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PROMISE-1084s and PROMISE-ND

Growth deficits among HIV Exposed Uninfected (HEU) children with perinatal ARV drug exposures

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Physical growth restriction among HEU children in SSA

- About 1.5 million HEU children/per year projected by 2020 (>90% from SSA)[1]
- Majority will have peripartum ARV drug exposures (mART and iNVP)
- Pre-ART era:
  - Growth restriction reported among HEU vs. HIV unexposed uninfected (HUU) children[2]
  - *Maternal viral load* associated with increased risk of physical growth deficits among HEU vs. HUU[3-5]
- ART era – reports persist of physical growth deficits among HEU with peripartum ARV drug exposures, vs. HUU children[6,7]
- Childhood growth restriction is associated with infectious disease severity, malnutrition & death; cognitive & early school learning outcomes; adulthood NCDs, and potential intergenerational effect in the girl child[6,7,8]

[1]*UNAIDS: On the Fast Track;* [2] *Evans C et al, Lancet Infect Dis. 2016;* [3]Brocklehurst P, Br J Obstet Gynaecol 1998;105; 836-48; [4]Stratton P, et al. J Acquir Immune Defic Syndr Hum Retrovirol 1999;20:179-86; [5]Turner BJ et al, J Acquir Immune Defic Syndr Hum Retrovirol 1996;12:259-67.6; [6]*Jumare et al, JAIDS, 2019;* [7]*Roux SM et al, Lancet child Adolesc Heal. 2019;* [8]*Victora CG, Lancet, 2008;* [9]*Walker SP, 2011;* [10]*Grantham-mcgregor S, 2007*

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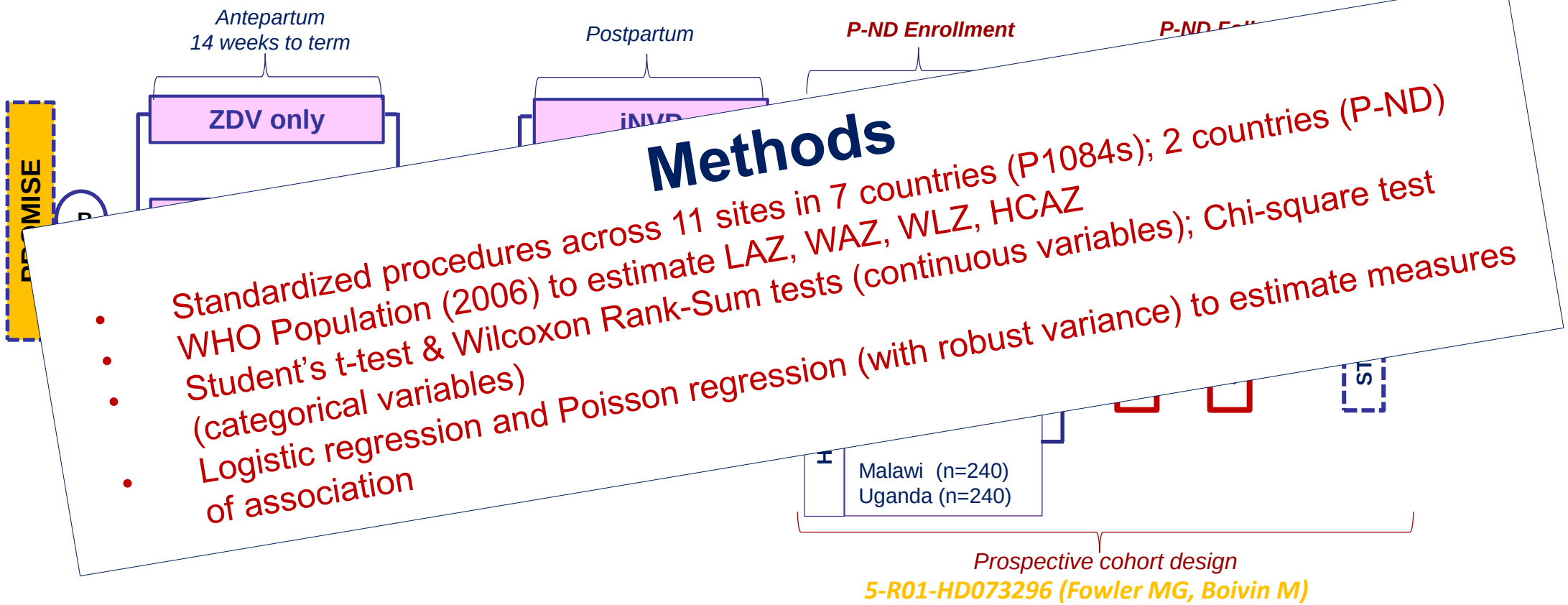

Methods

- Standardized procedures across 11 sites in 7 countries (P1084s); 2 countries (P-ND)
- WHO Population (2006) to estimate LAZ, WAZ, WLZ, HCAZ
- Student's t-test & Wilcoxon Rank-Sum tests (continuous variables); Chi-square test (categorical variables)
- Logistic regression and Poisson regression (with robust variance) to estimate measures of association

2011 → 2012 → 2013 → 2018

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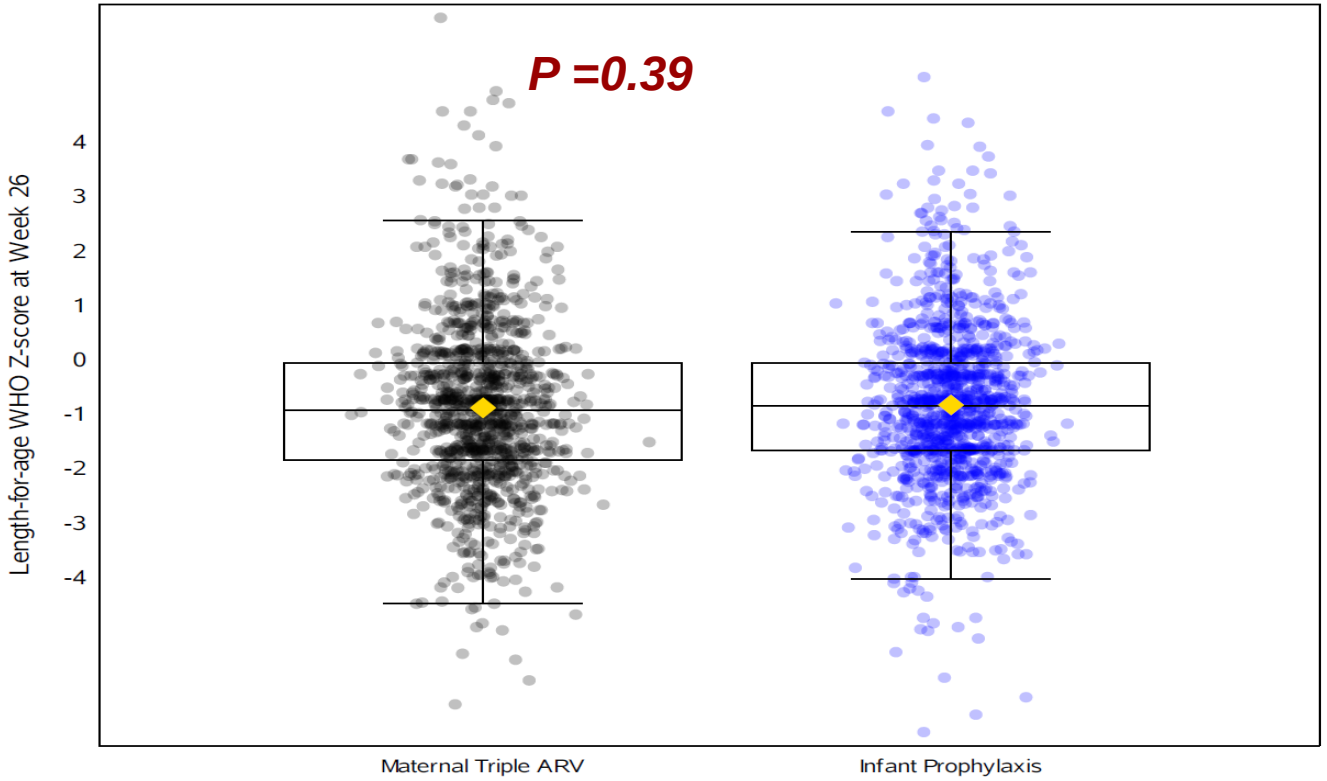
P1084s: Box plot summary of LAZ at week 26 (25th, 50th & 75th percentiles)



Primary outcome:

LAZ at week 26, mean (95% CI)

mART: -0.90 (-0.99, -0.81)
iNVP: -0.85 (-0.93, -0.76)
Mean diff: -0.05 (-0.18, 0.07)

No postpartum treatment effect – i.e. similarly no significant differences between mART vs iNVP observed in linear regression models: AP Rx (p=0.47); country (p=0.23); BF (p=0.23); TDF exposure at wk 26 (p=0.75).

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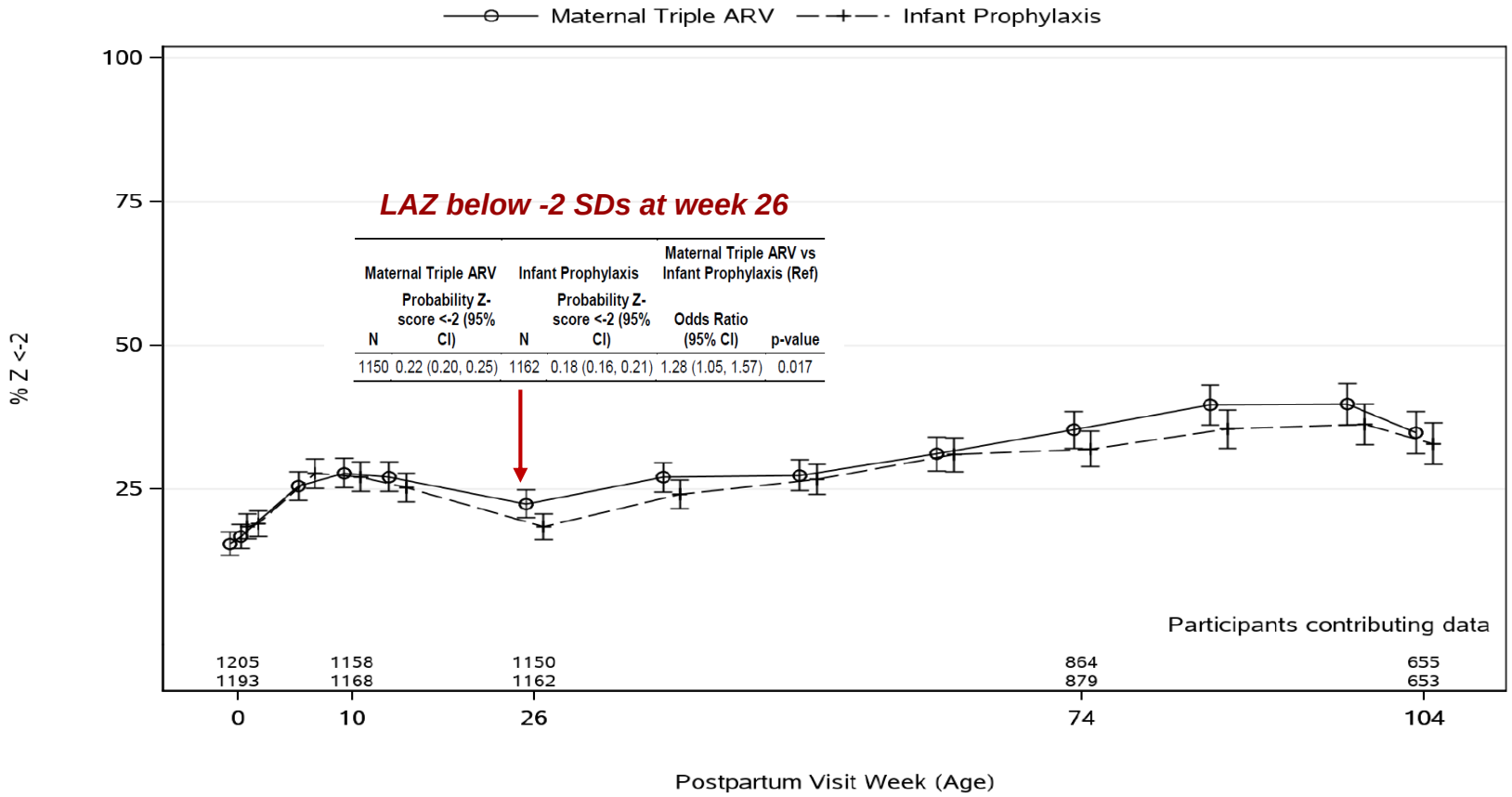
P1084s: Stunting (LAZ below -2 SDs) by postpartum visit (mean, 95% CI)



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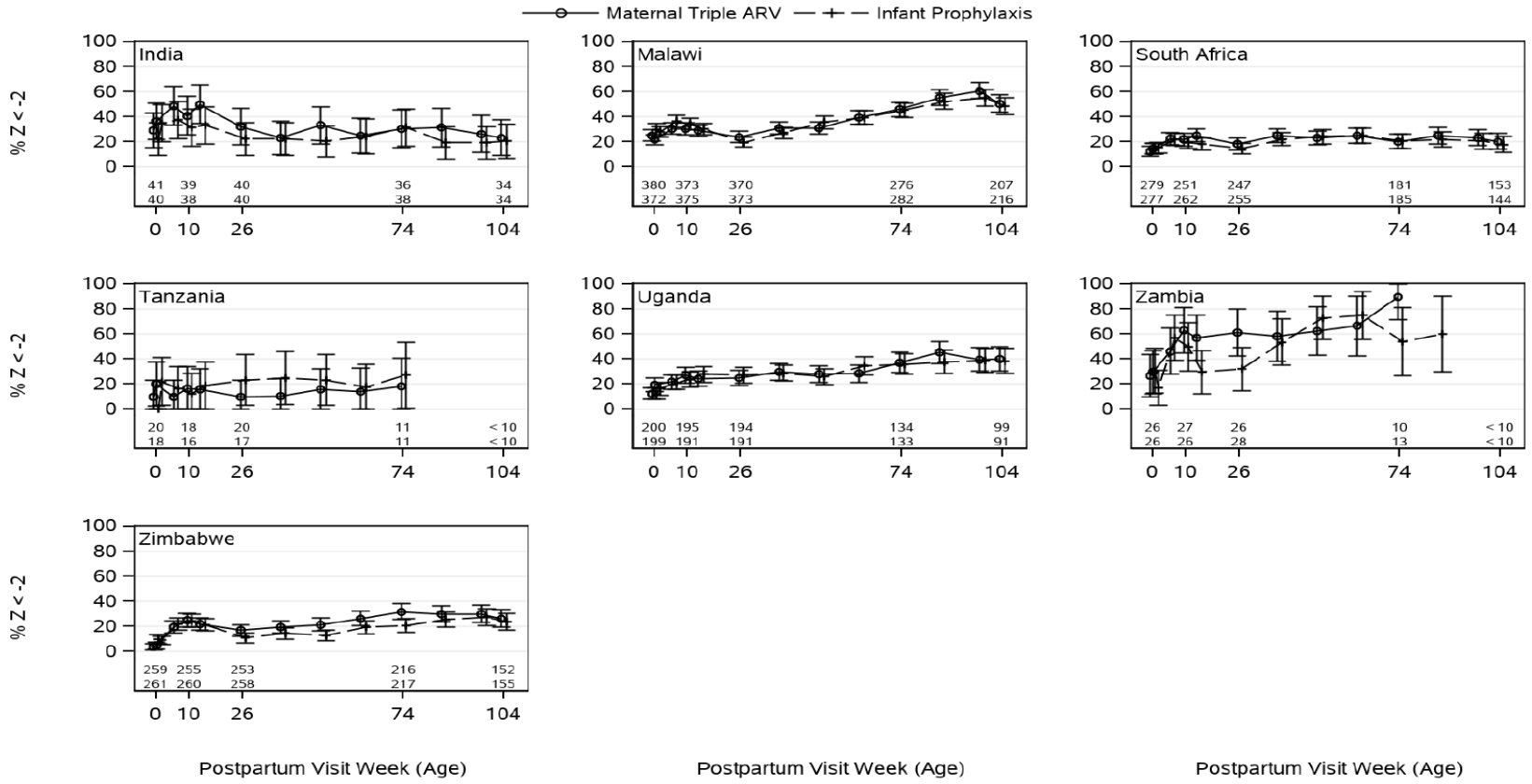
P1084s: Stunting (LAZ below -2) by postpartum visit & country (percent, 95% CI)



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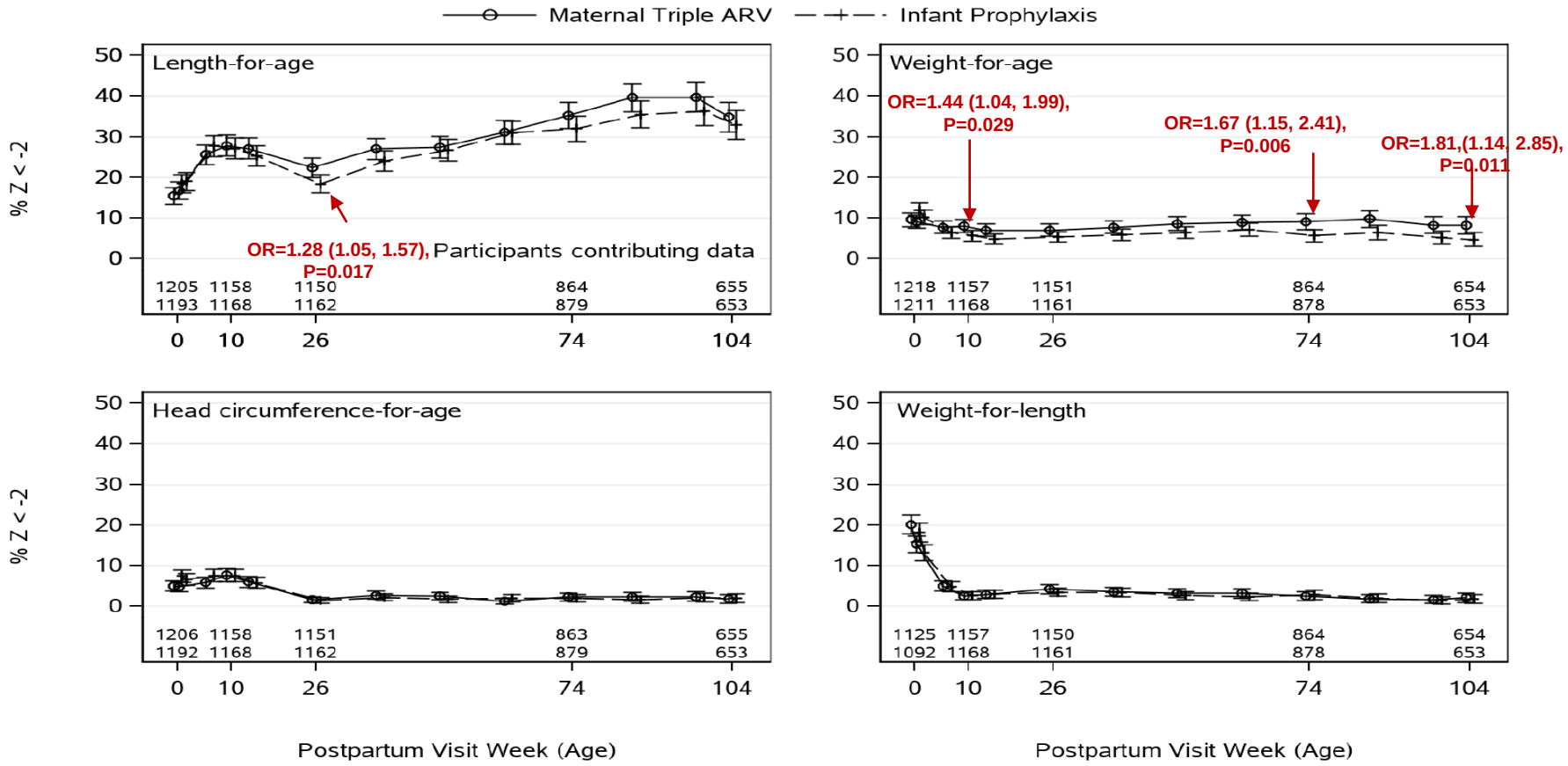
P1084s: Anthropometric Z-scores below -2 SDs by postpartum visit (mean, 95% CI)



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Summary

- **P1084s:** In an intention to treat analysis, the mART vs. iNVP exposed HEU children did not differ significantly for the primary outcome measure of mean LAZ at week 26 or any of the other secondary growth outcome measures.
- P1084s did find significantly increased risk of stunting (LAZ<2SD below the mean) at 26 weeks post delivery for the infants exposed to mART through breastmilk compared to those infants randomized to infant NVP
- P1084s in a *post hoc* analyses also found significantly increased risk of wasting (WAZ<2SDbelow the mean) at 10, 74 and 104 weeks post delivery for the mART arm infants versus those infants randomized to infant NVP.

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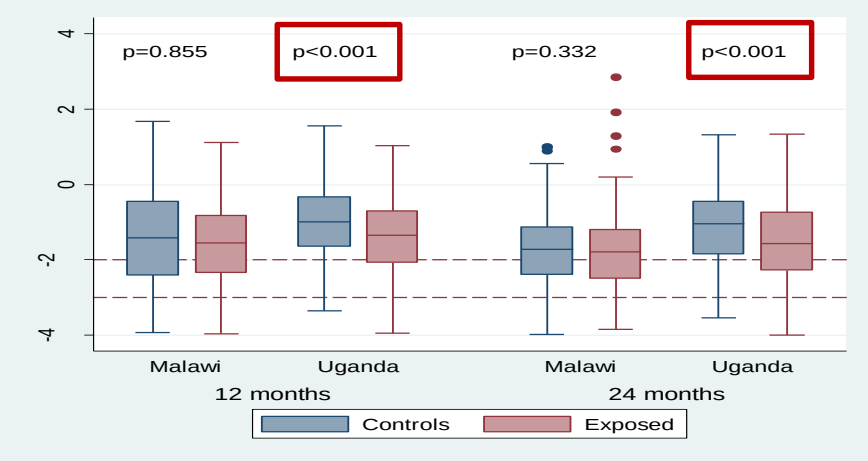
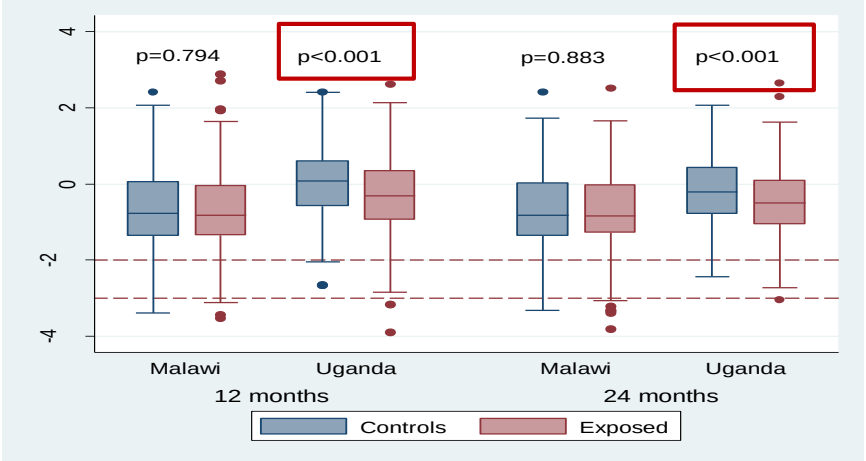
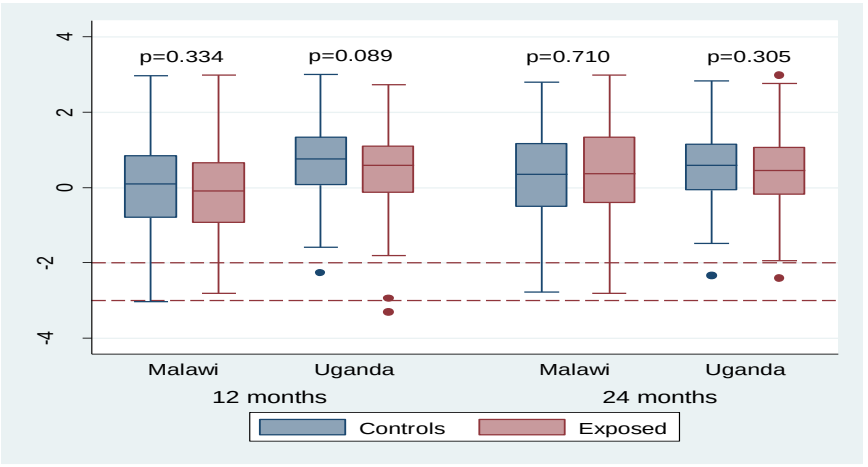
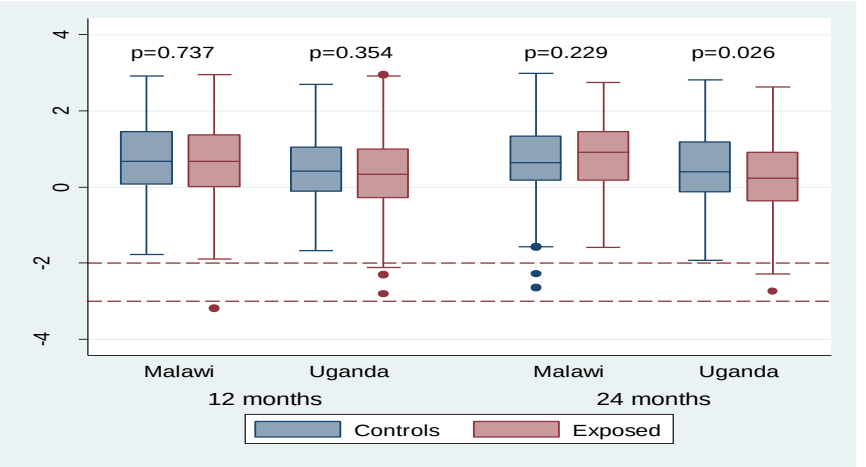
PROMISE-ND: Anthropometric z-scores by exposure and site









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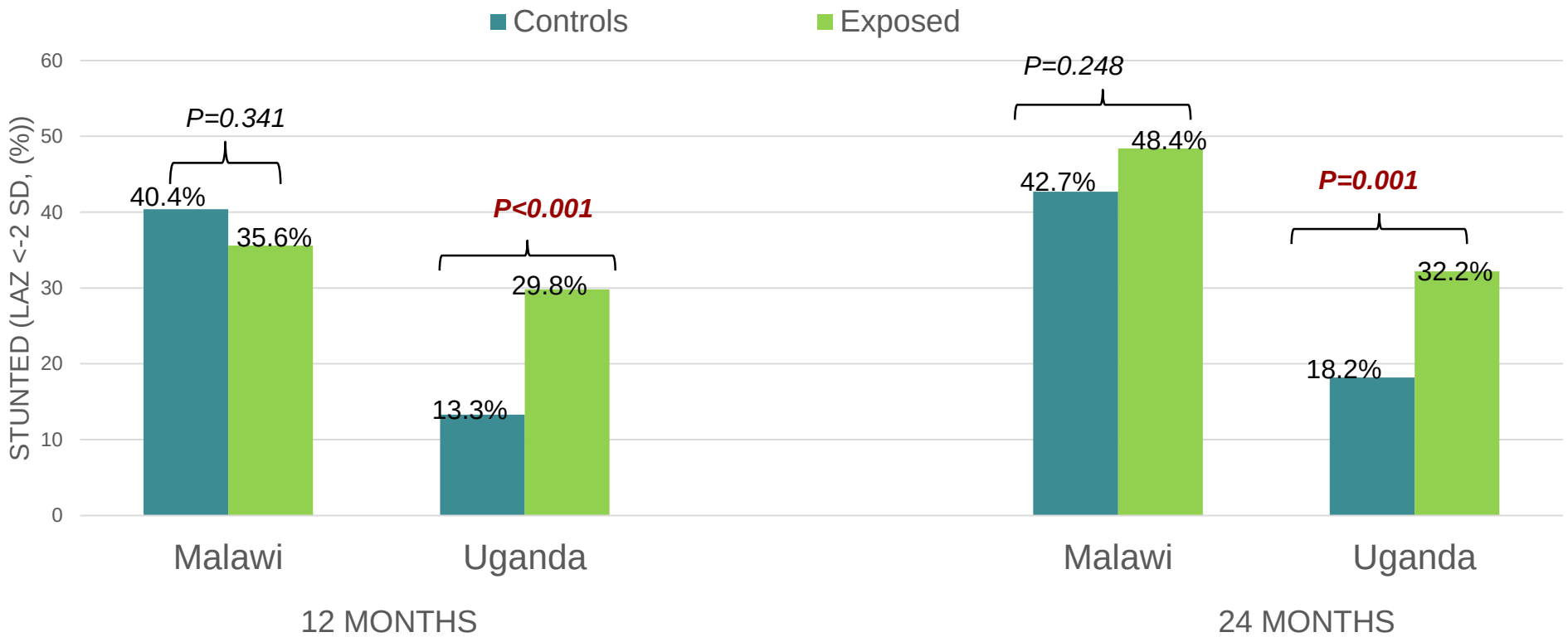
PROMISE-ND: Risk of stunting (LAZ < -2 SD) by age and site



aRR(95% CI), p-value	**0.99 (0.75, 1.32), p=0.982**	**1.79 (1.28, 2.52), p=0.001**	**1.32 (1.10, 1.66), p=0.018**	**1.67 (1.16, 2.41), p=0.006**

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Summary

- **PROMISE-ND:** PROMISE co enrolled HEU vs. age-& sex-matched HUU children at the Blantyre, Malawi and the MUJHU, Kampala Uganda sites
  - had lower median (IQR) of LAZ, WAZ and HCAZ but not WLZ
  - Increased stunting (extreme linear growth faltering) risk at 12 and 24 months-of-age; but did not differ with regard to wasting or underweight risk
  - Increased risk of HCAZ below WHO median at 24 months-age in Uganda but not Malawi
- The biologic mechanisms contributing to the stunting and WAZ findings in P1084s and stunting in the Malawi and Uganda ND study are not yet determined.

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Operations Center: M Allen, A Coletti, K George, K McCarthy, M Valentine
Laboratory Center: A Loftis, S Fiscus
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