




# Calcium Deficiency in Bangladesh: Burden and Proposed Solutions for the First 1000 Days

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## Abstract

**Background:** Bangladesh incurs among the highest prevalence of stunting and micronutrient deficiencies in the world, despite efforts against diarrheal disease, respiratory infections, and protein-energy malnutrition which have led to substantial and continuous reductions in child mortality over the past 35 years. Although programs have generally paid more attention to other micronutrients, the local importance of calcium to health has been less recognized.

**Objective:** To synthesize available information on calcium deficiency in Bangladesh in order to inform the design of an effective national calcium program.

**Methods:** We searched 3 online databases and a multitude of survey reports to conduct a narrative review of calcium epidemiology in Bangladesh, including population intake, determinants and consequences of deficiency, and tested interventions, with particular reference to young children and women of childbearing age. This was supplemented with secondary analysis of a national household survey in order to map the relative extent of calcium adequacy among different demographics.

**Results:** Intake of calcium is low in the general population of Bangladesh, with potentially serious and persistent effects on public health. These effects are especially pertinent to young children and reproductive-age women, by virtue of increased physiologic needs, disproportionately poor access to dietary calcium sources, and a confluence of other local determinants of calcium status in these groups.

**Conclusion:** A tablet supplementation program for pregnant women is an appealing approach for the reduction in preeclampsia and preterm birth. Further research is warranted to address the comparative benefit of different promising approaches in children for the prevention of rickets.

## Keywords

Bangladesh, calcium, maternal and child nutrition, pregnancy, birthweight, child growth

## Introduction

Calcium is essential for many biological processes, including provision of structural support for bones and teeth, signal transduction, muscle contraction, enzyme regulation, and blood clotting.<sup>1</sup> Adjusting for body size, more dietary calcium is often recommended for infants and children to support growth, the elderly population to ameliorate osteoporosis, and pregnant and

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**Table 1.** Recommended Nutrient Intakes of Calcium for Bangladesh.

	RNI, male, mg	RNI, Female, mg
Age group, years		
<1	300-400	300-400
1-3	500	500
4-6	600	600
7-9	700	700
10-18	1300	1300
19-50	1000	1000
51+	1000	1300
Pregnancy	-	1200
Lactation (0-6 months)	-	1000
Lactation (7-12 months)	-	1000

Abbreviations: FAO, Food and Agriculture Organization; RNI, recommended nutrient intake; WHO, World Health Organization.

<sup>a</sup>Nahar et al<sup>2</sup> based on WHO/FAO (2004).<sup>3</sup>

lactating women to meet increased physiologic requirements (Table 1),<sup>2,3</sup> although the evidence supporting recommended intakes for different groups has been controversial and may not apply across countries. For both reasons, dietary calcium recommendations have varied widely around the world.<sup>3</sup> A recent World Health Organization (WHO) guideline recommended that pregnant women living in regions of low calcium intake consume an additional 1.5 to 2.0 g of elemental calcium per day from 20 weeks of gestation until the end of pregnancy in order to reduce their risk of preeclampsia.<sup>4</sup>

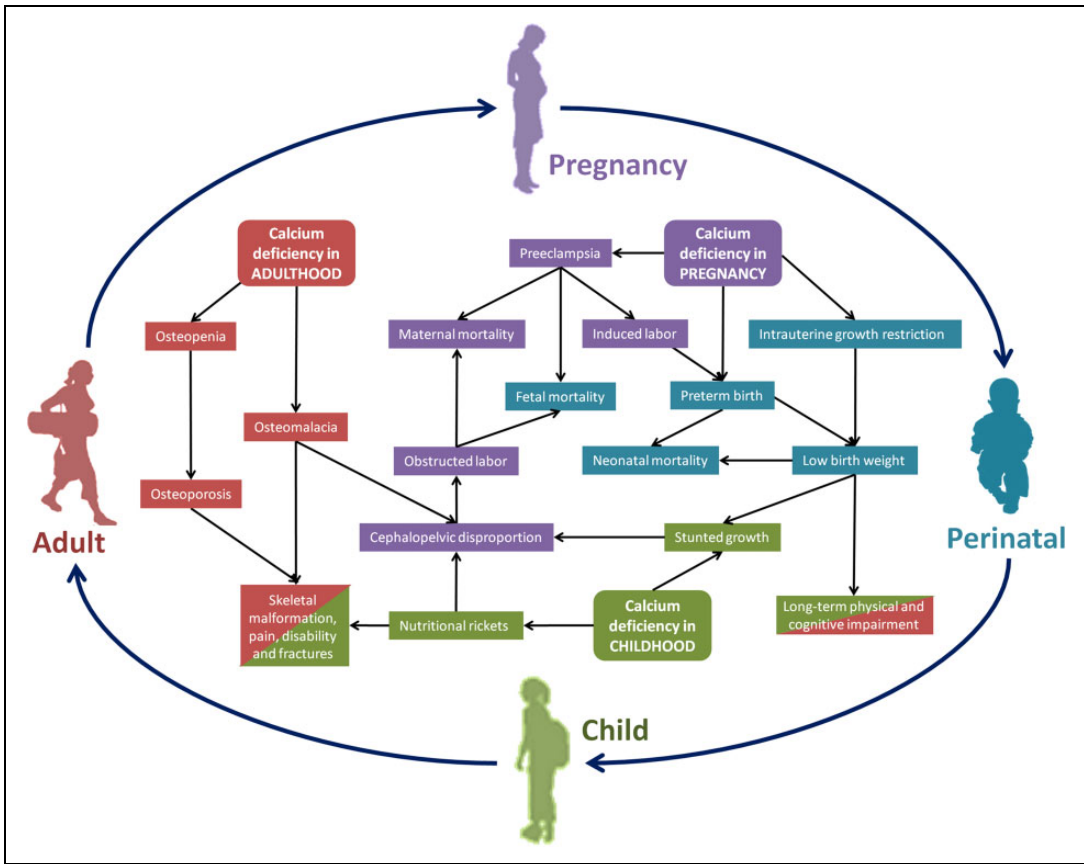
Mounting epidemiologic evidence has implicated calcium deficiency in the development of chronic hypertension, insulin resistance, obesity, and colon cancer.<sup>1</sup> More relevant to the developing country setting are calcium's potential roles in rickets and osteomalacia, hypertensive disorders of pregnancy, osteoporosis,<sup>1</sup> intrauterine growth restriction, and preterm birth.<sup>5</sup> In environments where extreme calcium deficiency is common, these disorders may be connected within and between generations (Figure 1).<sup>6-18</sup> One such environment is Bangladesh, where a multitude of factors converge to predispose the population to widespread deficiencies of calcium and other micronutrients.<sup>19</sup> At least 5 recent national surveys suggest extensive dietary calcium

inadequacy with respect to national guidelines (Table 2),<sup>2,20-24</sup> with evident disparities affecting female and rural populations. Compounding dietary inadequacy are indications of poor vitamin D status<sup>25</sup> and high availability of antinutrients.<sup>26,27</sup> High incidence of preeclampsia and nutritional rickets has been varyingly attributed to calcium deficiency and remains substantial sources of maternal and child morbidity and mortality in Bangladesh.<sup>28,29</sup>

The epidemiology of calcium nutrition in Bangladesh has been characterized from multiple perspectives, which this article seeks to integrate so as to provide a measured basis for designing an effective national calcium program. We reviewed PubMed, Bangladesh Journals OnLine, and Google Scholar for articles, survey reports, and national indicators related to calcium epidemiology and policy in Bangladesh, with respect to calcium intake, status and function, the ecologic, economic, community, and household factors that affect calcium nutrition and results of tested interventions. We also conducted a secondary analysis of a nationally representative household survey to map the relative extent of dietary calcium inadequacy among different regions, age-groups, and sexes according to local dietary guidelines.

## Burden

Fish, milk, vegetables, and rice are important sources of calcium in Bangladesh, the first 3 by virtue of their nutrient density and rice by its high consumption. From 1981 to 1995, calcium intake of 404 households in 2 rural areas revealed an increase of 40%; however, mean consumption did not exceed 400 mg/d during any season in either area.<sup>30</sup> Similar results were found in a 1995 national food consumption survey.<sup>31</sup> Twenty years later, calcium intake remains relatively low in most of Bangladesh, with nationally representative estimates ranging from 439 to 529 mg/d (Table 2).<sup>20-24</sup> National surveys suggest the intake of calcium in Bangladesh is right-skewed such that the mean exceeds the median and may provide a misleading idea of adequacy. By weighting the



**Figure 1.** Potential intragenerational and intergenerational effects of severe calcium deficiency. In pregnancy, severe deficiency of calcium may threaten the mother (increasing the risk of preeclampsia,<sup>6,7</sup> an important cause of maternal mortality in developing regions)<sup>8</sup> and fetus (calcium deficiency may contribute to spontaneous preterm birth,<sup>6</sup> and preeclampsia may contribute to loss of the fetus<sup>8</sup> or medically induced preterm birth,<sup>8</sup> the latter of which increases the risk of neonatal mortality).<sup>9</sup> Preterm birth and intrauterine growth restriction (the latter of which may itself result from calcium deficiency in pregnancy)<sup>10</sup> are both contributive to low birthweight, which is implicated in a variety of long-term physical and cognitive consequences,<sup>11</sup> including stunted growth (which may be independently related to childhood calcium deficiency).<sup>12,13</sup> Calcium-deficient children are at higher risk of nutritional rickets even in the absence of hypovitaminosis D,<sup>14</sup> which may lead to pain, deformity, and fractures throughout life. Skeletal disease may be exacerbated as calcium deficiency persists into adolescence and adulthood, during which rickets is replaced with osteomalacia (for which experimental evidence implicates vitamin D as a probable additional requisite)<sup>15</sup>; even without vitamin D deficiency, calcium deficiency in adulthood may also contribute to a different pathology in osteopenia, which may progress to osteoporosis. Osteoporosis and osteomalacia predispose individuals to a spectrum of acute and chronic bone and musculoskeletal symptoms.<sup>16</sup> The cycle repeats as various conditions—stunting, rickets, and osteomalacia—may contribute to cephalopelvic disproportion and obstructed labor.<sup>17</sup> Calcium in breast milk appears to be relatively protected even in mothers consuming very little calcium.<sup>18</sup>

recommended nutrient intakes (Table 1) according to the age and sex distribution of Bangladesh,<sup>32</sup> we calculate the mean per capita intake of calcium would need to be at least 993 mg/d for 95% of Bangladeshis to consume that is

recommended in local guidelines (this calculation does not account for the prevalence of pregnancy or lactation, which would otherwise increase this estimate to over 1 g/d). In sum, based on national surveys and dietary

**Table 2.** Selected Results of Recent Nationally Representative Dietary Surveys.

Reference	Method	Relevant Findings
Ahmed <sup>20</sup>	24-hour recall (rural areas only)	Mean per-capita calcium consumption, mg/d $\pm$ SD: both sexes: 195 $\pm$ 179, males: 207 $\pm$ 189, females: 184 $\pm$ 169. First/second/third quartiles of per-capita calcium consumption, mg/d: both sexes: 94/154/253, males: 84/133/223, females: 84/133/223.
Rahman <sup>21</sup>	Household survey	Dietary sources of calcium: fish 46%, vegetables 19%, cereals 15%, dairy 8%, potatoes 4%. Mean per-capita calcium consumption $\pm$ SD: 449 $\pm$ 273 mg/d.
Bangladesh Bureau of Statistics <sup>22</sup>	Household survey	Dietary sources of calcium: fish 36%, Indian spinach 9%, dried chapila 8%, milk 7%, rice 3%. Mean per-capita calcium consumption $\pm$ SD: 439 $\pm$ 227 mg/d.
Iyengar et al <sup>23</sup>	Market basket study	Median per-capita calcium consumption (range): 310 mg/d (250-350; based on analysis of 9 samples considered to be nationally-representative).
Akhtaruzzaman et al <sup>24</sup>	24-hour recall	Mean per-capita calcium consumption, mg/d (national): both sexes: 529, males: 539, females: 520. Mean per-capita calcium consumption, mg/d (urban): both sexes: 534, males: 561, females: 512. Mean per-capita calcium consumption, mg/d (rural): both sexes: 526, males: 530, females 523.

Abbreviation: SD, standard deviation.

<sup>a</sup>Analysis of Ahmed<sup>20</sup> is based on prior nutritional analysis by Sununtnasuk, Lividini, and Quabili (International Food Policy Research Institute). Findings from Bangladesh Bureau of Statistics<sup>22</sup> are drawn from Nahar et al.<sup>2</sup> Estimated SDs are inflated due to within-person (day-to-day) variation in calcium intake.

guidelines, calcium requirements appear to be largely unmet in Bangladesh.

### *Intake Among Women and Adolescent Girls*

In Bangladesh, calcium assessment has placed emphasis on young women and adolescent girls. In an early survey of 384 Dhaka schoolgirls aged 10 to 16 years,<sup>33</sup> mean intake of calcium assessed by 24-hour recall was 399  $\pm$  294 mg/d. Intake of 79% of the girls fell short of the Indian recommended daily allowance (RDA) at the time (600 mg), with 48% at less than 50% of the RDA; this placed median intake at less than 300 mg/d. Milk and eggs were major contributors of dietary calcium (contributing 33% and 37%, respectively). Notably, calcium intake was not associated with income, food expenditure, or parents' education. Also concerned with determinants, Islam et al<sup>34</sup> studied the influence of anthropometry, calorie intake, and income on calcium intake measured using 3-day diet records in 191 women aged 16 to 40 years in Dhaka and Mymensingh. In high-income women, 47% did not meet the WHO's lowest RDA at the time (400-500 mg/d), and

63% of low-income women had intakes below 200 mg/d. A study by Khan and Ahmed<sup>35</sup> of 211 adolescent female factory workers aged 14 to 19 years in Dhaka found frequent consumption of fish (70.3% girls consumed it more than 4 times per week) but less of eggs, milk, meat, and green leafy vegetables, along with low mean intake of calcium (212 mg/d). Intake in 76% of the girls fell below half the Indian RDA. Major sources of calcium were dairy and poultry (contributing 45.5%) and dark green leafy vegetables (23.9%). A recent study of 200 garment workers aged 18 to 36 years found a high prevalence of dietary calcium and vitamin D inadequacy and low bone mineral density at multiple body sites.<sup>36</sup> These studies suggest significant calcium inadequacy among young, urban Bangladeshi women.

### *Intake Among Young Children*

Exclusive breast-feeding among children under 6 months was not common in Bangladesh during the 2 decades before 2007 (43%).<sup>37</sup> An increase to 64% in the 2011 Demographic and Health Survey (DHS)<sup>38</sup> may partly be explained by an increase in

the proportion of sampled infants aged 0 to 3 months and a surge of mass media campaigns.<sup>39</sup> The 2011 to 2012 Bangladesh Integrated Household Survey (BIHS) highlights practices in breast-feeding and complementary feeding that may compromise calcium nutrition in young children, including early introduction of foods and nonmilk liquids and late introduction of high-nutrient-value foods.<sup>20</sup> Kimmons et al<sup>40</sup> also attribute early dietary calcium inadequacy in Bangladesh to low nutrient density of complementary foods, estimating that 31.3 mg of calcium are provided by each 100 g of food to replace that lost by cessation of breast-feeding; the WHO recommends 60% of calcium for a 6- to 8-month breast-fed child be provided by foods.<sup>41</sup> This guideline is poorly met in Bangladesh. Weighed records of 116 Bangladeshi children indicated that calcium densities of complimentary foods were severely inadequate from 6 to 12 months,<sup>42</sup> and 24-hour recall data of 195 children aged 6 to 24 months found approximately 20% consumed adequate calcium from complimentary foods.<sup>43</sup>

After weaning, poor micronutrient intake in Bangladesh has been attributed to a widespread lack of dietary diversity. Arsenault et al<sup>44</sup> found that no individuals in a large rural cohort of 463 children aged 2 to 4 years and 478 women aged  $27.9 \pm 8.0$  years were calcium adequate (calcium was more commonly inadequate than any other nutrient) and that 71% of overall micronutrient inadequacy among children could be explained by the lack of dietary diversity. After weaning, Karim and Ahmad<sup>45</sup> found low intake of calcium in 600 thin, normal-weight, and overweight Bangladeshi children aged 5 to 14 years, and Combs and Hassan<sup>46</sup> found children of all ages in the Chakaria subdistrict to consume only 15% to 30% of the Indian RDA. Overall, poor breast-feeding, complimentary feeding, and dietary practices appear to contribute to calcium inadequacy in Bangladeshi infants and children.

### **Biomarkers, Antinutrients, and Arsenic**

Data on biomarkers of calcium status in the Bangladeshi population are limited. Berglund et al<sup>47</sup> observed considerable differences in urinary calcium excretion between rural Bangladeshi adults

and children, Bangladeshi men and women, and Bangladeshi and European children, although it is not clear how well these differences reflect differences in status. Actual differences in status between Bangladeshi men and women are at least partly independent of differences in diet. For example, Chowdhury et al<sup>48</sup> observed that the duration of lactational amenorrhea (a proxy for the length of breast-feeding) in 400 marginally nourished Bangladeshi women was negatively correlated with bone mineral density, controlling for parity, physical workload, and total duration of breast-feeding. Bangladeshi women are also at risk of calcium deficiency through deficiency of vitamin D, which maintains calcium status by promoting intestinal calcium absorption, promoting resorption of bone, and suppressing secretion of parathyroid hormone.<sup>1</sup> In a study of 189 urban and rural women, Islam et al<sup>49</sup> found 38% of high- and 50% of low-income women were vitamin D deficient ( $<37.5$  nmol/L), with higher prevalence among lactating women (46% and 63%, respectively). In a later study, Islam et al<sup>50</sup> did not find a significant difference in vitamin D status between veiled and nonveiled women in Dhaka.

Antinutrients may blunt the effect of dietary calcium on calcium status. In Bangladesh, the diet may contain high amounts of calcium-chelating agents, such as phytate in rice and oxalate in leafy vegetables. In India, Harinarayan et al<sup>51</sup> found higher mean phytate-to-calcium ratios in rural versus urban populations; despite rural populations' higher serum concentrations of 25-hydroxyvitamin D (higher by 13.0 nmol/L in men and 8.7 nmol/L in women, respectively), serum calcium was only marginally higher, suggesting that phytate may have attenuated calcium absorption. Although population phytate intake is not quantified in Bangladesh, high consumption is referenced in local nutrition surveys, epidemiologic and clinical studies, and studies of Bangladeshi emigrants and is suggested by comparison of international food composition data.<sup>26</sup> Cadmium is another local antinutrient and toxin of concern, now common in Bangladesh due to widespread use of cheap fertilizers and pesticides in cultivating rice.<sup>27</sup> Studies of Bangladeshi women by Kippler et al<sup>52,53</sup> found negative associations between calcium and cadmium in breast

milk and blood, suggesting cadmium is inhibitory of calcium transport to both compartments. In their latest study, Kippler et al<sup>54</sup> did not report a significant association between breast milk calcium status and cadmium toxicity in Bangladesh, but protective effects of calcium status on the effects of cadmium and other divalent cation pollutants have been shown in a variety of animal models.

Bangladesh and West Bengal, India, are home to the largest arsenic-exposed populations in the world.<sup>55</sup> Arsenic exposure has not been associated with decreased calcium intake in Bangladeshi children<sup>45</sup>; however, dietary calcium inadequacy was independently associated with increased susceptibility to arsenic lesions in West Bengal.<sup>56</sup> This is corroborated in Bangladesh by Melkonian et al<sup>57</sup> who also observed that as calcium intake decreased, females were increasingly susceptible to lesions. Complementary findings by Micka<sup>58</sup> did not show increased lesions as a result of vitamin D deficiency in Bangladeshi women. Heck et al<sup>59</sup> found that increasing quartiles of calcium intake in Bangladeshi women were independently associated with an increased fraction of inorganic arsenic relative to other chemical forms in urine, suggesting higher dietary calcium may displace arsenic from bone. These findings implicate arsenic reduction and calcium provision as complementary public health strategies in Bangladesh.

### *National Calcium and Vitamin D Serum Status*

In October 2011, the icddr,b (formerly the International Centre for Diarrheal Disease Research, Bangladesh) National Micronutrients Status Survey<sup>25</sup> collected nationally representative serum calcium and 25-hydroxyvitamin D (25[OH]D) data from 461 preschool-aged children, 557 grade school-aged children, and 631 nonpregnant nonlactating reproductive-age women living in rural, urban, and urban slum areas of Bangladesh. Mean serum calcium concentrations in these groups were 9.1 mg/dL (95% confidence interval [CI]: 8.8-9.5), 9.3 (9.1-9.6), and 8.9 (8.4-9.3), respectively; mean 25(OH)D status was 56.3 nmol/L (95% CI: 50.6-62.1), 50.7 (46.8-54.6), and 41.8 (37.5-46.2), respectively; and prevalence of

vitamin D sufficiency (>75 nmol/L), insufficiency ( $\geq 50$  and  $\leq 75$ ), and deficiency (<50) was 18.3%/42.1%/39.6%, 7.6%/46.9%/45.5%, and 6.4%/22.1%/71.5%, respectively. Within each group, mean serum calcium or 25(OH)D did not differ significantly by area or by quintiles of socioeconomic status or food security status. Most notably, this survey indicates widespread and severe vitamin D deficiency in Bangladeshi women and children.

### *Distribution of Relative Dietary Calcium Inadequacy*

To describe the national distribution of dietary calcium inadequacy, we conducted a secondary analysis of the 2011 to 2012 BIHS,<sup>20</sup> a household consumption and expenditure survey designed by the International Food Policy Research Institute [IFPRI]. The BIHS is nationally representative of rural Bangladesh at the division level (the survey is not nationally representative of urban Bangladesh, which is half the size of rural Bangladesh<sup>32</sup> and in which population calcium intake is generally higher).<sup>24</sup> The BIHS is important among household surveys in Bangladesh because in addition to including a broad set of conventional household survey modules, the survey also collected 1 day of individual measurements of every household member's diet using an integrated 24-hour recall + weighed diet records approach. The survey therefore allows calcium intake to be calculated directly without relying on assumptions about the intrahousehold distribution of food.<sup>60</sup>

Prior analysis of BIHS data by IFPRI has provided the estimated calcium intake of all 26 126 individuals in the data set using food composition data from Helen Keller International and assigned each individual an age- and sex-specific estimated average requirement (EAR) for calcium,<sup>61</sup> 1699 individuals having first been excluded for reporting no food consumed during the recall period. In a secondary analysis, we restricted these data to exclude 3954 double-counted individuals designated by "sample\_type = FTF Original." Next, we excluded 15 outliers consuming over 300% of their respective calcium EAR, 349 remaining individuals currently breast-feeding, ill, or fasting, and 1173 remaining individuals away, unwilling,

or otherwise unable to provide dietary measurements for at least 1 meal. The remaining 20 635 individuals were aggregated into 70 subgroups (7 national divisions  $\times$  5 age-groups  $\times$  2 sex groups).

Mean calcium intake was lower in the crude sample of 20 635 individuals than in other recent nationally representative surveys (Table 2); this may be due to the unavailability of local food composition data in the primary analysis. For this reason, we have presented relative rather than absolute measures of dietary calcium inadequacy for each subgroup. Although less useful than absolute measures, our relative measures are likely more accurate than those that might be estimated from prior household surveys in Bangladesh, which did not collect individual dietary measurements. The “relative mean adequacy” for each of the 70 subgroups is calculated as  $\text{Mean}(\text{Intake}_{ij}/\text{EAR}_{ij} \times 100\%) - 25.05\%$ , where  $\text{Intake}_{ij}$  and  $\text{EAR}_{ij}$  denote the calcium intake (in mg) and EAR of individual  $j$  in subgroup  $i$  (this quotient is termed the individual’s “adequacy”), and 25.05% is the mean adequacy of the entire population of Bangladesh. Relative mean adequacy describes how adequate a particular subgroup is with respect to the general population, where positive values indicate mean adequacy exceeds that of the general population and negative values indicate the converse. Population estimates are presented in terms of calcium EARs using the EAR cut-point method, based on assumptions about calcium’s requirement distribution.<sup>61</sup> Although there is uncertainty surrounding calcium EARs,<sup>62</sup> the use of relative rather than absolute adequacy measures may reduce bias resulting from selection of inappropriate EARs.

Figure 2<sup>20,61</sup> provides a map of relative mean adequacy for all 70 subgroups of interest. Confidence intervals for these means can be found in Supplemental Table 1 (these are inflated due to within-person [day-to-day] variation in calcium intake).<sup>20,61</sup> Our analysis reveals 3 key findings. First, overall, relative inadequacy is most severe in the divisions Barisal (−3.6% with respect to the general population), Rangpur (−3.1%), Rajshahi (−2.7%), and Chittagong (−1.5%), whereas Khulna (+0.4%), Dhaka (1.8%), and Sylhet (+3.5%) are relatively adequate. Second, the relative severity of inadequacy in females

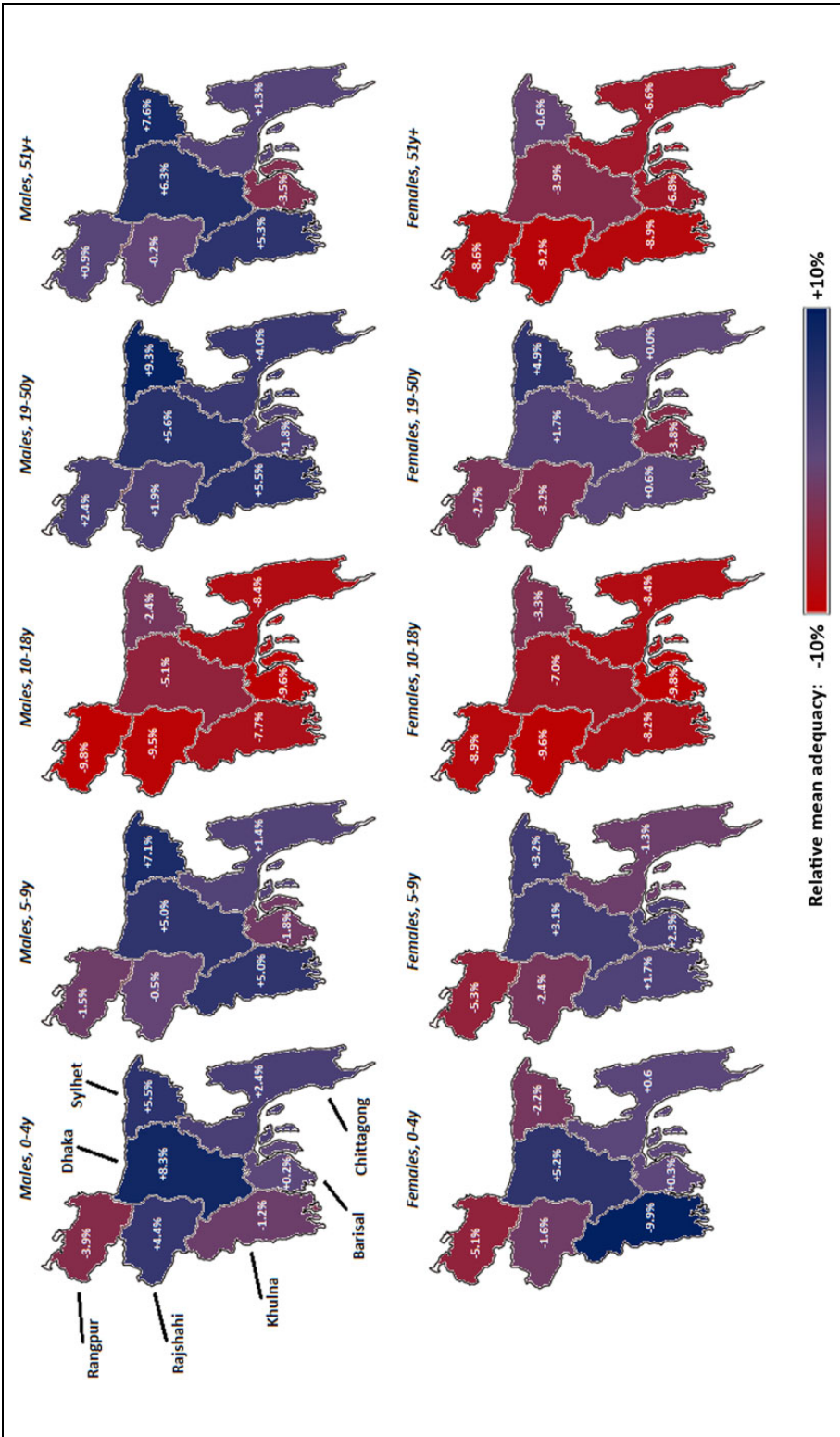
exceeds that of males in 30 of 35 age division groups analyzed. In the general population, mean adequacy is 3.4% lower in females than in males (95% CI −4.1% to −2.8%). Third, relative inadequacy is most severe among adolescents aged 10 to 18 years of both sexes (especially females) and women older than 50 years; this appears to be attributable to these groups’ higher EARs rather than disproportionately lower intake. If subgroups are weighted by population size, relative inadequacy is most severe among female adolescents in Dhaka (−7.0% with respect to the general population, 95% CI −8.3 to −5.7). This is perhaps the most striking finding of this analysis and suggests a need to prioritize this demographic.

## Consequences

The extent of calcium deficiency in Bangladesh is implicated in a variety of health consequences, which may persist throughout individuals’ lifetimes and persist further in the offspring of affected women (Figure 1). Accordingly, women and children are thought to bear the brunt of this burden by way of preeclampsia, rickets, and low birthweight; men are also affected insofar as the effects of rickets and low birthweight in boys extend into adulthood. Although the local contribution of calcium is better characterized for these 3 conditions, the intergenerational effects of extreme calcium deficiency in Bangladesh may also plausibly manifest through cephalopelvic disproportion (a cause of obstructed labor),<sup>17</sup> stunting related to subclinical calcium deficiency,<sup>12,13</sup> and a spectrum of bone pathologies in adulthood that are especially pernicious in postmenopausal women (including osteopenia and osteomalacia).

## Hypertensive Disorders of Pregnancy

Between 1990 and 2005, Bangladesh experienced a 70% reduction in the fraction of age-standardized disability-adjusted life years attributable to hypertensive disorders of pregnancy; this trend all but leveled off between 2005 and 2010.<sup>63</sup> Preeclampsia, a progressive and potentially fatal increase in blood pressure during pregnancy, presently remains a major cause of maternal and fetal mortality in Bangladesh and



**Figure 2.** Relative mean calcium adequacy (%) by sex, age group, and division (rural areas only). Analysis is based on prior nutritional analysis by Sununtnasuk, Lividini, and Quabii (International Food Policy Research Institute) of the 2011 to 2012 Bangladesh Integrated Household Survey.<sup>20</sup> Representative of rural Bangladesh. The “relative mean adequacy” for each of the 70 subgroups is calculated as  $\text{Mean}(\text{Intake}_i/\text{EAR}_{ij} \times 100\%) - 25.05\%$ , where  $\text{Intake}_{ij}$  and  $\text{EAR}_{ij}$  denote the calcium intake (in mg) and EAR of individual  $j$  in subgroup  $i$  (this quotient is termed the individual’s “adequacy”), and 25.05% is the mean adequacy of the entire population of Bangladesh. EARs are drawn from WHO/FAO (2004).<sup>61</sup> EAR indicates estimated average requirement; FAO, Food and Agriculture Organization; WHO, World Health Organization.



accounts for at least 20% of maternal deaths and 2.8% of total deaths among women of reproductive age.<sup>64</sup> A history of global research has implicated calcium deficiency as an important determinant in the development of preeclampsia.<sup>6,7</sup> Calcium deficiency is thought to contribute to preeclampsia by its independent effects on systemic blood pressure (through stimulation of parathyroid hormone or renin secretion and subsequent vasoconstriction) and its possible influence on intracellular magnesium concentrations.<sup>6</sup>

Local substantiation of the link between calcium and preeclampsia in Bangladesh is provided by a recent series of independent hospital-based cross-sectional and case-control studies (Supplemental Table 2).<sup>65-75</sup> Most studies have involved selection of cases with preeclampsia and eclampsia and matched normotensive controls, for whom paired serum or urinary calcium measurements were taken at either the same gestational duration or within the same time frame before delivery. Collectively, these studies suggest a decrease in total serum calcium during the third trimester, a cross-sectional association between lower calcium status and preeclampsia, and a dose-response relationship between severity of deficiency and severity of disease.

### Rickets

Rickets is a potentially crippling disease that occurs when calcium accretion per unit of bone matrix is too deficient to form a healthy microstructure. A survey in the district of Cox's Bazar found at least one sign of rickets in 8.7% of children aged 1 to 15 years, *pectus carinatum* being the most common in 33.3% of cases.<sup>76</sup> A less-detailed but national survey (accounting for visible deformities) found Cox's Bazar to have the highest district-level prevalence, 1.4%,<sup>77</sup> whereas no cases of rickets were observed in the neighboring Chittagong Hill Tracts; incidentally, the hill tract district of Khagrachari has the highest subnational mean calcium intake.<sup>24</sup> Nationally, visible deformities were found in 0.26% of 21 571 surveyed children aged 1 to 15 years in 2000 and in 0.12% of 10 005 children in 2004, although a more recent icddr,b survey of 20 000 children under 1 year of age found a much higher

prevalence of 0.99%.<sup>78</sup> This figure is more concerning given the graver implications of rickets in earlier childhood and may represent the tip of the iceberg of widespread subclinical deficiency in both calcium and vitamin D.<sup>79</sup> icddr,b found 49% of rachitic children with inadequate dietary calcium and 99% with biochemical vitamin D deficiency<sup>78</sup>; vitamin D deficiency in rural Bangladeshi infants is corroborated by Roth et al<sup>80</sup> and in children by the results of the National Micronutrients' Status Survey.<sup>25</sup>

Roth et al<sup>80</sup> invoke a moderate hypothesis in describing vitamin D deficiency to act synergistically with other causes of inadequate bone mineralization and suggest calcium has been afforded disproportionate attention in Bangladesh. For example, in a study of 199 Bangladeshi households with a rachitic family member and 281 neighboring control households,<sup>46</sup> dietary calcium inadequacy was common in both case and control households but was not associated with rickets. The investigators discounted vitamin D as a likely determinant, citing evidence for calcium from African countries; this position is seconded by Pettifor<sup>14</sup> who cites evidence from developing countries to suggest rickets in Bangladesh is less attributable to vitamin D deficiency by virtue of its sunny climate. In an early pilot study, Fischer et al<sup>81</sup> showed mean serum 25(OH)D was not much lower between 14 rachitic and 13 healthy children (20 vs 25 nmol/L, respectively) in Cox's Bazar and that rickets resembled that of calcium-inadequate rachitic African children. Although some disagreement remains, vitamin D may become more important as urbanization brings about increasingly indoor lifestyles.

### Low Birthweight and Other Outcomes

As many as 14% of births in Bangladesh are preterm.<sup>82</sup> Calcium deficiency may contribute to preterm birth by increasing uterine smooth muscle contractility, but its indirect effect through preeclampsia (severe cases of which must be treated by inducing delivery) is better established.<sup>6</sup> The contribution of calcium deficiency to preterm birth is not locally quantified in Bangladesh, though calcium deficiency may also

contribute to birthweight limiting mineralization or soft tissue growth.<sup>10</sup> In rural Bangladesh, Doi et al<sup>83</sup> studied the relationship between calcium concentration in fetal cord serum and size at birth using data from 223 women with live-born singleton deliveries. Calcium levels were positively associated with birthweight and length after multivariable adjustment. Mazumder et al<sup>84</sup> did not find a significant association between serum calcium and small for gestational age in a case-control study of 32 control and 32 case infants in Dhaka; however, hypocalcaemia was more prevalent in cases than controls (9.4% vs 6.3%, respectively).

Local data on the relationship between calcium or vitamin D and other outcomes in young children are limited. Baten et al<sup>85</sup> conducted a case-control study of 50 healthy neonates and 50 with recent idiopathic convulsions in Dhaka, measured serum calcium, and determined 60% of cases and 20% of controls were hypocalcaemic (mean serum concentration was 6.48 vs 8.28 mg/dL, respectively). In a case-control study of 87 hypocalcaemic and 246 normocalcaemic severely malnourished children admitted to a Dhaka ICU, Chisti et al<sup>86</sup> found a 26% prevalence of hypocalcaemia; acute watery diarrhea, convulsions, and lethargy were independent predictors of hypocalcaemia in this population. Vitamin D deficiency has been associated with acute lower respiratory tract infection in rural Bangladeshi children under 2 years.<sup>87</sup> These results, and calcium's effects on fetal growth, warrant further substantiation in Bangladesh and abroad.

## Interventions

### Supplements

It is estimated the risk of preeclampsia would be halved, and the risk of preterm birth and other pregnancy disorders or death would be reduced significantly if calcium supplements were provided to calcium-inadequate pregnant women.<sup>6</sup> In Bangladesh, calcium supplements may serve as an effective preventive measure in a population where 32% of women never attend an antenatal visit.<sup>38</sup> In a case-control study in

Rajshahi, 30 women with preeclampsia were administered 1 g/d of calcium upon suspected diagnosis of preeclamptic toxemia, and biochemical parameters were compared with 30 normotensive pregnant controls also receiving therapy.<sup>71</sup> A significant increase in mean urinary calcium:creatinine ratio (0.136-0.226) was observed in cases but not in controls. Herrera et al<sup>88</sup> conducted a small randomized controlled trial (RCT) of 30 Bangladeshi and 18 Columbian pregnant women, with half of each group receiving 600 mg calcium and 450 mg conjugated linoleic acid. The treatment group incurred reduced intracellular lymphocytic calcium, systolic blood pressure at delivery, and incidence of pregnancy-induced hypertension and increased plasma calcium:creatinine ratio and birthweight. In an RCT assessing preferences of 132 pregnant women in Dhaka to conventional calcium tablets, chewable tablets, unflavored powder, and flavored powder, conventional tablets were preferred by 62% of women.<sup>89</sup> As such, conventional tablets would likely be the most appropriate choice for mass distribution of calcium tablets among pregnant women in Bangladesh.

A growing body of research<sup>90</sup> regards vitamin D supplementation in pregnancy, with or without calcium, several trials of which have been conducted in Bangladesh. Islam et al<sup>91</sup> conducted a yearlong RCT among 4 study arms of premenopausal garment workers in Dhaka: placebo ( $n = 35$ ), daily 400 IU of vitamin D ( $n = 40$ ), vitamin D with 600 mg calcium ( $n = 41$ ), and multiple micronutrients with calcium ( $n = 37$ ). All treatment arms incurred significantly higher 25(OH)D, lower intact parathyroid hormone, and higher bone mineral density at multiple sites. Later, Roth et al<sup>92</sup> conducted an RCT of third-trimester pregnant women in Dhaka with 35 000 IU weekly ( $n = 80$ ) until delivery versus placebo ( $n = 80$ ). At delivery, all treated mothers and 95% of neonates were vitamin D sufficient ( $>50$  nmol/L), with a small increase in calcium levels, suggesting such treatment could produce benefits of improved vitamin D status while compensating for calcium losses normally observed in late pregnancy. Harrington et al<sup>93</sup> also conducted a 35 000 IU trial/wk of 160 pregnant women in Dhaka to study in more detail the effects of treatment on

maternal, fetal, and neonatal calcium homeostasis. The investigators also found a compensatory effect in infants: supplementation did not increase the risk of postnatal hypercalcemia, and attenuated the postnatal calcium nadir. In regard to infant growth, Roth et al<sup>94</sup> found weekly 35 000 IU maternal supplementation in the third trimester to produce a sex-adjusted mean increase of 1.1 cm (95% CI: 0.06-2.0) 1 year after birth, compared to infants born to control mothers. The results of these trials are encouraging, and vitamin D may represent a safe and effective therapy for improving calcium status and overall health in the Bangladeshi mother and infant dyad.

### Nutrient Powders

Use of micronutrient powders in improving children's nutrition is supported by a recent Cochrane review.<sup>95</sup> In Bangladesh, Combs et al<sup>96</sup> randomized one hundred fifty-eight 1- to 5-year-old rural children at risk of rickets (based on an alkaline phosphatase screener) living in a rickets-endemic area (incidence: 21.5%/year) to 6 d/wk of milk powder-based supplements with either 50, 250, or 500 mg calcium or 500 mg calcium plus multiple micronutrients (Cu, Fe, Mg, Zn, and vitamins A and D). At a 13-month rescreening, no child had rickets and carpal ossification was normal in all study arms, even 50 mg, while benefits of higher doses were marginal. The study did not measure iron status, however. Khan et al<sup>97</sup> administered a daily micronutrient powder with 12.5 mg iron and either 400 or 0 mg calcium to infants with anemia in rural Bangladesh (n = 48). Hemoglobin (Hb) response was attenuated in the with-calcium versus without-calcium group (mean Hb increased by 7.6 and 13.3 g/L, respectively) but was still notable. In an experiment to reduce competition between iron and calcium, microencapsulation of calcium failed to achieve desired calcium absorption in Bangladeshi pregnant women.<sup>98</sup> Karim et al<sup>99</sup> compared cost-effectiveness of a micronutrient premix (including calcium) versus fresh and dried fruits and vegetables in a large rural community nutrition project. Powders were more cost-effective and feasible in both children and pregnant and lactating women (relative to fresh red spinach,

powder provided the same amount of vitamin A at 71% of the cost and the same amount of iron at 2%-11% of the cost). Based on the potential savings elicited by micronutrient powders in Bangladesh, research should continue to incorporate calcium in them in such a way that it is compatible with iron.

### Food-Based Interventions

Despite the cost-effectiveness of powders, Karim et al<sup>99</sup> also noted that the provision of fruits and vegetables would provide additional dietary benefits and increase demand for local production. One large project investigated the effectiveness of a homestead gardening intervention on increasing dietary diversity and micronutrient intake in rural Bangladesh.<sup>100</sup> A difference in calcium intake of 626 versus 476 mg/d was observed between project and nonproject (control) adult women, with similar gains in adolescent girls (646 vs 425); this may have been due to an increase in the consumption of leafy vegetables among project households. Gains in children were smaller (358 vs 303), and intake by infants decreased (223 vs 483). Arnaud et al<sup>101</sup> found a nutrition education program was effective in reducing severity of rickets in 44 of 49 rachitic Bangladeshi children. Ahmed et al<sup>102</sup> show the results of a study in which locally available ingredients were used to develop rice/lentil- and chickpea-based, ready-to-use food products (RUSFs), naturally containing 286 and 413 mg calcium, respectively, per 50 g serving. Both foods were well accepted by study children. Yeasmin et al<sup>103</sup> found training Bangladeshi women to be effective in decreasing boiling times and the likelihood of using maximal heat when cooking vegetables, increasing nutrient retention (though fractional losses of calcium and vitamin D are usually small).<sup>104</sup> In a trial testing the effect of using aluminum cooking pots on children's calcium and vitamin D status, calcium concentrations were unchanged and vitamin D status decreased.<sup>105</sup>

The importance of fish to calcium intake in Bangladesh is recognized, particularly in rural areas where the landscape is permeated by small-scale aquaculture.<sup>106</sup> Wide-scale cultivation of

small fish in local ponds, fish farms, or rice fields has been suggested as a cost-effective and sustainable strategy for improving calcium and other micronutrients' status in Bangladesh,<sup>107-109</sup> but this has yet to be widely adopted. Hansen et al<sup>110</sup> and Larsen et al<sup>111</sup> implicate small fish in Bangladesh as a useful calcium source by virtue of their high bioavailability; small fish are also more nutritious as they are often eaten whole, bones included. Using the 2004 National Nutrition Programme Baseline Survey, Alam et al<sup>112</sup> found rural adolescent girls ate fish on an average of 3.4 days a week in 2004, with 41.1% eating it on 6 to 7 days (milk and green leafy vegetables were eaten only 1.9 and 1.7 days a week, respectively). Data from 84 poor rural households in the Kishoreganj District showed fish were responsible for 20%, 31%, and 16% of dietary calcium intake in February, October, and July 1997, respectively.<sup>113</sup> Hels et al<sup>30</sup> corroborate the seasonality of fish consumption. In rural Chakaria, Combs and Hassan<sup>46</sup> found that while dairy products were the most calcium dense and the only category of food whose consumption was associated with increased calcium status, fish and rice were the major calcium source for most of the 281 surveyed households. Given the wide scale production of fish in Bangladesh and recent development of technologies for small fish polyculture, efforts and implementation research should continue to scale up these technologies' adoption for the purpose of improving calcium and other micronutrients intake.

Efforts to improve dairy production and consumption have been limited, involving value chain improvement with emphasis on education and poverty reduction among farmers, in turn boosting access to markets. The Strengthening the Dairy Value Chain (SDVC) project by the Cooperative for Assistance and Relief Everywhere (CARE) showed a 46% increase in milk consumption by project households.<sup>114</sup> Further initiatives by CARE (SDVC II), Heifer International,<sup>115</sup> and Land O' Lakes International Development<sup>116</sup> are ongoing.

## Comment

Intake of calcium is low in the general population of Bangladesh, with potentially serious and

persistent effects on public health. These effects are especially pertinent to young children and reproductive-age women, by virtue of increased physiologic needs, poorer access to dietary calcium sources, and a confluence of other local determinants of calcium status in these groups. Although our review has aimed to be expansive, questions remain with regard to the design of a locally optimal program. In drawing together the available scientific and policy literature for this purpose, we have therefore included recommendations for further implementation research in Bangladesh.

A tablet supplementation program for pregnant women is an appealing approach, given evidence as to the acceptability and effectiveness of calcium tablets in Bangladesh, their quickness and low cost relative to other strategies, and the ability to target a subpopulation that is most in need while producing simultaneous reductions in fetal mortality. Recommendations for such a program and ancillary strategies build upon those proposed at the Asia Regional Meeting on Interventions for Impact in Essential Obstetric and Newborn Care<sup>29</sup> and are provided in Supplemental Table 3.

Home fortification by way of micronutrient powders may be an effective option for improving calcium status in Bangladeshi children. Locally, there are proven concerns around these powders' palatability in comparison with tablets, their ease of distribution, and to what degree calcium will interfere with iron absorption. A less expensive alternative may involve the addition of locally sourced calcium salts (slated lime) to rice while it is being cooked. Traditional fortification of corn with lime has been shown to increase the amount of calcium within and absorbed from tortillas among Mexican women<sup>117</sup> and has been implicated in reduced rates of preeclampsia among the Mayan Indians of Guatemala since 1980.<sup>118</sup> We observed that home fortification of rice with lime is practiced in Chakaria, where it is promoted by the local nongovernmental organization Social Assistance and Rehabilitation for the Physically Vulnerable (SARPV) to prevent and ameliorate rickets.<sup>119</sup> Any antirachitic effects of liming on rice have yet to be studied, however, and there is a need for research on the food

composition, bioavailability, efficacy, and acceptability of lime-fortified rice. Ready-to-use-therapeutic foods may provide a third practicable approach to improving calcium status of children. However, questions remain as to whether they will be eaten by intended beneficiaries, their mode of distribution and long-term compliance, and effects RUSFs will have on other aspects of diet and the local food economy.

In light of these knowledge gaps, we refrain from specific recommendations for program design for children. We suggest further research to address these gaps, from feasibility to adherence to effectiveness, for the primary purpose of preventing rickets in those areas most afflicted. An integrated strategy should also include educating mothers about the importance of dietary diversity in preventing and treating rickets and other symptoms of chronic dietary calcium inadequacy in childhood and education on the importance of exclusive breast-feeding.

Components of a longer term program for the general population may consider increasing dietary diversity by modifying agricultural practices,<sup>100</sup> industrialized fortification<sup>120</sup> with calcium and vitamin D, biofortification of staple crops or local fish aquaculture,<sup>106</sup> and strengthening the dairy value chain.<sup>114</sup> Given differences between urban and rural food systems in Bangladesh, a combination of strategies may be most effective; however, evidence is still limited as to how calcium can or should play a role in these strategies.

The most long-term strategies for improving calcium status may involve increasing supply and demand for more diverse foods. Past projects to diversify the country's diet succeeded in increasing consumption of potatoes, fruits, and certain vegetables, but increases in pulses, oil crops, or wheat were unsustainable.<sup>121,122</sup> At present, Bangladesh's food system is rice centric, and rice contains 67% of Bangladesh's total agricultural output of calcium.<sup>123</sup> Although potential benefits of increased dietary diversity are supported in Bangladesh,<sup>44,100</sup> research has yet to address questions as to how diversification could be practicably brought about in the general population, and policies have not favored such implementation or implementation research.

Research is needed to determine how supply- or demand-side price controls may increase production and consumption of nutrient dense-foods while reducing that of rice, without spreading hunger, marginalizing local firms, or limiting international trade. Research should also address how amenable Bangladeshis are to different forms of healthy diet modification, how practicably modifications may be effected by social marketing and health promotion, and as Bangladesh's food market continues to globalize, what policies will be warranted to reduce demand for foods that are nutrient dense and inexpensive while also obesogenic.

### Authors' Note

TA and WF conceived the study. SB and WF designed the study. SB acquired and analyzed data. SB, TA, and WF interpreted findings. SB drafted the manuscript. TA, WF, and SB critically revised the manuscript.

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### Supplemental Material

The online supplemental tables are available at <http://fnb.sagepub.com/supplemental>

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