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Effect of Early-Life Lipid-Based Nutrient Supplement and Home Environment on Autonomic Nervous System Regulation at 9–11 Years: A Follow-Up of a Randomized Controlled Trial

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ABSTRACT

Nutrition and the home environment contribute to the development of the autonomic nervous system (ANS). However, no study has examined the long-term effects of prenatal and postnatal small-quantity lipid-based nutrient supplements (SQ-LNS) and home environment on ANS regulation. We investigated the effect of early-life SQ-LNS and home environment on ANS regulation at 9–11 years. Participants were children born to women who participated in a randomized controlled trial in Ghana from 2009 to 2014. Women were randomized to receive daily, from pregnancy until delivery, either SQ-LNS, multiple micronutrients (MMN) or iron and folic acid (IFA) followed by SQ-LNS, MMN or placebo, respectively, until 6 months postpartum. Infants in the SQ-LNS group received SQ-LNS from 6 to 18 months. Quality of home environment was observed at 4–6 and 9–11 years. At 9–11 years, 965 children had their respiratory sinus arrhythmia (RSA) and pre-ejection period (PEP) measured at baseline and during two inhibitory control tasks, the RACER Simon and Emotion Go/No-Go (EGNG) tasks. PEP reactivity to the RACER Simon task was greater in the MMN (-2.54 ± 4.45, $p = 0.016$) and SQ-LNS (-2.31 ± 4.94, $p = 0.093$) groups than in the IFA group (-1.57 ± 3.51). A better home environment at 4–6 predicted longer baseline PEP ($\beta = 0.13$, 95% CI: 0.02, 0.23, $p = 0.016$) and more PEP reactivity during the EGNG task ($\beta = -0.06$, 95% CI: -0.00, -0.02, $p = 0.001$). Prenatal micronutrient supplementation appears to increase SNS reactivity. Children raised in disadvantaged early home environments had more tonic SNS activation and less SNS reactivity, suggesting a predisposition for stronger fight-or-flight activation and less likelihood to modulate arousal in response to acute situations.

Trial Registration: ClinicalTrials.gov identifier: NCT00970866

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Summary

- Evidence for the effect of prenatal and postnatal nutrient supplements and the home environment on autonomic nervous system development in children is needed.
- Children of mothers who received either small-quantity lipid-based nutrient supplements or multiple micronutrient supplements had better cardiac sympathetic activity compared to those who received iron and folic acid.
- The early childhood environment was also significantly associated with SNS regulation at 9–11 years.
- These findings highlight the importance of improving both early nutrition and the quality of the childhood home environment to improve ANS outcomes for children.

1 | Introduction

Adequate maternal and child nutrition during the first 1000 days and early childhood environmental experiences are critical to autonomic nervous system (ANS) development and regulation. For example, maternal zinc, iron and calcium status during pregnancy have been linked to foetal cardiovascular, brain and neural development and ANS regulatory function (Cerritelli et al. 2021; Christian and Stewart 2010; Georgieff 2007). The ANS coordinates communication between the brain and body and enables the body to maintain homoeostasis and adapt flexibly to environmental events (Caulfield et al. 2011). The ANS consists of two branches: the parasympathetic nervous system (PNS), which primarily regulates rest, restorative functions and recovery from stressors; and the sympathetic nervous system (SNS), which is involved in the physiological activation of the body, preparing the individual to deal with danger and stress (Bush et al. 2016; van Dijk et al. 2013; Vrijkotte et al. 2021). The PNS and SNS act in complementary ways to respond and adapt to environmental challenges (Alkon et al. 2011). Variations in ANS development and regulation are associated with an array of health outcomes, including differences in child and adult stress resilience (Mulkey and du Plessis 2019), the likelihood of obesity at an older age (Alkon et al. 2014; Lustig 2006; Nagai and Moritani 2004) and the likelihood of morbidity and all-cause mortality (Thayer, Yamamoto, and Brosschot 2010). ANS dysregulation also has been linked to the risk of developing and poor prognosis of cardiovascular disease (CVD) and its associated comorbidities such as type 2 diabetes, obesity, dyslipidemia, hypertension, cancer, dementia and atherosclerosis (Bush et al. 2016; Lopresti 2020; Speer et al. 2020; Thayer, Yamamoto, and Brosschot 2010). ANS dysregulation also has been implicated in internalizing and externalizing psychopathology in children including depression, anxiety, phobias, attention problems, conduct disorder and risk-taking behaviour (Beauchaine and Thayer 2015; Dietrich et al. 2007). Hence, studying the factors that promote healthy ANS development is of great importance for efforts to reduce life-long health problems.

Considering the importance of maternal and child diets, especially during the first 1000 days of life, to growth and development, various supplementation strategies to improve nutrient intakes during this period have been proposed and evaluated, including the provision of small-quantity lipid-based nutrient supplements (SQ-LNS). SQ-LNS were designed as a home fortification intervention to provide a full set of micronutrients and essential fatty acids (EFAs) to enrich local diets that may be low in these nutrients (Adu-Afarwuah et al. 2016; Prado et al. 2016). Meta-analyses of data from randomized trials revealed that the provision of SQ-LNS to children aged 6–24 months resulted in reduced mortality (Stewart et al. 2020), reduced prevalence of anaemia, iron deficiency anaemia, stunting, wasting and underweight (Dewey et al. 2021; Wessells et al. 2021) and improved motor, language and socio-emotional outcomes (Prado et al. 2021) in infancy and early childhood. Although several studies have reported effects of SQ-LNS on offspring in terms of physical development, as well as cognitive, socio-emotional, executive and motor function, to our knowledge, no study has assessed its effect on subsequent ANS regulation or considered the role of the home environment in this association.

Poor home environment and low socioeconomic status during childhood have the potential to negatively affect a child's ANS regulation (Alkon et al. 2014; Johnson et al. 2017). The amygdala and the prefrontal cortex, both of which play a role in ANS regulation, are sensitive to home environment influences during childhood and adolescence, respectively (Wesarg et al. 2022). Home environment may modify the effects of SQ-LNS, as observed in previous research. The effects of SQ-LNS on socio-emotional difficulties were larger among children from poorer early and middle childhood home environments than among children from better home environments (Ocansey et al. 2019; Prado et al. 2023), suggesting that SQ-LNS benefitted those children who were at greater environmental risk. Such types of interaction can also be interpreted as a buffering effect of SQ-LNS against the usual negative relation between a poor home environment and ANS regulation.

Respiratory sinus arrhythmia (RSA) and pre-ejection period (PEP) are indices of PNS and SNS activity, respectively. Baseline (resting) RSA and PEP serve as indicators of an individual's typical or usual ANS activity levels. Generally, at baseline, higher RSA (more PNS influence) and longer PEP (less SNS influence) are characteristics of well-regulated parasympathetic and sympathetic activities (Giuliano et al. 2018; Kahle et al. 2018; Zeytinoglu, Calkins, and Leerkes 2020). ANS reactivity (changes in RSA and PEP in response to stimuli relative to baseline) represents changes in ANS response during challenging periods. ANS reactivity is measured in laboratory studies by tasks that elicit modest ANS responses, such as inhibitory control (IC) tasks. IC, a core component of executive functions, is the ability to control one's emotions, thoughts, attention and/or behaviour by suppressing a prepotent or dominant response tendency when the task at hand requires a different response (Diamond 2013). Typically, modest RSA decreases (less PNS influence) and PEP shortening (more SNS influence) to IC tasks characterize well-regulated parasympathetic and sympathetic activity, respectively (Kahle et al. 2018; Tenenbaum et al. 2019; Zeytinoglu, Calkins, and Leerkes 2020).

In general, much of the existing knowledge of ANS development and regulation among children has been derived from samples in high-income countries (HICs), with little to no research among samples from low- and middle-income countries (LMICs). Compared to HICs, LMICs tend to have a higher prevalence of nutritional deficiencies and lower quality home environments (Lartey 2008; Walle et al. 2020). Thus, studying the relations between nutrition, home environment and children's ANS regulation in LMICs may reveal associations that are not evident in HIC populations.

In the current study, we examined the effect of prenatal and postnatal SQ-LNS compared to two control conditions on ANS regulation at 9–11 years of age, and the interactive effects of SQ-LNS and early and middle childhood home environment in relation to ANS regulation. To our knowledge, this is the first long-term follow-up of a randomized controlled trial (RCT) study assessing the effect of prenatal and postnatal supplementation with a fortified food-based product on ANS regulation. Our first hypothesis was that compared to children who were not exposed to SQ-LNS in early life, those exposed to SQ-LNS would have better ANS regulation (i.e., higher RSA and longer PEP at baseline, and moderate RSA withdrawal and PEP shortening during task relative to baseline). Our second hypothesis was that children in more disadvantaged home environments during early (4–6 years) or middle childhood (9–11 years) would have poorer ANS regulation. Our third hypothesis was that greater effects of SQ-LNS would be found among children from more disadvantaged home environments, with SQ-LNS buffering against the effects of disadvantaged home environments.

2 | Methods

2.1 | Original iLiNS Trial

Details of the International Lipid–based Nutrient Supplement (iLiNS) DYAD-Ghana trial conducted between 2009 and 2014 (Adu-Afarwuah et al. 2016; Adu-Afarwuah et al. 2015) have been described previously. Briefly, the iLiNS DYAD-G trial was a partially double-blind RCT that enroled 1320 pregnant women in the Yilo and Lower Manya Krobo Districts of Ghana. The women were randomized to one of three groups. One group received daily iron and folic acid (IFA; 60 mg iron and 400 μg folic acid) during pregnancy and placebo (200 mg/d calcium) during the first 6 months postpartum, with their offspring receiving no supplementation. The second group received daily multiple micronutrient (MMN) capsules providing 1–2 Recommended Dietary Allowances of 18 vitamins and minerals during pregnancy and the first 6 months postpartum, with their offspring receiving no supplementation. The third group received 20 g SQ-LNS daily during pregnancy and the first 6 months postpartum, with their offspring then receiving SQ-LNS formulated for infants daily from 6 to 18 months of age. In addition to containing the same micronutrients as the MMN capsule, the SQ-LNS contained EFAs and a small amount of protein, as well as calcium, potassium, magnesium and phosphorus (Supporting Information S1: Table 1). In 2016, when the children were 4–6 years of age, a first follow-up was conducted to assess the long-term effects of SQ-LNS on children's growth and development (Kumordzie et al. 2019; Ocansey et al. 2019).

2.2 | Follow-Up at 9–11 Years

The follow-up of the iLiNS DYAD-G trial conducted when the children were 9–11 years of age was carried out between December 2020 and December 2021. We aimed to locate caregivers of the 1217 known surviving children eligible for re-enrolment from the original trial. Field workers contacted the caregivers at their last known address. Caregivers were then visited at home where informed consent (caregivers) and assent (children) to participate were obtained, socio-demographic information was collected, the home environment was assessed and caregivers were scheduled to bring their children to the project office. At the project office, data on the children's growth and development and ANS regulation were collected. The original iLiNS trial was approved by the ethics committees of the University of California, Davis (UC Davis); the Ghana Health Service; and the University of Ghana Noguchi Memorial Institute for Medical Research. Ethical approval for the 4–6-year follow-up was obtained from the ethics committees of UC Davis, Ghana Health Service and the College of Basic and Applied Sciences of the University of Ghana. Ethical approval for the 9–11-year follow-up study was obtained from the Institutional Review Board of the University of California, Davis (IRB ID: 1489918) and the Ghana Health Service Ethical Review Committee (GHS-ERC: 027105119).

2.3 | Assessment of Background Characteristics and Home Environment

At enrolment into the original trial, field workers used a questionnaire to collect maternal and household information, including maternal age, education, marital status, parity, household assets and household food insecurity.

At the 4–6-year follow-up, the home environment was assessed using the Early Childhood Home Observation for the Measurement of the Environment (EC-HOME) Inventory designed for 3- to 6-year-old children (Caldwell and Bradley 2003), which was adapted to the local Ghanaian context. The adapted EC-HOME Inventory contained 46 items measuring language and academic stimulation, learning materials, physical environment, family lifestyle variety, caregivers' responsivity, desirable behaviour modelling and negative behaviour acceptance. In the study setting, the inventory showed high internal reliability (Cronbach's alpha = 0.86) and acceptable test–retest reliability (Pearson's $r = 0.63$) (Ocansey et al. 2019).

At the 9–11-year follow-up, the home environment was assessed using the Middle Childhood version of the HOME (MC-HOME) inventory (Grossman 1995), which is designed for children between 6 and 10 years. The adapted version contained 58 items measuring active stimulation, learning materials, physical environment, parental responsivity and involvement, emotional climate, encouraging maturity and family participation. The MC-HOME showed high test–retest reliability (Pearson's $r = 0.86$) and internal reliability (Cronbach's alpha = 0.77) (Prado et al. 2023).

2.4 | Assessment of Physiological Outcomes

ANS data were collected using Mindware Technologies (Westerville, OH, USA) ambulatory monitors with a sampling rate of 500 Hz, strapped to a belt placed around the waist of the children to allow for easy movement. To collect electrocardiography (ECG) and obtain RSA, three adhesive pre-gelled silver/silver chloride (Ag/AgCl) electrodes were attached in Einthoven's triangle configuration (right clavicle, right lower rib and left lower rib). To measure impedance cardiography (ICG) and obtain PEP, four more electrodes were placed on the child: two on the chest at the top of the sternum and over the xiphisternal junction and two on the child's back, placed at 3.8 cm above and below these locations.

Upon arrival at the project office site, the electrodes were attached to the child as described, after which children were seated on a straight, high-back chair and sat quietly for 5 min. Baseline ANS data were then collected, whereas children watched a 3-min penguin video from the March of Penguins (2005) documentary with gentle music and no narration. After this, children's autonomic activity was measured while they completed two challenging IC tasks on tablets: the Emotion Go/No-Go (EGNG) and Rapid Assessment of Cognitive and Emotional Regulation (RACER) Simon tasks.

2.5 | The IC Tasks

2.5.1 | EGNG

The EGNG task assesses children's IC in the presence of emotional stimuli. It was presented using E-Prime Software (Psychology Software Tools, Pittsburgh, PA). The stimuli consisted of happy, fearful and angry facial expressions from 20 African American adult individuals (10 male and 10 female) selected from the NimStim Set of Facial Expressions (http://www.macbrain.org/resources.htm) (Tottenham et al. 2009). The task consisted of four pseudo-randomized conditions with 144 go-trials and 48 no-go trials per condition: Happy Go/Fear No-Go, Fear Go/Happy No-Go, Happy Go/Angry No-Go and Angry Go/Happy No-Go. Each trial was presented for 500 ms and followed by a varied 750–1500 ms intertrial interval. Children were required to press the SPACEBAR on the tablet as quickly as possible when a 'Go' face was presented and to withhold a response when a "No-go" face was presented. On average, it took children 11.4 min to complete the task. We obtained RSA and PEP scores for each block of the task.

2.5.2 | RACER Simon Task

RACER Simon task is a tablet-based assessment tool assessing IC (Ford et al. 2019). The task had two conditions, same-side and opposite-side, with 30 randomized trials per condition. In the same-side trials, a solid yellow ball appeared on one side of the screen, and children were asked to touch the centre of the same side of the screen. In opposite-side trials, a pink and black striped ball appeared on one side, and children were asked to touch the centre of the opposite side of the screen from where the ball appeared. Each ball was presented until either the child touched the tablet screen or 2500 ms passed without a response, and then was followed by a 1000 ms intertrial interval. On average, it took children 2.9 min to complete the task. We obtained RSA and PEP scores for the total duration of the task.

2.6 | RSA and PEP Analysis

ECG data were edited in MindWare HRV Version 3.2.11. Trained editors visually inspected the duration of each child's physiological data and hand-corrected any misidentified R spikes. RSA was computed from the edited data, with respiratory frequency bands set to 0.24–1.04, the standard range for children (Kahle et al. 2018). Impedance data were edited in MindWare IMP Version 3.2.11; each Q point was inspected and placed at the R wave onset if the software did not automatically do so, and PEP was computed. RSA and PEP values were computed in 30-s epochs over the course of the baseline and RACER Simon tasks; baseline and RACER RSA and PEP values were computed from the averaged values across the 30-s epochs for each child. If the final epoch was less than 15 s, its data were discarded. RSA and PEP values for EGNG were computed for the total duration of each of the four emotion blocks separately.

2.7 | Sample Size

The final sample for analysis included 965 children (331 in the SQ-LNS group and 634 in the non-LNS group) who had ANS data at the 9- to 11-year follow-up. This sample size provided 80% power to detect a small effect size, defined as a mean difference between two groups of > 0.20 SD for continuous outcomes at a significance level of $p < 0.05$.

2.8 | Statistical Analyses

A statistical analysis plan was posted to Open Science Framework before conducting analyses (https://osf.io/bmv9d/). Analyses were conducted in R v4.1.1. Outliers in the raw RSA and PEP data, defined as more than 2 SD from the mean, were winsorized by reassigning the values that fell within 2 SDs of the mean (Horn et al. 2018; Nyitrai and Virág 2019). The number of outliers winsorized for the RSA and PEP data ranged from 3 to 9 (Supporting Information S1: Table 2).

We presented descriptive statistics for key baseline characteristics for children in the SQ-LNS and control (IFA + MMN) groups and examined whether these characteristics were similar for both groups. We evaluated potential bias in the sample by comparing baseline characteristics between the sample included in this analysis and the sample enroled in the original parent trial but lost to follow-up using *t*-tests for continuous variables and χ^2 for categorical variables.

Separate analyses were run for RSA and PEP measures. Our primary comparison groups of interest were SQ-LNS and the control group (IFA and MMN combined). However, we first conducted a sensitivity analysis comparing the IFA and MMN groups to check for any differences between these two groups. If we found differences between the IFA and MMN groups, we

conducted a three-group analysis and Tukey Kramer post hoc pairwise comparisons. To test the effect of the intervention, we examined the difference between the intervention (SQ-LNS) group versus the control group (IFA and MMN combined) using analysis of covariance (ANCOVA) models. For measures of ANS reactivity during the EGNG task, which had four levels of condition per child, the interaction of Intervention Group x Condition was used. Three versions of each model were assessed. In the first model, we adjusted only for the child's age at the time of ANS recording. The second models were additionally adjusted for child sex, developmental assessment data collector and any of the following baseline variables that were associated at the $p < 0.10$ level with the outcomes in bivariate analysis: maternal age, maternal education, maternal pre-pregnancy BMI, maternal haemoglobin concentration, household asset score and parity. In the third set of models, any factors collected after enrolment (birth weight) or at follow-up (child BMI at 9–11 years, baseline RSA or PEP for reactivity models) that were associated at the $p < 0.10$ level with the outcome in correlation analysis were adjusted for if they were not different between intervention groups ($p > 0.10$). Pre-specified potential effect modifiers were EC-HOME and MC-HOME. These were assessed with an interaction term in the ANCOVA models 1 and 3. Significant interactions ($p < 0.10$) were further examined with simple slope analyses with the moderator (home environment) at +1 and −1 SD. In the simple slope analyses, we examined whether the effect of SQ-LNS on ANS regulation outcomes differed at two values of the moderator (home environment). This approach allowed us to see whether the effect of SQ-LNS on ANS regulation outcomes differed for children in more advantaged (+1 SD) versus more disadvantaged (−1 SD) home environments. Regions of significance (ROS) analyses using the Johnson–Neyman technique were also used to identify whether there were differences between SQ-LNS and control groups at any values of the home environment and if so, at which values of the home environment scores those differences in ANS regulation were evident (Bauer and Curran 2005; Ugarte et al. 2023). The specific upper and lower bounds were interpreted as meaningful when they were within ±2 SD of the mean level of the home environment scores. However, if we conducted a three-group analysis for intervention differences, we added interaction terms to the ANCOVA three-group models and significant interactions ($p < 0.10$) were examined using stratified analyses.

3 | Results

3.1 | Background Characteristics

Out of the 1217 children eligible for re-enrolment in this follow-up study, 979 were enroled, and ANS data were obtained from 965 children (73.0% of the 1320 women enroled in the parent trial and 79.1% of the 1217 eligible children). Details of the study profile are presented in Figure 1. There were no significant differences in most background characteristics between children included in this analysis and those lost to follow-up, except for baseline maternal parity. A greater proportion of mothers of children lost to follow-up were nulliparous at enrolment (40.3% vs. 31.4%, $p = 0.003$) (Supporting Information S1: Table 3).

Table 1 shows the selected maternal and child characteristics of the sample included in the analysis. About 48% of the children were male, and the mean (SD) age was 9.9 (0.5) years. There were no significant differences in background characteristics between participants in the SQ-LNS and control groups, except for baseline household asset index (HAI) and pre-pregnancy BMI. Compared to the control group, the SQ-LNS group had lower HAI scores (−0.07 vs. 0.08, $p = 0.021$) and women in the SQ-LNS group had slightly higher pre-pregnancy BMI (24.9 vs. 24.3 kg/m^2, $p = 0.047$). Baseline HAI and pre-pregnancy BMI were measured at initial enrolment into the original trial, before randomization. At initial enrolment with the full sample of enroled families, there were no differences in HAI and pre-pregnancy BMI between the three groups (Adu-Afarwuah et al. 2015). However, small differences in HAI and pre-pregnancy BMI between the groups were seen in our analysis of the smaller sample after loss to follow-up. Therefore, the apparent differences between groups were the result of attrition, after HAI and pre-pregnancy BMI were assessed.

3.2 | Effects of SQ-LNS on Children's ANS Regulation (Hypothesis 1)

Children in the SQ-LNS group did not differ significantly from children in the control (IFA and MMN combined) group in any of the ANS outcome scores (Table 2). However, the IFA and MMN groups differed significantly in PEP reactivity scores for both RACER and EGNG tasks (Supporting Information S1: Table 4), with children in the MMN group showing more shortening of PEP during both tasks relative to baseline (hence, more SNS reactivity) compared compared to those in the IFA group. Therefore, three-group comparisons were conducted, revealing significant group differences only for PEP reactivity score to the RACER task ($p = 0.017$) (Supporting Information S1: Table 5), with children in the MMN group having the most PEP shortening, followed by those in the SQ-LNS group and then children in the IFA group. Post hoc analyses revealed no significant differences between the SQ-LNS and MMN groups, but there was a significant difference between the MMN and IFA groups ($p = 0.016$), and the difference between the SQ-LNS and IFA groups approached significance ($p = 0.093$) (Supporting Information S1: Table 5).

3.3 | Association of Home Environment With Children's ANS Regulation (Hypothesis 2)

Table 3 shows the associations between home environment (EC-HOME [4–6 years] and MC-HOME [9–11 years]) and children's ANS regulation. Children with lower EC-HOME showed shorter baseline PEP (hence, more SNS activation) and less shortening of PEP during the EGNG task relative to baseline (hence, less SNS reactivity). However, MC-HOME was not significantly associated with any of the ANS outcome scores. The associations of EC-HOME with baseline PEP and EGNG reactive PEP remained significant in the models with concurrent MC-HOME scores, suggesting that the quality of the early childhood home environment predicted future SNS regulation (Supporting Information S1: Table 6).

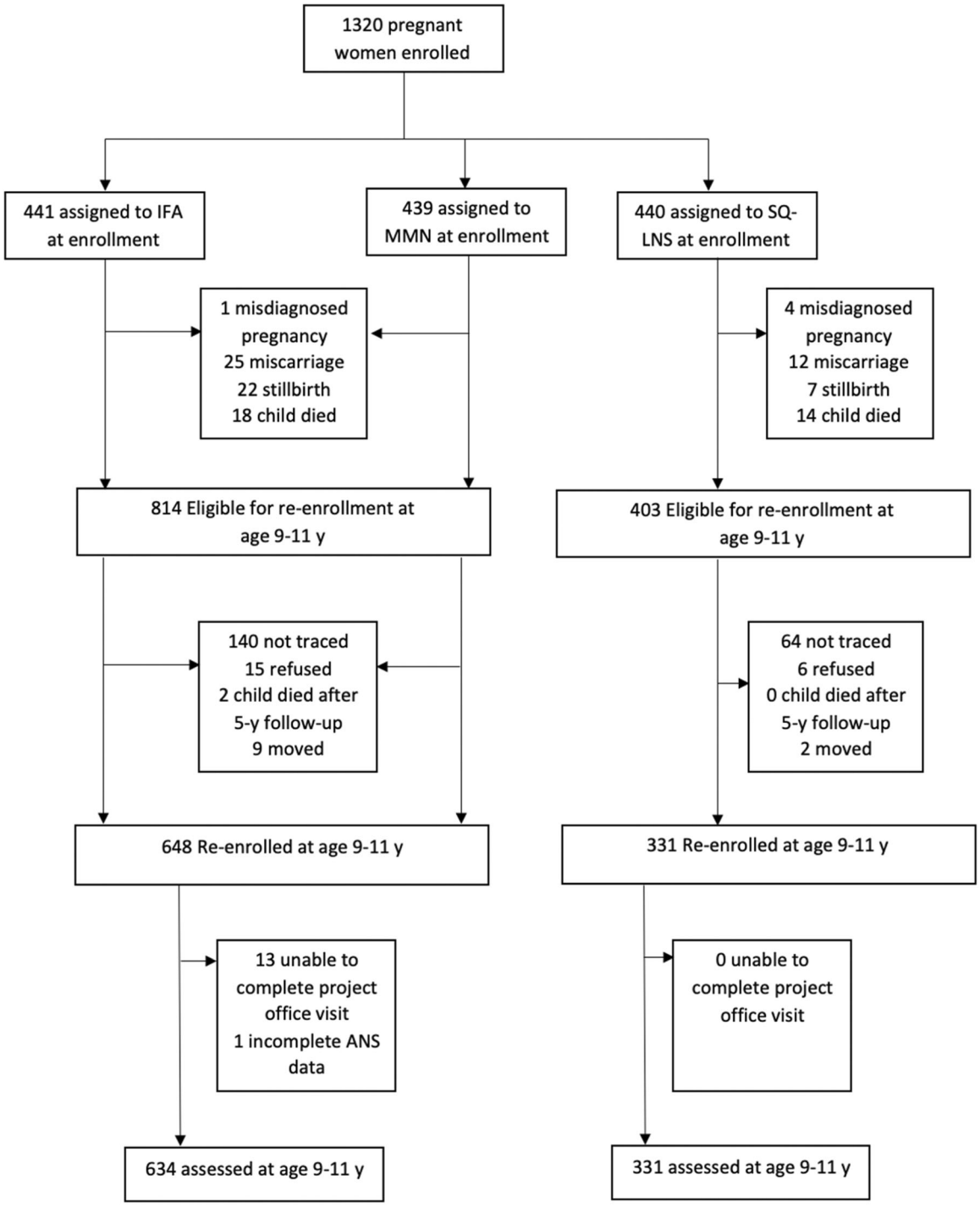

FIGURE 1 | Study profile. ANS, autonomic nervous system; IFA, iron and folic acid; MMN, multiple micronutrients; SQ-LNS, small-quantity lipid-based nutrient.

3.4 | Interaction of SQ-LNS and Home Environment (Hypothesis 3)

The interaction between the intervention group and MC-HOME was significant for RSA reactivity during RACER (P interaction = 0.076 in model 1; 0.111 in model 3) and EGNG tasks (P interaction = 0.0002 in model 1; 0.0008 in model 3). Although the interaction effect for RSA reactivity on the RACER task was weak, it showed that higher MC-HOME scores tended to predict more RSA reactivity to the RACER task only for children in the control group ($\beta = -0.087$, $p = 0.069$); MC-HOME did not predict RSA reactivity for children in the SQ-LNS group ($\beta = 0.050$, $p = 0.430$) (Figure 2a). However, the ROS analysis of the home environment as the moderator of the intervention group effect on RACER task RSA had an upper bound of 49.2, which was well beyond 2 SD above the mean of MC-HOME. The SQ-LNS and control groups did not differ in RSA reactivity at MC-HOME scores below 49.2. Therefore, the scores on MC-HOME at which the intervention groups diverged significantly for RSA reactivity on the RACER task were so extreme as to be uninterpretable, pertaining to only about 1% of the sample.

TABLE 1 | Background characteristics of women and children by intervention group at baseline and follow-up.[a]

Variable	SQ-LNS ($n = 331$)	Control ($n = 634$)	p value
Maternal characteristics at baseline			
Age (y)	27.0 (5.5)	26.8 (5.4)	0.741
Formal education (y)	7.6 (3.8)	7.7 (3.4)	0.871
Married or cohabiting (%)	91.8 [304/331]	94.0 [596/634]	0.255
Household asset index[b]	−0.07 (0.97)	0.08 (0.97)	0.017
Household food insecurity access score	2.3 (3.8)	2.7 (4.4)	0.091
Household water source (% improved)	99.1 [328/331]	97.9 [621/633]	0.366
Household toilet facility (% improved)	97.3 [322/331]	97.5 [618/631]	0.990
Height (cm)	159.1 (5.4)	158.7 (5.9)	0.377
Pre-pregnancy BMI[c] (kg/m^2)	24.9 (4.5)	24.3 (4.4)	0.047
Haemoglobin concentration (Hb) (g/L)	111.5 (11.2)	111.4 (12.6)	0.901
Nulliparous (%)	30.8 [102/331]	31.7 [201/634]	0.834
Child characteristics			
Sex (% male)	48.3 [160/331]	48.4 [307/634]	0.990
Age at 9–11 years (y)	9.9 (0.5)	9.9 (0.5)	0.728
BMI at 9–11 y (kg/m^2)	16.2 (2.6)	16.0 (2.4)	0.268
EC-HOME score at 4–6 year follow-up	28.0 (4.5)	28.0 (4.8)	0.970
MC-HOME score at 9–11 year follow-up	35.0 (5.5)	35.1 (6.1)	0.782

Note: Results are based on *t*-test or chi-square test.
Abbreviations: BMI, body mass index; EC-HOME, Early Childhood Home Observation for the Measurement of the Environment Inventory; MC-HOME, Middle Childhood Home Observation for the Measurement of the Environment; SQ-LNS, small-quantity lipid-based nutrient supplement.
[a]Values are mean (SD) or % (n/total). The control group refers to iron and folic acid (IFA) and multiple micronutrient (MMN) groups.
[b]Household asset score is a proxy for household socioeconomic status and was constructed based on household ownership of a set of assets and principal component analysis was used to create an index (mean of zero and standard deviation of one). A higher value represents a higher socioeconomic status.
[c]Estimated pre-pregnancy BMI was calculated from height at enrolment and estimated pre-pregnancy weight (based on polynomial regression with gestation age, gestational age squared and gestational age cubed as predictors).

Considering the interaction effect for RSA reactivity on the EGNG task, there was a similarly weak tendency for higher MC-HOME scores to predict RSA reactivity only for children in the control group ($\beta = -0.046$, $p = 0.101$), not in the SQ-LNS group ($\beta = 0.039$, $p = 0.419$) (Figure 2b). As with RACER, it was only for children in the control group that living in a lower-quality home environment tended to be associated with less RSA reactivity. The ROS analysis of the home environment as the moderator identified lower and upper bounds of 7.7 and 49.6, respectively. Both bounds were well beyond ±2 SD from the mean of MC-HOME, again indicating that the MC-HOME scores at which there was significantly different RSA reactivity between intervention groups represented only a very small proportion of the sample. As such, these moderation effects should be interpreted with caution.

For RACER PEP reactivity, we did not find significant interactions of the intervention group with EC- or MC-HOME scores in the three-group analysis.

4 | Discussion

To our knowledge, this is the first study to examine the long-term effects of prenatal and postnatal SQ-LNS on ANS regulation of children at 9–11 years. Although we did not find unique effects of SQ-LNS on most ANS measures at 9–11 years, we found that children in both the SQ-LNS and MMN groups showed more SNS reactivity during the RACER IC task compared to children in the IFA group. As hypothesized, children from less enriched early-childhood home environments had shorter baseline PEP, signifying increased SNS activity at baseline and reduced SNS reactivity to an emotionally evocative task, indicative of poorer modulation of SNS activity to acute challenges. Furthermore, we found interactions between the intervention group and middle childhood home environment with regard to RSA reactivity (PNS regulation) such that for children in the control group but not those in the SQ-LNS group, living in a lower quality home environment was associated with weaker RSA reactivity to IC tasks. However, these effects of nutritional intervention on PNS regulation were evident only at the extremes of home environment quality, representative of a small fraction of children.

Although there are no prior studies examining the effect of SQ-LNS on ANS functioning, some studies have examined the long-term effects on ANS development of other prenatal and postnatal macronutrient or micronutrient supplements (specifically zinc and long-chain polyunsaturated fatty acids, LCPUFAs). Both zinc and LCPUFAs have been shown to be involved in normal ANS development and regulation (Drewery,

TABLE 2 | Effect of SQ-LNS on ANS outcomes.

Variable	Mean (SD)		Model 1 *p* value[a]	Model 2 *p* value[b]	Model 3 *p* value[c]
	SQ-LNS	Control			
Baseline RSA	7.06 (1.11)	7.15 (1.25)	0.295	0.298	0.312
RSA reactivity					
RACER Simon	−0.9 (0.77)	−0.9 (0.72)	0.963	0.964	0.820
EGNG			0.601	0.595	0.938
Angry Go/Happy No-Go	−0.65 (0.85)	−0.65 (0.77)			
Fear Go/Happy No-Go	−0.61 (0.82)	−0.63 (0.77)			
Happy Go/Angry No-Go	−0.64 (0.83)	−0.64 (0.75)			
Happy Go/Fear No-Go	−0.62 (0.82)	−0.65 (0.75)			
Baseline PEP	84.63 (6.89)	83.86 (7.42)	0.117	0.101	0.101
PEP reactivity					
RACER Simon	−2.31 (4.94)	−2.07 (4.06)	0.451	0.452	0.638
EGNG			0.423	0.246	0.530
Angry Go/Happy No-Go	−2.85 (5.34)	−2.78 (4.76)			
Fear Go/Happy No-Go	−2.89 (5.49)	−2.72 (4.74)			
Happy Go/Angry No-Go	−2.82 (5.55)	−2.82 (4.92)			
Happy Go/Fear No-Go	−3.21 (5.59)	−2.85 (4.81)			

Note: Control group refers to iron and folic acid (IFA) and multiple micronutrient (MMN) groups. Results are based on ANCOVA.
Abbreviations: EGNG, emotion Go/No-Go; PEP, pre-ejection period; RACER, Rapid Assessment of Cognitive and Emotional Regulation; RSA, respiratory sinus arrhythmia; SQ-LNS, small-quantity lipid-based nutrient supplement.
[a]Model 1 was adjusted for child age at follow-up only.
[b]Model 2 was additionally adjusted for child sex, and any of the following baseline variables that were associated at the $p < 0.10$ level with the outcome(s) in correlation analysis: maternal age, maternal education, maternal pre-pregnancy BMI, maternal haemoglobin concentration, household asset score and parity.
[c]Model 3 was additionally adjusted for baseline RSA and PEP (for reactivity models), and any of the factors collected after enrolment (birth weight) or at follow-up (child BMI, maternal depression) that were associated at the $p < 0.10$ level with the outcome in correlation analysis.

Spedale, and Lammi-Keefe 2017; Georgieff 2007). Yet, findings from supplement studies have been mixed (Caulfield et al. 2011; Larnkjær et al. 2006; Rytter et al. 2012), consistent with results from this study where we found effects for SNS reactivity but not for other ANS regulation outcomes. In a zinc supplementation RCT in Peru where pregnant women received 60 mg iron and 250 μg folic acid with or without 25 mg zinc daily from enrolment until 1 month postpartum, children 4–5 years of age born to women who received zinc supplementation had slower heart rate and higher heart rate variability (HRV) at baseline, signifying better ANS regulation, compared to those who were in the no zinc supplementation group (Caulfield et al. 2011). Given that both MMN and SQ-LNS contain MMN, including zinc, and children in these two groups had better SNS regulation compared to those in the IFA group, our study reveals a novel association between MMN supplementation and SNS reactivity.

In the present study, it is uncertain why stronger, unique effects of SQ-LNS on most of the children's ANS regulation outcomes were not observed, but possible explanations emerge from studies showing that initial (baseline) nutritional status plays a role in determining the effect of nutritional supplements on certain developmental outcomes (Prado et al. 2017; Tofail et al. 2008). Greater nutritional deficiency increases the likelihood
of negative developmental outcomes and also increases the likelihood of a more positive response to, or benefit of, nutritional supplementation (Prado and Dewey 2014). In our cohort, during pregnancy, baseline maternal underweight prevalence was only 2.4% (Ocansey et al. 2019). As such, it is plausible that during their foetal development, children in our cohort were at a relatively low risk of malnutrition and hence were less likely to benefit from supplementation, translating to the lack of treatment effect observed for most of the ANS outcomes.

The finding that a less enriching and nurturing environment during early childhood was associated with poorer ANS regulation characterized by shorter baseline PEP (increased SNS activity at baseline) and less PEP reactivity during an emotional challenge supports findings from prior studies of ANS regulation (Alkon et al. 2014; Johnson et al. 2017). The HOME inventory measures the quality of the child's home environment, generally the cognitive stimulation and emotional support provided by the family. One prior study reported that lower maternal responsivity in infancy was associated with shorter baseline PEP across the early childhood years, indicating that poorer maternal care may prime children for stronger fight-or-flight activation (Johnson et al. 2017). A systematic review and meta-analysis of the relations between parenting behaviour and children's ANS activity found that, for longitudinal studies only, positive parenting predicted decreased baseline SNS activity (Alen et al. 2022). Our results may be the first to show that the quality of the home environment during early childhood predicts not only baseline SNS activity but also SNS reactivity

TABLE 3 | Association of home environment scores with each ANS outcome.

	Model 1[a] 5-year EC-HOME Beta (95% CI)	*p* value	Model 3[b] 5-year EC-HOME Beta (95% CI)	*p* value	Model 1[b,c] 10-year MC-HOME Beta (95% CI)	*p* value	Model 3[b,c] 10-year MC-HOME Beta (95% CI)	*p* value
Baseline RSA	−0.003 (−0.02, 0.01)	0.766	0.000 (−0.02, 0.02)	0.999	0.01 (−0.01, 0.02)	0.415	0.01 (−0.01, 0.02)	0.312
RSA reactivity								
RACER Simon	−0.003 (−0.01, 0.01)	0.574	−0.003 (−0.01, 0.01)	0.540	−0.005 (−0.014, 0.005)	0.326	−0.004 (−0.01, 0.01)	0.392
EGNG	−0.002 (−0.007, 0.004)	0.524	−0.003 (−0.008, 0.003)	0.354	−0.003 (−0.008, 0.001)	0.175	−0.003 (−0.007, 0.002)	0.227
Baseline PEP	0.13 (0.02, 0.23)	0.016	0.14 (0.04, 0.25)	0.009	0.03 (−0.06, 0.12)	0.471	0.04 (−0.05, 0.13)	0.429
PEP reactivity								
RACER Simon	−0.04 (−0.1, 0.02)	0.226	−0.02 (−0.09, 0.04)	0.449	0.04 (−0.02, 0.09)	0.179	0.04 (−0.01, 0.1)	0.122
EGNG	−0.06 (−0.09, −0.02)	0.001	−0.05 (−0.08, −0.01)	0.010	−0.004 (−0.035, 0.027)	0.804	−0.01 (−0.04, 0.02)	0.632

Abbreviations: EGNG, Emotion Go/No-Go; PEP, pre-ejection period; RACER, Rapid Assessment of Cognitive and Emotional Regulation; RSA, respiratory sinus arrhythmia; SQ-LNS, small-quantity lipid-based nutrient supplement.
[a]Model 1 was adjusted for child age at follow-up only.
[b]Model 3 was additionally adjusted for child sex, baseline RSA and PEP (for reactivity models) and any of the following variables that were associated at the $p < 0.10$ level with the outcome(s) in correlation analysis: baseline - maternal age, maternal education, maternal pre-pregnancy BMI, maternal haemoglobin concentration, household asset score and parity; after enrolment -birth weight; and at follow-up - child BMI, maternal depression.
[c]Models 1 and 3 for MC-HOME were also adjusted for EC-HOME scores.

to challenging tasks. Furthermore, the fact that predictive effects of EC-HOME for subsequent baseline and reactive PEP remained significant when included in the model with concurrent MC-HOME scores potentially points to the importance and long-lasting effects of early childhood environments on children's development of SNS regulation.

The interactions between MC-HOME and the intervention group with regard to RSA reactivity to the IC tasks should be interpreted with caution, as the ROS analyses indicated that the scores on MC-HOME at which the SQ-LNS and control intervention groups diverged significantly for RSA reactivity were extreme, pertaining to a very small percentage of the sample. For children in the control group, PNS regulation was related to the home environment, such that concurrently living in more disadvantaged homes was associated with less RSA reactivity, indicative of less mobilization of attention and resources by the PNS to manage the demands of the IC tasks (Hastings and Kahle 2019). Considered another way, more advantaged home environments were associated with more RSA reactivity for children in the control group. Conversely, for children in the SQ-LNS group, PNS regulation was unrelated to variations in the quality of the home environment. This pattern could be seen as consistent with differential susceptibility theory, which posits that children with greater vulnerabilities (in this case, children who had not received SQ-LNS) would disproportionately benefit in supportive environments, but also disproportionately falter under adverse conditions (Belsky 2016). Simultaneously, the findings are consistent with our expectation that SQ-LNS would protect children from the adverse effects of lower-quality environments on ANS regulation. In being buffered against the adverse physiological consequences of living in more economically and socially disadvantaged homes, children in the SQ-LNS group evinced average levels of RSA reactivity regardless of their concurrent home environments.

This study has several strengths and limitations. ANS regulation was measured at both baseline and during IC tasks known to elicit ANS changes to varying degrees for both the PNS and SNS branches of the ANS, giving a thorough portrayal of ANS physiology at 9–11 years. Repeated observations of the home environment were made across childhood at 4–6 years and 9–11 years. This study had a relatively low attrition rate and as a result, a large sample was retained from the parent trial (73.1% of those enroled during pregnancy) and from those eligible for follow-up (79.1%). During the original trial, participants could not be blinded to whether they received SQ-LNS compared to control (IFA and MMN), but for this follow-up study, field personnel who collected ANS data and analysts were blinded to group assignments to prevent bias. Background maternal, child and household characteristics were similar for SQ-LNS and control groups, suggestive of a low risk of bias. A limitation of this study is that a higher percentage of participants lost to follow-up were nulliparous compared to those included in the analysis. However, because the effect of intervention on outcomes did not differ by parity, it is unlikely that this difference led to bias in our results.

In conclusion, there was no overall effect of SQ-LNS on most ANS outcomes at 9–11 years in this cohort. However, children in the SQ-LNS and MMN groups showed more SNS reactivity compared to those in IFA group. There was evidence of middle

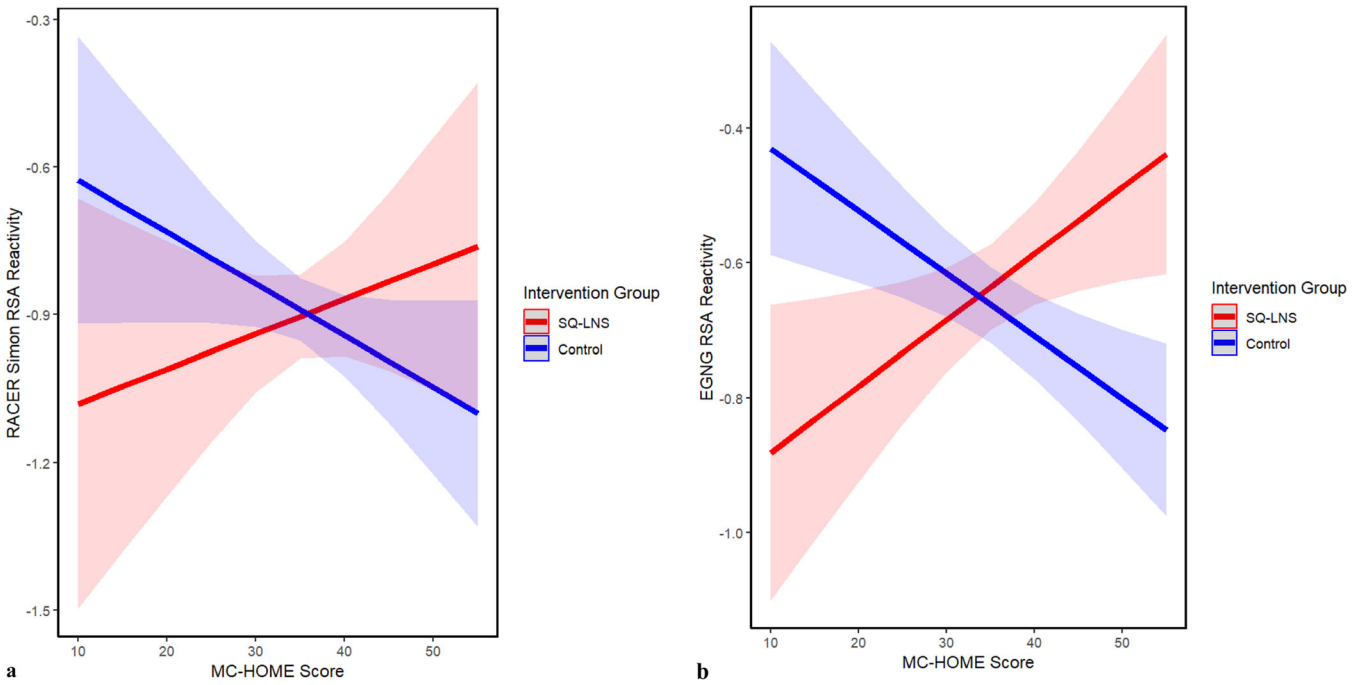

FIGURE 2 | Moderating Effects of Nutrition Group on the Associations of Middle Childhood Home Environment with RSA Reactivity to the (a) RACER Simon task and (b) Emotion Go/No-Go task. MC-HOME, Middle Childhood-Home Observation for the Measurement of the Environment; EGNG, Emotion Go/No-Go; RSA, respiratory sinus arrhythmia; SQ-LNS, small-quantity lipid-based nutrient supplement. The control group is a combination of iron and folic acid (IFA) and multiple micronutrients (MMN) groups.

childhood home environment moderating associations of SQ-LNS with PNS regulation. We found strong evidence for associations between early childhood home environment and later SNS regulation, suggesting the need to focus on improving the quality of the home environment in early childhood to support healthy ANS maturation across childhood.

Author Contributions

The authors' responsibilities were as follows: Lois M. D. Aryee, Kathryn G. Dewey, Elizabeth L. Prado, Seth Adu-Afarwuah, Paul D. Hastings, Amanda E. Guyer, Adom Manu, Benjamin Amponsah and Brietta M. Oaks designed the research; Lois M. D. Aryee, Seth Adu-Afarwuah, Mavis O. Mensah, Helena J. Bentil and Ebenezer Adjetey conducted the research; Lois M. D. Aryee, Paul D. Hastings and Charles D. Arnold analysed the data; Lois M. D. Aryee wrote the manuscript with critical input and comments from all other authors; Lois M. D. Aryee and Paul D. Hastings had primary responsibility for final content; all authors except Elizabeth L. Prado read and approved the final manuscript. Due to her death during the preparation of this manuscript, Elizabeth L. Prado was unable to read and approve the final manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

De-identified individual participant data (including data dictionaries) will be made available upon request to researchers who provide a methodologically sound proposal and statistical analysis plan contingent on approval by the Principal Investigators. Proposals should be submitted to the corresponding author.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.