Cognitive impairment in children and adolescents living with perinatal HIV disease in the ART era: a meta-analysis

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eClinicalMedicine
2024;72: 102602

Published Online 23 April 2024
https://doi.org/10.1016/j.eclinm.2024.102602

Summary

Background Despite improved survival and overall health outcomes from modern antiretroviral therapy (ART), children and adolescents living with HIV are facing pervasive impairments in neurodevelopment including cognitive impairment, but there remains a lack of consensus on the cognitive domains that are affected in those children and adolescents. The objective of this meta-analysis was to evaluate the impact of perinatal HIV-infection on executive function, working memory, and speed of information processing in the ART era.

Methods The PubMed database was searched for studies published between 1997 and 2024, plus additional search with the ScienceDirect, bioRxiv, and medRxiv databases. A meta-analysis was conducted on thirty-five studies published between 2012 and 2023 that encompassed a total of 4066 perinatally-infected HIV patients, 2349 HIV-exposed uninfected (HEU) controls, and 2466 HIV-unexposed, uninfected (HUU) controls. Performance scores on executive function, working memory, and processing speed were pooled using random-effects meta-analysis.

Findings Compared to HEU and HUU controls, perinatally HIV-infected children and adolescents presented with significant impairments in processing speed (*Hedges g* = –0.64, p < 0.00001), working memory (*Hedges g* = –0.69, p < 0.00001), and to a lesser degree, executive function (*Hedges g* = –0.35, p = 0.02). Meta-regression analysis suggested that the effect estimate of processing speed impairment negatively correlated with Gross National Income (GNI) per capita of the study countries (CALHIV vs HUU, p = 0.0016; CALHIV vs HEU, p = 0.0019), even though HIV-infected cases were compared to sociodemographically matched HUU controls from the same countries. Sub-group meta-analyses with participants from high-income or low-/middle-income countries provided further evidence suggesting that the performance gap between HIV-infected cases and HUU/HEU controls may be larger in low-/middle-income countries than high-income countries.

Interpretation In the ART era, cognitive impairment (especially reduced processing speed and working memory) persists in children and adolescents living with HIV. These impairments may be more pronounced among those children and adolescents living with HIV in low-income countries, suggesting that there may be global health inequities in treatment outcomes with perinatal HIV-infection. However, meta-analysis and meta-regression analysis have their limitations, which calls for future collaborative multi-country international studies to directly investigate this important topic. Nevertheless, there is an unmet need to assure equity in timely assessments and interventions to optimize neurocognitive development and outcomes among children and adolescents with perinatal HIV globally.

Funding This research was supported in part by NIH R01MH108466, NIH R56NS124422, and NIH R01NS124422.

Keywords: HIV; Children; Adolescents; Neurodevelopment; Executive function; Working memory; Processing speed

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Research in context

Evidence before this study

Despite improved survival and overall health outcomes, children and adolescents living with HIV (CALHIV) have been shown to face pervasive impairments in neurodevelopment, including impairments in cognitive and motor functions. However, there are inconsistent reports regarding cognitive domains affected in CALHIV. A previous meta-analysis by Philips et al. concluded that the most commonly affected cognitive domains among CALHIV are executive function and speed of information processing. However, this meta-analysis study was conducted more than seven years ago with very limited numbers of publications (i.e., the finding of significant processing speed impairment in HIV-infected children is based on a total of 96 participants from two studies). To expand the analysis to the most up-to-date studies and capture the large number of works published after 2016, we conducted an updated meta-analysis to investigate the impact of perinatal HIV-infection on cognitive functions.

Added value of this study

Compared to demographically matched HIV-uninfected controls, CALHIV presented with significant impairments in processing speed. By contrast, impairment in general executive function was rather mild. In addition, the effect estimate of processing speed impairment negatively correlated with Gross National Income (GNI) per capita of the study countries, even though HIV-infected cases were compared to sociodemographically matched controls from the same countries.

Implications of all the available evidence

In the era of antiretroviral therapy, cognitive impairment (especially reduced processing speed and working memory) persists in CALHIV. These impairments appear to be more pronounced among CALHIV in low-income countries, suggesting the existence of global health inequities in treatment outcomes with perinatal HIV-infection. There is an unmet need to assure equity in timely assessments and interventions to optimize neurocognitive development and outcomes among children and adolescents with perinatal HIV globally, especially those living in the low-income countries.

Introduction

Despite progress in the global HIV response, there still remains a substantial burden of HIV-disease among children around the world. It is estimated that there are approximately 2.8 million children and adolescents living with HIV (CALHIV) and approximately 310,000 new HIV infections in children and adolescents each year.[1] HIV in children is predominantly acquired through mother-to-child transmission (MTCT) during pregnancy, labor, and breastfeeding.[2] Medical advances—especially the scale of the access to antiretroviral therapy (ART) during pregnancy and postpartum throughout breastfeeding—have dramatically reduced the risk of mother-to-child transmission,[3,4] although progress has stalled in recent years and global targets on elimination of perinatal HIV transmission have not been reached.[5] Increased access to ART among pregnant women living with HIV as well as successes in the prevention of mother-to-child transmission have also resulted in a growing population of perinatally HIV-exposed uninfected (HEU) children and adolescents.[6–8]

Importantly, despite improved survival and overall health outcomes,[9] CALHIV and HEU have been shown to face pervasive impairments in neurodevelopment,[10–12] including impairments in cognitive and motor functions.[13] With regards to cognitive functions, a meta-analysis by Philips and colleagues in 2016 concluded that the most commonly affected cognitive domains among CALHIV are executive function and speed of information processing (or processing speed),[14] which is similar to adults living with HIV in the ART era.[15] However, this meta-analysis study was conducted eight years ago, and the number of studies focused on neurodevelopmental outcomes in CALHIV and HEU has since grown exponentially compared to the modest number of studies included in the previous analysis (i.e., the finding of significant processing speed impairment in HIV-infected children is based on a total of 96 participants from two studies).[14] To expand the analysis to the most up-to-date studies and capture the large number of works published after 2016, we conducted an updated meta-analysis to investigate the impact of perinatal HIV-infection on cognitive functions, with a focus on executive function, working memory, and processing speed—three tightly correlated cognitive domains during childhood development.[16,17] Our primary goal was to conduct an updated meta-analysis to assess neurodevelopment impairment in CALHIV, as compared to HIV-unexposed uninfected (HUU) and HEU controls. Our secondary goal was to investigate potential factors that may contribute to the potential neurodevelopment impairment in CALHIV.

Methods

Literature search

An online search of the PubMed database was conducted during March–April 2021, August 2023, and February 2024 using the following search criteria: "(hiv [Title/Abstract] OR hiv-infection [Title/Abstract] OR

HIV + [Title/Abstract] OR HIV1 [Title/Abstract] OR HIV-positive [Title/Abstract] OR HIV-infected [Title/Abstract] OR human immunodeficiency virus [Title/Abstract] OR HIV-disease [Title/Abstract]) AND (learning [Title/Abstract] OR cognitive [Title/Abstract] OR neurocognitive [Title/Abstract] OR neuropsychological [Title/Abstract] OR impairment [Title/Abstract]) AND (children [Title/Abstract] OR adolescent [Title/Abstract] OR pediatric [Title/Abstract] OR teenager [Title/Abstract] OR young [Title/Abstract] OR vertical [Title/Abstract])." Additional searches were conducted with the bioRxiv, medRxiv, and Science Direct databases in February 2024, as well as with citations in other studies. The following exclusion criteria were employed: (1) topic unrelated to neurocognitive functioning in perinatal HIV subjects; (2) published prior to 1997; (3) not original study; (4) only abstract available; (5) no control group; (6) no neuropsychological tests related to executive function, working memory, or processing speed; (7) no reporting of mean neuropsychological scores; (8) studies with less common neuropsychological tests (due to a lack of sufficient numbers of studies with scores from the same neuropsychological tests or test batteries); (9) same subject cohorts. Many studies met more than one exclusion criteria. Publications that used the same cohort of subjects were favored in the following respective order: studies with a larger sample size; studies published more recently (see Fig. 1). During the literature search process, we carefully reviewed all the articles to ensure quality control.[18,19]

We included several studies with the mean age of participants greater than 18 years old as these study participants developed HIV disease perinatally and were still at a relatively young age (i.e., mean age was less than 21). We conducted an additional sensitivity analysis with these studies excluded and confirmed the conclusions of the main study were not affected by the inclusion of these studies with young adults.

Measures of cognitive function

Composite scores for global executive function, working memory, and processing speed were extracted from each study. Executive function, as an umbrella term, is often defined as several high-level cognitive process components involving in goal-directed action and thought, including inhibition, working memory, and task shift.[20] Working memory measures one's ability to temporarily maintain and manipulate novel information and stimuli.[21,22] Speed of information processing, or processing speed measures the time required to monitor, process, and respond to new information in the environment.[23,24] The composite scores reported in each study were calculated by averaging the scores of all individual neuropsychological tests that comprised a particular cognitive domain.

Performance from several individual neuropsychological tests was also included in this meta-analysis, including the Digit Span test of the Weschler Adult Intelligence Scale, Trail Making Test Part A and Part B (TMT-A and TMT-B), and the Children's Color Trails Test 2 (CCTT-2). e-Table 1 provides further information on the neuropsychological tests included.

There were not enough published works with necessary data to conduct a meta-analysis on composite inhibitory control scores or some other neuropsychological tests (e.g., CCTT-1). Some studies reported z-scores, t-scores, or scores adjusted for various demographic variables, rather than raw test scores. e-Table 2 provides further details on the types of data that were extracted from each study.

Statistical analysis

The mean and standard deviation of executive function test scores were collected from each study included in the meta-analysis. The Review Manager software (version 5.4.1, https://www.cochrane.org) was utilized to create forest plots and perform statistical analysis of the study data. Pooled effect size estimates (*Hedges g*) were calculated for each of the executive function measures and each of the neuropsychological test scores. To account for between-study heterogeneity, a random-effects model weighted by inverse variance was used. The presence of between-study heterogeneity was tested using the Cochran's Q-Statistic and its magnitude was estimated using the I^2 statistic.[25] The Meta-Essentials Excel package (https://www.erim.eur.nl/research-support/meta-essentials)[26] was utilized to perform publication bias analyses, as well as moderator analyses for the following demographic and clinical characteristics: age, sex, usage of ART, and Gross National Income (GNI) per capita in 2019[27] (median publication date of all studies included in analysis). GNI per capita is defined as a country's total income earned by its residents divided by its population. The World Bank utilizes GNI per capita in order to classify countries into low-income, middle-income, and high-income status.[28,29] For studies involving multiple countries, an average of GNI per capita across countries was used. Publication bias was assessed through the Eggers test and funnel plot.[30] For the moderator analyses, a mixed-effects meta-regression model was used. The Meta-Essentials Excel package uses a weighted variance method that is slightly different from the RevMan package. We verified that both software packages produced equivalent results that led to the same conclusions.

Standard leave-one-*study*-out sensitivity analyses through the Review Manager software were conducted to investigate the robustness of findings. Specifically, each study was excluded once from the data analyses in order to assess how the pooled effect sizes and p-values were impacted. In addition, we conducted an additional sensitivity analysis to examine whether some of the results were biased by "overrepresented" research groups and/or cohorts. In this additional leave-one-*team*-out sensitivity analysis, we excluded all publications from each study team or cohort once.

Using the R package "meta" (https://cran.r-project.org/package=meta) and mixed-effects models with the

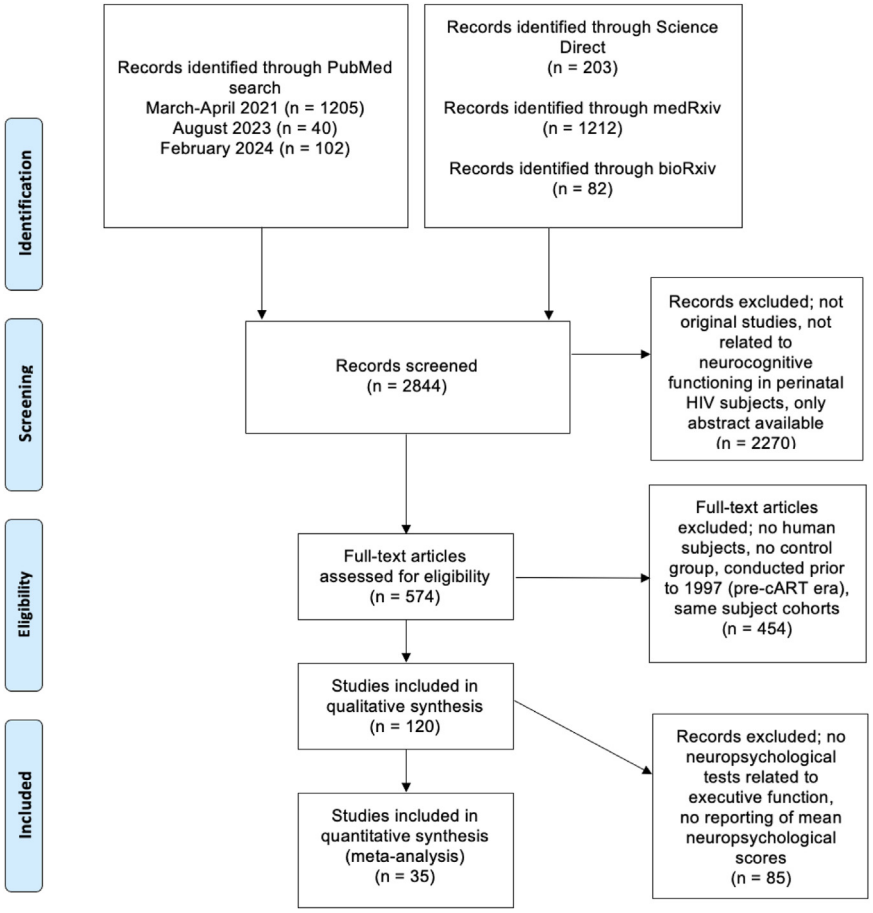

Fig. 1: PRISMA flow diagram of literature search and study selection.

default setting, additional meta-regression analyses were conducted to further investigate the effects of GNI per capita on the difference in processing speed between HIV-infected cases and HUU or HEU controls, after controlling for other potential confounding factors.

Please see Supplementary Materials for additional details on Methods.

Role of the funding source

This research was supported in part by NIH R01MH108466, NIH R56NS124422, and NIH R01NS124422. The funders had no role in study design, data collection and analysis, data interpretation, decision to publish, or preparation of the manuscript. Authors SD and XJ directly accessed data reported in manuscript. Authors SD, NR, and XJ contributed to decision to submit for publication.

Results

Study characteristics

Thirty-five studies were identified through the literature search (Table 1). Twenty-six studies examined the difference between perinatal CALHIV and HUU controls (including five studies with young adult participants, see Table 1). Fifteen studies examined the difference between HIV-infected cases and HEU controls. The publication date for the selected studies ranged from 2012 to 2023. Based on the World Bank country income classifications, fourteen of the selected studies took place in high-income countries, eighteen in middle-income countries, and five in low-income countries.[66] See e-Table 2 for additional information on the characteristics of each study included in this systematic review.

A total of 8881 participants were encompassed in this meta-analysis: 4066 perinatally-infected HIV patients, 2349 HIV-exposed uninfected controls, and 2466 HIV-unexposed, uninfected controls. The mean age of all the participants included was 11.6 years with a standard deviation of 4.6 years. The overall age range of participants was from 2 to 27 years of age. The demographic and clinical characteristics of perinatally-infected HIV patients included: mean age of 11.8 years, 46.8% male, 94.6% on ART, 78.1% with a suppressed viral load (as defined by each study criteria), and mean CD4 of 689.7 cells/mm^3. The demographic characteristics of

Study and Year	Country/region	HIV+					HEU		HUU	
		n	Age (years)	ART (%)	Suppressed VL (%)	Most Recent CD4 count/μL	n	Age (years)	n	Age (years)
Abrams 2018[31]	United States	206	12.7	94	64	491	97	12.4		
Ashby 2015[32]	United Kingdom	33	19.6	79	55	444			14	19.9
Bisiacchi 2017[33]	Italy	16	10.8	NA	NA	NA			28	11.8
Boivin 2020[34]	African Countries1	246	7.1	100	NA	NA	183	7.3	182	7.3
Chongwo 2023[35]	Kenya	43	4.33	NA	NA	NA	52	4.09	58	4.34
Cockcroft 2019[36]	South Africa	95	7.4	100	100	NA	86	7.4	92	7.1
Cohen 2015[37]	Netherlands	35	13.8	89	83	760			37	12.1
Ene 2014[38]	Romania	49	18.5	91.8	81.8	517			20	18.8
Ezeamama 2016[39]	Uganda	34	11.2	NA	77.6	772.0[a]	24	14.3	24	10.6
Familiar 2016[40]	Uganda	118	3.2	NA	NA	NA	164	2.8		
Haase 2014[41]	Brazil	41	11	100	NA	NA			82	11
Harris 2018[42]	United States	173	14.7	93.6	72.3	NA	85	12.6		
Heany 2023[43]	South Africa	60	13.8	100	68	747.5			36	13.5
Hermetet-Lindsay 2017[44]	United States	231	13.7	95	75	NA	151	13		
Hoare 2012[45]	South Africa	12	10.4	0[b]	91.7	585			12	9.8
Hoare 2020[46]	South Africa	168	10.8	100	82	980			43	10.7
Jago 2023[47]	Zambia	82	11.70	100	NA	NA	1045	12.32		
Judd 2016[48]	United Kingdom	296	16.0[a]	86	76	599			97	16.0[a]
Kapetanovic 2014[49]	United States	212	12.1	93	NA	713.0[a]	130	10.3		
Kerr 2019[50]	Thailand, Cambodia	232	14.9[a]	NA	86.4	741.0[a]	133	13.3[a]	148	12.8[a]
Lichtenstein 2021[51]	Tanzania	162	5.75	100	NA	NA	16	3–9	138	3–9
Linn 2015[52]	Myanmar	28	10.6	100	NA	827			31	10.7
Murthy 2018[53]	India	42	10.7	100	NA	NA			40	11.5
Paul 2018[54]	Thailand	100	11.4	71	67	683			100	10.6
Phillips 2019[55]	South Africa	203	10.4	100	65	952.7			44	10.4
Rachel 2023[56]	Kenya	270	9.56	NA	NA	NA			264	9.41
Ravindran 2014[57]	India	20	8–12	100	100	NA			20	8–12
Robbins 2021[58]	United States	33	NA	100	NA	475.0[a]	28	NA		
Ruiz-Saez 2021[59]	Spain	25	20.6	100	84	687.0[a]			25	20.4
Sherr 2018[60]	African Countries2	135	9.1	92.5	NA	NA			854	8.9
Shiau 2021[61]	United States	350	12.8[a]	94	69	NA	68	11.6[a]		
Sirois 2022[62]	United States	228	20.8	NA	64	NA	87	20.2		
Suter 2018[63]	Kenya	45	6.6	100	NA	NA			49	6.7
Van den Hof 2019[64]	Netherlands	14	10.5	100	100	NA			15	10.7
Willen 2017[65]	United States	29	20.3	76	NA	NA			13	21.9

HIV+, children/adolescents with HIV; HEU, HIV-exposed and uninfected; HUU, HIV unexposed and uninfected controls; NA, data were not available; ART, anti-retroviral therapy; VL, viral load. [a]Median. [b]No persons with HIV were on ART treatment due to their status as slow-progressors.

Table 1: **The list of studies included in the meta-analysis.**

HIV-exposed, uninfected controls included: mean age of 10.6 years and 50.9% male. The demographic characteristics of healthy controls included: mean age of 11.7 years and 46.3% male. Studies that only reported median age were excluded from the calculation of the mean age of the total sample. See e-Table 3 and e-Table 4 for additional demographic and clinical information for each group.

HIV-infected cases vs HIV-unexposed, uninfected (HUU) controls

Composite scores

HIV-infected subjects performed significantly worse relative to HUU controls on composite measures of executive function (*Hedges g* = –0.35, 95% CI: –0.64 to –0.07, p = 0.02, Fig. 2A), working memory (*Hedges g* = –0.69, 95% CI: –0.99 to –0.39, p < 0.00001, Fig. 2B), and processing speed (*Hedges g* = –0.64, 95% CI: –0.83 to –0.45, p < 0.00001, Fig. 2C) (Table 2).

Neuropsychological test scores

In comparison to HUU controls, HIV-infected subjects performed significantly worse on TMT-A (*Hedges g* = 0.67, 95% CI: 0.40–0.94, p = < 0.00001, Fig. 2D), TMT-B (*Hedges g* = 0.97, 95% CI: 0.23–1.72, p = 0.01, Fig. 2E), Digit Span (Forwards plus Backwards) (*Hedges*

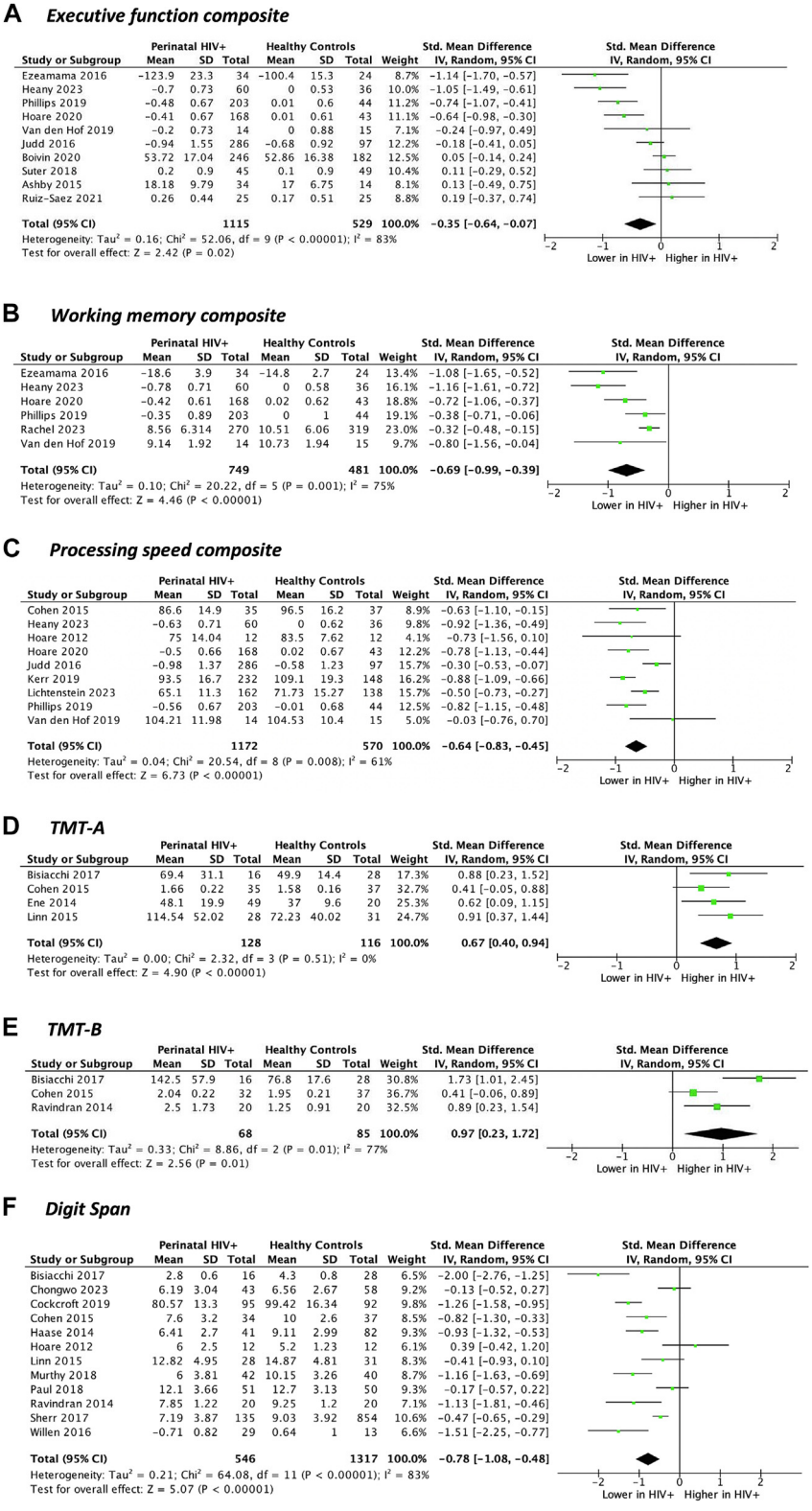

Fig. 2: Study effect sizes of children and adolescents with perinatal HIV-infection versus healthy controls. **(A)** Executive Function Composite; **(B)** Working Memory Composite; (**C**) Processing Speed Composite; **(D)** Trail Making Test Part A (TMT-A); **(E)** Trail Making Test Part B (TMT-B); **(F)** Digit Span (Forwards + Backwards). For both TMT-A (**D**) and TMT-B (**E**), higher values indicate longer reaction time and worse cognitive performance.

	NP Performance		Studies	Cases	Controls	Effect Size		Heterogeneity	
						95% CI	p	I^2 %	p
HIV + vs HUU	Composite Scores	Executive Function	10	1115	529	−0.35 (−0.64 to −0.07)	**0.02**	83.00	<0.00001
		Working Memory	6	749	481	−0.69 (−0.99 to −0.39)	**<0.00001**	75.00	0.001
		Processing Speed	9	1172	570	−0.64 (−0.83 to −0.45)	**<0.00001**	61.00	0.008
	Individual NP Test Scores	TMT A[a]	4	128	116	0.67 (0.40–0.94)	**<0.00001**	0.00	0.51
		TMT B[a]	3	68	85	0.97 (0.23–1.72)	**0.01**	77.00	0.01
		CCTT-2[a]	4	344	230	0.12 (−0.39 to 0.63)	0.64	82.00	0.0007
		Digit Span Scaled[b]	12	546	1317	−0.78 (−1.08 to −0.48)	**<0.00001**	83.00	<0.00001
HIV + vs HEU	Composite Scores	Executive Function	3	398	371	−0.17 (−0.48 to 0.14)	0.29	72.00	0.03
		Working Memory	5	1044	457	−0.18 (−0.37 to 0.02)	0.08	62.00	0.03
		Processing Speed	6	1404	582	−0.30 (−0.45 to −0.15)	**<0.0001**	52.00	0.07
	Individual NP Test Scores	Digit Span Scaled	6	577	1393	−0.26 (−0.41 to −0.12)	**0.0003**	27.00	0.23

CCTT-2, the Children's Color Trails Test 2; Healthy Controls, HIV unexposed and uninfected controls; HEU, HIV-exposed and uninfected; HIV+, HIV-infected cases; HUU, HIV unexposed and uninfected controls; NP, neuropsychological; TMT-A/TMT-B, Trail Making Test Part A/B. [a]Higher score is indicative of *less* favorable cognitive functioning. [b]Similar effects were observed for Forwards as well as Backwards scores from six studies with available data.

Table 2: **Summary of meta-analysis results.**

g = −0.78, 95% CI: −1.08 to −0.48, p < 0.00001, Fig. 2F), but not on CCTT-2 (p = 0.64) (Table 2).

HIV-infected cases vs HIV-exposed uninfected (HEU) controls

Composite scores

HIV-infected subjects performed significantly worse in composite processing speed measures relative to perinatally HEU controls (*Hedges g* = −0.30, 95% CI: −0.45 to −0.15, p < 0.0001, Fig. 3A), but not on Executive Function (p = 0.29) or Working Memory (p = 0.08) (Table 2).

Neuropsychological test scores

HIV-infected subjects performed significantly worse on Digit Span (forwards plus backwards) relative to HEU controls (*Hedges g* = −0.26, 95% CI: −0.41 to −0.12, p = 0.0003, Fig. 3B and Table 2).

Moderator and meta-regression analyses

A mixed-effects meta-regression model was used to investigate the effects of age, sex, ART usage, and country income-level on executive function in CALHIV compared to HUU controls. There were no

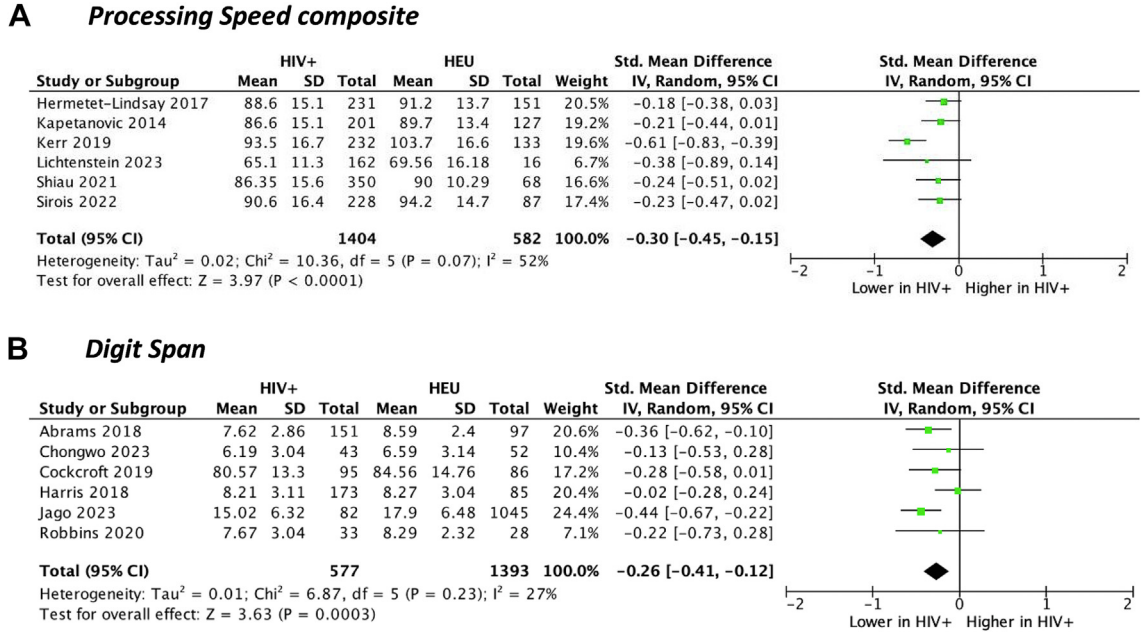

Fig. 3: Study effect sizes of children and adolescents with perinatal HIV-infection versus HIV-uninfected controls with perinatal HIV-infection exposure. **(A)** Processing Speed Composite; **(B)** Digit Span Forwards + Backwards.

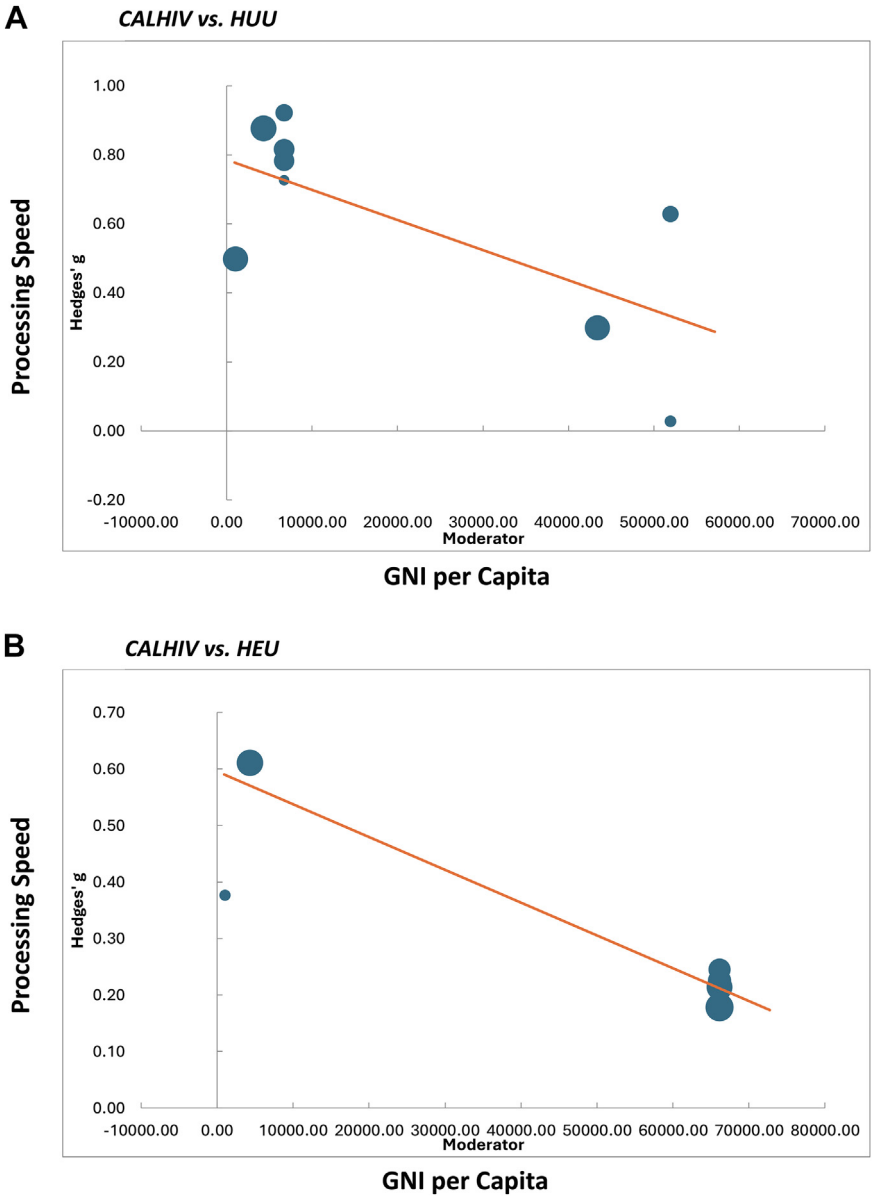

Fig. 4: The association between Gross National Income (GNI) per capita (moderator) and processing speed impairment in **A)** children and adolescents with perinatal HIV-infection (CALHIV) versus healthy controls (HUU), and **B)** CALHIV versus HIV-uninfected controls with perinatal HIV-infection exposure (HEU).

significant effects of mean age, gender/sex, and ART usage on the effect size for any of the executive function measures. By contrast, an association between country income-level and effect size for processing speed composite scores was observed for both CALHIV vs HUU and CAHIV vs HEU comparisons (Fig. 4). Overall, lower country income-level (measured as GNI per capita) tended to be associated with greater deficits in Processing Speed (measured as Composite Scores) among HIV-infected cases (CALHIV vs HUU: $z = -2.08$, $p = 0.038$; CALHIV vs HEU, $z = -3.02$, $p = 0.003$), even though CALHIV were compared to HUU or HEU controls from the same country (ies).

To further investigate the relationship between the GNI per capita and the observed processing speed deficit in CALHIV, we conducted a separate meta-regression analysis using the R package "meta", after controlling for other potential contributing factors, including age, % of ART usage, and % of HIV + participants with successful viral suppression (only age for CALHIV vs HEU due to lack of data on

ART usage and viral suppression). This additional meta-regression analysis provided additional evidence supporting the association between the GNI per capita and the effect size of Processing Speed deficit in HIV-infected participants (CALHIV vs HUU: p = 0.0016; CALHIV vs HEU: p = 0.0019).

In addition, we divided the studies into two subgroups based on the GNI per capita of the study countries, high-income or low-/middle-income countries, then investigated the difference in processing speed and other composite scores. Because there are not sufficient number of studies conducted in low-income countries, the studies conducted in low- and middle-income countries are combined together as one subgroup. These additional analyses provided further evidence suggesting worse cognitive deficits in CALHIV living in the low-/middle-income countries than those in the high-income countries (e-Table 8).

Heterogeneity, sensitivity analysis, publication bias, sociodemographic factors

A random effects model was used for all comparisons, as significant heterogeneity was observed for several executive function measures, as shown in Table 2. Furthermore, publication bias was identified in one comparison: Children's Color Trails Test Part 2 (e-Fig. 1). Both leave-one-*study*-out and leave-one-*team*-out sensitivity analyses suggested that the results were largely robust, with two exceptions: the working memory composite score for the CALHIV vs HEU comparison, and the executive function composite score for the CALHIV vs HUU comparison (see e-Table 5 and e-Table 6).

In addition, excluding studies with sociodemographically unmatched groups led to similar findings (e-Table 7).

Discussion

Our results suggest that in the ART era, compared to both HUU and HEU controls, impairment to processing speed, working memory, and to a lesser degree, executive function remain prevalent in CALHIV. Furthermore, meta-regression analysis suggests that processing speed impairment may be more severe in CALHIV in low-income countries, even when compared to HUU from the same countries.

Processing speed, or the speed of information processing, is one of the most commonly evaluated cognitive domains in studies related to neurodevelopment and neurodegeneration.[16,67] Previous studies have shown that in children and older adults, performance in the processing speed domain may underlie performance in many other cognitive domains, especially in domains related to fluid intelligence/function (including executive function),[68,69] but less so in young healthy adults.[70] For instance, the "cognitive developmental cascade" theory of neurodevelopment proposes a central role of processing speed on cognitive performance in children.[16,71] Based on this theory, processing speed has a direct impact on working memory, which in turn has a direct impact on fluid function (including executive function), thus a large portion of variations in general cognitive performance (especially fluid function) can be accounted for by variations in processing speed.[17] In studies with CALHIV, processing speed impairment has been widely reported,[37,45,46,48,50,55,64] and is further supported by data from the current meta-analysis study (Fig. 2C). Based on the cognitive developmental cascade theory[16,71] as well as findings from children,[17] the prevalent processing speed impairment may contribute to overall neurocognitive impairment in perinatally infected CALHIV, probably more so in young children as the development of processing speed is proposed to mature around age 14 years.[23]

Many potential factors may have contributed to processing speed impairment in CALHIV,[12] including HIV-related white matter injury[72,73] studies with HIV-uninfected individuals (both healthy controls and those with brain lesions or other neurological diseases) have demonstrated an important role of white matter integrity in processing speed performance.[74,75] Neural injury to other key brain regions such as prefrontal cortex[76] may play an important role in processing speed impairment as well. In addition to the biological factors such as white matter and prefrontal injury, socioeconomical factors may also contribute to processing speed impairment in CALHIV. Indeed, in this study, meta-regression analysis revealed a significant association between the effect size of processing speed impairment in HIV-infected cases and the GNI per capita of their countries (Fig. 4), even after controlling for other potential confounding factors (e.g., percentage on ART). Given the fact that both HIV-infected and -uninfected participants were recruited from the same country (ies), this significant association—while should be treated with caution due to limitations with meta-regression analysis[77]—has important implications: it suggests that limited resources in developing countries may not allow for timely assessment and interventions and therefore further exacerbate the impacts of HIV-infection on neurodevelopment.[13,78] Factors such as ART regimens,[79] nutrition,[80] the quality of health care,[11] and socioeconomic status[81] may independently or interactively contribute to the observed health inequity in CALHIV. Due to limitations with meta-regression analysis,[77] this association should be verified and directly investigated by future multi-site and multi-country studies, but nevertheless, its implications of limited country resources on neurodevelopment calls for global responses from WHO and other stakeholders,[82] especially since the vast majority of global perinatal HIV infections occur in resource-limited Sub-Saharan Africa area.[5]

In addition to processing speed, working memory impairment in CALHIV has been well documented by previous studies[39,46,55,64] and is further supported by

lower working memory composite score in our quantitative meta-analysis (Fig. 2B). The Digit Span neuropsychological test—a commonly used working memory cognitive instrument—provides additional support for working memory impairment in perinatal HIV-infection (Fig. 2F). Despite evidence supporting that backward and forward Digit Span may involve both overlapping and distinctive brain regions/networks,[83] we confirmed that using backward or forward scores alone produced highly similar findings (data not shown)—suggesting that working memory impairment is likely due to diffused neural injury (rather than focal injury) in perinatal HIV-disease, which may mirror the age-related decline in forward and backward Digit Span scores.[84] Reduced performance in Digit Span is also present when compared to HEU controls (Fig. 3B). Neural mechanisms underlying processing speed impairment (i.e., white matter[72,73] and prefrontal injury[76]) may contribute to working memory impairment in CALHIV as well,[85] especially given the direct relationship between processing speed and working memory in children.[16,71]

Although executive deficit in CALHIV has been previously reported[14] and is one of the main motivations for our study, we observed a relatively weak group difference in executive function between CALHIV and HUU controls, including marginally significant results with executive composite score (Fig. 2A). In addition, there is no significant group difference in CCTT-2 test score, a commonly used cognitive instrument to assess executive function in young children. Furthermore, even though CALHIV do perform poorly on TMT-B when compared to healthy controls (Fig. 2E), it is unclear whether the reduced performance on TMT-B can be largely accounted for by performance on TMT-A—a common assessment of processing speed. Future studies using a ratio of time, TMT-B/TMT-A, may help to control for confounds due to difference in processing speed and better answer this question.[86] There is no significant difference between CALHIV and HEU controls. However, the lack of strong difference in executive function between CALHIV and HUU and between CALHIV and HEU could be due to a ceiling or floor effect, i.e., the neuropsychological tests administered in these studies might be too easy or too challenging to reliably capture the difference between CALHIV and other participants.

This meta-analysis study does have limitations to be considered. First, other potential factors such as socioeconomic status, parental education and occupational status, and home language might contribute to the lower cognitive performance in CALHIV. However, similar results were obtained after excluding all studies with sociodemographically unmatched groups, providing further support of impaired processing speed in CALHIV. We also do not observe a significant effect of age at study-level, but future studies are needed to investigate the question at an individual subject level. Second, the findings from the moderator analysis and the meta-regression analysis should be treated with caution as indirect evidence, which will help to stimulate more research in this important direction but should not be used to make a decisive conclusion. In addition, the number of participants included in each individual study—as a common problem—is rather limited, and the meta-analysis is helpful to address some of limitations on sample size, but future large cohort studies are needed to directly compare cognitive performance of CALHIV living in low- and high-income countries to investigate the factors that contribute to health disparities among CALHIV living in low-/middle-versus high-resources countries. Finally, only one-third of the studies included in this meta-analysis took place in Sub-Saharan Africa, despite more than 90 percent of perinatal HIV cases occurring in Sub-Saharan Africa.[5] Therefore, caution should be exercised when generalizing the findings of this meta-analysis to Sub-Saharan African settings. Future investigations should explore the impact of perinatal HIV-infection on other cognitive domains such as language, memory, and motor function with modern ART, as well as the impact of confounding variables such as ART regimens, caregiver education, presence of malnutrition, and poverty on the neurological outcomes of CALHIV.

In summary, this meta-analysis demonstrates that despite ART treatment, perinatally infected CALHIV have impaired cognitive function compared to both HEU and HUU controls, particularly in processing speed and working memory, which might play an important role in impairments in other cognitive domains such as executive function, as well as in general neurodevelopment milestones. Importantly, processing speed impairment correlated with GNI per capita, suggesting that CALHIV in the resource-limited settings most heavily affected by the HIV epidemic may remain at a greater risk of cognitive and development impairment and related long-term outcomes.

Contributors

S.D., study concept, study design, literature review and data collection, data analysis, writeup and revisions; N.R. literature review, write up and revisions; X.J., study concept, study design, literature review and data collection, writeup and revisions.

Data sharing statement

Data is available in the supplementary materials.

Declaration of interests

None.

Acknowledgements

We wish to thank R. Craig Gallagher, Mikaley Bolden, Shuqi Wang, and Dr. Ruzong Fan for running the meta-regression analysis with the R software package. This research was supported in part by NIH R01MH108466, NIH R56NS124422, and NIH R01NS124422. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102602.

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