Guidelines

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

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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 recommended for infants, children and adolescents with at least one risk factor for low vitamin D and for pregnant women with at least one risk factor for low vitamin D at the first antenatal visit.
- Vitamin D deficiency can be treated with daily low-dose vitamin D supplements, although barriers to adherence have been identified. High-dose intermittent vitamin D can be used in children and adolescents. Treatment should be paired with health education and advice about sensible sun exposure. Infants at risk of low vitamin D should be supplemented with 400 IU vitamin D_3 daily for at least the first year of life.
- There is increasing evidence of an association between low vitamin D and a range of non-bone health outcomes, however there is a lack of data from robust randomised controlled trials of vitamin D supplementation.

Physiology

A summary of vitamin D physiology is provided in the adult vitamin D position statement.[1] During pregnancy, alterations to vitamin D and calcium homoeostasis allow calcium transfer to the developing fetus.[3] Maternal intestinal calcium absorption is doubled, serum 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) levels increase and parathyroid hormone (PTH) levels decrease to the lower end of the normal range in women with adequate calcium and vitamin D status. Maternal calcium absorption and fetal calcium accretion are maximal during the third trimester. Fetal vitamin D is derived from transplacental passage of maternal 25-hydroxyvitamin D (25(OH)D), with neonatal vitamin D status directly related to maternal vitamin D status. Cord blood 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]

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

1 Position statement development process

This position statement was developed by a working group, commissioned by the Australian and New Zealand Bone and Mineral Society (ANZBMS) and Osteoporosis Australia, with expertise in endocrinology (CFM, CPR, AS, RSM), paediatrics (GAP, MJT, CFM, CPR, AS), nutrition (CAN), sunlight exposure (RSM), obstetrics (GRT), brain development (JJM) and refugee health (GAP, MJT). The guidelines are based on articles on vitamin D dosing in paediatric age groups and during pregnancy and lactation, which were identified by a systematic search of the MEDLINE database (1946 to July 2011). Details of the search strategy and evidence tables are available on request. An initial draft was prepared for expert comment, the revised draft and evidence summaries were provided to ANZBMS members for feedback, and revisions were incorporated with consensus from the working group. Authors of the position statement on vitamin D and health in adults[1] were also consulted. Senior members of the ANZBMS and Australasian Paediatric Endocrine Group reviewed the final manuscript. ◆

levels and atmospheric ozone levels.[8] Sunscreens reduce transmission of ultraviolet A (UVA) and UVB radiation and have been reported to reduce skin synthesis of vitamin D,[9] but available evidence suggests that normal use of sunscreen does not result in low 25(OH)D levels in adults.[10] There are no data on cutaneous synthesis of vitamin D in Australian children, and no data on sunscreen use and vitamin D status in paediatric age groups.

The skin pigment, melanin, acts as a natural sunscreen and effectively absorbs UVB photons. Melanin determines skin colour and regulates how much UVB reaches 7-dehydrocholesterol in the basal skin layers to generate production of cholecalciferol (vitamin D_3). Adults with dark skin require three to six times the amount of UVB compared with those with light skin to achieve similar vitamin D levels.[10] No such data for paediatric age groups are available.

Although sunlight exposure is critical for vitamin D synthesis, caution is required when balancing competing risks associated with UVR exposure, which include skin cancers and photoageing.[11] Given the variation of UVR across Australia and New Zealand, multiple factors affecting available UVB and variation in skin colour, it is not possible to make a single recommendation on the sunlight exposure needed to achieve adequate vitamin D levels to suit all Australian and New Zealand children and adolescents. A pragmatic approach is shown in Box 2.

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Dietary sources

Breast milk, despite its other benefits, is a poor source of vitamin D, with a vitamin D content of 25 IU/L in mothers with normal 25(OH)D levels.[6] Infant formula in Australia is fortified with vitamin D to a concentration of 360–520 IU/L (9–13 μg/L). Few foods naturally contain vitamin D (eg, some fatty fish, including salmon, herring and mackerel), although the vitamin D_2 content of mushrooms can be increased by UV irradiation and a small amount of vitamin D is added to table margarines. Diet is a poor source of vitamin D for most Australians. Dietary intake of vitamin D in children is unlikely to be higher than the current adult intake of 48–104 IU/day (1.2–2.6 μg/day).[13] The US dietary reference intakes for vitamin D[14] are shown in Box 3, as the 2006 nutrient reference values for Australia have been acknowledged as being out of date.[1]

Defining normal levels of vitamin D

25(OH)D, the major circulating form of vitamin D, is the index of vitamin D input, and is used to assess vitamin D status, although there is a degree of imprecision in current testing (around 10%) and laboratories offering 25(OH)D testing are required to participate in external quality assurance programs.[1] Defining a normal level of vitamin D presents challenges. One physiological definition of vitamin D sufficiency is the level of 25(OH)D at which PTH production and bone resorption are minimised and intestinal

2 Sunlight protection and exposure guidelines for people in Australia and New Zealand, by skin type*

	Light to olive skin, Fitzpatrick types I–IV	Naturally dark (brown and dark brown or black) skin, Fitzpatrick types V and VI
Infants, children, adolescents		
Summer or UV index ⩾ 3†	Avoid sunburn; full sun protection with sunscreen, hat, clothing, shade and sunglasses‡ recommended	Avoid sunburn; intermittent sun exposure without sunscreen can be tolerated, but hat and sunglasses‡ still recommended
	Encourage active play or physical activity outside during and after school or preschool	
Winter	Sun protection recommendations vary with latitude and UV index; if UV index < 3, sun protection not required unless in alpine regions, outside for extended periods or near highly reflective surfaces such as snow or water	Sunscreen not needed in southern states of Australia and in New Zealand unless near highly reflective surfaces such as snow or water; it may not be possible to maintain recommended serum 25(OH)D levels through sun exposure alone in southern states of Australia and in New Zealand
	Encourage active play or physical activity outside during and after school or preschool	
Pregnant women, adults[12]		
Summer or UV index ⩾ 3†	6–7 minutes exposure with arms (or equivalent area) exposed mid-morning or mid-afternoon most days of the week; avoid sunburn; full sun protection with sunscreen, hat, clothing, shade and sunglasses recommended	15–50 minutes exposure with arms (or equivalent area) exposed mid-morning or mid-afternoon most days of the week; avoid sunburn; intermittent sun exposure without sunscreen can be tolerated, but hat and sunglasses still recommended
	Encourage physical activity outside	
Winter	7–40 minutes exposure (depending on latitude)§ with face, arms and hands exposed at lunchtime most days of the week; if UV index < 3, sun protection not required unless in alpine regions, outside for extended periods, or near highly reflective surfaces such as snow or water	Period of exposure depends on latitude; sunscreen not needed in southern states of Australia and in New Zealand unless near highly reflective surfaces such as snow or water; it may not be possible to maintain serum 25(OH)D levels through sun exposure alone in southern states of Australia or in New Zealand
	Encourage physical activity outside	

UV = ultraviolet. 25(OH)D = 25-hydroxyvitamin D. * Skin types are described by the Fitzpatrick scale, considering skin, eye and hair colour and response to sun exposure. † The peak UV index is ⩾ 3 throughout the year across most of Australia, including all of Queensland, all of the Northern Territory and most of Western Australia, South Australia and New South Wales. ‡ Sunglasses are generally recommended once children are old enough to wear them safely. § Increase time with more southerly latitude, or decrease time if a larger surface area of skin can be exposed. ◆

3 Estimated daily vitamin D requirements (United States, 2010) in paediatric age groups and during pregnancy and lactation, assuming minimal sun exposure*[14]

	AI	EAR	RDA
0–12 months old	400 IU	—	—
1–18 years old	—	400 IU	600 IU
Pregnant and lactating women	—	400 IU	600 IU

AI = adequate intake (used when EAR and RDA cannot be developed and represents an average intake, based on observed or experimental intake levels). EAR = estimated average requirement (reflects the estimated median requirement and is appropriate for applications related to planning and assessing intakes for groups of people). RDA = recommended dietary allowance (derived from the estimated average requirement and meets or exceeds the requirement for 97.5% of the population). * Concurrent daily calcium requirements: AI is 200–260 mg for 0–12-month-olds; RDA is 700 mg for 1–3 year-olds, 1000 mg for 4–8-year-olds and 1300 mg for 9–18-year-olds; and RDA for pregnant and lactating women is 1300 mg at ages 14–18 years and 1000 mg at ages 19–50 years.[14] ◆

4 Definitions of vitamin D status

	Serum 25(OH)D level
Severe deficiency	< 12.5 nmol/L
Moderate deficiency	12.5–29 nmol/L
Mild deficiency*	30–49 nmol/L
Sufficient†	⩾ 50 nmol/L
Elevated‡	> 250 nmol/L

25(OH)D = 25-hydroxyvitamin D. * The cut-point of 30 nmol/L has been used for consistency with the adult vitamin D position statement[1] and literature on vitamin D fortification of food as a population health measure. There is inadequate information in the literature to differentiate paediatric health outcomes (bone or other) between 25(OH)D levels of 25 nmol/L and 30 nmol/L. † Levels may need to be 10–20 nmol/L higher at the end of summer to allow for seasonal decrease. ‡ There are limited data on toxic levels of 25(OH)D in paediatric age groups and during pregnancy. Vitamin D toxicity can be caused by excessive oral intake, through supplementation, but not by prolonged exposure of the skin to sunlight. Levels > 500 nmol/L are likely to be toxic and toxicity may occur below this level. ◆

calcium absorption is stabilised, without adverse effects.[15] There are paediatric data which suggest that stabilisation of PTH occurs at 25(OH)D levels of 75–90 nmol/L,[16,17] and elevated PTH is seen at 25(OH)D levels below 40–60 nmol/L.[18-21] There are difficulties with this approach, as the interplay between vitamin D levels and dietary calcium intake in maintaining PTH suppression and the effect of PTH suppression on bone development in the growing skeleton are unclear. Further, there are no data to indicate that vitamin D supplementation during childhood to achieve 25(OH)D levels > 50 nmol/L is associated with improved bone mineral density.[22,23] Emerging data from studies in adults examining the relationship between vitamin D status and other health outcomes suggest that 25(OH)D levels of > 75 nmol/L may be optimal.[1]

Until there is stronger evidence, the recommended target level of 25(OH)D for infants, children and adolescents for optimal bone health remains ⩾ 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. Definitions of vitamin D status are shown in Box 4. Further data are required before recommendations for 25(OH)D levels in children can be based on non-calcaemic actions of vitamin D (Box 5, Box 6).

Defining normal vitamin D status during pregnancy is even more challenging, with the need to optimise both maternal and fetal health. No studies have addressed whether optimal 25(OH)D levels in pregnant women are different from optimal levels in non-pregnant women.[3] PTH levels tend to decrease during pregnancy, so PTH suppression may not be an appropriate measure of vitamin D status. Passage of maternal 25(OH)D to the fetus could, in theory, decrease maternal levels, although there is no evidence that clearly shows this. Alternatively, optimal 25(OH)D status during pregnancy could be defined as the level that ensures neonatal sufficiency, with cord blood levels being about 65% of maternal levels.[4] Until there is stronger evidence, the recommended adequate 25(OH)D levels for pregnant and lactating women remain the same as those for adults, at ⩾ 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. Some authors recommend a higher target level of 80 nmol/L during pregnancy,[35,49] and data emerging from randomised trials suggest improved pregnancy outcomes with 25(OH)D levels > 100 nmol/L.[48]

Effects of low vitamin D

Biochemical changes in people with vitamin D deficiency are variable and depend on the degree of deficiency, dietary calcium intake, and presence and duration of secondary hyperparathyroidism.[50] Vitamin D deficiency is often asymptomatic, although symptoms may include non-specific bone pain (often reported in the lower limbs in children and the axial skeleton in adults), muscle pain, poor exercise tolerance and fatigue. Young children may present with delayed gross motor milestones and irritability, rather than overt pain. Vitamin D deficiency is associated with osseous and non-osseous clinical findings (Box 7). Rickets is the best recognised association; it represents a generalised disruption of skeletal mineralisation (osteomalacia), together with abnormal growth plate mineralisation and development. Rachitic changes at growth plates are only seen during linear growth, with peak incidence during the rapid growth phase of infancy.[50] Rickets is usually associated with 25(OH)D levels < 30 nmol/L, although it may occur at higher 25(OH)D levels in situations of low calcium intake.[51]

Infants, children and adolescents with low vitamin D levels may present with symptoms of hypocalcaemia, including seizures (more common in infants younger than 6 months), stridor, muscle cramps, muscle weakness or carpopedal spasm.

A number of studies suggest an association between low vitamin D status during pregnancy and childhood and adverse health effects (Box 5), and several suggest that vitamin D supplementation during pregnancy or childhood is associated with improved health outcomes (Box 6). While these observational studies suggest early life vitamin D status may influence a range of non-bone health outcomes, there is a lack of data from robust randomised controlled trials of vitamin D supplementation.

Risk factors for low vitamin D

Risk factors for low vitamin D levels are shown in Box 8. People may have multiple concurrent risk factors for low

5 Results of studies on non-bone health outcomes associated with low serum 25-hydroxyvitamin D (25(OH)D) levels*

Outcome associated with low serum 25(OH)D levels	Effect size	Level of evidence†
Infants		
Respiratory or other infection, wheeze and asthma[24]		II
Increased risk of respiratory infection in first 3 months	AOR, 2.16; 95% CI, 1.35–3.46 (25(OH)D < 25 nmol/L v ⩾ 75 nmol/L)	
Increased risk of any infection in first 3 months	AOR, 2.21; 95% CI, 1.26–3.90 (25(OH)D < 25 nmol/L v ⩾ 75 nmol/L)	
Increased risk of parent-reported wheeze by age 5 years	AOR, 0.95; 95% CI, 0.91–0.99 (for each 10 nmol/L increase in cord blood 25(OH)D)	
No effect on incident asthma by age 5 years	AOR, 1.03; 95% CI, 0.97–1.10 (for each 10 nmol/L increase in cord blood 25(OH)D)	
Increased risk of schizophrenia, although risk also increased for highest quintile‡[25]	RR, 2.0–2.1 (95% CI, 1.3–3.5) for lower 3 quintiles v 4th quintile (40.5–50.9 nmol/L); RR, 1.71 (95% CI, 1.04–2.8) for highest quintile (⩾ 51 nmol/L) v 4th quintile	III-2
Children		
Allergic sensitisation (children and adolescents)[26]		IV
Increased odds of peanut sensitisation	AOR, 2.39; 95% CI, 1.29–4.45 (25(OH)D < 37.5 nmol/L v > 75 nmol/L)	
Increased odds of ragweed sensitisation	AOR, 1.83; 95% CI, 1.20–2.80 (25(OH)D < 37.5 nmol/L v > 75 nmol/L)	
Increased odds of oak sensitisation	AOR, 4.75; 95% CI, 1.53–4.94 (25(OH)D < 37.5 nmol/L v > 75 nmol/L)	
Adolescents		
Increased number of relapses in paediatric-onset multiple sclerosis[27]	Adjusted incidence rate ratio, 0.66 (95% CI, 0.46–0.95) for each 25 nmol/L increase in 25(OH)D	III-3
Pregnancy		
Decreased mean birthweight[28]	3245 g for maternal 25(OH)D ⩽ 25 nmol/L v 3453 g for maternal 25(OH)D > 25 nmol/L; adjusted difference, 151 g (95% CI, 50–250 g)	II
Short- and long-term health outcomes in offspring[29]		II
Decreased risk of eczema in offspring at age 9 months♦	OR, 3.26; 95% CI, 1.15–9.29 (maternal 25(OH)D > 75 nmol/L v < 30 nmol/L)	
Decreased risk of asthma at age 9 years¶	OR, 5.40; 95% CI, 1.09–26.65 (maternal 25(OH)D > 75 nmol/L v < 30 nmol/L)	
No difference in intelligence, or psychological or cardiovascular health at age 9 years¶	Many outcomes measured	
Wheeze and atopic outcomes in offspring[30]		II
No association with asthma in offspring at age 6 years	RR, 0.98 (95% CI, 0.92–1.04) for each 10 nmol/L change in maternal vitamin D at 34 weeks' gestation	
No association with wheeze in offspring at or before age 6 years	RR, 1.00 (95% CI, 0.98–1.02) for each 10 nmol/L change in maternal vitamin D at 34 weeks' gestation	
No association with skin-test sensitisation in offspring at age 1, 3 or 6 years	RR, 0.96 (95% CI, 0.90–1.03) at 1 year; RR, 0.99 (95% CI, 0.94–1.04) at 3 years; RR, 0.99 (95% CI, 0.95–1.04) at 6 years (for each 10 nmol/L change in maternal vitamin D at 34 weeks' gestation)	
No association with lung function (absolute FEV_1) in offspring at age 6 years	β, – 0.0001 (95% CI, – 0.0046 to 0.0043) for each 10 nmol/L change in maternal vitamin D at 34 weeks' gestation	
Increased risk of pre-eclampsia[31]	AOR, 2.4; 95% CI, 1.1–5.4 (for each 50 nmol/L decline in 25(OH)D)	III-3
Increased risk of pre-eclampsia[32]	AOR, 5.4; 95% CI, 2.0–14.5 (mid gestation 25(OH)D < 50 nmol/L v ⩾ 75 nmol/L)	III-3
Increased risk of gestational diabetes[33]	AOR, 2.66 (95% CI, 1.01–7.02) for 25(OH)D < 50 nmol/L v > 50 nmol/L; AOR, 1.29 (95% CI, 1.05–1.60) for each 12.5 nmol/L decline in 25(OH)D	III-3
Poorer glycaemic control in women with gestational diabetes mellitus in third trimester[34]	Glycated haemoglobin levels, – 0.41% (95% CI, – 0.16% to – 0.66%) for 25(OH)D > 50 nmol/L v ⩽ 50 nmol/L	III-3
Increased rates of caesarean section delivery[35]	AOR, 3.84; 95% CI, 1.71–8.62 (25(OH)D < 37.5 nmol/L v ⩾ 37.5 nmol/L	IV
Decreased risk of pregnancy-associated breast cancer**[36]	OR, 2.7; 95% CI, 1.04–6.7 (higher quintiles v lowest quintile)	III-3

AOR = adjusted odds ratio. RR = risk ratio. OR = odds ratio. FEV_1 = forced expiratory volume in 1 second. β = regression coefficient. * Evidence of the association between vitamin D supplementation and health outcomes in adults is summarised in the accompanying position statement.[1] † Based on National Health and Medical Research Council levels of evidence.[37] ‡ There was a U-shaped relationship between the level of 25(OH)D and schizophrenia. ♦ 74% follow-up. ¶ 30% follow-up. ** No increased risk of non-pregnancy breast cancer. ◆

vitamin D. Cultural practices that restrict UVR exposure, such as covering clothing or staying inside during the postpartum period, may increase the risk of low vitamin D for both the mother and infant. In Australia, a latitude gradient is seen in cohorts of pregnant women[28,52-54] and African refugee children,[55-57] with increased prevalence of vitamin D deficiency in the southern states. Obesity is associated with lower 25(OH)D levels after synthesis or ingestion of vitamin D in adults[58] and is associated with lower 25(OH)D levels in adolescents.[59] The effect of obesity on vitamin D status in children is not clear.

Prevalence of low vitamin D in Australia and New Zealand

Infants, children and adolescents

Population surveys from Australia[28] and New Zealand[24] have shown that 40%–57% of neonates have 25(OH)D levels < 50 nmol/L (and 11%–19% have 25(OH)D levels < 25 nmol/L) across seasons, and that breastfed infants have an increased risk of vitamin D deficiency (risk ratio, 5.7; 95% CI, 2.7–10.2).[60] Data from other population sur-

6 Results of studies on non-bone health outcomes associated with vitamin D supplementation*

Outcome associated with vitamin D supplementation	Effect size	Level of evidence†
Infants		
No effect on pneumonia incidence[38]	Incidence rate ratio, 1.06; 95% CI, 0.89–1.27	II
Decreased risk of repeat pneumonia within 90 days in infants with pneumonia‡[39]	RR, 0.78; 95% CI, 0.64–0.94	II
Decreased risk of type 1 diabetes[40]	OR, 0.67; 95% CI, 0.53–0.86	III-2
Decreased risk of type 1 diabetes[41]	OR, 0.71; 95% CI, 0.60–0.84	III-2
Decreased risk of schizophrenia in males[42]	RR, 0.08 (95% CI, 0.01–0.95) for irregular vitamin D supplementation; RR, 0.12 (95% CI, 0.02–0.90) for regular vitamin D supplementation	III-2
Decreased risk of pre-eclampsia in first pregnancy[43]	OR, 0.49; 95% CI, 0.26–0.92	III-2
Children		
Decreased risk of influenza A in 6–15-year-olds[44]	RR, 0.58; 95% CI, 0.34–0.99	II
Decreased risk of asthma exacerbations in 5–18-year-olds[45]	RR, 0.36; 95% CI, 0.13–0.98	II
Adolescents		
Possible improved muscle function in 12–14-year-old girls[22]	5% increase in jump efficiency ($P = 0.02$), although not significant when separated into components of jump velocity and height	II
Pregnancy		
Decreased risk of recurrent wheeze in offspring at age 3 years[46]	OR, 0.39 (95% CI, 0.25–0.62) for highest quartile v lowest quartile; OR, 0.81 (95% CI, 0.74–0.89) for each 100 IU/day increase intake	III-1
Decreased risk of pre-eclampsia[47]	OR, 0.73; 95% CI, 0.58–0.92 (400–600 IU/day v no supplementation)	II
Decreased risk of comorbidities of pregnancy (preterm labour, preterm delivery, diabetes and infection)[48]	RR, 0.5; 95% CI, 0.27–0.95 (4000 IU/day v 400 IU/day)	II♦

RR = risk ratio. OR = odds ratio. * Evidence of the association between vitamin D supplementation and health outcomes in adults is summarised in the accompanying position statement.[1] † Based on National Health and Medical Research Council levels of evidence.[37] ‡ No difference in time to recovery. ♦ Abstract form. ◆

veys have shown 25(OH)D levels < 50 nmol/L in 10% of 8-year-olds and 68% of 16–18-year-old males in Tasmania during winter and spring;[61,62] levels < 50 nmol/L in 78% of young children during winter in New Zealand;[18] and levels < 37.5 nmol/L in 31% of New Zealand children.[63] As expected, deficiency is more prevalent in high-risk groups, with 25(OH)D levels < 37.5 nmol/L in 59% of Pacific Islander children and 41% of Maori children in New Zealand,[63] and levels < 50 nmol/L in 61%–100% of predominantly African refugees in Victoria, New South Wales and South Australia[55-57,64] and 36% of Karen refugee children in Victoria.[65] In Australian studies of children with vitamin D deficiency rickets, this condition was associated with dark skin and maternal covering clothing, and 96%–98% of the children were migrants or born to migrant parents.[66-68] There are no published data on vitamin D status in Aboriginal children.

7 Clinical and radiological findings associated with vitamin D deficiency in infants, children and adolescents

Osseous signs
- Swelling of wrists and ankles
- Delayed fontanelle closure (normally closed by age 2 years)
- Delayed tooth eruption (no incisors by age 10 months, no molars by age 18 months)
- Leg deformity (genu varum, genu valgum, windswept deformity)
- Rachitic rosary (enlarged costochondral joints — felt anteriorly, lateral to the nipple line)
- Frontal bossing
- Craniotabes (softening of skull bones, usually evident on palpation of cranial sutures in first 3 months)

Non-osseous features
- Delayed gross motor development
- Poor linear growth
- Raised intracranial pressure
- Dilated cardiomyopathy

Radiological features
- Splaying, fraying, cupping and coarse trabecular pattern of metaphyses
- Osteopenia
- Minimal trauma fractures ◆

Pregnancy

Population surveys of pregnant women have found the prevalence of 25(OH)D levels < 50 nmol/L to be 10% in Queensland (during winter and spring),[54] 25.7% in Sydney (during spring and summer),[53] 25.8% in regional Victoria (during winter and summer),[52] 35% in Canberra (across seasons),[53] and 48% in a multiethnic population in NSW (across seasons).[28] In women attending a gestational diabetes clinic in NSW, the prevalence of 25(OH)D levels < 50 nmol/L was 41%.[34] Australian and New Zealand studies suggest that 60%–80% of veiled and/or dark-skinned women attending antenatal clinics have vitamin D levels < 25 nmol/L,[28,69,70] identifying these groups as being at particularly high risk.

Identification and treatment of low vitamin D

Infants, children and adolescents

There is inadequate evidence to recommend population-wide screening for vitamin D status in infants, children and adolescents in Australia and New Zealand. Those with one or more risk factors for low vitamin D (Box 8) should have their serum 25(OH)D, calcium, phosphate and alkaline phosphatase (ALP) levels measured; PTH should also be measured in those with symptoms or signs of deficiency, multiple risk factors or inadequate calcium intake. Infants,

8 Risk factors for low vitamin D

- Lack of skin exposure to ultraviolet B radiation from sunlight (due to lifestyle factors, chronic illness or hospitalisation, complex disability, covering clothing for religious or cultural reasons or southerly latitude)
- Dark skin (Fitzpatrick types V and VI)*
- Medical conditions or medications affecting vitamin D metabolism and storage (obesity, end-stage liver disease, renal disease, drugs that increase vitamin D degradation such as rifampicin and anticonvulsants, or fat malabsorption [eg, in cystic fibrosis, coeliac disease and inflammatory bowel disease])
- In infants, maternal vitamin D deficiency and exclusive breastfeeding combined with at least one other risk factor

* Dark skin is less likely to be a significant risk factor in people with regular sun exposure in climates with high incident ultraviolet radiation (eg, northern parts of Australia), but there is a lack of prevalence data for these populations. ◆

children or adolescents with low serum calcium or phosphate and those who have clinical signs of rickets require urgent specialist assessment and further investigations. Those presenting with hypocalcaemic seizures require emergency management and intravenous correction of calcium levels with continuous electrocardiographic monitoring for cardiac arrhythmia.

Infants, children and adolescents with low 25(OH)D levels should be treated to restore their 25(OH)D levels to the normal range (Box 9). A pragmatic approach is required, balancing levels, season, risk factors and capacity for behavioural change. The cost and convenience of daily vitamin D supplements may be prohibitive in large families, especially when needed for several children for prolonged periods, and adherence is often a problem. High-dose intermittent vitamin D therapy (≥ 50,000 IU/dose) may facilitate adherence, although there is insufficient evidence to support the use of high-dose therapy in children younger than 3 months. It is also important to provide education about vitamin D, risk factors for low vitamin D, and sun protection and exposure (Box 2), and to encourage regular outside play and physical activity. Infants, children and adolescents should have adequate calcium intake (typically through cows milk or calcium-fortified soy milk), and calcium supplements may be needed if dietary intake is poor.

Infants, children and adolescents with ongoing risk factors for low vitamin D require ongoing monitoring of vitamin D status with annual testing, as well as a long-term plan to maintain normal 25(OH)D levels and calcium status through behavioural change, where possible, and/or supplementation if behavioural change is inadequate. It may not be possible for people with risk factors (especially multiple risk factors) to maintain their 25(OH)D levels during winter in the southern parts of Australia and in New Zealand. Recently arrived migrant children at risk of low vitamin D may have normal 25(OH)D levels on initial health screening, so testing should be repeated at the end of their first winter in Australia or New Zealand. Some children with significant ongoing risk factors (eg, dark skin and covering clothing) may require high-dose vitamin D supplementation more than once a year. Levels at the start and end of winter can be useful to guide dosing frequency. Children who do not respond to high-dose vitamin D supplementation require specialist review.

Exclusively breastfed infants with at least one other risk factor for low vitamin D should be supplemented with 400 IU vitamin D_3 daily for at least the first year of life and adherence should be monitored, particularly after the first months of supplementation. Infants who are fed formula only should receive adequate vitamin D from this source. Consider checking 25(OH)D levels or adding daily vitamin D supplements in infants with other risk factors for low vitamin D who are fed a mixture of breast milk and formula, or who have appropriately reduced their formula intake after the introduction of solids.

Pregnancy and lactation

Pregnant women with one or more risk factors for low vitamin D (Box 8) should have their serum 25(OH)D levels measured at their first antenatal visit. Although there is a case for routine screening of all pregnant women in Australian and New Zealand (based on the high prevalence of vitamin D deficiency in pregnancy and potential for adverse effects on maternal and fetal health), there is geographic variation in the prevalence of vitamin D deficiency and insufficient evidence on the impact of vitamin D supplementation during pregnancy on maternal and child health to support a stronger recommendation for universal screening. While the cost of measuring 25(OH)D levels is significant, pregnant women undergo screening for conditions of much lower prevalence, and there are no data or cost-effectiveness studies on alternative management strategies (such as supplementation without testing during winter).

Pregnant women found to have low 25(OH)D levels should be treated to achieve 25(OH)D levels ≥ 50 nmol/L, although data on the optimal dosing regimen are lacking. Vitamin D doses < 1000 IU/daily are inadequate to ensure 25(OH)D levels > 50 nmol/L during pregnancy.[71,72] Pregnant women with 25(OH)D levels < 50 nmol/L should be started on 1000 IU vitamin D_3 daily, and women with levels < 30 nmol/L should be started on 2000 IU vitamin D_3 daily. Testing should be repeated at 28 weeks' gestation; in women whose 25(OH)D levels have corrected to > 50 nmol/L, a minimum of 600 IU vitamin D_3 daily should be given throughout the remainder of pregnancy.[14] Given the supplements available in Australia, 1000 IU daily may be more practical. Doses of 4000 IU vitamin D_3 daily during pregnancy from 12 to 16 weeks gestation until birth appear to be safe.[48,73] There is inadequate evidence to support the use of intermittent high-dose vitamin D during pregnancy.

A small study of vitamin D supplementation during lactation found 1000 IU daily for 6 weeks was inadequate to increase 25(OH)D levels to > 50 nmol/L in women with low baseline 25(OH)D levels.[74] Small trials in breastfeeding women suggest that 2000 IU vitamin D daily to the mother can raise low infant levels to the sufficient range (in a cohort of women with 25(OH)D levels > 50 nmol/L)[5,75,76] and can raise both maternal and infant levels (in a cohort of women with low 25(OH)D levels).[77] At present, given the lack of evidence, a pragmatic approach is to achieve adequate 25(OH)D levels during pregnancy, give 1000 IU vitamin D_3 daily during lactation to women with ongoing 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 25(OH)D levels should be started on 2000 IU vitamin D_3

9 Management of mild and moderate or severe vitamin D deficiency in infants, children and adolescents*

		Oral doses of vitamin D_3†	
		Treatment	Maintenance and prevention in those with ongoing risk factors
Preterm	Mild deficiency‡	200 IU/kg/day, maximum 400 IU/day	200 IU/kg/day, maximum 400 IU/day
	Moderate or severe deficiency§	800 IU/day, review after 1 month	200 IU/kg/day, maximum 400 IU/day
< 3 months old (term)	Mild deficiency‡	400 IU/day for 3 months	400 IU/day
	Moderate or severe deficiency§	1000 IU/day for 3 months	400 IU/day
3–12 months old	Mild deficiency‡	400 IU/day for 3 months	400 IU/day
	Moderate or severe deficiency§	1000 IU/day for 3 months, or 50 000 IU stat and review after 1 month (consider repeating dose)	400 IU/day
1–18 years old	Mild deficiency‡	1000–2000 IU/day for 3 months, or 150 000 IU stat	400 IU/day or 150 000 IU at start of Autumn
	Moderate or severe deficiency§	1000–2000 IU/day for 6 months, or 3000–4000 IU/day for 3 months, or 150 000 IU stat and repeat 6 weeks later	400 IU/day or 150 000 IU at start of Autumn

25(OH)D = 25-hydroxyvitamin D. * Based on a review of 98 clinical trials of vitamin D supplementation in infants, children and adolescents. References available on request. † Vitamin D_3 is the only form of vitamin D supplement currently available. ‡ Mild vitamin D deficiency is defined as 30–49 nmol/L serum 25(OH)D. § Moderate or severe vitamin D deficiency is defined as < 30 nmol/L serum 25(OH)D. **Dosing:** There is a relative lack of safety data regarding high-dose vitamin D in children and adolescents. No adverse events have been observed in trials using vitamin D dosing of 50 000–150 000 IU, although few of these trials measured serum and urine calcium in the week after dosing. Other treatment and maintenance regimens are used by clinicians with expertise in the area. Stat doses of 300 000–600 000 IU vitamin D_3 (depending on age) are used in the treatment of vitamin D deficiency and rickets in specialist clinical practice. **Monitoring:** Adherence with daily dosing should be monitored and follow-up blood tests should be performed: for neonates with moderate or severe deficiency, follow-up at 1 month is recommended; in other groups, follow-up at 3 months is usually more practical; and in the long term, annual testing is recommended. Very frequent testing should be avoided. Follow-up blood tests should include tests for serum 25(OH)D, calcium, phosphate and alkaline phosphatase. Repeat high-dose therapy may be required if 25(OH)D levels are low at follow-up. ◆

daily. There is inadequate evidence to support the use of high-dose vitamin D during lactation.

Treatment of low vitamin D during pregnancy and lactation should be paired with health education and advice on sensible sun exposure and regular outside physical activity.

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