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In utero exposure to malaria is associated with metabolic traits in adolescence: The Agogo 2000 birth cohort study

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Summary *Objectives:* Malaria in pregnancy (MiP) contributes to fetal undernutrition and adverse birth outcomes, and may constitute a developmental origin of metabolic diseases in the offspring. In a Ghanaian birth cohort, we examined the relationships between MiP-exposure and metabolic traits in adolescence.
Methods: MiP at delivery was assessed in 155 mother-child pairs. Among the now teenaged children (mean age, 14.8 years; 53% male), we measured fasting plasma glucose (FPG), body mass index (BMI), and systolic and diastolic blood pressure (BP). Associations of MiP with the adolescents' FPG, BMI, and BP were examined by linear regression.
Results: At delivery, 45% were MiP-exposed, which increased FPG in adolescence, adjusted for mother's age at delivery, parity and familial socio-economic status (infected vs. uninfected: mean ΔFPG = 0.20 mmol/L; 95% confidence interval (CI): 0.01, 0.39; p = 0.049). As a trend,

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this was discernible for BP, particularly for microscopic infections (mean Δsystolic BP = 5.43 mmHg; 95% CI: 0.00, 10.88; p = 0.050; mean Δdiastolic BP = 3.67 mmHg; 95% CI: −0.81, 8.14; p = 0.107). These associations were largely independent of birth weight, gestational age and teenage BMI. Adolescent BMI was not related to MiP.

Conclusions: In rural Ghana, exposure to malaria during fetal development contributes to metabolic conditions in young adulthood.

Introduction

Sub-Saharan Africa (SSA) is facing a rapid emergence of metabolic disorders, including type 2 diabetes, obesity and hypertension.[1–3] In Ghana, West Africa, 10% of adults have type 2 diabetes, while 20% are obese and 41% are affected by hypertension.[2,4] Population aging and accelerating urbanization that imposes changes in diet and physical activity contribute to the observed epidemic of metabolic conditions.[5] Still, infectious diseases constitute the major public health challenge to SSA. Among young children and pregnant women in Ghana, malaria remains abundant with an annual incidence of about 10,000 cases per 100,000 at risk.[6] This vector-borne disease causes life-threatening manifestations, particularly in young children, including severe anemia, coma, convulsions, acidosis, and renal failure, among others.[7] In highly endemic regions, malaria in pregnancy (MiP) frequently is asymptomatic but induces maternal anemia, placental inflammation and impaired fetal development, resulting in low birth weight (LBW) and preterm delivery (PD).[8] Lately, the concept of developmental programming of metabolic diseases has been extended to MiP, insofar as it may fuel the upsurge of type 2 diabetes, obesity and hypertension in SSA.[9,10] The concept of developmental programming proposes that pre- and early post-natal malnutrition induce metabolic adjustments, thereby increasing the survival chances of the offspring. Such adaptations, however, may become detrimental when energy and nutrient supplies improve, e.g. in later life.[11] In fact, intrauterine growth retardation is associated with impaired glucose metabolism.[11,12] cardiovascular disease,[13] and obesity in adulthood.[14]

Despite the detrimental potential of MiP, causing disrupted nutrient supply and adverse birth outcome, its potential contribution to metabolic disorders in the adult life of previously exposed fetuses has not been examined so far. The present study from rural Ghana aimed at investigating the importance of fetal exposure to MiP for metabolic traits in adolescence, comprising fasting plasma glucose (FPG), body mass index (BMI), and systolic and diastolic blood pressure (BP).

Methods

Study site, design and population

The present study was conducted in Agogo, which has some 30,000 inhabitants and is located in the forested hills of the Ashanti Akim North District, central Ghana. The main income sources are subsistence farming, trading and mining. Malaria transmission is hyper- to holoendemic.[15]

For this population-based birth cohort, the baseline recruitment of the mother-child pairs was carried out at Agogo Presbyterian Mission Hospital in the year 2000. We then included 839 delivering women with their life-singleton newborns. After 15 years, the follow-up assessments were conducted among 201 of these children, now aged 15 years. Details of the recruitment procedures and the baseline examinations have been described elsewhere.[16] In brief, from January 2000 to January 2001, pregnant women who presented for delivery were consecutively recruited. All women were clinically examined, socio-demographic data were documented, and venous blood samples were collected into EDTA. Malaria parasites were counted microscopically per 500 white blood cells (WBCs), and parasite density was calculated assuming a WBC count of 8000/μL. In addition, following DNA extraction (QIAmp, Qiagen, Germany), *Plasmodium species* and submicroscopic infections were ascertained by nested PCR assays,[17] taking advantage of the almost complete sensitivity in detecting placentally confined *Plasmodium falciparum* infections.[18]

Of note, in this population, MiP increased the odds of LBW by 70% and of PD by 80%.[16] From June to August 2015, we retrieved 200 of the former newborns, now aged 15 years, and invited them for a follow-up visit. We performed physical and anthropometric examinations, including BP measurements. Socio-demographic data and medical history were documented, and fasting venous blood samples were collected. For the present analysis, we excluded individuals with missing data on maternal malaria (n = 45), leading to a final sample size of 155 adolescents.

In 2000, all pregnant women gave written informed consent. In 2015, adolescents and their caregivers provided written informed consent, and the study protocols were reviewed and approved by the Committee on Human Research Publications and Ethics, School of Medical Sciences, University of Science and Technology, Kumasi.

Assessments of metabolic traits

From the adolescents, we collected fasting venous blood samples into EDTA, and FPG was measured (Accu-Check Performa + Accu-Check Inform II test strips, Roche Diagnostics, Germany). In light clothes and without shoes, teenage weight (kg; Person Scale DT602, Camry, Hong Kong, China) and height (cm; SECA 213, Germany) were measured by trained study personnel. BMI was calculated as weight/(height)^2

in kg/m^2. Sex-specific BMI-for-age z-scores (BAZ) were calculated for the adolescents based on the WHO reference population using the software package AnthroPlus (version 1.0.4, World Health Organization), and overweight was defined as $1 < BAZ \leq 2$. BP measurements among the teenagers were performed with an automated device (Tel-O-Graph BT, I.E.M. Stolberg, Germany) at 0, 3, and 6 min using appropriate cuffs after 5 min of resting time. The last two measurements were used to calculate the mean systolic and the mean diastolic BP (mmHg). We calculated age-, sex- and height-specific percentiles of systolic and diastolic BP using reference data of a large ethnically mixed US American reference population.[19] Teenage hypertension was defined as being above the 95th percentile.

Birth outcome and covariates

In the former newborns, birth weight (g) and gestational age (weeks) had been assessed within 24 h after delivery. LBW was defined as a birth weight <2500 g and PD as gestational age <37 weeks applying the Finnström score.[20] Socio-demographic and medical history data that had been collected for the mother in 2000 included: age at delivery, parity, residence, education and occupation. For adolescents at follow-up, we documented age, sex, residence, literacy and the number of people in the household.

Statistical analysis

The characteristics of the study population at baseline and at follow-up after 15 years are presented as mean and standard deviation (SD) or as median and interquartile range (IQR) for continuous variables. The characteristics of boys and girls were compared by t-test or Wilcoxon rank-sum test. Categorical data are shown as percentage and number, and were compared by χ^2-test or Fisher's exact test. Also, we compared teenagers who were lost to follow-up (n = 684) with cohort participants. The group lost to follow-up resided less frequently in Agogo and exposure to MiP had been more common than in the cohort group. Otherwise, baseline characteristics were similar (Supplementary Table 1).

To examine the relationships of MiP (defined as PCR-detected infection) with metabolic traits in the teenaged offspring, we compared adolescent FPG, BMI and BP between previously MiP-unexposed and MiP-exposed individuals, applying Wilcoxon rank-sum test. As a next step, linear regression analyses were performed for the associations of MiP with FPG, BMI and BP in adolescence. As depicted in the conceptual framework (Fig. 1), mother's age at delivery, parity and familial socio-economic status (SES) were considered as confounders in our analysis, because they are established risk factors for malaria in pregnancy[17,21] and metabolic conditions in adulthood.[22] Due to sample size limitations, we applied principal component analysis (PCA) as a data reduction technique to obtain an SES score. PCA was used to rank the adolescents according to familial SES (maternal education, maternal occupation, number of people in the household). Further, we adjusted the associations with FPG and BP for teenage BMI as a potential mediator for metabolic conditions.

For those adolescents with complete data on birth outcome (n = 141), we evaluated the previously reported associations of exposure to MiP with birth weight and gestational age,[16] and whether these could mediate the relationships with metabolic traits in adolescence.

As a first step, Wilcoxon rank-sum test and χ^2-test for non-normally distributed variables were used to compare birth weight (g), gestational age (weeks), and the proportions of LBW (%) and PD (%) between unexposed and exposed participants, respectively. Next, we examined linear

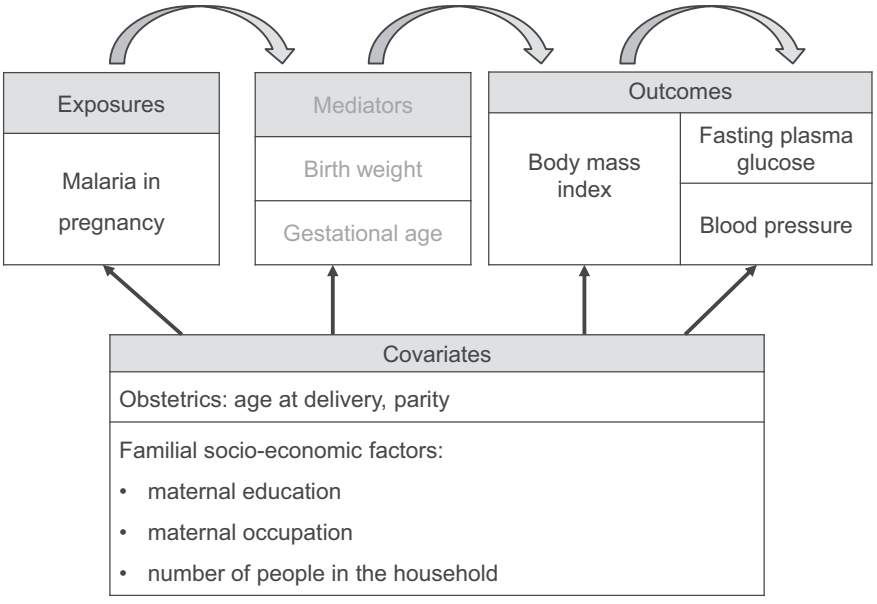

Figure 1 Conceptual framework of the relationships between malaria in pregnancy at delivery and metabolic traits at adolescent age.

associations of birth weight and gestational age with teenage FPG, BMI and BP using the above-mentioned adjustments and applying regression diagnostics to test for linearity. Lastly, we included birth weight and gestational age in the linear regression models as potential mediators for significant associations between MiP and metabolic traits in adolescence.

Results

Study population

In Table 1, we present the socio-demographic and medical characteristics of the study population at delivery and at follow-up after 15 years. At baseline, 45% of mothers had had malarial parasites in peripheral blood (microscopic, 14%; submicroscopic, 31%) at overall low geometric mean parasite density (737/μL; 95% CI: 282–1925/μL). The mean birth weight of the newborns had been 2936 g (SD: 453 g) and mean gestational age 38.6 weeks (SD: 2.7 weeks). Accordingly, 16/144 (11%) children had had LBW and 23/144 (16%) infants had been delivered preterm. Mothers' mean age at delivery had been 25·7 years (SD: 6 0 years) and two-thirds had resided in Agogo. The majority of mothers had completed primary education (77%) and had worked as traders (57%). These maternal baseline characteristics were similar between boys and girls (Table 1).

At follow-up, the teenagers presented with a mean age of 14·8 years (SD: 0·2 years); 68% resided in Agogo and 90% were able to read. The mean adolescent FPG was normal (4·2 mmol/L; SD: 0·6 mmol/L), while mean teenage BP was slightly increased (110/68 mmHg; 48th/59th percentile) and hypertension was seen in 10% (16/155) of the juveniles. Mean adolescent BMI and BAZ were higher in girls than in boys (Table 1), and overweight was present in 6% (9/155) of them.

Table 1 Socio-demographic and clinical characteristics of 155 mother-child pairs in rural Ghana.

Characteristics	Total (155)	Boys (82)	Girls (73)	p
Baseline				
Malaria in pregnancy				
Uninfected	54.8 (85)	50.0 (41)	60.3 (44)	0.258
Infected	45.2 (70)	50.0 (41)	39.7 (29)	
Microscopic infection	14.2 (22)	11.0 (9)	17.8 (13)	
Submicroscopic infection	31.0 (48)	39.0 (32)	21.9 (16)	
GMPD (/μL; 95% CI)	737 (282–1925)	2269 (591–8707)	338 (93–1230)	0.062
Birth weight (g) (n = 141)	2936 ± 453	2938 ± 422	2934 ± 491	0.715
Gestational age (weeks) (n = 141)	38.6 ± 2.7	38.4 ± 3.1	38.7 ± 2.0	0.802
Mother's age at delivery (years)	25.7 ± 6.0	25.6 ± 5.3	25.8 ± 6.8	0.845
Parity (number)	2 (1–4)	2 (1–4)	2 (1–4)	0.997
Residence (Agogo)	67.7 (105)	69.5 (57)	65.8 (48)	0.617
Mother's education				0.182
None	11.7 (18)	12.2 (10)	11.1 (8)	
Primary	77.3 (119)	72.0 (59)	83.3 (60)	
Secondary	9.7 (15)	13.4 (11)	5.6 (4)	
Other	1.3 (2)	2.4 (2)	0 (0)	
Mother's occupation				0.310
Farmer	23.2 (36)	29.3 (24)	16.4 (12)	
Trader	56.8 (88)	48.8 (40)	65.8 (48)	
Public servant	2.6 (4)	2.4 (2)	2.7 (2)	
Other	14.2 (22)	17.1 (14)	11.0 (8)	
Unemployed	3.2 (5)	2.4 (2)	4.2 (3)	
Follow-up after 15 years				
Age (years)	14.8 ± 0.2	14.8 ± 0.2	14.8 ± 0.2	0.557
Fasting plasma glucose (mmol/L)	4.2 ± 0.6	4.2 ± 0.6	4.2 ± 0.6	0.636
Body mass index (BMI) (kg/m^2)	19.5 ± 3.1	18.7 ± 2.1	20.3 ± 3.7	0.006
BMI-for-age z-score (BAZ)	−0.44 ± 1.12	−0.64 ± 1.05	−0.22 ± 1.17	0.042
Mean systolic BP (mmHg)	110 ± 11	112 ± 12	108 ± 10	0.054
Mean diastolic BP (mmHg)	68 ± 9	68 ± 10	67 ± 9	0.954
Residence (Agogo)	68.4 (106)	69.5 (57)	67.1 (49)	0.750
Literacy (able to read)	89.7 (139)	85.4 (70)	94.5 (69)	0.174
Number of people in the household	10 (7–17)	11 (8–17)	10 (7–20)	0.504

Note. Characteristics were compared between boys and girls by t-test for normally-distributed continuous variables (mean ± standard deviation), by Wilcoxon rank-sum test for non-normally distributed continuous variables [median (range)], and by χ^2-test for categorical variables [% (n)]. GMPD, geometric mean parasite density; BP, blood pressure.

Table 2 Associations of malaria in pregnancy at delivery with metabolic traits at adolescent age among 155 rural Ghanaians.

Metabolic trait	Mean ± SD				Adjusted mean difference (95% CI)			
	Uninfected	Infected	Microscopic	Submicroscopic	Uninfected vs. infected	Uninfected vs. microscopic	Uninfected vs. submicroscopic	Microscopic vs. submicroscopic
N	85	70	22	48				
FPG (mmol/L)	4.1 ± 0.6	4.3 ± 0.6*	4.3 ± 0.5	4.3 ± 0.7	0.20 (0.01, 0.39)*	0.16 (−0.13, 0.45)	0.21 (−0.01, 0.43)	0.07 (−0.25, 0.39)
BMI (kg/m^2)	19.8 ± 3.6	19.1 ± 2.3	19.1 ± 2.1	19.1 ± 2.4	−0.63 (−1.64, 0.38)	−0.59 (−2.08, 0.90)	−0.65 (−1.78, 0.48)	−0.07 (−1.30, 1.16)
Systolic BP (mmHg)	109 ± 11	111 ± 11	114 ± 10*	110 ± 12†	2.23 (−1.50, 5.97)	5.43 (0.00, 10.88)*	0.75 (−3.40, 4.91)	−5.12 (−10.71, 0.47)
Diastolic BP (mmHg)	66 ± 9	69 ± 10	70 ± 8	68 ± 11	2.10 (−0.95, 5.16)	3.67 (−0.81, 8.14)	1.38 (−2.03, 4.79)	−2.25 (−7.19, 2.69)

Note. Adjusted mean differences and 95% confidence intervals (CIs) were calculated by linear regression, adjusted for mother's age at delivery (years), parity and familial socio-economic status. FPG, fasting plasma glucose; BMI, body mass index; BP, blood pressure.
*$p \leq 0.05$ compared to uninfected; †, $p < 0.05$ compared to submicroscopic.

In utero exposure to malaria and metabolic traits

In Table 2, we present associations of previous exposure to MiP with teenage FPG, BMI, and systolic and diastolic BP. Mean FPG was higher in the adolescents of mothers showing MiP at delivery than in the offspring of back then uninfected mothers (ΔFPG: 0·2 mmol/L; p = 0·040). As a trend, this was also seen for teenage systolic and diastolic BP (Table 2). For systolic BP, the difference was more pronounced with respect to microscopic infections as compared to the descendants of uninfected mothers. No differences were observed for adolescent BMI (Table 2).

In the multiple-adjusted linear regression, exposure to MiP remained directly associated with the adolescents' FPG (adjusted ΔFPG: 0.20; p = 0.049). This association was virtually unchanged after adjusting for teenage BMI (adjusted ΔFPG: 0.18; 95% CI: −0·01, 0.38; p = 0.069) (Table 2). Also, we observed trends for positive associations of exposure to MiP with systolic and diastolic BP at teenage. Particularly, microscopic infection (vs. uninfected) significantly increased systolic BP by 5·4 mmHg (p = 0.050), and this association was independent of BMI at teenage (adjusted Δsystolic BP: 5.68; 95% CI: 0.25, 11.12; p = 0.041). The lack of association between MiP-exposure and BMI at teenage remained in the multiple-adjusted model (Table 2).

Birth outcome and metabolic traits

MiP at delivery did not confer significant effects on birth outcomes, also when stratifying the analysis for parity. Still, the proportion of PD was more than doubled in infants of infected mothers (Table 3). Nevertheless, we analyzed linear associations of birth weight and gestational age with metabolic traits in adolescence (Table 4). Pediatricians commonly use units of 200 g to describe physiologically meaningful differences in birth weight. In the present study of moderately underweight adolescents, teenage BMI decreased by 0.45 kg/m^2 per 200 g birth weight reduction. The mean diastolic BP among adolescents was rather high and increased by 0.62 mmHg per 1 gestational week reduction. Mother's age at delivery, parity and familial SES did not change the effects. Birth outcome neither influenced FPG nor systolic BP at teenage (Table 4). Still, we tested whether birth weight and gestational age were mediators of the observed associations of MiP at delivery with FPG and systolic BP in adolescence (Table 5). The sample size reduction (n = 141) and adjustments for birth weight and gestational age rendered the associations of MiP with teenage FPG and systolic BP non-significant; yet, the strengths of associations (adjusted mean difference) remained.

Discussion

In this rural Ghanaian birth cohort, we investigated MiP at delivery as a risk factor for metabolic traits among the teenage offspring. Indeed, MiP was common (45%) and was associated with an FPG increase of 0.2 mmol/L in the 15-years old offspring. Such a relationship was also seen for microscopic infection and adolescent systolic BP, and the findings were

Table 3 Birth outcome according to exposure to malarial infection at fetal age among 141 adolescents in rural Ghana.

Birth outcome	Uninfected	Infected	p	Microscopic infection	p	Submicroscopic infection	p
N	78	63		20		43	
Birth weight (g)	2895 (2630, 3280)	2937 (2823, 3052)	0.911	2900 (2525, 2940)	0.454	3000 (2660, 3230)	0.635
Low birth weight (<2500 g)	10.3 (8)	12.7 (8)	0.650	15.0 (3)	0.551	11.6 (5)	0.816
Birth weight (g) by parity							
1	2640 (2500, 2885)	2740 (2400, 2900)	0.987	2530 (2320, 2840)	0.303	2795 (2500, 3080)	0.451
2–3	2920 (2700, 3250)	3005 (2900, 3270)	0.360	2940 (2900, 3305)	0.336	3030 (2875, 3270)	0.513
>3	3150 (2820, 3420)	2915 (2785, 3475)	0.758	2930 (2820, 3300)	0.614	2900 (2750, 3500)	0.921
Gestational age (week)	38.4 (37.6, 40.3)	38.6 (38.0, 39.2)	0.858	39.2 (36.5, 40.3)	0.912	38.4 (37.6, 40.3)	0.789
Preterm delivery (<37 weeks)	11.5 (9)	29.6 (19)	0.140	25.0 (5)	0.134	18.6 (8)	0.288
Gestational age (week) by parity							
1	38.4 (37.3, 39.9)	38.4 (35.7, 40.3)	0.720	37.6 (35.0, 39.4)	0.867	38.4 (36.0, 40.3)	0.529
2–3	38.4 (37.6, 40.3)	39.0 (37.3, 40.3)	0.848	40.3 (38.0, 40.3)	0.539	38.2 (37.3, 40.3)	0.932
>3	39.0 (38.0, 40.3)	39.4 (38.4, 39.9)	0.731	39.4 (38.4, 39.4)	0.935	39.4 (38.4, 40.3)	0.715

Note. Data are presented as median (interquartile range) for continuous variables and as % (n) for categorical variables. None of the comparisons with the uninfected group were statistically significant ($p < 0.05$).

Table 4 Linear associations of birth outcome variables with metabolic traits at adolescent age among 141 rural Ghanaians.

Outcome	Birth weight (per 200 g)		Gestational age (per 1 week)	
	Adjusted mean difference (95% CI)	p-value	Adjusted mean difference (95% CI)	p-value
Fasting plasma glucose (mmol/L)				
Crude	−0.02 (−0.06, 0.03)	0.476	0.03 (−0.01, 0.06)	0.171
Adjusted	−0.01 (−0.06, 0.04)	0.727	0.03 (−0.01, 0.07)	0.193
Body mass index (kg/m^2)				
Crude	0.45 (0.22, 0.69)	0.0002	0.04 (−0.17, 0.24)	0.721
Adjusted	0.47 (0.21, 0.73)	0.0005	−0.09 (−0.30, 0.12)	0.411
Systolic blood pressure (mmHg)				
Crude	0.69 (−0.15, 1.54)	0.106	−0.23 (−0.93, 0.47)	0.522
Adjusted	0.64 (−0.32, 1.60)	0.188	−0.30 (−1.04, 0.44)	0.452
Diastolic blood pressure (mmHg)				
Crude	0.35 (−0.39, 1.08)	0.356	−0.62 (−1.23, −0.01)	0.045
Adjusted	0.31 (−0.52, 1.14)	0.459	−0.64 (−1.29, 0.02)	0.051

Note. Adjusted mean differences, 95% confidence intervals (CIs) and p-values were calculated by linear regression, adjusted for mother's age at delivery (years), parity and familial socio-economic status. Associations for fasting plasma glucose and blood pressure were additionally adjusted for teenage body mass index (kg/m^2).

largely independent of familial socio-economic status, adolescent BMI and former birth outcome.

Indirect effects of exposure to MiP on metabolic traits

Overall, MiP increases the risks of LBW and PD,[9,16] and as a trend, this was also seen in a sub-sample analyzed in the present study. At the same time, there is abundant evidence from developed countries that *in utero* conditions impact on the adult metabolic state *via* a U-shaped relationship of birth outcome measures with diabetes, obesity and hypertension in later life.[22] In the present group with a mean birth weight of <3000 g and low teenage BMI, higher birth weight increased adolescent BMI, possibly reflecting the bottom part of the right-hand side of this U-curve. In contrast, this cohort was characterized by a mean gestational age of 39 weeks and slightly elevated teenage BP. Thus, the increased diastolic BP by reduced gestational age may reflect the left-hand side of the U-curve.

Despite the lack of mediation by birth outcome for the observed associations of MiP with adolescent FPG and systolic BP, such indirect effects are conceivable. A recent review from low- and middle-income countries (Latin America and China) revealed strong associations of perinatal exposures to infections and malnutrition with adult diabetes.[23] With respect to malaria in childhood, one large, retrospective study among Costa Rican adults (age 60+ years) reported an associated increased risk of cardiovascular diseases, but not of diabetes.[24] Malaria in pregnancy impairs placental function due to the infiltration of the intervillous space by

Table 5 Associations of malaria in pregnancy at delivery with fasting plasma glucose and systolic blood pressure at adolescent age among 141 rural Ghanaians.

Outcome	Adjusted mean difference (95% CI)			
	Uninfected vs. infected	Uninfected vs. microscopic	Uninfected vs. submicroscopic	Microscopic vs. submicroscopic
Fasting plasma glucose (mmol/L)				
Crude	0.09 (–0.10, 0.29)	0.14 (–0.15, 0.43)	0.08 (–0.14, 0.30)	–0.06 (–0.37, 0.25)
Adjusted	0.10 (–0.10, 0.30)	0.14 (–0.16, 0.43)	0.09 (–0.14, 0.31)	–0.04 (–0.36, 0.27)
+ Birth weight (200 g)	0.10 (–0.10, 0.31)	0.14 (–0.16, 0.43)	0.09 (–0.14, 0.31)	–0.03 (–0.35, 0.29)
+ Gestational age (1 week)	0.09 (–0.11, 0.30)	0.13 (–0.16, 0.43)	0.08 (–0.15, 0.30)	–0.05 (–0.37, 0.27)
Systolic blood pressure (mmHg)				
Crude	1.69 (–19.7, 5.36)	5.01 (–0.39, 10.40)	0.15 (–3.93, 4.24)	–4.85 (–10.43, 0.72)
Adjusted	1.45 (–2.30, 5.21)	5.12 (–0.30, 10.54)	–0.28 (–4.44, 3.88)	–6.03 (–11.24, –0.82)
+ Birth weight (200 g)	1.24 (–2.53, 5.01)	5.06 (–0.36, 10.47)	–0.61 (–4.80, 3.58)	–6.47 (–11.63, –1.31)
+ Gestational age (1 week)	1.51 (–2.26, 5.28)	5.14 (–0.29, 10.58)	–0.22 (–4.40, 3.97)	–6.09 (–11.35, –0.82)

Note. Adjusted mean differences, 95% confidence intervals (CIs) and *p*-values were calculated by linear regression, adjusted for mother's age at delivery (years), parity, familial socio-economic status (principal component of maternal education, maternal occupation and number of people in the household), and teenage body mass index (kg/m^2).

pro-inflammatory cells and damage to the surface of fetal villi. Inflammation, subsequent placental structural alteration, and disturbed utero-placental blood flow eventually impair materno-fetal nutrient transfer (reviewed in [9]), leading to intrauterine growth retardation, reduced infant weight, and impaired development of major organs, including pancreas and skeletal muscle. In LBW children, β-cell mass is reduced and insulin-to-glucose ratio low, despite more efficient pro-hormone conversion compared to normal birth weight infants.[25] As for the skeletal muscle, structural and functional adaptations among LBW children have been suggested.[26] These comprise higher proportions of more glycolytic fibers,[27] impaired oxidative capacity and reduced amount of transport proteins for glucose uptake.[28] It appears logical that these young children are prone to insulin resistance and cardiovascular problems in adult life.

Direct effects of exposure to MiP on metabolic traits

To the best of our knowledge, we are the first to report that exposure to malarial infection during fetal development, i.e. MiP at delivery, can confer direct health risks at teenage. Exposure to malaria during pregnancy increased FPG and systolic BP at adolescent age, and this was barely mediated by teenage BMI and former birth outcome. In fact, prenatal infections are suggested to influence fetal body fat accumulation through alterations of the gut microbiome and of appetite signaling from the brain.[29] These processes may give rise to the deposition of visceral and abdominal fat with unfavorable consequences for the child's metabolism. Pregnant women show increased susceptibility to malarial infection,[30] and hypoglycemia frequently occurs under this condition not lastly because of the parasite's intense glucose consumption.[31] This, together with MiP-related reduced materno-fetal nutrient transfer,[9] may affect the fetal expression of glucose-transporters, appetite-regulating hormones and glucocorticoid-receptors leading to disturbances in peripheral glucose uptake, appetite control and vascular plasticity, respectively.[32,33] On the molecular level of the child, DNA methylation patterns of corresponding genes and other epigenetic mechanisms might be responsible for such programming effects.[34] Moreover, skeletal muscle damage of the fetus exposed to MiP and thus, loss of metabolic function is suggested to contribute to hyperglycemia and insulin resistance.[35] As a consequence of reduced muscle mass in previously MiP-exposed individuals, muscle strength might be also reduced,[36] promoting an inactive lifestyle, which is an established risk factor for diabetes, obesity and hypertension.[37] Not at last, MiP-exposure is associated with an increased risk of malaria during infancy,[38] which is partly attributed to familial socio-economic status.[39] Still, cumulative effects of early-life exposure to malaria on the metabolic health in adult age are conceivable.

Strengths and limitations

Long-term birth cohorts into adulthood are scarce for SSA. Thus, our findings contribute uniquely to respective knowledge. This cohort study from rural Ghana showed a direct link between MiP at delivery and metabolic health of the exposed offspring in later life. Still, 81% of the pregnant women who were recruited in the year 2000 could not present with their children for re-assessment in 2015. Despite similarities between the group lost to follow-up and the analytical sample, we cannot exclude that selection bias has distorted our findings in either direction. Still, in this small sample of 155 participants, physiologically meaningful differences were observed for teenage FPG and systolic BP with respect to *in utero* malaria exposure. The temporal sequence of exposure and outcome in the present study argues for a causal relationship. Yet, no data were available for the time period between delivery and adolescence, and cumulative effects cannot be investigated. While unmeasured confounding might have affected our results, we accounted for established demographic, socio-economic and anthropometric factors in our analyses. Malaria in pregnancy and metabolic state in adolescence were objectively

measured, strengthening the potential for their causal relationship.

Conclusions

From a public health perspective, malaria prevention appears even more important in the light of effects on metabolic health for the next generation. At the same time, these findings require verification in independent sub-Saharan African cohorts. Further investigations of the molecular mechanisms including epigenetic processes are warranted.

Conflict of interest

The authors declare to have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jinf.2017.08.010.

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