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Components of metabolic syndrome associated with lower neurocognitive performance in youth with perinatally-acquired HIV and youth who are HIV-exposed uninfected

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Abstract

Objective(s): We investigated the association of metabolic syndrome (MetS) and its components [abdominal obesity, elevated triglycerides (TG), low HDL cholesterol, elevated blood pressure (BP), and impaired fasting glycemia (IFG)] with neurocognitive impairment in youth with perinatally-acquired HIV (YPHIV) or who are perinatally HIV-exposed uninfected (YPHEU).

Design: Observational study with a comparison group of 350 YPHIV and 68 YPHEU ages 10–19 years.

Methods: Youth with MetS components measured between 1 year before and 3 months after a baseline neurocognitive assessment (Wechsler Intelligence Scale) were selected from the Pediatric HIV/AIDS Cohort Study (PHACS). A sub-group completed another assessment 3 years later. We assessed the association of each baseline MetS component with five standardized neurocognitive indices at baseline and changes in indices over time.

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Results: At baseline, 15% of YPHIV and 18% of YPHEU met criteria for ≥2 MetS components. Among YPHIV, there was no association between MetS components and neurocognitive indices at baseline; however, over time, elevated baseline BP was associated with a greater decrease in mean Perceptual Reasoning scores (−4.3;95%CI: −8.8,0.3) and ≥2 MetS components with a greater decrease in mean Processing Speed scores (−5.1;95%CI: −9.4,−0.8). Among YPHEU, elevated TG was associated with lower mean Verbal Comprehension, Perceptual Reasoning, and Full-scale IQ scores at baseline, and IFG with lower mean Verbal Comprehension scores.

Conclusions: Components of MetS in YPHIV (elevated BP) and YPHEU (elevated TG and IFG) were associated with lower neurocognitive performance index scores. Studies to elucidate how modifying metabolic risk factors early in life may improve neurocognitive outcomes in this population are warranted.

Keywords

neurocognitive function; perinatally-acquired HIV; HIV-exposure; children; metabolic syndrome

Introduction

The increased effectiveness of combination antiretroviral therapy (ART) has led to substantial declines in morbidity and mortality in adults living with HIV (ALWH); however, neurocognitive complications of HIV remain prevalent (Eggers et al., 2017; Heaton et al., 2010; Michael et al., 2020). Neurodevelopmental deficits have also been reported in youth with HIV, even among those initiating ART early in life (Hoare et al., 2018; Laughton et al., 2013, 2018; Ruel et al., 2012; Strehlau et al., 2016; Yadav et al., 2017). In addition, metabolic complications of HIV infection and ART, including dyslipidemia (Tassiopoulos et al., 2008), fat redistribution (Dzwonek et al., 2006; Jacobson et al., 2011), and insulin resistance (Frigati et al., 2019; Geffner et al., 2018; Gojanovich et al., 2020), have been documented extensively and may be the result of complex interactions between HIV infection, ART, age, race/ethnicity, socioeconomics, diet, and other factors including inflammation (Wohl et al., 2006).

The term metabolic syndrome (MetS) was popularized in 1977 to identify individuals at increased risk for cardiovascular disease (Alberti et al., 2009). Definitions of MetS in adults have been developed by, among others, the National Cholesterol Education Program (NCEP) and the International Diabetes Federation (IDF) (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). Components include (1) abdominal obesity, (2) elevated triglycerides (TG), (3) low high-density lipoprotein (HDL) cholesterol, (4) elevated blood pressure (BP), and (5) impaired fasting glycemia (IFG), with only slight differences among the various definitions. The IDF definition has also been adapted for children (Zimmet et al., 2007).

MetS is commonly present in ALWH (Jacobson et al., 2006). In the general HIV-uninfected adult population, cardiovascular risk factors, including components of MetS, have been linked to lower cognitive performance and brain abnormalities (Anstey et al., 2008; Debette et al., 2010; Levin et al., 2014; Siervo et al., 2014; Vieira et al., 2011). Studies in ALWH on ART have reported associations between cardiovascular risk factors and cognitive

impairment (Fabbiani et al., 2013; Macaluso et al., 2020; McCutchan et al., 2012; Sattler et al., 2015; Valcour et al., 2005, 2006). Recent studies also suggest MetS is associated with global neurocognitive deficits, and that these associations may differ between adults with and without HIV (Yu et al., 2019).

It is unclear whether these associations extend to youth living with perinatally-acquired HIV (YPHIV) or who are perinatally HIV-exposed uninfected (YPHEU), as the intersection of metabolic and neurocognitive health has not been well-studied in these groups. YPHIV have lifelong exposure to HIV and ART which may drive persistent inflammation and immune activation, and these processes, in turn, may underlie metabolic and cognitive problems (Benki-Nugent et al., 2019; Wilkinson et al., 2018). While some studies report stable neurocognitive performance among YPHIV on a group level, unfavorable changes in neurocognitive performance over time in some domains has also been reported for YPHIV; it is possible this could be due to changing HIV disease or metabolic dysfunction (Kerr et al., 2019; Malee et al., 2017; Robbins et al., 2020; Van den Hof et al., 2020). As such, YPHIV are a critical population to investigate, particularly since earlier identification of the association between MetS and poor neurocognition may provide a window for screening and intervention that is lost in older adult populations. In addition, understanding whether perinatal HIV modifies this association even at earlier ages is important. The aim of our study was to examine the association of individual MetS components with neurocognitive outcomes at baseline in YPHIV and YPHEU, and the association between individual MetS components at baseline and change in neurocognitive outcomes over time in YPHIV.

Methods

Study Population

Participants for this study were selected from the Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study (PHACS) network, a prospective cohort study designed to define the impact of HIV infection and antiretroviral therapy on pre-adolescents and adolescents with perinatal HIV infection with a group of HIV uninfected children with perinatal exposure to HIV as a comparison group. PHACS enrolled 451 YPHIV and 227 YPHEU from March 2007 through November 2009 at 15 clinical sites in the United States (US) including Puerto Rico, with annual follow-up visits. The analytic dataset included youth with a neurocognitive assessment at age ≥10 years (with the first assessment defined as “baseline”) and all five MetS components [based on International Diabetes Federation (IDF) criteria] measured between 1 year before and 3 months after that baseline assessment (Alberti et al., 2006, 2009; Zimmet et al., 2007). Participants with a second neurocognitive examination approximately 3 years after baseline (hereafter called “year 3”) were included in longitudinal analyses. Participants who were pregnant at baseline were excluded. Participating sites and the Harvard T.H. Chan School of Public Health obtained Institutional Review Board (IRB) approvals. Written informed consent was obtained from the parent/legal guardian and assent was obtained from participants according to local IRB guidelines.

Outcomes of Interest: Neurocognitive Function

The primary outcomes of interest were neurocognitive function at baseline and change in neurocognitive function between the baseline and year 3 evaluation, for each neurocognitive measure separately. Neurocognitive function was measured using either the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) if the participants were 10-<16 years of age, or the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) if the participants were ≥16 years at the assessment (Wechsler, 2003, 2008). Specific indices included Full-scale IQ (FSIQ) which represents overall cognitive ability, as well as standardized index scores (mean=100, SD=15) for the Verbal Comprehension, Perceptual Reasoning, Working Memory, and Processing Speed domains. Change over time in each neurocognitive index score was defined as the year 3 score minus baseline score. All tests were administered by a psychologist/psychometrist under direct supervision by a psychologist. Protocol neuropsychologists reviewed any test results suggesting unusual assessment circumstances, and only scores determined to be valid were included in the analysis.

Exposures of Interest: MetS Components

The primary exposures of interest were the individual components of MetS at baseline as binary variables based on the IDF criteria: abdominal obesity (waist circumference ≥90th percentile for 10-<16 years and ≥94 cm or ≥80 cm for males and females ≥16 years, respectively), elevated TG (≥150 mg/dL), low HDL cholesterol (<40 mg/dL for 10-<16 years for both sexes and males ≥16 years, and <50 mg/dL for females ≥16 years), high BP (systolic BP ≥130 mm Hg or diastolic BP ≥85 mm Hg), and IFG (≥100 mg/dL) (Supplementary Table 1) (Alberti et al., 2006, 2009; Zimmet et al., 2007). Blood samples were collected after a >8-hour fast to assay lipid sub-fractions, including TG and HDL cholesterol, and glucose levels according to standardized protocols (Geffner et al., 2018; Miller et al., 2012). Anthropometric and BP measurements were measured at the same visit. For this analysis, we used two definitions for MetS – the first meeting ≥3 and the second ≥2 of the five individual components.

Covariates

Covariate information was obtained from clinical charts, questionnaires, or physical examinations. For both groups, the following covariates were considered as potential confounders: sex, age, self-reported race/ethnicity (non-Hispanic Black vs. not non-Hispanic Black), primary language (English vs. Bilingual/Other), household income at baseline (≤$20,000 vs. >$20,000), and Tanner stage at baseline (1–2 vs. 3–4 vs. 5). For YPHIV, in addition to the above, we considered age at ART initiation, nadir CD4 cell count, peak HIV RNA level, and antiretroviral (ARV) use at baseline in categories [≥3 ARV classes, protease inhibitor (PI)-based combination ART, integrase strand transfer inhibitor (INSTI)-based combination ART, non-nucleoside reverse-transcriptase inhibitor (NNRTI)-based combination ART, 3 nucleoside reverse transcriptase inhibitors (NRTIs), other, and not on ARV].

Statistical Analysis

Baseline sociodemographic and clinical characteristics, as well as the distribution of exposure and outcome measures, were compared between YPHIV and YPHEU using t-, Wilcoxon, and Chi-square tests as appropriate.

Baseline: Within YPHIV and YPHEU separately, we assessed the association between each binary MetS component and each neurocognitive index at baseline by fitting linear regression models using generalized estimating equations (GEE) with robust variance, unadjusted and adjusted for *a priori* confounders (age, sex, race/ethnicity, primary language, household income, and Tanner stage, plus age at ART initiation, nadir CD4 cell count, peak HIV RNA level, and ARV use for YPHIV). Given limited power, we did not conduct a formal test for effect modification by HIV status. We presented stratified findings and qualitatively assessed effect modification of associations between each MetS component and each neurocognitive index by HIV status.

Longitudinal: To assess the representativeness of the subset with longitudinal neurocognitive assessments, distributions of baseline binary exposures and continuous outcomes were compared between participants with and without longitudinal measurements, separately within YPHIV and YPHEU, using t-, Wilcoxon, and Chi-square tests. Given the small sample size of YPHEU with available longitudinal measurements and apparent lack of change in neurocognitive indices from baseline to year 3 in YPHEU, the longitudinal association between each binary MetS component at baseline and change in each neurocognitive index over time was only assessed in YPHIV. This was done by fitting linear regression models using GEE with robust variance, specifying the distribution as normal and the identity link, unadjusted and adjusted for *a priori* confounders (age, sex, and race/ethnicity) and other potential confounders that had associations of $p<0.10$ with at least one of the neurocognitive indices. Additional analyses considering each of the MetS components on a continuous scale were conducted to determine if findings were consistent with those where we considered dichotomous MetS components.

Statistical analyses were performed using SAS® 9.4 (SAS Institute, Cary, NC). All statistical tests were two-sided; emphasis was placed on consistency of results across analyses under various assumptions.

Results

Study Population

Of the 678 AMP participants, 599 (398 YPHIV, 201 YPHEU) completed either a WISC-IV or WAIS-IV (Figure 1). Seventy-nine participants were excluded because they did not have a neurocognitive assessment completed ≥10 years of age, were missing scores for all outcomes of interest, or were pregnant at the time of the assessment. A total of 418 participants (350 YPHIV and 68 YPHEU) had all five MetS components measured between 1 year before and up to 3 months after the neurocognitive assessment and included in baseline analyses. Among YPHIV, median time between the MetS measurement and neurocognitive assessment was 0 days [IQR (interquartile range): −19, 0]. Among YPHEU,

median time between the MetS measurement and neurocognitive assessment was −1 day (IQR: −19, 0). In addition, 183 YPHIV and 58 YPHEU completed a neurocognitive assessment at both baseline and year 3.

Participant Characteristics

Participant characteristics are shown in Table 1. YPHIV were slightly older (median age 12.8 vs 11.6 years) and more often Non-Hispanic Black, living in a household with income >$20,000, and reporting English as a primary language compared to YPHEU. Approximately one-third (37%) of YPHIV reported that their biological mother was one of their primary caregivers compared to 68% of YPHEU. There were no differences in the distribution of sex, Tanner stage, caregiver education, and physical activity between groups. At baseline, 89% of YPHIV had a CD4 count >350 cells/μL, 69% had a viral load ≤400 copies/mL, and 58% were on PI-based combination ART. Median age at ART initiation was 2.96 years; 26% had a nadir CD4 T-cell >500 cells/μL, and 73% had a peak viral load >100,000 copies/mL.

Prevalence of MetS Components

A smaller proportion of YPHIV had abdominal obesity (17% vs 34%, p=0.002) and IFG (3% vs 7%, p=0.045), and a higher proportion had elevated TG (22% vs 7%, p=0.006) compared to YPHEU (Table 2). No differences were observed in the other categorical MetS components—reduced HDL and elevated BP. Among YPHIV, no participants with IFG were diagnosed with Type 2 DM at or prior to glucose measurement, but two participants without IFG were. Among YPHEU, no participants with or without IFG were diagnosed with Type 2 DM.

At baseline, 3% of YPHIV and 7% of YPHEU met criteria for ≥3 MetS components; 15% of YPHIV and 18% of YPHEU met criteria for ≥2 MetS components. Among those who met criteria for ≥2 MetS components, the most common MetS components were reduced HDL (65%) and elevated TG (63%) in YPHIV, whereas the most common were abdominal obesity (100%) and reduced HDL cholesterol (67%) in YPHEU.

Baseline Analysis of Neurocognitive Indices

Neurocognitive outcomes at baseline are shown in Table 2. Among YPHIV, no associations between baseline MetS components and baseline neurocognitive indices were observed in unadjusted models or models adjusted for age, sex, race/ethnicity, primary language, household income, Tanner stage, age at ART initiation, nadir CD4, peak HIV RNA, and ARV use (Supplementary Table 2). Among YPHEU, however, elevated TG was associated with lower mean Verbal Comprehension (−10.0; 95% CI: −17.7, −2.2), Perceptual Reasoning (−7.9; 95%CI: −13.2, −2.5), and FSIQ (−7.5; 95%CI: −14.6, −0.5) scores. In addition, IFG was associated with a lower mean Verbal Comprehension score (−12.7; 95%CI: −24.7, −0.7) in models adjusted for age, sex, race/ethnicity, primary language, household income, and Tanner stage. This was consistent with additional analyses treating TG as a continuous variable: a one-unit increase in TG (mg/dL) was associated with a 0.14 lower Verbal Comprehension score (95%CI: −0.21, −0.07), 0.07 lower Perceptual Reasoning score (95%CI: −0.11, −0.03), and 0.05 lower FSIQ score (95%CI: −0.10, 0.00), and a

one-unit increase in IFG (mg/dL) was associated with a 0.33 lower Verbal Comprehension score (95%CI: −0.65, −0.00).

Longitudinal Analysis of Neurocognitive Indices

Proportions of YPHIV and YPHEU meeting each MetS criterion at baseline were similar between participants with and without longitudinal measurements (Supplementary Table 3). At year 3, 34% of YPHIV and 19% of YPHEU with neurocognitive assessments completed the WAIS-IV. Neurocognitive scores at baseline, year 3, and the change are shown in Figure 2. All neurocognitive scores except Processing Speed score declined on average, between 1.5 and 2.1 points, from baseline to year 3 for YPHIV, while there were no changes in mean scores for YPHEU. Due to the lack of change in neurocognitive scores over time and the small sample of YPHEU, we chose to focus on longitudinal models in YPHIV.

Characteristics of the 183 YPHIV included in the longitudinal analyses were mostly similar to those without longitudinal measurements, with a few exceptions (data not shown). YPHIV included in the longitudinal analyses had a lower mean nadir CD4 count (320 vs. 386 cells/μL, $p<0.001$) and higher HIV RNA viral load (2.6 vs. 1.8 $\log_{10}$ copies/mL, $p<0.001$) near their baseline neurocognitive assessment, and initiated ART slightly later (3.8 vs. 2.1 years, $p<0.001$) than those excluded from longitudinal analyses.

Among 183 YPHIV with longitudinal data, elevated BP at baseline was associated with a greater decrease in mean Perceptual Reasoning scores over time (−4.3; 95%CI: −8.8, 0.3) in adjusted analyses (Table 3). In addition, meeting criteria for ≥2 MetS components was associated with a greater decrease in mean Processing Speed scores over time (−5.1; 95%CI: −9.4, −0.8) in adjusted analyses.

Abdominal obesity was associated with a greater decrease in mean Verbal Comprehension scores over time in unadjusted models (−3.2; 95%CI: −6.9, 0.4), but this association was attenuated after adjusting for potential confounders (−2.3; 95%CI: −6.3, 1.6). On the continuous scale, for every one-unit increase in waist circumference Z-score at baseline, there was an additional mean decrease of 1.64 (95%CI: −3.00, −0.27) points in Verbal Comprehension over time (data not shown).

Discussion

To our knowledge, this is the first study to examine the association between components of MetS and neurocognitive outcomes in YPHIV and YPHEU. In our cohort of youth aged 10–19, 3% of YPHIV and 7% of YPHEU met criteria for ≥3 MetS components and 15% of YPHIV and 18% of YPHEU met criteria for ≥2 MetS components. For YPHIV, the most prevalent MetS components were reduced HDL and elevated TG and, for YPHEU, the most prevalent components were abdominal obesity and reduced HDL cholesterol. We found that some components of MetS in YPHIV (raised blood pressure) and YPHEU (elevated TG and IFG) were associated with lower neurocognitive performance in childhood/adolescence.

A systematic review of 85 studies found a median MetS prevalence (based on ≥3 MetS components) of 3.3% (range 0–19.2%) in the general pediatric population (Friend et al.,

2013). MetS prevalence for YPHIV in our study was similar to this estimate, while the MetS prevalence for YPHEU was higher than in the general population. Another study, using nationally-representative data from 1999–2014 in youth ages 12–19 years in the US, found MetS prevalences ranging from 6.25% in the Northeast to 11.42% in the Midwest (DeBoer et al., 2019). MetS prevalence for YPHIV in our study fell below this range, while the MetS prevalence for YPHEU fell within this range. It is important to note that there is no consensus definition for pediatric MetS currently. For example, in the IDF criteria, the US definition of elevated fasting glucose is used for IFG, rather than the European definition of elevated fasting insulin. Use of different definitions may lead to different classifications for MetS. Thus, for youth, the focus on individual components may be more meaningful (Magge et al., 2017). There is some debate over whether incremental MetS risk (*e.g.*, meeting one or two, but not three or more, criteria for MetS) is as important as full-fledged MetS when investigating cognitive impairment in adults in the general population. Some studies suggest that meeting one or two factors may be as detrimental as meeting three or more (Lamar et al., 2015; Vieira et al., 2011). We found 15% YPHIV and 18% YPHEU exhibited MetS by meeting criteria for ≥2 components, raising the notion that these youth may also benefit from further monitoring.

Prevalence estimates of MetS among populations with HIV are varied. A meta-analysis using various MetS definitions estimated the global pooled prevalence of MetS among people with HIV to range from 16.7 to 31.3%, with substantial heterogeneity by age and other factors (Nguyen et al., 2016). This meta-analysis included few pediatric studies. In a study of Spanish youth with HIV ages 2–18 years, MetS prevalence was 1.97% by the IDF criteria and 5.92% by the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) criteria (Espiau et al., 2016). Our estimate of 3% in YPHIV was in this range. In young adults, a recent Thai study found MetS prevalence (NCEP-ATP III criteria) to be 10.6% in YPHIV ages 15–25 years (Aurpibul et al., 2020). Another cohort of young adults ages 18–30 years in France with perinatally-acquired HIV found a MetS prevalence of 13.2% in men and 10.4% in women (Arrive et al., 2018). Additional follow-up is necessary to understand whether the prevalence of MetS observed in our study will continue to increase as these adolescents age into young adulthood.

Among YPHIV who met criteria for ≥2 MetS components, the most common components were reduced HDL (65%) and elevated TG (63%). The profile of abnormal lipids without abdominal obesity observed among the YPHIV in our study falls in line with reports of a “thin and hypercholesterolemic” pattern in other studies of YPHIV (Lindsey et al., 2012), a pattern that continues to persist at older ages. For example, in the aforementioned French study of young adults with HIV, the most common cluster of abnormalities for those with MetS was reduced HDL, elevated TG, and elevated BP (Arrive et al., 2018). In another study of MetS in ALWH ages 25–64 years, most with MetS (77%) had reduced HDL, elevated TG, and one additional abnormality (Jacobson et al., 2006). On the other hand, for YPHEU who met criteria for ≥2 MetS components in this study, the most common were abdominal obesity (100%) and reduced HDL cholesterol (67%).

Among YPHIV, we found that elevated BP was associated with a decrease in Perceptual Reasoning scores over time. Hypertension could mediate the effects of HIV and ART on

cognition and has been linked to cognitive function in the general population (Asiimwe et al., 2020; Jiménez-Balado et al., 2019; Pasipanodya et al., 2019). An earlier study in the AMP cohort found an association between fibrinogen, a marker of coagulation, and Perceptual Reasoning scores (Kapetanovic et al., 2010). Together with our BP finding, this suggests a cascade of microvascular events could be associated with neurocognitive impairment in the context of pediatric HIV.

We found that, among YPHIV, meeting criteria for ≥2 MetS components was associated with lower Processing Speed scores over time. In a study of 109 ALWH, DM and elevated TG were the MetS components most strongly associated with increased global neurocognitive deficits (Yu et al., 2019). Monitoring these components of MetS as YPHIV continue to age will be increasingly important, particularly since YPHIV are less likely to exhibit frank obesity as a MetS component. Though the mechanism linking MetS and cognitive decline is not well-understood, microvascular dysfunction and inflammation from metabolic perturbations may offer an explanation. For example, YPHIV have been shown to have endothelial dysfunction, an early marker of subclinical cardiovascular disease risk compared to youth without HIV (Dirajlal-Fargo et al., 2017; Mahtab et al., 2020). Endothelial dysfunction reflects potentially reversible vascular damage (Flammer et al., 2012) and has been shown to be associated with cognitive impairment (Gorelick et al., 2011; Wright & Flores, 2015), making it an important parameter to consider in the context of cardiometabolic and neurocognitive health among YPHIV.

Of note, Perceptual Reasoning and Processing Speed were the domains associated with MetS components in our study among YPHIV. Processing Speed is a domain that has been repeatedly shown to be affected in youth with HIV (Phillips et al., 2016). In addition, there have been studies done indicating deficits in perceptual-performance domains in young children ages 6–8 years with HIV (Kandawasvika et al., 2015).

In cross-sectional analyses, YPHEU with elevated TG had lower Verbal Comprehension, Perceptual Reasoning, and FSIQ scores, and those with IFG had a lower mean Verbal Comprehension score. These associations have been reported in HIV-unexposed and uninfected adults. Among African-Americans adults in the general population, elevated TG and IFG have both been shown to be associated with poorer verbal scores (Sims et al., 2008; Skinner et al., 2015). As Verbal Comprehension can be affected by knowledge and cultural experience, there may be sociodemographic factors, such as parental education or food insecurity reflecting healthcare inequities, that contribute to decreased Verbal Comprehension scores (Wechsler, 2003, 2008).

Our study was limited by the lack of a comparison group of HIV-unexposed and uninfected youth. Eligible YPHEU for this analysis was also a small group (n=68) and may be subject to selection bias since they represent the first YPHEU enrolled in PHACS when metabolic assays were not performed routinely on this group (Geffner et al., 2018; Miller et al., 2012). This may also affect the generalizability of results to the larger YPHEU population. Lastly, as discussed above, there is the issue that there are no consensus guidelines or validated diagnostic criteria for MetS in youth (Weiss et al., 2013). We chose to use the US definition to more closely align with our study population, and our decision to evaluate each MetS

component separately as a predictor of interest allowed us to more closely investigate associations with neurocognitive domains.

In conclusion, in our study, 15% of YPHIV and 18% of YPHEU met criteria for ≥2 of the individual MetS components. Components of MetS in YPHIV (elevated BP) and YPHEU (elevated TG and IFG) were associated with lower neurocognitive performance index scores in childhood and adolescence. Future studies to elucidate how modifying metabolic risk factors early in life may improve short- and long-term neurocognitive outcomes in this population are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest:

Shiau: none

Yu: none

Jacobson: none

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Jao: none

Appendix

Appendix

The following institutions, clinical site investigators and staff participated in conducting PHACS AMP and AMP Up in 2019, in alphabetical order: **Ann & Robert H. Lurie Children's Hospital of Chicago**: Ellen Chadwick, Margaret Ann Sanders, Kathleen Malee, Yoonsun Pyun; Baylor College of Medicine:, Mary Paul, Shelley Buschur, Chivon McMullen-Jackson, Lynnette Harris; **Bronx Lebanon Hospital Center**: Murli Purswani, Mahboobullah Mirza Baig, Alma Villegas; **Children's Diagnostic & Treatment Center:** Lisa- Gaye Robinson, Sandra Navarro, Patricia Garvie; **Boston Children's Hospital:** Sandra K. Burchett, Rebecca Pinsky, Adam R. Cassidy; **Jacobi Medical Center:** Andrew Wiznia, Marlene Burey, Ray Shaw; **Rutgers - New Jersey Medical School**: Arry Dieudonne, Linda Bettica, Juliette Johnson, Karen Surowiec; **St. Christopher's Hospital for Children:** Janet S. Chen, Taesha White, Mitzie Grant; **St. Jude Children's Research Hospital:** Katherine Knapp, Jamie Russell-Bell, Megan Wilkins, Erick Odero; **San Juan Hospital Research Unit/Department of Pediatrics, San Juan Puerto Rico:** Midnela Acevedo-Flores, Heida Rios, Vivian Olivera; **Tulane University School of Medicine:** Margarita Silio, Medea Gabriel, Patricia Sirois; **University of California, San Diego:** Stephen A. Spector, Megan Loughran, Veronica Figueroa, Sharon Nichols; **University of Colorado Denver Health Sciences Center:** Elizabeth McFarland, Carrie Chambers, Emily Barr, Mary Glidden; **University of Miami:** Gwendolyn Scott, Grace Alvarez, Juan Caffroni, Anai Cuadra

Note: The conclusions and opinions expressed in this article are those of the authors and do not necessarily reflect those of the National Institutes of Health or U.S. Department of Health and Human Services.

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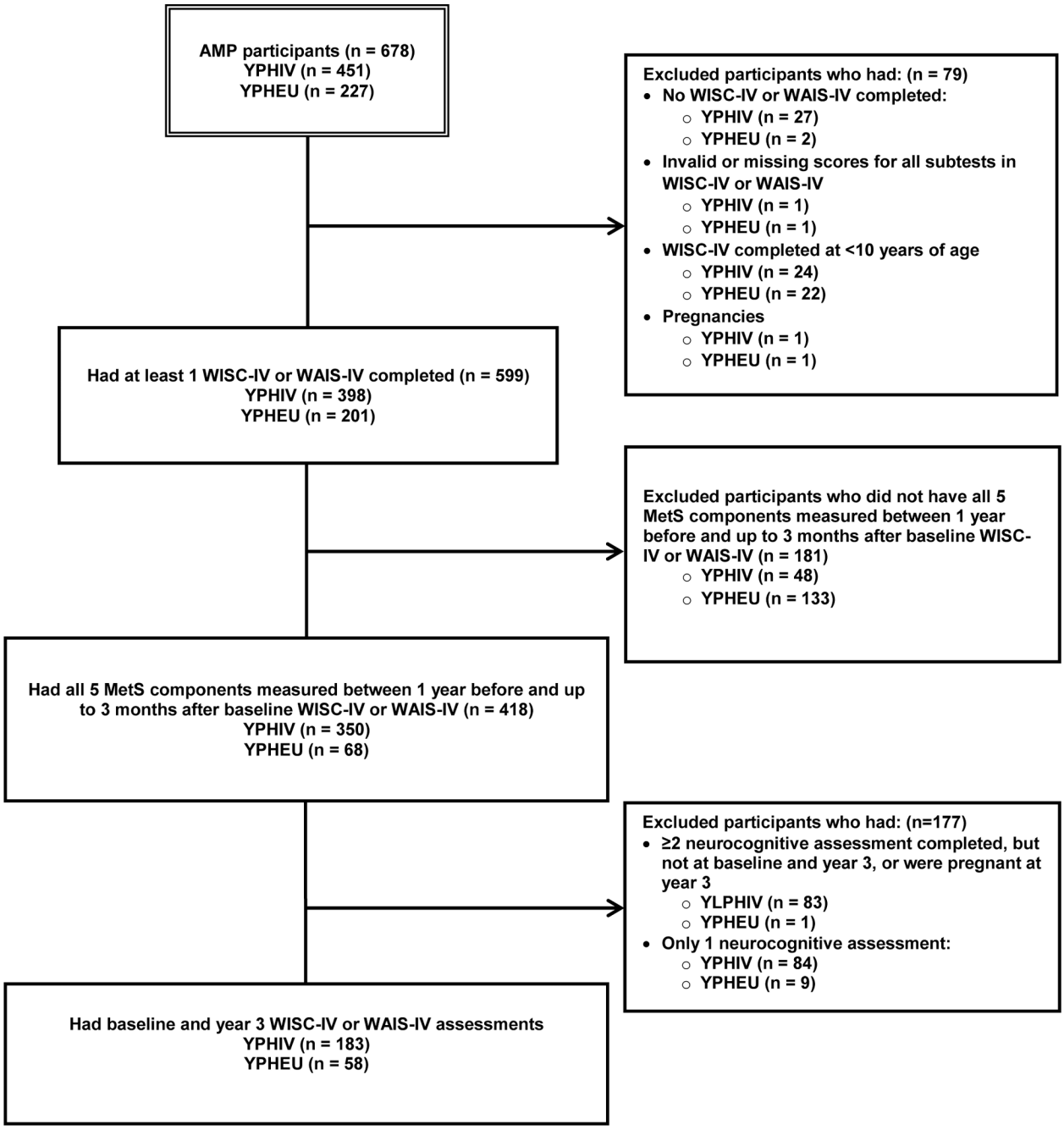

Figure 1:

Study population derivation for current analysis of youth with perinatally-acquired HIV (YPHIV) and youth who are HIV-exposed uninfected (YPHEU) from the Adolescent Master Protocol (AMP) of the Pediatric HIV/AIDS Cohort Study (PHACS) network

Abbreviations: WISC-IV – Wechsler Intelligence Scale for Children, Fourth Edition; WAIS-IV – Wechsler Adult Intelligence Scale, Fourth Edition; MetS – metabolic syndrome

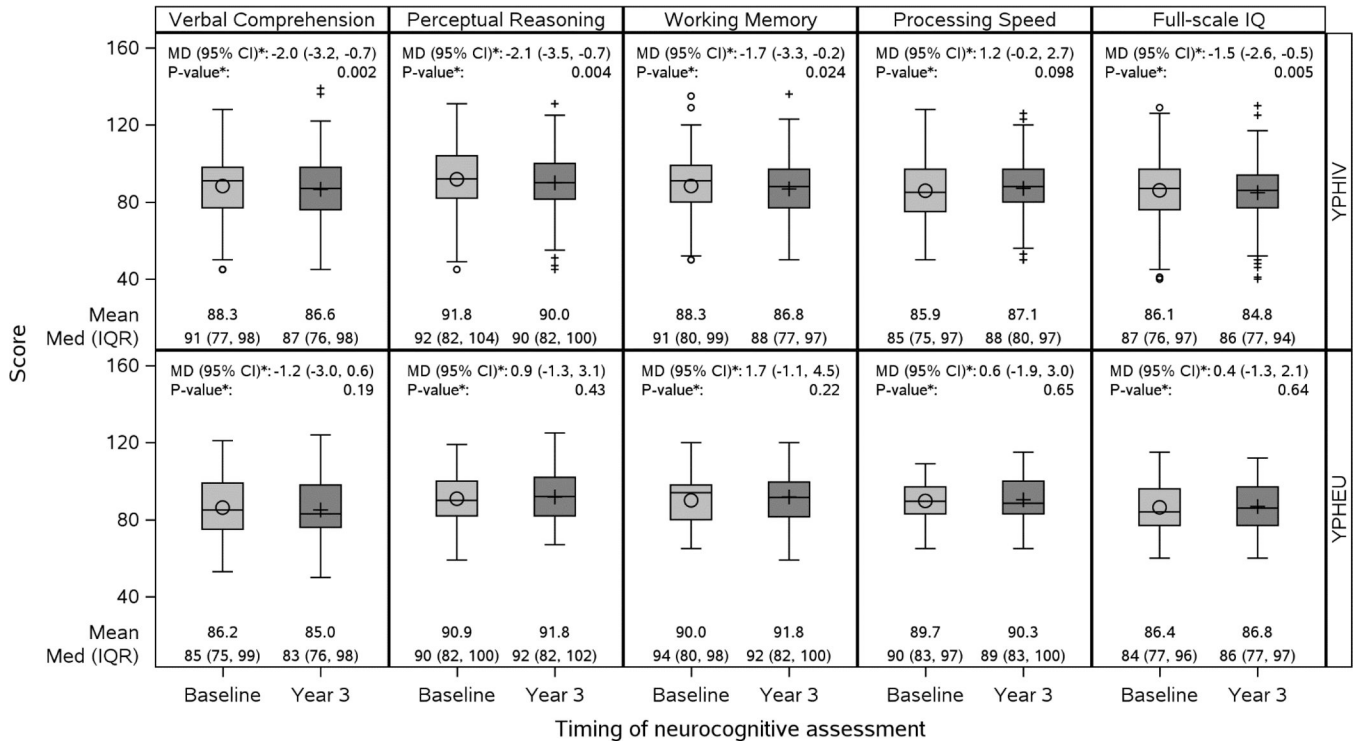

Figure 2:

Boxplot of baseline and year 3 neurocognitive scores and mean difference between baseline and year 3 for youth with perinatally-acquired HIV (YPHIV) and youth who are HIV-exposed uninfected (YPHEU) in the longitudinal sample

Abbreviations: Med – median; IQR – interquartile range; MD – mean difference; CI – confidence interval

*From paired t-tests

Table 1:

Demographic characteristics of youth with perinatally-acquired HIV (YPHIV) and youth who are HIV-exposed uninfected (YPHEU) in the baseline sample

Characteristic		YPHIV (N=350)	YPHEU (N=68)	P-value
Age at WISC-IV or WAIS-IV[1], years	Median (IQR)	12.8 (11.5, 14.5)	11.6 (10.7, 13.4)	<0.001*
	Min, Max	10.0, 18.6	10.0, 15.8	
Sex	M	160 (46%)	32 (47%)	0.84**
	F	190 (54%)	36 (53%)	
Weight Z-score[2]	Mean (s.d.)	0.10 (1.27)	0.78 (1.33)	<0.001***
	Min, Max	−4.15, 2.93	−2.23, 3.53	
Height Z-score[2]	Mean (s.d.)	−0.33 (1.17)	0.36 (1.21)	<0.001***
	Min, Max	−4.57, 3.09	−2.22, 4.41	
BMI Z-score[2]	Mean (s.d.)	0.31 (1.15)	0.76 (1.21)	0.006***
	Min, Max	−3.28, 2.93	−2.45, 2.71	
Tanner stage[2]	1–2	122 (35%)	31 (46%)	0.24**
	3–4	165 (47%)	27 (40%)	
	5	63 (18%)	10 (15%)	
Race/ethnicity	Not non-Hispanic Black	126 (36%)	33 (49%)	0.054**
	Non-Hispanic Black	223 (64%)	35 (51%)	
	Unknown	1	0	
Caregiver education[2]	High school or below	195 (56%)	41 (60%)	0.53**
	Greater than high school	152 (44%)	27 (40%)	
	Missing	3	0	
Annual household income[2]	≤$20,000	151 (46%)	44 (68%)	0.001**
	>$20,000	180 (54%)	21 (32%)	
	Missing	19	3	
Number of household members supported by income[1]	Median (Q1, Q3)	4 (3, 5)	4 (3, 5)	0.49*
Primary language reported in WISC-IV or WAIS-IV	English	304 (87%)	50 (74%)	0.002**
	Spanish	27 (8%)	15 (22%)	
	Bilingual/Other	19 (5%)	3 (4%)	
One of the primary caregivers is the biological mother	Yes	127 (37%)	46 (68%)	<0.001**
	No	219 (63%)	22 (32%)	
	Unknown	4	0	
Physical activity (vigorous minutes of activity per day >75th percentile)[3]	Yes	54 (20%)	16 (26%)	0.30**
	No	218 (80%)	46 (74%)	
	Unknown	78	6	
Age at ART initiation, years	Median (IQR)	2.96 (1.09, 5.59)		
	Min, Max	0.15, 19.65		
Nadir CD4 T-cell, cells/μL	>500	90 (26%)		

Characteristic		YPHIV (N=350)	YPHEU (N=68)	P-value
	201–500	177 (51%)		
	51–200	53 (15%)		
	≤50	30 (9%)		
Peak HIV RNA, copies/mL	≤10,000	14 (5%)		
	10,001–100,000	69 (22%)		
	100,001–1,000,000	225 (73%)		
Baseline CD4 count, cells/μL	>500	265 (76%)		
	351–500	44 (13%)		
	200–350	29 (8%)		
	<200	11 (3%)		
	Missing	1		
Baseline HIV RNA, copies/mL	≤400	239 (69%)		
	401–1000	20 (6%)		
	1001–10,000	46 (13%)		
	>10,000	42 (12%)		
	Missing	3		
Antiretroviral (ARV) treatment at baseline	≥3 ARV classes	42 (12%)		
	PI-based cART	200 (58%)		
	INSTI-based cART	7 (2%)		
	NNRTI-based cART	53 (15%)		
	3 NRTIs	8 (2%)		
	Other	14 (4%)		
	Not on ARV	20 (6%)		
	Missing	6		

*Wilcoxon Test

**Chi-Square Test

***T-Test

[1]WISC-IV: 411/418 (98%); WAIS-IV: 7/418 = 2%

[2]Data on weight Z-score, height Z-score, BMI Z-score, Tanner stage, caregiver education, and household income were retained if reported up to 1 year before and 3 months after WISC-IV or WAIS-IV.

[3]Data on physical activity was retained if reported within 2 years of age at WISC-IV or WAIS-IV. This is due to the fact that we only have approximate age at which physical activity was measured.

Abbreviations: BMI – body mass index; NRTI – nucleoside reverse transcriptase inhibitor; NNRTI – non-nucleoside reverse transcriptase inhibitor; PI – protease inhibitor; INSTI – integrase strand transfer inhibitor (INSTI); IQR – interquartile range; cART – combination antiretroviral therapy

Table 2:

Metabolic syndrome (MetS) components and neurocognitive indices from WISC-IV or WAIS-IV between YPHIV and YPHEU in baseline sample

		YPHIV (N=350)	YPHEU (N=68)	P-value
MetS components [1]				
Abdominal obesity	N (%)	60 (17%)	23 (34%)	0.002
Elevated triglycerides	N (%)	76 (22%)	5 (7%)	0.006
Low HDL cholesterol	N (%)	74 (21%)	9 (13%)	0.13
Elevated blood pressure	N (%)	21 (6%)	2 (3%)	0.31
Impaired fasting glycemia	N (%)	9 (3%)	5 (7%)	0.045
Fulfilled criteria for ≥2 MetS components	N (%)	52 (15%)	12 (18%)	0.56
Fulfilled criteria for ≥3 MetS components	N (%)	12 (3%)	5 (7%)	0.13
Neurocognitive indices				
WISC-IV or WAIS-IV	WISC-IV	343 (98%)	68 (100%)	0.24 *
	WAIS-IV	7 (2%)	0 (0%)	
Verbal Comprehension score	Median (IQR)	89 (77, 98)	85.00 (75.00, 99.50)	0.56 **
	Mean (SD)	87.37 (15.65)	86.71 (16.96)	
	Min, Max	45, 138	53, 130	
Perceptual Reasoning score	Median (IQR)	92 (82, 102)	91 (82, 103)	0.65 **
	Mean (SD)	90.15 (15.81)	91.66 (14.67)	
	Min, Max	45, 131	59, 121	
Working Memory score	Median (IQR)	91 (80, 99)	94 (80, 99)	0.62 **
	Mean (SD)	88.25 (16.27)	89.96 (13.08)	
	Min, Max	50, 135	65, 120	
Processing Speed score	Median (IQR)	87 (78, 97)	91 (83, 97)	0.077 **
	Mean (SD)	86.35 (15.60)	90.00 (10.29)	
	Min, Max	50, 128	65, 115	
Full-scale IQ score	Median (IQR)	86 (76, 95)	84.50 (77.00, 98.00)	0.80 **
	Mean (SD)	85.32 (16.11)	86.97 (14.40)	
	Min, Max	40, 130	60, 117	

*Chi-Square Test

**Wilcoxon Test

Abbreviations: WISC-IV - Wechsler Intelligence Scale for Children, Fourth Edition; WAIS-IV - Wechsler Adult Intelligence Scale, Fourth Edition; YPHIV - youth living with perinatally-acquired HIV; YPHEU – youth who are HIV-exposed uninfected; HDL - high-density lipoprotein; SD – standard deviation; IQR – interquartile range

[1]Refer to Supplementary Table 1 for definitions of MetS components

Table 3:

Unadjusted and adjusted models assessing the association of each MetS component at baseline with change over time[1] in each neurocognitive index in YPHIV over time

Outcome	Unadjusted			Adjusted[2]		
	N	Estimates (95% CI)	P-value	N	Estimates (95% CI)	P-value
Exposure 1) Abdominal obesity						
Change in Verbal Comprehension	180	−3.2 (−6.9, 0.4)	0.080	166	−2.3 (−6.3, 1.6)	0.25
Change in Perceptual Reasoning	180	0.8 (−2.7, 4.3)	0.65	166	0.7 (−2.9, 4.2)	0.72
Change in Working Memory	177	−1.5 (−4.7, 1.7)	0.37	163	−0.7 (−4.5, 3.0)	0.70
Change in Processing Speed	182	−1.0 (−4.8, 2.9)	0.63	168	0.2 (−3.7, 4.2)	0.90
Change in Full-scale IQ	181	−1.2 (−3.9, 1.6)	0.40	167	−0.4 (−3.4, 2.7)	0.81
Exposure 2) Elevated triglycerides						
Change in Verbal Comprehension	180	−0.2 (−3.1, 2.7)	0.89	166	−0.5 (−3.5, 2.6)	0.76
Change in Perceptual Reasoning	180	0.7 (−3.0, 4.4)	0.72	166	0.9 (−3.3, 5.1)	0.67
Change in Working Memory	177	1.9 (−1.5, 5.3)	0.27	163	2.3 (−1.4, 6.1)	0.22
Change in Processing Speed	182	−0.9 (−4.4, 2.6)	0.62	168	−1.2 (−4.7, 2.2)	0.48
Change in Full-scale IQ	181	0.5 (−2.2, 3.3)	0.70	167	0.3 (−2.5, 3.1)	0.82
Exposure 3) Low HDL-cholesterol						
Change in Verbal Comprehension	180	−1.4 (−4.2, 1.3)	0.30	166	−2.3 (−5.1, 0.5)	0.10
Change in Perceptual Reasoning	180	−0.2 (−4.1, 3.6)	0.91	166	0.7 (−3.4, 4.8)	0.74
Change in Working Memory	177	−1.9 (−5.5, 1.8)	0.32	163	−1.1 (−5.2, 3.0)	0.60
Change in Processing Speed	182	−2.5 (−6.6, 1.6)	0.23	168	−3.5 (−7.9, 0.8)	0.11
Change in Full-scale IQ	181	−1.8 (−4.2, 0.7)	0.16	167	−2.0 (−4.8, 0.7)	0.15
Exposure 4) Raised blood pressure						
Change in Verbal Comprehension	180	0.8 (−4.2, 5.8)	0.76	166	0.7 (−4.1, 5.5)	0.78
Change in Perceptual Reasoning	180	−4.2 (−8.4, 0.0)	0.051	166	−4.3 (−8.8, 0.3)	0.068
Change in Working Memory	177	2.9 (−3.2, 9.0)	0.35	163	4.6 (−2.0, 11.3)	0.17
Change in Processing Speed	182	−0.1 (−5.6, 5.4)	0.97	168	−1.0 (−7.2, 5.1)	0.74
Change in Full-scale IQ	181	−0.8 (−4.5, 2.9)	0.67	167	−0.7 (−5.0, 3.5)	0.74
Exposure 5) Impaired fasting glycemia						
Change in Verbal Comprehension	180	−1.6 (−7.3, 4.1)	0.59	166	−1.8 (−7.5, 4.0)	0.55
Change in Perceptual Reasoning	180	−2.7 (−9.2, 3.8)	0.42	166	−2.0 (−8.8, 4.8)	0.56
Change in Working Memory	177	2.8 (−3.5, 9.2)	0.38	163	3.3 (−1.9, 8.5)	0.21
Change in Processing Speed	182	−0.9 (−6.3, 4.5)	0.74	168	0.4 (−4.5, 5.3)	0.87
Change in Full-scale IQ	181	−0.5 (−5.6, 4.6)	0.85	167	0.4 (−4.2, 5.0)	0.86
Exposure 6) Fulfilled criteria for ≥2 MetS components						
Change in Verbal Comprehension	180	−1.2 (−4.4, 2.1)	0.48	166	−0.6 (−4.1, 2.9)	0.73
Change in Perceptual Reasoning	180	1.5 (−2.6, 5.5)	0.48	166	1.6 (−2.9, 6.1)	0.50
Change in Working Memory	177	−0.7 (−4.3, 2.8)	0.68	163	0.5 (−3.6, 4.5)	0.82
Change in Processing Speed	182	−4.2 (−8.2, −0.1)	0.045	168	−5.1 (−9.4, −0.8)	0.019
Change in Full-scale IQ	181	−1.3 (−4.2, 1.6)	0.37	167	−1.1 (−4.4, 2.1)	0.49

[1]Change over time in each neurocognitive index score was defined as year 3 score minus baseline score

[2]Models are adjusted for age at neurocognitive assessment (years), sex, race/ethnicity (NH Black vs not NH Black), primary language reported in WISC/WAIS (English vs Bilingual/Other), household income (≤$20,000 vs >$20,000), Tanner stage (3–4 and 5 vs 1–2), age (years) first started HAART, nadir CD4, and ARV use.