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Effects of Maternal Worm Infections and Anthelminthic Treatment during Pregnancy on Infant Motor and Neurocognitive Functioning

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Abstract

We tested the hypothesis that maternal worm infections in pregnancy affect infant motor and neurocognitive development, and that anthelminthic treatment during pregnancy can reverse these effects. We used measures which examine infant motor, cognitive and executive function, including inhibition. We assessed 983 Ugandan infants aged 15 months, using locally appropriate measures within the Entebbe Mother and Baby Study, a trial of anthelminthic treatment during pregnancy. Key exposures were maternal worm infections and anthelminthic treatment during pregnancy. Effects of other health and social factors were controlled for statistically. Of the five major worm species found in the pregnant women, two had influences on the developmental measures: Maternal *Mansonella perstans* and *Strongyloides stercoralis* infections showed negative associations with the A-not B-task, and Language, respectively. Performance on other psychomotor and cognitive measures was associated with illnesses during infancy and infants' behavior during assessment, but not with maternal worm infections. There were no positive effects of maternal anthelminthic treatment on infant abilities. *Mansonella perstans* and *Strongyloides stercoralis* infection during pregnancy seem associated with impaired early executive function and language, respectively, but single-dose anthelminthic treatment during pregnancy was not beneficial. The biological mechanisms that could underlie these neurocognitive effects are discussed. (*JINS*, 2012, *18*, 1019–1030)

Keywords: Pregnancy, Helminths, De-worming, Infancy, Psychomotor, Executive function

INTRODUCTION

Early cognitive development underlies individual differences in children's behavior and academic performance (Cooper & Farran, 1988; Rohde & Thompson, 2007; see Tramontana, Hooper, & Selzer, 1988, for a review). In the developing world, poverty, disease and malnutrition inhibit children from attaining their developmental potential. Several studies suggest that worms, affecting approximately 90 million school-age children (Brooker, Clements, & Bundy, 2006), impair cognitive functions (e.g., Boivin et al., 1993; Ezeamama et al., 2005; Jukes et al., 2002; Nokes et al.,1992, 1999; Sakti et al., 1999).

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Worms also infect approximately a third of pregnant women in Sub-Saharan Africa (Bundy, Chan, & Savioli, 1987). We hypothesized that maternal worm infections might influence the development of cognitive function in infants. Animal studies suggest that by depleting nutrients available to the fetus, maternal worm infections may interfere with processes such as myelination and the development of neurotransmitter systems vital for neurological and cognitive functioning (Beard et al., 2007). Beard et al. (2005) found that offspring of iron-deficient rats had lower iron content, lowered activity in the dopamine transporter system in the caudate nucleus and substantia nigra, reduced motor activity, and higher anxiety levels than controls. In humans, dopamine influences the limbic system and frontal cortex: disruptions in the dopamine system interfere with psychomotor and executive function (Goto & Grace, 2005; Smith & Kieval, 2000). Hence, we postulated that early human executive function might be

particularly vulnerable to effects of maternal worm infections. Executive function comprises processes involved in goal-directed behavior or planning and consists of complementary sub-skills including working memory, inhibitory control and attentional flexibility (Hughes, 1998; Miyake et al., 2000).

Maternal worm infections co-exist with several important potential confounders, such as maternal under-nutrition (Goldenberg, Hoffman, & Cliver, 1998; Hack, 1998), maternal infections, including HIV and malaria (Gay et al., 1995; Gentile, Boll, Stagno, & Pass, 1989) and exposures in infancy including malaria (Dugbartey & Spellacy, 1997), recurrent diarrhea (Berkman, Lescano, Gilman, Lopez, & Black, 2002), anemia (Clarke, Grantham-McGregor, & Powell, 1991; Lozoff, Brittenham, & Wolf, 1987), malnutrition (Galler, Ramsey, Solimano, Kucharski, & Harrison, 1984; Grantham-McGregor, Powell, Walker, Chang, & Fletcher, 1994), and inadequate social stimulation (Bradley et al., 1989; Grantham-McGregor, Powell, Walker, & Himes, 1991; Ramey & Ramey, 1998).

Measuring executive function in young children in resource-limited settings is difficult. Measures that take into account immature verbal and motor skills and low attentional spans, and adapted to local conditions, are required (Espy, 2004). One task designed to test motor inhibition that has been translated and adapted for various cultures is the A-not-B task. In this test, an object is hidden repeatedly at location A and then at location B. Infants who persistently search at A show poor motor inhibition. Devised by Piaget (1954) to study object permanence in infants, initial cognitive explanations regarding this task focused on short term memory (Schacter, Moscovitch, Tulving, McLachlan, & Freedman, 1986). Subsequently, it was suggested that executive functions were important (Diamond, 1988; Diamond & Goldman-Rakic, 1989): two meta-analyses of over 100 studies (Marcovitch & Zelazo, 1999; Wellman, Cross, & Bartsch, 1986) both proposed that the infant's response is driven by interaction between representation of the location and inhibition of the motoric tendency to search at the previous location. Initial findings suggested that younger infants perseverate more than older infants. Subsequent longitudinal studies (e.g., Clearfield et al., 2006) showed that at first infants do not perseverate, that this is followed by a stage of perseveration and then at around 12 months competence on the task. Thus Clearfield and colleagues argue that performance on A-not-B may be determined by competition between active (faster) and latent (slower) memory processes, and perseveration may be a consequence of immaturity in processes that guide application of past experience. Initially, Thelen and Smith (1994) attributed perseveration to motoric rather than cognitive schemes, but more recently Smith, Thelen, Titzer, and McLin (1999) proposed that infants' reaching is guided by a dynamic interplay between cognitive, motor, and visuospatial systems. While processes that underlie the A-not-B task are yet to be ascertained, the task covers a wide age-group, is sensitive for even very young infants (e.g., Clearfield et al., 2006; Diamond & Doar, 1989) and, hence, seems suitable for measuring early executive function.

A second important aspect of executive function is delay inhibition. Conflict inhibition tasks such as A-not-B require inhibiting an inappropriate prepotent response while activating a conflicting novel response. Delay inhibition tasks (e.g., the Self Control task) require the child simply to refrain from responding until a given signal, and may be purer measures of inhibition (Carlson, Davis, & Leach, 2005).

Executive function emerges in infancy (Diamond, 1985; Thompson & Nelson, 2001), and is thought to integrate input from several developing systems including attention (Rothbart & Ahadi, 1994), memory and language (Kopp, 1982), and psychosocial functioning (Londerville & Main, 1981; Stayton, Hogan, & Ainsworth, 1971). Psychomotor skills, language and socioemotional skills develop concurrently, but draw less upon executive mechanisms and may therefore be less affected by maternal worm infections.

We aimed to examine effects of maternal worm infections and anthelminthic treatment in pregnancy on motor and cognitive outcomes in infants at age 15 months. Our hypothesis was that two measures known to have high executive loads (the A-not-B and Delay Inhibition tasks) would be particularly sensitive to effects of maternal worm infections. In a large sample, we therefore examined different subtests of a locally appropriate assessment battery, the Kilifi Developmental Inventory-KDI (Abubakar, Holding, Van Baar, Newton, & Van de Vijver, 2008), to establish effects of maternal worm infections and their treatment on infants' developing executive functions, and other developing cognitive and psychomotor skills.

METHODS

Design and Participants

This research was part of the Entebbe Mother and Baby Study (EMaBS), a double-blind randomized placebo-controlled trial of anthelminthic treatment during pregnancy (Elliott et al., 2007). Between 2003 and 2005, a total of 2507 pregnant women were enrolled, investigated for parasitic infections and hemoglobin level, and randomized to receive albendazole (400 mg) or its matching placebo and praziquantel (40 mg/kg) or its matching placebo in a 2×2 factorial design. Albendazole treats roundworms (nematodes), and has some antiprotozoal effects. Praziquantel targets flatworms (trematodes), including schistosomiasis. Neither drug has known effects on bacterial infections. All mothers including those who had received placebos during pregnancy were treated effectively soon after delivery.

Infants underwent psychomotor assessments at 15 months using a modification of the KDI. Cognitive and social abilities were assessed using additional measures. Of 2507 women enrolled, there were 2345 live births of whom 1022 children were assessed but 39 were excluded from analysis because they were not tested within 2 months of age 15 months. Of those not tested, 94 had died (complications of labor or neonatal sepsis) before reaching age 15 months

(infant mortality was not related to maternal worm infections [unpublished data] or their treatment [Webb et al., 2011]), 174 were lost to follow-up, 427 were seen at 15 months before the developmental assessments were introduced, 628 missed the 15 month visit. Of the 983 children (500 boys) tested, mean age was 15.59 months (*SD* 0.49; min 14.23 months; max 17 months). Of their mothers, 249 received praziquantel and albendazole; 241 praziquantel and albendazole-matching placebo; 251 albendazole and praziquantel-matching placebo; and 242 received both placebos.

Ethics

This research was approved by the Science and Ethics Committee of the Uganda Virus Research Institute and the Uganda National Council of Science and Technology. Written informed consent was obtained from all eligible participants. In 1996, WHO recommended mass treatment of pregnant women in the second and third trimester with albendazole (400 mg) (WHO, 1996) in settings with high prevalence of hookworm and anemia. In 2002, WHO recommended treatment of schistosomiasis with praziquantel (40 mg/kg) during pregnancy and breast-feeding (WHO, 2002) but there was limited evidence on the risk-benefit ratio of this intervention. There was concern that anthelminthic drugs might lead to adverse birth outcomes (Bradley & Horton, 2001) and that among HIV positive women anthelminthic treatment might lead to an increase in HIV load and increased vertical HIV transmission (Elliott et al., 2003). Thus a condition of equipoise was considered to exist (Elliott et al., 2007). Indeed, WHO subsequently called for placebo-controlled trials of praziquantel during pregnancy (WHO, 2006). Our population had a moderate prevalence of hookworm (45%) and schistosomiasis (18%) but rates of anemia were relatively low and women with severe anemia (hemoglobin level less than 8.0 g/dL) were excluded from the study and treated. Hence a placebo-controlled study design was considered justified.

Motor and Cognitive Assessments

We used two executive function measures, the A-not-B task and a Self Control (delay inhibition) task, previously translated and used in rural Kenya (Abubakar, Holding, Van de Vijver, Bomu, & Van Baar, 2010). Infants' skills on Language, Self Care and Recognition of Self and Others were determined using parental reports (Abubakar et al., 2010). Fine-motor and gross-motor function, and non-task behavior (mood, interaction, and activity) were assessed using ratings originally developed for the KDI (Abubakar et al., 2008). Details of measures are described below.

Fine Motor

Control of small hand-movements was assessed using items such as building a tower with blocks and scribbling with a pen. Twenty-seven items were scored as pass/fail and summed to give a score.

Gross Motor

Control of the limbs was assessed using 35 items such as kicking a ball or climbing onto a platform; a total was calculated.

Child's mood, activity, and interaction

The assessor observed the child's activity, mood, and level of interaction and rated them on a six-point scale. High scores indicated good mood, activity, or interaction.

Self Control (delay inhibition)

In two trials, a biscuit (trial 1) or wrapped gift (trial 2) was presented to the child who was instructed not to take it until the assessor had completed what he/she was doing. Waiting time (in seconds) was recorded to a maximum of 150 s. Average waiting time for the two trials was computed.

The A-not-B task

A biscuit was placed in one of two wells as the child watched and both wells were then covered with opaque cups. The board was taken out of sight for 10 s during which the child was distracted with a song. The board was then brought back and the child asked to point to the well with the biscuit. The child was given the biscuit if she or he successfully located it. The location of the biscuit was switched to the other well after two consecutive correct responses. Ten trials were given; the number of correct responses was scored.

Language

This was assessed by interviewing the mother or guardian, asking whether the infant produced common pre-speech items such as vowels (e.g., aa, aa), babble (e.g., ma, ma) or gestures (e.g., waving for "bye'), spoke definite words, or named and identified common household objects (11 items overall).

Recognition of Self and Others

The caregiver was asked whether the infant reacted to his/her name, or distinguished his mother and other familiar people from strangers (altogether 12 items).

Self Care

The interview collected information about behaviors such as how much the infant helped during dressing and feeding (15 items).

Piloting, training, and scale reliability

The measures were translated into Luganda and piloted on 50 children. Seven nurses and two doctors were trained. To assess reliability, every 10th infant was rated by two assessors on all measures. Comparisons of 80 paired records showed inter-rater reliability coefficients ranging from 0.75 to 1.00 (Table 1). Scores showed normal distributions on all

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Table 1. Inter-rater reliability and internal consistency of the measures and factor loadings

Measure	Inter-rater reliability coefficient $N = 80$	Cronbach's alpha $N = 983$	Component 1	Component 2
Fine Motor	.71	.72	.62	−.32
Gross Motor	.77	.78	.63	−.19
Language	1.00	.76	.42	.70
Self Control	1.00	N/A	−.31	.60
Self Care	1.00	.64	.70	.18
Self Recognition	1.00	.62	.41	.16
A not B	1.00	N/A	.27	.13

measures except Self Control. Overall psychomotor performance (mean 29.58; *SD* 3.79) was found to be similar to that of an age-matched sample of Kenyan infants (Abubakar et al., 2008). Internal consistency was examined using Cronbach's alpha and poorly correlated items were deleted. The edited measures had internal consistency coefficients ranging from 0.62 to 0.78 (Table 1). Principal component analysis confirmed that motor measures loaded on one component, cognitive measures on another. There was a negative correlation ($r = -0.04$; $p = .26$) between the two measures of executive function (A-not-B and Self Control) which was not statistically significant. Psychomotor items in the KDI had exhibited high test–retest reliability in the Kenyan sample suggesting that the tool was stable over time (Abubakar et al., 2008). These psychometric features are summarized in Table 1.

Testing Procedure

Testing at age 15 months was postponed if mother or clinician judged the child to be unwell. Sessions lasted 45 to 65 min. Short breaks were allowed as judged by the assessor and mother. After the session, a small age-appropriate gift was given to the child and transport money reimbursed to the parent.

Additional Data

Parasitology

Stool samples of the pregnant women and infants were examined for helminth ova using Kato Katz technique (Katz, Chaves, & Pellegrino, 1972), and cultured for *Strongyloides stercoralis*. Blood was examined for *Mansonella perstans* using the modified Knott's method (Melrose, Turner, Pisters, & Turner, 2000) and for malaria parasites using thick smears.

Antenatal history and delivery data

We recorded information on maternal illnesses, medications and vaccines during pregnancy, mode of delivery, Apgar score at 10 min, birth weight, congenital abnormalities, and immunization received at birth.

HIV status of the child

Overall, 97 mothers tested HIV positive during pregnancy. At 6 weeks of age, their infants were tested for HIV using DNA and RNA polymerase chain reaction. Specific management of HIV positive women and exposed children is elaborated elsewhere (Elliott et al., 2007; Mpairwe et al., 2005).

Growth monitoring

Infants' weight, height, head circumference, and mid upper arm circumference were recorded at week 6, 10, and 14, and at 6, 9, and 12 months. At 1 year, hemoglobin levels were measured.

Illnesses in infancy

Numbers of episodes of malaria, diarrhea, lower respiratory tract infections, and upper respiratory tract infections were recorded at the study clinic.

Sociodemographic data

Sociodemographic data including marital status, gravidity, age, education, occupation, income, and number of people in the home, were collected at enrolment, by interview. Household socioeconomic status was derived from items owned, building material of the house and number of rooms.

RESULTS

Participants' Characteristics

Characteristics of the 983 participating mothers and children are summarized in Table 2. Characteristics of mothers of participating and non-participating children were similar with respect to education, household socioeconomic status, and prevalence of *Schistosoma mansoni* infection. However, mothers of participants were older and less likely to be primigravida, and had a lower prevalence of HIV and hookworm ($p < .01$). Children who participated had mean birth weight, height and weight for age, and hemoglobin level within WHO normal ranges.

Descriptive Statistics for Psychomotor and Cognitive Measures

Descriptive statistics for the various measures are summarized in Table 3. The numbers of infants who completed the

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Table 2. Characteristics of participating women and infants

Demographic and clinical characteristics	Treatment arms	Alb+praz $N = 249$	Praziquantel $N = 241$	Albendazole $N = 251$	Placebos $N = 242$	Overall $N = 983$	p value
Mothers' age (years)	Mean	23.9	23.9	24.4	23.2	24.1	.789
Mothers' education	None/primary	141 (56.9)[a]	118 (49.2)	141 (56.2)	129 (53.5)	529 (54.0)	.325
	Secondary/tertiary	107 (43.1)	122 (50.8)	110 (43.8)	112 (46.5)	451 (46.0)	
Household SES	Lower	105 (43.0)	113 (47.5)	107 (43.3)	105 (44.5)	430 (44.6)	.509
	Upper	139 (57.0)	125 (52.5)	140 (56.7)	131 (55.5)	535 (55.4)	
Mothers' occupation	Fishing/farming	10 (3.9)	9 (3.5)	13 (5.1)	11 (4.4)	43 (4.2)	.278
	Unskilled manual	20 (7.8)	22 (8.7)	9 (3.5)	11 (4.4)	44 (6.1)	
	Bar/hotel	10 (3.9)	7 (2.8)	16 (6.2)	11 (4.4)	44 (4.3)	
	housewife	169 (61.9)	174 (68.5)	166 (64.6)	167 (67.1)	666 (65.5)	
	business	32 (12.5)	25 (9.8)	33 (12.5)	35 (14.1)	125 (12.3)	
	student	6 (2.3)	5 (2.0)	5 (1.9)	1 (.4)	17 (1.7)	
	professional	20 (7.8)	12 (4.7)	15 (5.8)	13 (5.2)	60 (5.9)	
Fathers' occupation	None	2 (.8)	2 (.8)	3 (1.2)	3 (2.1)	5 (1.2)	.859
	Farmer/fishing	29 (12.2)	37 (15.4)	30 (12.1)	29 (12.2)	125 (13.0)	
	Unskilled manual	81 (34.2)	84 (35.0)	74 (30.0)	81 (34.0)	320 (33.3)	
	Bar/hotel	6 (2.5)	2 (.8)	3 (1.2)	3 (1.3)	14 (1.5)	
	Business	37 (15.6)	33 (13.8)	40 (16.2)	41 (17.2)	151 (15.7)	
	Student	4 (1.7)	6 (2.5)	3 (1.2)	3 (1.3)	16 (1.7)	
	Professional	78 (32.9)	76 (31.7)	94 (38.1)	76 (31.9)	324 (33.7)	
Mothers' income	<30,000 (£10)	208 (82.5)	208 (83.9)	212 (85.1)	216 (88.2)	844 (84.9)	.096
(Uganda Shillings)	30,000–60,000	31 (12.3)	28 (11.3)	15 (6.0)	20 (8.2)	94 (9.5)	
	60,001–100,000	7 (2.8)	4 (1.6)	11 (4.4)	4 (1.6)	26 (2.6)	
	>100,000	6 (2.4)	8 (3.2)	11 (4.4)	5 (2.0)	30 (3.0)	
Family size	mean	3.8	4.0	3.79	3.77	3.84	.602
Mothers' HIV status	Positive	22 (8.8)	19 (7.9)	26 (10.4)	25 (10.3)	92 (9.4)	.973
Mothers' gravidity	Primigravida	72 (28.9)	61 (25.3)	59 (23.5)	54 (22.3)	246 (25.0)	.310
Mothers' hookworm status	Positive	108 (43.7)	111 (46.0)	89 (35.7)	97 (40.1)	405 (41.4)	.150
Mother's *S. mansoni* status	Positive	44 (17.8)	50 (20.8)	47 (18.9)	46 (19.0)	187 (19.1)	.857
Sex of the child	Female	110 (44.2)	127 (52.7)	122 (48.6)	124 (51.2)	483 (49.1)	.122
Age of the child (months)	Mean (*SD*)	15.6 (.50)	15.6 (.50)	15.6 (.50)	15.6 (.50)	15.6 (.50)	.561
	Min.	14.2	14.3	15.1	15.0	14.2	
	Max.	17.0	17.0	17.0	16.9	17.00	
Gestation age at birth	full term (≥38 wks)	240	234	245	233	952	.212
	preterm	8	6	6	6	26	
Gestation age in weeks	Mean (*SD*)	39.30 (3.41)	39.29 (3.64)	39.68 (3.23)	39.46 (3.48)	39.42 (3.44)	.558
Birth weight (kg)	Mean (*SD*)	3.11 (.47)	3.15 (.48)	3.21 (.48)	3.21 (.50)	3.17 (.48)	.172
Apgar Score at 10 minutes	Mean (*SD*)	9.82 (.54)	9.68 (.53)	9.83 (.59)	9.77 (.65)	9.77 (.71)	.172
Weight at 15 months (kg)	Mean (*SD*)	9.56 (1.18)	9.55 (1.19)	9.63 (1.38)	9.64 (1.27)	9.59 (1.26)	.740
Height at 15 months (cm)	Mean (*SD*)	75.51 (3.26)	75.54 (3.61)	75.73 (3.31)	75.66 (3.11)	75.61 (3.33)	.813
Infant hemoglobin (g/dL)	Mean (*SD*)	10.06 (1.37)	10.05 (1.34)	10.10 (1.48)	10.28 (1.45)	10.12 (1.41)	.334

[a]Figures are proportions (percent) unless otherwise indicated.

tasks varied. Fewer completed the A-not-B task because they cried for the treat on the first trial and refused to continue. Scores on five of the seven measures were normally distributed. Performance on Self Control was slightly positively skewed and Recognition of Self and Others was negatively skewed. Appropriate transformations were conducted before analysis.

Prevalence of Worms in Mothers

Prevalence of worm species identified in the mothers is shown in Table 4. Hookworm had the highest prevalence followed by *Mansonella perstans*. Thirty percent of mothers had mixed infections with some women having up to five species of worms. A total of 352 (34.9%) women did not have any worm. Only effects of maternal worms with at least 2% prevalence were subsequently analyzed.

Effects of Albendazole and Praziquantel

T tests were used to compare performance between children born to treated versus untreated mothers first across the whole sample to assess the benefit of mass treatment, and then just those where the mothers had worms susceptible to the drugs.

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Table 3. Descriptive statistics of infants' scores on the various measures

Domain	*N*	Min	Max. (max. possible)	Mean	*SD*
Fine Motor	978	1	22 (32)	13.16	1.74
Gross Motor	982	12	25 (35)	17.62	2.32
Language	983	1	22 (22)	15.39	4.29
Self Control	832	1	150 (150)	6.60	17.55
Self Care	982	0	29 (30)	17.14	4.22
Self Recognition	982	0	18 (24)	10.25	.99
A not B task	792	0	10 (10)	4.01	2.36

Note. The numbers under each domain are discrete scores therefore no units are available.

We found no interactions between albendazole and praziquantel ($p > .05$). Therefore, the effect of each drug was examined separately (albendazole *vs*. placebo; praziquantel *vs*. placebo). Overall neither albendazole nor praziquantel had significant effects on developmental outcomes (all values of $p > .05$). Of note, after delivery stool analysis showed a significant decline of the prevalence of hookworm and schistosomiasis among albendazole or praziquantel-treated women, respectively, but no reductions in *Mansonella perstans*, *Trichuris trichiura*, and *Strongyloides stercoralis* (Ndibazza et al., 2010).

We found, however, a significant effect of praziquantel on the A-not-B task and Self Control in children whose mothers were infected with schistosomiasis during pregnancy. Children whose mothers were treated for schistosomiasis during pregnancy performed better on Self Control than those who were not treated [$t(140) = 2.58$; mean difference = 5.96; $p = .01$; Cohen's d = 0.47]. However for the A-not-B task, children whose mothers were treated performed more poorly than those whose mothers were not treated [$t(145) = -2.23$; mean difference = −0.93; $p = .03$; Cohen's d = .37]. We found no effect of albendazole among infants of mothers with the principal susceptible species, hookworm.

Table 4. Prevalence of the various worms in the pregnant women whose infants were assessed on the motor and cognitive measures at 15 months

Worm species	Infected *N* (%)
Hookworm	405 (41)
Mansonella perstans	192 (20)
Schistosoma mansoni	187 (19)
Strongyloides stercoralis	123 (13)
Trichuris trichiura	84 (9)
Ascaris lumbricoides	21 (2)
Trichostrongylus	6 (.60)
Hymenolepsis nana	2 (.20)
Fasciola hepaticus	1 (.10)
Dicrocoelium dendriticum	1 (.10)
Enterobius vermicularis	1 (.10)

ASSOCIATIONS BETWEEN MATERNAL WORM INFECTIONS AND OTHER EXPOSURES, AND INFANT OUTCOMES

Raw Correlations

First, raw correlations between child test scores and exposure variables were explored to identify factors that might mediate or mask effects of maternal worm infections. Maternal worms included were *Schistosoma mansoni*, hookworm, *Mansonella perstans, Ascaris lumbricoides, Trichuris trichiura,* and *Strongyloides stercoralis*.

Background factors included were mother's age, education, occupation, income, gravidity, HIV status, and hemoglobin at enrolment; household socioeconomic status, family size and father's occupation; and the child's sex, gestational age at birth, birth weight, Apgar score at 10 min, malaria, diarrhea, and respiratory infections in the first year, activity, mood and interaction level during assessment, hemoglobin, weight, and height. These correlations and regressions were examined across the entire sample irrespective of treatment status since neither treatment showed any overall effect.

Three maternal worms showed correlations with the infant test scores: *Strongyloides stercoralis* correlated positively (in the opposite to expected direction) with scores on Self Control and negatively with Language. *Trichuris trichiura* and *Mansonella perstans* correlated negatively with scores on the A-not-B task. Other factors variably correlated with performance on the motor and cognitive measures. Of 112 correlations calculated, 34 were significant at the 0.05 cutoff, even after adjusting for multiple comparisons with false discovery rate. Only exposures with at least one significant correlation with the outcomes are shown in Table 5.

Multivariate Regression Analysis

To test the hypothesis that maternal worm infections would independently affect performance of children on measures of executive function, we performed a series of hierarchical linear regression analyses in which associations with maternal worms were examined taking into account associations with potential confounding factors. Using this technique we explored the unique contribution of maternal worm infections over and above effects of additional exposures. The independent variables were entered in a single model which comprised three blocks: maternal-related factors (SES and family factors, health factors), child-related factors (gender, health, and behavioral factors), and maternal worms (entered in that order). Each subtest of the motor and cognitive assessment was examined separately. Categorical measures (worm exposure and drug treatment) were loaded as dummy variables. Non-significant explanatory variables were dropped from the model one at a time leaving only the significant factors and therefore the best model that accounts for performance on each of the measures. Associations between maternal worm infections, and other factors, and each of the outcomes are summarized in Table 6 and described below; the order of entering variables into the analysis is also listed in this table.

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Table 5. Pearson correlations between maternal worms and other health and sociodemographic exposures, and the outcomes

	Fine Motor	Gross Motor	Language	Sociocognition	Self Care	A not B	Self Control
Maternal worms in pregnancy							
Trichuris trichiura	.08	−.07	−.07	−.04	−.05	−.14*	.01
Strongyloides stercoralis	.09	−.03	−.14*	−.03	−.04	.03	.18**
Mansonella perstans	.07	−.01	−.04	.07	−.04	−.20**	.00
Maternal & birth related factors							
Maternal income	.10	.13*	.12	.04	.08	.06	−.03
Maternal education	−.14*	−.13*	.10	−.03	−.03	.10	−.05
Maternal occupation	−.01	−.004	.03	.08	−.03	−.09	−.01
Father's occupation	−.07	.12	−.03	−.11	.02	.07	−.10
Household SES	−.03	−.03	.16*	−.10	.02	.08	.01
HIV exposure	.18**	−.12	.05	−.02	−.01	.07	−.05
Mother's hemoglobin	−.15*	.10	−.01	−.05	.09	−.01	−.05
Gestation age	−.06	.09**	.06	−.05	−.02	.04	−.07
Gender	.01	−.12	−.14*	.12	.03	−.06	.01
Nutritional factors							
Weight at 15 months	−.02	.23**	.07	−.07	.08	.00	−.05
Height at 15 months	−.13	.17**	.06	−.10	.01	−.02	−.10
MUAC	.05	.13*	.14*	−.04	.05	−.02	−.06
Infections							
Malaria episodes	.03	−.17**	.05	.10	.00	−.02	.20**
Diarrhea episodes	.01	−.04	.08	−.08	.11	−.11	.18*
Respiratory infections	−.02	−.04	−.07	−.05	.06	.04	.22*
Child's behavior during the testing session							
Mood	−.04	.24**	.13*	−.20**	.12	.15**	−.21**
Activity	−.23**	.19**	.25**	−.31***	.22**	.29**	−.20**
Interaction	−.17**	.25**	.06	−.25**	.20**	.18*	−.18**

Note. MUAC = mid upper-arm circumference.
*$p < .05$.
**$p < .01$.
***$p < .001$.

Fine motor

Child's mood and maternal HIV status were positively associated with fine motor function, whereas activity, interaction and height were negatively associated with this outcome ($R^2 = 0.08$; $F(5,956) = 15.89$; $p < .001$). Maternal worm infections had no association.

Gross Motor

Performance on *Gross Motor* was positively associated with the child's hemoglobin level at 1 year, height and weight at 15 months, mood and interaction during assessment and child's age ($R^2 = 0.13$; $F(6,884) = 21.76$; $p < .001$). Maternal worms had no association.

Language

Maternal *Strongyloides stercoralis* showed a negative association with infants' Language. Household socioeconomic status, child's activity and height at the time of assessment showed positive associations with Language; and child's interaction during assessment showed a negative association ($R^2 = 0.06$; $F(6,860) = 9.42$; $p < .001$). This model accounted for more variance than the model without maternal worms ($\Delta R^2 = 0.005$).

Self Care

This measure was positively associated with child's sex, activity, and weight at the time of assessment ($R^2 = 0.05$; $F(3,974) = 16.90$; $p < .001$). Maternal worms had no association.

Recognition of Self and of Others was negatively associated with maternal gravidity and activity of child during assessment ($R^2 = 0.03$; $F(2,975) = 16.29$; $p < .001$). Maternal worm infections had no association.

Self Control

Performance on *Self Control* was negatively associated with infant's height, activity, and interaction during assessment and positively related with malaria episodes in infancy. The raw association with maternal *Strongyloides stercoralis* infection was no longer significantly associated with the function when we controlled for the other exposures ($R^2 = 0.11$; $F(5,810) = 19.94$; $p < .001$).

A-not-B task

Child's activity, interaction, and height were positively associated, while malaria episodes in infancy and maternal *Mansonella perstans* were negatively associated on this

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Table 6. Effects of maternal worm infections and of other health and sociodemographic exposures on the various functions

Measure	Worm/other exposure	Unstandardized coefficients (B)	Standardized coefficients (B)	Std. Error of B
Fine motor				
	Maternal HIV	.41*	.07*	.19
	Mood	.11*	−.10*	.05
	Activity	−.39***	−.20***	.08
	Interaction	−.12*	−.11*	.05
	Height	−.07***	−.13***	.02
Gross Motor				
	Mood	.21**	.14**	.06
	Interaction	.24***	.16***	.06
	Hb at 1 yr	.10*	.06*	.05
	Height	.07*	.09*	.03
	Weight	.20**	.11**	.08
	Child's age	.45**	.09**	.16
Language				
	Household SES	.33**	09**	.12
	Activity	1.10***	.23***	.21
	Interaction	−.30*	−.11*	.12
	Height	.11*	.08*	.04
	Strongyloides stercoralis	−.90*	−.07*	.44
Self Control	Activity	−.10***	−.16***	.03
	Interaction	−.06***	−.17***	.01
	Height	−.02***	−.10***	.01
	Malaria episodes	.06***	.11***	.02
Self Care				
	Activity	.71***	.16***	.15
	weight	.26*	.08*	.11
	Sex	1.32***	.16***	.27
Recognition of self and others				
	Activity	−.18***	−.17***	.03
	Gravidity	−.11*	−.07*	.05
A not B task				
	Activity	−.75***	−.26***	.12
	Interaction	.22***	.14***	.07
	Height	.08***	.11***	.02
	Malaria	−.18*	−.08*	.08
	Mansonella perstans	−.40*	−.07*	.20

Note. Maternal-related factors were entered into the model in this order: mother's age, education level, occupation, income, gravidity, HIV status, and hemoglobin level at enrollment; household socioeconomic status, family size, and father's occupation. Child factors were entered into the model in this order: child's sex, gestation age at birth, birth weight, Apgar score, malaria, diarrhea, and respiratory infections in the first year, activity, mood, and interaction level during assessment, hemoglobin level, weight, and height. Hb = hemoglobin; SES = socioeconomic status.
*$p < .05$.
**$p < .01$.
***$p < .001$.

outcome. The raw association with maternal *Trichuris trichiura* was no longer significant when we controlled for other factors ($R^2 = 0.16$; $F(5,774) = 28.71$; $p < .001$). The model with *Mansonella perstans* infection accounted for more variance than the model without the worm ($\Delta R^2 = 0.004$).

In summary, significant maternal worm effects were observed between *Mansonella perstans* and performance on the A-not-B task, and between *Strongyloides stercoralis* and performance on Language. Hookworm and schistosomiasis did not show significant associations with the outcomes although these were the most prevalent worms in the sample.

DISCUSSION

The Impact of Anthelminthic Treatment During Pregnancy

Treating pregnant women with albendazole or praziquantel had no significant effects on infant developmental measures. The absence of treatment effects in a setting with high prevalence of worm infection suggests that there is not much benefit of single-dose mass anthelminthic treatment during pregnancy for cognitive and psychomotor outcomes in the child.

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Subgroup analysis suggested that praziquantel treatment in mothers who had *Schistosoma mansoni* infection had significant effects on both the A-not-B and Self Control tasks even though the worm did not have significant effects on these outcomes. We observed a positive effect on Self Control. However, the negative effect of the drug on the A-not-B task is difficult to explain since *Schistosoma mansoni* infection has been associated with cognitive deficits and treatment was therefore expected to be beneficial. This result could have occurred by chance, or the negative effect of praziquantel might be linked to changes in the host immune responses following treatment. Treatment of schistosomiasis is associated with an increase in circulating proinflammatory as well as anti-inflammatory cytokines (Azim, Sedky, el-Tahawy, Fikry, & Mostafa, 1995; Mwatha et al., 1998); the killing of schistosomes following praziquantel treatment results in release of worm antigens and a boost in anti-worm responses (Tweyongyere et al., 2008; Walter et al., 2006). The infection may be effectively cleared but the high concentration of cytokines induced might perhaps interfere with neurotransmitter systems, particularly the dopaminergic systems, thereby affecting cognitive functioning (Reichenberg et al., 2001).

Effects of Maternal Worm Infections

The results provide some support for the main hypothesis that maternal worm infections in pregnancy might have negative effects, particularly on infant executive function, but this is restricted to only two species. In line with our prediction, certain maternal worm infections were associated with performance on both the A-not-B and Self Control tasks. We observed a negative association between maternal *Mansonella perstans* and infants' later performance on the A-not-B task and a positive correlation between *Strongyloides stercoralis* and Self Control. The latter was contrary to our predictions and might be an incidental finding, as it suggests that infection improves infant's skills on this function. It could be that children born to mothers with this infection are not more self-controlled but rather less active and less interested in their environment, and hence less interested in the treat. Indeed infant malaria and respiratory infections likewise showed positive associations with performance on this measure. Thus apathy may mediate the effect of ill-health on Self Control. However, delay tasks may not be reliable measures of inhibitory control since performance on these measures varies greatly with the task, including the type of treat used (Carlson et al., 2005).

The results suggest that executive functions might be particularly susceptible to influences of maternal worms; the effect observed on language has been reported in earlier childhood studies of worms (e.g., Ezeamama et al., 2005), and this might be secondary to effects on executive function given that the two domains emerge within the same period and are reported to be interdependent throughout life. Moreover, the two domains often show comorbidity (Ribeiro et al., 2011; Tannock & Schachar, 1996; Willinger et al., 2003 for a review). Rebiero et al. explored the comorbidity between language and executive functions and found that early executive function (attention) impairment predicted later language problems but not vice-versa. Therefore, the disruption of executive function by worms may explain the effect observed on language. Given these specific influences, the results suggest that maternal worm infections during pregnancy do not cause generalized cognitive deficits in infancy. Plausible explanations for the selective nature of maternal worm effects in infancy have been proposed. Maternal worms are believed to compete with the fetus for nutrients that are vital for formation of neurological systems (Beard et al., 2007).

Naismith (1969) suggests that, in cases of moderate deprivation (e.g., due to mild worm infections), the fetus takes priority over the nutrients that remain and thrives with minimal effects. Executive functions may however be more vulnerable due to more specific metabolic effects. It has been proposed, for example, that the availability of certain neurotransmitters is dependent on the dietary supply of their amino acid precursors (Wainwright & Colombo, 2006); for example, tryptophan is the dietary precursor of serotonin, and tyrosine is the precursor for dopamine and norepinephrine (Fernstrom, 1990). Reduced levels of tyrosine may lead to impaired executive function in children with phenylketonuria (Sharman, Sullivan, Young, & McGill, 2009). Therefore, changes in the availability of different amino acids may result in disturbances of specific brain functions and behavior. Dopamine, in particular, acts in the prefrontal cortex in which executive functions including planning, inhibition, and attention are represented, both in animals (Gaarlen, Brueggeman, Bronius, Schoffelmeer, & Vanderschuren, 2006) and humans (Goto & Grace, 2005; Smith & Kieval, 2000).

However, in worms as in other organisms, tyrosine is an essential nutrient (Moran, 2005). Impaired tyrosine catabolism in worms is associated with dramatic effects including a short life span, destruction of the intestine, and decreased fertility. Given that intestinal worms depend on the host's digestive contents for this amino acid, prolonged infestation of worms may deprive the body of this nutrient and this may in turn impact on dopamine synthesis resulting in impairment of the executive function.

The associations observed in this study were based on only two measures of executive function. It is possible that worms affect other executive skills not measured by the Delay inhibition task, and by the A not B task. Moreover, because assessments were done later in infancy, we may not completely rule out the possibility that earlier in life worms could show more generalized cognitive deficits. These are important issues that need to be resolved by longitudinal studies measuring various cognitive abilities.

Effects of maternal worm infections on infant cognitive functioning could also be mediated by iron deficiency. However, in this study we found very weak associations between maternal worm infections and maternal anemia (Muhangi et al., 2007), or benefit of anthelminthic treatment for anemia (Ndibazza et al., 2010). Moreover, all women

were routinely treated with iron and folic acid during pregnancy, perhaps compensating for any iron loss due to worm infections. Worms were not causing major iron deficiency anemia in these mothers, so cognitive effects of worms mediated by maternal anemia would not have been detectable in this study.

In addition to worm infections, infant abilities were examined in relation to other factors. Common infections in infancy, particularly repeated malaria, were found to influence infants' performance. As expected, child nutritional factors (hemoglobin, height, and weight) showed significant positive correlations with developmental outcomes. Infant mood, activity, and interaction level also consistently influenced scores on the various developmental measures highlighting the role non-task behavior plays in performance. Given that numerous factors were affecting infants' development before and after birth, a relatively small amount of variance explained by worms alone might be expected. However, worms affect millions of mothers and children, and hence, the global impact of even a small effect on child development may be important enough to raise concern. Regardless of the effect size, these findings are in keeping with our prediction and deserve further exploration.

Our study had an experimental design, and this was a strength of our analysis of the effects of anthelminthic intervention. However, it is of note that the majority of pregnant women who participated had a low intensity of worm infections; mothers with hemoglobin below 8 g/dL were excluded from the study, and iron and folic acid were given during antenatal care. These characteristics limit the extrapolation of our findings to other populations. It could be that, where infections are heavy and nutritional and micronutrient status is marginal, maternal worms have stronger and more diverse effects on the development of the executive system. Future studies should aim specifically to investigate effects in populations with high intensities of worms.

Furthermore, in early infancy, cognitive processes are not yet fully developed, which undermines the validity of developmental effects measured. Moreover, future studies should assess effects of worms on other aspects of executive functions, other than those measured in this study. We continue to follow-up these infants and reassess the worm effects at older ages and to include aspects of executive functions not examined in this study to re-evaluate the selectivity of these effects.

In conclusion, the results of this study suggest that certain maternal worm infections during pregnancy may have negative influences on early executive function in the offspring but anthelminthic treatment is unlikely to reverse these effects. Further research should aim to replicate these findings in the light of the limitations mentioned above.

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