Tessema et al. BMC Nutrition (2016) 2:54
DOI 10.1186/s40795-016-0089-z

BMC Nutrition

STUDY PROTOCOL Open Access

Translating the impact of quality protein maize into improved nutritional status for Ethiopian children: study protocol for a randomized controlled trial

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Abstract

Background: Linear growth failure is the most common form of undernutrition. Childhood stunting impairs human development and health and productivity in adulthood. Ethiopia has a high prevalence of stunting, with diets reliant on staple crops with low nutrient content. Maize is the most highly produced crop in Ethiopia. Unfortunately, conventional maize has poor protein quality due to a poor balance of essential amino acids. Quality protein maize (QPM) varieties are biofortified with these essential amino acids and, in controlled trials, improve child growth. However, evidence on the impact of QPM adoption and consumption on protein status and linear growth of children under natural circumstances is not yet available.

Methods/design: A randomized controlled trial was carried out to evaluate the impact of a) nutrition-focused adoption encouragement and provision of QPM seed in small seed packs, and b) a consumption encouragement intervention primarily targeting female caregivers and encouraging earmarking and integration of QPM into diets for infants and young children. The trial (n = 1611) had three randomly assigned arms: a control group; a first intervention group receiving adoption encouragement only; and a second intervention group receiving both adoption and consumption encouragement. The primary outcomes of this study are QPM consumption, protein status, and linear growth of children, assessed using questionnaires, biological specimen collection, and anthropometry over one cycle of agricultural production and post-harvest consumption. Secondary outcomes include child stunting, acute malnutrition, underweight, total intake of utilizable protein, and caregivers' cooking and child feeding practices.

Discussion: This study addresses important behavioral barriers between the development of a biofortified crop, QPM, and its impact on children's nutrition and health in a natural setting. The randomized controlled trial design, collection of data in multiple domains along hypothesized impact pathways, and assessment of nutritional status using both biomarkers and anthropometry allow greater understanding on mechanisms of impact. This trial is the first such study to be conducted with a biofortified staple crop in a natural setting and supports the Government of Ethiopia's current targets for nutrition and agriculture.

Protocol Registration Number: Prospectively registered in the AEA RCT Registry (AEARCTR # 0000786) on 24 July, 2015, and retrospectively registered on ClinicalTrials.gov (NCT02710760) on 30 January, 2016.

Keywords: Randomized controlled trial, Biofortification, Linear growth, Protein status, Maize, Ethiopia

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Background

Poor linear growth of children, manifested as stunting, is the most prevalent form of under-nutrition globally [1] and is associated with higher child mortality and morbidity [2, 3], poorer motor and cognitive development [4], and lower educational attainment and economic productivity [5] as well as higher risk of metabolic diseases during adulthood [1]. Despite the international commitment to reduce the number of stunted children under 5 years by 40 % by 2025 [6], current nutritional interventions alone are unlikely to meet this target [7]. Understanding the effectiveness of multi-sectoral approaches such as nutrition-sensitive agriculture in addressing the underlying determinants of malnutrition can accelerate progress in improving nutritional status globally [8].

Recent evidence indicates that protein and amino acids play biological roles in protein and lipid synthesis, bone elongation, and the regulation of these and other processes necessary for linear growth. Similarly, linear growth is stimulated by insulin-like growth factor 1 (IGF-1), which is also responsive to dietary protein intake [9, 10]. However, dietary intakes of utilizable protein, i.e., protein adjusted for quality (determined by the content of essential amino acids) and digestibility [11], may be inadequate, particularly in sub-Saharan Africa [12]. Furthermore, current estimates of protein requirements do not address (1) children's protein needs for optimal linear growth; (2) increased requirements due to frequent infections, growth faltering, or energy deficit; and (3) the roles of protein and amino acids in growth regulation and immune function [13–15]. Adjusting protein requirements to account for increased needs due to recurring infections and energy deficits significantly increases estimates of the prevalence of inadequate protein intakes in developing countries [12].

At the country level, the per capita supply of utilizable protein is significantly and negatively associated with the prevalence of child stunting, even after controlling for the supply of dietary energy [12]. In an observational cohort of Danish children, protein intake at 9 months of age was correlated with length at that age and height at 10 years [16]. A cross-sectional comparison of children aged 12–59 months in rural Malawi found that stunted children had lower serum concentrations of most amino acids including all the essential amino acids, which are not synthesized by the body and therefore must be obtained through dietary intake [17]. Randomized controlled trials in China [18] and Pakistan [19] found that fortification of wheat flour with lysine, which is globally the most limiting essential amino acid [20], increased linear growth in children.

Growth faltering is widespread among Ethiopian children, and the annual cost of undernutrition to the country has been estimated at US$4.7 billion, which amounts to 16.5 % of the gross domestic product (GDP) [21]. Among children under 5 years, 40 % are stunted, 9 % have acute malnutrition, and 25 % are underweight [22]. The Government of Ethiopia has committed to significantly reduce child stunting by 2020 in its Second Growth and Transformation Plan (GTP II) and to eradicate child malnutrition by 2030 in its Seqota Declaration [23, 24]. To achieve these goals, it has called for a multi-sectoral approach for implementation of the National Nutrition Program II (NNP 2) through integration of nutrition into the agricultural and health sectors and development of a strategic plan for nutrition-sensitive agriculture [23, 25]. However, despite these commitments, evidence is still limited, both globally and in Ethiopia, on how agriculture can be effectively leveraged to improve nutrition and health [26].

Dietary quantity and quality are poor among infants and young children in Ethiopia, with less than half (49 %) of all children aged 6–23 months receiving the minimum recommended number of meals and only 5 % consuming a sufficiently diversified diet [27]. Children of this age who receive the minimum recommended number of meals and number of food groups (i.e., consuming a minimum acceptable diet) have significantly higher height-for-age Z-scores (HAZ, standardized for child age and sex), indicating better linear growth [28]. Diets of both children and adults in Ethiopia are heavily dependent on cereals and, in the last 20 years, maize has become the dominant source [29]. However, conventional maize has low levels of the essential amino acids lysine and tryptophan, and the resulting poor protein quality increases the risk of inadequate intakes of utilizable protein and essential amino acids [30, 31].

Efforts to improve the protein quality of maize date back to the 1950s [32, 33]. In the early 1960s, the natural *o2* mutation was identified as responsible for changing the protein composition of the maize endosperm, nearly doubling its lysine and tryptophan content [34]. As a result, *o2* maize grain had improved protein quality, while its protein quantity remained the same. Subsequent conventional plant breeding efforts (i.e., methods not using genetic modification) resulted in agronomically competitive maize varieties adapted to target environments, particularly in sub-Saharan Africa [35]. To differentiate them from the earlier *o2* maize varieties and from 'conventional' maize varieties, these new varieties are collectively referred to as quality protein maize (QPM) and are an example of biofortification, or the genetic improvement of the nutritional quality of food crops [36]. Several randomized controlled trials (RCTs) have been conducted in which young children or households with young children were provided QPM or conventional maize in the form of seed, grain, dough, or prepared food, with specific instructions to use the maize for child feeding [37–39]. A meta-analysis of these studies found that provision of QPM instead of conventional maize led to a 12 % increase in the rate of growth in weight and a 9 % increase in the rate of growth in height in infants and young children with mild to moderate undernutrition from populations in which maize is the major staple food [37].

Despite these efforts, knowledge gaps remain in assessing the potential for QPM to positively impact the nutritional status of Ethiopian children in practice. Most prior RCTs on QPM did not directly measure children's consumption of QPM or conventional maize, and all RCTs largely or exclusively relied on anthropometric outcomes, which are affected by many factors beyond quality protein intake [1]. Therefore, despite the randomization in these studies, it is not possible to establish whether provision of QPM led to children's consumption of a critical amount or whether consumption of QPM led to changes in protein or amino acid status, which in turn led to improved growth.

Furthermore, little is known about QPM's impact on children's nutritional status in a natural setting in which households make their own decisions whether to adopt QPM, how much to adopt and cultivate, and whether and how to incorporate QPM into children's diets. In Ethiopia, maize seed is sold in a package with a mandated size of 12.5 kg, compared with 2-kg bags that are typically sold in other East African countries where seed markets are liberalized [40]. The larger seed package size may be a barrier to adoption of QPM or any other improved maize variety, particularly at the initial stage when farmers may prefer to allocate only a small area to a new variety. If farmers are convinced of the agronomic performance of a QPM variety and can access seed in appropriate quantities, additional gains in adoption could be achieved by nutrition-focused extension efforts in which farmers are provided with knowledge of the benefits, particularly for their children's nutrition.

Following adoption, QPM must be separated from conventional maize at all stages of production, harvest, post-harvest handling, storage, milling, cooking, and consumption to prevent dilution of the quality protein trait [41]. This requires knowledge of QPM, its nutritional benefit, and good management practices to maintain the quality protein trait. However, many of the steps between household adoption and children's consumption of QPM are handled by women, and women often have less access to agricultural extension and other sources of agricultural information [42]. Their lack of knowledge about the technology could lead to a reduction or loss of the quality protein trait in maize consumed by target individuals in the household, ultimately limiting the nutritional impact of QPM. Consumption by children in particular also depends on feeding practices, typically controlled by women, and on how women choose to incorporate QPM into children's diets in a natural setting. Therefore, this study aimed (1) to estimate the causal effect of adoption encouragement focused on nutritional benefits on adoption decisions and protein status among infants and young children in a major maize-growing area of Ethiopia; and (2) among QPM adopters in the same area, to estimate the causal effect of QPM consumption encouragement on children's QPM consumption, protein status, and linear growth.

Methods/design

Study overview

This study is superimposed upon the Nutritious Maize for Ethiopia (NuME) Project, which develops, promotes, and disseminates QPM varieties in the country's major maize-growing areas. NuME is a collaboration of the International Maize and Wheat Improvement Center (CIMMYT) with the Ethiopian Institute of Agricultural Research (EIAR), Sasakawa Global 2000, the Ethiopian Public Health Institute (EPHI), and other national and international partners. Households in this study had at least one member who had been exposed to QPM varieties by attending field demonstrations organized by NuME.

This study evaluates two randomized interventions related to household-level QPM production and consumption. Both focus on children who were 6–35 months old at enrollment. The first intervention, QPM adoption encouragement (AE), consists of a household visit by the research staff. The visit was targeted towards the household head, the primary decision-maker on the adoption of new maize varieties [42], although the primary caregiver for the household's young children was encouraged to join if present, and in 81 % of households was present. The message (Additional file 1) focused on the nutritional benefits of QPM varieties for young children, and the households were offered seed of QPM varieties they had observed in NuME field demonstrations to plant during the coming agricultural season.

While encouraging the adoption and production of QPM is an important first step in increasing QPM consumption, the ultimate purpose of the study is to understand whether greater production and consumption of QPM can improve childhood nutrition. To examine how to nudge families to feed QPM to their children, half of households assigned to the AE intervention were selected to receive an additional encouragement campaign. In this second intervention, the consumption encouragement (CE), targeting the caregiver of the household's young children, the study team explained why households should prioritize children's consumption of QPM (Additional file 2). The caregiver was provided with extension materials and specific storage containers to 'earmark' QPM grain and flour for young children.

Both parts of this second intervention could plausibly have large effects on children's consumption of QPM. Primary caregivers tend to have relatively little information about how to use QPM effectively, but generally make food preparation decisions for the household, suggesting that provision of even minimal education about QPM could result in significant changes in behavior and consumption patterns. Additionally, studies on financial decision-making suggest that earmarking (e.g., labeling a cash transfer as intended for education, but not enforcing how the money is spent) can have surprisingly large effects [43, 44].

Besides testing for the effect of these two interventions on household-level adoption of QPM and consumption of QPM by children in the target age range, we ultimately aim to evaluate the impact of these interventions on nutritional outcomes for infants and young children, including biochemical indicators of protein status and linear growth. Additionally, we will consider how other relevant outcomes, including allocation of food within the household and knowledge of QPM, are influenced by these interventions.

Overall, the selected households will be followed over one agricultural cycle, starting prior to planting, when adoption decisions are made, through production, harvest, and the period of storage and consumption that follows. Data collection includes a baseline survey (July-September 2015), a midline survey (February-March, 2016) and an endline survey (June-August 2016). Given the nature of the interventions, it was not possible to blind either study participants or staff.

We hypothesize that the first intervention, adoption encouragement, will increase the adoption and use of QPM, and have an observable effect on the outcomes, compared to households who only observed the varieties in the demonstration. Further, we hypothesize that the second intervention, consumption encouragement, with its focus on targeting the QPM to the young child, will have a larger effect compared to the adoption encouragement alone. Finally, as many confounders affect the outcomes, particularly overall dietary intake and morbidity, these variables will be included in the analysis.

The chronology of the study reflects the seasonality of the outcomes and main factors (Table 1). The households were first contacted after they participated in the demonstrations during the main season of 2014. They were visited again before the next planting season in 2015 and offered QPM seed in the adoption encouragement. The baseline survey took place at the peak of food insecurity, after planting but before harvest, in the main season of 2015, and included biological specimen collection. Consumption encouragement was offered before the harvest of 2015. The midline survey, including collection of biological specimens, took place at roughly 3-4 months after the harvest, when the peak effect on biomarkers was expected, while the endline, with anthropometrics, will take place in 2016 during the same season as the baseline, between planting and harvest, as households' maize stores are diminishing.

Table 1 Timetable of activities planned and implemented

Time of activity	**Control**	**Adoption Encouragement Only**	**Adoption and Consumption Encouragement**
Nov 2014-Jan 2015	QPM demonstrations		
Mar 2015	***DA listing of households & Stage 1 Randomization***		
Mar-Apr 2015		Adoption Encouragement	
Apr-May 2015		QPM seed distributed	
May-Jun 2015	*Households plant maize seed (QPM and conventional)*		
Jul-Sep 2015	***Stage 2 Randomization, Enrollment,& Baseline Survey***		
			Consumption Encouragement
Aug-Sep 2015	*Green maize consumption began*		
Nov 2015			Group Consumption Encouragement meeting + tools distributed
Dec 2015-Jan 2016	*Maize harvest*		
Feb-Mar 2016	***Midline Survey***		
			Consumption Encouragement Refresher
Jun-Aug 2016	***Endline Survey***		

The different treatments are presented in bold, the different stages of the study are presented in bold italics, agricultural activities that occurred in the community independent of the study are presented in italics, and activities related to the study are presented in plain text

Site description

Administratively, Ethiopia is divided into nine regional states, which are further divided into zones, then districts or *woredas*, and finally peasant associations or *kebeles. Kebeles* are the smallest official administrative unit and comprise about 500 to 1000 or more households each. The NuME project is being implemented over a 5-year period, starting in 2012, in three agro-ecological zones (drought-prone, moist mid-altitude and highland zones) where impact is expected to be greatest, as identified by GIS analysis combining agro-climatic, nutritional and poverty databases [45].

Within the NuME project areas, the study team conducted extensive focus groups with more than 100 men and women in the Oromia and Amhara regions. Interviews with the women focused on existing child feeding habits (e.g., age of solid food initiation, foods fed to young children, etc.), while interviews with the men focused on details of their planting seasons, including when and how seed variety choices are made, as well as general acceptance of and desire for QPM varieties. Based on the results of these focus group discussions, the study is being conducted in two zones of the Oromia region, given their higher likelihood for potential impact.

The entire Oromia region is a third of the total area of Ethiopia and has a population of 27 million people [46]. The average household size in the region is 4.8 members. Agriculture is the primary economic activity of the region, engaging about 90 % of the population, with home production used to meet a significant portion of household food needs.

The study area comprises one to two *kebeles* each from the *woredas* of Boneya Bushe, Gobu Seyo, Gudeya Billa, Guto Gida, and Sibu Sire in the East Wollega zone and two *kebeles* each of the *woredas* of Omo Nada and Mena from the Jimma zone. The12 *kebeles* in total are in rural, maize-growing areas.

Study population

This study focuses on households in the target areas where QPM was demonstrated prior to the main growing season in 2015. The primary focus is on children who were 6–35 months during the baseline survey in July-September 2015. The target age range excludes the first 6 months when exclusive breastfeeding is recommended and otherwise includes the critical first 2 years of life when children are particularly vulnerable to growth faltering and the third year when they are increasingly dependent on solid foods.

Households in the study area were eligible for inclusion if they met the following criteria: (1) the household had at least one child aged 6–35 months at recruitment in July-September 2015; (2) the household had at least one member who had attended a field demonstration conducted by the NuME Project in November 2014-January 2015; and (3) the household provided informed consent to participate in the study. Households were excluded if (1) the primary caregiver or index child were not intending to remain in the study area for the study duration; (2) the household did not have access to land for crop cultivation in the main 2015 season; or (3) the household had produced QPM in an on-farm demonstration in the previous year. Additionally, households in the treatment groups were excluded if the primary caregiver for the target child was not in a 'one to five' group, since this information was used for randomization between the two treatment groups. The one to five groups, formally called the Health Development Army (HDA), consist of about five women and are formed to help local health extension personnel with the outreach of the health and nutrition program at the community level.

Study design

The study is a randomized controlled trial, with two interventions related to household-level QPM production and consumption. The overall study has three treatment arms (Fig. 1). A third of households were allocated to the control arm, where the household's participation was limited to data collection. The remaining households were split between those receiving the AE intervention only and those receiving both the AE and CE interventions.

Randomization and recruitment

In the 12 selected *kebeles*, a list of households who participated in the field days and who were eligible for inclusion in the study was established with the help of the local administration, in particular the *kebele*-level development agents, which are government extension officers for agriculture and rural development. These households (1779 in total) were randomly assigned to the control (one third) and two treatment groups (each one third), sequentially in two stages, and stratified by *kebele* (so resulting in the same proportions in each *kebele*). In the first stage, control vs. AE, randomization was done at the household level, while at the second stage, which was AE only vs. AE plus CE, randomization was done at the group or cluster level.

In the first stage of randomization, a third of study households (587) were assigned to the control group and the remainder (1192) to the AE treatment using simple randomization, stratified by kebele. This stage took place prior to the planting season in April 2015. In the second stage of randomization, half of the households that had participated in the AE intervention were assigned to the CE intervention. This occurred prior to the baseline survey, during which the initial CE messages were presented. Among the 1192 households that had been assigned to the AE intervention, 1024 met the eligibility requirements and ordered QPM seed, forming

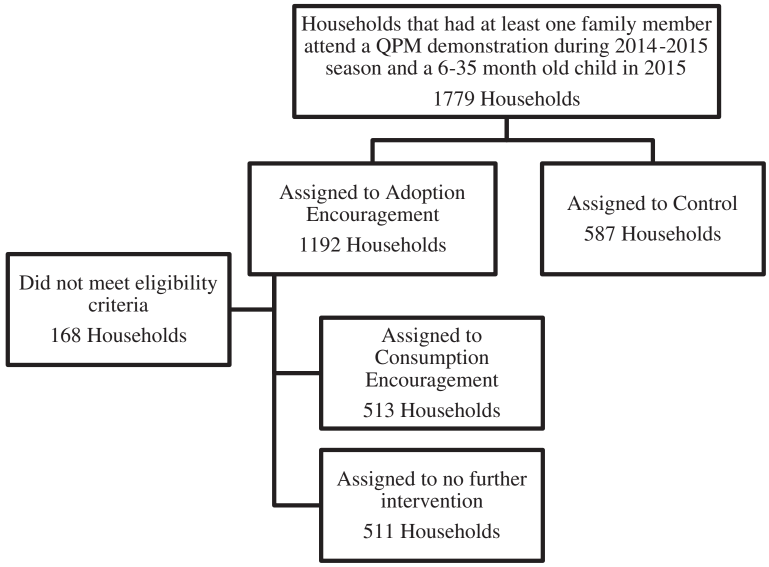

Fig. 1 Summary of study design

the set of potential households to be included in this stage.

Given that a large component of the CE intervention was based on information for the caregiver, the second stage of randomization was conducted at the 'one to five' group level. Therefore, all cases where the caregiver did not belong to a 'one to five' group were excluded, reducing the sample to 1024 households, now organized in 562 women's groups or clusters. Half of the clusters were assigned to each treatment group, stratified by *kebele*, using the Stata (software) command "randomize". This command maximized balance on each cluster's average values for caregiver being present during AE messages, household having a telephone number, and number of study households in the cluster (which ranged from 1 to 13 households, and averaged 3.0 households). After randomization, balance was confirmed at the household level on the number of bags of QPM of each variety that were ordered during AE, the total number of bags of QPM that was ordered during AE, and the three factors used during randomization. As in the first stage, this randomization was stratified by *kebele*. Overall, this resulted in 280 clusters (with 511 households) assigned to AE only, and 282 clusters (with 513 households) assigned to AE plus CE. Initially, 587 households were assigned to the control group, but power calculations suggested fewer households were needed to identify plausible treatment effects. Therefore, 467 of these households were selected by simple randomized sampling, stratified by *kebele*, for data collection.

A subsample was additionally selected from each study arm for biomarker collection, hemoglobin tests, and malaria rapid diagnostic tests. In the control group, this subsample was selected using simple random selection, stratified by *kebele*. In the treatment groups, this subsample was selected in two stages: (1) stratifying by *kebele*, an equal proportion of clusters was selected using simple random selection; and (2) within each of these randomly-chosen clusters, one household was chosen using simple random selection. After performing these two stages of random selection, balance was confirmed on the relevant household characteristics described above.

Given the multiple stages of randomization and the need to distribute QPM seed prior to the growing season, all randomization of households to treatment groups was conducted prior to informed consent and enrollment. Provision of QPM seed to households in the groups receiving AE was not contingent on study participation, and households which were later found to be ineligible or declined to provide informed consent were free to use the QPM seed even though they did not participate in the study or data collection. Households that were allocated to receive CE but were found to be ineligible or declined to provide informed consent did not receive the CE intervention or otherwise participate in the study.

Interventions

Adoption encouragement

In the Adoption Encouragement (AE) intervention, households were offered guidance about the benefits of QPM consumption for young children and the opportunity to order a small amount of QPM seed to plant on their own land. Qualitative evidence suggests that, especially for new products, higher rates of adoption occur when farmers can try seeds in smaller quantities [47, 48]. Prior to the intervention, we calculated that a package size of 2 kg—yielding enough to provide 150 g of QPM grain per target child per day with sufficient leftover grain for further household use—would be the minimum level of adoption required to see meaningful impact on nutritional status in young children over a period of 6 months.

This intervention is driven by the insight that while it is important for children to have nutritionally dense foods, they do not eat much food, particularly while they are also breastfeeding. Farmers are likely only willing to experiment with a small portion of their land before they have experience growing QPM, but even growing a relatively small amount of QPM could greatly impact their children's health.

The study team, assisted by local development agents, visited the households selected for the AE intervention in March–April 2015, and held a discussion with the head of household and the caregiver for the household's young children, if she was available. This discussion focused on (1) the nutritional benefits of QPM, especially compared to conventional maize varieties; (2) the special vulnerability children faced regarding nutritional deficiency and malnutrition and QPM's potential to mitigate these risks; (3) details about the two varieties of QPM available – one, AMH760Q, has white grain and is late maturing and drought tolerant while the second, BHQPY545, has yellow grain, has intermediate maturity and is also drought tolerant; and (4) information about how QPM is similar to other maize varieties agronomically and for food preparation and consumption. After this discussion, the enumerators offered the option to order up to three 2-kg bags of QPM seed, emphasizing that the farmer had no obligation to order, but was also asked not to share the seed with anyone outside of his household if he did choose to place an order. If the farmer was interested, the enumerators took orders for QPM seed to plant in the coming month. The seed was offered free of charge, but household heads were required to come to a central location to pick up the seed a few weeks later.

Consumption encouragement

In the consumption encouragement (CE) intervention, household heads and particularly caregivers for young children were offered (1) further guidance on the nutritional benefits of QPM for young children; (2) guidance on the importance of keeping QPM separate from conventional maize to prevent dilution of the nutritional benefits; and (3) tools to help them separate and 'earmark' QPM grain and flour for child consumption. The first component of the intervention, guidance on nutritional benefits for children, was adopted and developed based on the health belief model [49, 50]. The second component, guidance on QPM management, was based on recommendations by breeders and agronomists on production and utilization of QPM. The third component, tools for earmarking, was motivated by evidence from interventions in financial decision-making, which suggests that earmarking can have surprisingly large effects. In Morocco, cash transfers with a non-binding education label were shown to lead to significant increases in school participation, similar to conditioning the payments on participation [43]. Experiments have shown that allowing for multiple accounts increased savings rates, and this was enhanced by earmarking one account with a visual reminder of children [51]. In this study, the consumption encouragement intervention explores the hypothesis that providing a way to separate nutritional resources (improved maize) with a label with reference to children increases the quantity that reaches them.

The CE messages were presented during three different sessions over the study period: two one-on-one sessions during the baseline and midline surveys, immediately following data collection, and one group session in between these surveys prior to the harvest. The timing, content, and participants in these sessions depended on the agricultural calendar and the roles of men and women in agricultural, child care, and feeding practices.

The first CE message was offered at the household during the baseline survey in July-September 2015, immediately following data collection. The message was given prior to the availability of green maize in farmers' fields, at which point children may begin consuming QPM. During this visit, enumerators (1) discussed with the caregivers and heads of household the benefits of QPM relative to conventional maize and the special benefit young children receive from QPM consumption; (2) discouraged participants from selling QPM or feeding it to livestock; (3) discussed the importance of keeping QPM separate from other grains and flours; and (4) informed caregivers that they would be offered tools to help keep QPM grain and flour separate later in the year. Heads of household were encouraged to build separate cob storage cribs or to partition existing storage cribs, in order to keep their QPM separate from conventional maize while it was drying. The messages overall took less than 10 min.

The second session was conducted in November 2015, prior to the grain harvest. Caregivers in the CE intervention group were invited to participate in a group meeting at a nearby location, usually a health extension post or farmer training center. During this visit, enumerators used an education poster (Fig. 2a) to re-emphasize messages that had been presented earlier and engaged

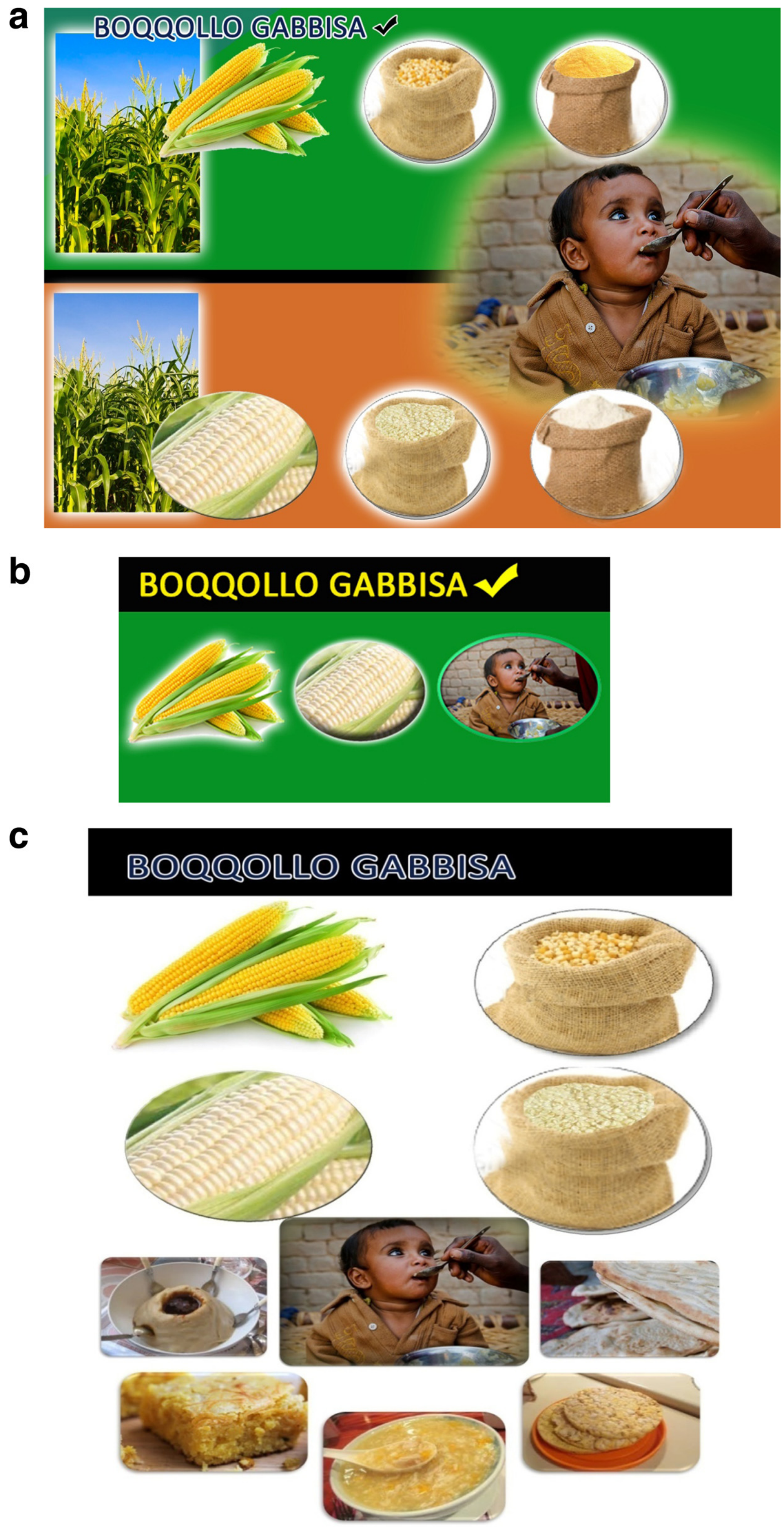

Fig. 2 (See legend on next page.)

(See figure on previous page.)
Fig. 2 Posters and label for consumption encouragement. "Boqqollo gabbisa" is the local term used for QPM in the Oromo language. **a** Poster for discussion during consumption encouragement group meeting, illustrating the yellow and white varieties offered in the study in the field, as grain and flour, and as complementary food; **b**) Label used for grain and flour storage bags; **c**) Poster for household use, illustrating complementary foods that could be made with QPM. Consent to use the image of the child in these posters and label was obtained from the child's mother by a staff member from the Ethiopian Public Health Institute (EPHI)

participants in a group dialogue to help identify ways to better target QPM to their young children. When participants identified aspects that might be difficult (e.g., cooking separate meals for their young children), the enumerator facilitated a group discussion to help participants think of ways to make these challenges easier to overcome. At the end of the visit, caregivers were offered several tools to help them separate QPM grain and flour from other grains and flours, and to remember to do so. Each caregiver was given four standard bags for storing grain (each capable of holding 100 kg), one bag for storing flour (capable of holding 50 kg), and a bowl and spoon for feeding the index child. All of these items were marked with a colorful label that had a picture of an infant eating and images of white and yellow maize, and "quality protein maize" written in the local language (Fig. 2b). Additionally, each caregiver was given a poster (60 cm × 41 cm) displaying complementary foods that could be made with QPM (Fig. 2c). Overall, the group events took 30–35 min. Caregivers who were unable to attend a group session received a one-on-one session and all materials in their homes.

In the third session, the CE educational messages were re-emphasized for caregivers for a final time during the midline survey, immediately after data collection. Enumerators reviewed a short set of the most key messages, focusing on the benefits of QPM consumption for young children and targeting QPM-based foods.

Outcome measures

The primary outcomes in this study are linear growth of the index child, measured as height-for-age Z-score (HAZ) [52], protein status measured using prealbumin (transthyretin) [53], and measures of QPM consumption. The secondary outcomes include child stunting (HAZ < -2), acute malnutrition (weight-for-height Z-score < -2) underweight (weight-for-age Z-score < -2), and total intake of utilizable protein measured using a 24-h dietary recall [53].

Data collection

Data were collected at three times: the baseline, midline and endline survey. Prior to beginning any data collection at baseline, written informed consent was obtained from all respondents. Much of the data collected focused on one target child (i.e., the "index child"), who was between 6 and 35 months old at the time of the baseline survey. In cases where there was more than one eligible child in the household, the youngest was selected to be the index child. All households received a small, non-monetary incentive such as soap and iodized salt at each data collection event.

Questionnaires were administered to the caregiver and the household head at baseline and midline, and the caregiver alone at endline. Topics in the caregiver surveys included demographics; household roster (baseline only); 24-h dietary recall for the index child; seven-day food frequency for key household members; cooking practices; growth perceptions; child health and illness; former pregnancies (baseline only); household food security; nutrition knowledge; QPM knowledge; water supply and sanitation access (baseline only); sources of information; gender responsibilities; and bargaining. Topics in household head surveys included demographics; household assets (baseline only); details about crop production, area, and sale; specific information about maize production by variety; seasonality in crop storage, sale, purchase, and consumption; agricultural input use; livestock ownership; income sources; expenditures; growth perceptions; gender responsibilities; bargaining; participation in rural institutions; and sources of information.

Anthropometrics

Anthropometrics (i.e., height or recumbent length, weight, and mid-upper arm circumference) were collected on all index children and their biological mothers (among the caregivers) during baseline, midline, and endline. Weight of index children was measured with light clothing and without shoes to the nearest 100 g using a standard SECA digital scale. The scale was calibrated after moving from one household to the next. The caregivers were weighed without ornaments, shoes and heavy clothes to the nearest 100 g using the same scale.

Length of younger children (6–23 months) was measured in a recumbent position to the nearest 0.1 cm using a locally made board with an upright wooden base and movable headpiece. Height of children older than 23 months of age was measured in a standing position to the nearest 0.1 cm using a locally made vertical board with a detachable sliding headpiece. Similarly, caregivers' height was measured by a portable measuring height board with moveable headboard.

Mid-upper arm circumference (MUAC) was measured for the index child and caregiver with a standard MUAC tape on the upper left arm. After locating the mid-point for measurement between the end of the shoulder (acromion) and the tip of the elbow (olecranon), this point was then marked. The arm was then allowed to hang freely and MUAC was measured at the marked midpoint. Referrals to the local kebele's health post were made whenever a participant was identified as severely malnourished (MUAC < 110 mm and/or bilateral oedema for children, MUAC < 210 mm for pregnant or lactating women, or body mass index (BMI) < 16 kg/m^2 for non-pregnant, non-lactating women).

Dietary recall

Dietary recall interviews were used to collect the specific type and amount of food consumed by the index child during the full day (24 h, sunrise to sunrise) prior to the survey. The questionnaire was developed based on the internationally-recognized multiple pass method described by Gibson and Ferguson [54], adjusted to the Ethiopian context. Each interview involved a stepwise series of questions and typical household utensils and food substitutes (play dough, flour, lentils, water) to improve the memory of the respondents and assist in completing the questionnaires. A digital food scale was be used to measure the gram amount of food consumed and of ingredients used in food preparation. The interviews were conducted on all 7 days of the week to capture changes in intakes across various days of the week. Collection days included market days and holidays that occurred while the team was in the study area. In addition to this, a seven-day food-frequency questionnaire asked the following details from the index child's primary caregiver: consumption of any QPM by the index child in the last 24 h, amount of QPM consumed by the index child in the last 24 h, index child's proportion of total maize consumption that was QPM in the last 24 h, consumption of any QPM by the index child in the last week, and number of days in the last week that the index child ate any QPM. Other household behaviors related to QPM targeting include number of days in the last week that the caregiver cooked a QPM-based food that was primarily for target children, amount of QPM reserved for home consumption (both self-reported), and proportion of grain that is QPM in the source most recently used to cook food for the index child.

This dietary recall module provides very rich data, but it only captures information about the previous day, which may not be representative of a child's overall eating habits. To identify the degree of within-person and between-person variation in food consumption, a subset of households was selected to revisit within 1 week of the midline survey, on a non-consecutive different day of the week, to conduct a repeated dietary recall [55]. Fifty households were randomly selected from each study group (control, AE and AE+ CE) for the repeated dietary recall using simple random sampling. If the household was not available during the repeat dietary recall, it was randomly replaced with another household from the same *kebele*. This information will allow estimation of the usual intake of dietary protein and other nutrients.

Specimen collection and analysis

In the subset of households identified for specimen collection, caregivers and index children were assessed for anemia and malaria infection and venous blood and stool samples were collected from index children. These assessments and specimen collection were conducted at baseline and midline. Given the seasonal pattern of maize consumption, midline was chosen over endline as it represented a period of high maize consumption approximately 3 to 4 months after harvest, which in turn followed a period of green maize consumption. At endline, it is expected that maize consumption will have tapered with declining maize stores. Venous blood samples were taken to assess serum prealbumin (transthyretin) and IGF-1 for protein status and alpha-1-glycoprotein (AGP) and C-reactive protein (CRP) for inflammation, which has been implicated in stunting [1, 56].

Phlebotomists collected blood samples from participants' arm by venipuncture using a trace metal-free evacuated tube collection system, and collected whole blood into a vacutainer. The vacutainer contained a separator gel, free from trace metals, with a non-rubber stopper. If the caregiver refused collection of venous blood from the child, blood was taken by finger prick to assess hemoglobin concentration for diagnosis of anaemia and malaria infection using a rapid diagnostic test (RDT) only.

Anemia was assessed by measuring hemoglobin in red blood cells, using a HemoCue (Hb-201) instrument. Liquid controls (high, medium and low) were used at the beginning of each day for quality control of the HemoCue instrument. Hemoglobin concentrations were read immediately using the HemoCue. Participants were considered to have severe anemia if their hemoglobin level was less than 8 g/dL and were referred to local health services [57]. Cut-off values for anemia will be adjusted per published recommendations [57, 58] on the basis of age, sex, pregnancy status and the altitude where the person lived. The adjustment for altitude will be done (Hb adjustment = -0.032 x [altitude (m) x 0.0032808] + 0.022 x [(altitude (m) x 0.0032808)]^2) for children and caregivers living at an altitude of 1000 meters above sea level or higher [58], where the Hb adjustment will be the value subtracted from each individual's observed hemoglobin level. The malaria parasite burden was measured using a RDT for *Plasmodium* species [59].

In each kebele a temporary field lab was set up in a central location such as a school, farmer training center, health center or other location for a lab technologist to immediately centrifuge samples transported from the field and aliquot the serum into labeled cryovials. Blood samples were transported from the household to the temporary field lab promptly after collection in cold boxes containing frozen gel packs (<8 °C) by local guides appointed specifically to assist each lab technician in rapidly carrying the samples to the centralized temporary field lab site. When electricity was not available, the field lab was set up in a vehicle. The laboratory team vehicle maintained a self-contained field laboratory that included a portable centrifuge to allow for immediate centrifugation and aliquoting of serum into cryovials. This vehicle also included a -20 °C freezer, powered with electricity from the grid or a battery for fast freezing of serum samples in the field. This freezer was also used to maintain the frozen gel packs to be used with the cool boxes that went to the field during sample collection. All samples were processed within 2 hours of collection. Cryovials were stored at – 80 °C. Specimen identifiers were labeled directly on the cryovial.

Stool samples were placed in a clean stool cup either during the visit with the lab team or by the caregiver later if no stool was available at the time of the visit. The examination of faeces for parasitological diagnosis was done to detect adult worms, cysts, ova and larvae using microscopes in the field using Kato Katz techniques [60, 61]. The remaining stool samples were transported to the EPHI parasitology laboratory and stored at – 80 °C for later analysis of intestinal helminth infections [61].

AGP, CRP, IGF-1, and prealbumin (transthyretin) will be assessed using the immuno-turbidimetry method using Roche kits. The change in turbidity, proportional to the AGP and CRP concentration, will be measured on the modular Cobas Integra 600 clinical analyzer and the presence of inflammation will determined by a standard method [62].

Grain sample

During the midline survey, the study team collected a sample of about 100 grains of maize from each household, from the source where the index child's most recent maize-based meal was made, to analyze if the grain came from a QPM variety. This is done by testing for QPM's endosperm modifiers along with the *o2* mutant allele using a rapid and low-cost method of selection, whereby light is projected through the vitreous grains or blocked by the opaque grains respectively [35].

Sample size calculation

Sample size calculations were based on the nutritional outcomes for which effects of QPM were observed under controlled conditions and plausible biological mechanisms exist: height-for-age Z-score (HAZ), hemoglobin (Hb), and prealbumin (transthyretin). HAZ is standardized, so its standard deviation was assumed to be 1. Hb is typically symmetric and a standard deviation of 2.0 g/dL is based on the expectation that physiologically plausible values will fall within a range of 12 g/dL (six standard deviations) in the relevant age group. The mean and standard deviation for transthyretin were assumed to be 20 and 30, per published reference distributions [53]. All calculations are based on intent-to-treat analyses, which assumes a 78 % overall QPM adoption rate in the treatment groups, and a 30 % adoption rate in the control group (both are conservative estimates to account for potential spillovers). When comparing the treatment groups to each other, the effect of adoption was assumed to be 50 % higher in the group receiving both adoption and consumption encouragement than in the group receiving adoption encouragement only.

Statistical analysis

Primary outcomes will be analyzed based on an 'intention-to-treat' principle. Baseline socio-demographic characteristics will be summarized with percentages for categorical variables and mean ± SD (or median and range) for continuous variables. To examine the impact of QPM adoption and consumption, generalized linear mixed effects models for repeated measures will be estimated for all outcomes. All hypothesis tests will be two-sided with a 0.05 significance level.

Trial status

Data collection is ongoing.

Discussion

Global commitment to reduce childhood stunting and improve nutritional outcomes is growing. There is an urgent need for evidence on the impact of agricultural interventions on nutrition and health, which requires rigorous assessments of effectiveness. Quality protein maize has the potential to improve the nutrition status of young children due to its higher lysine and tryptophan content. However, there are important challenges in ensuring appropriate adoption and use of QPM. This study seeks to address two important behavioral barriers between the development of QPM and its impact on children's nutrition and health in practice: the decision by households to adopt QPM, and the subsequent decision to allocate the improved maize to young children. It addresses the question of whether a biofortified crop can passively have an impact on children's nutritional status through adoption and typical household use, or whether additional intervention addressing behaviors affecting nutrition or targeting women as caregivers is needed for impact. Collection of data on production; decisions on storage, processing, intra-household food allocation and diets; and nutritional status using both biomarkers and anthropometry will provide greater understanding on the mechanisms through which QPM impacts child nutrition. This trial is the first such study to be conducted with a biofortified staple crop in a natural setting.

The Government of Ethiopia has set a target to have QPM varieties cultivated on 20 % of the country's total maize area in the coming few years. The results of this randomized controlled trial will be used to inform the Ethiopian and other governments and other stakeholders and implementers addressing nutrition, agriculture, and rural development in maize-growing areas on how to integrate QPM and similar biofortified crops into their programming. This trial will further add to the global database on evidence for linkages among agriculture, nutrition, and health and for strategies to maximize the impact of nutrition-sensitive agricultural interventions.

Additional files

Additional file 1: Message delivered during the Adoption Encouragement. (PDF 188 kb)

Additional file 2: Consumption Encouragement Guide. (PDF 341 kb)

Acknowledgements
The authors would like to thank the Regional Bureau, Zonal Bureaus, and Woredas (districts) and their personnel who facilitated the implementation of this study. We would also like to thank the study enumerators for their efforts and especially the study participants for their time and support of this study. We would further like to thank Kathy Sinclair for editing the manuscript.

Funding
This work is funded by the Agricultural Technology Adoption Initiative (ATAI) and the Nutritious Maize for Ethiopia (NuME) Project. The NuME Project is led by the International Maize and Wheat Improvement Center (CIMMYT) and funded by Global Affairs Canada. The donors had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results to peer-reviewed journals.

Availability of data and materials
As this study is ongoing, data are not available at this time. De-identified data will be available after publication of primary analyses, upon communication with the authors and according to the requirements of applicable IRBs and institutional policies.

Authors' contributions
MT, NSG, KD, and HDG drafted the manuscript. NSG and HDG conceived the original idea, the effect of QPM on nutritional outcomes within an RCT; MM and JC added the consumption encouragement intervention component; all critically commented on protocol. All authors contributed to the refinement of the study protocol and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Ethical approval and consent to participate
This study has been approved by Ethiopian Public Health Institute Scientific and Ethical Review Committee and the Harvard University Institutional Review Board (IRB). Prior to any data collection, research staff sought written informed consent from study participants in their homes. If participants were unable to sign their name, they affixed their thumbprint to the consent form and a witness to the consent process signed the consent form.

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Received: 16 July 2016 Accepted: 11 August 2016
Published online: 22 August 2016

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