Effects of food supplementation on cognitive function, cerebral blood flow, and nutritional status in young children at risk of undernutrition: randomized controlled trial

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ABSTRACT

OBJECTIVE
To assess the effects of food supplementation on improving working memory and additional measures including cerebral blood flow in children at risk of undernutrition.

DESIGN
Randomized controlled trial.

SETTING
10 villages in Guinea-Bissau.

PARTICIPANTS
1059 children aged 15 months to 7 years; children younger than 4 were the primary population.

INTERVENTIONS
Supervised isocaloric servings (≈1300 kJ, five mornings each week, 23 weeks) of a new food supplement (NEWSUP, high in plant polyphenols and omega 3 fatty acids, within a wide variety and high fortification of micronutrients, and a high protein content), or a fortified blended food (FBF) used in nutrition programs, or a control meal (traditional rice breakfast).

MAIN OUTCOME MEASUREMENTS
The primary outcome was working memory, a core executive function predicting long term academic achievement. Additional outcomes were hemoglobin concentration, growth, body composition, and index of cerebral blood flow (CBF_i). In addition to an intention-to-treat analysis, a predefined per protocol analysis was conducted in children who consumed at least 75% of the supplement (820/925, 89%). The primary outcome was assessed by a multivariable Poisson model; other outcomes were assessed by multivariable linear mixed models.

RESULTS
Among children younger than 4, randomization to NEWSUP increased working memory compared with the control meal (rate ratio 1.20, 95% confidence interval 1.02 to 1.41, P=0.03), with a larger effect in the per protocol population (1.25, 1.06 to 1.47, P=0.009). NEWSUP also increased hemoglobin concentration among children with anemia (adjusted mean difference 0.65 g/dL, 95% confidence interval 0.23 to 1.07, P=0.003) compared with the control meal, decreased body mass index z score gain (−0.23, −0.43 to −0.02, P=0.03), and increased lean tissue accretion (2.98 cm^2, 0.04 to 5.92, P=0.046) with less fat (−5.82 cm^2, −11.28 to −0.36, P=0.04) compared with FBF. Additionally, NEWSUP increased CBF_i compared with the control meal and FBF in both age groups combined (1.14 $mm^2/s\times10^{-8}$, 0.10 to 2.23, P=0.04 for both comparisons). Among children aged 4 and older, NEWSUP had no significant effect on working memory or anemia, but increased lean tissue compared with FBF (4.31 cm^2, 0.34 to 8.28, P=0.03).

CONCLUSIONS
Childhood undernutrition is associated with long term impairment in cognition. Contrary to current understanding, supplementary feeding for 23 weeks could improve executive function, brain health, and nutritional status in vulnerable young children living in low income countries. Further research is needed to optimize nutritional prescriptions for regenerative improvements in cognitive function, and to test effectiveness in other vulnerable groups.

TRIAL REGISTRATION
ClinicalTrials.gov NCT03017209.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Undernutrition in the early years of life is thought to cause permanent damage to cognitive function that is not reversed by later nutritional supplementation

Normal brain development is known to involve substantial ongoing changes, including neurogenesis, myelination, and synaptogenesis throughout childhood, suggesting that nutritional supplementation might promote regenerative improvements

An increasing body of preclinical research has suggested that traditional supplementary foods for young children might lack key food constituents that could support regenerative changes in the brain

WHAT THIS STUDY ADDS

Randomization to a new food supplement (NEWSUP) had a beneficial effect on working memory in children younger than 4, especially in those who consumed at least 75% of their supplement, compared with a traditional rice breakfast

NEWSUP also increased cerebral blood flow, improved body composition (more lean tissue with less fat), and had a beneficial effect on hemoglobin concentration in children younger than 4

Nutritional supplementation for 23 weeks could improve cognitive function in vulnerable young children living in low income countries, with additional benefits for brain health and nutritional status

Introduction

Undernutrition remains prevalent among young children worldwide and is associated with impaired cognition and reduced educational attainment.[1-5] Supplementary feeding programs and single nutrient trials in low income countries have not produced clear improvements in cognition,[6-10] and have contributed to the widespread view that inadequate nutrition in early life has irreversible effects on brain structure and function.[11-13] Nevertheless, normal brain development is known to involve substantial ongoing changes, including neurogenesis, myelination, and synaptogenesis, especially up to age 5,[14 15] and clear evidence exists of neuronal plasticity to at least age 17.[16] This evidence suggests that nutritional supplementation might, in principle, promote regenerative improvements in brain structure and function in children who have consumed an inadequate diet.

Current supplementary foods used in food assistance programs are fortified with only a subset of the vitamins and minerals that are defined as essential to prevent acute deficiency symptoms and death. An increasing body of preclinical research suggests the potential for additional nutrients and specific food constituents to support regenerative changes in the brain.[17] In particular, polyphenols, including those that cross the blood-brain barrier, increase cerebral blood flow, reduce cerebral inflammation and oxidative damage, and promote neurogenesis in animal models.[18-28] The omega 3 fatty acids docosahexaenoic acid and eicosapentaenoic acid, which are involved in myelination, regulation of microglial activation, and other aspects of brain structure and function, might not be synthesized endogenously in adequate amounts.[29-38] Other nutrients defined as essential that are not included in current supplementary foods include choline, a neurotransmitter precursor,[39 40] and the trace elements chromium and molybdenum, which have essential roles in brain metabolism.[41-44] Furthermore, the amounts of many micronutrients and protein (needed for structural growth and maintenance of brain tissue, and metabolic processes[45]) might be inadequate in traditional supplementary foods when taking into account the low nutrient levels in other foods consumed by children.[45 46] Despite these concerns, there have been no clinical trials testing wider multicomponent formulations, and the available data from focused testing of individual nutrients in children and older populations provide inconsistent results.[21-24 37 40 47]

We report a randomized controlled trial in children aged between 15 months and 7 years (primary age group: 15 months to <4 years; secondary age group: 4-7 years), which tested the effects of a new multicomponent supplementary food (NEWSUP) on cognition and nutrition parameters compared with traditional feeding practices (control meal). A fortified blended food (FBF) widely used in international food assistance programs was also tested. The primary outcome was working memory, which is a core executive function linked to a wide range of developmental changes, and arithmetic and reading ability,[48 49] emotion regulation,[50] and long term academic and social competence.[51] Additional study outcomes included cerebral blood flow, a sensitive marker of brain health,[52] which we measured non-invasively using near infrared spectroscopy (NIRS) and diffuse correlation spectroscopy (DCS). This method agrees with gold standards such as arterial spin labeled MRI (magnetic resonance imaging), fluorescent microspheres, and phase encoded velocity mapping MRI.[53-57] We also assessed hemoglobin concentrations and growth as standard indices of nutritional status, and body composition to determine if any of the supplements might promote an increased susceptibility to obesity later in life[11 58] through excessive body fat gain.

Methods

This randomized controlled trial was conducted during 2017 in young children living in 10 rural villages in the Oio and Cacheu regions of Guinea-Bissau, West Africa. Families were predominantly from Mandinka (Muslim) and Balanta (Christian) tribes. Guinea-Bissau is a low income country with a population of 1.7 million. The country has high rates of adult illiteracy, stunted growth in childhood, and anemia, as typically seen in low income countries in Africa.[59-61] Families living in villages in Guinea-Bissau cultivate much of the food they eat, including rice (the staple food), millet, corn, sorghum, groundnuts, cassava, sweet potatoes, and mangoes. Additionally they rear domestic animals, catch wild fish and small mammals, and grow cashews that they sell for additional rice and other popular foods including sugar, oil, and bread. Mothers typically breastfeed children to 2 years old, and report introducing complementary foods at about 6 months old.

The study design was a within village cluster randomized controlled trial with the family (defined as the father in this polygamous community) as the unit of randomization. We did not use block randomization by age or family size to prevent implementation mistakes, and to our knowledge no errors in randomization occurred. The supplementary appendix describes randomization in detail. Briefly, allocation concealment[62] was achieved by enrolling families, assigning study IDs, and using the Bissau field team, who had no role in randomization, to conduct baseline testing. Additionally, randomization was performed with a random number generator (Stata version 14.2) by the Tufts University study coordinator, who did not know the local families and created lists that assigned families to their randomized group after baseline testing. All major outcomes are reported here, and additional outcomes will be published elsewhere.

Families were randomized to receive NEWSUP, FBF, or a control meal that replicated the traditional local breakfast for five days each week. The interventions were implemented for an average of 23 weeks (range 20-25) and outcome measures were performed at baseline and shortly before the end of supplementation. Figure 1 shows the number of children who had baseline outcomes in the two predefined age groups (15 months to <4 years, and 4-7 years), dropouts, and the number of children in the intention-to-treat analysis and per protocol analysis (defined as children consuming ≥75% of total supplement; 89% (820/925) of those completing the intervention).

Participants

The villages approached for study participation were typical in terms of household occupations (predominantly farming) and family structure, while being sufficiently large and accessible to make oversight feasible. We enrolled villages in two cohorts starting five months apart. All approached villages agreed to participate after community level meetings to discuss the project. Once we had enrolled a village, all interested and eligible families could participate. The inclusion criterion was age (from 15 months to 7 years). Exclusion criteria were the child having severe acute malnutrition (mid-upper arm circumference <11.5 cm,[63] triggering a referral to a malnutrition clinic), the primary care giver reported the child had a relevant food allergy, or the family was planning to leave the village.

Mothers or legal guardians provided their informed consent with a signature or thumbprint in the presence of a researcher and local community health worker. The Data Safety and Monitoring Plan involved chain telephone reporting for serious and unexpected adverse events from village community health workers to the local study physician (CB) to the Tufts University study physician (ES). No serious adverse events or unexpected events occurred. After study completion, families were given rice to thank them for participation.

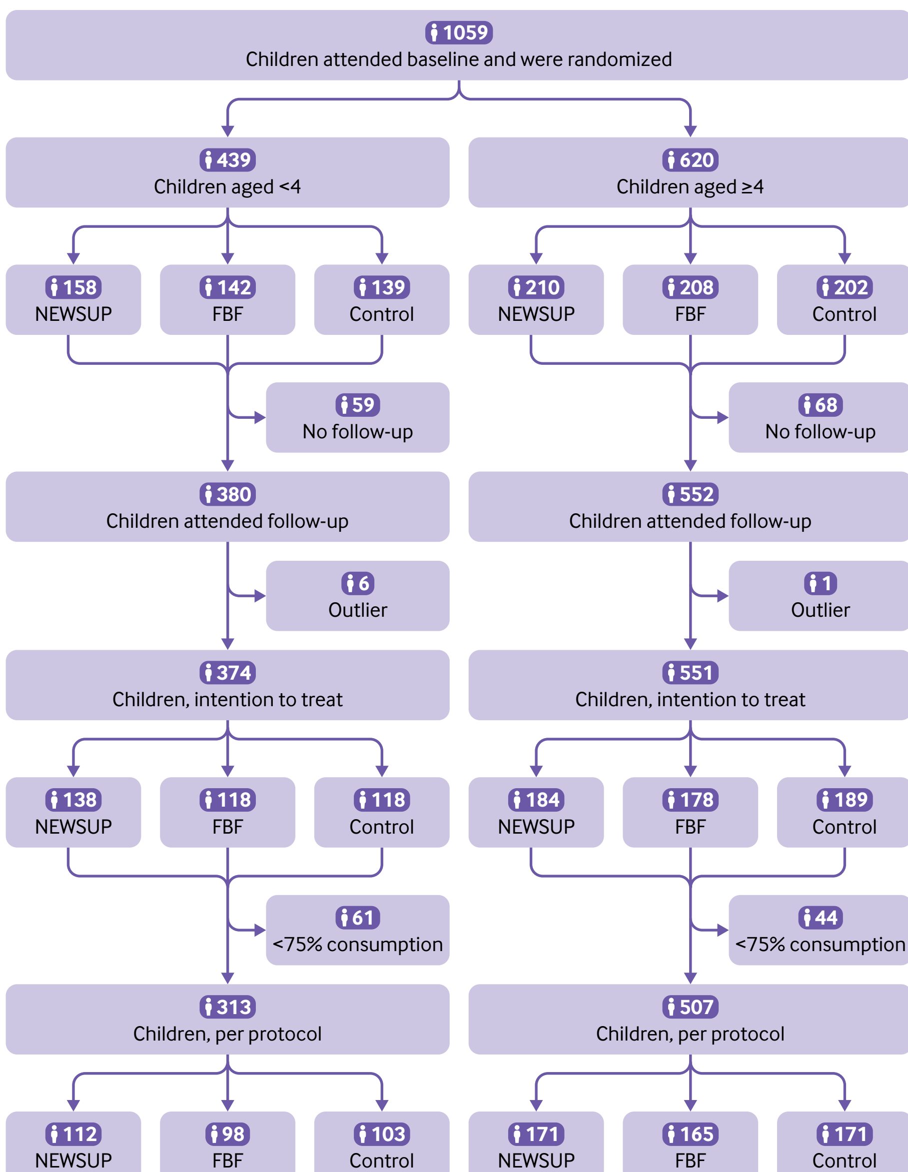

Fig 1 | Consort diagram showing primary trial populations for intention-to-treat and per protocol analyses (≥75% adherence to supplement consumption) for three randomized groups (new supplement (NEWSUP), fortified blended food (FBF), control meal). Age groups were children younger than 4 and children aged 4 and older

Intervention

After baseline outcome assessments and randomization, trained teams of villagers who had no role in study design or outcome measurements provided children with their randomized meal as a supervised breakfast. The food was the whole intervention (that is, no social or educational elements were used) and was provided on five days each week. Separate sites were established in each village to distribute each supplement. The supplementary appendix describes the training and supervision provided for intervention delivery and quality control measures. We did not make any recommendations about the food children received at home, and this information was not recorded owing to concerns that the data would be unreliable[64] and recording could change food practices.

NEWSUP was previously pilot tested in a similar nutritional formulation provided in a baked bar[65]; in our study it was served as a raw paste that contained an average of 98% of the recommended daily micronutrients for children younger than 4. Our micronutrient fortification goal was to satisfy USAID (United States Agency for International Development) guidelines for therapeutic foods[66] and US dietary reference intakes[31-35] as far as possible without negatively influencing taste. Most children consumed the supplement as a paste, but some younger children preferred it as porridge mixed with water. The FBF was USAID corn soy blend plus[67] cooked as porridge with fortified vegetable oil,[68] sugar, and salt as recommended, and contained an average of 16% of the recommended daily micronutrients. The control meal, which replicated a traditional breakfast for children, was imported white rice cooked with water, a small amount of soybean oil and salt, which contained an average of 1% of the recommended daily micronutrients. We provided the control meal to maximize intervention fidelity, and because our previous work in Guinea-Bissau indicated that not giving a control meal could result in compensation in home food.[69]

Study outcomes

Trained per diem staff who had conducted outcomes for previous nutrition studies,[60 61 65] had no role in the intervention, and were blinded to randomization measured outcomes. Measurements were made at a separate time from supplement distribution to prevent any accidental knowledge of randomization, and were supervised by the study coordinator (SFT) and the lead scientist for NIRS-DCS (MAF).

Cognition. The primary outcome was the number of stickers found in an established test of working memory. Working memory was chosen for three reasons. Firstly, working memory is a core component of executive function[70] and is also linked to IQ.[71] Secondly, this test can be implemented without verbal instruction in 10-15 minutes, whereas other measures of executive functions (eg, cognitive flexibility and inhibitory control) typically require verbal instructions and longer testing time than would be feasible for all children in this study. Thirdly, working memory can be tested without the use of food, which would have introduced potential confounding.

The specific working memory task was a variant of the classic spin the pots task, a widely used test similar to a hide-and-seek game.[72-78] This test has been used in several countries in children with a wide age range and with developmental delay, and by our team.[65] Completion does not require verbal instruction because even very young children with limited vocabulary can quickly and easily engage in searching behaviors.[79] One parent was allowed in the room so that the child could sit on a familiar knee if required, but the parent was instructed not to talk or provide any verbal or non-verbal cues.

The test administrator was trained to implement the test[65] by using a script in the local language for all verbal instructions and narration, and by using non-verbal communications. Children were presented with an array of small opaque cups, each covered by a lid with a distinct color or pattern and placed upon a circular base platform. Children were shown that the lids could be removed for stickers to be hidden inside each cup. Stickers were then hidden in a subset of the cups while the children watched (young children: 4 of 6 total cups; older children: 8 of 10 total cups). The entire array was covered with an opaque cover, which was lifted and children were allowed to search for stickers. Children who found stickers could keep them; if no sticker was found the child was shown the bottom of the empty cup and told there was no sticker. After each search, the lid was replaced and the circular base rotated 180°; searches continued for a predetermined number of trials (young children: 12 trials; older children: 18 trials) or until the child found all the stickers. The test administrator kept track of the number of searches on a worksheet, and test sessions were video recorded for coding by trained staff at Tufts University. Coders were masked to randomization and used an established protocol.[65] A randomly selected subset of tests (n=20) was evaluated by all coders and interrater reliability was high (r>0.9). Children's performance was assessed by the total number of stickers found (possible range from zero to total number of hidden stickers; no child reached the limit for trials allotted).

Cerebral blood flow. An index of cerebral blood flow (CBF_i) was measured non-invasively using a combination NIRS-DCS instrument (MetaOx, ISS, Campaign, IL).[80] This validated method integrates frequency domain NIRS to measure hemoglobin concentration and oxygenation, with DCS to measure an index proportional to blood flow.[81] Numerous studies in humans and in animals have shown that CBF_i relative changes (obtained with DCS alone) and absolute values (obtained by correcting for tissue optical properties as measured by frequency or time domain NIRS) agree well with cerebral blood flow measured with gold standard methods such as arterial spin labeled MRI, fluorescent microspheres, bolus tracking time domain NIRS, and phase encoded velocity mapping MRI.[53 56 57 80-82] Additionally, our method has high test-retest reliability in children living in low resource settings.[83] CBF_i was measured at 1.5 cm source separation at the beginning and end of the study,[80] and the same system was used to measure cerebral oxygen metabolism ($CMRO_{2i}$), so these data are also reported. Four locations in the forehead were tested: lower left and lower right over the Brodmann areas BA 10 and 46 (ventrolateral prefrontal cortex), and upper left and upper right over BA 9 (dorsolateral prefrontal cortex). A subset of children (n=119-125 for different brain sites) had NIRS-DCS measures because we had mechanical issues in the field and only the children in the first scheduled villages could be measured.

Hemoglobin concentration, weight for age z score, height for age z score, body mass index z score, mid-upper arm circumference, and head circumference were measured using standard techniques.[84-87] We excluded participants from all analyses when baseline values for weight for age z score, height for age z score, and body mass index z score were implausible based on World Health Organization criteria (−6.0 to 5.0 for weight for age z score and body mass index z score, and −6.0 to 6 for height for age z score; n=7). We used a validated multicompartment method that combined data from mid-upper arm circumference and skinfold thicknesses to measure lean tissue and fat areas at the mid-upper arm circumference site.[88 89] The supplementary appendix provides further details of each method.

Sample size calculation

Our pilot study[65] observed a mean difference of 0.56 stickers between the intervention (standard deviation 0.63) and control groups (0.62) in children younger than 4. Sample sizes in this study were calculated with 80% power to detect half the mean pilot effect observed in the pilot (0.28 stickers; pooled standard deviation 0.625; n=80/intervention/age group). Target enrollment was n=150/intervention/age group (total n=900) to account for an estimated 25% attrition and possible clustering within age groups within families. A total of 1059 children enrolled because it would have been unacceptable to enroll a subset of eligible families within villages. We performed a post hoc calculation based on the mean family size (n=2 children) and the observed intraclass correlation coefficient (0.01). A design effect of 1.01 and an effective sample size of n=1048 were calculated, indicating that our enrolled sample was sufficient to detect the intended mean difference in working memory.

Predefined populations of interest

All statistical analyses were conducted for the intention-to-treat population. A per protocol analysis of the children who completed the intervention and consumed at least 75% of their supplement (89%) was predefined in the statistical analysis plan (supplementary appendix) before study completion. Children who were not in the per protocol population tended to live further away from the supplement centers and consumed 43% of the supplement on average.

All analyses were conducted separately for the predefined age groups. Young children were aged 15 months to up to 4 years (called "3 years" in our protocol and clinical trial registration, to be consistent with the field team's use of integer years) at baseline, and were the predefined cohort of interest; older children were aged 4-7 years. The specific age groups were based on the previous pilot, which identified children younger than 4 as the likely beneficiaries.[65] Children aged 4 and older were included even though our pilot suggested they would not benefit. Although the synthesis of new brain cells and their integration into functionally effective brain tissue is intense until age 5, it can continue at a reduced rate throughout life.[14-16 90]

Statistical analysis

We compared baseline measurements for each randomized group separately for the intention-to-treat and per protocol populations. Cluster adjusted means were compared for continuous variables and were calculated by linear mixed models. We used the χ^2 test to compare categorical variables.

We assessed the primary outcome (working memory) by using the discrete number of stickers found at follow-up by multivariable Poisson models, with the natural log of the total number of searches given included as an offset. The control group served as the reference. We also compared NEWSUP and FBF groups in an exploratory analysis. Two models evaluating changes in working memory were applied. Model 1 was adjusted for age in years, sex, study cohort, and baseline working memory. The fully adjusted model 2 additionally included baseline and six month changes in weight for age z score and hemoglobin concentration. Both models were also applied after the exclusion of children with severe anemia at baseline.

We assessed changes in secondary outcomes (NIRS-DCS measurements, hemoglobin concentration, anthropometry, and body composition) by multivariable linear mixed models. Each model was adjusted for age, sex, study cohort, and baseline measurement. The assumptions for linear mixed models were verified, and all residuals were approximately normally distributed. Changes in hemoglobin concentration were assessed only among children with mild, moderate, or severe anemia at baseline. For children younger than 5, mild anemia was defined as 10.0-10.9 g/dL hemoglobin, moderate anemia was 7.0-9.9 g/dL, and severe anemia was less than 7.0 g/dL. For children aged 5 and older, mild anemia was defined as 11-11.4 g/dL hemoglobin, moderate anemia was 8.0-10.9 g/dL, and severe anemia was less than 8.0 g/dL. As the NIRS-DCS measurements were obtained on a subset of children, the two age groups were combined and models were adjusted for age, sex, baseline head circumference,[91] and baseline NIRS-DCS measurement.

We calculated intraclass correlation coefficients for each outcome to assess the degree of similarity between children from the same family. We also assessed the degree of similarity between children from the same village and observed no substantial evidence of clustering (intraclass correlation coefficient=0.02 for the primary outcome). Therefore, all statistical models account for the clustering of children within families as a random effect, but do not account for additional clustering within village. We conducted two sensitivity analyses on the primary outcome to verify that a three level hierarchical model (with children clustered within families, within villages) was not required. Firstly, models including a random effect for village were applied to a sample with one randomly selected child per family (effectively removing the family level clustering), with results consistent with those reported for models 1 and 2. Secondly, models were applied to the full sample, with village included as an additional covariate; we found no statistically significant effect of village when it was included as a fixed effect.

We assessed effect modification of supplementation by age group for the primary and secondary outcomes by using an interaction term in models including all children, and these results are considered exploratory. A P value less than 0.05 was considered the threshold for statistical significance. We did not adjust for multiplicity because a single primary outcome was used and the three randomized groups provided distinct dietary interventions.[92] All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). We report results for the primary outcome as rate ratios and 95% confidence intervals, and results for secondary outcomes as adjusted mean differences and 95% confidence intervals.

Participant and public involvement

Village meetings were held to obtain community level support for village enrollment, and additional discussions involved community members in study planning. Community health workers recommended the specific control breakfast, recommended the plan for all children to receive their supplement at one of the three separate feeding centers within the villages, and also asked for five days each week of supplementation to balance their other responsibilities. Community health workers and parents were additionally consulted about ingredients and preparation of NEWSUP at the end of the earlier pilot[65]; based on their request we reduced the amount of moringa in the NEWSUP recipe and changed the production from a baked good to a raw formula (to prevent burning and improve taste), and implemented a gradual increase in consumption during the first study week to allow children to become accustomed to the taste.

Results

Study population

Table 1 shows baseline characteristics for the intention-to-treat population. No differences in anthropometry were found between intervention groups at baseline in either age group. Additionally, we did not find any major differences in the distribution of anemia classifications between interventions in either age group, and mean hemoglobin concentration did not differ between interventions in the older children. However, young children in the NEWSUP group had higher mean hemoglobin concentration at baseline, primarily because of a smaller number of children with severe anemia (0.0% (0/113) *v* 1.9% (2/103) and 5.4% (6/111) for control and FBF groups, respectively). Family sizes ranged from one to six children. Among 552 households, 43% (239) were one child homes; 34% (185) were two child homes; 15% (84) were three child homes; 6% (34) were four child homes; and 2% (10) of homes had more than four children.

Supplementary table A shows the proportion of children who had poor nutritional benchmarks at baseline, defined as weight for age z score, height for age z score, or body mass index z score less than −2.0, or the presence of mild, moderate, or severe anemia. We found a 32% (332/1051) prevalence of height for age z score less than −2.0 and a 73% (553/762) prevalence of anemia; these values are similar to national data for Guinea-Bissau[59 93] and other countries in sub-Saharan Africa.[93 94] Supplementary table B shows baseline characteristics for the per protocol population (defined as children who consumed ≥75% of their supplement; 89%), which were similar to the intention-to-treat population. Supplementary table C compares the baseline characteristics of the per protocol children with the children who consumed less than 75% of their supplement. The per protocol children tended to be older, living in larger families (2.3 *v* 1.8 children on average; P<0.001), and were more likely to have a normal hemoglobin concentration (29% (172/599) *v* 22% (37/168); P=0.04), but did not differ in terms of weight for age z score, height for age z score, body mass index z score, or mid-upper arm circumference.

The supplements

Table 2 gives the composition, ingredients, and consumption of each supplement. The supplements were isocaloric (≈1300 kJ/daily serving). NEWSUP had more total protein and fat and less carbohydrate than FBF and the control meal, a greater range and fortification of essential micronutrients, and more omega 3 fatty acids, total polyphenols, catechin, and epicatechin. Supplement adherence was high across groups: in the intention-to-treat population, consumption was approximately 80% in children younger than 4 and 86% in children aged 4 and older. Supplement consumption in the per protocol population averaged 92% for children younger than 4 and 93% for children aged 4 and older, and was slightly higher for FBF and control meals than for NEWSUP in children younger than 4 (P=0.001).

Effects of supplementation on working memory (primary outcome)

Table 3 shows the multivariable effects of supplement type on working memory for the intention-to-treat and per protocol populations for children younger than 4 (primary population) and aged 4 and older.

Intention-to-treat population. For children younger than 4, we found a positive effect of NEWSUP compared with the control meal in crude model 1 adjusting only for age, sex, study cohort, and baseline working memory (rate ratio 1.16, 95% confidence interval 1.02 to 1.32). These results were retained in the fully adjusted model 2 after additional adjustment for baseline and six month changes in weight for age z score and hemoglobin concentration (1.20, 1.02 to 1.41), indicating that the beneficial effect of NEWSUP on working memory was independent of baseline nutritional status and changes in growth and hemoglobin. Consistent results were observed after excluding children with severe anemia at baseline to address the differences in mean hemoglobin across groups. We found no statistically significant effect of FBF compared with the control meal in any model and no statistically significant difference between NEWSUP and FBF.

Among children aged 4 and older, no statistically significant effect of NEWSUP was found compared with the control group. We found a small but statistically

Table 1 | Baseline characteristics of young children and older children in three randomized intervention groups

Characteristics	Intention-to-treat population				Intraclass correlation coefficient‡
	NEWSUP (mean (95% CI))*	FBF (mean (95% CI))*	Control (mean (95% CI))*	P value†	
Children younger than 4					
Demographic (n=157, n=141, n=135)					
Age	2.9 (2.7 to 3.0)	2.7 (2.6 to 2.9)	2.8 (2.7 to 3.0)	0.38	—
Male sex	77 (49.0)	71 (50.4)	84 (62.2)	0.05	—
Female sex	80 (51.0)	70 (49.6)	51 (37.8)		
Anthropometry (n=157, n=141, n=135)					
Weight for age (z score)	−1.2 (−1.4 to −1.0)	−1.2 (−1.5 to −1.0)	−1.3 (−1.6 to −1.1)	0.80	0.14
Height for age (z score)	−1.8 (−2.0 to −1.6)	−1.7 (−1.9 to −1.5)	−1.8 (−2.1 to −1.6)	0.59	<0.01
Body mass index for age (z score)	−0.2 (−0.4 to −0.1)	−0.2 (−0.4 to −0.04)	−0.2 (−0.4 to −0.05)	0.99	0.19
Mid-upper arm circumference (cm)	15.5 (15.3 to 15.7)	15.6 (15.4 to 15.8)	15.5 (15.3 to 15.7)	0.88	0.08
Lean tissue area (cm^2)	14.1 (12.0 to 16.3)	12.6 (10.3 to 14.9)	13.0 (10.7 to 15.3)	0.59	0.06
Fat tissue area (cm^2)	178.9 (173.8 to 184.0)	181.3 (176.0 to 186.6)	179.1 (173.7 to 184.6)	0.78	0.07
Cognitive (n=97, n=83, n=80)					
Stickers hidden	6.1 (5.7 to 6.5)	5.5 (5.0 to 5.9)	5.9 (5.4 to 6.3)	0.13	—
Searches offered	8.6 (8.2 to 9.1)	8.0 (7.5 to 8.4)	8.4 (7.9 to 8.8)	0.11	—
Stickers found	3.6 (3.3 to 3.9)	3.2 (2.8 to 3.6)	3.1 (2.7 to 3.5)	0.11	0.01
Hemoglobin (n=113, n=111, n=103)					
Hemoglobin concentration (g/dL)	10.3 (10.0 to 10.6)	9.6 (9.3 to 9.9)	9.9 (9.6 to 10.2)	0.002§	0.44
Anemia classification (%; n=113, n=111, n=103)					
Normal	38 (33.6)	16 (14.4)	26 (25.2)	0.07	—
Mild	34 (30.1)	31 (27.9)	30 (29.1)		
Moderate	41 (36.3)	58 (52.3)	45 (43.7)		
Severe	0 (0.0)	6 (5.4)	2 (1.9)		
Children aged 4 and older					
Demographic (n=202, n=207, n=209)					
Age	6.0 (5.8 to 6.1)	5.8 (5.7 to 6.0)	5.8 (5.7 to 6.0)	0.36	—
Male sex	110 (54.5)	102 (49.3)	110 (52.6)	0.57	—
Female sex	92 (45.5)	105 (50.7)	99 (47.4)		
Anthropometry (n=202, n=207, n=209)					
Weight for age (z score)	−1.4 (−1.5 to −1.2)	−1.4 (−1.6 to −1.3)	−1.4 (−1.5 to −1.3)	0.92	0.14
Height for age (z score)	−1.3 (−1.4 to −1.1)	−1.3 (−1.5 to −1.2)	−1.3 (−1.4 to −1.1)	0.85	<0.01
Body mass index for age (z score)	−0.8 (−1.0 to −0.7)	−0.8 (−1.0 to −0.7)	−0.9 (−1.0 to −0.7)	0.91	0.19
Mid-upper arm circumference (cm)	16.3 (16.1 to 16.4)	16.2 (16.0 to 16.4)	16.1 (16.0 to 16.3)	0.44	0.08
Lean tissue area (cm^2)	36.8 (33.0 to 40.5)	32.1 (28.4 to 35.9)	35.5 (31.8 to 39.2)	0.21	0.06
Fat tissue area (cm^2)	175.2 (170.4 to 180.0)	178.2 (173.4 to 182.9)	172.5 (167.8 to 177.3)	0.26	0.07
Cognitive (n=165, n=175, n=162)					
Stickers hidden	8.0 (7.9 to 8.0)	7.9 (7.9 to 8.0)	8.0 (7.9 to 8.0)	0.31	—
Searches given	10.1 (9.9 to 10.2)	10.1 (10.0 to 10.2)	10.0 (9.8 to 10.1)	0.27	—
Stickers found	5.3 (5.1 to 5.5)	5.2 (5.0 to 5.5)	5.3 (5.1 to 5.5)	0.90	0.01
Hemoglobin (n=142, n=145, n=148)					
Hemoglobin concentration (g/dL)	10.5 (10.2 to 10.8)	10.4 (10.1 to 10.7)	10.4 (10.1 to 10.7)	0.69	0.44
Anemia classification (%; n=142, n=145, n=148)					
Normal	42 (29.6)	43 (29.7)	44 (29.7)	0.80	—
Mild	24 (16.9)	25 (17.2)	23 (15.5)		
Moderate	70 (49.3)	67 (46.2)	72 (48.7)		
Severe	6 (4.2)	10 (6.9)	9 (6.1)		

FBF=fortified blended food; NEWSUP=new supplement.
*Continuous data presented as cluster adjusted means (95% confidence intervals); categorical data presented as number (%) of children. Numbers of children in groups vary by characteristic and are indicated in the table.
†Comparisons between three randomized groups in the intention-to-treat population are calculated by linear mixed models for continuous data and the x^2 test for categorical data.
‡Intraclass correlation coefficients were calculated for both age groups combined and assess the degree of similarity between children from the same family, and data are therefore the same for both age groups in the table.
§FBF versus NEWSUP=0.0004; NEWSUP versus control=0.03; FBF versus control=0.13.

Table 2 | Nutritional composition of the supplements (amount/serving/day) by supplement intervention

Composition	NEWSUP	FBF	Control
Energy and macronutrients			
Energy (kJ)	1322	1322	1314
Protein (g)	18.1	5.2	3.6
Total fat (g)	18.6	15.0	14.8
Total carbohydrate (g)	19.5	25.7	40.7
Vitamins and minerals included in fortified foods for nutrition assistance programs			
Vitamin A (µg)	664	688	0
Vitamin D (µg)	24.9	10.0	0
Vitamin E (mg)	29.6	4.69	1.25
Vitamin K (µg)	102	41.6	26.8
Vitamin C (mg)	150	36.5	0
Vitamin B1 (thiamine; mg)	1.36	0.27	0.04
Vitamin B2 (riboflavin; mg)	1.54	0.70	0.03
Vitamin B3 (niacin; mg)	22.2	4.50	0.8
Vitamin B5 (pantothenic acid; mg)	10.0	0.6	0.5
Vitamin B6 (pyridoxine; mg)	1.92	0.60	0.08
Vitamin B9 (folic acid; µg)	362	80	4
Vitamin B12 (cobalamin; µg)	1.81	0.80	0
Potassium (mg)	193	290	59
Calcium (mg)	207	205	14
Iron (mg)	19.7	4.7	0.4
Iodine (µg)	209	16.0	0
Zinc (mg)	14.0	3.1	0.6
Additional essential nutrients not included in fortified foods for food assistance preparations			
Choline	22.1	—	3.0
Vitamin B7 (biotin; µg)	36.2	—	0
Magnesium (mg)	49.6	—	13.0
Copper (µg)	1.81	—	0
Total omega 3 (mg)	534	—	0
Selenium (µg)	38.5	—	0.6
Manganese (µg)	1.51	—	0
Chromium (µg)	0.015	—	0
Molybdenum (µg)	22.5	—	0
Additional dietary constituents not defined as essential			
Docosahexaenoic acid (mg)	255	—	0
Eicosapentaenoic acid (mg)	171	—	0
Total plant polyphenols (mg)	468	—	0
Catechin (µg)	8.0	—	0
Epicatechin (µg)	22.3	—	0
Adherence to supplement consumption, mean % (95% CI)			
Intention-to-treat cohort: children aged <4; P=0.98	80.1 (75.7 to 84.4)	80.2 (75.7 to 84.7)	80.7 (76.2 to 85.2)
Per protocol cohort: children aged <4; P=0.001	90.0 (88.9 to 91.1)	91.9 (90.7 to 93.0)	93.0 (91.9 to 94.2)
Intention-to-treat cohort: children aged ≥4; P=0.21	86.8 (83.2 to 90.4)	83.1 (79.5 to 86.6)	87.1 (83.6 to 90.6)
Per protocol cohort: children aged ≥4; P=0.59	92.9 (92.0 to 93.8)	92.5 (91.6 to 93.4)	93.1 (92.2 to 94.0)

FBF=fortified blended food; NEWSUP=new supplement.
NEWSUP ingredients in order of weight: peanut butter, honey, soy protein isolate, cacao, fortified vegetable oil, whey protein, sugar, fish oil, matcha, moringa, vitamin-mineral mix, and flavorings. FBF porridge ingredients in order of weight: USAID supercereal plus,[67] sugar, and fortified vegetable oil.[68] Control breakfast ingredients in order of weight: white rice, fortified vegetable oil, and salt.

significant effect of FBF compared with the control meal in crude model 1 (1.07, 1.01 to 1.13) that was not retained when children with anemia were excluded or in model 2.

Per protocol population. Changes in working memory were also observed in children younger than 4 who consumed at least 75% of their supplement. We found a statistically significant effect of NEWSUP compared with the control meal in all models, with a greater effect size than in the intention-to-treat population in the fully adjusted model (1.25, 1.06 to 1.47). We found no significant effect of FBF compared with the control meal. The effect of NEWSUP tended to be greater than for FBF in the fully adjusted models (1.17, 0.99 to 1.39, P=0.06; and 1.19, 1.00 to 1.42, P=0.05, after excluding children with severe anemia).

In children aged 4 and older, we found no significant effect of NEWSUP in any model. A small improvement in working memory was suggested in children consuming FBF (1.07, 1.00 to 1.13), but was not retained when children with anemia were excluded or in the fully adjusted model 2. No significant difference was found between NEWSUP and FBF. The effect of supplementation on working memory did not differ by age group. An exploratory analysis of potential effect modification of supplementation by age group on the primary outcome was not statistically significant. Supplementary table D presents the results.

Effects of supplementation on cerebral hemodynamics

Figure 2 and figure 3 show adjusted mean changes over time in CBF_i and $CMRO_{2i}$ for the four predefined brain

Table 3 | Multivariable Poisson models predicting effects of three randomized supplement interventions on working memory*

Cohort	Model 1† Adjusted rate ratio (95% CI)	Model 1† P value	Model 2‡ Adjusted rate ratio (95% CI)	Model 2‡ P value	Model 1§ Adjusted rate ratio (95% CI)	Model 1§ P value	Model 2¶ Adjusted rate ratio (95% CI)	Model 2¶ P value
Children younger than 4								
Intention-to-treat cohort								
NEWSUP *v* control	1.16 (1.02 to 1.32)	0.03	1.20 (1.02 to 1.41)	0.03	1.16 (1.02 to 1.32)	0.03	1.20 (1.02 to 1.41)	0.03
FBF *v* control	1.09 (0.93 to 1.27)	0.30	1.09 (0.91 to 1.32)	0.35	1.08 (0.92 to 1.27)	0.33	1.08 (0.89 to 1.32)	0.41
NEWSUP *v* FBF	1.06 (0.93 to 1.22)	0.35	1.10 (0.93 to 1.29)	0.28	1.07 (0.93 to 1.23)	0.34	1.11 (0.93 to 1.31)	0.24
Per protocol cohort								
NEWSUP *v* control	1.18 (1.03 to 1.35)	0.02	1.25 (1.06 to 1.47)	0.009	1.18 (1.03 to 1.35)	0.02	1.25 (1.06 to 1.47)	0.007
FBF *v* control	1.07 (0.90 to 1.26)	0.44	1.06 (0.87 to 1.30)	0.56	1.06 (0.90 to 1.26)	0.50	1.05 (0.86 to 1.29)	0.65
NEWSUP *v* FBF	1.10 (0.96 to 1.27)	0.17	1.17 (0.99 to 1.39)	0.06	1.11 (0.96 to 1.29)	0.16	1.19 (1.00 to 1.42)	0.05
Children aged 4 and older								
Intention-to-treat cohort								
NEWSUP *v* control	1.03 (0.97 to 1.10)	0.31	1.02 (0.95 to 1.10)	0.58	1.03 (0.96 to 1.09)	0.43	1.02 (0.94 to 1.10)	0.70
FBF *v* control	1.07 (1.01 to 1.13)	0.02	1.07 (0.99 to 1.14)	0.08	1.05 (0.99 to 1.12)	0.08	1.05 (0.98 to 1.14)	0.18
NEWSUP *v* FBF	0.97 (0.92 to 1.02)	0.20	0.96 (0.90 to 1.02)	0.21	0.97 (0.92 to 1.03)	0.32	0.96 (0.90 to 1.03)	0.30
Per protocol cohort								
NEWSUP *v* control	1.03 (0.96 to 1.10)	0.41	1.02 (0.94 to 1.11)	0.63	1.02 (0.95 to 1.10)	0.50	1.02 (0.93 to 1.11)	0.66
FBF *v* control	1.07 (1.00 to 1.13)	0.05	1.08 (0.99 to 1.16)	0.07	1.05 (0.99 to 1.12)	0.13	1.07 (0.98 to 1.16)	0.12
NEWSUP *v* FBF	0.97 (0.91 to 1.02)	0.24	0.95 (0.88 to 1.02)	0.16	0.97 (0.92 to 1.03)	0.38	0.96 (0.89 to 1.03)	0.24

FBF=fortified blended food; NEWSUP=new supplement.
*Number of stickers found in the spin the pots working memory test.
†Model 1: calculated by a Poisson regression model accounting for clustering of children within families, adjusted for age, sex, study cohort, and baseline cognitive function. The natural logarithm of the total number of searches given is included as an offset.
‡Model 2: calculated by a Poisson regression model accounting for clustering of children within families, adjusted for age, sex, study cohort, baseline cognitive function, baseline weight for age (z score), baseline hemoglobin concentration (g/dL), change in weight for age (z score), and change in hemoglobin (g/dL). The natural logarithm of the total number of searches given is included as an offset.
§Model 1 (excludes children with severe anemia at baseline): calculated by a Poisson regression model accounting for clustering of children within families, adjusted for age, sex, study cohort, and baseline cognitive function. The natural logarithm of the total number of searches given is included as an offset.
¶Model 2 (excludes children with severe anemia at baseline): calculated by a Poisson regression model accounting for clustering of children within families, adjusted for age, sex, study cohort, baseline cognitive function, baseline weight for age (z score), baseline hemoglobin concentration (g/dL), change in weight for age (z score), and change in hemoglobin (g/dL). The natural logarithm of the total number of searches given is included as an offset.

regions of interest. Supplementary table E presents baseline measurements, and supplementary table F shows the multivariable effects of supplementation on changes in CBF_i and $CMRO_{2i}$.

Intention-to-treat population. Substantial increases were found in CBF_i (1.14 $mm^2/s\times10^{-8}$, 95% confidence interval 0.10 to 2.23) and $CMRO_{2i}$ (4.54 arbitrary units (AU), 95% confidence interval 0.64 to 8.44) in the left ventrolateral prefrontal cortex of children in the NEWSUP group compared with the control group. We also observed a positive and statistically significant effect of NEWSUP on both measures compared with FBF in this brain region. Additionally, a negative effect of FBF compared with the control meal was found in the left dorsolateral prefrontal cortex (−1.02 $mm^2/s\times10^{-8}$, −1.93 to −0.11 for CBF_i and −3.81 AU, −7.26 to −0.37 for $CMRO_{2i}$).

Per protocol population. Mean changes in CBF_i and $CMRO_{2i}$ were consistent with the intention-to-treat population, with additional differences between groups. The NEWSUP group had greater changes in CBF_i and $CMRO_{2i}$ than the control group in the left ventrolateral prefrontal cortex. An increase in both measures was also detected in the right ventrolateral prefrontal cortex compared with the control group (0.87 $mm^2/s\times10^{-8}$, 0.04 to 1.70 for CBF_i and 3.14 AU, 0.21 to 6.06 for $CMRO_{2i}$). Additionally we observed greater changes in both measures for NEWSUP compared with FBF in the left ventrolateral and dorsolateral prefrontal cortices.

Effects of supplementation on hemoglobin concentration and growth

Table 4 shows the multivariable effects of supplementation on changes in hemoglobin concentration, growth, and body composition. We summarize changes for the intention-to-treat population; similar results were seen for the per protocol population. Figure 4 shows the adjusted mean changes in body composition. Supplementary tables G and H present an exploratory analysis of effect modification of supplementation by age group for the secondary nutrition outcomes.

Children younger than 4 in all interventions had increased weight and body mass index z score and decreased height for age z score over time. NEWSUP (but not FBF) increased hemoglobin concentration in children with anemia compared with the control meal (0.65 g/dL, 95% confidence interval 0.23 to 1.07). Additionally, NEWSUP decreased body mass index z score gain (−0.23, −0.43 to −0.02), increased lean tissue accretion (2.98 cm^2, 0.04 to 5.92), and reduced fat accretion (−5.82 cm^2, −11.28 to −0.36) compared with FBF.

Children aged 4 and older also gained weight, but in contrast to the effects in younger children, neither NEWSUP nor FBF had significant effects on body mass index z score or height for age z score. Additionally no significant effects were found for NEWSUP on hemoglobin concentration in children with anemia compared with the control meal. However, the older children randomized to NEWSUP had an increase in

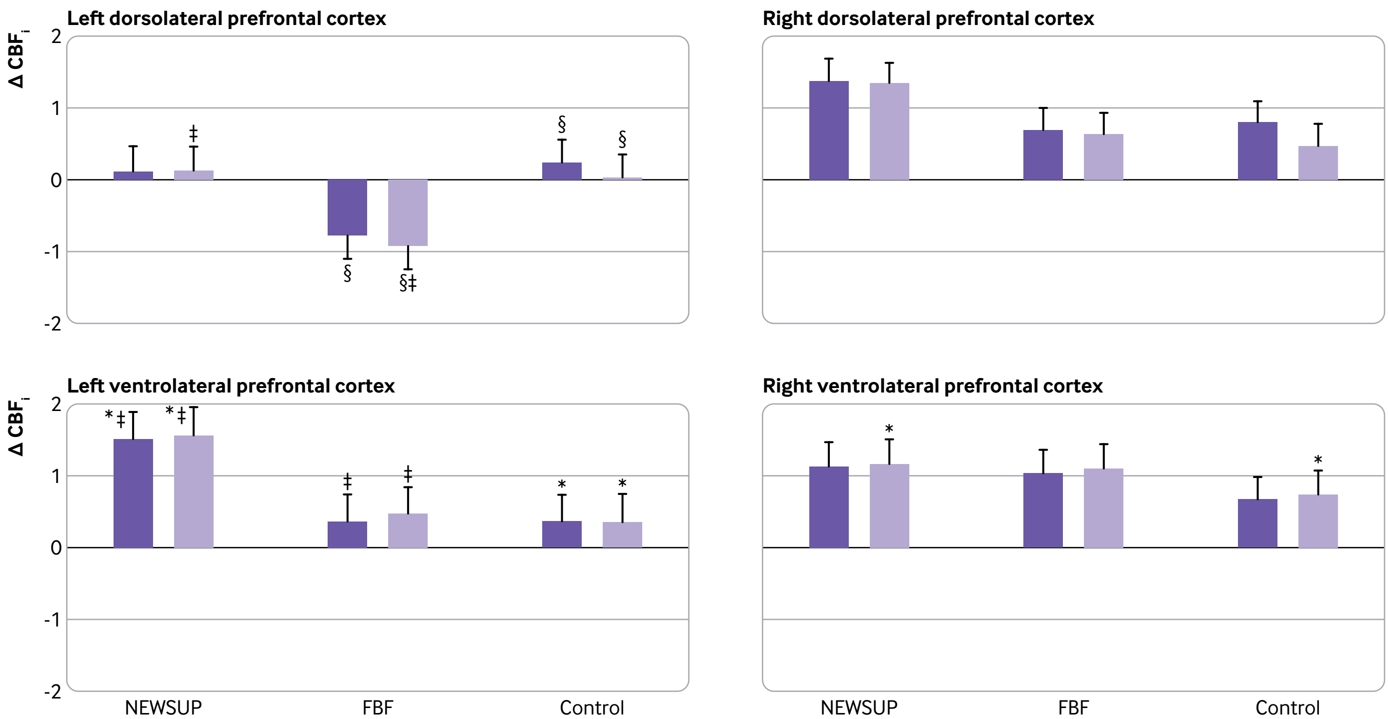

Fig 2 | Changes in cerebral blood flow index (CBF$_i$) in four prefrontal cranial sites with consumption of new supplement (NEWSUP), fortified blended food (FBF), or control meal. The four cranial sites correspond approximately to Brodmann areas BA 10 and 46 (ventrolateral prefrontal cortex), and upper left and upper right over BA 9 (dorsolateral prefrontal cortex). Cluster adjusted means adjusted for age, sex, baseline head circumference, and baseline CBF$_i$ are given with standard errors, and models are summarized in supplementary appendix. Means are adjusted for age, sex, baseline head circumference, and baseline CBF$_i$. Significant differences between groups are indicated by same superscript. Dark purple bars indicate results for intention-to-treat cohort and light purple bars represent per protocol cohort

lean tissue and reduced fat compared with the control meal, and greater lean tissue accretion than FBF.

Discussion

Summary of principal findings

At least 250 million children worldwide younger than 5 fail to reach their cognitive developmental potential.[5] While inadequate nutrition is not the only cause, it is recognized as an important contributing factor.[11 91 93 95-104] We conducted a randomized controlled trial in villages in Guinea-Bissau to test a new approach to supplementary food formulation, based on the theory that enhancing cognition after nutritional deprivation could potentially require simultaneous provision of a wide panel of nutrients supporting neurogenesis, myelination, and remodeling, while reducing inflammation and oxidative damage. Compared with traditional feeding practices, NEWSUP improved working memory among children younger than 4 in the intention-to-treat analysis, and in the predefined per protocol analysis of the children who consumed at least 75% of their supplement (rate ratio 1.25, 95% confidence interval 1.06 to 1.47). Furthermore, the effects seemed to be unrelated to changes in hemoglobin, a finding that is consistent with previous documentation of no effect of supplementary iron on working memory in children with anemia.[105] Working memory is a core executive function, making this an important benefit for children's education and national development. These results show that nutritional supplementation for 23 weeks can improve cognitive function in vulnerable children, and highlight the need for more research to optimize the composition of supplementary foods.

Interpretation of NEWSUP

We used a single test of working memory as the primary outcome, rather than a composite cognitive score derived from a lengthy battery of different tests of all aspects of cognition, because the lack of games for children in the community indicated the need for simple testing of short duration. The development of working memory early in life plays a critical role in long term academic and social competence,[48 49 51 106 107] theory of mind,[108 109] and emotion regulation,[50] and deficits in executive function abilities are linked to developmental delay.[110 111] Furthermore, training programs specifically targeting executive function abilities in childhood improve reading[112] and arithmetic.[113] These observations suggest that NEWSUP could have long lasting impacts on educational attainment and cognition.[114 115] Additionally, because only one cognitive function was tested, additional benefits might be identified in future studies that use wider testing. Importantly, observed benefits were restricted to children younger than 4, as seen in our earlier pilot study.[65] Older children might have a reduced capacity to benefit from supplementary foods,

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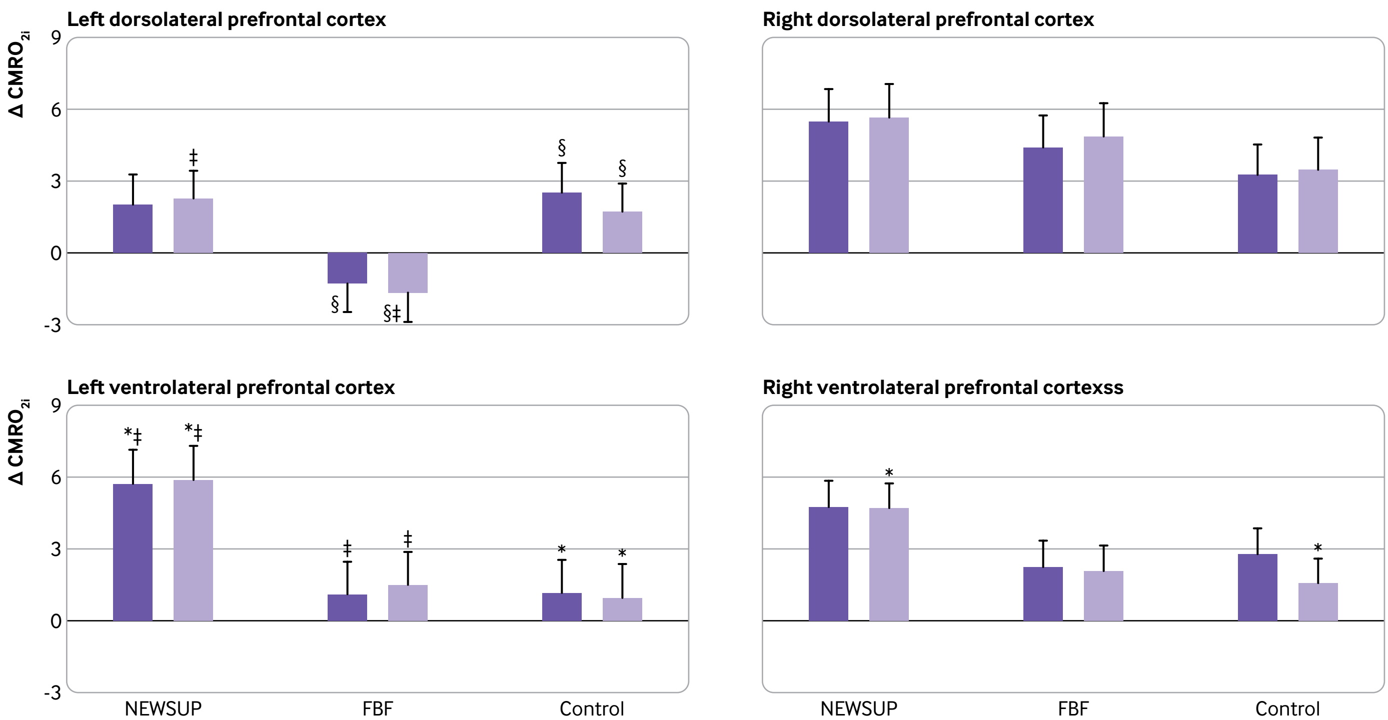

Fig 3 | Changes in cerebral oxygen metabolism index ($CMRO_{2i}$) in four prefrontal cranial sites with consumption of new supplement (NEWSUP), fortified blended food (FBF), or control meal. The four cranial sites correspond approximately to Brodmann areas BA 10 and 46 (ventrolateral prefrontal cortex), and upper left and upper right over BA 9 (dorsolateral prefrontal cortex). Cluster adjusted means adjusted for age, sex, baseline head circumference, and baseline $CMRO_{2i}$ are given with standard errors, and models are summarized in supplementary appendix. Means are adjusted for age, sex, baseline head circumference, and baseline $CMRO_{2i}$. Significant differences between groups are indicated by same symbols. Dark purple bars indicate results for intention-to-treat cohort and light purple bars represent per protocol cohort

but it is also possible that the length of the intervention or the supplement quantity was insufficient for older children (to minimize field errors, the supplement quality and quantity were identical across age groups).

NEWSUP also caused an increase in cerebral blood flow, which supports the finding of improved working memory. Cerebral blood flow (and oxygen metabolism, measured by the same instrumentation in this study) is a widely used measure representing neuronal activity.[14] Cerebral blood flow is also important for maintaining proper brain perfusion. Chronically low cerebral blood flow has been reported to contribute to cognitive decline and dementia in older adults,[52 116-118] and has been associated with autism in children.[119] The increases in cerebral blood flow and oxygen metabolism in children consuming NEWSUP, especially those consuming at least 75% of their supplement, suggest changes in brain health that could be either a cause or a consequence of improved cognitive function.[22 120-124] Also noteworthy is the finding that the largest measured changes were in the ventrolateral prefrontal cortex, an area that is known to be particularly vulnerable to adverse childhood environments.[125-127] Mechanistic studies are needed to examine the underlying causes of improved cerebral blood flow, including the potential for acute effects of plant polyphenols on flow mediated vasodilation and blood flow through production and availability of endothelial nitric oxide.[22 120-124]

NEWSUP also had effects on health, specifically an increase in hemoglobin in children younger than 4 with anemia, and improved quality of growth (more lean tissue and less fat). These beneficial changes occurred in the absence of changes in height for age z score, emphasizing the importance of measuring body composition, not just anthropometry which is typical in studies of nutritional interventions. The reasons for the changes in body composition could include several aspects of the supplement composition, including protein content. Greater lean tissue accretion with lower fat accretion might have implications for long term health because young children who experience undernutrition seem to be at greater risk of adult obesity and associated non-communicable diseases.[11 58]

Interpretation of FBF and comparison with previous work

In contrast to NEWSUP, we found no clear benefit of a widely used FBF (a USAID product used worldwide) on working memory, and the non-significant effect size was a quarter to a half of NEWSUP. However, differences between NEWSUP and FBF were not significant, and thus FBF might have a major impact on working memory in a larger trial. Nevertheless, our results are consistent with meta-analyses reporting a small effect of traditional supplementary foods on cognition in young children in low income countries (effect size 0.09 standard deviation[6-8]). Most of

Table 4 | Multivariable linear mixed models predicting effects of three randomized supplement interventions on anthropometry and hemoglobin measures

	NEWSUP *v* control		FBF *v* control		NEWSUP *v* FBF	
Measures	Adjusted mean difference (95% CI)	P value*	Adjusted mean difference (95% CI)	P value*	Adjusted mean difference (95% CI)	P value*
Children younger than 4						
Intention-to-treat cohort						
Hemoglobin concentration (g/dL) in children with anemia only	0.65 (0.23 to 1.07)	0.003	0.25 (−0.16 to 0.66)	0.23	0.40 (−0.01 to 0.80)	0.06
Weight (kg)	−0.20 (−0.41 to 0.02)	0.07	−0.01 (−0.23 to 0.21)	0.91	−0.19 (−0.40 to 0.03)	0.09
Weight for age (z score)	−0.14 (−0.27 to −0.01)	0.04	0.02 (−0.12 to 0.15)	0.80	−0.16 (−0.29 to −0.03)	0.02
Height for age (z score)	−0.04 (−0.18 to 0.09)	0.54	−0.06 (−0.20 to 0.09)	0.44	0.01 (−0.12 to 0.15)	0.85
Body mass index	−0.24 (−0.50 to 0.02)	0.07	0.04 (−0.24 to 0.31)	0.80	−0.28 (−0.54 to −0.01)	0.04
Body mass index for age (z score)	−0.18 (−0.39 to 0.02)	0.08	0.04 (−0.17 to 0.26)	0.69	−0.23 (−0.43 to −0.02)	0.03
Mid-upper arm circumference (cm)	−0.17 (−0.35 to 0.001)	0.05	−0.04 (−0.22 to 0.14)	0.64	−0.13 (−0.31 to 0.04)	0.14
Lean tissue area (cm^2)	0.71 (−2.22 to 3.65)	0.63	−2.26 (−5.31 to 0.78)	0.14	2.98 (0.04 to 5.92)	0.046
Fat tissue area (cm^2)	−4.94 (−10.41 to 0.52)	0.08	0.88 (−4.78 to 6.53)	0.76	−5.82 (−11.28 to −0.36)	0.04
Per protocol cohort						
Hemoglobin concentration (g/dL) in children with anemia only	0.73 (0.27 to 1.19)	0.002	0.16 (−0.28 to 0.61)	0.47	0.56 (0.12 to 1.01)	0.01
Weight (kg)	−0.25 (−0.49 to −0.01)	0.04	−0.09 (−0.34 to 0.16)	0.47	−0.16 (−0.40 to 0.08)	0.19
Weight for age (z score)	−0.16 (−0.31 to −0.02)	0.03	−0.02 (−0.17 to 0.13)	0.76	−0.14 (−0.29 to 0.01)	0.06
Height for age (z score)	−0.08 (−0.23 to 0.07)	0.32	−0.06 (−0.22 to 0.09)	0.43	−0.01 (−0.17 to 0.14)	0.86
Body mass index	−0.24 (−0.53 to 0.05)	0.11	−0.01 (−0.31 to 0.29)	0.95	−0.23 (−0.53 to 0.07)	0.13
Body mass index for age (z score)	−0.19 (−0.42 to 0.04)	0.10	0.01 (−0.23 to 0.25)	0.93	−0.20 (−0.43 to 0.03)	0.09
Mid-upper arm circumference (cm)	−0.20 (−0.39 to −0.02)	0.03	−0.05 (−0.24 to 0.14)	0.60	−0.15 (−0.34 to 0.04)	0.11
Lean tissue area (cm^2)	0.77 (−2.44 to 3.98)	0.64	−3.11 (−6.43 to 0.21)	0.07	3.88 (0.64 to 7.12)	0.02
Fat tissue area (cm^2)	−5.60 (−11.51 to 0.31)	0.06	1.51 (−4.60 to 7.63)	0.63	−7.11 (−13.07 to −1.15)	0.02
Children aged 4 and older						
Intention-to-treat cohort						
Hemoglobin concentration (g/dL) in children with anemia only	0.33 (−0.04 to 0.70)	0.08	0.09 (−0.28 to 0.45)	0.63	0.24 (−0.13 to 0.61)	0.20
Weight (kg)	0.11 (−0.07 to 0.28)	0.23	0.09 (−0.09 to 0.27)	0.33	0.02 (−0.16 to 0.20)	0.82
Weight for age (z score)	0.04 (−0.04 to 0.11)	0.32	0.03 (−0.05 to 0.10)	0.44	0.01 (−0.07 to 0.08)	0.82
Height for age (z score)	0.07 (−0.003 to 0.13)	0.06	0.03 (−0.04 to 0.10)	0.39	0.04 (−0.03 to 0.11)	0.32
Body mass index	0.02 (−0.12 to 0.16)	0.77	0.03 (−0.11 to 0.17)	0.67	−0.01 (−0.15 to 0.13)	0.90
Body mass index for age (z score)	−0.002 (−0.11 to 0.11)	0.98	0.02 (−0.09 to 0.13)	0.75	−0.02 (−0.13 to 0.09)	0.73
Mid-upper arm circumference (cm)	−0.03 (−0.17 to 0.11)	0.66	0.04 (−0.10 to 0.18)	0.60	−0.07 (−0.21 to 0.07)	0.34
Lean tissue area (cm^2)	6.27 (2.36 to 10.18)	0.002	1.96 (−1.98 to 5.89)	0.33	4.31 (0.34 to 8.28)	0.03
Fat tissue area (cm^2)	−6.47 (−12.13 to −0.81)	0.03	−1.22 (−6.91 to 4.48)	0.67	−5.25 (−10.99 to 0.48)	0.07
Per protocol cohort						
Hemoglobin concentration (g/dL) in children with anemia only	0.38 (−0.01 to 0.77)	0.06	0.08 (−0.30 to 0.47)	0.67	0.30 (−0.10 to 0.68)	0.14
Weight (kg)	0.11 (−0.08 to 0.30)	0.27	0.08 (−0.11 to 0.27)	0.41	0.03 (−0.16 to 0.22)	0.78
Weight for age (z score)	0.04 (−0.04 to 0.12)	0.34	0.03 (−0.05 to 0.11)	0.49	0.01 (−0.07 to 0.09)	0.80
Height for age (z score)	0.08 (0.01 to 0.15)	0.04	0.04 (−0.04 to 0.11)	0.31	0.04 (−0.03 to 0.11)	0.28
Body mass index	0.005 (−0.14 to 0.15)	0.95	0.01 (0.14 to 0.16)	0.85	−0.01 (−0.16 to 0.14)	0.90
Body mass index for age (z score)	−0.01 (−0.13 to 0.10)	0.80	0.003 (−0.11 to 0.12)	0.95	−0.02 (−0.13 to 0.10)	0.76
Mid-upper arm circumference (cm)	−0.06 (−0.20 to 0.09)	0.44	0.03 (−0.12 to 0.17)	0.72	−0.08 (−0.23 to 0.06)	0.26
Lean tissue area (cm^2)	6.10 (1.91 to 10.28)	0.004	1.75 (−2.45 to 5.96)	0.41	4.34 (0.12 to 8.57)	0.04
Fat tissue area (cm^2)	−7.20 (−13.23 to −1.16)	0.02	−1.47 (−7.54 to 4.59)	0.63	−5.72 (−11.81 to 0.36)	0.07

FBF=fortified blended food; NEWSUP=new supplement.
*Calculated by linear mixed models accounting for clustering of children within families, adjusted for age, sex, study cohort, and baseline measurement.

the summarized studies used composite cognitive scores across several measures of development (eg, attention, language, motor skills) and standardized tests of cognitive development that have not been normed to international populations or children at risk of undernutrition.[7 8 128] Our inconclusive results for FBF suggest that focusing on measuring a single domain general ability that widely supports cognitive development throughout childhood (executive functions) might identify the benefits of traditional supplementary foods for specific key aspects of cognition. Nevertheless, in contrast to NEWSUP, FBF did not have significant beneficial effects on cerebral blood flow or hemoglobin, and a disproportionate increase in fat mass was found, with less lean tissue accretion indicating low quality weight gain.

Strengths and limitations

The methodological strengths of this study included providing the supplement to all groups and directly observing the children eating the meals provided (to maximize intervention fidelity and adherence, and limit confounding by inaccurate parent reported supplement consumption); and blinded assessment, coding, and analysis of outcomes data by people who were not involved in intervention design and delivery.

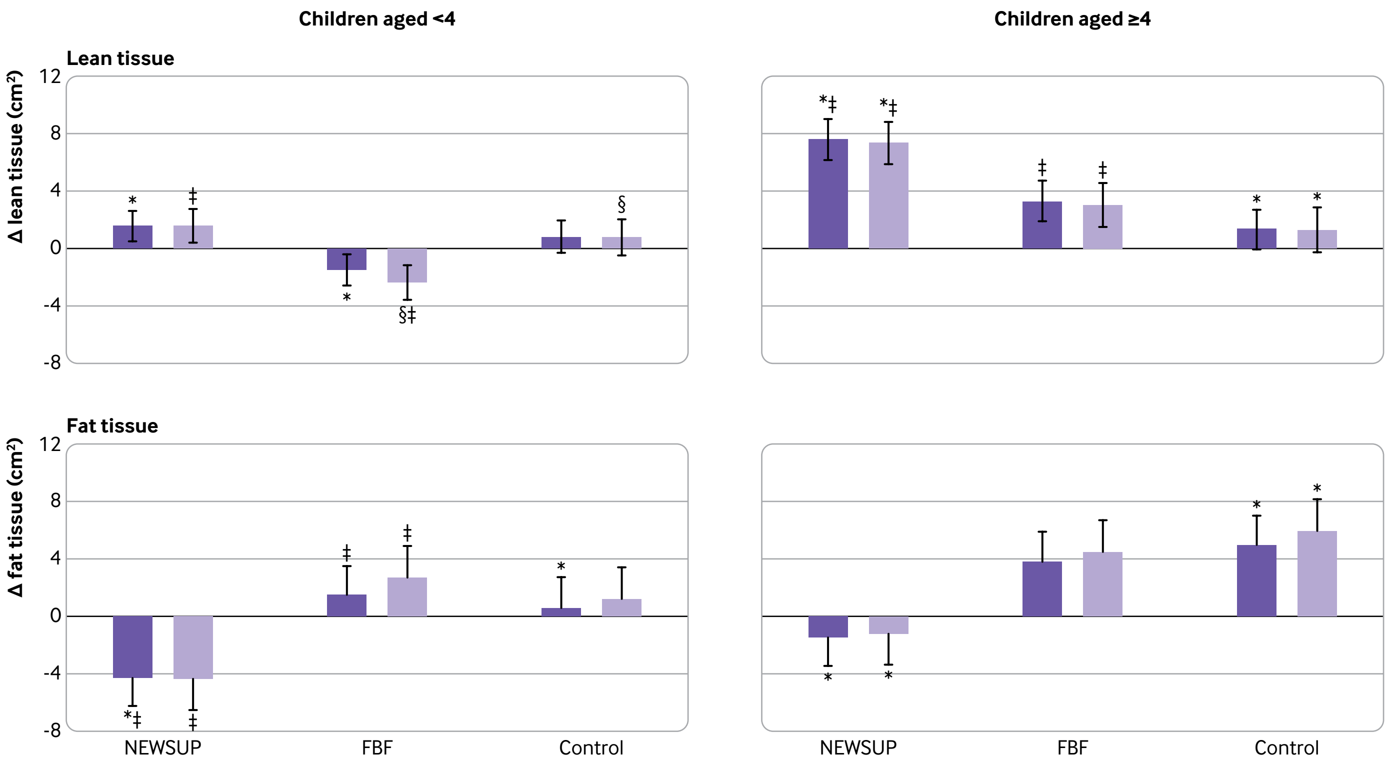

Fig 4 | Changes in lean and fat tissue with consumption of new supplement (NEWSUP), fortified blended food (FBF), or control meal. Cluster adjusted means and standard errors are given for tissue areas at the mid-upper arm circumference site. Means are adjusted for age, sex, study cohort, and baseline measurement. Significant differences between groups are indicated by same symbol. Dark purple bars indicate results for intention-to-treat cohort and light purple bars represent per protocol cohort

Additionally, the availability of an experienced field team allowed us to randomize within villages rather than cluster randomize by village. Therefore, we could study fewer participants to achieve statistical power, which allowed for more detailed measures than are usual in nutrition trials in low and middle income countries.

The study also had limitations. Data analysis revealed unequal mean hemoglobin concentrations at baseline across the groups of young children. No such differences were seen in the older children who came from the same families, which argues against some undetected flaw in the randomization. To address this issue we adjusted for baseline values, and also applied models excluding children with severe anemia (to make hemoglobin concentrations similar across groups). We found comparable results. Nevertheless, the possibility cannot be excluded that randomization was compromised in some undetected way. Further study limitations were that we did not screen for color vision deficiency,[129] it was only feasible to distribute the supplements five days a week, and we did not measure possible compensation in home food supply.[130] All of these factors might have resulted in the effects of supplements being underestimated. Additionally, by using a single cognitive measure we were limited to interpreting the results for working memory, and the study was not powered to detect a difference between NEWSUP and FBF.

Future research directions

Our results are a proof-of-concept demonstration that nutritional supplements can improve cognition in vulnerable young children. Additional research is needed to replicate the findings and support the development of scaled interventions for vulnerable children. Importantly, such work can determine whether all the components of NEWSUP are required for supplement effectiveness. Furthermore, the amounts of the different constituents can be optimized. This work will also inform commercial scaling because some NEWSUP ingredients (eg, cocoa and moringa) could be sourced locally, while others (eg, protein sources) are currently more expensive as international commodities than those used in FBF. Furthermore, such studies can be powered to determine whether NEWSUP has greater effects than FBF because a trend to significance was found in the per protocol cohort, and whether caffeine (through natural concentrations in some ingredients) in NEWSUP contributed to positive effects. However, caffeine by itself decreases brain blood flow and does not improve performance in executive function tasks that depend on working memory in adults.[43 44] Additionally, studies are needed to address the potential for improved nutritional formulations to have lasting effects on a wider range of cognitive functions and educational achievement at different ages, and the potential for synergistic effects with psychosocial interventions.[8]

Conclusions and implications for public health

The results of this trial show that nutritional supplementation for 23 weeks can improve cognitive function in young children living in communities with high rates of undernutrition. These beneficial effects were seen in children up to 4 years old with a new food supplement. This supplement was based on emerging evidence from regenerative nutrition research that incorporated a wider panel of essential nutrients in greater amounts than traditional formulations, and included new ingredients such as cocoa, moringa, and green tea. Although further research is needed to optimize the supplement composition and examine cognition more extensively for NEWSUP and traditional supplementary foods, the positive effects of the new formulation suggest that decisions about supplementary feeding programs should take cognitive benefits into account. Moreover, NEWSUP improved hemoglobin concentration and quality of growth, which are long recognized goals for supplementary nutrition programs. These results could be relevant for supplementary nutrition programs in low and middle income countries, for children living in affluent countries who consume an unhealthy diet, and for other groups such as older adults with inadequate nutrition and cognitive impairment.

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Contributors: SBR planned the study with expert input from MAF, PM, PW, BLR, NS, WP, and SKD, and also drafted the manuscript for input by all authors. All authors critically reviewed drafts of the manuscript and approved the final version. AK and AT created the methodology for supplement distribution, which was supervised by RC and AS. PM designed the cognitive testing methods and trained coders to extract data from the videotaped sessions blinded and interpreted those results. MAF developed the method for cerebral activity measures and led blinded testing in the field with PYL. ES designed the data safety and monitoring plan, which was overseen in the field by CB. CYC provided input on flavonoids and measured levels in the supplement ingredients. ABdS led the field team, and was responsible for obtaining local IRB permission and recruiting villages, assisted by RC and AS who also supervised supplement production and supplies. SBR led development of a plan for staff training and quality control, which was implemented by SFT, who also supervised the field team for outcomes, entered data for analyses, and supervised the team coding the cognitive testing videos. RES was responsible for data cleaning, development of the statistical analysis plan with advice from PM, MAF, and SBR, and statistical analyses with input from KKHC. SBR and RES affirm that the manuscript is an honest, accurate, and transparent account of the study being reported, and RES (all supplement data and anthropometry), PM (cognition), and MAF (cerebral data) are guarantors of the data. The corresponding author attests that all listed authors meet authorship criteria, and that no others meeting the criteria have been omitted.

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Ethical approval: The protocol was approved by all relevant committees in January 2017: the National Committee of Ethics in Health of Guinea-Bissau; Tufts University Institutional Review Board (all study components except NIRS-DCS); the Institutional Review Board at Massachusetts General Hospital (for NIRS-DCS as a substudy).

Data sharing: Requests for access to data and statistical code should be addressed to SBR.

SBR and RES affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: Formal village and national stakeholder meetings will be held in Guinea-Bissau after the results are published, and feedback will be used to inform future work. Preliminary conversations with community health workers indicate that the results are considered highly significant, and the hoped-for outcome will be a national delivery including not only young children but also pregnant mothers.

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Web appendix: Supplementary appendix