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Impact of maternal malaria and under-nutrition on intrauterine growth restriction: a prospective ultrasound study in Democratic Republic of Congo

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SUMMARY

Maternal malaria and under-nutrition are established risk factors for small-for-gestational-age (SGA) births; however, whether malaria is associated with intrauterine growth restriction (IUGR) is unknown. We investigated IUGR risk among 177 HIV-negative pregnant women enrolled in a longitudinal ultrasound study conducted in Democratic Republic of Congo from May 2005 to May 2006. Malaria infection, maternal anthropometrics, and ultrasound estimated fetal weight were measured monthly. All positive malaria cases were treated and intermittent presumptive therapy (IPTp) provided. Log-binomial regression models for IUGR were fitted using generalized estimating equations to account for statistical clustering of repeat IUGR measurements. Twenty-nine percent of fetuses experienced an episode of IUGR with the majority occurring in the third trimester. The risk of IUGR associated with malaria was greatest after three or more cumulative infections (RR 3·3, 95% CI 1·3–8·2) and was two- to eight-fold higher among women with evidence of under-nutrition. Receiving antimalarial treatment in the previous month (for IPTp or treatment) was significantly protective against IUGR (RR 0·5, 95% CI 0·3–0·7). The interaction observed between malaria and under-nutrition suggests that antenatal programmes in malaria endemic areas should incorporate nutritional screening and supplementation in addition to IPTp.

Key words: Congo, intrauterine growth restriction, malaria, maternal nutrition.

INTRODUCTION

Each year, over 20 million infants worldwide are born with low birth weight (LBW), increasing their risk of neonatal mortality and childhood morbidity [1]. LBW in resource-poor settings consists largely of small-for-gestational-age (SGA) births [2–4]. Although some SGA births are genetically determined, most result from intrauterine growth restriction (IUGR), which is characterized by insufficient transfer of nutrients and oxygen to the fetus and impaired growth of fetal organs and tissues. IUGR may result from limited availability of maternal micro- and macro-nutrients (maternal under-nutrition), or from

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medical conditions (e.g. hypertension or infection), that impede proper vascularization of the placenta and restrict the transfer of essential nutrients from mother to fetus [2, 5, 6].

In resource-poor settings such as sub-Saharan Africa, pregnant women are frequently undernourished and at increased risk of malaria infection, making them particularly vulnerable to delivering an SGA infant. Malaria infection [7–13] and maternal anthropometric indicators of under-nutrition, including short stature [2, 14], low pre-pregnancy weight [14, 15] or low body mass index (BMI) [2, 16], low upper arm fat mass [2], and inadequate pregnancy weight gain [17, 18] are independently associated with an increased risk of SGA at delivery.

To date, studies of fetal growth in sub-Saharan Africa have been limited to describing risk factors for occurrence of SGA births. Studies describing *in utero* fetal growth are limited, due largely to a lack of ultrasound resources necessary to diagnose IUGR. The objective of our prospective cohort study was to assess the effects of maternal malaria and under-nutrition on the risk of IUGR in an urban, resource-poor African population.

MATERIALS AND METHODS

Study population and recruitment

This longitudinal prospective cohort study was conducted between May 2005 and May 2006 among pregnant women seeking antenatal care at Binza Maternity Hospital in Kinshasa, Democratic Republic of Congo. Binza Maternity Hospital is one of the oldest maternities in Kinshasa and serves a predominately urban population. The study was designed to assess feasibility and refine ultrasound protocols in preparation for a larger subsequent trial; no formal sample size calculations were conducted as the sample was selected for convenience.

During routine antenatal registration, all women identified as aged $\geqslant$18 years with a fundal height or last-menstrual-period-derived gestational age of $\leqslant$23 weeks were invited to receive an ultrasound examination to confirm gestational age. All women with an ultrasound-confirmed gestational age $\leqslant$22 weeks were invited to participate in the longitudinal study. Women with high blood pressure at baseline (systolic $\geqslant$140 mmHg and/or diastolic $\geqslant$90 mmHg), multiple gestations, or an ultrasound detected fetal abnormality were excluded. Participant HIV status was determined through Binza Maternity Hospital's routine HIV voluntary counselling and testing programme and reported to our study staff through a linked patient identification number. HIV-positive women were included in the longitudinal follow-up, but excluded from the analyses described here. All participants provided written informed consent; ethical and study protocol approval were obtained by the Institutional Review Boards at the University of North Carolina at Chapel Hill, USA and the University of Kinshasa School of Public Health, Democratic Republic of Congo.

Baseline and follow-up visits

During a baseline interview, sociodemographic characteristics, alcohol, tobacco and drug use, medical and obstetric history, malaria symptoms and current use of anti-malarial drugs were collected. Using standard techniques [19], maternal weight was measured to the nearest 0·1 kg (SECA digital scale Model 890), and maternal height (without footwear or head cover) and mid upper arm circumference (MUAC) to the nearest 0·1 cm. Blood pressure and body temperature were recorded and a malaria thick smear and haematocrit were prepared from a finger-prick blood sample. All women received an insecticide-treated bed net.

Participants returned for monthly routine follow-up visits until delivery during which the ultrasound examination, medical, and laboratory examinations (including malaria thick smears) were repeated. In accordance with Congolese National Policy, intermittent presumptive therapy in pregnancy (IPTp) with sulfadoxine-pyrimethamine (SP) was provided to all women between 16–27 weeks' and 28–32 weeks' gestation, regardless of malaria status. In addition, all women with positive parasitemia were treated; SP was the first-line treatment, however, quinine, artesunate or camoquine was prescribed if the woman had received SP within the preceding month. Women were instructed to return to the maternity hospital between follow-up visits if they experienced any pregnancy complications or symptoms of malaria. At these interim visits, a malaria thick smear was prepared and medical care was provided at Binza Maternity Hospital's outpatient clinic.

Ultrasound measurements

Fetal biometric measurement of the biparietal diameter (BPD), head circumference (HC), abdominal

circumference (AC), and femur length (FL) were taken to estimate gestational age and fetal weight. In the first trimester (gestational age <14 weeks), crown–rump length was used to estimate gestational age. All ultrasounds were performed by a single ultrasonographer (V.L.) with a GE Logiqbook System using standard fetal biometric techniques [20]. A 10% sample of ultrasound images was assessed for quality by a maternal-fetal medicine physician at UNC–Chapel Hill. Gestational age in weeks and days (first ultrasound scan only) and fetal weight in grams (all ultrasound scans) were calculated using Hadlock algorithms programmed into the Logiqbook software [21, 22].

Laboratory methods

One microscopist read all malaria thick smears on site during study visits. However, for quality assurance, a 10% sample of all malaria thick smears was assessed independently by a second laboratory technician. Smears were stained with Giemsa and read counting the number of asexual parasites against 200 white blood cells and converted to numbers of parasites/μl under the assumption that there were 6000 white blood cells/μl [23]. Anaemia was assessed from finger-prick blood samples and the percent haematocrit was recorded (Clay Adams Readacrit; Becton Dickinson & Co., Franklin Lakes, NJ, USA).

Definitions

IUGR was defined as a binary outcome of <10th percentile of fetal weight for attained gestational age using the Hadlock fetal weight nomogram [24]. Socioeconomic status (SES) was defined as a binary composite variable, with those who were currently employed (participant or her partner) and living in a home with toilet facilities, a nearby water source and electricity characterized as high SES. Anaemia was defined as a haematocrit of <30% at each visit.

The 'recent malaria parasitaemia' variable is a time-dependent measure that represents whether a woman had a positive smear at any time (including an interim visit) in the interval from her previous routine visit up to and including the visit in which the IUGR measurement was obtained (roughly equivalent to the past month). The 'cumulative malaria parasitaemia' variable represents a time-dependent measure of the number of positive smears starting at enrolment up to and including the routine follow-up visit in which the IUGR measurement was obtained. Short stature was defined as height <150 cm and low MUAC as <23 cm at enrolment. BMI was calculated using maternal weight and height at enrolment with low BMI defined as $<19{\cdot}8$ kg/m^2. Change in maternal weight was calculated between each monthly visit, and categorized as low ($<1{\cdot}5$ kg) or adequate ($\geqslant 1{\cdot}5$ kg) monthly weight gain. The change in MUAC between around 14 and 27 weeks (second trimester) and 27 and 40 weeks (third trimester) was calculated and dichotomized as a loss in MUAC (<0 cm difference over the trimester) *vs.* no change or gain ($\geqslant 0$ cm difference over the trimester). These anthropometric cut-points have been used previously to indicate women at risk of poor birth outcome [25, 26].

Statistical methods

All analyses were performed in SAS, version 8.2 (SAS Institute, Cary, NC, USA). Log-binomial regression models were fitted to estimate risk ratios (RR) and 95% confidence intervals (CI) for IUGR before and after adjusting for potential confounders. To account for repeat outcome measures over the course of pregnancy, the regression models were estimated based on the method of generalized estimating equations with an exchangeable working correlation structure [27]. Owing to reduced variability in fetal weight during the first trimester, IUGR is not typically seen until the second trimester; we therefore left-truncated all person-time observations at 22 weeks' gestation, resulting in 758 study visits for which data on both recent and cumulative malaria infections, and IUGR measurements, were available for analyses.

We discovered a malfunction in the scale used to weigh mothers that affected measurements taken during a 3–4 week period. All suspect data-points were removed before calculation of the weight gain variable leaving 588 visits with complete data for all covariates. A second set of log-binomial models was fitted for these 588 visits; the distribution of maternal sociodemographics, under-nutrition, malaria status, and gestational age of IUGR for the excluded visits were similar to those of the entire study population (data not shown).

Models were fitted separately for the incident and cumulative malaria exposure variables and for several maternal anthropometric indicators of under-nutrition. As there is evidence that maternal weight gain and MUAC may have differential fetal effects

depending on pre-pregnancy nutritional status and timing during pregnancy, models for these exposures were also stratified for baseline BMI status and trimester of pregnancy, respectively [28, 29].

To evaluate effect measure modification of the malaria–IUGR relationship by under-nutrition, an interaction term for malaria and each anthropometric indicator was added to the models. A P value of $<0{\cdot}15$ for the interaction term was selected *a priori* to indicate statistical significance. As previous studies have shown that the negative impact of malaria on birth outcome is more pronounced in primigravid women, we also investigated maternal gravidity as a possible modifier of the malaria–IUGR relationship. In this population however, gravidity was not a significant modifier and we therefore combined all gravidities together for the remainder of the analyses and considered gravidity only as a possible confounder. Other confounders included in adjusted models were identified using a backward elimination procedure with 10% change in estimation criterion or were determined to be *a priori* confounders of the effect as identified from previous studies of SGA or LBW. We considered maternal age, SES, gravidity and anthropometrics as potential confounders in the malaria exposure models and maternal age, SES, gravidity, and malaria exposure in the models utilizing maternal anthropometrics as the main exposure. In Table 3, risk ratios are presented with and without adjustment for maternal weight gain due to the loss of some data for the weight gain variable as described above.

RESULTS

Recruitment and follow-up

Of 1111 new antenatal care attendees, 33% ($n=370$) met all initial screening criteria and were scanned to determine gestational age. Of those, 182 were eligible and consented to enrol in the longitudinal study. Reasons for ineligibility included: gestational age >22 weeks ($n=154$), absent for dating ultrasound ($n=24$), twin pregnancy ($n=6$), and no viable fetus present ($n=4$). Five participants identified as HIV-positive (4%) were retained for longitudinal follow-up, but excluded from the analyses described here, yielding a final analysis sample size of 177 women. Women received on average five ultrasound scans (range 2–8). One maternal death and one loss to follow-up occurred before delivery. Mean gestational age at enrolment was 18 weeks [standard deviation (S.D.) = 3].

Quality control

Of 140 malaria thick smears examined twice (10% of all smears), there was one discordant positive and one discordant negative between the two technicians (kappa = 0·91, 95% CI 0·78–1·00). Of 750 ultrasound images assessed for quality by a maternal-fetal medicine physician at UNC–Chapel Hill (10% of all ultrasounds images), 92% were deemed adequate for clinical assessment; 7% of questionable quality and 1% poor quality (i.e. not all biometry landmarks clearly visible, shadowing in the image or poor tracing of the length or circumference).

ANTENATAL MALARIA

During the entire study period, a total of 157 malaria infections were identified (14 probable recrudescent episodes that occurred within 14 days of a previous positive, despite receiving treatment, were excluded from all analyses). Sixty percent of women had at least one positive smear during pregnancy; 38% had a single incident infection, 15% had two incident infections, and 8% were infected three or more times.

During the 758 study visits after 22 weeks' gestation included in this analysis, a total of 110 recent positive malaria parasitaemias occurred. Three quarters of these infections (78%) were identified at routine study visits and 22% during an interim visit. The majority of infections were *P. falciparum* only (96%); 1% were *P. malariae* only and 3% mixed infections (*P. falciparum* plus *P. malariae* or *P. ovale*). The parasite density ranged from 29 to 13380 parasites/μl (geometric mean 98 parasites/μl). The majority of infections were subclinical, with only one accompanied by fever.

Maternal under-nutrition

At baseline, mean BMI was 23·7 kg/m^2 (S.D. = 3·6). Eleven percent of women were underweight (BMI $<19{\cdot}8$ kg/m^2), 66% were normal weight (19·8–26 kg/m^2), 14% overweight (26–29 kg/m^2) and 8% obese ($\geqslant 30$ kg/m^2). Three percent of women had short stature (mean height 161·4 cm, S.D. = 6·6) and 14% had a MUAC <23 cm. Mean monthly weight gain was 1·6 kg (S.D. = 1·5).

Table 1. *Baseline and visit-specific characteristics of pregnant women and risk of intrauterine growth restriction (IUGR), Democratic Republic of Congo, 2005–2006*

	Number (%)*	RR	95% CI
Maternal age (years)			
18–24	56/177 (32)	1·7	0·8–3·4
25–29	57/177 (32)	1·0	Ref.
⩾30	64/177 (36)	1·4	0·7–2·9
Socioeconomic status			
Low	153/177 (86)	1·0	Ref.
High	24/177 (14)	1·1	0·5–2·4
Gravida			
⩾3	105/177 (59)	1·0	Ref.
1–2	72/177 (41)	1·5	0·8–2·6
Fetal gender			
Female	94/177 (53)	1·0	Ref.
Male	82/177 (47)	0·6	0·3–1·0
Treated in previous month			
No	383/758 (51)	1·0	Ref.
Yes	375/758 (49)	0·5	0·3–0·7
Haematocrit at visit			
⩾30	347/388 (89)	1·0	Ref.
<30	41/388 (11)	0·9	0·4–2·1

RR, Risk ratio; CI, confidence interval.

* Maternal age, socioeconomic status and gravidity recorded at enrolment only ($n=177$); treatment recorded at enrolment and each follow-up visit ($n=758$); haematocrit recorded at enrolment and every other follow-up visit ($n=388$).

IUGR

After 22 weeks' gestation, a total of 52 fetuses (29%) experienced 76 episodes of IUGR. Of these, 17% were IUGR at only one scan, 8% were IUGR at two scans and 5% at three or more ultrasound scans. Eighty-two percent of the IUGR episodes occurred in the third trimester, with peak prevalence between 28 and 33 weeks' gestation. Receiving antimalarial treatment in the previous month (for IPTp or treatment) was significantly protective against IUGR (RR 0·5, 95% CI 0·3–0·7) (Table 1). Male fetuses were less likely to have IUGR than female fetuses (RR 0·6, 95% CI 0·3–1·0). Maternal anaemia, younger (18–24 years) and older (⩾30 years) maternal age, and gravidity <3 were not significantly associated with IUGR on univariate analyses (Table 1).

Fetuses that ever experienced an episode of IUGR were significantly more likely to be born LBW (<2500 g) or SGA (Table 2). They were also more likely to be born pre-term, however this finding was not statistically significant. Nearly 50% of fetuses who had IUGR at one or two ultrasound scans, and 86% of fetuses who had IUGR three or more times, went on to be born SGA. IUGR fetuses also had significantly smaller length, head circumference, abdominal circumference and ponderal index at birth. There was no difference in gestational length by IUGR status.

Malaria and IUGR

We observed no significant effect of a recent malaria infection on IUGR risk in either the unadjusted analysis (RR 1·1, 95% CI 0·7–1·9) or after adjustment for maternal age, gravidity and weight gain in the past month (RR 1·5, 95% CI 0·9–2·5) (Table 3). The cumulative malaria parasitaemia data suggest a trend of increasing risk of IUGR with increasing number of malaria episodes; however this trend is not statistically significant. In the fully adjusted cumulative malaria model, a three-fold increase in the risk of IUGR was observed among women infected three or more times (RR 3·3, 95% CI 1·3–8·2) compared to women with no previous infections.

Under-nutrition and IUGR

None of the baseline anthropometric indicators of under-nutrition was significantly associated with IUGR (Table 4). Inadequate maternal weight gain (defined as <1·5 kg/month) was more strongly associated with an increased risk of IUGR in women with low baseline BMI (RR 2·7, 95% CI 0·9–8·5) compared to women with adequate baseline BMI (RR 1·4, 95% CI 0·9–2·2).

Low monthly weight gain during the second trimester (RR 5·7, 95% CI 1·3–25·0), but not the third trimester (RR 1·1, 95% CI 0·7–1·7) was significantly associated with an increased risk of IUGR. A similar pattern was observed for MUAC change per trimester. Women with a loss in MUAC in the second trimester were nearly three times as likely to have an IUGR fetus (RR 2·7, 95% CI 1·0–7·7) as women who had no change or gain in MUAC, whereas a third trimester loss in MUAC was not associated with IUGR (RR 1·1, 95% CI 0·6–1·9).

Combined effects of malaria and under-nutrition on IUGR

A detrimental effect of both recent and cumulative malaria infection on IUGR risk was stronger among

Table 2. *Association between intrauterine growth restriction (IUGR), birth outcome, length of gestation and fetal anthropometrics at delivery, Democratic Republic of Congo, 2005–2006*

	Ever IUGR *n* (%) or mean	Never IUGR *n* (%) or mean	95% CI for mean difference	*P* value
Low birth weight (<2500 g)	11/57 (22)	5/123 (4)		<0·001
Small for gestational age (<10th centile of standard)*	26/57 (52)	33/123 (27)		0·002
Preterm delivery (<37 weeks)	6/57 (12)	5/123 (4)		0·056
Gestational age (weeks)	39·1	39·3	−0·8 to 0·4	0·469
Birth weight (g)	2778	3068	−435 to −145	<0·001
Birth length (cm)	48·8	49·8	−1·7 to −0·3	0·008
Head circumference (cm)	33·4	34·4	−1·8 to −0·3	0·001
Abdominal circumference (cm)	26·9	28·2	−2·1 to −0·5	0·001
Ponderal index (kg/m^3)	24·0	24·8	−1·7 to −0·1	0·033

CI, Confidence interval.
* Small for gestational age defined as birth weight for gestational age less than the 10th percentile of the Wilcox standard curve [40].

Table 3. *Risk ratios and 95% confidence intervals for the association between intrauterine growth restriction (IUGR) and incident and cumulative malaria infection, Democratic Republic of Congo, 2005–2006*

	Number (%)*	RR	95% CI	aRR†	95% CI	aRR‡	95% CI
Visits in model (*n*) …		758		758		588	
IUGR episodes in model (*n*) …		76		76		66	
Recent malaria parasitaemia							
Negative	648/758 (85)	1·0	Ref.	1·0	Ref.	1·0	Ref.
Positive	110/758 (14)	1·1	0·7–1·9	1·1	0·7–1·9	1·5	0·9–2·5
Cumulative malaria parasitaemia							
0	397/758 (52)	1·0	Ref.	1·0	Ref.	1·0	Ref.
1	256/758 (34)	0·9	0·5–1·7	0·9	0·5–1·7	0·8	0·4–1·5
2	76/758 (10)	1·2	0·5–2·6	1·2	0·5–2·7	1·6	0·8–3·3
⩾3	29/758 (4)	2·4	0·9–6·5	2·2	0·8–6·1	3·3	1·3–8·2
		P_{trend} = 0·31		P_{trend} = 0·33		P_{trend} = 0·11	
<2 positive	653/758 (86)	1·0	Ref.	1·0	Ref.	1·0	Ref.
⩾2 positive	105/758 (14)	1·5	0·8–2·9	1·5	0·8–2·8	2·1	1·2–3·6

RR, Risk ratio; aRR, adjusted risk ratio; CI, confidence interval.
* Malaria parasitaemia recorded at all visits after 22 weeks' gestation (*n* = 758).
† Adjusted for age and gravidity.
‡ Adjusted for age, gravidity and weight gain. Note that this fully adjusted model was fitted using only the 588 observations that had complete weight gain data (see Methods section for further explanation).

undernourished women (Table 5), regardless of which anthropometric indicator was examined. For example, among women with low baseline BMI, the risk of IUGR associated with a recent malaria infection was nearly three times that (RR 2·8, 95% CI 1·0–8·1) of women unexposed to malaria. However, at normal baseline BMI levels, there was no observed association between malaria and IUGR (RR 0·9, 95% CI 0·5–1·7). A similar pattern was seen among shorter women, women with low MUAC, and women with monthly weight gain <1·5 kg. Analyses of the cumulative malaria parasitaemia variable resulted in a similar pattern, with the joint effect of low baseline BMI and cumulative malaria associated with the largest risk (RR 8·2, 95% CI 3·6–18·5).

DISCUSSION

A longitudinal study of IUGR has never previously been carried out in a malaria-endemic area. We

Table 4. *Risk ratios and 95% confidence intervals for the association between intrauterine growth restriction (IUGR) and maternal anthropometric indicators, Democratic Republic of Congo, 2005–2006*

	Number (%)*	RR	95% CI	aRR†	95% CI	aRR‡	95% CI
Visits in model (*n*) …		758		758		588	
IUGR episodes in model (*n*) …		76		76		66	
At enrolment							
BMI							
⩾19·8 kg/m²	157/177 (89)	1·0	Ref.	1·0	Ref.	—	—
<19·8 kg/m²	20/177 (11)	1·1	0·6–2·2	1·0	0·5–2·0	—	—
Short stature							
⩾150 cm	171/177 (97)	1·0	Ref.	1·0	Ref.	—	—
<150 cm	6/177 (3)	1·5	0·4–5·4	1·4	0·4–4·7	—	—
MUAC							
⩾23 cm	153/177 (86)	1·0	Ref.	1·0	Ref.	—	—
<23 cm	24/177 (14)	0·8	0·5–4·2	0·7	0·4–1·5	—	—
Visit specific							
Maternal weight gain per month							
All women							
⩾1·5 kg/month	308/588 (52)	1·0	Ref.	—	—	1·0	Ref.
<1·5 kg/month	280/588 (48)	1·4	0·9–2·2	—	—	1·5	1·0–2·3
Low baseline BMI							
⩾1·5 kg/month	39/75 (52)	1·0	Ref.	—	—	1·0	Ref.
<1·5 kg/month	36/75 (48)	2·7	0·9–8·5	—	—	2·7	0·9–8·5
Normal baseline BMI							
⩾1·5 kg/month	269/513 (52)	1·0	Ref.	—	—	1·0	Ref.
<1·5 kg/month	244/513 (48)	1·3	0·8–2·0	—	—	1·4	0·9–2·2

RR, Risk ratio; aRR, adjusted risk ratio; CI, confidence interval; BMI, body mass index; MUAC, mid upper arm circumference.

* BMI, height and MUAC as recorded at enrolment ($n=177$); weight gain data reflects change per month ($n=588$ for all women, $n=75$ for low baseline BMI, $n=513$ for normal BMI).

† Adjusted for age.

‡ Adjusted for age. Models that included weight gain as the exposure were fitted using only the 588 observations that had complete data for this variable (see Methods section for further explanation).

measured fetal growth *in utero* and identified IUGR in nearly one third of fetuses in this urban, sub-Saharan Africa population. This analysis focused on two component causes of IUGR that have heightened relevance in resource-poor settings: malaria infection and maternal under-nutrition. In this Congolese population, we found that a significant independent effect of malaria was seen only among women with three or more incident infections during gestation. We also found that the effect of maternal malaria varied significantly by maternal nutritional status, and that the highest risks of IUGR were evident among the most undernourished women.

Antenatal malaria may lead to IUGR through accumulation of *P. falciparum*-infected erythrocytes, and immunity-related monocytes and pro-inflammatory cytokines, in the placental intervillious space [30]. Haemozoin, a product of parasite haemoglobin digestion, can also be found in phagocytic leucocytes and within fibrin deposits in the intervillous space. This build-up can lead to thickening of the trophoblast basement membrane and effect uteroplacental arterial development, thus decreasing maternal–fetal nutrient exchange [31].

Previous studies conducted in areas of high *P. falciparum* transmission have consistently reported associations between SGA and both antenatal [7, 12, 13] and placental malaria infection [7, 8, 10, 12, 13]. Our findings are at variance with these earlier studies, with differences probably stemming from the fact that we screened for malaria at monthly intervals and treated

Table 5. *Risk ratios and 95% confidence intervals for the association between intrauterine growth restriction (IUGR) and malaria, stratified by maternal anthropometrics, Democratic Republic of Congo, 2005–2006*

	RR	95% CI	aRR†	95% CI	aRR‡	95% CI
Visits in model (*n*) …	758		758		588	
IUGR episodes in model (*n*) …	76		76		66	
Recent malaria parasitaemia (positive *vs.* negative)						
BMI < 19·8 kg/m²	**2·7**	**1·0–7·7**	**2·8**	**1·0–8·1**	—	—
BMI ⩾ 19·8 kg/m²	**0·9**	**0·5–1·6**	**0·9**	**0·5–1·7**	—	—
Height < 150 cm	2·6	0·5–13·1	2·9	0·6–14·0	—	—
Height ⩾ 150 cm	1·1	0·6–1·8	1·1	0·6–1·9	—	—
MUAC < 23 cm	**3·7**	**1·2–11·3**	**3·7**	**1·2–11·0**	—	—
MUAC ⩾ 23 cm	**0·9**	**0·5–1·6**	**0·9**	**0·5–1·6**	—	—
Weight gain < 1·5 kg in past month	1·6	0·8–3·1	—	—	1·7	0·9–3·4
Weight gain ⩾ 1·5 kg in past month	1·3	0·7–2·4	—	—	1·3	0·7–2·4
Cumulative malaria parasitaemia (⩾2 positive *vs.* <2 positive)						
BMI < 19·8 kg/m²	**7·3**	**3·3–15·9**	**8·2**	**3·6–18·5**	—	—
BMI ⩾ 19·8 kg/m²	**1·1**	**0·5–2·3**	**1·1**	**0·5–2·3**	—	—
Height < 150 cm	2·1	0·2–24·3	2·4	0·2–25·0	—	—
Height ⩾ 150 cm	1·5	0·7–2·9	1·5	0·8–2·9	—	—
MUAC < 23 cm	**5·4**	**2·4–12·3**	**6·5**	**2·9–14·7**	—	—
MUAC ⩾ 23 cm	**1·3**	**0·6–2·6**	**1·3**	**0·6–2·6**	—	—
Weight gain < 1·5 kg in past month	2·4	1·2–4·5	—	—	2·3	1·3–4·3
Weight gain ⩾ 1·5 kg in past month	1·7	0·8–4·0	—	—	1·8	0·8–3·9

RR, Risk ratio; aRR, adjusted risk ratio; CI, confidence interval; BMI, Body mass index; MUAC, mid upper arm circumference.

† Adjusted for age and gravidity.

‡ Adjusted for age and gravidity. Models that included weight gain were fitted using only the 588 observations that had complete data for this variable (see Methods section for further explanation).

Risk ratio pairs highlighted in bold indicate a significant *P* value for the interaction term between malaria and the anthropometric indicator (*P* value <0·15).

all positive antenatal parasitaemia. Further, virtually all women received two presumptive doses of SP. Routine screening and treatment may have eliminated parasites before they had adequate time to sequester in the placenta and cause damage to the placental vasculature, potentially minimizing the effect of malaria infection. In this study, receiving an antimalarial drug (for treatment or IPTp) in the previous month was independently protective against both incident malaria infection and IUGR, and led to higher attained fetal weight (data not shown), further supporting this hypothesis. Our findings are consistent with two studies of low malaria transmission areas (the Thai–Burmese border and highlands of Ethiopia) that also had frequent monitoring and treatment of antenatal parasitaemia [32, 33]. Collectively, these data lend support to the WHO recommendations for malaria prevention and control during pregnancy by showing that even in areas of high malaria transmission, the combination of IPTp, prompt identification and treatment of subclinical malaria infections (case management), and use of insecticide-treated bed nets may prevent fetal growth restriction [34].

Maternal under-nutrition was both an independent risk factor for IUGR and a significant modifier of the association between malaria and IUGR. Chronic pre-pregnancy under-nutrition, low weight gain and inadequate accumulation of fat stores during pregnancy can render a woman incapable of meeting the substantial metabolic demands of pregnancy [35]. The mean monthly weight gain of 1·6 kg for these Congolese women was similar to weight gain reported in other resource-poor settings [26]. As suggested in

previous studies, we found that insufficient maternal weight gain was more strongly associated with IUGR in women with low baseline BMI [18, 29], and that low weight gain in the second trimester increased IUGR risk [36, 37]. Our data also corroborate previous findings that failure to accrue arm fat during the second trimester, but not the third trimester, is associated with lower fetal weight [28].

The association between malaria and IUGR was consistently two- to eight-fold higher among women with evidence of under-nutrition. In resource-poor settings, it has long been recognized that childhood malnutrition and attendant sequelae influence susceptibility to and severity of malaria infection [38]. Repercussions of childhood under-nutrition and malaria infection, such as stunting and low BMI, place pregnant women at increased risk of poor birth outcomes. Further, the joint effects of adult under-nutrition and malaria infection may act on similar physiological pathways to reduce uteroplacental blood flow [35] and decrease maternal–fetal oxygen transfer [39].

Limitations and strengths

Although malaria and under-nutrition are common causes of IUGR, other risk factors, such as chromosomal abnormalities, pre-eclampsia or substance use may have played a role. We attempted to minimize the effects of other medical factors through our exclusion criteria and found that reported tobacco, alcohol and drug use were minimal. The extent to which fetuses in our cohort were constitutionally SGA *vs.* truly pathological IUGR cases remains unknown. Moreover, our IUGR definition utilized a fetal weight-for-age nomogram created from an industrialized country, which may have overestimated the proportion of IUGR fetuses in this resource-poor population. However, sensitivity analyses utilizing other industrialized nomograms, as well as a Congolese-specific nomogram we developed from these ultrasound data, showed that the results were highly robust to different definitions of IUGR (data not shown). We may have also overestimated true pre-pregnancy weight by using maternal weight at enrolment as a proxy; however, any resultant bias is probably minimal because participants were enrolled early in pregnancy, before women in resource-poor countries tend to gain significant pregnancy weight [26]. Last, this study was designed as a pilot to prepare laboratory, ultrasound and clinical operating procedures for a larger subsequent trial, and thus the sample size was selected for convenience, rather than to maximize power. A larger longitudinal study to replicate these findings is warranted.

CONCLUSIONS

The heightened risk of IUGR seen among women who were both undernourished and malaria-infected underscores the importance of incorporating maternal anthropometric screening and nutritional supplementation into existing antenatal care and IPTp programmes in malaria endemic areas.

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DECLARATION OF INTEREST

None.

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