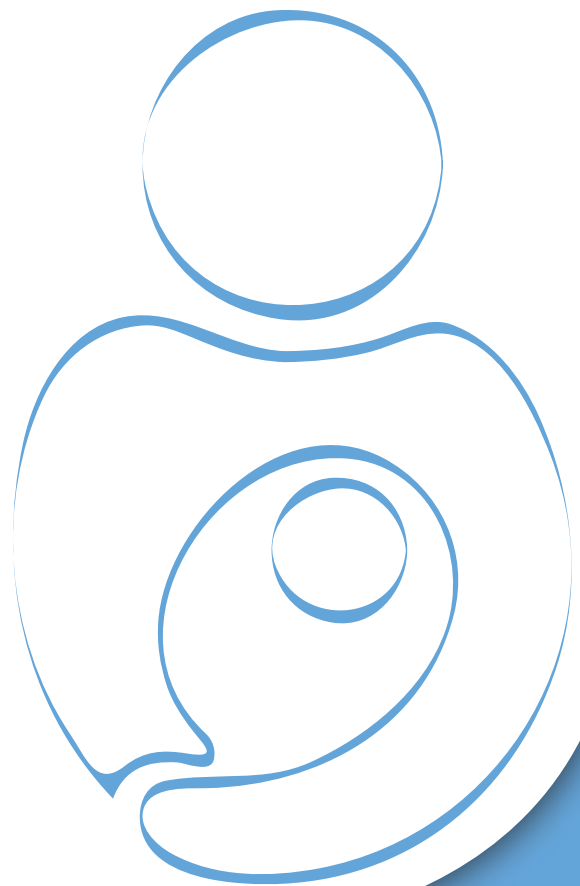




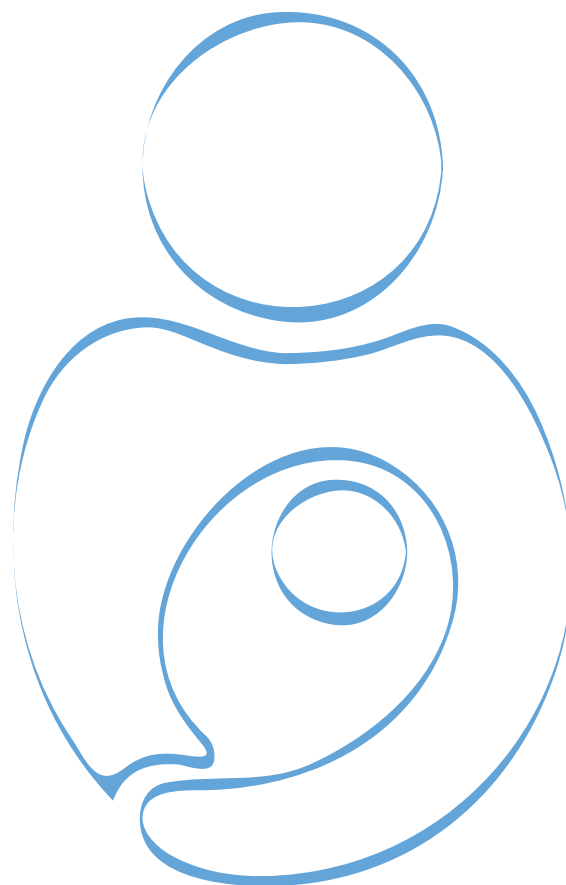
World Health
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Guideline:
**Vitamin D supplementation
in pregnant women**



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Executive summary

Purpose of the guideline: Vitamin D deficiency is thought to be common among pregnant women, particularly during the winter months, and has been found to be associated with an increased risk of pre-eclampsia, gestational diabetes mellitus, preterm birth, and other tissue-specific conditions. Recent scientific literature has reported the effects of vitamin D supplementation on adverse maternal and infant outcomes. Member States have requested guidance from the World Health Organization (WHO) on the effects and safety of vitamin D supplementation in pregnant women as a public health strategy, in support of their efforts to achieve the Millennium Development Goals and the global targets set in the maternal, infant and child nutrition comprehensive implementation plan. This guideline is intended for a wide audience including policy-makers, their expert advisers, and technical and programme staff at organizations involved in the design, implementation and scaling-up of nutrition actions for public health.

Guideline development methodology: WHO developed the present evidence-informed recommendations using the procedures outlined in the [WHO handbook for guideline development](#). The steps in this process included: (i) identification of priority questions and outcomes; (ii) retrieval of the evidence; (iii) assessment and synthesis of the evidence; (iv) formulation of recommendations, including research priorities; and (v) planning for dissemination, implementation, impact evaluation and updating of the guideline. The Grading of Recommendations Assessment, Development and Evaluation ([GRADE](#)) methodology was followed to prepare evidence profiles related to preselected topics, based on up-to-date systematic reviews. The guideline development group for nutrition interventions, the Nutrition Guidance Advisory Group, consisted of content experts, methodologists, and representatives of potential stakeholders, consumers and guideline users. These experts participated in two WHO technical consultations concerning this guideline, held in 2011 in Geneva, Switzerland, and Washington DC, United States of America. Members of the External Experts and Stakeholders Panel were identified through a public call for comments, and this panel was involved throughout the guideline development process.

Available evidence: A Cochrane systematic review assessed whether supplements with vitamin D alone or in combination with calcium and/or other vitamins and minerals given to pregnant women can safely improve maternal and neonatal outcomes. There was no evidence of an effect on either maternal pre-eclampsia in pregnant women receiving vitamin D plus calcium supplementation or on the risk of having a low birth weight infant (less than 2500 g) in pregnant women receiving vitamin D supplementation alone compared with pregnant women not receiving supplementation or receiving a placebo. Pregnant women who received vitamin D supplementation alone had significantly higher serum concentrations of 25-hydroxyvitamin D at term compared with those not receiving supplementation or placebo. Only one trial reported on side-effects, with the results indicating no difference in the prevalence of nephritic syndrome as a side-effect in pregnant women receiving vitamin D supplementation alone as compared with women not receiving supplementation or receiving a placebo. Thus currently there is insufficient evidence to directly assess the benefits or harms of vitamin D supplementation during pregnancy on maternal and infant health outcomes.

Recommendations: Vitamin D supplementation is not recommended during pregnancy to prevent the development of pre-eclampsia and its complications (*strong recommendation*). In addition, due to the limited evidence currently available to directly assess the benefits and harms of the use of vitamin D supplementation alone in pregnancy for improving maternal and infant health outcomes, the use of this intervention during pregnancy as part of routine antenatal care is also not recommended (*conditional recommendation*).

¹ A WHO guideline is any document, whatever its title, containing WHO recommendations about health interventions, whether they be clinical, public health or policy interventions. A recommendation provides information about what policy-makers, health-care providers or patients should do. It implies a choice between different interventions that have an impact on health and that have ramifications for the use of resources. All publications containing WHO recommendations are approved by the WHO Guidelines Review Committee.

Remarks:

- In cases of documented deficiency, vitamin D supplements may be given at the current RNI (5 µg (200 IU) per day as recommended by WHO/FAO or according to national guidelines). Vitamin D may be given alone or as part of a multiple micronutrient supplement, to improve maternal serum vitamin D concentrations. The benefit of this intervention for other maternal or birth outcomes remains unclear.
- Pregnant women should be encouraged to receive adequate nutrition, which is best achieved through consumption of a healthy balanced diet, and to refer to guidelines on healthy eating during pregnancy.
- There is limited evidence on the safety of vitamin D supplementation during pregnancy.
- There are at least 10 ongoing trials assessing the effects of vitamin D supplementation in pregnancy, five of which are expected to report on maternal vitamin D status, two on pre-eclampsia, and three on birth weight or low birth weight.

Research priorities: Guideline group members and stakeholders identified several research priorities to improve the body of evidence on the benefits or harms of this intervention among pregnant women, at the basic, epidemiological and programmatic levels.

Scope and purpose

This guideline provides global, evidence-informed recommendations on vitamin D supplementation during pregnancy as a public health intervention for the purpose of improving maternal and infant health outcomes.

The guideline will help Member States and their partners in their efforts to make informed decisions on the appropriate nutrition actions to achieve the Millennium Development Goals, in particular, reduction of child mortality (MDG 4) and improvement of maternal health (MDG 5). It will also support Member States in their efforts to achieve global targets on the maternal, infant and young child nutrition comprehensive implementation plan (1). The guideline is intended for a wide audience including policy-makers, their expert advisers, and technical and programme staff at organizations involved in the design, implementation and scaling-up of nutrition actions for public health.

This document presents the key recommendations and a summary of the supporting evidence. Further details of the evidence base are provided in Annex 1 and other documents listed in the references.

Background

Vitamin D, a lipid-soluble vitamin and prohormone, is known to play an important role in bone metabolism through regulation of calcium and phosphate homeostasis. Although relatively few countries have nationally representative data available on the vitamin D status of their population, vitamin D deficiency is suspected to be a public health problem in many parts of the world (2, 3). In addition, vitamin D deficiency or insufficiency is common in pregnancy in some populations (4). The main risk factors of vitamin D deficiency are those that inhibit the body's production of vitamin D in the skin, including dark pigmentation, too little exposure to sunlight, clothing that limits exposure of skin to sunlight, living in latitudes above 40° (both north and south), the season of the year, environmental pollution, use of sunscreen and ageing (5–9). Vitamin D status is also affected by dietary consumption of vitamin D and factors affecting its absorption or metabolism (10, 11), as well as obesity (12).

Vitamin D deficiency in pregnancy has been associated with an increased risk of pre-eclampsia (13–17), gestational diabetes mellitus (18), preterm birth (19, 20), small-for-gestational age infants (21), impaired fetal skeletal formation causing infant rickets (softening of bones commonly leading to deformities and/or fractures) and reduced bone mass (22–24), as well as other tissue-specific conditions. Immune dysfunction, placental implantation, angiogenesis (abnormal growth of new blood vessels from pre-existing vessels), excessive inflammation and hypertension in the mother have also been associated with vitamin D deficiency, although the underlying pathogenic mechanisms are not well understood (12, 25–28).

Vitamin D status is most commonly assessed through measurement of serum 25-hydroxyvitamin D (25(OH)D or calcidiol) levels, which reflect the vitamin D produced cutaneously and that obtained from foods or supplements (29). There is still controversy regarding adequate or optimal levels of serum 25(OH)D for overall health. The United States Institute of Medicine has recently defined levels of serum 25(OH)D greater than 50 nmol/L (or 20 ng/mL) as adequate for pregnant women (30); however, other investigators argue that optimal levels should be set higher (>75 nmol/L or 30 ng/mL) (31, 32). Vitamin D supplementation in pregnancy improves maternal vitamin D status (33, 34) and may positively affect the availability of vitamin D to the fetus and the neonate (35). The fetus is dependent on the mother for acquiring vitamin D, and 25(OH)D readily crosses the human placenta (36).

The World Health Organization/Food and Agriculture Organization of the United Nations (WHO/FAO) recommended nutrient intake (RNI) for vitamin D in pregnant women is 5 µg (200 IU) per day (37). Dietary sources of vitamin D include both food and dietary supplements. Vitamin D occurs naturally in oily fish such as salmon, mackerel and herring, cod liver oil, and egg yolk. Some countries also fortify food products

with vitamin D, such as milk, margarine, vegetable oils and ready-to-eat breakfast cereals (37). Vitamin D supplements exist in two forms, ergocalciferol (vitamin D₂) and cholecalciferol (vitamin D₃). Supplementation with cholecalciferol appears to be more efficacious at increasing serum vitamin D concentrations than that with ergocalciferol (38, 39). Vitamin D is also included in a multiple micronutrient supplement formulation developed by WHO, the United Nations Children's Fund (UNICEF) and the United Nations University (UNU), for use in pregnant and lactating women (40). Supplementation has been shown to have minimal toxicity in adults receiving doses of up to 10 000 IU per day (41–43). Vitamin D toxicity generally becomes evident at doses of 20 000 IU per day and can lead to hypercalcaemia, hypercalciuria, and elevated (200 nmol/L) levels of serum 25(OH)D (44). There are few safety studies in pregnant women, however, in one recent study up to 4000 IU vitamin D₃ was provided to pregnant women from the twelfth to sixteenth weeks of pregnancy until delivery with no reported cases of hypercalcaemia or hypercalciuria (45).

Summary of evidence

A Cochrane systematic review (46) was updated to assess whether supplements with vitamin D alone or in combination with calcium and/or other vitamins and minerals given to pregnant women safely improved maternal and neonatal outcomes. The maternal outcomes considered critical by the Nutrition Guidance Advisory Group were high blood pressure with significant proteinuria (pre-eclampsia), occurrence of one or more convulsions (fits) in association with pre-eclampsia (eclampsia) and serum levels of vitamin D (25(OH)D). Low birth weight (<2500 g) was the only infant outcome considered to be critical for decision-making.

The review included six trials (n = 1023 women) conducted in the United Kingdom, France and India. Five trials (n = 623 women) compared the effects of supplementation with vitamin D alone versus no supplementation or placebo, and one trial (n = 400 women) compared the effects of supplementation with vitamin D and calcium versus no supplementation. Supplemental vitamin D was provided either daily (dose ranging from 800 to 1200 IU daily) or in high doses (200 000–600 000 IU) given once or twice during pregnancy. The source of vitamin D in the supplements provided in these trials was mostly vitamin D₂, with some supplements providing vitamin D₃ or a combination of the two. Overall, one trial provided a dosage of less than 56 000 IU vitamin D in total during pregnancy, four trials provided between 56 000 and 200 000 IU, and one trial provided more than 200 000 IU.

None of the trials reported on the critical maternal outcome of eclampsia, and only one trial (n = 400 women) reported on the maternal critical outcome of pre-eclampsia. Women receiving vitamin D plus calcium supplementation were as likely to have pre-eclampsia as women not receiving supplementation or placebo (risk ratio (RR) 0.67, 95% confidence interval (CI) 0.33–1.35). Four trials with a total of 414 women reported the maternal vitamin D status at term. The results consistently showed that women who received vitamin D supplements had higher 25(OH)D concentrations than those women who received no intervention or a placebo. The response to supplementation was highly heterogeneous ($T^2 = 517.96$, $I^2 = 98\%$, χ^2 test for heterogeneity $P < 0.00001$) and ranged from 11.00 to 151.80 nmol 25(OH)D per litre.

Three trials reported on low birth weight. Pregnant women receiving vitamin D supplementation were less likely to have a baby with a birth weight below 2500 g compared with the women receiving no treatment or placebo. However, the difference just missed being statistically significant (9.6% versus 19.6%, average RR 0.48, 95% CI 0.23–1.01, 463 women). Only one trial reported on side-effects, with the results indicating no difference in the prevalence of nephritic syndrome as a side-effect in pregnant women receiving vitamin D supplementation alone as compared with women not receiving supplementation or placebo (RR 0.17, 95% CI 0.01–4.06, 135 women). Due to the small number of studies, planned subgroup analyses by total dose of supplemental vitamin D, gestational age at which supplementation was initiated, supplementation regimen and by latitude of residence could not be conducted.

The overall quality of the available evidence for vitamin D supplementation alone or in combination with calcium and/or other vitamins and minerals in pregnant women was low to very low for the critical outcomes of maternal vitamin D status and low birth weight (Annex 1).

Recommendations

- Vitamin D supplementation is not recommended during pregnancy to prevent the development of pre-eclampsia and its complications (47) (*strong recommendation*)^{1,2}.
- In addition, due to the limited evidence currently available to directly assess the benefits and harms of the use of vitamin D supplementation alone in pregnancy for improving maternal and infant health outcomes, the use of this intervention during pregnancy as part of routine antenatal care is also not recommended (*conditional recommendation*)^{2,3}.

Remarks

- In cases of documented deficiency, vitamin D supplements may be given at the current RNI (5 µg (200 IU) per day as recommended by WHO/FAO (37) or according to national guidelines). Vitamin D may be given alone or as part of a multiple micronutrient supplement, to improve maternal serum vitamin D concentrations. The benefit of this intervention for other maternal or birth outcomes remains unclear.
- Pregnant women should be encouraged to receive adequate nutrition, which is best achieved through consumption of a healthy balanced diet, and to refer to guidelines on healthy eating during pregnancy (48).
- There is limited evidence on the safety of vitamin D supplementation during pregnancy.
- There are at least 10 ongoing trials assessing the effects of vitamin D supplementation in pregnancy, five of which are expected to report on maternal vitamin D status, two on pre-eclampsia, and three on birth weight or low birth weight.

¹ A *strong recommendation* is one for which the guideline development group is confident that the desirable effects of adherence outweigh the undesirable effects. Implications of a strong recommendation for patients are that most people in their situation would desire the recommended course of action and only a small proportion would not. Implications for clinicians are that most patients should receive the recommended course of action, and adherence to this recommendation is a reasonable measure of good-quality care. With regard to policy-makers, a strong recommendation means that it can be adapted as a policy in most situations, and for funding agencies it means the intervention likely represents an appropriate allocation of resources (i.e. large net benefits relative to alternative allocations of resources).

² Considerations of the guideline development group for determining the strength of the recommendation are summarized in Annex 2.

³ A *conditional recommendation* is one for which the guideline development group concludes that the desirable effects of adherence probably outweigh the undesirable effects, although the trade-offs are uncertain. Implications of a conditional recommendation for patients are that while many people in their situation would desire the recommended course of action, a considerable proportion would not. Implications for clinicians are that they should help patients make a decision that is consistent with their values. With regard to policy-makers, a conditional recommendation means that there is a need for substantial debate and involvement from stakeholders before considering the adoption of the recommendation, and for funding agencies it means that the intervention may not represent an appropriate allocation of resources (i.e. alternative uses of resources may produce greater benefits).

Implications for future research

Discussions with the Nutrition Guidance Advisory Group and stakeholders highlighted the limited evidence available in some areas, meriting further research on vitamin D supplementation in pregnant women, in particular in the following areas:

- possible associations between an increase in maternal serum 25(OH)D concentrations and maternal and infant outcomes, as well as the likely mechanisms of action;
- isolating the effect of vitamin D supplementation in pregnancy. This will require randomized controlled trials with an adequate sample size, using comparable techniques and supplemental chemical form to determine: (1) the adverse effects of vitamin D supplementation; (2) the most effective and safe dose of vitamin D; (3) the optimal supplementation regimen (daily, intermittent, single dose); (4) the optimal timing of initiation of supplementation; and (5) any additive benefits or harms of vitamin D when combined with other vitamins and minerals¹;
- assessing pre-conceptional vitamin D status in trials;
- clear reporting of total diet and nutrition, in combination with vitamin D supplementation; and
- incorporating measurements of short- and long-term maternal and fetal/child outcomes for health and development in trials.

Most studies that informed this guideline reported large losses to follow-up. Researchers are encouraged to carefully document attrition rates in future studies.

Dissemination, adaptation and implementation

Dissemination

The current guideline will be disseminated through electronic media such as slide presentations, CD-ROMs and the World Wide Web, through the WHO Nutrition mailing list (into which the Micronutrients mailing list was merged) and United Nations Standing Committee on Nutrition ([SCN](#)) mailing list, social media, the [WHO nutrition web site](#), and the WHO e-Library of Evidence for Nutrition Actions ([eLENA](#)). The WHO e-Library of Evidence for Nutrition Actions compiles and displays WHO guidelines related to nutrition, along with complementary documents such as systematic reviews and other evidence that informed the guidelines, biological and behavioural rationales, and additional resources produced by Member States and global partners. In addition, the guideline will be disseminated through a broad network of international partners, including WHO country and regional offices, ministries of health, WHO collaborating centres, universities, other United Nations agencies and nongovernmental organizations. It will also be published in and disseminated via the [WHO Reproductive Health Library](#).

Adaptation and implementation

As this is a global guideline, it should be adapted to the context of each Member State. Prior to implementation, a public health programme that includes the provision of vitamin D supplements to pregnant women should be carefully evaluated in each context to determine whether to adopt and implement this guideline. Countries that are already implementing this intervention may reassess the objectives of their programmes to ensure that the expected outcomes are supported by evidence.

¹ Studies should control for exposure to sunlight, skin pigmentation, access to vitamin D fortified foods, body mass index and seasonality.

To ensure that WHO global guidelines and other evidence-informed recommendations for nutrition interventions are better implemented in low- and middle-income countries, the Department of Nutrition for Health and Development works with the WHO Evidence-Informed Policy Network ([EVIPNet](#)) programme. EVIPNet promotes partnerships at country level between policy-makers, researchers and civil society to facilitate policy development and implementation through use of the best available evidence.

Monitoring and evaluation of guideline implementation

A plan for monitoring and evaluation with appropriate indicators is encouraged at all stages. The impact of this guideline can be evaluated across countries (i.e. the adoption and adaptation of the guideline globally). For evaluation at the global level, the WHO Department of Nutrition for Health and Development has developed a centralized platform for sharing information on nutrition actions in public health practice implemented around the world. By sharing programmatic details, specific country adaptations and lessons learnt, this platform will provide examples of how guidelines are being translated into nutrition actions.

Guideline development process

This guideline was developed in accordance with the WHO evidence-informed guideline development procedures, as outlined in the [WHO handbook for guideline development](#) (49).

Advisory groups

The WHO Steering Committee for Nutrition Guidelines Development (Annex 3), led by the Department of Nutrition for Health and Development, was established in 2009 with representatives from all WHO departments with an interest in the provision of scientific nutrition advice, including Maternal, Neonatal, Child and Adolescent Health and Development and Reproductive Health and Research. The WHO Steering Committee for Nutrition Guidelines Development meets twice yearly. This Steering Committee both guided and provided overall supervision of the guideline development process. Two additional groups were formed: a guideline development group and a panel of external experts and stakeholders.

The Nutrition Guidance Advisory Group was established in 2009. A subgroup for micronutrients was established for the biennium 2010–2011 (Annex 4). Its role was to advise WHO on the choice of important outcomes for decision-making and in the interpretation of the evidence. The Nutrition Guidance Advisory Group includes experts from various [WHO expert advisory panels](#) and those identified through open calls for specialists, taking into consideration a balanced gender mix, multiple disciplinary areas of expertise and representation from all WHO regions. Efforts were made to include content experts, methodologists, representatives of potential stakeholders (such as managers and other health professionals involved in the health-care process) and consumers. Representatives of commercial organizations may not be members of a WHO guideline development group.

The External Experts and Stakeholders Panel (Annex 5) was consulted on the scope of the guideline, the questions addressed and the choice of important outcomes for decision-making, as well as with regard to review of the completed draft guideline. This was done through the WHO Micronutrients and [SCN](#) mailing lists that together included over 5500 subscribers, and through the [WHO nutrition web site](#).

Scope of the guideline, evidence appraisal and decision-making

An initial set of questions (and the components of the questions) to be addressed in the guideline was the critical starting point for formulating the recommendation. The questions were drafted by technical staff at the Evidence and Programme Guidance Unit, Department of Nutrition for Health and Development, based on policy and programme guidance needs of Member States and their partners. The population, intervention, control, outcomes (PICO) format was used (Annex 6). The questions were discussed and reviewed by the WHO Steering Committee for Nutrition Guidelines Development, and feedback was received from seven stakeholders.

A Nutrition Guidance Advisory Group meeting was held on 14–16 March 2011 in Geneva, Switzerland, to finalize the scope of the questions and rank the outcomes and populations of interest for the recommendations on vitamin D supplementation in pregnant women for the improvement of maternal and neonatal outcomes. The Nutrition Guidance Advisory Group – Micronutrients Subgroup discussed the relevance of the questions and modified them as needed. The guideline group scored the relative importance of each outcome from 1 to 9 (where 7–9 indicated that the outcome was critical for a decision, 4–6 indicated that it was important and 1–3 indicated that it was not important). The final key questions on this intervention, along with the outcomes that were identified as critical for decision-making, are listed in PICO format in Annex 6.

A systematic review (46) was used to summarize and appraise the evidence using the Cochrane methodology for randomized controlled trials¹. WHO staff prepared evidence summaries according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the overall quality of the evidence (50). GRADE considers: the study design; the limitations of the studies in terms of their conduct and analysis; the consistency of the results across the available studies; the directness (or applicability and external validity) of the evidence with respect to the populations, interventions and settings where the proposed intervention may be used; and the precision of the summary estimate of the effect.

Both the systematic review and the GRADE evidence profiles for each of the critical outcomes were used for drafting this guideline. The draft recommendation was discussed by the WHO Steering Committee for Nutrition Guidelines Development and at a second consultation with the Nutrition Guidance Advisory Group, held on 7–9 November 2011 in Washington DC, United States of America. At the second consultation, the guideline development group members independently voted on the strength of the recommendation, taking into account: (i) the desirable and undesirable effects of the intervention; (ii) the quality of the available evidence; (iii) values and preferences related to the intervention in different settings; and (iv) the cost of options available to health-care workers in different settings (Annex 2). The results of the vote and the summary of the considerations for establishing the strength of the recommendation were disclosed before the end of the meeting and further discussed as needed. Consensus was defined as agreement by simple majority of the guideline group members. WHO staff present at the meeting as well as other external technical experts involved in the collection and grading of the evidence were not allowed to vote. There were no strong disagreements among the guideline group members.

A public call for comments on the final draft guideline was released in 2012. All interested stakeholders became members of the External Experts and Stakeholders Panel but were allowed to comment on the draft guideline only after submitting a signed Declaration of Interests form. Feedback was received from 45 stakeholders. WHO staff addressed each comment and then finalized the guideline and submitted it for clearance by WHO before publication.

An additional group of international experts participated in a WHO technical consultation on the prevention and treatment of pre-eclampsia and eclampsia, held on 7–8 April 2011 in Geneva, Switzerland, to finalize the recommendation on vitamin D supplementation in pregnancy for the prevention of pre-eclampsia and its complications, which states that vitamin D supplementation in pregnancy to prevent the development of pre-eclampsia and its complications is not recommended (47).

¹ The detailed methods used in the systematic review, as well as their search dates, are published and available (open access) via *The Cochrane Library*. As part of the Cochrane pre-publication editorial process, this review was commented on by external peers (an editor and two referees external to the editorial team) and the group's statistical adviser (<http://www.cochrane.org/cochrane-reviews>). The *Cochrane handbook for systematic reviews of interventions* describes in detail the process of preparing and maintaining Cochrane systematic reviews on the effects of health-care interventions.

Management of conflicts of interest

According to the rules in the WHO [Basic documents](#) (51), all experts participating in WHO meetings must declare any interest relevant to the meeting prior to their participation. The conflicts of interest statements for all guideline group members were reviewed by the responsible technical officer and the relevant departments before finalization of the group composition and invitation to attend a guideline group meeting. All guideline group members and participants of the guideline development meetings submitted a Declaration of Interests form along with their curriculum vitae before each meeting. In addition, they verbally declared potential conflicts of interest at the beginning of each meeting. The procedures for management of conflicts of interest strictly followed the WHO [Guidelines for declaration of interests \(WHO experts\)](#) (52). The potential conflicts of interest declared by the members of the guideline group are summarized below.

- Dr Héctor Bourges Rodriguez declared being chair of the executive board of the Danone Institute in Mexico, a non-profit organization promoting research and dissemination of scientific knowledge in nutrition, and receiving funds as chair honorarium from this organization. Some activities of the Danone Institute in Mexico may generally relate to nutrition and are funded by Danone Mexico, a food producer.
- Dr Emorn Wasantwisut declared serving as a technical/scientific adviser to the International Life Sciences Institute (ILSI)/South East Asia's Food and Nutrients in Health and Disease Cluster and as a reviewer of technical documents and speaker for Mead Johnson Nutritionals. Her research unit received funds for research support from Sight and Life and the International Atomic Energy Agency (IAEA) for the use of stable isotopes to define interactions of vitamin A and iron.

Plans for updating the guideline

This guideline will be reviewed in 2016. At least 10 ongoing trials are scheduled to be completed by March 2014, which may provide the evidence that is currently lacking. The Department of Nutrition for Health and Development at the WHO headquarters in Geneva, along with its internal partners, will be responsible for coordinating the guideline update, following formal [WHO handbook for guideline development](#) procedures (49). WHO welcomes suggestions regarding additional questions for evaluation in the guideline when it is due for review.

References

1. Resolution WHA65.11. Nutrition. Maternal, infant and young child nutrition: draft comprehensive implementation plan. In: *Sixth-fifth World Health Assembly, Geneva, 21–26 May 2012. Resolutions and decisions, and list of participants*. Geneva, World Health Organization, 2012 (A65/11) Annex: 5–23 (http://apps.who.int/gb/ebwha/pdf_files/WHA65/A65_11-en.pdf, accessed 18 December 2012).
2. Holick MF. Vitamin D deficiency. *New England Journal of Medicine*, 2007, 357:266–281.
3. Bandeira F et al. Vitamin D deficiency: a global perspective. *Arquivos Brasileiros de Endocrinologia e Metabologia*, 2006, 50:640–646.
4. Dror DK, Allen LH. Vitamin D inadequacy in pregnancy: biology, outcomes, and interventions. *Nutrition Reviews*, 2010, 68:465–477.
5. Nicolaidou P et al. Low vitamin D status in mother-newborn pairs in Greece. *Calcified Tissue International*, 2006, 78:337–342.
6. O’Riordan MN et al. Prevalence of suboptimal vitamin D status during pregnancy. *Irish Medical Journal*, 2008, 101:240, 242–243.
7. Sloka S et al. Seasonal variation of maternal serum vitamin D in Newfoundland and Labrador. *Journal of Obstetrics and Gynaecology Canada*, 2009, 31:313–321.
8. Holick MF. Too little vitamin D in premenopausal women: why should we care? *American Journal of Clinical Nutrition*, 2002, 76:3–4.
9. van der Meer IM et al. High prevalence of vitamin D deficiency in pregnant non-Western women in The Hague, Netherlands. *American Journal of Clinical Nutrition*, 2006, 84:350–353.
10. Holick MF et al. Vitamin D and skin physiology: a D-lightful story. *Journal of Bone and Mineral Research*, 2007, 22(Suppl. 2):V28–V33.
11. Maghbooli Z et al. Vitamin D status in mothers and their newborns in Iran. *BioMed Central Pregnancy and Childbirth*, 2007, 7:1.
12. Arunabh S et al. Body fat content and 25-hydroxyvitamin D levels in healthy women. *Journal of Clinical Endocrinology and Metabolism*, 2003, 88:157–161.
13. Bodnar LM et al. Maternal vitamin D deficiency increases the risk of preeclampsia. *Journal of Clinical Endocrinology and Metabolism*, 2007, 92:3517–3522.
14. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *American Journal of Clinical Nutrition*, 2008, 87:1080S–1086S.
15. MacKay AP, Berg CJ, Atrash HK. Pregnancy-related mortality from preeclampsia and eclampsia. *Obstetrics and Gynecology*, 2001, 97:533–538.
16. Baker AM et al. A nested case-control study of midgestation vitamin D deficiency and risk of severe preeclampsia. *Journal of Clinical Endocrinology and Metabolism*, 2010, 95:5105–5109.
17. Wei SQ et al. Longitudinal vitamin D status in pregnancy and the risk of pre-eclampsia. *BJOG: International Journal of Obstetrics and Gynaecology*, 2012, 119:832–839.
18. Zhang C et al. Maternal plasma 25-hydroxyvitamin D concentrations and the risk for gestational diabetes mellitus. *Public Library of Science One*, 2008, 3:e3753.
19. Dawodu A, Nath R. High prevalence of moderately severe vitamin D deficiency in preterm infants. *Pediatrics International*, 2011, 53:207–210.
20. Morley R et al. Maternal 25-hydroxyvitamin D and parathyroid hormone concentrations and offspring birth size. *Journal of Clinical Endocrinology and Metabolism*, 2006, 91:906–912.
21. Leffelaar ER, Vrijkotte TG, van Eijsden M. Maternal early pregnancy vitamin D status in relation to fetal and neonatal growth: results of the multi-ethnic Amsterdam Born Children and their Development cohort. *British Journal of Nutrition*, 2010, 104:108–117.

22. Greer FR. 25-Hydroxyvitamin D: functional outcomes in infants and young children. *American Journal of Clinical Nutrition*, 2008, 88:529S–533S.
23. Javaid MK et al. Maternal vitamin D status during pregnancy and childhood bone mass at age 9 years: a longitudinal study. *The Lancet*, 2006, 367:36–43.
24. Wagner CL et al. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. *Pediatrics*, 2008, 122:1142–1152.
25. Cardús A et al. 1,25-Dihydroxyvitamin D₃ stimulates vascular smooth muscle cell proliferation through a VEGF-mediated pathway. *Kidney International*, 2006, 69:1377–1384.
26. Evans KN et al. Effects of 25-hydroxyvitamin D₃ and 1,25-dihydroxyvitamin D₃ on cytokine production by human decidual cells. *Biology of Reproduction*, 2006, 75:816–822.
27. Hewison M. Vitamin D and the immune system. *Journal of Endocrinology*, 1992, 132:173–175.
28. Li YC et al. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. *Journal of Clinical Investigation*, 2002, 110:229–238.
29. Jones G. Pharmacokinetics of vitamin D toxicity. *American Journal of Clinical Nutrition*, 2008, 88:582S–586S.
30. Food and Nutrition Board, Institute of Medicine. *Dietary reference intakes for calcium and vitamin D*. Washington DC, National Academy Press, 2010.
31. Dawson-Hughes B et al. Estimates of optimal vitamin D status. *Osteoporosis International*, 2005, 16:713–716.
32. Holick MF. Vitamin D status: measurement, interpretation, and clinical application. *Annals of Epidemiology*, 2009, 19:73–78.
33. Delvin EE et al. Vitamin D supplementation during pregnancy: effect on neonatal calcium homeostasis. *Journal of Pediatrics*, 1986, 109:328–334.
34. Yu CK et al. Vitamin D deficiency and supplementation during pregnancy. *Clinical Endocrinology*, 2009, 70:685–690.
35. Brooke OG et al. Vitamin D supplements in pregnant Asian women: effects on calcium status and fetal growth. *British Medical Journal*, 1980, 280:751–754.
36. Salle BL et al. Perinatal metabolism of vitamin D. *American Journal of Clinical Nutrition*, 2000, 71(Suppl.):S1317–S1324.
37. WHO, FAO. *Vitamin and mineral requirements in human nutrition*, 2nd ed. Geneva, World Health Organization, 2004.
38. Armas LA, Hollis BW, Heaney RP. Vitamin D₂ is much less effective than vitamin D₃ in humans. *Journal of Clinical Endocrinology and Metabolism*, 2004, 89:5387–5391.
39. Tripovic L et al. Comparison of vitamin D₂ and vitamin D₃ supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. *American Journal of Clinical Nutrition*, 2012, 95:1357–1364.
40. UNICEF, WHO, UNU. *Composition of a multi-micronutrient supplement to be used in pilot programmes among pregnant women in developing countries: report of a United Nations Children's Fund (UNICEF), World Health Organization (WHO), United Nations University (UNU) workshop held at UNICEF Headquarters, New York, July 9, 1999*. New York, United Nations Children's Fund, 2000 (<http://apps.who.int/iris/handle/10665/75358>, accessed 29 August 2012).
41. Hathcock JN et al. Risk assessment for vitamin D. *American Journal of Clinical Nutrition*, 2007, 85:6–18.
42. Heaney RP. Vitamin D: criteria for safety and efficacy. *Nutrition Reviews*, 2008, 66(Suppl. 2):S178–S181.
43. Vieth R, Chan PC, MacFarlane GD. Efficacy and safety of vitamin D₃ intake exceeding the lowest observed adverse effect level. *American Journal of Clinical Nutrition*, 2001, 73:288–294.
44. Aloia JF et al. Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration. *American Journal of Clinical Nutrition*, 2008, 87:1952–1958.

45. Hollis BW et al. Vitamin D supplementation during pregnancy: double-blind, randomized clinical trial of safety and effectiveness. *Journal of Bone and Mineral Research*, 2011, 26:2341–2357.
46. De-Regil LM et al. Vitamin D supplementation for women during pregnancy. *Cochrane Database of Systematic Reviews*, 2012, (2): CD008873 (<http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD008873.pub2/abstract>, accessed 16 February 2012).
47. *WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia*. Geneva, World Health Organization, 2011 (http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9789241548335/en/index.html, accessed 28 October 2011).
48. *Healthy eating during pregnancy and breastfeeding*. Copenhagen, WHO Regional Office for Europe, 2001 (http://www.euro.who.int/_data/assets/pdf_file/0020/120296/E73182.pdf, accessed 28 October 2011).
49. *WHO handbook for guideline development*. Geneva, World Health Organization, 2012 (http://apps.who.int/iris/bitstream/10665/75146/1/9789241548441_eng.pdf, accessed 29 August 2012).
50. Guyatt G et al. GRADE guidelines: 1. Introduction – GRADE evidence profiles and summary of findings tables. *Journal of Clinical Epidemiology*, 2011, 64:383–394.
51. *Basic documents*, 47th ed. Geneva, World Health Organization, 2009 (<http://apps.who.int/gb/bd/>, accessed 19 May 2011).
52. *Guidelines for declaration of interests (WHO experts)*. Geneva, World Health Organization, 2010.

Annex 1

GRADE “Summary of findings” tables

Vitamin D supplementation in pregnant women

Patient or population: Pregnant women

Settings: All settings

Intervention: Supplementation with vitamin D alone

Comparison: Placebo or no intervention (no vitamins or minerals)

Outcomes	Relative effect or mean difference (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)*	Comments
Pre-eclampsia (as defined by the trialists)	Not estimable	0 (0 studies)		None of the studies reported on this outcome
Maternal vitamin D status at term (serum 25-hydroxyvitamin D in nmol/L)	MD 47.08 nmol/L (23.76–70.39)	414 (4 studies)	⊕⊕⊖⊖ low ¹⁻³	
Eclampsia	Not estimable	0 (0 studies)		None of the studies reported on this outcome
Low birth weight (less than 2500 g)	RR 0.48 (0.23–1.01)	463 (3 studies)	⊕⊕⊖⊖ low ¹⁻³	

CI, confidence interval; RR, risk ratio; MD, mean difference.

*GRADE Working Group grades of evidence:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We have moderate confidence in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

¹Two of the included trials have high risk of performance of detection bias as they were not blinded. All trials had unclear allocation concealment.

²High statistical heterogeneity but consistency in the direction of the effect.

³Wide confidence interval.

For details of studies included in the review, see reference (46).

Vitamin D supplementation in pregnant women

Patient or population: Pregnant women

Settings: All settings

Intervention: Supplementation with vitamin D plus calcium

Comparison: Placebo or no intervention (no vitamins or minerals)

Outcomes	Relative effect or mean difference (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)*	Comments
Pre-eclampsia (as defined by the trialists)	RR 0.67 (0.33–1.35)	400 (1 study)	⊕⊖⊖⊖ very low ^{1,2}	Only one study reported on this outcome
Maternal vitamin D status at term (serum 25-hydroxyvitamin D in nmol/L)	Not estimable	0 (0 studies)		None of the studies reported on this outcome
Eclampsia	Not estimable	0 (0 studies)		None of the studies reported on this outcome
Low birth weight (less than 2500 g)	Not estimable	0 (0 studies)		None of the studies reported on this outcome

CI, confidence interval; **RR**, risk ratio.

*GRADE Working Group grades of evidence:

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We have moderate confidence in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

¹Wide confidence interval.

²This study is unclear about lack of blinding or differential loss to follow-up in the compared groups as biochemical data were completed only for those who developed pre-eclampsia and some of those with no pre-eclampsia and a group of non-pregnant controls.

For details of studies included in the review, see reference (46).

Annex 2

Summary of the Nutrition Guidance Advisory Group's considerations for determining the strength of the recommendation

- Quality of evidence:**
- The evidence for low birth weight and maternal vitamin D status was considered to be of low quality
- Values and preferences:**
- Vitamin D supplementation will probably have the most benefit in populations of poor countries, those with darker skin colour and in populations with a high prevalence of vitamin D deficiency
 - It is expected that this intervention would be acceptable to women who are not exposed to adequate amounts of sunshine
- Trade-off between benefits and harms:**
- Vitamin D is important for bone formation and cellular differentiation
 - Improved vitamin D status may have health effects that have not been measured
 - Vitamin D supplementation may decrease the prevalence of infants born with a low birth weight
 - There are no confirmed disadvantages of vitamin D supplementation in pregnancy
- Costs and feasibility:**
- This intervention may be better implemented as part of a multiple micronutrient supplement
 - If the intervention is combined with other interventions, the additional resources required would be small
 - This intervention would be most feasible when distributed as part of existing delivery mechanisms

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Annex 6

Questions in Population, Intervention, Control, Outcomes (PICO) format

Effects of vitamin D supplementation in pregnant women

- a. Should vitamin D supplements be given to pregnant women for the improvement of maternal and infant health outcomes?
- b. If so, at what dose, frequency and duration for the intervention, and in which settings?

- Population:**
- Pregnant women
 - Subpopulations (listed in order of priority):
 - Populations with low versus adequate baseline dietary calcium and vitamin D intakes
 - Populations with limited sun exposure versus populations with normal sun exposure
 - Populations with low or average risk versus above average risk of hypertensive disorders of pregnancy
 - Sedentary populations versus populations with moderate physical activity
- Intervention:**
- Any oral vitamin D supplements alone
 - Oral vitamin D supplements given in combination with other micronutrients
 - Subgroup analyses (listed in order of priority):
 - By dose of vitamin D (low versus high)
 - By trimester of pregnancy in which supplementation was started
 - By duration of supplementation
 - By regimen: daily versus weekly versus monthly
- Control:**
- Placebo or no treatment
 - Micronutrient supplements without vitamin D (to assess the additive effect of vitamin D)
- Outcomes:**
- Maternal
- Critical*
- High blood pressure with significant proteinuria (pre-eclampsia)
 - Blood levels of vitamin D (serum 25(OH)D)
 - Eclampsia (the occurrence of one or more convulsions (fits) in association with pre-eclampsia)
- Important*
- High blood pressure with or without proteinuria
 - Any adverse effects
 - Premature delivery (<37 weeks' gestation)
 - Bone density
 - Gestational diabetes
 - Complications at delivery (assisted delivery)
 - Immune function
 - Muscular strength
 - Vascular function
 - Physical performance
- Infant
- Critical*
- Low birth weight (<2500 g)
- Important*
- Birth weight
 - Stillbirth or death in early neonatal period (0–7 days of life)
 - Any adverse effects
 - Small for gestational age
 - Neonatal blood levels of vitamin D (serum 25(OH)D)
 - Admission to a neonatal intensive care unit
 - Length at birth
- Setting:** All settings/global

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