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Protein-Energy Supplementation in Early-Life Decreases the Odds of Mental Distress in Later Adulthood in Guatemala

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ABSTRACT

Background: The prevalence of mental health concerns is growing worldwide, along with lack of access to and receipt of needed treatment. Current gaps in treatment provision have led to exploring alternative methods of prevention, with research linking nutrition and mental health, of particular relevance in low- and middle-income countries, with a high prevalence of undernutrition.

Objectives: To examine whether exposure to a protein-energy nutritional supplement during the first 1000 d of life decreased odds of mental distress in adulthood among men and women in Guatemala compared with receiving a low energy-no protein supplement or supplementation outside the 1000-d window.

Methods: Data from participants (n = 1249) in a longitudinal cohort protein-energy supplementation trial (early-life, supplementation data from 1969 to 1977, ages 0–7 y; life course, outcome data from 2017–2018 follow-up, ages 40–57 y) were analyzed for associations between nutrition in the first 1000 d and mental distress in adulthood (WHO Self-Reporting Questionnaire 20 [SRQ-20]), controlling for early-life variables and current life stress; life course variables (e.g. education) were examined as potential mediators of this relation. Generalized linear mixed models and zero-inflated Poisson generalized linear mixed models were utilized.

Results: Both partial and full supplementation with *Atole* during the first 1000 d were associated with 63% (95% CI: 0.16, 0.87) and 56% (95% CI: 0.19, 1.03) lower odds, respectively, of experiencing mental distress in adulthood. Results did not differ by sex. These inverse relations remained relatively unchanged (partial OR = 0.34 [95% CI: 0.14, 0.83]; full OR = 0.38 [95% CI: 0.16, 0.92]) after controlling for early-life and life course variables, including life stress.

Conclusions: Protein-energy supplementation during the first 1000 d of life in Guatemala, where undernutrition is prevalent, may reduce the prevalence of later mental distress in adulthood. This effect appears to occur directly, rather than indirectly, through pathways of life course variables such as education, wealth, and marital status. *J Nutr* 2022;152:1159–1167.

Keywords: early childhood nutrition, protein-energy supplementation, adult mental distress, longitudinal cohort, prevention, low- and middle- income countries

Introduction

The prevalence of mental health concerns has continued to grow worldwide, with increased recognition as a significant public health issue (1). The WHO estimates that globally, 7.4% of disability-adjusted life years (DALYs; number of years lost) are caused by disorders in the mental and behavioral disorders category, with depressive disorders as one of the major contributors (2). Demand for mental health services has increased with the COVID-19 pandemic, along with significant disruptions in access to already underfunded services (3). In Latin America and the Caribbean, 5% of the adult population suffers from depression, with 6 out of 10 affected people not receiving any mental health treatment (4).

The current gaps in treatment provision for mental health globally have led to the exploration of alternative methods of prevention. One area of growing interest is research linking nutrition and mental health, leading to the growing field of psychoneuro-nutritional medicine (5). An increasing body of evidence from observational studies suggests that poor

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nutritional status (e.g. protein malnutrition, iron deficiency) during early childhood may be associated with behavioral difficulties among children as they get older (e.g. externalizing problems; impaired social behavior) even after controlling for social adversity (6–9). For example, Jacka et al. (6) in the large prospective Norwegian Mother and Child Cohort Study found that children with postnatal diets of lower nutritional quality had higher levels of both internalizing and externalizing problems at 5 y, independently of potentially confounding factors. In another study, young children with indicators of malnutrition (i.e. protein malnutrition, vitamin B-12 deficiency, anemia) showed impaired social behavior compared with children in a control group with adequate nutritional status (7).

Intervention and review studies suggest that amino acid or micronutrient supplementation may also reduce mental health and behavioral concerns (e.g. aggression, anxiety, depression, inattention) in early childhood and adolescence (10–13). Berglund et al. (10) found that low birthweight infants aged 6 wk to 6 mo supplemented with iron exhibited fewer behavioral problems at 3 y compared with controls. Reductions in behavior problems among children aged 8–16 y (11) and in antisocial and aggressive behavior among young offenders (mean age 19 y) (12) have also been found following supplementation with Omega-3. Amino acid supplements have been found to reduce symptoms of depression in adolescence, as they are converted to neurotransmitters which in turn alleviate depression and other mental health disorders (13). Few, if any, studies have examined the impact of protein-energy supplementation early in life on the mental health of children and adults, particularly in areas where malnutrition is high.

Protein-energy deficiency in early-life may affect mental health directly or indirectly via various pathways throughout the life course (see **Figure 1**). The basic architecture of the brain develops through an ongoing process that begins before birth and continues into adulthood, with foundations for optimum health, growth, and neurodevelopment established in the first 1000 d of life (14). Optimal nutrition during this period is critical for brain growth and neurodevelopment, potentially affecting lifelong health and mental health (15). Protein intake and the individual amino acids that make up protein can affect brain functioning and mental health through their effects on the development of neurotransmitters in the brain which are made from amino acids. For example, the neurotransmitter dopamine is made from the amino acid tyrosine and the neurotransmitter serotonin is made from tryptophan. Low dietary intake of these amino acids can result in reduced synthesis of the respective neurotransmitters which is associated with low mood and aggression (13, 16). Having adequate protein early in life may directly impact the neurochemical pathways necessary for optimal mental health and behavior.

Several sociocultural factors associated with mental health may also be impacted by nutritional intake, suggesting a possible indirect effect of early supplementation on later mental health (Figure 1). Studies have shown positive associations of level of education (17, 18), socioeconomic status (19), and marital status (20) with mental health. Early childhood nutrition, including protein-energy supplementation, has been shown to have positive effects on schooling (21, 22), and on later health and economic productivity (23, 24), which may affect later relationship status. For example, early protein-energy supplementation with *Atole* positively impacted schooling and income in a longitudinal cohort in Guatemala (22, 24). Thus, in addition to a potential direct effect on later mental health, early protein-energy supplementation may influence mental health indirectly through effects on various relevant sociocultural factors.

Data pertaining to the long-term effects of early childhood malnutrition on behavioral outcomes in adulthood are limited. Some studies have suggested behavioral effects from poor nutrition in early childhood persist into adulthood, including natural experiment data from the Chinese famine showing that women born during the famine years had an increased risk of mental illness during adulthood compared with women who were unexposed and born a few years later (25, 26). However, it is difficult to ascertain what other factors related to the famine (e.g. parental stress over lack of food availability, etc.) may have also influenced women's mental health later in life. The Institute of Nutrition of Central America and Panama (INCAP) Nutrition Trial Cohort Study in Guatemala (27) provides an excellent opportunity for the current study to examine the long-term impact of a protein-energy nutritional supplement (*Atole*) provided to mothers and children during the first 1000 d on adult mental distress measured 40–50 y later, controlling for various sociocultural factors that may also influence mental health, including current life stress (28). Data are available on early nutritional status, intermediate sociocultural variables such as education, socioeconomic and marital status, and older adult measures of current life stressors and mental distress.

Methods

All data collection followed protocols that were approved by the Institutional Review Boards of Emory University (Atlanta, GA; Protocol 95960) and the INCAP Institutional Ethics Committee (Guatemala City, Guatemala). All participants gave written informed consent at each survey wave before participation.

Participants

The INCAP Nutrition Trial Cohort Study (27) was initiated as an experimental nutrition supplementation program (1969–77) for mothers and children aged 0–7 y belonging to 4 villages in Guatemala. Children were included if they were < 7 y at the time of the study launch or born during the supplementation period, with follow-up until age 7 y or until the study ended in 1977. For children born during the study period, pregnancies were prospectively followed from detection to determine if the child was born at term. All participants born into the study were born at term; this information was not available for those born prior to the study.

Protein deficiency was identified as the main cause of malnutrition at the time the study was planned so the focus was on improving protein malnutrition while assuring enough extra energy to allow for protein use; the supplement was designed to be additive to the children's diet (29). Random allocation of *Atole* – an energy and protein drink or *Fresco* – a lower energy drink with no protein or fat was done among 4 villages in the department of El Progreso, a mountainous area

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Abbreviations used: CMD, common mental disorders; DALY, Disability Adjusted Life Year; INCAP, Institute of Nutrition of Central America and Panama; LMIC, low- and middle-income countries; SRQ-20, WHO Self-Reporting Questionnaire 20.

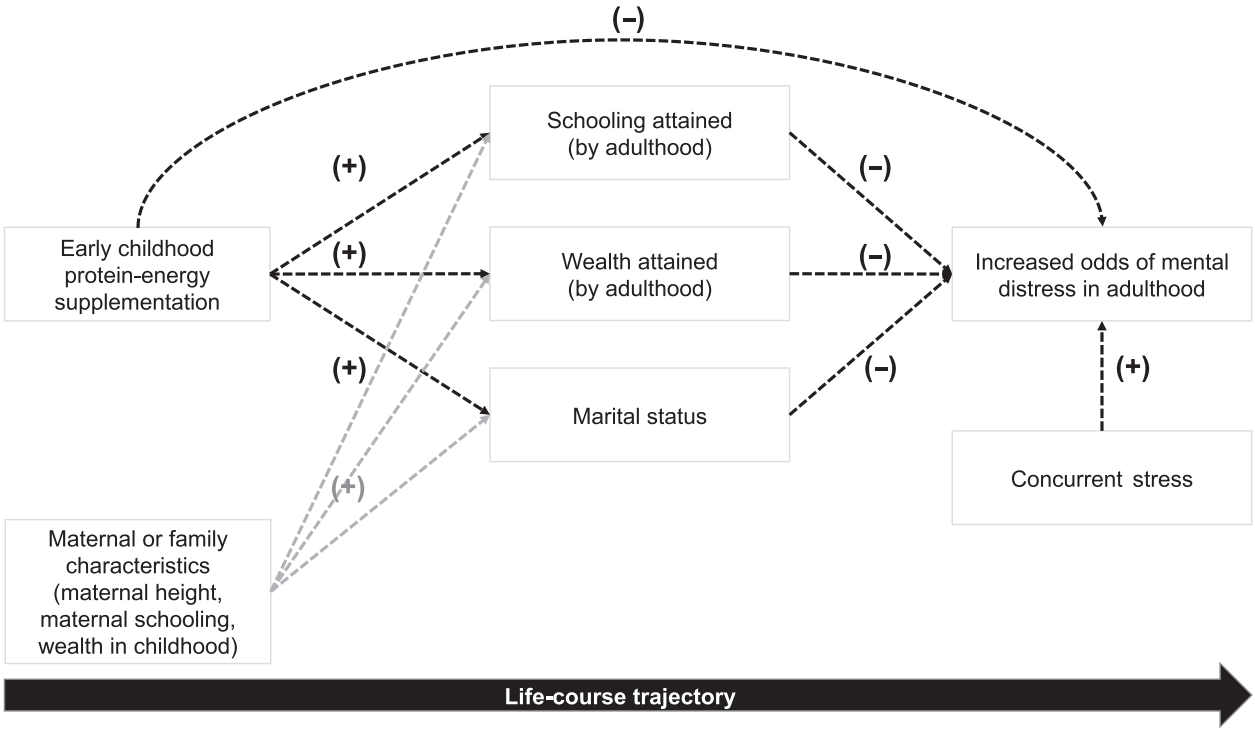

FIGURE 1 Potential direct and indirect effects of early protein-energy supplementation on mental distress in Guatemalan adults.

northeast of Guatemala City, paired to be as similar as possible; 1 pair of villages was relatively large (~900 people) and the other pair was small (~500 people). Villages were selected and matched on ethnicity (100% Spanish speaking, Ladino culture), population, birth rate, death rate, age distribution, family composition, population mobility, social isolation, transportation, housing, income, education and health, and nutrition indicators (more details in Habicht & Martorell [29] and Melgar et al. [30]). Data from the initial study showed that protein-energy malnutrition was initially prevalent among mothers and children, and that children supplemented with *Atole* exhibited significantly greater positive changes in growth than those supplemented with *Fresco*, taking into account participation and ingestion rates (29, 31, 32). For example, during the first year of life, each 100 kcal/d of *Atole* supplement was associated with ~9 mm in additional length gain and 350 g in additional weight gain; the benefit decreased to ~5 mm in length gain and 250 g in weight gain during the second year of life. *Atole* intakes represented ~10–16% of the RDA for energy intake and *Fresco* intakes about 1–7% of RDA (32).

Among the 2392 original participants, 1267 (53.0%) participated in the study follow-up conducted in 2017–18 (ages 40–57 y) which forms the basis of the current study. Our analytic sample consisted of the original participants residing in Guatemala who provided data for the WHO Self-Reporting Questionnaire 20 (SRQ-20) and the Holmes–Rahe Stress Inventory during 2017–18 (n = 1249; see **Supplementary Figure 1**).

Measures

Exposure: Early nutritional supplementation with Atole.

The current study assesses the impact of receiving *Atole* during the first 1000 d on the odds of experiencing mental distress in adulthood. The original study participants were assigned to *Atole* or *Fresco* by their village of birth. *Atole* was composed of 13.5 g of Incaparina (a nutritious gruel with high vegetable protein and moderate energy content highly accepted in Guatemala), 21.6 g of dry skim milk, and 9 g of sugar, totaling 163 kcal of energy and 11.5 g of protein per 180 mL/cup serving, compared with *Fresco* which was composed of 13.3 g of sugar, with 59 kcal of energy, and 0 g of protein. Both drinks were similarly fortified with micronutrients (e.g. iron, riboflavin, vitamin A) in equal quantities per unit volume (see Habicht and Martorell Table 3 for more specific details on the supplement composition) (29). We classified the level of exposure in the first 1000 d of life (from conception through to age 24 mo) to either intervention (*Atole* or *Fresco*) as a nominal variable – full exposure, partial exposure, or no exposure, by date of birth, and duration of trial (1 March, 1969 to 28 February, 1977). The referent group for the study included those who received *Fresco* at any age or those who may have received *Atole* but outside the 1000-d window. We used an intent-to-treat analysis, in which exposure was defined solely on the basis of village of birth (which defines exposure to *Atole* or to *Fresco*) and date of birth, which defines the age at which the participant was exposed. We have previously reported that consumption of the supplement varied by village, by age, and by distance from the participant's home to the study feeding center (33); however, modeling individual intakes is beyond the scope of the current article.

Outcome: Mental distress.

The SRQ-20 (34) was collected to assess symptoms of psychological distress in the 2017–2018 follow-up. The SRQ-20 is a 20-item (4 physical items; 16 emotional items) screening instrument used to identify suspected cases of Common Mental Disorders (CMD). The instrument has been used successfully in multiple low- and middle-income countries (LMIC), and has been found to be reliable, valid, and adaptable for screening CMD in many countries (35–37). Each question is answered as a "Yes" = 1 or "No" = 0; total scores can range from 0–20, with higher scores indicating higher psychological morbidity. The outcome variable for this study is mental distress, defined as an SRQ-20 score ≥7 for both males and females, based on cut-offs used previously in Brazil (37). We included only those individuals who had completed the SRQ-20 as this was the main outcome of interest. Information on available behavioral and mental health resources was provided to participants who reported higher levels of mental distress.

Covariates.

Early-life variables. Maternal schooling (in years), maternal height (in cm), and birth year of the child were collected at enrollment and included as continuous variables. Household wealth was computed as the first component of a principal component analysis which used

assets and housing characteristics during early life (1969–77) (38). Maternal height was standardized by subtracting the mean and dividing by the SD to ensure models ran smoothly.

Life course events. Years of completed schooling and relationship status (married or in a relationship = 1; else = 0) were collected in 2017–2018. Household wealth was also collected in adulthood (2017–2018) and computed similarly to the early-life variable. Current residence was categorized as urban or rural.

Current life stress. Adult life stress was measured in 2017–2018 with the Holmes–Rahe Stress Inventory (39, 40). The Holmes–Rahe consists of 43 major stressful life event items, each of which has a weighted score based on the degree of upheaval or change the event may cause in one's life. The greater number of events over the last year, and the higher the score, the higher the likelihood of the individual experiencing a stress-related illness. A total score of ≤150 suggests a low level of stress and a low probability of developing a stress-related disorder. Scores ≥300 suggest an 80% chance of getting ill in the next 2 y (40). We categorized scores of ≥300 points as high stress. The Holmes–Rahe has been used successfully across several different cultures and countries (40).

Statistical analyses

Continuous variables were reported as means and SDs (if normally distributed) or median and IQR (for nonnormally distributed). Categorical variables were reported as frequency and percentage. We reported descriptive statistics for the sample overall and after visually examining the distribution of the SRQ-20, we reported descriptive statistics by category of mental distress (score ≥7) for males and females. We used a generalized linear mixed model with logit link adjusting for clustering by maternal identifier (since many participants in our study were siblings). We adjusted for early-life and adult life course characteristics to study the differential association of periods of exposure in the first 1000 d and nutritional intervention on mental distress. We fitted the double difference model:

$$\begin{aligned} logit(E[Mental\ Distress_{im}]) &= \beta_0 + \gamma_m + \beta_1 ATOLE_{im} \\ &+ \beta_2 (PERIOD = FULL)_{im} + \beta_3 (PERIOD = PARTIAL)_{im} \\ &+ \beta_4 (PERIOD = FULL)_{im} \times ATOLE_{im} \\ &+ \beta_5 (PERIOD = PARTIAL)_{im} \times ATOLE_{im} \\ &+ \delta X \gamma_m \sim N(0, \tau^2) \end{aligned} \quad (1)$$

where X describes the covariates adjusted for in the model.

Models addressed the relations diagramed in Figure 1, examining the direct impact of *Atole* on mental distress, and the relations when including potential life course mediating variables and current life stress.

Model 1 assesses the direct impact of *Atole* in early-life on adult mental distress, while adjusting for the early-life variables of sex, birth year, early wealth, maternal height, and maternal schooling.

Model 2 assesses the potential mediating role of certain life course variables (attained schooling, marital status, wealth in 2017–2018, current rural residence) on the direct effects of *Atole* on adult mental distress, while also controlling for the early-life variables in Model 1.

Model 3 assesses whether the addition of current life stress alters the impact of *Atole* on later mental distress or relations with potential mediating life course variables, while also controlling for the early-life variables in Models 1 and 2.

We additionally modeled the SRQ-20 score as a discrete outcome, with each reported symptom treated as a count. We used zero-inflated Poisson generalized linear mixed models with log link. Such models are useful when the underlying assumption is that the outcome follows a log-linear distribution but there is an excess of zero counts reported. We adjusted for clustering by maternal identifier. The model consists of 2 parts for the 2 processes: a logistic regression to predict reporting excess zero counts, and a log-linear (Poisson) model for counts. We modeled the logistic part of the zero-inflated model using sex as a predictor and assessed the extent of zero-inflation after model fitting using simulated zeros. Coefficients from the log-linear part of the model could be interpreted as RRs of expected outcome for unit change in the exposure variable after adjusting for covariates. We followed progressive adjustment for covariates, similar to the generalized linear mixed model with logit link.

We explored interactions with sex in the models; as these were not significant, we present results for the pooled sample of men and women.

As a sensitivity analysis, we varied the SRQ-20 threshold to define mental distress separately for males (using cut-off scores ranging from 2 to 5) and females (using cut-off scores ranging from 4 to 7) to assess if the associations observed were an artifact of the thresholds used. We also examined results with a cut-off of ≥9 to identify more severe mental distress. Based on these analyses, we confirmed use of the cut-off ≥7 to define general mental distress for men, women, and the pooled sample (data not shown).

All analysis was carried out using R 3.5.1, package 'lme4' 0.6.3, package 'glmmTMB' 1.0.1, package 'DHARMa' 0.3.1, and tidyverse 1.3.0.

Results

Sample characteristics

Among the final sample of 1249 participants for whom data on the SRQ-20 were available, 56% were female (**Table 1**). Early-life characteristics included low maternal schooling (median = 1 y) and short maternal stature (148 ± 5.1 cm). In midlife, participants reported a median of 6 y of attained schooling; the majority of participants were married or in a relationship (77.4%) and living in a rural residence (72.8%). A total of 19.5% reported mental distress and 13.9% reported a high level of life stress.

A total of 48 (8.7%) males and 196 (28.2%) females reported mental distress as per a prespecified cut-off. Those who reported mental distress were similar to those who did not on early-life characteristics such as birth year, early-life wealth, maternal schooling, and maternal height. There were differences between the 2 groups among both males and females by attained years of schooling, adult wealth, rural residence, and the Holmes–Rahe stressful life events score; a higher percentage of distressed participants noted elevated stressful life events scores compared with those not experiencing mental distress. Table 1 includes a summary of these characteristics.

Early-life and life course variables with mental distress in adulthood

Bivariate relations of various early-life and life course variables with mental distress, controlling for sex are noted in **Table 2**. In logistic regressions, number of years of attained schooling, being married or in a relationship, being higher on the wealth index, and rural residence were all significantly inversely associated with experiencing mental distress in adulthood. Having higher scores on the stressful life events scale was significantly associated with higher odds of experiencing mental distress. Similar results, with the exception of rural residence (still inversely associated but not significant), were found when mental distress was considered as a discrete outcome using Zero-inflated Poisson regression (RR) (Table 2).

Early childhood nutrition and mental distress in adulthood

Table 3 shows results from a series of sequential models examining the impact of early nutritional supplementation on mental distress in adulthood, controlling for sex, early-life factors, and subsequently life course variables and current

TABLE 1 Summary of participant characteristics at baseline and at follow-up in 2017–2018, overall and by category (yes/no) of mental distress ($n = 1249$)[1]

		Pooled			Male			Female		
	All ($n = 1249$)	No ($n = 1005$, 80.5%)	Yes ($n = 244$, 19.5%)	*P* value	No ($n = 505$, 91.3%)	Yes ($n = 48$, 8.7%)	*P* value	No ($n = 500$, 71.8%)	Yes ($n = 196$, 28.2%)	*P* value
SRQ-20 Score Median (IQR)	3 (1; 6)	2 (0; 4)	9 (8; 12)	<0.001	1 (0; 3)	9 (8; 11)	<0.001	3 (1; 4)	9 (8; 12)	<0.001
Early-life variables										
Atole village *n*(%)	657 (52.6%)	508 (50.5%)	149 (61.1%)	0.004	253 (50.1%)	35 (72.9%)	0.004	255 (51.0%)	114 (58.2%)	0.106
Exposure in first 1000 d, *n* (%)										
None	304 (24.3%)	245 (24.4%)	59 (24.2%)	0.726	114 (22.6%)	13 (27.1%)	0.776	131 (26.2%)	46 (23.5%)	0.553
Partial	435 (34.8%)	345 (34.3%)	90 (36.9%)	—	177 (35.0%)	16 (33.3%)	—	168 (33.6%)	74 (37.8%)	—
Full	510 (40.8%)	415 (41.3%)	95 (38.9%)	—	214 (42.4%)	19 (39.6%)	—	201 (40.2%)	76 (38.8%)	—
Birth year, median (IQR)	1970 (1967; 1974)	1970 (1967; 1974)	1970 (1967; 1974)	0.932	1970 (1967; 1974)	1970 (1966; 1973)	0.500	1970 (1966; 1973)	1970 (1967; 1974)	0.635
Wealth in 1969–1977,[2] mean ± SD	-0.30 ± 1.42	-0.30 ± 1.43	-0.31 ± 1.39	0.906	-0.33 ± 1.43	-0.29 ± 1.18	0.818	-0.26 ± 1.44	-0.31 ± 1.44	0.672
Maternal height (cm),[3] mean ± SD	148 ± 5.10	148 ± 5.13	149 ± 4.61	0.295	148 ± 5.05	148 ± 3.99	0.893	148 ± 5.21	149 ± 4.72	0.255
Maternal schooling (y),[4] median (IQR)	1 (0; 2)	1 (0; 2)	0 (0; 2)	0.508	1 (0; 2)	1 (0; 2)	0.959	0 (0; 2)	0 (0; 2)	0.726
Life course events										
Wealth in 2017–2018,[2]										
Mean ± SD	0.21 ± 0.64	0.25 ± 0.63	0.04 ± 0.65	<0.001	0.24 ± 0.64	-0.12 ± 0.72	0.002	0.27 ± 0.63	0.08 ± 0.62	0.001
Attained schooling (y), median (IQR)	6 (2; 6)	6 (2; 6)	3 (1; 6)	<0.001	6 (3; 6)	3 (1; 6)	<0.001	5 (2; 6)	3 (1; 6)	0.036
Married or in a relationship *n* (%)	967 (77.4%)	798 (79.4%)	169 (69.3%)	0.001	426 (84.4%)	33 (68.8%)	0.011	372 (74.4%)	136 (69.4%)	0.213
Rural residence *n* (%)	909 (72.8%)	746 (74.2%)	163 (66.8%)	0.024	377 (74.7%)	33 (68.8%)	0.471	369 (73.8%)	130 (66.3%)	0.061
Current life stress										
Stressful Life Events Score ≥300 *n* (%)	174 (13.9%)	124 (12.3%)	50 (20.5%)	0.001	85 (16.8%)	14 (29.2%)	0.053	39 (7.80%)	36 (18.4%)	<0.001

[1]Continuous variables were summarized as mean ± SD (if normally distributed) or median (IQR). Categorical variables were summarized as *n* (%). Cut-off for Self-Reporting Questionnaire-20 (SRQ-20) to signify mental distress was ≥7 for both males and females.

[2]Household wealth was computed as the first component of a principal component analysis which used assets and housing characteristics during early life (1969–1977) and later in adulthood (2017–2018); a higher value indicates a higher relative wealth.

[3]Information on maternal height available for 455 males and 581 females; the WHO considers maternal height <150 cm as extremely short (47, 48).

[4]Information on maternal schooling available for 535 males and 677 females.

TABLE 2 Bivariate relations between early-life and life course variables and mental distress among adults in Guatemala ($n = 1249$; SRQ-20 ≥7)[1]

Early-life and life course variables	Logistic regression: OR (95% CI)	Zero-inflated Poisson regression: RR (95% CI)
Birth year	1.00 (0.96, 1.04)	0.99 (0.99, 1.00)
Wealth in 1969–1977	0.99 (0.88, 1.11)	1.03 (0.99, 1.07)
Maternal height (z-scores)[2]	1.07 (0.9, 1.26)	1.02 (0.96, 1.09)
Maternal schooling (years)	0.98 (0.88, 1.1)	0.99 (0.95, 1.02)
Attained schooling (years)	0.91 (0.87, 0.95)	0.96 (0.95, 0.97)
Marital status (married or in relationship)	0.66 (0.46, 0.94)	0.91 (0.83, 0.99)
Wealth in 2017–18	0.69 (0.59, 0.81)	0.85 (0.82, 0.88)
Current rural residence	0.70 (0.49, 0.99)	0.98 (0.89, 1.08)
Stressful Life Events Score ≥300	2.57 (1.67, 3.94)	1.36 (1.23, 1.50)

[1]Final analyses restricted to participants with stressful life events and Self-Reporting Questionnaire-20 (SRQ-20) in 2017–2018. Cut-off for SRQ-20 to signify mental distress was ≥7. All analyses adjusted for sex.
[2]One z-score is equal to 4.4 cm in males and 4.6 cm in females.

life stress. Results from Model 1 demonstrated that partial supplementation with *Atole* was associated with lower odds of experiencing later mental distress in adulthood when compared to nonexposure; full supplementation with *Atole* demonstrated similar results (Model 1, Table 3). In Model 2, after accounting for life course variables such as attained wealth and schooling, marital status and rural residence, both partial and full supplementation with *Atole* during the first 1000 d were associated with 63% and 59% lower odds, respectively, of experiencing mental distress in adulthood when compared with those who were not exposed (Model 2, Table 3). The direct impact of *Atole* on mental distress remained unchanged from Model 1, suggesting that the effects of *Atole* were not mediated through these life course variables. Finally, results from Model 3 demonstrated that the impact of *Atole* on mental distress remained relatively unchanged even after controlling for current life stress (Model 3, Table 3).

When examining mental distress as a discrete outcome, simulated zeros suggested no deviation from the expected count of zeros under fitted models (Model 1 to Model 3 in Table 4) suggesting that the models were able to account for excess observed zeros. Results paralleled those found when examining mental distress as a dichotomous outcome. Both full and partial supplementation with *Atole* were inversely associated with mental distress, with results relatively unchanged across the 3 models. (Table 4). Early nutrition was not associated with education, wealth attainment, rural residence, or marital status in this sample (**Supplementary Table 1**).

Discussion

We tested the hypothesis that providing protein-energy supplementation during the first 1000 d of life to individuals in communities where nutritional deficiencies are common (27) may be helpful in addressing later mental distress in adulthood. In a study with 50 y of follow-up, we found that

TABLE 3 Results from generalized linear mixed models for dichotomous SRQ-20 outcomes examining exposure to *Atole* supplementation, controlling for early-life variables, life course events and current stress among adults in Guatemala ($n = 1249$)[1]

	Logistic regression: OR (95% CI)		
	Model 1	Model 2	Model 3
Partial *Atole*[2]	0.37 (0.16, 0.87)	0.37 (0.15, 0.88)	0.34 (0.14, 0.83)
Full *Atole*[2]	0.44 (0.19, 1.03)	0.41 (0.17, 0.98)	0.38 (0.16, 0.92)
Attained schooling[3]	—	0.93 (0.88, 0.99)	0.92 (0.87, 0.98)
Marital status	—	0.78 (0.54, 1.12)	0.78 (0.54, 1.13)
Wealth in 2017–2018	—	0.69 (0.57, 0.82)	0.68 (0.56, 0.82)
Rural residence	—	0.46 (0.32, 0.68)	0.46 (0.31, 0.68)
Stressful Life Events Score ≥300	—	—	5.14 (3.46, 7.62)

[1]Final analyses restricted to participants with stressful life events and Self-Reporting Questionnaire-20 (SRQ-20) in 2017–2018. Cut-off for SRQ-20 to signify mental distress was ≥ 7. All analyses control for sex, birth year, early wealth, maternal height, and maternal schooling; Model 1 assesses the direct impact of *Atole* in early-life on adult mental distress controlling for these early-life variables; Model 2 assesses the potential mediating role of attained schooling, marital status, wealth in 2017–2018, and current rural residence on the direct effects of *Atole* on adult mental distress, while also controlling for the early-life variables in Model 1; Model 3 assesses whether the addition of current life stress alters the impact of *Atole* on later mental distress or relations with potential mediating life course variables, while also controlling for the early-life variables in Models 1 and 2.
[2]Interactions with *Atole* (reference: *Fresco*) and level of exposure (reference: no exposure to supplement in the first 1000 d).
[3]Participant years of completed schooling was median centered to improve model convergence.

TABLE 4 Results from generalized linear mixed models for discrete SRQ-20 outcomes examining exposure to *Atole* supplementation, controlling for early-life variables, life course events, and current stress among adults in Guatemala ($n = 1249$)[1]

	Zero-inflated Poisson regression: RR (95% CI)		
	Model 1	Model 2	Model 3
Partial *Atole*[2]	0.90 (0.74, 1.10)	0.90 (0.74, 1.10)	0.87 (0.72, 1.07)
Full *Atole*[2]	0.83 (0.68, 1.02)	0.82 (0.67, 1.00)	0.79 (0.64, 0.96)
Attained schooling[3]	—	0.98 (0.96, 0.99)	0.97 (0.96, 0.98)
Marital status	—	0.98 (0.9, 1.07)	0.98 (0.9, 1.07)
Wealth in 2017–2018	—	0.86 (0.82, 0.9)	0.85 (0.82, 0.89)
Rural residence	—	0.84 (0.76, 0.92)	0.83 (0.75, 0.91)
Stressful Life Events Score ≥300	—	—	1.44 (1.30, 1.59)

[1] Final analyses restricted to participants with stressful life events and Self-Reporting Questionnaire-20 (SRQ-20) in 2017–18. All analyses controlling for sex, birth year, early wealth, maternal height, and maternal schooling; Model 1 assesses direct impact of *Atole* in early-life on adult mental distress controlling for early-life variables; Model 2 assesses the mediating role of attained schooling, marital status, wealth in 2017–2018, current rural residence on direct effects of *Atole* on adult mental distress, controlling for early-life variables in Model 1; Model 3 assesses whether the addition of current life stress alters the impact of *Atole* on later mental distress or relations with potential mediating life course variables, controlling for early-life variables in Models 1 and 2.
[2] Interactions with *Atole* (reference: *Fresco*) and level of exposure (reference: no exposure to supplement in the first 1000 d).
[3] Participant years of completed schooling was median centered to improve model convergence.

supplementation with *Atole* (moderate energy and protein) in the first 1000 d was associated with lower odds of experiencing significant mental distress in adulthood when compared with supplementation with *Fresco* (lower energy, no protein). The inverse association of early childhood protein-energy supplementation with later mental distress was not modified by sex and was robust to controlling for various factors known to influence mental distress (e.g. current life stress) and potentially mediate effects on mental distress (e.g. education, wealth, marital status). This suggests a potential direct influence of providing a protein-energy supplement during the first 1000 d of life that may protect individuals from experiencing significant mental distress in adulthood, independent of difficult external circumstances that people may subsequently find themselves in. This observation is supported by earlier studies suggesting that optimal protein and micronutrient intake is important for brain development, particularly areas of the brain involved in emotional regulation, and that protein is essential for the amino acids needed for the development of neurotransmitters involved in mood and mental health (5, 13, 15, 16, 41). Although previous studies have shown *Atole* to be positively associated with attained schooling and wealth in this population (22, 24), in this analysis, we did not, perhaps given the timing of exposure (during the first 1000 d) or the sample included; therefore, it is unlikely that *Atole* supplementation during the first 1000 d in the current study was associated with decreased odds of later mental distress through these indirect pathways. Future analyses may want to explore different timing of the exposure; however, research supports the importance of the first 1000 d for neurodevelopment. In addition, it is possible that other factors not explored in the current study may mediate this relation. Although several life course variables (i.e. attained schooling, wealth) were related to adult mental distress in expected directions, their addition to the models did not attenuate the coefficients for the relation between supplementation with *Atole* in the first 1000 d and later mental distress suggesting that these factors did not fully explain the lower odds of experiencing mental distress. In addition to the known effects of early optimal nutrition on growth and development (42), this study supports a long-term association of protein-energy supplementation during the first 1000 d with adult mental health in a population where protein-energy malnutrition was prevalent. This is particularly significant given the growing prevalence of mental health concerns in Latin America and globally (43, 44).

Having an elevated score on stressful life events was strongly associated with increased odds of experiencing mental distress in adulthood. This finding confirms in this population in Guatemala what is known in the general literature about the relation between stress and distress (28, 45, 46), and supports the validity of using these measures with this study sample. Despite this strong relation between stress and distress, early childhood protein-energy supplementation was inversely associated with adult mental distress, even after adjusting for concurrent stress. Early supplementation may interact with later stressful life events to influence the odds of experiencing mental distress; however, our sample was not adequately powered to test this interaction. Future studies may want to further examine how supplementation with protein-energy or certain micronutrients may interact with stressful life events and other external factors to better understand how and under what conditions early childhood nutrition may be associated with mental health throughout the lifespan.

Our study's strengths lie in the experimental nature of the design, longitudinal nature of the data collected prenatally through older adulthood, as well as the breadth and quality of data collected on nutrition, early-life and life course variables, and stress and distress in later adulthood, with the use of several standardized measures. Potential limitations include the one-time measure of mental distress in adulthood and the lack of rigorous studies examining the validity of the stress and distress measures in this population; however, both measures were pilot tested in these communities and strong expected relations were found among these measures and the covariates. The study lacks statistical power to test for heterogeneity between early-life nutrition and adult life stress and given that the focus of the original study was to examine the association between protein-energy supplementation and growth and development, we lack neurological and other behavioral measures in childhood, limiting our ability to fully assess the effects of supplementation on brain architecture, neural pathways, and childhood behavior. Finally, the supplementation was randomized at a cluster

(village) level rather than at the individual level; however, our analytic design using the difference in difference model controls for birth period and village fixed effects.

In conclusion, the current longitudinal study suggests that protein-energy supplementation during the first 1000 d of life in communities in Guatemala where undernutrition, particularly protein-energy malnutrition, is prevalent may reduce the prevalence of later mental distress in adulthood. This association between early supplementation and later mental distress appears to occur directly, rather than indirectly through pathways of life course variables such as education, wealth, and marital status. Our study provides evidence of additional benefits to later health of supplementation with balanced energy and protein during the first 1000 d in settings where undernutrition is prevalent.

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Data Availability

The datasets generated and/or analyzed during the current study are not publicly available. There are ethical or legal restrictions on sharing a de-identified data set. We cannot anonymize the data from this cohort as all individuals come from 1 of 4 previously named villages and hence are readily re-identifiable once their demographic characteristics are known. We will not post data to a public archive, but we will make a replication data set available to bona fide researchers who agree to sign a Limited Data Use Agreement (LDUA) and are covered under an IRB. Please contact the INCAP Research Center for the Prevention of Chronic Diseases (CIIPEC) at the Institute of Nutrition of Central America and Panama for requests. The local data protection manager is Dina Roche (email: droche@incap.int; phone: +502 5499 7220). The code is available at https://github.com/jvargh7/incap-distress-nutrition.

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