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A Bayesian framework for estimating a latent placental malaria recency signal from delivery histology and its association with birthweight: A retrospective analysis in western Kenya

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Tables 1 to 3 are available in the Supplementary Files section.

A Bayesian framework for estimating a latent placental malaria recency signal from delivery histology and its association with birthweight: A retrospective analysis in western Kenya

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Abstract

Background: Placental malaria causes poor pregnancy outcomes, such as low birth weight. Histology at delivery can identify broad placental infection states, but does not differentiate the week of gestation at which the infection occurred. This study aimed to assess whether the delivery histology could serve as a model-based latent signal of recency and whether this recency signal was related to birthweight.

Methods: All 174 pregnancies with evaluable placental histology from a biobank in Bungoma County, western Kenya (54 without previous or current placental malaria, 28 with past, and 92 with active Placental malaria) were included in this retrospective secondary analysis. An ordered three-class histology outcome was related to a latent gestational recency process via a hierarchical Bayesian model, fitted in R with Stan, with birthweight as a covariate. For the 120 pregnancies with active or past placental malaria, a recency summary was reported. Birth weight was adjusted for maternal age, primigravidity, and intermittent preventive treatment in pregnancy. Four chains were run each for 4,000 iterations, 2,000 of which were warm-up iterations.

Results: The average birth weight of the 174 evaluable pregnancies was 3,086 g (SD 571). The mean of the pregnancy-specific posterior median recency values was 32.3 weeks (SD 1.9, range 24.8-39.2) for active placental malaria cases and 23.0 weeks (SD 1.8, range 15.2-25.9) for past placental malaria cases. The first and second-trimester-centred birthweight coefficients were -62.6 g (95% credible interval -293.3 to 170.5) and 4.0 g (-235.8 to 232.9). The third-trimester-centred coefficient was -264.8 g (-485.5 to -47.8). The largest R-hat was 1.013, and the smallest bulk effective sample size was 432.6.

Conclusions: Delivery histology provides minimal information on relative placental malaria recency or persistence, but not the observed date of infection. The late-gestation coefficient was linked to lower birth weight in this model with latent processes, but the estimate is subject to the

assumptions of the latent processes model and should not be interpreted as a causal trimester-specific effect. The framework needs to be tested by prospective longitudinal studies where malaria is measured at multiple time points, treatment records are maintained, and fetal growth is assessed.

Keywords: placental malaria; birthweight; Bayesian inference; latent recency; placental histology; pregnancy; Kenya

Background

Pregnancy-associated malaria remains a significant health problem for pregnant women and fetuses in endemic areas. The events of placental malaria involve sequestration of P. falciparum-infected erythrocytes in the intervillous space of the placenta via VAR2CSA and chondroitin sulfate A binding. This can lead to an inflammatory response, which may impair placental perfusion and fetal exchange, and may play a role in maternal anaemia, foetal growth restriction, preterm birth, and low birth weight (1–4). Fetal nutrient and oxygen demands rise with advancing gestation, and there are structural and functional changes in the placenta during gestation (5–8). The effects of a placental infection can therefore be different depending on the nature of the infection – whether it's new, ongoing, recurring or cleared up. But the time of the infection during the fetus/embryo stage cannot be seen directly during histology at delivery. It can differentiate between past and active placental malaria, where haemozoin pigment is found in the absence of infected erythrocytes (2,9). The absence of parasites and malaria pigment can be considered a histologically uninfected type.

The categories only give coarse information about relative recency or persistence. They are unable to date the infection to a specific gestational week, differentiate between primary infection, reinfection or long-term sequestration or reconstruct the treatment or parasite clearance history. It is important, therefore, that the latent quantity studied in this investigation be recognized from the beginning as a model-based evaluation of recency, rather than the actual date of infection.

Usually, an infection time would have to be directly observed or fixed to include birthweight in a conventional regression. Both requirements were not fulfilled. Because no information is available on the recency process, it was chosen to be treated as unobserved, in addition to imposing explicit monotonic structure linking elapsed time to histological class, and propagating uncertainty in the recency process to the birthweight coefficients as opposed to considering an estimated time as

known without error (10). The goal was not to determine a causal trimester-specific critical window but to evaluate an analytical framework designed to determine a critical window.

Methods

Study design, setting and data source

This was a retrospective secondary analysis of placental histopathology and linked maternal, obstetric, and neonatal data from a previously described placental biobank in Bungoma County, western Kenya (11). Placental specimens were collected at delivery and processed using standard histopathological procedures in the parent study. The present analysis used archived histology classifications and de-identified linked clinical variables. Reporting was guided by the STROBE recommendations (12). The raw file contained 186 pregnancies. Twelve records were excluded because formalin-fixed paraffin-embedded placental material was absent, and histology could not be evaluated. All remaining 174 eligible records were included in the dataset. Because the study used all eligible archived samples rather than recruiting a prospectively defined cohort, no prospective sample-size calculation was undertaken.

Histological classification

Placental histology was represented by three ordered categories using established pathological criteria (2,9). Active placental malaria was defined by infected erythrocytes in the intervillous space at delivery. Past placental malaria was defined by haemozoin pigment in fibrin or intervillous macrophages without detectable infected erythrocytes. No placental malaria was assigned when neither infected erythrocytes nor malaria pigment was detected. The model-ready dataset contained 92 active, 28 past, and 54 no-placental-malaria records.

Bayesian modelling framework

A hierarchical model with three linked elements: a pregnancy-specific latent gestational recency process, an ordered histology component with two class thresholds, and a Gaussian birthweight component was developed. The model contained latent timing, elapsed-time, and three trimester-burden parameters for each of the 174 evaluable pregnancies. Joint estimation allowed uncertainty in the latent process to pass into the birthweight coefficients.

For pregnancy i, the model-derived gestational timing and elapsed interval were represented as:

$$u_i \sim \text{Uniform}(0,1),\ \tau_i = \text{GA}_i u_i,\ d_i = \text{GA}_i - \tau_i$$

Where:

u_i = latent position of the dominant infection signal expressed as a proportion of gestational age, with values between 0 and 1.

GA_i = gestational age at delivery for pregnancy i, measured in weeks.

τ_i = model-derived gestational timing of the dominant infection signal for pregnancy i, measured in weeks.

d_i = elapsed interval between the dominant infection signal and delivery for pregnancy i, measured in weeks; smaller values indicate a signal closer to delivery.

i = index for pregnancy.

Birthweight outcome model

Birthweight was represented using a Gaussian likelihood:

$$BW_{\mathrm{i}} \sim Normal(\mu_{\mathrm{i}}, \sigma BW)$$

$$\mu_i = \beta_0 + \beta_{GA}(\mathrm{GA}_i - 40) + \beta_{age}(\mathrm{Age}_i - \bar{\mathrm{Age}}) + \beta_{prim}\mathrm{Prim}_i + \beta_{IPTp}\mathrm{IPTp}_i + \sum_{k=1}^{3} \gamma_k B_{ik}$$

Where: BW_i = observed birthweight for pregnancy i, measured in grams.

μ_i = expected birthweight for pregnancy i, conditional on the model covariates and latent-recency basis functions.

σ_{BW} = residual standard deviation of the Gaussian birthweight model, measured in grams.

Normal = Gaussian probability distribution

μ_i = expected birthweight for pregnancy i.

β_0 = birthweight intercept at the reference covariate values.

βGA = coefficient for gestational age at delivery, with GA_i centred at 40 weeks.

GA_i = gestational age at delivery for pregnancy i, measured in weeks.

βage = coefficient for maternal age.

Age_i = maternal age for pregnancy i, measured in years.

$\bar{Age}$ = mean maternal age in the primary analytic sample, used for centring.

$\beta prim$ = coefficient for primigravidity.

$Prim_i$ = primigravidity indicator for pregnancy i, coded 1 for a first pregnancy and 0 otherwise.

$\beta IPTp$ = coefficient for receipt of intermittent preventive treatment in pregnancy.

$IPTp_i$ = indicator of recorded IPTp receipt for pregnancy i.

γ_k = coefficient for the trimester-centred latent-recency basis function k.

B_{ik} = value of the trimester-centred Gaussian basis function k for pregnancy i.

k = basis-function index, k = 1, 2, 3, corresponding to the first, second, and third-trimester centres.

The trimester-centred basis functions were:

$$B_{ik} = \exp[-\frac{(\tau_i - c_k)^2}{2s^2}]$$

Where:

B_{ik} = trimester-centred Gaussian basis-function value for pregnancy i and basis k.
τ_i = model-derived gestational timing of the dominant infection signal for pregnancy i.
c_k = centre of basis function k; 7, 20.5, and 34 weeks for k = 1, 2, and 3, respectively.
s = basis-function spread parameter, fixed at 6 weeks.
exp = exponential function.
i = index for pregnancy.
k = index for the trimester-centred basis function.

Table 1 shows the prior distribution of the parameter used in the model.

Model identifiability and interpretation

The latent timing parameter was not identified by a direct antenatal measurement. The posterior distribution was generated by the gestational prior and the monotonic posterior relation of elapsed time and ordered histological class. Since no observations of density were made in the model-ready parasite-density field, density did not provide any timing information. As a result, the numerical values are subject to the assumptions of the model, and should be read as only relative positions on a continuum of recency or persistence. They are unable to determine the week of infection, to make an estimate of the incidence at each trimester and to differentiate between newly acquired infection and persistent or recurrent infection.

The implementation and evaluation of the model.

The model was implemented in R (13) through cmdstanr as an interface to Stan (14). There were 4 Markov chains, each with 4,000 draws, 2,000 of which were warm-up draws, for a total of 8,000 post-warm-up draws. Rank-normalized R-hat, bulk effective sample size, and visual sampling diagnostics (15,16) were used for assessing convergence. There were a total of 1,057 parameters exported, with a maximum R-hat of 1.013 and a minimum bulk effective sample size of 432.6. The vast majority of parameters were near 1.00; one parameter was greater than the recommended R-hat value of 1.01, as shown in Figure 1. There was no apparent major sampling failure.

The probability integral transform, histogram and posterior predictive comparison of observed and replicated birth weight densities were used as predictive assessment measures, as shown in Figure 2 and Figure 3, respectively. The values of the probability integral transform were used in the Kolmogorov-Smirnov test and resulted in $p = 0.6172$. It was a description calibration check and not a specification correct proof. The biological interpretation of the latent process of recency is not checked by the computational diagnostics and posterior prediction.

Model assumptions

1. one dominant latent infection signal per pregnancy;
2. latent timing restricted to the pregnancy with a Uniform(0,1) prior;
3. Active-PM probability decreases monotonically with time since infection;
4. parasite burden is assumed to decrease with increasing elapsed time;
5. inferred timing is a model-dependent relative recency signal, not an observed infection date.

Results

Study population

The analysis included 174 pregnancies with evaluable placental histology: 54 (31.0%) had no placental malaria, 28 (16.1%) had past placental malaria, and 92 (52.9%) had active placental malaria. Mean birthweight was 3,086 g (SD 571), mean maternal age among 173 recorded values was 25.2 years (SD 5.4), and mean gestational age among 166 recorded values was 38.6 weeks (SD 1.8). Fifty pregnancies (28.7%) were primigravid, and 154 (88.5%) had recorded IPTp use as shown in Table 2. Maternal age was available for 173 pregnancies and gestational age for 166 pregnancies. Active-PM, active placental malaria; Past-PM, past placental malaria; IPTp, intermittent preventive treatment in pregnancy.

Model-derived recency among infected pregnancies

The mean of the pregnancy-specific posterior median recency values for active placental malaria was: 32.3 weeks (SD 1.9, range 24.8-39.2). There were 92 active cases, of which 89 (96.7%) were in the third trimester, and three (3.3%) were in the second trimester. The mean for those with past placental malaria was 23.0 weeks (SD 1.8; range 15.2-25.9), and all 28 posterior medians were in the second trimester as shown in Figure 4. Values are summarizations of the pregnancy-specific posterior medians, and the reported ranges are observed ranges of those summarizations and not credible intervals for the group. Many of the distinctions between active and past placental malaria

are provided by the ordered histological classification and the presumed monotonic association with elapsed time. The contrast thus illustrated is a form of internal consistency with the model assumptions and not independent evidence of gestational week.

Sensitivity analysis

A sensitivity analysis was conducted to determine if the error due to missing GA information affected the birthweight estimates by trimester. The primary complete-case analysis included only the 113 pregnancies making up the Active-PM/Past-PM group with observed gestational age, but the seven missing gestational age values were substituted with 39 and the sensitivity analysis included all 120 pregnancies in the infected group. The posterior mean estimates of the first, second, and third-trimester centered coefficients were similar both in sign and value for both approaches, with large overlap of the corresponding 95% credible intervals as illustrated in Figure 6. Both approaches resulted in a third-trimester-centered coefficient that stayed negative, reflecting the direction of the late-gestation association. The strength of evidence varied, however, depending on the way the fetuses were handled at different gestational ages, with the complete-case analysis giving a more conservative estimate. These results suggest that the overall shape of the trimester-centered associations was not substantially affected by the choice of modeling for the missing gestational age, although there was sensitivity to this modeling choice for the statistical certainty of the late-gestation estimate.

Association between latent recency and birthweight

The coefficient for the first-trimester version was -62.6 g (-293.3 to 170.5), and the second-trimester version was 4.0 g (-235.8 to 232.9), after adjustments were made for primigravidity and maternal age and for IPTp use. The third-trimester-centred coefficient was -264.8g, with a 95% credible interval of -485.5 to -47.8, which did not include zero as shown in Figure 5. The other factor associated with lower birthweight was primigravidity, which had a posterior mean of -205.6 g (-335.6, -68.7). Zero was included in the intervals of maternal age and IPTp use. Third-trimester-centred estimate suggested that birthweight in the fitted model was lower for pregnancies with a latent pattern most similar to those that happened in the previous few months of pregnancy around the time of delivery. The coefficient should not be interpreted as evidence that an infection occurring during the third trimester would result in a 264.8 g reduction or that late pregnancy is a distinct critical window in which pregnancy infection can cause a 264.8 g reduction. Table 3

represents the Posterior birthweight coefficients from the R and Stan models, and negative coefficients indicate lower expected birthweight. The trimester terms are overlapping latent-recency basis functions, not observed treatment effects at fixed gestational times.

Discussion

This proof-of-concept analysis assessed delivery histology to characterize a latent placental malaria recency signal, and its uncertainty was propagated in the birth-weight model. The active placental malaria was scored with later recency patterns than past placental malaria, while the latent coefficient based on the third trimester was linked with reduced birth weight. The main methodological contribution is that an unobserved infection date was not considered as a known exposure in the analysis. There is no single trimester found to be damaging in all cases in longitudinal studies. Low birth weight risk was found to be higher with an increasing number of malaria episodes and greater for infections detected in the second trimester compared to the third trimester or delivery in Malawi (17). A cohort study in Benin showed that malaria infection detected earlier in pregnancy was associated with reduced birthweight, with infections occurring during the first trimester showing important effects on fetal growth (18). Similarly, a study in Burkina Faso showed that malaria infection during pregnancy was associated with adverse birth outcomes, with infections occurring earlier in gestation, particularly during the first trimester, being associated with an increased risk of low birth weight (19). These studies were conducted prospectively, whereas the present analysis has used a latent recency signal based on histology at delivery. The trimester-specific results reported in these studies are therefore not directly comparable with the trimester-centred coefficients reported in the present analysis. This is consistent with an equivocal ‘active-placental-malaria' signal. A late model-derived value could be due to a recent infection, an early infection that was maintained at low density, a more recent exposure, prolonged placental sequestration, or a mix of these events. This late-recency association is biologically plausible because, during this time of rapid fetal growth and increasing placental demand, placental sequestration and inflammation could interfere with maternal to fetal exchange (1,2,5,8). However, the coefficient is not capable of separating out the duration of the exposure, the intensity of the exposure, whether it was treated or not, or whether it was detected at delivery or not. The presence of active placental malaria indicates that the infection is still visible in the placenta at the time of birth and infections that have previously been resolved may be described as past placental malaria or may not be visible. The clustering of active-malaria recency estimates

around time of delivery is thus not indicative of a high proportion of infections occurring in the final trimester.

There are a number of strengths in the study. It leveraged all available samples from a characterized biobank, employed standard histological categories, assumed a three-class outcome for histology as an ordered categorical variable, and propagated uncertainty of the latent process to the birthweight coefficients. It also provided convergence and posterior predictive diagnostics. Summary of recency information was limited to histologically infected pregnancies, and the no-placental-malaria group included in the fitted model provided information on the ordered histology thresholds. The restrictions are significant. It was not possible to directly observe infection timing or to seek external confirmation of it. The latent process was not explicitly modeled to include reinfection, treatment, partial clearance, persistent sequestration, or hemozoin persistence, but rather it represented a single dominant infection signal. Although the parasite burden data were available as a separate raw data field, no values were entered in the model-ready parasite-density variable, and the recency process was not informed by parasite burden. The sample is from one setting, residual confounding is possible, and IPTp receipt is not a complete measure of malaria prevention/treatment history. The results of these studies do not warrant any changes in trimester-specific prevention or treatment guidelines. Validation should be done in a prospective study of women at the beginning of pregnancy, with repeated microscopy or molecular malaria testing, complete treatment and IPTp documentation, serial fetal-growth monitoring, and Placental histology at the time of delivery. These data would enable direct comparison of observed infection histories and model-generated recency, a framework for assessing recurrent-infection structures, sensitivity analysis for prior assumptions and external validation of birthweight predictions.

Conclusion

Placental histology at delivery contains coarse information about the relative recency or persistence of placental malaria, but it cannot reveal an observed infection date. Active placental malaria was assigned later latent recency patterns than past placental malaria, and a third-trimester-centred latent signal was associated with lower birthweight. These estimates are conditional on the model structure and should not be interpreted as proof of a causal critical window. Prospective longitudinal studies with repeated parasitological measurements, treatment histories, and fetal-growth assessment are required to validate the framework and determine whether trimester-specific inference is clinically meaningful.

List of abbreviations

Active-PM, active placental malaria; CrI, credible interval; ESS, effective sample size; FFPE, formalin-fixed paraffin-embedded; GA, gestational age; IPTp, intermittent preventive treatment in pregnancy; MCMC, Markov chain Monte Carlo; No-PM, no placental malaria; Past-PM, past placental malaria; PIT, probability integral transform; PM, placental malaria; R-hat, potential scale reduction factor; SD, standard deviation; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

Declarations

Ethics approval and consent to participate

The present study was a secondary analysis of de-identified data and archived placental histology from the parent biobank study (11). Ethical approval and written informed consent for specimen collection, storage, and secondary use of linked data were obtained in the parent study. No additional participant contact or specimen collection occurred for this analysis.

Consent for publication

Not applicable.

Availability of data and materials

The de-identified data and model summaries used in this analysis are available from the corresponding author on reasonable request, subject to the governance requirements and ethical conditions of the parent biobank.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

PMM, BNK, and JG conceived the study and developed the analytical framework. PMM, RW, PO, and WK performed the formal analysis and interpreted the results. PO, BNK, and JG provided methodological oversight and refined the modelling approach. PMM drafted the manuscript. FMK and BNK critically reviewed the manuscript. All authors read and approved the final manuscript.

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Not applicable.

Authors' information

Not applicable.

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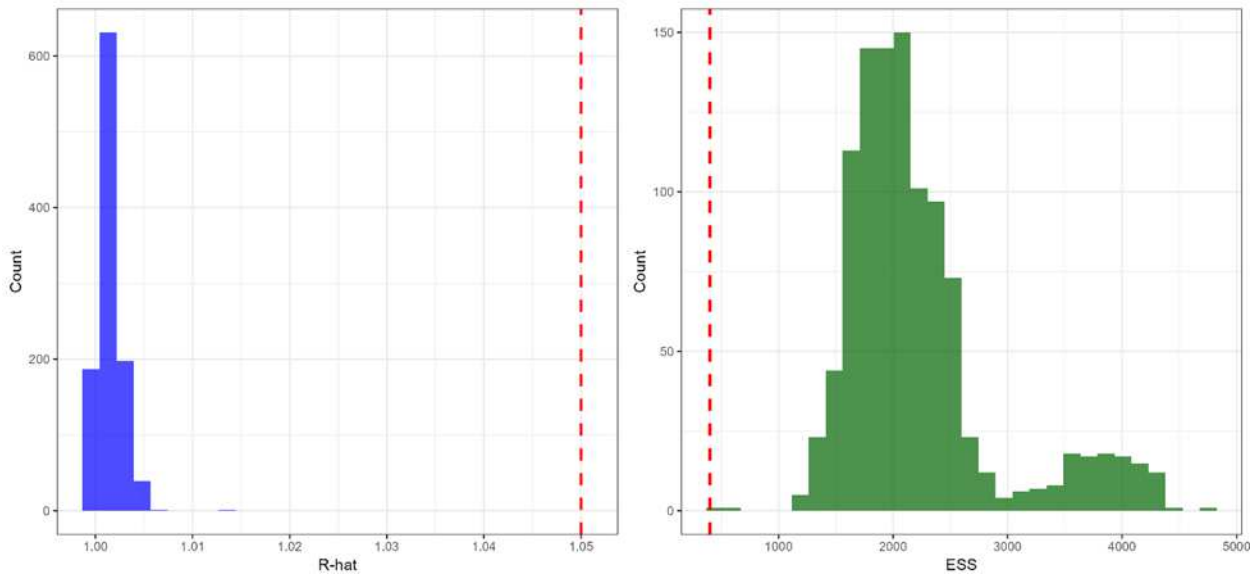


Figure 1. Convergence diagnostics for the Bayesian model. Panel A shows the distribution of rank-normalised. The vast majority of parameters were near 1.00; one parameter was greater than the recommended R-hat value of 1.01. Panel B shows the distribution of bulk effective sample sizes with a dashed line at 400 minimum threshold.

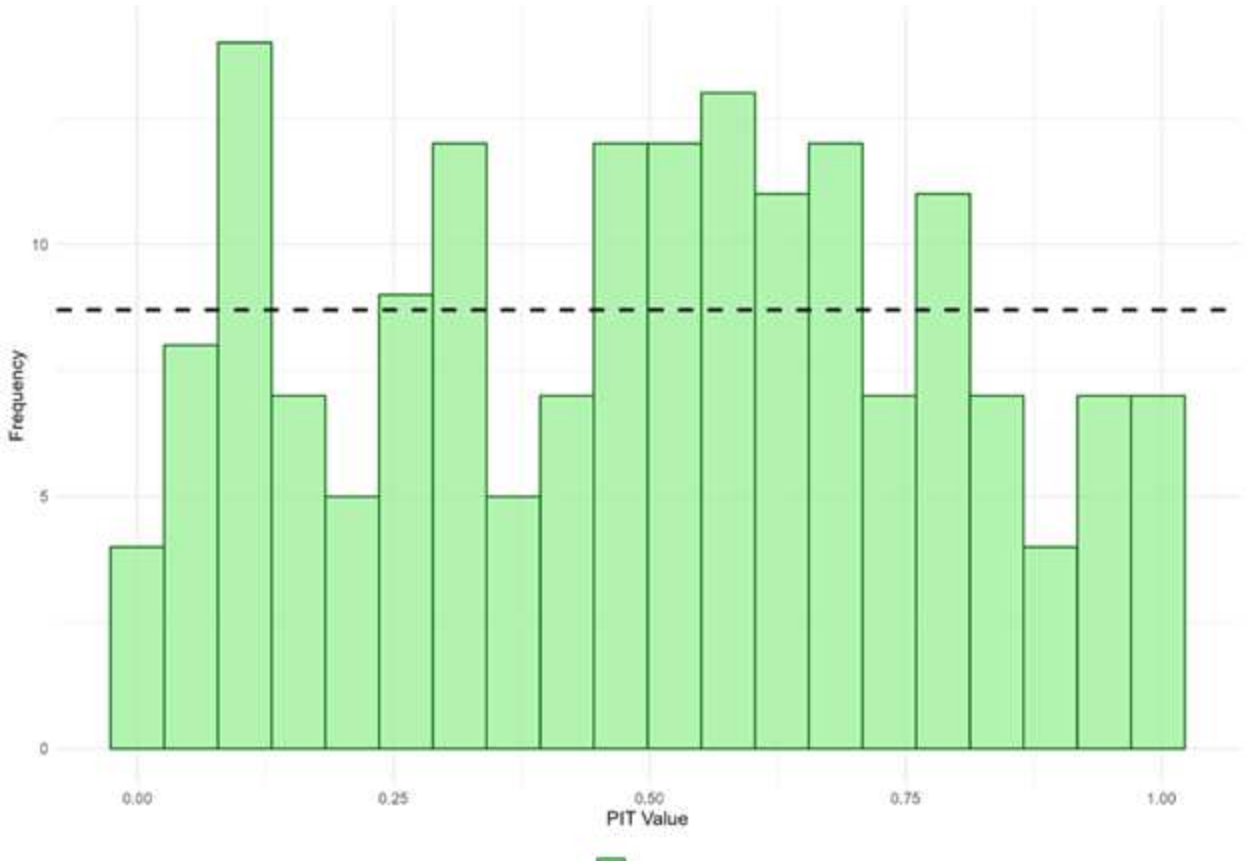


Figure 2. Probability integral transform histogram used as a descriptive calibration check. The dashed horizontal line represents the expected count per bin under approximate uniformity. The Kolmogorov-Smirnov test gave $p = 0.6172$.

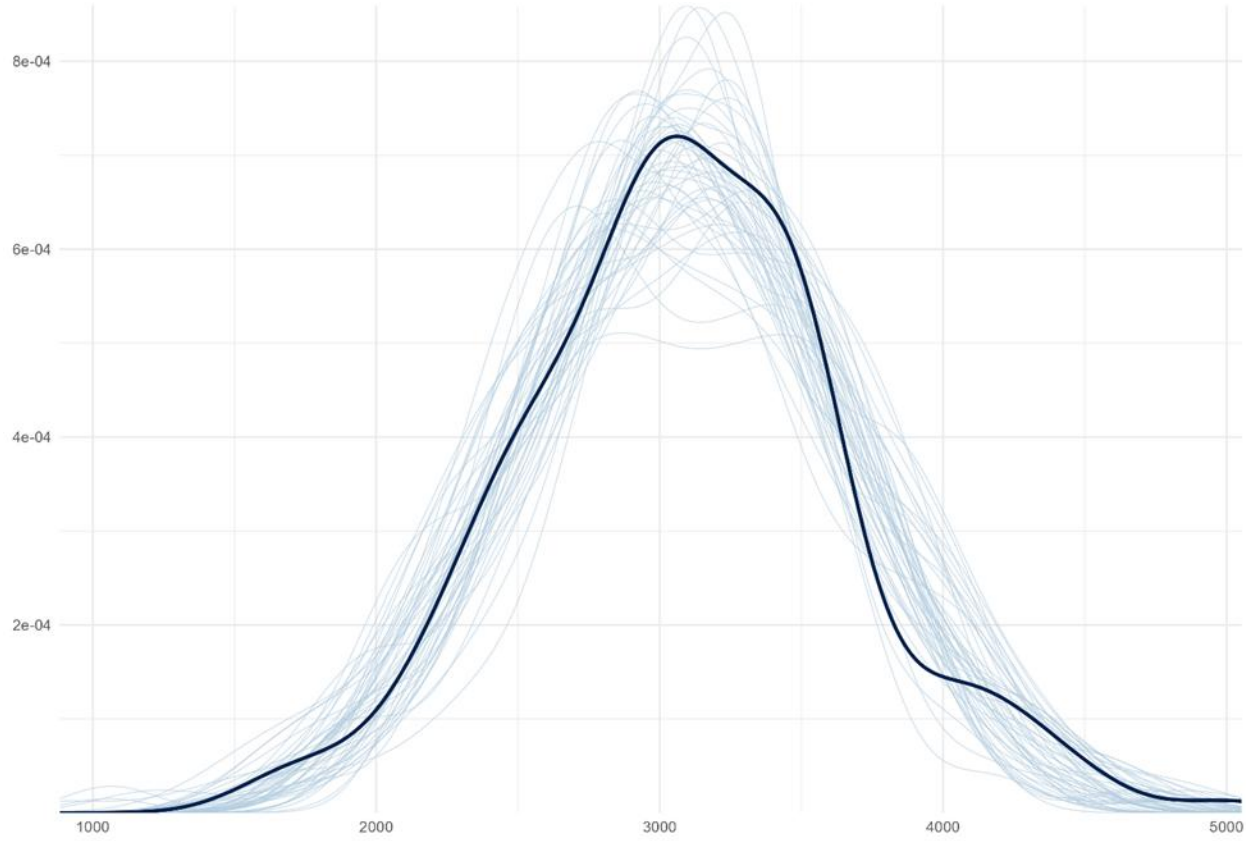


Figure 3. Posterior predictive check for birthweight density. The dark curve represents the observed birthweight density, and the lighter curves represent densities from posterior predictive replicates.

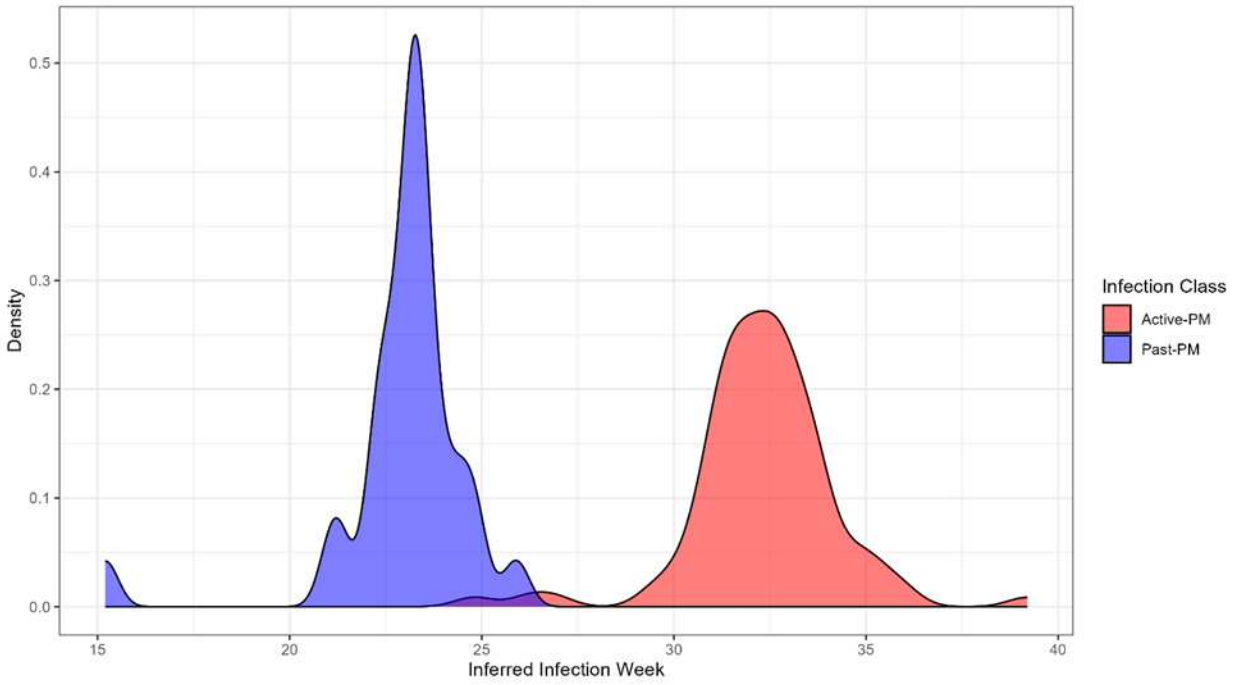


Figure 4. Distribution of pregnancy-specific posterior median recency values among active and past placental malaria cases. These values are conditional on the ordered histology model and should not be interpreted as observed infection dates.

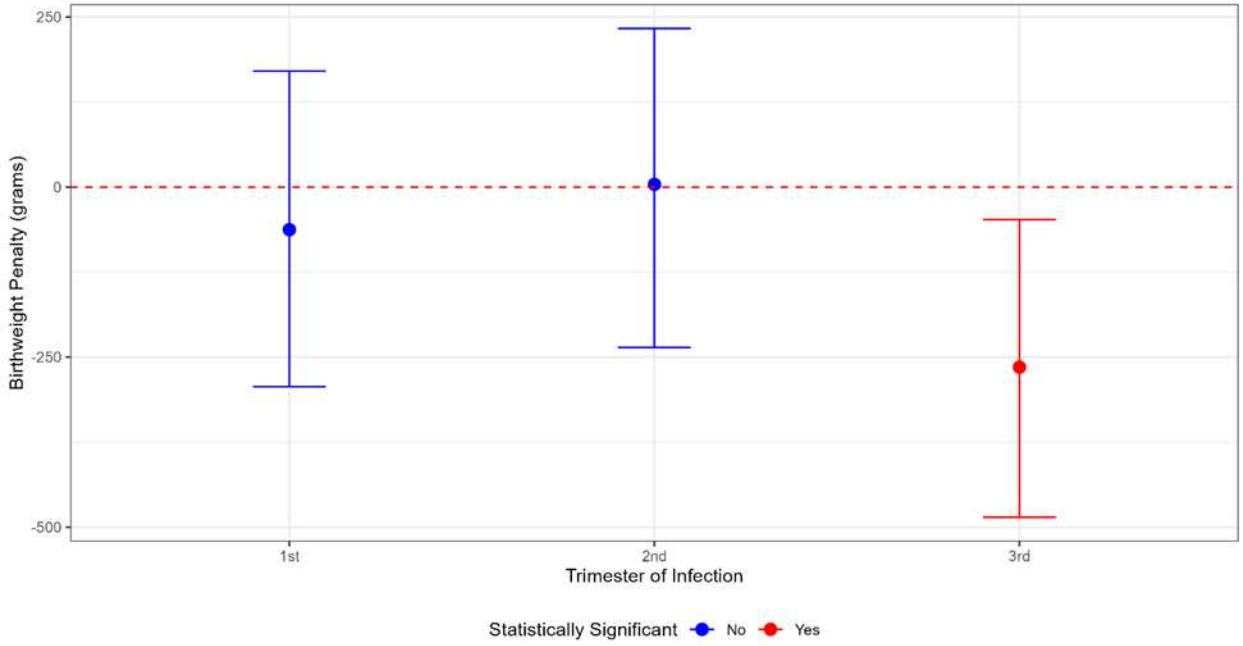


Figure 5. Posterior means and 95% credible intervals for the trimester-centred birthweight coefficients, adjusted for maternal age, primigravidity, and IPTp use. The third-trimester-centred interval excludes zero; this is a model-based association rather than evidence of a causal critical window.

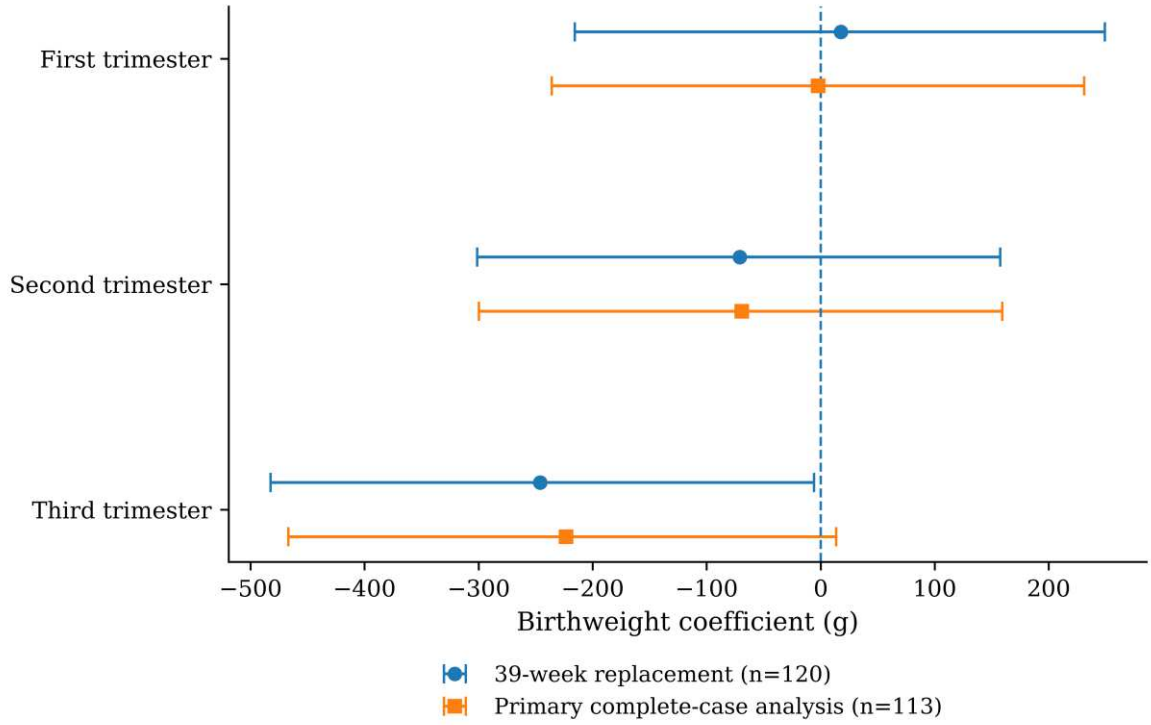


Figure 6. Sensitivity of trimester-centred birthweight coefficients to gestational-age handling. The 39-week replacement analysis includes all 120 Active-PM/Past-PM pregnancies; the primary complete-case analysis includes 113 pregnancies with observed gestational age. Points show posterior means and horizontal bars show 95% credible intervals.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TABLES.docx