Original Research Article

Household-Level Predictors of Maternal Mental Health and Systemic Inflammation Among Infants in Mwanza, Tanzania

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Objectives: Household conditions and culturally/socially variable childcare practices influence priming of the inflammatory response during infancy. Maternal mental health may partially mediate that effect. Among mother–infant dyads in Mwanza, Tanzania, we hypothesized that poorer maternal mental health would be associated with adverse household ecology, lower social capital, and greater inflammation among infants under the age of one; and that mental health would mediate any effects of household ecology/social capital on inflammation.

Methods: We collected dried blood spots from mother–infant dyads ($N = 88$) at health centers near Mwanza, Tanzania. To assess household ecology and social capital, we conducted interviews with mothers using the Household Food Insecurity Access Scale, the MacArthur Subjective Social Status Scale, and a household wealth inventory. We employed the Hopkins Symptom Checklist to assess maternal mental health. A high-sensitivity C-reactive protein (CRP) assay was used to quantify inflammation.

Results: Severe food insecurity (OR: 5.16), lower subjective social status ($r = -0.32$), and lower household wealth ($r = -0.26$) were associated with high symptoms of maternal depression. Lower household wealth ($r = -0.21$) and severe food insecurity (OR: 2.52) were associated with high anxiety. High depression symptoms (OR: 2.56) and severe food insecurity (OR: 2.77) each were associated with greater-than-median infant CRP. However, mediation was not supported.

Conclusions: Maternal mental health should be considered alongside nutritional status, pathogen exposure, and education as a potential driver of very early innate immune system development. Proximal mechanisms warrant further investigation. Am. J. Hum. Biol. 00:000–000, 2015.

Convincing evidence now connects lifetime chronic and infectious disease risk to early life experiences (Barker, 2012; Kuzawa and Quinn, 2009; McDade, 2012). Yet knowledge gaps remain regarding social exposures that influence the early development of the immune system, a physiological mediator of lifetime health risk. The social ecology of the immune system in infants is a challenging subject of study because of rapid developmental change. For instance, Th1/Th2 balance, cytokine profiles, and adaptive immune functioning change considerably over the first 60 months of postnatal life (Field, 2005; Holt and Jones, 2000). The innate immune response also is subject to developmental priming, driven at minimum by early pathogen exposures and by immune factors found in human milk (Field, 2005). Such exposures are highly variable across human experience, depending in part on culturally, socioeconomically, and individually distinctive childcare practices and household conditions.

Early innate immune system priming has long-term implications for health risk. In the Cebu Longitudinal Study (Philippines), two markers of pathogen exposure—episodes of diarrhea and exposure to animal feces under 1 year of age—were associated with *lower* serum levels of the inflammatory mediator C-reactive protein (CRP) in young adulthood (McDade et al., 2009). The authors interpreted this finding in terms of the hygiene hypothesis, wherein early pathogen exposures entrain the immune system, preventing harmful overreaction to antigens later in life. Repeated bouts of inflammation in infancy due to higher microbial exposure might lead to greater long-term competency in balancing pro- and anti-inflammatory components of the immune response (Garn and Renz, 2007; McDade, 2012; Yazdanbakhsh et al., 2002). Conversely, when pro- and anti-inflammatory responses are not well balanced, chronic inflammation may carry forward into adulthood. Even at levels considered subclinical, chronic adult inflammation contributes to allostatic load and can increase cardiovascular risk (Danese and McEwen, 2012), although it remains unclear whether subclinical adult inflammation is a cardiovascular risk factor in less-affluent populations (McDade, 2012).

Hadley and DeCaro (2014), using a nationally representative cross-section of children 6–59 months of age from Tanzania, found that age, sex, maternal literacy, maternal illness, household size, and household wealth each were independently associated with elevated CRP. Surprisingly, many other proxy measures for household sanitation, such as water treatment and shared toilet facilities, were not. Household food insecurity also did not predict CRP, and combining all significant covariates into a model only accounted for 4% of the variance. To gain more explanatory power the authors suggested paying closer attention to how social variables in specific local contexts mediate infant and young child inflammation.

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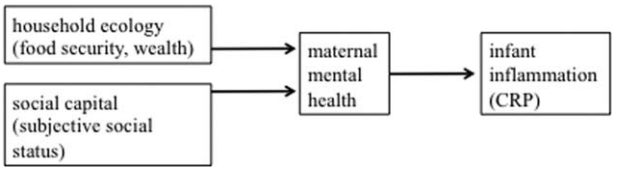

Fig. 1. Predicted relationships among variables.

A parallel line of research has investigated household wealth or poverty, food insecurity, and maternal mental health (particularly depressive symptoms) as psychosocial variables that influence early developmental trajectories across multiple physiological systems. Mental health appears to be particularly influential as a predictor of young children's health outcomes. This is likely because mental health serves as a sensitive marker of household-level adversity from multiple sources, balanced against resources for resiliency, and because anxiety and depression themselves mediate some of the effects of chronic adversity on child wellbeing through changes in caretaker behavior (Black et al., 2009; Bronte-Tinkew et al., 2007; Hadley and Patil, 2006; Hadley et al., 2008; Stewart, 2007; Weaver and Hadley, 2009).

The present study complements existing large-scale survey research with a focused examination of how three variables linked to household ecology and social capital—household food insecurity, household wealth, and the mother's subjective social status—are associated with maternal mental health and systemic inflammation for infants under 1 year of age in Mwanza, Tanzania. We focus on infants for three reasons. First, predictors of sub-clinical inflammation among infants are poorly understood. Second, as noted above with respect to findings from the Cebu study (McDade et al., 2009), pro-inflammatory exposures under 12 months of age may have long-term implications for the development of the inflammatory response. Finally, maternal influences are likely to be particularly critical in the first year of life, when children are least mobile and most dependent on the mother for their general care and for interactions with the physical environment.

We hypothesized that maternal mental health would serve as a proximal mediator of the effects of household ecology and social capital on infants' inflammation (Fig. 1). Hence, we predicted that food insecurity, lower wealth, and lower subjective social status each would be associated with greater maternal symptoms of anxiety and depression. We further predicted that maternal symptoms of anxiety and depression would be associated with higher CRP. Finally, we hypothesized that maternal mental health would partially mediate any effects of household-level variables on infant CRP.

METHODS

Study setting

We recruited our sample in Mwanza, Tanzania. Tanzania spent 7% of its gross domestic product in 2012 on health, compared to the global average of 10%, ranking it 79th out of 188 countries (World Bank, 2014). In 2006, Tanzania had 0.1 physicians per 1,000 people, ranking it last out of 194 countries (CIA, 2014). Life expectancy at birth in 2012 was 61 years, compared to the global average of 71, ranking Tanzania 166th out of 197 countries (World Bank, 2014). In 2012, Tanzania's infant mortality rate (IMR) was 38 deaths per 1,000 compared to the global average of 35, ranking it 139th out of 192 countries. The mortality rate for under-5-year olds (CMR) is 54 per 1,000, ranking it at 142nd out of 192 countries. In common with much of sub-Saharan Africa (SSA), Tanzania is making progress in reducing infant and child mortality; between 2004 and 2012, their IMR declined by 38% and CMR by 45%. In 2012, 43% of Tanzanian children had a height-for-age more than two standard deviations below the median for the international reference population, a measure of chronic nutritional stress, compared to 35% for developing countries in SSA and 25% globally (World Bank, 2014). In 2010, 12% of Tanzanian children had a weight-for-age more than two standard deviations below the median for the international reference population, a measure of acute nutritional stress, compared to 22% for developing countries in SSA and 16% globally (World Bank, 2014). The economy in the region around Mwanza is based primarily on smallholder agriculture, which employs about 85% of the population. Agriculture is complemented by an expanding fishing sector. Commercial fishing is carried out by large companies using modern gear and vessels.

Sample and general procedures

Participants were recruited opportunistically at five regional health centers in and around Mwanza, where all interviews took place, as part of a broader study regarding food insecurity and child health. In April to May 2011, 150 mother–child dyads were recruited, of whom 88 were eligible for this analysis because the child was under 12 months of age and both the mother and the child provided blood spots. The data collection team consisted of three medical residents in their last 1–2 years at the Catholic University of Health and Allied Sciences and a senior anatomy laboratory technician. WW trained the team in data collection procedures over a period of 7 days and subsequently supervised data collection.

Written informed consent was received from all participants. The research was approved by the National Institute for Medical Research in Tanzania's Ministry of Health and Social Welfare, the Conjoint Health Research Ethics Board in the Faculty of Medicine at the University of Calgary (Ethics ID: 23245), and the University of Alabama Institutional Review Board.

Demographic, socioeconomic, and mental health variables

Independent variables included household wealth, household food insecurity, maternal mental health, and subjective social status. In addition, standard sociodemographic information such as age, marital status, and family size were collected. The mother's age was determined by asking her age upon her last birthday and her date of birth. The child's age was determined by asking the mother the child's date of birth. If possible, the mother's and child's age were confirmed using their antenatal cards.

To measure household wealth we recorded the type and number of assets that a household owned (Knueppel et al., 2010). Wealth measures included material and livestock assets. For each asset, a household was given a score of 1 (low wealth), 2 (medium wealth), or 3 (high wealth),

TABLE 1. Composition and scoring of the household wealth measure

Household assets	Low wealth (score = 1)	Medium wealth (score = 2)	High wealth (score = 3)
Kiosk (*n*)	0	1	>1
Goat (*n*)	0	1–3	>3
Cow (*n*)	0	1	>1
Sheep (*n*)	0	1–3	>3
Chicken (*n*)	0	1–5	>5
Pig (*n*)	0	1–2	>2
Donkey (*n*)	0	1	>1
Plow (*n*)	0	1	>1 (score = 2)
No. of different crops planted (*n*)	0	1–2	>2
Radio (*n*)	0	1–2	>2
Bed (*n*)	0	1	>1
Land (acres)	0	0.25–1	>1
Bicycle (*n*)	0	1–2	>2
Sewing machine (*n*)	0	1	>1
Watch (*n*)	0	1	>1
Television (*n*)	0	1	>1
DVD player (*n*)	0	1	>1
Satellite dish (*n*)	0	1	>1 (score = 2)
Generator (*n*)	0	1	>1 (score = 2)
Mosquito net (*n*)	0–1	2–3	>3
Brick house (Y/N)	No	Yes	Yes (score = 2)
Metal roof (Y/N)	No	Yes	Yes (score = 2)

based on information from key informants during focus groups. For example, key informants stated that a household of low wealth would own no chickens, a household of medium wealth would own one to five chickens, and a household of high wealth would own more than five chickens. A household wealth score was produced by summing the scores for both material and livestock assets. The composition and scoring of the household wealth scale are displayed in Table 1.

In addition to objective household wealth, subjective social status, a strong predictor of health (Singh-Manoux et al., 2003), was measured using the MacArthur Subjective Social Status Scale. This instrument presents social status using the image of a ladder and has been validated for use in developing countries with minor adaptations to local contexts (Goodman et al., 2001). Scores range from 1 to 10, with higher scores signaling greater subjectively perceived social status.

Food insecurity was measured using the Household Food Insecurity Access Scale (HFIAS). This instrument was designed to capture the experience of household food insecurity across cultures and has been validated for use in developing countries including Tanzania with minor adaptations to local contexts (Coates et al., 2007; Knueppel et al., 2010). The instrument comprises nine occurrence questions that represent a generally increasing level of food insecurity, and nine frequency-of-occurrence questions asked as a follow-up to each occurrence question. Scores range from 0 to 27; higher scores indicate greater food insecurity. Additionally, since items on the HFIAS vary considerably in the severity of their implications for household food insecurity, there are established coding procedures based on individual item responses rather than total scores for classifying households as food secure, or as mildly, moderately, or severely insecure (Coates et al., 2007).

Maternal symptoms of anxiety and depression were assessed using the Hopkins Symptom Checklist 25-question screening tool (HSCL-25), an instrument that shows high validity (Winokur et al., 1984) and has been used extensively in vulnerable populations across a range of cultural contexts, including Tanzania (Hadley and Patil, 2006, 2008). The HSCL-25 elicits information about common psychoneurotic complaints and can be completed within five minutes, enabling researchers to rapidly screen patients in a busy medical setting where it would be impractical to perform more extensive evaluations of emotional symptomatology (Winokur et al., 1984).

The HSCL-25 contains 10 items to address symptoms of anxiety (e.g., suddenly scared for no reason; faintness, dizziness, or weakness) and 13 items to address symptoms of depression (e.g., feeling low in energy, slowed down; crying easily; feeling hopeless about the future). It also contains two items, "poor appetite" and "difficulty falling asleep or staying asleep," that contribute in this version of the instrument to the depression factor score (Winokur et al., 1984). Participants were asked to score their experience with each of these symptoms during the previous 2 weeks on a 4-point Likert scale ranging from "not at all" [1] to "extremely" [4]. The HSCL-25 score was calculated by averaging the participant's responses, with a lower score indicative of better mental health. One question from the HSCL-25, #14 concerning sexual activity, was found to be culturally inappropriate during pilot testing and was removed. As a result, our HSCL-25 depression score is based on the average score from 1 (not at all) to 4 (extremely) among 14 items rather than 15. The HSCL-25 is a rapid screening instrument, and while it has been employed successfully cross-culturally including elsewhere in Tanzania (Hadley and Patil, 2006), it is limited insofar as there are no cross-culturally valid a priori cut-points for depression or anxiety (Lee et al., 2008; Ventevogel et al., 2007).

Instrument refinement and team training

The data collection team adapted the sociodemographics questionnaire and the MacArthur Subjective Social Status Scale, HSCL-25, and HFIAS instruments to the local context in three steps. First, the team spent one day practicing with the instruments. As all team members, other than WW, were from the region, their local knowledge led to refinements of each instrument. Second, the team spent one day at a health post in Mwanza conducting focus group interviews with two groups of six key informants who were familiar with the conditions and experiences of mothers in the region to ensure that the instruments were culturally relevant. Focus group members were mothers from the Mwanza region with children under the age of 5 years. The instruments were altered accordingly after the focus groups. Third, on the following day, the refined instruments were used in individual interviews with eight mothers of children under five years of age from the Mwanza region. Pooled-respondent feedback was then used to rephrase portions of the interview that were unclear. The team received three days of training with the refined questionnaires, and a half-day of training in the collection of anthropometric and dried blood spot data. Training elements included explanation and discussion of each item, and learning how to interview by role-playing and with real respondents. Training was followed by a half-day field test with seven participants at a health post in Mwanza.

Inflammation and anthropometric measures

To assess inflammation, dried blood spots (DBS) were collected through finger stick for adults, and heel stick for infants, according to standard procedures (McDade et al.,

2007). After the skin was punctured with a single-use spring loaded lancet, the first drop of capillary blood was wiped away, and up to five additional drops were deposited onto Whatman 903 protein saver cards. After drying, DBS were placed individually into sealed plastic bags with a desiccant, placed into a −40°C freezer, and then shipped from Tanzania to the University of Alabama where they were placed into a −30°C freezer until analysis. Total time at ambient temperature, including drying time and transport, was 6 days and was uniform across the samples that were shipped together in a single package. Because this is close to the maximum acceptable exposure to ambient temperatures for CRP in DBS (Brindle et al., 2010), weather station reports throughout the transport route during shipment in June 2011 were monitored for both East Africa and the United States. When not indoors at room temperature, the samples were exposed to outdoor temperatures no greater than 30°C, with an average outdoor ambient temperature of approximately 22°C. Hence, we consider temperature control prior to the assay acceptable for reliable CRP determinations. However, our measured CRP values are likely modestly but uniformly underestimated, given a laboratory simulation that showed 15% decline over 7 days in measured CRP values after storage at 21°C relative to matched frozen DBS (Brindle et al., 2010).

Anthropometric data, used to calculate body mass index as a covariate in this analysis, were collected following standard procedures (Lohman et al., 1988). Participants were measured without their shoes and wearing only light clothing. Weight was measured with an electronic scale to the nearest 100 g (Beurer BG64). The stature of adults was measured using a portable stadiometer (Seca 213). The length of infants was measured recumbently using a portable measuring mat (Seca 210). All linear measurements were to the nearest mm and collected twice for each subject and averaged.

CRP assay

Dried blood spots were analyzed in the Developmental Ecology and Human Biology (DEHB) laboratory on the University of Alabama campus, using a published immunoassay for C-reactive protein in DBS (Brindle et al., 2010; McDade et al., 2004). In brief, DBS samples were removed from the freezer and warmed to room temperature, and a single 3.2 mm disc punched from an area of fully saturated filter paper near the edge of a blood spot. Whole capillary blood was eluted overnight from each disc at 4°C in 250 μl of a phosphate/NaCl/Tween sample dilution buffer, and then 100 μL transferred in duplicate from each sample to microtiter plate wells pre-coated with Biodesign mouse monoclonal anti-human-CRP #M86005M. Pre-prepared standards (0–10.7 mg/l) and controls (low, medium, high) on DBS also were eluted and transferred to microtiter plate wells in duplicate. Biodesign mouse monoclonal anti-human-CRP #M86284M, conjugated with horseradish peroxidase, was used to quantify CRP in each sample based on a four parameter logistic standard curve, detecting absorbance at 490 nm with a BioTek Powerwave HT plate reader. Assay sensitivity is 0.03 mg/l.

Data reduction and modeling strategy

Child body mass index (BMI) was converted into BMI-for-age *z*-scores using WHO reference standards (WHO Multicentre Growth Reference Study Group, 2006). For infant CRP and maternal symptoms of anxiety and depression, the sample was split into equal "low" vs. "high" categories using a median split. With respect to infant CRP, the distributional skew toward low values was sufficiently profound to make transformation impossible, and modeling as a continuous variable problematic. We also do not expect continuous linear associations with infant CRP, because variation among the lowest detectable values is unlikely to reflect any meaningful differences in pathogen exposure or other pro-inflammatory processes. There is, however, no convincing *a priori* threshold to apply for this age and population. While thresholds for elevated CRP from 2–10 mg/l have been reported in the literature, the most comparable and well-documented is a sensitivity/specificity analysis suggesting 1.1 mg/l as indicative of acute infection in children ages 3–5 years (Wander et al., 2012). In the present case, however, the children were much younger, and we expect a modest, uniform underestimation of CRP levels based on storage/transport times. Hence, we chose the empirical approach of a median split.

Similar concerns required the use of a median split for the HSCL-25. HSCL-25 scores, like infant CRP levels, were too profoundly skewed to be normalized using the ladder of powers. Moreover, the HSCL-25 is a rapid screening instrument, and the cut-points that discriminate between elevated and non-elevated symptomatology vary profoundly across contexts and by gender. For instance, among HIV-positive women in Tanzania, one study found that the optimal cut-point for identifying clinically significant depressive symptoms was 1.06 (Kaaya et al., 2002). Yet this would result in 100% of the present sample being classified as symptomatic. By contrast, in Afghanistan, Ventevogel et al. (2007) found that a cut-point of 1.50 for men but 2.25 for women best correlated with findings from a diagnostic psychiatric interview. Lee et al. (2008) argued against clinical use of the HSCL-25 in Tanzania, due to concerns about contextual variability in the manifestation of depression even within-country. Hence HSCL-25 cut-points are inherently arbitrary in the absence of detailed local validation studies which are not available for the population of the Mwanza region of Tanzania.

The first hypothesis, that household wealth, subjective social status, and food insecurity would be associated with maternal mental health, was tested as a series of three separate bivariate associations in logistic regression in order to estimate odds ratios. Then, covariates selected a priori for their potential as confounders of mental health symptoms were added into each model; specifically, household size, maternal age, child age, child sex, breastfeeding, maternal education, maternal BMI, and the presence of a father at home.

The second hypothesis, that maternal mental health would be associated with infant CRP, was also tested in logistic regression. First, this relationship was modeled as a bivariate association, and then covariates were added for their potential to confound CRP levels. These covariates were modeled after the findings of Hadley and DeCaro (2014), and include household size, mother's CRP (as a marker of maternal health), child fever reported in the past 2 weeks, child age in months, child sex, breastfeeding, maternal education, and child BMI-for-age *z*-scores. To determine whether the inclusion of symptoms

TABLE 2. Descriptive statistics

Variable	Mean or %	Median	SD	Range
Child age (months)	5.66	6	2.97	1–11
Household size	5.07	4	2.51	2–19
Maternal education (years)	6.91	7	2.86	0–11
Maternal BMI	22.99	22.48	3.68	16.19–36.16
Child BMIz	0.22	0.18	1.48	−4.68 to 4.02
HFIAS	6.10	6	5.79	0–27
Household wealth	28.40	28	2.70	23–36
Subjective social status	3.96	4	1.96	1–10
Maternal depression symptoms	1.61	1.43	0.60	1–3.36
Maternal anxiety symptoms	1.59	1.40	0.55	1–3.60
Maternal CRP (mg/l)	1.36	0.87	1.52	0.01–8.58
Child CRP (mg/l)	1.18	0.26	2.08	0.06–9.53
Child sex (male)	58.16%			
Fever in the past 2 weeks	45.74%			
Breastfeeding	94.85%			
Severe food insecurity	48.86%			

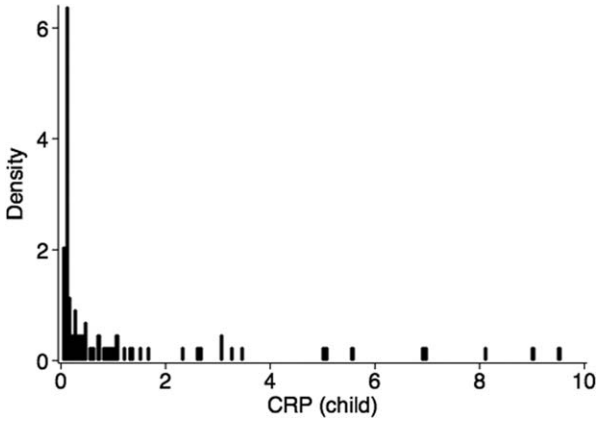

Fig. 2. Distribution of child CRP values.

of depression or anxiety improved overall model fit, one final model was constructed with the control variables only. Log likelihoods, Akaike information criteria (AIC) and Bayesian information criteria (BIC) were compared between the models.

Finally, to identify mediation, confidence intervals around the indirect (mediated) effect in logistic regression were established through 500 bootstrap replications (Preacher and Hayes, 2004), using the binary_mediation program in STATA 14.0.

RESULTS

Descriptive statistics

General characteristics of the sample are displayed in Table 2. The average child was 5.66 months in age, and lived in a household with 4 other members, although household size varied widely from 2 – 19. The average level of maternal education was 6 years of formal schooling, again with substantial variability, from 0 – 11 years. Maternal BMI and child BMIz values were generally within the normal range. Among mothers, 20.5% of mothers displayed BMI < 20, consistent with moderate prevalence of underweight. However, only 6.1% of infants displayed BMIz < −2, consistent with low prevalence of wasting.

On the HSCL-25, mean scores on the depression subscale (M = 1.61) and anxiety subscale (M = 1.59) were high by comparison to the best available validation sample, from primary care clinics in Dar es Salaam where mean values were 1.15 and 1.16, respectively (Lee et al., 2008). As a marker of socioeconomic well-being, HFIAS scores suggest widespread and significant adversity, with 48.9% of households reporting severe food insecurity. This is not, however, atypical; a survey in rural Iringa, Tanzania, for instance, found a nearly identical 48.1% prevalence of severe food insecurity (Knueppel et al., 2009). However, all socioeconomic/household status indicators showed considerable variability. For instance, household food insecurity varied across the entire range of the HFIAS measure, from 0 – 27. This sample spans a broad spectrum in terms of general economic and social security, from solidly secure households to those at very serious risk. Moderate associations existed among all household social variables. Severe food insecurity was associated with lower subjective social status (point biserial r = -.46, P < .001) and lower wealth (point biserial r = -.45, P < .001). Subjective social status and wealth were also correlated with one another (r = .34, P < .01)

CRP levels for infants (M = 1.18 mg/L, SD = 2.08, median = .26) and mothers (M = 1.36 mg/L, SD = 1.52, median = .87) were low on average, although not exceptionally so relative to other samples drawn from low and middle income countries (LMICs) (McDade, 2012). Both distributions were skewed. While maternal CRP could be log transformed to approximate normality, no power transformation could sufficiently normalize infant CRP. This reflects a distribution with a very large peak near the lowest detectable limits of the high sensitivity CRP assay, with 40% of the sample between .06 and .15 mg/L, followed by a long, flat tail (Fig. 2).

Wealth, social status, and food insecurity predict mental health symptoms

Lower household wealth (point biserial r = -.26, P = .013), lower subjective social status (point biserial r = -.32; P = .003), and severe household food insecurity (OR: 5.16; P < 0.001) all were associated with high depression symptoms among mothers. Lower household wealth (point biserial r = -.21, P = .045) and severe food insecurity (OR: 2.51, P = .035) were significantly associated with high anxiety symptoms, but subjective social status was not (point biserial r = -.05, P = .629). A complete set of comparisons is displayed in Table 3.

Each of these potential mental health risk factors was entered individually into logistic regression models with household size, maternal age, child age, child sex, breastfeeding, maternal education, maternal BMI, and father at home as covariates (Table 4). Associations remained largely unchanged, except that subjective social status lost statistical significance as a predictor of depression symptoms, and severe food insecurity lost significance as a predictor of anxiety symptoms. None of the covariates were statistically significant.

Symptoms of depression but not anxiety predict child CRP

Odds that a child's CRP would be high, relative to the sample median, were greater if mothers reported elevated symptoms of depression (OR: 2.56; P = 0.03). This effect was further tested in a logistic regression model that

TABLE 3. Bivariate associations of household variables with maternal depression and anxiety symptoms

Variable	Low depression	High depression	Test statistic	Low anxiety	High anxiety	Test statistic
Household wealth	29.07 (2.45)	27.63 (2.84)	$t(86) = 2.53$*	28.89 (3.05)	27.72 (2.27)	$t(86) = 2.03$*
Subjective social status	4.62 (2.16)	3.36 (1.64)	$t(85) = 3.08$**	4.07 (2.14)	3.86 (1.87)	$t(85) = 0.49$
Severe food insecurity	29.6%	67.4%	$\chi^2(1) = 13.24$***	37.8%	60.5%	$\chi^2(1) = 4.53$*

Values in parentheses are standard deviations.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

TABLE 4. Logistic regression models predicting high depression and anxiety symptoms

		High depression symptoms ($n = 75$)				High anxiety symptoms ($n = 75$)			
Model	Independent variable	OR	SE	*P*	95% CI	OR	SE	*P*	95% CI
1	Household wealth	0.74	0.09	0.016	0.58–0.95	0.79	0.09	0.042	0.63–0.99
	Household size	1.07	0.16	0.646	0.80–1.43	0.94	0.13	0.649	0.72–1.23
	Maternal age (years)	1.11	0.07	0.067	0.99–1.26	1.02	0.05	0.664	0.92–1.13
	Child age (mo)	0.96	0.09	0.699	0.80–1.16	1.11	0.10	0.260	0.93–1.33
	Breastfeeding (1=yes)	14.53	21.65	0.072	0.78–269.5	5.89	7.60	0.169	0.47–73.9
	Maternal education (years)	0.92	0.09	0.416	0.76–1.12	0.95	0.09	0.624	0.79–1.15
	Maternal BMI	1.00	0.07	0.967	0.87–1.15	0.88	0.07	0.089	0.76–1.02
	Father at home (1 = yes)	2.65	2.55	0.311	0.40–17.4	3.72	3.51	0.162	0.59–23.5
2	Subjective social status	0.75	0.12	0.067	0.55–1.02	0.95	0.14	0.777	0.72–1.28
	Household size	0.93	0.12	0.580	0.72–1.20	0.84	0.14	0.315	0.61–1.17
	Maternal age (years)	1.11	0.06	0.074	0.99–1.24	1.03	0.05	0.572	0.93–1.14
	Child age (mo)	0.98	0.09	0.806	0.82–1.17	1.10	0.10	0.274	0.92–1.32
	Breastfeeding (1=yes)	8.94	12.07	0.105	0.63–126.0	4.25	5.49	0.262	0.34–53.3
	Maternal education (years)	0.91	0.09	0.326	0.75–1.10	0.93	0.09	0.416	0.77–1.12
	Maternal BMI	1.00	0.07	0.986	0.87–1.14	0.88	0.06	0.068	0.76–1.01
	Father at home (1=yes)	1.53	1.36	0.634	0.27–8.71	1.86	1.63	0.481	0.33–10.4
3	Severe food insecurity (1=yes)	4.69	2.91	0.013	1.39–15.8	2.60	1.58	0.117	0.79–8.56
	Household size	0.99	0.14	0.941	0.75–1.30	0.88	0.12	0.372	0.67–1.16
	Maternal age (years)	1.06	0.06	0.326	0.95–1.18	0.99	0.05	0.905	0.89–1.10
	Child age (mo)	0.96	0.09	0.668	0.80–1.15	1.11	0.10	0.266	0.93–1.32
	Breastfeeding (1=yes)	11.22	15.47	0.079	0.75–167.2	5.03	6.60	0.219	0.38–66.0
	Maternal education (years)	0.92	0.09	0.368	0.75–1.11	0.95	0.09	0.573	0.79–1.14
	Maternal BMI	1.05	0.08	0.491	0.91–1.22	0.91	0.07	0.211	0.78–1.06
	Father at home (1=yes)	1.42	1.32	0.707	.23–8.82	2.18	1.91	0.374	0.39–12.2

included household size, mother's CRP (as a marker of household-level pathogen load), child fever reported in the past two weeks, child age in months, child sex, breastfeeding, and child BMI *z*-scores. The full model is displayed in Table 5. Greater child age (OR: 1.25; $P = .029$), lower maternal education (OR: .75; $P = 0.018$), and elevated maternal symptoms of depression (OR: 3.35; $P = .033$) were associated with higher odds of above-median CRP. Compared to a reduced model including covariates only, log likelihoods, AIC, and BIC indicate a modest improvement in model fit when maternal depressive symptoms are included. Specifically, including depression improved log likelihood from −45.71 to −43.28, AIC from 109.42 to 106.57, and BIC from 130.51 to 130.00.

There was no significant relationship between child CRP and elevated symptoms of anxiety (OR: 1.89; $P = 0.14$). When this association was tested in a logistic regression model as described above, it remained non-significant (Table 5).

Food insecurity associated with infant CRP but without mediation

Mediation was tested by comparing direct, indirect, and total effects in logistic regression using bootstrap replications. Household wealth, subjective social status, and severe food insecurity were entered as the independent variables, in three separate analyses. High maternal depression symptoms were entered as the mediator variable. High child CRP was entered as the dependent variable. Anxiety was not tested as a mediator, since it is not related to child CRP.

In none of the three models was a significant indirect effect detected. When household wealth was the independent variable, the indirect effect ($B = -0.067$; SE = 0.049; $P = 0.165$), direct effect ($B = -0.092$; SE = 0.132; $P = 0.488$), and total effect ($B = -0.160$; SE = 0.124; $P = 0.199$) were all non-significant. Similarly, with subjective social status as the independent variable, the indirect effect ($B = -0.088$; SE = 0.055; $P = 0.112$), direct effect ($B = 0.007$; SE = .139; $P = 0.960$), and total effect ($B = -0.081$; SE = 0.130; $P = 0.534$) were nonsignificant. Finally, entering severe food insecurity as the independent variable, the indirect effect ($B = 0.072$; SE = 0.056; $P = 0.200$) and direct effect ($B = 0.206$; SE = 0.123; $P = 0.094$) were non-significant, but there was a significant total effect ($B = 0.28$; SE = 0.108; $P = 0.010$). This reflects a modest association between severe household food insecurity and high infant CRP (OR = 2.77; SE = 1.22; $P = 0.021$).

DISCUSSION

We aim to contribute to a small but growing literature on correlates of subclinical inflammation among very young children in low- and middle-income countries (Hadley and DeCaro, 2014; McDade et al., 2005). Interest in this question derives from two sources. First, even in the

TABLE 5. Logistic regression models predicting above-median CRP from high maternal depression and anxiety symptoms (n = 77)

	Model 1				Model 2			
Independent variable	OR	SE	*P*	95% CI	OR	SE	*P*	95% CI
Household size	1.01	0.10	0.937	0.82–1.24	1.05	0.11	0.636	0.86–1.28
Recent fever (1 = yes)	1.45	0.84	0.516	0.47–4.48	1.30	0.73	0.644	0.43–3.90
Log maternal CRP	0.84	0.20	0.455	0.52–1.33	0.91	0.21	0.671	0.57–1.43
Child age (months)	1.25	0.13	0.029	1.02–1.52	1.20	0.12	0.060	0.99–1.46
Child sex (1 = male)	0.65	0.37	0.457	0.22–2.00	0.71	0.39	0.536	0.24–2.08
Breastfeeding (1 = yes)	7.77	13.23	0.229	0.27–218	8.08	13.8	0.222	0.28–231
Child BMIs	0.90	0.17	0.604	0.62–1.32	0.94	0.18	0.743	0.65–1.36
Maternal education (years)	0.75	0.09	0.018	0.58–0.95	0.73	0.09	0.010	0.58–0.93
Maternal depressive symptoms (1 = high)	3.35	1.90	0.033	1.10–10.2				
Maternal anxiety symptoms (1 = high)					1.94	1.03	0.213	0.68–5.54

absence of observable clinical pathology, elevated inflammation is a marker of pathogen exposure and subclinical infection that sheds light on near-term health risk (McDade et al., 2005; McDade et al., 2008; Thurnham et al., 2005; Wander et al., 2012). Second, early episodes of acute inflammation may have long-term developmental implications for the innate immune response. If these exposures do not lead to serious acute pathology, they may eventually be protective by preventing the development of an excessively pro-inflammatory phenotype in adulthood (Garn and Renz, 2007; McDade, 2012; McDade et al., 2009; Yazdanbakhsh et al., 2002). Yet CRP elevation in young children also has been found prospectively to predict reduced growth (Blackwell et al., 2010; McDade et al., 2008). We did not test the predictive value of elevated inflammation for child growth in our analysis, given the complexity of the model that would result relative to sample size, and the cross-sectional nature of our data. However, as prior findings illustrate, there are complex energetic and health trade-offs between the need to develop immunocompetence on one hand, and the risks associated with excessive childhood immunostimulation on the other.

We first tested the hypothesis that low subjective social status, severe household food insecurity, and low material wealth would be associated with greater reported symptoms of anxiety and depression among the mothers. All three of these indicators of household adversity were associated with greater odds of higher-than-average maternal depressive symptoms, although only household food insecurity and wealth were associated with maternal anxiety. The effect of household food insecurity for depression was particularly strong: severe food insecurity increased more than five-fold the odds of high depression symptoms.

Second, we hypothesized that higher symptoms of depression and anxiety would be associated with elevated CRP among infants. This was supported for depression symptoms, even after controlling for a range of likely confounding variables. The odds of above-median infant CRP increased 2.5-fold if the mother displayed greater than average depression symptoms. This effect only grew stronger in regression models controlling for other correlates of child inflammation, such as maternal education and child age. We do not have data to identify the specific proximal pathways though which maternal depression translates into child inflammation. However, there are a number of possible ways this form of adversity could "get under the skin," which will be discussed in greater detail below.

Finally, we hypothesized that any association between household socioeconomics and infant inflammation would be mediated by maternal mental health. This final hypothesis was not supported. While a modest, significant association between food insecurity and infant CRP was identified in mediation analysis as a total effect, the indirect effect was not statistically significant. Hence, the social conditions of the household and maternal mental health may be best understood as correlated variables with independent effects on child outcomes (Hadley et al., 2012). A larger sample size, ideally including prospective data, would be required to conclusively rule out mediation, however.

Maternal depression was robustly associated with social conditions *and* with infant CRP; hence, even in the absence of mediation, maternal depression occupies a central position in the evaluation of household well-being. This special role for symptoms of depression hearkens to recent work documenting the considerable global disease burden of mental illness (Murray et al., 2012); the social forces that produce adverse mental health outcomes (Patel et al., 2010); and the profound consequences for the physical health of adults and their children. Psychiatric epidemiologists have described widespread untreated or undertreated mental illness, hitting residents of LMICs with overtaxed mental health infrastructures particularly hard (Patel and Prince, 2010). Yet improving treatment is not the only lens through which global mental health should be understood. Depression and other forms of mental illness have well-documented social and economic determinants, and they interact with (frequently exacerbating) somatic disease (Mendenhall and Weaver, 2014). For instance, in rural Tanzania, Pike and Patil (2006) found that a confluence of social forces—including gender inequity, illness, hunger, poverty, social isolation and violence—create profound emotional burdens that manifest as the psychophysiological and psychological symptoms of anxiety and depression.

The strong association we found between food insecurity and maternal mental health is consistent with an extensive literature showing similar effects across the developing world (Clarke et al., 2014; Cole and Tembo, 2011; Hadley and Patil, 2006; Hadley and Patil, 2008; Hadley et al., 2008; Nanama and Frongillo, 2012; Weaver and Hadley, 2009). In a comprehensive review, Weaver & Hadley (2009) outline three principal reasons food insecurity may be associated with common mental disorders such as anxiety or depression. As they note, to the extent that food insecurity translates into poorer nutrition, there may be physiologically mediated effects on mental health.

Yet even where food insecurity does not translate into poor nutrition it is characterized by uncertainty about reliable access to culturally appropriate food, and is a potentially powerful signal of inferior relative social status. Uncertainty, social inequality, and shame produce chronic stress, which increases the risk for depressed affect (Hammen, 2005; McEwen, 2003; McEwen, 2005). Among mothers, food insecurity also frequently provokes buffering strategies, in which the child is protected from direct nutritional consequences, but often at some cost to the mother (Piperata et al., 2013). The caretakers in this study may be buffering children, including older children in the household besides the focal infant, and this in turn may carry an emotional cost.

While the contextualization of depressive symptoms in terms of household adversity is important, the most distinctive finding of this study is that maternal depressive symptoms predict higher inflammation among infants under the age of one. In general, mental health morbidity for the primary caretaker, especially maternal depression, is among the most widely replicated and powerful predictors of adverse health outcomes for young children. For instance, poorer maternal mental health has been linked to poorer infant growth (Black et al., 2009; Harpham et al., 2005; Patel et al., 2004; Rahman et al., 2004; Stewart, 2007; Stewart et al., 2008), higher infectious disease morbidity (Nguyen et al., 2014; Rahman et al., 2004; Ross et al., 2011), and numerous other adverse developmental outcomes (Wachs et al., 2009). These studies typically have not provided insight into immune system development, however. Where correlates of elevated inflammatory mediators such as CRP have been studied among very young children in LMICs, the focus instead has been on nutritional status (Frongillo et al., 2014; Thurnham et al., 2005), pathogen exposure or hygiene (Hadley and DeCaro, 2014; McDade, 2012), and maternal literacy or education (Hadley and DeCaro, 2014; McDade et al., 2005). Maternal mental health should be added to the inventory of such considerations.

Our study leaves open the question of what specific behaviors, environments, or interactions connect maternal depression to subclinical inflammation in infants. There are a number of potential pathways that would be fruitful for future research. Human milk contains factors that prime the innate immune response (Field, 2005), and there is limited evidence that greater intensity and/or duration of breastfeeding downregulates CRP over the long term (Cook et al. 2000; Rudnicka et al. 2007). Hence, while nearly all these infants were breastfed to some extent, differences in specific feeding practices may have influenced variation in CRP levels. We do not, however, have the detailed data on infant feeding required to test this. Maternal depression also may be a marker for broader pathogenic characteristics of the household, or may impede caretaking behaviors that otherwise would shield infants from pathogen exposure (Rahman et al., 2004). However, attempts to demonstrate this in previous studies have been inconclusive, since effects of maternal depression on infectious disease risk have been found independent of household conditions and health-promoting practices (Rahman et al., 2004; Ross et al., 2011). Finally, an intriguing line of inquiry recognizes that communication between the central nervous system and peripheral immune regulation is bidirectional. Among adults, inflammation has a role in the pathogenesis of depression (Raison et al., 2006), and depression alters the behavior of the immune system (Stewart et al., 2009). For infants, sensitivity to the affective and motivational states of primary caretakers is a basic survival adaptation (Chisholm, 1996), and infants respond to maternal distress with socioemotional, behavioral, and physiological changes (Brennan et al., 2008; Kingston et al., 2012). Hence, the infants may be regulating inflammation in response to maternal affect partially through their own developing capacity for psychoneuroimmunological responses. Each of these possibilities, while plausible, is beyond the scope of the present study.

Given its limitations, we caution against interpreting these findings as supporting specific applied public health interventions. First, we neither collected nor do we assert direct linkages to clinical outcomes. To our knowledge, data do not yet exist that would conclusively establish whether slight elevations in inflammation such as those demonstrated here are damaging, protective, neutral, or—most likely—highly context-dependent in their health implications. Second, it was necessary to dichotomize key variables including depression scores and infant CRP levels, which eliminates some of the variance and can increase risk of statistical artifacts. Ideally, this study would be repeated using a more sensitive depression measure that could be treated as continuous and/or one with securely validated clinical cut-points. Additionally, it would be helpful to follow changes in CRP among infants over time. Third, the cross-sectional design and limited depth of information about household ecology provided by the three survey instruments used in this study may have weakened the apparent influence of social and economic variables. Yet addressing household adversity is critical from an intervention standpoint. An over-simplistic view might lead unproductively toward attempts to solve essentially social and economic problems strictly at the individual level or by focusing on a single dimension of health to the exclusion of others (Mendenhall and Weaver, 2014). While mental health treatment is important for its own sake, the solution to childhood developmental processes adversely impacted by maternal depressed affect is not merely to treat symptoms, but to fully understand proximal mechanisms; to address the root causes of hopelessness among mothers who cannot provide for themselves and their children; and to identify resources for resiliency (cf. Patel, 2015).

These findings contribute to the research base regarding the global ecology of mental health and of immune functioning in several important respects. First, our findings are consistent with a growing body of evidence that pathogenic environments do not necessarily produce stark elevations in CRP; indeed, in some cases the opposite may be true. Yet we also provide evidence that even at very young ages, poorer maternal mental health may be associated with elevations—however slight—in inflammation levels. Given that poorer maternal mental health is an unsurprising outcome of systematic adversity at the household and community level, these associations warrant further exploration in prospective research regarding proximal pathways through which social adversity gets under the skin.

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