

HEU BLOOD mtDNA CONTENT REMAINS ELEVATED FROM BIRTH INTO EARLY LIFE (0-3Y)

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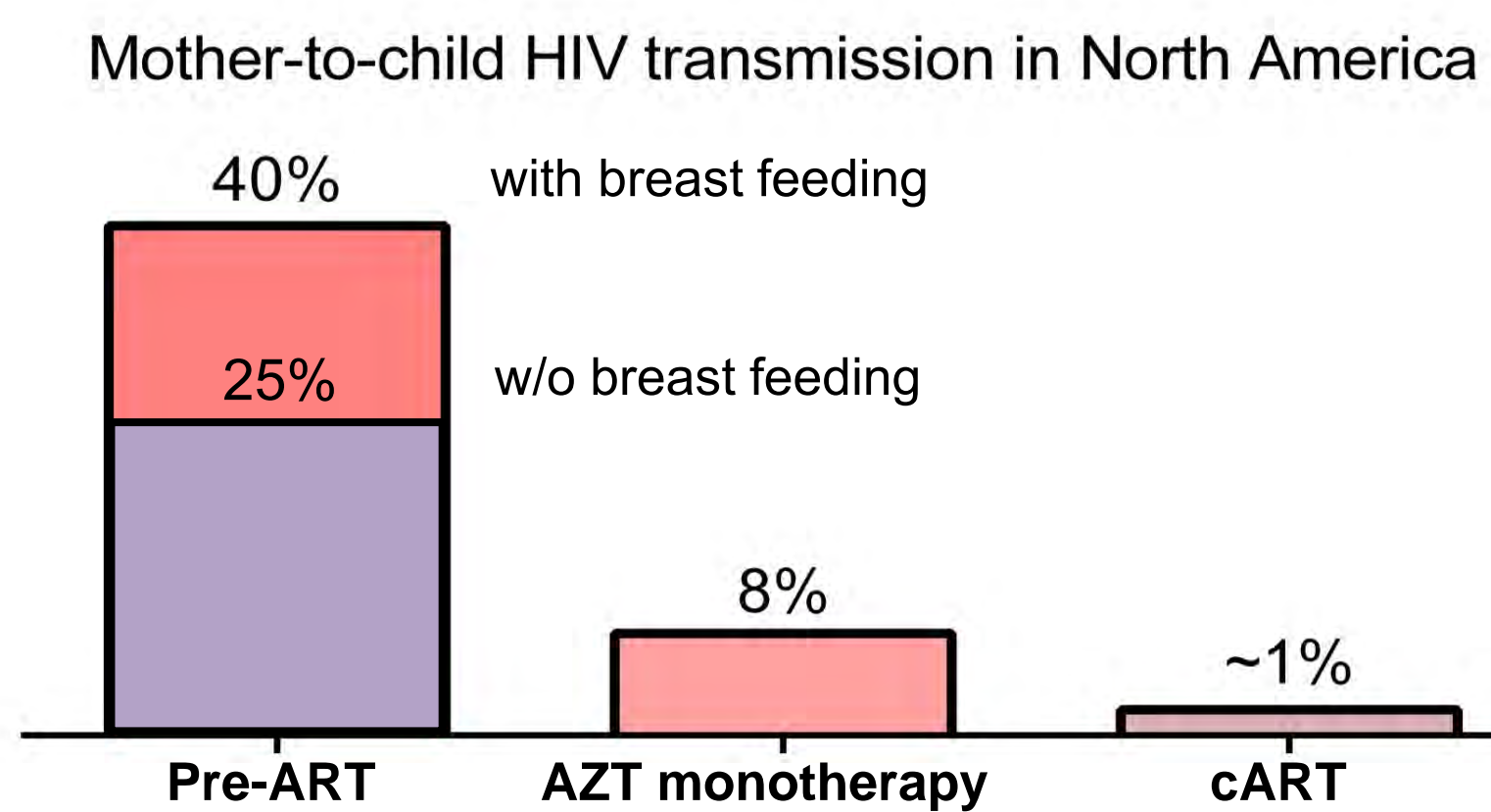
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Abstract #879

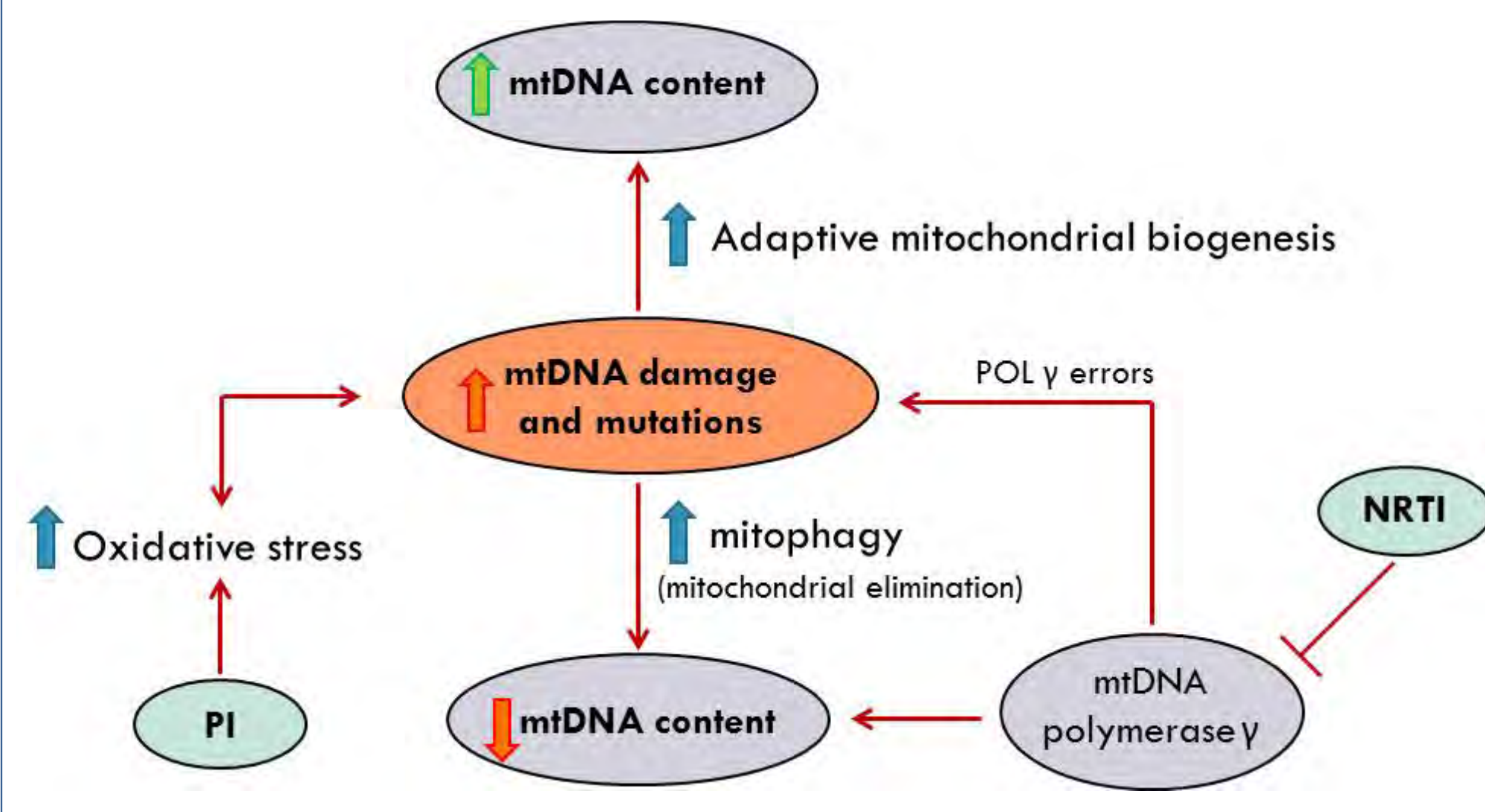
Introduction

- The introduction of **Zidovudine (AZT)** treatment in pregnancy during the mid-90s, followed by **dual and triple-drug combination antiretroviral therapy (cART)** led to a **significant decline in the risk of vertical transmission**



- Many antiretroviral drugs can cross the placenta
 - Some antiretrovirals can cause mitochondrial toxicity and affect mitochondrial DNA (mtDNA) quantity and quality

ART and mitochondrial damage



Objective

To compare HIV-exposed uninfected (HEU) and HIV-unexposed uninfected (HUU) infant blood mtDNA content at birth and over the first 3 years of life, and to investigate any relationship with *in utero* cART exposure

Methods

- Peripheral blood mtDNA content was measured by monochrome multiplex qPCR in 324 HEU (0-3y, of whom 214 had ≥ 2 blood samples) and 306 HUU children (0-3y, each with a single blood sample). Of those, 114 HEU and 86 HUU had a blood specimen collected at birth.
- Univariate analyses investigated the association between blood mtDNA content at birth and the following infant and maternal characteristics:



- ✓ Infant sex
- ✓ Birth weight
- ✓ Gestational age (GA) at birth
- ✓ Small for GA
- ✓ Maternal age
- ✓ Ethnicity
- ✓ Preterm delivery (<37 weeks GA)
- ✓ Smoking (ever) during pregnancy
- ✓ HIV viral load closest to delivery
- ✓ Duration of cART during pregnancy
- ✓ Type of cART regimen

- Factors important univariately ($p < 0.10$) were considered in multivariable linear regression analyses

Conclusions

- Being **HEU** and being born **preterm** is associated with **higher mtDNA content at birth**.
- Among children born at term:
 - **HEUs have higher mtDNA at birth and this persisted at least up to age three**
 - HEUs exposed *in utero* to **AZT+3TC+LPV/r** and **ABC+3TC+PI/r** had **higher mtDNA content at birth**
- These may represent a long-term effect of HIV/cART exposure, possibly resulting from adaptive mitochondrial biogenesis in response to *in utero* stresses

Results

Table 1. Infant demographic and clinical characteristics

| Characteristics | HEU n=114 | HUU n=88 | p value |
|--|-----------------------|-----------------------|------------|
| Male sex | 64 (56) | 47 (53) | 0.70 |
| Gestational Age, w | 38.3 (31.3 - 41.6) | 39.4 (28.9 - 42.1) | < 0.001 |
| Preterm delivery (<37 w) | 23 (20) | 9 (10) | 0.055 |
| Birth weight, kg | 3.1 (1.6 - 4.1) | 3.4 (1.4 - 5.2) | < 0.001 |
| Small for gestational age | 19 (17) | 12 (14) | 0.55 |
| Duration of <i>in utero</i> cART exposure, w | 20.6 (0.0 - 41.1) | NA | |
| <i>In utero</i> cART exposure | | | |
| AZT + 3TC + NVP | 7 (6) | NA | |
| AZT + 3TC + NFV | 34 (30) | NA | |
| AZT+3TC+LPV/r | 45 (39) | NA | |
| ABC+3TC+PI/r | 10 (9) | NA | |
| TDF+FTC(3TC)+PI/r | 10 (9) | NA | |
| Other | 8 (7) | NA | |

Data are presented as N (%) or median (range)

Table 2. Maternal demographic and clinical characteristics

| Characteristics | HEU n=114 | HUU n=88 | p value |
|--------------------------------------|-----------------------|-----------------------|------------|
| Maternal age, y | 31.0 (17.4 - 42.4) | 32.5 (21.3 - 43.0) | 0.063 |
| Maternal ethnicity | | | < 0.001 |
| Indigenous | 33 (29) | 7 (8) | |
| Black/African Canadian | 28 (25) | 2 (2) | |
| White | 39 (34) | 55 (63) | |
| Asian | 10 (9) | 16 (18) | |
| Other/Unknown | 4/0 (4) | 1/7 (9) | |
| Smoking ever in pregnancy | 63 (55) | 38 (43) | 0.09 |
| Detectable HIV pVL close to delivery | 12 (12) (n=99) | NA | |

Data are presented as N (%) or median (range)

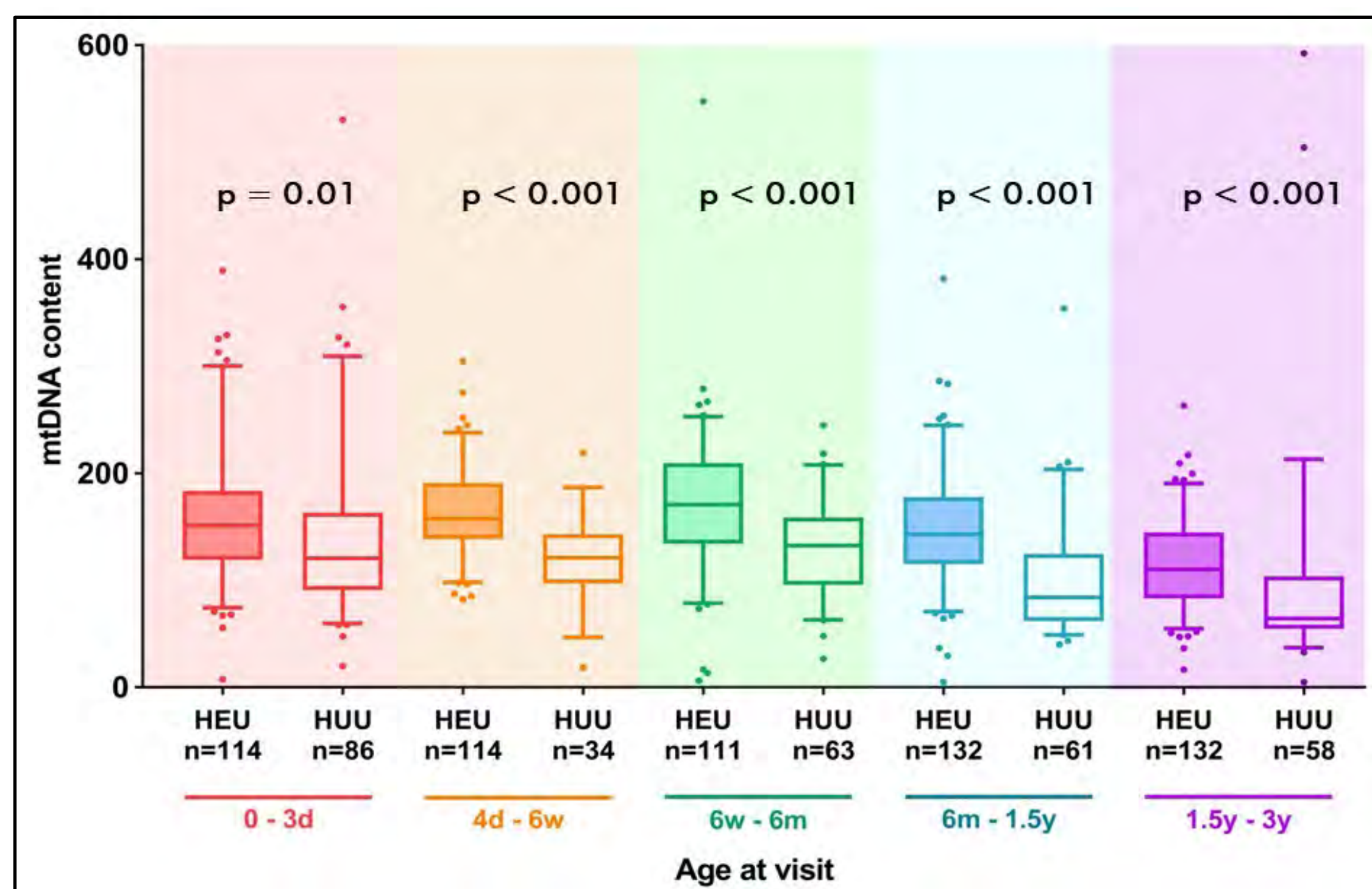


Figure 1. Comparisons of HEU and HUU mtDNA content at different age bins

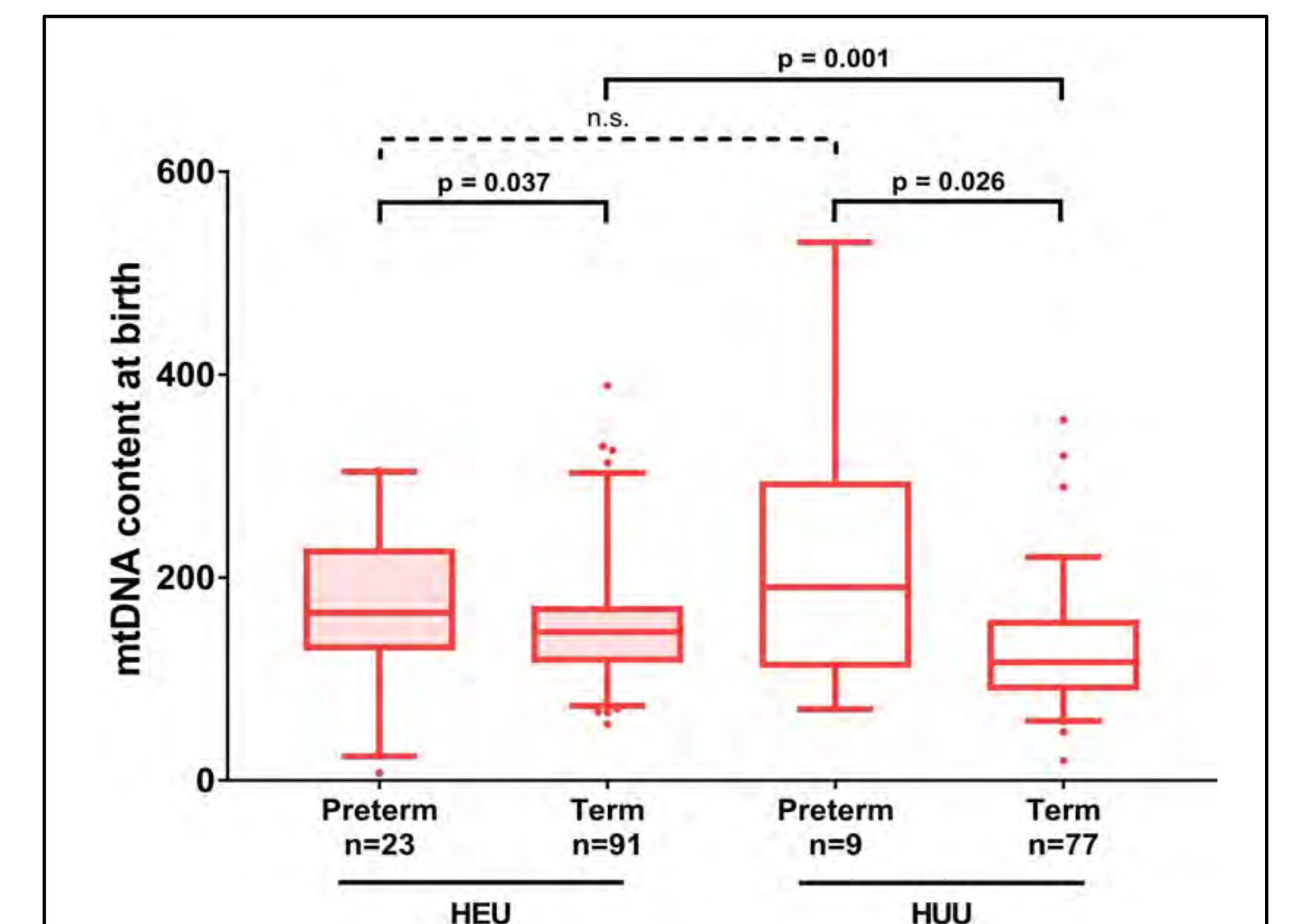


Figure 2. Comparisons of mtDNA content at birth among HEU and HUU infants born preterm and at term

- Among all infants, lower GA was the only factor associated with **higher mtDNA content at birth** (Figure 3A)
- In a sensitivity analysis of infants born at term, HEUs exposed *in utero* to **AZT+3TC+LPV/r** and **ABC+3TC+PI/r** regimen had **higher mtDNA content at birth** compared to HUUs (Figure 3B)

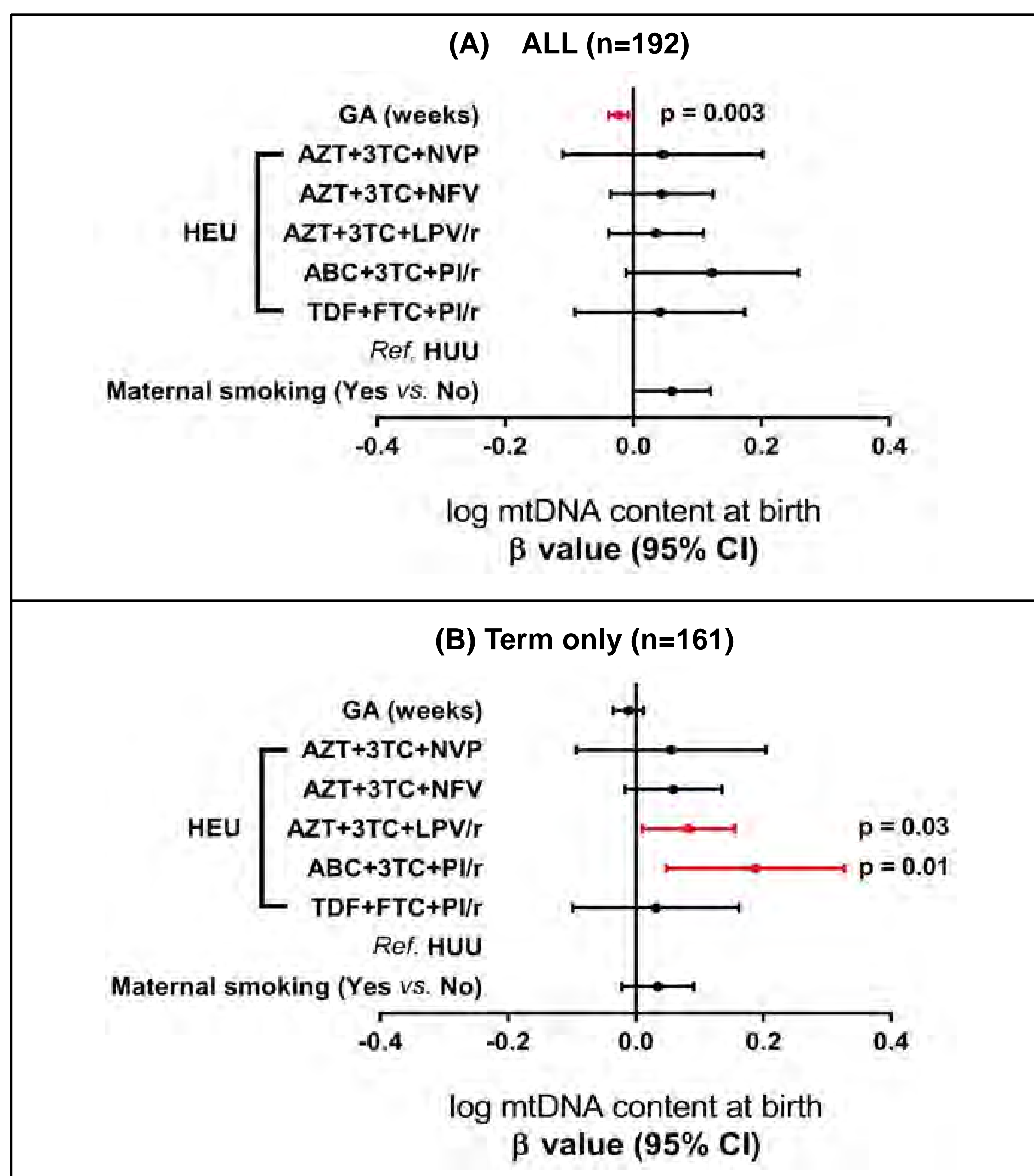


Figure 3. Multivariable analyses of mtDNA content at birth among (A) all participants (B) infants born at term

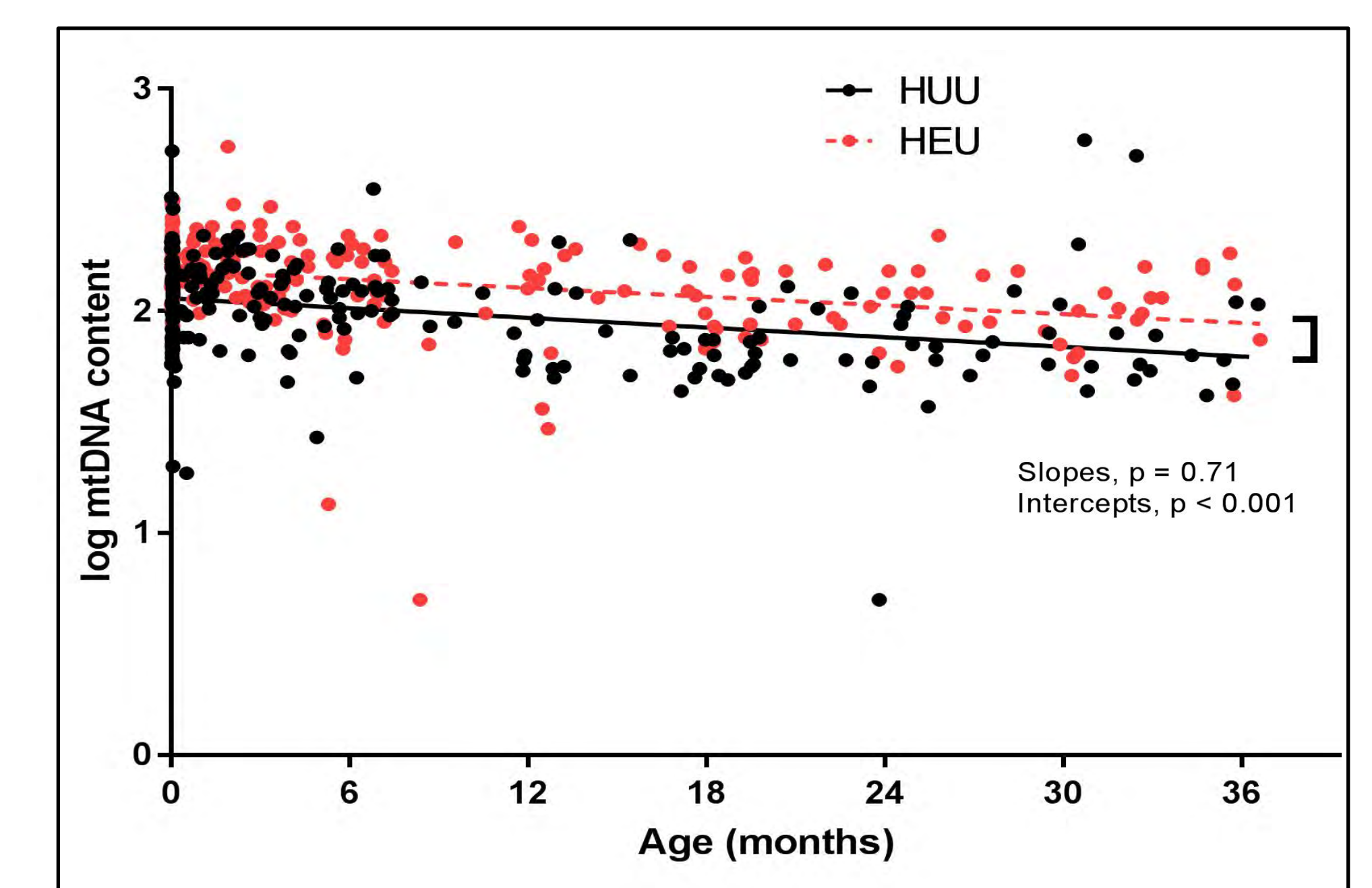


Figure 4. Relationship between mtDNA content and age during the first 3y of life among age- and sex-matched HEU and HUU children

- Among age and sex-matched children (n=214:214), **HEU children** continued to have **higher mtDNA content** than HUUs ($p < 0.01$) **throughout the first three years of life**

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