Summary of the Second Meeting of the Calcium Task Force
By Hallie Kapner

Overview

The Nutrition Science Program of the New York Academy of Sciences (NYAS) hosted the second of two meetings of the Calcium Task Force — an international group of experts on nutrition science, public health, maternal and child health, and food fortification — on April 26-28, 2021. Discussions centered around the benefits, risks, feasibility, and implementation of interventions and policies to improve global calcium intake. The work of the Calcium Task Force is supported by the Children's Investment Fund Foundation (CIFF).

Key Takeaways

The Task Force unanimously agrees that calcium is part of a healthy diet, as specified by all dietary recommendations worldwide. Yet due to an inconsistent relationship between calcium intakes and health outcomes, billions of people— especially in low- and middle-income countries (LMICs)—routinely consume far less calcium than recommended often with no increased risk of bone fracture. Bone health is the primary outcome upon which calcium recommendations are based. Efforts to define adequate calcium status and set dietary reference values often do not include data from LMICs where calcium intake is low, nor do they account for genetic differences or other elements of the diet, which can impact calcium absorption and retention.

The task force did not reach consensus on recommending a population-level intervention, such as food fortification, to increase calcium intakes—even in countries with extremely low calcium consumption. The group cited the following factors: the absence of a specific biomarker that reflects calcium status and is easily assessed; the inability to identify a population-level health outcome beyond bone health that could be impacted by increasing calcium intake; and the potential risks of some populations exceeding the upper limit (UL) for calcium, although this was deemed a relatively low risk in most LMICs. Fortification was considered desirable as a means for increasing preconception calcium for women of reproductive age, however, the group did not agree that this necessarily justified a population-level intervention in most settings.

The lack of an agreed-upon biomarker of calcium status is perhaps the greatest hurdle in assessing low calcium intake. Without it, efforts to identify populations with low calcium intake must rely on proxy measures, such as food balance sheets or national intake data, which is inconsistently available for calcium in LMICs. Monitoring and assessing the effectiveness of food fortification or supplementation is more challenging absent a biomarker, as is advocating for calcium to be included in national nutrition surveys.

The task force recognizes the benefits of calcium supplementation for reducing rates of preeclampsia, preterm birth, and maternal morbidity and mortality in women with low calcium intakes. While the WHO guidelines for calcium supplementation in pregnancy call for high-dose supplementation, the group eagerly awaits the results of forthcoming research on the efficacy of low-dose supplementation to achieve similar outcomes. Lower dose supplementation may also ease implementation challenges by reducing pill burden and cost.

Participants

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Meeting Summary

I. Defining Adequate Calcium Status

Calcium status depends on many factors, including consumption of calcium-rich foods, the presence or absence of calcium fortification or supplements, age, sex, and intake of foods that impair calcium absorption. Calcium retention and absorption also vary by race and ethnicity.[1,2,3]

Assessing calcium status is challenging. There is no biomarker that is both specific and sensitive to calcium, and the relationship between low calcium intakes and health outcomes is inconsistent. Not all populations with intake below the recommendations have negative health consequences—in fact, much of the world's population falls well below[4] the values set by the Institute of Medicine (IOM)[5], European Food Safety Authority (EFSA)[6] and others, and agencies differ in the amount of calcium they recommend per day. Calcium intake recommendations are based strictly on bone health outcomes in high-income settings, yet many other factors and nutrients play a role in this area.

Recommended intakes

Connie Weaver described researchers' efforts to derive a set of harmonized nutrient reference values[7] as a means for setting global, rather than national or regional, intake recommendations. These values would form a common basis from which to assess population intakes and address nutrient gaps through food fortification or supplementation.

The Harmonized Average Requirement (H-AR) for calcium[7] is closely aligned with EFSA recommendations for calcium intake.

H-AR Calcium (mg/d)

Source Life Stage					
Children		**Males**		**Females**	
1-3 y	390	11-14 y	960	11-14 y	960
4-6 y	680	15-17 y	960	15-17 y	960
7-10 y	680	18-24 y	860	18-24 y	860
		25-50 y	750	25-50 y	750
		51-70 y	750	51-70 y	750
		>70 y	750	>70 y	750

The task force discussed the potential value of harmonized reference values. A primary concern regarding the proposed values is that EFSA guidance is based on European populations and does not represent intakes of billions of people in Asia, South and Southeast Asia, and Africa, where calcium intake is much lower. Calcium data is not as readily available in LMICs, although some data exist. The group discussed organizing an effort to compile the available data to add to analyses of calcium intake and shortfalls relative to IOM recommendations and the proposed

H-AR. “However, any way we slice it, there will be a considerable part of the world below any of these recommendations,” Weaver said.

Biomarkers

Prashanth Thankachan led a discussion about the challenges of assessing calcium status in the absence of a sensitive, specific biomarker. While there are multiple methods for measuring calcium in the body, all have significant limitations. Serum calcium is tightly regulated and not reflective of recent intakes, biochemical markers in urine or blood may be associated with nutrient deficiencies besides calcium, and emerging techniques including urine metabolomics and assessing variability in stable calcium isotope ratios in urine require additional validation and are not “field friendly.” Dual-energy x-ray absorptiometry (DXA) provides an accurate measure of total body bone content (and, by derivation, total body calcium) as well as bone mineral density (BMD), but it is expensive and only reveals bone changes associated with late-stage deficiency in adults. DXA can reveal changes in BMD somewhat earlier in children and may be helpful in assessing the impact of small-scale supplementation programs. However, it is not a population-level tool. No clear solution to this issue is forthcoming.

The lack of a biomarker is likely to hinder large-scale nutritional programs, including food fortification, as monitoring and evaluation often depend on the ability to gauge the impact of these interventions on biomarkers and health outcomes.

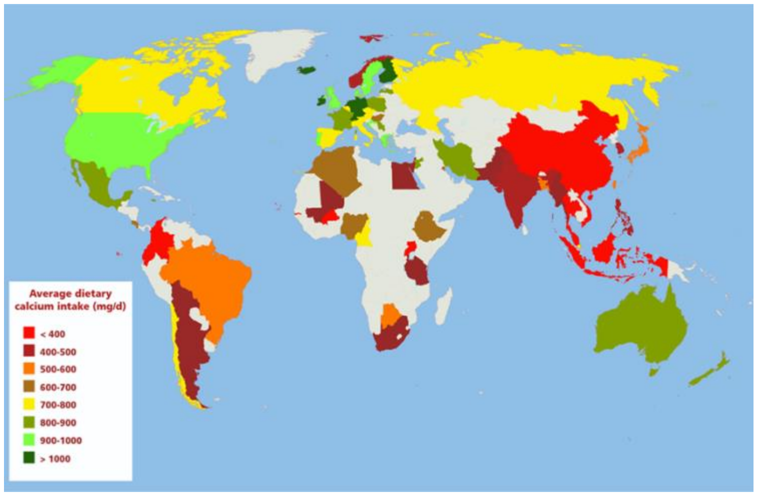
Calcium status beyond bone

While 99% of calcium in the body is found in bone, there are several medical conditions associated with either an excess or deficiency of serum or tissue calcium. **Steven Abrams** reviewed these conditions, noting that while hypocalcemia can cause neurological and cardiac issues and even death in extreme cases, conditions of excess calcium are a greater, albeit still minimal, concern when considering population-level interventions such as fortification.

Risks associated with excess calcium are greatest in early life and among the elderly. In preterm infants, use of loop diuretics raises the risk of hypercalcemia and renal stones. On the other end of the age spectrum, milk alkali syndrome—characterized by hypercalcemia, renal failure, and metabolic acidosis— has been reported from excess intake of calcium supplements, often in the form of calcium carbonate antacids. Overall, conditions associated with excess calcium intake are not common in adults, and almost nonexistent in adolescents, Abrams said.

Identifying populations with low calcium intake

Anuradha Khadilkar described several approaches for identifying populations with low calcium intake—a difficult task in light of the fact that calcium is not well represented in national intake surveys in LMICs. A 2017 systematic review of global calcium intakes[4] among adults not only reveals very low intakes throughout Asia, India, and Southeast Asia, but highlights large areas of the globe where there is no available calcium data, including most of Africa, Mongolia, and parts of Eastern Europe. Data on global consumption of calcium among children is scarce.



Many tools are used for assessing calcium and dairy consumption among adults. One paper[8] identified 36 different tools, yet their reliability and validity vary greatly, which also complicates efforts to assess intake levels.

Khadilkar suggests that in the absence of intake data, countries may consider using the prevalence of calcium deficiency states — including rickets, osteomalacia, osteoporosis, and fracture risk — as indicators of low calcium status. Factors such as food security, cultural habits and norms including vegetarian diets and consumption of dairy, as well as intake of nutrients that impact calcium absorption such as vitamin D, protein, oxalates, and phytates, should also be considered.

Gabriela Cormick noted that food balance sheets, which indicate the availability of calcium in the diet, have been used as a proxy for consumption[9] and can be helpful in identifying populations with low intakes. "If the country doesn't have enough calcium to cover the needs of the population, then you know there is low calcium consumption," she said. In these instances, a biomarker or other status indicator may be less critical as a benchmark for taking action.

Kate Dicken and **Lynnette Neufeld** commented that outdated or incomplete food composition tables also hinder calcium intake assessments, along with limited information on calcium bioavailability of some local foods consumed in LMICs.

Cristina Palacios brought the group's attention to the Global Dietary Database,[10] a new resource for information on individual nutrient and food intake data stratified by country, region (including rural/urban), life stage, and pregnancy/lactation status. Calcium is included in this database. Other task force members noted that this is a welcome addition to the field but cautioned that the database draws from many different sources, which vary in reliability.

According to Khadilkar, calcium is "not a public health priority" in LMICs, in part because there is no clear biomarker and no simple test for calcium deficiency. Calcium has also been largely left out of global efforts to encourage countries to include biomarkers in national nutrition surveys. “There’s no easy answer of what biomarker we would even put into a national survey,” said Lynnette Neufeld, “but resolving this might help resolve the [intake] data availability challenge.”

II. Summary and Research Gaps: Epidemiology and Health Outcomes

Daniel Roth facilitated a discussion of knowledge gaps in the areas of epidemiology and health outcomes. He noted that some gaps could potentially be filled by analysis of existing data, particularly in the areas of assessing calcium intake in LMICs. Other gaps require additional research, especially pertaining to biomarkers of calcium status.

The group agreed that the lack of a biomarker of calcium status remains a significant hurdle. Additional research on emerging methodologies may help alleviate this challenge, but at present, there is no obvious option for a biomarker that would be suitable for assessing population status or gauging the impact of large-scale nutritional interventions (fortification or supplementation). Additional questions remain regarding which health outcomes might trigger governments to consider including a calcium biomarker or intake assessment in national nutrition surveys, as budgets are often constrained, and nutrients often compete for inclusion.

The group acknowledged interest in adding calcium intake data in LMICs (where available) to estimates and analyses of population average intake. There was additional interest in exploring the idea of convening an international group to consider harmonized reference values, as well as a discussion of considering recommended intakes in the context of other nutrients that impact calcium availability. These include vitamin D, sodium, oxalate, phytate, and particularly in infants, phosphorous and magnesium.

III. Calcium Supplementation for Pregnant Women

Concerns around calcium supplementation in pregnancy and lactation

Calcium demand during pregnancy

Pregnancy and lactation are times of high demand for calcium, both to aid in fetal bone mineralization *in utero* and as a component of breastmilk.[11] Changes in calcium and bone metabolism occur during both pregnancy and lactation to meet that demand. Pregnancy is associated with increased intestinal calcium absorption and increased urinary calcium excretion, while lactation is marked by bone demineralization and decreased urinary excretion.[12] As **Ann Prentice** explained, the degree of bone mobilization that takes place during breastfeeding is directly related to the frequency and duration of nursing, and whether menses return during the breastfeeding period.[13] The longer the duration of breastfeeding, the greater the degree of bone demineralization. This state is transient, however, and three months post-weaning there is no significant difference in bone mineral content (BMC) between mothers regardless of breastfeeding duration.[13] Breastmilk volume, genetics, and maternal height also influence the degree of bone demineralization during lactation.[14] One factor that has no impact on this phenomenon is maternal calcium intake, as Prentice explained, which is why dietary reference values do not recommend additional calcium during pregnancy and lactation.

"It is the consensus around the world that lactation physiology is largely independent of maternal calcium intake," she said.

Trials of calcium supplementation during pregnancy and lactation in The Gambia

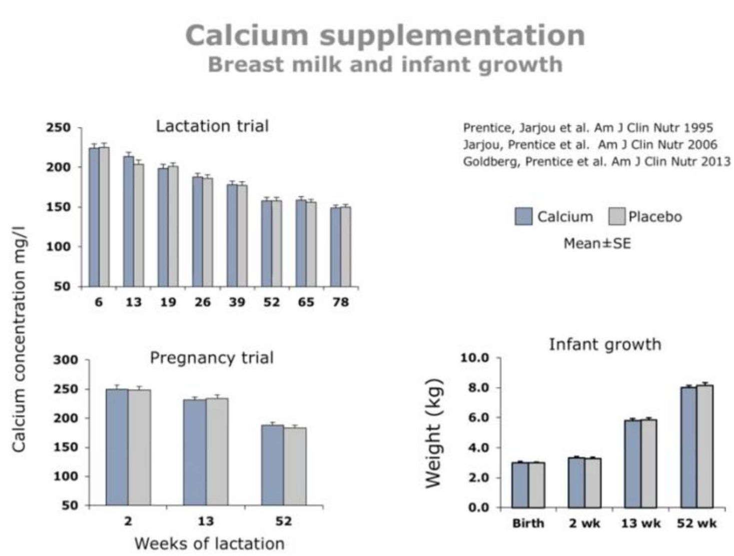
WHO guidance[15] recommends high-dose calcium supplementation (1.5-2 g/day) for pregnant women with low calcium intake to prevent preeclampsia. However, several long-term studies in The Gambia raise questions and concerns about the potential for short and long-term bone health outcomes among women supplemented with calcium during pregnancy.

Prentice reviewed the results of two trials in pregnant and lactating Gambian mothers, noting that all participants had low calcium intakes—300-400 mg/day, which is typical for the region—and all breastfed their infants for 18 months or longer.

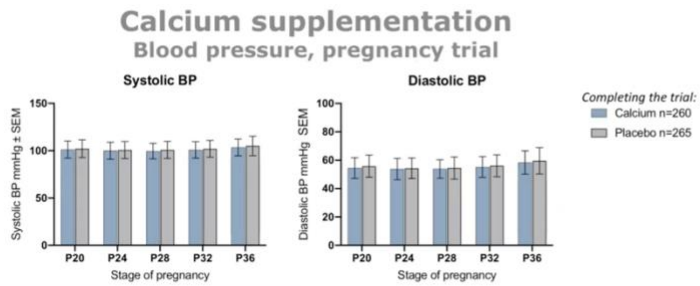
The first trial[16] examined the effect of calcium supplementation during lactation on breastmilk composition, bone mineral content, urinary excretion, and infant growth. The trial included 60 women given 1000 mg calcium carbonate supplements 5 days/week starting 2 weeks postpartum and continuing for 12 months. Mothers and infants were followed for an additional 6 months of lactation following cessation of supplementation.

The second trial[17] looked primarily at the impact of high-dose calcium during pregnancy on maternal blood pressure and infant growth. Over 500 participants were randomized to receive either 1500 mg/day of calcium carbonate or a placebo from 20 weeks of gestation through delivery, and were followed for 12 months. Breastmilk composition, BMC, and biochemical markers of bone metabolism were analyzed in a subset of 120 participants.[18]

Women supplemented during lactation did not have higher breastmilk calcium, nor was there an impact on infant growth. Calcium supplementation also had no effect on biochemical markers of bone metabolism in lactating women.[16,19]



In the pregnancy trial, no significant differences in maternal blood pressure or infant growth were observed between the control and supplementation cohorts.[17] While the study was not designed to examine incidence of preterm or stillbirth, Prentice noted that “nothing suggests any group differences in birth outcomes.” Notably, women with underlying health issues — including those at high risk of preeclampsia — were excluded from the trial.



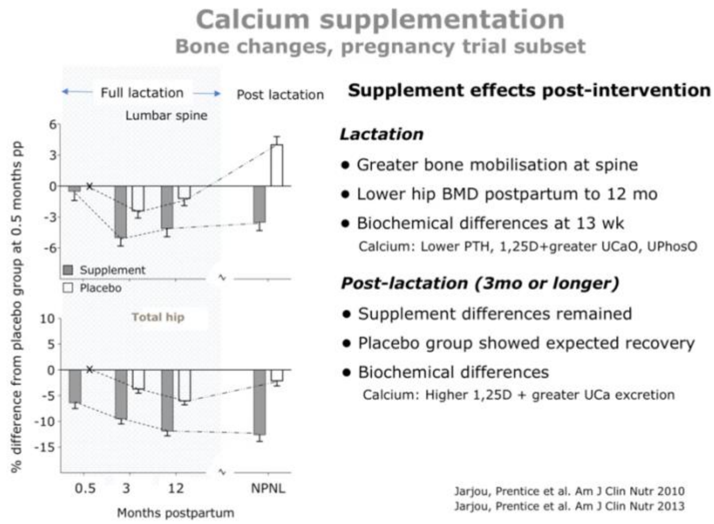
	Calcium	Placebo
Maternal death	1 (0.3%)	1 (0.3%)
Neonatal death	3 (0.9%)	2 (0.6%)
Spontaneous abortion+stillbirth	12 (3.6%)	18 (5.4%)
Those completing the trial:		
P36 BP>140/90 mmHg	0 (0.0%)	1 (0.4%)
Increase SBP>30 mmHg	1 (0.4%)	1 (0.4%)
Increase DBP>15 mmHg	24 (9.2%)	30 (11.3%)
Low birth weight <2.5kg*	16%	12%
Gestation <37 wk by Dubowitz*	16%	19%

* born at home; measured 0-7d pp

- No significant differences in BP
- Not powered for birth outcomes
- Nothing to suggest group differences
- Underlying health conditions excluded

Goldberg, Prentice et al. Am J Clin Nutr 2013

Analysis of bone changes in the subset of pregnancy trial participants did show effects of calcium supplementation, “and they were in the opposite direction of what we expected to find,” Prentice said. Compared to a placebo group, mothers supplemented with calcium during pregnancy showed evidence of *greater* bone mobilization at the spine and lower hip as early as 2 weeks postpartum, and these changes persisted for at least 12 months.[20] Supplemented women also had lower parathyroid hormone (PTH) levels and higher urinary calcium excretion 3 months postpartum. Surprisingly, these differences remained for at least 3 months — and often longer — following weaning.[21] “These results suggest that women who receive high-dose calcium carbonate during pregnancy had a disrupted ability to readapt to low calcium intake once the supplementation had stopped”, Prentice said. She and her collaborators recently concluded a 20-year follow-up study to determine whether supplemented women show midlife differences in BMD (data not yet available).



Effects on offspring following maternal calcium supplementation during pregnancy

Prentice has also observed sex-specific differences in growth[22] among children whose mothers received calcium during pregnancy. Male children grew faster (height and weight) and had higher levels of insulin-like growth factor 1 (IGF-1)[23] and greater prepubertal BMC, while female children grew slower and had lower IGF-1 and prepubertal BMC. A follow-up study of these children (now adults) is underway.

The phenomenon of sex-specific differences in growth within the context of calcium supplementation is also evident in a previous trial of prepubertal children in The Gambia.[24] A regimen of 1000 mg of calcium 5 days/week for 12 months resulted in faster growth for supplemented boys, who hit pubertal peak height velocity sooner than their un-supplemented peers but were ultimately 3.5 cm shorter than those in the placebo group.[25,26] Supplementation also resulted in higher BMC and BMD in boys. No effects were observed in girls.

Prentice acknowledged that much is unknown about the results of these studies, including whether the effects are specific to calcium carbonate. Additionally, the Gambian trials are from a single country and, according to Prentice, "need to be refuted or replicated in other populations."

A group discussion followed, during which some task force members broached the question of whether low-dose calcium supplementation during pregnancy might result in similar findings. **Wafaie Fawzi** commented that potential follow-up studies of the cohorts currently participating in a non-inferiority trial of low-dose calcium[27] during pregnancy may add to knowledge this subject.

Mechanisms of prenatal calcium supplementation on preterm birth

Many trials of calcium supplementation provide empirical evidence of an impact on the incidence of preeclampsia and preterm birth, especially in women with low calcium intake.[28] The mechanisms of these effects are not known, however. **Justus Hofmeyr** offered a brief summary of potential mechanisms by which calcium supplementation may affect preterm birth, with emphasis on possible effects from early-pregnancy supplementation as well as late-pregnancy supplementation.

He reviewed the hypothesis that low serum calcium increases PTH levels, which in turn increases intracellular calcium in smooth muscle tissue, causing vasoconstriction and possibly hypertension. Supplementing with calcium may reverse this process, lowering PTH and reducing smooth muscle contractility.[29] Researchers have theorized that this effect may include the relaxation of uterine smooth muscle, thus inhibiting preterm labor.[30] Calcium supplementation may affect incidence of spontaneous preterm birth directly via this reduction in uterine contractility in late pregnancy, or secondarily through an effect on placentation in early pregnancy. Supplemental calcium may also lower the incidence of preterm inductions of labor by lowering blood pressure and reducing the risk of preeclampsia.

Outcomes of calcium supplementation trials during pregnancy vary widely, with some showing significant effects on hypertension, preeclampsia, and preterm birth, and others showing more moderate benefit or no benefit. [28] A recently published umbrella review[31] mapping evidence of the effects of various nutrients on pregnancy outcomes related to placental disorders and maternal mortality summarizes the evidence for calcium supplementation during pregnancy.

Table 1

Evidence map of direction of effect, strength of association and certainty of the evidence.

	PE	SGA	LBW	PTB	Stillbirth	Maternal Mortality
Calcium	RR 0.52 (0.41–0.65, I^2 67%, 24 studies, *n* = 27,442) ●●	RR 1.01 (0.83–1.23, I^2 20%, 9 studies, *n* = 6407) ●●●	RR 0.84 (0.73–0.96, I^2 43%, 11 studies, n =7800) ●●●	RR 0.53 (0.33–0.86, I^2 95%, 18 studies, *n* = 14,078) ●●	RR 0.55 (0.24–1.23, I^2 75%, 7 studies, *n* = 10,687) ●●	RR 0.59 (0.18–1.92, I^2 40%, 5 studies, *n* = 10,057) ●●●

Benefit—Strong effect (RR < 0.40)	Benefit—Moderate effect (RR 0.40–0.69)	Benefit—Weak effect (RR 0.70–0.89)	Benefit—Not discernible (RR 0.90–0.99)	No significant effect (95% CI crosses 1.00)
Harm—Not discernable (RR 1.01–1.09)	Harm—Weak effect (RR 1.10–1.49)	Harm—Moderate effect (RR 1.50–2.99)	Harm—Strong effect (RR ≥ 3.00)	Not available

Certainty of the evidence

High ●●●● Moderate ●●● Low ●● Very low ●

Calcium supplementation appears to have greater benefit for women with low calcium intakes, and the greatest evidence for impact on maternal and infant outcomes is on preeclampsia and preterm birth. While most trials supplemented women from 20 weeks of gestation through delivery — allowing for evidence of late-pregnancy effects, perhaps mediated by a reduction in blood pressure — the Calcium and Preeclampsia Trial (CAP)[32] offered low-dose supplementation (500mg) from pre-pregnancy through 20 weeks' gestation, then switched to high-dose supplementation for all participants. This allowed for observation of early-pregnancy effects of calcium on preterm birth and preeclampsia. While the reductions (~20%) were not statistically significant, Hofmeyr believes there is sufficient evidence to suggest that calcium supplementation limited to both early pregnancy or late pregnancy can impact preterm birth and preeclampsia, but both points need confirmation.

IV. Implementation Questions Regarding Calcium Supplementation

Calcium supplementation during pregnancy is not widely implemented, in part due to the burdensome dosing schedule (500mg 3x/day), cost, and concerns about interactions between calcium and the iron in iron containing supplements. **Kate Dickin** led a discussion of outstanding implementation questions for the task force to consider prior to creating guidance for countries wishing to implement calcium supplementation for pregnant women.

Timing and targeting

WHO guidelines[15] do not specify a time interval for initiating calcium supplementation during pregnancy. In light of data suggesting that calcium supplementation may have a moderate effect on the genesis of preeclampsia during placentation,[3232] countries may wish to consider strategies for reaching women preconceptionally. This is a particularly challenging task for supplementation, and as the success of folic acid fortification has shown,[33] may be more feasible through food fortification. Identifying target age groups for any intervention — and determining if adolescent girls should be included — is also a priority.

Integration of calcium into antenatal care

In many LMICs, IFA or multiple micronutrient supplements (MMS) are routinely offered as part of antenatal care (ANC) services. Introducing calcium supplementation into this ecosystem is likely more cost-effective than starting a new program. However, establishing and integrating supply chains, updating national supplementation protocols, and training ANC staff requires significant effort and investment. Dicken highlighted that the logistics of administering calcium supplementation programs will vary among countries based on ANC schedules.

Adherence

Dicken's research has shown that adherence to calcium supplementation is higher when women are provided with counseling and information on the benefits of supplements.[34,35] Even so, the pill burden is significant, and can impact adherence even among women committed to taking supplements. As more data on the effectiveness of low-dose calcium become available, lowering the recommended dose — which also lowers the number of daily pill-taking events as well as program cost — may be feasible and desirable.

Interactions between calcium and iron

WHO guidance states that calcium supplements should be taken several hours before or after IFA or other iron-containing supplement, such as MMS, due to potential negative impacts of calcium on iron absorption. This recommendation further complicates adherence to calcium supplementation. Many studies[36,37] indicate that any interaction between calcium and iron is transient in lactating women,[38] non-pregnant women,[39] and young girls.[40] The authors of a recent systematic review[41] of calcium intake and iron status concluded that prescribing separation of calcium and iron supplements in pregnant women is unlikely to affect the anemia burden. **Connie Weaver** commented that daily calcium and iron supplementation triggers a homeostatic upregulation of iron absorption,[42] thus there is no long-term impact on iron stores when supplements are taken simultaneously. The task force unanimously agreed that separation of the two supplements is unnecessary. "The negative effects of recommending three or four pill-taking events a day are probably greater than any negative impact on absorption," concluded Dicken.

V. Research Gaps: Calcium Supplementation During Pregnancy

Chris Sudfeld summarized research gaps surrounding calcium supplementation during pregnancy. These spanned four key areas including calcium intake levels and supplementation dose; supplementation timing; mechanisms; and program implementation.

Calcium intake and supplementation

What level of calcium intake during pregnancy — whether through diet, supplementation, or a combination of both — provides "optimal" effects on maternal and offspring outcomes? Sudfeld and the task force discussed this longstanding question, navigating concerns about how to maximize the potential benefits (reduced risk of preeclampsia and preterm birth) while minimizing potential risks of negative maternal and offspring bone and growth outcomes. These questions require additional research—including dose-response trials to determine a threshold for effects—as well as consideration of the fact that calcium intakes vary, and women will require different amounts of calcium to achieve a threshold level of intake. "We've been talking about low-dose or high-dose supplementation, but it depends where you start," said Connie Weaver.

The efficacy and safety of combining calcium supplementation with other interventions, such as vitamin D and aspirin, are not known. The task force agreed that while this is valuable information, trials would be complex and costly. **Daniel Roth** offered a "reality check," commenting that there may be limited appetite among funders for such investigations. **Wafaie Fawzi** suggested the possibility of mining serum or plasma repositories from previous calcium trials to examine whether baseline vitamin D level is a modifier for the effect of calcium.

Supplementation timing

Research on the potential benefits of preconception calcium supplementation is largely limited to the CAP trial. As the genesis of preeclampsia occurs during early pregnancy, more research on preconception calcium may be warranted.

Mechanisms

The mechanisms that contribute to the effect of calcium on preterm birth, preeclampsia, maternal morbidity, and other maternal or offspring outcomes are unknown, as are the critical periods for affecting them. Sudfeld noted the possibility that some of these mechanisms are shared, while others may be specific to certain outcomes. "I think we need to learn more about each of these multifactorial effects of calcium," he said.

Calcium supplementation during pregnancy, much like MMS, appears to have sex-specific effects on offspring. These too are not well understood, but Sudfeld deemed them "an important aspect of nutritional supplementation in pregnancy," commenting that "there is clearly more to learn here."

Implementation

Integrating calcium into existing supplementation programs for pregnant women is desirable from an implementation perspective, and the task force agreed upon the need to develop best practices for this, as well as for counseling and guidance to promote adherence. Issues of packaging (blister packs, bottles), tablet form (chewable, gummy, standard tablet), shelf-stability, and provisioning (monthly supply vs 180 days) were also discussed. Cost-effectiveness of calcium supplementation also impacts feasibility and is another area for greater research.

VI. Considerations for Prompting Action on Calcium

Lynnette Neufeld proposed a framework for considering which indicators may trigger action on calcium, be it a large-scale intervention such as fortification or universal supplementation of pregnant women, or a targeted approach to reach at-risk women during pregnancy. Neufeld acknowledged that the topic prompts "more questions than suggestions," highlighting the need for more discussion and, in some cases, more information.

Neufeld suggested different thresholds for taking action depending upon which intervention is under consideration. In the presence of evidence beyond a reasonable doubt that population calcium intakes are below an agreed-upon level of sufficiency — for example, in countries where there is very little calcium in the national food supply — fortification generally offers a favorable cost/benefit ratio with less risk than supplementation. It is not clear, however, how large the gap between population intakes and a nutrient requirement level should be in order to prompt action.

"For supplementation, the burden of 'need' should probably be higher," Neufeld said, noting that cost and possibly risk are higher with supplementation, but the potential benefits may also be greater. Universal supplementation of pregnant women may be relevant for areas with low calcium intakes during pregnancy and high prevalence of calcium-responsive negative health outcomes, such as preterm birth. Another approach is medically-targeted supplementation of women at high risk of preeclampsia.

All of these scenarios rest on data sets that are currently lacking or incomplete. These include: a consensus regarding what constitutes adequate intake and whether a single set of recommendations is applicable across regions or countries; calcium intake data or a proxy for reliably identifying populations with low intake (e.g. food balance sheets); an agreed-upon biomarker of calcium status and field-friendly option for assessment; and methods for identifying populations at high risk of negative outcomes from low calcium (e.g. women at high risk of preeclampsia, especially in early pregnancy).

Group discussion on indicators for action

Connie Weaver proposed that populations with calcium intakes less than half of current requirements be considered at highest risk of negative outcomes and thus potential candidates for fortification. This very low benchmark avoids subtleties surrounding differences in national recommendations. "These are large, hit-you-over-the-head-with-a-hammer gaps between intake and requirement," she said. Fortification of an inexpensive, widely consumed staple food should be considered in these cases to address what Weaver termed "negative, chronic, persistent calcium balance."

John Pettifor and **Steven Abrams** voiced concern about a blanket fortification approach, as many populations, including those in Africa, have intakes that fall below half of the recommendation with little evidence of population-level bone health issues. Both support supplementation during pregnancy, although Pettifor noted that more research is needed on the non-inferiority of low-dose calcium, as well as additional studies to ensure that the negative outcomes reported in The Gambia are not generalizable to other populations. **Jean Humphrey** added a different perspective, citing the potential for calcium fortification in Africa to deliver preconception calcium and ease the "stubborn, recalcitrant" problem of high preterm birth rates, which reach 20% in some countries.

Gabriela Cormick emphasized the need to take action in populations with extremely low intakes, even in the presence of some concerns. "If we decide not to do anything because of a lack of information or the fear of risks that I think are very unlikely, we are accepting that the [calcium intake] recommendations are not valid and questioning the general recommendation that calcium is part of a healthy diet," she said.

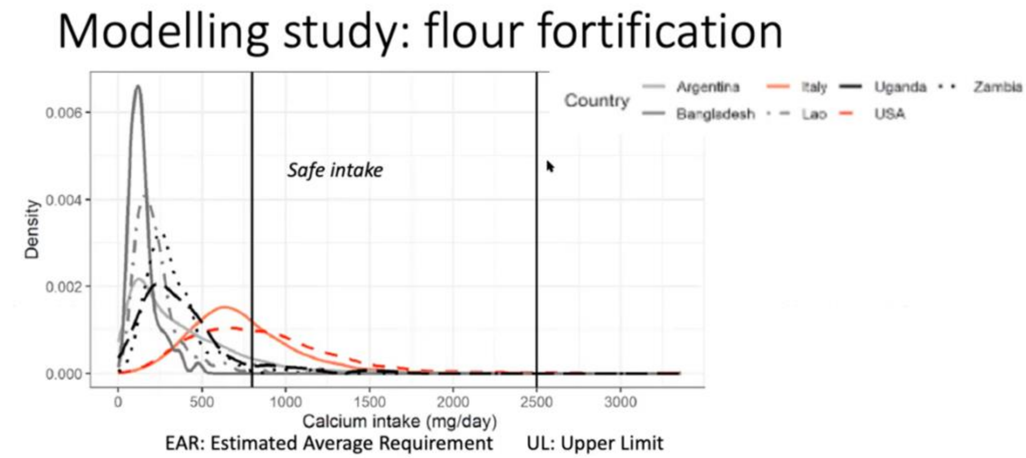
VII. Food-based Interventions to Improve Calcium Intake

Simulations of water and flour fortification

Gabriela Cormick presented the results of two studies modeling the impact, effectiveness, and safety of flour[43] and water[44] fortification with calcium. Using dietary intake data from a mix of high-income countries (HICs) and LMICs, Cormick and her collaborators simulated a flour fortification level aligned with the mandatory standard in the UK[45] (156 mg/calcium per 100 g/flour). Water fortification was simulated at the maximum level of 500 mg/L. As water intake is not frequently assessed, the group simulated intakes of 1 L/day. This is an overestimate for infants and children, and an underestimate in some populations, mostly in HICs.

Results were analyzed based on the percentage of the population with intakes below the EAR for calcium specified by IOM[5] before and after fortification, as well as the percentage of the population exceeding the UL following fortification.

LMICs where industrial flour is regularly consumed fared well in the simulation, with improved intakes and little or no risk of exceeding the UL. In nations like Bangladesh or Lao PDR, where flour is not a routine component of the diet, there was no impact. HICs also showed improvement in calcium intakes following flour fortification, but unsurprisingly, also had higher likelihood of a small fraction of the population reaching or exceeding the UL.



Distribution of mg of adjusted daily calcium intake of NPW aged between 31 and 50.9 years

Water fortification yielded similar benefits in improved intakes, with little or no risk of populations in LMICs reaching the UL. In the United States, however, water fortification would trigger safety issues, even at levels far lower than the maximum amount (500 mg/L) modeled here. Water fortification is likely a strategy best reserved for countries with low calcium intake.

Group discussion of this subject focused mainly on feasibility issues. For flour fortification, it was noted that many countries either don't consume flour or purchase whole grain which is locally milled into flour. Cormick described a successful work-around strategy that has been tested in Ethiopia, where local millers have been trained and provided with fortificants.

Many questions arose regarding water fortification, primarily surrounding logistics in regions where tap water is not available or is not used directly, but rather treated or boiled prior to use, as well as regions that rely heavily on bottled water. Cormick and **José Belizán** previewed prototype devices for in-home calcium fortification at the tap, although these technologies are still in development. It was also noted that many municipalities have limits on calcium fortification levels due to concerns about pipe corrosion.

Novel food processing techniques to improve calcium intakes

Victor Taleon updated the group on two efforts to develop novel methods of increasing calcium intake through food processing. Both aim to produce calcium-rich products that can easily replace existing staple foods in LMICs.

The first is a technique suited for populations in South and Southeast Asia and sub-Saharan Africa that rely heavily on polished white rice, which is typically milled multiple times to increase the grain's whiteness. Incidentally, this process also depletes crucial nutrients by removing the rice bran. By contrast parboiled rice is pre-cooked in water, then dried before being cooked once more. Taleon is experimenting with adding calcium lactate or calcium hydroxide to the initial cooking water, which increases calcium in the endosperm and significantly whitens the rice without milling. He reported a goal level of 100 mg of calcium per

100 g of rice, and the group is working to improve the amount of endosperm calcium absorbed during the initial cooking stage. Currently, only one-third of calcium in the cooking water is absorbed.

The second technique adapts the well-known process of nixtamalization for areas of sub-Saharan Africa where cassava, maize, and rice are used to make dough not unlike the tortilla doughs of Mexico and Central America. Rather than using nixtamalized corn fresh, however, Taleon proposes grinding it into a calcium-fortified flour that could replace local flours. Target fortification levels are still in development, but Taleon envisions 100 mg calcium per 100 g flour.

Acceptability of calcium-fortified foods

Studies of a diverse array of calcium-fortified foods in populations around the world demonstrate that these foods are not only well-accepted, but in many cases, they are preferred. A study of wheat tortillas fortified with different calcium salts[46] showed no issues with taste, texture, or any other factor, and participants preferred the taste of calcium carbonate-fortified tortillas over controls. Likewise, wheat bread flour fortified with ground eggshell powder was rated as more visually appealing and better-tasting than control bread.[47] In Nigeria, a study of ground fish as a calcium fortificant for children showed higher compliance with that approach than with a calcium supplement tablet.[48]

Despite the range of fortificant options and fortification vehicles, calcium fortification programs are uncommon compared to those for other micronutrients. Palacios hypothesized that calcium is not a priority because low calcium is not associated with acute or life-threatening illness outside of the context of preterm infants and children with rickets. Additionally, populations in LMICs may be slower to embrace fortified foods than Western populations, potentially due to a lack of knowledge about the benefits of micronutrients or cultural ties to specific foods and food preparation practices.

Countries wishing to consider calcium fortification may lower their costs and ease acceptability by adding calcium to one of the many food vehicles already included in mandatory fortification programs operating around the world.[49] As Palacios commented, "There is no way to recommend one [fortification] option for everyone, as it depends on the population and the amounts that need to be added—but at least we have options that are already in place in many countries."

VII. Food-Based Approaches: Discussion and Research Gaps

A recurrent theme in task force discussions is the lack of a biomarker for assessing calcium status or monitoring the effects of interventions. **Lynnette Neufeld** noted that this is not an uncommon issue with fortification programs. While there are tools for assessing coverage and consumption to understand the contribution of a fortified food to dietary intakes of a particular micronutrient, "going from that step to analyzing biological outcomes is a big problem due to the nature of interventions and the complexity of evaluating," Neufeld said. For calcium, the problem is greater due to a lack of consensus on what health measures would be addressed by increasing population-level calcium. Neonatal mortality and preterm birth rates may be candidate outcomes; however, it remains to be seen if fortification can deliver enough calcium to affect them, or if the results from tightly controlled experimental settings translate to a population-level effect.

Beyond the biomarker issue, many knowledge gaps remain surrounding food-based approaches to increasing calcium. **Erick Boy** concluded the meeting with a summary of topics for future research.

Biofortification: Agronomic biofortification, which was discussed in the prior task force meeting, is a promising but costly approach to increasing calcium intake. It relies on incentivizing farmers to participate in an intervention that improves nutrient content but not crop yields, and techniques for increasing calcium in staple foods are still being refined and developed. Traditional or transgenic approaches to biofortification may also be useful for increasing the calcium content of staple foods — or increasing its bioavailability by reducing phytate and other antinutrient content — but this research is still early-stage. As calcium is not a frequently used fortificant outside of HICs, it is not known whether calcium fortification is adaptable to an appropriately diverse basket of foods to reach vulnerable populations around the world.

Supply and cost-effectiveness issues: Cost-effectiveness is a significant driver of policy. Additional research is needed to understand the cost-effectiveness of various food-based approaches to increasing calcium, as well as different food fortification vehicles. In the interim, it may be possible to make policy recommendations to increase or optimize the existing supply of calcium-containing foods for vulnerable populations.

Water fortification: Municipal water fortification is not well-studied, with real-world information gaps in the areas of effectiveness, cost-effectiveness, and potential impacts on water delivery infrastructure.

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