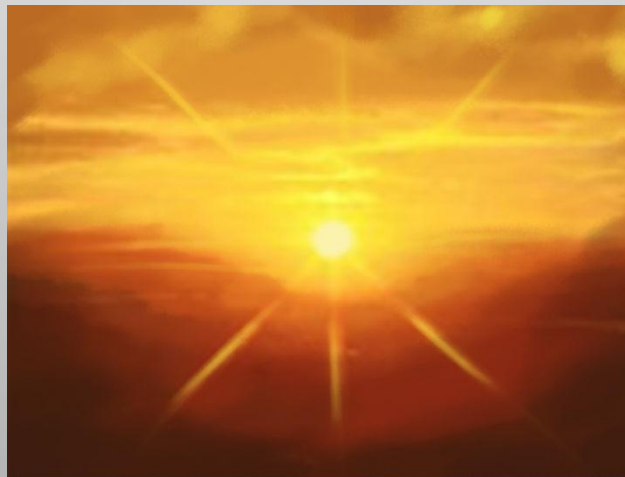


Vitamin D: Implications for Alaskan Children

Presentation to the Alaska Native Health Board
February 4th, 2013



Representative Paul Seaton

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Australia

Language Impairment

Maternal Serum Vitamin D Levels During Pregnancy and Offspring Neurocognitive Development

Andrew J. O. Whitehouse, Barbara J. Holt, Michael Serralha, Patrick G. Holt, Merci
M. H. Kusel and Prue H. Hart

Pediatrics 2012;129:485; originally published online February 13, 2012;
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Maternal Serum Vitamin D Levels During Pregnancy and Offspring Neurocognitive Development

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KEY WORDS

vitamin D, neurocognitive, language impairment, behavioral problems, emotional problems, Raine study

ABBREVIATIONS

95% CI—95% confidence interval

CBCL—Child Behavior Checklist

OR—odds ratio

PPVT-R—Peabody Picture Vocabulary Test—Revised

Ms Kusel and Dr Hart contributed equally to this work.

Drs Whitehouse, Kusel, and Hart developed the hypotheses; Ms Holt, Mr Serralha, Dr Holt, and Dr Hart analyzed serum samples for 25(OH)-vitamin D concentrations; and Dr Whitehouse conducted the statistical analyses and wrote the main drafts of the manuscript. All authors contributed to the interpretation and discussion of the results and other sections of the manuscript.

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WHAT'S KNOWN ON THIS SUBJECT: Vitamin D levels in the general population have decreased considerably over the past decade. The implications of maternal vitamin D insufficiency during pregnancy for offspring neurocognitive development remain unclear.

WHAT THIS STUDY ADDS: Studying a large sample and using a prospective longitudinal design, this study demonstrates a link between maternal vitamin D insufficiency during pregnancy and offspring language impairment. There was no association with childhood behavioral or emotional problems.

abstract

OBJECTIVE: To determine the association between maternal serum 25(OH)-vitamin D concentrations during a critical window of fetal neurodevelopment and behavioral, emotional, and language outcomes of offspring.

METHODS: Serum 25(OH)-vitamin D concentrations of 743 Caucasian women in Perth, Western Australia (32°S) were measured at 18 weeks pregnancy and grouped into quartiles. Offspring behavior was measured with the Child Behavior Checklist at 2, 5, 8, 10, 14, and 17 years of age (n range = 412–652). Receptive language was assessed with the Peabody Picture Vocabulary Test—Revised at ages 5 (n = 534) and 10 (n = 474) years. Raw scores were converted to standardized scores, incorporating cutoffs for clinically significant levels of difficulty.

RESULTS: χ^2 analyses revealed no significant associations between maternal 25(OH)-vitamin D serum quartiles and offspring behavioral/emotional problems at any age. In contrast, there were significant linear trends between quartiles of maternal vitamin D levels and language impairment at 5 and 10 years of age. Multivariate regression analyses, incorporating a range of confounding variables, found that the risk of women with vitamin D insufficiency (≤ 46 nmol/L) during pregnancy having a child with clinically significant language difficulties was increased close to twofold compared with women with vitamin D levels > 70 nmol/L.

CONCLUSIONS: Maternal vitamin D insufficiency during pregnancy is significantly associated with offspring language impairment. Maternal vitamin D supplementation during pregnancy may reduce the risk of developmental language difficulties among their children. *Pediatrics* 2012;129:485–493

Figure 1 data format changed and notes added by Rep. Seaton From Whitehouse, A. (2012) Maternal Serum Vitamin D Levels during pregnancy and offspring neurocognitive development. *Pediatrics* 485-493

Proportion (%) of offspring with language impairment

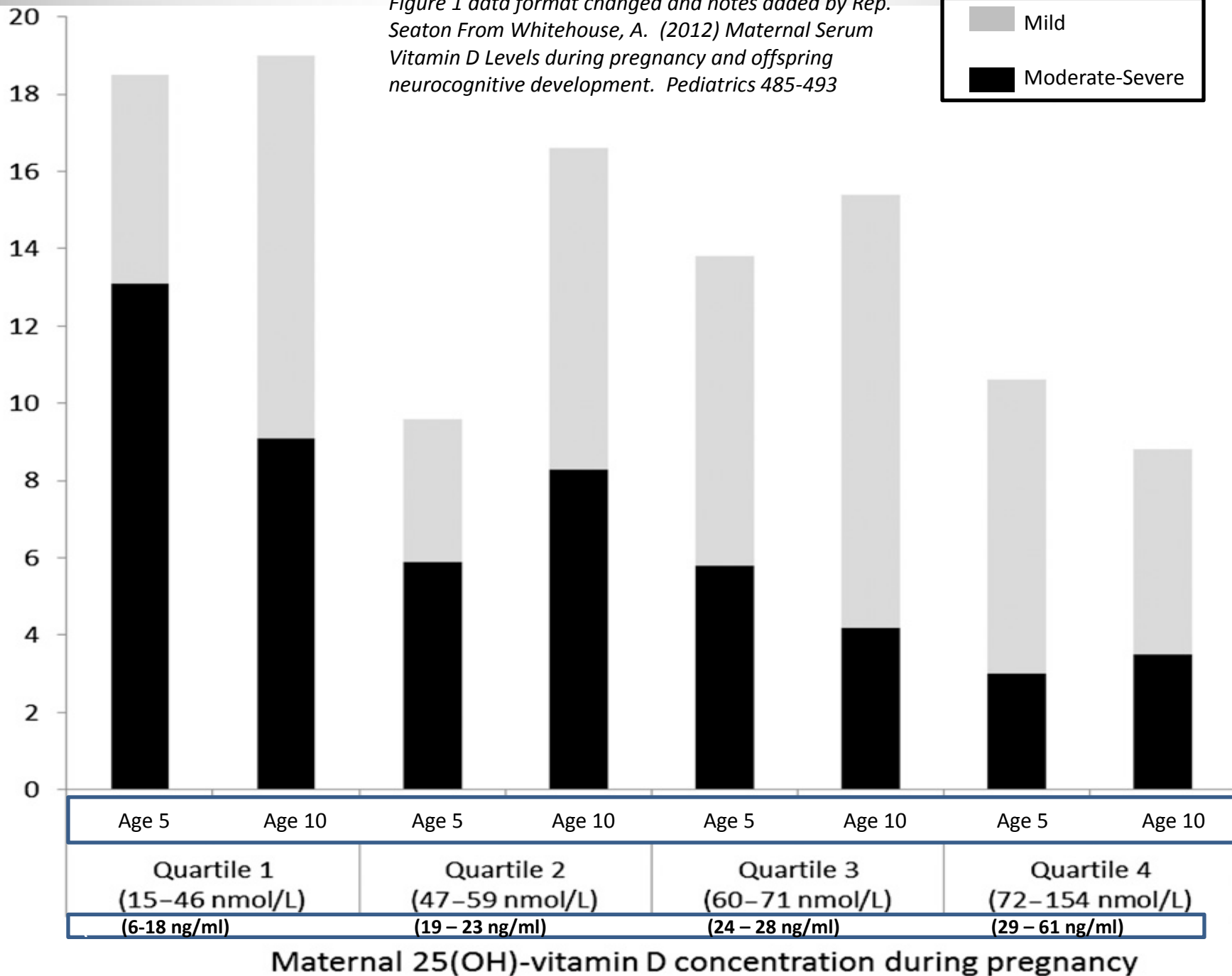
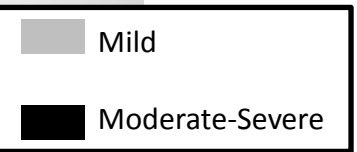


Figure 1 data format changed and notes added by Rep. Seaton From Whitehouse, A. (2012) Maternal Serum Vitamin D Levels during pregnancy and offspring neurocognitive development. Pediatrics 485-493

Moderate-Severe

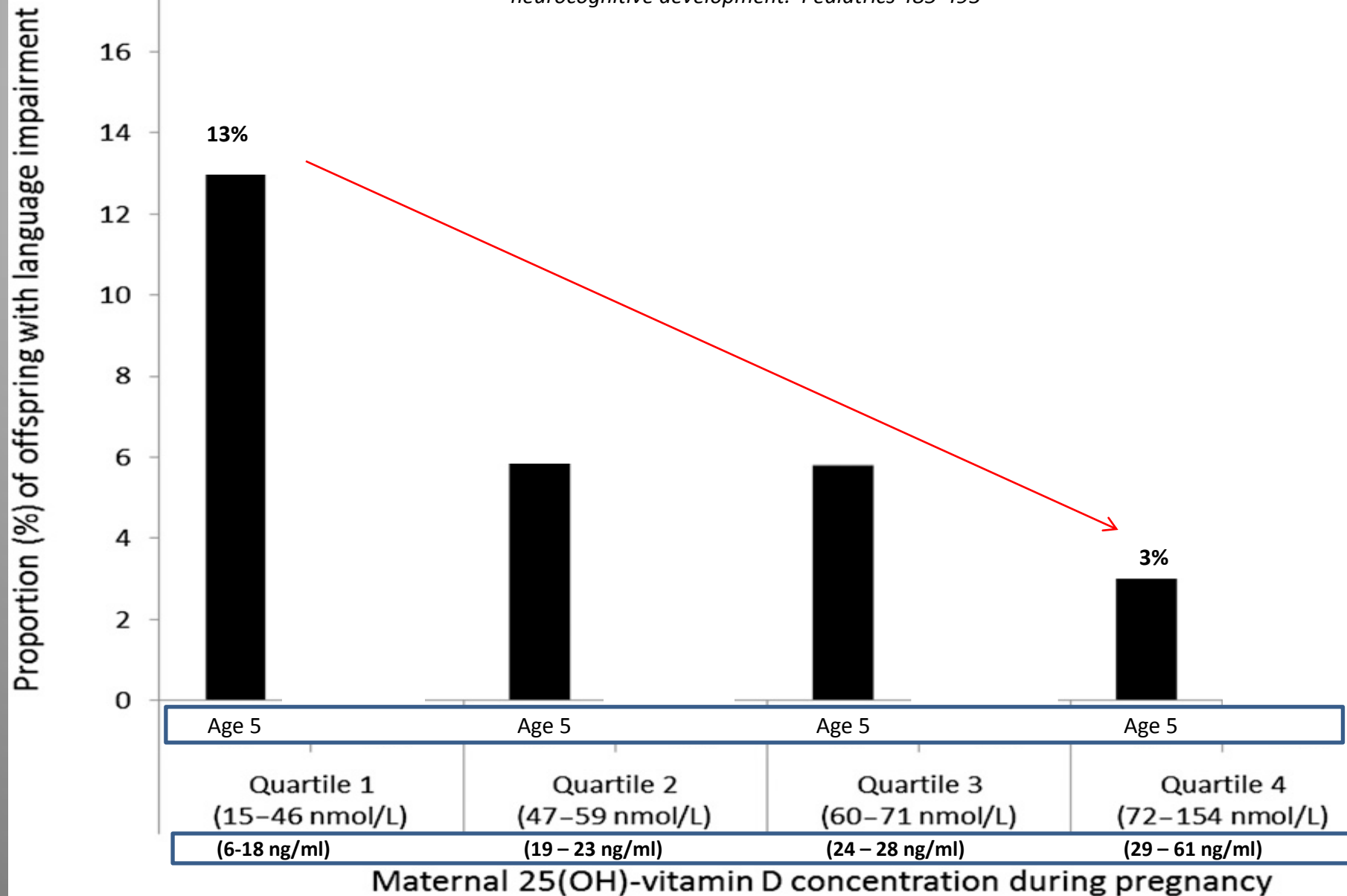
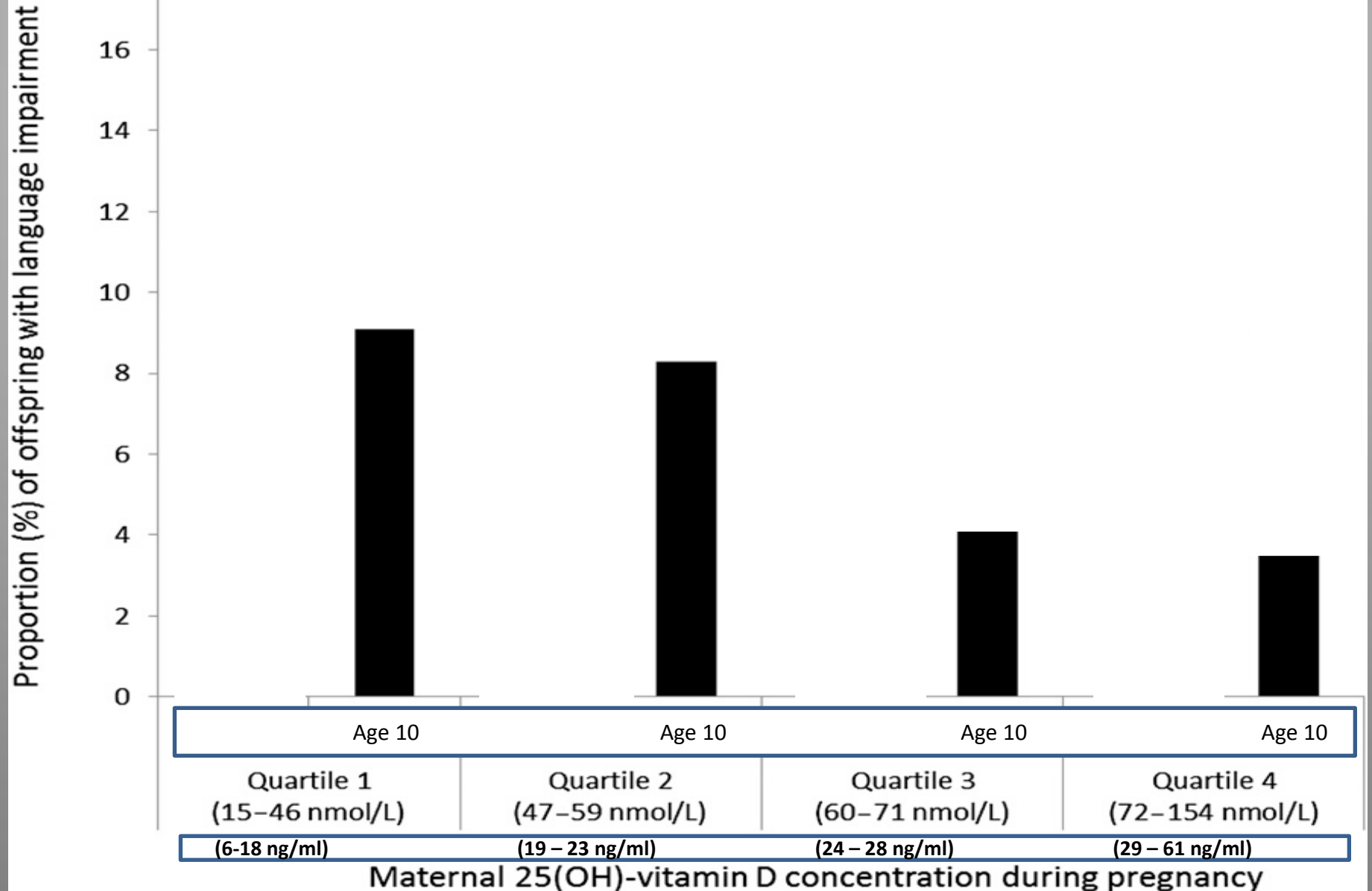


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Spain

Mental and Psychomotor Development

Circulating 25-Hydroxyvitamin D₃ in Pregnancy and Infant Neuropsychological Development

Eva Morales, Mònica Guxens, Sabrina Llop, Clara L. Rodríguez-Bernal, Adonina Tardón, Isolina Rjaño, Jesús Ibarluzea, Nerea Lertxundi, Mercedes Espada, Agueda Rodríguez and Jordi Sunyer

Pediatrics 2012;130:e913; originally published online September 17, 2012;

DOI: 10.1542/peds.2011-3289

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<http://pediatrics.aappublications.org/content/130/4/e913.1.full.html>

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HB 90 Support Implications, 7-19

Circulating 25-Hydroxyvitamin D₃ in Pregnancy and Infant Neuropsychological Development

AUTHORS: Eva Morales, MD, PhD, MPH,^{a,b,c,*} Mónica Guxens, MD, MPH, PhD,^{a,b,c,*} Sabrina Ulló, MSc, PhD,^{a,d} Clara L. Rodríguez-Bernal, DDS, MPH,^{a,d} Adonina Tardón, MD, PhD,^{a,e} Isolina Riaño, MD, PhD,^f Jesús Ibarluzea, MSc, PhD,^g Nerea Lertxundi, MSc,^{h,i} Mercedes Espada, PhD,^j Agueda Rodríguez, MD,^k and Jordi Sunyer, MD, PhD,^{a,b,c,l} on behalf of the INMA Project

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KEY WORDS

child development, cognition, infancy, intelligence, vitamin D

ABBREVIATIONS

CI—95% confidence intervals

FP—fractional polynomial

25(OH)D₃—25-hydroxyvitamin D₃

*Drs Morales and Guxens contributed equally to this work.

Dr Sunyer had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Morales, Guxens, Sunyer were responsible for study concept and design; Drs Guxens, Ulló, Tardón, Ibarluzea, Espada, and Sunyer were responsible for acquisition of data; Drs Morales and Guxens were responsible for drafting of the manuscript; Drs Ulló, Rodríguez-Bernal, Tardón, Riaño, Ibarluzea, Lertxundi, Espada, Rodríguez, and Sunyer were responsible for critical revision of the manuscript for important intellectual content; Dr Guxens was responsible for statistical analysis; and Drs Ibarluzea, Tardón, and Sunyer obtained funding.

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(Continued on last page)

WHAT'S KNOWN ON THIS SUBJECT: Adequate vitamin D status in mothers during pregnancy may influence the health status of offspring later in life. Growing evidence based on animal studies is linking vitamin D to brain development and functioning, but studies in humans are lacking.

WHAT THIS STUDY ADDS: This large-scale prospective pregnancy cohort study examines the association between maternal circulating 25-hydroxyvitamin D₃ concentrations in pregnancy and offspring neuropsychological development. Higher circulating concentration of 25-hydroxyvitamin D₃ in pregnancy was associated with improved mental and psychomotor development in infants.

abstract

OBJECTIVE: To investigate whether circulating 25-hydroxyvitamin D₃ [25(OH)D₃] concentration in pregnancy is associated with neuropsychological development in infants.

METHODS: The Spanish population-based cohort study Infancia y Medio Ambiente Project recruited pregnant women during the first trimester of pregnancy between November 2003 and February 2008. Completed data on 1820 mother-infant pairs were used. Maternal plasma 25(OH)D₃ concentration was measured by high-performance liquid chromatography in pregnancy (mean 13.5 ± 2.1 weeks of gestation). Offspring mental and psychomotor scores were assessed by trained psychologists at age 14 months (range, 11–23) by using the Bayley Scales of Infant Development. β -Coefficients with 95% confidence intervals (CIs) of mental and psychomotor scores associated with continuous or categorical concentrations of maternal plasma 25(OH)D₃ were calculated by using linear regression analysis.

RESULTS: The median plasma value of 25(OH)D₃ in pregnancy was 29.6 ng/mL (interquartile range, 21.8–37.3). A positive linear relationship was found between circulating concentrations of maternal 25(OH)D₃ concentrations in pregnancy and mental and psychomotor scores in the offspring. After adjustment for potential confounders, infants of mothers with 25(OH)D₃ concentrations in pregnancy >30 ng/mL showed higher mental score (β = 2.60; 95% CI 0.63–4.56) and higher psychomotor score (β = 2.32; 95% CI 0.36–4.28) in comparison with those of mothers with 25(OH)D₃ concentrations <20 ng/mL.

CONCLUSIONS: Higher circulating concentration of maternal 25(OH)D₃ in pregnancy was associated with improved mental and psychomotor development in infants. *Pediatrics* 2012;130:e913–e920

TABLE 1 Characteristics of Participants According to Maternal Circulating 25(OH)D₃ Concentrations in Pregnancy

	Serum 25(OH)D ₃ Concentration			P Value Trend
	<20 ng/mL (n = 356)	20–30 ng/mL (n = 574)	>30 ng/mL (n = 890)	
Area of study				
Valencia (39°N latitude)	20.2	29.6	37.2	<.001
Sabadell (41°N latitude)	30.3	23.2	26.4	
Gipuzkoa (42°N latitude)	24.7	27.2	23.4	
Asturias (43°N latitude)	24.7	22.2	13.0	
Child's gender (male)	51.1	48.8	48.8	.722
Birth weight, g	3300 (435)	3302 (419)	3302 (419)	.685
Maternal weight at birth, kg	71.5 (15)	71.5 (15)	71.5 (15)	.004
Parity				.053
Maternal BMI			7.4	.460
Parity				
I/II			36.0	.037
III			26.5	
IV			37.5	
Maternal BMI				
Pri			22.3	.273
Sec			39.4	
Un			38.3	
Maternal BMI				
Normal			75.6	.086
Overweight (25–29.99)	22.5	19.0	16.6	
Obese (≥30)	22.5	19.0	7.8	
Smoking at the time of delivery		16.4	13.9	.022
Alcohol during pregnancy (yes)	18.0	16.4	22.4	.013

Area of study

Valencia (39°N latitude)

Sabadell (41°N latitude)

Gipuzkoa (42°N latitude)

Asturias (43°N latitude)

Alaska (53° to 71° N latitude)

>30 ng/mL
(n = 890)

?

Values are percentages for categorical variables and mean (SD) for continuous variables.

HB 90 Support Implications, 9-19

To our knowledge this is one of the first large-scale prospective pregnancy cohort studies to examine the association between maternal circulating 25(OH)D₃ concentrations in pregnancy and offspring neuropsychological development in infancy. Higher concentrations of circulating 25(OH)D₃ in pregnancy were associated with improved mental and psychomotor scores. Infants of mothers with 25(OH)D₃ concentrations >30 ng/mL (clinically considered as optimal levels) showed an advantage of 2.6 and 2.3 points in mental and psychomotor scores, respectively, in comparison with those of mothers with 25(OH)D₃ concentrations <20 ng/mL (considered as deficient levels). The association remained significant after adjusting for a wide range of potential confounding and intermediate factors.

The main strengths of this study include its population-based prospective design and large sample size as well as examination of the associations with

A positive linear relationship was found between circulating concentrations of maternal 25(OH)D₃ in pregnancy and both mental (Fig 3A) and psychomotor (Fig 3B) development scores in the offspring. In multivariable models, each 10 ng/mL increase in 25(OH)D₃ in pregnancy resulted in up to 0.79 and 0.88 points increase in mental and psychomotor development scores in offspring, respectively (Table 2). In the basic model with adjustment for area of study, infants of mothers with 25(OH)D₃ concentrations >30 ng/mL showed an advantage of 3.17 and 2.42 points in the mental and psychomotor scores, respectively, in comparison with those of mothers with 25(OH)D₃ concentrations <20 ng/mL (model 1) (Table 2). Although attenuated, these associations remained significant after adjustment for potential confounders including child's gender, birth weight, maternal country of origin, maternal age, parental socioeconomic status, maternal education level, parity, maternal pre-pregnancy BMI, and

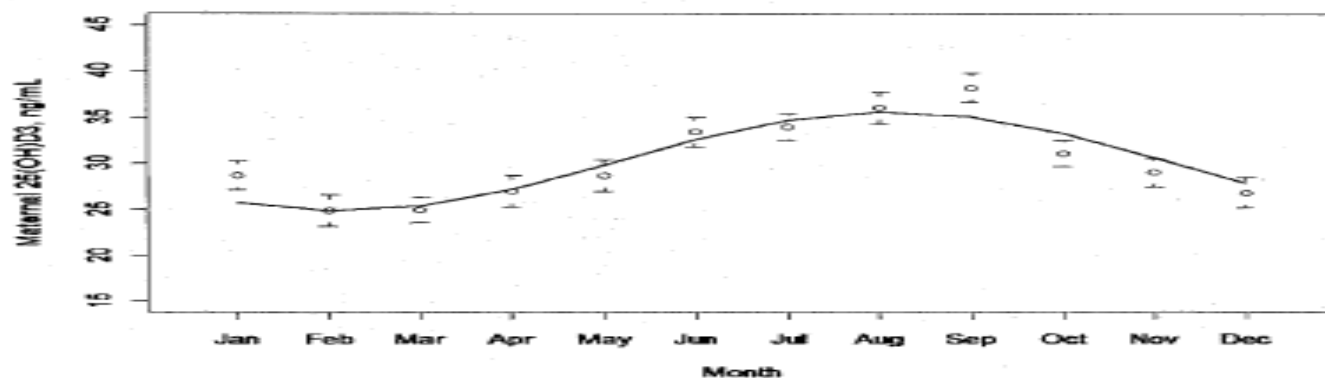


FIGURE 2

Fitted sinusoidal model for observed maternal circulating concentration of 25(OH)D₃ superimposed on plot of observed monthly mean and 95% CI values for 25(OH)D₃ concentration among 2112 participants in the INMA Project.



High Prevalence of Vitamin D Insufficiency in Black and White Pregnant Women Residing in the Northern United States and Their Neonates¹

Lisa M. Bodnar,^{2-4*} Hyagriv N. Simhan,²⁻⁴ Robert W. Powers,^{3,4} Michael P. Frank,⁴ Emily Cooperstein,⁴ and James M. Roberts²⁻⁴

²Department of Epidemiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, PA 15261; ³Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213; and ⁴Magee-Women's Research Institute, Pittsburgh, PA 15213

Abstract

In utero or early-life vitamin D deficiency is associated with skeletal problems, type 1 diabetes, and schizophrenia, but the prevalence of vitamin D deficiency in U.S. pregnant women is unexplored. We sought to assess vitamin D status of pregnant women and their neonates residing in Pittsburgh by race and season. Serum 25-hydroxyvitamin D [25(OH)D] was measured at 4–21 wk gestation and predelivery in 200 white and 200 black pregnant women and in cord blood of their neonates. Over 90% of women used prenatal vitamins. Women and neonates were classified as vitamin D deficient [25(OH)D <37.5 nmol/L], insufficient [25(OH)D 37.5–80 nmol/L], or sufficient [25(OH)D > 80 nmol/L]. At delivery, vitamin D deficiency and insufficiency occurred in 29.2% and 54.1% of black women and 45.6% and 46.8% black neonates, respectively. Five percent and 42.1% of white women and 9.7% and 56.4% of white neonates were vitamin D deficient and insufficient, respectively. Results were similar at <22 wk gestation. After adjustment for prepregnancy BMI and periconceptional multivitamin use, black women had a smaller mean increase in maternal 25(OH)D compared with white women from winter to summer (16.0 ± 3.3 nmol/L vs. 23.2 ± 3.7 nmol/L) and from spring to summer (13.2 ± 3.0 nmol/L vs. 27.6 ± 4.7 nmol/L) ($P < 0.01$). These results suggest that black and white pregnant women and neonates residing in the northern US are at high risk of vitamin D insufficiency, even when mothers are compliant with prenatal vitamins. Higher-dose supplementation is needed to improve maternal and neonatal vitamin D nutriture. J. Nutr. 137: 447–452, 2007.

Introduction

Rickets, once thought to have been nearly eradicated in the United States in the 1930s (1), has again become a major public health problem. Several reports have been published describing recent cases of rickets in infants, most of whom were black and exclusively breastfed (2–5). The reemergence of rickets is thought to be due to an epidemic of vitamin D deficiency in mothers and children (6). A newborn's vitamin D stores are completely reliant on vitamin D from the mother (7). Not surprisingly, poor maternal vitamin D status during pregnancy is a major risk factor for infant rickets (8–10).

In addition to causing poor global mineralization of the skeleton, vitamin D deficiency has implications for numerous other nonskeletal health outcomes. In utero or early life vitamin D deficiency has been linked to an increased risk of type 1 diabetes (11), asthma (12), and schizophrenia (13,14). Fascinating new data also show that vitamin D regulates placental development and function (15), which suggests that maternal vitamin D

status may be associated with adverse outcomes of pregnancy, such as miscarriage, preeclampsia, and preterm birth.

The most important source of vitamin D is the skin's synthesis of the vitamin from UV B solar radiation (16). Any process that reduces UV B photons from entering the epidermis will diminish cholecalciferol (vitamin D-3) production. The skin pigment melanin absorbs UV B photons and can reduce vitamin D-3 synthesis by >90% (17). Consequently, African Americans are at high risk of vitamin D deficiency. The most recent data from the National Health and Nutrition Examination Survey (1988–1994) indicated that vitamin D deficiency [25-hydroxyvitamin D [25(OH)D] ≤ 37.5 nmol/L] was prevalent in 42% of black childbearing-aged women and only 4% of white childbearing-aged women residing throughout the United States (18). Vitamin D status is also worsened in winter months (November through March), when, at latitudes above 37°, less UV B radiation reaches the earth and little or no vitamin D can be synthesized in the skin (16,19). Indeed, vitamin D deficiency in U.S. childbearing-aged women was more than 3 times as common in winter than summer in both blacks and whites (18).

Despite the striking racial disparity in vitamin D deficiency and the strong influence of season, there are few recent investigations into the vitamin D status of U.S. black and white pregnant women and their neonates throughout the year. Given

Babies at birth deficient or insufficient = 92.4% = 66.1%

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¹ Supported by NIH grants PPG 2P01 HD30367 and 5MO1 RR00056. Dr. Bodnar was supported by NIH grant K01 MH074092. Dr. Simhan was supported by NIH grants R01 HD041663 and R01 HD062732. The authors do not declare any conflicts of interest.

* To whom correspondence should be addressed. E-mail: bodnar@edc.pitt.edu.

TABLE 2 Vitamin D status of white and black pregnant women and their neonates¹

	White women, <i>n</i> = 200	Black women, <i>n</i> = 200
4–21 wk gestation		
Serum 25(OH)D, ² nmol/L	73.1 (69.4, 76.9)	40.2 (37.9, 42.7)*
Vitamin D status, %		
Deficient: 25(OH)D <37.5 nmol/L	2.0	44.9**
Insufficient: 25(OH)D 37.5–80 nmol/L	60.3	51.0
Sufficient: 25(OH)D >80 nmol/L	37.3	4.1
37–42 wk gestation		
Serum 25(OH)D, nmol/L	80.4 (76.0, 85.1)	49.4 (46.1, 52.9)*
Vitamin D status, %		
Deficient: 25(OH)D <37.5 nmol/L	5.0	29.2**
Insufficient: 25(OH)D 37.5–80 nmol/L	41.2	54.1
Sufficient: 25(OH)D >80 nmol/L	53.8	16.7
Cord blood		
Serum 25(OH)D, nmol/L	67.4 (63.8, 71.3)	39.0 (36.3, 41.8)*
Vitamin D status, %		
Deficient: 25(OH)D <37.5 nmol/L	9.7	45.6**
Insufficient: 25(OH)D 37.5–80 nmol/L	56.4	46.8
Sufficient: 25(OH)D >80 nmol/L	33.9	7.6

¹ Values are geometric means [95%CI] or %. *Different from white women, *P* < 0.001 (student's *t* test); **different from white women, *P* < 0.001 (chi-square test).

² Log-transformed to ensure normality.

Vitamin D status of exclusively breastfed infants aged 2-3 months.

Wall CR, Grant CC, Jones I.

Source: Discipline of Nutrition, Faculty of Medical and Health Sciences, University of Auckland, Auckland, New Zealand.

Abstract

BACKGROUND: New Zealand in 2008 adopted WHO policy which recommends that all infants are exclusively breast fed until 6 months of age. The benefits of this policy for the infant are undisputed; however, this policy has the potential to adversely impact on infant vitamin D status. A number of countries now recommend that all breastfed infants receive daily vitamin D supplementation of 400 IU to prevent rickets. New Zealand has no policy on the vitamin D supplementation of 'low-risk' breastfed infants. There are no data on the vitamin D status of exclusively breastfed infants in the first few months of life in New Zealand.

AIM: To describe serum 25-hydroxy-vitamin D (25(OH)D) concentrations in exclusively breastfed infants aged 2-3 months.

DESIGN/METHODS: Healthy term exclusively breastfed infants who were receiving no vitamin D supplements were enrolled over a 15-month period. A capillary blood sample was obtained from each infant. Serum 25(OH)D was measured using isotope-dilution liquid chromatography-tandem mass spectrometry.

RESULTS: 94 infants were enrolled (mean age 10 weeks). Median 25(OH)D concentration was 53 nmol/l (IQR 14-100 nmol/l). 23 (24%) infants had serum 25(OH)D concentration <27.5 nmol/l. Infants enrolled during winter had a median (IQR) 25(OH)D serum concentration of 21 nmol/l (14,31). Infants enrolled during summer had a median (IQR) 25(OH)D concentration of 75 nmol/l (55-100) (winter vs summer, $p < 0.0001$).

CONCLUSIONS: Vitamin D deficiency is prevalent in exclusively breastfed infants in New Zealand. Vitamin D supplementation should be considered as part of New Zealand's child health policy.

PMID:23303428[PubMed - as supplied by publisher]

Vitamin D levels of infants converted from nmol/l to the US common measurement for blood serum concentrations, ng/ml:

-Entire study:

Median = 21.2 ng/ml

24% of infants < 11 ng/ml

-Infants enrolled in winter:

Median = 8.4 ng/ml

Highest level = 12.4 ng/ml

-Infants enrolled in summer:

Median = 30 ng/ml

Conversion notes by the office of Representative Seaton

VITAMIN D AND SUICIDE RISK FACTORS

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Abstract

Low vitamin D levels are negatively associated with certain prosuicidal factors such as exacerbation of depression, anxiety, psychosis, and certain medical conditions. Therefore, we hypothesize that they may also be associated with completed suicides. In particular, lower vitamin D levels at the end of winter, secondary to the lower vitamin D production in the skin, (as a result to reduced skin surface exposure as well as reduced duration of exposure, an after effect of uncomfortably low heat index and lower solar radiation). In preparation to test this hypothesis in future research, we now briefly review the existent literature on vitamin D, its deficiency and its reported association with certain risk factors for suicide.

Introduction

Suicide is the 10th leading cause of death worldwide and the second leading cause of death in adolescents and adults ages 15-35 years (1-3). Suicide attempts are 2 to 3 times more likely than fatal completions (4). Approximately 90% of individuals who die by suicide are diagnosable with a psychiatric illness. About 9.5% of the United States population suffers from a mood disorder including 6.7% suffering from major depressive disorder, 18.1% diagnosed with an anxiety disorder and 1.1% with a psychotic disorder expressed by

Vitamin D news

Research reveals link between low vitamin D and military suicide

07 January 2013



Research published this past week is the first to report that low vitamin D levels are associated with an increased risk for suicide in US military personnel.

John C. Umhau, MD, and colleagues in Bethesda, Maryland conducted a prospective, case-control study using serum samples stored in the Department of Defense Serum Repository. The researchers matched 495 verified suicide cases to 495 controls by rank, age and sex.

The researchers found that more than 30% of all participants had vitamin D levels below 20 ng/ml. The subjects with the lowest vitamin D status (<15.5 ng/ml) had the highest risk of suicide, while participants with higher 25(OH)D status showed a decreased risk. The authors conclude,

“Future studies could determine if additional sunlight exposure and vitamin D supplementation might reduce suicide by increasing 25(OH) D levels.”

Source:

[Umhau JC, et al. Low vitamin D status and suicide: A case-control study of active duty military service members. PLOS ONE. Jan 2013.](#)

Is low vitamin D linked to military suicide?

Posted on [January 10, 2013](#) by [John Cannell, MD](#)

The authors studied 495 cases of suicide among active duty military personnel who had their blood drawn within 2 years of their suicide. They compared them to 495 matched cases controls.

[Umhau JC et al. Low Vitamin D Status and Suicide: A Case-Control Study of Active Duty Military Service Members. Plos One](#)

More than 30% of the soldiers had vitamin D levels lower than 20 ng/ml, even in the summer. When sampled in the winter, more than 60% of the soldiers had levels less than 20 ng/ml. They then grouped the soldiers in octiles; in other words, they divided the soldiers into 8 equal groups by grouping them according to vitamin D levels. **They found that soldiers with the lowest levels of vitamin D were twice as likely to complete suicide as were soldiers with higher levels.**

The authors made the following points in their paper:

Sunlight may exert benefits over and above that of making vitamin D. For instance, sunlight is involved in melatonin physiology and melatonin can affect mood.

Low vitamin D status has recently been connected with, low cognitive performance, psychotic-like symptoms, and depression.

A depressive episode does not always precede suicide. The development of suicidal thoughts can be sudden and occur within 10 minutes of a suicide attempt. Impulsivity plays a major role in military suicides.

Low serotonin occurs during the winter; and as most know, serotonin is popularly thought to be central to feelings of happiness. This fact may confound the relationship between vitamin D levels and risk of suicide.

A recent study found the vitamin D levels of soldiers in basic training in South Carolina fell at the end of 8 weeks of basic training due to the heavy clothing worn by soldiers.

Dr. Umhau and colleagues concluded,

“Studies are urgently needed to develop an appropriate strategy to insure that service members do not suffer the ill effects of a preventable deficiency of vitamin D.”

We agree but would add that the military should take immediate steps to treat vitamin D deficiency that is rampant among their soldiers.

Vitamin D₃ supplementation in patients with frequent respiratory tract infections: a randomised and double-blind intervention study

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PB and ACN contributed equally to this study.

ABSTRACT

Background: Low serum levels of 25-hydroxyvitamin D₃ are associated with an increased risk of respiratory tract infections (RTIs). Clinical trials with vitamin D₃ against various infections have been carried out but data are so far not conclusive. Thus, there is a need for additional randomised controlled trials of effects of vitamin D₃ on infections.

Objective: To investigate if supplementation with vitamin D₃ could reduce infectious symptoms and antibiotic consumption among patients with antibody deficiency or frequent RTIs.

Design: A double-blind randomised controlled trial.

Setting: Karolinska University Hospital, Huddinge.

Participants: 140 patients with antibody deficiency (selective IgA subclass deficiency, IgG subclass deficiency, common variable immune disorder) and patients with increased susceptibility to RTIs (>4 bacterial RTIs/year) but without immunological diagnosis.

Intervention: Vitamin D₃ (4000 IU) or placebo was given daily for 1 year.

Primary and secondary outcome measures: The primary endpoint was an infectious score based on five parameters: symptoms from respiratory tract, ears and sinuses, malaise and antibiotic consumption. Secondary endpoints were serum levels of 25-hydroxyvitamin D₃, microbiological findings and levels of antimicrobial peptides (LL-37, HNP1-3) in nasal fluid.

Results: The overall infectious score was significantly reduced for patients allocated to the vitamin D group (202 points) compared with the placebo group (249 points; adjusted relative score 0.771, 95% CI 0.604 to 0.985, p=0.04).

Limitations: A single study centre, small sample size and a selected group of patients. The sample size calculation was performed using p=0.02 as the significance level whereas the primary and secondary endpoints were analysed using the conventional

ARTICLE SUMMARY

Article focus

- Recent evidence suggests that vitamin D₃ has potent extraskeletal effects, such as suppression of inflammation and strengthening of mucosal immunity by induction of antimicrobial peptides.
- Data from observational studies suggest that low levels of 25-hydroxyvitamin D₃ are associated with an increased risk of respiratory tract infections.
- Results from a limited number of randomised controlled trials on the protective role of vitamin D₃ against respiratory tract infections are inconclusive and thus additional studies are warranted.

Intervention: Vitamin D₃ (4000 IU) or placebo was given daily for 1 year.

- The main conclusion is that vitamin D₃ supplementation reduces symptoms and antibiotic consumption among patients with an increased frequency of respiratory tract infections. Thus, vitamin D₃ supplementation may be an alternative strategy to reduce antibiotic use among patients with recurrent respiratory tract infections.

Strengths and limitations of this study

- A high daily dose of vitamin D₃ was used, the study time was a full year covering all seasons and patients with an increased frequency of respiratory tract infections were studied.
- A single study centre, small sample size (n=140) and a selected group of patients.

INTRODUCTION

Vitamin D was discovered when it was noted that rachitic children were improved by expos-

but a reduction of *S aureus* and fungal species that often colonise the airways was observed. This could be explained by specific effects by vitamin D₃ on immunity against *S aureus*. In fact, vitamin D₃ induces human β -defensin-2 (HBD-2) with bactericidal activity against *S aureus*.²⁹ A recent study showed that low vitamin D₃ levels were associated with an increased risk of being colonised by this bacterium.³⁰ Further, vitamin D₃ affects immunity against *C albicans*, which indicates direct effects of vitamin D₃ on human immunity.³¹ Alternatively, it is possible that vitamin D₃ may have prevented symptomatic viral infections, which prompted patients to leave a bacterial sample from the airways. Interestingly, there is both mechanistic and clinical evidence that vitamin D₃ can prevent viral infections,^{32–34} although we did not address this in the current study.

Notably, we observed a prominent increase in the serum concentration of 25-hydroxyvitamin D₃, which indicated good compliance and tolerability of the study drug. In fact, there was a trend towards adverse events being reported more often in the placebo group, suggesting that vitamin D₃ possibly could be efficient against other diseases, but this observation requires further studies. No clinically relevant changes of blood chemistry (calcium, phosphate, albumin or creatine) were observed. Despite few adverse events and high tolerability, 16 exclusions occurred during the study year. The main reason was problems to adhere to the protocol and 6/16 patients dropped out of the study after a few weeks. The rest failed to send in blood samples, did not leave blood for monitoring of safety parameters or did not take the study drug. One patient was excluded based on symptoms that could be attributed to vitamin D₃ (facial paraesthesia). However, this patient was later confirmed to have been allocated to placebo.

In summary, we found that supplementation with vitamin D₃ reduced the total infectious score with 47 points per patient (23% reduction in the adjusted analysis) during the study year. The observed reduction was lower than the assumed reduction of 70 points per patient (predefined assumption: 210 points→140 points; a reduction of 30%) that formed the basis for the power calculation. However, despite the predefined level of a reduction of infectious score by 30% as a clinically meaningful effect, we believe that effects lower than this also could be relevant for the individual patient. We base this line of reasoning on the fact that a reduction of 47 points per patient can be translated into 47 days with cough (47 points), 23 days with ear and sinus symptoms (23×2=46 points) or 9 days with ear and ear symptoms together with malaise and antibiotics (9×5=45 points). In addition, our data indicate that vitamin D₃ supplementation reduces the odds of taking antibiotics by approximately 60% in patients with frequent respiratory tract infections. Thus, supplementation with vitamin D₃ could provide a novel strategy to reduce antibiotic use among high consumers and indirectly prevent the emerging epidemic of bacterial resistance.

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Contributors PB designed the study, collected, analysed and interpreted data, wrote the paper. A-CN designed the study, collected and interpreted data, wrote the paper. SH designed and coordinated the study, collected and interpreted data. RSR carried out experimental work and analysed data. BA analysed and interpreted data, wrote the paper. LB-B analysed and interpreted data, wrote the paper. LE analysed and interpreted data. JL analysed and interpreted data, wrote the paper. JA designed the study, interpreted data, wrote the paper.

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