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BIBLIOGRAFÍA RECOMENDADA

"TALLA BAJA EN GUATEMALA: INTERPRETACIÓN DE LA EVIDENCIA PARA LA ACCIÓN"

SIMPOSIO
NUTRICIÓN PARA EL DESARROLLO

"Dra. Ana Victoria Román Trigo"

Guatemala, 5 de septiembre de 2019

Ilustración: Fragmentos del mural "Las Fuentes de la Vida", autor Dagoberto Vásquez, 1954. Técnica mosaico.
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Coordinadora: Carolina Siu, MPH, Directora INCAP

Moderadora: Ana Lucía Garcés, MD MPH, INCAP

Expositores:
Astrid Arriaza, MPH, Consultora INCAP
Nancy F. Krebs, MD, MS, Universidad de Colorado
Omar Dary, PhD, Experto en Nutrición y Micronutrientes
Michael Hambidge, MD, BChir, ScD, FRCP, Universidad de Colorado
Jef Leroy, PhD, International Food Policy Research Institute - IFPRI

Diseño y Diagramación: Diego Taylor, INCAP

Fotografías: Roberto Luna, INCAP

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Contenido

La estatura media de la mujer guatemalteca: un siglo detrás

Expositor: Astrid Arriaza, MPH, Consultora INCAP

Antecedentes: La estatura alcanzada es un indicador a largo plazo de salud y bienestar durante la niñez. La mejora de las condiciones de vida mundiales en el último siglo se ha visto reflejado en el crecimiento de la mujer. Las mujeres de algunos países han aumentado su estatura media en 0.0249 cm cada año. Guatemala es el país con la estatura media más baja en mujeres adultas del mundo.

Objetivo: Analizamos la tendencia secular de la estatura media de las mujeres entre los 18 y 49 años de edad, nacidas en Guatemala entre 1945 y 1997 e identificamos las diferencias étnicas y los factores socioeconómicos relacionados con dicha tendencia.

Métodos: Usamos datos representativos a nivel nacional de 45,043 mujeres de cinco Encuestas de Salud Materno Infantil (DHS, por sus siglas en inglés) llevadas a cabo entre 1995 y 2015. Se usó un modelo de regresión lineal multinivel para identificar la tendencia secular y se modeló la estatura como función del año de nacimiento, grupo de edad, nivel económico, nivel educativo, ubicación geo-administrativa, y altitud.

Hallazgos: La estatura media de las mujeres en Guatemala aumentó 0.021 cm cada año de 147.6 cm en 1945 a 148.6 cm en 1997. Hubo una fuerte relación positiva entre la estatura de la mujer, su nivel educativo y su nivel económico. La altura de las mujeres indígenas fue en promedio 4.77 cm menor a la de las mujeres no-indígenas. La de las mujeres indígenas aumentó 0.027 cm por año (2.7 cm en cada 100 años) y la de las mujeres no-indígenas 0.017 cm (1.7 cm por cada 100 años). La estatura se redujo por 1.00 cm por cada mil metros de elevación sobre el nivel del mar. En 1995, la estatura promedio en la región metropolitana fue de 151.6 cm y en la suroriente 0.79 cm más alta. En la región noroccidente fue 1.17 cm más baja, en la suroccidente 1.27 cm más baja y en la central, 0.75 cm más baja.

Conclusiones:

El lento crecimiento de la tendencia secular de la estatura podría explicar por qué Guatemala tiene la estatura media de mujeres más baja del mundo. Las mujeres indígenas maya tienen una estatura media más baja que las mujeres no-indígenas. Un mayor nivel educativo está fuertemente asociado a una mayor estatura. Se ha demostrado que la ubicación geográfica influye en la estatura a lo largo del tiempo. Nuestros hallazgos resaltan las inequidades que han persistido para las mujeres indígenas durante medio siglo.

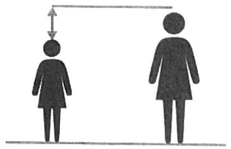
La talla media de una mujer que nació en Guatemala en el año 2000 es 149.4 cm

La talla media de una mujer en Colombia en 1903 era 150.2 cm (Meisel and Vega 2007)

(WHO 2007)

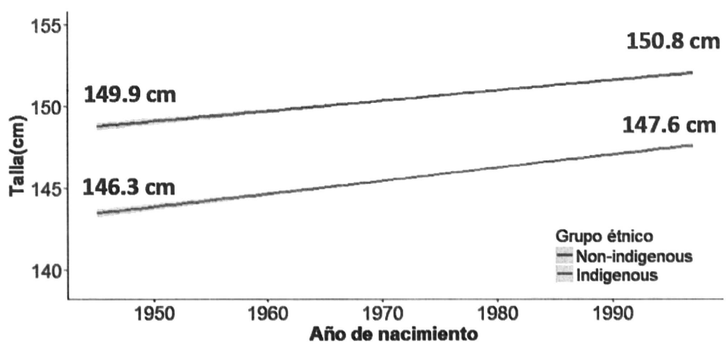
La talla media de una niña de 11 años bien nutrida es 149.0 cm

La talla media de una mujer indígena que nació en el año 1995 es 147.6 cm



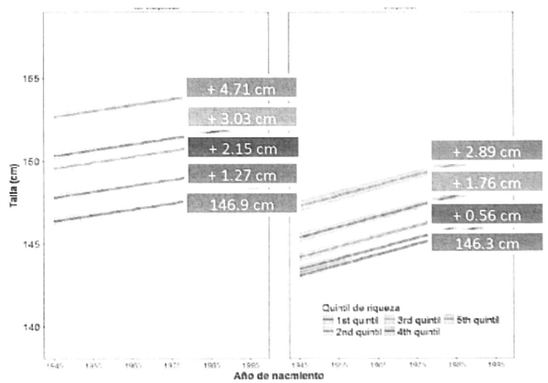
La talla media de una mujer no indígena que nació en el año 1995 es 150.8 cm

Aumento de la talla por década de mujeres indígenas y no indígenas nacidas en Guatemala entre 1945 a 1995

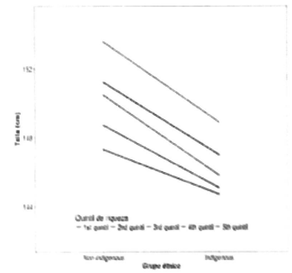


	Aumento de la talla por década	Intervalo de confianza [95%]
Todas las mujeres	0.20 cm	0.20 – 0.21
Mujeres indígenas	0.27 cm	0.27 – 0.27
Mujeres no indígenas	0.17 cm	0.17 – 0.17

Talla de mujeres indígenas y no indígenas nacidas entre 1945 y 1995, según nivel económico



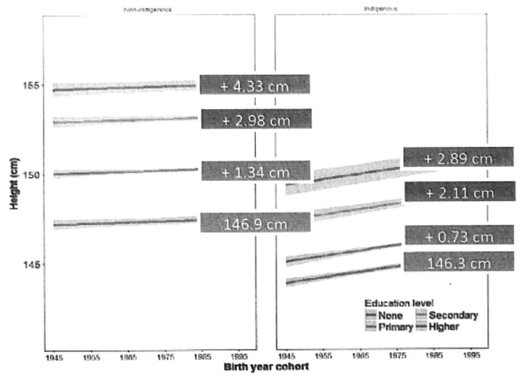
El aumento de la talla se asocia a un mayor nivel económico



Existe interacción entre etnicidad y nivel económico.

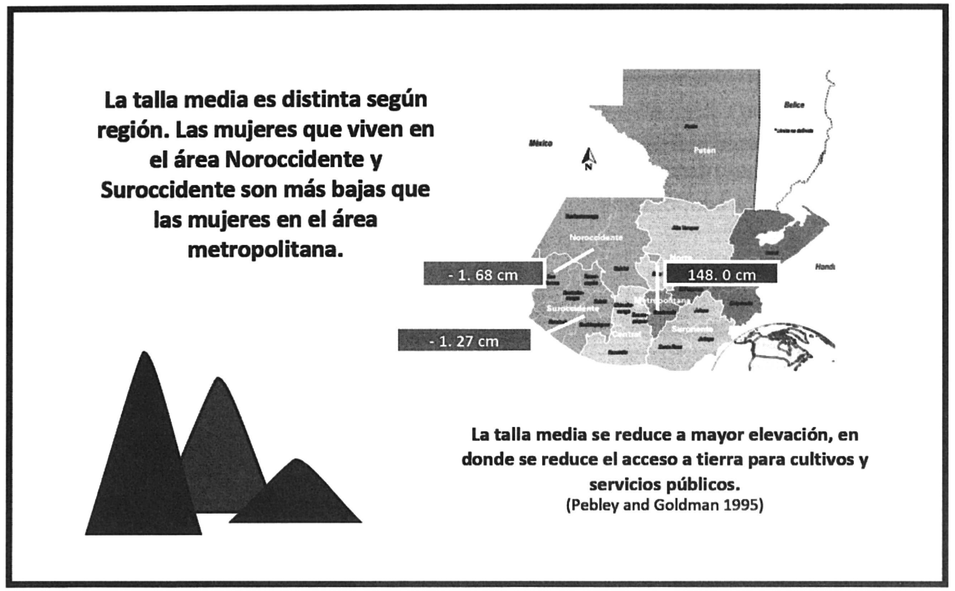
La brecha de la talla entre niveles económicos es más pequeña para mujeres indígenas que no indígenas.

Talla de mujeres indígenas y no indígenas nacidas entre 1945 y 1995, según nivel educativo



A Guatemala le llevará 130 años alcanzar la talla media de una mujer México de 1995.

A una mujer indígena le llevará 147 años alcanzar la talla media de una mujer no indígena



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Resultados del Estudio Preconcepcional "Women First"

Expositor: **Nancy Krebs**, MD, MS, Universidad de Colorado

Antecedentes: Se han reportado beneficios limitados del uso de suplementos nutricionales maternos comenzados durante el embarazo en poblaciones de escasos recursos.

Objetivos: Este estudio evaluó los efectos sobre el crecimiento del recién nacido, particularmente la talla, que tuvo el comenzar a tomar suplementos nutricionales para mujeres en poblaciones de escasos recursos ≥3 meses antes de concebir (Grupo 1), comparados con el mismo suplemento tomado a finales del primer trimestre del embarazo (Grupo 2), o sin suplemento (Grupo 3, de control).

Métodos: "Women First" fue un ensayo controlado aleatorizado con tres grupos. La intervención consistió en un suplemento de micronutrientes basado en lípidos. También había un suplemento enérgico/proteínico, el cual se usó en casos donde el índice de masa corporal (kg/m2) de la madre era menor a 20 o si el aumento de peso gestacional era menor al indicado. El estudio se realizó en áreas rurales en la República Democrática del Congo (RDC), Guatemala, India y Pakistán. El resultado primario fue el punteo "Z" longitud-a-edad (LAZ), para el cual las medidas antropométricas se obtuvieron en las primeras 48 horas post-parto. Dado que las edades gestacionales no estaban disponibles en la RDC, los resultados de las cuatro áreas se determinaron según estándares neonatales de la OMS (no-ajustados según la edad gestacional, NGAA por sus siglas en inglés), al igual que estándares fetales Intergrowth-21st (3 áreas, ajustados según edad gestacional, GAA por sus siglas en inglés).

Resultados: En total, 7387 mujeres no embarazadas fueron asignadas aleatoriamente. De ahí, hubo 2451 nacimientos con resultados primarios no ajustados según edad gestacional (NGAA), y 1465 con resultados ajustados según edad gestacional (GAA). El punteo LAZ medio, al igual que otros resultados, no varió entre el grupo 1 y grupo 2, ya sea usando NGAA o GAA. La LAZ media (NGAA) para el grupo 1 fue mayor que para el grupo 3 (tamaño del efecto: +0.19; 95% CI: 0.08, 0.30, P=0.0008). En los resultados GAA, las tasas de crecimiento reducido o bajo según la edad gestacional fueron menores en el grupo 1 que en el grupo 3 (RR: 0.69; 95% CI: 0.49, 0.98, P=0.0361, y RR: 0.78; 95% CI: 0.70, 0.88, P<0.001, respectivamente). Las tasas de nacimientos prematuros no tuvieron diferencias entre los grupos.

Conclusiones:

El uso de suplementos nutricionales, comenzado antes de la concepción o a finales del primer trimestre, benefició los resultados al nacer relativos al crecimiento fetal en poblaciones de escasos recursos.

See corresponding editorial on page 249.

A multicountry randomized controlled trial of comprehensive maternal nutrition supplementation initiated before conception: the Women First trial

K Michael Hambidge,[1] Jamie E Westcott,[1] Ana Garcés,[2] Lester Figueroa,[2] Shivaprasad S Goudar,[3] Sangappa M Dhaded,[3] Omrana Pasha,[4,5] Sumera A Ali,[4] Antoinette Tshefu,[6] Adrien Lokangaka,[6] Richard J Derman,[7] Robert L Goldenberg,[8] Carl L Bose,[9] Melissa Bauserman,[9] Marion Koso-Thomas,[10] Vanessa R Thorsten,[11] Amaanti Sridhar,[11] Kristen Stolka,[11] Abhik Das,[11] Elizabeth M McClure,[11] and Nancy F Krebs,[1] on behalf of the Women First Preconception Trial Study Group

[1]Department of Pediatrics, Section of Nutrition, University of Colorado Anschutz Medical Campus, Aurora, CO; [2]INCAP (Instituto de Nutrición de Centro América y Panamá), Guatemala City, Guatemala; [3]KLE Academy of Higher Education and Research's Jawaharlal Nehru Medical College, Belagavi, India; [4]Aga Khan University, Karachi, Pakistan; [5]Johns Hopkins University, Baltimore, MD; [6]Kinshasa School of Public Health, Kinshasa, Democratic Republic of the Congo; [7]Thomas Jefferson University, Philadelphia, PA; [8]Columbia University, New York, NY; [9]University of North Carolina, Chapel Hill, NC; [10]National Institute of Child Health and Human Development/NIH, Bethesda, MD; and [11]RTI International, Durham, NC

ABSTRACT

Background: Reported benefits of maternal nutrition supplements commenced during pregnancy in low-resource populations have typically been quite limited.

Objectives: This study tested the effects on newborn size, especially length, of commencing nutrition supplements for women in low-resource populations ≥3 mo before conception (Arm 1), compared with the same supplement commenced late in the first trimester of pregnancy (Arm 2) or not at all (control Arm 3).

Methods: Women First was a 3-arm individualized randomized controlled trial (RCT). The intervention was a lipid-based micronutrient supplement; a protein-energy supplement was also provided if maternal body mass index (kg/m^2) was <20 or gestational weight gain was less than recommendations. Study sites were in rural locations of the Democratic Republic of the Congo (DRC), Guatemala, India, and Pakistan. The primary outcome was length-for-age *z* score (LAZ), with all anthropometry obtained <48 h post delivery. Because gestational ages were unavailable in DRC, outcomes were determined for all 4 sites from WHO newborn standards (non-gestational-age-adjusted, NGAA) as well as INTERGROWTH-21st fetal standards (3 sites, gestational age-adjusted, GAA).

Results: A total of 7387 nonpregnant women were randomly assigned, yielding 2451 births with NGAA primary outcomes and 1465 with GAA outcomes. Mean LAZ and other outcomes did not differ between Arm 1 and Arm 2 using either NGAA or GAA. Mean LAZ (NGAA) for Arm 1 was greater than for Arm 3 (effect size: +0.19; 95% CI: 0.08, 0.30, $P = 0.0008$). For GAA outcomes, rates of stunting and small-for-gestational-age were lower in Arm 1 than in Arm 3 (RR: 0.69; 95% CI: 0.49, 0.98, $P = 0.0361$ and RR: 0.78; 95% CI: 0.70, 0.88, $P < 0.001$, respectively). Rates of preterm birth did not differ among arms.

Conclusions: In low-resource populations, benefits on fetal growth–related birth outcomes were derived from nutrition supplements commenced before conception or late in the first trimester. This trial was registered at clinicaltrials.gov as NCT01883193. *Am J Clin Nutr* 2019;109:457–469.

Keywords: preconception, pregnancy, birth length, stunting, lipid nutrient supplement

Introduction

Linear growth restriction continues to be a major public health challenge globally for poor communities in low- and middle-income countries (1–3). Stunting before 2 y of age is prominent among the nutrition factors related to disease burden and mortality in early childhood (4, 5). Longer-term associations of early linear growth faltering include impairment of motor development, cognition, educational and economic achievement, chronic disease, and low offspring birth size (6). Fetal growth restriction is another major predictor of adverse outcomes beyond the neonatal period, including mortality, stunting, and impaired neurodevelopment (7–10). Recognition of the unique and compelling opportunities for optimizing the environment of both the fetus and young child has given prominence to the concept of "The First 1000 Days" (6, 11) and has prompted

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numerous trials directed either to early postnatal life or, by means of improving maternal nutrition, to life during gestation. The environmental factors underlying stunting and adverse birth outcomes are undoubtedly complex and potentially synergistic, but maternal undernutrition can clearly result in deficits of nutrients required for physical growth. Trials of maternal supplements, typically initiated during the second trimester of gestation, consisting of iron and folate, multimicronutrients with or without lipids, or protein-energy supplements, have frequently had some positive effect on offspring birth size, including length. However, the effect sizes of such maternal interventions have typically been quite modest (12–15).

Advantages of initiating maternal nutrition supplements before conception have been suggested, particularly to correct both maternal underweight and micronutrient deficiencies before conception (16–18). Evidence of a beneficial effect of improved nutrition during the periconceptional period is supported by animal and epigenetic studies (19, 20). Currently, however, information is too limited to reach definitive conclusions regarding the potential benefits to the offspring of prevention or treatment of maternal undernutrition before conception in resource-poor settings (18, 21–24).

To address this gap in knowledge, we undertook a trial known as Women First. The broad goal of the trial was to evaluate the potential benefits on birth outcomes of promoting optimal maternal nutrition for ≥3 mo before conception (25). We hypothesized that for women living in poor environments with high rates of stunting, starting a comprehensive nutrition supplement during the preconception period would result in significantly greater newborn length than starting the same intervention at the junction of the first and second trimesters or not being provided this supplement at all. In addition, we report here the impact of the intervention on other birth outcomes.

Methods

Study design

This was an individually randomized, nonmasked, multisite controlled efficacy trial (NCT01883193, initial release 18 June 2013) to determine the effect of a preconception nutrition supplement on birth length and other anthropometry outcomes at birth. The trial included 3 arms: one that started the supplement ≥3 mo before conception and continued through delivery (Arm 1); a second arm that started the same intervention late in the first trimester (Arm 2); and a third that received no nutrition supplements besides those self-administered or prescribed through local health services (Arm 3).

The trial was conducted in rural or semirural locations in the Democratic Republic of the Congo (DRC; Equateur), Guatemala (Chimaltenango), India (Belagavi, North Karnataka), and Pakistan (Thatta, Sindh Province). Each of these 4 sites is a member of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Global Network (GN) for Women's and Children's Health Research. Trial participants were recruited from a total of 53 GN clusters, which were geographic catchment areas, each of which has ~300 deliveries/y. Communication between the investigators based at the University of Colorado and study partners in the 4 sites was facilitated by the Data Coordinating Center (DCC) at RTI International (Durham, NC) and included monthly data monitoring reports and conference calls and periodic site visits by the lead investigators to review study progress, share strategies, and conduct refresher training as needed.

Participants

Women were identified through the GN Maternal and Newborn Health Registry (26), household surveys, local health centers, word-of-mouth, and local advertising. Community sensitization meetings were held to explain the study to prospective participants and families. All women were screened for the following inclusion criteria: age 16–35 y; parity 0–5, with site-specific strategies to include nulliparous participants; no current or planned contraceptive use; and expectation to conceive during the following 18 mo. Consent of parous women was delayed until ≥2 mo postpartum. Women with a known history of obstetric complications or those who were unwilling to deliver in hospital were excluded (25). If an otherwise eligible woman had a hemoglobin concentration of ≤8 g/dL at screening, enrollment was delayed until successfully treated, if at all. No women were excluded on the basis of height, weight, or BMI (kg/m^2). Diets were predominantly based on staple foods, including grains and tubers, and were generally low in dietary diversity (27).

Randomization

The DCC created the randomization scheme, centrally generating the allocation sequence for each site. To ensure geographic balance, a permuted block design stratified by GN clusters was used for assigning individual participants to a trial arm. The allocation ratio was 1:1:1 within blocks which randomly varied between sizes of 3, 6, or 9 for each site. Once the responsible home visitor research assistant identified an eligible participant, they received the random assignment generated by the site data manager from the centralized computerized data management system maintained by the DCC.

Women First Preconception Trial Study Group collaborators are listed at the end of this article.

Supported by Bill & Melinda Gates Foundation grant OPP1055867 (KMH, NFK) and *Eunice Kennedy Shriver* National Institute of Child Health and Human Development and Office of Dietary Supplements, NIH grant U10 HD 076474 (NFK, KMH).

Supplemental Tables 1–8 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

Address correspondence to NFK (e-mail: nancy.krebs@ucdenver.edu).

Abbreviations used: BMIAZ, BMI-for-age *z* score; CRL, crown-rump length; DCC, Data Coordinating Center; DRC, Democratic Republic of the Congo; GA, gestational age; GAA, gestational-age-adjusted; GN, Global Network; HC, head circumference; HCAZ, HC-for-age *z* score; LAZ, length-for-age *z* score; LBW, low birth weight; NGAA, non-gestational-age-adjusted; PTB, preterm birth; RCT, randomized controlled trial; SGA, small-for-gestational age; WAZ, weight-for-age *z* score; WLRAZ, weight to length ratio-for-age *z* score.

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Procedures

Intervention.

The nutrition intervention, termed Supplement 1, has been described in detail in the published protocol (25) (**Supplemental Table 1**). Briefly, it was a lipid-based micronutrient supplement (Nutriset) and provided micronutrients, polyunsaturated fats in a favorable balance, and modest quantities of protein and energy (2.6 g protein and 118 kcal) (25, 28). For Arm 1, the duration of the primary supplement was from the time of random assignment until delivery; participants were required to be on the primary supplement for ≥3 mo before conception. For Arm 2, the primary supplement covered the second and third trimesters of pregnancy and was also stopped at delivery. Participants in Arm 3 were not provided any nutrition supplement by the study.

In addition, in Arms 1 and 2, women were provided a second daily lipid-based protein-energy supplement (termed Supplement 2, Supplemental Table 1) if they had a BMI <20 at any time while receiving Supplement 1, or had weight gain in the second or third trimesters of pregnancy less than the Institute of Medicine's guidelines (29). If consumed completely, this supplement provided 300 kcal and 11 g protein (~15% of energy) without additional supplemental micronutrients (Nutriset). Supplement 2 was initiated before conception on the basis of BMI for participants in Arm 1 as well as for gestational weight gain during pregnancy (1.7–2.0 kg/mo). For Arm 2, Supplement 2 was started after the initiation of Supplement 1 when either of the criteria became evident. For both arms, once initiated, Supplement 2 was provided until delivery. Unlike the primary supplement, high compliance was not required for the second supplement because of our intention to minimize reduction in habitual food intake and for participants to consume a quantity "to appetite." Recipients were encouraged to consume ≥50% of the protein-energy supplement (Supplement 2) on a daily basis. Participants in Arms 1 and 2 were cautioned not to take other micronutrient supplements or fortified food products while taking the trial supplements.

Home visits and compliance.

Participants in all 3 arms were visited by the home visitor research assistants every 2 wk to record interim health history and to administer a urine pregnancy test. The pregnancy testing was combined with calendar records of menses to ascertain last menstrual period and to guide the timing of ultrasounds to be obtained between 10 and 12 weeks of estimated gestation. For Arms 1 and 2, these visits were also used to replenish the supply of trial supplements. Compliance with use of supplements was documented by inspection of calendars the women completed daily and by collection of empty, partially eaten, and unused intervention sachets. Compliance was calculated for Supplement 1 as the total number of sachets fully eaten divided by the number of days between starting Supplement 1 and delivery. Supplement 2 compliance was calculated similarly; however, the numerator was the total number of Supplement 2 sachets fully or partially eaten.

Anthropometry.

Maternal height and weight measurements were obtained at enrollment, and maternal weight was obtained at ~12 and 32 wks of gestation for all arms. Additionally, monthly weights were obtained once Supplement 1 was initiated (e.g., at enrollment for Arm 1 and after the 12 wk gestation measurement for Arm 2). Newborn anthropometry was obtained within 48 h of delivery (neonatal stadiometer, Ellard Instrumentation, Ltd; seca 334 electronic scale and seca 201 measurement tape, seca North America). All anthropometry was performed by trained assessment teams who were not involved in the biweekly home visits. Assessment teams were extensively trained by study coordinators to use standardized anthropometric methods and were certified before data collection. The assessment teams' procedures were observed by study coordinators at each site on a monthly basis and were recertified at least quarterly. Infant recumbent length and weight measurements were obtained in triplicate and entered into the database; the median value was used for analysis.

Gestational age determination.

First trimester ultrasound crown-rump length (CRL) measurements were obtained for participants at 3 of the sites, allowing for newborn anthropometry to be adjusted for gestational age (GA). In the DRC, ultrasonography was not possible owing to the absence of equipment, trained personnel, and reliable power sources at the initiation of the study. In addition, the calendars and pregnancy testing were not reliably implemented to determine women's last menstrual period. Thus, plausible GA determinations were not possible for this site.

Outcomes.

The primary outcome, newborn length-for-age z score (LAZ), was based on length measurements obtained by the assessment teams before 48 h of age. Secondary outcomes reported here by arm and site include weight, head circumference (HC), and BMI, and the respective z scores: weight-for-age (WAZ), HC-for-age (HCAZ), and BMI-for-age (BMIAZ) z score (30) Gestational-age-adjusted (GAA) outcomes were determined based on INTERGROWTH-21st fetal growth charts (31). In addition to GAA LAZ, WAZ, and HCAZ, further outcomes included: instead of BMIAZ, weight to length ratio-for-age z score (WLRAZ), the proportions of infants with z scores < -1 and < -2, low birth weight (LBW, <2500 g), small-for-gestational age (SGA), and preterm birth (PTB).

Assessment of adverse events and safety monitoring.

Adverse events were monitored continuously as per protocol (25) and reported to the overall study principal investigators and the DCC within 48 h for all deaths and within 7 d for other adverse events, including adverse pregnancy outcomes, adverse neonatal events, hospitalizations, and allergic reactions. A federally constituted Data Monitoring Committee reviewed the study progress for safety, trial progress, data completion, supplement compliance, and protocol violations twice yearly.

Ethics

The project was approved by the Colorado Multiple Institutional Review Board, University of Colorado, the local and/or national ethics committees for each of the 4 sites (registered with

the US Office of Human Research Protection and with Federal-wide Assurance in place), and the DCC. Written informed consent was obtained from all participants. The study protocol is available online (25).

Statistical methods

Sample size determination was based on testing 2 co-primary hypotheses (comparison of Arm 1 with Arm 2 and Arm 1 with Arm 3), for the primary outcome of LAZ at birth. The sample size was based on also having 80% power within each site and maintaining a study-wide Type I error rate of 0.05 across all planned primary hypothesis tests (2 tests at each of 4 sites, for a total of 8 tests). Thus, an α-level of 0.00625 for single-site outcomes was specified to account for the 8 planned primary comparisons. Assuming an α-level of 0.00625, a 2-sided test, and an SD of 1.0 for the primary outcome, 192 evaluable women per arm in each site were needed to detect an effect size of 0.37 with 80% power. To account for 20% attrition during pregnancy required that 240 women per arm enter Phase 2 (pregnancy) within each site. The assumption that 50% of women randomly assigned at Phase 1 would get pregnant and move to Phase 2 required 480 women per arm to be enrolled in each site. Given 192 evaluable women per arm in each site for a total of 768 women per arm over all 4 sites, an α-level of 0.025 for each primary hypothesis test across all sites would allow detection of an effect size of 0.18 with 90% power for each pooled comparison of Arm 1 with Arm 2 and Arm 1 with Arm 3.

For the primary and secondary outcomes, newborn LAZ, WAZ, HCAZ, and BMIZ were based on the WHO Child Growth Standards (30), which account for infant sex and age at measurement but are not adjusted for GA at delivery. Owing to the lack of GA determinations in the DRC, we applied these standards to all births in all sites in the same manner across the 3 arms. Rates of LBW were also determined for the 4-site data set. In addition, for the 3 sites with GA determination (Guatemala, India, Pakistan), the INTERGROWTH-21st fetal growth standards were also applied to birth measurements and binary outcomes (31). These GAA analyses are a post hoc exploration, with P values provided for descriptive purposes.

We assessed the study outcomes using a modified intention-to-treat approach. The overall treatment effect and pairwise comparisons for the primary outcome and continuous secondary outcomes were obtained from linear models for the outcome of interest. Model-generated measures of effect size with 95% CIs and P values were adjusted for site and cluster-nested within site. For binary secondary outcomes, generalized linear models with generalized estimating equations were utilized to calculate RRs with 95% CIs and P values after adjusting for site while controlling for cluster correlations. The comparisons of Arm 1 with Arm 2 and Arm 1 with Arm 3 were prespecified in the protocol. The comparison of Arm 2 with Arm 3, also presented in this article, is a post hoc comparison. P values from chi-square tests for categorical variables and ANOVA analysis of means were calculated to assess differences between maternal baseline characteristics by treatment arm. In addition, for the primary outcome, we investigated potential confounding by baseline maternal factors by first assessing differences in the maternal factors by treatment arm and then adjusting the aforementioned models for any factor which varied by treatment at an α-level of 0.10. These maternal factors included age, parity, education, BMI, height, and socioeconomic status.

As a statistical check to ensure that evaluating only a subset of those randomly assigned (women who became pregnant and delivered a live birth, with birth length evaluated) was not unexpectedly skewing the results, we constructed a composite binary secondary outcome that was evaluated alongside the primary outcome. Among the randomly assigned women who became pregnant, this outcome is defined as live birth free of growth failure. Specifically, the outcome compared women who delivered a live birth with LAZ ≥−1 to all other women who became pregnant (i.e., delivered a live birth with LAZ <−1 and women who did not deliver a live birth due to medical termination of pregnancy, miscarriage, stillbirth, and intrapartum death). Women without birth outcome data, including women (all 3 arms) who became pregnant too soon (i.e., enrolled in the study for <3 mo before conception), were excluded from this analysis. For this composite outcome, P values for the overall treatment effect and pairwise comparisons were obtained from a generalized estimating equation model adjusting for country and controlling for cluster correlations. All analyses were performed by the DCC using SAS/STAT software version 9.4 (SAS Institute).

Results

Participant flow and characteristics

Between December, 2013 and October, 2014, 12,551 women were screened; 7686 (61.2%) were determined to be eligible for the trial. Of these, 7376 (96.0%) consented, enrolled, and were randomly assigned to 1 of the 3 study arms (**Figure 1**). In addition, 11 women who were subsequently found to be outside the inclusionary age range also consented and were enrolled for a total of 7387 randomly assigned women (Figure 1). Fifty-six percent (n = 4136) of those randomly assigned exited the study in Phase 1 (preconception) (Figure 1). Prominent among reasons for exiting were conception before 3 mo post–random assignment (n = 1261), especially in Pakistan and India; no longer wanted to participate (n = 773), primarily in Guatemala; and had not conceived by the time the target sample size was reached [i.e., completion of Phase 1 (n = 1572)] (Figure 1). An additional 88 women exited the study after becoming pregnant. As such, the delivery outcome was obtained for 3163 of 3251 (97.2%) eligible pregnancies, which included 25 multiple births, for a total of 3188 infants.

There were 520 miscarriages or medical terminations of pregnancy before 20 weeks of gestation (15.0% Arm 1; 16.7% Arm 2; 17.2% Arm 3) (Figure 1). Eighty-two stillbirths (≥20 wk) accounted for 2–3% of births across each arm. Of the 2586 live births, 2459 (95.1%) had newborn measurements within 48 h of delivery; 2451 (99.7%) had z scores within the biologically plausible range according to WHO standards and were included in the primary analysis. Among live births, 68 newborns died within 48 h of birth; of these newborns, 30 were measured before death.

Sixty percent of those with newborn primary outcome measurements (n = 1465) also had CRL ultrasound measurements between 6 weeks, 0 days and 13 weeks, 6 days of gestation and were available for analysis, including 85.8% from India, 80.3% from Guatemala, 68.5% from Pakistan, and none from DRC. Numbers were equally distributed among arms. Mean ± SD GA

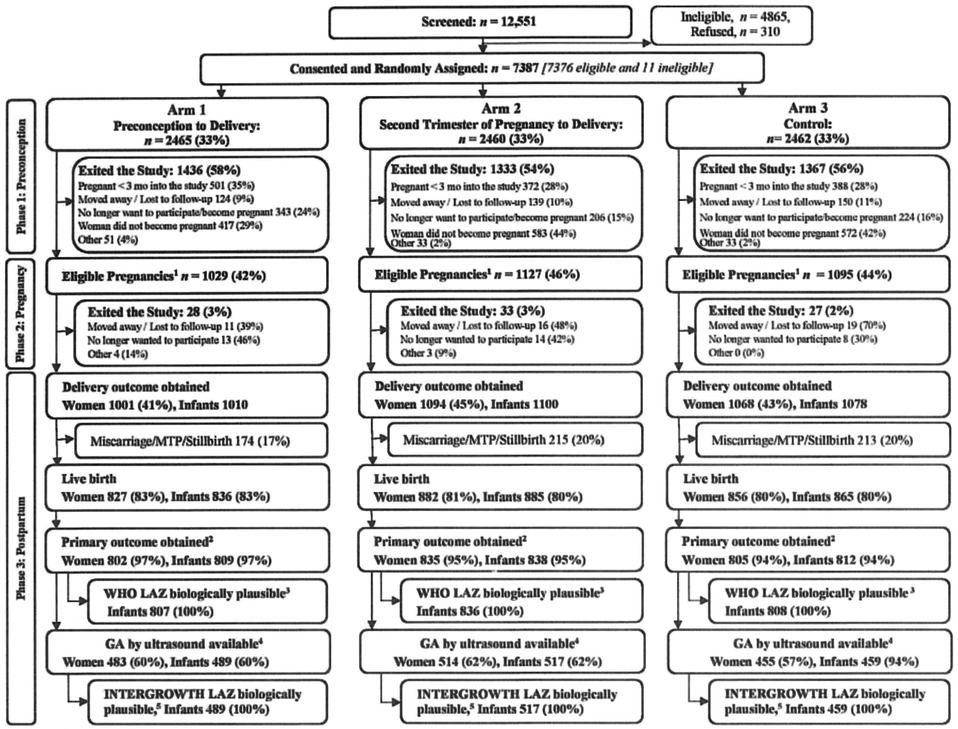

FIGURE 1 CONSORT diagram. Overall screening, random assignment, and obtainment of primary outcome by treatment arm. [1]Percentage of those randomly assigned. Excludes women who became pregnant <3 mo into the study. The women who had eligible pregnancies may have had delivery data obtained or they may have exited the study before delivery. [2]Primary outcome was obtained for live newborns with 3 length measurements taken within 48 h of delivery. Among women, primary outcome obtained from ≥1 infants of the woman. [3]LAZ for birth length, based on actual birth length measured by 48 h of age, calculated using the expanded tables of the Child Growth Standards published by the WHO (30) that provide scores by day of measurement. The same standards were used to calculate the weight-for-age, head circumference-for-age, and BMI-for age *z* scores (WAZ, HCAZ, and BMIAZ). [4]GA at birth is defined as the age at the time of the ultrasound based on the ultrasound plus time until birth if the ultrasound was done between 6 wk + 0 d and 13 wk + 6 d and the GA at birth was between 24 wk + 0 d and 42 wk + 6 d. If the ultrasound was not conducted during the GA previously mentioned, then the GA at birth is missing. [5]LAZ, WAZ, HCAZ, and weight to length-ratio-for age (WLRAZ) *z* scores and percentiles based on measurements within 48 h of delivery are calculated using the INTERGROWTH-21st International Standards for Newborn Size (32) and International Standards for Newborn Size for Very Preterm Infants (33), which provide *z* scores by sex and GA at birth for infants between 33 wk + 0 d and 42 wk + 6 d GA at birth and between 24 wk + 0 d and 32 wk + 6 d GA at birth, respectively. CONSORT, Consolidated Standards of Reporting Trials; GA, gestational age; LAZ, length-for-age *z* score; MTP, medical termination of pregnancy.

at the time of the ultrasound measurements was 11.73 ± 1.13 wk with minimal differences between arms and with a slightly higher mean GA of 12.2 wk for India.

Baseline anthropometric characteristics of all women randomly assigned have been reported previously (34). For women who had primary outcome data collected, these and other characteristics are given by site in **Table 1**. The only baseline difference between those with a primary outcome and the entire randomly assigned group was for parity: 20.4% and 27.5% were nulliparous, respectively (data not shown).

Overall baseline characteristics by arm among women who had the primary outcome obtained differed only in terms of maternal education, with a higher percentage of women in Arm 1 having no formal education ($P = 0.0081$, **Table 2**).

Compliance, protein-energy supplement use, and maternal weight gain

The mean ± SD length of exposure for Supplement 1 for Arm 1 during the preconception period was 37.3 ± 21.5 wk, with mean compliance of 88% (i.e., for every 100 d of exposure women consumed 88 sachets). During the first 12 wk of pregnancy, compliance for this group was similar at 87.3% ± 16.1%. From 12 wk to delivery, exposure for Arm 1 was 27.2 ± 1.9 wk and compliance was 84.2% ± 17.4%. Total length of exposure for Arm 1 from enrollment to delivery was 76.6 ± 21.6 wk with overall compliance of 87.2% ± 13.2%. For Arm 2, total length of exposure for Supplement 1 was 25.4 ± 3.2 wk, and compliance was 84.3% ± 17.4%.

TABLE 1 Baseline characteristics among women who had the primary outcome for newborns, by site[1]

Variable	DRC	Pak	Ind	Guat
Randomly assigned, *n*	1741	2015	1823	1808
Women who had a live birth, *n*	608	697	609	651
Women who had the primary outcome obtained for a newborn,[2] *n* (%)	576 (94.7)	663 (95.1)	591 (97.0)	612 (94.0)
Maternal age, *n* (%)				
<20 y	141 (24.5)	116 (17.5)	147 (24.9)	90 (14.7)
20–24 y	228 (39.6)	222 (33.5)	317 (53.6)	247 (40.4)
≥25 y	207 (35.9)	325 (49.0)	127 (21.5)	275 (44.9)
Height, cm	156.1 ± 6.2	152.4 ± 6.3	151.4 ± 5.7	145.5 ± 4.9[3]
BMI, kg/m^2				
Mean ± SD	20.6 ± 2.6	19.7 ± 2.9	20.1 ± 3.4	25.4 ± 4.2[3]
<20.0	253 (43.9)	381 (57.5)	327 (55.3)	39 (6.4)
<18.5	101 (17.5)	235 (35.4)	219 (37.1)	8 (1.3)
Maternal education, *n* (%)				
No formal schooling	135 (23.4)	562 (84.8)	45 (7.6)	49 (8.0)
Primary	342 (59.4)	66 (10.0)	93 (15.7)	410 (67.0)
Secondary or more	99 (17.2)	35 (5.3)	453 (76.6)	153 (25.0)
Parity, *n* (%)				
0 (nulliparous)	121 (21.0)	190 (28.7)	151 (25.5)	35 (5.7)
1	135 (23.4)	152 (22.9)	243 (41.1)	234 (38.2)
≥2	320 (55.6)	321 (48.4)	197 (33.3)	343 (56.0)
Tally of indicators of higher SES,[4] *n* (%)				
None (0 present)	308 (53.5)	19 (2.9)	0 (0.0)	0 (0.0)
1–2 present	260 (45.1)	302 (45.6)	58 (9.8)	73 (11.9)
3–4 present	8 (1.4)	241 (36.3)	376 (63.6)	366 (59.8)
5–6 present	0 (0.0)	101 (15.2)	157 (26.6)	173 (28.3)

[1]Values are *n*, *n* (%), or means ± SDs. DRC, Democratic Republic of the Congo; Guat, Guatemala; Ind, India; Pak, Pakistan; SES, socioeconomic status.
[2]Primary outcome obtained from ≥1 newborns of the woman.
[3]$n = 611$ for height and BMI in Guatemala.
[4]The SES tally provides the number of indicators available from the following list: electricity, improved water source, sanitation, man-made flooring, improved cooking fuels, and household assets.

Supplement 2, the protein-energy supplement, was started in >90% of the women in Arm 1 in DRC, India, and Pakistan, and in 88–96% of the women in these sites for Arm 2 (after 12 weeks of gestation). Less than 10% of the women in Guatemala for either Arm 1 or Arm 2 started Supplement 2. Mean overall Supplement 2 compliance for both arms was 84%, with total duration of exposure 55.4 ± 29.4 and 22.0 ± 5.8 wk for Arms 1 and 2, respectively.

From baseline (preconception) to 12 weeks of gestation, mean ± SD weight gain was greater for women in Arm 1 than for those in both Arms 2 and 3: 0.8 ± 3.9 kg, 0.0 ± 3.8 kg, and 0.3 ± 3.7 kg, respectively ($P < 0.0010$). BMI figures at 12 wk were 21.8 ± 3.8, 21.4 ± 3.8, and 21.6 ± 3.9, for Arms 1, 2, and 3, respectively ($P = 0.082$). Change in weight from baseline to 32 wk was also greater for Arm 1 than for the other 2 arms: 6.9 ± 4.5 kg, 6.4 ± 4.1 kg, and 6.2 ± 4.4 kg, respectively ($P < 0.0015$).

Newborn anthropometry

Analysis of non-GAA data.

For neither all sites combined nor for any individual site was the LAZ for Arm 1 significantly greater than the LAZ for Arm 2 (**Table 3, Supplemental Tables 2–5**). In Guatemala, the mean LAZ for Arm 1 was lower than that of Arm 2 (−0.27, $P = 0.0044$). The mean LAZ, however, was higher for Arm 1 than for Arm 3 for combined sites ($P < 0.01$) and for DRC and Pakistan ($P < 0.00625$). A small positive effect size was observed for India (+0.17, $P = 0.1244$). Post hoc comparison of Arm 2 with Arm 3 also revealed a significantly higher LAZ for combined sites and for Pakistan. The LAZ effect size for Arm 1 compared with Arm 3 was low (<0.2) for combined sites and in the moderate range (0.20–0.39) for DRC and Pakistan (Supplemental Tables 2 and 3). Effect sizes for WAZ were the same as or lower than for LAZ but followed the same pattern, with both Arms 1 and 2 greater than Arm 3 (Table 3, Supplemental Tables 2–5). Mean *z* scores for all anthropometric outcomes for the non-GAA (NGAA) data are shown by site (**Figure 2**). The incidence of LBW for combined sites trended lower in both Arm 1 and Arm 2 compared with Arm 3, with an RR of 0.86 (95% CI: 0.75, 0.98, $P = 0.0263$) and 0.81 (95% CI: 0.70, 0.93, $P = 0.0038$), respectively.

No differences between arms or sites were observed for either HCAZ or BMIAZ (Table 3). The analysis of live births free of growth failure, constructed as a statistical check of the primary outcome, demonstrated patterns consistent with that of the primary LAZ outcome: a significant treatment arm effect ($P = 0.0021$) and a difference between Arm 1 and Arm 3 ($P = 0.0009$) and Arm 2 and Arm 3 ($P = 0.0166$).

TABLE 2 Overall baseline characteristics among women who had the primary outcome for newborns, by treatment arm[1]

Variable	Arm 1 ($n = 802$, 97.0%)[2]	Arm 2 ($n = 835$, 94.7%)[2]	Arm 3 ($n = 805$, 94.0%)[2]
Maternal age, *n* (%)			
<20 y	154 (19.2)	184 (22.0)	156 (19.4)
20–24 y	352 (43.9)	339 (40.6)	323 (40.1)
≥25 y	296 (36.9)	312 (37.4)	326 (40.5)
Maternal education,* *n* (%)			
No formal schooling	287 (35.8)	252 (30.2)	252 (31.3)
Primary	263 (32.8)	320 (38.3)	328 (40.7)
Secondary or more	252 (31.4)	263 (31.5)	225 (28.0)
Height, cm	151.4 ± 6.6	151.2 ± 7.1[3]	151.2 ± 7.0
BMI, kg/m^2			
Mean ± SD	21.4 ± 4.0	21.4 ± 4.1[3]	21.5 ± 3.9
<20.0	324 (40.4)	347 (41.6)	329 (40.9)
<18.5	189 (23.6)	196 (23.5)	178 (22.1)
Parity, *n* (%)			
0 (nulliparous)	186 (23.2)	165 (19.8)	146 (18.1)
1	244 (30.4)	262 (31.4)	258 (32.0)
≥2	372 (46.4)	408 (48.9)	401 (49.8)
Tally of indicators of higher SES,[4] *n* (%)			
None (0 present)	107 (13.3)	111 (13.3)	109 (13.5)
1–2 present	240 (29.9)	234 (28.0)	219 (27.2)
3–4 present	313 (39.0)	345 (41.3)	333 (41.4)
5–6 present	142 (17.7)	145 (17.4)	144 (17.9)

[1]Values are *n* (%) or means ± SDs. Differences between treatment arms were assessed by chi-square tests and ANOVA. *Significant difference among arms, $P = 0.0081$. SES, socioeconomic status.

[2]Primary outcome obtained from ≥1 live newborns of the woman.

[3]$n = 834$ for height and BMI in Arm 2.

[4]The SES tally provides the number of indicators available from the following list: electricity, improved water source, sanitation, man-made flooring, improved cooking fuels, and household assets.

Given that baseline maternal education varied by treatment arm, the same analyses were repeated adjusting for maternal education. The results did not change in direction or magnitude (data not shown). Similarly, a primary outcome sensitivity analysis adjusted for other maternal factors, including age, parity, and BMI, did not change the results. No important differences were observed according to interpregnancy interval, season of delivery, or mode of delivery among arms (data not shown).

TABLE 3 Combined sites (Democratic Republic of the Congo, Pakistan, India, and Guatemala): growth outcomes by treatment arm among live births with length at birth; comparison of effect sizes and 95% CIs[1]

				Arm 1 vs. 3		Arm 2 vs. 3		Arm 1 vs. 2	
Variable	Arm 1 809 (96.8)[2]	Arm 2 838 (94.7)[2]	Arm 3 812 (93.9)[2]	Effect size (95% CI)	*P* value	Effect size (95% CI)	*P* value	Effect size (95% CI)	*P* value
Length, cm	47.56 ± 2.29	47.59 ± 2.11	47.24 ± 2.17						
LAZ	−1.05 ± 1.22	−1.02 ± 1.11	−1.22 ± 1.14	0.19 (0.08, 0.30)	0.0008	0.20 (0.09, 0.31)	0.0004	−0.01 (−0.12, 0.10)	0.87
Weight, g[3]	2800.1 ± 448.9	2802.7 ± 424.3	2751.6 ± 423.3						
WAZ[3]	−1.13 ± 1.06	−1.12 ± 1.01	−1.25 ± 1.01	0.14 (0.04, 0.24)	0.0054	0.13 (0.03, 0.23)	0.0095	0.01 (−0.09, 0.11)	0.83
BMI[4]	12.33 ± 1.28	12.35 ± 1.21	12.27 ± 1.18						
BMIAZ[4]	−0.93 ± 1.12	−0.91 ± 1.06	−0.97 ± 1.05	0.06 (−0.04, 0.17)	0.21	0.07 (−0.03, 0.17)	0.19	−0.00 (−0.10, 0.10)	0.96
HC, cm[5]	33.21 ± 1.51	33.24 ± 1.42	33.18 ± 1.49						
HCAZ[5]	−0.79 ± 1.21	−0.75 ± 1.14	−0.82 ± 1.18	0.07 (−0.04, 0.18)	0.23	0.08 (−0.03, 0.19)	0.14	−0.02 (−0.13, 0.09)	0.79

[1]*P* values and effect sizes with corresponding 95% CIs comparing mean LAZ, WAZ, BMIAZ, and HCAZ for pairwise comparisons obtained from linear models for the outcome of interest, adjusted for country and cluster-nested within country. For the primary outcome of LAZ at birth, the comparisons of Arm 1 with Arm 2 and Arm 1 with Arm 3 were evaluated at a significance level of $\alpha = 0.025$ when combining data from all sites. *P* values are also provided for the secondary analyses. Because these are exploratory analyses, no correction for multiple comparisons has been made. Values are *n* (%), means ± SDs, or effect size (95% CI). BMIAZ, BMI-for-age *z* score; HC, head circumference; HCAZ, HC-for-age *z* score; LAZ, length-for-age *z* score; WAZ, weight-for-age *z* score.

[2]The primary outcome is among those who completed the assessment visit <48 h after delivery and had length measurements obtained. *z* Scores were calculated using the expanded tables of the Child Growth Standards published by the WHO (30) and are based on term infants. LAZ and WAZ are within the biologically plausible ranges according to the WHO standards. Numbers in parentheses in the column headers are percentages of live births with birth length obtained <48 h of age.

[3]Weight and WAZ: $n = 807$, 836, and 808 for Arms 1, 2, and 3, respectively.

[4]BMI and BMIAZ: $n = 804$, 831, and 806 for Arms 1, 2, and 3, respectively.

[5]HC and HCAZ: $n = 805$, 832, and 806 for Arms 1, 2, and 3, respectively.

GAA newborn anthropometry.

The lower sample size for each outcome compared with corresponding numbers for the NGAA data also reflects the lower numbers for each site who had CRL measurements (**Table 4**). Across the 3 sites and all arms, when we subset to the infants with GA available, adjustment for GA age resulted in 16–45% higher (less negative) LAZ compared with the NGAA data. For example, the overall mean LAZ for Arm 3 in the NGAA analysis was −1.22, compared with −0.88 for the GAA data (Table 4). As for the NGAA data, Arm 1 LAZ did not differ from LAZ for Arm 2. The Arm 1 compared with Arm 3 effect size was again positive for combined sites (+0.20), for India (+0.23), and for Pakistan (+0.35) (**Figure 3**).

Similarly to the continuous outcomes for GAA data, none of the binary outcomes differed between Arm 1 and Arm 2 (**Table 5**). However, there was a reduction in RRs for stunting (LAZ <−2) for combined sites (Table 5) and for both Pakistan and India for Arm 1 compared with Arm 3, but not for Arm 2 compared with Arm 3. There were also reductions in RR for wasting (WLRAZ <−2) for Arm 1 compared with Arm 3 but not Arm 2 compared with Arm 3, for combined sites and for India. Substantial reductions in RR for SGA were evident for Arm 1 compared with Arm 3, for combined sites and for both Pakistan and India (Table 5, **Supplemental Tables 6–8**, and **Figure 4**). A decrease in RR for SGA also occurred for Arm 2 compared with Arm 3, for combined sites and for India but not for Pakistan. No reductions in RRs were observed for Guatemala for any of the aforementioned newborn anthropometric outcomes except WAZ <−2 for Arm 2 compared with Arm 3. The deficits in mean HCAZ were small in comparison with other outcomes; no effects of the interventions on HCAZ were observed (Table 4, Supplemental Tables 6–8).

For combined sites, the incidence of PTB by arm was 12.5%, 8.6%, and 11.5% ($P = 0.0407$) for Arm 1, Arm 2, and Arm 3, respectively, among all live newborns, and 11.7%, 7.4%, and 9.4% ($P = 0.0047$) among live newborns with birth length obtained, respectively (Table 5, Supplemental Tables 6–8). For Guatemala, the incidence of PTB by arm was 11.3%, 6.5%, and 8.0% ($P = 0.1645$) for Arm 1, Arm 2, and Arm 3, respectively, among all live-born infants, and 10.3%, 5.1%, and 3.8% ($P = 0.0123$) among live-born infants with birth length obtained, respectively. The apparent drop in Arm 3 was due to not getting birth measurements on 8 of 14 (57%) of the preterm live births in this group.

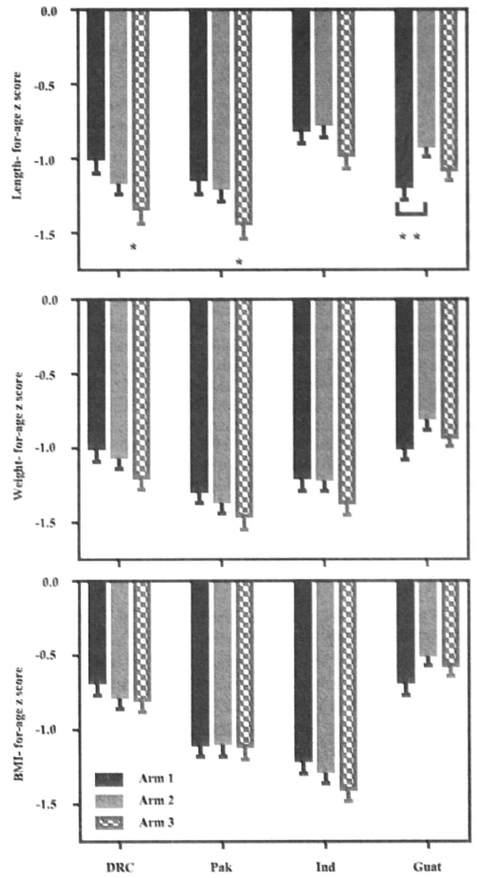

FIGURE 2 Mean ± SEM length-, weight-, and BMI-for-age *z* scores for each site by treatment arm for non-gestational-age-adjusted data. *P* values comparing mean *z* scores for pairwise comparisons of the treatment effect were obtained from linear models for the outcome of interest, adjusted for cluster. Pairwise comparisons of treatment arms within an individual site are evaluated at a significance level of $\alpha = 0.00625$. *Mean length-for-age *z* score for Arm 1 differs from Arm 3 in Pak ($P = 0.0057$) and in DRC ($P = 0.0042$). **Arm 1 differs from Arm 2 in Guat ($P = 0.0044$). Sample size for each arm within a site ranged as follows: $n = 183$–199 (DRC), $n = 201$–236 (Pak), $n = 199$–200 (Ind), and $n = 189$–216 (Guat). DRC, Democratic Republic of the Congo; Guat, Guatemala; Ind, India; Pak, Pakistan.

Discussion

The results of this 4-site trial add substantially to the evidence that poor fetal growth, including linear growth, in low-resource countries can be improved with maternal nutrition supplementation. Specifically, the intervention initiated before conception or late in the first trimester resulted in greater mean birth size (LAZ, WAZ, WLRAZ) and improved rates of stunting, underweight, wasting (WLRAZ < −2), and SGA in comparison with the control arm. Moreover, these benefits are evident in women who were selected without regard for anthropometric or biochemical evidence of malnutrition other than exclusion for severe anemia at baseline. Furthermore, overall improvements in fetal growth occurred despite the wide heterogeneity of the participating sites. With the exception of Guatemala, the mean effect sizes compare favorably with overall results of reported maternal nutrition interventions with either multimicronutrients alone, lipid-based nutrient supplement preparations, or a similar lipid-based protein-energy supplement commencing in mid-gestation (14, 15, 35–38). However, starting the supplement before conception did not result in significantly greater newborn LAZ than starting the same intervention late in the first trimester.

TABLE 4 Combined GAA sites (Pakistan, India, and Guatemala): continuous growth outcomes by treatment arm among live births with GA and length at birth; comparison of effect sizes with 95% CIs[1]

				Arm 1 vs. 3		Arm 2 vs. 3		Arm 1 vs. 2	
Variable	Arm 1 ($n = 489$)[2]	Arm 2 ($n = 517$)	Arm 3 ($n = 459$)	Effect size (95% CI)	*P* value	Effect size (95% CI)	*P* value	Effect size (95% CI)	*P* value
Length, cm	47.57 ± 2.19	47.64 ± 2.36	47.31 ± 2.31						
LAZ	−0.69 ± 0.97	−0.69 ± 1.04	−0.88 ± 1.04	0.20 (0.07, 0.33)	0.0027	0.19 (0.07, 0.32)	0.0029	0.00 (−0.12, 0.13)	0.95
Weight, g	2783.6 ± 441.5	2784.4 ± 438.8	2740.2 ± 408.7						
WAZ	−0.90 ± 0.93	−0.95 ± 0.94	−1.06 ± 0.93	0.17 (0.06, 0.29)	0.0036	0.12 (0.00, 0.23)	0.0455	0.06 (−0.06, 0.17)	0.33
WLR[3]	5.85 ± 0.72	5.84 ± 0.71	5.79 ± 0.66						
WLRAZ[3]	−1.22 ± 1.34	−1.31 ± 1.31	−1.43 ± 1.31	0.22 (0.06, 0.38)	0.0081	0.14 (−0.02, 0.30)	0.10	0.08 (−0.08, 0.24)	0.30
HC, cm[4]	33.01 ± 1.42	33.05 ± 1.48	33.00 ± 1.49						
HCAZ[4]	−0.47 ± 1.03	−0.47 ± 1.05	−0.52 ± 1.08	0.06 (−0.08, 0.19)	0.40	0.06 (−0.07, 0.19)	0.37	0.00 (−0.13, 0.13)	0.96

[1] *P* values and effect sizes with corresponding 95% CIs comparing mean LAZ, WAZ, HCAZ, and WLRAZ for pairwise comparisons obtained from linear models for the outcome of interest, adjusted for country and cluster-nested within country. Because these are exploratory analyses, no correction for multiple comparisons has been made. Values are mean ± SD or effect size (95% CI). GA, gestational age; GAA, gestational-age adjusted; HC, head circumference; HCAZ, HC-for-age *z* score; LAZ, length-for-age *z* score; WAZ, weight-for-age *z* score; WLR, weight to length ratio; WLRAZ, WLR-for-age *z* score.

[2] Number of participants with primary outcome and GA determined. The primary outcome is among those who completed the assessment visit <48 h after delivery and had length measurements obtained. LAZ, WAZ, HCAZ, and WLRAZ calculated using the INTERGROWTH-21st Project standards which provide *z* scores by sex and GA at birth for infants between 33 wk + 0 d and 42 wk + 6 d GA at birth (32) and between 24 wk + 0 d and 32 wks + 6 d GA at birth (33). GA at birth is defined as the GA at the time of the ultrasound based on the ultrasound plus time until birth if the ultrasound was done between 6 wk + 0 d and 13 wk + 6 d and GA at birth was between 24 wk + 0 d and 42 wk + 6 d. If the ultrasound was not conducted during this time, GA at birth was set to missing.

[3] WLR and WLRAZ: $n = 484$, 514, and 455 for Arms 1, 2, and 3, respectively.

[4] HC and HCAZ: $n = 488$, 516, and 459 for Arms 1, 2, and 3, respectively.

The RRs for binary outcomes and some of the effect sizes for continuous variables reported here were not included in the original proposal and should be regarded as exploratory. In this context, however, there are informative differences illustrating the heterogeneity between sites. Effect sizes for comparison of LAZ between the preconception and control arms were substantial in both Pakistan and DRC where they approached the effect size hypothesized in the original proposal (25). A similar pattern was evident for RRs of binary measures of linear growth, especially for stunting (LAZ <−2) and also to a lesser degree for impaired linear growth (LAZ <−1), which has predictive value for postnatal growth (7, 39). Corresponding responses to the intervention compared with controls were observed for weight-related outcomes, both continuous and binary. SGA was especially high in India, and substantial reductions in RRs for both SGA and WLRAZ were associated with the intervention, most notably with the preconception intervention (Figure 3). Consistent with this, effects of the intervention on LBW were also observed for the 4 sites combined (NGAA data). In Guatemala, no positive outcomes were observed for either continuous or binary variables for Arm 1 and Arm 3 comparisons.

The primary intervention for which we have detailed information on compliance was similar to a widely used small-quantity lipid-based nutrient supplement with modest protein and energy content and micronutrient amounts appropriate for pregnancy

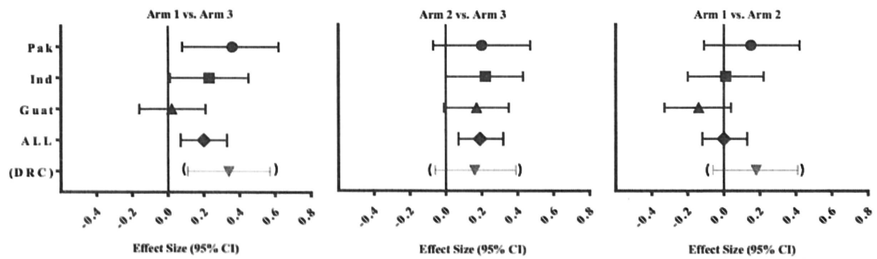

FIGURE 3 Effect sizes and 95% CIs for pairwise comparisons of the difference in mean length-for-age *z* scores at birth by treatment arm, by site and for combined sites. Effect sizes with corresponding 95% CIs obtained from linear model, adjusted for clusters. The combined site analysis is adjusted for country and cluster-nested within country. GAA data (31) presented for all individual sites except for the DRC which is not adjusted for gestational age (30). "All" represents combined data from the 3 sites with GAA data available (Pak, Ind, and Guat; $n = 459$–517 per arm). Sample size for each arm within a site ranged as follows: $n = 141$–160 (Pak), $n = 158$–184 (Ind), $n = 156$–177 (Guat), and $n = 183$–199 (DRC). DRC, Democratic Republic of the Congo; GAA, gestational-age adjusted; Guat, Guatemala; Ind, India; Pak, Pakistan.

TABLE 5 Combined GAA sites (Pakistan, India, and Guatemala): binary growth outcomes by treatment arm among live births with GA and length at birth; comparison of RRs with 95% CIs[1]

				Arm 1 vs. 3		Arm 2 vs. 3		Arm 1 vs. 2	
Variable	Arm 1 ($n = 489$)[2]	Arm 2 ($n = 517$)	Arm 3 ($n = 459$)	RR (95% CI)	*P* value	RR (95% CI)	*P* value	RR (95% CI)	*P* value
LAZ <−1	175 (35.8)	194 (37.5)	201 (43.8)	0.82 (0.72, 0.93)	0.0019	0.86 (0.75, 0.98)	0.0205	0.95 (0.81, 1.12)	0.57
LAZ <−2	49 (10.0)	57 (11.0)	65 (14.2)	0.69 (0.49, 0.98)	0.0361	0.78 (0.57, 1.07)	0.12	0.89 (0.64, 1.24)	0.48
WAZ <−2	62 (12.7)	59 (11.4)	79 (17.2)	0.71 (0.56, 0.90)	0.0049	0.66 (0.50, 0.85)	0.0017	1.08 (0.85, 1.38)	0.51
WLRAZ <−2[3]	128 (26.4)	157 (30.5)	155 (34.1)	0.76 (0.65, 0.89)	0.0005	0.88 (0.76, 1.02)	0.09	0.87 (0.75, 1.00)	0.0435
HCAZ <−2[4]	36 (7.4)	33 (6.4)	35 (7.6)	0.93 (0.62, 1.40)	0.73	0.83 (0.59, 1.18)	0.31	1.12 (0.71, 1.76)	0.63
SGA	161 (32.9)	185 (35.8)	188 (41.0)	0.78 (0.70, 0.88)	<0.001	0.87 (0.78, 0.96)	0.0047	0.90 (0.79, 1.04)	0.15
LBW	118 (24.1)	119 (23.0)	125 (27.2)	0.86 (0.72, 1.04)	0.11	0.85 (0.70, 1.02)	0.08	1.02 (0.80, 1.29)	0.88
Incidence of PTB, all live	63 (12.5)	46 (8.6)	56 (11.5)	1.05 (0.79, 1.41)	0.73	0.74 (0.50, 1.09)	0.12	1.43 (1.08, 1.89)	0.0117
Incidence of PTB, with LAZ	57 (11.7)	38 (7.4)	43 (9.4)	1.18 (0.82, 1.71)	0.38	0.77 (0.50, 1.20)	0.25	1.52 (1.18, 1.97)	0.0014

[1] *P* values and RRs with corresponding 95% CIs comparing proportion of LAZ <−1, LAZ <−2, WAZ <−2, HCAZ <−2, WLRAZ <−2, SGA, and LBW for the pairwise comparisons are obtained from generalized linear models with generalized estimating equations to estimate parameters while controlling for cluster correlations. Models are adjusted for country. Because these are exploratory analyses, no correction for multiple comparisons has been made. Values are *n* (%) or RR (95% CI). GA, gestational age; GAA, gestational-age adjusted; HCAZ, head circumference-for-age *z* score; LAZ, length-for-age *z* score; LBW, low birth weight; PTB, preterm birth; SGA, small-for-gestational-age; WAZ, weight-for-age *z* score; WLRAZ, weight to length ratio-for-age *z* score.

[2] Number of participants with primary outcome and GA determined. The primary outcome is among those who completed the assessment visit <48 h after delivery and had length measurements obtained. LAZ, WAZ, HCAZ, and WLRAZ were calculated using the INTERGROWTH-21st Project standards which provide *z* scores by sex and GA at birth for infants between 33 wk + 0 d and 42 wk + 6 d GA at birth (32) and between 24 wk + 0 d and 32 wk + 6 d GA at birth (33). GA at birth is defined as the GA at the time of the ultrasound based on the ultrasound plus time until birth if the ultrasound was done between 6 wk + 0 d and 13 wk + 6 d and GA at birth was between 24 wk + 0 d and 42 wk + 6 d. If the ultrasound was not conducted during this time, GA at birth is set to missing.

[3] WLRAZ <−2: $n = 484$, 514, and 455 for Arms 1, 2, and 3, respectively.

[4] HCAZ <−2: $n = 488$, 516, and 459 for Arms 1, 2, and 3, respectively.

and lactation (28). An additional protein-energy supplement was provided to women who were underweight or had low gestational weight gain. The latter reason accounted for provision of the second supplement to >90% of women in both Arms 1 and 2 (except for Guatemala) starting at some stage in the second or third trimester and continuing until delivery. Participants were encouraged to consume this second supplement but the actual amount was left to the woman's discretion in order to minimize interference with consumption of the habitual diet. That this guideline was effective for Arm 1 was indicated by the lack of any difference in energy consumption from local food between Arms 1 and 2 during the first trimester in a random subsample (27). Despite provision of the protein-energy supplement, the average gestational weight gain through 32 wk remained low relative to international recommendations (40). Both low prepregnancy weight and gestational weight gain <8 kg have been associated with LBW and SGA rates, and these factors may have been relevant to outcomes in the current trial (22).

This trial coincided with growing interest in the potential value of preventing or correcting maternal undernutrition before conception (11, 18, 41). One trial of preconception multimicronutrient maternal supplements conducted in Vietnam demonstrated a modest improvement in iron stores but no impact on birth outcomes (24). Results of an a priori secondary analysis from a food-based intervention trial targeting a poor urban population in India were consistent with an increase in birth weight if the supplement was commenced ≥3 mo before conception. The

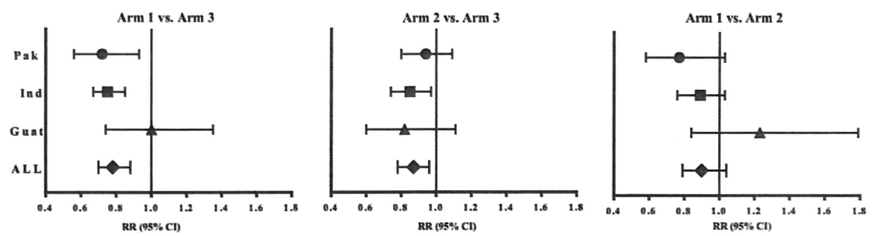

FIGURE 4 RRs and 95% CIs for pairwise comparisons of SGA by treatment arm, by site, and for combined sites (31). RRs with corresponding 95% CIs comparing proportions of SGA for the pairwise comparisons are obtained from generalized linear models with generalized estimating equations to estimate parameters while controlling for cluster correlations. For combined data, models are adjusted for country. Women First newborn measurements based on those with gestational age data. "All" comprised combined data from Pak, Ind, and Guat. Sample sizes for each arm within a site ranged as follows: $n = 141$–160 (Pak), $n = 158$–184 (Ind), $n = 156$–177 (Guat), and $n = 459$–517 (All). Guat, Guatemala; Ind, India; Pak, Pakistan; SGA, small for gestational age.

results of that trial also differed by maternal prepregnancy weight status, with no overall impact of the intervention on birth weight, the primary outcome, but a significant interaction such that birth weight, birth length, and rates of LBW were improved in women with BMI >21.8 at baseline (21).

A major weakness of the trial was the inability to determine GA in the DRC with the resultant loss of the sub-Saharan African site for the GAA data. This loss detracted from the global scope of the trial. Moreover, the DRC had the most favorable Arm 1 compared with Arm 3 improvement in mean LAZ based on the NGAA data. Subject numbers were further reduced for GAA data, both combined and in the other 3 sites, especially in Pakistan, due to failure to obtain a first-trimester ultrasound in all participants. Final numbers for this post hoc GAA analysis were thus well below those available for the trial primary outcome analysis predicated on NGAA LAZ at birth. Another factor adversely affecting effect sizes and RRs for combined sites was the negative Arm 1 result for the Guatemala site. We speculate that this outcome was attributable, in part, to the high proportion of Arm 3 preterm infants who did not have primary outcome measures. These losses were for diverse reasons apparently unrelated to the trial. Support for this explanation has been derived from disappearance of the negative Arm 1 compared with Arm 3 results for LAZ for Guatemala newborns delivered at term only (data not presented). However, it remains disappointing and unexplained that there was no indication of a positive effect on fetal linear growth in this indigenous population with exceptionally high rates of stunting but with a substantially lower proportion of maternal underweight than in the other 3 sites (34). It is possible that potential benefits of the Arm 1 intervention to the linear growth of this population may be discernible in the next generation [i.e., those born to the female infants in the current study (42)]. Primary reliance on participants' reported consumption of the supplements represents a potential weakness. This was mitigated by the biweekly home visits which provided opportunities for the field staff to work closely with mothers to identify palatable ways to consume the supplements and frequently to observe consumption.

Notable features of this trial included the diverse low-resource sites in which it was conducted, in 4 countries across 3 continents. The participating women, who had wide differences in diet, culture, socioeconomic status, and education, were not selected on the basis of current evidence of undernutrition except for at least temporary exclusion if hemoglobin was <8 g/dL. The trial was unusual in testing the effects of a relatively comprehensive combination of nutrition products (i.e., those containing micronutrients as well as a protein-energy supplement). Finally, the trial is one of very few that have addressed the huge potential challenge of preventing or correcting undernutrition of both micronutrients and macronutrients in females of reproductive age before conception.

In resource-poor rural or semirural populations in which there is a high prevalence of stunting, fetal growth was improved with maternal nutrition supplements commenced either before conception or late in the first trimester and provided to women irrespective of their own nutritional status. This improvement was achieved without the support of nutrition education and without any attention to other environmental factors associated with impaired fetal and early postnatal growth. Results for sites were heterogeneous with improvements in newborn LAZ, the primary outcome, ranging from zero to more than one-third of deficits. Results were more favorable than most reported data for maternal nutrition supplements initiated during pregnancy, which could be attributable to the timing of the initiation of the supplements. Despite the trial's failure to achieve optimal maternal gestational weight gain and to support its principal primary hypothesis, the results of data analyses undertaken within a hypothesis-generating framework suggest that further work is needed. Meanwhile, the results are strongly supportive of strategies to improve inadequate nutrition in women, commencing before conception or very early in gestation.

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The authors' responsibilities were as follows—KMH and NFK: conceived the original idea and designed the initial protocol; KMH, NFK, JEW, EMM, and AD: wrote the final protocol in collaboration with all members of the trial group (NFK, KMH, JEW, AG, LF, SSG, SMD, OP, SAA, AT, AL, RJD, RLG, CLB, MB, MK-T, VRT, AS, KS, AD, EMM, and members of the Women First Preconception Trial Group listed below); KMH, NFK, and JEW: prepared the manuals for field operations in collaboration with the staff members of the Data Coordinating Center (KS, VRT, EMM, AD); NFK, KMH, JEW, KS, VRT, and EMM: coordinated the overall execution of the trial; AG, LF, SSG, SMD, OP, SAA, AT, and AL: coordinated the implementation of the study at the country level; AD: wrote the plan of analysis in collaboration with VRT, EMM, NFK, and KMH; VRT, AS, and AD: performed the statistical analysis in collaboration with EMM; NFK and KMH: wrote the report with close collaboration with VRT, AS, EMM, AD, and with input from all authors; and all authors: read and approved the final version of the manuscript. None of the authors reported a conflict of interest related to the study.

Women First Preconception Trial Study Group: Rebecca L. Lander, Instructor (University of Colorado Anschutz Medical Campus, United States); Gabriela Tejeda, Nutritionist (INCAP, Guatemala); Bhalchandra Kodkany, Professor, Manjunath S Somannavar, Professor, and Veena Herekar, Assistant Professor (KLE Academy of Higher Education and Research's Jawaharlal Nehru Medical College, Belagavi, India); Sarah Saleem, Professor, and Umber Khan, Nutritionist (Aga Khan University, Pakistan); Menachem Miodovnik, Medical Officer and Tonse NK Raju, Chief (Pregnancy and Perinatology Branch, National Institute of Child Health and Human Development/NIH, United States).

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Estado de micronutrientes en madres y niños de Guatemala

Expositor: Omar Dary, PhD
Experto en Nutrición y Micronutrientes

Sistema de Vigilancia Epidemiológica de Salud y Nutrición -SIVESNU- 2016

Informe Final

Octubre 2018

E. Seguridad alimentaria en el hogar

1. Índice de seguridad alimentaria

En el año 2016 se utilizó la metodología de la Escala Latinoamericana y Caribeña de Seguridad Alimentaria – ELCSA -, la cual había sido incorporada a los esfuerzos de la Encuesta Nacional de Condiciones de Vida – ENCOVI – en los años 2011 y 2014 (17). En el cuadro a continuación se presenta el consolidado de las respuestas correspondientes a las ocho preguntas centrales de la ELCSA que utilizan un marco de referencia de los tres meses previos a la entrevista. Con base en estas ocho preguntas de la escala para evaluar niveles de inseguridad alimentaria, se puede concluir que 20.5% de las familias visitadas tienen un nivel adecuado de seguridad alimentaria, 58.4% se ubican en inseguridad alimentaria leve y moderada y 15.2% en severa.

Cuadro E.1
Distribución de hogares según condiciones de seguridad e inseguridad alimentaria en el hogar, SIVESNU 2016

Condición	Hogares	
1. En los últimos 3 meses, por falta de dinero u otros recursos, alguna vez, ¿usted se preocupó de que los alimentos se acabaran en su hogar?	n	% (n = 2382)
Si	1668	70.0
No	708	29.7
No sabe/no responde	1	0.0
2. En los últimos 3 meses, por falta de dinero u otros recursos, alguna vez, ¿en su hogar se quedaron sin alimentos?	n	% (n = 2382)
Si	815	34.2
No	1559	65.4
No sabe/no responde	5	0.2
3. En los últimos 3 meses, por falta de dinero u otros recursos, alguna vez, ¿en su hogar dejaron de tener una alimentación saludable y balanceada?	n	% (n = 2382)
Si	1155	48.5
No	1216	51.0
No sabe	6	0.2
4. En los últimos 3 meses, por falta de dinero u otros recursos, alguna vez, ¿usted o algún adulto en su hogar tuvo una alimentación basada en poca variedad de alimentos?	n	% n = 2382
Si	1249	52.4
No	1119	47.0
No sabe	5	0.2
5. En los últimos 3 meses, por falta de dinero u otros recursos, alguna vez, ¿usted o algún adulto en su hogar dejó de desayunar, almorzar o cenar?	n	% n = 2382)
Si	522	21.9
No	1849	77.6
No sabe	4	0.1
6. En los últimos 3 meses, por falta de dinero u otros recursos, alguna vez, ¿usted o algún adulto en su hogar comió menos de lo que debía?	n	% n = 2382)
Si	809	34.0
No	1547	64.9
No sabe	11	0.4
7. En los últimos 3 meses, por falta de dinero u otros recursos, alguna vez, ¿usted o algún adulto sintió hambre, pero no comió?	n	% n = 2382)
Si	589	24.7
No	1775	74.5
No sabe	9	0.4

Condición	Hogares	
8. En los últimos 3 meses, por falta de dinero u otros recursos, alguna vez, ¿usted o algún adulto en su hogar comió solo una vez al día o dejó de comer todo un día?	n	% (n =2382)
Si	408	17.1
No	1955	82.1
No sabe	7	0.3
Categorías de Seguridad Alimentaria*	n	% (n =2382)
Seguridad	488	20.5
Inseguridad leve	892	37.4
Inseguridad moderada	501	21.0
Inseguridad severa	362	15.2
Total	2382	100.0

2. Disponibilidad y uso de alimentos fortificados en el hogar

Los datos sobre el tipo de sal utilizada en el hogar se presentan en el cuadro E.2 y gráfica E.1 a continuación. Se observa que la mayor parte de familias utilizaba la sal gruesa (88.6%) y la sal fina (21.9%) y que únicamente 31 familias indicaron consumir sal de mina. La disponibilidad diaria per cápita de sal gruesa o fina que se obtuvo en esta encuesta oscila entre los 15.9 y los 9.4 gramos, respectivamente. Del total de hogares visitados que reportaron usar algún tipo de sal, fue posible observar paquetes de sal gruesa en 88.1% y de sal fina en 57.9% de esos hogares. En 59.0% de los hogares en que se consumió sal gruesa se observó que ésta no tiene marca, y que en 67.2% de los hogares en que se consumió sal fina tampoco mostraron sal con marca, lo que imposibilita la revisión de la etiqueta para observar si la etiqueta de sal dice que está o no yodada. En la parte inferior del cuadro se incluyen las marcas de sal que fueron identificadas en la visita al hogar y de las que se obtuvo muestra para análisis.

Cuadro E.2
Distribución de hogares según adquisición y uso de sal en el hogar, SIVESNU 2016

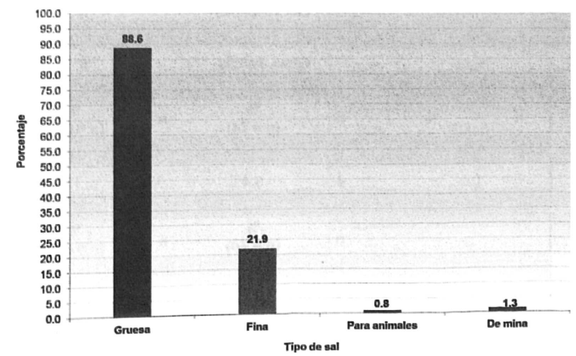
Característica de adquisición/uso de sal	Tipo de sal							
	Gruesa		Fina		Para animales		De mina	
Tipo de sal que se usa en el hogar	n	%* (n=2381)	n	%* (n=2381)	n	%* (n=2381)	n	%* (n=2381)
	2110	88.6	522	21.9	20	0.8	31	1.3
Disponibilidad per cápita/día (gramos)	n	Media	n	Media	n	Media	n	Media
	2101	15.9	521	9.4	20	39.7	nd**	nd**
Informante mostró sal cuando tenía en el hogar	n	% (n=2110)	n	% (n=522)	n	% (n=20)	n	%
Si mostró sal	1861	88.1	302	57.9	10	50.0	--	--
Marca de sal en el hogar	n	% (n=1859)	n	% (n=302)	n	% (n=10)	n	%
Sin marca	1245	59.0	203	67.2	10	100.0	--	--
Marca nacional	611	29.0	64	21.2	0	0.0	--	--
Marca importada	3	0.1	35	11.6	0	0.0	--	--

Sal Gruesa			Sal Fina		
Nombres de marcas	**N**	**%**	**Nombres de marcas**	**n**	**%**
La Joya	55	9.0	Oso Blanco	6	9.2
Diamante	57	9.3	Ya está	15	23.1
Agua Marina	25	4.1	Beatriz	1	1.5
Marea Azul (Marca azul)	46	7.5	Sabemas	13	20.0
Alibas	39	6.4	Radiante	3	4.6
Oso Blanco	11	1.8	Agua Marina	3	4.6
Guadalupana	39	6.4	San Pablo	2	3.1
Mariposa	10	1.6	Gallo Pinto	2	3.1
San Pablo	27	4.4	Del Mar	5	7.7
El Ancla	38	6.2	Guadalupana	1	1.5
Rama Blanca	21	3.4	La Fina	4	6.2
Salita - San Juan	20	3.3	Marea Azul	5	7.7
Probasal	7	1.1	San Pedro Salinas	2	3.1
Oriental	12	2.0	La Joya	1	1.5
Sabemas	10	1.6	Sal de Mesa Refinada	1	1.5
Blanquita	13	2.1	Salita	1	1.5
B & Z	27	4.4	**TOTAL**	**65**	**100.0**
San Francisco	7	1.1			
Gallo Pinto	18	2.9			
Salinda	10	1.6			
El Cristal	12	2.0			
La Ola Azul	14	2.3			
Sal del Mar	26	4.2			
Saltrasa	10	1.6			
San Pedro Salinas	13	2.1			
El Semillero	6	1.0			
Rosario	8	1.3			
Otras	31	5.3			
TOTAL	**612**	**100.0**			

*Opciones de respuesta múltiple
**No disponible porque no se hizo estimación de este tipo de sal

Indicación de yodo en etiqueta	Gruesa		Fina		Para animales		De mina	
	n	% (n=614)	n	% (n=99)	n	%	n	%
Dice yodada	610	99.3	99	100.0	0	0.0	0	0.0
No dice yodada	4	0.7	1	0.2	0	0.0	0	0.0

Gráfica E.1
Distribución de hogares (n=2381) según tipo de sal que se usa, SIVESNU 2016



La mayor parte de familias (91.1%) utilizaba el azúcar normal o estándar, según el cuadro E.3 y la gráfica E.2. La disponibilidad diaria per cápita de azúcar normal, cuyo consumo es casi universal, fue de 63.7 gramos. Del total de hogares visitados que reportaron usar algún tipo de azúcar fue posible observar paquetes de azúcar normal en 85.5% de los que la usan y de azúcar morena en 50.7% de los hogares que la usan. En 52.5% de los hogares en que se consumió azúcar normal que fue mostrada, los paquetes no tenían marca, lo cual imposibilita cotejar si la etiqueta dice que está o no fortificada por observación. Se destaca, además, que del total de paquetes de azúcar normal que fueron mostrados en la visita al hogar y que tenían etiqueta de marca, el 98.6% de ellos indicaba que el azúcar tenía vitamina A y tenían, también, ojo rojo o verde el 98.9%.

Cuadro E.3
Distribución de hogares según adquisición y uso de azúcar en el hogar, SIVESNU 2016

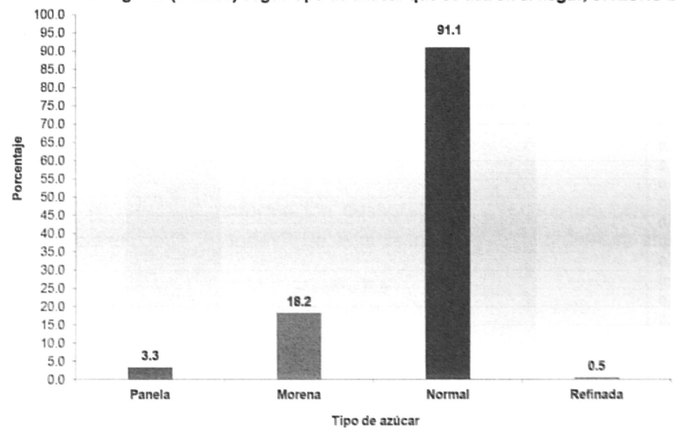
Característica de adquisición y uso de la azúcar	Tipo de azúcar							
	Panela		Morena		Normal		Refinada	
Tipo de azúcar que se usa en el hogar	n	%* (n=2380)	n	%* (n=2380)	n	%* (n=2380)	n	%* (n=2380)
	78	3.3	432	18.2	2169	91.1	13	0.5
Disponibilidad per cápita/día (gramos)	n	Media	n	Media	n	Media	n	Media
	--	--	430	56.7	2162	63.7	13	55.1
Informante mostró azúcar cuando tenía en el hogar	n	%	n	% (n=432)	--	% (n=2169)	n	% (n=13)
Si mostró azúcar	--	--	219	50.7	1854	85.5	7	53.8
Marca de azúcar en el hogar	n	%	n	% (n=219)	n	% (n=1854)	n	% (n=7)
Sin marca	--	--	146	66.7	974	52.5	4	57.1
Marca nacional	--	--	70	32.0	892	48.1	3	42.9
Marca importada			4	1.8	5	0.6	---	---

* Respuesta múltiple

Morena			Normal		
Nombres de marcas	**n**	**% (n=70**	**Nombres de marcas**	**n**	**% (n=890)**
Los Tulipanes	69	98.6	La Montaña	328	36.9
La Montaña / Morenaza	1	1.4	Caña Real	473	53.1
			Los Tulipanes	3	0.3
			Don Justo Cabal	82	9.2
			Otras marcas	6	0.5

	Panela		Morena		Normal		Refinada	
Indicación de Vitamina A en etiqueta	n	%	n	% (n = 74)	n	% (n = 895)	n	%
Dice Vitamina A	--	--	69	93.2	882	98.6	--	--
No dice Vitamina A	--	--	4	5.4	11	1.2	--	--
No tiene etiqueta	--	--	1	1.4	2	0.2	--	--
Empaque tiene ojo rojo o verde			n	% (n = 74)	n	% (n = 889)	n	%
Tiene	--	--	70	94.6	879	98.9	--	--
No tiene	--	--	2	2.7	7	0.8	--	--
Fecha de vencimiento			n	% (n = 73)	n	% (n = 877)	n	%
Hay fecha	--	--	73	100.0	865	98.6	--	--
No hay fecha	--	--	-	-	8	0.9	--	--

Gráfica E.2
Distribución de hogares (n=2380) según tipo de azúcar que se usa en el hogar, SIVESNU 2016



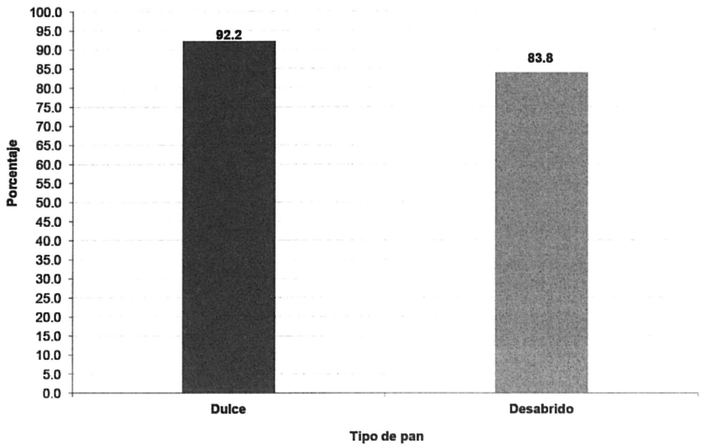
El porcentaje de hogares que indicó que consumían pan dulce y desabrido o francés fue 92.2% y 83.8%, respectivamente (cuadro E.4 y gráfica E.3), y la disponibilidad diaria per cápita de ambos fue de 1.0 y 1.2 unidades, también respectivamente. Se destaca que la totalidad del pan dulce y el 96.5% del pan desabrido que fueron mostrados no tenían marca, por lo que es imposible verificar si la etiqueta dice que esta fortificado con hierro.

Cuadro E.4
Distribución de hogares según adquisición y uso de pan en el hogar, SIVESNU 2016

Característica de adquisición y uso de pan	Tipo de pan			
	Dulce		Desabrido	
Consumo de pan en el hogar	n	%* (n = 2375)	n	%* (n =2377)
Consumen pan en el hogar	2189	92.2	1993	83.8
No consumen pan en el hogar	186	7.8	384	16.2
Disponibilidad per cápita por día (unidades)	n	Media	n	Media
	2188	1.0	1988	1.2
Informante mostró pan cuando tenía en el hogar	n	% (n = 305)	n	% (n = 205)
Si mostró pan	276	90.5	174	84.9
Marca de pan	n	% (n = 276)	n	% (n = 173)
Sin marca	276	100.0	167	96.5
Marca nacional	0	0.0	6	3.5
Marca importada	0	0.0	0	0.0
Etiqueta indica hierro	n	%	n	% (n = 6)
Etiqueta dice hierro	--	--	3	50.0

*Respuesta múltiple

Gráfica E.3
Distribución de hogares que consumieron pan dulce (n=2375) y pan desabrido (n=2377) en el hogar el día de la entrevista, SIVESNU 2016



El 28.3% de las familias indicaron consumo de harina de maíz, como se aprecia en el cuadro E.5. Del total de paquetes que fueron mostrados, 72.4% tenían marca nacional. 21.8% marca importada y el resto no tenían marca. La etiqueta en 96.2% de los paquetes revisados indicaba que el producto estaba fortificado con hierro.

Cuadro E.5
Distribución de familias según adquisición y uso de harina de maíz en el hogar, SIVESNU 2016

Característica de adquisición y uso de harina de maíz	Hogares	
Disponibilidad de harina de maíz en el hogar	n	% (n = 2377)
Usan harina de maíz en el hogar	672	28.3
Disponibilidad per cápita por día (gramos)	n	Media
	671	48.9
Informante mostró harina	n	% (n = 184)
Si mostró harina de maíz	165	89.7
Marca de harina de maíz	n	% (n = 170)
Sin marca	10	5.9
Marca nacional	123	72.4
Marca importada	37	21.8
Etiqueta indica hierro	n	% (n = 157)
Dice hierro en la etiqueta	151	96.2
Marca	n	% (n = 157)
MASECA	118	75.2
Del Comal	24	15.3
Otras	18	9.5

3. Niveles de fortificación de los alimentos en el hogar

a. Yodo en sal

Del total de muestras de sal obtenidas (553), 30.7% presentaron niveles de 15-39.9 mg de yodo/kg de sal, categoría que corresponde a niveles adecuados de yodo en sal según el Fondo de las Naciones Unidas para la Infancia (UNICEF) (19). El promedio de yodo en las muestras fue de 24.0 mg/kg.

En el cuadro E.6 se resume la información desagregada en diferentes concentraciones, evidenciándose que el programa todavía no alcanza los niveles de cobertura esperados.

Cuadro E.6
Yodo en muestras de sal, muestras de hogar, SIVESNU 2016

Información	Categorías							
	< 5.0 Sin yodo	5.0-14.9 Inadecuado	15.0-39.9 Adecuado	≥ 40.0 Sobre-yodado	n	Media (mg/kg)	DE	Rango (mg/kg)
Total de casos	175	96	170	112	553	24.0	26.1	0.4 -147.2
%	31.6	17.4	30.7	20.3				
% acumulado	31.6	49.0	79.7	100.0				

En Guatemala, el Acuerdo Gubernativo 29-2004 – 'Reglamento para la Fortificación de la Sal con Yodo y Sal con Yodo y Flúor' – indica que los niveles de yodo en sal en centros productores/fortificadores y expendios deben estar entre 20 y 60 mg de yodo/kg de sal. Los resultados que se presentan a continuación corresponden a muestras recolectadas en hogares que no están sujetas al cumplimiento de los niveles de yodo estipulados en el Acuerdo Gubernativo en mención.

Sin embargo, para que el programa tenga el efecto esperado, se debe cumplir con los niveles indicados en la ley para asegurar niveles de yodo adecuados en la sal que se consume en los hogares. El monitoreo a nivel de hogar aborda tres aspectos clave del desempeño del programa: provisión, utilización y cobertura. En este informe únicamente se analiza la cobertura de fortificación en las muestras tomadas en los hogares seleccionados.

Con esta información se evidencia que el programa de fortificación de sal con yodo no está cumpliendo con la cobertura de fortificación que se espera encontrar en 90% de hogares con niveles de yodo de 15-39.9 mg/kg. Sólo 30.7% de las muestras cumplía con este criterio, 31.6% no contenían yodo, 17.4% presentaron nivel inadecuado. Adicionalmente el 20.3% (n=112) de muestras presentaron niveles de yodo por arriba de 40 mg/kg.

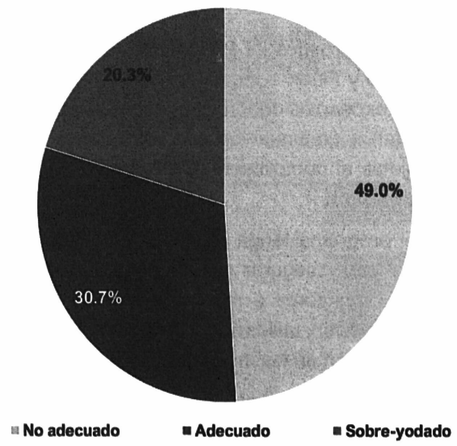
Esta variación es de esperar debido a que la fortificación de la sal con yodo todavía es un proceso que produce alta variabilidad debido a que la sal tiene un alto contenido de humedad incidiendo en la homogeneidad del proceso de fortificación cuya variación puede ser de hasta el 100%. Los valores altos no son de preocupación, pero indican que se debe prestar atención al programa para mejorar la cobertura y variabilidad del proceso de fortificación.

La legislación no incluye los niveles de yodo que deben contener las muestras de sal en los hogares. Sin embargo, para que en hogares se llegue a los niveles de ingesta necesarios para cubrir el requerimiento de yodo al día, asumiendo un consumo de 10 gramos de sal por persona al día, la concentración de yodo en sal debiera ser de 15 mg/kg, para llegar a un consumo promedio, o de 150 µg al día, que cubre las Recomendaciones Dietéticas Diarias (RDD) de casi todos los grupos, exceptuando las mujeres embarazadas cuyos requerimientos son mayores (220 µg).

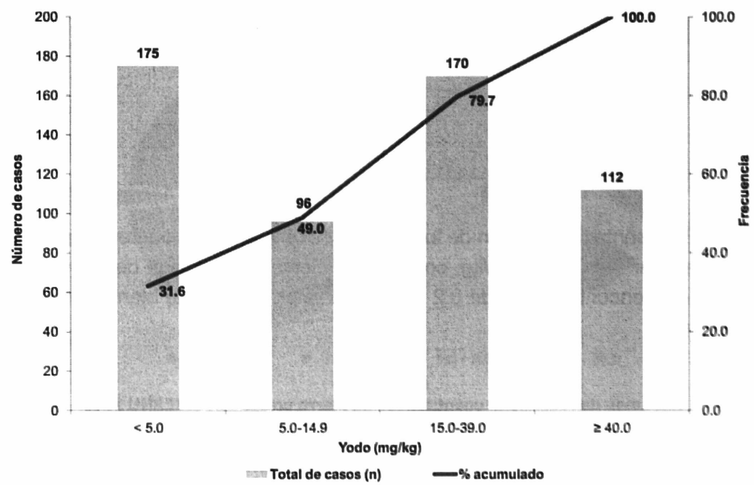
El Reglamento de fortificación de sal exige el cumplimiento de la yodación de la sal para la industria alimentaria, lo que explicaría que, a pesar de una cobertura baja en la concentración de yodo esperado en los hogares como concentración mínima (15 mg/kg), los datos de yoduría no evidencian un problema serio de deficiencia para la mayoría de la población, con la excepción de mujeres embarazadas.

En la Gráfica E.4 se observa la baja cobertura a nivel de hogares del programa de fortificación de la sal con yodo adecuado (30.7%).

Gráfica E.4
Muestras de sal en hogares (n=553) con niveles adecuados de yodo (15-39.9 mg/kg), SIVESNU 2016



Gráfica E.5
Yodo en sal (n = 553), frecuencias y porcentaje acumulado, SIVESNU 2016



b. Hierro en azúcar

Se detectó hierro en el 100% de las muestras de azúcar (Cuadro E.7). El 60.8% de muestras tenían niveles de hierro por debajo de 1.4 mg/kg, 15.5% tenían niveles de hierro entre 1.4 y 5.0 mg/kg, y 19.0% entre 5.0 y <12.0 mg/kg. Es importante mencionar que según la Tabla de Composición de Alimentos de Centroamérica (16) del Instituto de Nutrición de Centro América y Panamá (INCAP), la azúcar blanca granulada (Código 15001) y la azúcar blanca granulada fortificada con vitamina A (Código 15002) contienen 1.0 mg de hierro intrínseco por kg de azúcar. Estos datos son previos a la fortificación del azúcar con hierro. El contenido intrínseco para azúcar morena o negra (Código 15003) es de 1.91 mg de hierro por kg de azúcar.

Con base en esto, es probable que el contenido de hierro abajo de 1.0 y 2.0 mg de hierro/kg de azúcar obtenido en las muestras corresponda al contenido intrínseco de hierro en todo el azúcar. Los productores reportan que el nivel de fortificación con hierro es de 6 a 12 mg/kg. Se calcularon algunos percentiles de interés para los datos de microgramos por kilogramo[7].

[7] Se obtuvieron los siguientes resultados: para 5%, 0.40; para 25%, 0.60; para 50%, 0.90; para 75%, 4.25, y para 95%, 8.92.

Cuadro E.7
Distribución del contenido de hierro en muestras de azúcar seleccionadas, SIVESNU 2016

Hierro (mg/kg)	n	%
<0.5	38	14.7
0.5 – <1.4	119	46.1
1.4- 5.0	40	15.5
>5.0 -12	59	22.9
> 12	2	0.8
Total	**258**	**100.0**

El Cuadro E.8 presenta un resumen de los resultados obtenidos. El contenido promedio de hierro en el azúcar fue de 2.6 mg/kg, con un coeficiente de variación del 95.5%. El valor mínimo de hierro encontrado fue de 0.2 mg/kg. El valor máximo de hierro encontrado fue de 13.9 mg/kg.

Cuadro E.8
Resumen de resultados cuantitativos de hierro en azúcar, SIVESNU 2016

Parámetro	Valor
n análisis estadístico	258
Hierro promedio (mg/kg)	2.6
Desviación estándar	3.0
Valor mínimo de hierro (mg/kg)	0.2
Valor máximo de hierro (mg/kg)	13.9

c. Vitamina A en azúcar

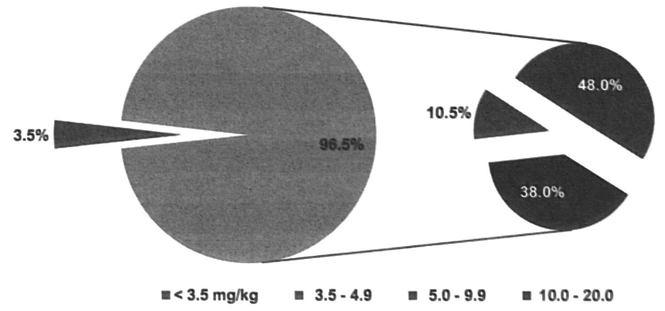
Se recolectaron muestras individuales de azúcar en hogares para evaluar la cobertura del programa de fortificación de azúcar con vitamina A. Del total de 258 muestras obtenidas, el 95% presentaron niveles iguales o mayores a 3.5 mg de retinol /kg de azúcar. El promedio de retinol en las muestras fue de 8.9 mg/kg.

En el Cuadro E.9 y la Gráfica E.6 se resume la información desagregada en rangos de concentración: el 86.1% de las muestras se encontraron entre 5 y 20 mg/kg, rangos que la legislación indica como niveles de fortificación requeridos durante el proceso de fortificación y la vida de comercialización del azúcar. El 3.5% de muestras estuvieron por abajo del mínimo establecido con importancia biológica en hogares. Se concluye que la mayoría del azúcar que llega a los hogares guatemaltecos está siendo fortificada de forma adecuada.

Cuadro E.9
Análisis general de retinol (mg/kg) en muestras de azúcar a nivel de hogares, SIVESNU 2016

Información	Retinol (mg/kg)					n	Media	DE	Mediana	Rango (mm-MM) (mg/kg)
	>20	10.0-20.0	5.0-9.9	3.5-4.9	<3.5		(mg/kg)		(mg/kg)	
Total de casos (n)	0	98	124	27	9	258	8.9	3.4	8.9	0.6-18.7
%	0	38.0	48.0	10.5	3.5					
% acumulado	0	38.0	86.0	96.5	100.0					

Gráfica E.6
Retinol en azúcar (mg/kg), hogares (n=258), SIVESNU 2016



d. Hierro en pan

Se analizaron 96 muestras de pan. La media de hierro fue de 5.49 mg/100g de pan, similar a la mediana de 5.32 mg hierro/100g de pan. El valor mínimo encontrado fue de 3.86 mg de hierro/100 g y el máximo de 10.76 mg de hierro/100g.

Cuadro E.10
Resumen del contenido de hierro en las 95 muestras de pan del SIVESNU 2016

Parámetro	Hierro (mg/100g de pan)
Promedio	5.49
Mediana	5.32
D.S.	1.03
Coeficiente de variación (%)	18.76
Valor mínimo	3.86
Valor máximo	10.76
N	96

El Cuadro E.11 presenta la distribución de resultados de hierro en las muestras analizadas. El 55.2 % de las muestras contiene niveles entre 3.5 < 5.5 mg de hierro/100g. El 44.8% contiene niveles de 5.5 mg hierro/100 g y arriba. El Reglamento Técnico Centroamericano RTCA 67.01.15:06 para la harina de trigo fortificada indica que ésta debe contener como mínimo 5.5 mg de hierro/100 g de harina. Asumiendo que la receta estándar de pan contiene 60% de harina de trigo, se podría decir que el pan debería contener como mínimo 3 mg de

hierro/100 g. Con base en esto, se puede concluir que la fortificación de la harina de trigo con hierro está llegando a la población a través del pan.

Cuadro E.11
Distribución del contenido de hierro en las 96 muestras de pan recolectadas en el SIVESNU 2016

Clase	Frecuencia	%	% acumulado
<3.5	0	0.0	0.0
3.5- <4.0	1	1.0	1.0
4.0 - <4.5	14	14.6	15.6
4.5 - <5.0	16	16.7	32.3
5.0 - <5.5	22	22.9	55.2
5.5 - <6.0	22	22.9	78.1
6.0 - <6.5	7	7.3	85.4
≥6.5	14	14.6	100.0

Los efectos de factores intergeneracionales en el crecimiento

Expositor: Michael Hambidge, MD, BChir, ScD, FRCP
Universidad de Colorado

INCAP ha estado consciente del rol que cumplen los factores intergeneracionales / transgeneracionales en el crecimiento de los jóvenes en Guatemala desde 1975 y antes (Reynaldo Martorell et al; Acta Paediatr Scand 66: 579-584, 1977). Más recientemente, Martorell R. y Zongrone A. han aportado una evaluación más extensa de las influencias intergeneracionales sobre el crecimiento infantil y desnutrición, la cual ha resultado invaluable (Epidemiología Pediátrica y Perinatal 2012 26, suplemento 10 302-314).

Esta presentación se enfocará en los retos específicos a los que se enfrenta la población indígena de Guatemala, resaltando la importancia del ambiente a corto y largo plazo. Se dará especial atención a la importancia de factores seculares y socio-culturales en la interpretación de adaptaciones a largo plazo (herencia poligénica) y corto plazo (epigenética) al ambiente, tomando en cuenta la "transmisión intergeneracional de la pobreza".

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Intergenerational Influences on Child Growth and Undernutrition

Reynaldo Martorell,[a] Amanda Zongrone[b]

[a]Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, GA, and [b]Division of Nutritional Sciences, Cornell University, Ithaca, NY, USA

Abstract

Intergenerational effects on linear growth are well documented. Several generations are necessary in animal models to 'wash out' effects of undernutrition, consistent with the unfolding of the secular trend in height in Europe and North America. Birthweight is correlated across generations and short maternal stature, which reflects intrauterine and infant growth failure, is associated with low birthweight, child stunting, delivery complications and increased child mortality, even after adjusting for socio-economic status. A nutrition intervention in Guatemala reduced childhood stunting; it also improved growth of the next generation, but only in the offspring of girls. Possible mechanisms explaining intergenerational effects on linear growth are not mutually exclusive and include, among others, shared genetic characteristics, epigenetic effects, programming of metabolic changes, and the mechanics of a reduced space for the fetus to grow. There are also socio-cultural factors at play that are important such as the intergenerational transmission of poverty and the fear of birthing a large baby, which leads to 'eating down' during pregnancy. It is not clear whether there is an upper limit for impact on intrauterine and infant linear growth that programmes in developing countries could achieve that is set by early childhood malnutrition in the mother. Substantial improvements in linear growth can be achieved through adoption and migration, and in a few selected countries, following rapid economic and social development. It would seem, despite clear documentation of intergenerational effects, that nearly normal lengths can be achieved in children born to mothers who were malnourished in childhood when profound improvements in health, nutrition and the environment take place before conception. To achieve similar levels of impact through public health programmes alone in poor countries is highly unlikely. The reality in poor countries limits the scope, quality and coverage of programmes that can be implemented and modest impact should be expected instead. The Lancet series on Maternal and Child Undernutrition estimated that implementation to scale of proven interventions in high burden countries would reduce stunting by one-third; this is perhaps a realistic upper bound for impact for high quality programmes, unless accompanied by sweeping improvements in social services and marked reductions in poverty. Finally, because so much can be achieved in a single generation, intergenerational influences are unlikely to be an important explanation for lack of programme impact aimed at the window of the first 1000 days. Failure to prevent linear growth failure in developing countries has serious consequences for short- and long-term health as well as for the formation of human capital. The nutrition transition has created a double burden by adding obesity and related chronic diseases to the public health agenda of countries still struggling with the 'old' problems of maternal and child undernutrition. The challenge ahead is to increase efforts to prevent linear growth failure while keeping child overweight at bay.

Keywords: *Intergenerational influences, child growth, child undernutrition, nutrition transition.*

Intergenerational influences have been defined as 'conditions, exposures, and environments experienced by one generation that relate to the health, growth and development of the next generation'.[1]

Correspondence: Reynaldo Martorell, PhD, Hubert Department of Global Health, Rollins School of Public Health, Emory University, 1599 Clifton Road, NE, Atlanta, GA 30322, USA.
E-mail: rmart77@emory.edu

This review concerns intergenerational influences on birth size and growth in length, particularly up to 2 years of age. The two key objectives are to review the evidence for intergenerational influences and their possible mechanisms, and to discuss whether intergenerational influences impose an upper limit on the possible impact of programmes in developing countries on intrauterine and early childhood linear

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growth. Emphasis is given, when appropriate, to studies from resource-poor countries. We also provide a discussion on the achievement of healthy growth in the context of the double burden of disease, as countries undergo the nutrition transition.

Conceptual framework

A conceptual framework for intergenerational relationships on linear growth is presented in Figure 1. For simplicity, we depict only two generations, although studies, particularly in animal models, indicate that influences can be sustained over several generations. We begin with the mother's early life environment which influences her pre-pregnancy constitution (height, fat free mass), organ size (e.g. placenta, uterus, ovaries), metabolism, and ultimately newborn and child characteristics. Babies may be small because of a poor nutrient supply and/or because they have limited room to growth. A narrow pelvic inlet and a large newborn head circumference may lead to obstetrical complications, and this may explain the phenomenon of eating less during pregnancy to reduce the size of the baby at birth. Availability of obstetrical services may lessen this fear.

Underpinning these relationships are broad factors such as genetic endowment, metabolic programming, epigenetics and selection, and the intergenerational transmission of poverty. These factors form the basis for general, potential explanations for intergenerational effects.[2] Apparent intergenerational effects may reflect shared genetic characteristics, for example, a familial disposition to be small and/or shared environments across generations: in the economic development literature about poor societies the latter is sometimes referred to as the intergenerational transmission of poverty. Other explanations include effects of an adverse environment in early life on maternal child growth and reproductive organ size and/or metabolism, aspects that will influence fetal and infant growth of the next generation. Metabolism may also be influenced by epigenetic changes that alter, for example, gene expression in the mother.

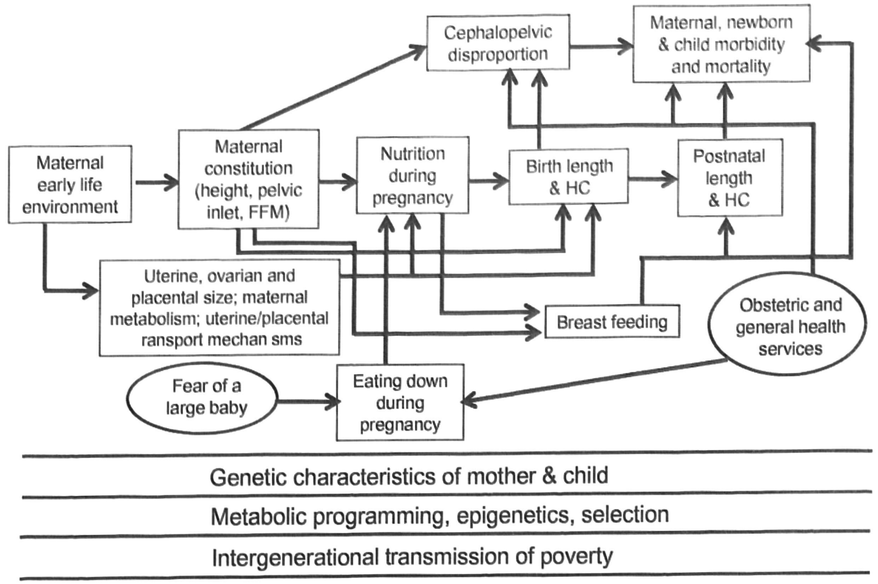

Figure 1. Intergenerational influences on child nutrition. FFM, fat free mass; HC, head circumference.

The animal literature

The animal literature offers conclusive support for intergenerational influences. A range of programming effects on size and metabolism, as well as epigenetic changes, have been demonstrated as reviewed by Drake *et al.*[3] Cross-breeding studies of Shetland ponies and Shire horses in 1938 established that maternal size places a limit on intrauterine growth.[4] The birth size of offspring of a Shetland pony and a massive Shire stallion were not intermediate between what is typical of these two breeds, which would have been too large a fetus for the Shetland mare, but closer to what is typical for purebred Shetland offspring. The constrain on fetal growth is probably driven by physical limitations but likely involves maternal metabolic processes or uterine/placental transport mechanisms that limit nutrient provision to the fetus and thus growth, as suggested by studies in rhesus monkeys.[5]

Intergenerational and multigenerational relationships in birth and adult size have been shown in animal models. Studies in rhesus monkeys, living in a permissive laboratory, demonstrated a strong matrilineal influence on birthweight across five generations, underscoring the role of the intrauterine environment in producing these birthweight patterns.[5,6] Stewart *et al.*[7] conducted classic studies over 12 generations with black and white hooded rats that were kept on protein deficient diets and compared with controls. Birth and adult sizes were reduced as well as organ sizes, with differences with respect to controls increasing over generations. In a later study Stewart *et al.*[8] reported that it took three generations with a normal diet for the malnourished rats to achieve the adult size of control rats, although there may have been some residual, negative effects on learning and behaviour. However, in other experiments testing dietary restrictions using other types of rodents, it took only one generation with a normal diet to restore normal size (i.e. the F2 generation was normal).[9] This suggests that the effects of undernutrition in only a single generation are more amenable to intervention than the effects of multigenerational restrictions in Stewart's studies.[7,8] Until a generation or two ago, the common condition in poor counties was that of chronic nutritional deficiencies across generations.

Epigenetic inheritance, non-genomic effects that are transmissible through the germline, has been demonstrated in animals, most famously at the agouti locus in the mouse, where the diet of a pregnant mouse apparently affects not only her offspring's coat colour but also the coat colour of future generations.[3,10] Epigenetic changes have been hypothesised but not yet demonstrated unequivocally in humans.[3,10,11]

In summary, animal models have been useful for understanding intergenerational effects observed or hypothesised in human populations. Models of investigation in animals are quite varied and include various types of dietary restriction during pregnancy and lactation, hormonal interventions as well as surgical procedures.[12] Besides the usual caveats of extrapolation of findings from animals to humans, the variety of experimental conditions and the type of species and breeds used in studies pose challenges in interpretation.

The human literature

Intergenerational transmission of poverty

Because of the importance of poverty in influencing health and nutrition outcomes we consider the case of the intergenerational transmission of poverty, the notion that the strongest risk factor for being poor is being born to poor parents. A framework for understanding these transfers considers different kinds of capital (human, socio-cultural, socio-political capital, financial/material and environmental/natural) and private and public channels of transmission; it also goes beyond the familiar transfers from parents to children to also consider transfers from younger to older generations.[13] Poor health and nutrition reflect as well as cause poverty and are important elements of the intergenerational transfer of poverty in developing countries.[14] For example, pathways out of poverty include investments in maternal and child nutrition, which can improve offspring cognition, schooling and future wages.[15]

Growth during the first 1000 days

The first 1000 days (conception to the first 2 years of life) is a critical period for human growth and development.[16] Evidence from around the world shows that growth failure begins *in utero*, is pronounced during the first year of life, and continues, but with lesser force, until around 2 years.[17] Even in very poor settings, such as rural India, growth in length after 2 years is similar to that in the reference population.[17] The only consistently known period of growth failure

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in populations in poor countries is the first 1000 days; if anything, there seems to be modest catch up in length/height after 2 years, perhaps because of delayed maturation and a longer period of growth.[18] Thus, the short stature one observes in adults from many developing countries probably reflects growth failure prior to 2 years of life; also, the intrauterine growth period may contribute equally to short adult height as do the first 2 years.[19]

Associations between maternal anthropometry and offspring outcomes

The association between maternal birthweight and offspring birthweight is well established.[2] A review of 14 studies (all from developed countries) that examined the intergenerational associations in birthweight found that for every 100 g increase in maternal birthweight there was a 10–20 g increase in offspring birthweight.[20] Data from Guatemala suggest an amplified relationship; for every 100 g increase in maternal birthweight, offspring birthweight increased by 29 g (adjusted for various confounding factors).[20] A study using the 1958 British national birth cohort found intergenerational birthweight associations that were little affected by controlling for parental height or body mass index (BMI) at 7 years of age, suggesting that intergenerational associations in birthweight are largely independent of the postnatal growth of the parents, although the latter also had an independent, positive effect on offspring birthweight.[21] Mothers who were born small for gestational age (SGA) have significantly increased risk of delivering SGA newborns;[22,23] however, in mothers themselves born at preterm gestational ages, there is no increased risk of delivering at preterm gestations.[23] This suggests that intergenerational associations in birthweight may be largely driven by fetal growth rather than gestational age. A small study reported that adolescents girls born SGA had a smaller uterus and a reduced ovarian volume compared with those born adequate for gestational age (AGA),[24] offering a possible mechanism for the intergenerational transmission of SGA.

Evidence from studies that have used multigenerational designs indicates that birthweight influences are more strongly transmitted through the maternal line,[2] as also found in studies in rhesus monkeys.[5,6] Intergenerational relationships in birthweight were strongest between mothers and daughters[25] and most studies report a stronger association of low birthweight (LBW) across generations for mothers compared with fathers.[21,26–28] It has been suggested that the weaker influence of fathers may reflect non-paternity in some cases[21] but this cannot be the explanation because studies in rhesus monkeys carefully controlled breeding.[6]

Few studies have examined how parental childhood growth influences offspring birthweight. In meta-analyses of four prospective cohorts from middle- and low-income countries, maternal height, birthweight and intrauterine growth restriction (IUGR) status as well as maternal weight for age and height for age z-score at 2 years of age were related to offspring birthweight.[16] Analyses of one of these cohorts, the 1982 Pelotas cohort from Brazil, focused on influences of parental birthweight and child growth on offspring birthweight.[28] Maternal but not paternal birthweight was associated with offspring birthweight. In analyses that used conditional growth variables that were uncorrelated with each other and with birthweight, it was found that parental growth in weight from birth to 20 months, but not from 20 to 42 months, was significantly related to offspring birthweight *but only in mothers*. Each z-score change in growth from 0 to 20 months was associated with 62 g [95% confidence interval (CI) 11, 112] of offspring birthweight in mothers and only 37 g [95% CI 40, 113] in fathers, after adjusting for confounders. Lack of birth length information did not allow these analyses to be done for growth in length, independent of birth length, but it is likely they would have reached the same conclusion because the relationship between length for age and weight for age z-scores at 20 months of age with offspring birthweight were similar. These findings suggests that there is a qualitative difference in the accretion of weight or length in the first 2 years of life compared with later in childhood and that this matters for offspring birthweight only in mothers. In a British cohort, leg length, a possible marker of early life influences, was found to be the component of maternal childhood height (single measure taken between 2 and 14 years of age) that was related to offspring birthweight, independent of maternal birthweight and final height.[29]

Maternal height has the advantage that it is commonly available in studies, resulting in a large literature on its relationship to child size. In particular, the availability of national Demographic Health Surveys (DHS or equivalent types) has allowed examination of the relationship between maternal height with child-

hood outcomes in specific countries such as India[30,31] and in pooled analysis of low- and middle-income countries,[32,33] while controlling for potentially confounding factors. A study using data from 54 countries,[32] found that a 1 cm increase in maternal height was associated with a decreased risk in stunting [relative risk (RR), 0.968, [95% CI 0.967, 0.968]] and mortality in the first 5 years of life (RR 0.988, [95% CI 0.987, 0.988]). Relative to the highest height category (≥160 cm), children of women in the lowest of five categories (<145 cm) were more than twice likely to be stunted (RR 2.13, [95% CI 2.10, 2.16]) and 40% more likely to die (RR 1.40, [95% CI 1.37, 1.42]). To put the findings in context, the effect on mortality of being in the lowest height category relative to the highest height category was approximately 80% of the effect of being in the poorest compared with the highest wealth quintile.[32] An analysis based on Indian data reported similar findings for maternal height; however, paternal height was associated with stunting but not with child mortality.[31]

Human evolution, cephalopelvic disproportion and eating down during pregnancy

Cephalopelvic disproportion (CPD) occurs when there is a mismatch between the size of the fetal head and the size of the maternal pelvis, which can lead to obstructed labour and serious risks for mother and child.[34,35] According to the World Health Organization (WHO), CPD is responsible for 8% of maternal deaths worldwide.[36] Smaller women have smaller pelvises and are at greater risk for caesarean delivery.[37]

Evolution made delivery in humans very complicated and dangerous compared with what happens in our closest relatives, the higher primates, among whom delivery is relatively simple, fast and safe.[35] Evolutionary forces narrowed the birth canal and increased the fetal head, making obstructed labour all too common.[35]

Bipedal locomotion, an ancient trait, led to major anatomical modifications that made the pelvis narrow and birthing difficult, despite some modifications to the female pelvis to facilitate delivery. Encephalisation, or the increase in brain size throughout our history, more recent than bipedalism, increased appreciably some 600 000 years ago, eventually leading to the appearance of large brained, anatomically and behaviourally modern humans 40 to 50 000 years ago.[35,38,39] Some adaptations in humans have reduced but not eliminated the difficulties of delivery. Rapid brain growth continues after birth, which keeps the fetal head smaller, and there is remarkable malleability of the human fetal head to ease its passage through the narrow birth canal.[35] A unique aspect of human delivery is the elaborate rotation of the head during delivery, followed by that of the shoulders and body, in order to align the largest dimensions of the fetal head with the largest dimensions of each plane of the pelvis as labour progresses; as a result, the fetus emerges, most commonly, face down, which does not allow the mother to clear her baby's airways or help ease its head out of the body.[35] The relative difficulty of childbirth in our species has led some to speculate that social adaptations emerged long time ago to help women, such as the presence of birth attendants.[35]

A unique study from Guatemala examined the role of maternal height and fetal head circumference in predicting intrapartum caesarean delivery.[37] The study took place in the Social Security Hospital in Guatemala City, where all women presenting were covered by insurance and where physicians had no incentives for carrying out caesareans. Cases with planned caesareans and assisted deliveries (e.g. use of forceps) were excluded, leaving some 4614 nulliparous women, among whom 27% had intrapartum caesareans. The population was divided into quartiles of maternal height and quartiles of newborn head circumference. The incidence of caesarean delivery increased in babies with larger heads and in shorter mothers, apparently in an additive model. The lowest incidence, 11.1%, occurred in the tallest mothers (>157 cm) with the babies with the smallest head circumferences (< 33.0 cm); the highest incidence, 53%, occurred in the shortest mothers (≤ 148 cm) with the largest head circumference (≥34.7 cm). Birthweight also predicted risk of intrapartum caesareans but head circumference was a somewhat stronger predictor.

Intergenerational influences can also be mediated by culture. Eating less during pregnancy is widely reported in developing countries for varying reasons.[40–43] Some have called this practice 'eating down' and in some areas a reason given for it is to keep the baby small to avoid obstructed labour.[40–43] This may be an ancient practice, deep in cultural memory. 'Eating down' may be also a factor limiting the potential participation of women in prenatal programmes, such as food supplementation or educational interventions to increase food intake during pregnancy;[43] one solution is to offer such programmes

along with accessible obstetric care.[40] This would lessen the fear of delivery complications and also protect women if indeed the programmes prove effective in increasing birth size.

Quasi-experimental evidence in humans

Experimental evidence of intergenerational influences in humans is very limited if we exclude interventions during pregnancy on birth outcomes; technically, the fetus was alive during the intervention, blurring the concept of intergenerational influences. The literature on interventions during pregnancy and birth outcomes identify efforts to improve nutrition (macro and micronutrients) and prevent infection as being very important for prematurity and birth size.[44]

Pre-conceptional micronutrient nutrition interventions in the mother are probably very important for newborn outcomes but the evidence in humans is scant, except in the case of folate and the prevention of neural tube defects.[45] Pregnancy is probably too late to correct nutritional deficiencies and even less for building nutrient stores. Pre-conceptional iron supplementation allows women to enter pregnancy in better status;[46,47] given that iron supplementation during pregnancy improves birth outcomes,[48,49] pre-conceptional iron supplementation should also do so but experimental data regarding such an association is lacking.

Findings from long-term follow-up studies of a nutrition intervention carried out by the Institute of Nutrition of Central America and Panama (INCAP) showed that improved nutrition up to 3 years of life led to adult increases in height, work capacity, schooling (women), reading comprehension, intelligence and wages (men).[50] The largest effects on wages (46%) were observed on those provided with improved nutrition through age 2 years.[15] Findings for cardiovascular disease risk factors were heterogeneous; however, they suggest that improved nutrition in early life is unlikely to increase cardiovascular disease risk later in life and may indeed lower risk.[51] The INCAP studies underscore that investments in women and children in the first 1000 days improve human capital and productivity, and thus help break the cycle of the intergenerational transmission of poverty.

The INCAP follow-up studies are unique in showing intergenerational effects.[52–54] Offspring of women themselves exposed to the nutritious supplement in childhood (relative to women exposed to the control supplement) were heavier at birth and were taller and had greater head circumferences in childhood. No effects on measures of adiposity were found. Effects were greater in sons. Father's exposure to the supplements in childhood, on the other hand, did not influence their offspring characteristics,[54] mirroring the findings from Brazil that were reviewed above about the relationship between growth from birth to 20 months and offspring birthweight in mothers but not fathers.[28]

Famines provide a quasi-experimental setting for research on the long-term effects on human development. While most famines of the 20th century occurred in developing countries, little attention has been paid to studying consequences for human development in these settings. The best-studied famine is the Dutch 'hunger winter' at the end of World War II.[55] The Dutch famine had a well-defined but brief duration (~6 months) and, while severe, it occurred in the context of an otherwise well-nourished population who may have been somewhat buffered. The Chinese famine was of longer duration (3 years; 1959–61) and was superimposed on widespread chronic undernutrition; some 30–50 million people died, with greater severity in rural compared with urban areas.[56,57]

Fetal exposure to the Dutch famine during pregnancy was not associated with adult height and body proportions,[58] mental retardation,[59] IQ[60,61] or offspring birthweight.[62–64] Exposure to the Chinese famine over windows of exposure that included prenatal as well as postnatal life reduced height, income and wealth.[56,57] Income effects were substantial for the 1959 cohort, exposed from 0 to 2.5 years of age, in whom annual per capita income was reduced by 33%.[56] Intergenerational effects on birth outcomes have also been shown.[65] Birth sizes of offspring of women born prior to the famine (1957–58; exposure of the mothers between 0.5 and 4.5 years of age), during the famine (1959–61; exposure prenatally and up to 2.5 years) and after the famine (1962; some exposure early in pregnancy) were compared with those of women never exposed to the famine (born 1963). In rural areas, and in pre-famine and famine cohorts, exposure to famine was associated with *increases* in offspring weight (71 g, [95% CI 30, 113]), length (0.3 cm, [95% CI 0.0, 0.6 cm]) and BMI (0.1 kg/m^2, [95% CI 0.0, 0.2]) at birth. In urban areas, however, exposure to famine was not associated with offspring birth size. The authors speculate that very high mortality rates in rural areas resulted in intense survival selection pressure for hardier individuals with greater growth potential (but

shorter adult heights because of early life exposure to the famine), which becomes expressed in their offspring as greater birth size. This may be an example of natural selection for taller people.

Secular trends, adoption and migration studies

We turn now to indirect evidence about the response in birth outcomes and in child growth to improvements in living conditions. Changes in height over time (i.e. secular trends) in different countries, particularly in those undergoing economic development, are one form of evidence. Also relevant are adoption studies of children born in developing countries and adopted by families in wealthy nations; these tell us about the degree to which the effects on growth of adverse conditions in early life can be overcome by an improved environment. We also consider studies of migrants to wealthy nations, with particular attention to children born in their adopted country to mothers exposed to lifetime malnutrition prior to arrival but to an improved environment after arrival and prior to conception.

Secular trends

Secular trends in height in Northern Europe and North America have been studied extensively;[66,67] these trends began in the second half of the 19th century and ceased 30 to 40 years ago in these regions. The Dutch are the tallest people in the world; in 1865 Dutch recruits were over 16 cm shorter than in 1990, a difference reduced to 10.5 cm by 1917 and 5.2 cm by 1960; in 1978 differences became 1.0 cm or less for the first time and since 1984, heights have differed by no more than 0.1 cm from the 1990 value.[65,68] These trends reflect improvements in living standards and are consistent with animal studies in that they show that it took several generations to 'wash out' malnutrition. Trends are evident in many but not all developing countries. In Brazil, for example, a steady decline in stunting over 33 years (1974–2007) has been documented, from 37.1% to 7.1%; the decline was particularly steep in the last 10 years of the period studied (1996–2007) when inequalities have narrowed, although they persist.[69,70] The recent rapid decline in stunting and the improvement in other health indicators have been attributed to 'progress in social determinants of health and to implementation of a comprehensive national health system with strong social participation'.[71]

Adoption studies

There is a large literature about the growth and development of children from developing countries adopted by Europeans and North Americans.[72–75] The findings are very consistent: most studies report poor growth status on arrival and substantial but incomplete catch-up in height and head circumference that depends on age at arrival, better for children under 2 years than for older children. Proos[76] states 'What is lost in growth early in life can only partially be recovered by catch-up growth'. In older children, the risk of precocious puberty is enhanced as faster growth likely triggers endocrine responses that hasten puberty; the end result is that final adult height is reached at a younger age, which shortens the childhood growth period and limits final height.[76–78]

Migrant studies

When migrant families from poor societies migrate to wealthy countries they experience a substantial improvement in their living conditions. In a remarkable study of Southeast Asian refugees (Cambodia, Laos, Vietnam) that settled in the US from 1977 to 1980 – and who were enrolled, along with low-income US born families, in public health clinics – researchers at the US Centers for Disease Control and Prevention showed that over 15 years the prevalence of LBW and of stunting declined dramatically and became similar to that of the white and Hispanic populations.[78–80] The prevalence of LBW declined in Black and Asian newborns but the decline in the latter was substantial, from 15% in 1978 to 8.5% in 1989.[78] Also, the prevalence of low height-for-age in children 1–23 months of age declined from 24.8% in the peak year of 1982 to 13.5% in 1989, a reduction of 45%.[79] These trends continued into 1993, when the last study was carried out.[79] These refugee children were born to mothers who suffered from malnutrition prior to arrival in the US. Over the period of the study, refugee mothers' nutritional status prior to conception and during pregnancy and lactation undoubtedly improved and they were able to have children who grew as well as other low-income children of other ethnic groups in the US. A similar situation may have occurred among Bhutanese refugees to camps in Nepal that provided basic needs (food and micronutrients, water and sanitation, antenatal care and education); the prevalence of LBW fell from 18–16% in 1994–95 to 10–8% in 2000–01.[81]

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Preventing growth failure in the context of the nutrition transition

A dual nutrition agenda has emerged in low- and middle-income countries.[82] The problems of yesterday – such as stunting, early childhood wasting and micronutrient deficiencies – coexist with a pandemic of obesity and related chronic diseases. Obesity in women in many countries is now common and is driving diabetes rates rapidly, in part through intergenerational influences.[83,84] Obesity increases the risk of gestational diabetes mellitus (GDM) and this in turn increases the risk of obesity and diabetes in the offspring as well as the risk of diabetes in the mother, affecting her future pregnancies adversely. Over time, this intergenerational effect increases the prevalence of obesity and diabetes in the population and, in a number of settings, as much as one-third of cases of diabetes can be attributed to GDM exposure.[82,83,85] The causes of the epidemic of obesity are complex but can be traced to economic development and urbanisation, the engines of the nutrition transition, which has ushered such changes as improved food security and diversity, inexpensive vegetable oils, increased exposure to media, increased eating away from home, less physically demanding jobs and labour-saving devices, availability of public transit, sedentary recreation and decreased opportunities for physical activity; these factors have led to increased energy intakes, decreased physical activity and obesity.[82] The rapidity of the obesity epidemic as well as the greater severity and earlier onset, for example of diabetes, has led some to look for additional causes.[84] One cause that has gained wide acceptance is the mismatch between the environment of undernutrition in early life, which programmes individuals for lifelong scarcity, and the obesogenic milieu of the nutrition transition.[86,87] Such individuals may be more efficient in using energy, may be inclined to eat more and move less and may store more fat; although there is considerable evidence for this interaction, the extent to which it helps explains the epidemic of obesity has not been quantified.

Tension has arisen between the Developmental Origin of Health and Disease (DOHaD) paradigm presented by Gluckman *et al.*[85] and the perspective of the international nutrition community, best characterised by the Lancet series on Maternal and Child Undernutrition.[44] The series is focused on improving health, nutrition and linear growth during the first 1000 days, but without explicit attention to the problem of maternal and child obesity. Reports from developed countries, mostly involving preterm newborns, have been used to caution against promoting faster growth in infants in poor countries because many were born small.[88] Indeed, about half of all LBW babies in low- and middle-income countries are preterm, a higher proportion than previously believed.[89] Gluckman *et al.*[86] state '. . . interventions in early life aimed at essential short term gains, such as infant survival, could have longer term effects on individuals throughout their life-course, and such outcomes might not always be beneficial. Programmes aimed at increasing birthweight might raise risk for later diabetes, amplified by accelerated fat gain in childhood, a possible result of universal supplementation programmes'. These are very strong statements that could have a paralysing effect on policies and programmes. The first point that can be made is that certainly, many lives will be saved; about 2.8 million deaths in children under 5 years occur because of growth failure (IUGR, stunting, wasting).[90] Involving research from five low- and middle-income countries, the COHORTS collaboration is providing findings highly relevant to the relationships between growth during the life cycle and future health in poorer countries; among the findings is that better linear growth in the first 1000 days is associated with improved human capital.[91] Also, growth *in utero* and the first 2 years is essential for building lean mass; later rapid weight mainly results in fat mass deposition.[92] Other findings from COHORTS are that birthweight is not related to blood pressure but is protective against fasting glucose.[93,94] The INCAP nutrition intervention trial resulted in improved linear growth but not increased adiposity[50,54] and may have been beneficial to adult health.[51] An intervention in India with balanced protein–calorie supplements to pregnant women and children reported reductions in the burden of cardiovascular disease.[95]

Comments

The period of consistent growth failure in poor settings is the first 1000 days: from conception through the first 2 years. Growth failure is an indicator of poor nutrient availability at the cellular level and reflects widespread functional impairment. Through a variety of research designs, including cohort studies, follow-up evaluations of nutrition interventions or assessments of the long-term impact of natural

experiments such as famines, we have learned, unequivocally, that poor nutrition early in life, as reflected in poor growth, has lifelong adverse-consequences, including short stature, diminished work capacity, delayed cognition, less schooling and reduced incomes. Many types of studies indicate the need to act within the first 1000 days for maximal benefit; the earlier the better.

Intergenerational effects on growth are well documented. The mechanisms are complex and range from the purely biological to the socio-cultural and are not mutually exclusive. Several generations are necessary in animal models to 'wash out' effects of undernutrition, consistent with the unfolding of the secular trend in growth in Europe and North America. Birthweight is correlated across generations and short maternal stature, which reflects intrauterine and infant growth failure, is associated with LBW, child stunting, delivery complications and increased child mortality, even after adjusting for socio-economic status. A nutrition intervention in Guatemala reduced childhood stunting; it also improved growth of the next generation, but only in the offspring of girls. Possible mechanisms explaining intergenerational effects are not mutually exclusive and include, among others, shared genetic characteristics, epigenetic effects, programming of metabolic changes, and the mechanics of a reduced space for the fetus to grow. There are also socio-cultural factors at play that are important such as the intergenerational transmission of poverty. The intergenerational transmission of poverty leads to similarities across generations in birthweight and stunting. In a sense, this form of transmission is a confounder for those wishing to interpret intergenerational influences as purely biological, for example, as sole reflections of programming *in utero*. In the same sense, metabolic programming, epigenetics and shared genetic characteristics become confounders to those examining intergenerational influences from a narrow social science angle. In reality, nature and nurture are always intertwined in intergenerational influences.

Intergenerational influences are powerful and are directly responsible for perpetuating the so-called 'intergenerational cycle of growth failure'.[20] This involves young girls who grow poorly and become stunted women who are more likely to have small babies; these babies, if girls, will continue the cycle.[20] Human evolution has made this intergenerational cycle of growth failure dangerous for both mother and newborn. Women have narrower pelvises compared with other higher primate and stunted women have even narrower ones, which may also be misshapen by deficiencies such as rickets. Giving birth to a child with a relatively large head circumference can be tragic and CPD remains an important cause of maternal mortality. In many parts of the world, the fear of birthing a large baby leads to 'eating down' during pregnancy. For ethical reasons and in order to improve compliance, programmes that improve food intakes during pregnancy in populations with significant stunting should also include access to effective obstetrical care in the package of services.

There is clear agreement that this intergenerational cycle of growth failure must be broken by improving socio-economic, nutrition and health conditions, as is happening in countries such as Brazil. But, is there an upper limit for impact on intrauterine and infant growth that could be achieved by programmes in developing countries that is set by early childhood malnutrition in the mother? Are the typical, ambitious goals of programmes in developing countries for reducing LBW and stunting also unrealistic because, even if the programmes had state-of-the-art designs and efficient delivery and uptake, intergenerational influences will constrain what can be achieved because the pregnant women in the programme suffered growth failure early in life?

A direct test of this question is impossible. This would require evaluation studies of well-funded, ambitious, comprehensive, wide-coverage, effective programmes aimed at vulnerable populations and specifically targeting the first 1000 days and for best results, also the preconception period. Evaluations of bold programmes are unlikely. First, programmes are seldom evaluated with robust designs.[96] Second, bold programmes may be rare, if they exist at all. Typically, designs are limited to what is possible given limited resources, at best a package of interventions of proven efficacy but only addressing a facet of the problem, with delivery generally poor and coverage low. The Lancet Series on Maternal and Child Undernutrition estimated that implementation to scale of proven interventions in high burden countries would reduce stunting by one-third by taking impact evaluations from mostly efficacy studies and modelling overall impact.[44] The approach was limited by what has been learned to date and is therefore conservative. The estimate itself has been used as an advocacy tool to show that significant progress can be achieved through implementation of proven interventions.

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Other experiences reviewed here tell us that much more could be achieved with bold but likely expensive programmes. Adoption from settings of malnutrition to wealthy countries results in significant but incomplete catch-up in growth, worse if the child is adopted after 2 years of age. Poor health, nutrition and care during pregnancy and during postnatal life prior to adoption explain the poor status on arrival and the incomplete extent of catch-up growth. Migration of families from settings of malnutrition to wealthy countries leads to more remarkable results. In a few years after arrival, children of migrant families begin to resemble local populations in birthweight and stunting prevalence, even though the mothers suffered from malnutrition in early life. This may reflect improved nutrition and health prior to conception and in the first 1000 days. It would seem, therefore, that despite clear documentation of intergenerational effects, nearly normal lengths can be achieved in children born to mothers who were malnourished in childhood when profound improvements in health, nutrition and the environment take place before conception. Marked improvements in growth are also evident in a few selected countries, following rapid economic and social development. To achieve similar levels of impact through public health programmes in poor countries is highly unlikely. The reality in poor countries limits the scope, quality and coverage of programmes that can be implemented and modest impact should be expected instead. The Lancet series on Maternal and Child Undernutrition estimated that implementation to scale of proven interventions in high burden countries would reduce stunting by one-third; this is perhaps a realistic upper bound for impact for high quality programmes, unless accompanied by sweeping improvements in social services and marked reductions in poverty. Finally, because so much can be achieved in a single generation, intergenerational influences are unlikely to be an important explanation for lack of programme impact.

We are moving towards convergence of the DOHaD and international nutrition agendas.[84,91,97] According to Cesar Victora[91] 'Promotion of good nutrition in early life is essential for health later in life because either undernutrition or overnutrition can cause lifelong, irreversible damage'. The challenge, therefore, is how to prevent linear growth failure in the first 1000 days, prevent wasting where it is a problem, but avoid overweight after age two. There is increasing recognition that policies and programmes need to consider the double burden (stunting and obesity) as a related set of problems that share common causes and thus interventions and that need to be addressed throughout the life cycle beginning in the first 1000 days. Healthy body composition and weight gain during pregnancy, good maternal micronutrient stores, exclusive breast feeding for the first 6 months and continued breast feeding for longer, dietary intakes that provide adequate levels of energy but are nutrient dense, diets in which children are exposed to fruits and vegetables, and environments that encourage physical activity and play are some of the interventions that would promote linear growth but not fatness. Fortified complementary foods from 6 to 24 months may or not be necessary depending on the setting; in some populations, micronutrient powders will suffice to improve dietary quality. The consumption of sugared drinks, juices and junk food, seen in alarming levels in many countries, must be discouraged through education and other programmes. Achieving healthy growth is among the most important challenges of the 21st century for both poor and wealthy nations.

Conflicts of interest

The authors have not declared any conflicts of interest.

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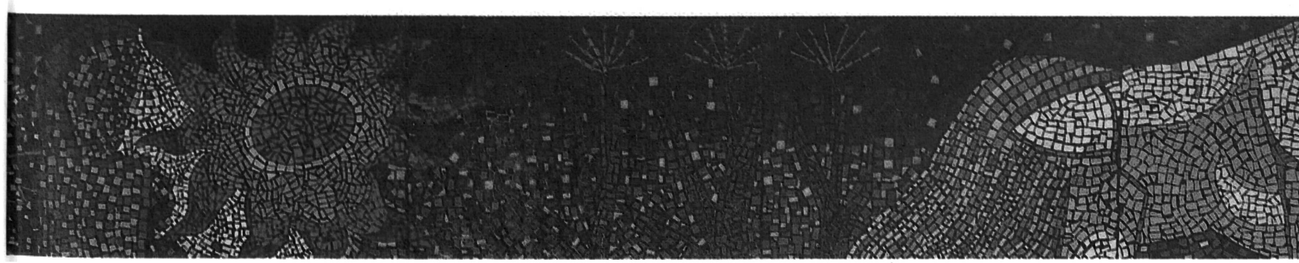
La Talla como indicador del bienestar

Expositor: Jef Leroy, PhD
International Food Policy Research Institute - IFPRI

Durante la última década, se ha evidenciado un aumento sin precedentes a la atención prestada a la desnutrición y se ha asumido como una meta de desarrollo global la reducción drástica de la talla baja (stunting en inglés) en la niñez. El fuerte enfoque en el retraso de crecimiento lineal la talla baja ha facilitado el apoyo efectivo a la nutrición. Sin embargo, junto con este enfoque, han surgido confusión y malentendidos sobre el significado del retraso de crecimiento lineal y talla baja entre investigadores, donantes y agencias que participan en el campo de la nutrición.

Motivados por la convicción de que un enfoque agudo puede acelerar el progreso en la reducción de la desnutrición, revisamos las evidencias de manera crítica. La atención global a la talla baja se basa en la premisa de que cualquier intervención enfocada a mejorarla resultará en mejoras posteriores del crecimiento lineal y talla baja. Sin embargo, la evidencia actual y la comprensión de los mecanismos implicados no apoya este pensamiento causal, con dos excepciones: el retraso en crecimiento lineal si es causa de nacimientos dificultosos y pobres resultados de salud neonatal. El retraso del crecimiento lineal se asocia (pero no es la causa) con el desarrollo tardío del niño, ingresos reducidos en su edad adulta y padecimiento de enfermedades crónicas.

Nosotros proponemos dos maneras diferentes de comprender el retraso del crecimiento lineal y la talla baja. En primer lugar, la relación entre el retraso del crecimiento lineal (o talla baja) y estado de salud desfavorable la hace un indicador muy útil. En segundo término, los vínculos causales entre los nacimientos dificultosos y los pobres resultados en salud neonatal le dan un valor intrínseco. En muchos casos, un enfoque en el retraso del crecimiento lineal y el crecimiento reducido no es necesario para mejorar el bienestar de los niños. En muchos otros casos este enfoque no es suficiente alcanzar esta meta para mejorar la salud; para lograr otros resultados, el fomento del crecimiento lineal no es la estrategia más costo efectiva. Nosotros requerimos a los donantes, a los planificadores de los programas y a los investigadores que sean específicos en la selección de los resultados de nutrición y en que aborden estos resultados de manera directa.



PERSPECTIVE

Perspective: What Does Stunting Really Mean? A Critical Review of the Evidence

Jef L Leroy[1] and Edward A Frongillo[2]

[1]Poverty, Health, and Nutrition Division, International Food Policy Research Institute, Washington, DC and [2]Department of Health Promotion, Education, and Behavior, University of South Carolina, Columbia, SC

ABSTRACT

The past decade has seen an unprecedented increase in attention to undernutrition, and drastically reducing child stunting has become a global development objective. The strong focus on linear growth retardation and stunting has enabled successful advocacy for nutrition, but with this focus has come some confusion and misunderstanding about the meaning of linear growth retardation and stunting among researchers, donors, and agencies active in nutrition. Motivated by the belief that a sharp focus will further accelerate progress in reducing undernutrition, we critically reviewed the evidence. The global attention to stunting is based on the premise that any intervention aimed at improving linear growth will subsequently lead to improvements in the correlates of linear growth retardation and stunting. Current evidence and understanding of mechanisms does not support this causal thinking, with 2 exceptions: linear growth retardation is a cause of difficult births and poor birth outcomes. Linear growth retardation is associated with (but does not cause) delayed child development, reduced earnings in adulthood, and chronic diseases. We thus propose distinguishing 2 distinctly different meanings of linear growth retardation and stunting. First, the association between linear growth retardation (or stunting) and other outcomes makes it a useful marker. Second, the causal links with difficult births and poor birth outcomes make linear growth retardation and stunting outcomes of intrinsic value. In many cases a focus on linear growth retardation and stunting is not necessary to improve the well-being of children; in many other cases, it is not sufficient to reach that goal; and for some outcomes, promoting linear growth is not the most cost-efficient strategy. We appeal to donors, program planners, and researchers to be specific in selecting nutrition outcomes and to target those outcomes directly. *Adv Nutr* 2019;0:1–9.

Keywords: stunting, linear growth retardation, undernutrition, causality, marker, child development, earnings, chronic disease, birth outcomes, global development objective

Introduction

Child undernutrition remains an important global health problem. Undernutrition increases susceptibility to illness and fatality, and if removed, 45% of child deaths would not occur. For surviving children, undernutrition has severe short-term (e.g., delayed cognitive development), medium-term (e.g., lower school achievement), and long-term consequences (e.g., lower earnings and higher probability of adult noncommunicable chronic diseases) (1).

The past decade has seen an unprecedented attention to undernutrition, as witnessed by examples of worldwide nutrition initiatives, global goal setting for nutrition, and high-level publications (2) (**Supplemental Text**). The goal of drastically reducing child stunting has taken center stage: the World Health Assembly's first global nutrition target is a 40% reduction by 2025 in the number of children <5 y old who are stunted (3).

The focus on linear growth retardation and stunting (see **Box 1** for definitions) has facilitated communication with policy makers, enabled successful advocacy for nutrition, and mobilized policy makers and donors to pay attention to undernutrition and its consequences. Rallying around stunting has contributed to garnering wide global support for nutrition which has been beneficial to the world. Building the strong and convincing stunting narrative, however, required leaving out important details about stunting's actual consequences. In this paper, we argue that along with the strong emphasis on linear growth retardation and stunting has come some confusion and misunderstanding about its meaning among researchers, donors, and agencies active in nutrition. Our paper is motivated by the concern that the current framing of stunting as the key global nutrition challenge has blurred our thinking. Not delivering on the ambitious stunting-reduction agenda may damage the current global nutrition momentum.

Box 1:
Linear growth retardation and stunting: what's the difference?

Linear growth retardation (or linear growth faltering) is defined as a failure to reach one's linear growth potential. Linear growth retardation implies that (groups of) children are too short for their age, but does not imply that they are stunted (see below). As explained in the text, the number of children suffering from linear growth retardation is much higher than the number of children that are stunted.

Stunting is defined as having a height-for-age *z* score (HAZ) <−2SD. HAZ is calculated by subtracting an age- and sex-appropriate median value from a standard population and dividing by the SD of the standard population (4). The 2006 WHO growth standards are the recommended standard (5). In a healthy population, ~2.5% of all children have a HAZ <−2SD. A higher percentage <−2SD is indicative of a deficient growth environment. Children who are stunted are a subset of those with linear growth retardation.

Our objective is to show that many outcomes commonly presented as consequences of linear growth retardation and stunting are not causally linked. We first illustrate how the nutrition community has emphasized the consequences of linear growth retardation and stunting and how this "causal" view has been widely adopted. Second, we critically review the scientific evidence linking linear growth retardation and stunting to other outcomes. Third, we recommend a fundamentally different evidence-based way of making use of linear growth retardation and stunting as measures of global development.

What the Nutritional Science Community Is Telling the World about Linear Growth Retardation and Stunting

Linear growth retardation and stunting are associated with undesirable short-, medium-, and long-term outcomes in 5 domains: *1)* delayed child development (6), leading to lower school achievement and reduced earnings; *2)* reduced physical strength and work capacity (7), leading to reduced earnings; *3)* physiologic changes, contributing to adult noncommunicable diseases and increased mortality (8, 9); *4)* increased risk of cephalopelvic disproportion, leading to dystocia, mortality, and morbidity (1); and *5)* undesirable birth outcomes in the next generation (10), i.e., low birth weight or small-for-gestational-age (SGA) infants more likely to die or not grow adequately.

The scientific literature commonly presents these associations as being causal, i.e., claiming that linear growth retardation and stunting are a cause of the negative outcomes in these 5 domains (**Figure 1A**). A recent comprehensive literature review on the association between undernutrition in childhood and economic outcomes shows that this is a widely held view; over half of the 68 papers on linear growth or height made direct causal claims linking linear growth retardation (or stunting) to the 5 outcome domains (11).

If linear growth retardation (or stunting) is a cause of these negative outcomes, then it logically follows that improving child linear growth will improve these outcomes. The causal claims imply that any intervention aimed at improving linear growth will subsequently and automatically lead to improved outcomes in these 5 domains. We argue below that this causal evidence exists only for the last 2 domains.

This causal view is strongly embedded in the nutrition community. An informal survey of agencies and donors active in nutrition shows that they have generally adopted the view that linear growth retardation and stunting is a cause of developmental delays, lower levels of schooling, reduced earnings, and chronic disease risk. Eliminating linear growth retardation and stunting have become a primary development objective, based in part on believing that their elimination will lead to meaningful benefits in a large number of other domains. The causal thinking has also triggered research on, for example, aflatoxin and catch-up growth.

Aflatoxin

The possible role of chronic exposure to aflatoxin (a mycotoxin produced by the fungus *Aspergillus* sp.) in the etiology of linear growth retardation and stunting is receiving increasing attention in the research and development community. The premise is that if aflatoxin exposure is a confirmed cause of linear growth retardation and stunting in children, then reducing aflatoxin exposure will ameliorate the negative consequences of poor growth (12–16). Since these consequences are limited (see subsequent sections), this motivation for researching the link between aflatoxin and linear growth is questionable. We add 2 nuances. First, effective aflatoxin control is important because aflatoxin is a group 1 carcinogen, and aflatoxin contamination of food crops impairs the ability of low- and middle-income countries to access export markets (16, 17). Second, aflatoxin (and mycotoxin) exposure may contribute to environmental enteric dysfunction, systemic inflammation, immunomodulation, and changes in the hepatic metabolism of micronutrients (14, 18). These short-term consequences (if confirmed) all warrant immediate preventive action. Furthermore, they all potentially limit

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Address correspondence to JLL (e-mail: j.leroy@cgiar.org).

Abbreviations used: BMIZ, BMI-for-age *z* score; HAZ, height-for-age *z* score; SGA, small for gestational age.

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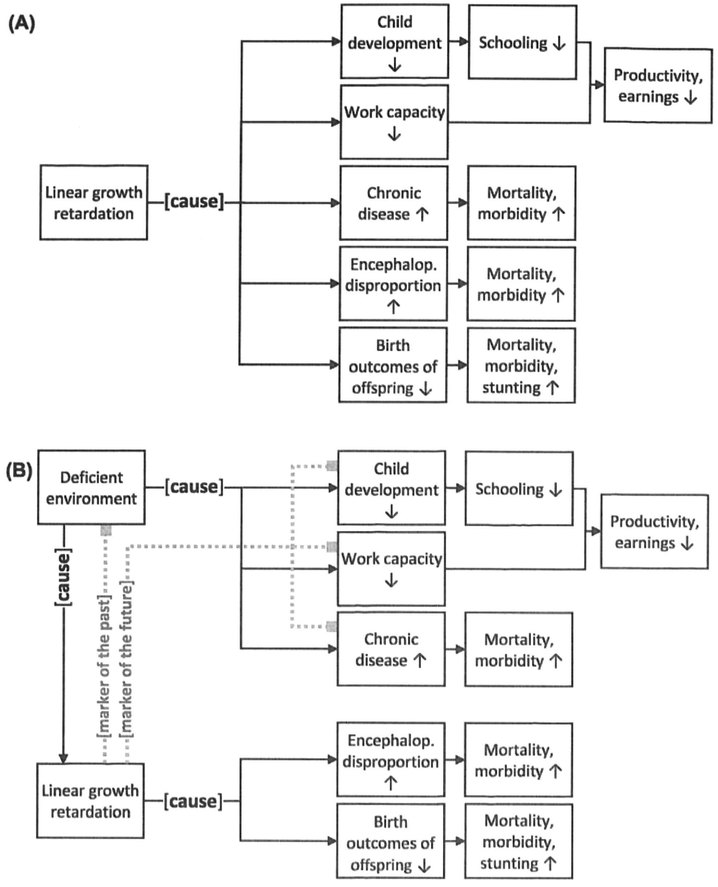

FIGURE 1 Commonly accepted framework showing the importance of linear growth retardation (A); and proposed framework distinguishing between child linear growth as an indicator reflective of the past, as indicator predicting the future, and as an outcome in its own right (B).

young children's ability to fully develop into healthy and productive adults (19–21). Research should focus on these potential consequences of mycotoxin exposure, rather than on its contribution to linear growth retardation and stunting.

Catch-up growth

Catch-up growth refers to accelerated growth that reduces a child's accumulated height deficit (22). Much recent work has reported catch-up growth in the absence of any nutrition intervention (23–28). Some studies reported an association between catch-up growth and child development, concluding that promoting growth during infancy and early childhood might contribute to better child development (25–28). These reports have received media attention (29). These conclusions are misleading for 2 reasons. First, much of the catch-up growth work has assumed that linear growth retardation and stunting negatively affect child (cognitive) development, and recovery from linear growth retardation or stunting is presented as if it will lead to improved cognitive outcomes (23–28). We show below that there is no evidence that linear growth and cognitive development are causally linked. Second, the recent studies use height-for-age *z* scores (HAZ), a measure that is statistically inappropriate to assess catch-up growth (22). In conclusion, none of these studies provided evidence of catch-up growth or determined that

catch-up growth has long-term positive consequences on child development. Rather, they confirm that better linear growth is associated with better cognitive development, which is in line with existing knowledge (6). We add 2 caveats. First, the motivation for a much-cited study on catch-up growth is maternal short stature as a cause of poor birth outcomes (30), but the analyses used the statistically inappropriate HAZ (22). Second, recovery from child linear growth retardation or stunting may or may not be possible, but the reviewed studies do not provide evidence that it is.

What Is the Evidence about Outcomes of Linear Growth Retardation and Stunting?

Linear growth retardation and developmental delays

Linear growth retardation is associated with reduced cognition and motor development in middle- and low-income countries (6); the association between stunted growth and socioemotional development has received less attention (6). Linear growth retardation and poor development are associated through a set of shared determinants (suboptimal nutrition, inadequate care, and repeated infections). Based on current understanding, however, linear growth retardation is not part of the mechanistic path leading to delayed cognitive, motor, or socioemotional development (31). Two mechanisms have been raised as potentially causal. The first one is the hypothesized direct effect of smaller body size on reduced motor activity, which would limit the child's ability to explore and access stimulation (6, 32) and reduce opportunities for language, socioemotional, and cognitive development (33). Motor development, however, appears to be a consequence of factors including balance, myelination, muscle strength, and endurance, but not of body length (34). The second potential mechanism is the Rosenthal effect, whereby short child stature lowers caregivers' expectations about children's developmental potential, which could then reduce the stimulation these children receive (31). This mechanism is not likely to be important in societies in which the majority of children suffer from some degree of linear growth retardation. In conclusion, there is no evidence that linear growth retardation (or stunting) causes delays in child development, and based on our current understanding of mechanisms, it is not likely that they are causally related.

Linear growth retardation and earnings

In both developed economies and low-income settings, earnings are associated with height (7). Taller individuals have more schooling and better skills, which could explain the association, but the height-earnings association remains after controlling for cognitive and socioemotional capacity (7). There are several reasons to question the causality of this association. First, we could not find evidence for a credible biological (or other) mechanism that would explain the effect of stature on earnings at the population level. Second, the height-earnings association in developed economies indicates that relative height (rather than height in absolute terms) is of importance. The association will therefore not disappear when linear growth retardation is eliminated since that would not remove the distribution of heights at the population level. Third, with the use of longitudinal data from the Oriente study in Guatemala, Behrman et al. (35) statistically separated the effects of physical and intellectual human capital on wages, treating both types of human capital as statistically endogenous. We are not aware of other studies that used this method. In this population largely active in the agricultural sector, only intellectual and not physical human capital increased annual income (35). We conclude that a causal link between linear growth retardation (or stunting) and lower earnings is not supported by current evidence.

Linear growth retardation and chronic diseases

Environmental influences during early development, such as poor nutrition, increase chronic disease risk later in life (36). Much early work on the developmental origins of disease focused on birth weight and infant size as measures of exposure (36, 37), which may have contributed to the belief that linear growth retardation and stunting are a cause of adult chronic disease risk (8, 9). Three interrelated categories of mechanisms underlying the effect of early environmental influences on chronic disease have been identified: changes in the structure and function of critical organs such as the brain, the pancreas, and the kidney; changes in gene expression; and changes in cellular senescence (37). Based on current knowledge, however, linear growth retardation and stunting are not part of the mechanistic path. Additionally, recent evidence from carefully conducted epidemiologic studies does not show an association between linear growth retardation (or stunting) and a number of chronic disease risk factors. Analyses of pooled data from 5 birth cohort studies in low- and middle-income countries (India, the Philippines, South Africa, Guatemala, and Brazil) showed that neither lower birthweight (birth length was not included) nor lower linear growth rates in the first 2 y of life were associated with increases in adult cardiovascular risk or plasma glucose concentration (38). A long-term follow-up of a South African cohort showed that children not stunted at 24 mo had a higher BMI-for-age *z* score (BMIZ) at 18 y than those who were stunted at 24 mo (39). Likewise, stunting at 12 mo of age in Peru was associated with a decreased risk of having a high BMIZ (40). We conclude that the evidence does not support a causal link between linear growth retardation (or stunting) and chronic disease.

Linear growth retardation and encephalopelvic disproportion

Linear growth retardation at childhood reduces adult height. Shorter stature in women at adulthood, in turn, is associated with a higher risk of dystocia or difficult labor (1). Mechanical dystocia, or cephalopelvic disproportion, is a major cause of maternal and neonatal mortality and morbidity; the sequelae have important social, economic, and marital consequences (41). The association between maternal height and difficult labor is mediated by the size of the pelvic inlet; shorter women have a smaller pelvic inlet and are thus more likely to

suffer from a mismatch between the size of fetal head and the dimensions of the birth canal (42, 43). Since both stature and pelvic size are linked to skeletal size, we can assume that the association between linear growth retardation at childhood and obstructed labor at adulthood is causal. Obstructed labor accounts for a small proportion (3%) of all maternal mortality or ~10,000 deaths/y (44). Its disability burden is important (40% of the total number of years lost due to disability among all maternal disorders), but has dropped significantly over time (45). Which proportion of the mortality and disability burden could be averted by eliminating maternal short stature is not known. In conclusion, short stature and obstructed labor are causally linked, their mortality and morbidity burden is relatively small and declining, and the fraction of the mortality and morbidity burden attributable to linear growth retardation earlier in life is not known.

Linear growth retardation and birth outcomes

A short mother (which could be due to linear growth retardation during her childhood) is more likely to have SGA children. This association is considered causal and due (in part) to maternal physical constraints associated with short stature (10). SGA children are at increased risk of neonatal and infant mortality and morbidity during the neonatal period and beyond (46). Being SGA is also responsible for up to 20% of stunting in children between the ages of 1 and 5 y (47). Maternal short stature is associated with an estimated 6 million SGA births in low- and middle-income countries annually (or ~18.4% of the total) (44). Reducing SGA from its current prevalence of 19.3% in these countries to 10% would reduce neonatal deaths by 9.2% (or prevent 254,600 deaths) (48). Combining both estimates, eliminating SGA births that are due to maternal short stature would reduce neonatal deaths by an estimated 3.6% (or 97,200 deaths globally), a small proportion of the global total. Which proportion of the SGA-associated morbidity could be averted when eliminating maternal short stature is unknown. In conclusion, linear growth retardation at childhood is causally linked to an increased risk of giving birth to SGA children. Eliminating maternal short stature would have a modest effect on neonatal mortality and an unknown effect on child morbidity.

Distinguishing between Linear Growth Retardation and Stunting as a Marker Compared with as an Outcome

Linear growth retardation and stunting are associated with—but based on available evidence do not cause—delayed child development, reduced earnings at adulthood, and chronic diseases. Linear growth retardation is a cause of difficult birth and poor birth outcomes. From these findings, we identify 2 distinct uses of linear growth retardation and stunting. First, the association between linear growth retardation (or stunting) and other outcomes makes it a useful marker. Second, the causal links with difficult birth and poor birth outcomes makes linear growth retardation and stunting outcomes of intrinsic value (Figure 1B). This marker compared with outcome distinction in relation to linear growth retardation and stunting has been made previously (49, 50).

Linear growth retardation and stunting as markers reflective of past and predictive of future

Healthy linear growth requires children to consume adequate diets, to receive proper care, and to be healthy. These immediate determinants depend on food security, caregivers' nutrition and health knowledge, and access to and proper use of health services (1). A change in the severity of linear growth retardation (or stunting) is indicative of changes in these immediate and underlying determinants. Linear growth retardation and stunting are markers of the inadequacy of the environment to which children have been exposed.

Since linear growth retardation and poor cognition share many of the same determinants (including suboptimal nutrition, inadequate care, and repeated infections), improvements in these determinants can be expected to improve both growth and cognition. Improved linear growth does not lead to improved cognition per se, but it can predict better cognition. Linear growth retardation and stunting in groups of children predict future poor school achievement and progress, lower cognition, reduced earnings, and a higher probability of living in poverty (51, 52).

Linear growth retardation and stunting often are used implicitly as markers of both the past and future. When a high stunting prevalence is reported for a region, 2 messages are implied. First, children grow up in a deficient growth environment. Second, as a consequence of growing up in this environment, they are unlikely to realize their full developmental and economic potential in the future.

Linear growth retardation and stunting as outcomes of intrinsic value

Linear growth retardation is causally linked to difficult child birth and poor birth outcomes. Linear growth retardation is therefore an outcome of intrinsic value, since a reduction in linear growth retardation (or stunting) is expected to directly improve these outcomes. Linear growth here is part of the mechanistic path and not just a marker of other outcomes (Figure 1B).

Just Semantics?

A more careful distinction between linear growth retardation (or stunting) as a marker compared with an outcome has a number of practical implications.

Improving linear growth is often not necessary

Interventions may positively and meaningfully affect important nutrition outcomes without providing the dose or inputs necessary to improve linear growth. That is, for many nutrition outcomes (e.g., infant and young child feeding

practices, dietary adequacy, and micronutrient status), nutrition interventions will have positive, meaningful, and observable effects before linear growth improves. For example, a combination of interpersonal counseling, a national mass media campaign, and community mobilization in Vietnam and Bangladesh successfully improved complementary feeding practices, but not linear growth (53, 54). Impacts on linear growth retardation or stunting possibly required larger improvements in feeding practices or improvements in other determinants such as health. Furthermore, equating lack of impact on linear growth to program failure discounts the importance of other outcomes and interventions to improve them. Finally, several nutrition interventions are highly effective at improving children's well-being but have no effect on linear growth. Optimal breastfeeding and vitamin A supplementation, for instance, reduce morbidity and mortality but do not improve linear growth (1).

Improving linear growth is not sufficient

Eliminating linear growth retardation is not sufficient to ensure children develop to their full potential. Children who grow adequately, but who lack adequate stimulation at home or attend poor-quality preschool and primary education, are unlikely to fully develop.

Improving linear growth may not efficiently address other outcomes

Addressing outcomes associated with linear growth retardation or stunting directly is likely more efficient than addressing these outcomes indirectly through linear growth. The effect size of nutrition interventions on cognitive outcomes is an estimated 4–5 times smaller than that of interventions providing stimulation (31). Other examples include addressing the problems of obstructed labor and SGA for which other strategies are more efficient than reducing linear growth retardation (Supplemental Text).

Eliminating fatalism

The observation that the first 2 y of life are the period of most rapid growth failure (55) and interventions beyond this age have little or no impact on child linear growth (56) have led to a view that interventions outside this window are unlikely to have meaningful effects (30). Linear growth retardation continues beyond the first 1000 d (57), however, and the biological window of opportunity for improving linear growth does not necessarily coincide with windows for other outcomes. Regions in the brain responsible for higher cognition (e.g., reasoning, problem solving) have a maturational course that extends into adolescence (58). The focus on the first 1000 d should be maintained, but nutrition, health, and development efforts need to extend beyond this period. Current evidence does not provide good guidance on which interventions to implement after 2 y of age or what improvements in which domains could be expected. Research is needed to assess the potential to improve nutritional status beyond 2 y of age (59), to test the impact of different packages of interventions on undernutrition and its functional consequences, and to identify optimal timing for improving these outcomes cost effectively, without increasing chronic disease risk.

Getting other sectors on board for nutrition-sensitive interventions

Solving the world's nutrition problems will require both nutrition-specific and nutrition-sensitive interventions (60). Nutrition-sensitive interventions both address the underlying causes of undernutrition (e.g., poverty and food insecurity) and incorporate specific nutrition goals and actions. The narrow focus on linear growth as a nutrition outcome, however, may create a barrier for other sectors to engage. Nutrition-sensitive agriculture programs, for instance, can contribute to improving access to and consumption of high-quality diets, but these programs cannot alone improve linear growth (61). Likewise, nutrition-sensitive social protection can reduce poverty and improve food security, but should not be expected to directly improve child growth.

Proposed Way Forward

The need for specificity

Donors, program planners, and researchers in nutrition should be specific in using terminology and avoid using undernutrition and linear growth retardation (or stunting) as synonyms, as is often done. Many forms of undernutrition are biologically unrelated to linear growth retardation and stunting, and linear growth retardation and stunting are not merely a consequence of nutritional inadequacy. Linear growth retardation and stunting are not synonyms (Box 1). Donors, program planners, and researchers should be explicit about reasons for focusing on linear growth: is it used for population assessment, to count those affected, or in program design and evaluation? In programs, is it used as a marker of another outcome (and why is that outcome not addressed directly) or is it an outcome of immediate interest (and why was it chosen as an objective)?

Population assessment

Because linear growth retardation and stunting mark the inadequacy of the environment to which children have been exposed, they provide a good indicator for population assessment. The severity of linear growth retardation and stunting in groups of children can be used to compare countries or regions within a country, and can be used to monitor progress of children of the same age distribution over time.

Counting cases

The use of stunting (defined as an HAZ <−2SD) to count the number of children affected has inherent limitations (62). First, there is no biological or clinical basis for the arbitrary cut-off; nothing changes just above or below −2SD. Second, the number of stunted children vastly underestimates the number of children who are affected by an inadequate growth environment, as the entire HAZ distribution is shifted in

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populations with a prevalence of stunting >2.5% (62, 4). In Burundi, for instance, 65% of children between 24 and 42 mo of age were counted as stunted (63). The entire HAZ distribution was shifted to the left, which implies that a much larger percentage, if not all children, suffered from a deficient growth environment. Moreover, estimates that use stunting to count those affected will be inaccurate. For instance, estimating the cost per case of stunting averted assigns all program costs to the (few) children who crossed the cut-off and ignores the benefits incurred by others, thus underestimating impact and inflating costs relative to effectiveness. Nevertheless, relative differences in stunting prevalence are useful for population assessment, e.g., to compare countries or changes in populations with the same age distribution over time.

Programs, interventions, and impact evaluation

Although relatively easy to assess, linear growth retardation and stunting should not be a primary outcome for the purposes of evaluating programs and interventions. Linear growth retardation and stunting are causally linked to only 2 negative outcomes which can be more effectively addressed through direct interventions. Donors and implementers should select primary outcomes that are directly relevant, such as early childhood development, dietary adequacy, nutrient status, and health, thereby eliminating the risk of reducing a program's success to its ability to improve linear growth. Assessing outcomes such as early childhood development, dietary adequacy, and nutrition status are currently more difficult and costly than measuring child length or height. A wider use of these outcomes may, however, spark investments in the development of more field-friendly measures. Assessing linear growth as a secondary outcome might be useful to evaluate if a program was successful in improving the full set of conditions necessary for linear growth.

Conclusions

The current global attention to undernutrition provides an unprecedented opportunity to improve the well-being of billions of people, with positive consequences for their health, development, schooling, and earnings. Rallying around linear growth retardation and stunting has resulted in extraordinary nutrition momentum, but a narrow focus on these outcomes could have important downsides going forward. Equating lack of impact on linear growth retardation or stunting to program failure unnecessarily discounts other important outcomes and interventions to improve these conditions. In many cases a focus on linear growth retardation and stunting is not necessary to improve the well-being of children; in many other cases, it is not sufficient to reach that goal; and for some outcomes, promoting linear growth is not the most cost-efficient strategy. To maintain global nutrition momentum, a sharp focus of nutrition investments, policies, and programs on outcomes that truly matter will help accelerate progress towards the well-being of children in disadvantaged communities.

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