



# The Promise of Vitamin D

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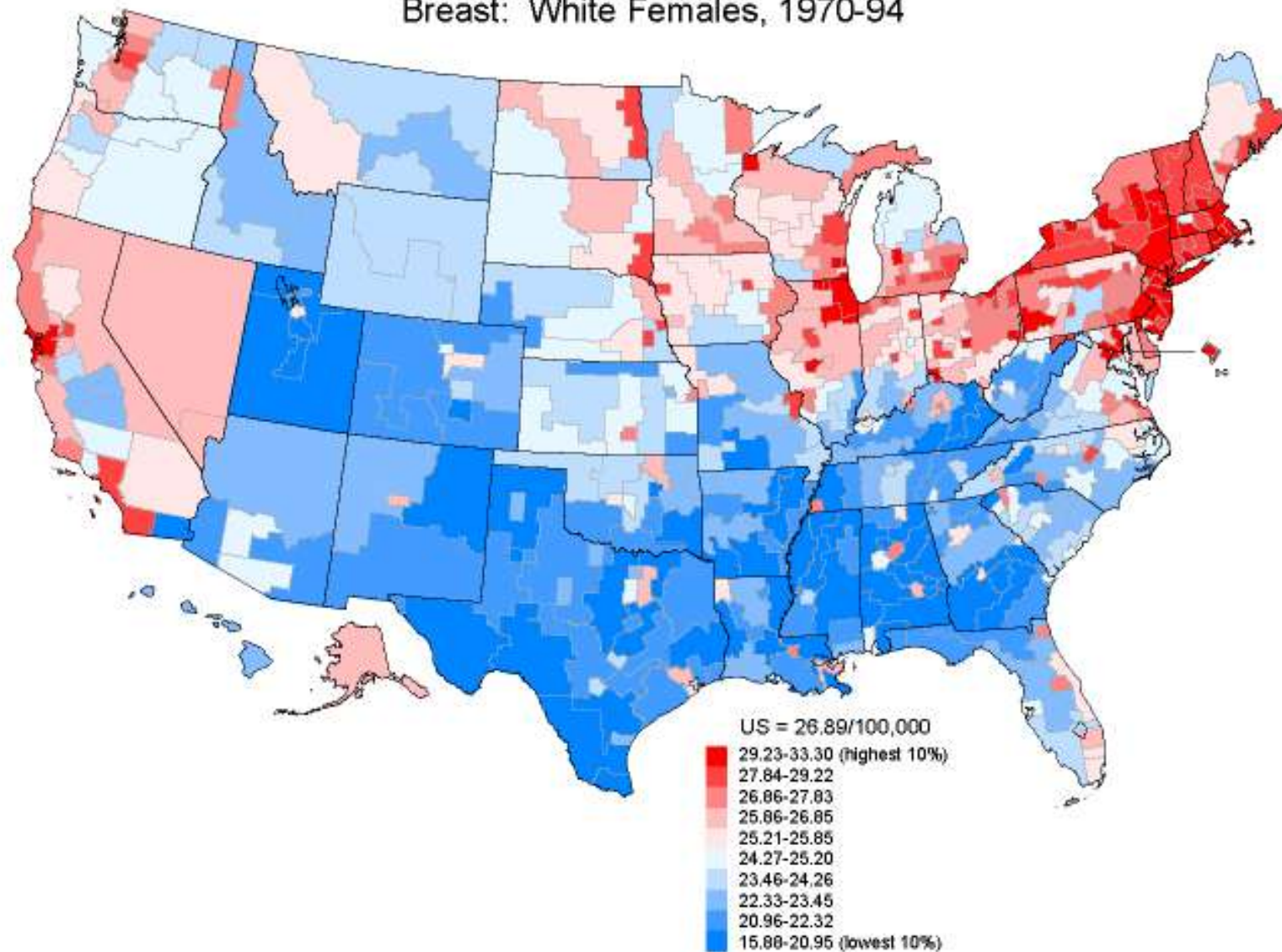
Whangarei Hospital

# Latitude and Disease

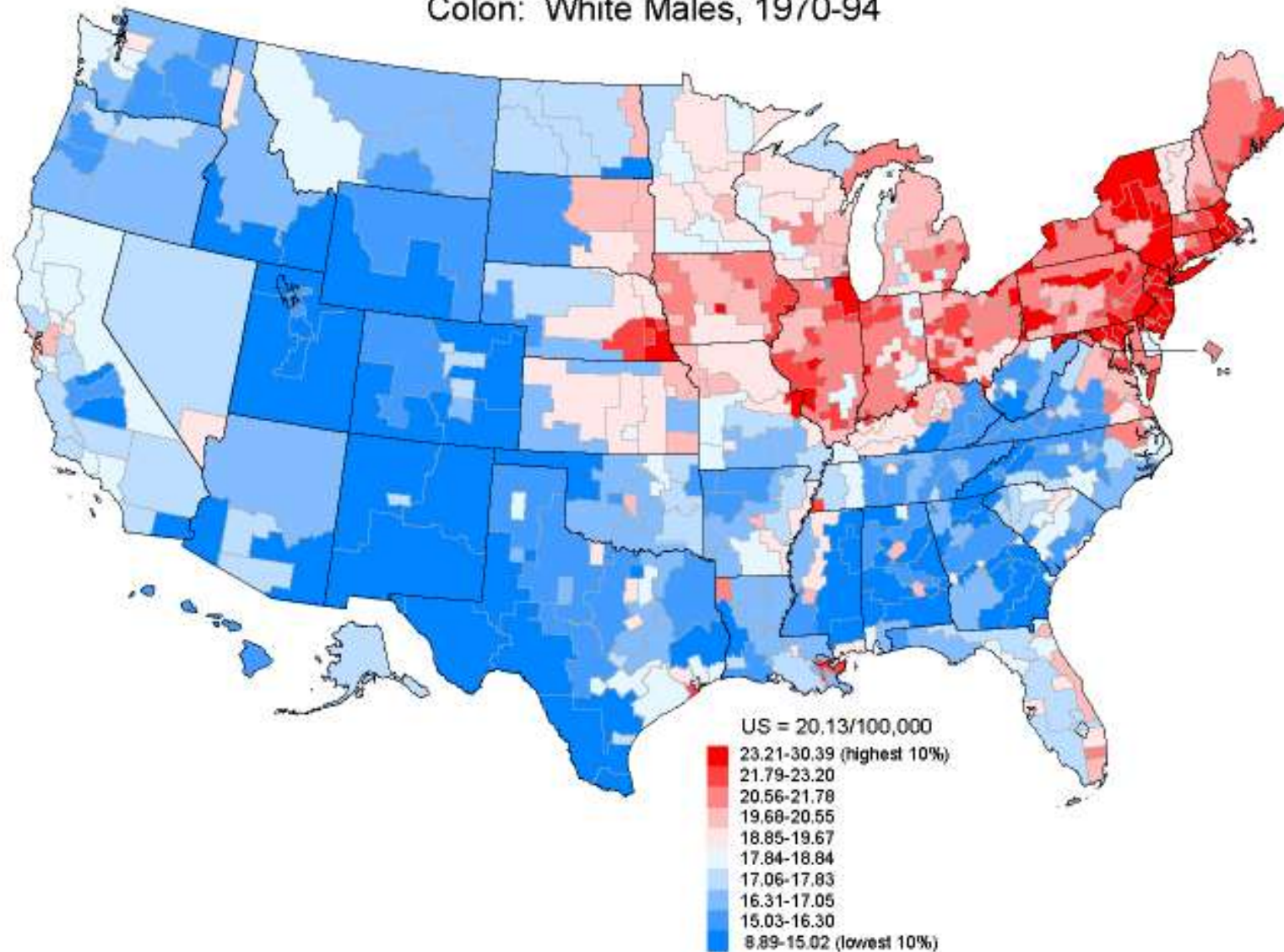
- Latitude  $>30^{\circ}\text{S}$  or N (NZ  $35^{\circ}\text{S} - 47^{\circ}\text{S}$ )
  - Cancers (breast, prostate, colon, melanoma etc.)
  - T1, T2 Diabetes
  - Multiple sclerosis
  - Rheumatoid arthritis/SLE
  - Osteoarthritis
  - Cardiovascular disease
  - Crohn's disease



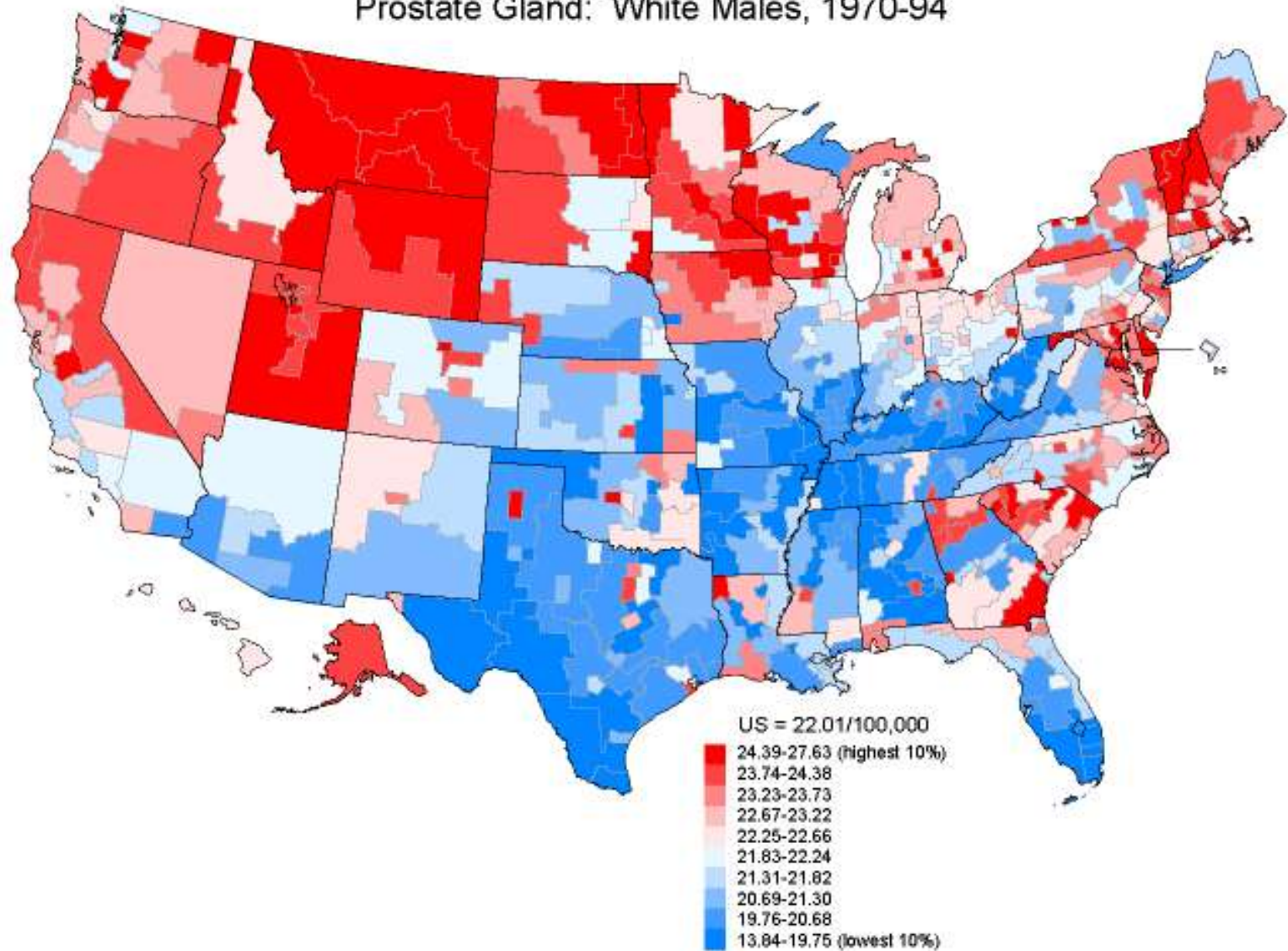
Cancer Mortality Rates by State Economic Area (Age-adjusted 1970 US Population)  
Breast: White Females, 1970-94



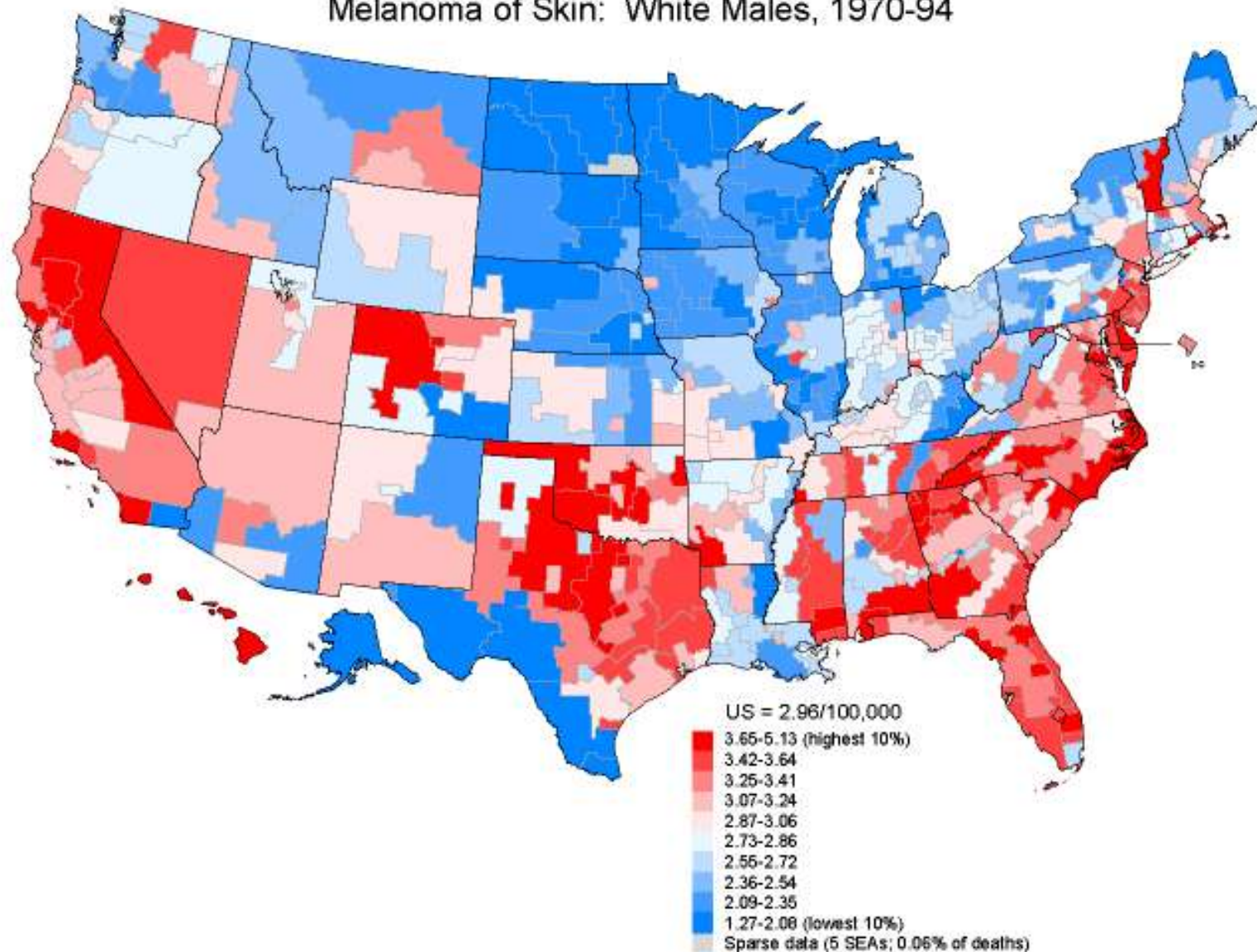
Cancer Mortality Rates by State Economic Area (Age-adjusted 1970 US Population)  
Colon: White Males, 1970-94



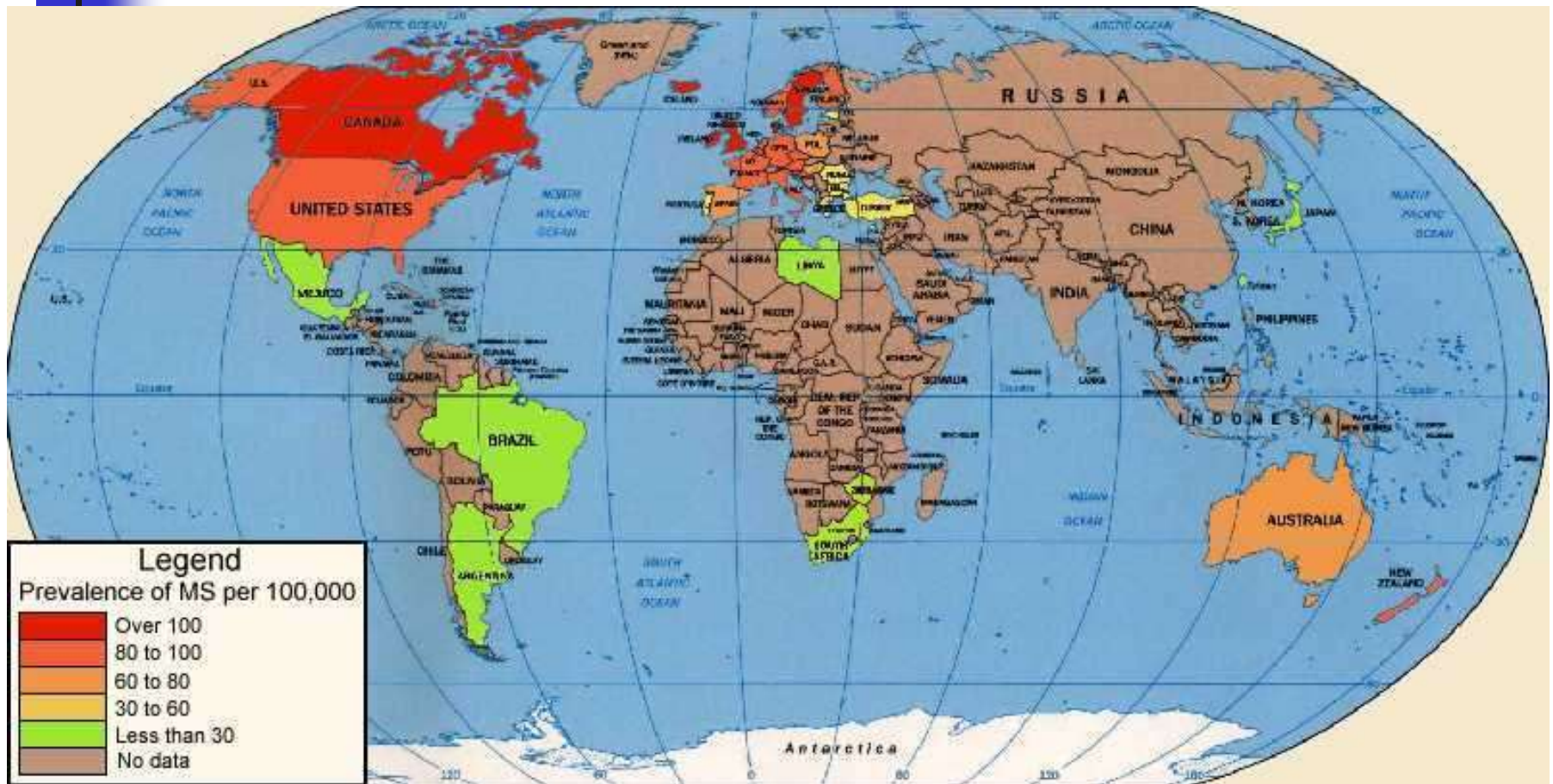
Cancer Mortality Rates by State Economic Area (Age-adjusted 1970 US Population)  
Prostate Gland: White Males, 1970-94



Cancer Mortality Rates by State Economic Area (Age-adjusted 1970 US Population)  
Melanoma of Skin: White Males, 1970-94



# Prevalence of MS worldwide



*Sunshine (Vitamin D) is the Elixir of Life?*





It couldn't be that simple...could  
it?

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Why not??

- Vitamin D directly or indirectly controls over 1000 genes (3% of genome)



# Rickets

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- 2<sup>nd</sup> Century AD – Roman Physician Soranus of Ephesus – children’s bony deformities more in Rome than Greece
- 17-18<sup>th</sup> Century – Industrial Revolution
- 1645 – 1<sup>st</sup> description of Rickets – Dr Whistler (as a medical student)
- 1789 – cod liver oil – Dr Darbey (for rheumatism)
- 1861 – association with sunlight – Dr Trousseau
- 1890 – sunlight sunbaths – Dr Palm
- 1919 – Mercury vapour lamps cure Rickets – Dr Huldchinsky

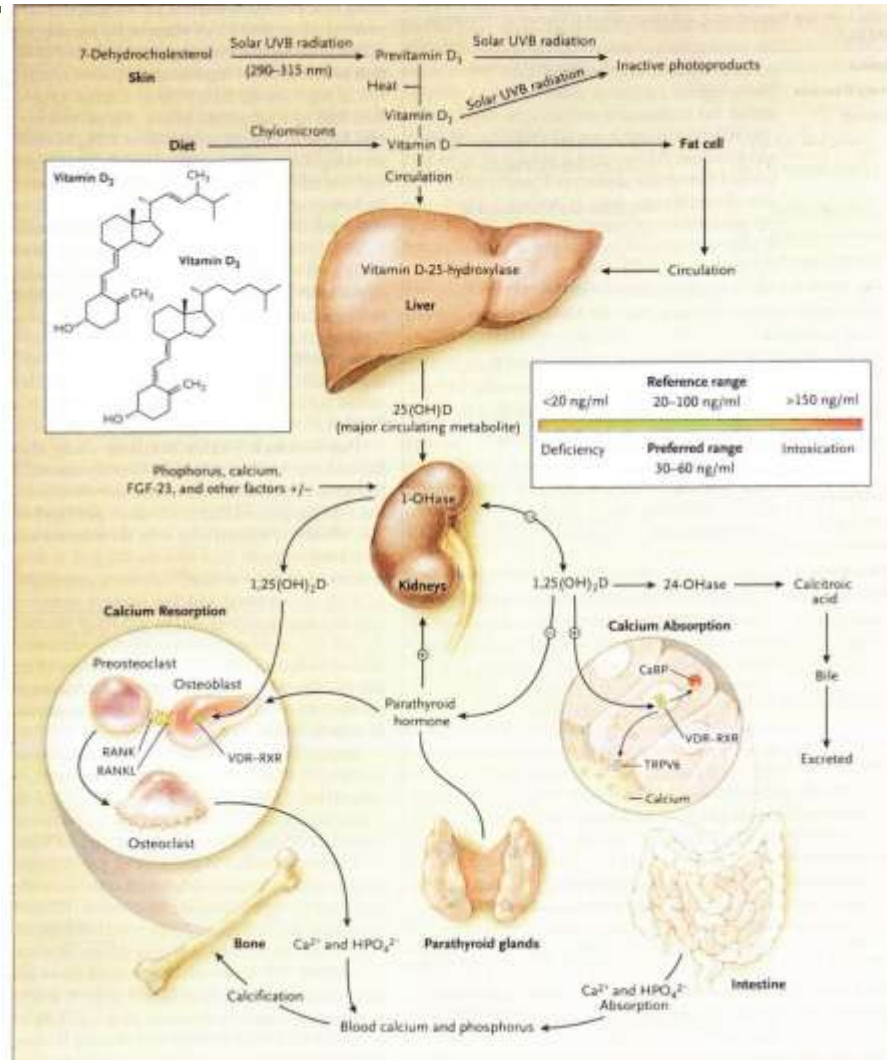


# The Vitamin D story

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- 1918 – animal experiments; fat soluble substance – designated Vitamin D ( Sir Edward Mallenby, Dr Elmer McCollum)
- 1930s – Vitamin D2 and D3 identified
- 1968 – 25(OH) Vitamin D – the liver
- 1971 – 1,25(OH) Vitamin D – the kidneys

# Vitamin D – refresher





# Non-bone effects of Vitamin D

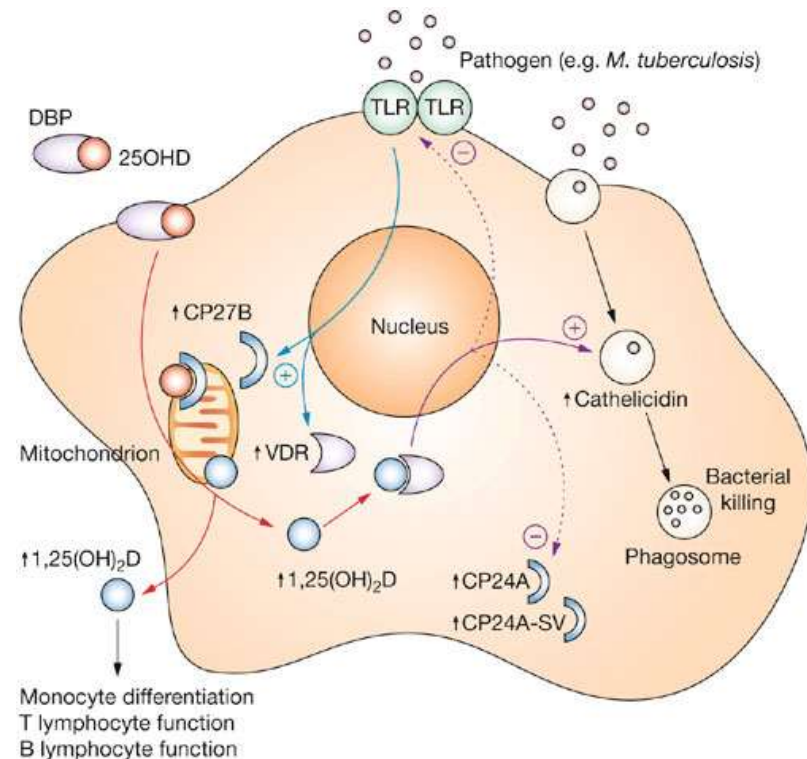
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- Immunity
  - Innate
  - Adaptive
- Diabetes
- Cardiovascular disease
- Cancer

# Vitamin D and Immunity

(Gombart M. BMC Genomics. 2009;July12)

- Innate - immune response to attack by microorganisms
  - Vitamin D dependant via regulation of **cathelicidin** antimicrobial peptide (CAMP)





# Influenza and Vitamin D

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- **Antimicrobial Peptides**
- **Defensins and Cathelicidins:**
  - Protect mucosal epithelial surfaces with a hostile antimicrobial shield with antiviral effects that bind to Haemagglutinin–A and inactivate influenza virus (Leikina et al. Nature Immunol. 2005;6(10):995-1001)
  - Effects on secreted neutrophils, NK cells, macrophages (down regulating proinflammatory Interferon- $\gamma$ , TNF- $\alpha$  and IL-12)





# Vitamin D in the tissues

(Journal of Immunology. November 2008)

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- Directly or indirectly  $1,25(\text{OH})_2\text{D}$  controls > 200 genes involved in:
  - Cellular proliferation (reduces cellular proliferation in normal and cancer cells and induces cellular terminal differentiation)
  - Increases Apoptosis
  - Reduces Angiogenesis



# Vitamin D – Optimal levels

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- “Expert consensus”: (Holick MF. N Eng J Med. 2007;357 (3):266-280)
  - Deficiency =  $<50$  nmol/l
  - Relative insufficiency =  $<75$  nmol/l
    - (Inverse relationship between 25-OH and parathormone until parathormone suppressed at 75-100nmol/l Vit D)
  - Sufficient Vit D =  $>75$  nmol/l
  - Optimal ??
  - Vit D Intoxication only if levels  $> 150$  nmol/l



# Recommended Daily Allowance

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- 400 IU daily
- 2000IU considered safe maximum intake



# Recommended Daily Allowance

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- 400 IU daily
- 2000IU considered safe maximum intake
  
- BUT we can make up to 20,000 IU in the sun!

# Blood Levels indicating deficiency have been identified:

- Rickets/Osteomalacia <25 nmol/l
- **Deficiency** <50 nmol/l
- **Insufficiency** 50-75 nmol/l
- **Sufficiency** >75 nmol/l
- Dramatic suppression of parathormone\* >50 nmol/l
- Maximum gut calcium absorption\*\* >85 nmol/l
- Max. neuromuscular perform. in Elderly\*\*\* 125 nmol/l
- Optimal for cancer prevention ?? ??>100nmol/l
- Prevention of Colds & Influenza??? ?? 125 nmol/l

\* Lips. P. J Clin Endocrin & Metab. 2001;86:1212

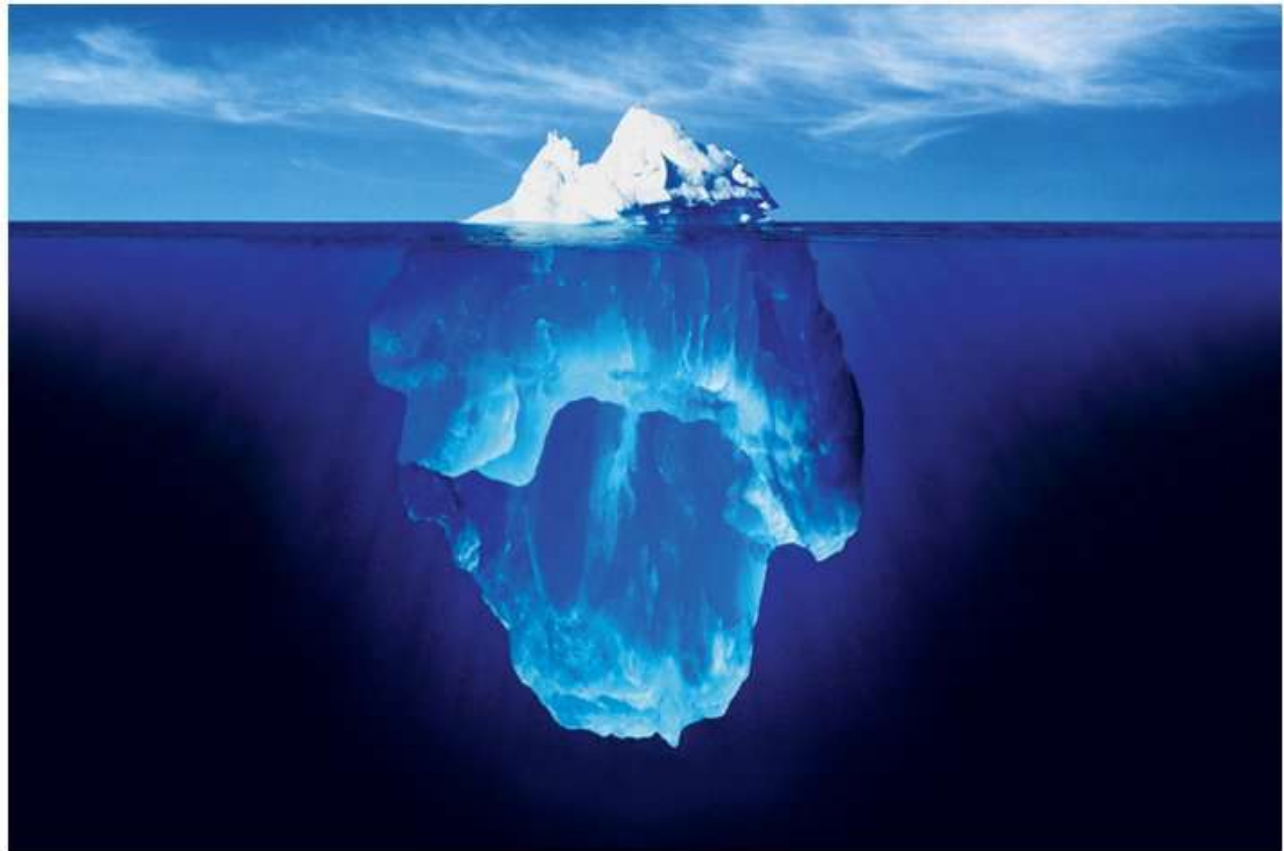
\*\* (Delucca et al. Am J Clin Nutr. 2004;80(Suppl):1689S-1696S)

\*\*\* Biscoff-Ferrara. Am J Clin Nutr. 2003;22:142-146

nmol/l = ng/ml x 2.5

# The extent of **D**eficiency

>75 nmol/l



<75 nmol/l



# Vitamin D Deficiency

(Holick M. N eng J Med. 2007;357(3):266-281)

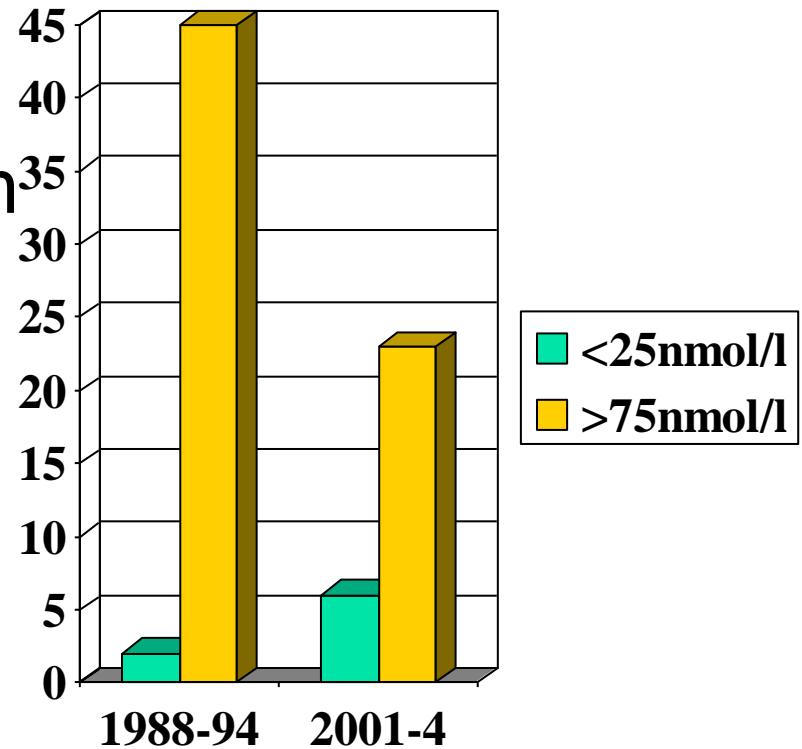
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- Estimated 1 billion people worldwide
- 40-100% of U.S. and European elderly women and men in the community (not rest homes)
- >50% women on medication for osteoporosis were deficient
- 52% black/Hispanic adolescents (Boston)
- 48% white preadolescent girls (Maine)

# Vitamin D levels declining

(Archives Internal Medicine; March 23<sup>rd</sup>, 2009)

- 18,883 participants of NHANES 1988-1994 compared with 13,369 participants of NHANES 2001-2004





# The sunny areas?

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- Saudi Arabia, UAE, Australia (NZ), Turkey, India and Lebanon:
  - 30-50% of children and adults deficient
  - D levels < 50nmol/l



# Vitamin D Deficiency in New Zealand

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- Surveys within NZ found deficiency in the **majority** of:
  - Indoor Workforce
  - Auckland elderly
  - Pregnant women in Wellington
  - Dunedin elderly
  - Children throughout the country

(Seasonal variation in vitamin D levels in the Canterbury, New Zealand population in relation to available UV radiation. Livesey J et al. NZMJ. 2007;120 no 1262)



# Vitamin D Deficiency in New Zealand

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- “Most Christchurch people are vitamin D deficient most of the time and a daily supplement of 2600 IU vitamin D3 would correct this”

(Seasonal variation in vitamin D levels in the Canterbury, New Zealand population in relation to available UV radiation. Livesey J et al. NZMJ. 2007;120 no 1262)



# U.S. Children

(Paediatrics. August 2009)

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- 6000 children, ages 1-21 (NHANES survey 2001-2004)
- **61%** had insufficient Vit D <75nmol/l
  - Equates to **50.8 million children**
- **9%** deficiency (<38 nmol/l)
  - Equates to **7.6 million children**



# New Zealand Teenagers

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- Tasmanian Study
- Age 16 boys
- In winter > 68% had levels < 50nmol/l



# Why such deficiency?

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- Sunscreens with a sun protection factor (SPF) of 15 reduce the capacity of the skin to produce vitamin D by about 98%.
- Poor diet
  - Fish and liver oils, liver, fortified foods (margarine, milk, orange juice in USA)

# Rickets is back!



- **“Rickets Making Comeback in American Kids”** – “....because parents are actually following the advice of pediatricians, many children are not getting enough vitamin D”  
(WebMD Medical News, Oct 30, 2000 (Chicago))



# Teens need more Vitamin D

(AHA Conference presentation March 11<sup>th</sup> 2009)

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- NHANES survey 2001-4: 3577 boys and girls aged 12-19
- Caucasians – D level mean 62 nmol/l
- Mexicans/African American mean 53 and 38 nmol/l
- Lowest quartile vs highest quartile for Vit D
  - OR **2.36** for hypertension
  - OR **2.54** for hyperglycaemia
  - OR **3.99** for Metabolic syndrome



# Arterial stiffness in Teens

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- **Endocrine Society** (Dong Y et al. JCEM. Accepted for publication)
- **44 Black teenagers in sunny Georgia**
  - Supplemented with 400IU vs 2000IU
  - Pulse-wave velocity measurement of arterial stiffness
  - 400IU – failed to reach sufficiency level. Stiffness unchanged
  - 2000IU reached sufficiency and arterial stiffness fell (vascular protective effect of Vitamin D)



# Pregnant women?

(Lee J. Clin Pediatrics (Phila) 2007;46:42-44)

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- 40, mainly Black, Pregnant and lactating women
  - 70% taking prenatal multivitamins containing 400 IU Vitamin D
  - 90% ate fish
  - 93% drank 2-3 glasses of milk per day



# Pregnant women!!

(Lee. J. Clin Pediatrics (Phila) 2007;46:42-44)

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- 50% of the women and 65% of their infants were severely Vitamin D deficient at the time of birth  
(D < 30nmol/l)

# Mothers and Babies in Wellington (Dr Judkins – GP antenatal population)

(Judkins A. et al. NZ Med J. 2006;119(1241))

- 90 women
- Universally low levels D, including African, Asian, Veiled, Maori, Pacific and European
- 78% had levels < 50nmol/l
- **None** had levels > 75nmol/l
- All the African/veiled had very low to **unrecordable** levels



# ICU pts – The Critically Ill

(Lee et al. N Eng J Med. 2009;360(18):1912-1914)

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- Australian study
- 42 pts prospectively evaluated
  - Mean Vit D = 41(19-63) nmol/l
  - Sufficient (>60) 3 (7%)
  - Insufficient (>30 to 60) 23 (55%)
  - Deficient (>15 <30) 16 (38%)
- Vitamin D inversely correlated with SAPS II severity score (Simplified Acute Physiology Score)
- Deaths – 3 (all undetectable Vitamin D)
- **All had Vit D levels < 75nmol/l**



# Vitamin D Deficiency – associations

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- Osteoporosis and osteomalacia/Rickets
- Cancers
- CVD
- Diabetes (Types 1 and 2)
- Neurological conditions – Alzheimer's, Seizures, Inflammatory brain lesions
- Depression, Schizophrenia
- Infection susceptibility and responses
- Allergic asthma
- Chronic Pain
- Autoimmune diseases



# Muscle aches and Bone Pain

Mayo Clinic Proceedings 2003;78:1463-70

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- ED Presentations with non-specific muscle aches and bone pain – wide variety of diagnoses including:
  - Fibromyalgia, chronic fatigue, growing pains, depression
- 93% Vitamin D deficient



# Falls and the Elderly

(Bischoff-Ferrari H. BMJ.

2009;339:843-846)

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Meta analysis of 8 DBPC trials Vit D<sub>2</sub> and D<sub>3</sub>  
700-1000IU +/- Calcium

- High Dose Vit D<sub>2</sub> reduced falls 19%
- High dose Vitamin D<sub>3</sub> reduced falls by up to 26%
- Vitamin D level achieved >65 nmol/l reduced falls by 23% compared with <65 nmol/l
- Trials with 1,25(OH)<sub>2</sub>D reduced falls by 22% but more likely to cause hypercalcaemia



# Asthma and Vitamin D

(Sutherland ER. Am J Respir Crit Care Med. 2010;181(7):699-704)

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- 54 adults (non-smokers)
- 25-OH Vit D level related to airway responsiveness and glucocorticoid sensitivity
- Higher Vit D ass'd with higher lung function
  
- Vit D < 75nmol/l
  - Impaired lung function
  - greater airway hyper-responsiveness
  - Reduced glucocorticoid response



# Type 1 Diabetes

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- Children with D-deficiency
  - Risk of Type-1 diabetes increased by 200%
- Increasing Vitamin D intake during pregnancy reduced development of Islet cell antibodies in offspring

(Am J Clin Nutr. 2004;79:820-5)



# Vitamin D and Type-1 Diabetes

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- 10,366 children in Finland (Lancet 2001;358:1500-3)
  - 2000 IU Vitamin D3 daily in first year of life
  - Relative risk of Type 1 Diabetes reduced by 78%



# Chronic kidney Disease

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- Levels of 25OH D inversely associated with PTH levels whatever the degree of renal failure
- **25-OH Vitamin level to be maintained > 75nmol/l with D3 supplements**  
(Recommendation of National Kidney Foundation)
- May need active analogue (1,25(OH<sub>2</sub>)D) to maintain calcium homeostasis



# Vitamin D in Cardiovascular disease

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- Young science:
  - Many Observational studies
    - Association between lower Vitamin D levels and higher CV mortality
  - Intervention studies:
    - None designed specifically to evaluate the effect of supplementation



# Vitamin D and Carotid Intima-Media Thickness in T2 Diabetics

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- Strong independent association with D deficiency and increasing CIMT
- ? D plays a part in atherosclerosis  
(Targher G et al. Clin Endocrinol. 2006;65(5):593-597)



# Problems with CVD trials so far

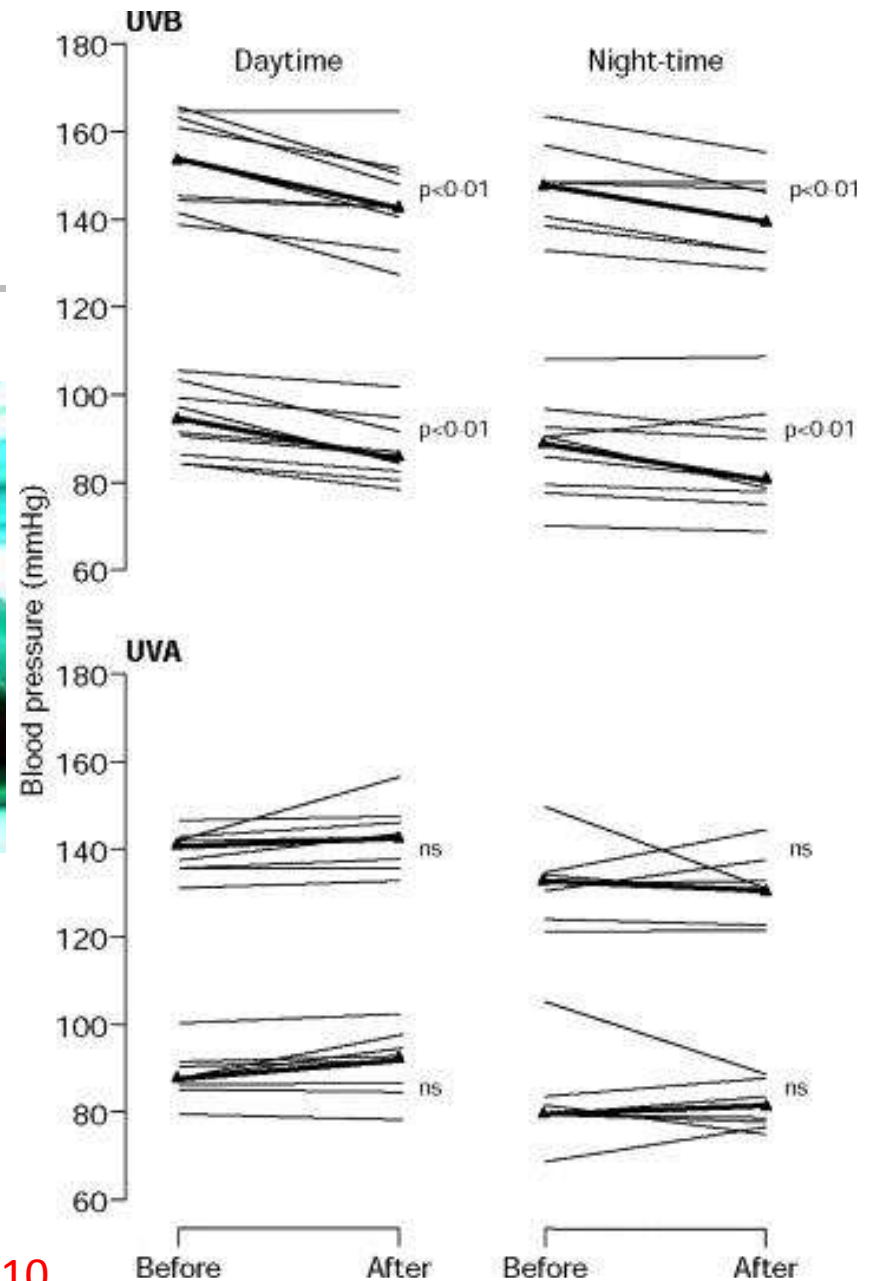
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- Not set up to evaluate the effect of Vit D
  - Levels of 25-OH D either not measured or levels *now* considered necessary not achieved
  - Doses used too small
  - Ergocalciferol vs Cholecalciferol
- 
- Calcium supplements alone however are not protective vs CVD and may be detrimental  
(Bolland et al. BMJ;2008;336:262-6)

# UVB and hypertension



- 18 patient with mild untreated hypertension (age 26-66)
- UVB vs. UVA 3 x weekly for 6 weeks
- 162%** increase in Vitamin D (UVB)
- Significant fall in both systolic and diastolic day and night-time BP



[The Lancet 1998; 352:709-710](#)



# Vitamin D supplementation in heart failure

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- 123 CCF patients (Am J Clin Nutr. April 2006)
- 2000IU Vitamin D daily (placebo controlled trial)
- Reduction in inflammatory activity in CCF patients with use of D supplements
  - Reduced TNF- $\alpha$  and IL-10
- (Previous study with 400 IU showed no effect on cytokines)



# Vitamin D and Cancer

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- Higher latitudes:
  - Increased Hodgkin's, colon, pancreatic, prostate, ovarian, breast compared with lower latitudes
- 25-OH D below 50nmol/l associated with:
  - 30-50% increased risk of incident colon, prostate and breast
  - Higher mortality from these cancers



# Prostate Cancer

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- Vitamin D levels in young men studied: (Ahonen. Cancer Causes Control. 2000;11(9):847-52)
  - D levels < 40nmol/l
    - 3 x more likely to develop prostate cancer
    - 6 x more likely to develop invasive cancers
- Hanchette and Schwartz (Cancer. 1992;70(12):2861-9)
  - USA men 10x risk of Japanese for prostate cancer
  - Japanese - High fish intake and consequent vitamin D
  - Soy – Genistein inhibits breakdown of calcitriol in prostate tissue.



# Breast Cancer and Vitamin D

(Crew KD et al. J Clin Oncol. 2009;27(13):2151-6)

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- “High prevalence of Vitamin D deficiency despite supplementation in premenopausal women undergoing adjuvant chemotherapy”
- 74% women were frankly D deficient (median 42nmol/l)
- After D supplementation (400 IU D<sub>3</sub>+ 1000mg Ca) for 1 year
  - <15% white and Hispanic had sufficient D
  - No Black women had sufficient D
- Recommended supplement level (400 IU) insufficient to raise levels



# Lung Cancer Surgery and survival

(Zhou.W et al. Cancer Epid Biom Prev. 2005;10: 2303-9)

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- Early non-small cell lung cancer
- Patients with highest vitamin D intake operated in Summer vs. Lowest D intake operated in winter:
  - 3 – fold disease free survival rate
  - 4 – fold overall survival rate



# All cause mortality

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- Meta analysis of 18 trials
- 57,311 randomly assigned participants
- Vitamin D supplementation reduced all cause mortality by 7% (CI 1%-13%)



# How Much Vitamin D do we need to take?

(Am J Clin Nutr. June 2008)

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- Dose adjusting study over 6 months in 38 men and women
- Optimal level > 75 nmol/l
  - Patients with D > 55nmol/l need **3800 IU/day**
  - Patients with D < 55nmol/l need **5000 IU/day**
- *“The selection of 2000 IU as a safe upper limit of intake is based on insufficient evidence”*



# How much in Pregnancy? (Wagner C

et al. Presented to Paediatric Academic Societies, Vancouver, May 2010)

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- Approx. 500 women
  - 2<sup>nd</sup> and 3<sup>rd</sup> trimester
- 400IU vs 2000IU vs 4000IU per day
- Pregnancy-related complications (gestational diabetes, pregnancy-associated hypertension, preeclampsia)
  - **Reduced by 50%** with 4000 IU per day as compared with 400IU/day
  - **4000 IU/day Vitamin D3 safe in pregnancy**



# A pragmatic approach - Assume everyone is Vitamin D deficient

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- Elderly
- Pregnant women and infants
- Children (teeth, asthma, painful bones)
- All chronic illness (Autoimmune, diabetes, cardiovascular disease, hypertension)
- Cancer and Chemotherapy
- Liver and renal disease (conversion issues)
- Brain – depression/schizophrenia/dementia



# The Elderly - A pragmatic approach

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- The elderly generally: High risk for Falls/infections/cancer
  - Oral Vitamin D3 (loading) then 1.25mg (50,000 IU) fortnightly
- Rest Home residents: falls/infections
  - Oral Vitamin loading then D3 1.25mg (50,000 IU) fortnightly
  - 600,000 IU depot intramuscularly 6-monthly or annually? **Increased fracture risk??**



# Vitamin D deficiency

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- Vitamin D deficiency is a real and present danger
  - Big interventional trials are required with adequate dosing to achieve levels  $> 75$  nmol/l
- Huge potential to influence human health
- It is very cheap and probably supplementation is the most cost-effective intervention we can undertake in Medicine.



# Thoughts to ponder.....

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- All the drug trials in chronic diseases have been done on Vitamin D deficient people
- If they had been D-replete
  - Would they have developed the disease at all?
  - Would the drugs have had the same statistically significant benefit?



# Summary

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- Vitamin D is essential to health not only of the bones but immune system, CV health, mental health and cancer prevention
- Widespread deficiency has been demonstrated from cradle to grave
- Small clinical trials have shown benefits of supplementation
- RDA is woefully inadequate
- Supplementation at 4000 IU per day is safe in pregnancy
- Big interventional trials needed
  
- In the meantime..... Be pragmatic



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Think Vitamin D  
Deficiency in every  
patient

# Dietary sources of Vitamin D

(Holick M. N Eng J Med. 2007;357(3):266-281)

■ Salmon	<i>Approx. levels</i>
■ Fresh wild (3.5 oz)	600-1000 IU D <sub>3</sub>
■ Fresh, farmed (3.5 oz)	100-250 IU
■ Canned (3.5 oz)	300 IU
■ Sardines	
■ Canned (3.5 oz)	300 IU
■ Tuna	
■ Canned (3.5 oz)	230 IU
■ Shitake mushrooms	
■ Sun-dried (3.5 oz)	1600 IU (D <sub>2</sub> )
■ Cod liver oil (1 tsp)	400-1000 IU



# Warnings

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- Hypercalcaemia

- Primary hyperparathyroidism
- Granulomatous diseases (lung/activated mononuclear cell production of  $1,25(\text{OH})_2\text{D}$  outside control of renal parathormone feedback) (**NB Vitamin D level can be low**)
  - TB
  - Sarcoidosis
  - Coccidioidomycosis
- Malignancy – Hodgkin's ( $1,25(\text{OH})_2\text{D}$  or PTHrP), Ca Lung