.¹⁴⁰ The lifetime additive societal cost of autism is \$3.2 million per case.¹⁴¹ However, the epidemiology of autism suggests its genetics confer predisposition, not predestination. That same epidemiology suggests that vitamin D deficiency during pregnancy and childhood may contribute to autism. If that is true, and to the extent it is true, the disease is iatrogenic, brought on by medical advice to avoid the sun, advice that failed to compensate for the consequent “epidemic of vitamin D deficiency.”¹⁴² Several types of studies could easily test this theory.

‘The Vitamin D Council’.

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DECLARATIONS OF INTEREST

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