# Vitamin D supplementation in reducing the risk of vitamin D insufficiency during infancy

An evidence based review of the literature

Carmen Hayward

# Patient presentation

- 20 day-old Caucasian infant
- From Adelaide
- Mother exclusively breastfeeding

- Will baby need vitamin D???

# Should breastfed babies receive vitamin D supplementation?

# Vitamin D

- Via the placenta during fetal life
- Sunlight after birth

# Measuring vitamin D

- Measured as the serum concentration of 25-hydroxyvitamin D [25(OH)D]
- Increased risk low bone density and rickets
  - Below 40 – 45 nmol/L
- Insufficiency:
  - Less than 50 nmol/L

# Risk factors

Source: www.telegraph.co.uk

Clinical focus

Guidelines

Vitamin D and health in pregnancy, infants, children and adolescents in Australia and New Zealand: a position statement

Georgia A. Paxton
Gwyn R Teale
Caryl A Nowson
Rebecca S Mason
Jonn J McGrath
Maunie J Thompson
Aris Siafarikas

Low vitamin D levels are a major public health concern across the lifespan. This position statement of the Australian and New Zealand Bone and Mineral Society and Osteoporosis Australia accompanies a position statement on vitamin D and health in adults[1] and updates a 2006 position statement.[2] It is intended for primary care providers and specialists involved in the care of children and pregnant women, and is endorsed by the Australasian Paediatric Endocrine Group, Royal Australasian College of Physicians and Royal Australian and New Zealand College of Obstetricians and Gynaecologists. The consensus process is described in Box 1.

Summary

- The recommended level for serum 25-hydroxyvitamin D (25(OH)D) in infants, children, adolescents and during pregnancy and lactation is ≥ 50 nmol/L. This level may need to be 10–20 nmol/L higher at the end of summer to maintain levels ≥ 50 nmol/L over winter and spring.
- Sunlight is the most important source of vitamin D. The US recommended dietary allowance for vitamin D is 600 IU daily in children aged over 12 months and during pregnancy and lactation, assuming minimal sun exposure.
- Risk factors for low vitamin D are: lack of skin exposure to sunlight, dark skin, southerly latitude, conditions affecting vitamin D metabolism and storage (including obesity) and, for infants, being born to a mother with low vitamin D and exclusive breastfeeding combined with at least one other risk factor.
- Targeted measurement of 25(OH)D levels is

Physiology

A summary of vitamin D physiology is provided in the

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25(OH)D levels are about 65% of maternal levels,[4] hence neonates born to vitamin D deficient mothers will also be vitamin D deficient.[3] Further, premature infants have low vitamin D stores solely due to prematurity.[5]

During lactation, maternal $1,25(OH)_2D$ levels decrease and PTH levels remain low, but the combination of elevated parathyroid hormone-related protein produced by the lactating breast and low oestradiol levels stimulate maternal bone resorption and increased renal calcium reabsorption, enabling adequate calcium to be transferred to breastfeeding infants.[3] This results in transient loss of maternal bone mineral content, with recovery after weaning. Infants depend on their own synthesis, ingestion and metabolism of vitamin D, as there is little vitamin D in breast milk.[6]

controlled trials of vitamin D supplementation.

Sources of vitamin D

Sunlight

Sunlight exposure is the most important determinant of vitamin D levels, even in exclusively breastfed infants,[7] and is estimated to provide over 90% of vitamin D in humans. Skin synthesis of vitamin D occurs through the action of ultraviolet B (UVB) radiation in sunlight, and varies with skin colour, ultraviolet radiation (UVR) protection (eg, clothing, shade, sunscreen), time spent outside, latitude, season, time of day, amount of cloud cover, air pollution



risk factors for low vitamin D, and give 400 IU vitamin $D_3$ daily to exclusively breastfed infants with other risk factors for low vitamin D. Breastfeeding women with low

Source: Paxton G, et al. Vitamin D and health in pregnancy, infants, children and adolescents in Australia and New Zealand: a position statement. Medical Journal of Australia. 2013;198(3):142-3.

# Additional risk factors

- Lack of skin exposure to sunlight
- Dark skin
- Southerly latitude
- Conditions affecting vitamin D metabolism and storage
- Being born to a mother with low vitamin D

# The clinical questions

In healthy breastfed infants with no confirmed maternal history of vitamin D insufficiency:

- Does vitamin D supplementation reduce the risk of vitamin D insufficiency during infancy ?
- If so, is it without increasing the risk of adverse events?

# Relevant publications

| Database of origin | Citation | Type of study |
|---|---|---|
| **Dynamed** | Pham, 2015 | Clinical practice guideline |
| | Grant et al., 2014 | Randomised controlled trial |
| **Pubmed** | Onal et al., 2010 | Cross-sectional study |
| **Pubmed / Medline** | Merewood et al., 2012 | Prospective cohort study |
| **Medline** | Dawodu et al., 2014 | Prospective cohort study |
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| **Turning Research into Practice** | Green et al., 2015 | Cross-sectional study |
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# Vitamin D During Pregnancy and Infancy and Infant Serum 25-Hydroxyvitamin D Concentration

**AUTHORS:** Cameron C. Grant, MBChB, PhD,[a] Alistair W. Stewart, BSc,[b] Robert Scragg, MBBS, PhD,[b] Tania Milne,[a] Judy Rowden,[a] Alec Ekeroma, MBBS,[c] Clare Wall, PhD,[d] Edwin A. Mitchell, MBBS, DSc,[e] Sue Crengle, MBChB, PhD,[f] Adrian Trenholme, MB, BChir,[g] Julian Crane, MBBS,[h] and Carlos A. Camargo Jr, MD, DrPH[h]

[a]*Paediatrics: Child and Youth Health,* [b]*Epidemiology and Biostatistics,* [c]*Obstetrics and Gynaecology,* [d]*Nutrition, and* [f]*Te Kupenga Hauora Maori, University of Auckland, Auckland, New Zealand;* [e]*Women and Children's Health, Middlemore Hospital, Auckland, New Zealand;* [g]*Medicine, University of Otago, Wellington, New Zealand; and* [h]*Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts*

**KEY WORDS**
vitamin D, 25-hydroxyvitamin D, pregnancy, infancy, supplementation

**ABBREVIATIONS**
25(OH)D—25-hydroxyvitamin D
NZ—New Zealand
RDI—recommended dietary intake

Dr Grant conceived and designed the study, developed the data collection instruments, analyzed and interpreted the data, and completed the first and final drafts of the manuscript; Mr Stewart conceived and designed the study, analyzed and interpreted the data, reviewed and revised the manuscript, and approved the final manuscript as submitted; Dr Robert Scragg conceived and designed the study, developed the data collection instruments, critically reviewed the manuscript, and approved the final manuscript as submitted; Ms Milne and Ms Rowden developed the recruitment and retention strategy for the study, designed the data collection instruments, coordinated the collection of the data, and approved the final manuscript as submitted; Dr Ekeroma conceived and designed the study, developed the data collection instruments, and approved the final manuscript as submitted; Drs Wall and Crengle developed the data collection instruments, critically reviewed the manuscript, and approved the final manuscript as submitted; Dr Mitchell conceived and designed the study, developed the data collection instruments, reviewed and revised the manuscript, and approved the final manuscript as submitted; Dr Trenholme supervised the collection of safety data, critically reviewed the manuscript, and approved the final manuscript as submitted; Dr Crane developed the data collection instruments, reviewed and revised the manuscript, and approved the final manuscript as submitted; and Dr Camargo conceived and designed the study, developed the data collection instruments, analyzed and interpreted the data, reviewed and revised the manuscript, and approved the final manuscript as submitted.

*(Continued on last page)*

**WHAT'S KNOWN ON THIS SUBJECT:** A serum 25-hydroxyvitamin D (25(OH)D) concentration of 20 ng/mL meets the requirements of at least 97.5% of the population older than 1 year. A recommended dietary intake to achieve this serum 25(OH)D concentration has not been established during infancy.

**WHAT THIS STUDY ADDS:** Daily maternal (during pregnancy) and then infant vitamin supplementation with 1000/400 IU or 2000/800 IU increases the proportion of infants with 25(OH)D ≥20 ng/mL during infancy with the higher dose sustaining this increase for longer.

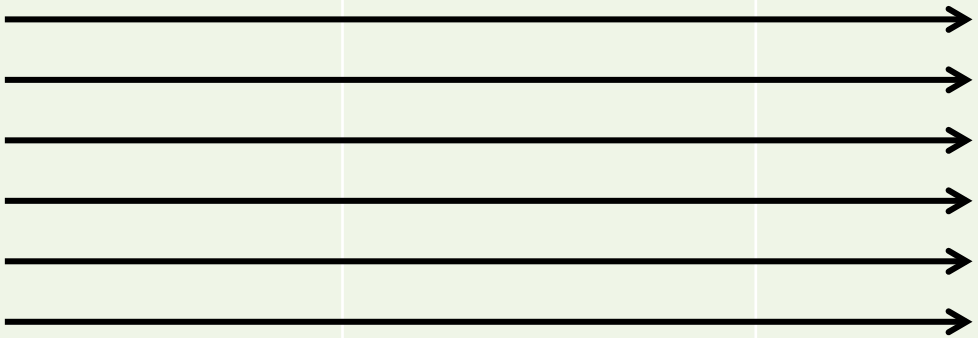
## abstract

**OBJECTIVE:** To determine the vitamin D dose necessary to achieve serum 25-hydroxyvitamin D (25(OH)D) concentration ≥20 ng/mL during infancy.

**METHODS:** A randomized, double-blind, placebo-controlled trial in New Zealand. Pregnant mothers, from 27 weeks' gestation to birth, and then their infants, from birth to age 6 months, were randomly assigned to 1 of 3 mother/infant groups: placebo/placebo, vitamin $D_3$ 1000/400 IU, or vitamin $D_3$ 2000/800 IU. Serum 25(OH)D and calcium concentrations were measured at enrollment, 36 weeks' gestation, in cord blood, and in infants at 2, 4, and 6 months of age.

**RESULTS:** Two-hundred-and-sixty pregnant women were randomized. At enrollment, the proportions with serum 25(OH)D ≥20 ng/mL for placebo, lower-dose, and higher-dose groups were 54%, 64%, and 55%, respectively. The proportion with 25(OH)D ≥20 ng/mL was larger in both intervention groups at 36 weeks' gestation (50%, 91%, 89%, $P < .001$). In comparison with placebo, the proportion of infants with 25(OH)D ≥20 ng/mL was larger in both intervention groups to age 4 months: cord blood (22%, 72%, 71%, $P < .001$), 2 months (50%, 82%, 92%, $P < .001$), and 4 months (66%, 87%, 87%, $P = .004$), but only in the higher-dose group at age 6 months (74%, 82%, 89%, $P = .07$); higher dose versus placebo $P = .03$, lower dose versus placebo $P = .21$).

**CONCLUSIONS:** Daily vitamin D supplementation during pregnancy and then infancy with 1000/400 IU or 2000/800 IU increases the proportion of infants with 25(OH)D ≥20 ng/mL, with the higher dose sustaining this increase for longer. *Pediatrics* 2014;133:e143–e153

| Group | Placebo (n = 87) | Low dose vitamin D (n = 87) | High dose vitamin D (n = 86) |
|---|---|---|---|
| **Intervention** | | | |
| **Mother** | Daily placebo from enrolment until child birth | 1000 IU vitamin $D_3$ daily from enrolment until childbirth | 2000 IU vitamin $D_3$ daily from enrolment until childbirth |
| **Infant** | Daily placebo from birth until 6 months of age | 400 IU vitamin $D_3$ daily from birth until 6 months of age | 800 IU vitamin $D_3$ daily from birth until 6 months of age |
| **Blood 25(OH) vit D** | | | |
| **Enrolment (Mother)** |  | | |
| **36 weeks (Mother)** | | | |
| **Cord blood** | | | |
| **2 months** | | | |
| **4 months** | | | |
| **6 months** | | | |

## Similar characteristics between study groups

- Formula milk volume consumed
- Time spent outdoors each day
- Reported compliance with taking study medication

# Treatment effect

| | Absolute risk (95% confidence interval)[a] | | | Absolute risk reduction (Number needed to treat[b]) | |
|---|---|---|---|---|---|
| **Infant Age** | Placebo | Low dose vit D | High dose vit D | Low dose vit D vs placebo | High dose vit D vs placebo |
| **At birth** | 0.78 | 0.28 (0.19 - 0.40) | 0.29 (0.19 - 0.41) | 0.50 (2) | 0.49 (3) |
| **2m** | 0.50 (0.39 - 0.61) | 0.18 | 0.08 | 0.32 (4) | 0.42 (3) |
| **4m** | 0.34 (0.24 - 0.46) | 0.13 | 0.13 | 0.21 (5) | 0.21 (5) |
| **6m** | 0.26 (0.17 - 0.37) | 0.18 | 0.11 | 0.08 (13) | 0.15 (7) |

**[a] Confidence intervals have only been calculated where the categorical data rule for calculation was satisfied (i.e. $np \geq 15$ and $n(1-p) \geq 15$ where n is the total number of participants in the subgroup and p is the proportion of these that were insufficient**

**[b] Rounded up to nearest whole number by convention (Straus et al., 2011)**

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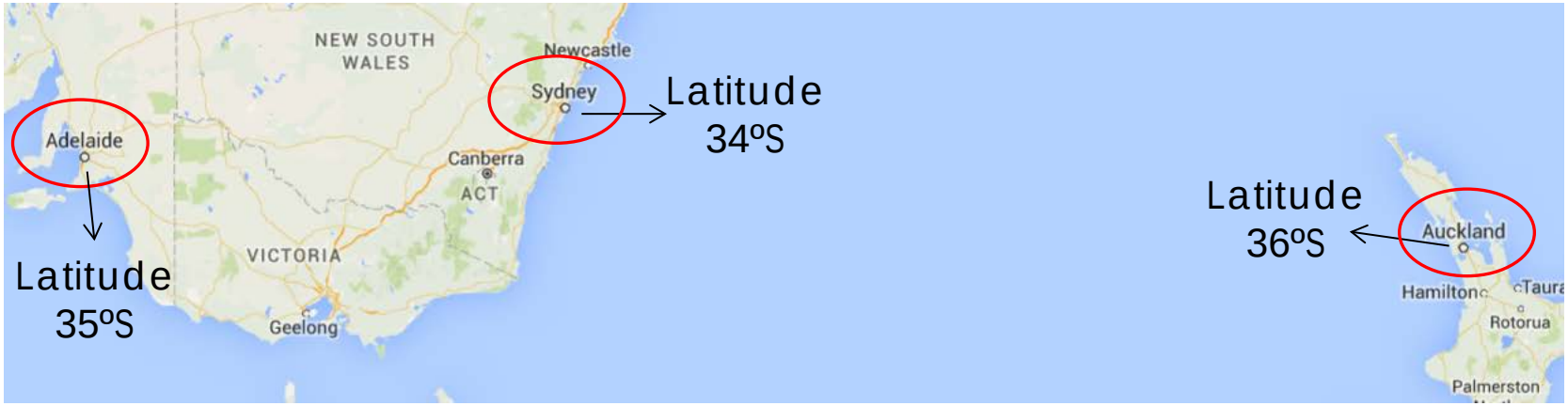
# Applying the results to infants in Adelaide




Adapted from: https://www.google.com.au/maps/@-36.4815576,157.071088,5z

# Vitamin D insufficiency in Sydney, Australia

| Mother's skin type: | | % of neonates born with vitamin D insufficiency in Sydney, Australia* |
|---|---|---|
| I | Always burns, never tans | 16 |
| II | Usually burns, tans less than average (with difficulty) | 22 |
| III | Sometimes mild burns, tans about average | 30 |
| IV | Rarely burns, tans easily | 30 |
| V | Rarely burns, tans very easily (brown-skinned person) | 36 |
| VI | Never burns (black-skinned person) | 40 |

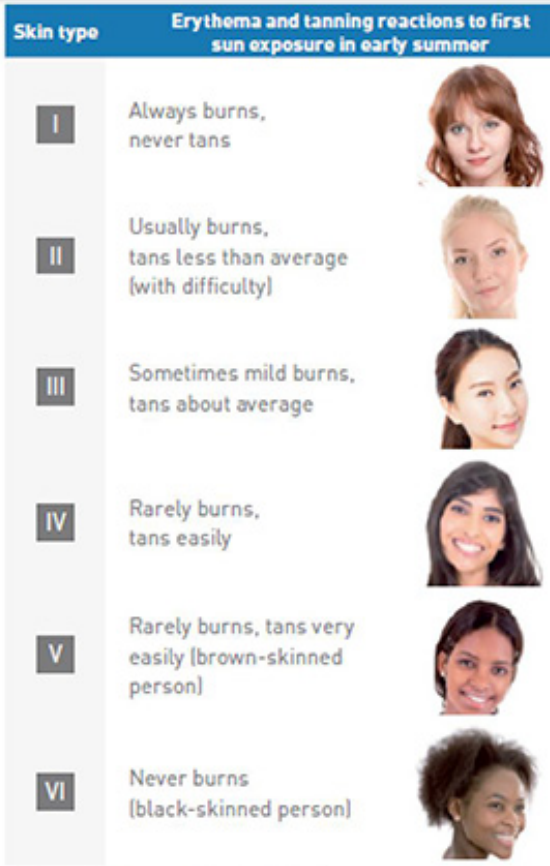



Table 1: the Fitzpatrick's classification

*Bowyer L et al. Vitamin D, PTH and calcium levels in pregnant women and their neonates. *Clinical Endocrinology*. 2009;70(3):372-7.

Source: http://www.cosmeticsbusiness.com

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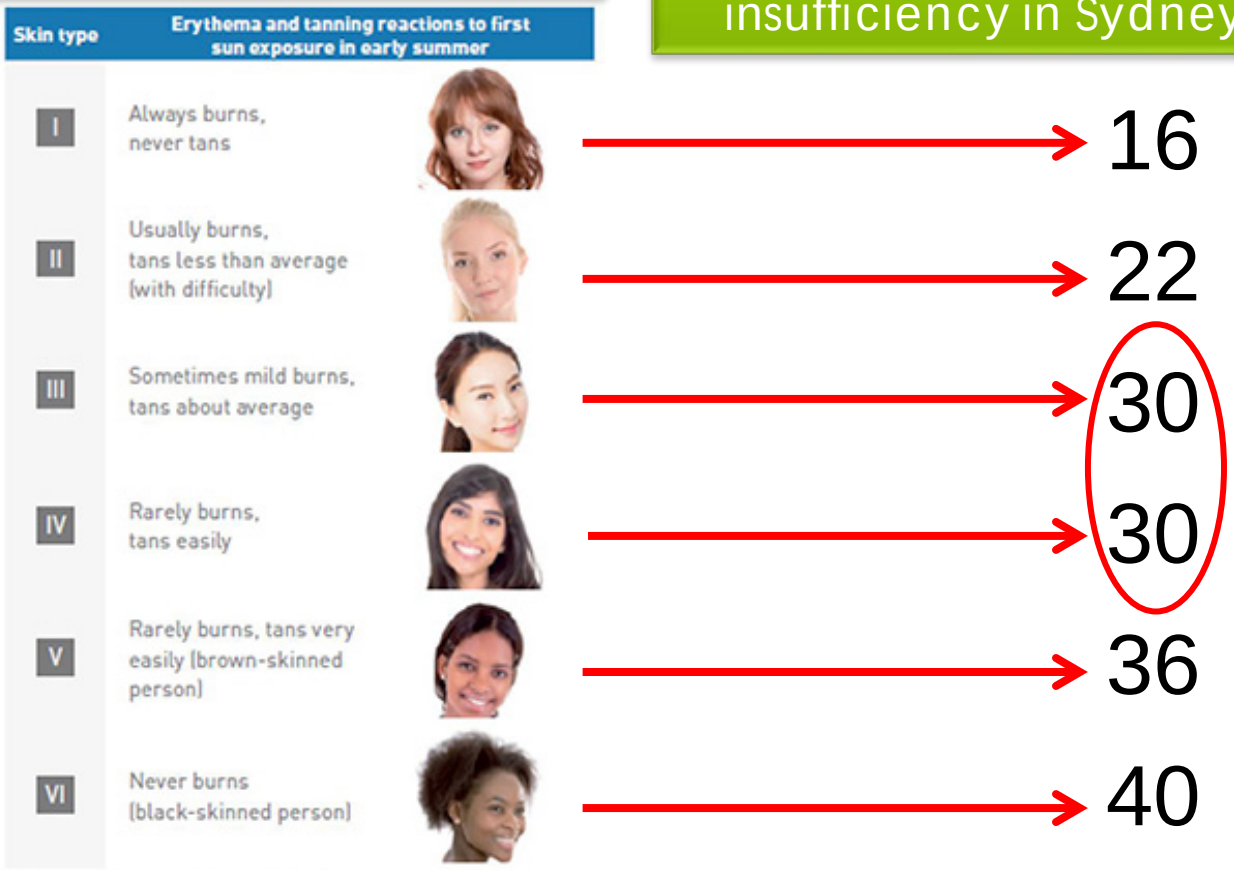


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# Using these results to estimate risk in Adelaide

$$\frac{30\% + 78\%}{2} = 54\%$$

# Applying the results to Adelaide

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# Implications for policy and practice

1. Risk
   - No adverse effect in this RCT
2. Cost
   - Relatively inexpensive and easy to access
3. Minimum difficulty
   - Integrate recommendations into policy and practice

# AFPHM competency elements

**3.1.4 ‘Conduct effective literature reviews’**

**3.1.5 ‘Critically assess published literature and other evidence’**

# AFPHM competency elements

## 3.1.4 ‘Conduct effective literature reviews’

- clearly identify the public health question and scope
- systematically search published and ‘grey’ literature
- document the search strategy
- present findings in a clear, well structured manner.

## 3.1.5 ‘Critically assess published literature and other evidence’

- Grade evidence
- interpret results of trials and measures of effectiveness
- interpret meta analyses
- present well-reasoned conclusions.

# AFPHM competency elements

**3.2.4 ‘Perform suitable epidemiological analyses’**

# AFPHM competency elements

## 3.2.4 ‘Perform suitable epidemiological analyses’

- define the objectives
- use analytical software
- use suitable statistical methods
- document the methodology
- perform descriptive analyses
- standardise rates
- calculate confidence intervals
- interpret multivariate analyses
- consider issues of causality (chance, bias, confounding)
- detect effect modification
- present the results of the analysis in written and oral form.

# AFPHM competency elements

**1.1.5 ‘Use evidence as the basis for public health practice’**

# AFPHM competency elements

**1.1.5 'Use evidence as the basis for public health practice'**

- critically assess the strength of evidence for one's own practice
- present limitations and uncertainty honestly when communicating findings to others.

# Thank you

- Dr Louise Flood
- Dr Doug Shaw

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