THE EFFICACY AND ACCEPTABILITY OF PRENATAL CORN SOYA BLEND PLUS DIETARY SUPPLEMENTATION AMONG WOMEN IN RURAL CAMBODIA

by

Amynah Janmohamed

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

(Integrated Studies in Land and Food Systems)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

December 2015

Abstract

Corn Soya Blend (CSB) Plus is a micronutrient-fortified dietary supplement designed for women in Cambodia and elsewhere to help meet their nutritional needs in pregnancy, though little is known about its acceptance and ability to improve pregnancy outcomes. This research utilized a mixed methods approach to investigate the efficacy and acceptability of prenatal supplementation with CSB Plus among rural Cambodian women. A cluster-randomized trial was conducted in 75 villages in Kampong Chhnang Province, in which 547 women received the food supplement (treatment) on a monthly basis from the first trimester until delivery or continued their normal diet (control). Participants included women receiving antenatal care at a health facility in the first trimester. The primary outcome was birth weight and secondary outcomes were low birth weight (< 2500 grams), small for gestational age, birth length and head circumference, preterm birth (< 37 weeks), maternal weight gain, and anemia prevalence at 24-28, 30-32, and 36-38 weeks gestation. Cluster-adjusted linear mixed effect and logistic regression models were used to examine group differences. Acceptability of CSB Plus was investigated through structured interviews to understand consumption preferences and practices and six focus group discussions to explore perceptions, attitudes, and behaviors related to supplement utilization. CSB Plus resulted in a non-significant 46 g increase in birth weight (95% CI: -31, 123) and did not increase maternal weight gain or other measures of birth size. However, maternal anemia at 36-38 weeks (OR: 0.51; 95% CI: 0.34, 0.77) and preterm birth (OR: 0.33; 95% CI: 0.12, 0.89) were lower in the CSB Plus group. A significantly higher rate of fetal loss occurred in the treatment group. Acceptability was influenced by the product's organoleptic qualities, family support, peer influences, trust in the provider of the supplement, and attitudes related to nutrition and weight in pregnancy. Acceptance was lower among first-time mothers, mainly due to fears of a large baby and resulting delivery complications. The findings of this research provide insight that can be used to guide future policy and programming decisions on the provision of Corn Soya Blend Plus and other prenatal dietary supplements in the Cambodian context.

Preface

This research was facilitated through a collaboration between the University of British Columbia and International Relief & Development, Cambodia. I designed the research in consultation with my doctoral co-supervisors Dr. Judy McLean and Dr. Tim Green. I developed the research protocol and data collection instruments and conducted the data analyses. I carried out the research with the assistance of a Cambodia-based team that collected the data. The research was approved by the University of British Columbia Clinical Research Ethics Board (H11-00801).

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ANC	Antenatal care
BMI	Body mass index
CDHS	Cambodia Demographic and Health Survey
CSB	Corn Soya Blend
FBF	Fortified-blended-food
FFS	Fortified food supplement
Hb	Hemoglobin
IFA	Iron folic acid
LBW	Low birth weight
MOH	Ministry of Health
MMS	Multiple micronutrient supplement
OR	Odds ratio
PLW	Pregnant and lactating women
RCT	Randomized controlled trial
RDA	Recommended dietary allowance

RR	Relative risk
SGA	Small for gestational age
UNIMMAP	United Nations International Multiple Micronutrient Preparation
WFP	World Food Programme
WHO	World Health Organization
WRA	Women of reproductive age

Acknowledgements

In my doctoral program, I have been privileged to be guided by individuals who epitomize excellence. My supervisors, Dr. Judy McLean and Dr. Tim Green, have my enduring gratitude for taking me as their student and for their continued guidance, support, flexibility, patience, and utmost kindness. Thank you, Dr. McLean, for creating the opportunity for me to do this important and amazing work that took me to Cambodia for 33 months and for trusting in my abilities. Thank you, Dr. Green, for always encouraging me to believe in myself, to aim higher, and for being so very generous with your time, involvement, and compliments on my work. The experience of celebrating my successes and working through the challenges with you both is beyond words. To my committee members, Dr. Gwen Chapman and Dr. Patti Janssen, I hold you in such high esteem and was immensely honored to be under your guidance. Thank you for your invaluable insights and contributions to making my work better every step of the way.

I am deeply indebted to the wonderful and incredibly hard-working group at International Relief & Development in Cambodia for the opportunity to be part of their extraordinary team. I learned so much from them and will forever be appreciative of my time there. To my fellow lab mates, thank you for the unwavering encouragement, inspiring conversations, for being great listeners, for selflessly offering your knowledge and experience, and for your infectious enthusiasm. You are truly amazing individuals and it was a pleasure to work with you each day. I know our friendships will extend well beyond the confines of FNH 208. To my fellow residents of St. John's College, my home away from home, thank you for being my family around the dinner table each evening. Finally, I am immeasurably grateful to my parents, family, and friends for being my biggest supporters and for reminding me that nothing is impossible. They have always stood proudly by my side no matter the distance. I know they have longed to witness this achievement and I could not have made it without their love, comfort, and care. This has been our journey and I share my joy with them.

Lastly, I would like to express my deepest appreciation to the warm and generous people of Kampong Chhnang Province who allowed me into their homes, shared their stories with me, and graciously gave of their time for my research, and to those who went above and beyond to make my long stay in Cambodia as happy and comfortable as possible. I could not have asked for better hosts. I wish them and their families much good fortune in the years ahead.

Chapter 1: Introduction and Review of Literature

1.1 Background and Rationale

Food security is critical for a population's health and development. Despite immense growth and economic progress since the Khmer Rouge-led genocidal regime decimated Cambodia 40 years ago, undernutrition remains one of the country's most pressing challenges. In particular, chronic child undernutrition and the poor nutritional status of women are of major concern (1). Adequate fetal, infant, and child nutrition during the 1000 day period from conception to a child's second birthday is critical for preventing long term, and potentially irreversible, consequences of undernutrition (2). This necessitates women being well-nourished during pregnancy and lactation. However, in resource-poor countries like Cambodia that are highly dependent on external assistance, donor-led nutritional investments have almost solely focused on infant and young child feeding and it is only relatively recently that maternal nutrition has started to receive greater attention.

In countries like Cambodia where economic constraints place limits on achieving dietary adequacy, food-based interventions are one approach to improve the nutritional status of vulnerable populations such as pregnant women. Cereal-based (e.g., maize, rice, wheat) products are commonly used by the United Nations and other donor agencies in both emergency contexts and in supplementary feeding programs in non-emergency settings (3). Supplementary feeding programs assist pregnant and lactating women and young children in areas with high levels of poverty, food insecurity, and undernutrition (4). The objective of such programs is to provide macro and micronutrients lacking in staple diets to enable these vulnerable segments of populations to meet their nutritional needs. Fortified-blended-foods (FBF) are the most commonly used commodities in supplementary feeding programs (5). However, despite decades of use, little is known about their nutritional efficacy and acceptability among beneficiaries. This has both ethical and resource implications for providers and recipients of these products. The continued use of FBFs needs to be supported by scientific evidence. My research involved investigating the efficacy and acceptability of a prenatal FBF supplement called Corn Soya Blend (CSB) Plus among women in rural Cambodia. To my knowledge, there are no published studies on the use of CSB Plus in pregnancy in Cambodia or elsewhere.

This research opportunity was facilitated through a partnership between the University of British Columbia's Food, Nutrition & Health Program and International Relief & Development's (IRD) Cambodia country office. This collaboration was created and formalized in 2010 by my doctoral co-supervisor Dr. Judy McLean. IRD is a non-governmental organization (NGO) with active projects in more than 40 countries that span numerous sectors including infrastructure, civil society, governance, conflict mitigation, disaster/emergency response, agriculture, food, and health. IRD has been operational in Cambodia since 2004 and community-based nutrition is a key focus of their work in the country. IRD's nutrition projects have been implemented in Kampong Chhnang Province, one of the country's 24 provinces, located in the central region of the country. The area has high levels of child mortality and undernutrition and is largely underserved by NGOs, compared to other provinces (1,6). In the most recent Cambodia Anthropometric Survey (7), Kampong Chhnang was the only province in the country with a rate of childhood underweight above 35%.

My research was a component of IRD's ENRICH (Evidence-based Interventions for Improved Nutrition to Reinforce Infant, Child, and Maternal Health) Project that was implemented during a four-year period (October 2010 to September 2014) and funded under the USAID Child Survival and Health Grants Program. The ENRICH Project's strategic objectives reflected an integrated approach to addressing child undernutrition through mutually-reinforcing activities and included: reducing the prevalence of child malnutrition; reducing the burden of diarrheal diseases; increasing healthy timing and spacing of pregnancies; and improving pregnancy and newborn outcomes. The project targeted a total population of about 100,000 using primarily community-based nutrition-focused interventions. In my research, which addressed the last objective, I was able to leverage IRD's longstanding footprint in the province and the collaborative relationships established with provincial and local authorities, as well as other stakeholders.

I was based at the IRD office in Kampong Chhnang town, the provincial capital, from November 2010 to June 2013. My responsibilities included: conceptualizing and designing the research; developing the research methodology; writing the research protocol; obtaining local and UBC ethics approval; hiring local research officers; developing recruitment, education, and training materials; developing data collection instruments; overseeing field activities; conducting all data analyses; and disseminating findings to local, provincial, and national government authorities, the nutrition community in Cambodia, and the funding agency USAID. These activities were conducted in consultation with my doctoral supervisors and in collaboration with my IRD colleagues.

The process for selecting the intervention (Corn Soya Blend Plus) to be tested in the efficacy trial first involved a situation analysis, primarily through a literature review, to better understand the major causes of undernutrition in the country and the specific nutritional challenges facing women of reproductive age. This was followed by a series of formative in-country consultations over a period of three months with officials at the Cambodia Ministry of Health, National Nutrition Programme, United Nations agencies (WFP, UNICEF, WHO), World Bank, and local and international NGOs working in maternal and child health. The reason for these consultations was so that I could become better informed about what interventions had been tried and tested in the country, what the unmet needs were, and what was of key interest and relevance to government and other stakeholders, as related to the country's health and nutrition agenda. This valuable exercise generated a list of intervention ideas that were evaluated in accordance with what was feasible within IRD's operating and budgetary constraints.

In chapter 1, the reader is introduced to the global problem of maternal undernutrition, its causes and consequences, and the magnitude of the problem in Cambodia. This discussion presents an argument for the global and Cambodia-specific public health need for effective nutrition-focused interventions during pregnancy. This is followed by an overview of the scientific literature on three strategies for prenatal nutritional supplementation: protein-energy foods, multiple micronutrient supplements, and micronutrient-fortified protein-energy foods, as well as a discussion of FBFs, including Corn Soya Blend products, in the context of global food assistance. I discuss key studies, highlighting their strengths and weaknesses. The chapter concludes with a statement of the research goal, the research objectives, and the study hypotheses tested.

1.2 Literature Review

1.2.1 The Problem of Maternal Undernutrition

Undernutrition is defined as "being underweight for age, too short for age (stunted), too thin relative to height (wasted) and functionally deficient in vitamins and minerals (micronutrient malnutrition)" (8; p. 2). Despite the WHO declaring in 2002 that undernutrition was the "single greatest threat to health worldwide" (9; p.1), it remains responsible for one-third of deaths in children under five years of age more than one decade later (10). The condition disproportionately affects women and children in developing countries due to multiple physiological, socio-economic, and cultural factors (11-12). As women's requirements for energy and many nutrients increase during pregnancy, there is a need for more calories and foods with high nutritive value during the prenatal period.

A newborn's size at birth is a predictor of neonatal and infant survival (13). Babies born underweight often experience a reduced ability to feed properly, due to a lack of energy and/or immature gastrointestinal tract, and a compromised immune system which increases susceptibility to infection, a major cause of infant mortality (13). In 2013, about 22 million babies were recorded as having low weight (< 2500 g) at birth worldwide, a prevalence of approximately 16%, and the vast majority of these cases (> 95%) occurred in developing countries (14). Poor nutritional status at birth is associated with physical and cognitive impairments into infancy and childhood that may persist into adulthood (15). Research from animal models and epidemiological studies indicates that the metabolic adaptations that occur in suboptimal intrauterine environments are associated with the onset of cardiovascular disease, diabetes, and other chronic illnesses later in life (15). These changes, referred to as fetal programming, underpin the "fetal origins of adult disease" hypothesis (16).

Size at birth reflects the rate of fetal growth and duration of gestation. Underweight babies are either born preterm (before 37 completed weeks gestation) or at term (37-42 completed weeks gestation). Weight, length, head, and chest circumference are standard anthropometric measurements to assess a neonate's nutritional status at birth (17). Birth weight, in particular, is routinely measured following delivery in health facilities in countries where there is general availability of infant weighing scales and where birth weight is a reportable indicator in national health information tracking systems (18). Moreover, the prevalence of low birth weight (LBW) babies is commonly used for making inter-country comparisons and for monitoring individual country progress over time. Finally, the extensive knowledge base on socio-demographic, nutritional, physiological, and lifestyle factors associated with birth weight creates a robust research platform for using birth weight and LBW as study outcomes (19).

However, despite its widespread use, birth weight data do not distinguish between preterm and “small” term babies, which have very different risk profiles (20-21). Babies born smaller for their age - below the 10th percentile as compared to a sex-specific reference population of babies at the same gestational age - are considered to be small for gestational age (SGA) (22). Though it is important to note that non-nutritional factors (e.g., age, genetics, infection, lifestyle) have etiologic roles, many SGA births in developing countries are due to intrauterine growth restriction arising from nutrition-related factors in undernourished mothers (23). Two-thirds of LBW babies in developing countries are attributed to intrauterine growth restriction (23). Though SGA is a more precise and informative indicator of birth size than LBW, the rather complicated process of calculating and interpreting SGA in field settings, as compared to the simpler task of determining the proportion of babies born < 2500 g, makes SGA an infrequently used indicator in developing countries, especially when gestational age is unknown or difficult to determine.

Women who are nutritionally-disadvantaged when becoming pregnant are at higher risk for maternal mortality, preterm birth, and delivering LBW and or SGA babies (24-26). A newborn’s body size is greatly influenced by the mother’s anthropometric status, determined using height and weight measurements and assessed using the indicators of height-for-age and pre-pregnancy weight-for-height (20). Short maternal stature, defined using specific cutoffs for individual country contexts (e.g., < 145 cm in Cambodia) (1), is associated with underweight neonates, stunted infant growth, and a higher risk of child mortality (27-28). Stunted growth indicates chronic undernutrition as it stems from stunting in early life (29-31). The repercussions of uncorrected nutritional deficits over the life course create an intergenerational cycle of malnutrition, also known as the intergenerational transmission of growth failure (Figure 1.1) (32).

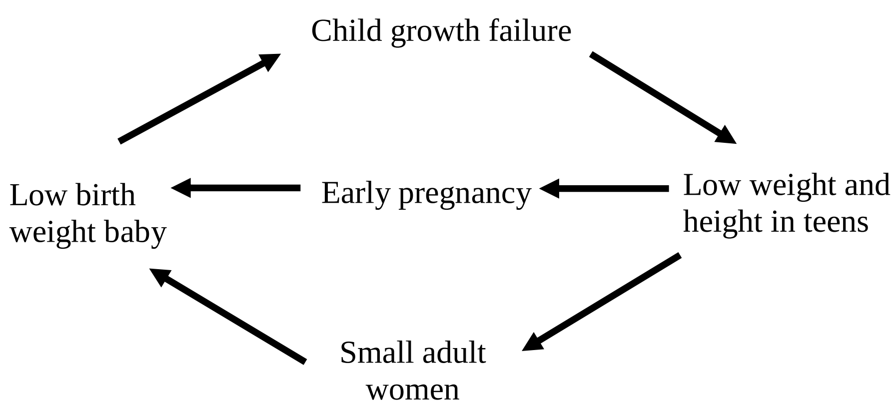

Figure 1.1 Intergenerational cycle of growth failure. Adapted from Second Report on the World Nutrition Situation Volume 1: Global and regional results. UN Administrative Committee on Coordination - Subcommittee on Nutrition, 1992.

Low maternal weight-for-height, expressed as low body mass index (< 18.5 kg/m^2), is also associated with reduced fetal growth potential (20, 33). This condition, known as wasting, reflects the degree of thinness caused by energy imbalance due to an inadequate intake of calories to meet energy requirements. Evidence showing lower birth weights and/or SGA among babies born to women with low BMI in early pregnancy, compared to those with BMI ≥ 18.5 kg/m^2 , is partially attributed to the intrauterine partitioning of energy that occurs between mother and child that favors maternal fat deposition in underweight women (34-37). It is for this reason that recommendations for weight gain in pregnancy are based on women's pre-pregnancy BMI status (38). In addition to a woman's anthropometric status when becoming pregnant, newborn size at birth is also influenced by her nutritional status during gestation (26). This is assessed through monitoring gestational weight gain and screening for anemia and vitamin and mineral deficiencies using biochemical methods and or clinical diagnosis in field settings. After the first trimester, a woman needs about 300 extra kcal per day for the duration of pregnancy (39). The association between gestational weight gain and fetal growth is well established (40) and is not described in further detail here.

Anemia is a serious global public health problem and merits some discussion. The condition affects about 500 million women of childbearing age each year and more than half of all pregnant women are anemic (41). The magnitude of this global burden is alarming as anemic women have elevated risks for maternal mortality, stillbirth, preterm birth, LBW, and SGA (42-43). Apart from adverse pregnancy outcomes, the effects of anemia are also apparent in compromised physical and cognitive performance (41-42), posing economic hardships for agriculture-based societies in developing countries due to the loss of women's productivity. Though there are many etiologic pathways for anemia to occur, nutritional factors are of major importance in places where staple diets offer low bioavailability of iron and other nutrients (41). Iron-deficiency-anemia occurs when insufficient amounts of iron-rich foods are consumed and when the amount of iron absorbed from food is insufficient to meet physiological requirements during specific life stages such as pregnancy and infancy (42).

In addition to iron, deficiencies of vitamins A, B6, B12, C, E, folate, and riboflavin contribute to anemia directly or indirectly through their roles in hemoglobin synthesis, iron absorption and mobilization, and other iron-related functions (41, 44-47). As these deficits are quite often not perceptible, vitamin and mineral deficiencies are commonly referred to as "hidden hunger" (48). The estimated two billion people with micronutrient undernutrition worldwide is astounding

(48). The majority of attention and effort has focused on iron deficiency as it is the most common nutritional deficiency among women of reproductive age (WRA) and is thought to account for half of the global anemia prevalence in this demographic group (41-42). Iron needs increase during pregnancy from 8.1 mg/day to 22 mg/day (49) due to the hemodilution that results from blood plasma volume expansion and the rapid fetal growth that occurs during the second and third trimesters. As this requirement is hard to meet for most women, the WHO recommends supplementation with iron and folic acid throughout pregnancy for women in all settings (50). However, achieving high coverage has been challenging in many countries due to low/late antenatal care attendance, supply issues, and low compliance due to side effects (51).

Though anemia prevalence tends to be used as a proxy indicator for the level of iron deficiency among women in developing countries, given that more than half of all anemia episodes are purportedly attributed to iron deficiency, the major contribution of endemic helminth, malarial, and other parasitic infections cannot be overlooked (52-55). Undernutrition and infection are mutually reinforcing and, in places where both are highly prevalent, result in perpetual states of poor health and nutrition. Unsafe water and sanitation facilities create an environment for recurring acute or prolonged infections from enteric pathogens, intestinal parasites, and other infectious agents. Nutrient deficiencies (e.g., vitamin A) that occur during episodes of illness, when appetite and nutrient absorption are diminished, increase susceptibility to and the potential severity of infections through reduced immune function (56-57). The negative effects of nutritional depletion from frequent infection and illness on birth outcomes are mediated through suboptimal gestational weight gain and poor micronutrient status. The cyclical relationship between undernutrition and infection is presented in Figure 1.2.

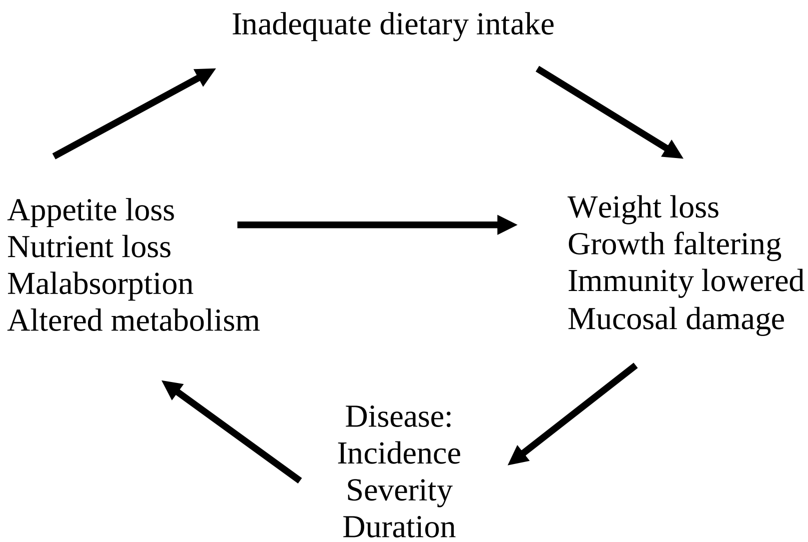

Figure 1.2 Malnutrition infection cycle. Adapted from Nutrition Policy Discussion Paper No. 5. UN Administrative Committee on Coordination – Subcommittee on Nutrition, 1989.

In conclusion, women who are nutritionally-challenged during gestation experience a higher likelihood of adverse pregnancy outcomes. Aside from the nutritional marginalization that occurs in populations having staple diets that provide inadequate sources of macro and micronutrients and a reduced nutrient absorptive capacity due to recurring infection and illness, other factors also play a role. A lack of health and nutrition knowledge to enable individuals to make informed dietary choices in contexts of relative food and economic security and reproductive expectations add to women's ongoing nutritional challenges. Closely-spaced pregnancies provide short recuperative periods for necessary nutrient repletion (58). This underlies the inclusion of healthy timing and spacing of pregnancies as one of IRD's strategic project objectives mentioned in section 1.1. Finally, heavy physical workloads of agriculture-centered communities can further compromise women's nutritional status if energy intake is insufficient to support high energy expenditures.

1.2.2 Maternal Undernutrition in the Cambodian Context

The nutritional profile of women and children in Cambodia is poor. According to the 2010 Cambodia Demographic and Health Survey (CDHS) (1), one in five WRA are wasted, that is they have a low BMI (< 18.5 kg/m2), which is considered to be of public health significance according to the WHO (59). The prevalence of anemia in this demographic group is 44% and is above 50% in pregnancy, also indicating a severe public health problem for the country (1, 42). Though there has been a reduction in the national anemia prevalence among WRA during the past decade, in large part due to the improvement in coverage of IFA supplementation, which increased from 21% in 2000 (60) to 58% in 2005 (61) to 89% in 2010 (1), the nutritional status of women in Cambodia remains poor as shown in Table 1.1 These indicators are concerning as they reflect the large number of women who are nutritionally-compromised when becoming pregnant.

Table 1.1 Nutrition indicators for Cambodian women of childbearing age

	2000	**2005**	**2010**
% of women with BMI <18.5 kg/m^2	20.7%	20.3%	19.1%
% of women with anemia (Hb <12.0 g/dL)	57.8%	46.6%	44.4%
% of pregnant women with anemia (Hb <11.0 g/dL)	66.4%	57.1%	52.7%

Source: Cambodia Demographic and Health Surveys – 2000, 2005, 2010

The magnitude of chronic child undernutrition in Cambodia is also large. Almost half of all children under five years of age have stunted growth, meaning they are short for their age (1). In the 2010 CDHS, 8% of babies were born with LBW during the preceding five years, though this likely underestimates the problem as 30% of surveyed births did not have a reported weight, either recorded or based on the mother's recall, and about half of all births in Cambodia occur outside of a health facility (1). Home births tend to be higher-risk pregnancies as can be inferred from the disproportionately larger percentage of weighed babies from households in high wealth quintiles (1). Recent UNICEF data indicate a LBW prevalence of 11% in Cambodia based on aggregated data from the CDHS, other national household surveys, and administrative data (62).

The burden of undernutrition is especially high in Kampong Chhnang Province, the location of my research. Anemia prevalence among WRA is 57% in the province, 13% higher than the national prevalence and the second highest rate in the country (1). Eight percent of women have a height under 145 cm, the marker for short stature in Cambodia (1), which corresponds to a value 3 standard deviations (SD) below the average expected height of a healthy woman at 19 years of age (164 cm) according to the WHO Growth Standard (63). Rates of severe (< -3 SD according to WHO Growth Standard) wasting, severe stunting, and severe underweight in children under five are higher in Kampong Chhnang, compared to respective national rates (1). Further, an alarmingly high 64% of children 6-59 months of age are anemic in the province, substantially exceeding the national rate of 55% (1). Finally, Kampong Chhnang has the second highest neonatal mortality rate in Cambodia (45/1000 live births) and the third highest infant (78/1000 live births) and under five (97/1000 live births) mortality rates (1), in large part, reflecting the burden of undernutrition during these critical periods.

These statistics, which portray a rather bleak picture of the health of many Cambodians, can be explained by understanding the factors that place limits on achieving nutritional adequacy for much of the population. Despite the steady economic growth that has taken place following decades of war and political turmoil, Cambodia has remained one of the world's poorest countries. Cambodia was ranked 136th out of 187 countries in the 2014 Human Development Report (64) and the 2013 Global Hunger Index classified Cambodia as having a "serious" level of hunger (65). The country is largely dependent on foreign aid (30-40% of the government's budget depends on donor aid) (66) and government under-investment in health and education has left much of the population marginalized. National poverty estimates vary depending on the poverty metric used, which is subject to politically-driven change. United Nations data report poverty rates declined from 26% of the population living under USD 1.25/day in 2010 to 19% in 2013 (67). Most of the poor are rural subsistence farmers who grow rain-fed lowland rice that produces one annual harvest. More than half of rural households report experiencing seasonal food shortages (68). Women are major contributors to the agricultural work force and actively engage in physically-demanding work, particularly during rice planting and harvesting seasons. The shortage of a skilled and educated work force, a consequence of the Khmer Rouge reign, and little subsequent government investment in the social sector, including improving livelihoods, have undermined the country's reconstruction and development.

Population representative data on micronutrient status are not available for Cambodia. However, multiple deficiencies are acknowledged in the population based on proxy data (e.g., anemia rates) and available data suggesting limited dietary diversity and low intake of nutrient-dense foods. The staple food of Cambodians is white rice and, according to the Food and Agriculture Organization, 74% of dietary energy is supplied from cereals, roots, and tubers, while under 10% is derived from animal foods (69). Rice noodle soup (kuyteav) or rice porridge (borbor) is commonly eaten for breakfast, though plain white rice is sometimes eaten at the morning meal and is the mainstay of all other meals. Small local fish such as trey lingh and trey riel are widely consumed, especially in the rainy season when they are most plentiful. Fish constitutes a major source of animal protein and freshwater crabs, shrimp, frogs, and snails harvested from rice fields are also common protein sources (70-72). However, for severely food insecure households without access to fish or other protein sources, cooked rice is likely the main protein source –

providing ~4 g protein/cup (73). In households with some access to high-value foods such as beef, chicken, larger fish, and eggs, individual portions tend to be very small as these foods are typically cooked with other items in a large family pot. In a small dietary intake study among women 25-75 years of age in Kandal Province that used a 24-hour dietary recall, Wallace et al. (74) concluded 97% of the women did not meet their daily recommended intake of iron and most consumed less than 50% of the recommended intake. These results emerged despite reported consumption of iron-rich foods such as pork and fish, which were determined to be consumed in inadequate amounts in the study.

Though fish provides a good source of iron, most dietary iron in the Cambodian population is obtained from plant (non-heme) sources, which precludes optimal absorption due to the low bioavailability of iron in non-animal foods (75). Though rice has a high phytate content, which is known to inhibit non-heme iron absorption (76), the antinutrient is not of major concern for Cambodians as polished white rice is the staple food. Deficits of vitamin A and zinc may also be of concern as regular access to bioavailable sources of these nutrients (i.e. animal foods) is cost-prohibitive and the majority of Cambodians do not have access to fortified foods. Gibson et al. (77) concluded insufficient availability of vitamin A, calcium, iron, riboflavin, thiamin, and zinc in the Cambodian food supply. Whitfield et al. (78) documented a high (~90%) prevalence of riboflavin deficiency and suboptimal thiamin status (~60%) among WRA in Prey Veng Province. Finally, it is important to recognize the low contribution of fat to the Cambodian diet (~14% of dietary energy) (79), in light of the minimum 20% required in pregnancy (80). A low fat intake affects not only overall energy intake, but absorption of fat-soluble vitamins, most importantly vitamin A.

Interestingly, serum ferritin levels (indicator of iron storage) in women in Prey Veng Province indicate a very low prevalence of iron deficiency (81). This challenges the prevailing assumption that 50% of anemia episodes are attributed to dietary iron deficiency and, therefore, highlights the potential need for caution when interpreting anemia prevalence as an indicator of iron deficiency in the Cambodian population. In Cambodia, anemia should be viewed in the context of evidence suggesting that other nutritional deficiencies, high rates of thalassemia and other genetic hemoglobinopathies, and a large burden of infection are major contributors to anemia (81-82). Endemic helminth infections, particularly those caused by hookworms, whipworms, and roundworms, are an important contributor to undernutrition in Cambodia (83). These worms feed on the intestinal epithelium and cause fecal blood loss, which can progress to anemia. Based on studies in Zanzibar and Nepal, Stolfzus et al. (84) concluded the amount of iron lost from a moderately severe hookworm infection may exceed required amounts of iron in pregnancy. A 26% prevalence (egg-positive rate) of intestinal soil-transmitted and food-borne helminthes was seen in fecal samples collected from adults and children in 19 provinces in Cambodia during 2006-2011 (83). The prevalence in Kampong Chhnang was 28%, based on a sample of ~1800 adults and children. The fact that about half of Cambodian households consume drinking water from an unsafe source during the six-month dry season (November to April) and the majority of rural households (~70%) do not have access to a proper toilet are major factors underlying the helminth burden, as well as recurring infections from other food and waterborne pathogens (1). Furthermore, as Cambodian women comprise ~60% of the agricultural work force and are mainly responsible for rice planting and harvesting, they are particularly susceptible to soil-transmitted helminthes (1). Given the morbidity associated with intestinal worm infections, prenatal deworming treatment with the drug mebendazole is provided to all women after the first trimester as part of antenatal care in Cambodia (85). Though coverage has been low, coinciding with poor ANC attendance in recent years, treatment is now increasing as 45% of women reported taking deworming medication during their last pregnancy in the 2010 CDHS (1), compared with only 11% in the 2005 survey (61).

The Cambodia Ministry of Health (MoH) has acknowledged the need to improve the nutritional status of women during pregnancy. In the National Nutrition Strategy: 2009 – 2015 (86), the "reduction of protein energy malnutrition and micronutrient deficiencies in women and improving care for pregnant women, including extra dietary intake and rest for increased weight gain during pregnancy" (86; p. 12), were stated priorities. Key MoH recommendations for women during pregnancy include: (i) total weight gain of at least 7 kg; (ii) consumption of one extra daily meal (unspecified); (iii) a course of 90 IFA tablets (provided at ANC); and (iv) attendance at a minimum of four ANC visits (85). Though ANC attendance in Cambodia is increasing, as indicated by the fact that 89% of women who gave birth in the five years preceding the 2010 CDHS survey received antenatal care at least once from a skilled provider (compared to 69% in the 2005 survey), many women do not come early enough to fully avail themselves of these services. In the 2010 survey, about 60% of women had their first ANC visit at a health center in the first trimester of pregnancy. This means that 40% of women were unable to obtain IFA supplements in early pregnancy as community-based distribution of these tablets does not exist in the country. For those who do attend, nutritional counseling during ANC is sparse and, when provided, is often inadequate and based on outdated guidelines and messages (87). Moreover, general recommendations such as eating one extra daily meal are not specific enough to inform individual practice on food choices and portion sizes.

In conclusion, attaining adequate nutritional status during gestation is challenging for many women in Cambodia, as the best sources of protein, vitamins, and minerals tend to be costlier foods. For places where the staple diet offers little dietary diversity and immediate improvements are out of reach, nutritional supplementation may be an effective way to achieve gains in maternal and child health.

1.2.3 Nutritional Supplementation in Developing Countries

Three strategies to improve nutritional status are: dietary interventions that promote increased consumption of a greater variety of nutritious locally-available foods; fortification of commonly consumed foods/condiments; and nutritional supplements to help individuals achieve required intakes of certain nutrients that are lacking in staple diets (88). Though interventions such as homestead food production models have produced reductions in micronutrient deficiencies, the need to incorporate more animal protein for broader nutritional impact is recognized (89). The introduction of fortified foods resulted in large declines in micronutrient deficiencies and associated morbidities in western populations (90-91), though this process has proven to be challenging in developing countries due to uncertainties surrounding fortificant composition and choice of food vehicle, the existence of multiple millers and producers, unlegislated initiatives, and high investment costs (92). Further, poor rural households are unlikely to benefit from fortified products due to distribution and cost factors and pregnant women require amounts in excess of quantities present in most fortified products.

In Cambodia, maternal dietary supplementation is considered a potentially-effective interim intervention for improving pregnancy outcomes, until development transitions such as poverty reduction increase purchasing power and enable consumption of a greater variety of local foods. This section includes a discussion of the scientific evidence surrounding three prenatal nutrition supplementation strategies: protein-energy supplements, multiple micronutrient supplements, and fortified protein-energy supplements. These approaches have produced nutritional benefits in undernourished populations and continue to receive attention in the nutrition research community.

1.2.3.1 Protein-energy Supplementation

Early research involving women in various countries who experienced severe food shortages during the World War II years showed energy deprivation during pregnancy was strongly associated with reduced newborn size at birth (93). Further work conducted by Lechtig and colleagues in the 1970s in Guatemala demonstrated a significant reduction in LBW among newborns of women who received high-calorie prenatal food supplements (94). This spurred much interest in the potential utility of protein-energy supplements to repair macronutrient deficiencies in undernourished pregnant women. Findings from studies conducted in the 1980s and 1990s, including research in developing countries, consistently demonstrated positive effects of balanced protein-energy supplements, those in which protein provides < 25% of total energy content, on birth weight. Kramer et al.'s (95) Cochrane review published in 2003 revealed balanced protein-energy supplementation was associated with a 38 g (95% CI: 0, 75; 12 trials) increase in birth weight and a 32% reduction in risk of SGA (RR 0.68; 95% CI: 0.56, 0.84; 6 trials).

Imdad and Bhutta's (93) more recent pooled analysis (Table 1.2) indicated a positive impact of protein-energy supplementation on birth weight (73 g; 95% CI: 30, 117; 16 trials). Further, a 32% reduction in risk of LBW was shown in a combined analysis of five of these studies (RR 0.68; 95% CI: 0.51, 0.92), as well as a 34% reduction in risk of SGA (0.66; 95% CI: 0.49, 0.89; 9 trials). Nine trials in the Imdad study included fortified supplements and 11 of the trials that examined birth weight were also included in Kramer's analysis. Ota et al.'s (96) 2012 update of Kramer's Cochrane review included 11 protein-energy supplement studies, of which 10 were included in Imdad's meta-analysis. Ota's findings revealed supplementation increased birth weight by 41 g (95% CI: 5, 77; 11 trials) and reduced the risk of SGA (RR 0.79; 95% CI: 0.69, 0.90; 7 trials). All three of these meta-analyses showed an approximate 40% reduction in risk of stillbirth in the supplemented group. As shown in Table 2, supplements used in these early studies ranged from locally-produced foods to specially formulated energy-dense beverages, biscuits, powders, and spreads.

Table 1.2 Studies included in the Imdad and Bhutta meta-analysis[1]

Location, Author, Year	Design	Sample (for birth weight analysis)	Study Groups	Supplement duration	Results
England Atton 1990 (97)	RCT	N = 148 (undernourished women)	Intervention: Daily 200 ml flavored milk (~400 kcal; 14.6 g protein; vit/min) Control: no supplement	28 weeks to delivery	Birth weight: -60 g (-188, 68)
Taiwan Blackwell 1973 (98)	RCT	N = 223 (under and adequately nourished women with at least 1 male child)	Intervention: Chocolate flavored liquid (800 kcal; 40 g protein; vit/min) Control: vit/min only	Started after prior birth through index pregnancy	Birth weight: Undernourished: +140 g (7, 273) Adequately nourished: -6 g (-129, 117) LBW: RR 0.61 (0.25, 1.54) SGA: RR 0.56 (0.21, 1.48)
Scotland Campbell Brown 1983 (99)	RCT	N = 180 (undernourished primiparous women)	Intervention: 1 pint flavored milk drink or 1 pint fresh milk or 75 g cheddar cheese (~300 kcal; 15-20 g protein) Control: no supplement	27 weeks to delivery	Birth weight: +37 g (-75, 149)
Gambia Ceesay 1997 (100)	RCT	N = 2047 (undernourished women)	Intervention: 2 biscuits (groundnuts, rice flour, sugar, oil); 2 biscuits =1017 kcal; 22 g protein; 56 g fat; 47 mg calcium; 1.8 mg iron) Control: no supplement	20 weeks to delivery	Birth weight: +136 g (57, 155) Harvest season: +94 g (p<0.01) Hungry season: +201 (p<0.001) LBW: RR 0.61 (0.47, 0.79) SGA: RR 0.65 (0.49, 0.87)
England Elwood 1981 (101)	RCT	N = 1153 (adequately nourished women)	Intervention: Tokens worth ½ pint milk Control: no intervention	Any time in pregnancy to child 5 years of age	Birth weight: +53 g (-6, 112) SGA: RR 0.88 (0.52, 1.50)

Location, Author, Year	Design	Sample (for birth weight analysis)	Study Groups	Supplement duration	Results
India Girija 1984 (102)	RCT	N = 20 (undernourished women)	Intervention: 50 g sesame cake, 40 g jaggery, 10 mL oil (~400 kcal, 30 g protein) Control: no supplement	Third trimester to delivery	Birth weight: +263 g (-101, 627) SGA: RR 0.09 (0.01, 1.45)
Burkina Faso Huybregts 2009 (103)	RCT	N = 1020 (under and adequately nourished women)	Intervention: Fortified spread (33% peanut butter, 32% soy flour, 15% vegetable oil, 20% sugar, vit/min); 72 g = ~400 kcal, 14.7 g protein Control: vit/min only	Any time in pregnancy to delivery	Birth weight: Undernourished: +111 g (-34, 256) Adequately nourished: 19 g (-31, 69) LBW (RR 0.79; 95% CI: 0.52, 1.19) SGA (RR 0.85; 95% CI: 0.65, 1.10)
Iran Kaseb 2002 (104)	RCT	N = 53 (adequately nourished women)	Intervention: Rice milk porridge, lentils, pottage, cheese, yoghurt, eggs, milk, bread (400 kcal; 15 g protein) Control: no supplement	Month 4 to delivery	Birth weight: +220 g (28, 412)
Chile Mardones-Santander 1988 (105)	RCT	N = 429 (undernourished women)	Intervention 1: Fortified powdered milk (~500 kcal, 27.9 g protein per 100 g) Intervention 2: Fortified powdered milk (470 kcal, 14.5 g protein per 100 g)	<20 weeks to delivery	Data for intervention 2: Birth weight: +187 g (69, 306) LBW: RR 0.88 (0.35, 2.24) SGA: RR 0.38 (0.32, 0.45)
USA Metcoff 1985 (106)	RCT	N = 410 (undernourished women)	Intervention: Vouchers for milk, eggs and cheese intended to provide 40-50 g protein and 900-1000 kcal daily. Control: routine care	19 weeks to delivery	Birth weight: +175 g (157, 193)

Location, Author, Year	Design	Sample (for birth weight analysis)	Study Groups	Supplement duration	Results
Colombia Mora 1978 (107)	RCT	N = 407 (undernourished women)	Intervention: 60 g dried skim milk, 150 g enriched bread, 20 g vegetable oil (856 kcal; 38.4 g protein) Control: no supplement	28 weeks to delivery	Birth weight: +51 g (-24, 126) SGA: RR 0.78 (0.37, 1.65)
Gambia Prentice 1987 (108)	Retrospective study	N = 379 (undernourished women)	Intervention: Groundnut biscuits (per 100 g: ~470 kcal, 17.4 g protein, 25.5 g fat + vit/min) and tea drink (~80 kcal, 2.9 g protein, 1.6 g fat + vit/min) Control: no supplement	Any time in pregnancy to delivery	Birth weight: +117 g (61, 173) LBW: RR 0.40 (0.23, 0.69) SGA: RR 0.76 (0.65, 0.90)
South Africa Ross 1985 (109)	RCT	N = 95 (adequately nourished women)	Intervention 1: mixture of beans and maize + vit/min (~800 kcal, 36 g protein) Intervention 2: porridge (dried skimmed milk, maize flour + vit/min (700 kcal, 44 g protein) Control: placebo pill	20 weeks to delivery	Birth weight: +58 g (-139, 255) (intervention groups combined in analysis and compared to control)
USA – Harlem, NY Rush 1980 (110)	RCT	N = 520 (undernourished women)	Intervention 1: 16 oz beverage (~300 kcal, 6 g protein + vit/min) Intervention 2: 16 oz beverage (~500 kcal, 40 g protein + vit/min) Control: vit/min only	≤ 30 weeks to delivery	Data for intervention 1 vs. control: Birth weight: +41 g (-49, 131) SGA: RR 0.70 (0.45, 1.07)

Location, Author, Year	Design	Sample (for birth weight analysis)	Study Groups	Supplement duration	Results
England Viegas 1982 (111)	RCT	N = 142 (adequately nourished women)	Intervention 1: glucose drink w/ iron and vit C (~300 kcal) Intervention 2: glucose drink w/ iron and vit C + chocolate flavored skimmed milk powder (~300 kcal, 11% protein) Control: carbonated water w/ iron and vitamin C	18-38 weeks	Birth weight: -32 g (-194, 130) (intervention groups combined in analysis and compared to control)
England Viegas 1982 (112)	RCT	N = 128 (under and adequately nourished women)	Intervention 1: glucose syrup (425 kcal) + multivitamin sachet Intervention 2: glucose syrup + chocolate flavored skimmed milk powder (10% protein) + multivitamin sachet Control: multivitamin sachet	28-38 weeks	Birth weight: Undernourished: +157 g (-75, 389) Adequately nourished: -118 g (-320, 84) (intervention groups combined in analysis and compared to control)

[1]RCT, randomized controlled trial; LBW, low birth weight; SGA, small for gestational age; RR, relative risk.

One study included in these pooled analyses is a large 5-year randomized controlled trial conducted by Ceesay et al. (100) in rural Gambia. This study looked at the effects of daily supplementation with high-energy groundnut biscuits (2 biscuit serving = ~1000 kcal, 22 g protein, 56 g fat, 47 mg calcium, 1.8 mg iron) starting at 20 weeks gestation on birth size, compared to no food supplement, among 1460 women. The supplemented group had a higher mean birth weight (136 g; $p < 0.001$), lower rate of LBW (OR 0.61; 95% CI: 0.47, 0.79), and a higher average head circumference at birth (3.1 mm; $p < 0.01$). I draw attention to this study for two reasons. First, it showed the effects of supplementation differed according to season, with a substantially greater impact in the "hungry" versus harvest season for birth weight (201 g vs. 94 g), head circumference (3.9 mm vs. 2.5 mm), and birth length (4.1 mm vs. -1 mm). These findings are important because the majority of nutritionally-vulnerable populations in developing countries like Cambodia are subsistence farmers that rely on one annual harvest and experience food shortages when supplies of the preceding harvest are exhausted. Therefore, the effects of undernutrition are usually more severe in the "lean" or "hungry" season. Secondly, this study is of interest because it is an example of a food intervention successfully delivered through the health system at the community level in a rural area in a developing country. The biscuits were prepared by local village women and distributed by birth attendants connected to the health system. This is noteworthy because Cambodia and other countries are grappling with how best to integrate facility and community-based care, including the delivery of nutrition interventions.

Few studies have been published in the past two decades to advance knowledge on the topic of protein-energy supplementation for undernourished populations in developing countries and account for the considerable socio-demographic, lifestyle, environmental, and other changes that have occurred globally and have affected food availability, access, preferences, and general dietary patterns. Of the 16 studies included in Imdad and Bhutta's recent meta-analysis, 13 were conducted during 1973-1990. Nine of the 11 trials included in Ota's recent review were conducted before 1990. These older studies were subject to variable methodological quality and many were determined to have a risk of bias with regard to participant selection, attrition, outcome measurement, and/or analysis of cluster trials.

As Liberato (113) points out, participant selection criteria should be carefully considered when interpreting pooled data. Though greater effects on birth weight were found in undernourished women (101 g) compared to adequately nourished women (23 g) in the Imdad analysis, only five studies used specific anthropometric or other nutrition-related criteria for recruiting undernourished women at study enrollment. Other criteria for identifying eligible study participants, such as geographic or ethnic profiling, socio-economic/poverty data, and or non-specific nutrition indicators such as history of a LBW baby, result in non-comparable populations (113). The resulting varied responses to supplementation potentially distort the outcome effects examined in combined analyses of such studies. As the effects of protein-energy supplementation during pregnancy on birth outcomes have shown to vary in adequately and undernourished women, combining studies conducted in these populations (as both Imdad and Ota did) also poses challenges for drawing conclusions about the overall effects of these interventions. Nonetheless, results generated from such meta-analyses form the basis for inclusion of protein-energy supplements as one of the 10 core interventions recommended in the 2013 Lancet series on maternal and child nutrition (114).

Since the early studies involving prenatal protein-energy supplements more than 30 years ago, three fundamental shifts have influenced international nutrition research: (i) the widespread recognition of the first 1000 days as the critical window for safeguarding human health and development; (ii) an increased interest in fetal programming and the association between birth outcomes and adult chronic disease based on emerging data from longitudinal studies (115-116); and (iii) increased knowledge and understanding of the roles of specific micronutrients in pregnancy, the topic of the next section.

1.2.3.2 Multiple Micronutrient Supplementation

Requirements for vitamins and minerals increase during periods of heightened physiological need, such as pregnancy. In addition to iron, vitamin A, the B vitamins, vitamin C, and folate are important during gestation due to their roles in immune function, energy metabolism, lipid and nucleic acid synthesis, hemoglobin synthesis, and other functions (117-119). As these nutrients cannot be synthesized in the body, needs are met through dietary sources, which is a problem for individuals with diets limited in naturally micronutrient-rich and fortified foods. Extensive basic science, epidemiological, and experimental research has been done in recent years to better understand the role of specific nutrients, causes and consequences of deficient states, and strategies that may be effective for addressing them. Further, with the establishment of the Millennium Development Goals (120) in 2000 came a greater call to address the unmet nutritional needs of women and children. It became widely thought that the persistently high rates of undernutrition in developing countries were due to micronutrient needs being unaddressed in these populations (121). This broadened the scope of micronutrient supplementation beyond iron and folic acid, based on the notion that repletion of just these nutrients is not sufficient to improve maternal and infant nutrition where multiple concurrent deficiencies exist.

Development of the UNICEF/WHO/United Nations University International Multiple Micronutrient Preparation (UNIMMAP) supplement in 1999 spearheaded the work on prenatal multiple micronutrient supplementation (MMS) in developing countries (122). UNIMMAP contains 15 micronutrients and includes a lower dose of iron (30 mg), compared to the routinely provided 60 mg dose in IFA supplements (122). With the exception of iron, it was developed to provide one recommended dietary allowance (RDA) for pregnant women. The effects of UNIMMAP were assessed in nine efficacy trials that involved approximately 50,000 women in eight developing countries (Bangladesh, Burkina Faso, China, Guinea-Bissau, Lombok Indonesia, Indramayu Indonesia, Nepal, Niger, Pakistan) during 2001 to 2006 (123). These studies were designed to generate evidence on the comparative advantage of prenatal UNIMMAP versus IFA, with a view to potential replacement of IFA in developing countries. Meta-analyses of these trials, specific to the outcome(s) examined, were commissioned by the UN agency partnership in 2005. Two of these pooled analyses on maternal anemia and birth size are discussed here.

In a meta-analysis of 13 studies that included four UNIMMAP trials (Guinea-Bissau, Indramayu Indonesia, Nepal, Pakistan) and nine studies that used other multiple micronutrient formulations, Allen et al. (124) looked at the effects of MMS on hemoglobin (Hb) concentration, serum ferritin, and anemia status in pregnancy. In the pooled analysis, MMS did not increase Hb (11 studies), increase serum ferritin (10 studies), or reduce the risk of anemia (4 studies) compared to iron supplements, with or without folic acid. The MMS and iron supplements produced comparable effects on these three outcomes, despite the MMS containing half the amount of iron (30 mg) as the control (60 mg) in the four UNIMMAP trials. Though there was no overall difference in Hb concentration with MMS, three of the individual studies showed a significant effect - two positive (125-126) and one negative (127). One of the studies that showed a positive effect on Hb in Tanzania is discussed below, along with a study in Mexico that showed a negative effect of MMS on Hb concentration.

In a placebo-controlled randomized trial conducted by Makola et al. (125) in Tanzania (n=259), MMS was provided in the form of a micronutrient-fortified powder (to be mixed with water) containing 11 micronutrients (2 daily servings = 10.8 mg iron). Women in the MMS and control (unfortified powder) groups also received 60 mg iron and 500 μg folic acid through routine ANC. The MMS produced a 4.2 g/L increase in Hb concentration, a 4.5 μg/L increase in ferritin, and a 51% reduction in risk of anemia. Moreover, a 70% reduction in risk of iron deficiency was observed in MMS-supplemented women who were iron-deficient at baseline (12-34 weeks gestation). The fortified powder (2 serving daily ration) contained more than twice the amount of vitamin C and vitamin B12 and 30% more vitamin A than the UNIMMAP which, along with the potentially positive effects of other nutrients such as riboflavin, was posited by the authors as one reason for the increase in Hb and related decrease in anemia. Supplementation with the MMS or placebo occurred for 8 weeks. Of the 259 women, ~70% reported consuming at least 90% of the intended dose of powder sachets. However, adherence to IFA was low in both groups as $< 1\%$ reported taking IFA supplements at study entry and ~30% took them at some point during the study, mainly the result of poor distribution. Therefore, the IFA likely had little impact on the study outcomes. The high 44% and 38% loss to follow-up in the intervention and placebo group, respectively, is a major limitation of the study and was mainly due to delivery prior to completion of the supplementation period. As mentioned, women were recruited between 12 and 34 weeks gestation, which presumably altered the response to supplementation.

In contrast to this positive result of MMS in Tanzania, a negative effect on average Hb (MMS 104.2 g/L vs. iron 108.1 g/L; $p < 0.01$) was observed at 32 weeks gestation in a trial conducted by Ramakrishnan et al. (127) in Mexico (n=453) that compared MMS and iron-only (60 mg) control supplements. The two supplements contained similar amounts of iron - 62 mg in the MMS and 60 mg in the iron control. Women were supplemented beginning in the first trimester and the duration of supplementation averaged 29 weeks. Compliance was high (average ~90%) in both groups. There are a few characteristics of this study worthy of mention. First, about 30% of the study population was overweight in the first trimester, as determined by BMI. Second, relationships were observed between anemia prevalence, iron deficiency, and iron deficiency anemia at baseline and 32 weeks gestation. At baseline, average serum ferritin was higher in the MMS group (14.5 µg/L vs. 9.7 µg/L; p=0.03), corresponding to a 13% lower prevalence (44% vs. 57%) of iron deficiency (serum ferritin < 12 µg/L) in the MMS group. Most women (> 90% in both groups) were iron-deficient at 32 weeks, while anemia prevalence increased from ~14% at baseline to > 40% at 32 weeks in both groups. In the analysis adjusted for the baseline difference in serum ferritin, higher risks of anemia and iron deficiency anemia were apparent in the MMS group at 32 weeks.

A possible explanation suggested by the authors for the lack of hematologic response to MMS supplementation was a likely low prevalence of vitamin A, B12, folate, and other deficiencies in the study population, which could have attenuated the treatment effect. Though this makes sense when considering the higher prevalence of iron deficiency compared to anemia prevalence and the fact that > 90% of women were iron-deficient at 32 weeks gestation, what is puzzling about these findings is that rates of iron deficiency increased by 47% and 36% in the MMS and iron-only groups, respectively, at 32 weeks, despite iron supplementation started in early pregnancy. It would seem that the effects of nutrients in the MMS such as vitamin C (66.5 mg/dose) would have exerted some positive impact on iron levels. As both groups received the same amount of iron and compliance was high, it is important to consider the possible interactions between nutrients in the MMS that could have inhibited iron absorption, as previously described in the literature (118), particularly zinc (mentioned by the authors) by virtue of its shared DMT-1 receptor in the duodenum. A relatively high dose of magnesium was included in the MMS (252 mg/dose) in this study in Mexico. In contrast, magnesium is not included in the UNIMMAP supplement and only 10 mg/dose was included in another MMS formulation containing magnesium used in a study in Nepal (128). Though unlikely to cause a reduction in non-heme iron absorptive capacity at moderate levels, I felt it was important to highlight this difference, given the magnesium dose was 25 times higher in the Mexico study. An important study limitation mentioned in the paper is the potential bias that occurred due to the higher percentage of anemic women at baseline who were lost to follow-up in the MMS group (17%), compared to the iron-only control group (7%). Finally, it is unusual that different cutoffs were used to assess anemia at baseline (< 13 weeks) and at 32 weeks - Hb < 110 g/L and Hb < 105 g/L, respectively, in the Mexico study.

In summary, from their meta-analysis of 13 studies conducted in developing countries, Allen et al. concluded: (i) MMS and IFA produced similar effects on hemoglobin, anemia, and iron status; (ii) 60 mg of iron was not more effective than 30 mg (UNIMMAP dose) for improving hemoglobin or iron status; and (iii) the additional micronutrients in the MMS did not appear to reduce the effects of iron supplementation. These findings are supported in a more recent meta-analysis by Haider et al. (129) which showed that MMS and IFA produced similar effects on the risk of maternal anemia in the third trimester (RR 1.03; 95% CI: 0.87, 1.22). This result was based on data from four trials conducted in China (130), Mexico (127), and Nepal (128, 131), three from which data were included in Allen's meta-analysis.

With regards to the effects of MMS on birth outcomes, a pooled analysis by Fall et al. (121) that included the nine UNIMMAP trials plus three that used similar formulations showed a mean birth weight increase of 22 g (95% CI: 8.3, 36.4; range: 5-75 g) in babies of MMS-supplemented mothers compared to a control. Marginal reductions in risk were also observed for LBW (OR 0.89; 95% CI: 0.81, 0.97) and SGA (OR 0.90; 95% CI: 0.82, 0.99). However, the meta-analysis did not reveal a significant difference in birth length or head circumference, nor was this observed in any of the 11 and 10 individual studies that measured these outcomes, respectively. Further, MMS did not increase average gestational age at delivery or reduce the risk of preterm birth in the pooled analysis. Interestingly, a mean increase of 39 g (95% CI: 22, 56) in birth weight occurred in babies born to women with a higher BMI ($\geq$ 20 kg/m^2) and a negative effect (-6 g; 95% CI: -9, 17) was observed in those born to women with BMI < 20 kg/m^2. The authors postulate this being due to micronutrients not being effectively utilized in energy-deficient women as they may lack the ability to metabolize/absorb them. Key characteristics of the 12 studies from which data were extracted and combined in Fall et al.'s meta-analysis are presented in Table 1.3.

Table 1.3 Studies included in the Fall et al meta-analysis[1]

Location Author, Year	Design	Sample (for bw analysis	Study Groups	Supplement Duration	Results
Bangladesh Tofail 2008 (132)	RCT	N = 1818	Intervention: UNIMMAP Control: 30 mg iron + 400 µg folic acid	2^{nd} trimester to delivery	Birth weight: +11 g (-27, 49) LBW: RR 0.86 (0.71, 1.05) SGA: RR 0.89 (0.66, 1.22)
Burkina Faso Roberfroid 2008 (133)	RCT	N = 1052	Intervention: UNIMMAP Control: 60 mg iron + 400 µg folic acid	Any time to 3 months postpartum	Birth weight: +52 g (4, 100) LBW: RR 0.84 (0.58, 1.20) SGA: RR 0.83 (0.65, 1.07)
China Zeng 2008 (130)	RCT	N = 4421	Intervention 1: UNIMMAP Intervention 2: 60 mg iron + 400 µg folic acid Control: 400 µg folic acid	<28 weeks to delivery	Data for UNIMMAP: Birth weight: +42 g (7, 78) LBW: RR 0.78 (0.56, 1.08) SGA: RR 0.95 (0.82, 1.12)
Guinea-Bissau Kaestel 2005 (134)	RCT	N = 1100	Intervention 1: UNIMMAP Intervention 2: 2 RDA of 14 micronutrients in UNIMMAP + 30 mg iron Control: 60 mg iron + 400 µg FA	<37 weeks to delivery	Birth weight: MMS1: +47 g (-24, 119) MMS2: +69 g (-2, 140) LBW: MMS1: RR 0.88 (0.57, 1.37) MMS2: RR 0.70 (0.44, 1.11)
Indonesia (Indramayu) Sunawang 2009 (135)	RCT	N = 745	Intervention: UNIMMAP Control: 60 mg iron + 250 µg folic acid	12-20 weeks to 30 days postpartum	Birth weight: +41 g (-22, 103) LBW: RR 0.84 (0.47, 1.50)
Indonesia (Lombok) Shankar 2008 (136)	RCT	N = 11101	Intervention: UNIMMAP Control: 30 mg iron + 400 µg folic acid	any time to 90 days postpartum	Birth weight: +21 g (-11, 53) LBW: RR 0.86 (0.73, 1.01)

Location Author, Year	Design	Sample (for bw analysis	Study Groups	Supplement Duration	Results
Mexico Ramakrishnan 2003 (137)	RCT	N = 633	Intervention: 62 mg iron + 12 micronutrients Control: 60 mg iron	<13 weeks to delivery	Birth weight (mean ± SE): 16.1 ± 31 g (p=0.60) LBW: OR 0.98 (0.55, 1.74)
Nepal (Sarlahi) Christian 2003 (128)	RCT	N = 4130	1) 400 µg FA + 1000 µg vit A 2) 400 µg FA + 60 mg iron + 1000 µg vit A 3) 400 µg FA + 60 mg iron + 30 mg zinc + 1000 µg vit A 4) #3 + 11 other micronutrients Control: 1000 µg vit A	1st trimester to 12 weeks postpartum	Data for Intervention 4: Birth weight: +64 g (12, 115) LBW: RR 0.86 (0.74, 0.99) SGA: RR 0.95 (0.87, 1.04)
Nepal (Janakpur) Osrin 2005 (131)	RCT	N = 1052	Intervention: UNIMMAP Control: 60 mg iron + 400 µg folic acid	≤20 weeks to delivery	Birth weight: +77 g (24, 130) LBW: OR 0.69 (0.52, 0.93)
Niger Zagre 2007 (138)	RCT	N = 2550	Intervention: UNIMMAP Control: 60 mg iron + 400 µg folic acid	1st trimester to delivery	Birth weight: +48 g (33, 62) LBW: UNIMMAP 7.2%; IFA 8.4% (p <0.001)
Pakistan Bhutta 2009 (139)	RCT	N = 1538	Intervention: UNIMMAP Control: 60 mg iron + 400 µg folic acid	<16 weeks to delivery	Birth weight: +70 g (p=0.01) LBW: UNIMMAP 17.7%; IFA 19.6% (p=0.17)
Zimbabwe Friis 2004 (140)	RCT	N = 1106	Intervention: 13 micronutrients with IFA through health system Control: placebo + routine IFA through health system	22–35 weeks to delivery	Birth weight: +49 g (-6, 104) LBW: 0.84 (0.59, 1.18)

[1]RCT, randomized controlled trial; FS, food supplementation; UNIMMAP, UNICEF/WHO/UNU International Multiple Micronutrient Preparation; RDA, recommended daily allowance; MMS, multiple micronutrient supplement; LBW, low birth weight; SGA, small for gestational age; RR, relative risk; OR, odds ratio.

The study conducted by Kaestel et al. (134) in Guinea-Bissau is interesting due to its unique characteristics, as are the two Nepal studies (128, 131) which found conflicting results in similar populations. In the Guinea-Bissau trial, two MMS were used: (i) the UNIMMAP containing 1 RDA of 14 micronutrients + 30 mg iron; and (ii) a supplement containing 2 RDA of the same 14 micronutrients + 30 mg iron. The effects of these formulations were compared with a control supplement (60 mg iron + 400 µg folic acid) among ~1100 babies born to ~1700 women enrolled at < 37 weeks gestation (average 22 weeks). Mean birth weight was non-significantly higher in the standard UNIMMAP (1 RDA) group (47 g; 95% CI: -24, 119) and significantly higher in the 2 RDA group (69 g; 95% CI: -2, 140), compared to the IFA control. This was reflected in the rates of LBW - UNIMMAP 12%, 2 RDA 10%, and control 14% - though these did not significantly differ (p=0.33). The effect of the 2 RDA supplement on birth weight was greatest among the ~30% of women who were anemic at baseline, with a large 218 g (95% CI: 81, 354) increase compared to anemic controls. This was apparent in the large (69%) reduction in risk of LBW in moderately anemic women (OR 0.31; 95% CI: 0.13, 0.73). Supplement compliance was similar and above 70% in all three groups and gestational age at enrollment did not pose an interaction effect on birth weight (p=0.39). These findings are indicative of a dose–response relationship, given the larger health effects produced with a doubling of the UNIMMAP nutrient composition (except for iron), and suggest benefits of providing supplemental micronutrients in addition to iron for improvements in birth size, particularly in anemic women.

The two Nepal studies conducted in Sarlahi and Janakpur included in both the Allen and Fall meta-analyses produced contrasting results in similar populations. Christian et al.'s (128) large study in Sarlahi compared five groups: (i) folic acid (400 µg) + vitamin A (1000 µg); (ii) folic acid (400 µg) + iron (60 mg) + vitamin A (1000 µg); (iii) folic acid (400 µg) + iron (60 mg) +

zinc (30 mg) + vitamin A (1000 µg); (iv) a MMS [15 micronutrients including folic acid (400 µg) + iron (60 mg) + zinc (30 mg) + vitamin A (1000 µg)]; and (v) a vitamin A control (1000 µg). The MMS provided 1 RDA for pregnant women, except for a double dose of iron (60 mg) and zinc (30 mg) as compared to the UNIMMAP. Average gestation at enrollment was about 11 weeks in all groups and median compliance with supplementation was approximately 90% in all groups. Among ~4000 infants, average birth weight increased by 37 g (−16, 90) in the folic acid + iron + vitamin A group and by 64 g (12, 115) in the MMS group, which resulted in respective LBW reductions of 16% (RR 0.84; 95% CI: 0.72, 0.99) and 14% (RR 0.86; 95% CI: 0.74, 0.99) in the two groups. Based on this, the authors concluded that MMS did not offer an advantage over IFA for reducing the incidence of LBW. As in the Guinea-Bissau study, no effect was observed on preterm birth in this study in Nepal.

Osrin et al.'s (131) trial in Janakpur Nepal compared the effect of prenatal UNIMMAP to IFA (60 mg iron + 400 µg folic acid) on birth weight among ~1000 babies born to women enrolled at < 20 weeks gestation. In contrast to Christian's study above, a higher average birth weight was observed in the MMS group (77 g; 95% CI: 24, 130), resulting in a greater reduction in incidence of LBW (RR 0.69; 95% CI: 0.52, 0.93). In Osrin's study, the prevalence of LBW was 25% in the control group, 18% lower than in Christian's study. Interestingly, mean birth weight was 130 g higher in babies born to MMS-supplemented women with BMI ≥ 18.5 kg/m^2, compared to MMS-supplemented women with a low (< 18.5 kg/m^2) BMI (2845 g vs. 2715 g). Among women with normal weight-for-height, average birth weight was 83 g higher (95% CI: 20, 146) in the MMS group compared to the control group. Among those with low BMI, average birth weight was 54 g higher (95% CI: –43, 152) in the MMS-supplemented group compared to the IFA controls. The authors attributed the larger effect of MMS on birth weight in women with a higher

BMI to babies of heavier women having greater fetal growth potential. Median supplement adherence was 97% and 98% in the MMS and control groups, respectively. As in the Guinea-Bissau and Nepal-Sarlahi studies, no difference was observed in gestational age at delivery or preterm birth between groups in this study in Nepal.

The more pronounced effect of MMS on birth weight in heavier women was a consistent finding of the studies included in Fall et al.'s meta-analysis. An explanation put forth by the authors is it may be that thinner women are unable to metabolize micronutrients as efficiently as those who are better nourished. It is well-established that women with a higher BMI tend to deliver babies with higher birth weights, compared to thinner women who generally carry smaller babies (36, 129, 141). This can be explained by the partitioning of energy that occurs between mother and child, with greater maternal fat deposition in energy-deficient women, and is the basis for the higher maternal weight gain recommendations for women with low BMI in early pregnancy (39). It is also noteworthy that Osrin et al. observed a larger average birth weight among multiparous women in the MMS group compared to primiparous women (104 g vs. 50 g). These findings are consistent with Roberfroid et al.'s (133) UNIMMAP study in Burkina Faso that showed a positive effect of MMS on birth weight in multiparous women (71 g) and in women with BMI ≥ 22 kg/m^2 at entry to pregnancy (119 g; p = 0.01).

It is informative to briefly comment on the Lombok, Indonesia trial conducted by Shankar et al. (136) as it was the largest of the UNIMMAP studies and included an analysis of ~11,000 live births. This study is also of interest because the control group was provided 30 mg iron and 400 µg folic acid, which is half the dose of iron provided as a control in most of the other studies. Women were enrolled at any time during pregnancy and were supplemented to 90 days postpartum. A 21 g increase in average birth weight (95% CI: -11, 53) occurred in the

UNIMMAP group, which corresponded to a non-significant 14% reduction in LBW (RR 0.86; 95% CI: 0.73, 1.01). However, significant effects were seen for birth weight (52 g; p=0.02) and LBW (RR 0.67; 95% CI: 0.51, 0.89) in women who were anemic at enrollment. In both groups, ~30% of women who enrolled in the first trimester were anemic and this approached 60% in both groups for women enrolled in the second and third trimesters. Women who had a mid-upper arm circumference (MUAC) ≥ 23.5 cm had a 37 g increase in birth weight (p=0.04) and a borderline reduction in LBW (RR 0.82; 95% CI: 0.67, 1.00), with no effects among women with MUAC < 23.5 cm. These positive results on birth size in anemic women and in energy-sufficient women (using MUAC as a proxy) following MMS supplementation are consistent with the studies described previously and highlight the potential contributions of micronutrients in the UNIMMAP, other than iron and folic acid, to the observed increase in birth size. Similar to the other studies, compliance with supplementation was high (median > 80%) in both groups.

The main objective of this large study conducted by Shankar et al. in Indonesia was to look at the effects of MMS on early infant mortality (90 days postpartum). A significant reduction in early infant mortality was observed in the MMS group (RR 0.82; 95% CI: 0.70, 0.95). It is noteworthy that among MMS-supplemented women with MUAC < 23.5 cm, there was a 25% reduction in risk of early infant mortality (RR 0.75; 95% CI: 0.62, 0.90), with no reduction in women with MUAC ≥ 23.5 cm. Also, a 38% reduction in risk of early infant mortality was observed in anemic (Hb < 110 g/L) women (RR 0.62; 95% CI: 0.49, 0.78), with no significant reduction in non-anemic women. I have commented on the mortality outcome because I found it curious that improved survival occurred despite no increase in birth weight, reduction in risk of LBW, or reduction in preterm birth. The authors speculate the reduction in early infant mortality was due to the physiological, metabolic, and other benefits of MMS that extend beyond birth size, especially in undernourished women. This is supported by other evidence suggesting positive postnatal effects of maternal micronutrient supplementation (142-144).

Despite the heterogeneity of studies included in the Fall meta-analyses with respect to study population characteristics, composition of the intervention and control supplements, and the duration of supplementation, the individual studies were high quality RCTs conducted in low-income countries and, therefore, provide a wealth of data on the effects of MMS in undernourished populations in developing countries. The following points summarize the key findings of these studies: (i) compliance with both MMS and IFA was high; (ii) the effect of MMS on birth weight was greater in heavier women; (iii) the effect of MMS on birth weight was greater in anemic women; (iv) MMS may have benefits beyond birth size, including improving early infant survival; and (v) MMS did not have an effect on gestational age at delivery or preterm birth, suggesting the effect on birth weight was due to improved fetal growth, rather than a longer gestation. Finally, the UNIMMAP contains 1 RDA of each micronutrient, which has been set to meet the needs of most healthy women in the United States. As shown in the Guinea-Bissau study, higher doses at safe limits may be more effective in similar settings due to the poorer nutritional status of women prior to and during pregnancy in these contexts because of diet and infection.

Positive effects on birth size, in terms of reductions in LBW and SGA, were also shown in more recent studies (145-148) that looked at the efficacy of a variety of MMS to build on the evidence generated from the UNIMMAP trials. These studies pooled data from the UNIMMAP trials, as well as other MMS studies, and included populations from both low and middle-income countries. In their 2012 Cochrane review of 21 studies (12 UNIMMAP trials) involving ~75,000 women recruited from early pregnancy to 36 weeks gestation, Haider et al. (148) showed reductions in LBW (RR 0.89; 95% CI: 0.83, 0.94; 14 studies) and SGA births (RR 0.87; 95% CI: 0.81, 0.95; 14 studies) among MMS-supplemented women, compared to IFA-supplemented controls. The effects of MMS on LBW and SGA were significant in women with BMI ≥ 20 kg/ m^2 [RR 0.88; 95% CI: 0.81, 0.96 for LBW and RR 0.85; 95% CI: 0.79, 0.91 for SGA]. A similar effect was observed in taller women. Those with average height ≥ 154.9 cm had a lower risk of LBW (RR 0.85; 95% CI: 0.76, 0.94) compared to shorter women < 154.9 cm (RR 0.90; 95% CI: 0.77, 1.04). Similarly, taller women had a lower risk of SGA (RR 0.82; 95% CI: 0.76, 0.89) compared to shorter women (RR 0.97; 95% CI: 0.90, 1.04). These findings corroborate those of Fall et al. as they show a greater effect of MMS on birth size in larger/heavier women. As there was no difference in the rate of preterm birth, the reductions in LBW and SGA were also likely mediated through improved fetal growth, rather than a longer gestation.

Finally, in a very large recently-published study that looked at the effects of multiple micronutrient supplementation on birth and postnatal outcomes in ~30,000 infants in Bangladesh, West et al. (149) compared prenatal supplementation with UNIMMAP to an IFA control (27 mg iron + 600 µg folic acid) from early pregnancy to 12 weeks postpartum. In this large study, compliance with supplementation was high as 80% of women in both groups reportedly took more than 80% of their tablets. An increase in mean birth weight (54 g; 95% CI: 41, 66), decreased risk of LBW (RR 0.88; 95% CI: 0.85, 0.91), and small increases in birth length (0.20 cm; 95% CI: 0.13, 0.27) and head circumference (0.20 cm; 95% CI: 0.15, 0.25) were observed in the MMS group. These effects on birth weight and LBW are consistent with the aforementioned studies. However, in contrast to the other studies hitherto described, a significant reduction was observed in preterm birth among MMS-supplemented women (RR 0.85; 95% CI: 0.80, 0.91) in this study in Bangladesh, reflected in a longer average gestation

(0.30 wk; 95% CI: 0.21, 0.40). As no difference was observed in SGA (RR 0.98; 95% CI: 0.96, 1.01) between the UNIMMAP and IFA groups, in contrast to Haider's and other studies, the larger babies born to MMS mothers was likely due to fewer preterm births in this group. Despite the increase in birth weight and reduction in preterm births, no effect was found on neonatal (≤ 28 days) or postneonatal (29-180 days) mortality. Though the authors are unclear as to the reason for this lack of observed effect on mortality, they state it "*may reflect a complex interplay between maternal and newborn sizes and differential responses to supplementation by causes of death*" (149; p. 2657). The authors attribute the gains in fetal growth and birth size to the potential benefits of MMS for reducing maternal, placental, and fetal inflammation through improved immune function and for increasing oxidative metabolism, which is required for energy production. A lower risk of infant mortality (up to 6 months) due to diarrheal disease and sepsis was observed in babies of MMS-supplemented mothers, suggesting a protective effect from infection and resulting inflammation.

In summary, the scientific evidence surrounding the use of MMS supports their potential value in increasing birth weight by improving fetal growth and reducing preterm birth. Though the comparative advantage of MMS over IFA for maternal anemia control is debated, if MMS are shown to be as effective as IFA (with half the iron dose) and confer other benefits such as improving immune function, then it seems prudent to expand the scope of maternal micronutrient supplementation beyond IFA in developing countries. That being said, as the effects of MMS have consistently shown to be greater in women with normal weight-for-height (BMI), then it would seem providing energy-deficient women with a mixture of macro and micronutrients is a better approach for achieving gains in maternal, newborn, and infant health. This is the topic of the next section.

1.2.3.3 Micronutrient-fortified Protein-energy Supplementation

Micronutrient-fortified protein-energy supplements are a strategy to enable pregnant women to meet their additional nutritional needs through dietary means. Such products have been developed based on the recognition that both macro and micronutrient deficiencies concomitantly exist in most undernourished populations in developing countries, and so protein-energy or micronutrients, alone, will only partially address the problem of maternal undernutrition in these contexts. Few well-designed studies have looked at the potential of fortified food supplements to improve pregnancy outcomes. Some are included in the meta-analyses described in section 1.2.3.1. However, it is necessary to more closely examine the related evidence in a separate discussion, as these products are most similar to the Corn Soya Blend Plus supplement used in my study.

A study conducted by Huybregts et al. (103) in Burkina Faso investigated a fortified food supplement (FFS) in the form of a spread consisting of 33% peanut butter, 32% soy flour, 15% vegetable oil, and 20% sugar that was fortified with a micronutrient premix equal to the UNIMMAP. A single dose (72 g) provided ~370 kcal, 14.7 g protein, and 27.6 g fat. The FFS was administered prenatally to women in rural Burkina Faso and effects on birth size were compared to a control group that received the UNIMMAP single daily tablet. Among ~1300 women who were enrolled at any time during gestation, compliance was about 75% in both groups. Average birth weight did not significantly differ (31g; 95% CI: -16, 78), nor was there a significant reduction in LBW (RR 0.79; 95% CI: 0.52, 1.19) or SGA (RR 0.85; 95% CI: 0.65, 1.10) in the FFS group. Babies born to women in the FFS group had a small, but significant, increase in birth length (4.6 mm; 95% CI: 1.8, 7.3), though this was only a significant result for multiparous women. Interestingly, the effect of FFS on birth length was greater in mothers who were underweight (low BMI) at enrollment (12.0 mm; 95% CI: 3.7, 20.2) and in women who were anemic at enrollment (7.3 mm; 95% CI: 2.7, 11.8). Though not statistically significant, the larger effects of FFS on birth weight in underweight women (111 g vs. 19 g) and in anemic women (49 g vs. 3 g) are noteworthy.

This study is important because it is one of very few that have shown a significant effect of FFS on birth length, an indicator of stunting in early life. Though the authors are uncertain as to the reason for this positive effect on birth length, they speculate it may be due to the micronutrients being provided in a high-fat food (67% of total energy). In a prior study (133) conducted by one of the authors in the same area in Burkina Faso that compared prenatal supplementation with UNIMMAP to IFA, birth length was significantly higher in the UNIMMAP group (3.6 mm; 95% CI: 0.8, 6.3) though, as in this study, was only significant in multiparous women. Thus, the posited assertion of a "boosted" effect of micronutrients in foods with a high fat content seems plausible and is supported by evidence showing a positive association between maternal dietary fat intake and birth length in India (150-151). Adding to this is the requisite fat intake for absorption of the four fat-soluble vitamins, three of which are contained in the UNIMMAP (vitamins A, D, E). In countries faced with serious nutrition challenges like Burkina Faso and Cambodia, fat intake for the majority of pregnant women is well below the recommended daily minimum of 20% of dietary energy (80).

A study conducted by Persson et al. (152) in Bangladesh is unique and interesting in that it involved comparing the effects of "early" versus "late" prenatal food supplementation, combined with a MMS, on maternal anemia and birth outcomes in ~ 3000 infants. Six groups were compared: food supplementation (FS) that began after pregnancy was detected plus UNIMMAP; early FS + 30 mg iron + 400 μg folic acid; early FS + 60 mg iron + 400 μg folic acid; and three groups that started FS at the time of their choosing, with each of the three respective micronutrient regimens. The daily FS consisted of a roasted rice powder (80 g), pulse powder (40 g), molasses (20 g), and soybean oil (12 mL) to be mixed with water and provided ~600 kcal and 18 g of protein. The MMS regimens started at 14 weeks gestation for women enrolled by then, or at the start of participation for later enrollees. Gestational age at enrollment averaged 9.3 to 9.5 weeks across the six groups. No significant differences were observed in Hb concentration ($p=0.97$) between the three micronutrient groups at 30 weeks gestation and no difference in anemia prevalence was noted across the six groups at this time point ($p=0.57$). Birth weight also did not differ across the six groups ($p=0.35$), the three micronutrient groups ($p=0.52$), or between early and late food supplementation ($p=0.27$). Birth length ($p=0.26$), head circumference ($p=0.18$), and gestational age at birth ($p=0.18$) were also similar across the six groups. Compliance with the MMS was significantly lower than the IFA regimens.

Despite no differences in newborn anthropometry, babies born to mothers who received early FS + UNIMMAP had lower risks of neonatal, infant, and under 5 mortality, as expressed by hazard ratios of 0.31 (95% CI: 0.13, 0.72), 0.38 (95% CI: 0.18, 0.78) and 0.34 (95% CI: 0.18, 0.65), respectively, compared to the late FS + 60 mg iron + 400 µg folic acid (reference) group. The lack of impact on birth size, but increased child survival is very interesting and points to other factors that may exert positive fetal, neonatal, and/or infant effects that are independent of birth size. The protective effects of micronutrients against neonatal infection and the potentially fatal stresses neonates experience during birth are explanations given by the authors for the lower rates of perinatal infection and asphyxia observed in the early FS + UNIMMAP group. These findings highlight the potential benefits of starting nutritional interventions, in this case protein-energy and micronutrient supplements, early in pregnancy and, similar to the West study described in section 1.2.3.2, draw attention to nutritional factors that may promote neonatal and infant survival apart from weight at birth. The FS + MMS study in Bangladesh has huge programmatic implications for countries where local production of fortified food supplements is challenging and non-traditional externally-provided fortified foods are not available or acceptable. Protein-energy foods produced in-country using local ingredients and micronutrient supplements delivered as dual concurrent strategies, as in this Bangladesh study, may be a viable policy option for such contexts.

The Huybregts and Persson studies described here used two different approaches for providing prenatal macro and micronutrient supplementation. Huybregts showed positive effects of a fortified peanut-soy supplement on newborn length and a trend toward increased birth weight, as compared to the UNIMMAP tablet, but no effect on neonatal mortality. In contrast, Persson showed no difference in birth size, but an improvement in postnatal survival among babies born to women provided supplementary food early in pregnancy in addition to the UNIMMAP tablet. Though it is difficult to speculate why these studies produced different impacts, the much higher fat content of the spread versus the rice-pulse powder (67% vs. 9%) and the fact that women received MMS earlier in the Persson study are major differences that shed light on the conceivable benefits of increasing maternal fat intake and starting women on MMS early in pregnancy. Lipid-based nutritional supplements are gaining more attention due to evidence suggesting improvements in birth anthropometry and acceptability among pregnant women (153-154). Whether MMS should be provided through a food vehicle as in the Huybregts study, or as a separate pharmacological formulation provided concomitantly with a protein-energy supplement as in the Persson study, is unclear. Corn Soya Blend Plus, the fortified food supplement used in my intervention trial, is an example of a combined product and is discussed in the next section.

1.2.3.4 Commodities Used in Global Food Assistance Programs

Access to sufficient quantity and quality of food at all times is considered a basic human right, as stated in 1999 by the United Nations Committee on Economic, Social and Cultural Rights (155): “The right to adequate food is realized when every man, woman and child, alone or in community with others, has physical and economic access at all times to food (in a quantity and quality sufficient to satisfy the dietary needs of individuals, free from adverse substances, and acceptable within a given culture) or means for its procurement” (155; p. 1). This follows from the Committee’s declaration of "the fundamental right to freedom from hunger and malnutrition" (155; p. 1). For decades, international agencies have provided food aid to reduce hunger as part of humanitarian relief efforts in crisis settings. In the more recent past, food assistance has broadened to include the provision of supplementary foods to vulnerable populations such as pregnant women and young children in non-emergency areas with high rates of poverty, food insecurity, and undernutrition (156). Foods used in these targeted programs are intended to fill the gaps created by nutritionally-poor staple diets and are meant to supplement daily foods to meet nutritional requirements. This contrasts to emergency situations where donated foods comprise the majority, if not all, of daily food intake. Aside from direct food transfers, food-based assistance in non-emergency contexts can be provided in the form of food-for-work, monetary transfers, and voucher systems to support broader development efforts in poor populations in developing countries (156). Food commodities provided as direct transfers mainly consist of micronutrient-fortified flours containing either maize or wheat and a pulse (typically soya). These products, known as fortified-blended-foods (FBF), are intended to be mainly consumed as gruels or porridges.

FBFs were developed in the 1960s to address the needs of malnourished children and have continued to be the mainstay of food aid programs to date (157). Corn Soya Blend (CSB) is an energy-dense, micronutrient-fortified maize and soybean flour that has been used for decades by the United Nations World Food Programme (WFP) and US government, the largest procurers and distributors of global food assistance. More recently, an improved version of CSB called Corn Soya Blend Plus was introduced into food aid programs. This product was developed to deliver an enhanced micronutrient profile for pregnant women and young children (158). Studies involving CSB supplementation are limited to a few trials conducted in children comparing it to energy-dense ready-to-use foods for treating moderate acute malnutrition, including studies in Malawi, Niger, and Ethiopia (159-162).

The WFP began distributing CSB in Cambodia in 2002. In 2011, CSB was replaced with CSB Plus in WFP's supplementary feeding programs for pregnant and lactating women (PLW) and young children in five provinces with active WFP operations in Cambodia. Kampong Chhnang (location of my study) was not part of WFP's food supplementation program. In Cambodia, the WFP provides food transfers to all individuals within a specific target group (e.g., PLW) in geographic areas selected based on economic and nutrition indicators (163). The provision of non-emergency food assistance to all persons in a specific physiological/age category, irrespective of their individual nutritional status, is known as blanket supplementary feeding (156). CSB Plus is comprised of 75-80% maize and 20-25% soya and is fortified with a pre-mix containing 19 vitamins and minerals (Table 1.4) (164). As shown in Table 1.4, there are some notable differences between the micronutrient composition of a single daily ration (200 g) of CSB Plus and one daily UNIMMAP tablet, specifically with regards to mineral content.

Table 1.4 Nutrient composition of CSB Plus flour and UNIMMAP tablet

Nutrient	CSB Plus (200 g dry matter)	UNIMMAP (1 tablet)
Energy	760 kcal	0
Protein	28 g	0
Fat	5 g	0
Vitamin A	3328 IU	800 µg RE
Thiamine	0.256 mg	1.4 mg
Riboflavin	0.896 mg	1.4 mg
Niacin	9.6 mg	18 mg
Pantothenic acid	13.4 mg	0
Vitamin B6	3.4 mg	1.9 mg
Folic acid	120 µg	400 µg
Vitamin B12	4 µg	2.6 µg
Vitamin C	200 mg	70 mg
Vitamin D	8 µg	5 µg
Vitamin E	16.6 mg	10 mg
Vitamin K	200 µg	0
Iodine	80 µg	150 µg
Iron	8 mg	30 mg
Iron-sodium EDTA	5 mg	0
Phosphorus	400 mg	0
Calcium	260 mg	0
Potassium	800 mg	0
Zinc	10 mg	15 mg
Copper	0	2.0 mg
Selenium	0	65 µg

Sources: (1) Composition of a multi-micronutrient supplement to be used in pilot programmes among pregnant women in developing countries: report of a UNICEF, WHO and United Nations University workshop, 1999.
(2) World Food Programme. Technical Specifications for the Manufacture of Corn Soya Blend Plus for Young Children and Adults. Version 2.1; Current March 2011.

Despite their long-standing and widespread use, there is little knowledge on the nutritional effects and acceptance of FBFs, including CSB products, in pregnancy. In general, it has been recognized that analyzing impact has been a weakness of food and other aid programs (165). This has, in turn, created an evidence gap due to the lack of clinical research and impact assessments for commonly used cereal-based flours. Reasons cited in the literature for this dearth of evidence include a lack of clarity around expected outcomes of food assistance programs and methods to measure impact, and the fact that research is expensive and involves expertise that is often lacking in the food aid sector (166). The merits of providing ongoing food assistance to countries like Cambodia that are politically stable, not experiencing severe environmental crises, and where markets generally function, livelihoods remain intact, and there is general year-round availability of staple foods, are highly debated in the international development literature. Negative impacts of food aid such as reduced agricultural production and the consequent destabilization of agricultural markets that have occurred in some countries, coupled with overarching concerns of sustainability and dependency, have substantiated arguments against supplementary feeding programs (167-168). Furthermore, critics of these programs say they disproportionately serve donor, rather than recipient, interests through profits generated from the export of surplus grain commodities and the operation of such programs being dependent on excess food availability in donor countries, rather than population needs (169). Solutions to hunger and malnutrition involve freeing individuals from their poverty traps and countries from their development traps according to those on this side of the debate (169).

The poor nutritional status of too many women and children in Cambodia is of major concern and is an obstacle to the country’s development. Corn Soya Blend Plus is a nutritional supplement provided to pregnant women in Cambodia and other countries, yet little is known about its ability to improve pregnancy outcomes. My research, which looked at the efficacy and acceptability of prenatal Corn Soya Blend Plus supplementation, sits at the intersection of the public health need, the scientific need, and the ethical need to investigate the potential benefits and limitations of this frequently used commodity for improving the nutrition of women and children.

1.3 Research Objectives and Hypotheses

1.3.1 Rationale and Goal of Research

Pregnancy comprises one-third of the critical '1000 Day' window for ensuring proper health and development into childhood, adolescence, and later life. Good maternal nutrition is, therefore, paramount for optimal maternal and child outcomes. The prevalence of maternal and child undernutrition, including low weight at birth, is high in Cambodia. The Cambodian diet is typically of low nutritional value and economic barriers make consumption of diverse nutrient-dense foods difficult, greatly increasing the risk of nutritional inadequacy. Micronutrient-fortified food supplements are used internationally to help nutritionally-vulnerable women meet their nutritional needs during pregnancy. The dietary supplement Corn Soya Blend (CSB) Plus is used extensively in global food assistance programs, including in some regions of Cambodia. Regrettably, little is known about its efficacy and/or acceptability in pregnancy. The goal of this research was to address the knowledge gap surrounding the use of prenatal CSB Plus by generating evidence on its ability to improve pregnancy outcomes and its acceptance among women in rural Cambodia.

1.3.2 Research Objectives

The objectives of the research were as follows:

1. To investigate the efficacy of prenatal CSB Plus supplements to improve maternal and newborn outcomes, through improved nutrition, using a cluster-randomized trial that compared CSB Plus-supplemented women to those on their normal diet.

2. To explore factors that affected the acceptance and utilization of CSB Plus supplements in pregnancy through a qualitative study that involved a subset of the trial participants.

1.3.3 Primary and Secondary Study Hypotheses (as related to objective 1)

1.3.3.1 Primary Hypothesis

Null hypothesis (H_0): The birth weight of babies born to women provided CSB Plus food supplements prenatally will be the *same* as the weight of babies born to women not provided the food supplement.

Research hypothesis (H_A): The birth weight of babies born to women provided CSB Plus food supplements prenatally will be *higher* than the weight of babies born to women not provided the food supplement.

1.3.3.2 Secondary Hypotheses

Hypothesis #1

Null hypothesis (H_0): The total gestational weight gain of women provided CSB Plus food supplements prenatally will be the *same* as the weight gain of women not provided the food supplement.

Research hypothesis (H_A): The total gestational weight gain of women provided CSB Plus food supplements prenatally will be *higher* than the weight gain of women not provided the food supplement.

Hypothesis #2

Null hypothesis (H_0): The birth length of babies born to women provided CSB Plus food supplements prenatally will be the *same* as the birth length of babies born to women not provided the food supplement.

Research hypothesis (H_A): The birth length of babies born to women provided CSB Plus food supplements prenatally will be *higher* than the birth length of babies born to women not provided the food supplement.

Hypothesis #3

Null hypothesis (H_0): The birth head circumference of babies born to women provided CSB Plus food supplements prenatally will be the *same* as the birth head circumference of babies born to women not provided the food supplement.

Research hypothesis (H_A): The birth head circumference of babies born to women provided CSB Plus food supplements prenatally will be *higher* than the birth head circumference of babies born to women not provided the food supplement.

The methods utilized to test these hypotheses and to conduct the qualitative study are described in chapters 2 and 3, respectively. Chapters 2 and 3 present the two main components of my research: (i) a cluster-randomized efficacy trial that examined the effects of CSB Plus on maternal and newborn nutrition outcomes; and (ii) a qualitative study that identified and explored factors affecting women's acceptance and utilization of CSB Plus during pregnancy. These two complementary aspects of my research are presented in the dissertation as adapted versions of manuscripts submitted for scientific publication. Chapter 4 concludes the dissertation with an overall synthesis of the research findings and a discussion of recommendations emanating from my results.

Chapter 2: Prenatal Corn Soya Blend Plus Supplementation and Maternal and Newborn Nutrition Outcomes: A Cluster-Randomized Trial

2.1 Summary

Corn Soya Blend (CSB) Plus is a fortified dietary supplement used to help women in Cambodia and elsewhere meet their nutritional needs in pregnancy, though little is known about its ability to improve pregnancy outcomes. We assessed the effects of prenatal CSB Plus supplementation on birth weight and secondary outcomes of low birth weight (LBW) (< 2500 grams), small for gestational age (SGA), birth length and head circumference, preterm birth (< 37 weeks), maternal weight gain, and anemia at 24-28, 30-32, and 36-38 weeks gestation among women in rural Cambodia. A cluster-randomized trial was conducted in 75 villages in Kampong Chhnang Province, in which 547 women received CSB Plus (treatment) from the first trimester until delivery or continued on their normal diet (control) based on their village residence. Participants were recruited on the basis of attending antenatal care (ANC) at a health facility in the first trimester. All women received iron folic acid (IFA) tablets per standard care and were treated with additional IFA if anemic (hemoglobin [Hb] < 11 g/dL). Cluster-adjusted linear mixed effects and logistic regression models were used to examine group differences. Consumption of CSB Plus resulted in a non-significant 46 gram (g) increase in birth weight (95% CI: -31, 123). Significant reductions were observed in anemia at 36-38 weeks (OR: 0.51; 95% CI: 0.34, 0.77) and preterm birth (OR: 0.33; 95% CI: 0.12, 0.89). There were no significant differences in LBW, SGA, birth length, head circumference, or maternal weight gain. A higher rate of fetal loss was observed in the treatment group (10.2% vs. 3.7%; $p < 0.01$). Though our findings raise doubt about the ability of prenatal CSB Plus supplements to confer benefits on birth size, the clinically

important treatment effects of reduced anemia and preterm birth suggest the food supplement may contribute to improving maternal and child health in the Cambodian context.

2.2 Introduction

Adequate maternal nutrition is important for both mother and child (26). In Cambodia, almost one in five women of reproductive age have a low body mass index (BMI) (< 18.5 kg/m^2) and almost half are anemic (hemoglobin [Hb] < 12 g/dL) (1). These women are especially vulnerable to poor pregnancy outcomes, as they are unlikely to meet the additional nutritional demands of gestation. Cambodia has one of the highest maternal mortality rates in the Asia-Pacific region at 206 deaths per 100,000 live births (1, 170). Low birth weight (LBW) (< 2500 g) is nearly 10%; however, this likely underestimates the true rate as it does not include most home births, which account for almost 50% of deliveries (1). Fetal undernutrition likely contributes to the high rate of stunting in Cambodia, which affects approximately 40% of children < 5 years of age (1, 25).

The staple diet in Cambodia consists mainly of white rice, which lacks sufficient protein, fat, and micronutrients that are required for pregnancy (75). In addition to an iron folic acid (IFA) supplement, the Cambodian Ministry of Health (MoH) recommends women increase their food intake during pregnancy by consuming one extra daily meal (85). Ideally, this meal should be nutrient-dense; however, this is difficult for most rural women due to a lack of ability to purchase available high-quality foods and limited access to fortified foods. An alternative approach is to provide a nutrient-dense food supplement during pregnancy. Findings from a recent meta-analysis of 16 studies suggest prenatal protein-energy supplementation can increase birth weight, reduce LBW, and decrease small for gestational age (SGA), compared to babies born to unsupplemented or only micronutrient-supplemented women (93). Based on this and other supporting evidence, protein-energy supplements are recommended for preventing undernutrition in pregnancy in nutritionally-vulnerable populations (114).

Corn Soya Blend (CSB) Plus is a fortified maize and soybean flour that is widely used as a dietary supplement in global food aid programs to assist pregnant and lactating women and young children in areas with high rates of undernutrition (158). CSB has been used in supplementary feeding programs operated by the United Nations World Food Programme in Cambodia since 2002. CSB Plus, which contains an enhanced micronutrient profile, was introduced in the country in 2011. Specialized fortified flour supplements, including CSB and CSB Plus, have not been rigorously evaluated for their potential to improve pregnancy outcomes in target populations. We examined the effects of CSB Plus, provided prenatally starting in the first trimester until delivery, on birth weight and, secondarily, on low birth weight, small for gestational age, birth length and head circumference, preterm birth, maternal weight gain, and gestational anemia among rural women in Kampong Chhnang Province.

2.3 Study Design

The study was a cluster-randomized trial with a treatment and control group. All 75 village clusters located in the geographic catchment area of four health centers were randomized to receive either CSB Plus supplements (referred to as the ‘treatment’ group) provided to women from the first trimester to delivery (treatment group: n=37) or to a control group that did not receive the food supplement (control group: n=38). The randomization procedure involved selecting cluster names from an opaque bag and assigning each to the treatment or control group. The 75 village clusters were target areas for a child survival project implemented by International Relief & Development. Women in both the treatment and control clusters received: IFA tablets (containing 60 mg iron and 400 µg folic acid) provided by midwives at health centers during antenatal visits as per standard care; Hb testing and treatment for anemia (2 IFA tablets/day for 14 days) provided by the midwives during routine prenatal sessions; and prenatal counseling provided by study personnel during enrollment in women's homes. The counseling focused on best practices related to diet, antenatal and delivery care, and general self-care during pregnancy, in accordance with Cambodian MoH guidelines (85).

2.4 Setting and Participants

The trial was conducted in 75 villages in two districts (Boribo and Rolea Phear) of Kampong Chhnang Province in central Cambodia. The average village population size was 660. The study area consisted primarily of subsistence rice-farming communities relying on one annual harvest. Seasonal migration is common in the province due to flooding of Lake Tonle Sap during the wet season from May to October. Based on the 2010 Cambodia Demographic and Health Survey (1) results for the province, almost 60% of women of reproductive age are anemic (Hb < 12 g/dL) and ~20% have a low BMI (< 18.5 kg/m^2). In addition, 40% of children < 5 years of age are stunted (height-for-age Z-score <-2 SD compared with 2006 WHO Child Growth Standards (171)) and 64% are anemic (Hb < 11 g/dL) (1).

The study sample comprised all women in each of the 75 village clusters who became pregnant during the study period and met the inclusion criteria. Recruitment occurred from August 2011 to June 2012 and was concurrent in the treatment and control groups. Potentially eligible women were identified from ANC registers at the four participating health centers based on specific criteria. To be eligible, women had to be at least 18 years; be in the first trimester; and be planning to stay in their home village for the duration of their pregnancy. Following identification from health center records, women were enrolled at their household, during which eligibility criteria were verified, informed consent was obtained, and a survey (Appendix A) was administered to establish socio-demographic characteristics and reproductive history. Women were enrolled in the first trimester and followed to delivery. The study was approved by the Cambodian National Ethics Committee for Health Research and the University of British Columbia Clinical Research Ethics Board. All women provided written informed consent to participate. The trial was registered at ClinicalTrials.gov (NCT01413776).

2.5 Treatment

CSB Plus is a maize (~80%) and soybean (~20%) flour that is fortified with a vitamin and mineral premix (Table 2.1). It is partially pre-cooked through extrusion or roasting to deactivate soya trypsin inhibitors that affect protein digestion (164). Each woman in the treatment group was provided a 6.75 kg bag of CSB Plus, containing 0.75 kg of pre-added sugar for palatability, on a monthly basis by the field researchers with the assistance of trained female village health workers (VHW). A 300 mL supply of vitamin A and D-fortified palmolein oil was provided each month along with the CSB Plus and was to be added during the cooking process (~10 mL per ration). The daily CSB Plus ration (200 g dry flour) provided approximately 760 kcal, 27 g protein (14% of total kcal), and 5 g fat (6% of total kcal). The 10 mL daily oil ration provided 90 µg of vitamin A (RE), 0.77 µg of vitamin D, and ~ 90 kcal of additional energy. CSB Plus is intended to be consumed as a porridge or gruel prepared by mixing 1 part flour with 4-5 parts water, depending on the desired thickness, followed by a boiling time of 5-10 minutes. Women were given a measuring bowl and provided education on cooking the flour. They were instructed to minimize product sharing within the household and with other relatives and neighbors. Women were asked to keep daily CSB Plus consumption records, which were collected by the VHWs and given to the researchers on a weekly basis. The consumption data from women's records were verified through a survey (Appendix B). Due to the variety of actual cooking methods, it was not possible for women who consumed non-porridge preparations to tally bowls of cooked product. Therefore, consumed amounts were extrapolated from quantities of raw product women cooked for themselves each day.

Table 2.1 Nutrient composition of Corn Soya Blend Plus (per 200 g dry matter)[1,2]

Nutrient	Quantity	Chemical form
Energy	760 kcal	
Protein	27 g	
Fat	5 g	
Vitamin A	3328 IU	Dry vitamin A palmitate 250 S/N
Thiamine	0.256 mg	Thiamine mononitrate
Riboflavin	0.896 mg	Riboflavin
Niacin	9.6 mg	Nicotinamide
Pantothenic acid	13.4 mg	Calcium d-pantothenate
Vitamin B6	3.4 mg	Pyridoxine hydrochloride
Folic acid	120 µg	Folic acid
Vitamin B12	4 µg	Vitamin B12 – 0.1% spray dried
Vitamin C	200 mg	Ascorbic acid
Vitamin D	8 µg	Dry vitamin D3 100 CWS
Vitamin E	16.6 mg	Vitamin E 50% CWS
Vitamin K	200 µg	Vitamin K1 5% CWS
Iodine	80 µg	Potassium iodate
Iron	8 mg	Ferrous fumarate
Iron	5 mg	Iron-sodium EDTA
Phosphorus	400 mg	Mono-calcium-phosphate
Calcium	260 mg	Mono-calcium-phosphate
Potassium	800 mg	Potassium chloride
Zinc	10 mg	Zinc oxide

[1]Source: WFP Technical Specifications for the Manufacture of CSB Plus (Version 2.1, updated 30 March 2011). CWS, cold water soluble.
[2]1 ration = 200 grams

2.6 Outcome Measurement

All outcome measurements were performed during ANC sessions and deliveries by 10 trained and experienced midwives who were staffed at the four health centers. Birth weight (Nhon Hoa NHBS-12 scale; Ho Chi Minh, Vietnam), recumbent length (UNICEF infant length board), and occipitofrontal head circumference (standard non-elastic flexible tape) were measured at delivery or within 48 hours for home births. Birth weight was measured to the nearest 100 g and length and head circumference to the nearest 1 cm, in accordance with routine practices at primary health centers in Cambodia. Maternal weight was measured using a non-digital scale (Nhon Hoa NHHS-120-K6; Ho Chi Minh, Vietnam) at four times (first trimester, 24-28, 30-32, 36-38 weeks) and maternal height was measured at the first visit using standard procedures. Capillary Hb (finger prick) concentration was determined at each of the four visits using a portable hemoglobinometer (HemoCue® Hb 201$^+$; Angelholm, Sweden). All four health centers used the same measuring equipment, which was provided for the study, and weighing scales were calibrated weekly by health center staff using standard weights.

Study outcome measures were defined as follows: LBW was defined as weight at birth < 2500 g; SGA was defined as birth weight below the 10th percentile for a given gestational age and sex using the INTERGROWTH-21st growth reference (172); preterm birth was defined as delivery prior to 37 completed weeks gestation; total maternal weight gain was calculated as the difference between the weight measurement taken at the first prenatal visit in the first trimester and the 36-38 week measurement; and maternal anemia was defined as Hb < 11 g/dL as per the WHO classification for anemia in pregnancy (173). Gestation week was determined from the first day of the woman's last menstrual period as reported at the first prenatal visit and from uterine fundal height measurements beginning at the 24-28 week session. We also examined the prevalence of stunting (low length-for-age) and small head circumference for gestational age at birth using the respective sex-specific INTERGROWTH-21st charts (172).

All 10 midwives participated in two study training sessions. Hemoglobin testing and treatment (based on the test result) were the only new services introduced into antenatal care for the purposes of the study. Midwives performing the study measurements were blinded to the randomization scheme, in that they did not know or ask whether the women were receiving CSB Plus. Observations of ANC sessions at health centers and interviews with midwives reinforced the fact that CSB Plus was not discussed during patient contacts. Further, enrollment cards used to record maternal weight and Hb measurements did not identify the women's study group.

2.7 Statistical Analysis

The required cluster sample size was calculated in consultation with a statistician and was based on 80% power to detect a 100 g difference in mean birth weight between the treatment and control group at the 0.05 significance level. Though pooled estimates of birth weight generated from meta-analyses of prenatal protein-energy supplementation trials have been lower, we estimated a greater effect of the high-calorie micronutrient-fortified CSB Plus on the basis of larger increases that have been observed in individual studies using high-calorie supplements (100,103,108,131,174). Participant characteristics and nutritional status at baseline (first trimester) were compared between study groups using standard t-tests and chi-square tests.

Linear mixed effects (LME) regression models were created to assess differences in the primary outcome of birth weight and secondary continuous outcomes of birth length, head circumference, and maternal weight gain. The LME models included the treatment as a two-level fixed effect and the cluster as a random effect. This accounted for both the intra-cluster correlation with respect to the study outcomes measured and the inter-cluster variation in the treatment effect. Results predicted by the models are expressed as differences in group means (β coefficient) with a 95% confidence interval.

Logistic regression was used to assess group differences in the dichotomous outcomes, adjusted for the cluster effect. Odds ratios and 95% confidence intervals are reported for LBW, SGA, preterm birth, maternal anemia, as well as stunting and small head circumference for gestational age. We adjusted for the variation in time intervals between women's hemoglobin measurements in the anemia analysis by incorporating the average number of days between the ANC 2 and ANC 4 visits as a continuous covariate in the logistic regression model, adjusting for clustering and anemia status at ANC 1 (baseline status). Only live-born singleton infants were included in the analysis for birth anthropometry. We examined whether pre-pregnancy BMI (using first trimester BMI as a proxy measurement) modified the treatment effect. All reported p values are two-sided with an alpha (α) of 0.05. Treatment was evaluated according to the intention-to-treat principle. Statistical analyses were performed using IBM SPSS Version 20.0 software (Armonk, NY: IBM Corp).

2.8 Results

A total of 547 pregnant women were enrolled in the study: 333 in the treatment group and 214 in the control group. The average number of cluster participants was higher in the treatment group (8 vs. 6). Fifty-two women (9.5%) did not complete the trial. Forty-two women (~8%) experienced a fetal loss (self-reported miscarriage or abortion), with a higher rate reported in the treatment group (10.2%, n=34) compared to the control group (3.7%, n=8) ($p = 0.006$). Ten women migrated outside the study area during the trial. Births to participants occurred from January 2012 to February 2013. Nine newborns were excluded from the analysis due to stillbirth (n=3), twin birth (n=2), and perinatal death (n=4). Among the 294 pregnancies in the CSB Plus group and 201 pregnancies in the control group, 289 and 197 live-born infants, respectively, were included in the birth weight analysis. The flowchart of study enrollment and completion is shown in Figure 2.1.

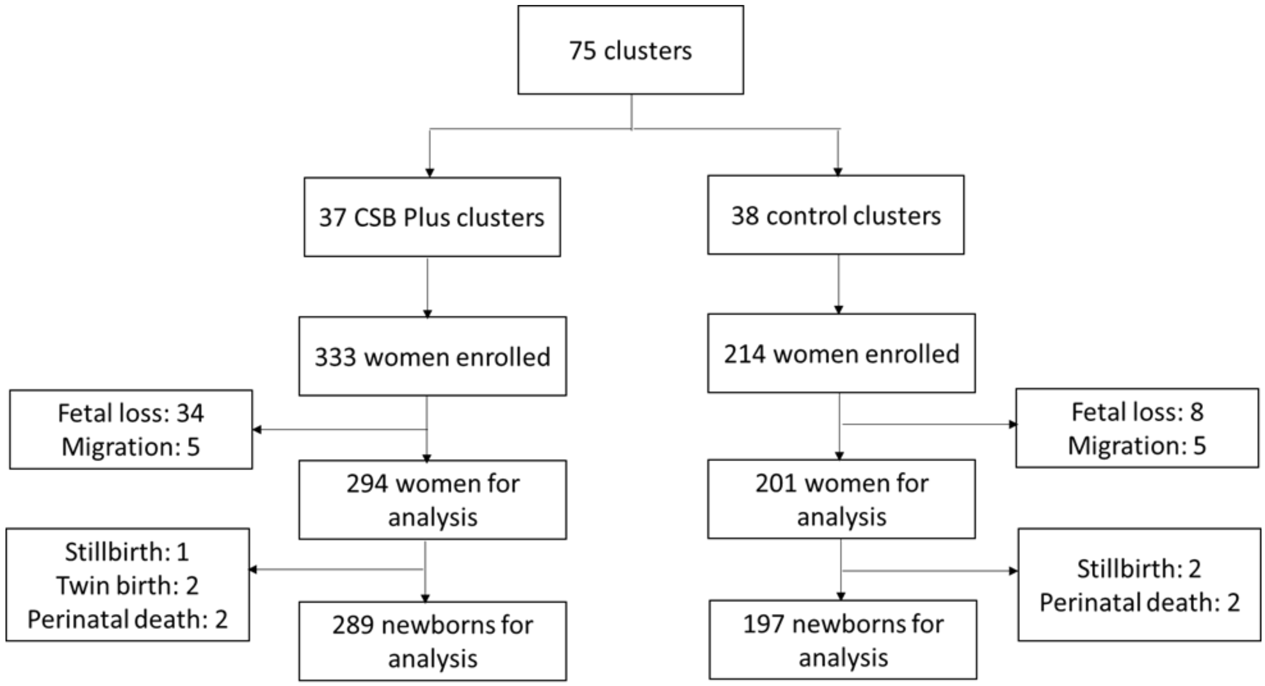

Figure 2.1 Flowchart of study enrollment and completion

2.8.1 Baseline Characteristics

Socio-demographic characteristics of participants at baseline (first trimester) were similar between the two groups (Table 2.2). The average age of women was 26.2 years in the treatment group and 26.9 years in the control group. Approximately 44% of women in both groups were primiparous and 48% and 43% had one or two children in the treatment and control group, respectively. Both groups had an average household size of four members. The majority of women (~70%) in both groups reported farming as their main occupation and the two groups were of comparable socio-economic status as assessed by income, land ownership, and livestock assets. Based on average reported household income, ~50% and ~40% of households in both groups were living under USD 1.25/day during the wet season (May to October) and dry (harvest) season (November to April), respectively. Further, about 60% of women in each group reported that their household had experienced a rice shortage following the preceding harvest.

Table 2.2 Baseline characteristics of enrolled women[1]

	CSB Plus (n=333)	Control (n=214)
Age, y	26.2 ± 5.1	26.9 ± 5.0
Parity		
0	147 (44.1)	96 (44.9)
1	123 (37.0)	61 (28.5)
2	36 (10.8)	31 (14.5)
3+	27 (8.1)	26 (12.1)
Number of household members	4.0 ± 1.6	4.0 ± 1.6
School attendance		
Yes	311 (93.4)	204 (95.3)
No	22 (6.6)	10 (4.7)
Duration of schooling, y	6.3 ± 2.8	6.6 ± 2.9
HH monthly median income dry season, USD[2]	50	40
HH monthly median income wet season, USD[2]	25	25
Land ownership		
Yes	291 (87.4)	176 (82.2)
No	42 (12.6)	38 (17.8)
Size of land, hectares	1.3 ± 1.5	1.4 ± 1.7

[1]Total n=547. Values are mean ± SD or n (%). CSB, corn soya blend; SD, standard deviation; HH, household; USD, United States Dollars.
[2]1 USD = 4,000 KHR (Cambodian Riel).

In both the treatment and control group, 60% of women had their first ANC visit during 5-8 weeks gestation and about one-third after 8 weeks. Average gestation at ANC 1 was 8.3 weeks in both groups. Nutrition indicators of women in the first trimester were similar and are presented in Table 2.3. In the treatment and control clusters, 37% and 33% of women were underweight with a BMI < 18.5 kg/m^2, respectively ($p = 0.30$). The prevalence of anemia was 28% in the treatment group and 33% in the control group ($p = 0.20$), with 65% and 52% ($p = 0.13$) of these cases classified as mild anemia (Hb 10.0-10.9 g/dL) and 34% and 48% ($p = 0.09$) as moderate anemia (Hb 7.0-9.9 g/dL) in the CSB Plus and control group, respectively, based on the WHO guidelines for anemia classification (173). There was one case of severe anemia at ANC 1, which occurred in the treatment group. Sixty-three women (treatment: 12%, n=36; control: 13%, n=27) had both a low BMI and were anemic at baseline. About 3% of women in both groups had a short stature, defined as height < 145 cm for Cambodian women (1).

Table 2.3 Maternal nutritional status at baseline (first trimester)[1]

	CSB Plus (n=294)[2]	Control (n=201)[2]
Gestational age at ANC 1, wk	8.3 ± 2.3	8.3 ± 2.5
Weight, kg	47.0 ± 6.8	46.9 ± 6.2
Height, m	1.55 ± 0.06	1.55 ± 0.06
BMI, kg/m^2		
Severely underweight, <16.5	17 (5.8)	15 (7.4)
Underweight, 16.5 - <18.5	93 (31.6)	51 (25.4)
Normal, 18.5 - <25.0	173 (58.8)	128 (63.7)
Overweight, 25.0 - <30.0	9 (3.1)	6 (3.0)
Obese, ≥30.0	2 (0.7)	1 (0.5)
Anemia, Hb g/dL		
Normal, ≥11.0	212 (72.2)	134 (66.7)
Mild, 10.0 - 10.9	53 (64.6)	35 (52.2)
Moderate, 7.0 - 9.9	28 (34.2)	32 (47.8)
Severe, <7.0	1 (1.2)	0 (0.0)

[1]Total n=495. Values are mean ± SD or n (%). ANC, antenatal care; CSB, corn soya blend; Hb, hemoglobin; SD, standard deviation.
[2]Values include women who completed the trial (39 and 13 women did not complete the trial in the CSB Plus and control group, respectively).

2.8.2 Birth Outcomes

The majority of deliveries occurred in primary (first level) health centers (81% treatment, 90% control). There were 21 (4.3%) home deliveries (18 treatment, 3 control), with 12 concentrated in one remote village where home births are common. The remainder of births took place in a private clinic (n=7) or hospital (n=47). Anthropometric outcomes at birth are presented in Table 2.4. Average birth weight was 3020 ± 386 g in the treatment group and 2975 ± 471 g in the control group (46 g; 95% CI: -31, 123 adjusted for cluster randomization). A non-significant reduction in LBW was observed in the CSB Plus group (treatment: 6.2%, n=18; control: 10.7%, n=21) in the cluster-adjusted model (OR: 0.65; 95% CI: 0.33, 1.26). Babies born to women with BMI < 18.5 kg/m^2 at study entry weighed less than infants born to women with normal weight-for-height status in both groups (Table 2.5). In the analysis adjusted for maternal baseline BMI, the difference in birth weight between groups was larger, though also not significant (55 g; 95% CI: -29, 138). The interaction between baseline BMI and supplementation was not significant ($p = 0.31$). The prevalence of SGA was 15.4% (n=44) in the treatment group and 14.8% (n=29) in the control group (OR: 1.21; 95% CI: 0.72, 2.03; cluster-adjusted analysis).

Average birth length was 49.98 ± 2.94 cm in the treatment group and 50.02 ± 2.97 cm in the control group. In the cluster-adjusted analysis, the mean difference was negligible and non-significant (-0.05 cm; 95% CI: -0.89, 0.80). The proportion of infants below the age and sex-specific 10th percentile for length at birth was 13.1% (n=31) in the treatment group and 12.3% (n=22) in the control group, which was not significant in the cluster-adjusted analysis (OR: 1.03; 95% CI: 0.57, 1.87). Average head circumference at birth was 31.16 ± 1.69 cm in the CSB Plus group and 30.85 ± 1.75 cm in the non-treatment group. As with birth length, there was no statistically significant treatment effect on head circumference in the cluster-adjusted analysis (0.31 cm; 95% CI: -0.02, 0.64). Further, in the treatment and control group respectively, 162 (68.4%) and 124 (69.3%) babies were born with a head circumference below the 10th percentile of the reference population for their sex-specific gestational age (OR: 0.90; 95% CI: 0.59, 1.38; adjusted for cluster effect). Average gestation at delivery was 38.8 ± 1.5 weeks in the treatment group and 38.6 ± 1.7 weeks in the control group ($p = 0.13$; cluster-adjusted analysis). Despite no significant increase in the duration of gestation overall, the rate of preterm birth favored the CSB

Plus group (treatment: 2.1%, n=6; control: 7.1%, n=14) and resulted in an odds ratio of 0.33 (95% CI: 0.12, 0.89) in the cluster-adjusted regression model.

Table 2.4 Birth anthropometry, low birth weight, small for gestational age, and preterm birth[1]

Birth Outcome	CSB Plus		Control		Mean Difference or OR	95% CI	P value
	n		n				
Birth weight, g	289	3020 ± 386	197	2975 ± 471	46	-31, 123	0.24
Low birth weight	18 (6.2%)	N/A	21 (10.7%)	N/A	0.65	0.33, 1.26	0.20
Birth length[2], cm	237	49.98 ± 2.94	179	50.02 ± 2.97	-0.05	-0.89, 0.80	0.91
Birth head circumference[2], cm	237	31.16 ± 1.69	179	30.85 ± 1.75	0.31	-0.02, 0.64	0.07
Small for gestational age	44 (15.4%)	N/A	29 (14.8%)	N/A	1.21	0.72, 2.03	0.48
Preterm birth	6 (2.1%)	N/A	14 (7.1%)	N/A	0.33	0.12, 0.89	0.03

[1]Values are mean ± SD, n (%), or otherwise indicated. CI, confidence interval; CSB, corn soya blend; N/A, not applicable; OR, odds ratio; SD, standard deviation.
[2]Data missing for n=52 infants in the treatment group and n=18 infants in the control group who were delivered at home or in a private clinic or hospital where birth length and head circumference were not measured.

2.8.3 Maternal Outcomes

Average maternal weight gain from ANC 1 to ANC 4 was 8.5 ± 3.1 kg in the treatment group and 8.1 ± 3.1 kg in the control group (0.43 kg; 95% CI: -0.19, 1.05 adjusted for cluster randomization). Overall, 13% (n=57) of women achieved their recommended weight gain based on their baseline BMI status, according to the Institute of Medicine (IoM) guidelines (38). Of these, 41 (72%) were in the treatment group and 16 (28%) in the control group. Women who had low weight-for-height at study entry exhibited higher average weight gain compared to their normal-weight counterparts in both groups [treatment: 1.2 kg; 95% CI: 0.42, 1.98; control: 0.70 kg; 95% CI: -0.28, 1.67]. Further, among women with low BMI in early pregnancy, 16 (17%) attained their target weight gain in the treatment group, compared to 2 (4%) in the control group ($p = 0.02$). As shown in Table 2.5, women with low BMI (who had the higher average weight gain) delivered infants with a lower average birth weight.

Table 2.5 Maternal weight gain and birth weight according to baseline BMI status[1,3]

	BMI < 18.5				BMI ≥ 18.5			
	CSB Plus		Control		CSB Plus		Control	
	n		n		n		n	
Weight gain[2], kg	97	9.3 ± 3.2	56	8.6 ± 2.4	162	8.1 ± 3.0	121	7.9 ± 3.3
Birth weight, g	109	2966 ± 369	65	2900 ± 456	180	3054 ± 394	132	3011 ± 475

[1]Values are mean ± SD. CSB, corn soya blend; SD, standard deviation.
[2]Weight gain could not be calculated for n=35 women in the treatment group and n=24 women in the control group due to a missed study visit at 36-38 weeks gestation.
[3]Interaction effect of maternal BMI x supplementation for birth weight: p = 0.31.

From baseline to 24-28 weeks, the prevalence of maternal anemia nearly doubled in the treatment group and increased by ~70% in the control group. No significant treatment effects on anemia were observed at 24-28 and 30-32 weeks gestation (Figure 2.2). However, relative to controls, anemia decreased over time in the treatment group and was significantly lower (34% vs. 50%) at 36-38 weeks (OR: 0.51; 95% CI: 0.34, 0.77; adjusted for cluster effect). Similarly, the estimate for the proportional change in the odds ratio (adjusted for baseline anemia status and clustering) for anemia risk in the treatment group, relative to controls, over 80 days (mean interval between ANC 2 and ANC 4) was 0.48 (95% CI: 0.25, 0.95).

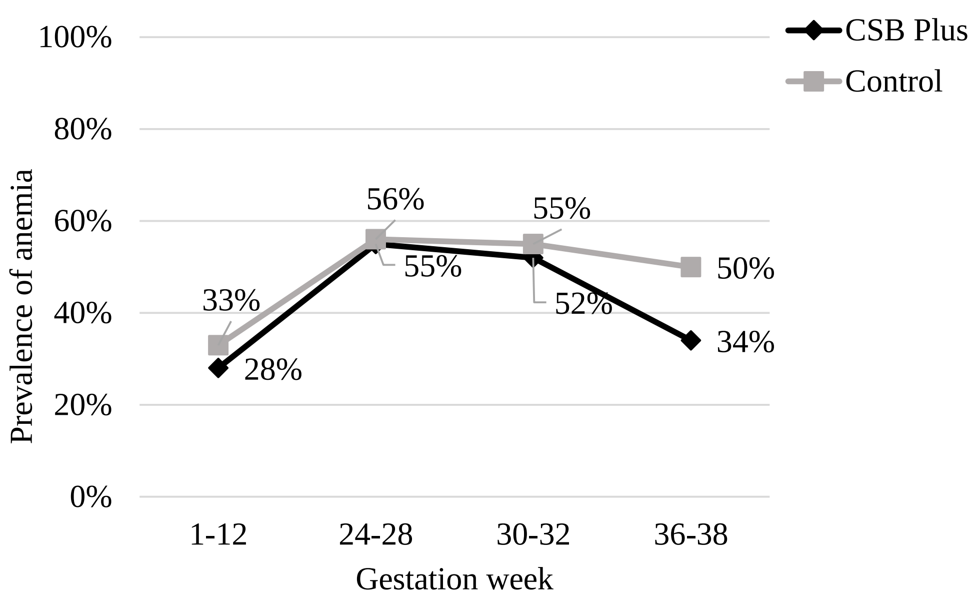

Figure 2.2 Prevalence of maternal anemia in CSB Plus and control group at each study visit

It is necessary to situate the observed prevalence of gestational anemia in the context of women's compliance with IFA supplements and deworming treatment, which were provided as part of routine antenatal care. Women in both groups reported high compliance with the standard 90 IFA (60 mg iron + 400 µg folic acid) tablet regimen for anemia prophylaxis and with the larger doses provided for anemia treatment as part of the study. Among women provided 90 pills, 95%

and 97% reported taking all their tablets in the treatment and control group, respectively. Among the more than half of women provided > 90 IFA tablets for single or multiple episodes of anemia, 90% and 96% reported completing their prescribed dosage in the treatment and control group, respectively. For women given > 150 tablets for repeated anemia (treatment: n=39; control: n=28), reported compliance was 77% in the treatment group and 100% in the control group. Adherence to the single 500 mg dose of mebendazole was reported by all women who received the deworming treatment (93% CSB Plus, 97% control). Women were shown samples of IFA and mebendazole tablets to help facilitate recall during the home visit.

2.8.4 Consumption of Corn Soya Blend Plus

The average duration of CSB Plus supplementation was 30 weeks. Mean and median monthly consumption was 18 rations (out of a maximum 30), which equated to ~0.6 rations or ~500 kcal per day, plus the amount of added oil (~90 kcal/ration). This was determined from the total number of rations women reported consuming during their enrollment in the study, as recorded in their daily consumption logs. Intake of CSB Plus was not supervised. Women cooked the flour in multiple ways, apart from the recommended porridge, and frying was the preferred mode of consumption.

We investigated dose-response relationships for total consumption level, categorized as low (< 100 rations), medium (100-150 rations), or high (> 150 rations), and birth weight, maternal weight gain, and duration of gestation. As shown in Table 2.6, higher total consumption was associated with a longer gestation. Women who reported consuming > 150 total rations experienced an average 0.8 week longer gestation, compared to women who reported an intake of < 100 rations. No significant differences were observed in average birth weight or maternal weight gain among women in the three consumption categories. Though ~80% of women reported sharing the food supplement with family members living in the household, about two-thirds reported sharing < 10% of the quantity they received each month. Inter-household sharing of CSB Plus was reported by ~20% of women and the reported amount shared was also small.

Table 2.6 Maternal weight gain, birth weight, and gestation at delivery by level of CSB Plus consumption[1]

CSB Plus consumption category	n (%)	Weight gain (kg)	Birth weight (g)	Gestation at delivery (wk)
< 100 rations	54 (19)	8.1 ± 3.1	2973 ± 351	38.4 ± 1.6
100-150 rations	188 (64)	8.6 ± 3.1	3026 ± 408	38.8 ± 1.4
> 150 rations	51 (17)	8.5 ± 3.2	3051 ± 338	39.2 ± 1.5[2]

[1]Values are mean ± SD or n (%). CSB, corn soya blend.
[2]Significantly different from < 100 rations ($p < 0.05$, ANOVA)

2.9 Discussion

In this trial in rural Cambodia, prenatal CSB Plus supplementation had no significant effect on our primary outcome of birth weight or secondary outcomes of LBW, SGA, birth length, head circumference, and maternal weight gain, compared to women not provided the food supplement. CSB Plus reduced rates of anemia in late gestation and preterm birth. The positive, though non-significant, effect on birth weight is possibly due to our study being underpowered to detect smaller (< 100 g) differences that have been reported in the literature (95, 96). In addition, we observed no significant treatment effect on stunting or small head circumference for gestational age at birth. The high prevalence of small head circumference for gestational age in our study (~70% in both groups) is concerning, as this indicator is a surrogate measurement for brain size and brain growth (175).

The lack of a significant increase in maternal weight gain was unexpected. The average reported CSB Plus daily intake (~120 g) was equivalent to ~500 kcal per day (not including the 10 mL

(~90 kcal) added oil), which should have resulted in a higher maternal weight gain in the treatment group. The null effect suggests comparable energy intake between the two groups, which could have been due to dietary substitution of regular household foods, in that women did not share much of the CSB Plus and intentionally ate less of other foods, or women were ‘full’ with the CSB Plus so they ate less of other foods. The lack of effect could also be due to over-reporting of CSB Plus consumption and/or underreporting of the extent of intra and/or inter-household sharing, as the flour is conducive to being prepared and consumed as a family food. Notwithstanding the lack of effect on total weight gain, the larger proportion of women who achieved their IoM recommended weight gain in the CSB Plus group is a positive finding of the study. In our subgroup analysis, women with pre-pregnancy BMI $\geq$ 18.5 kg/m^2 delivered babies weighing about 100 grams more, on average, than their underweight counterparts in both groups. This points to the need to address macronutrient deficits in pregnancy, as recommended by Bhutta et al. (114) in the recent Lancet series on maternal and child nutrition.

Though anemia in pregnancy is not uncommon, given the increased physiological need for iron to support fetal growth (50), the fact that ~30% of women in our study were anemic in the first trimester, and this increased to more than 50% at 24-28 weeks, is concerning. In Cambodia, anemia is caused by nutritional deficiencies, helminth and other parasitic infections, and/or hereditary hemoglobinopathies (82). The finding of lower anemia in the third trimester in the CSB Plus group suggests a benefit from the multi-micronutrients provided through the food supplement for multiple reasons. First, deficiencies of vitamins A, B6, B12, C, folate, and riboflavin can contribute to anemia as these nutrients play important roles in erythropoiesis, hemoglobin synthesis, iron mobilization, and/or iron absorption (41, 44-47). Multiple nutrient deficiencies have been observed in the Cambodian population (176). In their estimation of micronutrient density values for several countries, Gibson and Cavalli-Sforza concluded probable insufficiencies of vitamin A, calcium, iron, riboflavin, thiamin, and zinc in the Cambodian food supply (77). Therefore, even if the CSB Plus replaced other foods, those staple foods would have most likely provided less micronutrient value.

Second, both groups reported high IFA compliance. Had iron deficiency been the primary etiology of anemia in our population, we suspect the effects of iron repletion would have been similarly apparent with respect to anemia rates in both groups. This suggests iron deficiency was probably low, but cannot be confirmed in our study as we did not measure biomarkers of iron status. Further, high compliance with the deworming treatment in both groups likely minimized the risk of anemia due to intestinal helminth infections. Lastly, the randomized design of the study controlled for unmeasured confounders such as genetic hemoglobin disorders, which are known to contribute to anemia in Cambodian women (81). Therefore, any potential differential effects exerted by confounding factors on the study outcomes were highly improbable. Moreover, underlying group differences in non-nutritional factors such as rates of parasitic infection and hemoglobinopathies, that may have occurred by chance, would have been apparent at each study visit as these conditions do not respond to nutrient-based interventions. We have hypothesized that the reduction in anemia observed in our study was due to the additional micronutrients provided in the CSB Plus. It is important to note that this interpretation contradicts the evidence described in chapter 1 (124) that suggests multiple micronutrient supplements and IFA are equally effective for improving hemoglobin levels in pregnancy. This being said, the food-based delivery of micronutrients is an important difference of our study.

The reduction in preterm births in the treatment group is an important finding of this study, though we acknowledge the number of women with preterm deliveries was small (treatment:

n=6, control: n=14). Micronutrient deficiencies are associated with premature delivery (177-182) and macronutrient interventions have shown to reduce the incidence of preterm birth (183). It is, therefore, plausible that the protective effect of CSB Plus on preterm birth was due to nutrient repletion. However, it is important to acknowledge that the higher rate of fetal loss in the treatment group could partially explain the fewer preterm births that occurred among women who consumed the food supplement if more vulnerable fetuses terminated in utero in the CSB Plus group, but survived and became preterm babies in the control group. In a cross-sectional study using data from the Danish National Birth Cohort, Nohr et al. (184) reported multivitamin use from before conception to early pregnancy was associated with an increased risk of early fetal death. Though the authors were not able to explain this finding, they acknowledged that otherwise unviable pregnancies may be lengthened with multivitamin use, leading to more fetal losses after eight weeks gestation (184-185). As daily vitamin doses were within recommended ranges, more studies are needed to substantiate these findings. We are unable to explain the higher rate of fetal loss in the treatment group in our study. As women received multivitamin-fortified food in our study, there may have been other factors related to product components and/or storage practices that were possibly associated with this adverse outcome. This warrants further investigation.

A strength of our study was the cluster-randomized design with comparable groups at baseline. All live-born infants of study participants were weighed within 48 hours of delivery and had a recorded weight measurement. Midwives were blinded to the randomization scheme, which reduced the likelihood of bias in service delivery, measurement, and recording. Recruitment of women on the basis of having attended antenatal care early in pregnancy may have resulted in a sample of women who were more proactive in their health-seeking behaviors and, consequently, introduced some bias in our sample. Though data for Kampong Chhnang Province are not available, national data indicate that 56% of rural Cambodian women have their first prenatal care visit when less than four months pregnant (1). Measurement of birth weight to the nearest 100 g and birth length and head circumference to the nearest 1 cm resulted in a loss of precision in both groups. As measurement precision influences statistical power, the lack of precision of the scale used to measure birth weight possibly reduced our ability to detect important differences between groups. This may have resulted in under-ascertainment of babies below 2500 g. A study in Nepal (186) comparing two scales – one with a precision of 100 g and the other with a precision of 2 g – found that LBW was underestimated by 11% using the less precise scale. However, our randomized design would ensure that classification bias, if it exists, would be non-differential. Nonetheless, more precise measurement may still have revealed differences between groups. Additionally, missing birth length and head circumference measurements for deliveries that occurred at private clinics and hospitals could have altered the treatment effect. Finally, the use of last menstrual period and fundal height methods precludes precise measurements for gestational dating. However, recruiting women early in pregnancy shortened the recall interval from the time of last menstruation, which presumably decreased the error inherent in using the LMP method.

In conclusion, this is the first study to our knowledge to investigate the effects of prenatal CSB Plus supplementation on maternal and newborn nutrition outcomes. Despite having no effect on birth size, the reductions in maternal anemia and preterm birth are important and suggest potential benefits of the food supplement in this context. Notwithstanding this, the higher rate of fetal loss among women who consumed CSB Plus is concerning and requires further investigation. The merits of providing Corn Soya Blend Plus to improve pregnancy outcomes in poorly nourished populations should be evaluated with data from other contexts.

Chapter 3: Factors Affecting the Acceptability and Consumption of Corn Soya Blend Plus as a Prenatal Dietary Supplement: A Qualitative Study

3.1 Summary

Undernutrition is highly prevalent among pregnant women in Cambodia. The provision of fortified dietary supplements is one strategy to help pregnant women meet their nutritional needs. Corn Soya Blend (CSB) Plus is a widely used prenatal dietary supplement in areas with high rates of undernutrition. However, little is known about its acceptability during pregnancy. We identified factors that affected the acceptability and consumption of prenatal CSB Plus supplements in two districts in Kampong Chhnang Province, Cambodia. Participants were women (n=288) enrolled in a cluster-randomized trial of CSB Plus during pregnancy. Methods utilized were structured interviews with all participants to provide information on utilization practices and six focus group discussions (FGD) with a subset of women to further explore attitudes, perceptions, and experiences related to CSB Plus use. The acceptability of CSB Plus was influenced by the product's sensory attributes, family support, peer influences, and attitudes related to diet, nutritional status, and weight gain in pregnancy. Attaining adequate nutrition was considered less important than other concerns women had during pregnancy, particularly anxiety related to the costs of delivery and postpartum care. Acceptance was lower among first-time mothers due to fears of weight gain, a large baby, and delivery complications. CSB Plus was generally accepted in this population, though maximum compliance did not occur. Nutrition promotion and allaying fears of weight gain provide opportunities for greater adherence in this context.

3.2 Introduction

Adequate energy and nutrient intake during pregnancy is critical for optimal maternal and newborn health outcomes (187). Currently, the World Health Organization recommends iron and folic acid supplementation (50) for all pregnant women and calcium supplements (188) for pre-eclampsia prevention in areas where calcium intake is low, though increasing evidence suggests potential benefits of multiple micronutrient supplements to improve pregnancy outcomes (114).

Undernutrition is one of Cambodia's most pressing challenges. The prevalence of chronic child undernutrition is among the highest in Southeast Asia (189). Further, a large proportion of women of childbearing age are underweight and/or anemic and over half of women are anemic during pregnancy (1). While some progress has been made towards reducing early child undernutrition in recent years, mainly as a result of national breastfeeding and complementary feeding programs, maternal undernutrition remains a problem (1). Recommendations for pregnant women in Cambodia include consumption of an extra daily meal (85). However, the staple food in Cambodia, white rice, has low nutritional value, which prevents many women from meeting their nutritional needs when pregnant (75). The burden of undernutrition is especially high among women and children in Kampong Chhnang Province, where the prevalence of anemia among women of childbearing age is ~57%, which is 13% higher than the national average and the second highest in the country (1). Stunting (low height-for-age) among children < 5 in the province is 40% and the prevalence of anemia in this age group is 64%, the third highest in the country (1).

Reducing maternal and child undernutrition during the first 1,000 days between conception and 24 months is a key priority of donor and development agencies (190). One approach is targeted food supplements such as fortified-blended-foods (FBF), which are provided to pregnant women and other nutritionally-vulnerable populations (191). Such foods aim to supplement the local diet with macro- and micronutrients. The energy-dense, micronutrient-fortified maize and soybean flour Corn Soya Blend Plus is commonly used in supplementary feeding programs for pregnant women (158), though little is known about its acceptance in this population. For dietary supplements such as CSB Plus to improve the nutritional status of beneficiaries, they must be acceptable in the populations they are used. This entails exploring factors that facilitate or challenge their uptake. This gap in knowledge surrounding CSB Plus is significant and has resource and ethical implications for both suppliers and recipients of the supplement. To our knowledge, there are no published studies on the acceptability of CSB Plus among pregnant women.

We investigated factors that affected women's acceptability and consumption of CSB Plus during pregnancy in rural Cambodia. This study was embedded in a CSB Plus efficacy trial conducted in Kampong Chhnang Province between August 2011 and February 2013, in which 547 women received the food supplement, starting in the first trimester through the final month of pregnancy, or followed a normal diet.

3.3 Methods

3.3.1 Study Setting and Participants

As mentioned, women who participated in the qualitative acceptability study were part of an efficacy trial, in which they were provided CSB Plus supplements (daily ration: 200 g CSB Plus and 10 mL vegetable oil) while pregnant. During each month, from enrollment in the first trimester until delivery, women were provided approximately 7 kg of CSB Plus in durable plastic bags provided by the United Nations World Food Programme, the donor of the supplement. On average, participants began receiving the food supplement at 8 weeks gestation. Women were instructed to cook the CSB Plus and oil together as a porridge and were asked to track how much CSB Plus they consumed each day. The design, methods, participant characteristics, and results of the trial are discussed in chapter 2.

The study villages comprised mainly subsistence rice-farming communities. The importance of rice in the country's food culture is reflected in the Khmer language in which "eating" is literally translated as "eating rice" (192). Further, rice constitutes the main part of the Cambodian meal and a commonly used expression is "if a person has not eaten rice, a person has not eaten". Small amounts of vegetables and fish or meat (if available) are typically eaten with rice, but are not substantive components of the meal.

For the acceptability study, which was nested within the larger trial, structured interviews and focus groups were conducted. The structured interviews were conducted with all women in the CSB Plus (treatment) group who completed the trial and were administered individually at the household following delivery. Six focus groups were conducted with a subset of women in the treatment group after delivery (1-6 months post-delivery depending on the time of enrollment). As the number of trial participants from each village was small, all women who completed the trial were eligible to participate in their respective village's focus group. Focus group villages were purposively selected based on geographic representation in an attempt to achieve maximum sample variation. The informed consent procedure for the trial included participation in the qualitative study.

3.3.2 Data Collection and Analysis

The questionnaire for the structured interview was designed to collect information on the CSB Plus user experience and included primarily closed-ended questions on behaviors pertaining to supplement usage (cooking methods, frequency of consumption, household sharing), benefits and adverse effects, and motivators and barriers to consumption. We used open-ended questions to elicit suggestions for product improvement. The interview guide was pre-tested in the local community and revisions consisted mainly of terminology changes.

The FGDs were designed to expand on aspects of the interview (user preferences) and investigate in greater depth the factors that positively and negatively affected uptake of the CSB Plus intervention. Through the FGDs, we sought to gain a deeper understanding of and explanation for the supplement-related behaviors observed in our study population. We utilized focus groups instead of in-depth interviews given the advantage of this methodology to identify prevailing cultural and/or community norms and shared beliefs (193) and because we wanted to capture the rich data inherent in inter-participant interactions and behaviors fostered in a group discussion setting. As Kitzinger notes, "Focus groups reach the parts that other methods cannot reach, revealing dimensions of understanding that often remain untapped by more conventional data collection techniques" (194; p. 299). Furthermore, based on local input and circumstantial knowledge, we felt group discussions would engage women more fully in this cultural context. Table 3.1 presents the key topic areas explored in the interviews and focus groups.

Table 3.1 Key topics in structured interviews and focus group discussions[1]

No.	Topics
1	How did you like to consume CSB Plus?
2	How often did you consume CSB Plus?
3	What challenges did you experience when preparing CSB Plus?
4	Who else in the household ate CSB Plus?
5	How did eating CSB Plus affect your intake of other family foods?
6	Who provided support or discouraged you in regard to using CSB Plus?
7	What health benefits and side effects did you experience from eating CSB Plus?
8	What encouraged/motivated you to eat CSB Plus?
9	What discouraged you from eating CSB Plus?
10	How do you feel about eating CSB Plus next time you are pregnant?
11	How would you prefer to receive CSB Plus or other foods in the future?
12	How can CSB Plus be improved?

[1]CSB, corn soya blend.

Both the structured interviews and focus groups were conducted by International Relief & Development (IRD) research officers who were trained by senior IRD researchers and technical experts from a large multi-year child survival project. The interviews took place at women's homes within one month of delivery and took an average of 45 minutes to complete. Participant answers were recorded in writing by the interviewer and forms were checked by the research supervisor for completeness and obvious recording errors which were corrected. Automated quality control checks were built into the data entry process. Data were analyzed using simple descriptive methods and are presented as frequencies and percentages.

FGDs were conducted in each selected village after all women in the respective village delivered. They were held at the home of a village health worker, the village pagoda, or other convenient meeting place and lasted 90 to 120 minutes. The FGD guide contained key questions to direct the discussion, but allowed flexibility to explore topics as they emerged. Probing techniques were used as necessary to explore ideas and viewpoints in further detail. Each audio-taped focus group was facilitated by one moderator and two note-takers captured nuanced aspects of the discussions, including participant temperament, tone, and emotion. The moderator and note-takers prepared a detailed report of each discussion in the local language from the audio-recording and expanded field notes and then produced a synthesized summary in English. The summaries were assessed for completeness, accuracy, and quality of translation by bilingual IRD project staff who were external to the study team. A thematic content analysis was performed on the synthesized summaries. This entailed organizing text around relevant themes and subthemes that emerged during the discussions using an inductive coding scheme. The method allowed for iterative coding as we gained more in-depth understanding of the data. Coded segments were manually grouped and inserted into textual matrices in MS Word for interpretation. We used the constant comparison method (195) to examine findings of each focus group in relation to preceding discussions. Illustrative quotes of participants are included to reinforce key points and concepts raised. Perspectives of “deviant” cases, that is, opinions expressed by one or very few individuals, were described for completeness. All data entry, management, and analyses for the CSB Plus acceptability study were conducted locally at the IRD office premises in Kampong Chhnang, Cambodia.

Our analytical approach entailed organizing data based on a framework developed by Young et al. in their acceptability study of three nutritional supplements among pregnant and lactating women in Mexico (196). This innovative, grounded-theory approach involved examining three aspects of acceptability: organoleptic properties, ease of use, and positive and negative health effects. We chose to adapt this conceptual scheme as their study closely paralleled our research in terms of the aspects of acceptability investigated and it was also conducted in the context of a cluster-randomized efficacy trial that examined the impact of the three supplements on maternal nutrition outcomes. In addition to Young et al.'s three thematic categories, our framework included an exploration of women's attitudes and perceptions towards CSB Plus as we believed these to be important determinants underlying its use and acceptance in our study context. In this chapter, data obtained from the structured interviews and focus groups are combined and presented together according to the components of the conceptual framework: organoleptic qualities, feasibility of use, health effects, and attitudes and perceptions. The data source (interview or FGD) is specified, where relevant, to provide further clarity.

3.4 Results

A total of 288 women from 37 villages in Kampong Chhnang Province participated in the structured interview. Of these, 70 women from 6 villages also participated in the FGD component. The average age of participants was 26 years and, although most had some formal schooling, 40% did not complete primary school (grade 6). Most households (~70%) were classified as impoverished, according to the World Bank definition of living on less than 2 USD/day (197).

3.4.1 Organoleptic Qualities

Women were very sensitive to the organoleptic qualities of CSB Plus, particularly the sensory characteristics of smell and taste. Almost all women (> 90%) disliked the smell produced during the boiling process, which they referred to as an undesirable "corn smell", and the majority said the taste was bland and flavorless. Women's aversion to these attributes of CSB Plus was particularly acute during periods of morning sickness, which more than half of women experienced beyond the first trimester: '*I was having morning sickness and the smell when cooking (CSB Plus) porridge made me feel sick in my stomach and I had to vomit. It would be better if it did not smell when cooking*'.

Numerous women mentioned adding sugar to make the supplement more palatable, though some said having to purchase extra sugar meant they could consume limited quantities of CSB Plus: *'I could not eat it (CSB Plus) the way it was given to us because the taste was not good. I had to go to the market to buy sugar so I could eat it because they told me it was good for my baby. But I could not keep buying more sugar because my family is poor so I did not eat a lot'*. Aside from adding sweetness to improve the taste of the porridge, women cooked the flour in other ways such as frying, making a beverage, and preparing a thick mush, which was translated to mean "cake". Only a few women (~10%) stated they liked the CSB Plus as it was provided to them, as illustrated by one woman's comment: '*It was nice to eat when I roasted it on the fire. In the village we are poor. IRD gave us this food and we are happy. We never got food before'*.

3.4.2 Feasibility of Use

Information obtained from the interviews and focus groups revealed no major logistical or structural barriers to incorporating CSB Plus into women's daily routines. Preparatory requirements in terms of time, additional cooking fuel, and availability of water (for boiling) did not affect women's willingness or ability to prepare the food supplement. Most women felt it was easy to cook and reported an average cooking time of 12 to 13 minutes, which was considered minimal. One quarter of participants said family members, particularly mothers and husbands, assisted with cooking during times of illness, fatigue, and on days when women were too busy. This created an enabling environment for uninterrupted consumption: '*When I was* *close to delivery and did not have energy in my body, my mother told me I had to eat the vitamin food (CSB Plus) to be ready and she was cooking it for me'*.

Many women found it challenging to store the flour in the provided plastic bag in the household because it was not airtight once opened and was, therefore, easily penetrated by insects, rodents, and other pests. Instead, they said it would be better to receive CSB Plus in a reusable plastic or tin container that could be refilled each month. A few women said smaller quantities provided on a more frequent basis (weekly or fortnightly) would be preferable for easier home storage and management. Women were generally satisfied with the quantity of CSB Plus they received. However, based on consumption records maintained by the women, interview responses, and field observations of the researchers, intake was less than maximum (average 0.6 rations/day). A major reason for this was that most women opted to consume CSB Plus as a snack between meals, rather than as the intended extra porridge meal. The relative popularity of consuming CSB Plus as a "snack" food was also based on women's preferred methods for preparing the flour alluded to earlier (frying, beverage), which were more conducive to being eaten in small amounts, rather than as full meals. CSB Plus was not incorporated into daily meals as only 2% (n=5) of women said they consumed it with their normal "family" foods. This was due to preference and not to avoid sharing it at meal times.

As the food supplement was specifically targeted to pregnant women in the household, and most Cambodian households are multi-generational, we explored women's decision-making with regard to dietary choices and eating habits during pregnancy. Encouragingly, all women stated they were responsible for their food choices and controlled their eating behaviors, including consumption of CSB Plus, when they were pregnant. Moreover, the presence of an additional food source in the household did not exert any untoward pressures on women to cook it for their husbands and/or parental elders. Alternative uses such as feeding it to their children were voluntary choices made by few women. Family members were generally supportive and encouraged women to cook and eat the CSB Plus, which facilitated utilization. In the interviews, all women said their husband approved of them consuming the supplement.

We encountered mixed opinions regarding preferred forms of food supplements. Despite the undesirable flavor, more women liked having the uncooked flour because it could be customized to taste and cooking style. Such women said if they received a ready-to-eat food and did not like it, nothing could be done and it would be wasted: '*If they give us something else that tastes bad and we cannot change the taste, we cannot do much. With this (CSB Plus) even though we do not like the taste much we can make it better'.* Fewer women said a ready-to-eat food would be more convenient because it would not require cooking, could be eaten anywhere, and that a packaged product would be easier to store in the home: *'It would be better to have something we can eat any time and take to the (rice) field'*. Though 99% of women interviewed expressed willingness to receive CSB Plus during a future pregnancy if offered at no cost and delivered to them directly as occurred during the trial, fewer (80%) said they would be willing to collect it from the nearest health center, which we considered as a proxy point of distribution to gauge product demand. Willingness to pay for CSB Plus was not determined, given that the product is currently only provided at no-cost as part of donor-led global food assistance programs.

3.4.3 Health Effects

In the structured interviews, most women reported at least one perceived benefit from consuming CSB Plus. Benefits were primarily associated with the mother's health and well-being during pregnancy and the size, strength, and general health of the newborn (Table 2): *'After eating the food (CSB Plus), I had more energy. With my last child, I did not have much energy and felt* *dizzy and had to sleep a lot'*. One woman said the CSB Plus enabled her to produce more milk during lactation, compared to her previous breastfeeding experience. Specific to the newborn, positive effects mentioned were a healthy, normal-weight, and pretty baby and the infant being ill less frequently. In the FGDs, a few women cited indirect health benefits such as being able to take their other children to the health center and buy medicines because they were able to save some money due to having the additional CSB Plus food source. Other benefits mentioned by women during the group discussions were rapid infant growth and that their baby was clever, which was determined to mean active in the local language.

Negative effects of CSB Plus were reported by about 10% of interview respondents and consisted of adverse events experienced by the women. Diarrhea and nausea were the most common complaints. Three women reported stomach pain, one experienced dizziness, one reported headache, and one woman said CSB Plus induced a fever. The majority of women said side effects lasted a short time and were not bothersome. Three women said they experienced side effects often, or on a daily basis, and only one woman reported stopping the CSB Plus completely due to continuing nausea and stomach upset. In general, side effects did not appear to be a barrier to consumption of the supplement: '*The first week I ate it (CSB Plus) I had a pain in my stomach. I asked the village health worker and she told me it would go away and I should try eating it again because I need to eat good for my baby. I did what she told me and the pain got less'*. Table 3.2 presents the health benefits and adverse effects women associated with consuming the supplement, as reported in the structured interviews.

Table 3.2 Reported benefits and adverse effects of Corn Soya Blend Plus

	n	(%)
Reported benefit to mother (N=282)		
Felt healthier	204	(72)
Had more energy	189	(67)
Increased appetite/gained weight	9	(3)
Had easy delivery	4	(1)
Produced more breast milk	1	(<1)
Saved money	1	(<1)
Reported benefit to baby (N=282)		
Born with healthy/normal weight	210	(75)
Was not ill frequently/grew well	42	(15)
Born with pretty skin	22	(8)
Reported adverse effect to mother (N=30)		
Diarrhea	15	(50)
Nausea	7	(23)
Abdominal pain	3	(10)
Dizziness	1	(3)
Fever	1	(3)
Headache	1	(3)

3.4.4 Attitudes and Perceptions

Exploration of women's attitudes and perceptions revealed two dominant themes related to acceptance of CSB Plus: women's perspectives on health/nutrition status in pregnancy and views towards gestational weight gain. Nutritional adequacy held less importance than other concerns women had during their pregnancy. Lacking money for the cost of delivery and necessary supplies for the newborn was a major source of anxiety. Women said they often compromised on food purchases to save money for childbirth expenses. Some women expressed regret about not being able to have a better diet: '*I wanted to eat stronger food like beef, but I had to keep the money for delivery at the health center and for the blanket, bottle, and clothes for my baby'*.

Women's opinions about health/nutrition in pregnancy were reflected in the relative homogeneity between the pre-pregnancy and prenatal diet. In general, having good health was associated with eating “enough”. Therefore, eating well in pregnancy typically meant increasing intake of routinely consumed foods, namely rice, as opposed to seeking out higher-quality proteins such as meat and eggs. This was also due, in large part, to economic constraints that limited access to such costlier foods. The emphasis on food quantity was not only circumstantial, but was also influenced by messages typically provided during routine antenatal care sessions. At these visits, women were encouraged to eat more, though were provided little guidance on intake of specific foods, aside from leafy green vegetables which were strongly emphasized as dietary sources of iron. CSB Plus acceptance was also affected by women’s perceived household food availability. Women who reported having enough food, irrespective of quality, consumed less CSB Plus, while those living in households with less food available showed greater acceptance. In the structured interview, only 12% of women reported eating less of their normal daily food because they were given the additional food source.

The second dominant theme that emerged surrounding women’s attitudes towards the food supplement related to the topic of weight gain in pregnancy. Women who were pregnant for the first time during the study were less receptive to the CSB Plus due to fears of weight gain, a large fetus, and resulting delivery complications. Some underlying stigma surrounding being “cut”, that is, having a cesarean section, was inferred from some of the FGDs and could have contributed to these fears. Though women said they primarily consulted midwives at health centers for trusted advice during pregnancy, it became apparent that counseling on the risks of inadequate gestational weight gain was not standard practice. New mothers feared the unfamiliar childbirth experience and labor pain due to their tighter pelvic muscles. These fears influenced their willingness to consume a product that was partly promoted to increase infant weight. In contrast, women who had children more readily accepted the CSB Plus because they believed it would help them build up vitamins and "power" (energy) for delivery, which they wanted based on their previous childbirth experience(s). Also, several women said they did not want an underweight and weak baby with frequent illness as this would incur unmanageable costs for health center visits and medicines: '*My last child was born very small. The midwife said the baby had no power to drink mother's milk and grow well. I took my baby to hospital and they took much money from me. This time I ate more and the new food (CSB Plus) to make my baby grow enough inside'.* A few women were concerned about having a child with a deformity and some believed that the vitamins in the supplement would prevent a malformation: '*I ate the CSB Plus because I was afraid my baby would not have a full body'.* These divergent opinions regarding weight gain in pregnancy were reflected in how CSB Plus was incorporated into women's eating practices. For women who were eager to gain weight, eating CSB Plus fit with other weight-promoting practices such as increasing portion sizes, having more frequent meals and/or snacks, and consuming what they considered to be high-energy foods such as fruit "shakes" and duck fetus, if they were able to afford them. For women who wanted to control their weight gain, eating less CSB Plus was accompanied by weight-limiting behaviors such as reducing food intake and frequency and avoiding sweets and other foods they associated with weight gain.

In the structured interview, we explored the level of intra and inter-household sharing of CSB Plus. Though about 80% of women reported sharing the supplement within the household, two-thirds said they only shared the equivalent of one or two rations per month. Seven women said they shared it on a daily basis. Distribution outside the household was less common. Individual interpersonal messaging and the package label targeted only to pregnant women were intended to discourage sharing. The sale of CSB Plus by participants was not reported or observed in this setting. Finally, the knowledge and trust instilled through frequent interactions with the IRD study team, positive experiences of co-participants recruited earlier in the study (e.g., more energy, smooth delivery, healthy baby, pretty baby), as well as safety assurances provided through peer experiences cultivated positive attitudes towards CSB Plus and motivated later recruits: '*At first I was not sure about it (CSB Plus), but then I saw my neighbor eat it and she had a healthy and clever baby so I thought to eat it also'.* Lastly, CSB Plus was not associated with negative consequences other than women's perceived problems associated with excess weight gain. For example, it was not likened to a prevailing food taboo or traditional food avoidance in pregnancy. Therefore, such culturally-imposed potential barriers to consumption were unlikely.

3.5 Discussion

In this study, we explored women's experiences with Corn Soya Blend Plus dietary supplements during pregnancy in a rural Cambodian setting. Acceptance of the food supplement was examined through women's opinions and beliefs about palatability, ease of preparation, health effects, and attitudes and perceptions that motivated or inhibited use. The intervention, which was the participants' first exposure to CSB Plus, was generally accepted and tolerated, despite aversions to sensory characteristics and dislike of the porridge. Surprisingly, logistical considerations such as additional time and cooking fuel did not discourage preparation. This differs from the literature on infant and young child complementary feeding programs, which suggests a mother's lack of time is often a barrier to preparing special foods for children and nutrition supplements requiring active preparation are typically less well accepted than ready-to-use foods (5).

CSB Plus adherence was situated within the context of maternal nutrition being less important than other concerns requiring protective action such as the cost of health center visits, delivery, and postpartum care and amidst fears of gestational weight gain among new mothers. Parallels can be drawn between our findings and the literature on interventions to reduce malaria in pregnancy, which suggests vulnerability to illness should be viewed in relation to other needs and concerns women have during pregnancy and that perceived severity of illness can be a strong catalyst for uptake of preventive interventions (198). This was seen in the apparent similarity of the maternal diet prior to and during pregnancy in our population, which has also been observed in Burkina Faso (199), India (200), and Laos (201).

Women's perceptions of weight gain in pregnancy were an important determinant of CSB Plus acceptance in our study population. Positive attitudes, conceived experientially by women who had previously undergone childbirth and those who cared for a weak and ill newborn, were reflected in weight-promoting practices including willingness to consume the dietary supplement. In contrast, fears of a large baby and difficult labor and delivery reduced acceptance of CSB Plus among many first-time mothers. Similar concerns and purposive reductions in food intake during pregnancy have been identified in other settings, including Bangladesh and Indonesia (202-203). A study among Somali immigrants in Sweden identified negative attitudes towards "abnormal" cesarean delivery and decreased food intake to avoid the procedure (204). Our findings suggest women's views towards weight gain in pregnancy can considerably influence acceptance of a food supplement and, therefore, nutrition promotion and allaying fears of weight gain provide opportunities for greater CSB Plus adherence in our context. Moreover, specific challenges facing first-time mothers that may limit supplement consumption necessitate targeted efforts for this vulnerable group. More generally, nutrition-focused counseling should be a core component of antenatal care services as health center midwives were considered the most trusted source for advice and care in pregnancy in our context.

In this setting, women's control over their food choices in pregnancy facilitated acceptance of CSB Plus in the household. This is an important finding and points to the merits of targeting women directly with health and nutrition messages, while creating a supportive family environment to reinforce behaviors. This contrasts to a study conducted by Shannon et al. in Bangladesh which revealed the majority of food reduction in pregnancy was due to intra-household food allocation practices that disproportionately affected women (202). Other factors that influenced uptake of CSB Plus in our study population were positive health effects, few and mild adverse events, peer influences, family support, and trust in the provider of the supplement. Despite the fact that most women disliked the taste and smell of CSB Plus, almost all reported a health benefit, either for themselves or their baby, which they attributed to the supplement. This finding was also observed in a study involving a ready-to-use therapeutic food in Bangladesh, where health benefits in pregnancy were reported in a context of low supplement acceptability (205).

In our study population, CSB Plus was considered a food and not a medicine, though it was promoted as a source of vitamins and minerals. This likely contributed to lower acceptance among those fearing weight gain as food is typically associated with body size, and to increased acceptance among others as it was considered a healthy food and not a medicinal product with an unknown safety profile. This finding is consistent with the Young et al. study among rural Mexican women that partly attributed acceptance of a prenatal fortified powder beverage to it being perceived as a food, rather than a medicine, as compared to the other (tablet and micronutrient powder) interventions evaluated in the trial (196). We observed greater adherence to CSB Plus as the study progressed and women derived more confidence and motivation from others' experiences. Though most women reported sharing the food supplement in the household, the amounts shared were smaller than we expected. The fact that a large number (45%) of participants were first-time mothers may partially explain this, as they did not have the willingness and/or need to feed the supplement to children in the household. This being said, the possibility of under-reporting the extent of intra and inter-household sharing of the food source in these communities cannot be overlooked.

There is a dearth of evidence surrounding the acceptance and use of prenatal corn soya-based products by food aid recipients. However, our findings can be compared with field evaluations of Corn Soya Blend in communities in Guatemala, Malawi, and Uganda (206). In these contexts, where CSB was provided to assist all household members, porridge preparations were preferred and foods such as fruits and vegetables were added to make family meals out of the supplement. Contextual variation likely explains these differences. In Malawi and Uganda, beneficiaries were highly dependent on food assistance for their household needs. Also, frequent selling/trading of the product was reported in Uganda, indicating a high value and demand for the product and perhaps higher levels of overall food insecurity. Lastly, corn is a staple food in these countries, unlike in Cambodia, which supported incorporation of the flour into local dishes (e.g., tortillas in Guatemala) and likely contributed to the higher acceptability in these settings.

A strength of our study is that we captured a wide range of CSB Plus user experiences within a relatively homogeneous socio-economic context. In addition, we assessed the acceptability of CSB Plus over the duration of pregnancy. Further, all eligible women agreed to participate in the qualitative study. A limitation of this type of research is social desirability response bias (207). As utilization of CSB Plus was not observed, it is unknown whether participant responses reflected over-reporting of positive opinions and behaviors and a reluctance to provide truthful, albeit negative, opinions for fear of ridicule, intimidation, or jeopardizing future opportunities for food or other types of assistance. Also, data were collected after women had delivered and retrospective accounts of attitudes and experiences during pregnancy could have been magnified or attenuated with the elapse of time. This logistical arrangement was made to avoid introducing bias into the efficacy trial and, therefore, could not have been avoided.

The findings of this study provide valuable insight that can be used to guide future programming and policy on the provision of prenatal dietary supplements in Cambodia. We speculate that the individual, household, and community factors that influenced acceptance and consumption of CSB Plus during pregnancy in our context are generalizable to other rural settings in the country. Our findings were generated in the context of a controlled clinical trial, in which supplements were provided at the household and frequent interactions occurred between field researchers and participants, which likely contributed to utilization. Acceptability outside a research context should be investigated. Finally, the findings highlight potential factors that may also be inhibiting optimal acceptance and consumption of CSB Plus among populations in other geographical regions. Knowing how and why supplements are used and determining the impediments that challenge their acceptance in different contexts are important for adapting global food-based programs to local conditions.

Chapter 4: Discussion and Conclusion

This research conducted in rural Cambodia has contributed knowledge on the effects of prenatal supplementation with Corn Soya Blend Plus on maternal and newborn nutrition, and has provided insight into the social and behavioral context in which supplement usage occurred. The mixed methods approach that used a sequential explanatory design (208), whereby the collection of quantitative data was followed by qualitative data to further explain the measured results**,** is a strength of the research. It provided a fuller understanding of the supplement's impact among women in these communities than would have occurred using a single method.

I tested the hypothesis that infants born to women who consumed CSB Plus during pregnancy would have a higher average birth weight than those born to women on a routine, unsupplemented diet. Though not significant, the 46 g increase in birth weight observed in the treatment group is consistent with Kramer's (95) meta-analysis of prenatal protein-energy supplementation studies (38 g; -0.2, 75.5) and Ota's (96) update of this review (41 g; 5, 77). However, the result is lower than the pooled estimate of Imdad and Bhutta (93) (73 g; 30, 117), which included six additional studies. The lack of evidence for improved newborn anthropometry in the CSB Plus group raises doubt about the ability of the food supplement to confer benefits on birth size in this context. We expected an increase in birth weight, mediated through an increase in maternal weight gain, given that the average reported daily consumption (~120 g) of CSB Plus contributed close to 500 kcal per day. The fact that there was no difference in maternal weight gain suggests energy intake was probably similar between the treatment and control groups, despite the added food source. This was likely due to a combination of factors related to dietary substitution, household sharing, as well as potential overreporting of CSB Plus consumption.

For poor families, in which a large portion of household expenditure is spent on food, it is reasonable that women would want other family members, especially children, to eat the health-promoting food and/or that they would eat more of the provided supplement and less of their normal family foods to enable others in the household to have larger portions. Regarding women's reporting of the amounts of CSB Plus they consumed, the desire to avoid being perceived as 'non-compliant' is a limitation of such research and possible overreporting of 'good behavior' could have introduced social desirability bias (207) in the self-reported data. Further, adherence may have been overreported due to women not wanting to jeopardize receiving possible future benefits from the organization providing the food supplement. This is a likely reality in vulnerable communities facing extreme poverty and associated challenges. Finally, determining the amount of CSB Plus consumed may have been difficult for women, given the various methods they used to prepare the flour, which could have overestimated actual intake.

The qualitative study provided insight into factors that encouraged and limited acceptance of CSB Plus. Women's sensitivity to the product's sensory characteristics of taste and smell were barriers that influenced their willingness to consume the food. The majority of women had to modify the flour in some way to improve palatability, mainly by making it sweeter, though reducing the unpleasant smell during cooking proved to be more difficult, despite the addition of aromatics (e.g., vanilla). An important theme that emerged from the qualitative data was that women's views towards weight gain in pregnancy influenced acceptance of the supplement. Interestingly, attitudes towards weight gain were shaped experientially and were positive for many women who had undergone childbirth, especially those who had to care for a weak and frequently ill newborn. For many new mothers, concerns surrounding excess weight gain leading to a large baby and delivery complications outweighed their perceived risks associated with having a small baby. Though these concerns reportedly manifested in some women limiting their food intake, including the CSB Plus, when pregnant, this did not corroborate with the quantitative data that showed no significant difference in the average number of CSB Plus rations consumed by women who were pregnant for the first time during the study and those who had one or more children. The reason for this conflicting finding is unclear and may reflect greater overreporting of consumption among new mothers. Nonetheless, this has important implications for using food-based approaches that promote increased maternal energy and weight gain, as well as strong (commonly perceived as larger) babies. These findings suggest that improvements in the product's characteristics, allaying fears of weight gain, and nutrition promotion could potentially improve CSB Plus supplement adherence in this context.

It is useful to situate our results in the context of other prenatally-administered food supplements that have produced larger effects on birth size. More pronounced impacts on birth weight and length have been observed in studies using supplements containing a milk protein and a high percentage of dietary energy from fat. Lipid-based Nutrient Supplements (LNS) are semi-solid substances that contain a vegetable oil, peanut or groundnut paste, milk powder, sugar, and several micronutrients (209). In contrast to fortified flours like CSB Plus, these ready-to-eat supplements are provided in smaller, concentrated doses that provide less total energy, but the majority of dietary energy as lipids, along with a high-quality (animal source) protein. LNS are gaining donor popularity because they are easier to transport, do not require preparation, are less prone to environmental contamination, and are less conducive to sharing than a flour supplement.

LNS have mainly been used to treat acute malnutrition in children and are beginning to receive more attention as potentially effective options to enrich the maternal diet. Plumpy'nut® is a well-known LNS as it has been widely used to treat severe acute undernutrition in children (209). Nutributter® is a commercially available LNS developed to prevent undernutrition that contains a vegetable fat, peanuts, milk powder, sugar, and vitamins and minerals (209-210). Packaged in a 20 g dose, it provides ~110 kcal, 2.6 g (10%) protein, and 7 g (59%) fat (including linoleic and alpha-linolenic fatty acids) (210). In Ghana, Nutributter® provided during pregnancy resulted in a higher average birth weight (85 g; $p = 0.04$) and lower risk of low birth weight (RR: 0.61; 95% CI: 0.39, 0.96) than IFA (153). In Bangladesh, the same product resulted in a 17% reduction in risk of newborn stunting, compared to IFA supplementation (RR: 0.83; 95% CI: 0.70, 0.96) (211). Though these are impressive results, they need to be balanced with cost considerations as LNS are expensive (212). Thus, it would seem that to make commercially produced LNS more cost-effective for pregnant women, it would be necessary to target supplementation based on an individual's nutritional status, as opposed to pregnancy status in the case of CSB Plus, which may present logistical challenges in field settings.

Locally-produced supplements containing a high fat content in Burkina Faso and The Gambia also resulted in significant improvements in birth size. In Burkina Faso, a peanut-soy spread containing 67% of energy from fat significantly increased birth length (103). In The Gambia, high-energy groundnut biscuits providing 50% of energy from fat produced a large effect on birth weight (> 200 g) in the lean season (100). In contrast to the high fat content of these products and the commercially available LNS, only 6% of total calories in a daily ration of CSB Plus flour is provided from fat. The oil provided along with the monthly CSB Plus ration constituted an additional fat source, but it is unclear whether women regularly used it for cooking the flour as this was not supervised. Oil is a highly valued commodity in these communities and, consequently, could have been used for other purposes. Though some support in the nutrition sector exists for creating Cambodia-specific supplementary foods to help women meet their pregnancy requirements, the development of such products is rather challenging as it requires accurate and representative dietary and market data, fairly complete food composition tables, and, typically, the establishment of public-private partnerships. Moreover, there is no guarantee that combinations of local foods in the form of a supplementary food will be acceptable.

The reductions in maternal anemia and preterm birth in this study are clinically important treatment effects. However, further research is needed to ascertain whether these findings can be replicated in other studies. For example, further research could compare nutritional outcomes resulting from CSB Plus supplementation in pregnancy to alternative prenatal approaches for filling energy and nutrient gaps that involve increasing consumption of locally-available nutrient-dense foods, thereby preserving local dietary practices. Two of these approaches (cash transfers and the PD Hearth model) are discussed below. Further, as our data revealed higher rates of fetal loss associated with CSB Plus, this also requires further study.

Cash transfers function as food assistance mechanisms by increasing people's purchasing power, thereby creating access to better quality foods that are generally out of reach for poor households (213). Aside from helping people out of poverty, they provide other potential benefits as the transfers are often conditioned on certain health-promoting behaviors (e.g., child immunization, maternity care) and the cash inputs into local communities strengthen local markets and incentivize farmers and traders to produce and maintain food stocks for purchase (213). Conditional cash transfer (CCT) programs have been very successful in Latin America, particularly in Brazil and Mexico, and have resulted in major improvements in child health in these countries (214-216). Started in 2004, the *Bolsa Familia* program in Brazil is the largest CCT program in the developing world and is credited for helping millions of people out of poverty (214, 216). Cash transfers to poor pregnant women, conditioned on attending antenatal care where knowledge on good food sources during pregnancy is reinforced, would be especially suitable for Cambodian households with small land holdings that are unable to increase their home food production, as in much of the Lake Tonle Sap region. In this area, where long distances limit access to food markets, particularly during the wet season, transport costs could be offset by the cash transfer. A similar mechanism that could be used is cash vouchers that are exchanged for a choice of food items. This system offers advantages in terms of ensuring cash allowances are only used for food purchases and they more directly benefit producers and sellers by guaranteeing purchases of key food items in specific shops (213).

The Positive Deviance (PD) Hearth approach has been successfully used to reduce child undernutrition in many settings (217), though robust scientific evidence from randomized trials and studies involving large samples is limited (218). This strategy is based on the premise that many solutions to local problems already exist in communities and that, in every locality, there are “positive deviants”, that is people who share similar socio-economic characteristics but who are in better health (219). The approach involves identifying these individuals and promoting their practices through a community-based peer learning process. The system is empowering because it shows people what is possible, in spite of their common disadvantages. This tried and tested approach for children could be adapted to draw on local practices that promote good health and nutrition in pregnancy in the Cambodian context, given the demonstrated success of community PD Hearth sessions in rehabilitating acutely malnourished children in the country (220-221). This could also facilitate providing community knowledge and support to first-time mothers, who were identified as an especially vulnerable group in our research. Locally-inspired solutions to problems are compelling because, in my view, they have a greater chance of changing community norms and, thereby, effecting sustained improvements.

Additionally, based on the evidence generated from our research that suggests a positive impact of the micronutrient fortificant in the CSB Plus, the nutritional benefits of adding these additional nutrients to low-quality staple diets in the form of prenatal vitamin and mineral supplements should be investigated. Such supplements can be cheaply procured and easily integrated into prenatal care services through leveraging well-functioning distribution systems for IFA and deworming tablets. An advantage of multi-micronutrient tablets is that guaranteed dosing (e.g., 1 RDA) is ensured, as opposed to fortified food supplements where micronutrient intake is based on the quantity of food consumed. The highly anticipated results of the Cambodia national micronutrient status survey expected later this year will provide us with a better understanding of the unmet micronutrient needs in women and other demographic groups so we can better tailor our efforts to close the micronutrient deficiency gap in the country.

Our research findings have other implications for the health of Cambodian women. Despite the sizable reduction in anemia in the treatment group in our study, the prevalence remained above 30% in late gestation. Though we did not assess markers of iron status, other than proxy hemoglobin levels, this rate of anemia in the context of high reported IFA and deworming adherence suggests the presence of other factors that are unresponsive to iron repletion. This, in turn, supports the growing body of evidence suggesting that iron deficiency may not be as large a problem among women of childbearing age in the country as previously thought. The work of UBC Human Nutrition researchers has shown low levels of iron deficiency and a high prevalence of genetic hemoglobin disorders among women of reproductive age in another province in Cambodia (81), reinforced with data suggesting high levels of environmental sources of iron (222) and adequate dietary iron intake in the same area (unpublished data). These findings challenge the longstanding view that the high rate of anemia in Cambodian women is mainly due to poor coverage and compliance with iron supplements.

As part of the implementation of our study, we leveraged existing health infrastructure and capacities for the maternal and newborn measurements and management of anemia, which contributed to strengthening of antenatal care services in the study area. The incorporation of hemoglobin testing and anemia treatment into routine prenatal care, as part of our study, has been replicated in other health centers in an effort towards province-wide scale-up using our introduction model. Hitherto, anemia was diagnosed based on visual inspection, which left most cases untreated. A limiting aspect of the research is that the observed effects of CSB Plus on maternal and newborn nutrition status and participants' experiences with the product reflect those of women who were probably more health-focused by virtue of having sought antenatal care early in pregnancy. However, subsequent to the completion of the research, preliminary key indicators from the latest Cambodia Demographic and Health Survey (223) were released. These results, which were generated from data obtained during 2010 to 2014 and thus overlap with our study timeframe, indicate substantial improvements in antenatal care attendance and facility deliveries and a resulting reduction in maternal mortality. This, in large part, reflects the investments in maternity care made by the Cambodian government towards achieving the Millennium Development Goals (120). Preliminary results for Kampong Chhnang Province reveal 99.5% of women who gave birth in the five years preceding the survey sought antenatal care from a skilled provider (doctor, nurse, health center midwife) at least once and 86% had four or more prenatal visits at a health facility (223). Also, 97% of surveyed women in the province delivered at a health facility (223). In light of these findings, it could be that our study participants constituted a more representative sample of women in the province than we originally thought.

In conclusion, the serious, and potentially lifelong, consequences of fetal undernutrition demand immediate and effective action. Donor provision of corn and soy-based food rations to respond to the hunger and nutritional needs of populations is common practice. Not knowing whether these products are achieving their objectives in the places they are used has ethical and resource implications. This research is pioneering work in that, to our knowledge, there are no published studies on the efficacy, effectiveness, or acceptability of CSB Plus supplements in pregnancy, despite their extensive global use. Though the results suggest CSB Plus may have a role in improving maternal and child health in Cambodia, the positive effects need to be considered along with the higher number of fetal losses experienced by women who consumed the food supplement. Our findings suggest the risks may outweigh the benefits of CSB Plus consumption. Therefore, serious questions remain regarding the use of CSB Plus to improve pregnancy outcomes in Cambodia and other settings.

References

1. National Institute of Statistics, Directorate General for Health, and ICF Macro. Cambodia Demographic and Health Survey 2010. Phnom Penh, Cambodia and Calverton, Maryland, USA: National Institute of Statistics, Directorate General for Health, and ICF Macro, 2011.

2. Victora CG, Adair L, Fall C, Hallal PC, Martorell R, Richter L, Sachdev HS, Maternal and Child Undernutrition Study Group. Maternal and child undernutrition: consequences for adult health and human capital. Lancet 2008;371:340-57.

3. Improving the Nutritional Quality of WFP's Food Basket – An Overview of Nutrition Issues, Commodity Options and Programming Choices. Sight and Life Magazine 2008;3:4–14.

4. World Food Programme. Vulnerability Analysis and Mapping Food Security Analysis: Understanding Vulnerability. WFP, 2013.

5. De Pee S, Bloem MW. Current and potential role of specially formulated foods and food supplements for preventing malnutrition among 6- to 23-month-old children and for treating moderate malnutrition among 6- to 59-month-old children. Food Nutr Bull 2009;30:434–63.

6. World Food Programme, Cambodia. UN NGO Presence by Sector, 2013. Available at http://epmaps.wfp.org/maps/06013_20131022_KHM_A4_WFP_Cambodia,_UN_NGO_Presence_by_Sector_(as_of_21_October),_21_October_2013.jpg.

7. National Institute of Statistics. Cambodia Anthropometrics Survey 2008. National Institute of Statistics, Directorate General for Health, 2011.

8. PMNCH Knowledge Summary #18 (Nutrition). The Partnership for Maternal, Newborn and Child Health, 2012. Available at http://www.who.int/pmnch/knowledge/publications/summaries/ks18.pdf?ua=1.

9. World Health Organization. World Health Report 2002: Reducing Risks, Promoting Healthy Life. WHO, 2002.

10. UNICEF. Improving Child Nutrition: The Achievable Imperative for Global Progress. UNICEF, 2013.

11. Ransom E, Elder L. Nutrition of women and adolescent girls: why it matters. Population Reference Bureau, 2003.

12. World Health Organization. World Health Report 2005: Make Every Mother and Child Count. WHO, 2005.

13. Save the Children. Saving Newborn Lives: State of the world's newborns. Save the Children, 2001.

14. UNICEF. Monitoring the Situation of Children and Women. UNICEF, updated Nov 2014. Available at http://data.unicef.org/nutrition/low-birthweight.

15. Delisle H. Programming of chronic disease by impaired fetal nutrition: evidence and implications for policy and intervention strategies. World Health Organization, 2002.

16. Barker DJ. Fetal origins of coronary heart disease. BMJ 1995;311:171-4.

17. Villar J, Ismail LC, Victora CG, Ohuma EO, Bertino E, Altman DG, Lambert A, Papageorghiou AT, Carvalho M, Jaffer YA, Gravett MG, Purwar M, Frederick IO, Noble AJ, Pang R, Barros FC, Chumlea C, Bhutta ZA, Kennedy SH. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. Lancet 2014;384:857–68.

18. UNICEF and World Health Organization. Low Birthweight: Country, Regional and Global Estimates. UNICEF and WHO, 2004.

19. Ohlsson A, Shah P. Determinants and Prevention of Low Birth Weight: A Synopsis of the Evidence. Institute of Health Economics, 2008.

20. Kramer MS. Intrauterine growth and gestational duration determinants. Pediatrics 1987;80:502-11.

21. Schieve LA, Cogswell ME, Scanlon KS, Perry G, Ferre C, Blackmore-Prince C, Yu SM, Rosenberg D, the NMIHS Collaborative Study Group. Prepregnancy body mass index and pregnancy weight gain: associations with preterm delivery. Obstet Gynecol 2000;96:194-200.

22. Battaglia F, Lubchenco L. A practical classification of newborn infants by weight and gestational age. J Pediatrics 1967;71:159-63.

23. Pojda J, Kelley L. Nutrition Policy Paper No. 18. United Nations Administrative Committee on Coordination, Sub-Committee on Nutrition, 2000.

24. Rush D. Nutrition and maternal mortality in the developing world. Am J Clin Nutr 2000; 72:S212-40.

25. Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, de Onis M, Ezzati M, Grantham-McGregor S, Katz J, Martorell R, Uauy R, the Maternal and Child Nutrition Study Group. Maternal and child undernutrition and overweight in low-income and middle-income countries. Lancet 2013;382:427–51.

26. Abu-Saad K, Fraser D. Maternal nutrition and birth outcomes. Epidemiol Rev 2010;32:5–25.

27. Özaltin E, Hill K, Subramanian SV. Association of maternal stature with offspring mortality, underweight, and stunting in low-to middle-income countries. JAMA 2010;303:1507-16.

28. Hambidge KM, Mazariegos M, Kindem M, Wright LL, Cristobal-Perez C, Juárez-García L, Westcott JE, Goco N, Krebs NF. Infant stunting is associated with short maternal stature. J Pediatr Gastroenterol Nutr 2012;54:117-9.

29. Dewey K, Begum K. Why stunting matters. Alive & Thrive Technical Brief Issue 2, 2010.

30. Dewey KG, Begum K. Long-term consequences of stunting in early life. Matern Child Nutr 2011;7:5–18.

31. Martorell R, Zongrone A. Intergenerational influences on child growth and undernutrition. Paediatr Perinat Epidemiol 2012;26:302–14.

32. Second Report on the World Nutrition Situation. Volume I: Global and Regional Results. United Nations Administrative Committee on Coordination, Sub-Committee on Nutrition, 1992.

33. Black RE, Allen LH, Bhutta ZA, Caulfield LA, de Onis M, Ezzati M, Mathers C, Rivera J. Maternal and child undernutrition: global and regional exposures and health consequences. Lancet 2008;371:243–60.

34. Allen LH, Lung'aho MS, Shaheen M, Harrison GG, Neumann C, Kirksey A. Maternal body mass index and pregnancy outcome in the Nutrition Collaborative Research Support Program. Eur J Clin Nutr 1994;48:S68-77.

35. Prentice AM, Goldberg GR. Energy adaptations in human pregnancy: limits and long-term consequences. Am J Clin Nutr 2000;71:S1226–32.

36. Yu Z, Han S, Zhu J, Sun X, Ji C, Guo X. Pre-pregnancy body mass index in relation to infant birth weight and offspring overweight/obesity: a systematic review and meta-analysis. PLoS One 2013;8:e61627 doi 10.1371/journal.pone.0061627.

37. Ota E, Haruna M, Suzuki M, Anh DD, Tho le H, Tam NT, Thiem VD, Anh NT, Isozaki M, Shibuya K, Ariyoshi K, Murashima S, Moriuchi H, Yanai H. Maternal body mass index and gestational weight gain and their association with perinatal outcomes in Viet Nam. Bull World Health Organ 2011;89:127–36.

38. Institute of Medicine. Weight gain during pregnancy: reexamining the guidelines. Washington, DC: National Academies Press, 2009.

39. Institute of Medicine. Nutrition During Pregnancy: Part I Weight Gain: Part II Nutrient Supplements. US Committee on Nutritional Status During Pregnancy and Lactation. Washington, DC: National Academies Press, 1990.

40. Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. Bull World Health Organ 1987;65:663-737.

41. Kraemer K, Zimmermann MB, editors. Nutritional Anemia. Sight and Life Press, 2007.

42. World Health Organization. Iron Deficiency Anaemia Assessment, Prevention, and Control: A Guide for Programme Managers. WHO, 2001.

43. Levy A, Fraser D, Katz M, Mazor M, Sheiner E. Maternal anaemia during pregnancy is an independent risk factor for low birthweight and preterm delivery. Eur J Obstet Gynecol Reprod Biol 2005;122:182–6.

44. Fishman SM, Christian P, West KP. The role of vitamins in the prevention and control of anaemia. Public Health Nutr 2000;3:125–50.

45. Hisano M, Suzuki R, Sago H, Murashima A, Yamaguchi K. Vitamin B6 deficiency and anemia in pregnancy. Eur J Clin Nutr 2010;64:221–3.

46. Semba RD, Bloem MW. The anemia of vitamin A deficiency: epidemiology and pathogenesis. Eur J Clin Nutr 2002;56:271-81.

47. Van den Broek N. Anaemia and micronutrient deficiencies. Br Med Bull 2003;67:149–60.

48. International Food Policy Research Institute, Welthungerhilfe, Concern Worldwide. 2014 Global Hunger Index Data. International Food Policy Research Institute, Welthungerhilfe, Concern Worldwide (datasets). Available at http://dx.doi.org/10.7910/DVN/27557.

49. Institute of Medicine. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc. Washington, DC: National Academies Press, 2001.

50. World Health Organization. Guideline: Daily iron and folic acid supplementation in pregnant women. WHO, 2012.

51. Galloway R, Dusch E, Elder L, Achadi E, Grajeda R, Hurtado E, Favin M, Kanani S, Marsaban J, Meda N, Moore KM, Morison L, Raina N, Rajaratnam J, Rodriquez J, Stephen C. Women's perceptions of iron deficiency and anemia prevention and control in eight developing countries. Soc Sci Med 2002;55:529-44.

52. Pullan RL, Smith JL, Jasrasaria R, Brooker SJ. Global numbers of infection and disease burden of soil transmitted helminth infections in 2010. Parasit Vectors 2014;7:37.

53. Thurnham DI, McCabe GP. Influence of Infection and Inflammation on Biomarkers of Nutritional Status with an Emphasis on Vitamin A and Iron. World Health Organization, 2012.

54. Hotez PJ, Alvarado M, Basáñez MG, Bolliger I, Bourne R, Boussinesq M, et al. The global burden of disease study 2010: interpretation and implications for the neglected tropical diseases. PLoS Negl Trop Dis 2014;8:e2865 doi 10.1371/journal.pntd.0002865.

55. Murray CJL, Ortblad KF, Guinovart C, Lim SS, Wolock TM, Roberts DA, et al. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014;384: 1005–70.

56. Bhaskaram P. Micronutrient malnutrition, infection, and immunity: an overview. Nutr Rev 2002;60:S40–5.

57. Tomkins A, Watson F. Nutrition policy discussion paper No. 5: Malnutrition and Infection − A Review. United Nations Administrative Committee on Coordination, Subcommittee on Nutrition, 1989.

58. King JC. The risk of maternal nutritional depletion and poor outcomes increases in early or closely spaced pregnancies J. Nutr 2003;133:S1732-36.

59. World Health Organization. Physical status: the use and interpretation of anthropometry. Technical Report Series No. 854. WHO, 1995.

60. National Institute of Statistics, Directorate General for Health, and ORC Macro. Cambodia Demographic and Health Survey 2000. Phnom Penh, Cambodia, and Calverton, Maryland USA: National Institute of Statistics, Directorate General for Health, and ORC Macro, 2001.

61. National Institute of Public Health, National Institute of Statistics, and ORC Macro. Cambodia Demographic and Health Survey 2005. Phnom Penh, Cambodia and Calverton, Maryland, USA: National Institute of Public Health, National Institute of Statistics and ORC Macro, 2006.

62. UNICEF. The State of the World's Children 2015: Country Statistical Information. UNICEF, 2014.

63. De Onis M, Onyango AW, Borghi E, Siyam A, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. Bull World Health Organ 2007;85:660-7.

64. United Nations Development Programme. Human Development Report 2014. UNDP, 2014.

65. Von Grebmer K, Headey D, Olofinbiyi T, Wiesmann D, Fritschel H, Yin S, Yohannes Y, Foley C, von Oppeln C, Iseli B, Béné C, Haddad L. 2013 Global Hunger Index — The Challenge of Hunger: Building Resilience to Achieve Food and Nutrition Security. Welthungerhilfe, International Food Policy Research Institute, Concern Worldwide, 2013.

66. US Department of State, Bureau of East Asian and Pacific Affairs. Cambodia Fact Sheet, updated August 29, 2014. Available at http://www.state.gov/r/pa/ei/bgn/2732.htm.

67. World Bank. World Development Indicators 2013. Washington, DC: World Bank, 2013 doi 10.1596/978-0-8213-9824-1.

68. International Fund for Agricultural Development. Rural Poverty in Cambodia. Available at http://www.ruralpovertyportal.org/country/home/tags/cambodia; Accessed May, 2014.

69. Association of Southeast Asian Nations, European Union, FAO, UNICEF, WFP, WHO. Cambodia - Food and Nutrition Security Profiles. Updated June, 2014. Available at http://www.fao.org/3/a-at706e.pdf.

70. De Silva S, Johnston R, Try T. Investing in Water Management to Improve Productivity of Rice-Based Farming Systems in Cambodia Project. Issue brief #4: Rice and Fish: Impacts of Intensification of Rice Production. International Water Management Institute, Australian Centre for International Agricultural Research, 2013.

71. Food and Agriculture Organization. Fishery value chain analysis in Cambodia. FAO, 2011.

72. Halwart M. Commentary: Biodiversity and nutrition in rice-based aquatic ecosystems. J Food Comp Anal 2006;19:747–51.

73. United States Department of Agriculture. Household USDA Foods Fact Sheet. Updated October, 2012. Available at http://www.fns.usda.gov/sites/default/files/HHFS_RICE_WHITE_ENRICHED_LONGGRAIN_100491_100492_Oct2012.pdf.

74. Wallace LJ, Summerlee AJS, Dewey CE, Hak C, Hall A, Charles CV. Women's nutrient intake and food-related knowledge in rural Kandal province, Cambodia. Asia Pac J Clin Nutr 2014;23:263-71.

75. Ministry of Health, Cambodia. National Policy and Guidelines for Micronutrient Supplementation to Prevent and Control Deficiencies in Cambodia. Phnom Penh, Cambodia: Ministry of Health, 2011.

76. Hurrell R, Egli I. Iron bioavailability and dietary reference values. Am J Clin Nutr 2010;91:S1461–67.

77. Gibson RS, Cavalli-Sforza T. Using reference nutrient density goals with food balance sheet data to identify likely micronutrient deficits for fortification planning in countries in the Western Pacific Region. Food Nutr Bull 2012;33:S214-20.

78. Whitfield KC, Karakochuk CD, Liu Y, McCann A, Talukder A, Kroeun H, Ward M, McNulty H, Lynd LD, Kitts DD, Li-Chan EC, McLean J, Green TJ. Poor thiamin and riboflavin status is common among women of childbearing age in rural and urban Cambodia. J Nutr 2015;145:628-33.

79. Food and Agriculture Organization. 2010 Food Balance Sheets. Food and Agriculture Organization Statistics Division. Accessed March, 2011. Available at http://faostat3.fao.org/faostat-gateway/go/to/browse/FB/FB/E.

80. Institute of Medicine. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. Washington, DC: National Academies Press, 2002/2005.

81. Karakochuk CD, Whitfield KC, Barr SI, Lamers Y, Devlin AM, Vercauteren SM, Kroeun H, Talukder A, McLean J, Green TJ. Genetic hemoglobin disorders rather than iron deficiency are a major predictor of hemoglobin concentration in women of reproductive age in rural Prey Veng, Cambodia. J Nutr 2015;145:134-42.

82. Charles CV, Summerlee AJS, Dewey CE. Anemia in Cambodia: prevalence, etiology and research needs. Asia Pac J Clin Nutr 2012;21:171–81.

83. Yong TS, Chai JY, Sohn WM, Eom KS, Jeoung HG, Hoang EH, Yoon CH, Jung BK, Lee SH, Sinuon M, Socheat D. Prevalence of intestinal helminths among inhabitants of Cambodia (2006-2011). Korean J Parasitol 2014;52:661-6.

84. Stoltzfus RJ, Dreyfuss ML, Chwaya HM, Albonico M. Hookworm control as a strategy to prevent iron deficiency. Nutr Rev 1997;55:223-32.

85. National Nutrition Program, Cambodia. National Nutrition Training Curriculum – Minimum Package of Activities 10. Cambodia National Nutrition Program, Cambodia National Maternal and Child Health Center, A2Z Project, 2009.

86. National Nutrition Program, Cambodia. National Nutrition Strategy 2009-2015. Cambodia National Nutrition Program, Cambodia National Maternal and Child Health Center, 2009.

87. USAID (Cambodia). Integrated Nutrition Investment Framework. USAID Cambodia, 2012.

88. Harrison GG. Public health interventions to combat micronutrient deficiencies. Public Health Rev 2010;32:256-66.

89. Olney DK, Vicheka S, Kro M, Chakriya C, Kroeun H, Hoing LS, Talukder A, Quinn V, Iannotti L, Becker E, Roopnaraine T. Using program impact pathways to understand and improve program delivery, utilization, and potential for impact of Helen Keller International's homestead food production program in Cambodia. Food Nutr Bull 2013;34:169-84.

90. Williams LJ, Mai CT, Edmonds LD, Shaw GM, Kirby RS, Hobbs CA, Sever LE, Miller LA, Meaney FJ, Levitt M. Prevalence of spina bifida and anencephaly during the transition to mandatory folic acid fortification in the United States. Teratology 2002;66:33-9.

91. Bishai D, Nalubola R. The History of Food Fortification in the United States: Its Relevance for Current Fortification Efforts in Developing Countries. Economic Development and Cultural Change, University of Chicago Press 2002;51:37-53.

92. Haas JH, Miller DD. Overview of Experimental Biology 2005 symposium: food fortification in developing countries. J Nutr 2006;136:1053–4.

93. Imdad A, Bhutta ZA. Maternal nutrition and birth outcomes: effect of balanced protein-energy supplementation. Paediatr Perinat Epidemiol 2012;26:178-90.

94. Lechtig A, Habicht JP, Delgado H, Klein RE, Yarbrough C, Martorell R. Effect of food supplementation during pregnancy on birthweight. Pediatrics 1975;56:508-20.

95. Kramer MS, Kakuma R. Energy and protein intake in pregnancy. Cochrane Database Syst Rev 2003;(4):CD000032.

96. Ota E, Tobe-Gai R, Mori R, Farrar D. Antenatal dietary advice and supplementation to increase energy and protein intake. Cochrane Database Syst Rev 2012;(9):CD000032.

97. Atton C, Watney PJM. Selective supplementation in pregnancy: effect on birth weight. J Hum Nutr Diet 1990;3:381–92.

98. Blackwell RQ, Chow BF, Chinn KSK, Blackwell BN, Hsu SC. Prospective maternal nutrition study in Taiwan: rationale, study design, feasibility and preliminary findings. Nutr Rep Int 1973;7:517-32.

99. Campbell-Brown DM. Protein energy supplements in primigravid women at risk of low birth weight. In DM Campbell and MDG Gillmer, eds. Nutrition in Pregnancy: Proceedings of the Tenth Study Group in the Royal College of Obstetricians and Gynecologists, September, 1982. The Royal College of Obstetricians and Gynecologists, London: 1983.

100. Ceesay SM, Prentice AM, Cole TJ, Foord F, Weaver LT, Poskitt EM, Whitehead RG. Effects on birth weight and perinatal mortality of maternal dietary supplements in rural Gambia: 5 year randomised controlled trial. BMJ 1997;315:786-90.

101. Elwood PC, Haley TJ, Hughes SJ, Sweetnam PM, Gray OP, Davies DP. Child growth (0-5 years) and the effect of entitlement to a milk supplement. Arch Dis Child 1981;56:831-5.

102. Girija A, Geervani P, Rao GN. Influence of dietary supplementation during pregnancy on lactation performance. J Trop Pediatr 1984;30:79-83.

103. Huybregts L, Roberfroid D, Lanou H, Menten J, Meda N, Van Camp J, Kolsteren P. Prenatal food supplementation fortified with multiple micronutrients increases birth length: a randomized controlled trial in rural Burkina Faso. Am J Clin Nutr 2009;90:1593–1600.

104. Kaseb F, Kimiagar M, Ghafarpoor M, Valaii N. Effect of traditional food supplementation during pregnancy on maternal weight gain and birthweight. Int J Vitam Nutr Res 2002;72:389-93.

105. Mardones-Santander F, Rosso P, Stekel A, Ahumada E, Llaguno S, Pizarro F, Salinas J, Vial I, Walter T. Effect of a milk-based food supplement on maternal nutritional status and fetal growth in underweight Chilean women. Amer J Clin Nutr 1988;47:413-19.

106. Metcoff J, Costiloe P, Crosby WM, Dutta S, Sandstead HH, Milne D, Bodwell CE. Majors SH. Effect of food supplementation (WIC) during pregnancy on birth weight. Amer J Clin Nutr 1985;41:933-47.

107. Mora JO, De Navarro L, Clement J, Wagner M, De Paredes B, Herrera MG. The effect of nutritional supplementation on calorie and protein intake of pregnant women. Nutr Rep Int 1978;17:217-28.

108. Prentice AM, Cole TJ, Foord FA, Lamb WH, Whitehead RG. Increased birthweight after prenatal dietary supplementation of rural African women. Am J Clin Nutr l987;46:912-25.

109. Ross SM, Nel E, Naeye RL. Differing effects of low and high bulk maternal dietary supplements during pregnancy. Early Hum Dev 1985;10:295-302.

110. Rush D, Stein Z, Susser M. A randomized controlled trial of prenatal nutritional supplementation in New York City. Pediatrics 1980;65:683-97.

111. Viegas OA, Scott PH, Cole TJ, Mansfield HN, Wharton P, Wharton BA. Dietary protein energy supplementation of pregnant Asian mothers at Sorrento, Birmingham. I: Unselective during second and third trimesters. Br Med J 1982;285:589-92.

112. Viegas OA, Scott PH, Cole TJ, Eaton P, Needham PG, Wharton BA. Dietary protein energy supplementation of pregnant Asian mothers at Sorrento, Birmingham. II: Selective during third trimester only. BMJ 1982;285:592.

113. Liberato SC, Singh G, Mulholland K. Effects of protein energy supplementation during pregnancy on fetal growth: a review of the literature focusing on contextual factors. Food Nutr Res 2013;57:20499 doi:10.3402/fnr.v57i0.20499.

114. Bhutta ZA, Das JK, Rizvi A, Gaffey MF, Walker N, Horton S, Webb P, Lartey A, Black RE, Lancet Nutrition Interventions Review Group, Maternal and Child Nutrition Study Group. Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? Lancet 2013;382:452–77.

115. Huxley R, Owen CG, Whincup PH, Cook DG, Rich-Edwards J, Smith GD, Collins R. Is birth weight a risk factor for ischemic heart disease in later life? Am J Clin Nutr 2007;85:1244-50.

116. Lawlor DA, Ronalds G, Clark H, Smith GD, Leon DA. Birth weight is inversely associated with incident coronary heart disease and stroke among individuals born in the 1950s: findings from the Aberdeen Children of the 1950s prospective cohort study. Circulation 2005;112: 1414–8.

117. Allen LH. Multiple micronutrients in pregnancy and lactation: an overview. Am J Clin Nutr 2005;81:S1206–12.

118. Ladipo OA. Nutrition in pregnancy: mineral and vitamin supplements. Am J Clin Nutr 2000;72:S280-90.

119. Keen CL, Clegg MS, Hanna LA, Lanoue L, Rogers JM, Daston GP, Oteizazz P, Uriu-Adams JY. The plausibility of micronutrient deficiencies being a significant contributing factor to the occurrence of pregnancy complications. J Nutr 2003;133:S1597–1605.

120. Millennium Project. Available at http://www.unmillenniumproject.org/goals/.

121. Fall CHD, Fisher DJ, Osmond C, Margetts BM, the Maternal Micronutrient Supplementation Study Group. Multiple micronutrient supplementation during pregnancy in low-income countries: a meta-analysis of effects on birth size and length of gestation. Food Nutr Bull 2009;30:S533-46.

122. UNICEF, World Health Organization, United Nations University. Composition of a multi-micronutrient supplement to be used in pilot programmes among pregnant women in developing countries: report of a United Nations Children's Fund (UNICEF), World Health Organization (WHO) and United Nations University workshop, 1999.

123. Margetts BM, Fall CH, Ronsmans C, Allen LH, Fisher DJ. Multiple micronutrient supplementation during pregnancy in low-income countries: review of methods and characteristics of studies included in the meta-analyses. Food Nutr Bull 2009;30:S517–26.

124. Allen LH, Peerson JM, Maternal Micronutrient Supplementation Study Group. Impact of multiple micronutrient versus iron-folic acid supplements on maternal anemia and micronutrient status in pregnancy. Food Nutr Bull 2009;30:S527-32.

125. Makola D, Ash DM, Tatala SR, Latham MC, Ndossi G, Mehansho H. A micronutrient-fortified beverage prevents iron deficiency, reduces anemia and improves the hemoglobin concentration of pregnant Tanzanian women. J Nutr 2003;133:1339–46.

126. Ogunbode O, Otubu JA, Akeredolu OO, Akintunde EA, Olatunji PO, Jolyaemi ET. The effect of chemiron capsules on maternal and fetal hematologic indexes, including birthweight. Curr Therap Res 1992;51:634–6.

127. Ramakrishnan U, Neufeld LM, González-Cossío T, Villalpando S, García-Guerra A, Rivera J, Martorell R. Multiple micronutrient supplements during pregnancy do not reduce anemia or improve iron status compared to iron-only supplements in Semirural Mexico. J Nutr 2004; 134:898-903.

128. Christian P, Khatry SK, Katz J, Pradhan EK, LeClerq SC, Shrestha SR, Adhikari RK, Sommer A, West KP. Effects of alternative maternal micronutrient supplements on low birth weight in rural Nepal: double blind randomised community trial. BMJ 2003;326:571.

129. Haider BA, Yakoob MY, Bhutta ZA. Effect of multiple micronutrient supplementation during pregnancy on maternal and birth outcomes. BMC Public Health 2011;11:S19.

130. Zeng L, Dibley MJ, Cheng Y, Dang S, Chang S, Kong L, Yan H. Impact of micronutrient supplementation during pregnancy on birth weight, duration of gestation, and perinatal mortality in rural western China: double blind cluster randomised controlled trial. BMJ 2008;337:a2001.

131. Osrin D, Vaidya A, Shrestha Y, Baniya RB, Manandhar DS, Adhikari RK, Filteau S, Tomkins A, Costello AM. Effects of antenatal multiple micronutrient supplementation on birthweight and gestational duration in Nepal: double-blind, randomised controlled trial. Lancet 2005;365:955-62.

132. Tofail F, Persson LA, El Arifeen S, Hamadani JD, Mehrin F, Ridout D, Ekström E-C, Huda SN, Grantham-McGregor SM. Effects of prenatal food and micronutrient supplementation on infant development: a randomized trial from the Maternal and Infant Nutrition Interventions, Matlab (MINIMat) study. Am J Clin Nutr 2008;87:704-11.

133. Roberfroid D, Huybregts L, Lanou H, Henry MC, Meda N, Menten J, Kolsteren P, MISAME Study Group. Effects of maternal multiple micronutrient supplementation on fetal growth: a double-blind randomized controlled trial in rural Burkina Faso. Am J Clin Nutr 2008; 88:1330-40.

134. Kæstel P, Michaelsen KF, Aaby P, Friis H. Effects of prenatal multimicronutrient supplements on birth weight and perinatal mortality: a randomised, controlled trial in Guinea-Bissau. Eur J Clin Nutr 2005;59:1081–9.

135. Sunawang, Utomo B, Hidayat A, Kusharisupeni, Subarkah. Preventing low birthweight through maternal multiple micronutrient supplementation: a cluster-randomized, controlled trial in Indramayu, West Java. Food Nutr Bull 2009;30:S488-95.

136. Supplementation with Multiple Micronutrients Intervention Trial (SUMMIT) Study Group, Shankar AH, Jahari AB, Sebayang SK, Aditiawarman, Apriatni M, Harefa B, Muadz H, Soesbandoro SD, Tjiong R, Fachry A, Shankar AV, Atmarita, Prihatini S, Sofia G. Effect of maternal multiple micronutrient supplementation on fetal loss and infant death in Indonesia: a double-blind cluster-randomised trial. Lancet 2008;371:215-27.

137. Ramakrishnan U, González-Cossío T, Neufeld LM, Rivera J, Martorell R. Multiple micronutrient supplements during pregnancy do not increase birth size compared to iron-only supplements: a randomized controlled trial in a semi-rural community in Mexico. Am J Clin Nutr 2003;77:720-25.

138. Zagré NM, Desplats G, Adou P, Mamadoultaibou A, Aguayo VM. Prenatal multiple micronutrient supplementation has greater impact on birthweight than supplementation with iron and folic acid: a cluster-randomized, double-blind, controlled programmatic study in rural Niger. Food Nutr Bull 2007;28:317-27.

139. Bhutta ZA, Rizvi A, Raza F, Hotwani S, Zaidi S, Moazzam Hossain S, Soofi S, Bhutta S. A comparative evaluation of multiple micronutrient and iron-folic acid supplementation during pregnancy in Pakistan: impact on pregnancy outcomes. Food Nutr Bull 2009;30:S496-505.

140. Friis H, Gomo E, Nyazema N, Ndhlovu P, Krarup H, Kæstel P, Michaelsen KF. Effect of multimicronutrient supplementation on gestational length and birth size: a randomized, placebo-controlled, double-blind effectiveness trial in Zimbabwe. Am J Clin Nutr 2004;80:178-84.

141. Kramer MS. The epidemiology of adverse pregnancy outcomes: an overview. J. Nutr 2003;133:S1592-96.

142. Prado EL, Alcock KJ, Muadz H, Ullman MT, Shankar AH, SUMMIT Study Group. Maternal multiple micronutrient supplements and child cognition: a randomized trial in Indonesia. Pediatrics 2012;130:e536–46.

143. Gupta P, Ray M, Dua T, Radhakrishnan G, Kumar R, Sachdev HP. Multimicronutrient supplementation for undernourished pregnant women and the birth size of their offspring: a double-blind, randomized, placebo-controlled trial. Arch Pediatr Adolesc Med 2007;161:58–64.

144. Vaidya A, Saville N, Shrestha BP, Costello AM, Manandhar DS, Osrin D. Effects of antenatal multiple micronutrient supplementation on children's weight and size at 2 years of age in Nepal: follow-up of a double-blind randomised controlled trial. Lancet 2008;371:492-9.

145. Kawai K, Spiegelman D, Shankar AH, Fawzi WW. Maternal multiple micronutrient supplementation and pregnancy outcomes in developing countries: meta-analysis and meta-regression. Bull World Health Organ 2011;89:402–411B.

146. Ramakrishnan U, Grant FK, Goldenberg T, Bui V, Imdad A, Bhutta ZA. Effect of multiple micronutrient supplementation on pregnancy and infant outcomes: a systematic review. Paediatr Perinat Epidemiol 2012;26:153-67.

147. Shah PS, Ohlsson A, Knowledge Synthesis Group on Determinants of Low Birth Weight and Preterm Births. Effects of prenatal multimicronutrient supplementation on pregnancy outcomes: a meta-analysis. CMAJ 2009;180:E99-108.

148. Haider BA, Bhutta ZA. Multiple-micronutrient supplementation for women during pregnancy. Cochrane Database Syst Rev 2012;11:CD004905.

149. West KP, Shamim AA, Mehra S, Labrique AB, Ali H, Shaikh S, Klemm RD, Wu LS, Mitra M, Haque R, Hanif AA, Massie AB, Merrill RD, Schulze KJ, Christian P. Effect of maternal multiple micronutrient vs iron-folic acid supplementation on infant mortality and adverse birth outcomes in rural Bangladesh: the JiVitA-3 randomized trial. JAMA 2014;312:2649-58.

150. Kanade AN, Rao S, Kelkar RS, Gupte S. Maternal nutrition and birth size among urban affluent and rural women in India. J Am Coll Nutr 2008;27:137-45.

151. Rao S, Yajnik CS, Kanade A, Fall CHD, Margetts BM, Jackson AA, Shier R, Joshi S, Rege S, Lubree H, Desai B. Intake of micronutrient-rich foods in rural Indian mothers is associated with the size of their babies at birth: Pune Maternal Nutrition Study. J. Nutr 2001;131:1217-24.

152. Persson L, Arifeen S, Ekström E, Rasmussen KM, Frongillo EA, Yunus M. Effects of prenatal micronutrient and early food supplementation on maternal hemoglobin, birth weight, and infant mortality among children in Bangladesh: the MINIMat Randomized Trial. JAMA 2012;307:2050-9.

153. Adu-Afarwuah S, Lartey A, Okronipa H, Ashorn P, Zeilani M, Peerson JM, Arimond M, Vosti S, Dewey KG. Lipid-based nutrient supplement increases the birth size of infants of primiparous women in Ghana. Am J Clin Nutr 2015;101:835-46.

154. Adu-Afarwuah S, Lartey A, Zeilani M, Dewey KG. Acceptability of lipid-based nutrient supplements (LNS) among Ghanaian infants and pregnant or lactating women. Matern Child Nutr 2011;7:344-56.

155. UN Committee on Economic, Social and Cultural Rights. General Comment No. 12: The Right to Adequate Food, 1999. Available at http://www.refworld.org/docid/4538838c11.html.

156. World Food Programme. Nutrition at the World Food Programme: Programming for Nutrition-Specific Interventions. WFP, 2012.

157. Webb P, Rogers BL, Rosenberg I, Schlossman N, Wanke C, Bagriansky J, Sadler K, Johnson Q, Tilahun J, Masterson AR, Narayan A. Improving the Nutritional Quality of U.S. Food Aid: Recommendations for Changes to Products and Programs. Tufts University, 2011.

158. USAID. Corn Soy Blend/Plus Commodity Fact Sheet. Version current: April 24, 2015. Available at http://www.usaid.gov/what-we-do/agriculture-and-food-security/food-assistance/resources/implementation-tools/corn-soy.

159. Matilsky DK, Maleta K, Castleman T, Manary MJ. Supplementary feeding with fortified spreads results in higher recovery rates than with a corn/soy blend in moderately wasted children. J Nutr 2009;139:773-8.

160. Nackers F, Broillet F, Oumarou D, Djibo A, Gaboulaud V, Guerin PJ, Rusch B, Grais RF, Captier V. Effectiveness of ready-to-use therapeutic food compared to a corn/soy-blend-based pre-mix for the treatment of childhood moderate acute malnutrition in Niger. J Trop Pediatr 2010;56:407-13.

161. Karakochuk C, van den Briel T, Stephens D, Zlotkin S. Treatment of moderate acute malnutrition with ready-to-use supplementary food results in higher overall recovery rates compared with a corn-soya blend in children in southern Ethiopia: an operations research trial. Am J Clin Nutr 2012;96:911-16.

162. Patel MP, Sandige HL, Ndekha MJ, Briend A, Ashorn P, Manary MJ. Supplemental feeding with ready-to-use therapeutic food in Malawian children at risk of malnutrition. J Health Popul Nutr 2005;23:351-7.

163. World Food Programme. Cambodia Country Programme 2011-2016. WFP, 2011.

164. World Food Programme. Technical Specifications for the Manufacture of Corn Soya Blend Plus for Young Children and Adults. Version 2.1, March 2011.

165. Hofmann C-A, Roberts L, Shoham J, Harvey P. Measuring the impact of humanitarian aid: A review of current practice. Overseas Development Institute, 2004.

166. Lawson ML. Does Foreign Aid Work? Efforts to Evaluate U.S. Foreign Assistance. Congressional Research Service, 2013.

167. Murphy S, McAfee K. U.S. Food Aid: Time to Get It Right. The Institute for Agriculture and Trade Policy, 2005.

168. Barrett CB. Food Aid’s Intended and Unintended Consequences. ESA Working Paper No. 06-05. Food and Agriculture Organization, 2006.

169. Barrett CB. Food Aid as Part of a Coherent Strategy to Advance Food Security Objectives. ESA Working Paper No. 06-09. Food and Agriculture Organization, 2006.

170. The World Factbook 2013-14. Washington, DC: Central Intelligence Agency, 2013.

171. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. Geneva: World Health Organization, 2006.

172. Villar J, Altman DG, Purwar M, Noble JA, Knight HE, Ruyan P, Cheikh Ismail L, Barros FC, Lambert A, Papageorghiou AT, Carvalho M, Jaffer YA, Bertino E, Gravett MG, Bhutta ZA, Kennedy SH, International Fetal and Newborn Growth Consortium for the 21st Century. The objectives, design and implementation of the INTERGROWTH-21st Project. BJOG 2013;120:9-26.

173. WHO Vitamin and Mineral Nutrition Information System. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. World Health Organization, 2011. Available at http://www.who.int/vmnis/indicators/haemoglobin.

174. Huy ND, Le Hop T, Shrimpton R, Hoa CV. An effectiveness trial of multiple micronutrient supplementation during pregnancy in Vietnam: impact on birthweight and on stunting in children at around 2 years of age. Food Nutr Bull 2009;30:S506–16.

175. McElrath TF, Allred EN, Kuban K, Hecht JL, Onderdonk A, O'Shea TM, Paneth N, Leviton A for the ELGAN study investigators. Factors associated with small head circumference at birth among infants born before the 28th week. Am J Obstet Gynecol 2010;203:138.e1–138.e8. doi: 10.1016/j.ajog.2010.05.006.

176. Talukder A, Haselow NJ, Osei AK, Villate E, Reario D, Kroeun H, Sokhoing L, Uddin A, Dhunge S, Quinn V. Homestead food production model contributes to improved household food security and nutrition status of young children and women in poor populations. Field Actions Science Reports; Special Issue 1, 2010.

177. Hofmeyr GJ, Lawrie TA, Atallah AN, Duley L. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev 2010; 8:CD001059.

178. Mori R, Ota E, Middleton P, Tobe-Gai R, Mahomed K, Bhutta ZA. Zinc supplementation for improving pregnancy and infant outcome. Cochrane Database Syst Rev 2012;7:CD000230.

179. Ronnenberg AG, Goldman MB, Chen D, Aitken IW, Willett WC, Selhub J, Xu X. Preconception homocysteine and B vitamin status and birth outcomes in Chinese women. Am J Clin Nutr 2002;76:1385-91.

180. Scholl TO, Hediger ML, Bendich A, Schall JI, Smith WK, Krueger PM. Use of multivitamin/mineral prenatal supplements: influence on the outcome of pregnancy. Am J Epidemiol 1997;146:134–41.

181. Scholl TO, Hediger ML, Schall JI, Fischer RL, Khoo CS. Low zinc intake during pregnancy: its association with preterm and very preterm delivery. Am J Epidemiol 1993;137:1115–24.

182. Siega-Riz AM, Savitz DA, Zeisel SH, Thorp JM, Herring A. Second trimester folate status and preterm birth. Am J Obstet Gynecol 2004;191:1851–57.

183. Gresham E, Bisquera A, Byles JE, Hure AJ. Effects of dietary interventions on pregnancy outcomes: a systematic review and meta-analysis. Matern Child Nutr 2014. doi:10.1111/mcn.12142.

184. Nohr EA, Olsen J, Bech BH, Bodnar LM, Olsen SF, Catov JM. Periconceptional intake of vitamins and fetal death: a cohort study on multivitamins and folate. Int J Epidemiol 2014;43:174-84.

185. Poston L. Commentary: Multivitamins and early pregnancy loss. Int J Epidemiol 2014;43:184-6.

186. Mullany LC, Darmstadt GL, Katz J, Khatry SK, Tielsch JM. Effect of instrument precision on estimation of low birth weight prevalence. J Perinatol 2005;25:11-13.

187. United Nations Children's Fund. Tracking progress on child and maternal nutrition. New York: UNICEF, 2009.

188. World Health Organization. Guideline: Calcium supplementation in pregnant women. Geneva: WHO, 2013.

189. Bloem MW, de Pee S, Hop LT, Nguyen CK, Laillou A, Minarto, Moench-Pfanner R, Soekarjo D, Soekirman, Solon JA, Chan T, Wasantwisut E. Key strategies to further reduce stunting in Southeast Asia: Lessons from the ASEAN countries workshop. Food Nutr Bull 2013;34:S8-16.

190. Scaling Up Nutrition: A Framework for Action, 2011. Available at http://scalingupnutrition.org/wp-content/uploads/pdf/SUN_Framework.pdf.

191. World Food Programme, Cambodia. Maternal and Child Health and Nutrition Guidelines. Phnom Penh: WFP, 2013.

192. Nesbitt HJ, editor. Rice production in Cambodia. Manila: International Rice Research Institute, 1997.

193. Mack N, Woodsong C, Macqueen KM, Guest G, Namey E. Qualitative Research Methods: A Data Collector's Field Guide. Research Triangle Park: Family Health International, 2005.

194. Kitzinger J. Qualitative research: introducing focus groups. BMJ 1995;311:299-302.

195. Boeije H. A purposeful approach to the constant comparative method in the analysis of qualitative interviews. Qual Quant 2002;36:391–409.

196. Young SL, Blanco I, Hernandez-Cordero S, Pelto GH, Neufeld LM. Organoleptic properties, ease of use, and perceived health effects are determinants of acceptability of micronutrient supplements among poor Mexican women. J Nutr 2010;140:605-11.

197. World Bank. Poverty overview; updated April 6, 2015. Available at http://www.worldbank.org/en/topic/poverty/overview.

198. Pell C, Straus L, Andrew EVW, Meñaca A, Pool R. Social and cultural factors affecting uptake of interventions for malaria in pregnancy in Africa: a systematic review of the qualitative research. PLoS One 2011;6:e22452 doi: 10.1371/journal.pone.0022452.

199. Huybregts LF, Roberfroid DA, Kolsteren PW, Van Camp JH. Dietary behaviour, food and nutrient intake of pregnant women in a rural community in Burkina Faso. Matern Child Nutr 2009;5:211–22.

200. Kumar R, Aslesh OP, Kumar A, Kapoor A, Sanan D, Wadhwa E, Agarwal N. Urban poor women do not increase their diet during pregnancy: a study from an urban resettlement colony in Delhi, India. Int J Med Pub Health 2013;3:134-39.

201. De Sa J, Bouttasing N, Sampson L, Perks C, Osrin D, Prost A. Identifying priorities to improve maternal and child nutrition among the Khmu ethnic group, Laos: a formative study. Matern Child Nutr 2013;9:452–66.

202. Shannon K, Mahmud Z, Asfia A, Ali M. The social and environmental factors underlying maternal malnutrition in rural Bangladesh: implications for reproductive health and nutrition programs. Health Care Women Int 2008;29:826–40.

203. Setyowati. An ethnography study of nutritional conditions of pregnant women in Banten Indonesia. Makara Kesehatan 2010;14:5–10.

204. Essén B, Johnsdotter S, Hovelius B, Gudmundsson S, Sjöberg NO, Friedman J, Ostergren PO. Qualitative study of pregnancy and childbirth experiences in Somalian women resident in Sweden. BJOG 2000;107:1507-12.

205. Ali E, Zachariah R, Shams Z, Manzi M, Akter T, Alders P, Allaouna M, Delchevalerie P, Harries AD. Peanut-based ready-to-use therapeutic food: how acceptable and tolerated is it among malnourished pregnant and lactating women in Bangladesh? Matern Child Nutr 2013 May 6; doi: 10.1111/mcn.12050.

206. Rowe JP, Brodegard WC, Pike OA, Steele FM, Dunn ML. Storage, preparation, and usage of fortified food aid among Guatemalan, Ugandan, and Malawian beneficiaries: a field study report. Food Nutr Bull 2008;29:213-20.

207. Grimm P. Social Desirability Bias. In Wiley International Encyclopedia of Marketing. Hoboken: John Wiley & Sons, Inc, 2010.

208. Ivankova NV, Creswell JW, Stick SL. Using mixed-methods sequential explanatory design: from theory to practice. Field Methods 2006;18:3-20.

209. The International Lipid-Based Nutrient Supplements Project website. Available at http://ilins.org/resources#section-0.

210. Nutriset product information. Available at http://www.nutriset.fr/index.php?id=90.

211. Mridha M, Chaparro C, Paul R, Hussain S, Vosti S, Matias S, Harding K, Cummins J, Day L, Saha S, Peerson J, Dewey K. Lipid-based nutrient supplements (LNS) for pregnant women reduce newborn stunting in Bangladesh. FASEB J 2014;28:Supplement 256.6.

212. Greiner T. The advantages, disadvantages and risks of ready-to-use foods. The International Baby Food Action Network. Breastfeeding Briefs No. 56/57; September 2014.

213. World Food Programme. Vouchers and cash transfers as food assistance instruments: opportunities and challenges. WFP, 2008.

214. Mourão L, de Jesus AM. Bolsa Família (Family Grant) Programme: an analysis of Brazilian income transfer programme. Field Actions Science Reports; Special Issue 3, 2011. Available at http://factsreports.revues.org/1314.

215. Fernald LCH, Gertler PJ, Neufeld LM. Role of cash in conditional cash transfer programmes for child health, growth, and development: an analysis of Mexico's Oportunidades. Lancet 2008;371:828–37.

216. Soares S, Osorio RG, Soares FV, Medeiros M, Zepeda E. Conditional cash transfers in Brazil, Chile and Mexico: impacts upon inequality. International Poverty Centre Working Paper No. 35, 2007.

217. World Vision. Impact: Positive Deviance/Hearth. World Vision, 2013. Available at http://www.worldvision.ca/OURWORK/our-impact/Documents/pdf/PD-HearthReportInteractive.pdf.

218. Bisits BPA. The positive deviance/hearth approach to reducing child malnutrition: systematic review. Trop Med Int Health 2011;16:1354-66.

219. McNulty J. Positive Deviance/Hearth Essential Elements: A Resource Guide for Sustainably Rehabilitating Malnourished Children. Washington, DC: CORE Group, 2005.

220. Lopez DF. A community-based approach for improving child nutrition: experiences from a Positive Deviance/Hearth program in Kampong Chhnang. Presentation at American Public Health Association conference, 2014. Available at https://apha.confex.com/apha/142am/webprogram/Paper311367.html.

221. Lopez AK. PFD's Hearth Program in Cambodia. Program Research Document, 2005. Available at http://camnut.weebly.com/uploads/2/0/3/8/20389289/2005 assessmentofpfdshearthprogramen.pdf.

222. Karakochuk CD, Murphy HM, Whitfield KC, Barr SI, Vercauteren SM, Talukder A, Porter K, Kroeun H, Eath M, McLean J, Green TJ. Elevated levels of iron in groundwater in Prey Veng province in Cambodia: a possible factor contributing to high iron stores in women. J Water Health 2015;13:575-86.

223. National Institute of Statistics, Directorate General for Health, and ICF Macro. Cambodia Demographic and Health Survey 2014 Key Indicators Report. Phnom Penh, Cambodia and Calverton, Maryland, USA: National Institute of Statistics, Directorate General for Health, and ICF Macro, 2015.

Appendices

Appendix A Baseline Questionnaire for Trial Participants

BASELINE QUESTIONNAIRE	
GEOGRAPHIC AND RESPONDENT IDENTIFICATION DISTRICT: _________________ COMMUNE:________________ VILLAGE : _________________ ID OF RESPONDENT: [ ]	INTERVIEW RECORD Interviewer's Name ______________________________ Signature ___________________ Date _____________ Start time______________ End time ______________ Remarks:

MODULE 1: RESPONDENT AND SPOUSE CHARACTERISTICS	
1. What is your age?	_________Years
2. What is your date of birth?	____________
3. Have you attended school?	1 = Yes 2 = No → Skip to Q5
4. What is the highest grade you completed?	_________Grade
5. Are you able to read?	1 = Yes 2 = No
6. What is your marital status?	1 = Married 2 = Not married → Skip to Q8 3 = Widowed → Skip to Q8 4 = Separated or divorced → Skip to Q8
7. How long have you been married?	_________ Months __________Years
8. What is your main occupation? → Skip to Q10 if work at home	1 = Farmer 2 = Day laborer 3 = Garment factory worker 4 = Fishing 5 = Sell vegetables, fruit, eggs, etc. 6 = Shopkeeper 7 = Work at home 8 = Other (specify)________________
9. How many hours per day do you work outside the home? A. Rainy season B. Dry season	A. _________Hours B. _________Hours
10. How much money do you and your husband earn together per month? A. Rainy season B. Dry season	A. _________Riel B. _________Riel
11. Have you saved some money from your income every month?	1 = Yes 2 = No

12. What is your husband's age?	_________Years
13. Has your husband attended school?	1 = Yes 2 = No ⟶ Skip to Q15
14. What is the highest grade he completed?	__________Grade
15. What is your husband's main occupation?	1 = Farmer 2 = Day laborer 3 = Fishing 4 = Sell vegetables, fruit, eggs, etc. 5 = Shopkeeper 6 = Other (specify)_______________
MODULE 2: HOUSEHOLD CHARACTERISTICS	
16. Who is the head of your household?	1 = Respondent 2 = Husband 3 = Parents 4 = Other (specify)_____________
17. How many people live in your household? (eat from your food pot)	____________Persons
18. Do you own your house?	1 = Yes 2 = No
19. Do you own any land or jointly own land?	1 = Yes 2 = No ⟶ Skip to Q21
20. How many hectares of land do you own?	__________Hectares
21. Do you own any livestock or fish ponds?	1 = Yes 2 = No ⟶ Skip to Q23

22. Which of the following do you own? Ask all responses	1 = Cows 2 = Goats 3 = Chickens 4 = Ducks 5 = Pigs 6 = Water buffalo 7 = Fish 8 = Other (specify)____________________
23. Do you have a vegetable garden in your homestead?	1 = Yes 2 = No → Skip to Q25
24. What do you do with the vegetables that you grow?	1 = Eat 2 = Sell 3 = Sell and eat
25. Do you have any fruit trees in your homestead?	1 = Yes 2 = No → Skip to Q27
26. What do you do with the fruits you grow?	1 = Eat 2 = Sell 3 = Sell and eat
27. What is the main source of drinking water for your household?	1 = Pond/river 2 = Hand dug well 3 = Open ringwell 4 = Closed ringwell 5 = Handpump 6 = Rain water 7 = Bought water 8 = Other (specify)____________
28. Where is the water source located?	1 = In homestead 2 = Outside homestead
29. Who collects water for your household?	1 = Respondent 2 = Husband 3 = Child 4 = Other (specify)____________
30. How many times a day is water collected?	__________Times
31. How long does it take to go to the water source, get water, and come back?	_________Minutes or _________ Hours

32. Do you usually do anything to the water to make it safer to drink?	1 = Yes (specify)______________ 2 = No
33. What type of toilet facility do members in your household usually use?	1 = Closed latrine 2 = Pit 3 = River/pond 4 = Open field 5 = Other (specify)___________________
34. What is the main source of light for your household?	1 = Electricity 2 = Gas 3 = Battery 4 = Other (specify)___________________
35. What type of fuel does your household mainly use for cooking?	1 = Electricity 2 = Gas 3 = Kerosene 4 = Charcoal 5 = Wood 6 = Straw/grass 7 = Animal dung 8 = Other (specify)____________________
36. Do you have any of the following items in your house? Ask each response and circle those mentioned	1 = Radio 2 = Television 3 = Refrigerator 4 = Mobile phone 5 = Moto 6 = Bicycle 7 = Car

MODULE 3: REPRODUCTIVE HISTORY

37. How many children have you given birth to?	___________Children

38. Please tell me the sex and ages of your living children and whether they attend school.

	Sex	Date or Birth	Age in months/years	Attends school? (Yes or No)
1	M (1) F (2)	/ /		
2	M (1) F (2)	/ /		
3	M (1) F (2)	/ /		
4	M (1) F (2)	/ /		
5	M (1) F (2)	/ /		
6	M (1) F (2)	/ /		
7	M (1) F (2)	/ /		
8	M (1) F (2)	/ /		
9	M (1) F (2)	/ /		
10	M (1) F (2)	/ /		

39. Have you given birth to a child who was born alive but later died?	1 = Yes 2 = No → Skip to Q42
40. How many of your children were born alive but later died?	____________Children

41. What were the sex and ages of the children that died?

	Sex	**Age**
1	M (1) F (2)	
2	M (1) F (2)	
3	M (1) F (2)	

42. Have you ever had a pregnancy that miscarried, was aborted, or ended in a stillbirth?	1 = Yes 2 = No → Skip to Q44
43. How many times did this happen?	____________Times
44. How many months pregnant are you now?	____________Months
45. When you got pregnant, did you want to get pregnant at that time?	1 = Yes → Skip to Q47 2 = No

46. If no, why not?	1 = Wanted to have a child later 2 = Did not want any more children 3 = Other (specify)_______________
47. At ANC, did you receive information about the number of meals you should eat?	1 = Yes 2 = No
48. At ANC, did you receive information about what type of food you should eat?	1 = Yes 2 = No
49. At ANC did you receive any iron tablets?	1 = Yes 2 = No
50. How many iron tablets did you receive?	_________Tablets
51. Do you take the iron tablet every day?	1 = Yes → Skip to Q53 2 = No
52. If no, why not?	1 = Forget to take it 2 = Side effect 3 = Do not trust quality 4 = Other (specify)___________
53. Is it difficult for you to attend ANC?	1 = Yes 2 = No → Skip to Q55
54. What are the reasons why it is difficult for you to attend ANC?	1 = Need to get permission from husband/family 2 = Do not want to go alone 3 = Not enough money to go 4 = No transport to go 5 = Do not have time to go 6 = Midwife not always there 7= Other (specify) _______________
55. If the woman has other children, ask: During your last pregnancy, how many ANC visits did you have?	__________Visits
56. If the woman has other children, ask: Where did you deliver your last baby?	1 = Health center 2 = Home 3 = Other (specify) ____________________

57. If the woman has other children, ask: Was your last child born larger than average, average, smaller than average, very small?	1 = Larger than average 2 = Average 3 = Smaller than average 4 = Very small
58. If the woman has other children, ask: Are you breastfeeding now?	1 = Yes 2 = No
MODULE 4: HEALTH-SEEKING BEHAVIOR AND FOOD PRACTICES	
59. What is the distance from your house to the nearest health post or center?	___________Km 77. Don’t know
60. How do you get to the nearest health post or center when you need to go or you need to take your child?	1 = Walk 2 = Moto 3 = Taxi 4 = Bicycle 5 = Other (specify)________________
61. Who usually decides how the money you earn will be spent? Circle all responses	1 = Respondent 2 = Husband 3 = Parents 4 = Other (specify)_______________
62. Who usually makes decisions about which foods to buy for the family? Circle all responses	1 = Respondent 2 = Husband 3 = Parent 4 = Other (specify)_______________
63. How do you obtain most of your meat?	1 = Purchase 2 = Grow crops 3 = From livestock products (milk, meat) 4 = Exchange for labor or food for work 5 = Fishing 6 = Other (specify)_______________
64. How do you obtain most of your vegetables?	1 = Purchase 2 = Grow crops 3 = Exchange for labor or food for work 4 = Other (specify)_______________

65. How much of your income is spent on food per day for your family?	__________Riel
66. How many meals do you normally eat per day when you are not pregnant?	__________Meals
67. How many meals are you eating per day now that you are pregnant?	__________Meals
68. Who decides what you should eat during pregnancy? Circle all responses	1 = Respondent 2 = Husband 3 = Mother 4 = Mother in law 5 = Other (specify)_______________
69. If she has other children, ask: When you were pregnant with your last child, did you eat more, less or same number of meals per day as before pregnancy?	1 = More 2 = Less 3 = Same
70. How many meals and snacks did you have yesterday?	Number of meals________________ Number of snacks_______________
71. Which of the following foods did you eat yesterday during the day or night?	
FOOD	**CONSUMED FOOD YESTERDAY**
1) Rice	1 = Yes 2 = No
2) Noodles, bread	1 = Yes 2 = No
3) Pumpkin, yellow or orange sweet potatoes, carrots	1 = Yes 2 = No
4)White potatoes, cassava	1 = Yes 2 = No
5) Dark green leafy vegetable (e.g. morning glory or amaranth)	1 = Yes 2 = No
6) Other vegetables	1 = Yes 2 = No
7) Ripe mango or papaya	1 = Yes 2 = No
8) Other fruits	1 = Yes 2 = No
9) Meat (beef, pork, lamb, goat, chicken, duck, snail, frog)	1 = Yes 2 = No
10) Liver, kidney, blood, intestine other organs	1 = Yes 2 = No
11) Eggs	1 = Yes 2 = No

12) Fish (fresh or dried)	1 = Yes 2 = No
13) Beans, lentils, peas, nuts, tofu	1 = Yes 2 = No
14) Any food made with oil, butter, coconut milk, other fat	1 = Yes 2 = No
15) Fish sauce, fish paste	1 = Yes 2 = No
16) Any sweets, cakes biscuits, fried bananas	1 = Yes 2 = No
17) Milk- fresh, tinned, powder or cheese, yoghurt	1 = Yes 2 = No
72. Was this a typical day's food intake?	1 = Yes → Skip to Q74 2 = No
73. If not a typical day's diet, why not?	1 = Not hungry 2 = Sick 3 = Not enough food 4 = Other (specify)_________________
74. How often do you eat any meat or fish?	1 = 1-2 times per week 2 = 3-4 times per week 3 = More than 4 times per week 4 = Never 5 = Other (specify)_________________
75. Do you drink tea or coffee with meals?	1 = Yes 2 = No
76. How much rice was eaten by your family in the past 7 days?	__________ (kg)
77. Does your household usually run out of rice during the year?	1 = Yes 2 = No
78. In the past 30 days did you worry that your household would not have enough food?	1 = Yes 2 = No → Skip to Q80
79. How often did this happen?	1 = Never 2 = Rarely 3 = Sometimes 4 = Often
80. In the past 30 days were you or any household member not able to eat the kinds of foods you preferred because of a lack of resources?	1 = Yes 2 = No → Skip to Q 82
81. How often did this happen?	1 = Never 4 = Often 2 = Rarely 3 = Sometimes

82. In the past 30 days did you or any household member have to eat a limited variety of foods due to a lack of resources?	1 = Yes 2 = No ⟶ Skip to Q84
83. How often did this happen?	1 = Never 2 = Rarely 3 = Sometimes 4 = Often
84. In the past 30 days did you or any household member have to eat some foods that you really did not want to eat because of a lack of resources to obtain other types of food?	1 = Yes 2 = No ⟶ Skip to Q86
85. How often did this happen?	1 = Never 2 = Rarely 3 = Sometimes 4 = Often
86. In the past 30 days did you or any household member have to eat a smaller meal than you felt you needed because there was not enough food?	1 = Yes 2 = No ⟶ Skip to Q88
87. How often did this happen?	1 = Never 2 = Rarely 3 = Sometimes 4 = Often
88. In the past 30 days did you or any household member have to eat fewer meals in a day because there was not enough food?	1 = Yes 2 = No ⟶ Skip to Q90
89. How often did this happen?	1 = Never 2 = Rarely 3 = Sometimes 4 = Often
90. In the past 30 days, was there ever no food to eat of any kind in your household because of a lack of resources to get food?	1 = Yes 2 = No ⟶ Skip to Q92
91. How often did this happen?	1 = Never 2 = Rarely 3 = Sometimes 4 = Often
92. In the past 30 days, did you or any member go to sleep at night hungry because there was not enough food?	1 = Yes 2 = No ⟶ Skip to Q94

93. How often did this happen?	1 = Never 2 = Rarely 3 = Sometimes 4 = Often
94. In the past 30 days did you or any household member go a whole day and night without eating anything because there was not enough food?	1 = Yes 2 = No ⟶ Skip to Q96
95. How often did this happen?	1 = Never 2 = Rarely 3 = Sometimes 4 = Often
96. Do you sleep under a mosquito net every night?	1 = Yes ⟶ Skip to Module 5 2 = No
97. If no, why not?	1 = No net in house 2 = Other family members sleep under the net 3 = Other (specify)________________
MODULE 5: KNOWLEDGE AND ATTITUDES	
98. How many ANC visits should a woman have during pregnancy?	________Visits 77. Don't know
99. When during pregnancy should the first ANC visit be?	_________Month of Pregnancy 77. Don't know
100. Do you think women should eat more during pregnancy?	1 = Yes 2 = No 77. Don't know
101. Do you think women should try to gain weight during pregnancy?	1 = Yes 2 = No 77. Don't know
102. Do you think women should work less during pregnancy?	1 = Yes 2 = No 77. Don't know
103. How many meals should a woman eat every day when she is pregnant?	__________Meals
104. Do you think women should take iron tablets during pregnancy?	1 = Yes 2 = No ⟶ Skip to Q106

105. How important is it for women to take iron during pregnancy?	1 = Very important 2 = Somewhat important 3 = Not important 77. Don't know
106. What are reasons why it is important for a woman to take iron during pregnancy? List reasons.	1. ______________________ 2. ______________________ 3. ______________________ 77. Don't know
107. Do you know any foods that contain iron?	1 = Yes 2 = No → Skip to Q109 77. Don't know → Skip to Q109
108. Can you tell me 3 foods that contain iron? List foods.	1. ______________________ 2. ______________________ 3. ______________________
109. Are there foods that are important for women to eat during pregnancy?	1 = Yes 2 = No → Skip to Q111 77. Don't know → Skip to Q111
110. Can you tell me 3 foods that are important for women to eat during pregnancy? List foods.	1. ______________________ 2. ______________________ 3. ______________________
111. Are there foods that women should not eat during pregnancy?	1 = Yes 2 = No → Skip to Module 6 77. Don't know → Skip to Mod 6
112. Can you tell me which foods women should not eat during pregnancy? List foods.	1. ______________________ 2. ______________________ 3. ______________________ 77. Don't know
MODULE 6: ANEMIA ASSESSMENT	
113. Have you ever heard of anemia?	1 = Yes 2 = No → Skip to Q129
114. Have you ever been told by a health worker that you have anemia?	1 = Yes 2 = No → Skip to Q 117
115. Have you ever been treated for anemia?	1 = Yes 2 = No → Skip to Q 117

116. What treatment did you receive?	1. ______________________ 2.______________________ 3. ______________________
117. Do you think you have anemia now?	1 = Yes 2 = No 77. Don't know
118. Do you think anemia is a problem for women during pregnancy?	1 = Yes 2 = No 77. Don't know
119. Can an inherited disease or condition cause anemia?	1 = Yes 2 = No 77. Don't know
120. Can intestinal parasites cause anemia?	1 = Yes 2 = No 77. Don't know
121. Can eating too little cause anemia?	1 = Yes 2 = No 77. Don't know
122. What are common symptoms of anemia?	1 = Body has no power 2 = Dizziness 3 = Tired 4 = Headache 5 = Pale skin 6 = Other (specify)_____________ 77. Don't know
123. Are there ways to prevent anemia?	1 = Yes 2 = No → Skip to Q 126 77. Don't know → Skip to Q 126
124. What are ways to prevent anemia? List ways.	1. _________________ 2. _________________ 3. _________________ 77. Don't know
125. Are there foods you can eat to prevent anemia?	1 = Yes 2 = No → Skip to Q 127 77. Don't know → Skip to Q 127
126. What foods can prevent anemia? List foods.	1. ______________ 2. ______________

	3. ______________ 77. Don't know
127. Are there ways to treat anemia?	1 = Yes 2 = No ⟶ Skip to Q 129 77. Don't know ⟶ Skip to Q 129
128. What are ways to treat anemia? List ways.	1. ________________ 2. ________________ 3. ________________ 77. Don't know
129. Did you experience heavy or prolonged menstrual bleeding before you became pregnant?	1 = Yes 2 = No
130. Have you experienced any of the following recently? Ask all responses.	1 = Shortness of breath 2 = Palpitation 3 = Chest pain 4 = Fatigue/tiredness 5 = Headache
131. Do you ever experience tingling or numbness in the feet?	1 = Yes 2 = No
132. Are there health conditions for which you regularly see the doctor or take medicine all the time?	1 = Yes 2 = No ⟶ End of survey
133. If yes, for what conditions? List conditions.	1. ______________________ 2. ______________________ 3. ______________________
END OF SURVEY – THANK PARTICIPANT	

Appendix B Structured Interview Questionnaire for Qualitative Study

<table>
<tr><td colspan="2">CSB PLUS QUESTIONNAIRE</td></tr>
<tr><td>GEOGRAPHIC AND RESPONDENT IDENTIFICATION

DISTRICT: ____________________

COMMUNE:____________________

VILLAGE : ____________________

ID OF RESPONDENT: [ ]</td><td>INTERVIEW RECORD

Interviewer’s Name
____

Signature
____

Date _____________

Start time_______________

End time _______________

Remarks</td></tr>
</table>

1. Normally how many times per week did you eat CSB? Read all options but circle only 1 response	1 = 0 times per week → Skip to Q28 2 = 1-3 times per week 3 = 4-6 times per week 4 = ≥ 7 times per week
2. Normally how much CSB did you cook each time? Read all options but circle only 1 response	1 = Half bowl 2 = Full bowl 3 = Different every time 4 = Other (specify)____________
3. Normally how did you cook CSB? Wait for response and circle all responses **THEN ASK WHICH OF HER RESPONSES WAS THE MAIN WAY AND PUT (*) NEXT TO MAIN WAY**	1 = Borbor 2 = Fried 3 = Drink 4 = Other (specify)_______________
4. Normally how long did it take you to cook CSB?	___________Minutes
5. Normally how many times per day did you cook CSB?	_____Times
6. Normally how many times per day did you eat CSB?	_____Times
7. Normally what time of day did you eat CSB? Wait for response and circle all responses	1 = Morning 2 = Afternoon 3 = Evening 4 = Other (specify)______________
8. Normally did you cook CSB at the same time as normal food?	1 = Yes 2 = No
9. Normally did you eat CSB with normal food?	1 = Yes 2 = No
10. Normally did you finish all the CSB you cooked each day?	1 = Yes → Skip to Q69 2 = No
11. If no, what did you normally do with remaining cooked CSB? Wait for response and circle all responses	1 = Give to family 2 = Give to animals 3 = Throw it out 4 = Other (specify)_____________
12. Did anyone cook CSB for you sometimes?	1 = Yes 2 = No → Skip to Q72

13. If yes, who? Wait for response and circle all responses	1 = Husband 2 = Mother 3 = Other (specify)_____________
14. When did they cook CSB for you? Wait for response and circle all responses **THEN ASK WHICH OF HER RESPONSES WAS THE MAIN TIME AND PUT (*) NEXT TO MAIN TIME**	1 = When sick 2 = When tired 3 = When busy 4 = When not at home 5 = Other (specify)________________
15. Did you eat more, same, less of normal food because you were eating CSB?	1 = More 2 = Same 3 = Less
16. What motivated you to eat CSB? Wait for response and circle all responses **THEN ASK WHICH OF HER RESPONSES WAS THE MAIN REASON AND PUT (*) NEXT TO MAIN REASON**	1 = Not enough food 2 = Wanted baby to be strong 3 = Liked to eat CSB 4 = Had more energy 5 = Other (specify)___________
17. Did you experience any benefit from eating CSB?	1 = Yes 2 = No → Skip to Q75
18. If yes, what benefit? Circle all responses NOTE: Probe to make sure benefit is related to CSB	1. Had more energy 2. Mother was healthy 3. Baby was strong/healthy 4. Baby was not sick 5. Baby had pretty skin 6. Other (specify)________________
19. Did you have any negative effects after eating CSB?	1 = Yes 2 = No → Skip to Q78
20. If yes, what negative effect? Circle all responses NOTE: Probe to make sure negative effect is related to CSB	1. Dizziness 2. Nausea 3. Headache 4. Diarrhea 5. Other (specify)________________

21. How often did you have these negative effects? Wait for response and circle only 1 response	1 = Rarely (1-2 times per month) 2 = Sometimes (3-5 times per month) 3 = Often (over 5 times per month) 4 = Every day 5 = Other (specify)_______________
22. Did you share CSB with other family members (in household)?	1 = Yes 2 = No → Skip to Q80
23. If yes, how much did you share with other family members (in household)? Wait for response and circle only 1 response	1 = 1-2 rations per month 2 = 3-5 rations per month 3 = >5 rations per month 4 = Shared some every day 5 = Other (specify)_____________
24. Did you share CSB with your neighbor or relatives?	1 = Yes 2 = No → Skip to Q82
25. If yes, how much did you share with your neighbor or relatives? Wait for response and circle only 1 response	1 = 1-2 rations per month 2 = 3-5 rations per month 3 = >5 rations per month 4 = Shared some every day 5 = Other (specify)_____________
26. Did your husband approve of you eating CSB?	1 = Yes → Skip to Q85 2 = No
27. If no, why not? Wait for response and circle all responses **THEN ASK WHICH OF HER RESPONSES WAS THE MAIN REASON AND PUT (*) NEXT TO MAIN REASON**	1 = Did not trust it 2 = Wanted to feed CSB to children 3 = Feared difficult delivery 4 = Other (specify)_____________

28. If she did not eat CSB every day, ask why did you not eat CSB more often? Wait for response and circle all responses **THEN ASK WHICH OF HER RESPONSES WAS THE MAIN REASON AND PUT (*) NEXT TO MAIN REASON**	1 = Bad taste 2 = Bad smell 3 = Side effects 4 = Fear weight gain/difficult delivery 5 = Had enough food already 6 = No time to prepare 7 = Work outside home 8 = Boring to eat every day 9 = Other (specify)_______________
29. Was the education we provided about CSB helpful for you?	1 = Yes 2 = No
30. Did you understand how to cook CSB?	1 = Yes 2 = No
31. Did the village health worker come talk with you about CSB?	1 = Yes 2 = No ⟶ Skip to Q89
32. If yes, how many times did the VHW come?	___________Times 77. Don't know
33. Would you eat CSB next time you are pregnant if it is offered to you for free?	1 = Yes 2 = No ⟶ Skip to Q92
34. Next time how often would you like to receive CSB? Wait for response and circle only 1 response	1 = Every week 2 = Every month 3 = Other (specify)____________
35. Next time would you come to the health center to collect CSB?	1 = Yes 2 = No
36. How can we improve CSB next time? Wait for response and circle all responses	1 = Make smell better 2 = Make more sweet 3 = Change texture 4 = Other (specify)____________
37. Did you experience any severe illness during pregnancy?	1 = Yes 2 = No ⟶ Skip to Q96
38. If yes, what illness? Record all responses	1. ________________ 2. ________________ 3. ________________
END OF SURVEY – THANK PARTICIPANT	