

Vitamin-D and MS

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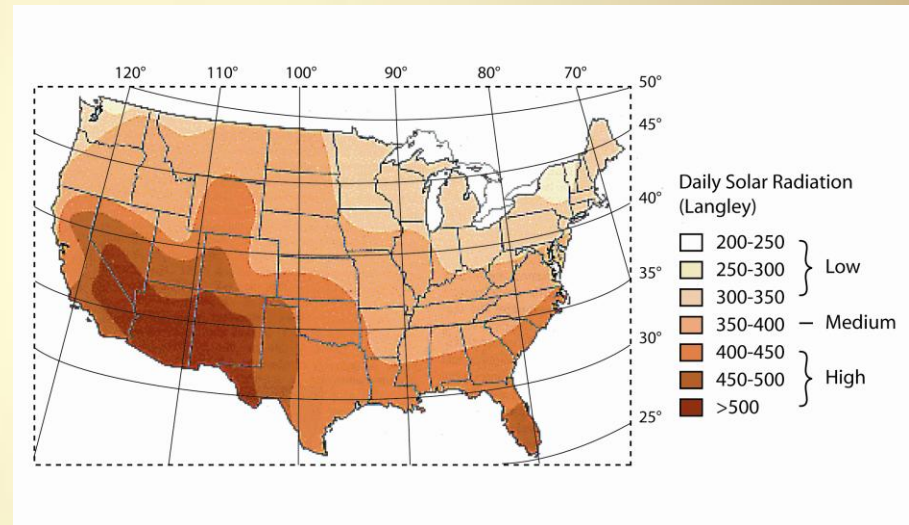
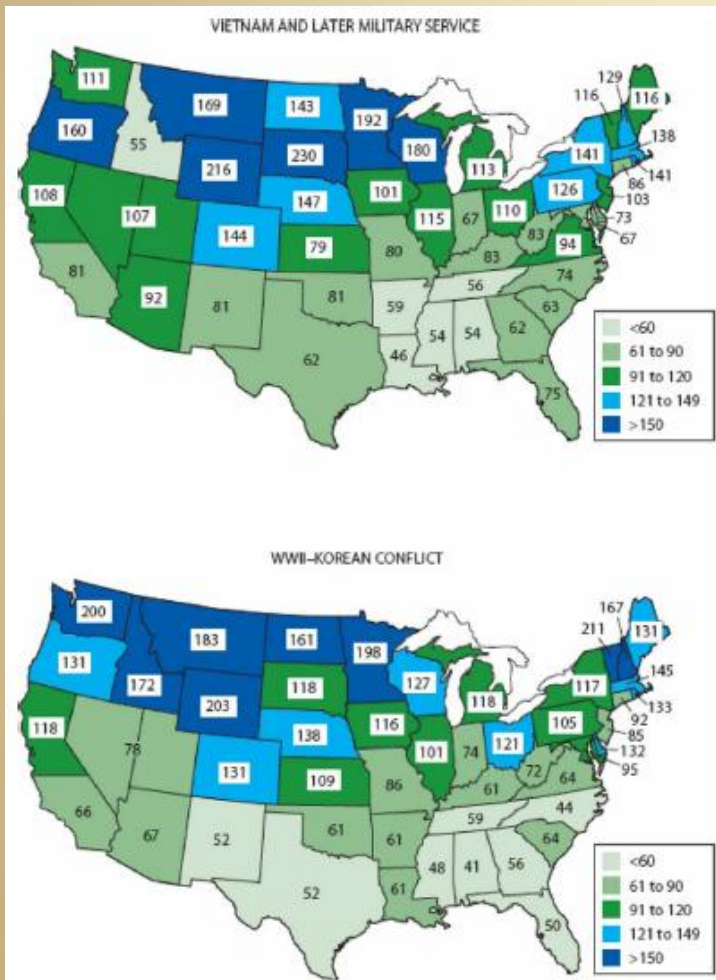
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Overview

- Historical context
- Literature Review by type of Vit-D exposure
 - UVR exposure (time in the sun)
 - Vit-D supplementation
 - Serum Vit-D levels
 - Aussie Immune Study
- Conclusions on the role of Vit-D on risk of MS
- Biologic Plausibility
- Unanswered Questions
- Next Steps...

Origin of Vitamin-D as an environmental risk factor for MS



From: US Department of Commerce, 1968

From: Kurtzke J., Multiple Sclerosis 2008; 14: 1007-12.

Origin of Vitamin-D Hypothesis

- First published report by Davenport in 1921¹
- Distribution of UVR exposure inversely related to prevalence of MS
- Speculation that lower prevalence of MS in areas with high UVR exposure mediated through Vit-D
- Majority of Vit-D produced in the skin in response to UVR exposure²
- Migration studies suggest environmental factor

Origin of Vitamin-D Hypothesis

- Migration studies³⁻⁸
 - Persons moving from low-risk to high-risk areas
 - Show increased risk of MS if migration during adolescence or earlier
 - Persons moving from high-risk to low-risk areas
 - Show decreased risk of MS if migration during adolescence or earlier
 - Genetics account for $\approx 30\%$ of MS risk and do not explain migration results
- Based on these observations it has been hypothesized that Vit-D is protective against MS

UVR Exposure and MS⁹

- Case-control study of 136 MS cases in Tasmania
 - 68% female
 - Mean age at DX: 35±9 years
 - Mean disease duration: 9.4±7.5 years
 - Relapsing disease: 92%
 - Mean EDSS: 3.5±2.2
 - Cases selected 2:1 matched on sex and year of birth
- Interview conducted survey to collect
 - Time in the sun during weekends/holidays during summer and winter
 - Actinic skin damage from the hand as objective measure of cumulative life-time sun exposure
 - Skin phenotype by spectrophotometer at multiple body sites

UVR Exposure and MS⁹

- Results

- Higher sun exposure in summer (>2hr/day) when aged 6-15 showed decreased risk of MS: adj OR 0.31 [95%CI: 0.16 – 0.59]
- Winter sun exposure had a stronger effect than did summer sun exposure
- Actinic skin damage was inversely associated with MS risk
 - OR of 0.32, 0.11 to 0.88 for grades 4-6 versus grade 3

- Conclusions

- Higher sun exposure during childhood and adolescence, particularly during winter months, is associated with a reduced risk of MS

UVR Exposure and MS⁹

- Limitations
 - Observational study (case-control design)
 - Self-reported sun exposure subject to bias
 - Accurate recall of time spent in the sun 20-30 years ago
 - Over reporting of sun exposure due to belief that sun exposure/UVR related to MS
- Study sample from a relatively homogenous source population in area with living in a relatively narrow latitudinal gradient
- Does not separate out the effects that may be independently due to UVR from those of Vit-D mediated mechanisms

Vitamin-D Supplementation¹⁰

- Nurses Health Study (I and II)
 - 92,253 and 95,310 female registered nurses
 - 25 to 42 years of age
- Assessment of Vit-D intake
 - Semi-quantitative food frequency questionnaire every 2-4 years
 - Questionnaire has been validated
 - Vit-D rich food (e.g., milk and fish)
 - Vit-D supplements (e.g., multi-vitamins assuming 400 IU/dose)
 - Vit-D intake correlated well with serum 25(OH)D in 323 women
 - Vit-D intake inversely related to hip fracture
- Primary covariates
 - Smoking
 - Latitude at birth

Vitamin-D Supplementation¹⁰

- MS ascertainment
 - Initial ascertainment based on self-report
 - Confirmed by treating neurologist/physician
 - DX confirmed as definite/probable in 90%
- Results
 - RR, comparing highest quintile of total Vit-D intake at baseline to lowest quintile was 0.67 [95%CI: 0.40 – 1.12]
 - RR, comparing Vit-D supplement of ≥ 400 IU to no Vit-D supplementation was 0.59 [95%CI: 0.38 – 0.91]
 - No association was found for Vit-D from food alone
- Conclusions
 - Results support a protective effect of Vit-D (supplements) on the risk of developing MS

Vitamin-D Supplementation¹⁰

- Limitations

- Observational study (cohort study design)
- Self-reported Vit-D intake subject to bias
 - Measurement error (particularly for supplements)
 - Nurses may over-report Vit-D intake if they believe Vit-D important for general health / prevent MS
- Only women were evaluated
 - Some data to suggest gender differences in Vit-D production/bioavailability
- Do current dietary practices correlate with those during childhood and adolescence

- Strengths

- Very large sample sizes & prospective design
- Efforts made to validate assessment of Vit-D and to confirm MS diagnosis
- Finding a 40% reduction in MS risk is a strong association

Serum Vit-D Levels¹¹

- DoD Serum Repository (data on >7 million military personnel)
 - Serum collected and banked on entry to active duty
 - 257 cases of MS identified from 1992 through 2004 confirmed by chart review
 - Controls selected at 2:1 matched by
 - Age, sex, race/ethnicity and date of blood collection
- Vit-D status was estimated by
 - Averaging 25-hydroxyvitamin-D levels across 2 or more samples
 - On samples collected prior to date of first symptom(s) of MS
- Analyses
 - Logistic regression used to generate OR
 - Stratified by race
 - Adjusted by latitude of residence at entry to active duty

Serum Vit-D Levels¹¹

- Results

- For each 50-nmol/L increase in 25-hydroxyvitamin-D the OR was 0.59 [95%CI: 0.36 – 0.97]
- Categorical analysis
 - Comparing highest quintile (>99 nmol/L) to the lowest quintile (≤ 63 nmol/L) the OR was 0.38 [95%CI: 0.19 – 0.75]
- In a small subsample with 25-hydroxyvitamin-D collected before age 20
 - OR was 0.09 [95%CI: 0.01 – 0.75] Comparing highest to lowest quintile
- The above results were observed only in white, non-Hispanics
 - For Black, non-Hispanics the OR was 0.66 [95%CI: 0.24 – 1.78]
 - For Hispanics the OR was 0.97 [95%CI: 0.28 – 3.33]

Serum Vit-D Levels¹¹

- Conclusions
 - High circulating levels of 25-hydroxyvitamin-D are associated with a reduced risk of MS
- Limitations
 - Effect observed only in non-Hispanic whites
 - Small numbers of Blacks and Hispanics
 - 25-hydroxyvitamin-D levels assessed in early adulthood beyond the typical exposure-window
 - Did not control for potential direct effects of UVR exposure
- Strengths
 - Large prospective study
 - Objective measure of Vit-D

Vit-D and First Demyelinating Event

- The Ausimmune Study
- Multicenter, incident case-control study –
 - 216 cases, 18-59 years of age with FDE between 11/01/03 to 12/31/06
 - 395 randomly selected controls matched on age, sex, region
- Assessment of Vit-D
 - Self-reported sun exposure at different time points
 - 6-10y, 11-15y, 16-20y, and last 3 y
 - Actinic skin damage
 - 25(OH)D serum Vit-D levels
- Analyses
 - ORs estimated by logistic regression adjusting for
 - Physical activity, smoking, Hx of mononucleosis

Vit-D and First Demyelinating Event

- Validations

- High coherence was observed between the different measures of Vit-D
 - Higher recent time in the sun predicted 25(OH)D levels
 - Leisure time UV dose (time in sun 6y to present) actinic skin damage

- Results

- Higher time in the sun in 3 years prior to interview and increasing leisure time in the sun (age 6 to present) were associated with reduced risk of FDE
 - OR of 0.88 [0.72 – 0.00] and 0.73 [0.56 – 0.95], respectively
- Grade 3-6 Actinic skin damage associated reduced risk of FDE
 - OR of 0.45 [0.29 – 0.69]

Vit-D and First Demyelinating Event

- Results (cont'd)
 - Cases had lower 25(OH)D levels than controls
 - FDE risk decreased with increasing 25(OH)D level
 - OR = 0.69 [0.48 – 0.98] per 50nmol/L increase
- When all Vit-D measures included in logistic regression
 - Independent protective effects were observed for each measure
- Summary
 - Higher recent or life-time sun exposure and higher serum 25(OH)D levels independently associated with risk of FDE

Conclusions

Vit-D an risk of MS

- These three studies are good examples of the better studies on Vit-D and MS
- Despite the limitations in study design, these three studies, as well as others, support the role of Vit-D as protective against MS
- This effect appears to be most pronounced when Vit-D is elevated during childhood and adolescence
- Appears to be a dose-response relationship with the higher the Vit-D level the greater the risk reduction

Conclusions

Vit-D an risk of MS (cont'd)

- There is an emerging literature that supports Vit-D and begins to identify potential mechanisms of action
 - Vit-D affects HLA-DR antigen expression /presentation¹³
 - HLA-DRB1*1501, main MS-related allele, regulated by Vit-D¹⁴
 - Variation in Vit-D receptor gene associated with MS¹⁵
 - Vit-D has associated with an increase in CD4+ CD25+ T-regulatory cells¹⁶
 - Serum levels of 25(OH)D correlate with suppression of T-cell proliferation in MS patients¹⁷
- In EAE models of MS, Vit-D can prevent disease onset¹⁷

Unanswered Questions

- Why does Vit-D appear to not have the same protective effect in African American and Hispanic patients?
- How does the Vit-D hypothesis fit with the recently reported increased incidence in MS in Kuwait?¹⁸
- Mechanism(s) of action need to be more precisely defined?
- Is there sufficient evidence to warrant prevention and treatment trials with Vit-D

Next Steps ?

- NMSS convened workshop in early 2009 to address role of Vit-D in MS
- General consensus was that
 - Primary prevention trials should be initiated
 - Trials to assess therapeutic benefit of Vit-D supplementation in MS patients should and have been initiated
- Need better data
 - To define normal serum levels of Vit-D and Vit-D toxicity
 - What constitutes a therapeutic dose/level
 - What form of Vit-D to use as supplement
 - What is the most appropriate measure of Vit-D status
- Prevention and Tx trials present many challenges

QUESTIONS

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