Children Exposed or Unexposed to Human Immunodeficiency Virus

Weight, Height, and Body Mass Index During the First 5 Years of Life—A Danish Nationwide Cohort

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Children exposed or unexposed to HIV: weight, height and BMI during the first five years of life. A Danish Nationwide Cohort Study

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Summary of main points

HIV exposed uninfected (HEU) children born in Denmark were smaller and shorter during early life compared to a matched control group of HIV unexposed children. This difference decreased with time and may not impact the overall health of HEU children.

Abstract

Background: Exposures to HIV and antiretroviral therapy in utero may have adverse effects on infant growth. We aimed to compare anthropometric outcomes of HIV exposed uninfected (HEU) children born in Denmark aged 0-5 years to children not exposed to HIV.

Methods: In a nationwide register-based study we included all singleton HEU children born in Denmark, 2000-2016. HEU children were individually matched by child sex, parity and maternal country of birth to five singleton controls born to HIV uninfected mothers. Weight-for-age (WAZ), Length-for-age (LAZ) and Weight-for-Length (WLZ)/BMI-for-age (BMI) z-scores were generated according to the WHO standards and the Fenton growth chart for premature infants. Differences in WAZ, LAZ and BMI z-scores were analyzed using linear mixed models, both univariate and adjusted for social and maternal factors.

Results: In total, 485 HEU children and 2.495 controls were included. Compared to controls, HEU children were smaller at birth with an adjusted difference in mean WAZ and LAZ scores of -0.29 (95%CI -0.46:-0.12: p=<0.001) and -0.51 (95%CI -0.71:-0.31: p=<0.001), respectively. Over time, there was a trend towards increasing WAZ and LAZ in HEU children, and there was no significant difference in adjusted WAZ z-scores after age 14 days (-0.13 (95% CI -0.27:0.01: p=0.07) and LAZ z-scores after age 6 months (-0.15 (95%CI -0.32:0.02: p=0.08).

Conclusion: Compared to a matched control group, HEU children were smaller at birth, but this difference decreased with time and is not considered to have a negative impact on the health and well-being of HEU children during early childhood.

Keywords: HIV exposed uninfected, child, growth, longitudinal

Background

The use of combination antiretroviral therapy (cART) during pregnancy has reduced the risk of perinatal transmission of human immunodeficiency virus (HIV) to less than 1% in Denmark and most Western countries [1,2]. As cART is now recommended and implemented globally to all people living with HIV, an increasing number of women living with HIV (WLWH) will either conceive or initiate cART during pregnancy, resulting in a growing population of HIV exposed, but uninfected (HEU) children [3].

Exposures to HIV and cART *in utero* may have adverse effects on infant development and growth [4]. HEU children have an increased risk of low gestational age and low birthweight compared to children born to HIV uninfected mothers (HU children) [5,6]. Studies from low-income settings have shown that HEU children are at higher risk of impairment during early growth [7–9], with some studies showing persistence into school age [9,10]. Social and economic factors have a big impact on infant and child development and well-being [11] and studies have reported less or no difference in growth among HEU and HU children when adjusting for socio-economic factors [10,12].

Exposure to cART *in utero* may also have adverse effect on growth in HEU children, although contradictory results have been published [13,14]. This could be due to differences in maternal cART regime and duration of cART exposure. Some studies have reported a negative effect of in utero exposure of Tenofovir on growth, while others cannot confirm these findings [15–17].

In the present study, we took advantage of the national registries in Denmark containing systematically collected data, covering the whole population during long periods of time [18]. The purpose was, on a national level, to compare anthropometric outcomes of HEU children born in Denmark to a matched control group of HU children, in the first five years of life. Our hypothesis was that HEU children were smaller than HU children at birth and during the first year of life, but that this difference decrease over time and any clinically significance would relate to the short term.

Methods

Setting

The Danish population consists of 5.7 million inhabitants with an estimated adult HIV prevalence of 0.1% [19,20]. In Denmark, WLWH are followed at eight specialized centers during pregnancy and four specialized centers for delivery. Their children are followed at four affiliated pediatric units. cART is provided free of charge to all residents in Denmark with HIV, and most WLWH are well treated with undetectable viral loads [21].

Data sources

We used the unique 10-digit Personal Identification Number (PIN) assigned to all Danish residents at birth (or with approved immigration status) to identify and track HEU children and controls in the following registries [22]:

The Danish HIV Birth Cohort

The Danish HIV Birth Cohort (DHBC) is a prospective, nationwide, population-based cohort study including all WLWH giving birth to one or more children in Denmark after 31 December 1999, with consecutive ongoing enrollment. The DHBC was setup by Nina Weis and the steering committee of the DHBC to investigate the consequences of HIV infection in pregnancy and delivery in women in Denmark and their children. Eligible women are identified and enrolled in the DHBC through the specialized clinical centers responsible for treatment and care of pregnant WLWH in Denmark. Hence, the risk that a woman is missed in the DHBC is negligible. The DHBC collects clinical and demographic data on both the mother and the child from the medical records. Annual updates are performed. For this study the following data was extracted: date of HIV diagnosis, mode of HIV acquisition, cART during pregnancy,

latest CD4 cell count and HIV-RNA viral load measurement prior to delivery and maternal intrapartum prophylaxis (intravenous zidovudine).

Statistics Denmark

From the registries at Statistics Denmark, we extracted data on maternal education, marital status, the family's socio-economic status defined by the adult with the highest income in the household, maternal country of birth, vital status of the child, and migration.

The Medical Birth Registry

The Medical Birth Registry (MBR) contains complete information on all births in Denmark since 1973 [23]. The following data was extracted for the child: date of birth, gestational age, sex, birth weight, Apgar score at 5 minutes, and singleton/twin birth; and for the mothers: parity, age at delivery and smoking during pregnancy.

National Patient Registry

The National Patient Registry (NPR) contains information on all in- and out-patient hospital admissions in Denmark since 1977 [24]. The discharge diagnoses are classified according to the International Classification of Diseases, 10th revision (ICD-10 codes). Information on mode of delivery was obtained using the ICD-10 codes DO800 – DO840.

The Children's Database

The Children´s Database (CDB) contains all height and weight measurements recorded by medical doctors and nurses during the annual preventive health checks offered to all Danish children until school

year 7. Weight and length (recumbent in children below 2 years of age and standing in children age 2 years or older) are measured by standardized procedures [25]. The CDB was established in 2009 and reporting became compulsory in 2011. Previously existing electronic data records dating back to the 1990´ies were included in the database, but with decreased completeness [26]. The following data was extracted: height, weight, date of measurement, duration of exclusive breastfeeding.

Study population

All singleton children in the DHBC born between January 1, 2000 and December 31, 2016 were included. Children were excluded if tested HIV-positive prior to or at 18-months of age, if emigrated after delivery or if their PIN was invalid. Definitive exclusion of HIV infection of the child was based on two negative virologic test results prior to or at 18-months of age. Using the Danish MBR, each of the HEU children were individually matched by child sex, parity (0, ≥1) and maternal country of birth (Denmark, Africa, Asia, Other) to five singleton controls born to HIV uninfected mothers. Women with unknown parity were set to be nulliparous. Potential controls that died or migrated within the first week of life were excluded.

Outcome

The primary outcomes were Weight-for-age (WAZ), Length-for-age (LAZ), Weight-for-Length (WLZ) and BMI-for-age (BMIz) z-scores, calculated using the 2006 WHO child growth standards for infants born at term [27]. WLZ is used in children under 2 years of age, while BMIz is used for children age 2 years or older [27]. Weight and length z-scores for premature infants (gestation <37 week) were adjusted for prematurity and calculated using the 2013 Fenton preterm growth charts (until 50 weeks of gestational age) [28]. The 2013 Fenton preterm growth charts do not include WLZ/BMIz, thus, WLZ/BMIz z-scores

could not be calculated for children born premature (children born <37 week: HEU=54 (11%) and HU=135 (5%), p=<0.001). Biological implausible z-scores was excluded according the WHO guidelines [27]. A z-score of 0 means that the child has the mean measurement of that age and sex as compared with the standard population [25,27].

Statistical analysis

Categorical variables are described as counts (%), and continuous variables are described as means (95% confidence intervals (CI)) or medians with the 25th to 75th interquartile ranges (IQR). Differences in baseline characteristics were summarized and compared between HEU – and HU children using the Pearson's χ2-test, Student's unpaired T-test or the Wilcoxon rank sum test, as appropriate.

Linear mixed regression models were used to assess the difference in WAZ, LAZ and WLZ/BMIz z-scores between HEU children and the HU control group. The WLZ/BMIz analysis only include children born at term. Since growth is not linear over time, we included age as a categorial variable to improve the fit of the models. Final model selection was based on the Akaike´s Information Criterion and included age divided into five categories (birth -<14 days, 14 days – 6 months, >6 - 12 months, >12 – 18 months and older than 18 months) with an interaction between age group and exposure group. As children with impairment in growth are more likely to have been followed closer with more measurements, the number of measurements for each child was also included in the models. Parity was included in the models to account for correlations between infants born to the same mother. Within-child residuals were modelled with an unstructured variance-covariance structure. These models account for correlations between repeated measurements of the same child over time and also include all available data, i.e. if a child had missing data at one time point they were not deleted from the analysis and the available data from previous time points was included resulting in more precise estimates.

Multivariable models were defined *a priori* and included covariates for maternal age, maternal marital status, family socio-economic group, maternal BMI prior to pregnancy and maternal smoking during pregnancy. The z-score already control for age, gestational age (for children born <37 week), and sex so these factors were not further controlled for.

We also performed a sub-group analysis adjusting for exclusive breastfeeding (>30 days, no and unknown). As information on breastfeeding was only available in children born after year 2008, this analysis is limited to children born in year 2009-2016.

Factors associated with WAZ and LAZ z-scores in HEU children age 0-5 years was explored in univariate and adjusted linear mixed models. Year of birth, gestational age, birthweight, maternal age at delivery, maternal country of birth, and smoking were included in the adjusted models in one single step. Individuals with missing explanatory values were excluded from the multivariable analyses. Analyses were carried out using STATA 13 (STAT Corporation, College Station, Texas, USA) and p-values of <0.05 were considered significant.

Ethics

The project was approved by the Danish Data Protection Agency (2012-58-0004; AHH-2017-027) and the Danish Medical Agency (3-3013-406/1/). Access to the different databases used in the study are granted by these regulatory agencies, and individual informed consent from the participating women are not required. Nonetheless, individual consent for collection of data for research purposes is provided from all women included in the DHBC. According to Danish Law, approval from the National Committee on Health Research Ethics was not required as no biomedical intervention was performed.

Results

Characteristics

A total of 504 singleton children born to 246 WLWH during the study period were identified. Of these, a total of 19 children were excluded: four children tested HIV positive and 15 children did not have a valid PIN. Thus, 485 HEU children and 2495 matched HU children were included in the analysis.

The characteristics of the cohort are presented in Table 1 and 2. All WLWH were on cART at delivery, with the majority having undetectable VL at the time of delivery. In total, 162 (33%) women were treated with tenofovir during pregnancy. Among HU children born between year 2009 – 2016, 53% (n=604) were exclusively breastfeed for more than 30 days. None of the HEU children were breastfed.

Primary analysis

A total number of 8,883 weights and 8,856 lengths were measured up to five years of age in the study population. The median number of measurements per child where 5 (IQR 3-7) among HEU children and 4 (IQR 3-7) in the control group. Table 3 and Figure 1 shows the results of the mixed regression analysis. Overall, anthropometric z-scores of both HEU and HU children were close to or above the average population mean of 0. Compared to controls, HEU children were smaller at birth in the adjusted analysis with a difference in mean WAZ and LAZ z-scores of -0.29 (95% CI -0.46: -0.12, p=<0.001) and -0.51 (95% CI -0.71 : -0.31: p=<0.001), respectively. Over time, there was a trend towards increasing WAZ and LAZ z-scores in HEU children and there was no significant difference in WAZ after 14 days of age (-0.13 (95% CI -0.27 : 0.01: p=0.07) and no difference in LAZ after 6 months of age (-0.15 (95% CI -0.32 : 0.02: p=0.08) after adjusting for social and maternal factors. The absolute difference in median height ranged from -0.40 cm to -1.53 cm, while the absolute difference in weight ranged from -123.9 grams to -529.4 grams (supplementary 1).

A higher proportion of HEU children were underweight (defined by a WAZ z-score = <-2) at birth (4% (n=12) versus 1% (n=18), p=<0.01) and at 6 months (6% (n=14) versus 4% (n=40), p=0.04). There was no difference in the proportion of children with a LAZ z-score <-2 (stunting) or a WLZ/BMIz z-score >2 (overweight) children at any age.

HEU children born ≥37 week had a higher mean WLZ z-score until 6 months of age compared to HU children (0.27 (95% CI 0.13 : 0.40), p=<0.001) in the adjusted analysis. After the age of 6 months, HEU children had smaller WLZ/BMIz z-scores compared to controls, however, this difference was not statistically significant in the adjusted analysis.

Sub-group analysis

The results of the analysis adjusting for breastfeeding is presented in Table 4. There was no significant difference in WAZ at any age group, after adjusting for breastfeeding. HEU children had lower LAZ z-scores and higher WLZ/BMI z-scores during the first year of life when adjusting for breastfeeding, maternal and social factors.

Factors associated with WAZ and LAZ z-scores among HEU

The analysis on factors associated with WAZ and LAZ z-scores in HEU children age 0-5 years are presented in Table 5. In the adjusted analysis, born in year 2009 or later, birthweight <2500 grams and maternal PI treatment was associated with lower WAZ z-scores, while a birthweight <2500 grams, social benefits/disability and maternal PI treatment was associated with lower LAZ z-scores.

Discussion

In this nationwide study, HEU children were smaller and shorter at birth compared to a matched control group of children born to HIV-uninfected mothers. WAZ and LAZ z-scores in HEU children increased over time, and there was no statistically significant difference between HEU and HU children after 18 months of age. A similar trend was seen when adjusting for maternal and sociodemographic factors, although the difference was only statistically significant in early life. The absolute difference in weight and length seen between HEU and HU children was relatively small. In a sub-group analysis adjusted for breastfeeding, HEU children was significantly shorter during the first year of life, while there was no difference in WAZ z-scores between groups. Thus, the difference in WAZ z-scores seen between groups may be related to infant feeding mode. None of the HEU children were breastfed, and it is well known that there are differences in growth between breastfed and formula-fed children, especially early life weight gain [29].

The finding that HEU children are consistently smaller and shorter at birth is a concern and warrants further examination. Low birthweight and preterm birth has been associated with cART exposure, particularly in relation to PI-based regiments and among women who initiate cART before conception [30,31]. Similarly, we found that maternal treatment with PI and being born after year 2009, where increasingly mothers were on treatment at the time of conception, was associated with lower WAZ and LAZ z-scores. Unfortunately, our study sample was too small to stratify by drug class.

The association between *in utero* cART exposure and adverse growth beyond infancy is not clear [4]. The European Collaborative study found minimal differences in weight and height between children exposed *in utero* to cART, monotherapy or no therapy [14]. In a US cohort, where 96% of the mothers were on cART at time of delivery, growth of HEU children were similar to a matched control group of HU children over the first 2 years of life [32]. Another US study among HEU children, whose mothers initiated cART

during pregnancy, reported that HEU children had lower average birth weight and length compared to reference standards, but catch up over time [33].

Low birthweight and rapid catch-up growth in early childhood may have a negative impact long-term on health, such as increased risk of obesity, insulin resistance, and increased risk of cardiovascular disease [34,35]. Thus, our finding that HEU children are smaller at birth, but seem to catch up during the first year of life may have implications into adulthood. Moreover, any possible difference in the timing of catch-up growth between HEU and HU children should be investigated in future studies.

Advanced maternal disease has been associated with poor growth in the offspring [36,37]. Our finding of no statistically significant association between maternal CD4 and HIV RNA levels and offspring WAZ and LAZ z-scores could be due to small numbers, as most mothers were well treated with fully suppressed viral loads at the time of delivery.

Strengths and limitations

Our study has several strengths. First, this study used a population-based approach, including a nationwide population of all HEU children born in Denmark during the study period. Second, using the MBR registry allowed us to include a matched control group of HU children born during the same period. Third, the use of registries ensures prospective, uniformly, and neutrally collected data on an individual level, which restrict the methodological problems of loss to follow-up, selection bias, and emigration. Finally, we were able to follow the children until their fifth birthday.

Our study also has some limitations. First, the CDB is a relatively new database. Thus, information on breastfeeding was limited to children born after year 2009. Moreover, valid information on exclusive breastfeeding for >1 month was not available. Second, it was not possible to identify the PIN for 15 children and follow-up information is therefore unknown for these children. Third, we excluded

premature children in the BMZ/WLZ analysis, and as more HEU children were born premature compared to HU children, the results should be interpreted accordingly. Finally, the overall population of HEU children in Denmark are relatively small, making it difficult to stratify data on for example maternal cART regime.

Conclusion

In a high-resource setting, exposure to HIV and/or antiretroviral therapy does not seem to be adversely associated with growth in early childhood. Compared to a matched control group, HEU children were smaller at birth, but this difference decreased with time and is not considered to have a negative impact on the overall health and well-being of HEU children. More data is needed to assess an effect on long-term health.

NOTES

Contributors

All authors contributed to study design, data collection, data interpretation, writing the report, and approved the final version. EML had full access to the data and did the statistical analysis together with HS and MH. EML wrote the first draft of the paper, and together with NW had the original concept for the study.

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Conflicts of interest

Outside of the submitted work, EML reports grants from the Novo Nordisk Foundation. NW reports personal fees from Abbvie, Bristol-Myers-Scuibb, Merck Sharp Dohme, Gilead, Glaxo Smith Kline, outside the submitted work, as well as honoraria paid to her institution. TK reports personal fees,grants, and other compensation from Gilead, grants from ViiV/Glaxo Smith Kline, and other compensation from CLS Behring, and Baxalta, outside of the submitted work. The remaining authors (MH, HS, GP, MS, ISJ) declare no conflicts of interests.

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Table 1: Characteristics of HIV exposed uninfected (HEU) and HIV unexposed (HU) children born in Denmark 2000-2016

	HEU children (n = 485)	HU children (n = 2495)	
Maternal characteristics			*p-value**
Maternal age at birth (mean (95% CI))	32.5 (32.00 – 32.96)	30.1 (29.87 – 30.28)	**<0.001**
Missing	0	0	
Married (n (%))	252 (52)	1.492 (60)	**0.01**
Missing	36	89	
Ethnicity (n (%))			
Danish	120 (25)	605 (24)	0.69
African	263 (54)	1330 (53)	
Asian	60 (12)	310 (12)	
Other	42 (9)	250 (10)	
BMI (median (IQR))	23.05 (20.80 – 26.42)	23.72 (21.05 – 27.24)	0.05
Missing	94	770	
Family Socio-Economic Group (n (%))**			
Working	236 (48)	1.227 (49)	**<0.001**
Unemployed	8 (2)	104 (4)	
Social benefits/disability	80 (16)	540 (22)	
Other	15 (3)	44 (2)	
Missing	146 (30)	580 (23)	
Smoking during pregnancy (n (%))	50 (11)	175 (7)	**0.003**
Missing	19 (4)	58 (2)	
Nulliparous (n (%))	205 (42)	943 (38)	0.06
Child characteristics			
Year of birth (n (%))			
2000 – 2006	152 (31)	1.088 (44)	**<0.001**
2007 – 2008	61 (13)	268 (11)	
2009 – 2016	272 (56)	1139 (46)	
Gestational age <37 weeks (n (%))	54 (11)	135 (5)	**<0.001**
Missing	<5	<5	
Delivered by caesarean section (n (%))	236 (49)	405 (16)	**<0.001**
Birth weight, grams (mean (95% CI))	3178 (3122 – 3235)	3445 (3421 – 3469)	**<0.001**
Missing	<5	<5	
Birth length, cm (mean (95% CI)	49.5 (48.91 – 50.12)	51.3 (51.08 – 51.49)	**<0.001**
Missing	9	21	
Male sex (n (%))	254 (53)	1.300 (52)	0.13
Missing	0	0	
Apgar score at 5 min <7 (n (%))	5 (1)	20 (1)	0.61
Missing	<5	11	

* P values are based on the χ2-test, Fischers exact or non-parametric Students T-test, as appropriate.

** The employment status of the adult with the highest income in the household was used to indicate socioeconomic status.

Table 2: Maternal HIV Characteristics (n=485)	
Time of maternal HIV diagnosis (n (%))	
Prior to pregnancy	385 (79)
During pregnancy*	93 (19)
During/after delivery	7 (1)
Mode of HIV acquisition (n (%))	
Sexual	296 (66)
Injection drug use	15 (3)
Other/unknown	174 (36)
ART treatment at delivery (n (%))	
3 NRTIs	28 (6)
2 NRTIs + NNRTI	66 (14)
2 NRTIs + PI	380 (78)
Other	11 (2)
Intrapartum prophylaxis (n (%))	218 (48)
Missing	41
CD4 cell count at delivery (n (%))	
>350 cells/µL	400 (82)
200-350 cells/µL	39(8)
<200 cells/µL	25 (5)
Missing	21
HIV viral load at delivery (n (%))	
<40 copies/mL	418 (86)
40 – 1000 copies/mL	47 (10)
>1000 copies/mL	11 (2)
Missing	9

* Timing of maternal HIV diagnosis during pregnancy: 1. Trimester: n=47 (51%), 2. Trimester: n=38 (41%) and 3. Trimester: n=8 (9%)

Table 3: Difference in Weight-for-age (WAZ), Length-for-age (LAZ) and Weight-for-Length/BMI-for-age (WLZ/BMIz) between HIV exposed uninfected (HEU) and HIV unexposed (HU) children from birth to five years of age.

	HEU children			HU children			Mean difference Unadjusted	*p-value*	Mean difference Adjusted**	*p-value*
Weight-for-age (WAZ)	n	mean z-score	95% CI	n	mean z-score	95% CI				
Birth	305	0.14	(-0.01 : 0.28)	1.361	0.48	(0.40 : 0.55)	-0.37 (-0.52 : -0.21)	**<0.001**	-0.29 (-0.46 : -0.12)	**<0.001**
0-6 months	901	0.14	(0.02 : 0.24)	3.599	0.32	(0.26 : 0.38)	-0.21 (-0.34 : -0.08)	**<0.001**	-0.13 (-0.27 : 0.01)	0.07
6-12 months	318	0.46	(0.33 : 0.52)	1.214	0.62	(0.56 : 0.68)	-0.19 (-0.32 : -0.04)	**0.01**	-0.10 (-0.25 : 0.06)	0.21
12-18 months	69	0.39	(0.19 : 0.52)	307	0.63	(0.53 : 0.72)	-0.26 (-0.48 : 0.05)	**0.02**	-0.23 (-0.47 : 0.01)	0.07
Older than 18 months	128	0.25	(0.02 : 0.48)	678	0.44	(0.33 : 0.55)	-0.21 (-0.47 : 0.04)	0.10	-0.19 (-0.47 : 0.09)	0.18
Length-for-age (LAZ)										
Birth	303	0.57	(0.40 : 0.73)	1.354	1.10	(1.01 : 1.18)	-0.55 (-0.73 : -0.37)	**<0.001**	-0.51 (-0.71 : -0.31)	**<0.001**
0-6 months	897	0.53	(0.40 : 0.66)	3.592	0.97	(0.90 : 1.02)	-0.46 (-0.60 : -0.31)	**<0.001**	-0.40 (-0.56 : -0.23)	**<0.001**
6-12 months	316	0.76	(0.63 : 0.86)	1.211	0.97	(0.90 : 1.04)	-0.22 (-0.37 : -0.06)	**<0.01**	-0.15 (-0.32 : 0.02)	0.08
12-18 months	69	0.51	(0.29 : 0.73)	305	0.61	(0.50 : 0.71)	-0.11 (-0.35 : 0.15)	0.37	-0.15 (-0.43: 0.12)	0.28
Older than 18 months	128	0.12	(-0.11 : 0.37)	678	0.28	(0.18 : 0.39)	-0.17 (-0.43 : 0.08)	0.18	-0.08 (-0.37 : 0.20)	0.57
Weight-for-length/BMI-for-age*										
Birth	262	-0.61	(-0.72 : -0.46)	1283	-0.81	(-0.89 : -0.73)	0.17 (0.01: 0.33)	**0.04**	0.24 (0.06 : 0.41)	**0.01**
0-6 months	872	-0.21	(-0.33 : -0.10)	3518	-0.46	(-0.52 : -0.41)	0.22 (0.10 : 0.34)	**<0.001**	0.27 (0.13 : 0.40)	**<0.001**
6-12 months	318	0.09	(-0.04 : 0.23)	1.213	0.21	(0.14 : 0.28)	-0.14 (-0.30 : 0.01)	0.07	-0.09 (-0.20 : 0.08)	0.28
12-18 months	69	0.17	(-0.07 : 0.42)	306	0.43	(0.31 : 0.55)	-0.29 (-0.56 : -0.01)	**0.04**	-0.25 (-0.55 : 0.05)	0.11
Older than 18 months	128	0.34	(0.09 : 0.58)	671	0.42	(0.31 : 0.54)	-0.10 (-0.37 :- 0.17)	0.47	-0.18 (-0.49 : 0.13)	0.25

*Analysis only includes children born after gestational week 37.

**Adjusted for maternal age, maternal marital status, family socio-economic group, maternal BMI prior to pregnancy and maternal smoking during pregnancy.

Significant results are highlighted in bold. n=number of measurements

Table 4: Difference in WAZ, LAZ, WLZ/BMIz in a sub-group analysis adjusting for breastfeeding

	Mean difference Unadjusted**	*p-value*	Mean difference Adjusted***	*p-value*
Weight-for-age (WAZ)				
Birth	-0.31 (-0.62 : -0.01)	0.05	-0.28 (-0.61 : 0.05)	0.09
0-6 months	-0.21 (-0.51 : 0.08)	0.15	-0.16 (-0.47 : 0.15)	0.31
6-12 months	-0.20 (-0.51 : 0.10)	0.18	-0.13 (-0.45 : 0.19)	0.42
12-18 months	-0.28 (-0.64 : 0.08)	0.13	-0.17 (-0.55. : 0.21)	0.37
Older than 18 months	-0.29 (-0.68 : 0.11)	0.15	0.21 (-0.62 : 0.21)	0.33
Length-for-age (LAZ)				
Birth	-0.72 (-1.06 : -0.37)	**<0.001**	-0.74 (-1.10 : -0.37)	**<0.001**
0-6 months	-0.62 (-0.94 : -0.29)	**<0.001**	-0.61 (-0.96 : -0.27)	**<0.001**
6-12 months	-0.41 (-0.75 : -0.08)	**0.01**	-0.39 (-0.74 : -0.05)	**0.03**
12-18 months	-0.34 (-0.75 : 0.05)	0.09	-0.36 (-0.78: 0.06)	0.10
Older than 18 months	-0.45 (-0.86 : 0.03)	**0.04**	-0.36 (-0.80 : 0.07)	0.10
Weight-for-length/BMI-for-age*				
Birth	0.36 (0.07: 0.65)	**0.02**	0.47 (0.15 : 0.78)	**<0.01**
0-6 months	0.36 (0.09 : 0.63)	**0.01**	0.46 (0.17 : 0.75)	**<0.01**
6-12 months	-0.02 (-0.31 : 0.27)	0.90	0.09 (-0.22 : 0.40)	0.56
12-18 months	-0.18 (-0.58 : 0.22)	0.37	-0.04 (-0.46 : 0.38)	0.86
Older than 18 months	-0.06 (-0.47 : 0.35)	0.77	0.02 (-0.41 : 0.45)	0.92

*Adjusted for breastfeeding

*Analysis only includes children born after gestational week 37.

**Adjusted for breastfeeding

***Adjusted for breastfeeding, parity, number of measurements per child, maternal age, maternal marital status, family socio-economic group, maternal BMI prior to pregnancy and maternal smoking during pregnancy. Significant results are highlighted in bold

Figure 1: Predicted effect over time of WAZ, LAZ and WLZ/BMIz z-scores from birth until the age of five years from the mixed regression models

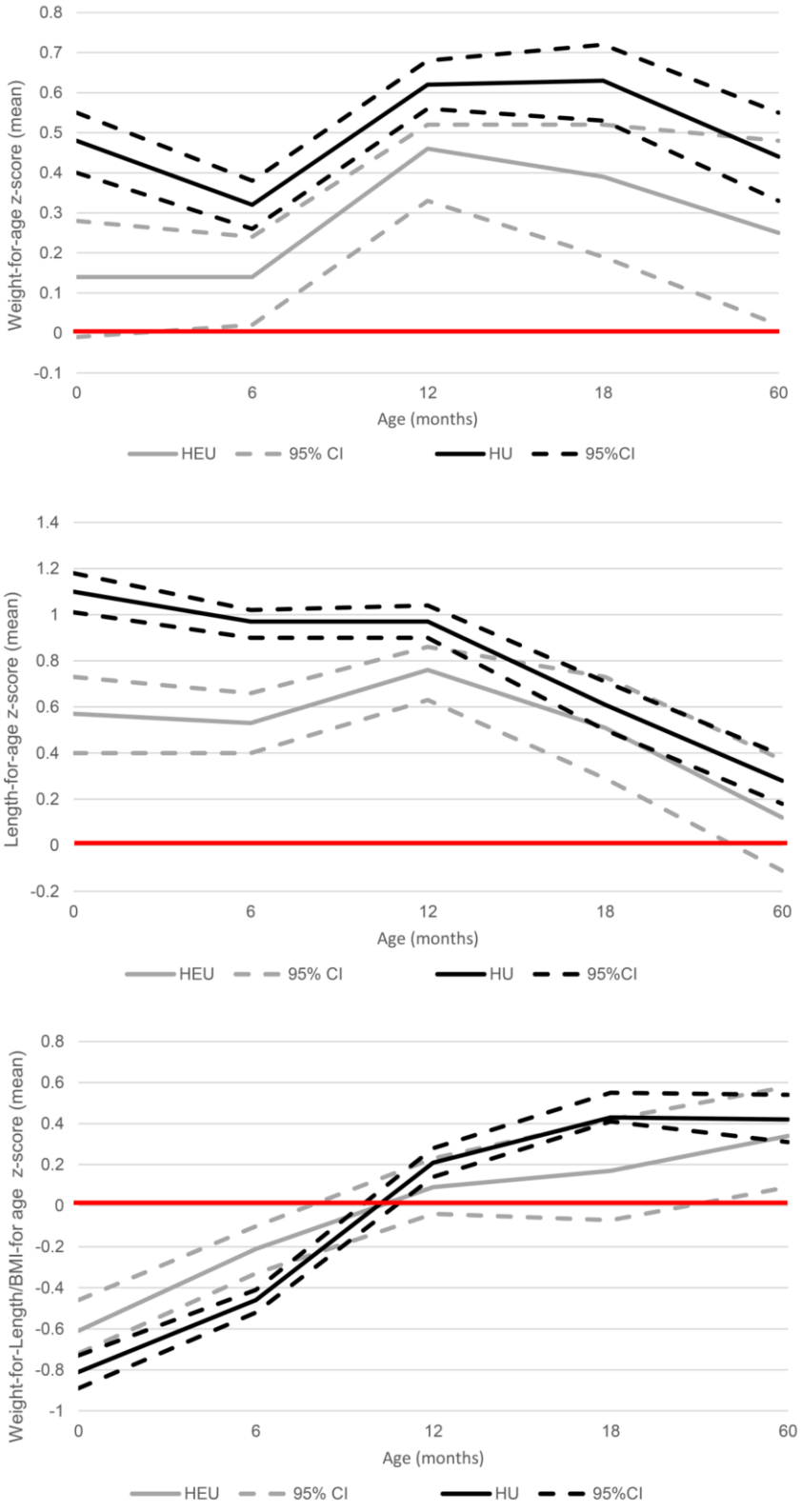

Table 5

Table 5: Factors associated with WAZ and LAZ z-scores among HIV-exposed uninfected children (total n=485)

	n	WAZ z-score univariate	*p-value*	WAZ z-score adjusted*	*p-value*	LAZ z-score univariate		LAZ z-score adjusted*	*p-value*
Child variables									
Gender									
Boy	254	1		1		1		1	
Girl	231	-0.003 (-0.25 : 0.25)	0.99	0.05 (-0.16 : 0.27)	0.64	0.01 (-0.26 : 0.28)	0.96	0.05 (-0.17 : 0.27)	0.67
Year of birth									
2000-2006	152	1		1		1		1	
2007-2008	61	0.004 (-0.53 : 0.54)	0.99	-0.20 (-0.68 : 0.29)	0.42	0.14 (-0.46 : 0.73)	0.48	-0.02 (-0.57 : 0.55)	0.96
2009-2016	272	0.08 (-0.29 : 0.45)	0.67	**-0.48 (-0.85 : -0.12)**	**0.01**	0.06 (-0.35 : 0.47)	0.79	-0.41 (-0.83 : 0.01)	0.05
Gestational age									
≥ 37 week	427	1		1		1		1	
< 37 week	54	**-1.04 (-1.36 : -0.71)**	**<0.001**	-0.29 (-0.71 : 0.14)	0.18	**-0.96 (-1.33 : -0.59)**	**<0.001**	-0.20 (-0.70 : 0.28)	0.41
Birthweight pr. 100 gramss									
≥2500 grams	436	1		1		1		1	
<2500 grams	45	**-1.71 (-2.04 : -1.39)**	**<0.001**	**-1.57 (-2.01 : -1.09)**	**<0.001**	**-1.61 (-2.00 : -1.23)**	**<0.001**	**-1.46 (-1.98 : -0.93)**	**<0.001**
Parity									
0	205	1		1		1		1	
≥1	280	0.21 (-0.04 : 0.46)	0.10	0.07 (-0.16 : 0.30)	0.56	-0.08 (-0.36 : 0.19)	0.55	-0,23 (-0.50 : 0.04)	0.09
Maternal variables									
Maternal age at delivery									
< 25 years	42	1		1		1		1	
25-35 years	287	0.11 (-0.41 : 0.63)	0.68	0.31 (-0.16 : 0.79)	0.19	-0.20 (-0.75 : 0.36)	0.49	0.01 (-0.53 : 0.54)	0.99
> 35 years	156	-0.08 (-0.61 : 0.45)	0.79	0.21 (-0.29 : 0.70)	0.41	-0.25 (-0.82 : 0.32)	0.39	-0.02 (-0.54 : 0.58)	0.95
Country of birth									
Danish	120	1		1		1		1	
African	263	**0.31 (0.02 : 0.61)**	**0.04**	0.16 (-0.12 : 0.46)	0.27	0.30 (-0.02 : -0.62)	0.07	0.20 (-0.12 : 0.52)	0.21
Asian	60	-0.07 (-0.49 : 0.35)	0.73	-0.16 (-0.45 : 0.23)	0.42	-0.16 (-0.63 : 0.31)	0.54	-0.28 (-0.78 : 0.16)	0.22
Family Socio-Economic Group**									
Working	236	1		1		1		1	
Unemployed	8	0.86 (-0.01 : 1.73)	0.06	0.56 (-0.20 : 1.33)	0.15	0.37 (-0.60 : 1.33)	0.46	0.15 (-0.72 : 1.02)	0.73
Social benefits/disability	80	-0.19 (-0.54 : 1.63)	0.33	-0.32 (-0.65 : 0.01)	0.06	**-0.41 (-0.81 : -0.02)**	**0.04**	**-0.46 (-0.84 : 0.08)**	**0.02**
Other	15	0.07 (-0.80 : 0.93)	0.80	0.04 (-0.87 : 0.78)	0.92	0.06 (-0.90 : 1.02)	0.90	-0.09 (-0.87 : 1.06)	0.86
Smoking									
No smoking	416	1		1		1		1	
Smoking during pregnancy	50	**-0.43 (-0.84 : -0.02)**	**0.04**	-0.13 (-0.51 : 0.25)	0.51	**-0.67 (-1.11 : -0.22)**	**<0.01**	-0.42 (-0.86 : 0.02)	0.06
Mode of HIV transmission									
Sexual	296	1		1		1		1	
Injection drug use	15	-0.55 (-1.23 : 0.12)	0.11	-0.27 (-0.88 : 0.33)	0.37	-0.55 (-1.29 : 0.18)	0.14	-0.30 (-0.98 : 0.38)	0.38
Other	174	0.06 (-0.20 : 0.33)	0.60	0.03 (-0.27 : 0.27)	0.82	0.14 (-0.17 : 0.43)	0.40	0.06 (-0.22 : 0.33)	0.68
ART treatment initiated									
Prior to pregnancy	385	1		1		1		1	
1. trimester	47	0.13 (-0.3 : 0.63)	0.61	-0.01 (-0.44 : 0.42)	0.97	-0.01 (-0.55 : 0.53)	0.96	0.11 (-0.59 : 0.36)	0.63
2./3. trimester	46	0.07 (-0.23 : 0.38)	0.64	-0.06 (-0.33 : 0.21)	0.67	-0.04 (-0.37 : 0.28)	0.80	-0.17 (-0.47 : 0.13)	0.26
ART treatment									
Without PI	105	1		1		1		1	
With PI	380	0.02 (-0.32 : 0.36)	0.90	**-0.31 (-0.62 : -0.01)**	**0.04**	-0.18 (-0.55 : 0.19)	0.34	**-0.41 (-0.75 : -0.07)**	**0.02**
CD4 cell count at delivery									
> 350 cells/µL	400	1		1		1		1	
<= 350 cells/µL	64	0.03 (-0.36 : 0.42)	0.81	0.10 (-0.44 : 0.24)	0.57	0.01 (-0.40 : 0.43)	0.96	-0.05 (-0.43 : 0.33)	0.80
HIV RNA prior to delivery									
≤ 40 copies/mL	418	1		1		1		1	
> 40 copies/mL	58	-0.32 (-0.73 : 0.08)	0.11	-0.18 (-0.53 : 0.17)	0.32	-0.39 (-0.83 : 0.04)	0.08	-0.24 (-0.64 : 0.15)	0.23
Mode of delivery									
Vaginal	249	1		1		1		1	
Caesarean section	236	-0.19 (-0.43 : 0.06)	0.14	-0.21 (-0.44 : -0.02)	0.08	-0.16 (-0.43 : 0.11)	0.25	-0.26 (-0.52 : 0.01)	0.05

*Adjusted for year of birth, gestational age, birthweight, maternal age at delivery, maternal country of birth and smoking

**The employment status of the adult with the highest income in the household was used to indicate socioeconomic status

Significant results are highlighted in bold. n=number of children.