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Maternal depression is the predominant persistent risk for child cognitive and social-emotional problems from early childhood to pre-adolescence: A longitudinal cohort study

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ABSTRACT

Rationale: Brain development occurs rapidly during early childhood and continues throughout middle childhood. Early and later windows of opportunity exist to alter developmental trajectories. Few studies in low- and middle-income countries have examined the importance of the timing of exposure to risks for poor pre-adolescent cognitive and social-emotional outcomes.

Methods: We assessed 359 children who participated in two follow-up studies of the Supplementation with Multiple Micronutrients Intervention Trial conducted in Indonesia in 2001–2004: at 3.5 years in 2006 and 9–12 years in 2012–2014. Using structural equation models, we examined indicators of early childhood (3.5 y) and pre-adolescent (9–12 y) exposure to risks (child height-for-age z-score [HAZ], hemoglobin [Hb], maternal depressive symptoms [MDS], home environment [HOME]), with two developmental outcomes: cognitive ability and social-emotional problems. We characterized patterns of change by calculating residuals of indicators measured earlier (3.5 y) predicting the same indicators measured later (9–12 y), for example, the residual of 3.5 y MDS predicting 9–12 y MDS (rMDS).

Results: Three early risk indicators (HOME, Hb, and MDS) were indirectly associated with pre-adolescent cognitive scores through early cognitive scores (HOME: 0.15, [95% CI 0.09, 0.21]; Hb: 0.08 [0.04, 0.12], MDS: −0.07 [-0.12, −0.02]). Pre-adolescent cognitive scores were also associated with change in MDS (rMDS: −0.13 [-0.23, −0.02]) and Hb (rHb: 0.10 [0.00, 0.20]) during middle childhood. For pre-adolescent social-emotional problems, both early childhood MDS (0.31 [0.19, 0.44]) and change in MDS during middle childhood (rMDS: 0.48 [0.37, 0.60]) showed strong direct associations with this outcome.

Conclusions: Our findings confirm those of previous studies that prevention of risk exposures during early childhood is likely to support long-term child development. It also adds evidence to a previously scarce literature for the middle childhood period. Prevention of maternal depressive symptoms and child anemia during middle childhood should be assessed for effectiveness to support child development.

1. Introduction

Poverty contributes to an estimated 250 million children under five years of age worldwide not fulfilling their developmental potential (Black et al., 2017). Building strong beginnings during early childhood may be easier and more cost-effective than facilitating repairs during

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later childhood, when brain architecture is less malleable (Couperus and Nelson, 2006). However, brain development and plasticity continue throughout childhood and adolescence, therefore later windows of opportunity also exist to alter developmental trajectories (Fuhrmann et al., 2015). Interventions during early childhood have shown beneficial effects in adulthood, such as increased wages and reductions in violent behavior, which provides strong economic justification for intervention during this early period (Hoddinott et al., 2013; Walker et al., 2011a). However, effects of many early interventions fade out over time (Bailey et al., 2017) and intervention during later childhood may also be needed to maintain early gains and reverse early deficits (Bundy et al., 2018).

The middle childhood years (age 5–9) have been largely neglected in public health programs and research in low- and middle-income countries (LMICs) (Bundy et al., 2018). An essential package of interventions for children age 5–14 has been proposed, which focuses on prevention of biomedical risk factors. For example, the proposed essential package includes health interventions, such as deworming and tetanus vaccination, as well as dietary interventions, such as school feeding programs and micronutrient supplementation (Bundy et al., 2018). Further understanding of how the timing and chronicity of exposures to risk and promotive factors impact children's development is needed. Timing refers to when during development children are exposed to risks, while chronicity refers to whether the exposure is transient or long in duration. Such understanding is important for planning and targeting interventions, including understanding both biomedical and socio-environmental risk factors.

Our aim in the current study was to examine the timing and chronicity of exposure to two biomedical and two socio-environmental risk factors in relation to cognitive ability and social-emotional problems at age 9–12 years in Indonesia. Longitudinal studies in high-income countries have found that chronic exposure to poverty leads to poorer cognitive and behavioral outcomes than temporary durations of exposure (Najman et al., 2010; National Institute of Child, 2005). While understanding the timing and chronicity of the effects of poverty on child development is important, informing the design of interventions requires understanding specific risk factors that occur in the context of poverty. Four reviews have identified 44 poverty-related risk factors associated with poor developmental outcomes in LMICs (Jensen et al., 2015; Wachs and Rahman, 2013; Walker et al., 2007, 2011b). These include poor sanitation and hygiene, exposure to toxins, lack of cognitive stimulation, and maternal and child undernutrition, infections, and stress (for a complete list, see Supplemental Material). In a sample of 2305 children age 9–12 years in Indonesia, we found that concurrent measures of the home environment and maternal depressive symptoms were the strongest predictors of pre-adolescent cognitive and social-emotional outcomes. Child linear growth and hemoglobin concentration were also associated with some pre-adolescent cognitive scores (Prado et al., 2017). However, in that study, we did not examine changes in exposures over time from early childhood to pre-adolescence.

Therefore, in this study, we focus on four measures for which concurrent associations were previously found with pre-adolescent outcomes and for which early childhood measures were also available: child height-for-age z-scores (HAZ) and haemoglobin concentration (Hb), maternal depressive symptoms (MDS), and the Home Observation for the Measurement of the Environment (HOME) Inventory, a measure of responsive care and learning opportunities in the home environment. Low child HAZ and Hb can be indicators of poor nutritional status due to inadequate dietary intake, and can also be related to illness, infection, and inflammation. Nutrients are both the building blocks and the fuel for the developing brain, with nutrient deficiencies leading to deficits in neuron proliferation, axon and dendrite growth, synaptogenesis, and myelination (Prado and Dewey, 2014). Structural deficits in the formation of the neural architecture that underlies cognitive and social-emotional function may lead to long-term effects on cognitive and social-emotional abilities. Socio-environmental factors also affect these neurodevelopmental and behavioral processes. For example, lack of sensory and social experiences leads to reduced axon and dendrite growth and myelination (Kolb and Whishaw, 1998) and long-term cognitive and behavioral deficits (Fox et al., 2011). Maternal depressive symptoms are associated with lower responsive care and developmentally enriching experiences, which may lead to poorer cognitive and social-emotional development (Scherer et al., 2019). Whereas negative biomedical exposures, such as inadequate nutrition, may impair neural and behavioral development, socio-environmental factors, such as enriched experiences, actually stimulate neural, cognitive, and behavioral development throughout the life span. For example, taxi drivers who are able to navigate the complex London city streets have larger posterior hippocampi, the brain area underlying spatial memory, compared to matched controls who do not drive taxis (Maguire et al., 2000).

While child HAZ and Hb, MDS, and the quality of the home environment are known to be associated with cognitive and behavioral development (Bradley, 2015; Larson et al., 2019; Sudfeld et al., 2015; Surkan et al., 2011), less is known about the importance of the timing of child exposure to these risk factors, as indicated by when during childhood the following occur: faltering in linear growth (HAZ), low Hb, high maternal depressive symptoms, and low HOME scores. Our first specific objective (objective 1) was to characterize the timing and chronicity from early childhood (3.5 y) to pre-adolescence (9–12 y) of exposure to two biomedical risk factors (HAZ and Hb) and two socio-environmental risk factors (MDS and HOME scores). Our second objective (objective 2) was to determine the association of these early childhood and pre-adolescent risk exposures with cognitive ability and social-emotional problems in pre-adolescence (9–12 y).

Specifically, we aimed to test three pathways, shown in Fig. 1, designed to inform intervention targeting. Pathway 1 shows associations of pre-adolescent abilities with early childhood risk exposures through early abilities. Pathway 2 shows associations of pre-adolescent abilities with early childhood risk exposures independent of early abilities. If either of these pathways show significant associations, that could imply that prevention of those risk exposures during early childhood might have long-term positive effects. Pathway 3 shows associations of pre-adolescent abilities with change in risk exposures during middle childhood. If this pathway shows significant associations, we would hypothesize that prevention of those risk exposures during middle childhood would result in improved outcomes. This should then be assessed in randomized trials. While such evidence exists for the early childhood period, as discussed above, evidence for the middle childhood period is scarce.

2. Methods

2.1. SUMMIT trial and follow-up studies

The Supplementation with Multiple Micronutrients Intervention Trial (SUMMIT) was a double-blind randomized controlled trial that provided maternal micronutrient capsules to pregnant women in Lombok, Indonesia in 2001–2004 (SUMMIT Study Group, 2008). Midwives employed by the government to provide prenatal care (n = 262) were randomly assigned to distribute either iron and folic acid or multiple micronutrients to 31,290 women during pregnancy and until three months postpartum. Two follow-up studies were conducted: one in 2006 when the children were preschool age (3.5 years; n = 487) (Prado et al., 2012). and one in 2012–2014 when the children were pre-adolescents (9–12 years; n = 2879) (Prado et al., 2017).

In 2001, the population of Lombok was about 2.7 million, and the infant mortality rate was estimated to be 89 per 1000 livebirths compared with 52 per 1000 for Indonesia. The Province of West Nusa Tenggara, which includes Lombok, had maternal mortality ratio estimates ranging from 400 to 890 per 100,000 livebirths, compared with 390 per 100,000 for Indonesia. West Nusa Tenggara has persistently been amongst the poorer of Indonesia's 34 provinces, ranking in the

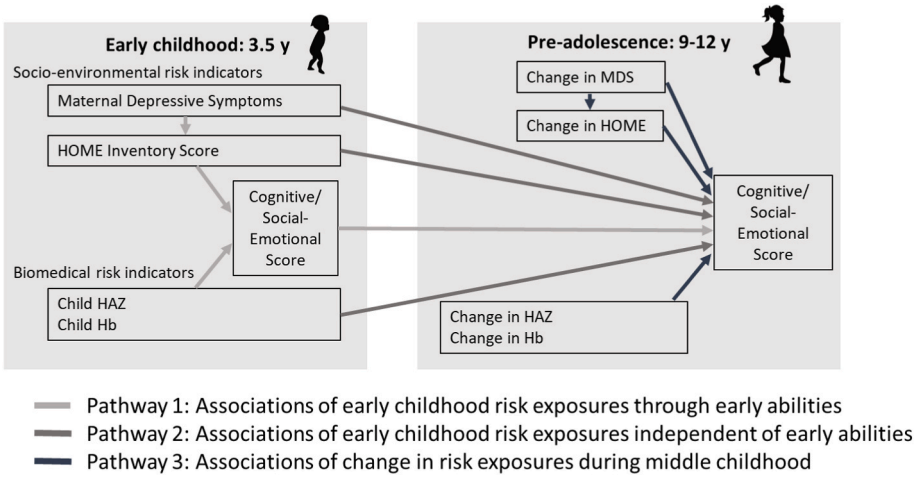

Fig. 1. Hypothesized pathways of associations of early and middle childhood risk exposures with cognitive ability and social-emotional problems at age 9–12 years.

lowest quartile in socioeconomic indices, health infrastructure, and health indicators such as childhood stunting and maternal anemia (Agustina et al., 2019).

All women provided written informed consent for themselves and their children. The study was registered as an International Standard Randomized Controlled Trial, number ISRCTN34151616. The protocols of the original study and follow-up studies were approved by the National Institute of Health Research and Development of the Ministry of Health of Indonesia.

2.2. Participants

Out of the 487 children who participated in the preschool (3.5 y) follow-up study and the 2879 children who participated in the pre-adolescent follow-up study (9–12 y), 359 children participated in both. For this study, we analyzed the data from these 359 children for whom data were available at both follow-up time points.

2.3. Adaptation and evaluation of assessment tools

All assessment tools were adapted to the local language, culture, and setting in Lombok, and were evaluated for internal reliability, test-retest reliability, and convergent validity. A full description of the adaptation, reliability, and validity of the preschool assessments (Prado et al., 2010) and pre-adolescent assessments (Prado et al., 2017) were reported previously.

2.4. Measurement of risk factors

In both the preschool and pre-adolescent follow-up studies, trained anthropometrists measured child height using a stadiometer (Seca model 213). For each time point, we calculated HAZ according to World Health Organization norms (WHO Multicentre Growth Reference Study Group, 2006). In both follow-up studies, child Hb concentration in capillary blood was measured using a HemoCue AB portable hemoglobin meter, and maternal depressive symptoms by self-report using the Centre for Epidemiological Studies Depression (CESD) Scale (Radloff, 1977). The CESD is a 20-item self-report scale that is designed to assess symptoms of depression in community populations, although it does not provide a clinical diagnosis of depression or diagnose the cause of depression. The adapted CESD in the local context showed high test-retest reliability ($r = 0.85$) and internal reliability (Cronbach's $\alpha = 0.83$).

To measure the amount and quality of responsive care and learning opportunities in the home environment, in both follow-up studies we used a locally adapted HOME Inventory (Caldwell and Bradley, 2003), which measures the amount and quality of stimulation a child receives from the home environment. Items probe parent-child communication and interactions, the types of toys available, specific events and other experiences that occur in the home, and the general quality of the physical home environment. The Early Childhood version of the HOME Inventory is designed for children age 3–6 years and the Middle Childhood version for age 6–10 years. Test-retest reliability of the adapted HOME Inventories (early childhood: $r = 0.82$, middle childhood: $r = 0.85$), as well as internal reliability (early childhood, 52 items: $\alpha = 0.77$; middle childhood, 57 items: $\alpha = 0.69$) were high (Prado et al., 2010, 2017).

2.5. Measurement of covariates

At enrollment, maternal anthropometric status and socio-demographic information were gathered, including maternal and paternal years of education and ownership of a set of household assets. These were used to construct an index of socio-economic status based on principal components analysis (Vyas and Kumaranayake, 2006). At pre-adolescence, we also administered an adapted version of the Petersen Pubertal Development Scale (Petersen et al., 1988).

2.6. Measurement of cognitive and social-emotional development

For the SUMMIT follow-up studies, we selected tests of cognitive, motor, and social-emotional development that assess specific abilities which develop during early and middle childhood and are likely to be sensitive to nutritional influences (listed in Table 1; for details, see Supplemental Table 1).

For each time point, we entered all age- and sex-adjusted z-scores into an exploratory factor analysis, to determine the underlying factors measured by the assessments. The first factor accounted for 84% of the variance in preschool scores and 86% of the variance in pre-adolescent test scores, showing that most cognitive scores assessed a single underlying construct, representing general cognitive ability. The other factors did not show a clear interpretable pattern of factor loadings. Therefore, we calculated a single factor score for each time point, representing cognitive ability. We included all test scores with a factor loading >0.3 (Table 1).

As expected, the social-emotional problems score did not load on the cognitive factor at either time point (Table 1). This demonstrates the discriminant validity of the social-emotional problems score as measuring a distinct underlying construct as compared to the cognitive tests. Therefore, we examined the social-emotional problems score as a separate outcome. For the preschool time point, we calculated the social-emotional problems z-score based on the distribution of our

Table 1
Factor loading of each score on the first factor in a maximum likelihood factor analysis.

Preschool (3.5 years)	Factor loading	Pre-adolescence (9–12 years)	Factor loading
Test		Test	
Included in cognitive factor score			
Block Design Test	0.37	Block Design Test	0.46
Picture Vocabulary Test	0.75	Information Test	0.72
Sentence Complexity Scale	0.64	Speeded Picture Naming Test	0.33
Fine Motor Scale	0.62	Purdue Pegboard Test Assembly Score	0.32
Gross Motor Scale	0.39	Visual Search Dual Task	0.36
Visual Search Test	0.49	Digit Span Forward	0.47
Windows Test	0.37	Digit Span Backward	0.37
		Stroop Numbers Test	0.31
		Dimensional Change Card Sort Test	0.39
		Word List Memory Test	
		Immediate Recall	0.50
		Delayed Recall	0.33
		Delayed Recognition	0.40
		Literacy Test	0.45
		Arithmetic Test	0.78
Excluded from cognitive factor score			
Snack Delay Test	0.21	Purdue Pegboard Test Average Score	0.26
		Visual Search Task	0.20
		Serial Reaction Time Task	0.05
Social-Emotional Problems			
Social-Emotional Problems[a]	−0.04	Social-Emotional Problems[b]	0.07

[a] Based on adapted Brief Infant-Toddler Social and Emotional Assessment.
[b] Based on adapted Child Behavior Checklist.

sample because all children were tested within 3 weeks of age 3.5 years. For the pre-adolescent time point, we calculated the social-emotional problems z-score by six-month age bands and by child sex. Thus, a child's z-score represents the difference of that child's score from the mean of children their age and sex in the full study sample (487 at preschool and 2879 at pre-adolescence) in units of standard deviation (SD). For example, a z-score of 0.3 is 0.3 standard deviations above the mean for that child's age and sex. IQ tests are typically standardized to a mean of 100 and a standard deviation of 15. Therefore, a z-score of 0.3 is equivalent to an IQ of about 105, while a z-score of −0.3 is equivalent to an IQ of about 95.

2.7. Statistical analysis

Analyses were conducted using SAS version 9.4 (SAS Institute) or Stata version 15.1 (StataCorp). For objective 1, to characterize patterns of change in risk factors over time, we used linear regression models of the earlier value of each risk factor predicting the later value to calculate the standardized residuals, which are the difference between the observed value and the value predicted by the regression equation (i.e., the residual variance). Because repeated measures of the same risk factor tend to be correlated over time, the later value can be predicted from the earlier value using regression equations. A residual value of zero indicates that the later value (e.g. HOME score at 9–12 y) was the same as what would be expected based on the earlier value (e.g. HOME score at 3.5 y). A positive residual value indicates a later score that was higher than predicted based on the earlier score, while a negative residual value indicates a later score that was lower than predicted based on the earlier score. Thus, these residuals can be considered the "change" from early to later conditions, with positive values indicating improved conditions (reduced risk) over time and negative values indicating worsening conditions (increased risk) over time.

This method is well established for modelling the consequences of linear growth faltering during different periods of childhood (Adair et al., 2013). To calculate residuals for child HAZ, we adjusted for child pubertal development score at age 9–12 y and for maternal height, as a proxy for growth potential.

For each indicator, we then calculated the percentage of children in four categories: (1) persistent high risk (2) persistent low risk, (3) early risk, later improvement, and (4) late-onset of risk. To categorize children with high risk at age 3.5 y, we used the following cut-offs: HAZ < -2, Hb < 110 g/L, CESD ≥ 14, and HOME < 40 (median of the sample distribution). For the CESD scale, the standard cut-off to screen positive for depressive symptoms is ≥ 16 out of a maximum possible 40 points from 20 items. However, our adapted version of the CESD scale was 17 items only, for a maximum possible 34 points, therefore we used a cut-off of ≥ 14. To categorize children with late-onset risk, we used residual < 0 for the three indicators for which lower is worse (HAZ, Hb, and HOME) and residual ≥ 0 for MDS, since a higher score is worse. Thus, we conceptualize late-onset risk as a pre-adolescent score that is worse than expected based on the early childhood score.

The creation of categories is useful for descriptive purposes, however it is problematic for hypothesis testing for several reasons, including the problem that differences in scores between children near the cut-off are not captured. In addition, measurement error can lead to misclassification of children. Therefore we used these categories for descriptive purposes only (Objective 1). For objective 2, we used the continuous scores and continuous residuals (as indicators of change over time) to test our hypotheses. To estimate the association of exposure to risks at different time points with cognitive ability and social-emotional problems, we used two structural equation models, one for each outcome. Both models were adjusted for socio-economic status, maternal and paternal years of education, and intervention group in the SUMMIT trial. Through these two models, we tested the three pathways shown in Fig. 1.

To test pathway 1, we tested the direct association of the early risk (e.g. HAZ at 3.5 y) with the early outcome (e.g., cognitive score at 3.5 y) and the direct association of the early outcome with the pre-adolescent outcome (e.g., cognitive score at 9–12 y), and estimated the indirect association of the early risk with the pre-adolescent outcome through the early outcome score (light grey arrows in Fig. 1). To test pathway 2, we specified the direct association of the early risk (e.g. HAZ at 3.5 y) with the pre-adolescent outcome (e.g. cognitive score at 9–12 y; medium grey arrows). To test pathway 3, we specified the direct association of the change in risk (e.g. rHAZ) with the pre-adolescent outcome (dark grey arrows). We also assessed the indirect association of MDS with child outcomes through HOME scores.

For most independent variables, less than 10% of values were missing, except child Hb at 3.5 y (13%) and 9–12 y (21%) and MDS at 3.5 y (32%). For the structural equation models, we used the *sem* command in Stata with the *mlmv* option to estimate the model on the full data set using maximum likelihood estimation for missing values. This method calculates the indirect effects coefficients using the product of the coefficients method, and the variance estimator using the observed information matrix (OIM).

3. Results

Background characteristics of the 359 children analyzed for this study were similar to the full group of 31,290 participants enrolled in the trial, demonstrating low risk that the sub-sample was biased (Table 2). Characteristics of the sample that was assessed at pre-school but not pre-adolescence ($n = 125$) and of the sample that was assessed at pre-adolescence but not pre-school ($n = 2520$) were also similar (Supplemental Table 2).

Fig. 2 shows the patterns of change in indicators of exposure to risks from early childhood (3.5 y) to pre-adolescence (9–12 y). For linear growth, a high percentage of the sample experienced stunted growth (HAZ < -2): 59% at 3.5 years and 44% at 9–12 years. Thirty percent of

Table 2
Sample characteristics.

	Sample assessed at both preschool and pre-adolescence	Full Cohort
	n = 359	*n* = 31,290
Baseline maternal age: *mean (SD)*	25.8 (5.7)	25.6 (6.1)
Maternal years of education: *mean (SD)*	6.8 (3.5)	6.3 (3.7)
Paternal years of education: *mean (SD)*	7.6 (3.8)	7.0 (4.0)
Baseline wealth quintile: *n/total (%)*		
Poorest	63/355 (18%)	6245/30014 (21%)
Second	71/355 (20%)	6094/30014 (20%)
Third	65/355 (18%)	5946/30014 (20%)
Fourth	77/355 (22%)	5958/30014 (20%)
Wealthiest	79/355 (22%)	5771/30014 (19%)
Parity at enrollment: *n/total (%)*		
First	112/359 (31%)	10829/30472 (36%)
2-3	181/359 (50%)	13415/30472 (44%)
4-5	53/359 (15%)	4529/30472 (15%)
≥6	13/359 (4%)	1699/30472 (6%)
Baseline maternal MUAC <23.5 cm: *n/total (%)*	106/326 (33%)	9363/27127 (35%)
Baseline maternal Hb < 110 g/L: *n/total (%)*	161/355 (55%)	8801/17892 (50%)
Child male: *n/total (%)*	185/359 (52%)	14103/27114 (52%)

children showed a pattern of persistent high risk (persistent growth faltering) throughout childhood, while only 17% showed persistent low risk (consistent positive growth). An additional 30% showed a pattern of early stunted growth with later catch-up growth, while 23% were not stunted at age 3.5 years, but showed late-onset faltering. At age 9–12 years, the cognitive z-scores of all four HAZ groups were within 0.1 SD (1.5 IQ points) of the overall mean z-score (Fig. 3). Likewise, for social-emotional problems, HAZ group means did not vary widely, ranging from 0.13 to 0.30 at 9–12 y (Fig. 4).

At 3.5 years, 49% of children in the sample were anemic (Hb < 110 g/L), which decreased to 35% at 9–12 years. For patterns over time, 23% of the sample had persistent high risk and 23% of children had persistent low risk. Thirty percent were anemic in early childhood then had later improved Hb, while 24% were not anemic in early childhood then showed late-onset risk. At age 9–12 years, children with persistent low risk had the highest cognitive z-scores, on average 0.18 or 3 IQ points above average for age and sex, while the other three groups scored near zero, though slightly below average for age and sex (means −0.02 to −0.08). For social-emotional problems, Hb group means did not vary widely, ranging from 0.16 to 0.24 at age 9–12 years.

For the largest group of mothers (45%), depressive symptoms were consistently low risk, while 35% showed early low depressive symptoms with late-onset risk (worsening depressive symptoms). Only 9% of mothers reported consistently high depressive symptoms and 11% of mothers with high depressive symptoms when their child was 3.5 y showed a later improvement. At age 9–12 y, mean cognitive z-score of mothers with consistently low MDS was higher (0.15 or 2 IQ points above average) than the other three groups, who scored on average −0.07 to −0.14 (1–2 IQ points below average). Children's social-emotional problems z-scores showed large differences between MDS groups. At age 9–12 y, children of mothers who had persistent high depressive symptoms showed very high social-emotional problems,

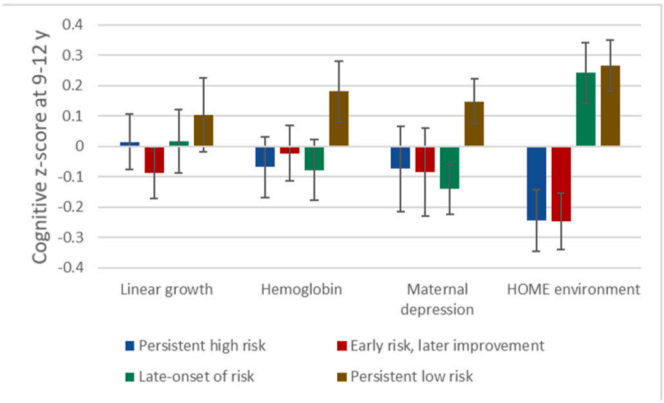

Fig. 3. Cognitive z-scores at age 9–12 years by risk groups.

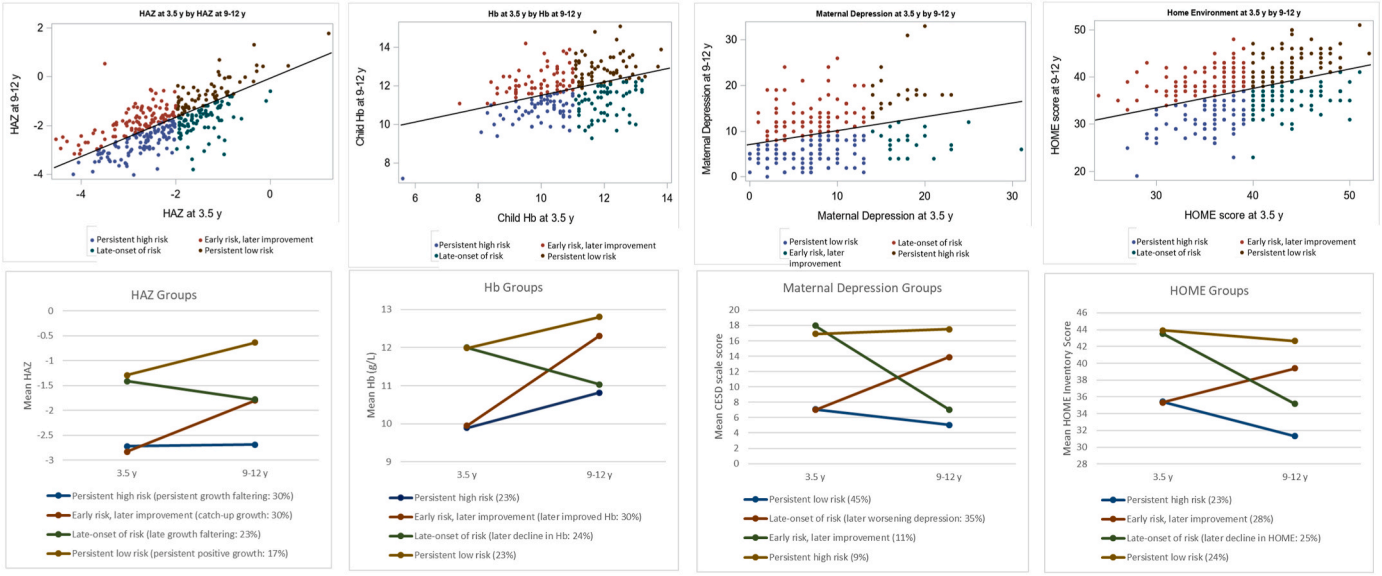

Fig. 2. Patterns of change in four indicators of exposure to risks from early childhood (3.5 y) to pre-adolescence (9–12 y).

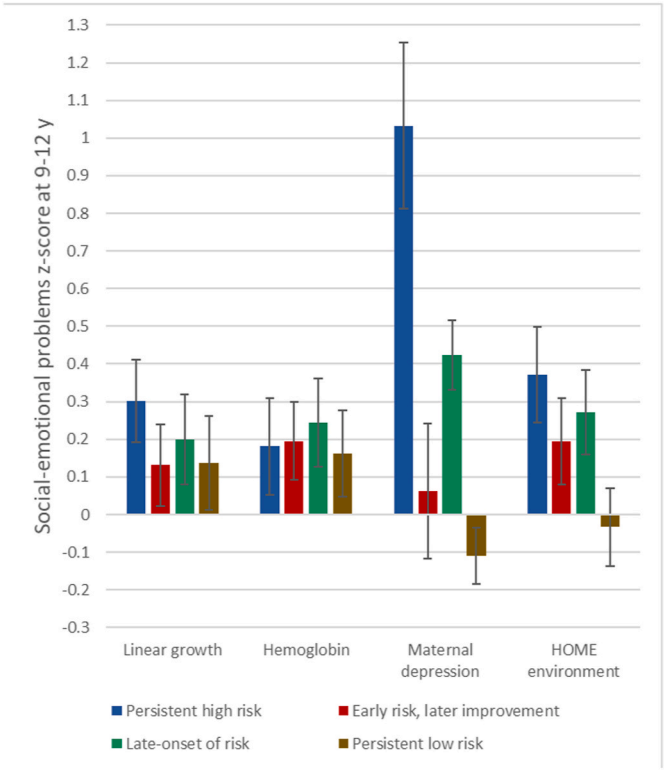

Fig. 4. *Social-emotional z-scores at age 9–12 years by risk groups.*[11]Mean social-emotional z-scores were slightly above zero because these z-scores were calculated based on the distribution of the full sample of 2879 children (see Methods). While the mean of the full sample was zero, the mean of this subsample was slightly above zero.

more than 1 SD above the overall mean (mean 1.03). In contrast, children of mothers with persistent low depressive symptoms had low social-emotional problems (mean −0.11). Children whose mothers experienced high depressive symptoms early, with later improvement, had social-emotional problems z-score on average 0.06, while children whose mothers experienced low depressive symptoms early, with late-onset risk, had social-emotional problems z-score on average 0.42.

HOME inventory scores were evenly distributed, with about a quarter of children in each category. Pre-adolescent cognitive z-scores (at age 9–12 y) of children with low-risk early HOME environments were high (mean 0.24 to 0.27; 4 IQ points above average), regardless of later change in HOME scores during middle childhood. Likewise regardless of middle childhood change in HOME, pre-adolescent cognitive z-scores of children with high-risk early HOME environments were low (mean −0.24 to −0.25; 4 IQ points below average). For social-emotional problems, children with persistent low-risk HOME scores had low social-emotional problems scores at 9–12 y (mean −0.03), while the other three groups had higher social-emotional problems (means 0.19 to 0.37).

We categorized children for objective 1 for descriptive purposes only. For hypothesis testing for objective 2 we examined structural equation models using the continuous indicators of exposure to risks during different periods of development; the results are presented in Tables 3 and 4 and Fig. 5. Results were similar for female and male children (Supplemental Tables 3 and 4).

The initial models did not result in good model fit (cognitive: χ^2 (23) = 98.54, $p < 0.001$, RMSEA = 0.096, CFI = 0.754; social-emotional: χ^2 (23) = 97.58, $p < 0.001$, RMSEA = 0.095, CFI = 0.626), which may have been due to the strong association of three covariates – socio-economic status, maternal and paternal education – with the early childhood HOME score, which were not specified as pathways in the models. When we added these pathways, model fit improved substantially (cognitive: χ^2 (20) = 16.71, $p = 0.67$, RMSEA = 0.00, CFI = 1.00; social-emotional: χ^2 (20) = 15.54, $p = 0.74$, RMSEA = 0.00, CFI = 1.00). The coefficient of determination (R^2) for cognitive scores was 0.40 and for social-emotional problems was 0.55.

Early childhood (3.5 y) Hb and HOME scores were significantly directly associated with early childhood cognitive scores and significantly indirectly associated with pre-adolescent (9–12 y) cognitive scores through early cognitive scores (Table 3). Early childhood MDS was indirectly associated with early childhood and pre-adolescent cognitive scores through early HOME scores. No early risk indicator was directly associated with pre-adolescent cognitive scores, independent of early cognitive scores. This confirmed that our hypothesized Pathway 1 (light grey arrows in Fig. 1) was the primary pathway through which early childhood environments were associated with pre-adolescent cognitive abilities. Change in maternal depressive symptoms from early to later childhood (rMDS) was significantly directly associated with pre-adolescent cognitive scores, indicating that children had lower cognitive performance if their mothers had a greater increase in depressive symptoms during middle childhood, but this was not mediated by middle childhood changes in the home environment. Change in child Hb between early childhood and pre-adolescence was also associated with pre-adolescent cognitive ability. This confirmed our hypothesized Pathway 3 (dark grey arrows in Fig. 1) for MDS and Hb, but not for linear growth or home environment.

For social-emotional problems, Pathway 1 (light grey arrows in Fig. 1) was not confirmed because early (3.5 y) social-emotional problems were not associated with pre-adolescent (9–12 y) social-emotional problems and there were no indirect associations of early risk indicators with pre-adolescent social-emotional scores. Maternal depressive symptoms were strongly associated with child social-emotional problems through both Pathways 2 and 3 (medium and dark grey arrows in Fig. 1). Higher early childhood MDS was significantly associated with higher early childhood social-emotional problems. Early childhood MDS was also significantly directly associated with pre-adolescent social-emotional problems independent of early childhood social-emotional problems. Change in maternal depressive symptoms during middle childhood (rMDS) was also significantly associated with pre-adolescent social-emotional problems, indicating that children had higher social-emotional problems if their mothers had a greater increase in depressive symptoms during middle childhood. Early childhood Hb was also significantly directly associated with pre-adolescent social-emotional problems, however, this association was in the opposite direction as expected, with higher Hb associated with higher social-emotional problems. For all other risk indicators, later changes during middle childhood in linear growth, Hb, and home environment were not significantly associated with social-emotional problems at age 9–12 y.

4. Discussion

This is the first study in a LMIC to model the timing and chronicity of exposure to multiple high impact biomedical and socio-environmental risk exposures on child cognitive outcomes and social-emotional problems in a longitudinal cohort of children during early and middle childhood. In a sample of 359 children, we observed variation in continuity of exposure to risks. Some children were exposed to early risks then experienced improved conditions. Others experienced positive conditions early with late-onset risk, while others were chronically exposed to high-risk or low-risk environments. Associations of early childhood risk exposures with pre-adolescent cognitive ability were more prevalent than associations with changes in exposures between early and middle childhood. For three indicators (Hb, MDS, and HOME), early childhood risk exposure (3.5 y) was indirectly associated with pre-adolescent cognition (9–12 y) through early childhood cognitive scores. This confirmed that Pathway 1 (light grey arrows in Fig. 1) was the primary pathway through which early risk exposures were associated

Table 3
Structural equation model coefficients for cognitive outcomes.

Outcome	*Predictor*	Direct association		Indirect association		Total association	
		Estimate (95% CI)	p-value	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
Early childhood (3.5 y) HOME score							
	Low socio-economic status (<median)	**−0.55 (-0.74, -0.36)**	**<0.001**	–	–	–	–
	Low paternal education (<6 years)	**−0.43 (-0.67, -0.18)**	**0.001**	–	–	–	–
	Low maternal education (<6 years)	**−0.47 (-0.71, -0.23)**	**<0.001**	–	–	–	–
	MDS at 3.5 y	**−0.18 (-0.30, -0.07)**	**0.001**	–	–	–	–
Early childhood (3.5 y) cognitive score							
	Low Socio-economic status (<median)	−0.03 (−0.2, 0.14)	0.727	**−0.20 (-0.29, -0.12)**	**<0.001**	**−0.23 (-0.41, -0.05)**	**0.011**
	Low paternal education (<6 years)	−0.05 (−0.28, 0.17)	0.650	**−0.16 (-0.25, -0.06)**	**0.002**	−0.21 (−0.45, 0.04)	0.096
	Low maternal education (<6 years)	0.10 (−0.11, 0.32)	0.346	**−0.17 (-0.27, -0.07)**	**0.001**	−0.07 (−0.30, 0.16)	0.555
	MDS at 3.5 y	−0.06 (−0.16, 0.04)	0.239	**−0.07 (-0.11, -0.02)**	**0.002**	**−0.13 (-0.24, -0.02)**	**0.018**
	HOME at 3.5 y	**0.37 (0.27, 0.46)**	**<0.001**	–	–	–	–
	HAZ at 3.5 y	0.05 (−0.04, 0.15)	0.280	–	–	–	–
	Hb at 3.5 y	**0.20 (0.11, 0.29)**	**<0.001**	–	–	–	–
Change in HOME 3.5 to 9–12 y (rHOME)[a]							
	Change in MDS 3.5 to 9–12 y (rMDS)[b]	**−0.13 (-0.25, -0.01)**	**0.040**	–	–	–	–
Pre-adolescent (9–12 y) cognitive score							
	Low Socio-economic status (<median)	−0.05 (−0.24, 0.13)	0.575	**−0.14 (-0.24, -0.05)**	**0.004**	**−0.20 (-0.39, 0.00)**	**0.049**
	Low paternal education (<6 years)	**−0.34 (-0.58, -0.11)**	**0.005**	−0.12 (−0.24, 0.00)	0.042	**−0.47 (-0.73, -0.21)**	**<0.001**
	Low maternal education (<6 years)	0.09 (−0.14, 0.33)	0.423	−0.07 (−0.18, 0.05)	0.235	0.02 (−0.22, 0.27)	0.845
	MDS at 3.5 y	0.01 (−0.10, 0.11)	0.902	**−0.07 (-0.12, -0.02)**	**0.009**	−0.06 (−0.18, 0.05)	0.277
	HOME at 3.5 y	0.09 (−0.02, 0.19)	0.107	**0.15 (0.09, 0.21)**	**<0.001**	**0.24 (0.13, 0.34)**	**<0.001**
	HAZ at 3.5 y	0.02 (−0.08, 0.12)	0.750	0.02 (−0.02, 0.06)	0.285	0.04 (−0.07, 0.15)	0.484
	Hb at 3.5 y	−0.02 (−0.12, 0.07)	0.656	**0.08 (0.04, 0.12)**	**<0.001**	0.06 (−0.04, 0.16)	0.239
	Change in HAZ 3.5 to 9–12 y (rHAZ)[c]	−0.08 (−0.18, 0.02)	0.107	–	–	–	–
	Change in Hb 3.5 to 9–12 y (rHb)[d]	**0.10 (0.00, 0.20)**	**0.048**	–	–	–	–
	Change in MDS 3.5 to 9–12 y (rMDS)[b]	**−0.13 (-0.23, -0.02)**	**0.019**	0.00 (−0.01, 0.01)	0.827	**−0.13 (-0.25, -0.01)**	**0.04**
	Change in HOME 3.5 to 9–12 y (rHOME)[a]	−0.01 (−0.10, 0.08)	0.825	–	–	–	–
	Early childhood (3.5 y) cognitive score	**0.41 (0.30, 0.52)**	**<0.001**	–	–	–	–

[a] rHOME: residual of Home Observation for the Measurement of the Environment (HOME) score at 9–12 y predicted by HOME at 3.5 y.
[b] rMDS: residual of maternal depressive symptoms (MDS) at 9–12 y predicted by MDS at 3.5 y.
[c] rHAZ: residual of child height-for-age z-score (HAZ) at 9–12 y predicted by HAZ at 3.5 y, pubertal development score at 9–12 y, and maternal height.
[d] rHb: residual of child haemoglobin (Hb) at 9–12 y predicted by child Hb at 3.5 y.

Table 4
Structural equation model coefficients for social-emotional outcomes.

Outcome	*Predictor*	Direct association		Indirect association		Total association	
		Estimate (95% CI)	p-value	Estimate (95% CI)	p-value	Estimate (95% CI)	p-value
Early childhood (3.5 y) HOME score							
	Low socio-economic status (<median)	**−0.54 (-0.73, -0.36)**	**<0.001**	–	–	–	–
	Low paternal education (<6 years)	**−0.43 (-0.68, -0.18)**	**0.001**	–	–	–	–
	Low maternal education (<6 years)	**−0.46 (-0.70, -0.23)**	**<0.001**	–	–	–	–
	MDS at 3.5 y	**−0.21 (-0.31, -0.10)**	**<0.001**	–	–	–	–
Early childhood (3.5 y) cognitive score							
	Low Socio-economic status (<median)	−0.10 (−0.32, 0.11)	0.328	0.03 (−0.03, 0.09)	0.354	−0.07 (−0.28, 0.13)	0.471
	Low paternal education (<6 years)	−0.05 (−0.33, 0.23)	0.737	0.02 (−0.03, 0.08)	0.364	−0.02 (−0.30, 0.25)	0.866
	Low maternal education (<6 years)	**−0.29 (-0.56, -0.03)**	**0.030**	0.03 (−0.03, 0.08)	0.362	**−0.27 (-0.52, -0.01)**	**0.044**
	MDS at 3.5 y	**0.28 (0.16, 0.40)**	**<0.001**	0.01 (−0.01, 0.04)	0.350	**0.29 (0.18, 0.40)**	**<0.001**
	HOME at 3.5 y	−0.06 (−0.17, 0.06)	0.347	–	–	–	–
	HAZ at 3.5 y	−0.03 (−0.14, 0.09)	0.653	–	–	–	–
	Hb at 3.5 y	−0.01 (−0.12, 0.10)	0.858	–	–	–	–
Change in HOME 3.5 to 9–12 y (rHOME)[a]							
	Change in MDS 3.5 to 9–12 y (rMDS)[b]	−0.11 (−0.23, 0.01)	0.08	–	–	–	–
Pre-adolescent (9–12 y) cognitive score							
	Low Socio-economic status (<median)	0.01 (−0.22, 0.25)	0.906	−0.01 (−0.08, 0.06)	0.740	0.00 (−0.22, 0.22)	0.982
	Low paternal education (<6 years)	0.22 (−0.08, 0.51)	0.151	−0.01 (−0.07, 0.04)	0.694	0.21 (−0.09, 0.50)	0.167
	Low maternal education (<6 years)	−0.05 (−0.33, 0.23)	0.707	0.00 (−0.07, 0.07)	0.965	−0.05 (−0.33, 0.22)	0.708
	MDS at 3.5 y	**0.31 (0.19, 0.44)**	**<0.001**	−0.02 (−0.07, 0.02)	0.310	**0.29 (0.17, 0.40)**	**<0.001**
	HOME at 3.5 y	0.03 (−0.09, 0.15)	0.641	0.00 (−0.01, 0.01)	0.493	0.03 (−0.09, 0.15)	0.605
	HAZ at 3.5 y	−0.02 (−0.14, 0.11)	0.794	0.00 (−0.01, 0.01)	0.684	−0.02 (−0.14, 0.11)	0.812
	Hb at 3.5 y	**0.16 (0.05, 0.27)**	**0.006**	0.00 (−0.01, 0.01)	0.860	**0.16 (0.05, 0.27)**	**0.006**
	Change in HAZ 3.5 to 9–12 y (rHAZ)[c]	−0.04 (−0.16, 0.08)	0.514	–	–	–	–
	Change in Hb 3.5 to 9–12 y (rHb)[d]	−0.06 (−0.18, 0.07)	0.391	–	–	–	–
	Change in MDS 3.5 to 9–12 y (rMDS)[b]	**0.48 (0.37, 0.60)**	**<0.001**	0.00 (−0.01, 0.02)	0.493	**0.49 (0.37, 0.60)**	**<0.001**
	Change in HOME 3.5 to 9–12 y (rHOME)[a]	−0.04 (−0.14, 0.06)	0.478	–	–	–	–
	Early childhood (3.5 y) social-emotional problems	−0.06 (−0.17, 0.06)	0.341	–	–	–	–

[a] rHOME: residual of Home Observation for the Measurement of the Environment (HOME) score at 9–12 y predicted by HOME at 3.5 y.
[b] rMDS: residual of maternal depressive symptoms (MDS) at 9–12 y predicted by MDS at 3.5 y.
[c] rHAZ: residual of child height-for-age z-score (HAZ) at 9–12 y predicted by HAZ at 3.5 y, pubertal development score at 9–12 y, and maternal height.
[d] rHb: residual of child haemoglobin (Hb) at 9–12 y predicted by child Hb at 3.5 y.

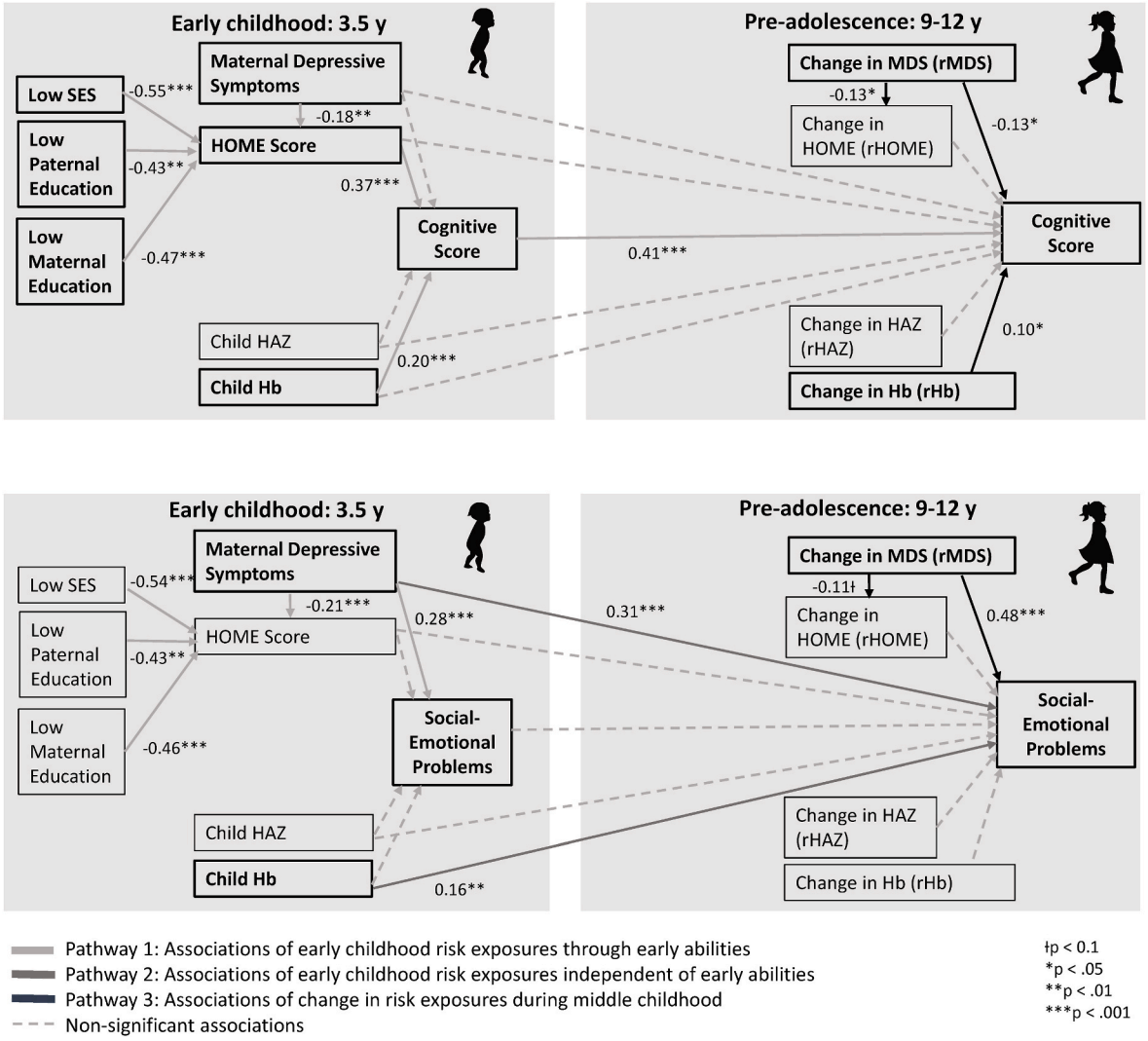

Fig. 5. Results of structural equation models.

with pre-adolescent cognitive ability, that is through early cognitive ability. Later changes in maternal depressive symptoms and child Hb during middle childhood were also associated with pre-adolescent cognitive scores, and this was not observed for middle childhood change in HAZ or HOME scores.

For social-emotional development, both early childhood maternal depressive symptoms and change in MDS during middle childhood were independently associated with pre-adolescent social-emotional problems. In contrast to cognitive outcomes, for which Pathway 1 was supported, this demonstrated that Pathways 2 and 3 (medium and dark grey arrows in Fig. 1) were the primary pathways through which maternal depressive symptoms were associated with child social-emotional problems. The lack of association between early childhood and pre-adolescent social-emotional problems may be due the difficulty measuring social-emotional problems during early childhood, which is a period during which children are learning social-emotional regulation and often outgrow behaviors such as tantrums and hitting. A striking finding was that the mother's change in MDS during middle childhood (from 3.5 to 9–12 y) showed the strongest association with this outcome.

Our findings highlight the potential importance of supporting maternal mental health throughout early and middle childhood to promote cognitive and especially social-emotional development. Most studies examining MDS in LMICs have focused on the postnatal and early childhood periods. MDS during these periods is associated with poor child health, growth, and development. Few have studied MDS throughout early and middle childhood (Surkan et al., 2011), thus our findings make an important novel contribution. Provision of maternal mental health services can be integrated into existing services in LMICs in several ways. One way is to integrate screening and referral for maternal depressive symptoms into ante-natal care and child health programs that provide services such as growth monitoring and vaccinations. Another is to train non-specialist community front-line workers to provide services based on proven interventions, such as cognitive behavioral therapy, interpersonal therapy, supportive therapy, and group therapy (Murray et al., 2020). Both screening and community-based interventions have been effective to reduce MDS and improve child outcomes in LMICs (Rahman et al., 2013). Further work is needed to integrate mental health services into existing health systems throughout the early and middle childhood, and pre-adolescent periods. An essential package of interventions for children age 5–14 has been proposed to support adolescent health and well-being (Bundy et al., 2018). The effectiveness of MDS interventions among mothers of school-age children should be evaluated to assess whether maternal mental health support should be part of an essential package of interventions for cognitive and social-emotional development during middle childhood and pre-adolescence.

Early childhood responsive care and learning opportunities in the home environment was the strongest predictor of pre-adolescent

cognitive outcomes. The importance of the early home environment is consistent with a study in Bangladesh, which found that the HOME Inventory score at age 18 months and the deviation from expected HOME score at age 5 years were both significantly associated with 5-year cognitive scores, with similar magnitude (Hamadani et al., 2014). Our study adds the novel finding that the early (3.5 y) home environment predicted pre-adolescent (9–12 y) cognitive scores indirectly through early cognitive scores. In contrast, the change in home environment during middle childhood was not associated with cognitive outcomes. This could be interpreted as a weaker influence of the later home environment on cognitive development. However, it is also possible that HOME scores do not adequately capture crucial aspects of the home environment at older ages, a notion supported by the lower concurrent association of HOME with cognitive scores at 9–12 y ($r = 0.15$ vs $r = 0.46$ for the correlation between early HOME and early cognitive score). In addition, later changes in our sample may not have been large enough to observe an effect of changes in the home environment over and above its effect at younger ages. Among the groups that showed early low risk and late-onset of risk, the change was on average a decrease of 8 points, or 1.5 SD, on the HOME Inventory. For the group exposed to early high risk and later improvement, the change was on average an increase of 4 points, or 0.8 SD. In the absence of intervention, these changes may reflect relatively small meaningful differences in the home environment over time. Studies of children who experienced adoption or foster care, which results in dramatic changes in the home environment, demonstrate substantial recovery in brain and cognitive development, albeit typically without full recovery of early deficits (Leroy et al., 2020). This supports the importance of both early intervention to prevent faltering and later intervention to reverse early deficits and maintain gains.

Our findings enrich the body of evidence on the consequences of the timing of linear growth faltering. Given the large number of studies that have examined the timing of linear growth faltering in relation to cognitive development (at least 13 studies, for references, see Supplemental Material), it is interesting that in our study linear growth was not associated with cognitive scores when adjusting for other risk factors. This suggests that other risk exposures, especially socio-environmental risks, are more important for developmental outcomes than linear growth faltering and should be taken into account in such studies. However, in our sample, even children classified as having consistent positive growth showed evidence of faltering. This group had, on average, HAZ of 1.4 SD below the median of WHO norms at age 3.5 years and 0.7 SD below the median of WHO norms at age 9–12 years. This suggests that the entire sample of children experienced conditions that constrained their linear growth, which is typical in LMIC contexts (Roth et al., 2017). The natural variation in the sample may not have been sufficient to observe functional consequences of linear growth faltering or catch-up growth.

Our study also contributes to the development of methodology to quantify catch-up in linear growth. Leroy et al. (2020) argue that four conditions must be met to define catch-up growth: (1) the child experiences a period of growth-inhibition, causing (2) a reduction in growth velocity, followed by (3) alleviation of the inhibiting condition, (4) leading to higher-than-normal velocity (Leroy et al., 2020). Using our method, the group we defined as experiencing catch-up growth met all of these criteria, with HAZ around 3 SD below the norm at age 3.5 y and improvement to less than 2 SD below the norm at age 9–12 y (Fig. 2). The growth velocity of children in the catch-up group was similar to the growth velocity of children in the persistent low-risk group (Fig. 2). Moreover, in our calculation of the residual (rHAZ) we adjusted for maternal height, as a proxy for growth potential, as well as pubertal development score, thus the influence of these factors on linear growth was controlled in our determination of growth velocity during middle childhood. Leroy and colleagues also argue that absolute height velocity (change in height in cm) should be used rather than change in standardized HAZ. We used HAZ because the position of a child relative to a healthy distribution is more clinically relevant than their absolute height. In growth monitoring, a child is considered "on track" if he or she remains at the same percentile relative to the growth curve norms, regardless of absolute distance from the mean. Therefore, using changes in HAZ is more appropriate to define faltering or catch-up growth.

Our findings also suggest that child anemia may be an important target for prevention during both early and middle childhood to promote cognitive development. We are aware of only two other studies that examined associations of Hb at various time points with child cognition. One study in the US measured Hb every six months from birth to 48 months and found a positive association of 48-month cognitive score with 36-month Hb only (Wasserman et al., 1994). Another study in Ghana found an association of haemoglobin at age 18 months, but not age 4–6 years, with cognitive scores at age 4–6 years, and no associations of Hb at any time point with social-emotional problems (Ocansey et al., 2019). Neither of these studies is directly comparable to our study because they did not analyze deviations from expected child Hb based on earlier time points. However, they also found associations of Hb at earlier time points (6 months) with later cognitive scores (4–6 years) in the opposite direction as expected, similar to our finding that early childhood Hb was associated with pre-adolescent social-emotional problems in the opposite direction as expected. Although in all cases, the unadjusted associations were not significant, it is not clear why early higher Hb would be associated with poorer cognitive and social-emotional outcomes when adjusting for Hb at later time points. The novel finding in our study that change in Hb during middle childhood predicted higher pre-adolescent cognitive scores suggests that both early and middle childhood are critical for anemia prevention to avoid negative long-term cognitive consequences, which should be evaluated in long-term follow-up studies of randomized trials.

4.1. Strengths and limitations

A strength of our study was the unique dataset comprised of a relatively large sample of children followed from pregnancy through age 9–12 years, which was representative of the full spectrum of households present in the parent trial (Table 2). The dataset included detailed measures of child cognitive and social-emotional development in both early and later childhood, along with multiple indicators of exposure to biomedical and socio-environmental risks. Our study took advantage of the natural variation in changes over time that occurred in the sample. However, a potential limitation is that these naturally occurring changes over time may have been insufficient to change developmental trajectories in later childhood. Further studies are needed that evaluate the relative effects of biomedical and socio-environmental interventions during different periods of childhood. Another limitation was that child social-emotional development was measured by parent report, which could be biased, especially in mothers with depressive symptoms. This may account for part of the association between maternal reported depression and child social-emotional scores. However, MDS was also significantly associated with cognitive scores, which were objectively measured. In addition, it is less likely that MDS at age 3.5 years would bias maternal report of children's behavior 6–8 years later. Thus, the significant association between early MDS and later child social-emotional development is robust.

5. Conclusions

Our findings validate and extend previous evidence supporting investment in early childhood to promote healthy long-term cognitive development, specifically investment in the prevention of anaemia and maternal depression, and promotion of responsive care and learning opportunities in the home environment. However, our findings also confirm and extend our previous findings (Prado et al., 2017) that socio-environmental factors (HOME, MDS) showed stronger and more consistent associations with pre-adolescent cognitive and social-emotional outcomes than biomedical factors (HAZ, Hb). As for

middle childhood, an essential package of interventions for children age 5–14 has been proposed, including health interventions, such as deworming and tetanus vaccination, as well as dietary interventions, such as school feeding programs and micronutrient supplementation. Our findings suggest that maternal mental health support services should also be considered as a part of an essential package of interventions to support cognitive and social-emotional development during middle childhood.

Author contributions

Dr. Prado designed the follow-up studies, coordinated and supervised data collection, analyzed the data, drafted the initial manuscript, and reviewed and revised the manuscript. Dr Sebayang designed and implemented the original SUMMIT study and follow-up studies, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. Ms Adawiyah designed and implemented the pre-adolescent follow-up study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. Dr Alcock and Dr Ullman designed the follow-up studies and critically reviewed the manuscript for important intellectual content. Dr Muadz and Dr Shankar designed and implemented the original SUMMIT study and follow-up studies, were principal investigators of the pre-adolescent follow-up study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted.

Data sharing statement

De-identified individual participant data (including data dictionaries) will be made available upon publication to researchers who provide a methodologically sound proposal and statistical analysis plan contingent on approval by the SUMMIT Data Oversight Committee. Proposals should be submitted to Anuraj Shankar: anuraj.shankar@ndm.ox.ac.uk.

Role of the funding source

The sponsors of the study had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Declaration of competing interest

The authors have no conflict of interest.

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We dedicate this paper to the memory of Dr. Husni Mu'adz, who passed away on July 24, 2021. He was a core member of our research team and a wonderful mentor and colleague. His dedication to improving the lives of others was inspiring and admirable. He devoted his life and career to improving the health and well-being of communities in Lombok and beyond through research, scholarly writing, community activism, and program leadership. His legacy will extend to benefit many future generations.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.socscimed.2021.114396.

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