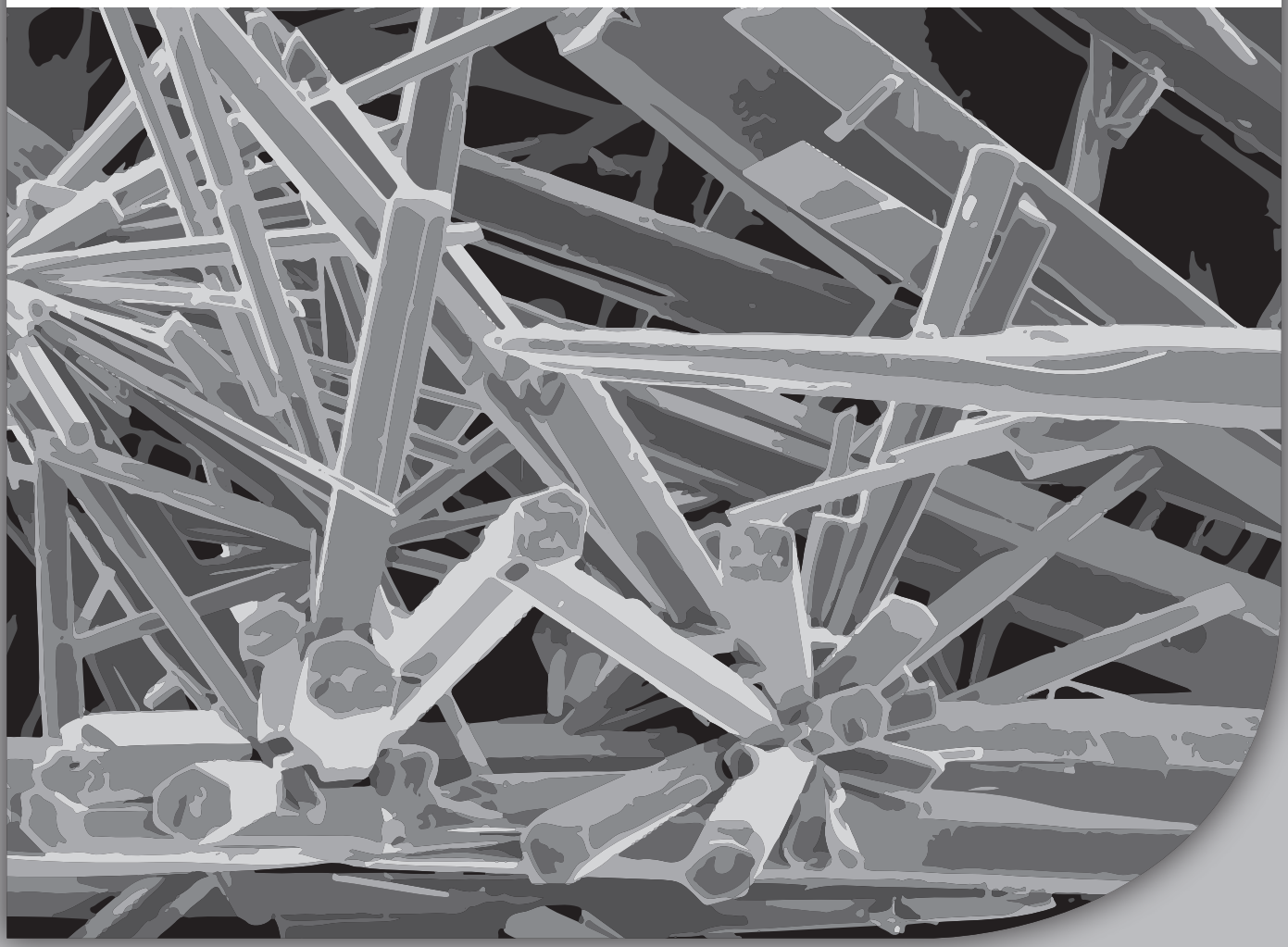
World Health Organization

Guideline:

# Calcium supplementation in pregnant women



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## Contents

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## Guideline[1]

**Calcium supplementation in pregnant women**

## Executive summary

**Purpose of the guideline:** Poor maternal and newborn health and nutrition remain significant contributors to the burden of disease and mortality. Calcium supplementation has the potential to reduce adverse gestational outcomes, in particular by decreasing the risk of developing hypertensive disorders during pregnancy, which are associated with a significant number of maternal deaths and considerable risk of preterm birth, the leading cause of early neonatal and infant mortality. Member States have requested guidance from the World Health Organization (WHO) on the efficacy and safety of calcium 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. 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.

**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, representatives of 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:** Two Cochrane systematic reviews investigated whether calcium supplementation on a daily basis during pregnancy safely improved maternal and infant outcomes. The findings revealed that this intervention significantly reduced the risk of pre-eclampsia and high blood pressure (with or without proteinuria). Women who received calcium supplements had a significantly higher risk of developing HELLP (haemolysis, elevated liver enzymes, and low platelet count) syndrome, a rare adverse event associated with severe pre-eclampsia. Calcium supplementation had no effects on the risk of developing eclampsia or maternal death or maternal admission to the intensive care unit.

[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.

In regard to infant outcomes, there was no effect of calcium supplementation on preterm birth (born before 37 weeks' gestation) overall. However, a subgroup analysis suggested that there were fewer preterm births among pregnant women who received between 1.5 g and 2 g of elemental calcium per day than among those women with a lower calcium intake. Calcium supplementation did not have a detectable effect on the risk of low birth weight, admission to a neonatal intensive care unit, stillbirth and neonatal death before hospital discharge.

**Recommendation**

- In populations where calcium intake is low, calcium supplementation as part of the antenatal care is recommended for the prevention of pre-eclampsia in pregnant women, particularly among those at higher risk of developing hypertension (*strong recommendation*)[1].

A suggested scheme for supplementation in pregnant women is presented in Table 1.

Table 1
**Suggested scheme for calcium supplementation in pregnant women**

| | |
|---|---|
| **Dosage** | 1.5–2.0 g elemental calcium/day[a] |
| **Frequency** | Daily, with the total daily dosage divided into three doses (preferably taken at mealtimes) |
| **Duration** | From 20 weeks' gestation until the end of pregnancy |
| **Target group** | All pregnant women, particularly those at higher risk of gestational hypertension[b] |
| **Settings** | Areas with low calcium intake |

[a] 1 g of elemental calcium equals 2.5 g of calcium carbonate or 4 g of calcium citrate.
[b] Women are regarded as being at high risk of developing gestational hypertension and pre-eclampsia if they have one or more of the following risk factors: obesity, previous pre-eclampsia, diabetes, chronic hypertension, renal disease, autoimmune disease, nulliparity, advanced maternal age, adolescent pregnancy and conditions leading to hyperplacentation and large placentas (e.g. twin pregnancy). This is not an exhaustive list, but can be adapted/complemented based on the local epidemiology of pre-eclampsia.

**Remarks:**

- Assessment of the risk of developing gestational hypertensive disorders is to be conducted by a clinician. The clinical management of women with pre-eclampsia or eclampsia requires consideration of other evidence-informed interventions.

[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 allocation of resources).

- Implementation of this recommendation requires close monitoring of women's total daily calcium intake (diet, supplements and antacids). The overall intake of calcium per day should not exceed the locally established upper tolerable limit. In the absence of such reference standards, an upper limit of calcium intake of 3 g/day can be used.
- The mechanisms through which calcium reduces the risk of gestational hypertension need further elucidation. Available evidence supports the theory that calcium supplementation may reduce the risk of developing pre-eclampsia by filling a dietary gap in calcium intake. In populations where consumption of calcium on average meets the recommended dietary calcium intake, either through calcium-rich foods or fortified staple foods, calcium supplementation is not encouraged as it may not improve the outcomes related to pre-eclampsia and hypertensive disorders of pregnancy but might increase the risk of adverse effects. Although antacids are a rich source of calcium, they are not part of the diet and their use should be limited to the treatment of heartburn or indigestion. The calcium content of any other vitamin and mineral supplements that are also being taken should be considered when recommending calcium supplementation, to reduce the risk of hypercalcaemia.
- Determination of the dietary calcium intake of an individual woman is a complex task. The target group for this recommendation comprises populations with observed low dietary calcium intake or those living in geographical areas where calcium-rich foods are not commonly available or consumed. Calcium intake at population level can be estimated through various means including dietary surveys using 24-hour recalls, food frequency questionnaires or food weighing, as well as through secondary data estimates derived from the Food and Agriculture Organization (FAO) food balance sheets or household consumption and expenditure surveys.
- Healthy dietary practices to promote adequate calcium intake through local calcium-rich foods should be encouraged in the general population, including pregnant women.
- Interaction between iron supplements and calcium supplements may occur, although the consequences of prolonged calcium supplementation for iron status among different age groups are still unclear. Therefore, the two nutrients should preferably be administered several hours apart (i.e. iron may be consumed between meals) rather than concomitantly.
- Selection of the most appropriate delivery platform should be context specific, with the aim of reaching the most vulnerable populations and ensuring a timely and continuous supply of supplements. Calcium supplementation could be delivered by lay health workers along with targeted monitoring and evaluation.
- Calcium supplements are available as tablets or capsules. Tablets (soluble tablets, effervescent tablets, chewable tablets for use in the mouth and modified-release tablets) are solid dosage forms containing one or more active ingredients.

**Research priorities:** Guideline group members and stakeholders identified several research priorities to improve the body of evidence at the basic, clinical, epidemiological and operational levels on both benefits and harms of this intervention among pregnant women. They are listed in the guideline.

## Scope and purpose

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

The guideline will help Members 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, especially global target 3, which entails achieving a relative reduction of 30% in the number of infants born with a weight <2500 g by the year 2025 (*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 escalation of nutrition actions in public health programmes.

This document presents the key recommendation and a summary of the supporting evidence. Further details of the evidence base are provided in Annexes 1 and 2 and other documents listed in the references.

## Background

Poor maternal and newborn health and nutrition remain significant contributors to the burden of disease. In 2010, 3.1 million babies died in the first 28 days of life, mostly due to low birth weight, severe infections, asphyxia and preterm birth. Every year, 15 million babies are born prematurely, of whom 1.1 million die in the neonatal period or in infancy. In addition, many of those who survive have a lifetime disability such as learning disabilities and/or visual and hearing problems (*2*).

Approximately 287 000 women died during pregnancy and childbirth in 2010, mostly due to maternal health complications (*3*). Hypertensive disorders of pregnancy include (pre-existing) chronic hypertension and gestational hypertension, pre-eclampsia and eclampsia (*4*,*5*). These disorders complicate approximately 2-8% of all pregnancies and have been associated with preterm and low birth weight and maternal mortality (*4*). Pre-eclampsia is diagnosed when gestational hypertension (maternal blood pressure ≥140/90 mmHg for the first time in the second half of pregnancy) is accompanied by proteinuria >300 mg in a 24-hour period. The pathogenesis of pre-eclampsia has not been thoroughly elucidated, however, it is related to disturbances in placentation in early pregnancy, followed by generalized inflammation and progressive endothelial damage. Pre-eclampsia can be classified as mild or severe. In severe pre-eclampsia, the blood pressure is ≥160/110 mmHg and there is proteinuria ≥2 g/24 h, with or without substantial maternal organ damage (*5*). Such end-organ damage as a result of pre-eclampsia can present with haemolysis, elevated liver enzymes and low platelet count, a constellation of symptoms known as HELLP syndrome (*5*). This is a rare condition that occurs in 10–20% of cases with severe pre-eclampsia (*6*).

Calcium is the most abundant mineral in the body and is essential for many diverse processes, including bone formation, muscle contraction, and enzyme and hormone functioning (*7*). Most of the body's calcium is found

in the bones and teeth; approximately 1% is present in the intracellular structures, cell membrane and extracellular fluids (*8*). Calcium absorption increases during pregnancy and no additional intake is needed (*9*). A dietary intake of 1200 mg/day of calcium for pregnant women is recommended by WHO and the Food and Agriculture Organization of the United Nations (FAO) (*7*). Inadequate consumption of this nutrient by pregnant women can lead to adverse effects in both the mother and the fetus, including osteopenia, tremor, paraesthesia, muscle cramping, tetanus, delayed fetal growth, low birth weight and poor fetal mineralization (*10*).

Serum calcium concentrations are maintained within narrow limits in the body and thus have limited use for the assessment of calcium nutritional status at both the individual and the population levels. Calcium intake could be a useful indicator of status at the population level. The main dietary sources of this nutrient are milk, dairy products, calcium-set tofu and fortified foods (*9*); some local foods such as lime-treated corn meal also have abundant calcium. There is no information on the adequacy of calcium intake worldwide. However, some studies at the regional and national levels suggest that low calcium intake at population level occurs frequently (*11, 12*).

Various studies have suggested that calcium supplementation during pregnancy has a beneficial effect on reducing the risk of pregnancy-induced hypertension (*10*). The results of trials evaluating the effect of supplementation on maternal bone mineral density, fetal mineralization, and preterm birth, however, are less conclusive (*13*). Excessive consumption of calcium may increase the risk of urinary stones and urinary tract infection, and reduce the absorption of other essential micronutrients (*13*).

In supplements, calcium is present in the form of carbonate, citrate, lactate or gluconate, and in general all these forms have good bioavailability (*14, 15*). At least one salt of calcium for oral administration (in a variety of doses) is included in most national essential medicines lists (*16*), calcium carbonate being the most common. As calcium carbonate has the highest content of elemental calcium (40%), it may have the best efficacy-cost ratio in pregnancy (*17*), but this needs to be confirmed in future analyses.

## Summary of evidence

An existing Cochrane systematic review was updated (*13*) and another review was newly developed (*18*) to specifically investigate whether daily calcium supplementation in pregnancy safely improves maternal and infant outcomes. The maternal outcomes considered critical for decision-making by the Nutrition Guidance Advisory Group were pre-eclampsia, eclampsia, high blood pressure with or without proteinuria, complications at delivery, and any adverse events. Important infant outcomes were preterm birth, low birth weight (<2500 g), stillbirth, death during the neonatal period, and any adverse effects such as being small for gestational age or admission to a neonatal care unit.

For the purposes of this guideline, the results of the two systematic reviews were combined, thus including the findings of 21 randomized controlled trials (RCT), involving more than 19 000 pregnant women from both developed and developing countries in all continents. These trials compared calcium supplementation with receiving a placebo or no

intervention in addition to regular antenatal care. The total daily dosage of supplemental calcium ranged between 300 mg (0.3 g) and 2000 mg (2 g). Most of the studies started supplementation at 20 weeks' gestation and were considered of high quality.

For all women, irrespective of the baseline risk of developing hypertension and calcium intake status, calcium supplementation more than halved the risk of pre-eclampsia when compared with a placebo (average risk ratio (RR) 0.48, 95% confidence interval (CI) 0.34–0.67, 15 trials, 16 490 women). The risk reduction was 41% in women at low risk of developing hypertension (RR 0.59, 95% CI 0.42–0.82, 10 trials, 15 903 women) whereas among those at high risk of hypertensive disorders, a much higher risk reduction of 78% was recorded (RR 0.22, 95% CI 0.12–0.42, five trials, 587 women). Although the women's response to calcium supplementation was heterogeneous in terms of the magnitude of the effect, there was a consistent protective effect of the intervention (Annex 1, Figure 1; Annex 2).

High blood pressure (with or without proteinuria) showed, in general, a similar pattern to that of pre-eclampsia. Overall, fewer women on calcium supplementation had high blood pressure compared with those receiving placebo (RR 0.65, 95% CI 0.53–0.81, 12 trials, 15 470 women). Women at high risk of developing hypertension showed the greatest reduction in risk (RR 0.47, 95% CI 0.22–0.90, four trials, 327 women), closely followed by those with a low baseline dietary calcium intake (RR 0.44, 95% CI 0.28–0.70, seven trials, 10 418 women).

With regard to the outcome of eclampsia, there were no significant differences between women on calcium supplementation and women receiving placebo or no treatment (RR 0.66, 95% CI 0.40–1.11, five trials, 14 185 women). Similar effects were found in a non-Cochrane review analysis restricted to developing countries (*19*).

A significant increase in the risk ratio for HELLP (haemolysis, elevated liver enzymes, low platelet counts) syndrome was observed in women who received calcium supplementation compared with those who received placebo (RR 2.67, 95% CI 1.05–6.82, two trials, 12 901 women). There were no effects on maternal death (RR 0.17, 95% CI 0.02–1.39, one trial, 8312 women) or maternal admission to the intensive care unit (RR 0.84, 95% CI 0.66–1.07, one trial, 8312 women).

In regard to infant outcomes (Annex 2), there was no effect of calcium supplementation on preterm birth, although a subgroup analysis by supplemental dose suggested that among pregnant women consuming ≥1.5 g of calcium per day fewer babies were born before 37 weeks' gestation than among those receiving <1.5 g per day (RR 0.78, 95% CI 0.63–0.98 vs. RR 0.72, 95% CI 0.08–6.52 (Annex 1, Figure 2)). There were no significant differences between women who received calcium supplements and those who did not in the risk of having a low-birth-weight baby (RR 0.85, 95% CI 0.72–1.01, nine trials, 14 883 infants) or in the risk of the baby being admitted to neonatal intensive care unit (RR 1.05, 95% CI 0.94–1.18, four trials, 14 062 women) and, stillbirth or neonatal death before hospital discharge (RR 0.90, 95% CI 0.74–1.09, 11 trials, 15 665 women). One of the systematic reviews assessed additional infant outcomes (*18*) and noted that a trial conducted in 1978 with 273 women reported that calcium supplementation might increase infant bone mineral density. There was no evidence of an effect of calcium

supplementation on intrauterine growth restriction, birth length or fetal head circumference.

The quality of the evidence for admission to a neonatal intensive care unit was high, while it was moderate for pre-eclampsia, high blood pressure, and maternal admission to an intensive care unit. The quality of the evidence was low for eclampsia, maternal death, HELLP (haemolysis, elevated liver enzymes, low platelet counts) syndrome, preterm birth, low birth weight and perinatal mortality.

## Recommendation

- In populations where calcium intake is low, calcium supplementation as part of the antenatal care is recommended for the prevention of pre-eclampsia among pregnant women, particularly among those at higher risk of hypertension (*strong recommendation*)[1,2].

A suggested scheme for supplementation in pregnant women is presented in Table 1.

Table 1
**Suggested scheme for calcium supplementation in pregnant women**

| | |
|---|---|
| **Dosage** | 1.5–2.0 g elemental calcium/day[a] |
| **Frequency** | Daily, with the total daily dosage divided into three doses (preferably taken at mealtimes) |
| **Duration** | From 20 weeks' gestation until the end of pregnancy |
| **Target group** | All pregnant women, particularly those at higher risk of gestational hypertension[b] |
| **Settings** | Areas with low calcium intake |

[a] 1 g of elemental calcium equals 2.5 g of calcium carbonate or 4 g of calcium citrate.
[b] Women are regarded as being at high risk of developing hypertension and pre-eclampsia if they have one or more of the following risk factors: obesity, previous pre-eclampsia, diabetes, chronic hypertension, renal disease, autoimmune disease, nulliparity, advanced maternal age, adolescent pregnancy and conditions leading to hyperplacentation and large placentas (e.g. twin pregnancy). This is not an exhaustive list, but can be adapted/complemented based on the local epidemiology of pre-eclampsia.

[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 allocation of resources).

[2] Considerations of the guideline development group for determining the strength of the recommendation are summarized in Annex 3.

**Remarks**

- Assessment of the risk of developing gestational hypertensive disorders is to be conducted by a clinician. The clinical management of women with pre-eclampsia or eclampsia requires consideration of other evidence-informed interventions (*5*).
- Implementation of this recommendation requires close monitoring of women's total daily calcium intake (diet, supplements and antacids). The overall intake of calcium per day should not exceed the locally established upper tolerable limit. In the absence of such reference standards, an upper limit of calcium intake of 3 g/day can be used (*7*).
- The mechanisms through which calcium reduces the risk of gestational hypertension need further elucidation. Available evidence supports the theory that calcium supplementation may reduce the risk of developing pre-eclampsia by filling a dietary gap in calcium intake (*5*). In populations where consumption of calcium on average meets the recommended dietary calcium intake, either through calcium-rich foods or fortified staple foods, calcium supplementation is not encouraged as it may not improve the outcomes related to pre-eclampsia and hypertensive disorders of pregnancy but might increase the risk of adverse effects. Although antacids are not a rich source of calcium, they are not part of the diet and their use should be limited to the treatment of heartburn or indigestion. The calcium content of any other vitamin and mineral supplements that are also being taken should be considered when recommending calcium supplementation, to reduce the risk of hypercalcaemia.
- Determination of the dietary calcium intake of an individual woman is a complex task. The target group for this recommendation comprises populations with observed low dietary calcium intake or those living in geographical areas where calcium-rich foods are not commonly available or consumed (*5*). Calcium intake at population level can be estimated through various means including dietary surveys using 24-hour recalls, food frequency questionnaires or food weighing, as well as through secondary data estimates derived from FAO food balance sheets or household consumption and expenditure surveys (*20, 21*).
- Healthy dietary practices to promote adequate calcium intake through local calcium-rich foods should be encouraged in the general population, including pregnant women (*5*).
- Interaction between iron supplements and calcium supplements may occur, although the consequences of prolonged calcium supplementation for iron status among different age groups are still unclear (*22–25*). Therefore, the two nutrients should preferably be administered several hours apart (i.e. iron may be consumed between meals) rather than concomitantly.
- Selection of the most appropriate delivery platform should be context-specific, with the aim of reaching the most vulnerable populations and ensuring a timely and continuous supply of supplements. Calcium supplementation could be delivered by lay health workers along with targeted monitoring and evaluation (*26*).
- Calcium supplements are available as tablets or capsules. Tablets (soluble tablets, effervescent tablets, chewable tablets for use in the mouth and modified-release tablets) are solid dosage forms containing one or more active ingredients (*27*).

## Implications for future research

Discussion with members of the Nutrition Guidance Advisory Group and stakeholders highlighted the limited evidence available in some areas, meriting further research on calcium supplementation in pregnant women, in particular, in the following areas:

- biological mechanisms underlying the relationships between calcium supplementation, pre-eclampsia and HELLP (haemolysis, elevated liver enzymes, low platelet counts) syndrome;
- minimal dose and optimal commencement of supplementation to achieve a positive effect on pre-eclampsia and other gestational outcomes such as preterm birth;
- effects of calcium supplementation on maternal and infant outcomes in conjunction with other nutrients (e.g. vitamin D) or as part of a supplement with multiple vitamins and minerals;
- effects of gestational calcium supplementation among adolescents;
- long-term effects of calcium supplementation during pregnancy on mother and infant health;
- additional benefit of calcium supplementation among pregnant women who are already receiving antihypertensive treatment; and
- operational research assessing delivery mechanisms, compliance, acceptability and costs of providing separate versus multiple micronutrients. Calcium supplementation programmes need careful monitoring and evaluation to assess their successes and failures in terms of integration into the overall antenatal care package.

## 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 calcium supplements to pregnant women should have well-defined objectives that take into account available resources, existing policies, suitable delivery platforms and suppliers, communication

channels, and potential stakeholders. Ideally, calcium supplementation should be implemented as part of an integrated programme for antenatal care and preceded by an assessment of the calcium intake at population level. The latter can be estimated through various means including dietary surveys using 24-hour recalls, food frequency questionnaires or food weighing, as well as through secondary data estimates derived from FAO food balance sheets or household consumption and expenditure surveys (*20, 21*).

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 within countries (i.e. monitoring and evaluation of the programmes implemented at national or regional scale) and across countries (i.e. the adoption and adaptation of the guideline globally). The WHO Department of Nutrition for Health and Development, Evidence and Programme Guidance Unit, jointly with the Centers for Disease Control and Prevention (CDC) International Micronutrient Malnutrition Prevention and Control (IMMPaCt) programme, and with input from international partners, has developed a generic logic model for micronutrient interventions in public health (*28*) to depict the plausible relationships between inputs and expected MDGs by applying the micronutrient programme evaluation theory. Member States can adjust the model and use it in combination with appropriate indicators, for designing, implementing, monitoring and evaluating the successful escalation of nutrition actions in public health programmes.

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 WHO evidence-informed guideline development procedures, as outlined in the *WHO handbook for guideline development* (*29*).

### Advisory groups

The WHO Steering Committee for Nutrition Guidelines Development (Annex 4), 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 and 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 (Annex 5) was established in 2009. A subgroup for micronutrients was established for the biennium 2010–2011. 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 6) 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 7). The questions were discussed and reviewed by the WHO Steering Committee for Nutrition Guidelines Development, and feedback was received from four 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 critical outcomes and populations of interest for the recommendation on calcium 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 7.

Two systematic reviews (*13, 18*) were used to summarize and appraise the evidence using the Cochrane methodology for randomized controlled

trials[1]. 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 (*30*). 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 reviews 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 3). It was noted how they balanced the decisions for each of the four domains. The voting results 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 46 stakeholders. WHO staff addressed each comment and then finalized the guideline and submitted it for clearance by WHO before publication.

This guideline complements the report of the WHO technical consultation on the prevention and treatment of pre-eclampsia and eclampsia, held on 7–8 April 2011 in Geneva, Switzerland (*5*).

## Management of conflicts of interest

According to the rules in the WHO *Basic documents* (*31*), 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

[1] The detailed methods used in each 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.

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 WHO *Guidelines for declaration of interests (WHO experts)* (*32*). 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 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. If new information is available at that time, a guideline review group will be convened to evaluate the new evidence and revise the recommendation if needed. 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* (*29*) procedures. WHO welcomes suggestions regarding additional questions for evaluation when the guideline is due for review.

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## Annex 1. Additional analyses

Figure 1. **Effect of gestational calcium supplementation on pre-eclampsia in comparison with receiving a placebo or no intervention, by risk of developing hypertension**

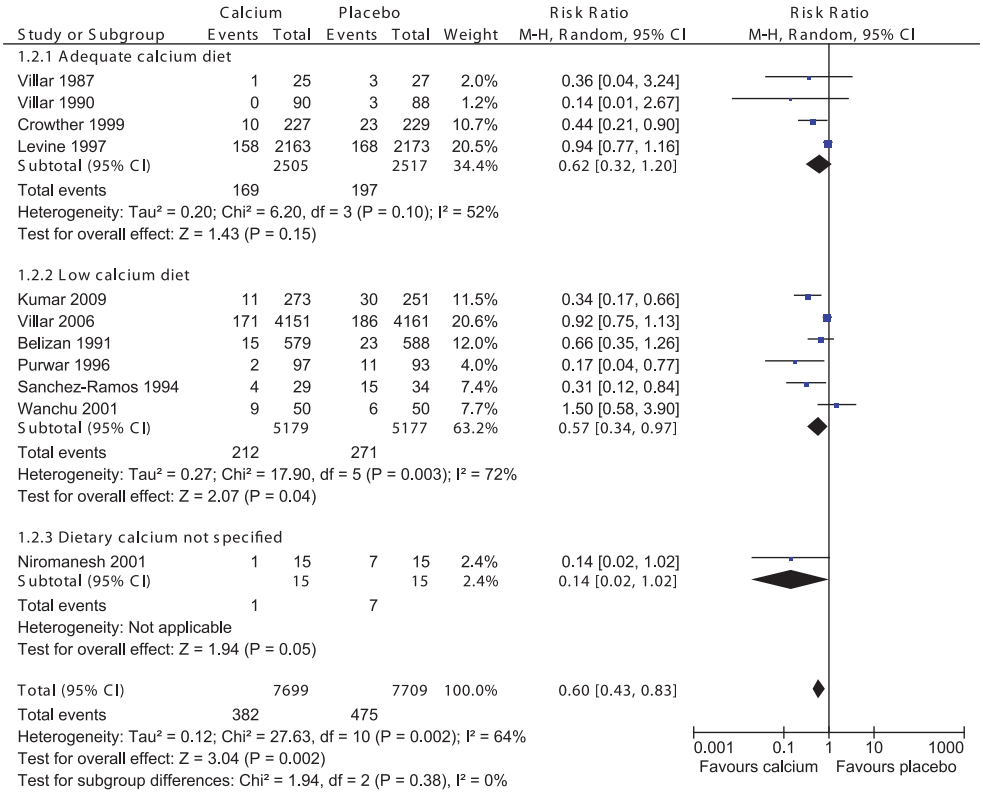
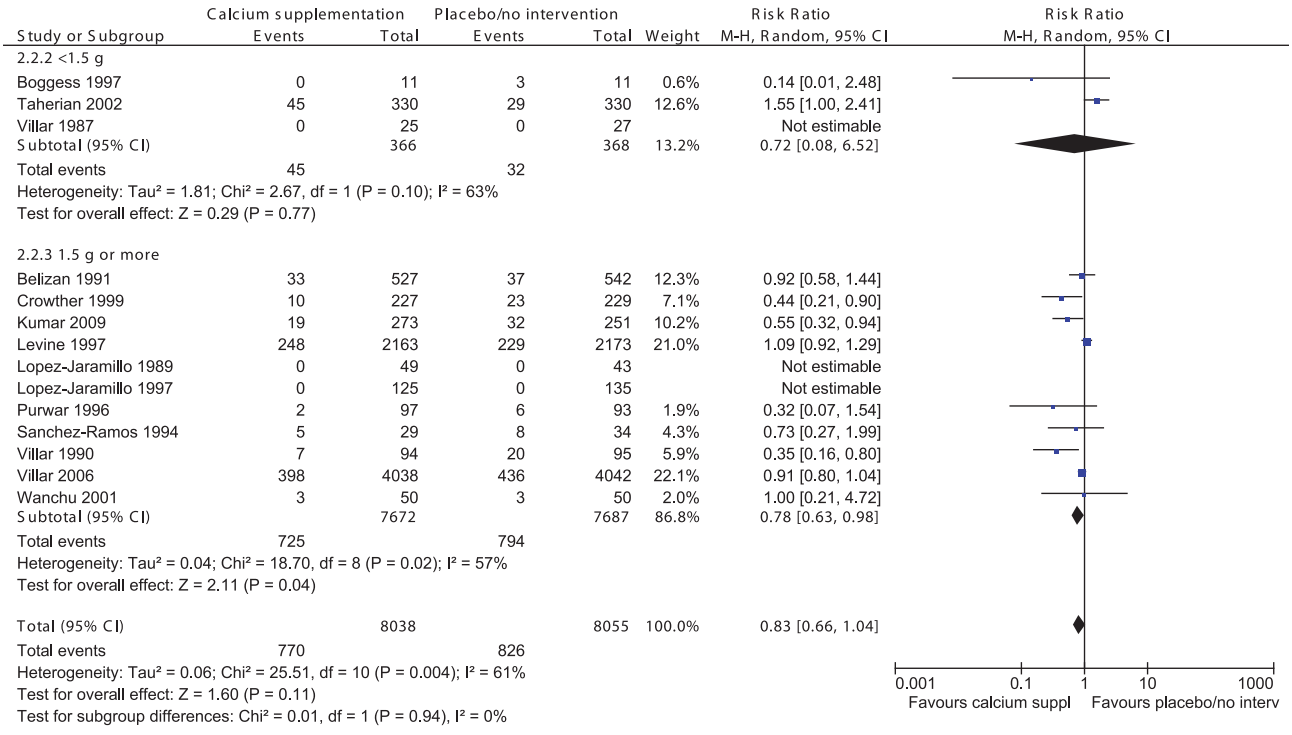



Figure 2. **Effect of gestational calcium supplementation on preterm birth in comparison with receiving a placebo or no intervention, by calcium supplementation dose**




* Boggess (1997) reported on premature labour
For details of studies, see reference (*13*, *18*).

## Annex 2. GRADE "Summary of findings" tables

**Calcium supplementation for pregnant women: maternal outcomes**
**Patient or population:** Pregnant women
**Settings:** All settings
**Intervention:** Calcium supplementation
**Comparison:** Placebo or no intervention

| Outcomes | Relative effect or mean difference (95% CI) | Number of participants (studies) | Quality of the evidence (GRADE)* | Comments |
|---|---|---|---|---|
| **Pre-eclampsia** | RR 0.48 (0.34–0.67) | 16 490 (15 trials) | ⨁⨁⨁⨀ **moderate**[1] | |
| **Eclampsia** | RR 0.66 (0.40–1.11) | 14 185 (5 trials) | ⨁⨁⨀⨀ **low**[1,2] | |
| **High blood pressure (with or without proteinuria)**+ | RR 0.65 (0.53–0.81) | 15 470 (12 trials) | ⨁⨁⨁⨀ **moderate**[1] | |
| **Maternal death**+♣ | RR 0.17 (0.02–1.39) | 8312 (1 trial) | ⨁⨁⨀⨀ **low**[2,3] | |
| **Maternal admission to intensive care unit**+♣ | RR 0.84 0.66-1.07) | 8312 (1 trial) | ⨁⨁⨁⨀ **moderate**[3] | |
| **Haemolysis, elevated liver enzymes, low platelet counts (HELLP) syndrome**+ | RR 2.67 (1.05–6.82) | 12 901 (2 trials) | ⨁⨁⨀⨀ **low**[2,4] | |

**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.

[1] Serious statistical heterogeneity possibly due to variation in baseline dietary intake of calcium, but there is consistency in the direction of the effect.
[2] Wide confidence intervals (imprecision).
[3] Only one study reported on this outcome.
[4] Few events.

+ For details of studies included in the review, see reference *(13)*.
♣ For details of studies included in the review, see reference *(18)*.

**Calcium supplementation for pregnant women: newborn outcomes**
**Patient or population:** Pregnant women
**Settings:** All settings
**Intervention:** Calcium supplementation
**Comparison:** Placebo or no intervention

| Outcomes | Relative effect or mean difference (95% CI) | Number of participants (studies) | Quality of the evidence (GRADE)* | Comments |
|---|---|---|---|---|
| **Preterm birth** | RR 0.83 (0.66–1.04) | 16 093 (14 trials) | ⨁⨁⨀⨀ **low**[1,2] | |
| **Low birth weight**+ | RR 0.85 (0.72–1.01) | 14 883 (9 trials) | ⨁⨁⨀⨀ **low**[1,2] | |
| **Perinatal mortality**♣ | RR 0.84 (0.61–1.16) | 5145 (7 trials) | ⨁⨁⨀⨀ **low**[1,2] | |
| **Admission to neonatal intensive care unit**+♣ | RR 1.05 (0.94–1.18) | 14 062 (4 trials) | ⨁⨁⨁⨁ **high** | |

**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.

[1] Serious statistical heterogeneity possibly explained by the supplemental dose of calcium, but there is consistency in the direction of the effect.
[2] There are some trials at high risk of bias, particularly due to high losses to follow-up and lack of blinding.

+ For details of studies included in the review, see reference *(13)*.
♣ For details of studies included in the review, see reference *(18)*.

## Annex 3. Summary of the Nutrition Guidance Advisory Group's considerations for determining the strength of the recommendation

| | |
|---|---|
| **Quality of evidence:** | • Low and moderate-quality evidence for most outcomes<br>• Clear impact on pre-eclampsia and possibly on preterm birth<br>• Low-quality evidence for adverse effects |
| **Values and preferences:** | • Effects greater in those with low calcium intake and larger doses of calcium<br>• Evidence is consistent for pre-eclampsia and preterm birth, both of which are responsible for a considerable proportion of the burden of maternal and infant morbidity and mortality<br>• Some members noted that the two largest studies do not show a clinical impact of this intervention |
| **Trade-off between benefits and harms:** | • Current evidence suggests that benefits outweigh disadvantages, particularly in populations with low calcium intake<br>• The possibility of developing HELLP syndrome and renal stones is a concern and more evidence is needed for this outcome |
| **Costs and feasibility:** | • This intervention may be adopted as a policy when adequate health systems and delivery platforms already exist<br>• There is a lack of information on the cost of this intervention<br>• This intervention may require intensive resources to target those women with an increased risk of hypertension |

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## Annex 7. Questions in Population, Intervention, Control, Outcomes (PICO) format

***Effects of calcium supplementation in women during pregnancy***

a. Should calcium supplements be given to pregnant women for improvement of maternal and infant health outcomes?

b. If so, at what dose, frequency and duration of the intervention?

| | |
|---|---|
| **Population:** | • **Pregnant women**<br>• Subpopulations (listed in order of priority):<br>– Populations with a low versus adequate baseline dietary calcium intake<br>– Populations with above average risk versus low or average risk of hypertensive disorders of pregnancy |
| **Intervention:** | • Oral calcium supplements<br>• Oral calcium supplements given in combination with other micronutrients<br>• Subgroup analyses:<br>– By dose of calcium<br>– By calcium compound: calcium carbonate, lactate, gluconate<br>– By regimen: daily versus other<br>– By duration of supplementation<br>– By trimester of pregnancy in which supplementation was started |
| **Control:** | • Placebo or no treatment<br>• Micronutrient supplements without calcium (to assess the additive effect of calcium) |
| **Outcomes:** | Maternal<br>• High blood pressure with or without proteinuria<br>• High blood pressure with significant proteinuria (pre-eclampsia)<br>• Eclampsia (the occurrence of one or more convulsions (fits) in association with pre-eclampsia)<br>• Complications at delivery (assisted delivery)<br>• Bone softness<br>• Osteoporosis<br>• Any adverse effects<br><br>Infant<br>• Low birth weight (<2500 g)<br>• Birth weight<br>• Preterm birth (<37 weeks' gestation)<br>• Length at birth<br>• Admission to a neonatal intensive care unit<br>• Stillbirth or death in early neonatal period (0–7 days of life)<br>• Any adverse effects<br>• Small for gestational age |
| **Setting:** | All settings/global |

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