ILSI SEAR Australasia and the National Committee for Nutrition, Australian Academy of Science

Should Australia and New Zealand allow more Vitamin D into the food supply?

Support for post graduate participation in this workshop from the Australian Nutrition Trust Fund is gratefully acknowledged.

Conference supported by:

NSA Melbourne Group

DEAKIN UNIVERSITY AUSTRALIA
Centre for Physical Activity and Nutrition Research
Overview:
Impact of vitamin D insufficiency/deficiency on health

Caryl Nowson
Chair Nutrition and Ageing
Other speakers today

- Vitamin D status of Adult Australians • Prof Rob Daly
- Vitamin D status of dark skinned groups • As/Prof Andre Renzaho
- Mandatory fortification in Canada • Prof Susan Whiting
- Sunlight exposure: adequate vitamin D • Prof Rebecca Mason
- Pregnancy and young children • Dr Georgia Paxton
- Vitamin D and mental health • Prof John McGrath
- Emerging areas • Prof Peter Ebeling
- Industry perspectives

Vitamin D and mental health
Emerging areas
Industry perspectives
Vitamin D2
Synthetic: supplements
irradiation of ergosterol

Vitamin D3
irradiation of a pro-vitamin molecule (7-dehydrocholesterol)
in the skin of mammals
Animal sources

Vitamin D2 & D3

- Originally classified as a nutrient:
  - cod liver oil antirachitic infants (1920)
- Exposure to sunlight/uv light also could prevent and cure rickets
- vitamin D
  - Hormone: synthesis partially dependent on the action of ultraviolet light
Classical Vitamin D Deficiency
Rickets and Osteomalacia

Growth plate does not mineralise

Bone biopsy remodelled bone does not mineralise

2nd biopsy shows resolution of the osteomalacia after treatment.
Vitamin D

Major Source: Sunlight

7-Dehydrocholestrol

Cholecalciferol (vitamin D₃)

Minor Source: Diet

Vitamin D₃ (Margarine, fish, meat)

Vitamin D₂ (irradiated fungi/previous supplements)

1-25-dihydroxyvitamin D₃

Urinary calcium reabsorption

Bone mineralisation

Calcium absorption (small intestine)

25-hydroxy D-alpha-hydroxylase (CYP27B1)

Renal

Extrarenal CYP27B1

Measured in serum. Indicator of vitamin D status.
Newly recognised Roles for vitamin D

- **Endocrine Modulators**
  - Act on $1\alpha$-hydroxylase
    - *estrogen, calcitonin, growth hormone*
    - *Prolactin, insulin, glucocorticoid*

- **$1\alpha-25(OH)_2D_3$ Nuclear Receptors**
  - *adipose, adrenal, bone, bone, marrow, brain, breast, cancer cells, cartilage, colon, epidymis, hair follicle, intestine, kidney, liver, lung, muscle, osteoblast, ovary, pancreas, parathyroid, parotid, placenta, prostate, retina, stomach, testes, thymus, thyroid, ureter*

- **Paracrine Production**
  - $1\alpha-25(OH)_2D_3, 24H,25(OH)_2D_3$
    - Macrophages, keratinocytes, astrocytes
  - $1\alpha-25(OH)_2D_3$ mediated cellular growth & differentiation
    - Haemopoietic cells
      - Skin, brain
  - $1\alpha-25(OH)_2D_3, 24H,25(OH)_2D_3$

- **Placental Production**
  - Foetal development

---

**EXTRA RENAL**

**CYP27B1**


---

- Vitamin D receptor (VDR) expressed in nucleated cells
- ~3% genome under control
  - 1,25-dihydroxyvitamin D
- $\geq$10 tissues kidney express $1\alpha$-hydroxylase (CYP27B1)

**25-(OH)D $\rightarrow$ 1,25(OHD)**

- Active hormone can be generated: autocrine or paracrine
- Activity of vitamin D endocrine system broad: resembles other ligands of nuclear receptors, such as thyroid hormone
Vitamin D: Disease Links

- Cardiovascular disease
- Diabetes Type 1
- Colorectal cancer
- Breast Cancer
- Cognition
- Autism
- Metabolic Syndrome
- Diabetes Type 2
- Tubererculosis
- Inflammatory Bowel Disease
- Schizophrenia
- Depression
- Falls
- Fracture
- Muscle Weakness
- Multiple Sclerosis
- Rheumatoid Arthritis
- Resistance to Infections
Sun rich cultures
135 - 220 nmol/L 25 (OH)D₃
Life guards 148 - 163 mmol/L

Nursing home residents
35 nmol/L 25 (OH)D₃
Vitamin D status (25OHD) and disease

Level 1

- Vitamin D (plus calcium) for falls
- and fractures
  (DIPART, 2010, Institute of Medicine (IOM), 2011)
- All cause mortality

Level II

- Insulin resistance
  (Mitri et al. 2011, von Hurst et al. 2010)
- Influenza type A
  (Urashima et al., 2010)
Evidence vitamin D status (25OHD) is related to disease

Level III
Secondary outcomes: cancer (Lappe et al. 2007), Asthma (Urashima et al. 2010) (Level III-1): RCT

• Low serum 25(OH)D associated with:
  Autoimmune disorders (Souberbielle et al. 2010), rheumatoid arthritis (Merlino et al. 2008), type 1 diabetes (Hyppönen et al. 2010), type 2 diabetes (Pittas et al. 2007), multiple sclerosis (van der Mei et al. 2007), cardiovascular disease (Wang et al. 2008, Melamed et al. 2008), schizophrenia (McGrath et al. 2010), cognitive decline (Buell 2009), depression (Milaneschi et al. 2010), active tuberculosis (Nnoaham et al. 2008), increased susceptibility to infection (Urashima et al. 2010), cancer [colon, breast] (Gandini et al. 2011) and neurological conditions (Parkinson’s disease) (Knekt et al. 2010) (Level III-2)
Vitamin D: Effect on falls/fracture (compliance >50%)

- 2-year randomised, double-blind placebo controlled
  - >25 & <90 nmol/l 25(OH)D (not deficient)
  - All 600 mg Calcium
  - vitamin D (10,000 IU D2 1/wk or 1000IU (25ug) 1/d)
  - placebo
- OR ever falling 0.70 (0.50–0.99) (30% reduction)
- OR ever fracture 0.68 (0.38–1.22)
  - 8 people needed to be treated for one year to prevent a fall occurring

Flicker et al. JAGS 2005 Nov
Meta analysis: vitamin D fracture:
RCT > 65 years: dose > 400 IU (10µg)

Non vertebral fractures

- ↓ 20% Non vertebral fractures
- (n=33,265) (9 trials)
- community-dwelling (−29%)
- institutionalized older (−15%)
  - (nb WHI classed high dose 400µg)

Hip fracture

- ↓ 18% Hip fracture (n=31,872) (5 trials)
- community-dwelling older (−21%)
- institutionalized older (−28%)

Meta-analysis: vitamin D & Falls

• 26: n= 45,782
• Most elderly females
• Vitamin D ↓ OR: 0.86 (0.77–0.96). 24% ↓
• Greatest effect:
  – vitamin D deficient + calcium
    0.86 (0.77 0.96)

Also Kalyani et al. 2010 J Am Geriatr Soc. ↓14% falls (RR)=0.86, Bischoff-Ferrari HA, et al. JAMA. 2004 Apr 28;291(16): ↓22% falls
Vitamin D Levels Predict All-Cause and Cardiovascular Disease Mortality in Subjects With the Metabolic Syndrome

- 1801 persons with metabolic syndrome in The Ludwigshafen Risk and Cardiovascular Health (LURIC) study of subjects referred for coronary angiography between 1997 and 2000
- Mortality tracked for a median of 7.7 years
- Multivariable survival analysis used to estimate the association between 25(OH)D levels and mortality
- Split by: <25, 25-50, 50-75 >75nmol/L serum OHD
  - Age (yrs) 66 64 62 62
  - Female% 47 28 30 23

Optimal 25(OH)D levels (≥ 75nmol/L) substantially lowered all-cause and CVD mortality in subjects with the metabolic syndrome.
Randomised Trial: Secondary outcome

Evidence Level II randomised controlled trial

- 4-y, population-based, double-blind, randomized, placebo-controlled trial.
- Primary outcome:
  - Fracture incidence
- Secondary outcome:
  - Cancer incidence
- 1179 post-menopausal
- (Ca-only) Ca 1400–1500 mg
- (Ca-D), Ca + 1100 IU(27ug) vitamin D3/d
- (PL) placebo
- unadjusted RR of cancer
  - CaD 0.402 (P<0.01)
  - Ca-only 0.532 (P<0.06)

Kaplan-Meier survival curves (ie, free of cancer) for the 3 treatment groups randomly assigned in the entire cohort of 1179 women. Sample sizes are 288 for the placebo group (n=18 (6.8%)), 445 (Ca-only) (n=15 (3.6%)) group, 446 calcium plus vitamin D (CaD) (n=8 (2.0%)). The survival at the end of study for the Ca-D group is significantly higher than that for placebo.

Evidence supports a key role of calcium and vitamin D in skeletal health, consistent with a cause-and-effect relationship and providing a sound basis for determination of intake requirements.

For extraskeletal outcomes, including cancer, cardiovascular disease, diabetes, and autoimmune disorders, the evidence was inconsistent, inconclusive as to causality, and insufficient to inform nutritional requirements.

Randomized clinical trial evidence for extraskeletal outcomes was limited and generally uninformative.

For vitamin D, RDAs:
- 600 IU/d (15µg) for ages 1–70 yr
- 800 IU/d (20µg) for ages 71 yr and older,

Corresponding to a serum 25-hydroxyvitamin D level of at least 50 nmol/L), meet requirements of < 97.5% of the population.
**Aust. Vitamin D: NRVs (AI) 2006**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>µg/day AI</th>
<th>µg/day IU</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-18 yrs</td>
<td>5</td>
<td>200</td>
</tr>
<tr>
<td>19-30 yrs</td>
<td>5</td>
<td>200</td>
</tr>
<tr>
<td>31-50 yrs</td>
<td>5</td>
<td>200</td>
</tr>
<tr>
<td>Pregnancy/Lact.</td>
<td>5</td>
<td>200</td>
</tr>
<tr>
<td>51-70 yrs</td>
<td>10</td>
<td>400</td>
</tr>
<tr>
<td>&gt;70 yrs</td>
<td>15</td>
<td>600</td>
</tr>
<tr>
<td>1 – 19+yr</td>
<td></td>
<td>UL 80 3200</td>
</tr>
</tbody>
</table>

**Explanatory Note**

For institutionalized or bed bound elderly, very restricted exposure to sunlight often accompanied by reduced food intake, affecting both dietary calcium and vitamin D, supplementation with vitamin D in the order of 10-25µg/day may be necessary.

IOM 2010 revised RDA Vitamin D:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>EAR (µg/day)</th>
<th>RDA (IU)</th>
<th>AI (µg/day)</th>
<th>EAR (IU)</th>
<th>RDA (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6M</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>6-12M</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>18-50 yrs</td>
<td>5 µg</td>
<td>200 IU</td>
<td>5 µg</td>
<td>200 IU</td>
<td>200 IU</td>
</tr>
<tr>
<td>51-70 yrs</td>
<td>10 µg</td>
<td>400 IU</td>
<td>10 µg</td>
<td>400 IU</td>
<td>400 IU</td>
</tr>
<tr>
<td>71+ yrs</td>
<td>15 µg</td>
<td>400 IU</td>
<td>15 µg</td>
<td>400 IU</td>
<td>400 IU</td>
</tr>
<tr>
<td>Preg/Lact.</td>
<td>10</td>
<td>15</td>
<td>10</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>1-70yrs</td>
<td>10</td>
<td>15</td>
<td>10</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>70+yrs</td>
<td>10</td>
<td>20</td>
<td>10</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>0-6M</td>
<td>25</td>
<td></td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-12M</td>
<td>38</td>
<td></td>
<td>38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-3yrs, 4-8yr</td>
<td>63,75</td>
<td></td>
<td>63,75</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>100</td>
<td></td>
<td>100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Estimated Average Requirement (EAR):** Reflects the estimated median requirement

**Recommended Dietary Allowance (RDA):** Derived from the EAR and meets or exceeds the requirement for 97.5 percent of the population.

Available from the National Academies Press at: [http://www.nap.edu/catalog/13050.html](http://www.nap.edu/catalog/13050.html)
Australian 
Dietary Vitamin D intake (1995 NNS)

- Margarine: 48%, canned fish: 16% Eggs: 14%, butter 3%
  
  Mean daily intake:
  - females 2µg (80IU)
  - males 2.6µg (104 IU)

Mandated margarine, (at low level) ≥5.5µg (220IU)/100g

### Current voluntary regulations (Vit D fortification)

<table>
<thead>
<tr>
<th>Food</th>
<th>Reference quantity</th>
<th>Max claim per ref Quantity (10μg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dried milks</td>
<td>200ml</td>
<td>2.5 μg (25%)</td>
</tr>
<tr>
<td><strong>Modified milks Low fat</strong></td>
<td>200ml</td>
<td>1.0 μg (40IU) (10%)</td>
</tr>
<tr>
<td>Cheese/ products</td>
<td>25g</td>
<td>1.0 μg (10%)</td>
</tr>
<tr>
<td>Yoghurts</td>
<td>150g</td>
<td>1.0 μg (10%)</td>
</tr>
<tr>
<td>Dairy desserts</td>
<td>150g</td>
<td>1.0 μg (10%)</td>
</tr>
<tr>
<td>Butter</td>
<td>100g</td>
<td>1.0 μg (10%)</td>
</tr>
<tr>
<td>Analogues from legumes/cereal - Beverages</td>
<td>200ml</td>
<td>1.0 μg (10%)</td>
</tr>
<tr>
<td>- Yoghurt</td>
<td>150g</td>
<td>1.0 μg (10%)</td>
</tr>
<tr>
<td>- Cheese</td>
<td>25g</td>
<td>1.0 μg (10%)</td>
</tr>
<tr>
<td>Formulated Beverages</td>
<td>600ml</td>
<td>2.5 μg (25%)</td>
</tr>
</tbody>
</table>

**Australia**

Formulated supplementary food

Anlene milk drink [5μg/250mL](4μg (160 IU /200mL)
4x level allowed in milk (40%)

Anlene yoghurt [5μg/200g serving]

“Just two servings a day provide at least 100% of the recommended dietary intake (RDI) of Calcium and 100% RDI of Vitamin D for most adults.”
*Ca 200mg/100ml

**Canada milk** (2μg (80IU) /200mL)
Fortification Practices: intake/day

- **USA and Canada (~3-6µg (120-240IU)/d)***
  - Voluntary/Mandated (2.5µg (100IU)/250ml)
  - Margarine (1.5µg (60IU)/100g)
  - Voluntary: infant formula & cereals routinely fortified with vitamin D, some juices
- **Europe (~2-4µg (80-160IU)/d)***
  - Voluntary: levels of fortification quite low
- **Australia (~2-3µg (80-120IU)/d)***
  - Mandated margarine, (at low level) ≥5.5µg (220IU)/100g
- **Voluntary low level in low fat milk products (1µg (80IU)/200ml)**
- **NZ (~1-2.5 (40-180IU)/µg/d)***
  - No mandated fortification
  - Voluntary low level in low fat milk products

*reported mean range of intake
Dietary source of vitamin D

- Few foods with significant amounts of vitamin D
- Small amount dietary cholecalciferol (fat of animals)
- Rich sources are fish, especially high fat fish such as salmon, herring and mackerel (north sea)
  - (farmed salmon 25% vitamin D content of wild salmon) (baked, farm salmon comparable vitamin D content raw salmon fried in vegetable oil, only 50% vitaminD₃)*

<table>
<thead>
<tr>
<th>Food</th>
<th>Vitamin D (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mackeral 100g</td>
<td>8.6</td>
</tr>
<tr>
<td>Sardines 100g</td>
<td>6.8</td>
</tr>
<tr>
<td>Cod liver oil 30g</td>
<td>34</td>
</tr>
</tbody>
</table>

Other sources:
- Margarine (>(>55–<160µg /kg) usual content 10µg/100g
- Red meat and liver (0.7-1.1µg/100g), Full cream milk and eggs (1.8µg/100g)
- New sources irradiated mushrooms (< 20µg/100g) D₂

*Lu Z. et al. An evaluation of the vitamin D₃ content in fish: Is the vitamin D content adequate to satisfy the dietary requirement for vitamin D? J Steroid Biochem Mol Biol. 2007 Mar;103(3-5):642-4
Vitamin D in Australian Food:
amount required to reach
10µg (400IU) /day (AI adults 51-70yrs or US EAR)NB RDA 15µg (600 IU)

20 teaspoons margarine /day

OR almost 1½ cans of sardines/day

OR 10 (200ml) glasses Aust. vitamin D fortified milk
Amount of Vitamin D required

- Amount of vitamin D to prevent rickets in infants and young children is less than 3µg/d
  - Most children with dietary intake 76 -100IU (1.9-2.5µg)/d maintain serum 25OHD levels >28nmol/L (Asknes & Aarskog 1982, Gulttekin et al. 1987)

- IOM (2011) risk of vitamin D deficiency, leading to rickets in infants and children and osteomalacia in adults is observed at serum 25(OH)D concentrations <30 nmol/l

  4-6 teaspoons margarine /day
  OR ½ - ¾ cans of sardines/day
  OR 1-1½ (200ml) glasses Canada’s vitamin D fortified milk
Vitamin D fortification of food

- Dietary vitamin intakes low: not possible to increase diet significantly with current food supply
- Dietary supplements are useful but uptake does not typically exceed 40%*
- Problems fortifying single food staple eg milk or dairy does not increase intake in non consumers
  - Need a variety/number of different foods eg cereals, flour, bread
- Meta-analysis: 16 with food (n=1513), 14 +ve 25OHD

- Intake 11 µg/d (440 IU/d)
  - ↑ 25OHD 19 nmol/L
- those 25OHD <50nmol/L
  - 11 µg/d ↑ 25OHD 25 nmol/L

Dietary Levels of dietary calcium & Vitamin D

UL 1-3yrs: 63 µg (2,520 IU)
UL 4-8yr : 75 µg (3,000 IU)
UL 100 µg (4,000 IU)

UL calcium 1.7 times RDA 71 yr old
UL vitamin D 4 times RDA 71 yr old
US IOM

UL calcium > 70 yr 2000mg
19-50yr 2500mg
9-18 yrs 3000mg US IOM
Questions Addressed today

- How widespread is vitamin D deficiency/insufficiency in Australia and which groups are at greatest risk?
- Can safe sun exposure be achieved simultaneously with maintaining adequate vitamin D status for most people: winter/summer?
- Is vitamin D fortification of the food supply an effective method of addressing:
  - Vitamin D deficiency – rickets and osteomalacia (serum 25OH < 30 nmol/L)
  - Vitamin D insufficiency (30 -50 nmol/L in some groups)
- Are there any risks in raising vitamin food fortification levels to those comparable with Canada? Would some people consuming supplements be at risk of consuming too much?
Questions II

- What would be the impact on rates of vitamin D deficiency /insufficiency of increasing vitamin D fortification of the food supply through mandatory fortification of all fluid milks and possibly yoghurt with vitamin D comparable to Canada?
- What would be the impact on rates of vitamin D deficiency /insufficiency of altering the Food Regulations to increase range of foods to be fortified with vitamin D at higher levels (in other countries) e.g. ready-to-eat breakfast cereals, fruit juice, yogurt?
- Is fortification of food supply with vitamin D a potentially safe, cost effective strategy to address vitamin D deficiency?