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# Autism and vitamin D

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**Summary** Any theory of autism's etiology must take into account its strong genetic basis while explaining its striking epidemiology. The apparent increase in the prevalence of autism over the last 20 years corresponds with increasing medical advice to avoid the sun, advice that has probably lowered vitamin D levels and would theoretically greatly lower activated vitamin D (calcitriol) levels in developing brains. Animal data has repeatedly shown that severe vitamin D deficiency during gestation dysregulates dozens of proteins involved in brain development and 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. Children with vitamin D deficient rickets have several autistic markers that apparently disappear with high-dose vitamin D treatment. 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, cytokines that have been associated with autism. Consumption of vitamin D containing fish during pregnancy reduces autistic symptoms in offspring. Autism is more common in areas of impaired UVB penetration such as poleward latitudes, urban areas, areas with high air pollution, and areas of high precipitation. Autism is more common in dark-skinned persons and severe maternal vitamin D deficiency is exceptionally common the dark-skinned. *Conclusion*: simple Gaussian distributions of the enzyme that activates neural calcitriol combined with widespread gestational and/or early childhood vitamin D deficiency may explain both the genetics and epidemiology of autism. If so, much of the disease is iatrogenic, brought on by medical advice to avoid the sun. Several types of studies could easily test the theory.


''I observe the physician with the same diligence as he the disease.'' John Donne (1623)

## Introduction

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 prevalence 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

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responsive genes. While the predisposing autistic lesion is genetic, the above epidemiological observations indicate something in the environment, prenatally or postnatally, is affecting expression of the genotype, probably through gene—environment interactions. Such interactions have not hirtherto ''received sufficient attention in autism genetics investigations'' [3] (p. 671).

The environment directly influences environmental responsive genes and they, in turn, directly influence the genome, the neurosteroid hormones are a good example. That is, while neurosteroids are under genetic organization, something in the environment may lower neurosteroid concentrations, which, in turn, fails to signal fully the genetic expression of the neural proteins that steroid regulates.

Furthermore, if current claims of autism's increasing prevalence over the last 20 years [4] (Fig. 1) are due to actual increases in incidence and not entirely due to diagnostic substitution [5] or increased diagnostic sensitivity [6] — and this seems increasingly likely [7,8] — then it is reasonable to search for neurosteroids that have declined over the same time autism has increased. Furthermore, if a neurosteroid exists that significantly affects brain development, whose brain levels vary with human behavior, are increased by estrogen but not testosterone, and whose levels show racial variations similar to the racial variations in autism prevalence (see below), then surely that neurosteroid may be autism's environmental genetic contributor.

Of the neurosteroids involved in brain development, activated vitamin D (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'' [9]. 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. They were the first to conclude that ''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 [10] (p. 363). In 2007, Kalueff and Tuohimaa reviewed the pleiotropic and nootropic properties of vitamin D in even more detail and concluded extant data ''stress the importance of prenatal, neonatal, and postnatal vitamin D supplementation for normal brain functioning'' [11] (p. 16).

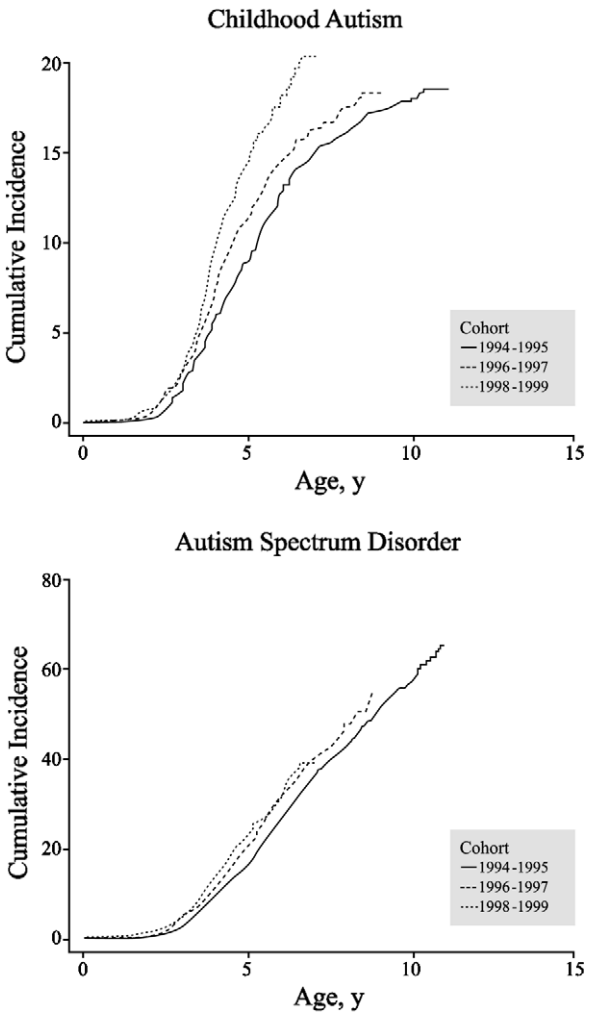


**Figure 1** Time trend of autism spectrum disorder and childhood autism among children born in Denmark, 1990—1999, and reported 1995—2004: cumulative incidence proportion (per 10,000) for each 2-year analytic birth cohort for each disorder. (Reproduced with permission of American Medical Association,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

## Candidate genes

If true, then candidate genes for autism should include all genes that code for the various proteins involved in the metabolism, catabolism, transport, or binding of calcitriol. Pseudo-vitamin D deficiency rickets, an inborn error of metabolism, involves the defective genetic production of CYP27B1, the enzyme that activates vitamin D. The disease is, nevertheless, responsive to high-doses of calcitriol's precursor, vitamin D [12]. 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 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). Even more interesting, children with the Williams syndrome [13], some of whom have greatly elevated calcitriol levels for several months in early infancy [14,15], often present in later life with remarkable sociability, overfriendliness, empathy, and willingness to initiate social interaction [16], strikingly the opposite phenotype of autism.

Thus, CYP27B1 is an enzyme of interest in autism. Due to the unique pharmacokinetics of calcitriol (see below), simple quantitative, not necessarily qualitative, variations of CYP27B1 will interact with variations in its environmentally determined substrate, 25-hydroxy-vitamin D [25(OH)D], resulting neural concentrations that are under genetic organization but that vary widely with human behavior.

## Vitamin D

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 [10]. 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 [17,18]. Large populations of pregnant women putting small amounts in their mouths — in the form of prenatal vitamins — 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 make up for diminished skin production. But the skin's production of vitamin D is remarkably rapid and extraordinarily robust, easily exceeding recognized dietary sources by an order of magnitude [19]. For example, when fair-skinned adults sunbathe in the summer (one, full-body, minimal erythemal dose of ultraviolet light), for 20 min, they input about 20,000 units of vitamin D to their systemic circulation within 24 h [20]. A pregnant woman would have to drink 200 glasses of milk (100 IU per glass) or take 50 prenatal multivitamins (400 IU per tablet) to input a similar amount.

Equally novel to human brain development is medical advice over the last several decades that humans should completely avoid sunlight, advice widely and successfully promulgated by medical and governmental bodies since the late 1980s. For example, in 1989 the American Medical Association's 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'' [21] (p. 383). The increase in autism appears to have begun at the same time [22]. Indeed, most of the graphs showing rising prevalence rates of autism over the last 20 years (Fig. 2) would be strikingly similar to graphs showing the rising rates of programs promulgating sun-avoidance. Of course, thousands of other environmental changes occurred during this same time and such associations, on their own, mean little.

Among the body's steroid hormone systems, the vitamin D system is unique. Unlike any other steroid hormone, substrate concentrations are absolutely rate-limiting for tissue calcitriol production [23]. The enzymes that first hydroxylate vitamin D in the liver and CYP27B1 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 not only depend on the amount of CYP27B1 available, they are directly dependent on 25(OH)D levels. That is, human

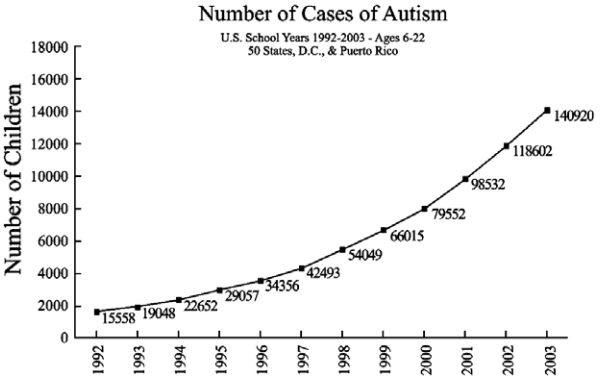


**Figure 2** Time trend of autism prevalence for the 50 states and Puerto Rico. (Reproduced with permission, Fighting Autism, http://www.fightingautism.org/idea/autism.php, accessed 05.08.07.)

behavior, be it the step into the sun, the step to the supplements, the step into the shade, or the step to the sunscreen, determine brain calcitriol levels. This is not only extraordinary for a steroid hormone, it is fundamental to understanding vitamin D's unique pharmacology.

## Calcitriol and the developing brain

In a series of recent animal experiments, an Australian group found severe maternal vitamin D deficiency in rats produces offspring with aberrant apoptosis and abnormal cell proliferation [24], reduced expression of a number of genes involved in neuronal structure [25], hyperlocomotion [26], and subtle alterations in both learning and memory [27]. When vitamin D deficiency is restricted to late gestation only, such deficiencies are sufficient to disrupt adult brain functioning [28].

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 [29]. 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 [30], anatomical abnormalities similar to those found in autism [31,32]. For a review of vitamin D's multiple effects on brain development and function, see Brachet et al. [33].

## Inflammation and heavy metals

Dysregulated immune responses are associated with both autism and vitamin D deficiency. For example, autistic individuals have T cell abnormalities and cytokine excesses [34] that show a striking similarity to the immune functions affected by vitamin D [35]. 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 [36].

Both the brain and the blood of autistic individuals show evidence of ongoing chronic inflammation and oxidative stress [34]. 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 [37]. Furthermore, calcitriol is remarkably neuroprotective by stimulating neurotropin release, reducing toxic calcium levels in the brain, inhibiting the production of nitrous oxide, and by its immunomodulating properties — especially in reducing inflammatory cytokines [38] — and by increasing brain glutathione [39].

This last function of vitamin D, increasing cellular levels of glutathione [40], may explain the purported link between heavy metals, oxidative stress, and autism. For example, calcitriol attenuates iron-induced [41] and zinc-induced [42] 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 [43]. Besides its function as a master antioxidant, glutathione acts as a chelating agent to remove heavy metals, including mercury [44].

## Sexual differences and vitamin D

Estrogen and testosterone appear to have strikingly 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'' [45], but after reviewing studies on testosterone, they found no similar effects (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.

## Vitamin D intake and autism

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 [46]. 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 normal childhood cognition (for a review, see Schoenthaler et al. [47]). 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 [48]

(Fig. 3). More interestingly, most studies showed no effect on most children but very significant effects (15% gains) in about 20% of the children, perhaps the vitamin D deficient subgroup.

Furthermore, the vitamin D theory of autism predicts that consumption of vitamin D-rich fish during pregnancy would improve the offspring's mentation. Consistent with the theory, higher fish consumption during pregnancy was associated with better infant cognition with the greatest effect for infants whose mothers consumed the most fish [49]. 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 [50], outcomes eerily similar to autism.

If postnatal, and not just prenatal, vitamin D deficiency can cause autism, then cases should appear around weaning in formula fed babies as infant formula contains significant amounts of vitamin D on a per pound basis. Although vitamin D/autism infant dietary studies do not exist, 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.[51] 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 some autistic children deteriorate, and the age many children begin drinking juice instead of vitamin D enriched formula [52].

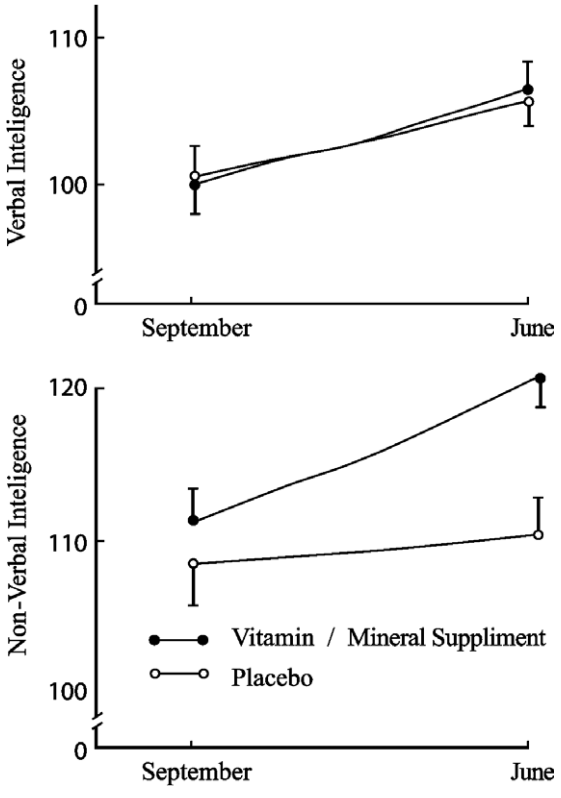


**Figure 3** Effects of vitamin D containing multivitamins versus placebo on verbal and non-verbal intelligence of 60 English schoolchildren, $p < 0.01$. (Reprinted with permission from Elsevier, Benton and Roberts, 1988.)

## UVB light and autism

If the theory is valid, anything that increases the amount of UVB light in the atmosphere should decrease the incidence of autism. For example, the disorder should be less common at more sunny equatorial latitudes, at least before modern sun-avoidance. Grant and Soles found a strong positive association between latitude and prevalence of autism in international cohorts born before 1985 [53]. 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 [54].

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, Stevens et al. reviewed the literature and found that at least seven studies found excessive autism births in the winter, especially March, (Fig. 4) when vitamin D levels are at their lowest [55]. A clear urban versus rural distribution occurs with autism, similar to that which exists for rickets, with significantly lower rates in rural areas [56]. The recent

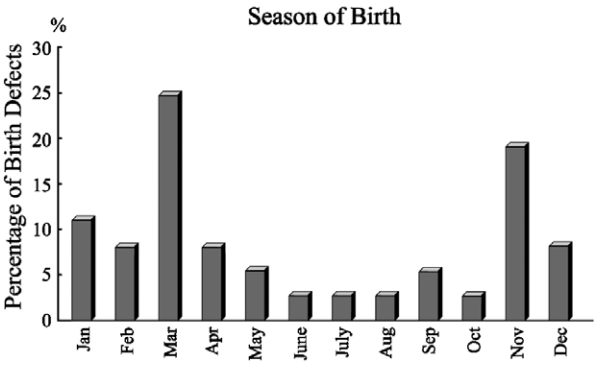


**Figure 4** Proportion of birth dates per month of the passive subgroup of 131 children with autism using Wing's Autistic Disorder Interview Checklist, social functioning classification. (Reprinted with permission, Taylor and Francis, Stevens et al., 2000.)

finding of strong positive associations between precipitation rates and autism [57] (where the authors used precipitation as a proxy for television viewing) also support the vitamin D theory as clouds and rain impair UVB atmospheric penetration. The report that the Amish of Pennsylvania, who have a rural manual farming lifestyle without electricity or gasoline powered farming equipment, have very low rates of autism [57] is also consistent with the theory. Furthermore, air pollution, which has also been associated with autism [58], dramatically lowers 25(OH)D levels [59].

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 [60] (Fig. 5). 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 [61]. 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 [62], as are parents with a higher education [63]. 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 their findings [64].

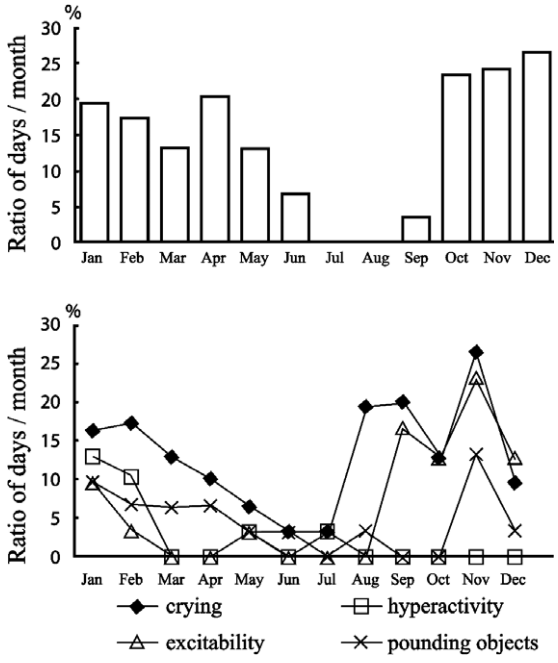


**Figure 5** Ratio of days with sleep problems (top) and ratio of days with behavioral problems (bottom) in each month for a 15-year-old Japanese male with autism. (Reprinted with permission, Blackwell Publishing, Hayashi, 2001.)

## Autism, rickets, medication, and seizures

If postnatal vitamin D deficiency caused autism, then autism would be common in vitamin D deficient rickets, although physicians treat rachitic children promptly with high-doses of vitamin D. To the best of my knowledge, no studies have looked at neuropsychological profiles of rachitic children, before or after treatment, although rachitic children are likely to be hypotonic, display decreased activity, and have developmental motor delays before treatment [65]. Interestingly, hypotonia is common in children with autism [66], as is decreased activity [67], and developmental motor delays are the rule [68].

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 is one of the few drugs that lower vitamin D levels [69] and one of the few gestational drugs that lead to autism [70]. Finally, seizures are common in autism [71] and calcitriol significantly increases the seizure threshold [72]. Furthermore, a controlled study found vitamin D reduced the incidence of seizures [73].

## Vitamin D and skin color

Vitamin D deficiency discriminates based on the amount of cutaneous melanin, a proficient 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 US studies found a higher incidence of autism in black children, sometimes appreciably higher [64,74–76]. Furthermore, in Europe, autism rates are higher in children of dark-skinned immigrants [77]. 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 15%, about 200 times higher than the general population [78].

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) [79] (Fig. 6). That is, 96% of pregnant black women and 63% of pregnant white women did not have adequate 25(OH)D blood levels. Their infants faired 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 400 IU of vitamin D (10 mcg) offered little protection for mother or infant, 90% of the women in the study reported taking them.

Nor is autism the only neurodevelopmental disease with higher incidence rates among black children. 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 [80,81]. While it is unknown how human 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.

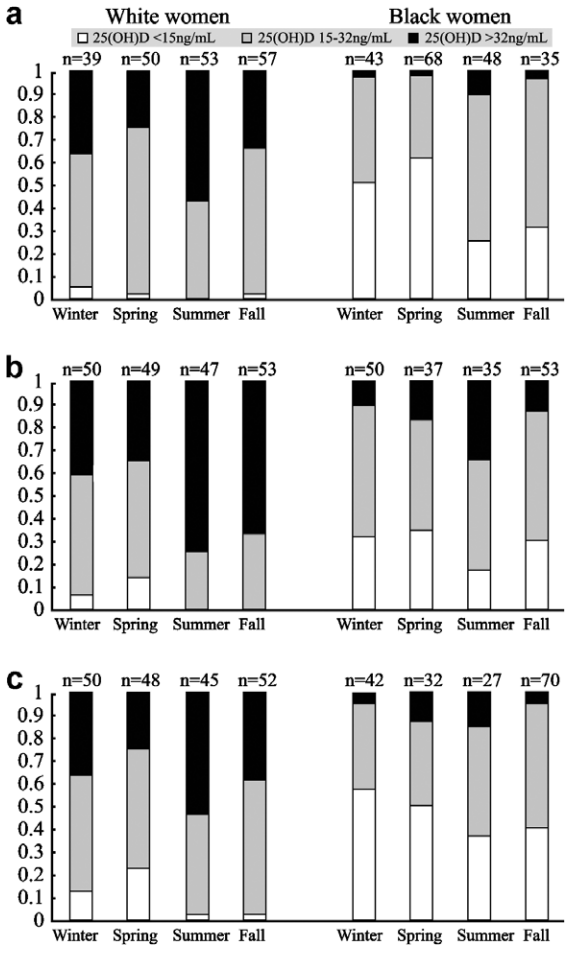


**Figure 6** Prevalence of vitamin D deficiency [25(OH)D < 15 ng/ml], insufficiency [25(OH)D 15—32 ng/ml], and sufficiency [25(OH)D > 32 ng/ml] among 200 white and 200 black women at 4—21 week gestation (a), at term (b), and in their neonates (c). (Reproduced with permission, American Society of Nutrition,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

## Discussion

The theory that vitamin D deficiency is a major cause of autism is of medical and social consequence, parsimonious, has a tenable mechanism of action, subsumes numerous other theories, implies simple prevention, hints at a widely available and inexpensive treatment effect, and is easily disprovable — all components of a useful theory. Predisposing genetic variations in some component of the vitamin D system — perhaps as simple as Gaussian variations in CYP27B1 — 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 environmentally determined variations in substrate levels during later life would explain its varying phenotype. Low vitamin D levels in the dark-skinned may explain its increased prevalence in African Americans, and falling vitamin D levels over the last 20 years explain its increasing incidence. Discrepant effects of sex steroids on calcitriol metabolism may explain male preponderance. Several types of studies could address the theory.

For example, is there is an association between sun-exposure during pregnancy or early 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? 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 latitudinal variations in autism? (Latitudinal studies would need to be controlled for race and 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? Does vitamin D supplementation with doses adequate to

achieve ideal 25(OH)D blood levels improve autistic symptoms?

The critical question is ''What is an ideal 25-hydroxy-vitamin D level?'' Given what science currently knows, adequate 25(OH)D levels are now thought to be somewhere above 30 ng/ml [82] and probably closer 40 ng/ml [83], and requires the daily ingestion of thousands — not hundreds — units to achieve [84]. 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 [85]. A simple risk/benefit analysis would seem to indicate that the wise course of action is to maintain natural vitamin D levels in pregnant women, autistic children (and the rest of us) until science completes its work.

## Conclusion

Baird et al. recently reported the prevalence of autism spectrum disorder in 56,000 British children was 1 in 86 children, numbers suggesting a calamitous epidemic [86]. It seems less and less likely that this entirely represents a change in diagnostic sensitivity or diagnostic substitution, but a real 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 a fatal illness [87]. The lifetime additive societal cost of autism is $3.2 million per case [88]. However, the epidemiology of autism suggests its genetics are predispositional, not predestinational. That same epidemiology suggests that current epidemic of autism may be caused by gestational and early childhood vitamin D deficiency, an iatrogenic deficiency brought on by medical advice to avoid the sun, advice that tragically failed to compensate for the consequent ''epidemic of vitamin D deficiency''[89].

## Declaration of Interest

Dr. Cannell heads the non-profit educational organization, the Vitamin D Council.

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