1-1-2023

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Recommended Citation
Koroma, Aminata S; Ellie, Mariama; Bangura, Kadiatu; Iversen, Per O; Hendrixson, David T; Stephenson, Kevin; and Manary, Mark J, "Supplementary feeding and infection control in pregnant adolescents-A secondary analysis of a randomized trial among malnourished women in Sierra Leone." Maternal & Child Nutrition. 19, 1. e13456 (2023).
https://digitalcommons.wustl.edu/oa_4/2538

Received: 9 August 2022 | Revised: 11 October 2022 | Accepted: 24 October 2022

DOI: 10.1111/mcn.13456

ORIGINAL ARTICLE

Maternal & Child Nutrition WILEY

Supplementary feeding and infection control in pregnant adolescents—A secondary analysis of a randomized trial among malnourished women in Sierra Leone

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Funding information

Children's Investment Fund Foundation

Abstract

Undernutrition during pregnancy in adolescence confers a high risk of maternal morbidity and adverse birth outcomes, particularly in low-resource settings. In a secondary analysis, we hypothesized that younger undernourished pregnant adolescents (<18 years) would benefit more than undernourished pregnant adults (>20 years) from the intervention of supplementary food and anti-infective treatments. The original trial in Sierra Leone enrolled 236 younger adolescents (<18 years), 454 older adolescents (aged 18–19 years), and 741 adults (≥20 years), all with a mid-upper arm circumference ≤23 cm. Younger adolescents had lower final fundal height as well as smaller newborns (−0.3 kg; 95% confidence interval [CI], −0.3, −0.2; $p < 0.001$) and shorter newborns (−1.1 cm; 95% CI, −1.5, −0.7; $p < 0.001$) than adults. The intervention's effect varied significantly between maternal age groups: adults benefited more than younger adolescents with respect to newborn birth weight (difference in difference, 166 g; 95% CI, 26, 306; interaction $p = 0.02$), birth length (difference in difference, 7.4 mm; 95% CI, 0.1, 14.8; interaction $p = 0.047$), and risk for low birth weight (<2.5 kg) (interaction $p = 0.019$). The differences in response persisted despite adjustments for maternal anthropometry, the number of prior pregnancies, and human immunodeficiency virus status. Older adolescents similarly benefited more than younger adolescents, though differences did not reach statistical significance. In conclusion, newborns born to younger adolescent mothers had worse outcomes than those born to adult mothers, and adults and their newborns benefited more from the intervention than younger adolescents.

KEYWORDS

adolescents, anthropometry, birth, child, pregnancy, supplementary foods, teen pregnancy, undernutrition

1 | INTRODUCTION

Adolescence (age 10–19 years) is characterized by physical, psychosocial, sexual, and cognitive maturation (Patton et al., 2016). During adolescence, approximately 50% of adult body weight and 15% of adult height are attained, requiring higher nutrient intakes than at any other stage in the lifecycle (Christian & Smith, 2018). Pregnant adolescents are vulnerable to undernutrition as the demand for continued growth and development is augmented by the nutritional requirements to support the fetus (Scholl & Hediger, 1993). When there is nutrient competition between the mother and fetus, and when the mother has inadequate nutrient intake and stores, it has been suggested that nutrition favors the fetus (Gigante et al., 2005; Nguyen et al., 2019; Rah et al., 2008). Chronic undernutrition can delay physical maturation and extend the adolescent growth period beyond 20 years of age, increasing its overlap with the age of the first pregnancy (World Health Organization [WHO], 2014).

Many adolescents exhibit poor growth and nutritional status, especially those in low- and middle-income countries (Gigante et al., 2005). Worldwide, one in five women has given birth by 18 years. In the world's poorest regions, this fraction rises to over one in three girls (Nguyen et al., 2019). About 95% of adolescent pregnancies occur in low- and middle-income countries, and within countries, adolescent births are particularly likely among poor, less educated, and rural populations (Nguyen et al., 2019). Adolescent pregnancy is a worldwide concern, especially in settings of poverty, social disadvantage, poor access to health services, lack of education and employment, and limited female autonomy (Black et al., 2013; Bongaarts & Cohen, 1998; Rogol et al., 2000). Adolescent pregnancy increases the risk of poor fetal growth, adverse birth outcomes, impaired infant and maternal health, and mortality (Malamitsi-Puchner & Boutsikou, 2006; Stewart et al., 2007).

Complications during pregnancy and delivery are the main causes of mortality among women of childbearing age in Sierra Leone, with a maternal mortality rate of 717 per 100,000. Such complications also contribute to the increased neonatal mortality rate of 31 per 1000 live births in Sierra Leone. For both outcomes, adolescent pregnancy is a risk multiplier. Among adolescent females, nearly half of all deaths are caused by complications during pregnancy or delivery, and the neonatal mortality rate is 1.5 times higher than that of older mothers (Wurie, 2017).

Given that pregnant adolescents are more vulnerable, we used a dataset from a randomized, controlled trial in Sierra Leone (Hendrixson et al., 2021) to test the post hoc hypothesis that malnourished pregnant adolescents would benefit more than pregnant adults from an intervention consisting of supplementary food and anti-infective treatments.

Key messages

- We performed secondary data analysis of a randomized controlled trial of a combined nutrition and anti-infective intervention for undernourished pregnant women, investigating the effect of maternal age on maternal and newborn outcomes and response to the intervention.
- Despite achieving similar gestational weight gain, younger adolescent mothers (<18 years) had newborns with lower birth weights, lengths, and mid-upper arm circumferences, as well as higher proportions of low birth weight and stunted newborns when compared with adult mothers (≥20 years).
- Younger adolescent mothers also derived less benefit from the combined intervention than adult mothers with respect to the rate of weight gain during pregnancy, infant birth weight, length, and rate of low birth weight (<2.5 kg).
- Further work is needed to identify interventions that benefit undernourished pregnant adolescents and their newborns.

2 | METHODS

2.1 | Study design and participants

This was a secondary analysis of clinical outcomes from a trial of malnourished pregnant girls and women in Sierra Leone (Hendrixson et al., 2021). Participants were categorized into three age groups: younger adolescents (<18 years), older adolescents (18–19 years), and adults (≥20 years). This categorization was chosen based on the WHO definition of an adolescent as <20 years old. The distinction between younger and older adolescents was made because marriage to a child <18 years old is illegal in Sierra Leone and adolescents <18 years old are more likely to have ongoing physical maturation than older adolescents. Maternal age was also modeled as a continuous variable to visualize its association with key maternal and infant outcomes.

Undernutrition was defined by a mid-upper arm circumference (MUAC) ≤ 23 cm. Eligible participants had a fundal height <35 cm and attended one of 43 health centers in Pujehun and Western Area Rural Districts. Exclusion criteria were known gestational diabetes, hypertension, or severe anemia.

Informed consent was obtained and documented by a signature or thumbprint. Women older than 16 years were eligible to consent for themselves, and girls younger than 16 years desiring to participate required consent from a parent or guardian. Ethical approvals were obtained from the appropriate local and international review committees. The original trial was registered at ClinicalTrials.gov.

2.2 | Content of the intervention

The intervention group received a package of care including two doses of 1 g azithromycin by mouth and monthly sulfadoxine-pyrimethamine (SP: 1500 mg/75 mg) given during the second and third trimesters. Participants were tested for vaginal dysbiosis, and if positive, they were treated with 500 mg metronidazole bid by mouth for 7 days. They also

received a daily ration of ready-to-use supplemental food (RUSF). The RUSF was composed of skimmed milk powder, whey protein isolate, vegetable oil, sugar, peanut paste, and pearl millet, providing 2180 kJ (520 kcal). The RUSF provided 18 g of protein and over 100% recommended daily allowance for most micronutrients during pregnancy (Hendrixson et al., 2018). The control group received standard care, 250 g/d of corn-soy blended flour (SuperCereal), and 25 g of palmolein oil daily, providing 2474 kJ (589 kcal) and 17.5 g of protein, as well as a ration for sharing per World Food Programme standards. In addition, the control group received three doses of malarial chemoprophylaxis, 60 mg/d iron, and 400 µg/d folic acids during the second and third trimesters. Nutritional supplementation was initiated at the time of enrolment and continued until delivery. A standardized questionnaire assessed adherence to the nutritional intervention at each visit. Azithromycin and SP were given under direct observation.

The study was conducted in conjunction with government-provided antenatal clinics. Upon enrolment, demographic information, time of last menses, an estimated delivery date, and clinical symptoms were recorded. Weight, height, MUAC, blood pressure and fundal height were measured. Fundal height was measured in the supine position with a nonelastic tape to the nearest 0.5 cm and used as a proxy for gestational length (WHO, 2007). Participants returned for follow-up every 2 weeks for anthropometric assessment and provision of the study foods and medications until delivery. Participants were considered lost-to-follow-up after missing three consecutive visits. Home visits were attempted for any patient lost to follow-up.

Clinic staff and participants were provided a telephone number and credit card to call the study coordinator at delivery. A birth measurement team was dispatched to conduct measurements of the infants within 48 h of delivery. Infant survival, weight, length, head circumference, MUAC, morbidity and feeding practices were assessed at each child visit. Maternal weight, MUAC and morbidity were also assessed at these visits. Full details of the intervention, food supplementation, and study procedures have been previously published (Hendrixson et al., 2018, 2021).

2.3 | Outcome variables

The primary outcomes of this secondary analysis were maternal rate of weight gain and birth weight. Key secondary outcomes were birth length, rates of low birth weight (<2.5 kg), and neonatal mortality.

2.4 | Data analysis

Data were first recorded on clinic management cards. Data from these cards were double-entered into a database (Microsoft Access) and cross-checked for discrepancies. All discrepancies were resolved by examination of the original data card. Once the content of the database was determined, it was locked for analysis. Anthropometric indices were calculated using WHO 2006 growth standards (Anthro version 3.2.2). Baseline characteristics were summarised as *n* (%) if categorical. The distributions of continuous variables were visualized with histograms and Q–Q plots and summarised as mean (SD) unless they were skewed, in which case they were summarised as median (interquartile range). The maternal rate of weight gain was calculated by subtracting the baseline weight from the final visit weight and dividing it by the time elapsed. No missing data were imputed.

Continuous outcomes, irrespective of the intervention group, were compared across the three maternal age cohorts using analysis of variance or Kruskal–Wallis test, depending on their distributions, while binary outcomes were compared using χ^2, or Fisher's exact test when any subgroup $n < 5$. For unadjusted comparisons between intervention groups, Student's *t*-test or the Mann–Whitney *U* test was used for continuous variables, while the test for equality of proportions was used for binary variables. To test for effect modification of the intervention by maternal age group, an interaction term between the intervention group and maternal age group was created within regressions. After assessing model assumptions and deeming them not violated, linear regression was used for continuous outcomes, while modified Poisson regression with robust variance estimates was used for binary outcomes. In both cases, a difference-in-difference analysis comparing the effect of intervention between different age groups was done, with an estimation of 95% confidence intervals (CIs) and *p* values for the interaction terms. Difference-in-difference results were reported as positive if the intervention was more beneficial in the adult or older adolescent age groups than the intervention's effect in the younger adolescent age group. These analyses were done both without adjustment and with adjustment for (i) baseline maternal anthropometry (body mass index, height and MUAC), (ii) the number of prior pregnancies, and (iii) human immunodeficiency virus (HIV) status. These adjustments were chosen based on previously identified associations with maternal and infant outcomes as well as differences at baseline between maternal age groups in the parent study, which, therefore, might have explained differential intervention effects.

Associations between maternal age and singleton infant birth weight and length and maternal rate of weight gain during pregnancy were also modeled with baseline maternal age as a continuous variable using linear regression. The associations between maternal age and these three outcome variables were visualized using loess curves; in all cases, the associations were nonlinear. As a result, restricted cubic splines were used to model age nonlinearly and to estimate the associations between age, intervention group, and outcomes (Harrell, 2016). Within these regressions, *p* values were computed using partial *F*-statistics (Harrell, 2022). All analyses were conducted using R version 4.1.2 (R Foundation for Statistical Computing).

3 | RESULTS

3.1 | Characteristics of the study participants

Among the 1489 pregnant women enrolled in the original trial, 1431 were included in the current secondary analyses, of whom 236 (16.5%) were younger adolescents (age < 18 years), 454 (31.7%) were older

adolescents (age 18–19 years), and 741 (51.8%) were adults (age ≥ 20 years) (Figure 1). A total of 45 women were excluded from this analysis for lack of age data, which was an essential variable for the current analysis. When compared with adult mothers, a higher proportion of younger adolescents were primigravid (difference, 75%; 95% CI, 70, 80; Table 1). They also attained more education, possessed a lower fundal height at the time of enrolment (−1.3 cm; 95% CI, −2.3, −0.3 cm; $p = 0.010$), and were less likely to have been diagnosed with HIV than adult mothers (−6.3%; 95% CI, −9.6, −3; $p < 0.001$). However, 30% of mothers in each group had not undergone testing (Table 1). Compared with adult mothers, fewer younger adolescents lived with the father of their child (−17%; 95% CI, −24, −9), while more slept with animals in their homes (14%; 95% CI, 6.5, 21). Similar findings were present when comparing younger adolescent mothers to older adolescent mothers, with higher rates of nulliparity as well as animals sleeping in the home and lower rates of fathers living in the home. Baseline characteristics were similar between women randomized to receive the intervention and the standard of care across all age strata (Supporting Information: Table S1).

3.2 | Pregnancy and birth outcomes among adolescents

When evaluating clinical outcomes by maternal age irrespective of the intervention group, younger adolescents had a similar rate of weight change as older mothers; however, younger adolescent mothers had lower average final fundal height, a crude measure of gestational age, than mothers ≥20 years of age (−0.75 cm; 95% CI, −1.3, −0.2; Table 2). Moreover, newborns of younger adolescents had lower birth weight (−0.3 kg; 95% CI, −0.3, −0.2) and length (−1.1 cm; 95% CI, −1.5, −0.7; Table 2) than those born to adults. Categorical pregnancy and neonatal mortality outcomes were similar in the three age groups ($p = 0.62$ and $p = 0.14$, respectively; Figure 1).

3.3 | Effect of the combined intervention versus standard of care across maternal age groups

Adherence with the intervention and the standard of care was high and did not differ with age (Supporting Information: Table S2). When age was modeled as a continuous variable, the combined intervention led to a higher rate of maternal weight gain during pregnancy (difference, 42 g/week; 95% CI, 14, 71; partial F-statistic = 8.5; $p = 0.004$; Figure 2). This benefit was primarily demonstrated among women ≥20 years (difference, 59 g/week; 95% CI, 21, 96; $p = 0.003$), while younger adolescents did not experience greater weight gain as a result of the intervention (difference, −11 g/week; 95% CI, −83, 61; $p = 0.76$; Supporting Information: Table S3), yielding a difference-in-difference response to the intervention of 70 g/week (95% CI, −11, 151; interaction $p = 0.09$; Figure 4). After adjustment for baseline

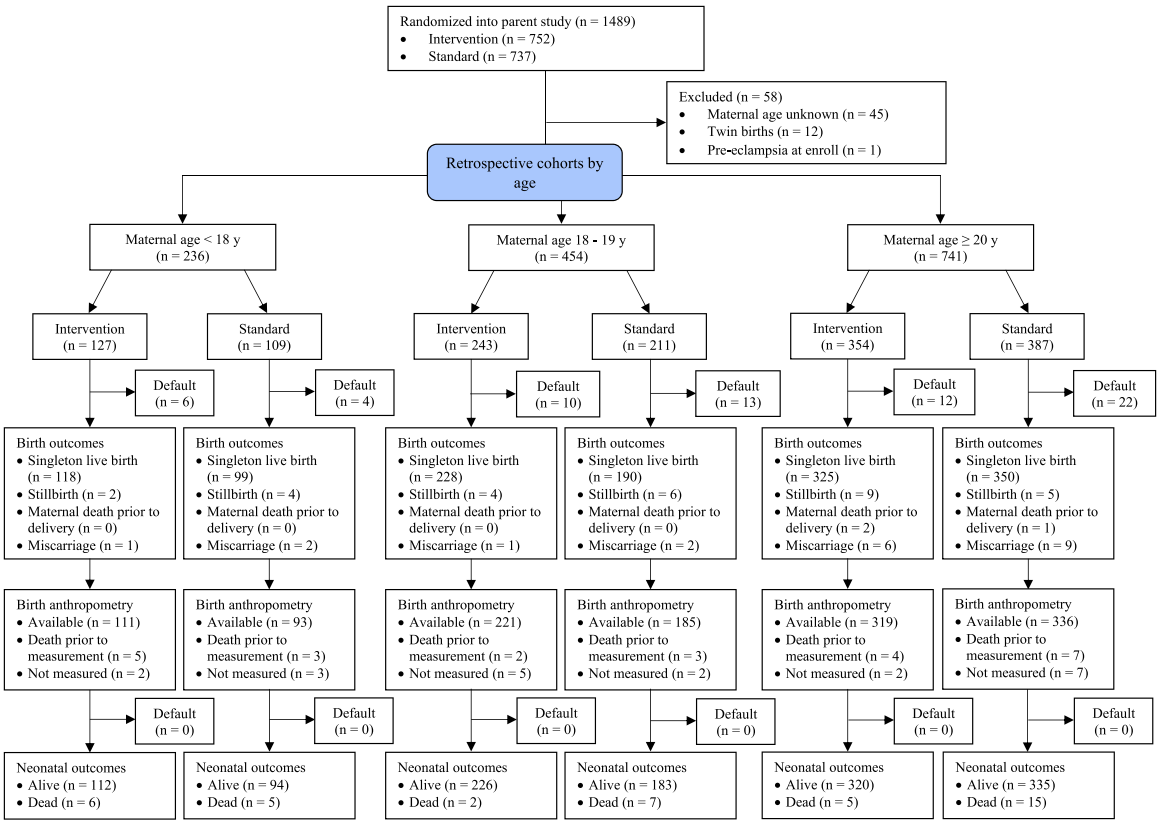

FIGURE 1 Flowchart of the participant inclusion process. Study flow diagram showing the number of subjects at each juncture of follow-up. Default refers to subjects who were lost to follow-up.

TABLE 1 Baseline sociodemographic and anthropometric characteristics of the three age groups

Characteristics[a,b]	Younger adolescent mothers (<18 y) (*n* = 236)	Older adolescent mothers (18–19 y) (*n* = 454)	Adult mothers (≥20 y) (*n* = 741)	*p* Value[c]
Maternal age, y	16.4 (0.9)	18.3 (0.5)	24.5 (4.6)	
Height, cm	155.1 (6.2)	156 (6.3)	155.9 (6.6)	0.21
MUAC, cm	22.2 (0.8)	22.3 (0.7)	22.3 (0.8)	0.07
BMI, kg/m^2	19.8 (1.5)	20.0 (1.7)	19.6 (1.7)	0.002
Fundal height, cm, median (IQR)	22 (18, 28)	24 (18, 28)	24 (18, 28)	0.013
HIV positive, *n* (%)[d]	2 (1.3)	5 (1.6)	41 (7.6)	<0.001
First pregnancy, *n* (%)	211 (89)	294 (65)	104 (14)	<0.001
Education status, *n* (%)				<0.001
None	35 (15)	93 (20)	321 (43)	
Primary	60 (25)	117 (26)	123 (17)	
Secondary or greater	141 (60)	244 (54)	297 (40)	
Father living in the home, *n* (%)	146 (62)	324 (71)	583 (79)	<0.001
Clean water source, *n* (%)[e]	145 (61)	299 (66)	475 (64)	0.51
Household with electricity, *n* (%)	20 (8.5)	44 (9.7)	67 (9.0)	0.86
Animals sleep in home, *n* (%)	166 (70)	266 (59)	419 (57)	<0.001

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; HIV, human immunodeficiency virus; IQR, interquartile range; MUAC, mid-upper arm circumference; y, year.

[a]Values expressed as mean (SD) unless otherwise indicated.

[b]Several variables had missing data, including height (maternal age 18–19 y, *n* = 2; maternal age ≥ 20 y, *n* = 6), BMI (maternal age < 18 y, *n* = 1; maternal age 18–19 y, *n* = 3; maternal age ≥ 20 y, *n* = 7), fundal height (maternal age < 18 y, *n* = 22; maternal age 18–19 y, *n* = 27; maternal age ≥ 20 y, *n* = 60), HIV status (maternal age < 18 y, *n* = 87; maternal age 18–19 y, *n* = 138; maternal age ≥ 20 y, *n* = 204), father in home (maternal age < 18 y, *n* = 1; maternal age ≥ 20 y, *n* = 2) and animals in the home (maternal age ≥ 20 y, *n* = 2).

[c]Continuous variables were compared using one-way ANOVA, except for the time from enrolment to delivery, using the Kruskal–Wallis test. Binary variables are compared using χ^2 or Fisher's exact test.

[d]Multiple participants had not undergone testing for HIV and thus status was unknown (maternal age < 18 y, *n* = 87 [37%]; maternal age 18–19 y, *n* = 138 [30%] and maternal age ≥ 20 y, *n* = 202 [27%]).

[e]Includes public tap and borehole, in contrast to well and river/stream source.

maternal anthropometrics, the number of prior pregnancies, or HIV status, mothers receiving the combined intervention still gained weight faster than those in the control group, and the difference in effect between adult mothers (benefitted more) and younger adolescents (benefitted less) remained similar (Supporting Information: Figures S1 and S2). For instance, after adjustment for HIV status, the difference in difference was 69 g/week for adult mothers compared with younger adolescents (95% CI, −12, 150; interaction $p = 0.09$). The intervention had no effect on maternal MUAC in any age group (Supporting Information: Table S3). Final fundal height was higher among women ≥20 years of age receiving the intervention when compared to those receiving the standard (difference, 0.6 cm; 95% CI, 0.2, 1.1; $p = 0.002$); however, this benefit was not seen among the younger age groups (Supporting Information: Table S3), though the interaction between the intervention group and maternal age group did not reach statistical significance. No significant differences were identified between the stratified groups for categorical pregnancy outcomes (Supporting Information: Table S3).

When age was modeled as a continuous variable, the effects of the combined intervention on newborn weight and length compared to the standard of care were +76 g (95% CI, 27, 125; partial *F*-statistic = 9.2; $p = 0.003$) and +3.8 mm (95% CI, 1.2, 6.4; partial *F*-statistic = 8.4; $p = 0.004$), respectively (Figure 3). Maternal age was a significant determinant of newborn weight (partial *F*-statistic = 61.5; $p < 0.001$) and length (partial *F*-statistic = 38; $p < 0.001$). The effect of the intervention on birth weight varied by maternal age group, with adult mothers benefitting more than younger adolescent mothers (difference in difference, 166 g; 95% CI, 26, 306; interaction $p = 0.02$; Figure 4). Similarly, adult mothers benefited more from the intervention with respect to risk for low birth weight compared with younger adolescents (interaction $p = 0.019$) and birth length (difference in difference, 7.4 mm; 95% CI, 0.1, 14.8; interaction $p = 0.047$) (Figure 4). Similar trends were seen when comparing younger and older adolescents, though these differences did not reach statistical significance (Figure 4). Adjustment for differences in baseline maternal anthropometry did not alter these findings for birth

TABLE 2 Study outcomes of mothers and their newborns stratified by maternal age

Characteristics[a]	Younger adolescent mothers (<18 y)	Older adolescent mothers (18–19 y)	Adult mothers (≥20 y)	*p* Value[b]
Maternal outcomes[c]	(*n* = 236)	(*n* = 454)	(*n* = 741)	
Time from enrolment to delivery, weeks; median (IQR)	16 (11, 21)	15 (10, 20)	15 (10, 21)	0.66
Change in weight from enrolment to final visit, kg	5.3 (3.6)	5.0 (3.7)	5.0 (3.7)	0.58
Rate of weight change, g/week[d]	366 (272)	358 (286)	337 (257)	0.27
Final MUAC > 23 cm, *n* (%)	56 (25)	134 (30)	203 (28)	0.31
Final fundal height, cm[e]	34.7 (3.8)	35.3 (3.4)	35.4 (4.2)	0.039
Final fundal height < 37 cm, *n* (%)	171 (74)	295 (66)	411 (57)	<0.001
Infant outcomes	(*n* = 217)	(*n* = 418)	(*n* = 675)	
Birth weight, kg	2.66 (0.44)	2.84 (0.44)	2.92 (0.45)	<0.001
Birth weight < 2.5 kg, *n* (%)	62 (30)	79 (19)	93 (14)	<0.001
Birth length, cm	46.3 (2.4)	47.1 (2.4)	47.4 (2.3)	<0.001
Neonatal mortality, *n* (%)	11 (4.7)	9 (2.0)	20 (2.7)	0.14

Abbreviations: ANOVA, analysis of variance; IQR, interquartile range; MUAC, mid-upper arm circumference; y, year.

[a]Values expressed as mean (SD) unless otherwise indicated.

[b]Continuous outcomes were compared using one-way ANOVA, except for the time from enrolment to delivery, using Kruskal–Wallis one-way ANOVA. Categorical outcomes were compared using Fisher's exact test.

[c]Maternal anthropometry unavailable to calculate weight change/rate (maternal age < 18 y, *n* = 13; maternal age 18–19 y, *n* = 17; maternal age ≥ 20 y, *n* = 37), MUAC rate/final (maternal age < 18 y, *n* = 8; maternal age 18–19 y, *n* = 9; maternal age ≥ 20 y, *n* = 13) and for fundal height (maternal age < 18 y, *n* = 4; maternal age 18–19 y, *n* = 4; maternal age ≥ 20 y, *n* = 15). Singleton lives births with missing anthropometry for maternal age < 18 y, *n* = 13; maternal age 18–19 y, *n* = 12 and maternal age ≥ 20 y, *n* = 20.

[d]Rates calculated as (final value – initial value)/time between measurements.

[e]Fundal height is used as a crude marker of gestational age. Birth <37 gestational weeks are considered late preterm, and birth <32 gestational weeks is considered very preterm.

weight (difference in difference, 150 g; 95% CI, 11, 289; interaction $p = 0.034$) or risk for low birth weight (interaction $p = 0.037$; Supporting Information: Figure S3), nor did adjustment for the number of prior pregnancies alter the findings for birth weight (difference in difference, 171 g; 95% CI, 33, 311; interaction $p = 0.016$; Supporting Information: Figure S4), the risk for low birth weight (interaction $p = 0.012$), or birth length (difference in difference, 7.6 mm; 95% CI, 0.3, 15; interaction $p = 0.042$). Similarly, adjustment for HIV status did not alter the findings, with newborns of older mothers still benefiting more from the intervention with respect to birth weight (difference in difference, 165 g; 95% CI, 24, 305; interaction $p = 0.02$), birth length and risk for low birth weight. Neonatal mortality was significantly reduced among infants of mothers receiving the intervention compared to the standard of care (Figure 4). There were fewer neonatal deaths of infants of mothers ≥20 years of age receiving the intervention (relative risk [RR], 0.36; 95% CI, 0.13, 0.99; $p = 0.034$), while there was no difference among younger adolescents (RR, 1.03; 95% CI, 0.32, 3.28; $p = 0.95$; Supporting Information: Table S3), though the interaction effect did not reach statistical significance ($p = 0.18$; Figure 4).

4 | DISCUSSION

Using data from a randomized, controlled clinical effectiveness trial in Sierra Leone (Hendrixson et al., 2021), we retrospectively tested the hypothesis that during pregnancy, undernourished adolescents would benefit more from a bundled intervention consisting of supplementary food and anti-infective treatments than adults. While the intervention proved effective when all ages were pooled together, there were significant differences in its effect by maternal age group, particularly with respect to infant anthropometric outcomes, wherein adult mothers derived more benefit from the intervention than did young adolescent mothers. Similar trends were seen when comparing older adolescent mothers with younger adolescent mothers, though these did not reach statistical significance. Contrary to our hypothesis, younger adolescents demonstrated less benefit from the combined intervention than adults.

Animal research offers potential insight into how malnutrition affects fetal development (Luther, Aitken, et al., 2007; Luther, Milne, et al., 2007). Histological studies of sheep placenta, as it develops during pregnancy, demonstrate that capillary density and blood flow are about 20% less when maternal undernutrition occurs, leading to

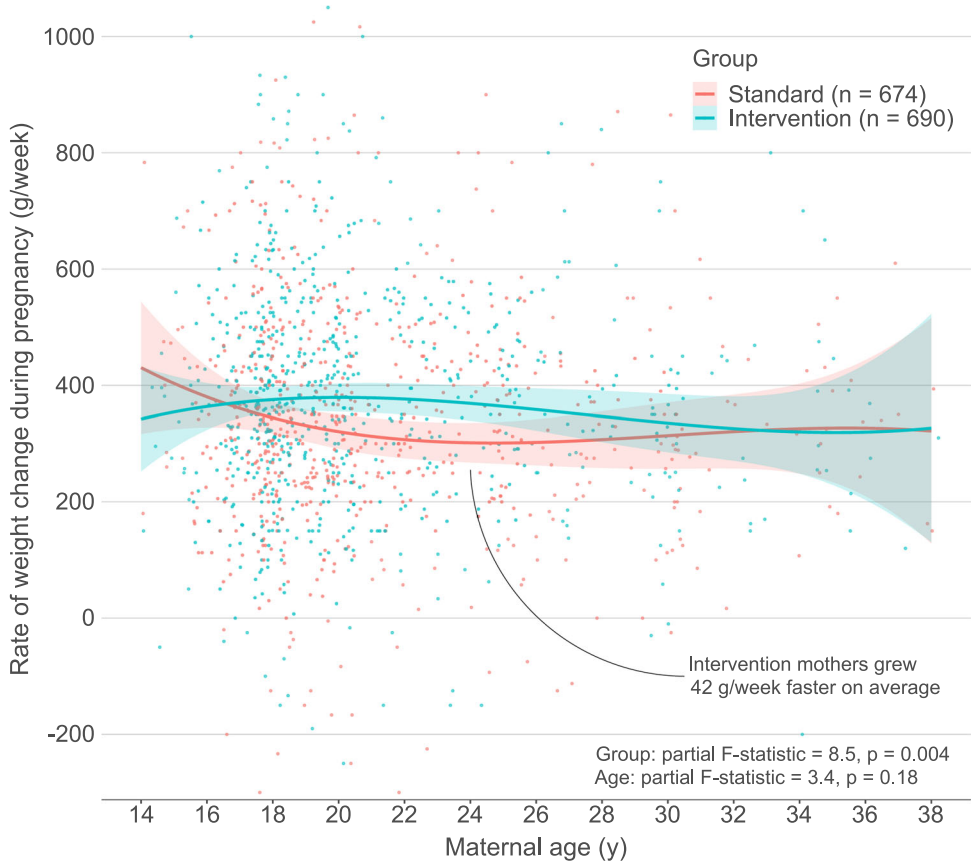

FIGURE 2 Maternal weight gain. Rate of weight change during pregnancy among undernourished Sierra Leonean women by baseline maternal age (years) and intervention group comparing a standard of care (standard) regimen consisting of the supplementary corn-soy blend, three doses of sulfadoxine-pyrimethamine for intermittent treatment for the prevention of malaria (IPTp), insecticide-treated bed nets, and albendazole with a novel bundle (intervention) composed of specially formulated ready-to-use supplementary food, azithromycin at the beginning of second and third trimesters, monthly IPTp, albendazole, and an insecticide-treated bed net. Each data point represents a participant and points have been randomly jittered to reduce overlap (Wickham, 2016). The association between baseline maternal age and maternal weight gain during pregnancy was modeled using restricted cubic splines with three knots. Linear regression was used to estimate this association as well as the effect of the intervention, and the beta coefficient for the intervention group and partial *F*-statistics for the intervention group and age are reported. The regression output is shown with lines surrounded by shaded areas, representing 95% CIs (Harrell, 2016). Mothers with rates of weight change <−250 g/week (intervention $n = 6$, standard $n = 17$) or 1000 g/week (intervention $n = 4$, standard $n = 8$) were clipped from the plot, but their data were included to estimate the smoothed lines and regression statistics. CI, confidence interval.

less maternal-to-fetal nutrient transfer (Luther, Milne, et al., 2007. Dietary supplements given to these undernourished sheep increased offspring birth weight (Wallace, 2019).

Our findings may be partly explained by biological differences between undernourished pregnant adolescents and undernourished pregnant adults (Scholl et al., 1990; Spear, 2002). Adolescents are still physically growing and there is likely more competition for nutrients between mother and fetus, such that the fetus of an adolescent would not receive as many nutrients as it would from an adult. Baseline anthropometrics varied slightly between age groups, while gravidity varied significantly, though adjustment for these differences did not meaningfully change either the intervention effect estimates or the interaction effects, suggesting these differences were not responsible for the differential intervention effect between age groups. In addition, the prevalence of HIV infection was fivefold higher in adults compared with adolescents. While there was no evidence that this difference impacted the intervention's benefit, particularly the greater benefit seen in adult mothers relative to young adolescents, nearly 1/3 of participants had not undergone HIV testing, which precludes firm conclusions. Added to the detrimental effects of HIV, the greater prevalence among adult mothers could represent a surrogate for higher rates of sexually transmitted diseases. The anti-infective treatments may have prevented or treated such infections, thus facilitating better fetal growth in this group.

Social determinants of health may also have a role in explaining our findings. Fewer mothers residing with their child's father imply that the youngest mothers are more likely to live with parents and siblings. This could lead to more food sharing in the family than an adult mother would experience with her own family. Pregnant adolescents also face higher social risks risk when compared to pregnant adults, including unemployment, discontinuation of education, low income, and social

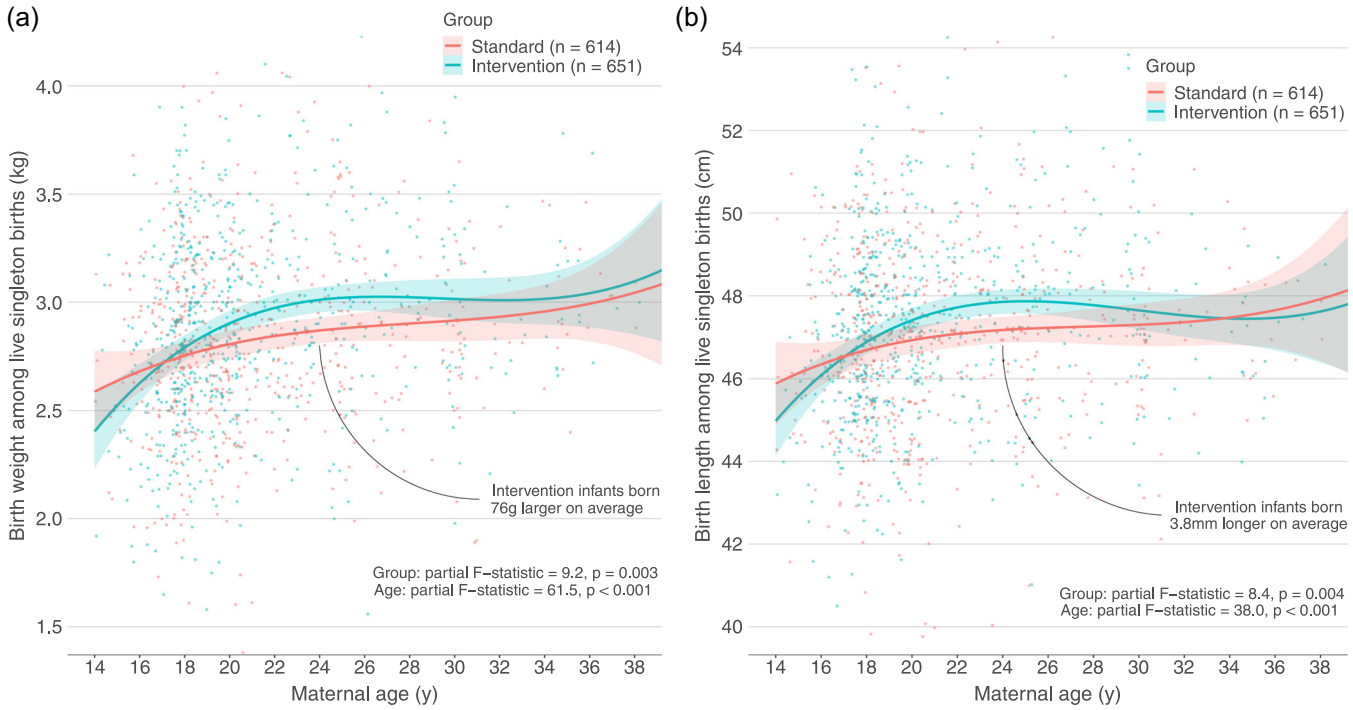

FIGURE 3 Infant birth outcomes stratified by maternal age. Singleton infant birth weight (a) and length (b) by maternal age (years) and intervention group, comparing a standard of care (standard) regimen consisting of the supplementary corn-soy blend, three doses of sulfadoxine-pyrimethamine for intermittent treatment for the prevention of malaria (IPTp), with a bundle (Intervention) composed of ready-to-use supplementary food, two doses of azithromycin, and monthly IPTp. Each data point represents a participant and points have been randomly jittered to improve visibility (Wickham, 2016). The associations between baseline maternal age and birth weight and length were modeled using restricted cubic splines with three knots. Linear regression was used to estimate this association as well as the effect of the intervention, and the beta coefficient for the intervention group and partial *F*-statistics for the intervention group and age are reported. The regression output is shown with lines surrounded by shaded areas representing 95% CIs (Harrell, 2016). CI, confidence interval.

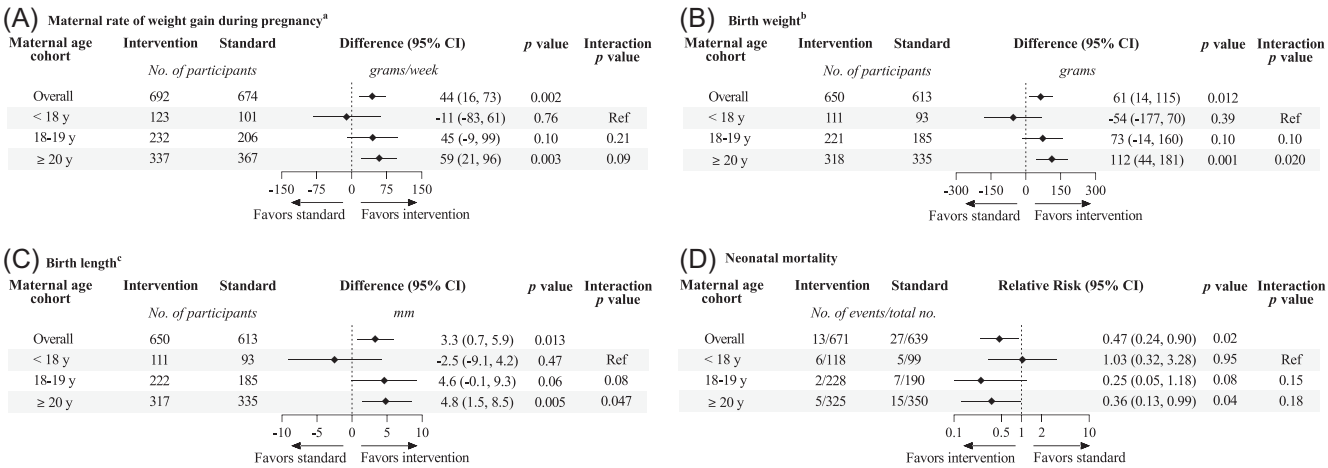

FIGURE 4 Maternal and infant outcomes among undernourished mothers receiving a bundle of nutritional and anti-infective interventions stratified by maternal age group. The rate of weight gain was calculated by subtracting the initial weight from the final weight and dividing it by the time between the two measurements. For the maternal rate of weight gain as well as birth weight and birth length, linear regression was used to estimate differences with 95% CIs and to calculate *p* values, including for the interaction between the treatment group (intervention vs. control) and maternal age group (<18, 18–19, and ≥20 y). For neonatal mortality, modified Poisson regression with robust variance estimates was used to estimate relative risk with 95% CIs and to calculate *p* values. (A) Maternal rate of weight gain during pregnancy[a]. (B) Birth weight[b]. (C) Birth length[c]. (D) Neonatal mortality. [a]No second weight was measured for several mothers <18 y (intervention *n* = 4, control *n* = 8), 18–19 y (intervention *n* = 11, control *n* = 5), and ≥20 y (intervention *n* = 17, control *n* = 20). [b]Missing measurements for infants from mothers <18 y (intervention *n* = 7, standard *n* = 6), 18–19 y (intervention *n* = 7, standard *n* = 5), and ≥20 y (intervention *n* = 6, standard *n* = 14) due to infant death before measurement or other. [c]Missing measurements for infants from mothers <18 y (intervention *n* = 7, standard *n* = 6), 18–19 y (intervention *n* = 6, standard *n* = 5), and ≥20 y (intervention *n* = 7, standard *n* = 14) due to infant death before measurement or other. CI, confidence interval; y, year.

isolation (Dubois et al., 1997). Interventions addressing socioeconomic hardships may be critical in addressing disparities in adolescent birth outcomes. Additionally, pregnant adolescents are at high risk of mental health disorders (Siegel & Brandon, 2014), and peripartum mood disorders are associated with poorer birth outcomes and growth (Iwata et al., 2019; Traviss et al., 2012).

Care must be exercised in the interpretation of these results. These findings do not indicate that food is not needed or not beneficial to treat undernourished adolescents; there was no 'supplementary food versus no supplementary food' comparison. Indeed, younger adolescent mothers gained weight at similar rates as their adult counterparts, suggesting similar benefits to the mothers themselves. Rather, the main differences lie in fetal outcomes, both irrespective of the intervention group and when comparing the effects of the intervention. This suggests there remain unaddressed barriers to nutrient transfer, improved length of gestation, and/or other factors essential for fetal development. It is plausible that a more nutrient-rich food could be necessary or that additional interventions for co-morbidities, such as mental health issues, are required. Holistic care, including nutritional, anti-infective, mental health care, and social support, may be necessary to attain optimal fetal growth outcomes, especially in the most vulnerable young adolescents.

The study has multiple limitations. It is a post hoc analysis which limits the strength of inference to be drawn from its findings. There are multiple comparisons, which increases the chance of false positive results. We only included undernourished pregnant women, so we do not know if well-nourished pregnant women would respond to the combined intervention in the same way. Our study was conducted in a humid, rainy tropical environment, so the results might have been different in other ecological environments, e.g., in regions where malaria is not omnipresent. While we did follow the national guidelines, in the typical day-to-day circumstances in antenatal clinics, food supplements are often out of stock for pregnant women. In our case, undernourished women represent about 20% of women attending antenatal clinics and this environment is thus similar for about 150 million women residing in West Africa. The major strengths of our study are the robust and pragmatic randomized design of the parent trial, the high adherence rate with the intervention and follow-up visits, and a sample size sufficient to assess differential effects by maternal age.

5 | CONCLUSION

In this secondary analysis comparing the effects of combined food and anti-infective intervention among undernourished Sierra Leonean pregnant women stratified by maternal age group, we found that infants born of young adolescent mothers benefited less than those of adult or older adolescent mothers with respect to birth anthropometry, including the risk of LBW, despite achieving similar rates of weight gain during pregnancy themselves. Further work is needed to identify interventions that benefit undernourished pregnant adolescents and their newborns.

AUTHOR CONTRIBUTIONS

Aminata S. Koroma, Mariama Ellie, and Kadiatu Bangura performed the research. Aminata S. Koroma and Mark J. Manary designed the research study. David T. Hendrixson and Kevin Stephenson analysed the data. Aminata S. Koroma, Mariama Ellie, Kadiatu Bangura, Per O. Iversen, David T. Hendrixson, Kevin Stephenson, and Mark J. Manary interpreted the data. Aminata S. Koroma, David T. Hendrixson, Per O. Iversen, Kevin Stephenson, and Mark J. Manary wrote the paper. All authors read and approved the final version of the manuscript.

ACKNOWLEDGMENT

This study was supported by the Children's Investment Fund Foundation funded the study.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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How to cite this article: Koroma, A. S., Ellie, M., Bangura, K., Iversen, P. O., Hendrixson, D. T., Stephenson, K., & Manary, M. J. (2023). Supplementary feeding and infection control in pregnant adolescents—A secondary analysis of a randomised trial among malnourished women in Sierra Leone. *Maternal & Child Nutrition*, 19, e13456. https://doi.org/10.1111/mcn.13456