Supplementary Appendix

Supplement to: Roh et al, Dihydroartemisinin-piperaquine versus sulfadoxine-pyrimethamine for intermittent preventive treatment of malaria in pregnancy: a systematic review and individual participant data meta-analysis

Table of Contents

Appendix 1. PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Paper title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	N/A
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Paragraphs 2-3
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Paragraph 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	"Search strategy and selection criteria" section
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	"Data extraction and quality assessment" section
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	"Study endpoints" section; Appendices 2-4
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Appendices 2-4
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	"Data extraction and quality assessment" section; Appendix 5

Section and Topic	Item #	Checklist item	Location where item is reported
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	"Statistical analysis" section
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	N/A
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	"Statistical analysis" section
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	"Statistical analysis" section
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	"Statistical analysis" section
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	"Statistical analysis" section; Appendix 4
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	"Description of studies" section; Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	"Description of studies" section
Study characteristics	17	Cite each included study and present its characteristics.	"Description of studies" section; Appendix 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	"Description of studies" section
Results of	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b)	Figures 2-6; Results

Section and Topic	Item #	Checklist item	Location where item is reported
individual studies		an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	section
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	"Description of studies" section
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	All pooled estimates are presented with 95% CIs and I^2 statistic for in Results section + Figures 2-6
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	95% CIs are presented with all outcomes
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Paragraph 1-3
	23b	Discuss any limitations of the evidence included in the review.	Paragraph 4
	23c	Discuss any limitations of the review processes used.	Paragraph 4
	23d	Discuss implications of the results for practice, policy, and future research.	Paragraph 5
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	"Data extraction and quality assessment" section of Methods
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Summary, "Role of funding source" section of Methods, "Acknowledgement"

Section and Topic	Item #	Checklist item	Location where item is reported
			section
Competing interests	26	Declare any competing interests of review authors.	"Declaration of interests" section
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	"Data sharing statement" section

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Appendix 2. Description of study characteristics and outcomes for each study

Study Information	Desai 2015[1]	Kakuru 2016[2]	Kajubi 2019[3]	Mlugu 2021[4]	Madanitsa 2023[5] studies	Gutman unpublished[6]
Study Details						
Source	PMID: 26429700	PMID: 26962728	PMID: 30910321	PMID: 33891721	PMID: 36913959	ClinicalTrials.Gov: NCT03009526
Study site(s)	4 health facilities in Siaya County, Kenya	Tororo District Hospital in Tororo District, E. Uganda	Masafu General Hospital in Busia District, E. Uganda	Kibiti District Center in Kibiti District, SE. Tanzania	12 ANC clinics in W. Kenya (n=4) S. Malawi (n=5), NE Tanzania (n=3)	Machinga District Hospital in Liwonde, S. Malawi
Prevalence of PfDHPS 540E mutation, %*	96%	85%	98%	90%	Kenya: 65%; Malawi: 90%; Tanzania: 52%	99%
Prevalence of PfDHPS 581G mutation, %*	6%	0%	3%	1%	Kenya: 11%; Malawi: 8%; Tanzania: 40%	8%
Number of Participants Randomized (Among Singleton Pregnancies)	1012	194	769	956	Kenya: 992; Malawi: 938; Tanzania: 1192	593
Sulfadoxine-Pyrimethamine	508	104	381	478	Kenya: 495; Malawi: 469; Tanzania: 597	297
Dihydroartemisinin-Piperaquine	504	90	388	478	Kenya: 497; Malawi: 469; Tanzania: 595	296
IPTp dosing regimen	every ANC	every 8 weeks	every 4 weeks	every 4 weeks	every 4 weeks	every 4 weeks
Number of IPTp doses, median (IQR)	2 (2-3)	3 (3-3)	6 (5-6)	3 (2-4)	Kenya: 4 (4-5); Malawi: 4 (4-5); Tanzania: 5 (4-6)	4 (3-5)

Study Information	Desai 2015[1]	Kakuru 2016[2]	Kajubi 2019[3]	Mlugu 2021[4]	Madanitsa 2023[5] studies	Gutman unpublished[6]
PCR positivity at enrolment, %	32%	58%	81%	14%	Kenya: 15%; Malawi: 11%; Tanzania: 18%	11%
Birth outcomes						
Foetal Loss	Available	Available	Available	Available	Available	Available
Small-for-Gestational Age	Available†	Available	Available	Available†	Available	Available
Preterm Delivery	Available†	Available	Available	Available†	Available	Available
Low Birthweight	Available	Available	Available	Available	Available	Available
Neonatal Death	Available	Available	Available	Available (no cases)	Available	Available
Continuous Birth Outcomes						
Mean Birthweight	Available	Available	Available	Available	Available	Available
Mean Gestational Age at Delivery	Available†	Available	Available	Available†	Available	Available
Mean Birthweight-for-Gestational Age Z-scores	Available†	Available	Available	Available†	Available	Available
Malaria Outcomes						
Incidence of Clinical Malaria Episodes in Pregnancy	Available	Available	Available	Available	Available	Available
Any Evidence of Pigment Only in Placental Tissue by Histopathology	Available	Available	Available	Available	Available	Available

Study Information	Desai 2015[1]	Kakuru 2016[2]	Kajubi 2019[3]	Mlugu 2021[4]	Madanitsa 2023[5] studies	Gutman unpublished[6]
Any Evidence of Parasites in Placental Tissue or Blood by Histopathology, PCR, Microscopy, or RDT	Available	Available; RDT not done on placental blood	Available; RDT not done on placental blood	Available; RDT not done on placental blood	Available	Available
Any Evidence of Parasites or Pigment in Placental Tissue or Blood by Histopathology, PCR, Microscopy, or RDT	Available	Available; RDT not done on placental blood	Available; RDT not done on placental blood	Available; RDT not done on placental blood	Available	Available
Any Evidence of Parasites in Maternal Peripheral Blood at Delivery by RDT, Microscopy, or PCR	Available	Available; RDT not done on maternal blood	Available; RDT and PCR not done on maternal blood	Available	Available	Available; PCR not done on maternal blood
Maternal Outcomes						
Any Evidence of Severe Anaemia (Hb <7 g/dl) During Pregnancy	Available; Assessed at routine visits	Available; Assessed at routine visits	Available; Assessed at routine visits	Available; Assessed at routine visits	Available; Assessed at routine visits	Not Available; Measured at Delivery Only
Any Evidence of Moderate Anaemia (Hb <9 g/dl) During Pregnancy	Available; Assessed at routine visits	Available; Assessed at routine visits	Available; Assessed at routine visits	Available; Assessed at routine visits	Available; Assessed at routine visits	Not Available; Measured at Delivery Only
Any Evidence of Mild Anaemia (Hb <11 g/dl) During Pregnancy	Available; Assessed at routine visits	Available; Assessed at routine visits	Available; Assessed at routine visits	Available; Assessed at routine visits	Available; Assessed at routine visits	Not Available; Measured at Delivery Only
MUAC at Delivery	Available; but unadjusted estimates b/c enrolment data was unavailable	Not available	Not available	Not available	Available	Available
Maternal weight gain per week‡	Available	Available	Available	Available	Available	Available

Study Information	Desai 2015[1]	Kakuru 2016[2]	Kajubi 2019[3]	Mlugu 2021[4]	Madanitsa 2023[5] studies	Gutman unpublished[6]
Infant Outcomes						
Any Evidence of Stunting (LAZ <2 SD) from Birth to 2 Months of Life	Available; Follow up data up to 6-8 weeks	Available; Follow-up data up to 8 weeks	Available; Follow-up data up to 8 weeks	Not available	Available; Follow up data up to 6-8 weeks	Available; Follow up data up to10 weeks
Any Evidence of Underweight (WAZ <2 SD) from Birth to 2 Months of Life	Available; Follow up data up to 6-8 weeks	Available; Follow-up data up to 8 weeks	Available; Follow-up data up to 8 weeks	Not available	Available; Follow up data up to 6-8 weeks	Available; Follow up data up to10 weeks
Any Evidence of Wasting (WLZ <2 SD) from Birth to 2 Months of Life	Available; Follow up data up to 6-8 weeks	Available; Follow-up data up to 8 weeks	Available; Follow-up data up to 8 weeks	Not available	Available; Follow up data up to 6-8 weeks	Available; Follow up data up to10 weeks
Mean LAZ at 2 Months of Life	Available; Follow up data up to 6-8 weeks	Available; Follow-up data up to 8 weeks	Available; Follow-up data up to 8 weeks	Not available	Available; Follow up data up to 6-8 weeks	Available; Follow up data up to10 weeks
Mean WAZ at 2 Months of Life	Available; Follow up data up to 6-8 weeks	Available; Follow-up data up to 8 weeks	Available; Follow-up data up to 8 weeks	Not available	Available; Follow up data up to 6-8 weeks	Available; Follow up data up to10 weeks
Mean WLZ at 2 Months of Life	Available; Follow up data up to 6-8 weeks	Available; Follow-up data up to 8 weeks	Available; Follow-up data up to 8 weeks	Not available	Available; Follow up data up to 6-8 weeks	Available; Follow up data up to10 weeks

Abbreviations: ANC = antenatal care visit; Hb = haemoglobin; IQR = interquartile range; LAZ = length-for-age z-score; MUAC = mid-upper arm circumference; WAZ = weight-for-age z-score; WLZ = weight-for-length z-score

* Prevalence of polymorphisms were reported as part of the published findings of the trial, except for the Kakuru et al (2016) and Kajubi et al (2019) studies which were reported separately in Conrad et al (2017)[7] NS Nayebare et al (2020)[8], respectively. Data were not available from Gutman et al (unpublished) and we therefore used estimates from a separate study (Gutman et al (2015)[9]) which was conducted at the same site eight years earlier.

† Gestational age dating not confirmed by ultrasound

‡ Maternal weight gain per week calculated using the following formula: $\frac{Weight_{last\ ANC\ visit\ before\ delivery} - Weight_{enrollment}}{\#\ of\ weeks\ between\ enrollment\ and\ last\ ANC\ v\square\square sit}$

Appendix 3. Definition of outcomes

Outcome	Description
Birth outcomes	
Any Adverse Pregnancy Outcome	Binary variable defined as a composite outcome of any one of the following conditions: miscarriage (stillbirth (foetal loss ≥28 gestational weeks), preterm birth (PTB; delivery <37 gestational weeks), small-for-gestational age (SGA; birthweight <10th percentile for gestational age using the INTERGROWTH-21st standard[10]); low birthweight (LBW; birthweight <2,500 grams), and neonatal loss (newborn death within the first 28 days of life).
Foetal Loss	Binary variable defined as a composite outcome of miscarriage or abortion that occurred at less than 28 gestational weeks
Small-for-Gestational Age	Binary variable defined as birthweight below the 10th percentile for a given gestational age and sex using the INTERGROWTH-21st standard[10]
Preterm Delivery	Binary variable defined as delivery occurring less than 37 gestational weeks among live births
Low Birthweight	Binary variable defined as newborn birthweight that was less than 2500 grams. Birthweights were assessed among live births. Corrected birthweights were used when available.
Neonatal Death	Defined as a binary variable indicating the death of live newborn within the first 28 days of life
Continuous Birth Outcomes	
Birthweight	Continuous measure of newborn birthweight in grams. Birthweights were assessed among live births. Corrected birthweights were used when available.
Gestational Age at Birth	Continuous measure of duration of gestation in weeks. Gestational age at birth was estimated using the gestational age at enrolment assessed by ultrasound, except for Desai 2015 and Mlugu 2021. Desai 2015 used the Ballard score, while Mlugu 2021 used last menstrual period to estimate gestational age at delivery.
Birthweight-for-Gestational Age Z-scores	Continuous measure of birthweight-for-gestational age z-scores. Z-scores were calculated based on INTERGROWTH-21st standards[10]
Malaria outcomes	
Incidence of Clinical Malaria Episodes in Pregnancy	Count outcome defined as the number of symptomatic malaria episodes experienced during the pregnancy follow-up period. Clinical malaria was defined as presence of documented fever (≥37·5°C or defined by study-specific definitions) or recent history of fever in the last 48 hours (or as defined by study-specific definitions) and a positive diagnosis of malaria by either rapid diagnostic test or blood smear microscopy.
Any Evidence of Pigment Only in Placental Tissue by Histopathology	Binary variable defined as the presence of pigment (but not parasites) in the placental tissue assessed by histopathology. For this outcome, active and chronic placental infections as defined by Rogerson et al[11] were excluded from the analysis.

Any Evidence of Parasites in Placental Tissue or Blood by Histopathology, PCR, Microscopy, or RDT	Binary variable defined as the presence of parasites in the placental tissue or blood assessed by histopathology, PCR, microscopy, or RDT. For this outcome, samples containing pigment with no indication of parasites in the placental tissue or blood were considered in the "No" category.
Any Evidence of Parasites or Pigment in Placental Tissue or Blood by Histopathology, PCR, Microscopy, or RDT	Binary variable defined as the presence of parasites or pigment in the placental tissue or blood assessed by histopathology, PCR, microscopy, or RDT. For this outcome, samples containing pigment with no indication of parasites in the placental tissue or blood were considered in the "Yes" category.
Any Evidence of Parasites in Maternal Peripheral Blood at Delivery by RDT, Microscopy, or PCR	Binary variable defined as the presence of parasites detected in maternal peripheral blood at delivery by PCR, microscopy, or RDT.
Maternal outcomes	
Any Evidence of Severe Anaemia (Hb <7 g/dl) During Pregnancy	Binary variable defined as the incidence of a severe anaemic episode detected during routine and/or unscheduled visits during pregnancy follow-up period. Severe anaemia was defined as a haemoglobin measurement that fell below 7 g/dL.
Any Evidence of Moderate Anaemia (Hb <9 g/dl) During Pregnancy	Binary variable defined as the incidence of a moderate anaemic episode detected during routine and/or unscheduled visits during pregnancy follow-up period. Moderate anaemia was defined as a haemoglobin measurement that fell below 9 g/dL.
Any Evidence of Mild Anaemia (Hb <11 g/dl) During Pregnancy	Binary variable defined as the incidence of a moderate anaemic episode detected during routine and/or unscheduled visits during pregnancy follow-up period. Moderate anaemia was defined as a haemoglobin measurement that fell below 11 g/dL.
MUAC at Delivery	Continuous measure of maternal mid-upper arm circumference measured at delivery.
Maternal weight gain per week‡	Continuous variable defined as the average weight gained per week from enrolment to last day of antenatal care visit before delivery. The following formula was used to define this outcome: $\frac{Weight_{last\ ANC\ visit\ before\ delivery} - Weight_{enrollment}}{\#\ of\ weeks\ between\ enrollment\ and\ last\ ANC\ visit}$
Infant Outcomes	
Any Evidence of Stunting (LAZ <2 SD) from Birth to 2 Months of Life	Binary variable defined as a length-for-age z-score that fell below two standard deviations below the median 2006 WHO Child Growth Standards[12] at birth and at routine scheduled neonatal care visits up to approximately two months of life. Infant follow-up periods varied between studies: six-eight weeks in the Desai 2015 and Madanitsa 2023 studies, eight weeks in the Kakuru 2016 and Kajubi 2019 studies, and ten weeks in the Gutman unpublished study.
Any Evidence of Underweight (WAZ <2 SD) from Birth to 2 Months of Life	Binary variable defined as a weight-for-age z-score that fell below two standard deviations below the median 2006 WHO Child Growth Standards[12] at birth and at routine scheduled neonatal care visits up to approximately two months of life. Infant follow-up

	periods varied between studies: six-eight weeks in the Desai 2015 and Madanitsa 2023 studies, eight weeks in the Kakuru 2016 and Kajubi 2019 studies, and ten weeks in the Gutman unpublished study.
Any Evidence of Wasting (WLZ <2 SD) from Birth to 2 Months of Life	Binary variable defined as a weight-for-length z-score that fell below two standard deviations below the median 2006 WHO Child Growth Standards[12] at birth and at routine scheduled neonatal care visits up to approximately two months of life. Infant follow-up periods varied between studies: six-eight weeks in the Desai 2015 and Madanitsa 2023 studies, eight weeks in the Kakuru 2016 and Kajubi 2019 studies, and ten weeks in the Gutman unpublished study.
LAZ at 2 Months of Life	Continuous variable defined as a length-for-age z-score based on 2006 WHO Child Growth Standards.[12]
WAZ at 2 Months of Life	Continuous variable defined as a weight-for-age z-score based on 2006 WHO Child Growth Standards.[12]
WLZ at 2 Months of Life	Continuous variable defined as a weight-for-length z-score based on 2006 WHO Child Growth Standards.[12]

Appendix 4. Details of causal mediation analyses methods

Causal mediation analyses were performed to quantify the contributions of placental malaria, gestational weight gain (GWG), and maternal mid-upper arm circumference (MUAC) on the differential impact of IPTp regimens on birthweight-for-gestational age z-scores.

Brief summary of causal mediation analysis. Mediation analyses were conducted following the "potential outcomes" framework as described by Rubin[13] and Pearl[14,15] and extended for mediation analyses by Imai.[16] Under this framework, potential outcomes are defined for each individual based on their counterfactual treatment condition. Let A, Y, and W denote the treatment, outcome, and confounder for each individual *i*. In the scenario where treatment is binary, an individual would have two potential outcomes: one had they been treated ($Y_i(a=1)$) and another if they had not been treated ($Y_i(a=0)$). The causal effect of the treatment on the outcome for individual *i* is defined as $Y_i(a=1) - Y_i(a=0)$ and $E[Y_i(a=1) - Y_i(a=0)]$ is defined as the average causal effect.

For mediation analyses, this framework is extended to further decompose the above causal effect (also known as the "total effect") into effects that are mediated and not mediated through some intermediate variable of interest, M. This requires the specification four potential outcomes for each individual:

$$Y_i(a=0, M_i(a=0)) \qquad Y_i(a=0, M_i(a=1))$$
$$Y_i(a=1, M_i(a=0)) \qquad Y_i(a=1, M_i(a=1))$$

where $Y_i(a, M_i(a))$ represents the outcome value for individual *i* had treatment been set to some value *a* and the mediator value was set to the value it would have taken on under *a*. For example, $Y_i(a=1, M_i(a=1))$ represents the outcome value for individual *i* had they been treated and their mediator value takes on what it would have "naturally" taken on had the individual been treated. By estimating potential mediator values, $M_i(a=0)$ and $M_i(a=1)$, we can separately estimate the **natural indirect effect (NIE)**, where NIE = $Y_i(a, M_i(a=1)) - Y_i(a, M_i(a=0))$ and is defined as the effect of the treatment on the outcome that is mediated through M (i.e., mediated effect). The **natural direct effect (NDE)** is defined as the effect of the treatment on the outcome via pathways not through mediator M (i.e., non-mediated effect), where NDE = $Y_i(a=1, M_i(a)) - Y_i(a=0, M_i(a))$.

Of these four potential outcomes, two can never be observed under real world conditions (i.e., $Y_i(a=1, M_i(a=0))$ and $Y_i(a=0, M_i(a=1))$) and depending the individual's actual treatment value, either one of the two remaining potential outcome values are actually observed ($Y_i(a=1, M_i(a=1))$ or $Y_i(a=0, M_i(a=0))$). However, these values are needed to derive NIE AND NDE; therefore, unobserved values must be estimated from data.

Required assumptions. To interpret NIE and NDE estimates causally, several assumptions need to be met[17], including:

- No unmeasured confounding between treatment-outcome, treatment-mediator, and mediator-outcome
- Treatment and mediator positivity
- Well-defined treatment and mediator
- Mediator and outcome values are unaffected by another individual's treatment and mediator condition
- No presence of a mediator-outcome confounder that is itself affected by the treatment

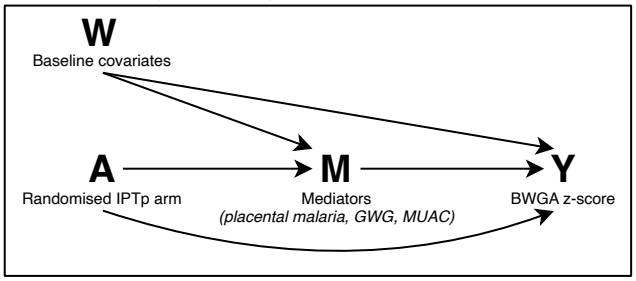
Targeted Maximum Likelihood Estimation Approach to Causal Mediation Analysis. We used the semi-parametric, doubly robust targeted maximum likelihood estimation (TMLE) approach to estimate NIE and

NDE. TMLE offers advantages over traditional parametric approaches by imposing fewer assumptions about the underlying data generating process. It does so by allowing data-adaptive, ensemble machine-learning approaches (e.g., SuperLearner via the sl3 package[18]) to flexibility accommodate interactions and non-linear relationships between variables, thereby reducing the risk of model misspecification.

A detailed description of the TMLE approach is provided in Zheng and van Der Laan (2012).[19] In brief, the observed data is used to generate an initial outcome model estimating the expected outcome conditional on treatment, mediator, and confounders (i.e., $Q[Y|A, M, W]$). The initial outcome estimates are then updated using "clever covariates" derived from two propensity score models: one estimating the conditional probability given confounders ($g(A|W)$) and one estimating the conditional probability of treatment given mediator and confounders ($g(A|M, W)$). This process, known as the "targeting step" of TMLE, is performed to ensure that the final estimates optimize the bias-variance trade-off, thereby enhancing the precision, efficiency, and robustness of causal effect estimates. Finally, this updated estimate is used to generate updated estimates of the four potential outcomes and NIE and NDE are calculated as the mean difference across these potential outcomes (using prior formulas).

Mediation analysis methods. The directed acyclic graph (DAG) on the right was used to represent our assumptions of the causal relationships between treatment mediator, outcome, and confounders. Mediators were analyses separately to prevent overly complex models given our small sample size and to reduce the risk of violating the treatment and mediator positivity assumption.

Directed Acyclic Graph



The `medoutcon` package in R[20] was used to estimate NIE, NDE, and the corresponding 95% confidence intervals. Definitions of the treatment, mediator, outcome, and confounders used in the analyses are provided in the table below. The algorithm library for the initial outcome model included elastic net regularization, lasso (L-1 penalized) regression, generalized linear regression, generalized additive models, and extreme gradient boosting. The algorithm library for propensity score models included simple intercept models, generalized additive models, and gradient boosted decision tree models. 10-fold cross-validation was used all applications. Observations with missing values were excluded from the analysis.

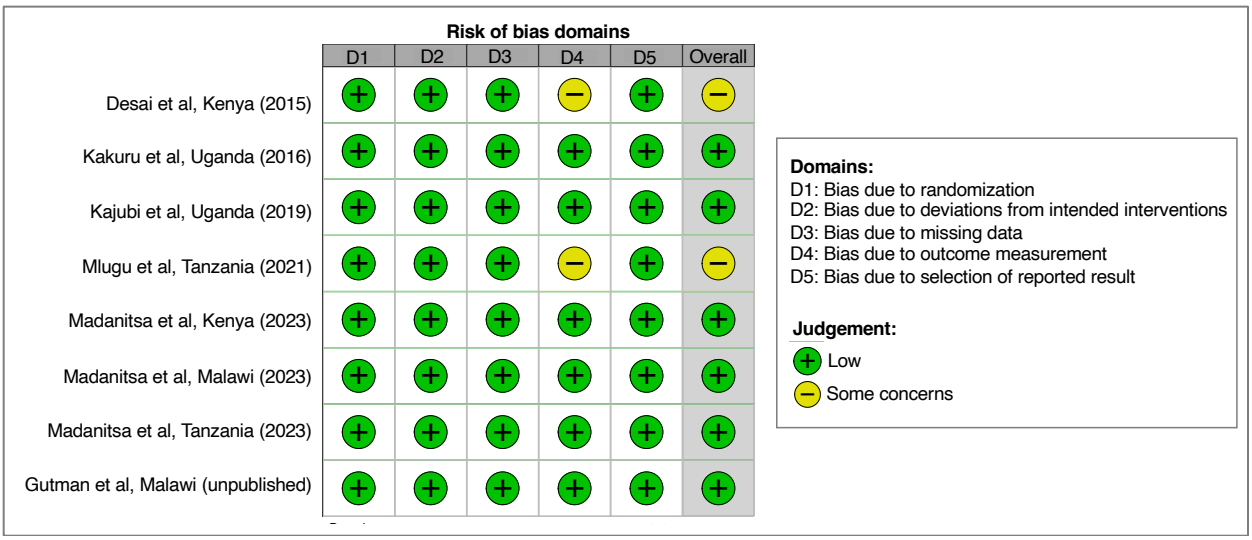
Variable definitions

Variable	Description
Treatment (A)	Randomized assignment to IPTp with sulfadoxine-pyrimethamine (A=1) or dihydroartemisinin-piperaquine (A=0)
Mediators (M)	• **Placental malaria**, defined as any evidence of pigment or parasites in the placental tissue or blood detected by histopathology, RDT, microscopy, and/or PCR • **Gestational weight gain**, defined as mean weight gain per week from enrolment to last antenatal care visit before delivery • **Maternal mid-upper arm circumference** in cm measured at delivery
Outcome (Y)	Birthweight-for-gestational age z-score using INTERGROWTH-21st birthweight standards
Confounders (W) *measured at enrolment*	Maternal age, BMI, weight, and gestational age; highest schooling level completed by mother (none, primary, secondary, or higher); and infant sex

Appendix 5. Bias assessment using the Cochrane Risk of Bias Tool 2.0

Summary. The Cochrane risk of bias tool for randomized trials (RoB 2.0) was applied to each study. As the primary outcome of the individual trials often differed from the primary outcome of our meta-analysis and varied between studies, we conducted the risk of bias assessment based on the primary outcome of the meta-analysis. Overall, six of the eight trials were considered to have a low risk of bias; two studies (Desai et al, 2015 and Mlugu et al, 2021) had some concerns regarding the primary outcome because gestational age dating was not confirmed by ultrasound. This may have resulted in misclassification of small-for-gestational age and preterm birth, both of which are included as components in the composite primary outcome. Detailed visualizations from the RoB 2.0 assessment are provided below. Plots were generated using the `robvis` package in R.[21]

Risk of bias traffic light plot



Risk of bias summary plot

Appendix 6. Participant characteristics at enrolment by arm

Table S-1. Desai et al, Kenya (2015)

Enrolment characteristics	Total N=1,012	IPTp-SP N=508	IPTp-DP N=504
Maternal age in years, mean (SD)	23·4 (5·7)	23·5 (5·9)	23·4 (5·5)
Gestational age in weeks, mean (SD)	22·9 (4·8)	22·8 (4·9)	23·0 (4·8)
Gravidity categories, n/N (%)			
Primigravidae	336/1012 (33%)	178/508 (35%)	158/504 (31%)
Secundigravidae	215/1012 (21%)	112/508 (22%)	103/504 (20%)
Multigravidae (3+)	461/1012 (46%)	218/508 (43%)	243/504 (48%)
Weight in kg, mean (SD)	61·6 (9·2)	61·5 (9·1)	61·7 (9·4)
Height in cm, mean (SD)	164·3 (6·8)	164·3 (6·9)	164·3 (6·7)
Maternal MUAC in cm, mean (SD)	--	--	--
Highest level of schooling completed, n/N (%)			
None	229/1004 (23%)	114/505 (23%)	115/499 (23%)
Primary	569/1004 (57%)	283/505 (56%)	286/499 (57%)
Secondary	183/1004 (18%)	96/505 (19%)	87/499 (17%)
Higher	23/1004 (2%)	12/505 (2%)	11/499 (2%)
Wealth index tertiles, n/N (%)			
Lowest tertile	328/1006 (33%)	172/505 (34%)	156/501 (31%)
Middle tertile	331/1006 (33%)	164/505 (32%)	167/501 (33%)
Highest tertile	347/1006 (34%)	169/505 (33%)	178/501 (36%)
Slept under a bed net last night, n/N (%)	725/1012 (72%)	364/508 (72%)	361/504 (72%)
Microscopy positivity, n/N (%)	154/984 (16%)	79/499 (16%)	75/485 (15%)
PCR/LAMP positivity, n/N (%)	322/1002 (32%)	167/504 (33%)	155/498 (31%)

Abbreviations: LAMP = loop-mediated isothermal amplification method MUAC = mid-upper arm circumference; PCR = polymerase chain reaction

Table S-2. Kakuru et al, Uganda (2016)

Enrolment characteristics	Total	IPTp-SP	IPTp-DP
	N=194	N=104	N=90
Maternal age in years, mean (SD)	21·7 (4·0)	21·3 (3·6)	22·2 (4·3)
Gestational age in weeks, mean (SD)	15·3 (2·0)	15·2 (2·0)	15·4 (2·0)
Gravidity categories, n/N (%)			
Primigravidae	73/194 (38%)	42/104 (40%)	31/90 (34%)
Secundigravidae	58/194 (30%)	30/104 (29%)	28/90 (31%)
Multigravidae (3+)	63/194 (32%)	32/104 (31%)	31/90 (34%)
Weight in kg, mean (SD)	55·6 (6·9)	55·5 (6·8)	55·7 (7·1)
Height in cm, mean (SD)	162·7 (6·8)	162·8 (6·8)	162·5 (6·9)
Maternal MUAC in cm, mean (SD)	--	--	--
Highest level of schooling completed, n/N (%)			
None	9/194 (5%)	6/104 (6%)	3/90 (3%)
Primary	143/194 (74%)	74/104 (71%)	69/90 (77%)
Secondary	39/194 (20%)	22/104 (21%)	17/90 (19%)
Higher	3/194 (2%)	2/104 (2%)	1/90 (1%)
Wealth index tertiles, n/N (%)			
Lowest tertile	67/194 (35%)	38/104 (37%)	29/90 (32%)
Middle tertile	66/194 (34%)	31/104 (30%)	35/90 (39%)
Highest tertile	61/194 (31%)	35/104 (34%)	26/90 (29%)
Slept under a bed net last night, n/N (%)	174/194 (90%)	91/104 (88%)	83/90 (92%)
Microscopy positivity, n/N (%)	--	--	--
PCR/LAMP positivity, n/N (%)	111/193 (58%)	58/104 (56%)	53/89 (60%)

Abbreviations: LAMP = loop-mediated isothermal amplification method MUAC = mid-upper arm circumference; PCR = polymerase chain reaction

Table S-3. Kajubi et al, Uganda (2019)

Enrolment characteristics	Total	IPTp-SP	IPTp-DP
	N=769	N=381	N=388
Maternal age in years, mean (SD)	23·7 (5·8)	23·8 (5·9)	23·7 (5·6)
Gestational age in weeks, mean (SD)	15·5 (2·4)	15·5 (2·4)	15·4 (2·3)
Gravidity categories, n/N (%)			
Primigravidae	193/769 (25%)	100/381 (26%)	93/388 (24%)
Secundigravidae	187/769 (24%)	83/381 (22%)	104/388 (27%)
Multigravidae (3+)	389/769 (51%)	198/381 (52%)	191/388 (49%)
Weight in kg, mean (SD)	55·9 (7·6)	56·1 (7·7)	55·6 (7·6)
Height in cm, mean (SD)	158·6 (6·0)	158·8 (6·2)	158·4 (5·9)
Maternal MUAC in cm, mean (SD)			
Highest level of schooling completed, n/N (%)			
None	63/769 (8%)	37/381 (10%)	26/388 (7%)
Primary	512/769 (67%)	248/381 (65%)	264/388 (68%)
Secondary	175/769 (23%)	89/381 (23%)	86/388 (22%)
Higher	19/769 (2%)	7/381 (2%)	12/388 (3%)
Wealth index tertiles, n/N (%)			
Lowest tertile	251/740 (34%)	122/366 (33%)	129/374 (34%)
Middle tertile	248/740 (34%)	116/366 (32%)	132/374 (35%)
Highest tertile	241/740 (33%)	128/366 (35%)	113/374 (30%)
Slept under a bed net last night, n/N (%)	242/740 (33%)	122/366 (33%)	120/374 (32%)
Microscopy positivity, n/N (%)	394/769 (51%)	192/381 (50%)	202/388 (52%)
PCR/LAMP positivity, n/N (%)	622/769 (81%)	313/381 (82%)	309/388 (80%)

Abbreviations: LAMP = loop-mediated isothermal amplification method MUAC = mid-upper arm circumference; PCR = polymerase chain reaction

Table S-4. Mlugu et al, Tanzania (2021)

Enrolment characteristics	Total	IPTp-SP	IPTp-DP
	N=956	N=478	N=478
Maternal age in years, mean (SD)	26·6 (7·1)	26·5 (7·1)	26·6 (7·1)
Gestational age in weeks, mean (SD)	21·5 (3·4)	21·4 (3·5)	21·7 (3·3)
Gravidity categories, n/N (%)			
Primigravidae	243/956 (25%)	128/478 (27%)	115/478 (24%)
Secundigravidae	213/956 (22%)	105/478 (22%)	108/478 (23%)
Multigravidae (3+)	500/956 (52%)	245/478 (51%)	255/478 (53%)
Weight in kg, mean (SD)	55·2 (8·9)	54·8 (8·5)	55·6 (9·3)
Height in cm, mean (SD)	152·2 (3·1)	152·1 (3·1)	152·4 (3·0)
Maternal MUAC in cm, mean (SD)	--	--	--
Highest level of schooling completed, n/N (%)			
None	183/956 (19%)	94/478 (20%)	89/478 (19%)
Primary	657/956 (69%)	336/478 (70%)	321/478 (67%)
Secondary	116/956 (12%)	48/478 (10%)	68/478 (14%)
Higher	0/956 (0%)	0/478 (0%)	0/478 (0%)
Wealth index tertiles, n/N (%)			
Lowest tertile	251/740 (34%)	122/366 (33%)	129/374 (34%)
Middle tertile	248/740 (34%)	116/366 (32%)	132/374 (35%)
Highest tertile	241/740 (33%)	128/366 (35%)	113/374 (30%)
Slept under a bed net last night, n/N (%)	695/956 (73%)	345/478 (72%)	350/478 (73%)
Microscopy positivity, n/N (%)	--	--	--
PCR/LAMP positivity, n/N (%)	136/956 (14%)	63/478 (13%)	73/478 (15%)

Abbreviations: LAMP = loop-mediated isothermal amplification method MUAC = mid-upper arm circumference; PCR = polymerase chain reaction

Table S-5. Madanitsa et al, Kenya (2023)

Enrolment characteristics	Total	IPTp-SP	IPTp-DP
	N=992	N=495	N=497
Maternal age in years, mean (SD)	23·8 (5·3)	23·8 (5·4)	23·8 (5·3)
Gestational age in weeks, mean (SD)	21·5 (3·6)	21·8 (3·7)	21·3 (3·4)
Gravidity categories, n/N (%)			
Primigravidae	355/992 (36%)	178/495 (36%)	177/497 (36%)
Secundigravidae	268/992 (27%)	131/495 (26%)	137/497 (28%)
Multigravidae (3+)	369/992 (37%)	186/495 (38%)	183/497 (37%)
Weight in kg, mean (SD)	65·1 (11·2)	66·1 (11·1)	64·1 (11·2)
Height in cm, mean (SD)	162·7 (6·8)	163·4 (6·7)	162·0 (6·9)
Maternal MUAC in cm, mean (SD)	27·0 (3·2)	27·2 (3·3)	26·8 (3·2)
Highest level of schooling completed, n/N (%)			
None	57/992 (6%)	28/495 (6%)	29/497 (6%)
Primary	454/992 (46%)	218/495 (44%)	236/497 (47%)
Secondary	334/992 (34%)	170/495 (34%)	164/497 (33%)
Higher	147/992 (15%)	79/495 (16%)	68/497 (14%)
Wealth index tertiles, n/N (%)			
Lowest tertile	46/992 (5%)	17/495 (3%)	29/497 (6%)
Middle tertile	473/992 (48%)	242/495 (49%)	231/497 (46%)
Highest tertile	473/992 (48%)	236/495 (48%)	237/497 (48%)
Slept under a bed net last night, n/N (%)	895/900 (99%)	440/445 (99%)	455/455 (100%)
Microscopy positivity, n/N (%)	127/981 (13%)	61/490 (12%)	66/491 (13%)
PCR/LAMP positivity, n/N (%)	127/865 (15%)	61/434 (14%)	66/431 (15%)

Abbreviations: LAMP = loop-mediated isothermal amplification method MUAC = mid-upper arm circumference; PCR = polymerase chain reaction

Table S-6. Madanitsa et al, Malawi (2023)

Enrolment characteristics	Total	IPTp-SP	IPTp-DP
	N=938	N=469	N=469
Maternal age in years, mean (SD)	24·5 (5·9)	24·3 (5·9)	24·7 (5·9)
Gestational age in weeks, mean (SD)	21·3 (3·1)	21·2 (3·1)	21·3 (3·1)
Gravidity categories, n/N (%)			
Primigravidae	287/936 (31%)	151/469 (32%)	136/467 (29%)
Secundigravidae	238/936 (25%)	112/469 (24%)	126/467 (27%)
Multigravidae (3+)	411/936 (44%)	206/469 (44%)	205/467 (44%)
Weight in kg, mean (SD)	58·7 (9·1)	58·4 (8·8)	59·0 (9·4)
Height in cm, mean (SD)	157·3 (6·3)	157·2 (6·1)	157·5 (6·6)
Maternal MUAC in cm, mean (SD)	26·3 (3·1)	26·2 (3·1)	26·4 (3·1)
Highest level of schooling completed, n/N (%)			
None	90/938 (10%)	42/469 (9%)	48/469 (10%)
Primary	586/938 (62%)	306/469 (65%)	280/469 (60%)
Secondary	236/938 (25%)	107/469 (23%)	129/469 (28%)
Higher	26/938 (3%)	14/469 (3%)	12/469 (3%)
Wealth index tertiles, n/N (%)			
Lowest tertile	649/938 (69%)	331/469 (71%)	318/469 (68%)
Middle tertile	165/938 (18%)	78/469 (17%)	87/469 (19%)
Highest tertile	124/938 (13%)	60/469 (13%)	64/469 (14%)
Slept under a bed net last night, n/N (%)	580/597 (97%)	283/293 (97%)	297/304 (98%)
Microscopy positivity, n/N (%)	104/934 (11%)	52/467 (11%)	52/467 (11%)
PCR/LAMP positivity, n/N (%)	159/867 (18%)	79/433 (18%)	80/434 (18%)

Abbreviations: LAMP = loop-mediated isothermal amplification method MUAC = mid-upper arm circumference; PCR = polymerase chain reaction

Table S-7. Madanitsa et al, Tanzania (2023)

Enrolment characteristics	Total	IPTp-SP	IPTp-DP
	N=1,192	N=597	N=595
Maternal age in years, mean (SD)	26·5 (6·5)	26·5 (6·6)	26·5 (6·5)
Gestational age in weeks, mean (SD)	20·0 (3·4)	19·9 (3·3)	20·1 (3·5)
Gravidity categories, n/N (%)			
Primigravidae	324/1187 (27%)	164/594 (28%)	160/593 (27%)
Secundigravidae	260/1187 (22%)	130/594 (22%)	130/593 (22%)
Multigravidae (3+)	603/1187 (51%)	300/594 (51%)	303/593 (51%)
Weight in kg, mean (SD)	59·5 (12·1)	59·5 (12·4)	59·5 (11·8)
Height in cm, mean (SD)	155·9 (6·1)	155·8 (6·0)	156·1 (6·3)
Maternal MUAC in cm, mean (SD)	27·5 (3·9)	27·6 (4·0)	27·5 (3·9)
Highest level of schooling completed, n/N (%)			
None	128/1189 (11%)	65/596 (11%)	63/593 (11%)
Primary	702/1189 (59%)	366/596 (61%)	336/593 (57%)
Secondary	326/1189 (27%)	147/596 (25%)	179/593 (30%)
Higher	33/1189 (3%)	18/596 (3%)	15/593 (3%)
Wealth index tertiles, n/N (%)			
Lowest tertile	336/1192 (28%)	177/597 (30%)	159/595 (27%)
Middle tertile	415/1192 (35%)	200/597 (34%)	215/595 (36%)
Highest tertile	441/1192 (37%)	220/597 (37%)	221/595 (37%)
Slept under a bed net last night, n/N (%)	932/956 (97%)	451/466 (97%)	481/490 (98%)
Microscopy positivity, n/N (%)	70/1192 (6%)	38/597 (6%)	32/595 (5%)
PCR/LAMP positivity, n/N (%)	114/1082 (11%)	56/543 (10%)	58/539 (11%)

Abbreviations: LAMP = loop-mediated isothermal amplification method MUAC = mid-upper arm circumference; PCR = polymerase chain reaction

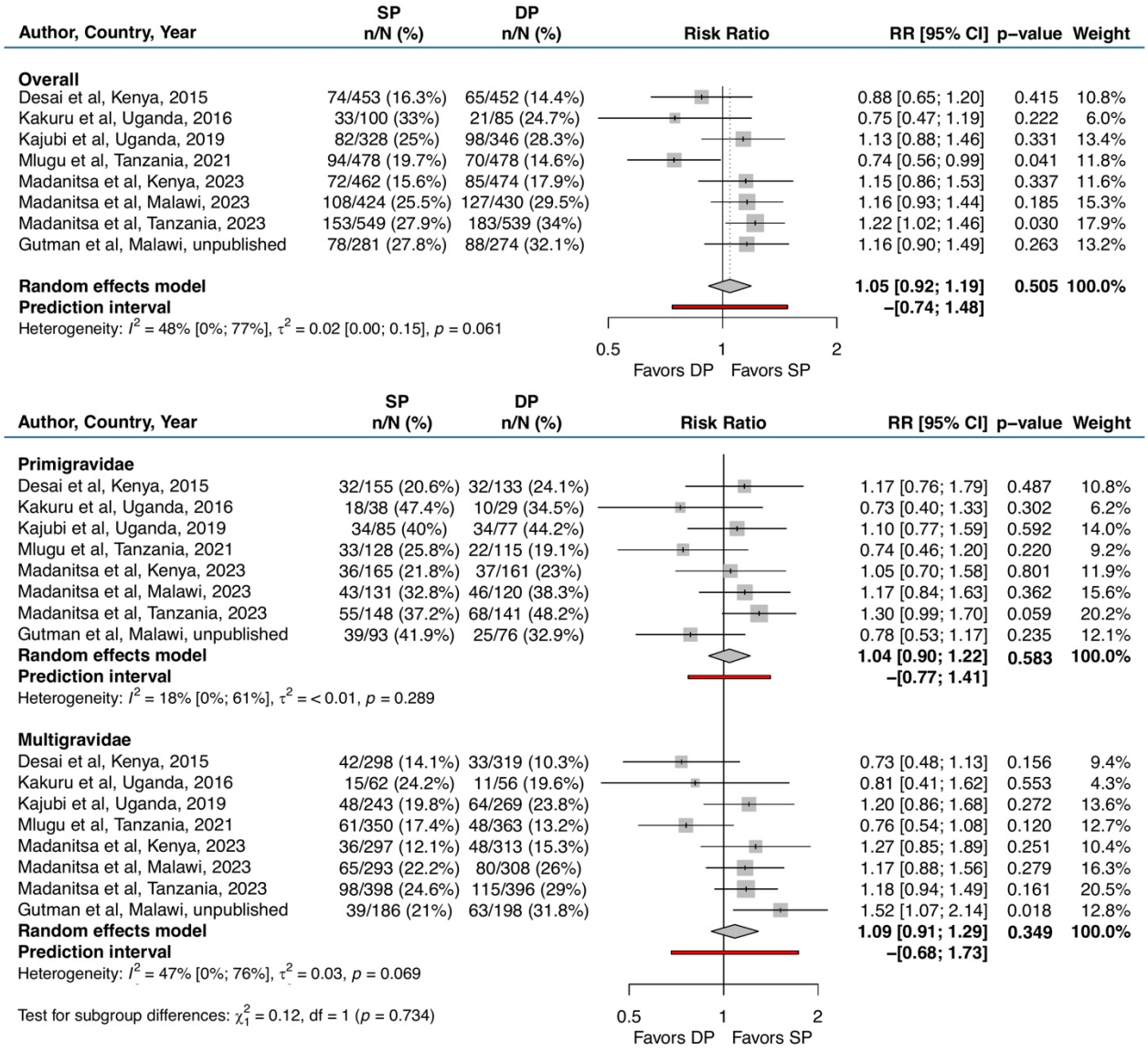
Table S-8. Gutman et al, unpublished

Enrolment characteristics	Total	IPTp-SP	IPTp-DP
	N=593	N=297	N=296
Maternal age in years, mean (SD)	24·6 (6·2)	24·5 (6·4)	24·7 (6·1)
Gestational age in weeks, mean (SD)	20·1 (3·2)	20·1 (3·2)	20·1 (3·1)
Gravidity categories, n/N (%)			
Primigravidae	184/589 (31%)	102/295 (35%)	82/294 (28%)
Secundigravidae	146/589 (25%)	73/295 (25%)	73/294 (25%)
Multigravidae (3+)	259/589 (44%)	120/295 (41%)	139/294 (47%)
Weight in kg, mean (SD)	58·4 (10·0)	58·6 (9·4)	58·3 (10·6)
Height in cm, mean (SD)	157·4 (6·2)	157·3 (6·6)	157·5 (5·7)
Maternal MUAC in cm, mean (SD)	26·2 (3·1)	26·4 (3·2)	26·1 (3·1)
Maternal education level, n/N (%)			
None	286/593 (48%)	146/297 (49%)	140/296 (47%)
Primary	209/593 (35%)	97/297 (33%)	112/296 (38%)
Secondary	89/593 (15%)	49/297 (16%)	40/296 (14%)
Higher	9/593 (2%)	5/297 (2%)	4/296 (1%)
Wealth index tertiles, n/N (%)			
Lowest tertile	200/593 (34%)	93/297 (31%)	107/296 (36%)
Middle tertile	196/593 (33%)	105/297 (35%)	91/296 (31%)
Highest tertile	197/593 (33%)	99/297 (33%)	98/296 (33%)
Slept under a bed net last night, n/N (%)	932/956 (97%)	451/466 (97%)	481/490 (98%)
Microscopy positivity, n/N (%)	--	--	--
PCR/LAMP positivity, n/N (%)	143/593 (24%)	66/297 (22%)	77/296 (26%)

Abbreviations: LAMP = loop-mediated isothermal amplification method MUAC = mid-upper arm circumference; PCR = polymerase chain reaction

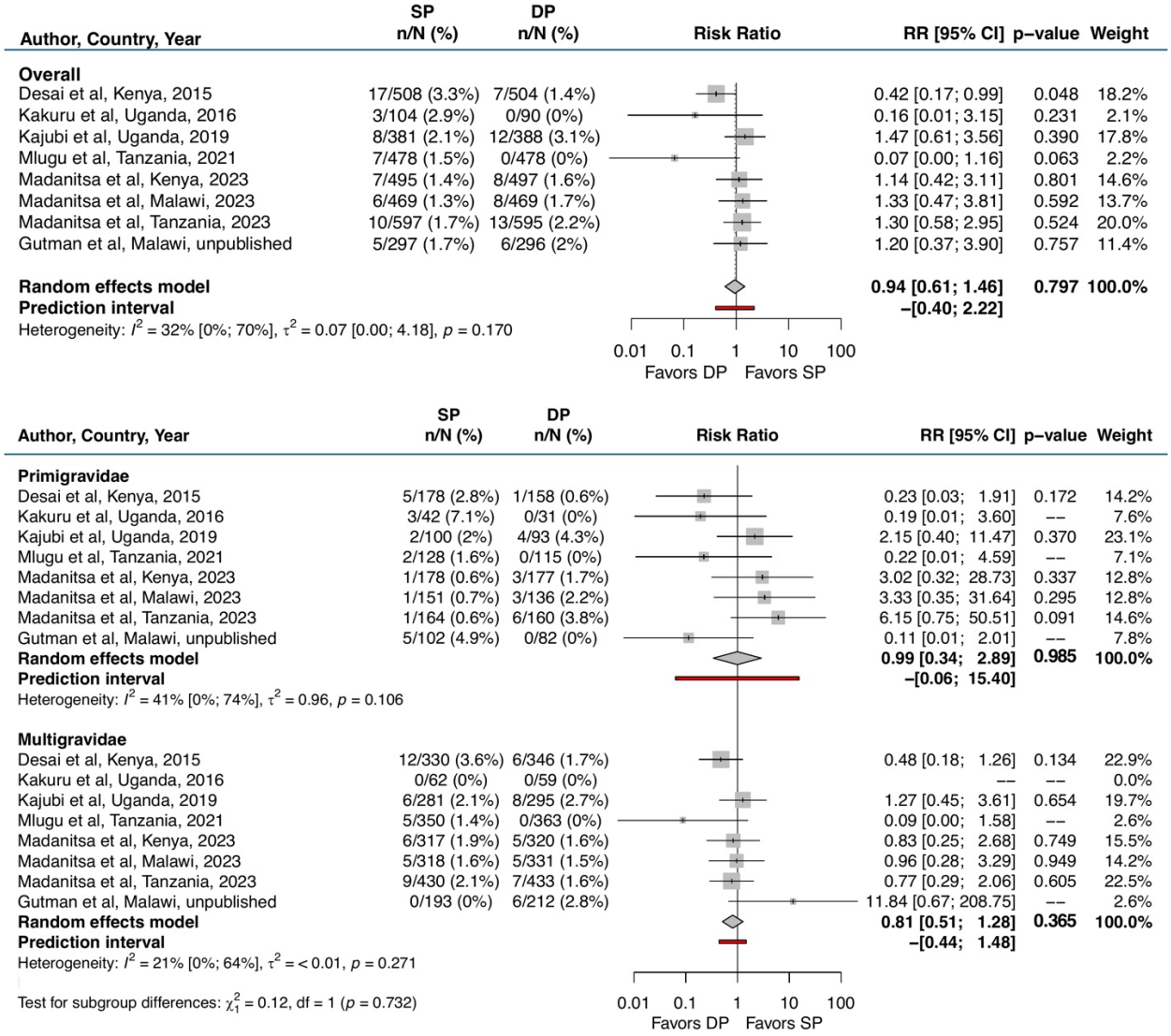
Appendix 7. Forest plot of study-specific estimates

Figure S-1. Any composite adverse birth outcome



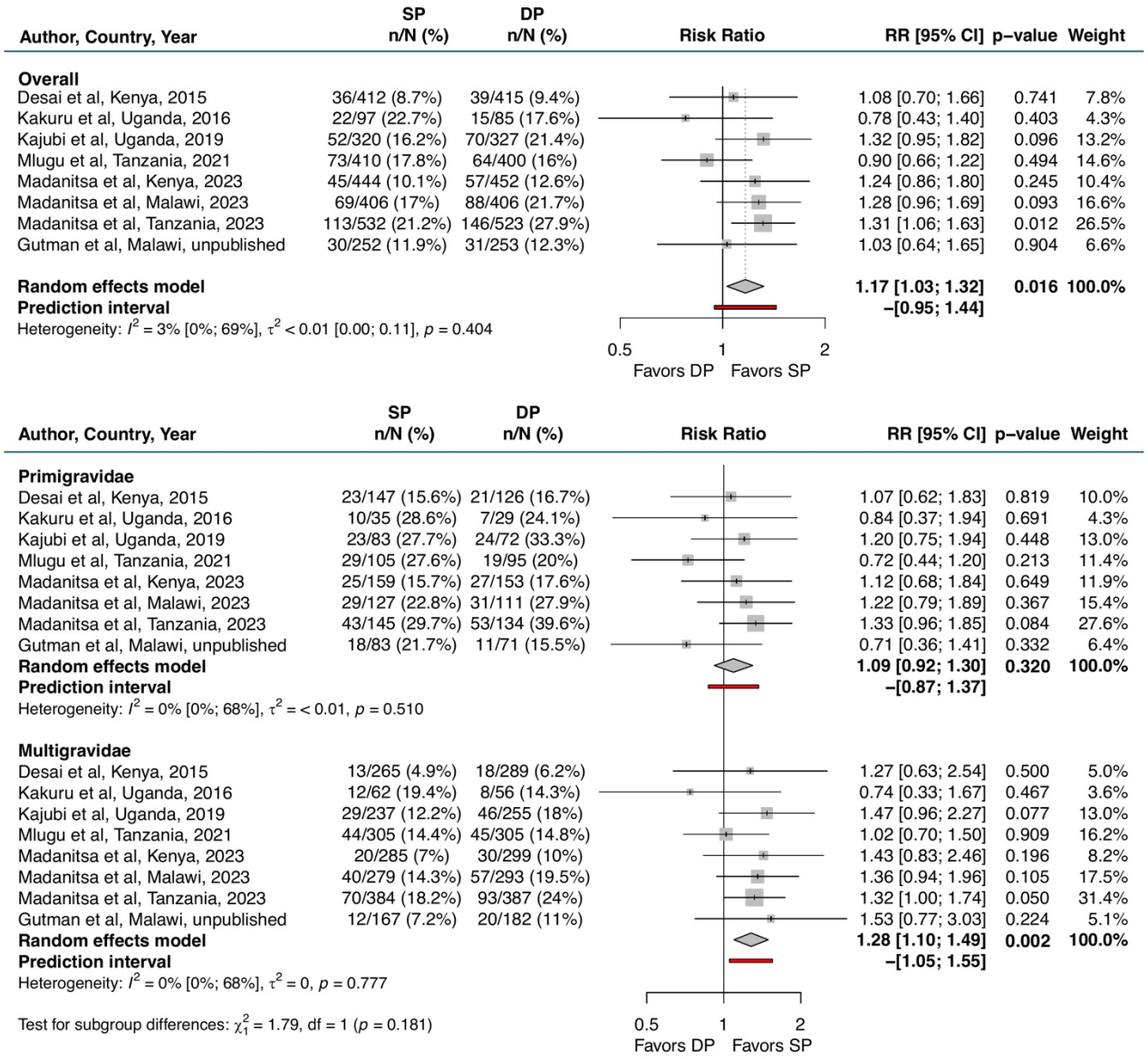
Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; LBW = low birthweight; RR = risk ratio; SGA = small-for-gestational age; SP = sulfadoxine-pyrimethamine

Figure S-2. Foetal loss



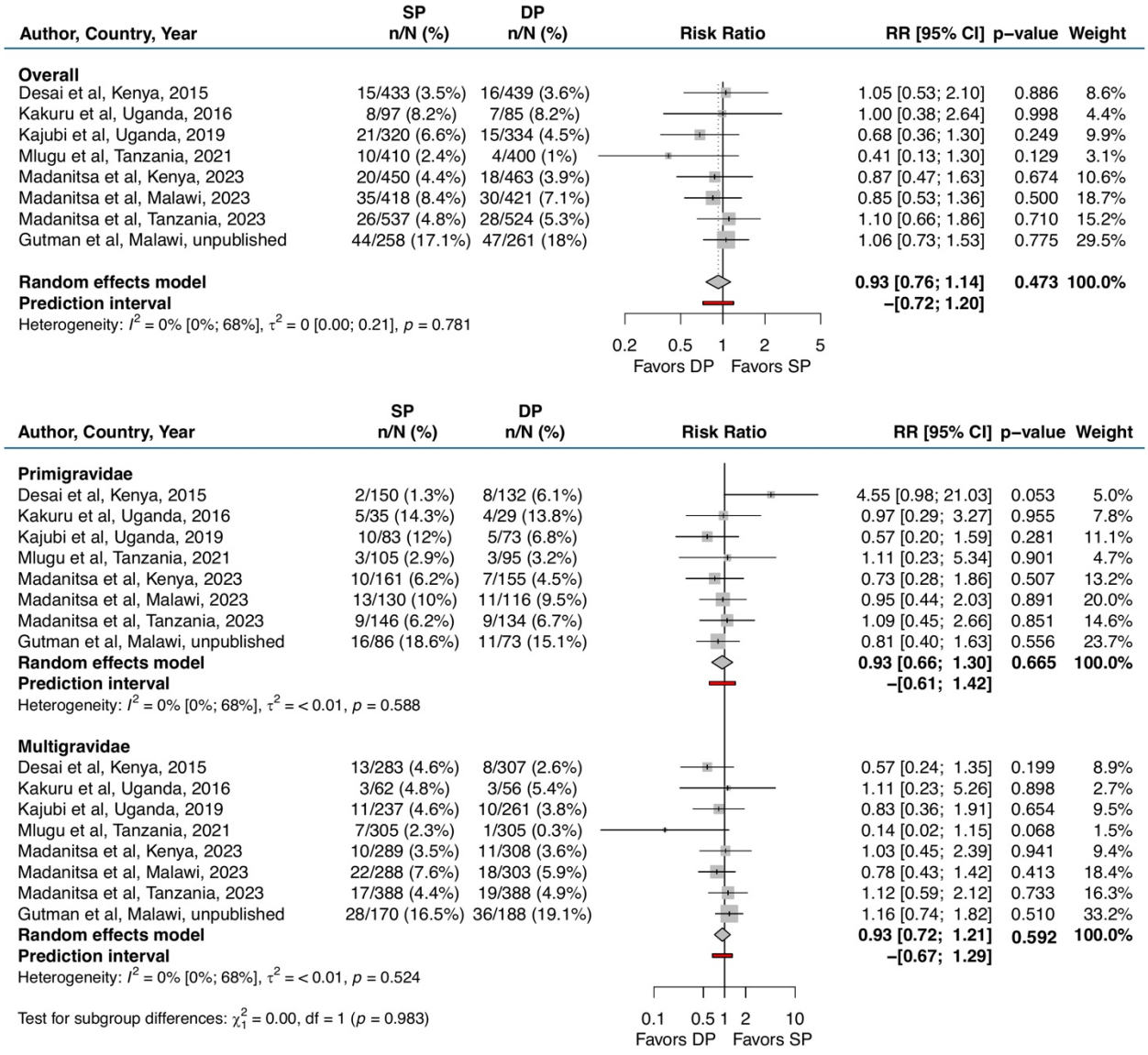
Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; RR = risk ratio; SP = sulfadoxine-pyrimethamine

Figure S-3. Small-for-gestational age (<10th percentile for birthweight-for-gestational age)



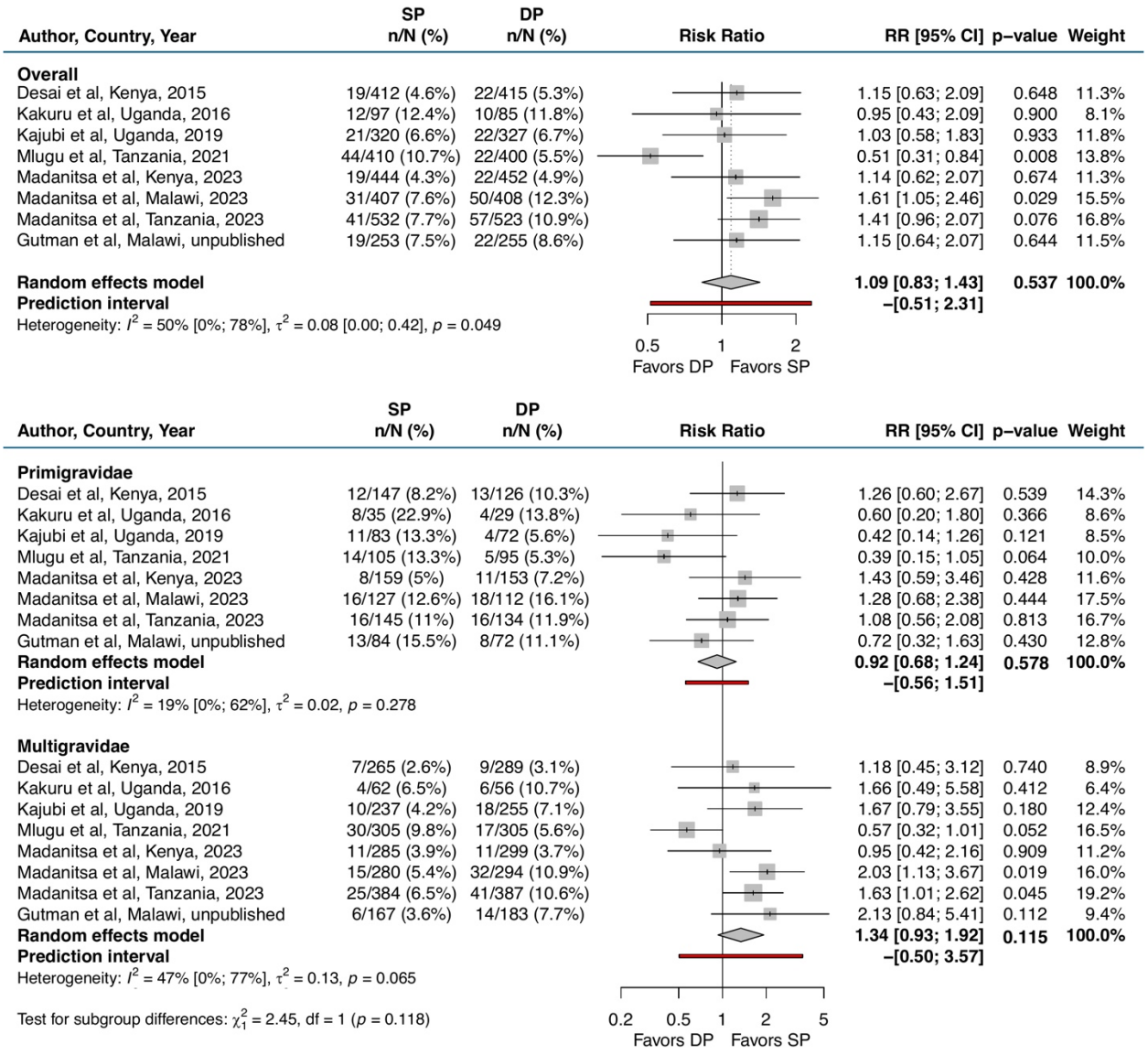
Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; RR = risk ratio; SP = sulfadoxine-pyrimethamine

Figure S-4. Preterm birth (<37 gestational weeks)



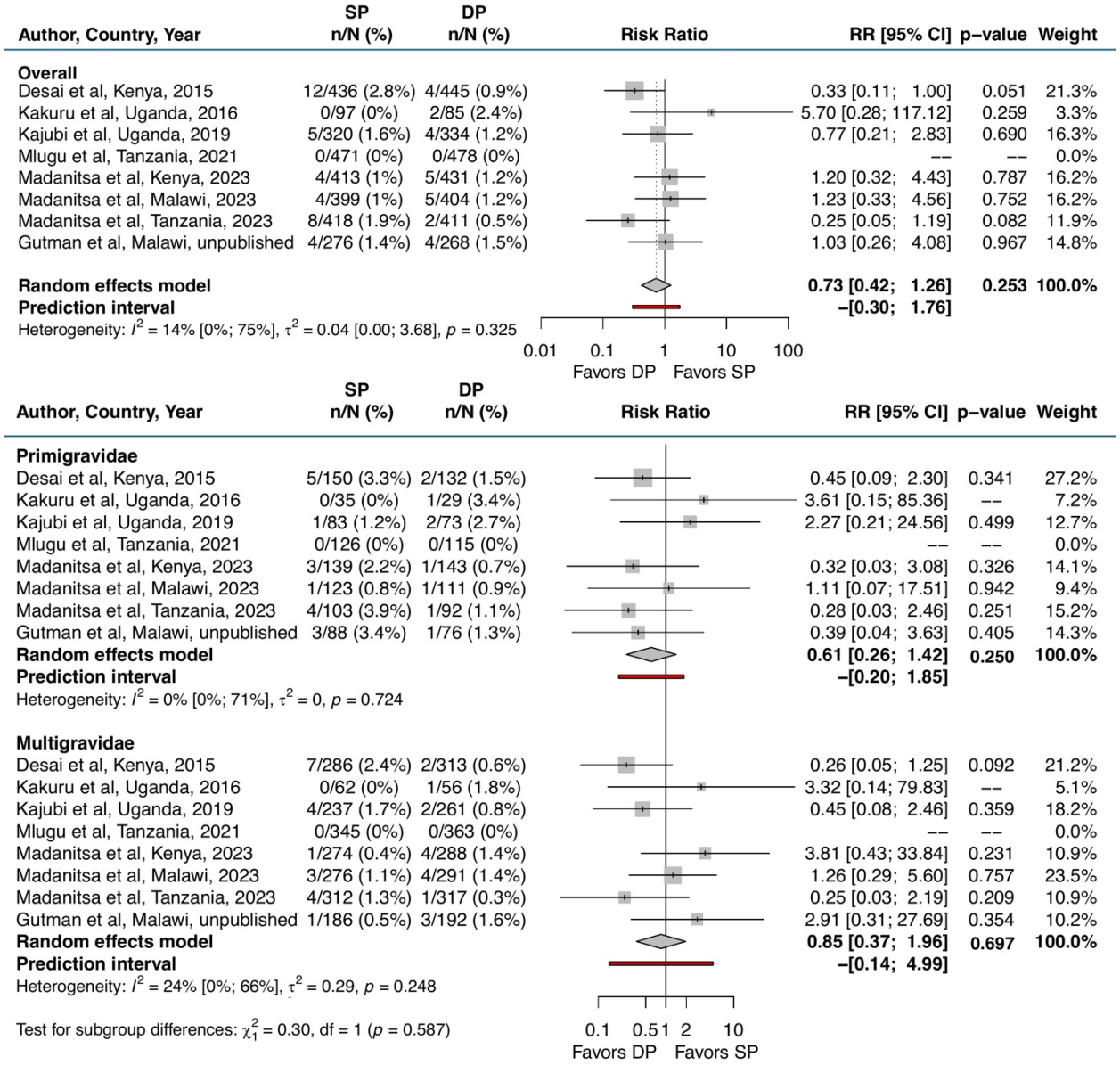
Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; RR = risk ratio; SP = sulfadoxine-pyrimethamine

Figure S-5. Low birthweight



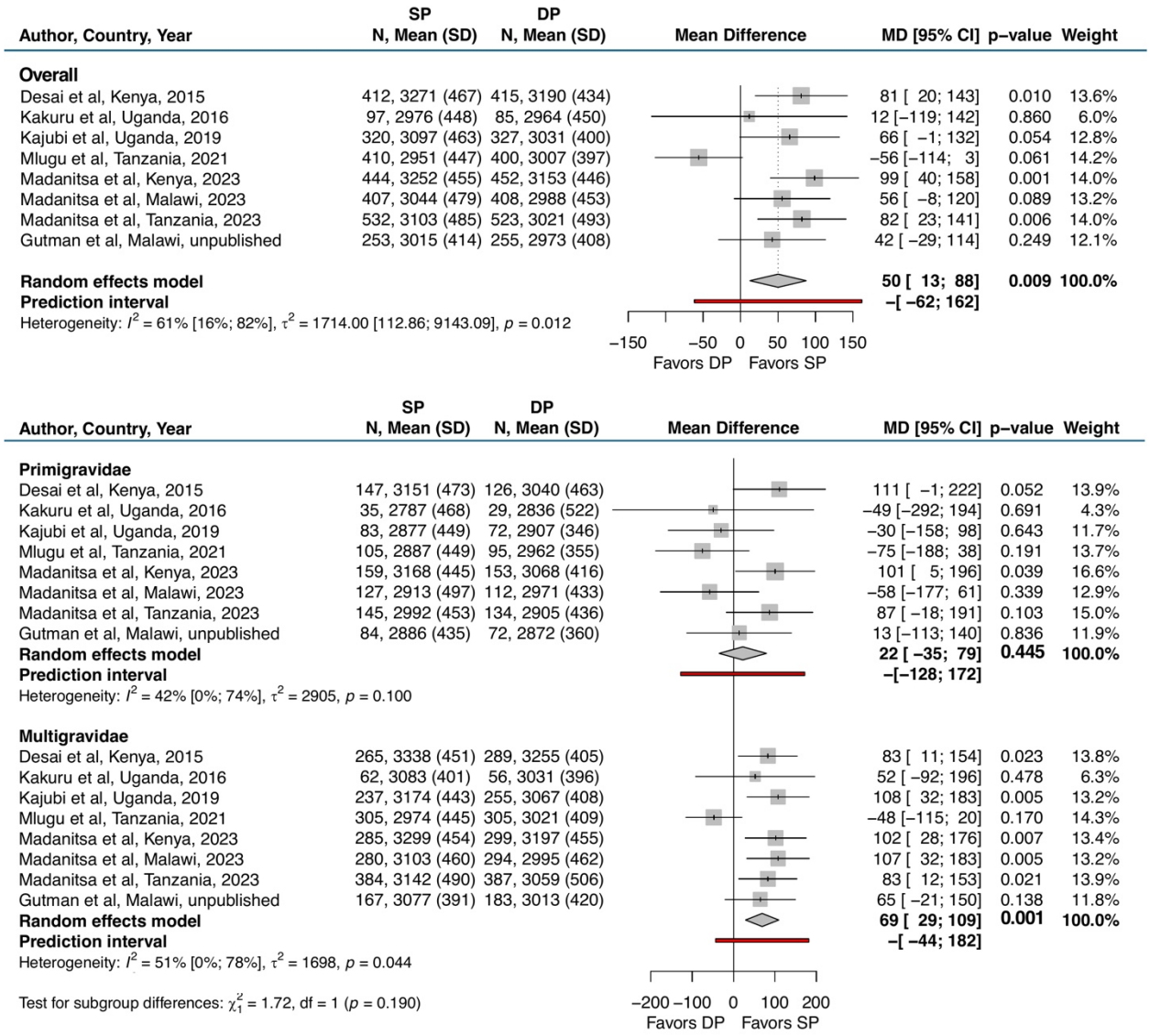
Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; RR = risk ratio; SP = sulfadoxine-pyrimethamine

Figure S-6. Neonatal death



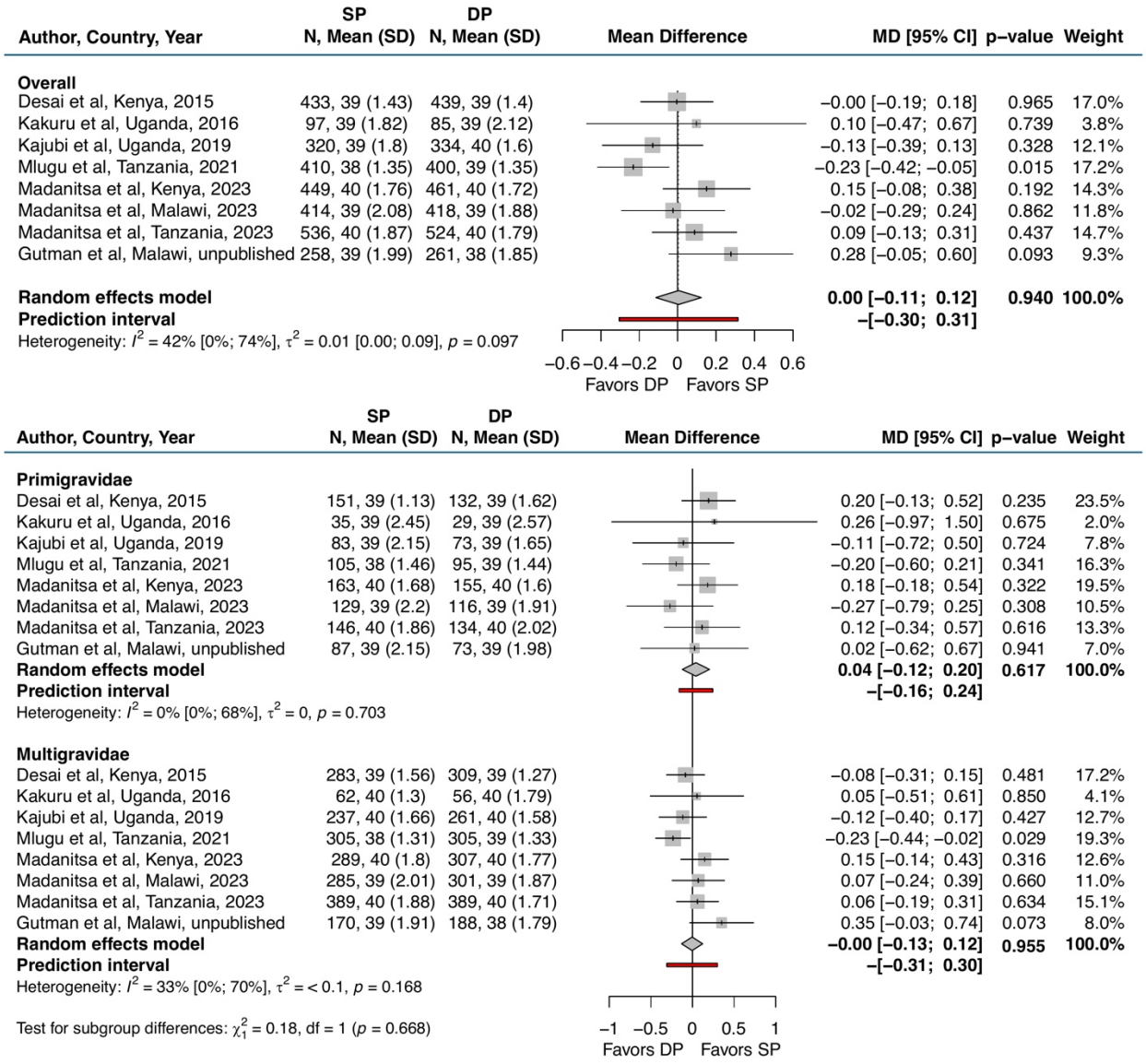
Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; RR = risk ratio; SP = sulfadoxine-pyrimethamine

Figure S-7. Mean birthweight in grams



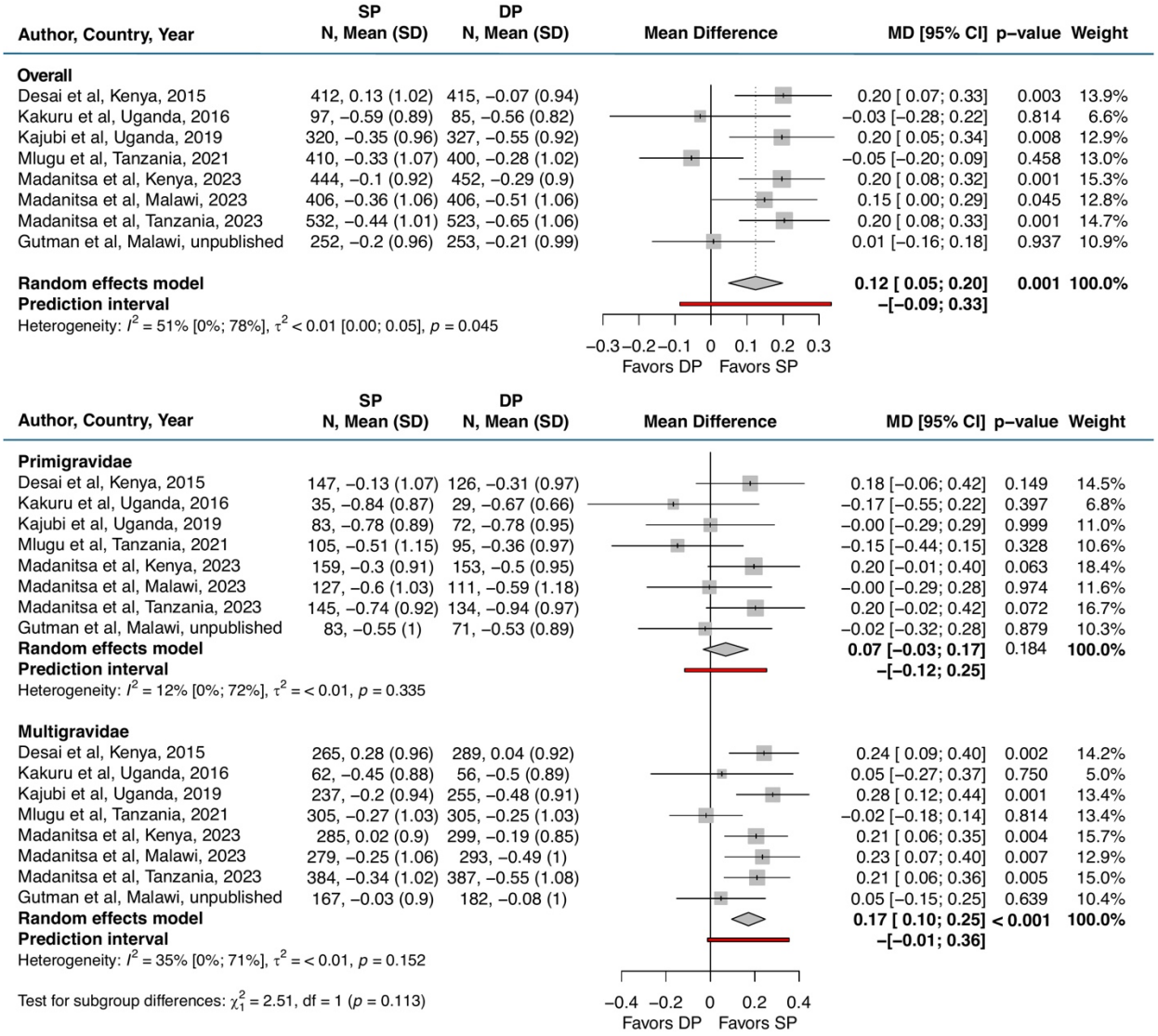
Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; MD = mean difference; SD = standard deviation; SP = sulfadoxine-pyrimethamine

Figure S-8. Mean gestational age at birth in weeks



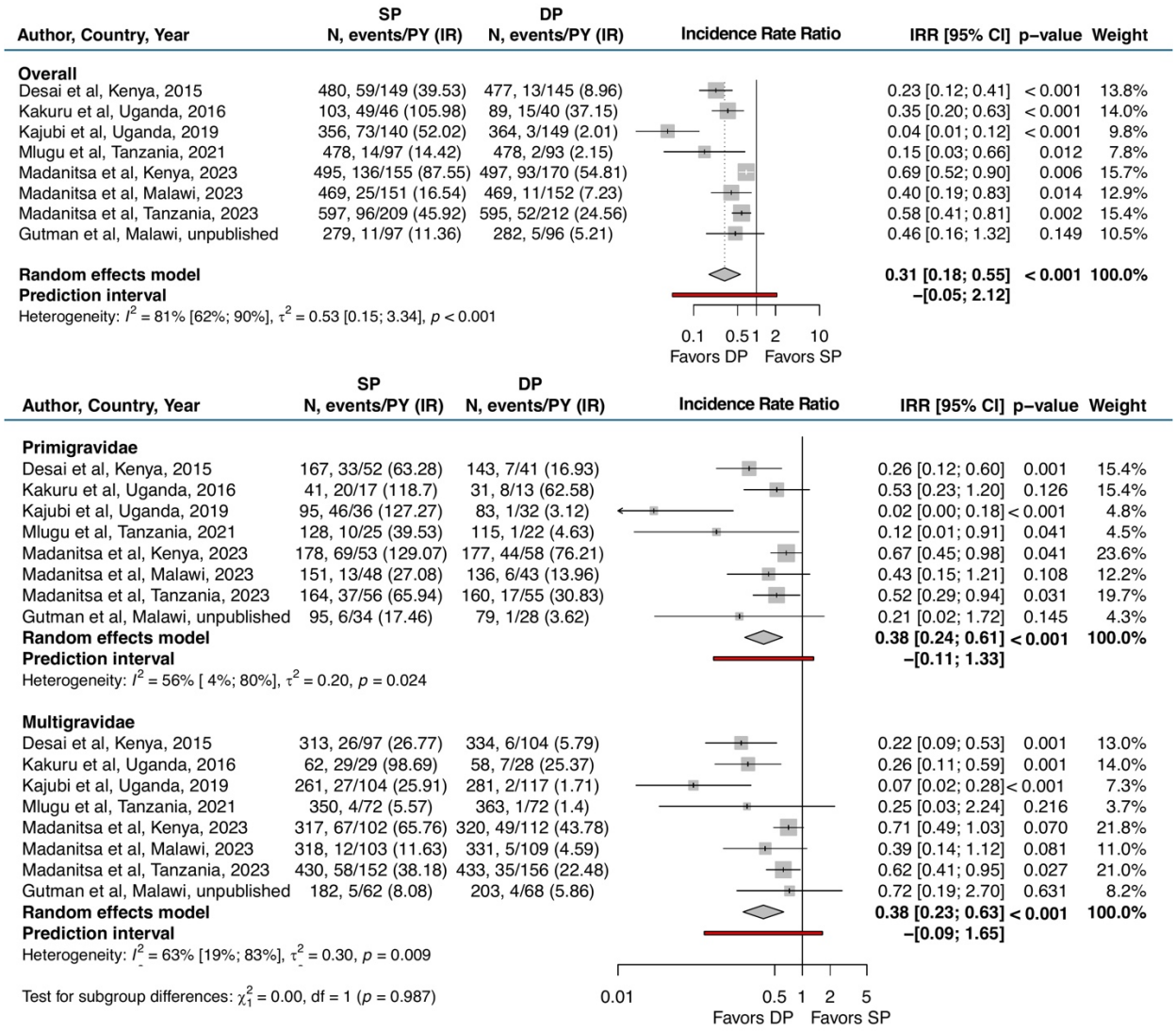
Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; MD = mean difference; SD = standard deviation; SP = sulfadoxine-pyrimethamine

Figure S-9. Mean birthweight-for-gestational age z-scores



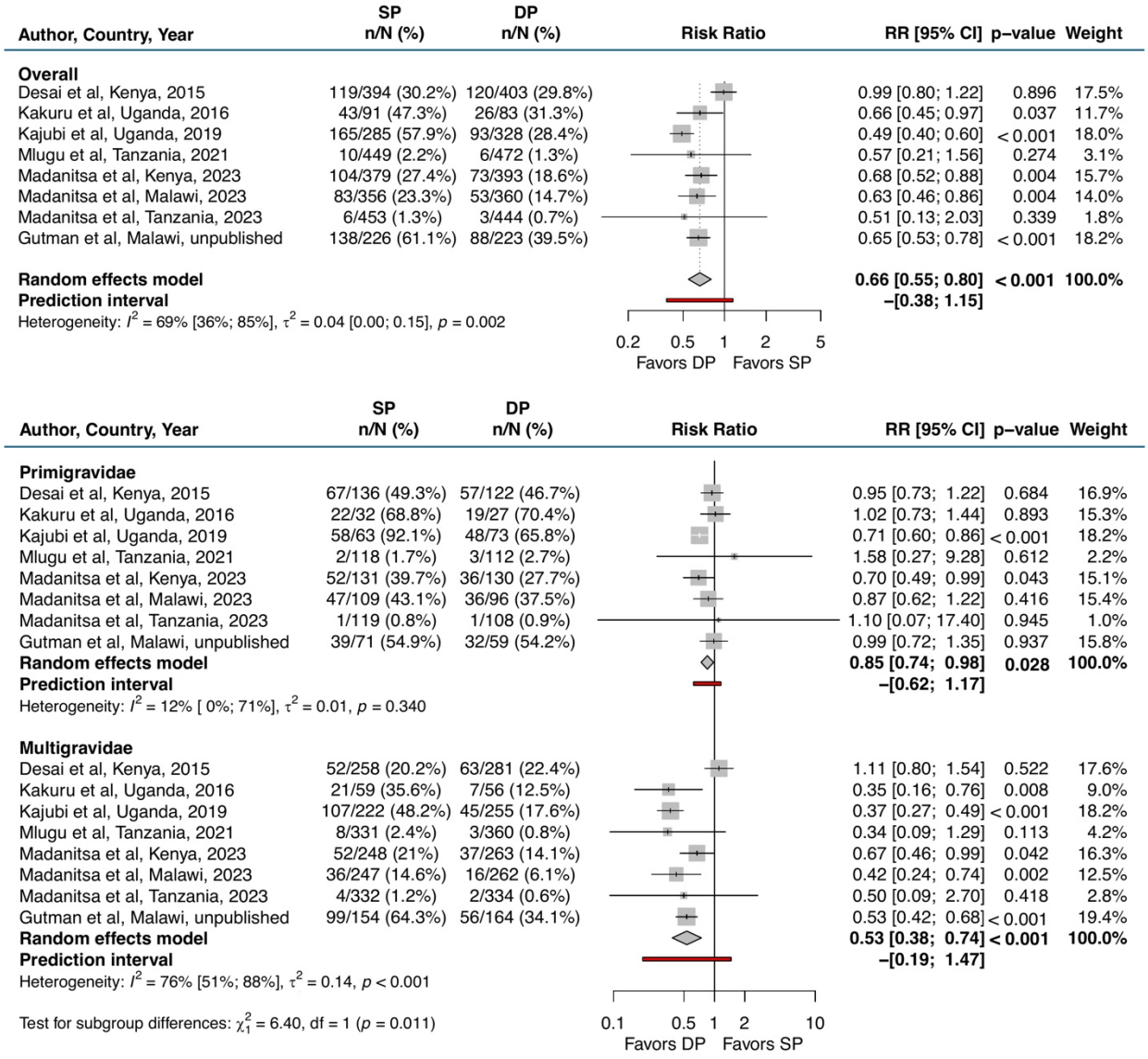
Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; MD = mean difference; SD = standard deviation; SP = sulfadoxine-pyrimethamine

Figure S-10. Incidence of clinical malaria during pregnancy



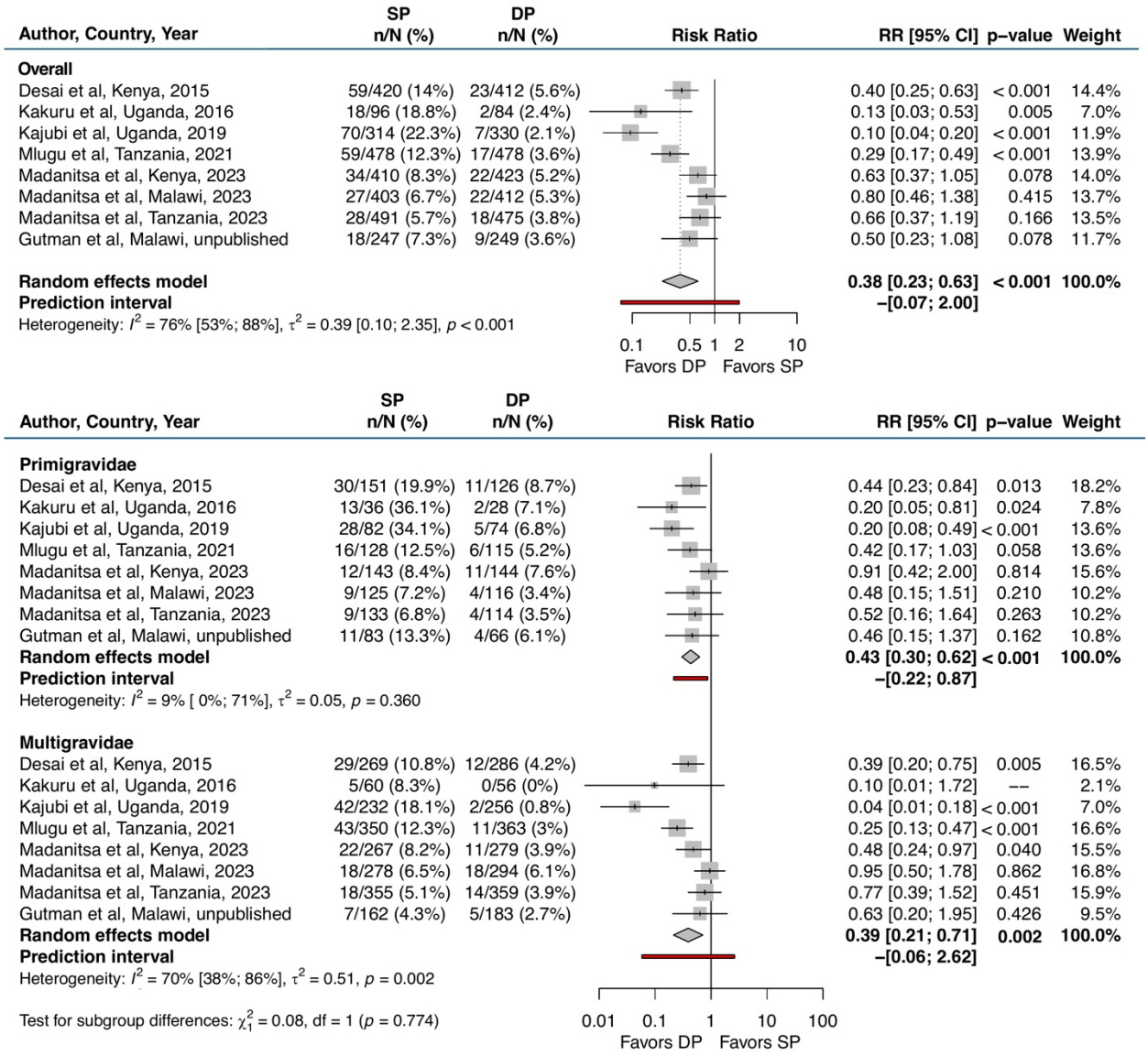
Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; IR = incidence rate (episodes per 100 person-years); IRR = incidence rate ratio; PY = person-years; SP = sulfadoxine-pyrimethamine

Figure S-11. Any evidence of pigment in placental tissue by histopathology



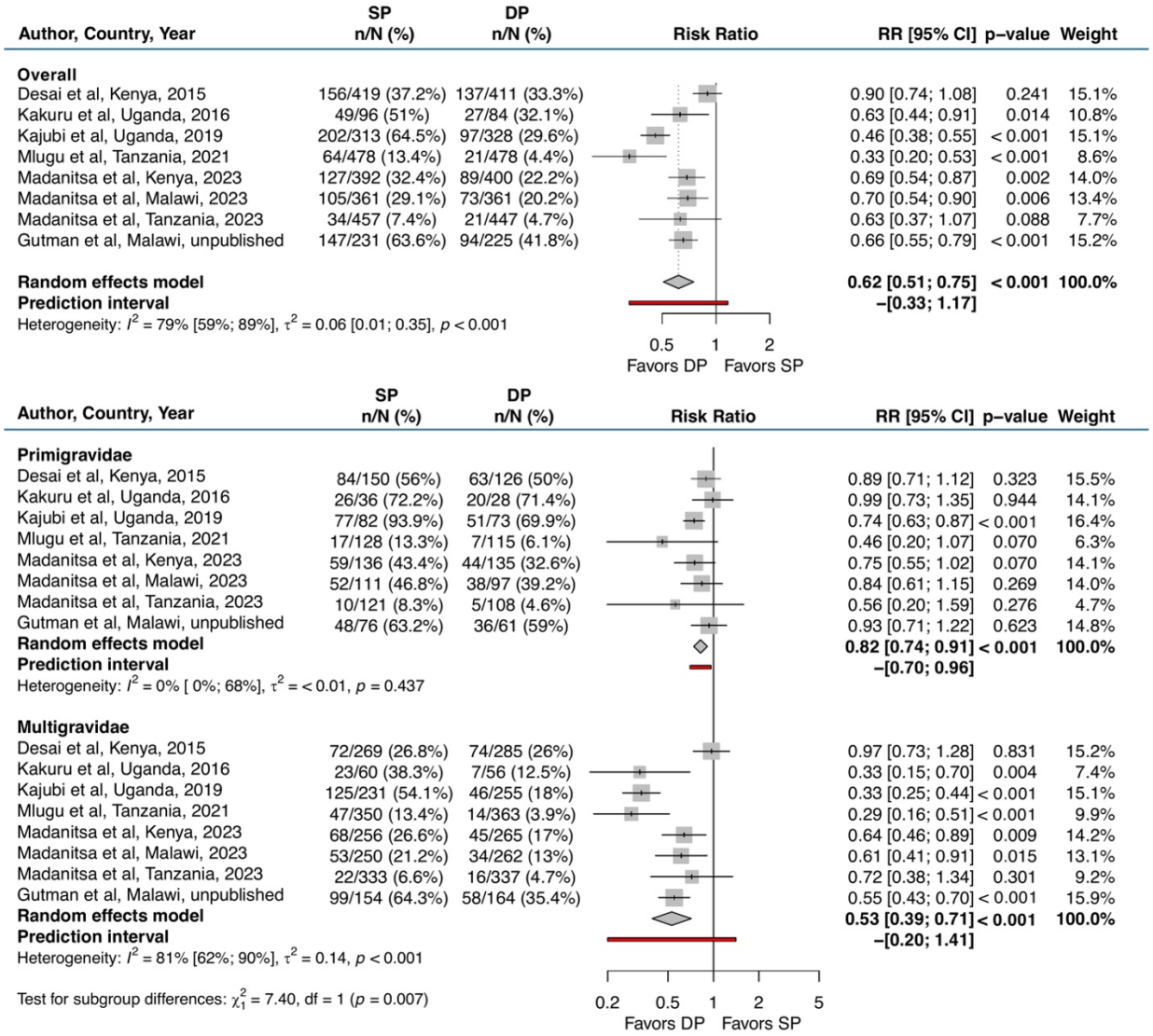
Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; RR = risk ratio; SP = sulfadoxine-pyrimethamine

Figure S-12. Any evidence of parasites in placental tissue or blood by histopathology, microscopy, PCR, or RDT



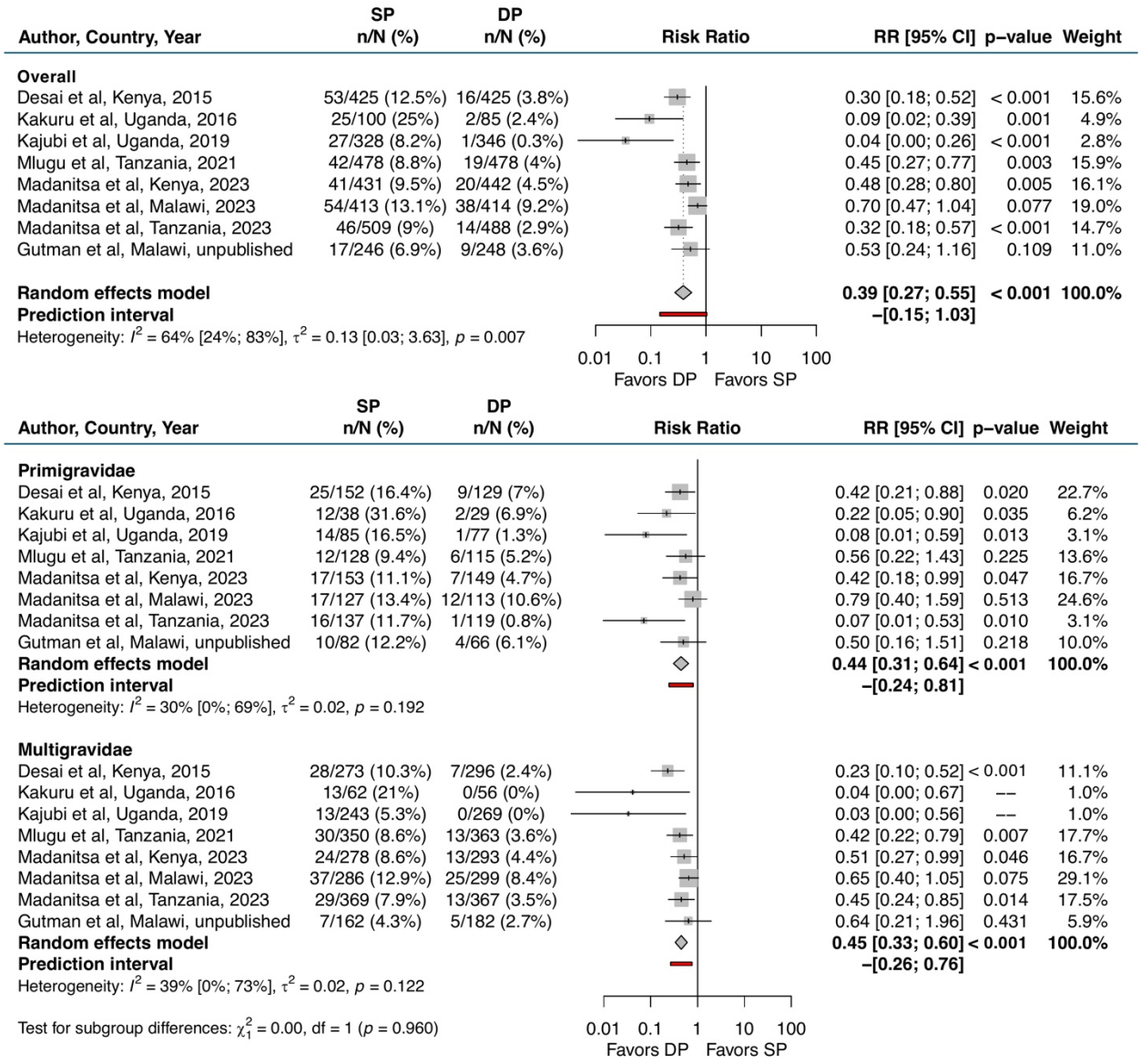
Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; PCR = polymerase chain reaction; RDT = rapid diagnostic test; RR = risk ratio; SP = sulfadoxine-pyrimethamine

Figure S-13. Any evidence of pigment or parasites in placental tissue or blood by histopathology, microscopy, PCR, or RDT



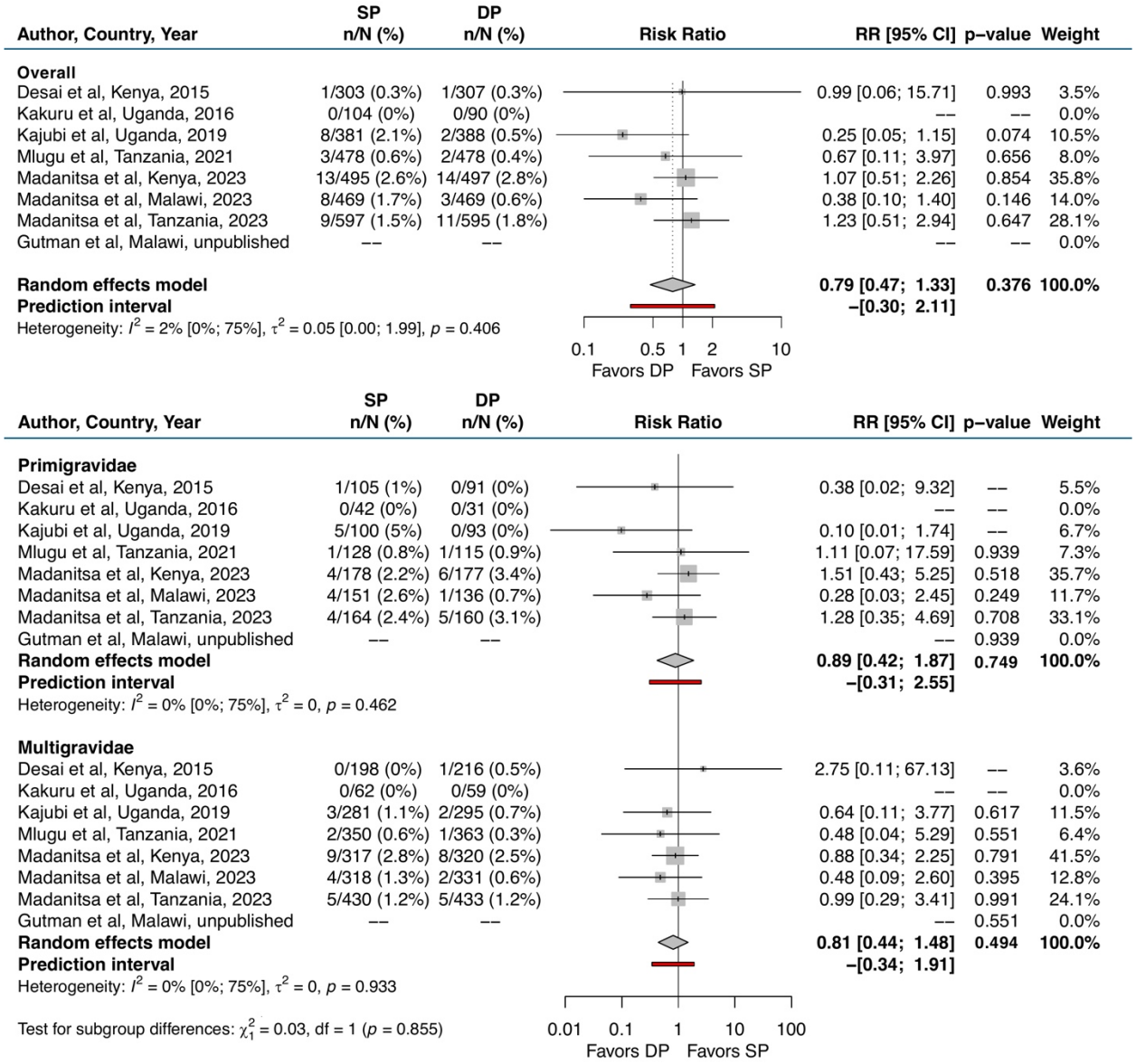
Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; PCR = polymerase chain reaction; RDT = rapid diagnostic test; RR = risk ratio; SP = sulfadoxine-pyrimethamine

Figure S-14. Any evidence of peripheral malaria at delivery by microscopy, PCR, or RDT



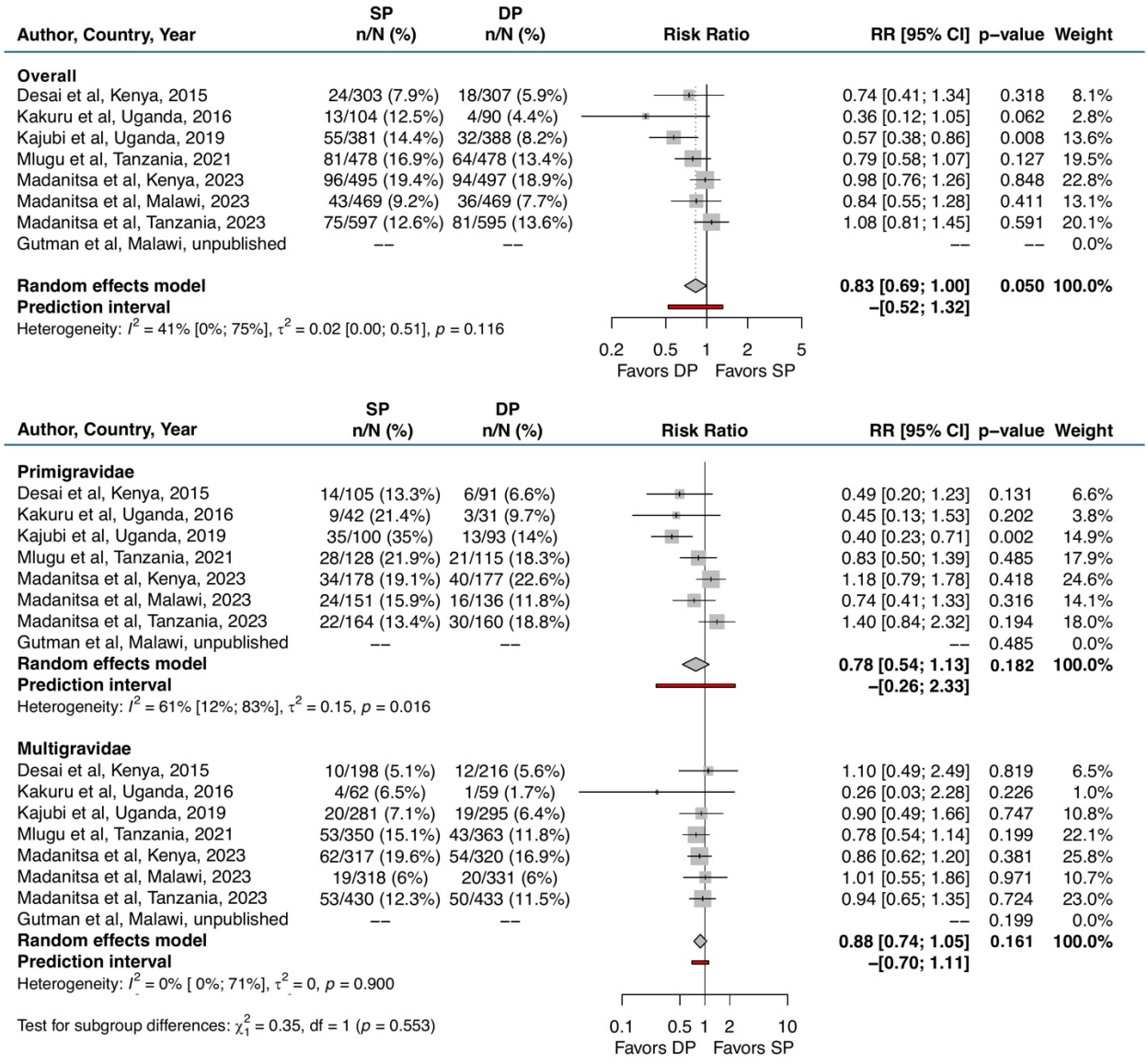
Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; PCR = polymerase chain reaction; RDT = rapid diagnostic test; RR = risk ratio; SP = sulfadoxine-pyrimethamine

Figure S-15. Any evidence of severe anaemia (Hb <7 g/dL) during pregnancy



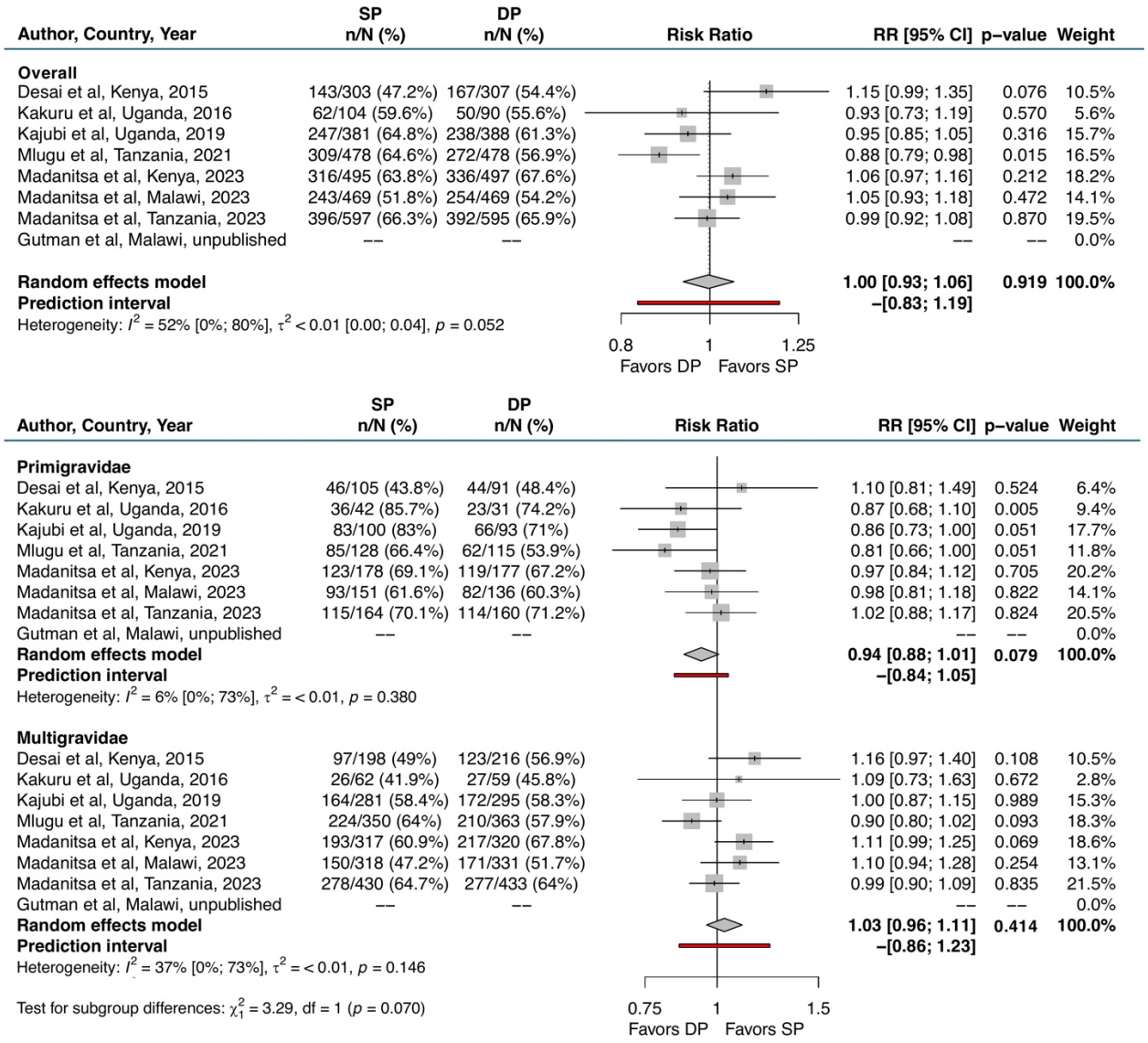
Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; g/dL = grams/deciliter; Hb = haemoglobin; RR = risk ratio; SP = sulfadoxine-pyrimethamine

Figure S-16. Any evidence of moderate anaemia (Hb <9 g/dL) during pregnancy



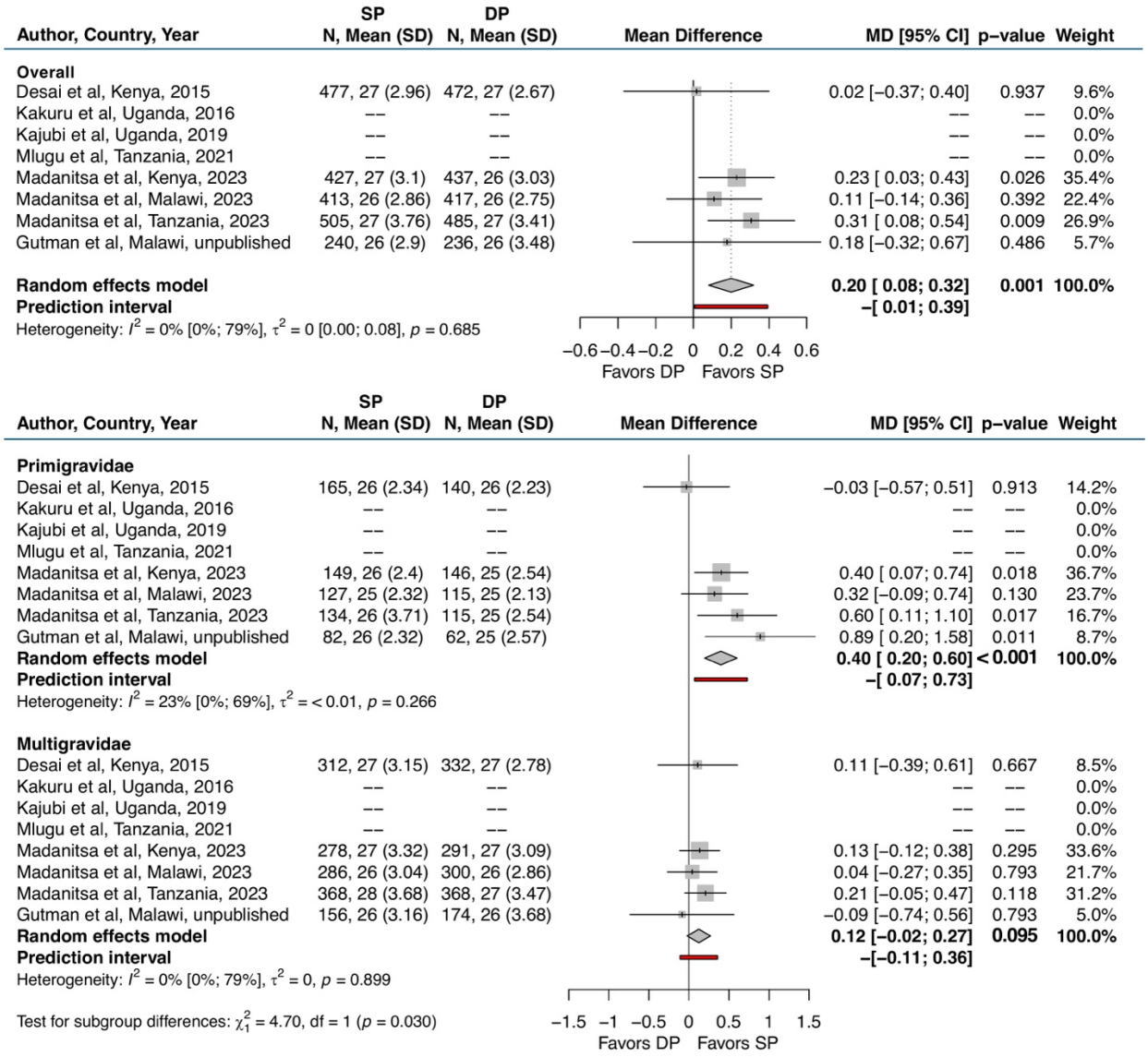
Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; g/dL = grams/deciliter; Hb = haemoglobin; RR = risk ratio; SP = sulfadoxine-pyrimethamine

Figure S-17. Any evidence of mild anaemia (Hb <11 g/dL) during pregnancy



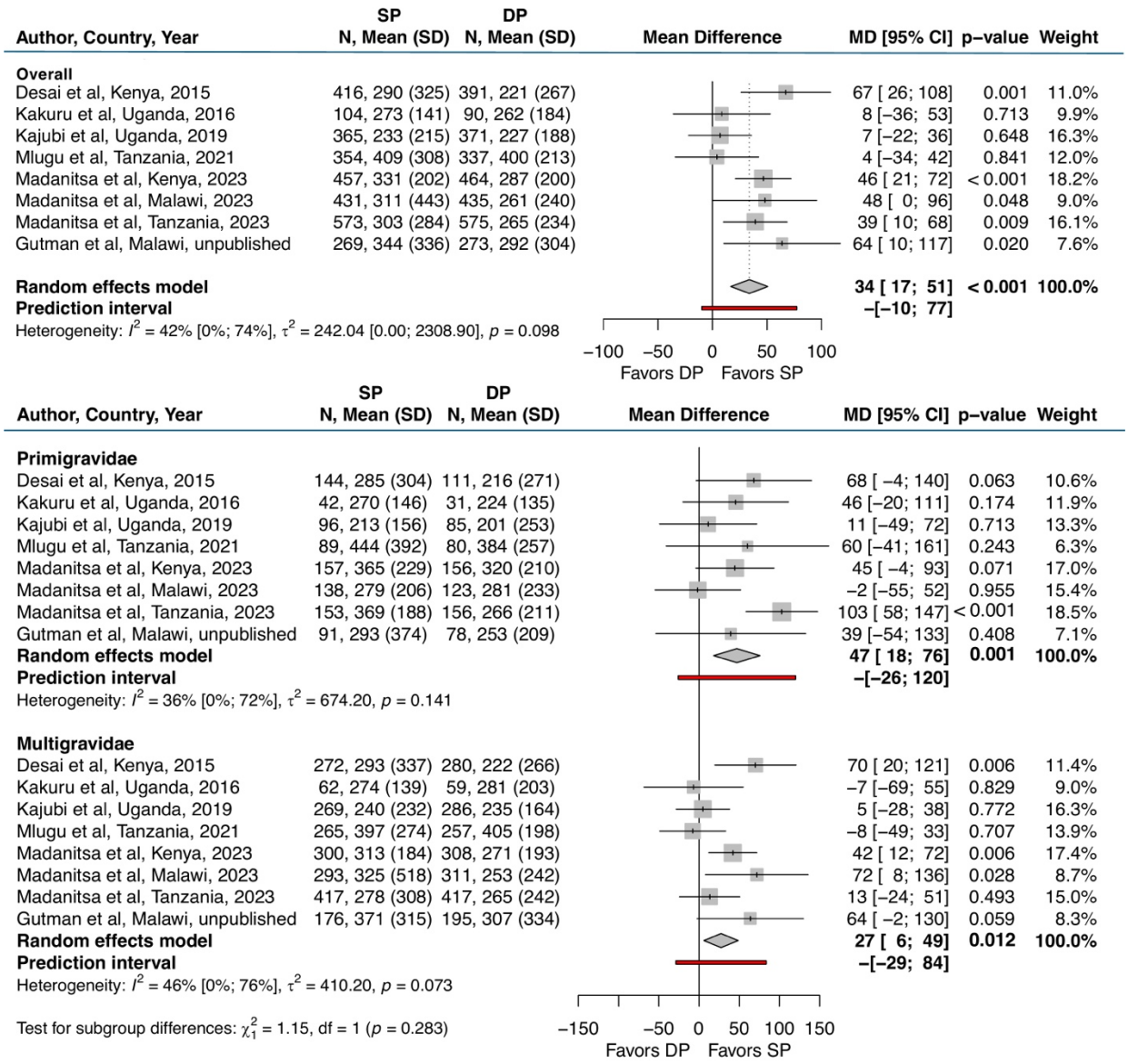
Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; g/dL = grams/deciliter; Hb = haemoglobin; RR = risk ratio; SP = sulfadoxine-pyrimethamine

Figure S-18. Mean maternal MUAC in cm at delivery



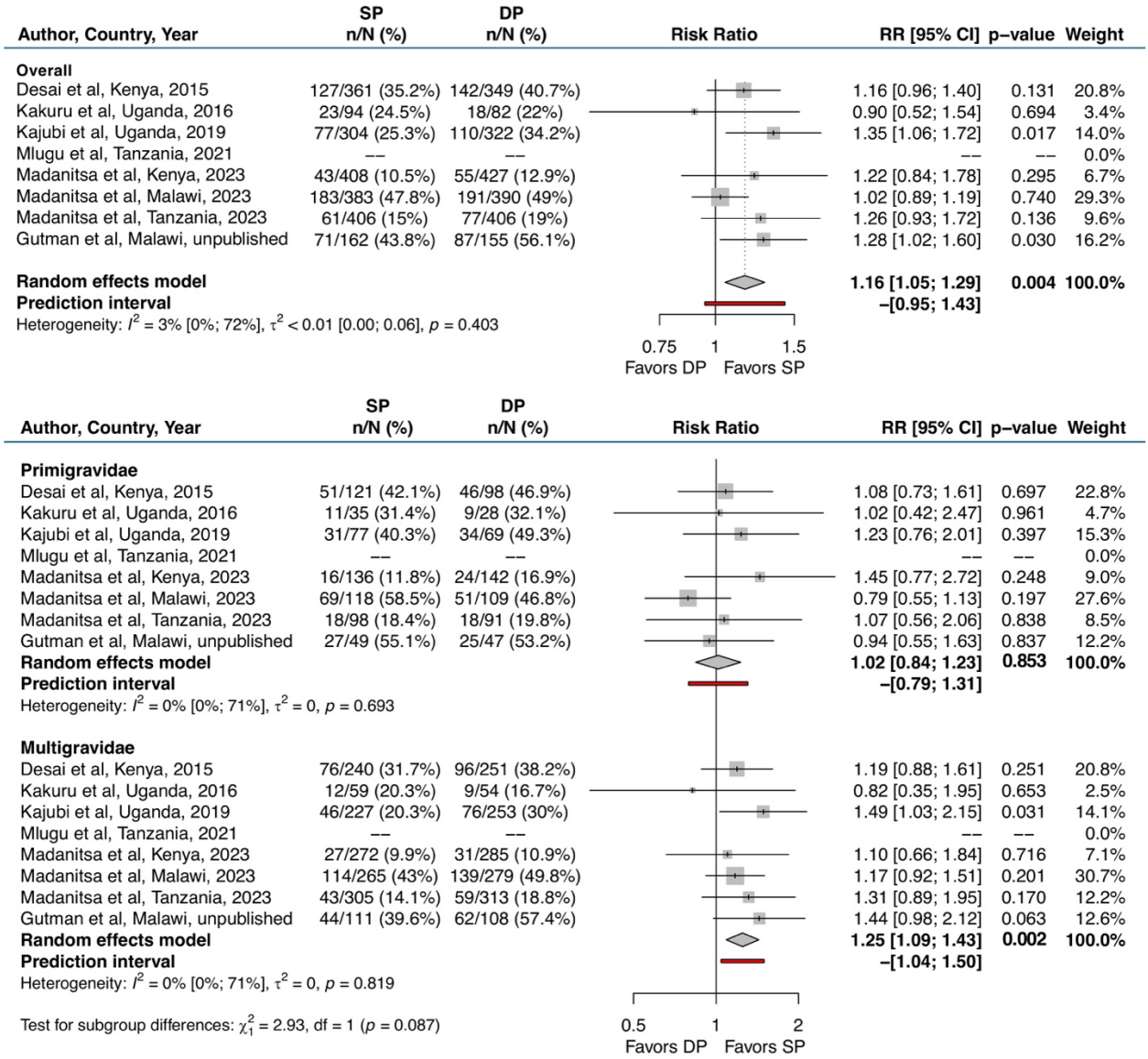
Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; MD = mean difference; MUAC = mid-upper arm circumference; SD = standard deviation; SP = sulfadoxine-pyrimethamine

Figure S-19. Mean maternal weight gain per week in grams



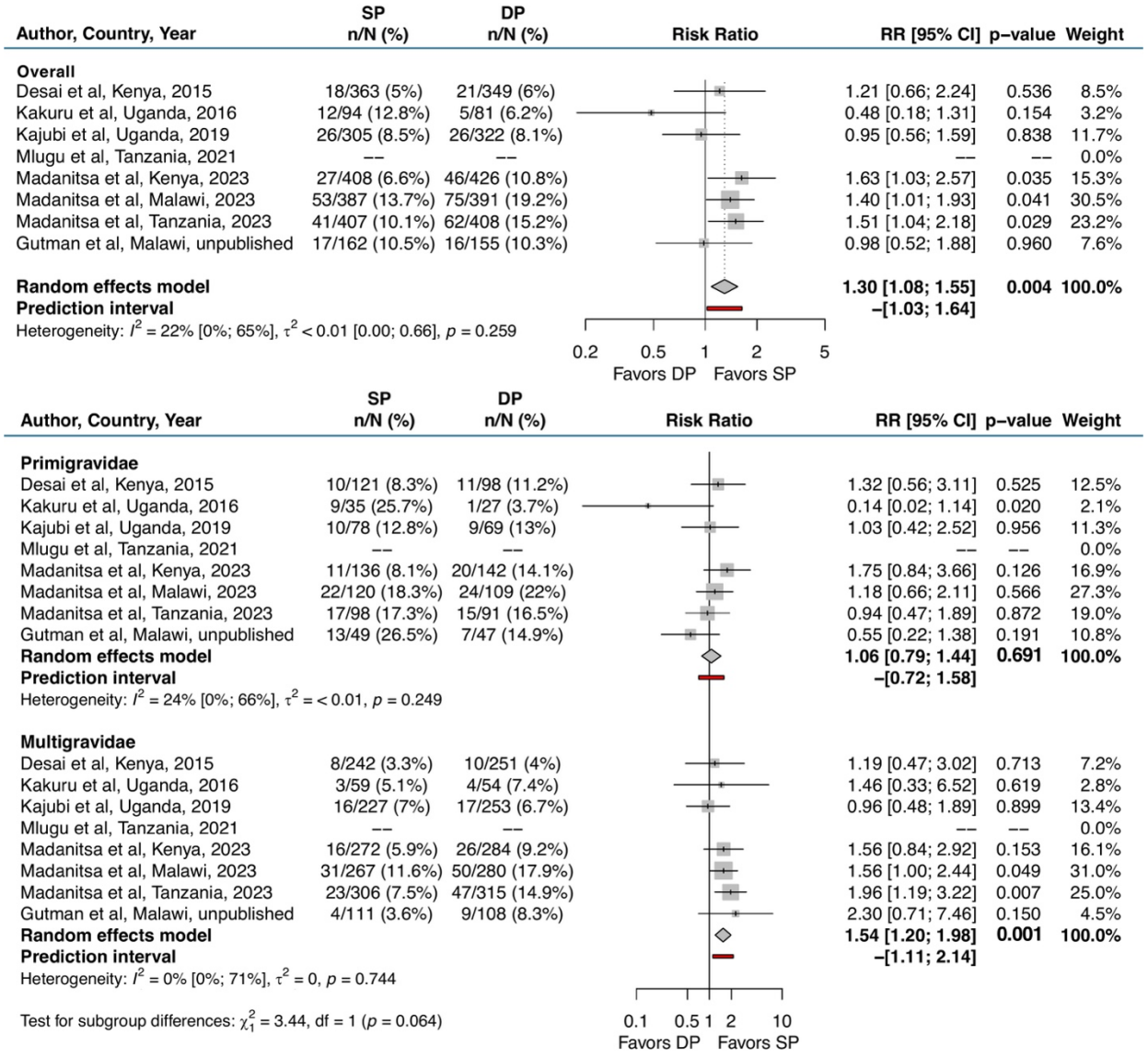
Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; MD = mean difference; SD = standard deviation; SP = sulfadoxine-pyrimethamine

Figure S-20. Any evidence of stunting (LAZ <2 SD) from birth to two months of life



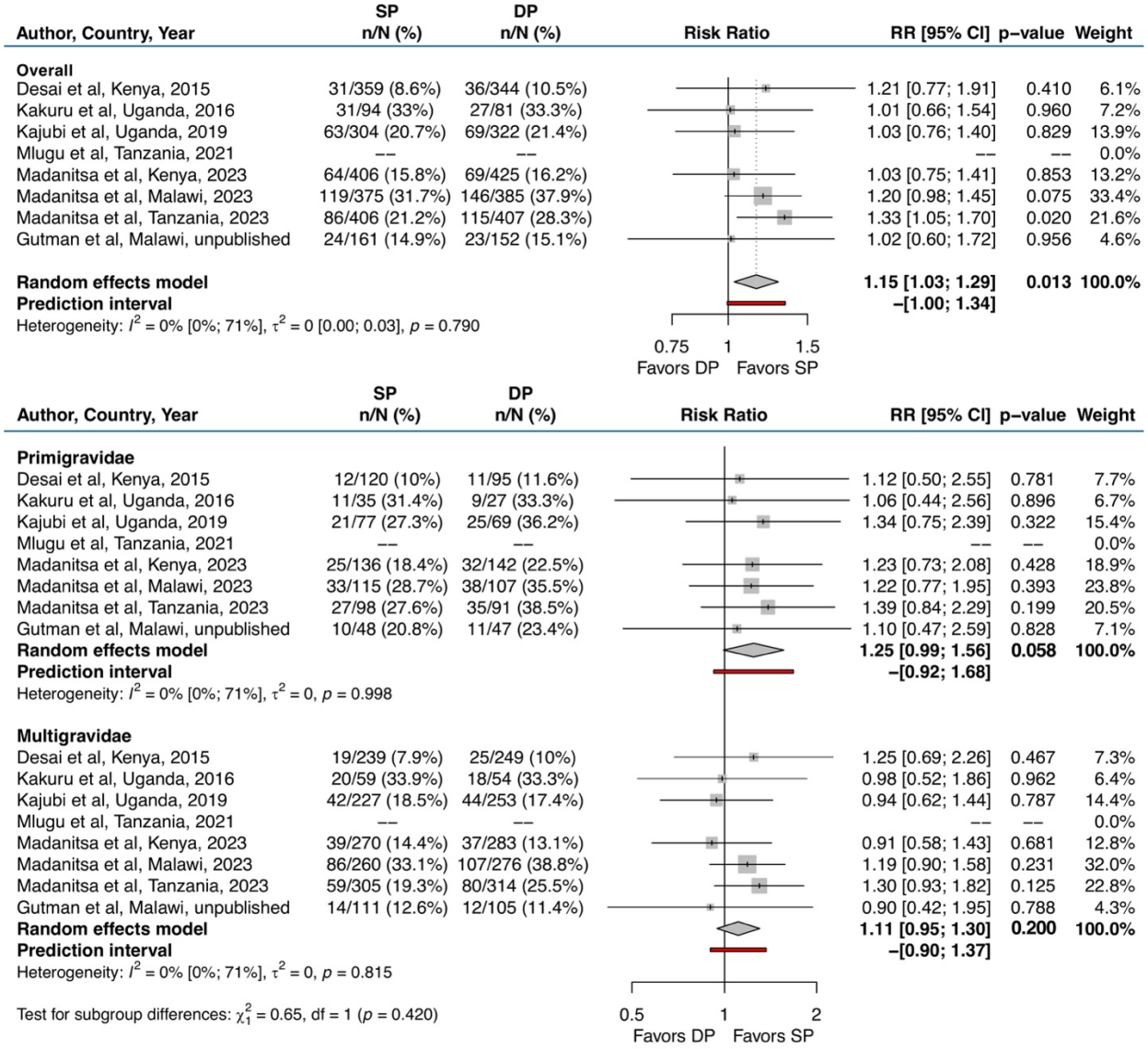
Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; LAZ = length-for-age z-score; RR = risk ratio; SD = standard deviation; SP = sulfadoxine-pyrimethamine

Figure S-21. Any evidence of underweight (WAZ <2 SD) from birth to two months of life



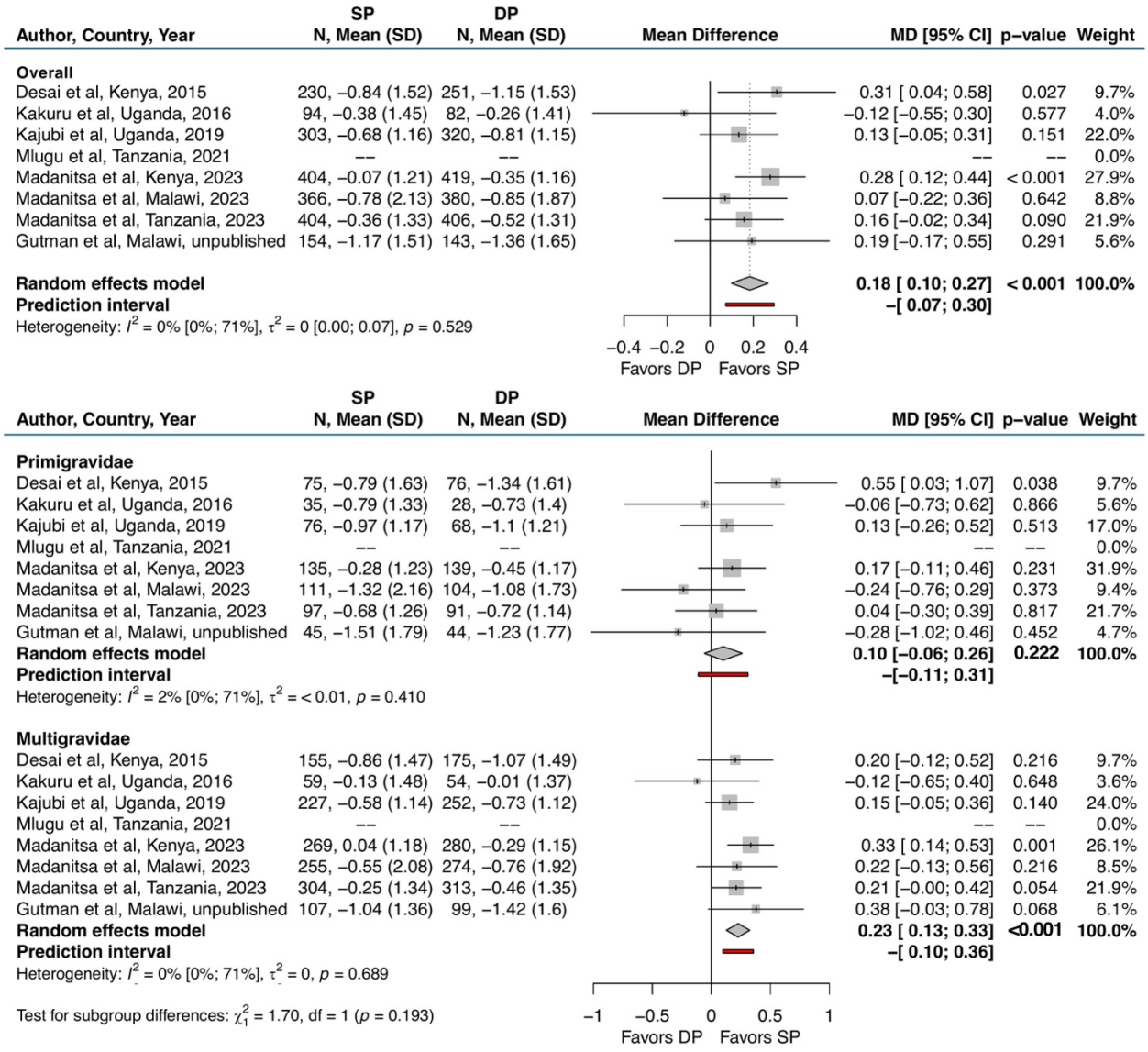
Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; RR = risk ratio; SD = standard deviation; SP = sulfadoxine-pyrimethamine; WAZ = weight-for-age z-score

Figure S-22. Any evidence of wasting (WLZ <2 SD) from birth to two months of life



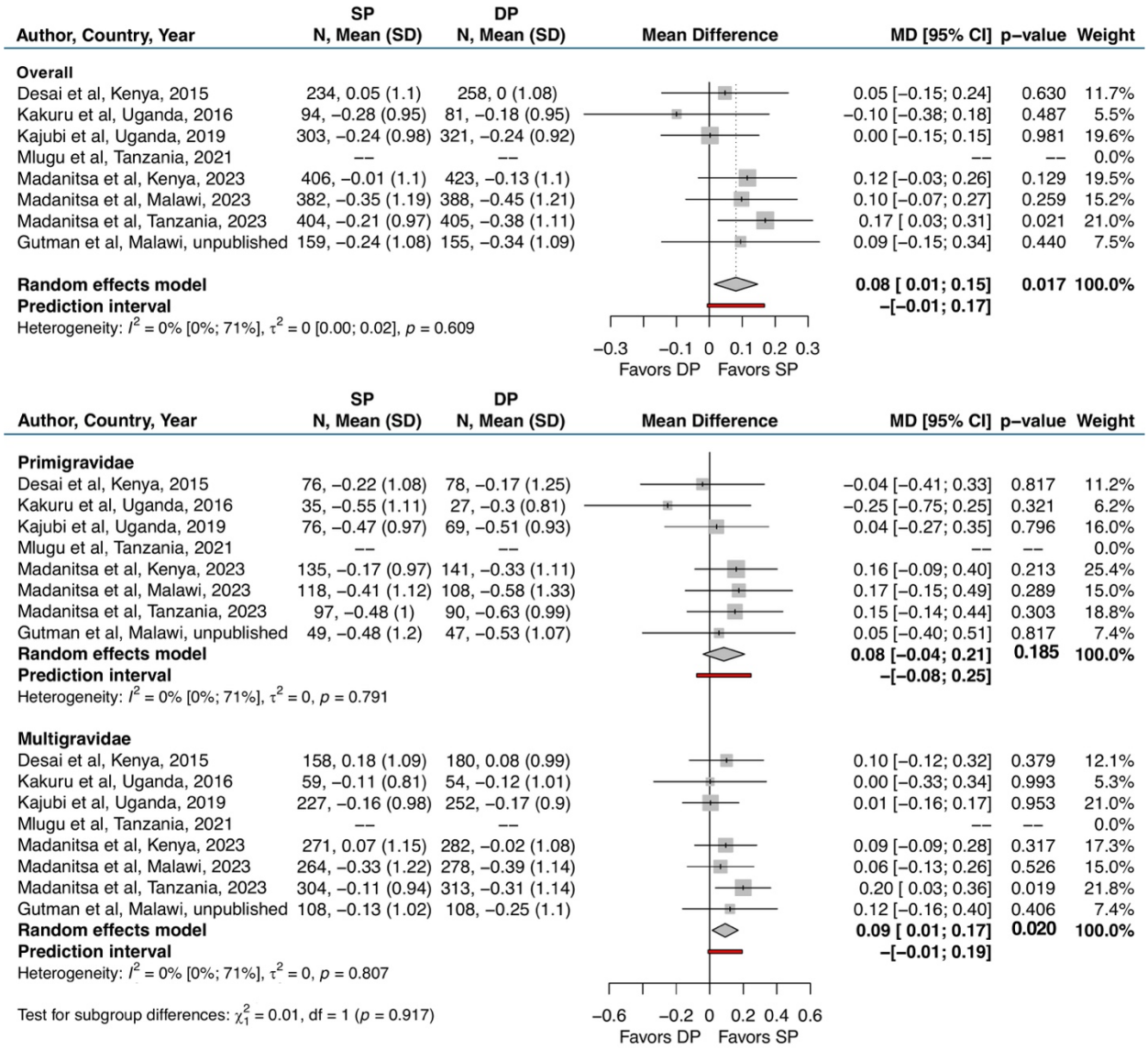
Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; RR = risk ratio; SD = standard deviation; SP = sulfadoxine-pyrimethamine; WLZ = weight-for-length z-score

Figure S-23. Mean length-for-age z-score at two months of life



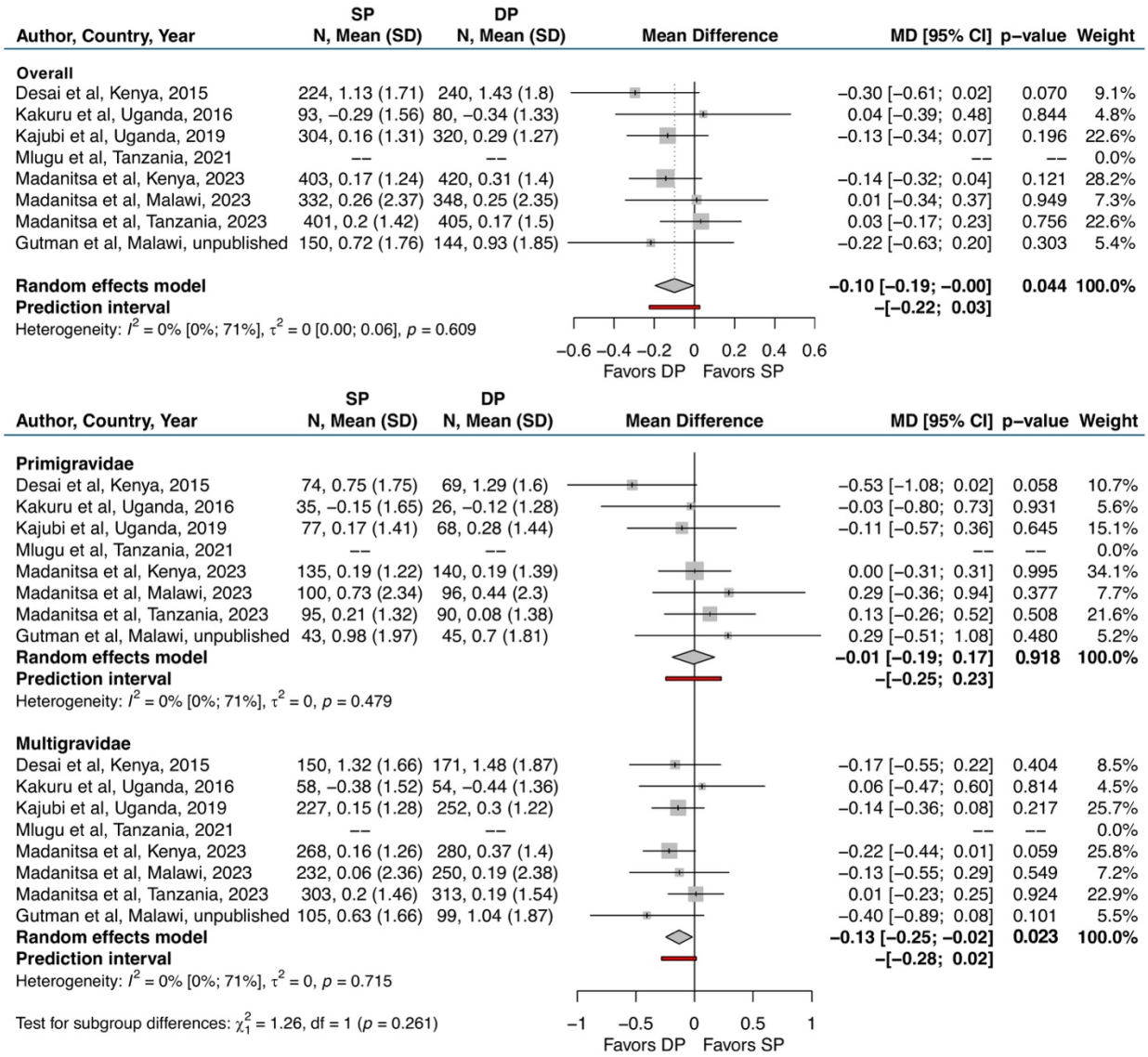
Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; MD = mean difference; SD = standard deviation; SP = sulfadoxine-pyrimethamine

Figure S-24. Mean weight-for-age z-score at two months of life



Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; MD = mean difference; SD = standard deviation; SP = sulfadoxine-pyrimethamine

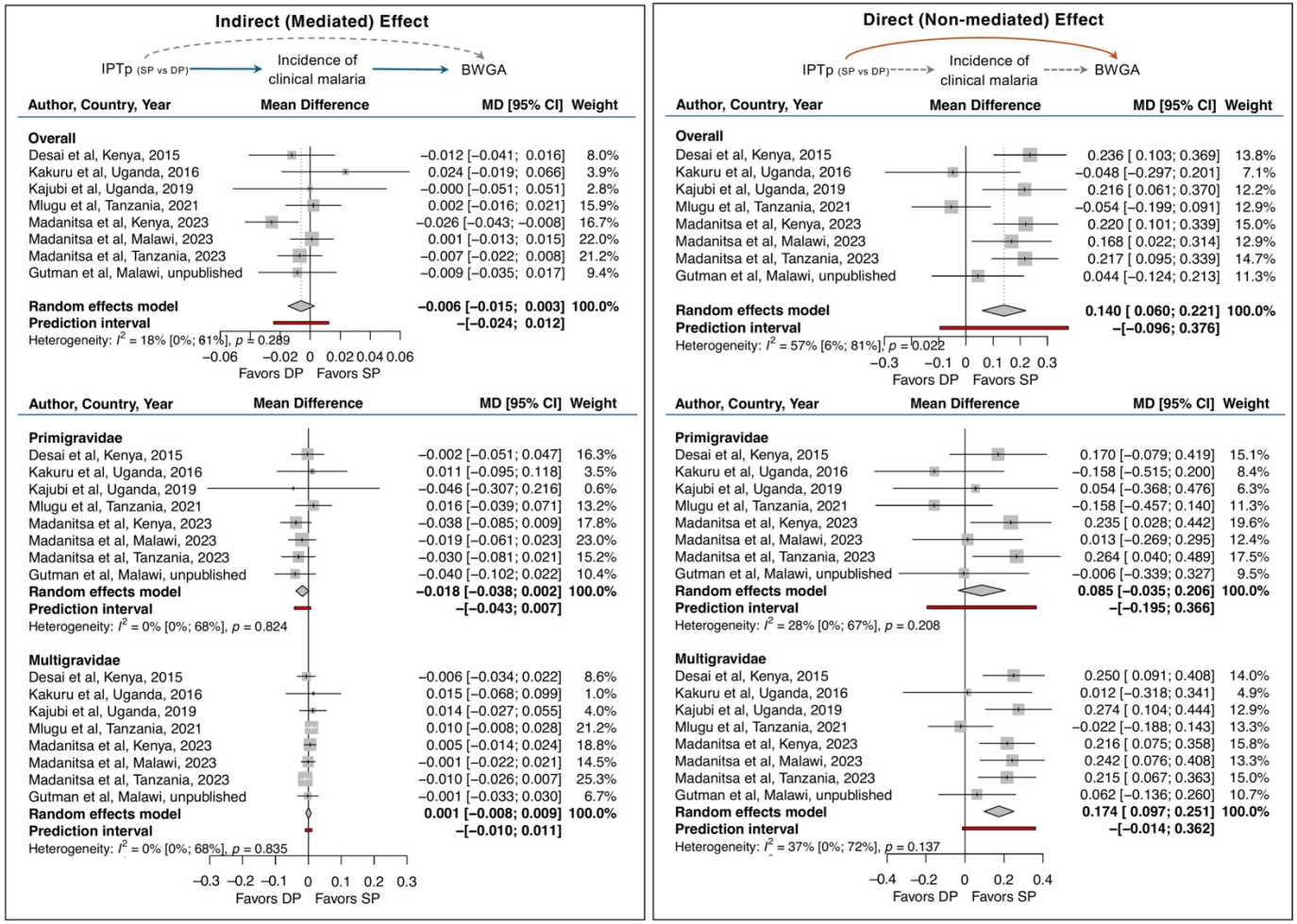
Figure S-25. Mean weight-for-length z-score at two months of life



Abbreviations: CI = confidence interval; DP = dihydroartemisinin-piperaquine; MD = mean difference; SD = standard deviation; SP = sulfadoxine-pyrimethamine

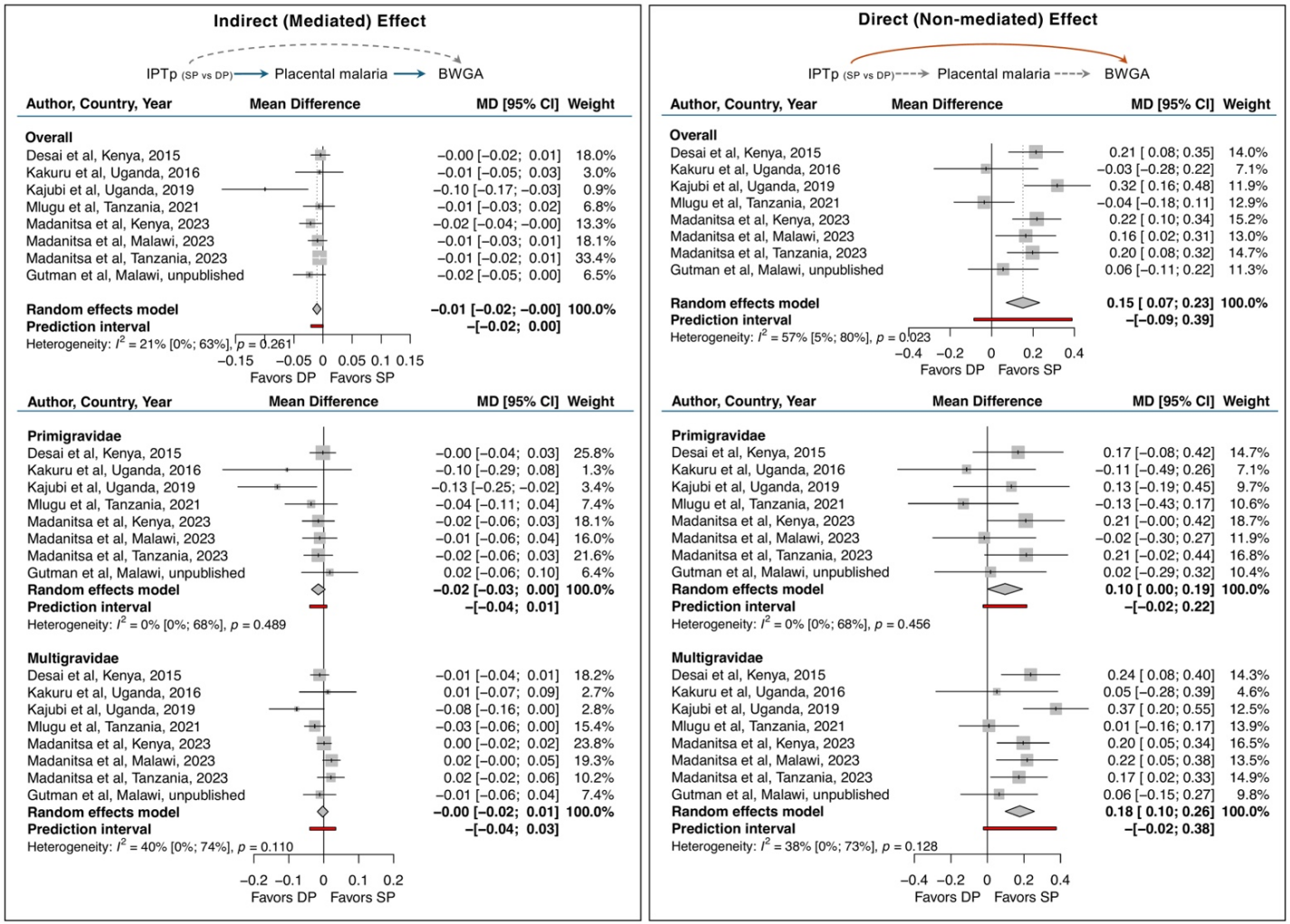
Appendix 8. Study-specific effect estimates from mediation analyses

Figure S-26. IPTp differences in BWGA z-scores mediated by incidence of clinical malaria during pregnancy



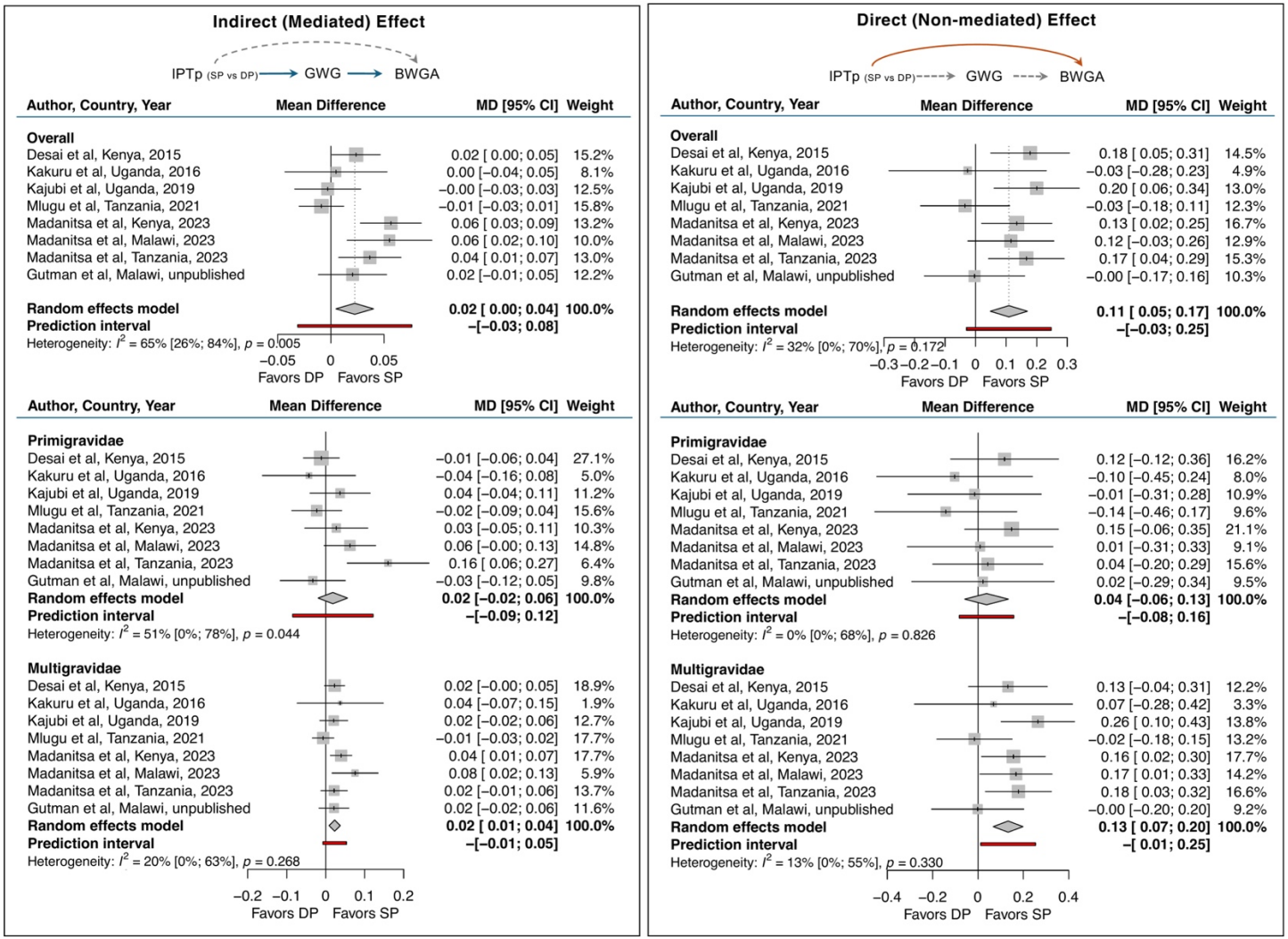
Abbreviations: BWGAz = Birthweight-for-gestational age, CI = confidence interval; DP = dihydroartemisinin-piperaquine; MD = mean difference; SP = sulfadoxine-pyrimethamine

Figure S-27. IPTp differences in BWGA z-scores mediated by placental malaria infection defined as any evidence of pigment or parasites detected by histopathology, microscopy, PCR, or RDT



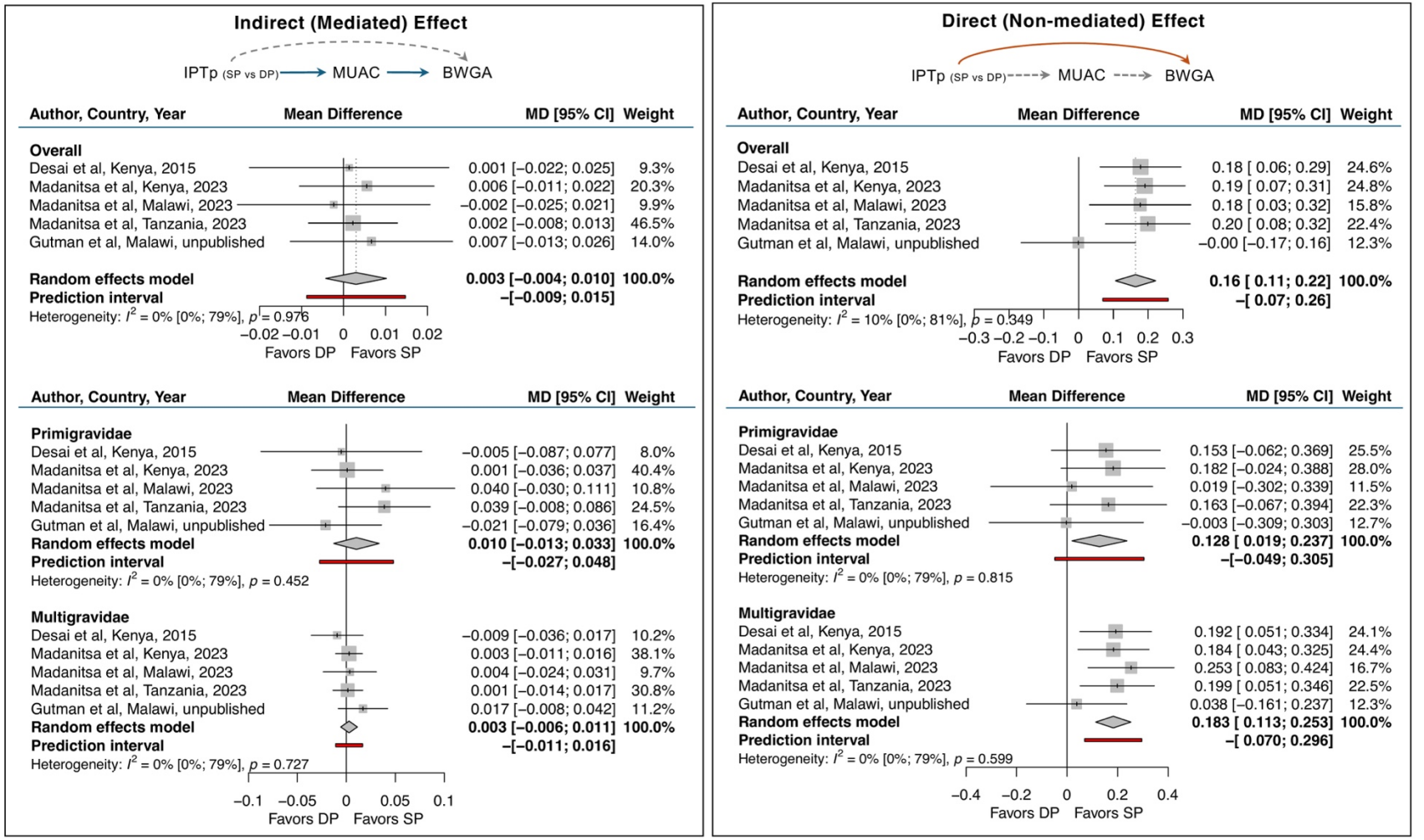
Abbreviations: BWGAz = birthweight-for-gestational age z-score; CI = confidence interval; DP = dihydroartemisinin-piperaquine; MD = mean difference; SP = sulfadoxine-pyrimethamine

Figure S-28. IPTp differences in BWGA z-scores mediated by gestational weight gain



Abbreviations: BWGAz = Birthweight-for-gestational age, CI = confidence interval; DP = dihydroartemisinin-piperaquine; GWG = Gestational weight gain; MD = mean difference; SP = sulfadoxine-pyrimethamine

Figure S-29. IPTp differences in BWGA z-scores mediated by MUAC



Abbreviations: BWGAz = Birthweight-for-gestational age, CI = confidence interval; DP = dihydroartemisinin-piperaquine; MD = mean difference; MUAC = mid-upper arm circumference; SP = sulfadoxine-pyrimethamine

Appendix 9. Results for excluded Okoro et al, Nigeria (2023) trial

Table S-9. Table 1 Participant characteristics

Enrolment characteristics	Total	IPTp-SP	IPTp-DP
	N=197	N=91	N=106
Maternal age in years, mean (SD)	27·4 (6·0)	27·7 (6·3)	27·0 (5·8)
Gestational age in weeks, mean (SD)	17·5 (1·6)	17·7 (1·6)	17·3 (1·5)
Gravidity categories, n/N (%)			
Primigravidae	68/197 (35%)	30/91(33%)	38/106 (36%)
Secundigravidae	25/197 (13%)	11/91 (12%)	14/106 (13%)
Multigravidae (3+)	104/194 (53%)	50/91 (55%)	54/106 (51%)
Weight in kg, mean (SD)	65·0 (15·6)	66·1 (14·9)	64·0 (16·1)
Height in cm, mean (SD)	158·7 (7·8)	159·0 (6·7)	158·3 (8·6)
Maternal MUAC in cm, mean (SD)	--	--	--
Highest level of schooling completed, n/N (%)			
None	--	--	--
Primary	--	--	--
Secondary	--	--	--
Higher	--	--	--
Wealth index tertiles, n/N (%)			
Lowest tertile	--	--	--
Middle tertile	--	--	--
Highest tertile	--	--	--
Slept under a bed net last night, n/N (%)	--	--	--
Microscopy positivity, n/N (%)	82/196 (42%)	41/91 (48%)	39/105 (37%)
PCR/LAMP positivity, n/N (%)	--	--	--

Abbreviations: LAMP = loop-mediated isothermal amplification method MUAC = mid-upper arm circumference; PCR = polymerase chain reaction

Table S-9. Description of study characteristics and outcomes collected

Study Information	Okoro et al[22]
Study Details	
Source	PACTR202002644579177
Study site(s)	Tertiary hospital in Maiduguri, Nigeria
Prevalence of PfDHPS 540E mutation, %*	0%
Prevalence of PfDHPS 581G mutation, %*	0%
Number of Participants Randomized (Among Singleton Pregnancies)	197
Sulfadoxine-Pyrimethamine	91
Dihydroartemisinin-Piperaquine	106
IPTp dosing regimen	3-course IPTp given at 16-20, 28, and 36 weeks
Number of IPTp doses, median (IQR)	2 (2-3)
Microscopy positivity at enrolment, %	42%
Birth outcomes	
Foetal Loss	Available (nne observed)
Small-for-Gestational Age	Infant sex not collected
Preterm Delivery	Available†
Low Birthweight	Available
Neonatal Death	Available (none observed)
Continuous Birth Outcomes	
Mean Birthweight	Available
Mean Gestational Age at Delivery	Available†
Mean Birthweight-for-Gestational Age Z-scores	Infant sex not collected
Malaria Outcomes	
Incidence of Clinical Malaria Episodes in Pregnancy	Not collected
Any Evidence of Pigment Only in Placental Tissue by Histopathology	Available
Any Evidence of Parasites in Placental Tissue or Blood by Histopathology, PCR, Microscopy, or RDT	Available; Testing of placental blood for parasitemia not done
Any Evidence of Parasites or Pigment in Placental Tissue or Blood by Histopathology, PCR, Microscopy, or RDT	Available; Testing of placental blood for parasitemia not done
Any Evidence of Parasites in Maternal Peripheral Blood at Delivery by RDT, Microscopy, or PCR	Available; Testing by microscopy only
Maternal Outcomes	
Any Evidence of Severe Anaemia (Hb <7 g/dl) During Pregnancy	Not collected

Study Information	Okoro et al[22]
Any Evidence of Moderate Anaemia (Hb <9 g/dl) During Pregnancy	Not collected
Any Evidence of Mild Anaemia (Hb <11 g/dl) During Pregnancy	Not collected
MUAC at Delivery	Not collected
Maternal weight gain per week‡	Not collected
Infant Outcomes	
Any Evidence of Stunting (LAZ <2 SD) from Birth to 2 Months of Life	Not collected
Any Evidence of Underweight (WAZ <2 SD) from Birth to 2 Months of Life	Not collected
Any Evidence of Wasting (WLZ <2 SD) from Birth to 2 Months of Life	Not collected
Mean LAZ at 2 Months of Life	Not collected
Mean WAZ at 2 Months of Life	Not collected
Mean WLZ at 2 Months of Life	Not collected

Abbreviations: ANC = antenatal care visit; Hb = haemoglobin; IQR = interquartile range; LAZ = length-for-age z-score; MUAC = mid-upper arm circumference; WAZ = weight-for-age z-score; WLZ = weight-for-length z-score

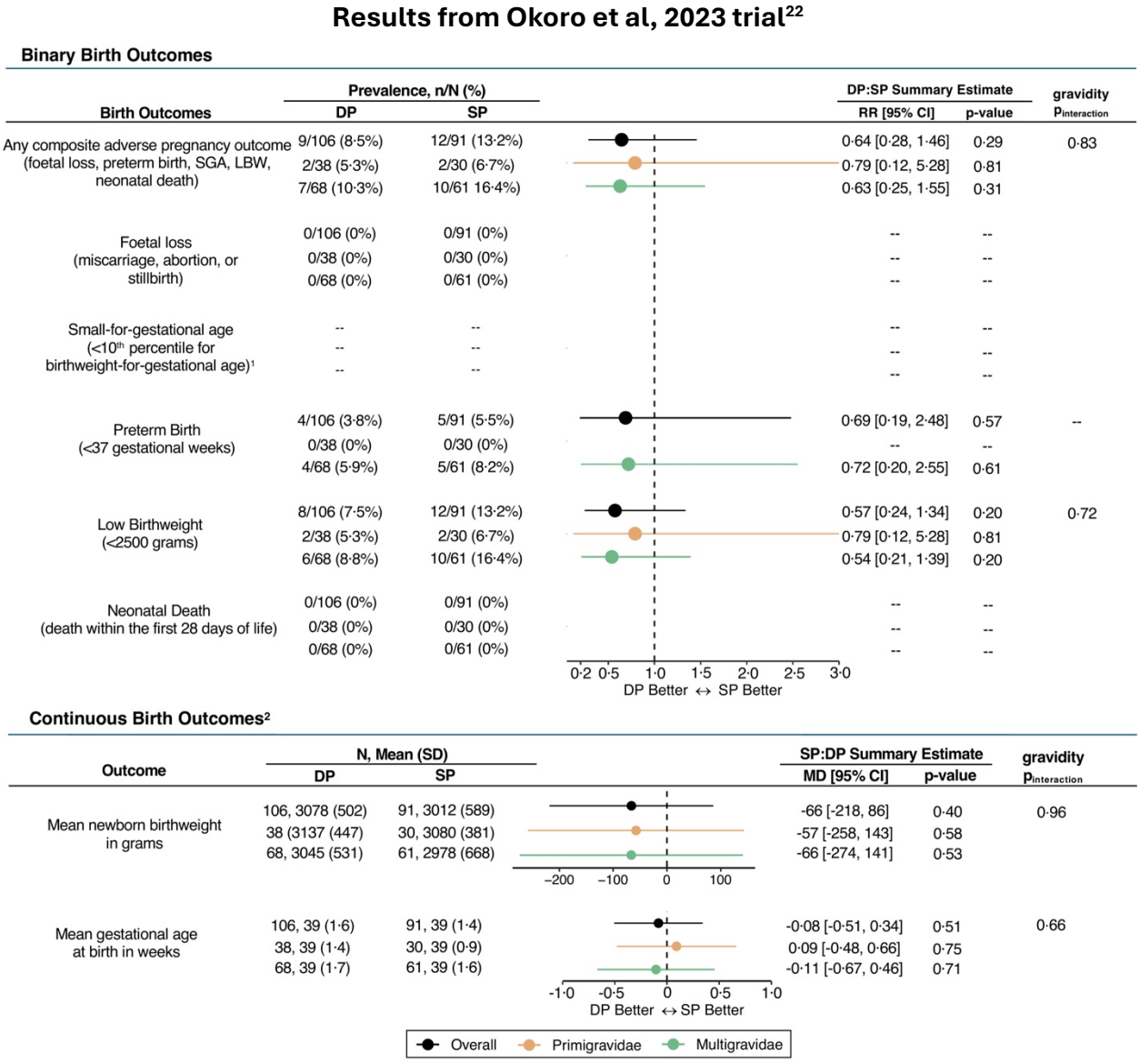
* Prevalence of polymorphisms were taken from another study from a neighboring site.[23]

† Gestational age dating not confirmed by ultrasound

‡ Maternal weight gain per week calculated using the following formula:

$$\frac{Weight_{last\ ANC\ visit\ before\ delivery} - Weight_{enrollment}}{\#\ of\ weeks\ between\ enrollment\ and\ last\ ANC\ visit}$$

Figure S-30. Birth outcomes

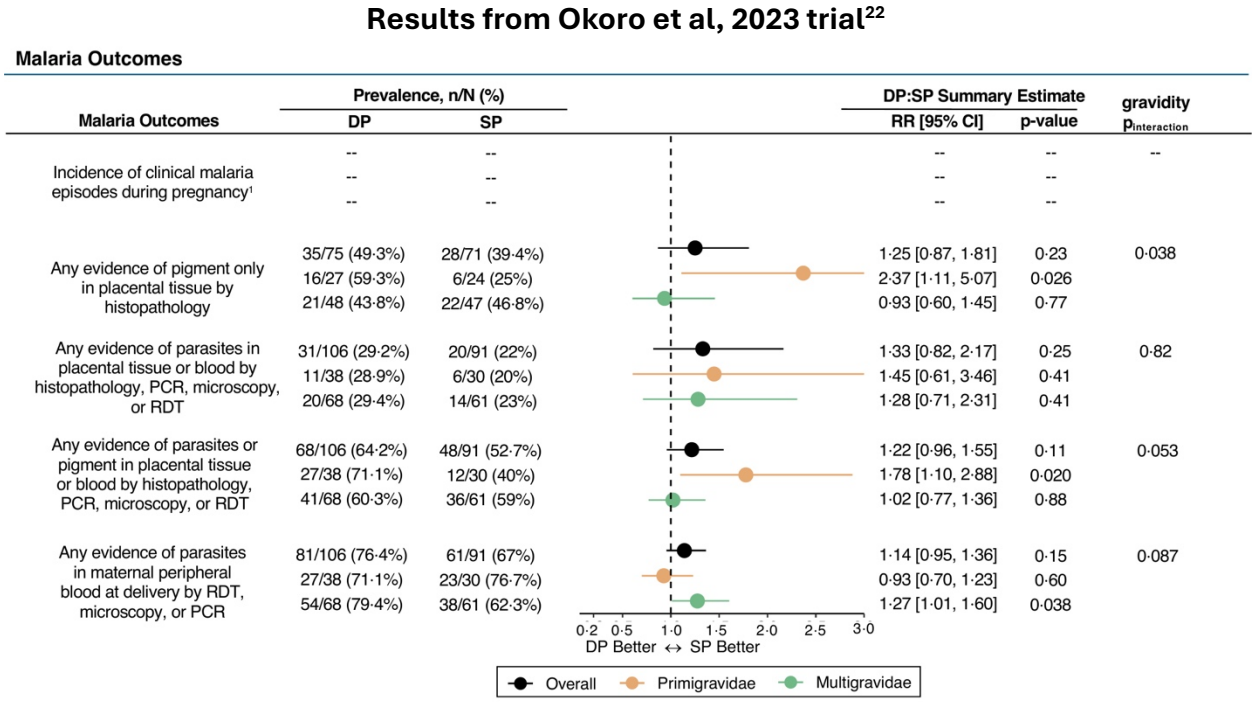


Abbreviations: CI=confidence interval; DP=dihydroartemisinin-piperaquine; MD=mean difference; RR = relative risk ratio; SD=standard deviation; SP=sulfadoxine-pyrimethamine

[1] Did not collect infant sex variable used to determine birthweight percentiles for gestational age

[2] Birthweight-for-gestational age z-scores missing due to unknown infant sex

Figure S-31. Malaria Outcomes



Abbreviations: CI=confidence interval; DP=dihydroartemisinin-piperaquine; PCR=polymerase chain reaction; RDT=rapid diagnostic test; RR=relative risk ratio; SP=sulfadoxine-pyrimethamine

[1] Outcome not collected

Appendix 10. Appendix References

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