The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Two Randomized Trials of Low-Dose Calcium Supplementation in Pregnancy

Pratibha Dwarkanath, Ph.D., Alfa Muhihi, M.D., M.P.H., Christopher R. Sudfeld, Sc.D., Blair J. Wylie, M.D., M.P.H., Molin Wang, Ph.D., Nandita Perumal, Ph.D., Tinku Thomas, Ph.D., Shabani M. Kinyogoli, B.Sc., Mohamed Bakari, M.Sc., Ryan Fernandez, M.B.L., John-Michael Raj, M.Sc., Ndeniria O. Swai, M.P.H., Nirmala Buggi, M.D., Rani Shobha, M.D., Mary M. Sando, M.D., M.P.H., Christopher P. Duggan, M.D., M.P.H., Honorati M. Masanja, Ph.D., Anura V. Kurpad, M.D., Ph.D., Andrea B. Pembe, M.D., Ph.D., and Wafaie W. Fawzi, M.B., B.S., Dr.P.H.

- Hypertensive disorders of pregnancy, which include preeclampsia, complicate 2 to 8% of pregnancies and are estimated to cause 45,000 maternal deaths annually.

- These disorders are also associated with an increased risk of preterm birth, the leading cause of death among children worldwide.

- Therefore, the implementation of effective strategies to prevent hypertensive disorders of pregnancy and preterm birth will be essential for countries to reach the maternal and child mortality targets of the United Nations Sustainable Development Goals by 2030.

Calcium supplementation in pregnancy has been recommended by the World Health Organization (WHO) since 2011 to reduce the risk of preeclampsia in populations with low dietary calcium intake.

In placebo-controlled trials, high-dose calcium supplementation of at least 1000 mg per day reduced the risk of preeclampsia by more than half and the risk of preterm birth by 24%; the reduction in the risk of preeclampsia appeared to be greater in trials that had been conducted in populations with lowcalcium diets.

On the basis of this evidence, the WHO has recommended calcium supplementation of 1500 to 2000 mg per day, divided into three doses, taken a few hours apart from iron–folic acid supplements.

Trials of low-dose calcium supplementation of less than 1000 mg per day in pregnancy, most of which evaluated a single 500-mg calcium supplement per day as compared with placebo and have had relatively small sample sizes, have generally shown a magnitude of reduction in the risks of preeclampsia and preterm birth similar to that seen in the trials of highdose supplementation.

- **We conducted two randomized, noninferiority trials to compare the efficacy of 500 mg of calcium supplementation per day with 1500 mg per day in India and Tanzania.**

Methods

We conducted two independent, individually randomized, parallel-group, double-blind, noninferiority trials of low-dose calcium supplementation as compared with high-dose calcium supplementation in nulliparous pregnant women in India and Tanzania. The trials were designed to have similar interventions, methods, and outcome definitions but were independently powered and were planned to be analyzed separately.

Participants were enrolled at health clinics in Bangalore, India, and in Dar es Salaam, Tanzania. Participants were adult (≥18 years of age) nulliparous pregnant women who were at less than 20 weeks' gestation (according to the date of the last menstrual period), who intended to stay in the trial area until 6 weeks post partum, and who provided written informed consent. Women were excluded from enrollment if they had a history, signs, or symptoms of nephrolithiasis; had a history of parathyroid disorder or had undergone thyroidectomy; or had a disease for which digoxin, phenytoin, or tetracycline therapy was indicated.

Interventions

Participants in India and Tanzania were randomly assigned to receive either 500 mg or 1500 mg of elemental calcium supplementation to be taken orally each day until delivery. The 500-mg calcium supplementation group received one tablet that contained 500 mg of elemental calcium as calcium carbonate and two placebo tablets each day, and the 1500-mg calcium supplementation group received three 500-mg tablets each day. In India, vitamin D3 is recommended to be taken with calcium supplements, and therefore the two groups in the India trial also received 250 IU of vitamin D3 per day. There was no vitamin D3 added to the tablets in the Tanzania trial.

- Participants had follow-up clinic visits each month during pregnancy, at delivery, and at 6 weeks post partum.

- The primary efficacy outcomes were **preeclampsia and preterm birth**. Preeclampsia was defined as the meeting of at least one of the following criteria from 20 weeks' gestation to delivery: gestational hypertension and proteinuria among participants without chronic hypertension, gestational proteinuria among participants with chronic hypertension (superimposed preeclampsia), clinical diagnosis of preeclampsia, or the development of preeclampsia with severe features with or without proteinuria.

- Blood pressure was assessed at each trial visit by means of digital blood-pressure monitors. Dipsticks were used to assess the presence of **protein in urine** samples at each pregnancy visit and at delivery.

- Preterm birth was defined as a live birth before 37 weeks' gestation.

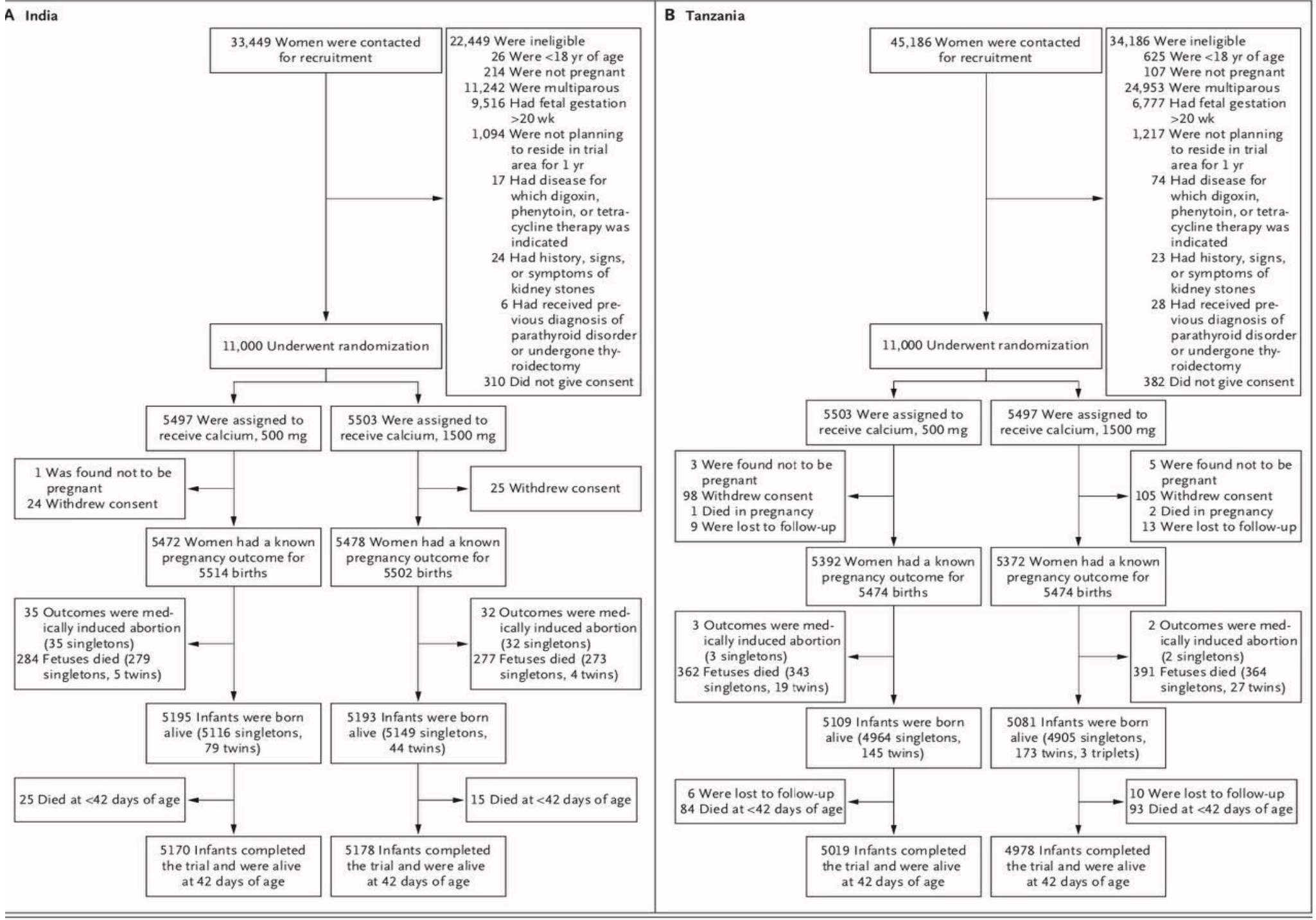
Secondary outcomes included gestational hypertension, preeclampsia with severe features, pregnancy-related death, fetal death, stillbirth (at ≥28 weeks' gestation), low birth weight (<2500 g), small-for-gestational-age.

and infant death before 42 days of age. Maternal hospitalization (excluding hospitalization for delivery) and third-trimester severe anemia (hemoglobin concentration, <7.0 g per deciliter) were evaluated as safety outcomes.

All the participants in India and Tanzania received standard-care antenatal and postpartum services that were aligned with the country-specific antenatal care guidelines. **In India**, pregnant participants received daily supplements that contained 5 mg of folic acid during the first trimester and then supplements that contained 60 mg of elemental iron and 0.4 mg of folic acid during the second and third trimesters. **In Tanzania**, pregnant participants received daily iron–folic acid supplements that contained 60 mg of elemental iron and 0.4 mg of folic acid starting at the first antenatal care visit.

Results

In the India trial, from November 2018 through February 2022, we screened 33,449 women and enrolled 11,000 pregnant participants. In the Tanzania trial, from March 2019 through March 2022, we screened 45,186 women and enrolled 11,000 pregnant participants.


A India
33,449 Women were contacted for recruitment
22,449 Were ineligible
26 Were <18 yr of age
214 Were not pregnant
11,242 Were multiparous
9,516 Had fetal gestation >20 wk
1,094 Were not planning to reside in trial area for 1 yr
17 Had disease for which digoxin, phenytoin, or tetracycline therapy was indicated
24 Had history, signs, or symptoms of kidney stones
6 Had received previous diagnosis of parathyroid disorder or undergone thyroidectomy
310 Did not give consent
11,000 Underwent randomization
5497 Were assigned to receive calcium, 500 mg
5503 Were assigned to receive calcium, 1500 mg
1 Was found not to be pregnant
24 Withdrew consent
25 Withdrew consent
5472 Women had a known pregnancy outcome for 5514 births
5478 Women had a known pregnancy outcome for 5502 births
35 Outcomes were medically induced abortion (35 singletons)
284 Fetuses died (279 singletons, 5 twins)
32 Outcomes were medically induced abortion (32 singletons)
277 Fetuses died (273 singletons, 4 twins)
5195 Infants were born alive (5116 singletons, 79 twins)
5193 Infants were born alive (5149 singletons, 44 twins)
25 Died at <42 days of age
15 Died at <42 days of age
5170 Infants completed the trial and were alive at 42 days of age
5178 Infants completed the trial and were alive at 42 days of age
B Tanzania
45,186 Women were contacted for recruitment
34,186 Were ineligible
625 Were <18 yr of age
107 Were not pregnant
24,953 Were multiparous
6,777 Had fetal gestation >20 wk
1,217 Were not planning to reside in trial area for 1 yr
74 Had disease for which digoxin, phenytoin, or tetracycline therapy was indicated
23 Had history, signs, or symptoms of kidney stones
28 Had received previous diagnosis of parathyroid disorder or undergone thyroidectomy
382 Did not give consent
11,000 Underwent randomization
5503 Were assigned to receive calcium, 500 mg
5497 Were assigned to receive calcium, 1500 mg
3 Were found not to be pregnant
98 Withdrew consent
1 Died in pregnancy
9 Were lost to follow-up
5 Were found not to be pregnant
105 Withdrew consent
2 Died in pregnancy
13 Were lost to follow-up
5392 Women had a known pregnancy outcome for 5474 births
5372 Women had a known pregnancy outcome for 5474 births
3 Outcomes were medically induced abortion (3 singletons)
362 Fetuses died (343 singletons, 19 twins)
2 Outcomes were medically induced abortion (2 singletons)
391 Fetuses died (364 singletons, 27 twins)
5109 Infants were born alive (4964 singletons, 145 twins)
5081 Infants were born alive (4905 singletons, 173 twins, 3 triplets)
6 Were lost to follow-up
84 Died at <42 days of age
10 Were lost to follow-up
93 Died at <42 days of age
5019 Infants completed the trial and were alive at 42 days of age
4978 Infants completed the trial and were alive at 42 days of age

In both trials, most of the pregnant participants were between 18 and 24 years of age and had normal blood pressure at baseline. The percentage of the participants with a baseline dietary calcium intake of less than 800 mg per day was approximately 87% in India and 67% in Tanzania.

Table 1. Characteristics of the Participants at Baseline in the India and Tanzania Trial Populations.*

Characteristic	India Trial (N=11,000)		Tanzania Trial (N=11,000)	
	500 mg Calcium (N=5497)	1500 mg Calcium (N=5503)	500 mg Calcium (N=5503)	1500 mg Calcium (N=5497)
Maternal age — no. (%)				
18–24 yr	3372 (61.3)	3436 (62.4)	3882 (70.5)	3879 (70.6)
25–29 yr	1616 (29.4)	1550 (28.2)	1299 (23.6)	1257 (22.9)
≥30 yr	509 (9.3)	517 (9.4)	322 (5.9)	361 (6.6)
Maternal education — no./total no. (%)				
No formal education	162/5496 (2.9)	168/5502 (3.1)	82/5496 (1.5)	94/5491 (1.7)
Primary education	215/5496 (3.9)	199/5502 (3.6)	1802/5496 (32.8)	1744/5491 (31.8)
Secondary or higher education	5119/5496 (93.1)	5135/5502 (93.3)	3612/5496 (65.7)	3653/5491 (66.5)
Wealth quintile — no./total no. (%)				
Quintile 1: Poorest	1104/5496 (20.1)	1096/5502 (19.9)	1099/5503 (20.0)	1099/5497 (20.0)
Quintile 2: Second poorest	1076/5496 (19.6)	1130/5502 (20.5)	1109/5503 (20.2)	1093/5497 (19.9)
Quintile 3: Middle	1122/5496 (20.4)	1071/5502 (19.5)	1119/5503 (20.3)	1081/5497 (19.7)
Quintile 4: Second richest	1077/5496 (19.6)	1131/5502 (20.6)	1055/5503 (19.2)	1145/5497 (20.8)
Quintile 5: Richest	1117/5496 (20.3)	1074/5502 (19.5)	1121/5503 (20.4)	1079/5497 (19.6)
Gestational age — no. (%)†				
<13 wk 0 days	1675 (30.5)	1718 (31.2)	1598 (29.0)	1699 (30.9)
13 wk 0 days to 16 wk 6 days	2231 (40.6)	2170 (39.4)	2085 (37.9)	2070 (37.7)
17 wk 0 days to 20 wk 0 days	1591 (28.9)	1615 (29.3)	1820 (33.1)	1728 (31.4)
Maternal height <155.0 cm — no./total no. (%)	3241/5496 (59.0)	3295/5502 (59.9)	1853/5503 (33.7)	1824/5497 (33.2)
Body-mass index — no./total no. (%)‡				
<18.5	898/5496 (16.3)	886/5502 (16.1)	452/5503 (8.2)	440/5497 (8.0)
18.5–24.9	2846/5496 (51.8)	2869/5502 (52.1)	3202/5503 (58.2)	3162/5497 (57.5)
25.0–29.9	1238/5496 (22.5)	1225/5502 (22.3)	1269/5503 (23.1)	1306/5497 (23.8)
≥30.0	514/5496 (9.4)	522/5502 (9.5)	578/5503 (10.5)	588/5497 (10.7)
Hemoglobin concentration — no. (%)				
≥11.0 g/dl	3018 (54.9)	3034 (55.1)	3241 (58.9)	3233 (58.8)
10.0–10.9 g/dl	1762 (32.1)	1679 (30.5)	1534 (27.9)	1531 (27.9)
7.0–9.9 g/dl	687 (12.5)	766 (13.9)	728 (13.2)	732 (13.3)

<7.0 g/dl	15 (0.3)	13 (0.2)	0	1 (<0.1)
Living with HIV infection — no. (%)	NA	NA	107 (1.9)	89 (1.6)
Family history of hypertension — no./total no. (%)	326/5496 (5.9)	325/5502 (5.9)	1025/5503 (18.6)	1050/5497 (19.1)
High blood pressure — no. (%)§	34/5482 (0.6)	45/5492 (0.8)	14/5503 (0.3)	18/5497 (0.3)
Taking antihypertensive drug — no. (%)	1/5496 (<0.1)	3/5502 (0.1)	10/5503 (0.2)	9/5497 (0.2)
Median caloric intake (IQR) — kcal¶	1169 (946–1421)	1166 (956–1421)	2862 (2144–3600)	2882 (2206–3647)
Median dietary calcium intake (IQR) — mg/day¶	431 (292–629)	440 (297–633)	413 (193–1143)	413 (190–1233)
Dietary calcium intake <800 mg/day — no./total no. (%)‖	4774/5497 (86.8)	4802/5503 (87.3)	3046/4535 (67.2)	3035/4526 (67.1)

* HIV denotes human immunodeficiency virus, IQR interquartile range, and NA not available.
† Gestational age was defined on the basis of the reported date of the last menstrual period (enrollment criterion). In the India trial, 11 participants (6 in the 500-mg group and 5 in the 1500-mg group) underwent randomization between 20 weeks 1 day of gestation age and 20 weeks 6 days of gestational age.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ High blood pressure was defined as a systolic blood pressure of at least 140 mm Hg or a diastolic blood pressure of at least 90 mm Hg.
¶ In the Tanzania trial, data on dietary intake were missing for 968 participants in the 500-mg group and for 971 in the 1500-mg group.
‖ An intake of 800 mg of calcium per day is the U.S. Institute of Medicine estimated average requirement for calcium intake among pregnant or lactating persons 19 to 50 years of age.

Primary Outcomes

In the India trial, the cumulative incidence of preeclampsia was 3.0% in the 500-mg group and 3.6% in the 1500-mg group (relative risk, 0.84; 95% confidence interval [CI], 0.68 to 1.03); in the Tanzania trial, the cumulative incidence of preeclampsia was 3.0% in the 500-mg group and 2.7% in the 1500-mg group (relative risk, 1.10; 95% CI, 0.88 to 1.36) (Table 2). In both trials, the 500-mg dose of calcium was shown to be noninferior to the 1500-mg dose with regard to the risk of preeclampsia. In sensitivity analyses, there were no between-group differences in the incidence of early-onset preeclampsia at less than 34 weeks' gestation or of preeclampsia onset at less than 37 weeks' gestation.

The incidence of preterm birth in the India trial was 11.4% in the 500-mg group and 12.8% in the 1500-mg group (relative risk, 0.89; 95% CI, 0.80 to 0.98); the incidence in the Tanzania trial was 10.4% in the 500-mg group and 9.7% in the 1500-mg group (relative risk, 1.07; 95% CI, 0.95 to 1.21). The findings were consistent with noninferiority in the India trial but not in the Tanzania trial.Results of the per-protocol analyses, sensitivity analyses, and analyses with adjustment for potential baseline imbalance were similar to the primary analyses in each trial.

Table 2. Primary Efficacy Outcomes in the India and Tanzania Trials.*

Outcome	India Trial				Tanzania Trial			
	500 mg Calcium	1500 mg Calcium	Relative Risk (95% CI)	P Value for Noninferiority	500 mg Calcium	1500 mg Calcium	Relative Risk (95% CI)	P Value for Noninferiority
Preeclampsia								
Primary intention-to-treat analysis	164/5497 (3.0)	196/5503 (3.6)	0.84 (0.68–1.03)	<0.001	165/5503 (3.0)	150/5497 (2.7)	1.10 (0.88–1.36)	<0.001
Per-protocol analysis†	156/5027 (3.1)	184/5022 (3.7)	0.85 (0.69–1.05)		148/4420 (3.3)	128/4448 (2.9)	1.16 (0.92–1.46)	
Sensitivity analysis excluding participants who had pregnancy loss or withdrew before 20 wk of gestation	164/5397 (3.0)	196/5408 (3.6)	0.84 (0.69–1.03)		165/5361 (3.1)	150/5297 (2.8)	1.09 (0.87–1.35)	
Preterm birth‡								
Primary intention-to-treat analysis	593/5195 (11.4)	665/5193 (12.8)	0.89 (0.80–0.98)	<0.001	531/5109 (10.4)	493/5081 (9.7)	1.07 (0.95–1.21)	0.10
Per-protocol analysis§	552/4852 (11.4)	629/4842 (13.0)	0.87 (0.78–0.97)		448/4279 (10.5)	430/4323 (9.9)	1.06 (0.93–1.20)	
Sensitivity analysis involving singleton live births	559/5116 (10.9)	637/5149 (12.4)	0.88 (0.79–0.98)		448/4964 (9.0)	412/4905 (8.4)	1.07 (0.95–1.22)	

* P values are for noninferiority. A post hoc Bonferroni correction was applied to the primary efficacy outcomes within each trial to account for tests of the two efficacy outcomes; two-sided 95% confidence intervals are shown, and a P value for noninferiority of less than 0.025 was considered to indicate statistical significance.

† The per-protocol analysis for preeclampsia included all the pregnant participants who had more than 75% adherence to the randomly assigned regimen, had a pregnancy of at least 20 weeks' gestation, and had a delivery outcome assessed (excluding withdrawal and loss to follow-up in pregnancy).

‡ Gestational age was determined on the basis of the best obstetrical estimate.

§ The per-protocol analysis for preterm birth included live births born to pregnant participants who had more than 75% adherence to the randomly assigned regimen.

Results of the per-protocol analyses, sensitivity analyses, and analyses with adjustment for potential baseline imbalance were similar to the primary analyses in each trial (Table 2). There were no apparent between group differences in the incidenc of preterm birth in post hoc sensitivity analyses that were restricted to spontaneous births.

Secondary and Safety Outcomes

Results of the secondary and safety outcomes in the two trials are shown in Table 3.

There was no evidence favoring the 1500-mg group over the 500-mg group with regard to the secondary or safety outcomes in either trial.

Table 3. Secondary and Safety Outcomes in the India and Tanzania Trials.*

Outcome	India Trial			Tanzania Trial		
	500 mg Calcium	1500 mg Calcium	Relative Risk or Incidence Rate Ratio (95% CI)	500 mg Calcium	1500 mg Calcium	Relative Risk or Incidence Rate Ratio (95% CI)
Secondary outcomes						
Gestational hypertension — no./total no. (%)†	176/5477 (3.2)	207/5468 (3.8)	0.85 (0.70–1.03)	225/5481 (4.1)	220/5469 (4.0)	1.02 (0.85–1.22)
Preeclampsia with severe features — no./total no. (%)	61/5497 (1.1)	97/5503 (1.8)	0.63 (0.46–0.87)	100/5503 (1.8)	94/5497 (1.7)	1.06 (0.80–1.40)
Pregnancy-related death — no./total no. (%)	2/5497 (0.04)	2/5503 (0.04)	1.00 (0.14–7.10)	4/5503 (0.1)	3/5497 (0.1)	1.33 (0.30–5.95)
Fetal death — no./total no. (%)	284/5479 (5.2)	277/5470 (5.1)	1.03 (0.87–1.20)	362/5471 (6.6)	391/5472 (7.2)	0.93 (0.81–1.07)
Stillbirth at ≥28 wk of gestation — no./total no. (%)	110/5305 (2.1)	120/5313 (2.3)	0.92 (0.71–1.18)	165/5274 (3.1)	158/5239 (3.0)	1.05 (0.85–1.30)
Birth weight <2500 g — no./total no. (%)	898/5195 (17.3)	910/5193 (17.5)	0.98 (0.90–1.06)	448/5095 (8.8)	438/5066 (8.7)	1.03 (0.90–1.18)
Small-for-gestational-age status <10th percentile — no./total no. (%)	1703/5195 (32.8)	1777/5193 (34.2)	0.96 (0.90–1.01)	1133/5095 (22.2)	1112/5066 (22.0)	1.02 (0.94–1.09)
Infant death at <42 days — no./total no. (%)	25/5195 (0.5)	15/5193 (0.3)	1.60 (0.84–3.06)	84/5109 (1.6)	93/5081 (1.8)	0.90 (0.67–1.22)
Safety outcomes						
Maternal hospitalization — no. of hospitalizations/no. of person-mo	11/43,223	24/43,332	0.46 (0.22–0.94)	40/38,164	25/38,705	1.60 (0.97–2.63)
Maternal third-trimester severe anemia — no./total no. (%)‡	1/4475 (<0.1)	2/4478 (<0.1)	0.50 (0.05–5.52)	0/4229	0/4215	—

* Relative risks are shown for all secondary and safety outcomes except for the repeatable safety event of maternal hospitalization, for which incidence rate ratios are shown. For these nonprimary outcome analyses, the 95% confidence intervals are not adjusted for multiplicity and should not be used to infer definitive treatment effects.

† The analysis of gestational hypertension excluded participants with chronic hypertension (20 participants in the 500-mg group and 35 in the 1500-mg group in the India trial, and 22 and 28 participants, respectively, in the Tanzania trial).

‡ Severe anemia was defined as a hemoglobin concentration of less than 7.0 g per deciliter.

Discussion

In two large, randomized trials conducted in India and Tanzania, each of which enrolled 11,000 nulliparous pregnant participants, the use of lowdose calcium supplementation at a dose of 500 mg per day was noninferior to standard high-dose supplementation of 1500 mg per day with respect to the incidence of preeclampsia. For preterm birth, the use of low-dose calcium supplementation was noninferior in the India trial but did not show noninferiority in the Tanzania trial. Metaanalyses of data from the two trials were consistent, with no material difference between low-dose and high-dose supplementation for the primary, secondary, and safety outcomes.

Our two trials showed that low-dose supplementation with 500 mg of calcium per day was noninferior to high-dose supplementation for the prevention of preeclampsia.

We found that low-dose calcium supplementation was noninferior to high-dose supplementation for preterm birth in the India trial; however, this was not the case in the Tanzania trial, in which the upper boundary of the confidence interval crossed the noninferiority margin. In the Tanzania trial, the risk of preterm birth in the 1500-mg group was slightly less than predicted in the power calculations, and therefore the confidence intervals were somewhat wider than expected.


با تشکر از توجه شما