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Burden of malaria in pregnancy among adolescent girls from five sub-Saharan African countries: a meta-analysis of individual-participant data

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Background

- In sub-Saharan Africa (SSA), an estimated **12 million pregnancies** were exposed to malaria infection in 2019
- Malaria in pregnancy increases the risk of maternal morbidity and mortality, adverse pregnancy outcomes, low birth weight, and infant mortality
- Adolescent motherhood is associated with increased risk of preterm birth, low birth weight, and childbirth complications such as asphyxia or neonatal mortality
- Previous studies carried out in SSA showed that malaria was among the most important causes of maternal mortality in pregnant adolescents in endemic areas

Objective

To estimate the burden of malaria in pregnancy among adolescent girls compared to adult women from five SSA countries.

Study design

This was a secondary analysis of data obtained prospectively from two EDCTP-funded clinical trials* coordinated by ISGlobal and conducted in five SSA countries, between 2009 and 2014

- Trial 1: randomized controlled open-label trial, performed in **Benin, Gabon, Mozambique, and Tanzania**, that evaluated the efficacy and safety of mefloquine (MQ) compared to sulfadoxine-pyrimethamine (SP) as intermittent preventive treatment of malaria during pregnancy (IPTp) among **HIV-uninfected pregnant women**
- Trial 2: randomised placebo-controlled trial carried out in **Mozambique, Kenya, and Tanzania**, among **HIV-infected pregnant women** on daily cotrimoxazole prophylaxis (CTXp) that evaluated the efficacy and safety of three doses of IPTp with MQ plus CTX compared to CTXp alone for prevention of malaria.

** Gonzalez et al. Plos Med 2014*

Study population

- **Pregnant women of all gravidities** attending the ANC clinic for the first time during the current pregnancy
- ≤ 28 weeks of gestation
- Resident in the study area
- Agreed to give birth in one of the maternity wards of the study area

The population subgroup of interest was **pregnant adolescents**.

- Following UNICEF, UNFPA and WHO definitions, we considered **adolescents** those women between **10 and 19 years of age**
- Women aged 20 or more were used as comparison group

Study variables

- **Principal study outcomes**:
  - Clinical malaria episodes during pregnancy
  - Peripheral malaria parasitaemia at delivery (measured by thick blood smear)
  - Placental malaria infection (measured by thick blood smear and histology)
- **Main independent variable**: adolescent (dummy variable Yes/No)
- **Covariates**:
  - Treatment arm
  - Gestational age at recruitment
  - MUAC
  - Literacy
  - Anaemia at recruitment
  - Adherence to study treatment (IPTp)
- **Subgroup analysis by**: HIV status and gravidity

Statistical analysis

- This was a pooled analysis using a **two-stage individual patient data meta-analysis** (IPD-MA) approach
  - Stage 1: multivariate logistic regression analyses
  - Stage 2: the regression results were pooled in a standard DerSimonian-Laird random-effects model
- Each country for each trial was considered a separate *study* to be able to control for **country** and **HIV status** at the same time

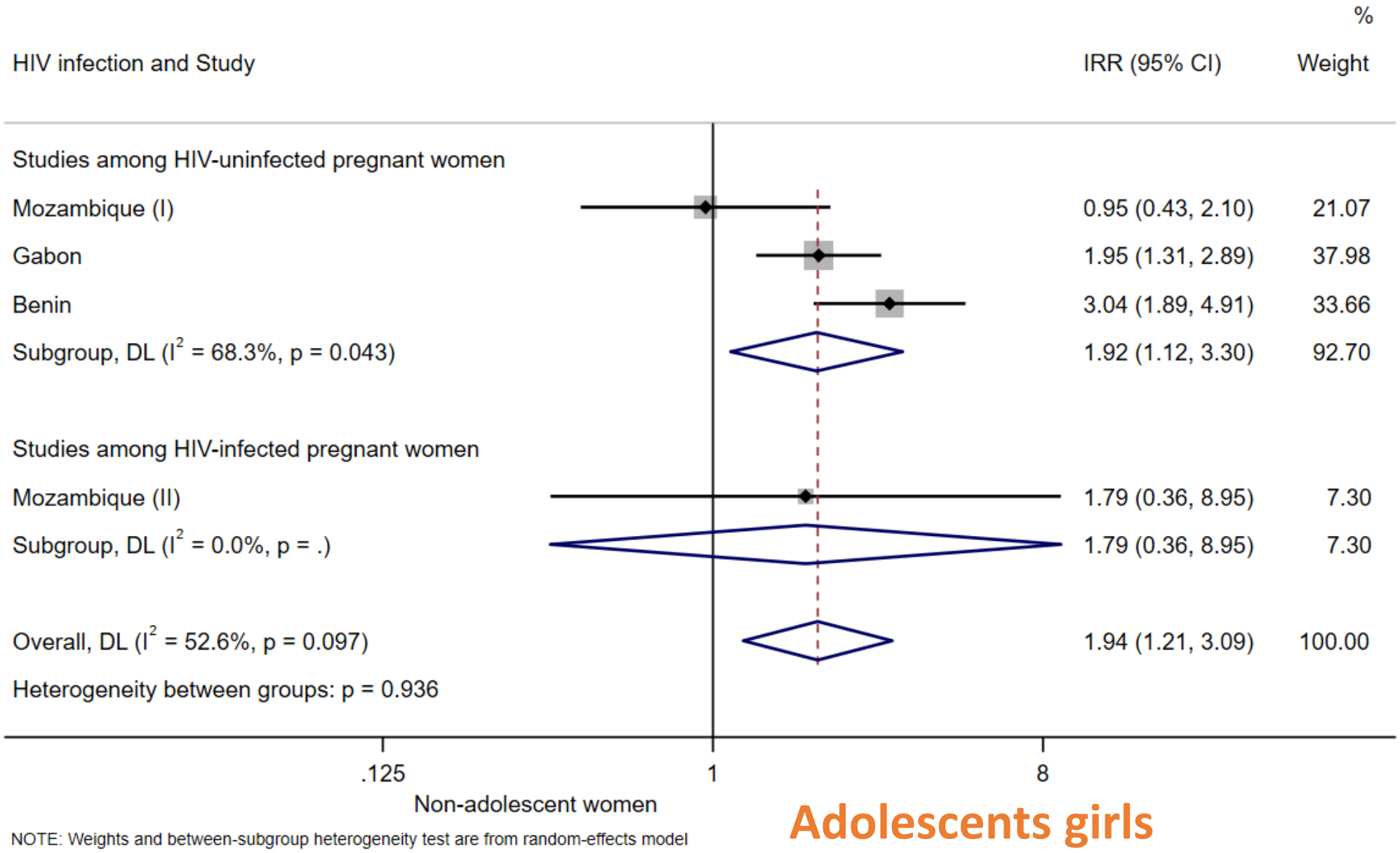
Trial 1 (HIV-uninfected women)	Trial 2 (HIV-infected women)
Mozambique (I)	Mozambique (II)
Gabon	Tanzania (II)
Tanzania (I)	Kenya
Benin	

Results: participant's characteristics

	Trial 1 N=4735		Trial 2 N=1069	
	≤19 years n=1101	>19 years n=3634	≤19 years n=100	>19 years n=969
Primigravidae [1]	832 (75.6%)	541 (14.9%)	54 (54.0%)	54 (5.6%)
Weight at baseline (kg) [2]	56.58 (8.0)	60.71 (11.7)	58.35 (8.3)	60.16 (8.4)
Gestational age at recruitment (weeks) [2]	19.69 (5.2)	20.43 (5.1)	20.73 (4.8)	20.05 (5.7)
Anaemia (<11 g/dl Hb) [1]	701 (63.7%)	2107 (58.0%)	73 (73.0%)	637 (65.7%)
MUAC at baseline ≤ 22 [1]	140 (12.7%)	250 (6.9%)	2 (2.0%)	19 (2.0%)
Illiterate [1]	154 (14.0%)	1288 (35.4%)	15 (15.0%)	187 (19.3%)
Adherent to treatment [1]	778 (70.7%)	2654 (73.0%)	82 (82.0%)	776 (80.1%)

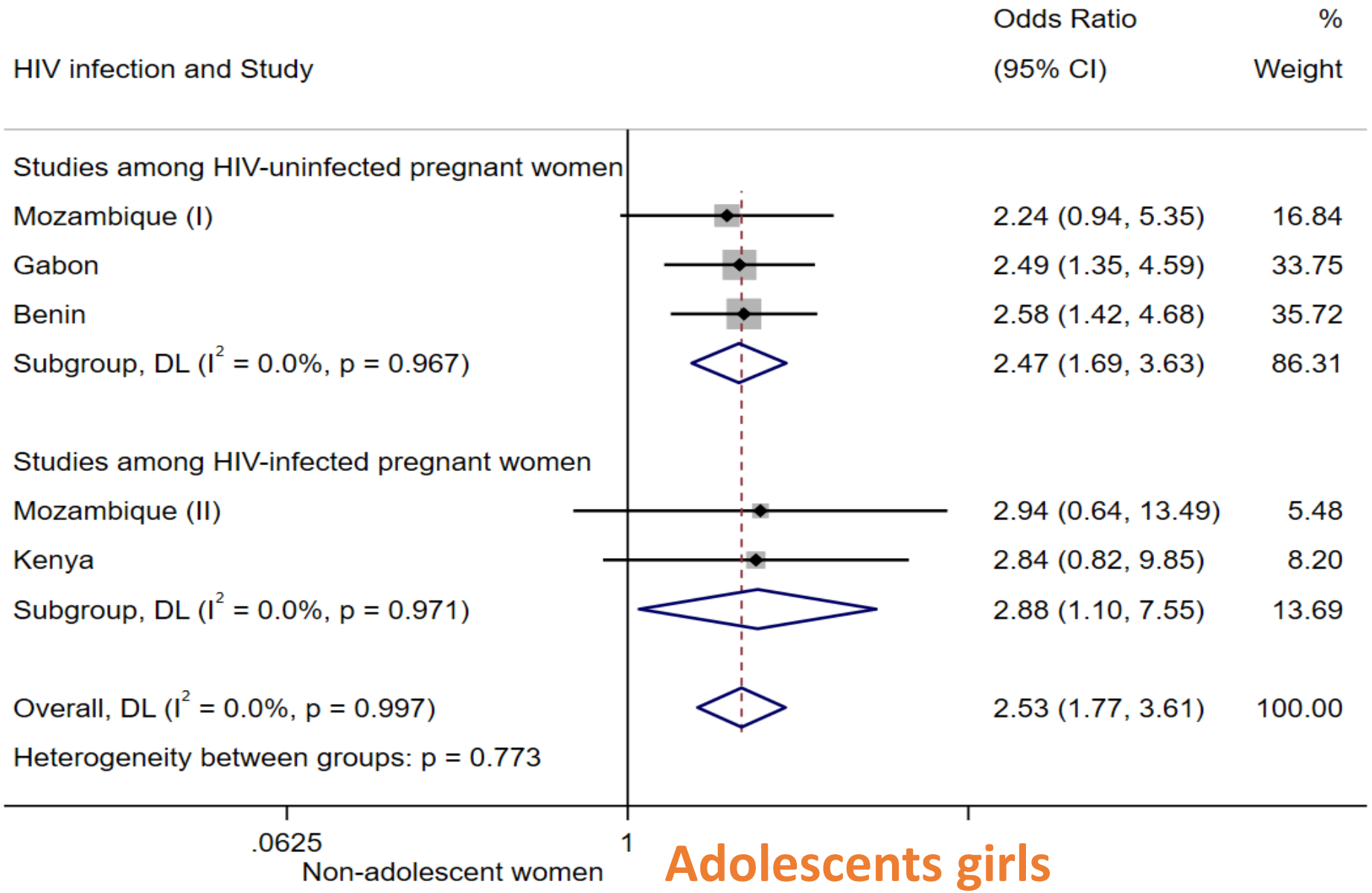
1: n (column percentage); 2: Arithmetic mean (SD)

Clinical malaria episodes during pregnancy



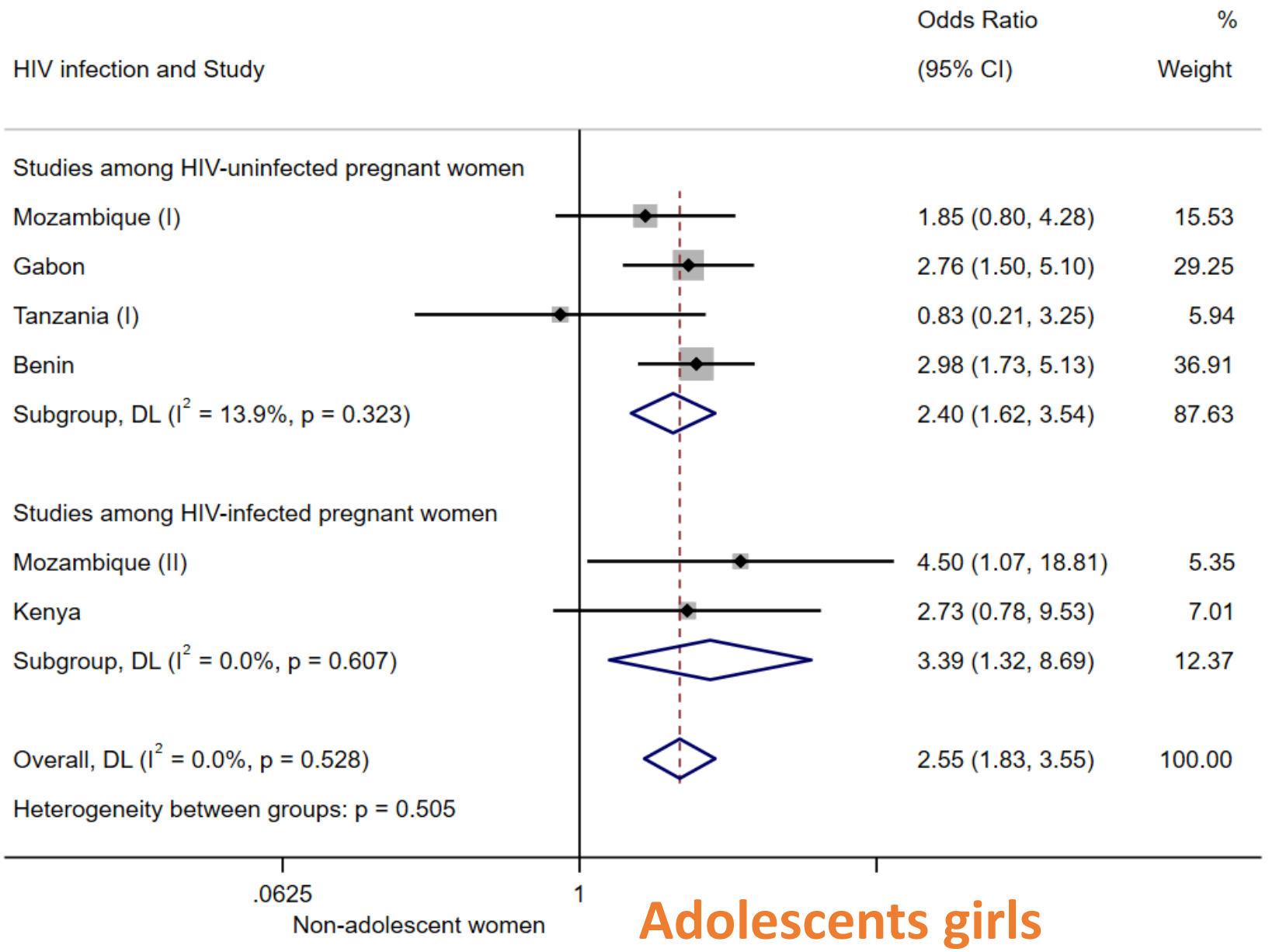
Adolescents girls

Parasitaemia at delivery



NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

Placental infection



Analysis stratified by gravidity

- Each study was split into two sub-studies: one with primigravidae and the other with multigravidae
- The associations of adolescence with the three malaria-related study outcomes remained despite stratifying by gravidity
- The results suggest that the **association between adolescence and the study outcomes is independent from the gravidity** of the woman

Conclusions

- Increased
  - Clinical malaria during pregnancy
  - Prevalence of malaria parasitaemia at delivery
  - Placental infection were significantly

} associated with being ≤19 years of age

- High consistency across studies
- Findings in line with the few available studies from different SSA countries
- These associations were also observed only among primigravidae and multigravidae → **gravidity is unlikely to be confounding our results**
- Results for HIV-infected and HIV-uninfected women point to the same direction → **adolescent girls suffer more from malaria in pregnancy regardless of their HIV status**

Discussion

Plausible explanation for the results:

- The **pubertal hormonal environment** could influence susceptibility to malaria → increased levels of the steroid dehydroepiandosterone sulfate (DHEAS)

- **Increased acquisition of malaria immunity with age** following repeated exposure to different Plasmodium strains

Recommendations

- Interventions to **prevent adolescent pregnancies** should be prioritized and urgently implemented in malaria-endemic settings
- Interventions to **prevent malaria** once adolescents become pregnant should also be developed
- Adolescent girls should be particularly targeted in **malaria control strategies**, including ITN distribution strategies even before they become pregnant

MiPPAD consortium partners

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Thank you for your attention

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