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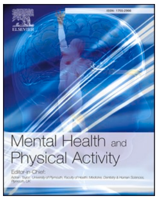

Cardiovascular health profile is favorably associated with brain health and neurocognitive development in adolescents

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ABSTRACT

Background and aims: Poor cardiovascular health has been linked to a higher risk of cognitive decline in adults, however this relation is not well established among adolescents. The purpose of this analysis was to test the associations of cardiovascular health behaviors (diet, physical activity, nicotine use, and sleep health) and health indicators (body mass index, blood lipids, blood glucose, blood pressure) with adolescents' brain development and executive and cognitive function.

Methods: We included 978 individuals from the Adolescent Brain and Cognitive Development (ABCD) Study who completed the year 2 follow-up assessment. Analysis was limited to those with complete data on cardiovascular health behaviors and health indicators which were used to compute composite cardiovascular health scores. Outcomes included estimates of general cognitive ability, executive function, and learning/memory through the NIH Toolbox neurocognitive battery, and MRI-derived brain morphometry. Associations were estimated by multilevel linear regression models using random effects.

Results: The mean (SD) age was 11.9 (0.2) years, 44.9% were girls, and 53.4% were white race/ethnicity. Individuals with more favorable cardiovascular health behaviors showed higher executive cognitive function scores ($\beta = 0.170$; CI 95%, 0.076 to 0.265; $p = 00.001$). Overall cardiovascular health was associated with a higher measure of executive cognitive function ($\beta = 0.209$; CI 95%, 0.067 to 0.351; $p = 00.002$) and total whole brain cortical volume ($\beta = 480.1$; CI 95%, 4.7 to 955.6; $p = 00.003$). r

Conclusion: Our findings reveal positive associations between adolescents' cardiovascular health behaviors and overall cardiovascular health with cognitive and executive function and brain cortical volume. Although our study is cross-sectional, the findings from a representative group of early adolescents add to the existing evidence suggesting a relationship between cardiovascular and brain health.

1. Introduction

Cardiovascular disease (CVD) is a major global health concern, with risk factors emerging early in life (Lloyd-Jones, Ning, et al., 2022). To address this, the American Heart Association (AHA) updated its concept of ideal cardiovascular health in 2022, introducing the Life's Essential 8 index. This index considers four modifiable health behaviors (sleep time, smoking, physical activity [PA], and diet) and four health factors (body

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mass index [BMI], blood pressure [BP], total cholesterol [TC], and fasting blood glucose) (Lloyd-Jones, Allen, et al., 2022).

Executive function (EF) and brain development are crucial for early adolescent academic and social achievements (Solis-Urra et al., 2023). EF is connected to brain morphology, particularly within critical cognitive regions such as the prefrontal cortex and hippocampus (Fjell & Walhovd, 2010). These areas, essential for decision-making, problem-solving, and emotional regulation, are sensitive to CVD risk factors like hypertension and hyperlipidemia (Gorelick et al., 2011). Such factors can impair cerebral vascular health and alter brain structure and function. Moreover, brain morphology undergoes significant changes with age, such as cortical thinning and volume reduction, which can be exacerbated by CVD risk factors. This growing body of evidence highlights the crucial role of maintaining cardiovascular health throughout life to support both the cognitive function and structural integrity of the brain (Debette & Markus, 2010).

Cardiovascular health (CVH) indicators are essential for understanding cerebral function, revealing mechanisms like reduced gray matter volume (Ranglani, Ward, Sattar, Strawbridge, & Lyall, 2023) and stroke in adults (Debette & Markus, 2010) that underlie brain health impairments. However, a comprehensive analysis of how clusters of cardiovascular health, as defined by the AHA (Lloyd-Jones, Allen, et al., 2022), affect EF and healthy brain development in early adolescence still needs to be made available, highlighting the need for advanced analytical approaches to elucidate these relationships.

Understanding this relationship is critical for designing interventions that can improve early adolescents' cardiovascular and cognitive health. Poor CVH can compromise neural development, leading to academic and behavioral challenges and raising the risk for neuropsychological disorders (Plaza-Florido, Rodriguez-Ayllon, Altmäe, Ortega, & Esteban-Cornejo, 2023). Cardiovascular health, intricately tied to efficient blood flow, oxygenation, and metabolic waste clearance, is pivotal in supporting this neural development (Gonzales et al., 2017). Poor cardiovascular health during this critical period could lead to compromised brain function and structure, potentially resulting in academic difficulties, behavioral issues, and elevated risks for neuropsychological disorders (Sedaghat et al., 2023).

Early identification and management of CVD risk factors in adolescents may lead to improved EF and brain development, positively impacting academic and social outcomes throughout the lifespan. Thus, the purpose of this paper is to examine the association between cardiovascular health behaviors and health indicators with executive function and structural brain MRI in a group of US early adolescents.

2. Methods

2.1. *Study design; sample size; eligibility criteria; ethical aspects*

The Adolescent Brain Cognitive Development (ABCD) study at abcdstudy.org represents the most extensive ongoing study in the U.S. focusing on brain development and overall health in adolescents. This study spans 21 research sites nationwide and is designed to track the progress of approximately 11,877 adolescents, starting from their preteen years and continuing into their early adult life. The participants were selected using a method that involved a random sampling of both public and private elementary schools. This strategy encompasses over 20% of the U.S. population in the eligible age group. Before any data gathering, appropriate consent was secured from the participants, including consent from parents or guardians. Trained field workers collected and managed data in this study as part of the ABCD study. These field workers conducted a series of standardized assessments, including neuroimaging, cognitive testing, and surveys on health and lifestyle, ensuring a comprehensive dataset on adolescent development (Barch et al., 2018). The study's methodology, including the approach to recruiting participants, the design of the tasks, the protocols for data collection, and the techniques used for processing neuroimaging data, are elaborated on in other publications (Casey et al., 2018; Garavan et al., 2018).

This research analyzed the initial cardiovascular data set, including blood pressure readings and biomarker assessments. These were obtained from fresh blood samples collected from 978 adolescents aged 11 to 12 who visited a research site and completed a battery of measures and questionnaires as part of the 2nd ABCD Study follow-up from 2018 to 2020. We did not collect any of the data analyzed in our study; rather, they were obtained through access to the ABCD study database. Our role as researchers was to design the analysis, interpret the findings, and formulate conclusions based on the comprehensive dataset provided by the ABCD study. These in-person visits, up to 4–5 h (Zucker et al., 2018), were meticulously structured to create a supportive and safe participant environment, ensuring high-quality, reliable data collection. All measurements followed this sequence: brain neuroimaging (116–137 min), cognitive testing (51 min), blood sample physical health assessments (43 min), lifestyle questionnaires (24 min), and environmental and social inquiries (20 min).

The current analysis was limited to participants who had provided complete data in several areas: healthy behavior patterns, blood sample information, and results from cognitive tests and other relevant variables (as illustrated in Fig. 1). To ensure the robustness of our findings, we conducted sensitivity analyses. These analyses compared the blood pressure readings and other critical variables between those who provided blood samples and those who did not. The findings revealed a statistically significant difference (p-value = 0.034) predominantly in the distribution of biological sexes, as detailed in **Supplement File 1**.

The foundational ABCD study received its ethical approval from the Institutional Review Board of the University of California, San Diego. This study was conducted in adherence to the moral guidelines outlined in the 1964 Declaration of Helsinki, as amended in Edinburgh, Scotland in 2000 (WMA, 2000). Our organization accessed the data through a formal agreement (specifically, the National Institute of Mental Health [NIMH] Data Archive Data Use Certification), which was established with the National Institutes of Health (NIH). Given that our analysis was based solely on de-identified data, it was categorized as exempt from a comprehensive review by the institutional review board at UTHealth Houston (referenced as HSC-SPH-22-0663).

2.2. *Outcomes*

2.2.1. *Executive function measures*

The ABCD Study incorporates a comprehensive neurocognitive assessment encompassing various aspects such as visual sharpness, handedness, brain hemisphere dominance, and overall neurocognitive growth (Lisdahl et al., 2018; Luciana et al., 2018). The executive functions were evaluated using the NIH Toolbox Cognition Battery. This battery is a validated, computer-based test designed to assess cognitive abilities across a broad age range, from early childhood to older adulthood. It evaluates several cognitive domains, including language comprehension, attention and inhibition control, working memory, cognitive flexibility, processing speed, memory recall, and reading decoding abilities (Akshoomoff et al., 2013). Skilled evaluators have consistently administered these assessments to all participants in the ABCD study across multiple stages of the study (Akshoomoff et al., 2013). A composite cognitive score was calculated based on the average scores of five tasks. Our analysis was confined to the unadjusted standard scores and the age-adjusted data (with a mean [M] of 100 and a standard deviation [SD] of 15) from the ABCD Study. This approach considers the performance of a normative sample, which is crucial as the neurodevelopmental stages vary significantly during childhood and adolescence (Casaletto et al., 2016).

2.2.2. *Brain morphometric measures*

The ABCD Data Analysis and Informatics Center (DAIC) performs centralized processing and analysis of magnetic resonance imaging

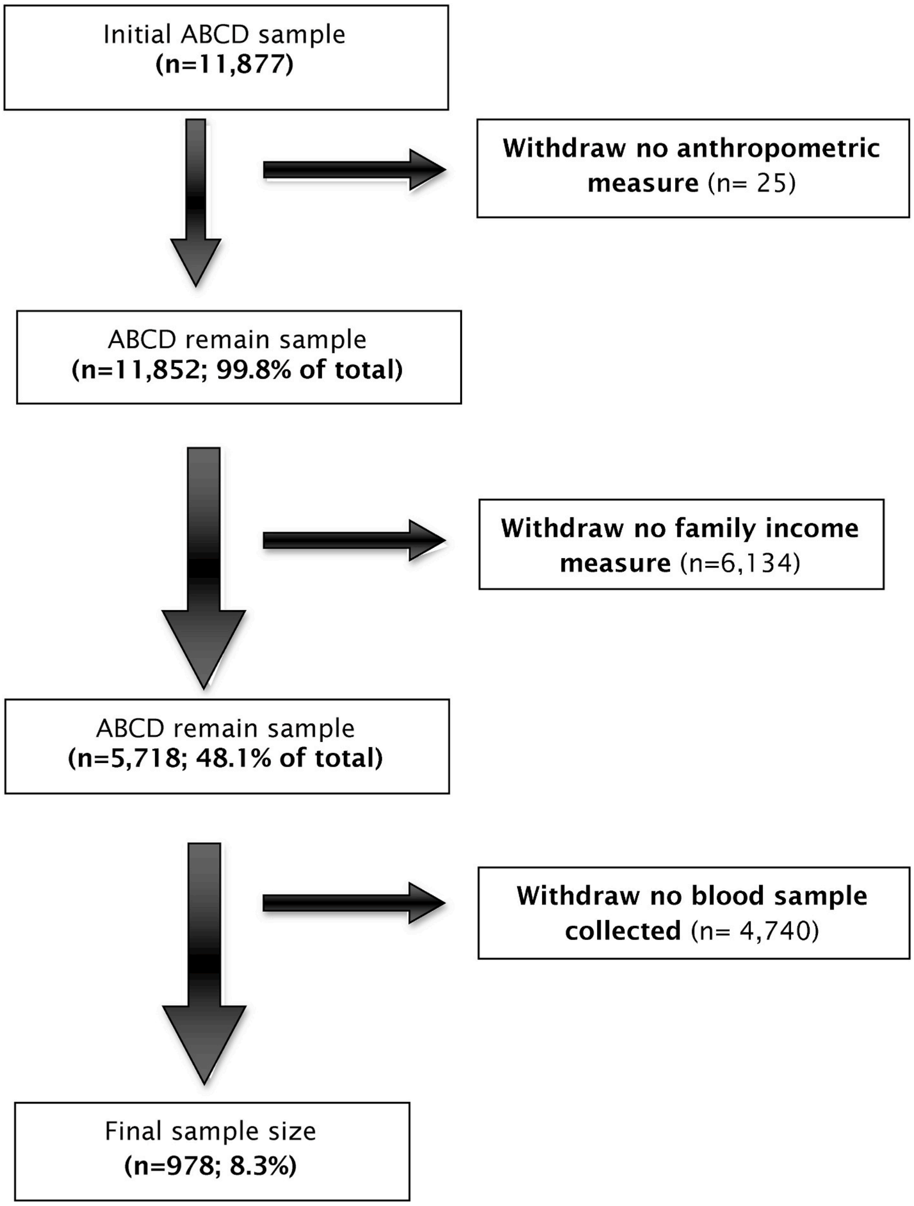

Fig. 1. Final sample size flowchart.

(MRI) data from each modality. The specifics of scanning parameters, preprocessing methods, and analytical frameworks for this study are detailed in other publications (Casey et al., 2018; Hagler et al., 2019). Briefly, our study leveraged the processed and analyzed neuroimaging data as part of the ABCD study, employing state-of-the-art multimodal brain imaging techniques to ensure comprehensive and accurate assessments of brain structure and function. The neuroimaging processing protocol includes modality-specific corrections for distortions and motion alongside advanced brain segmentation and cortical surface reconstruction derived from a structural MRI (Hagler et al., 2019).

The structural images of the cortical surfaces were generated from T1-weighted MRI scans. These images were then segmented to assess cortical thickness (CT) and cortical surface area (CSA) using FreeSurfer version 7.1.1, available at [https://surfer.nmr.mgh.harvard.edu], and the Destrieux atlas was employed for this study (Destrieux, Fischl, Dale, & Halgren, 2010). These procedures are meticulously designed to normalize and adjust for intracranial volume and other pertinent variables such as sex, facilitating robust comparisons across the diverse participant cohort. The meticulous approach to data processing and analysis ensures the integrity and comparability of neuroimaging data, providing an unparalleled resource for investigating both typical and atypical brain development (Saragosa-Harris et al., 2022).

The primary focus of our analysis was on three key metrics: *total whole brain cortical area in mm*^{3} *and mm*^{2}*, and average cortical thickness*. These parameters are extensively recognized and utilized in neuroimaging research, thus lending themselves to comparative studies and meta-analyses. We relied on standardized imaging data from the ABCD study, specifically using data that outlined various regions of interest (Giedd & Rapoport, 2010; Zhao et al., 2023). In terms of data quality, we limited our analysis to participants who had successfully passed the quality control checks for cortical surface reconstruction. This involved a manual inspection of the data. Consequently, only those participants whose structural data had been verified and approved by the ABCD study team were included in our final analysis (Hagler et al., 2019).

2.3. Main exposures

Life's Essential 8 (LE8®): Based on the methodology proposed by the

American Heart Association, Life's Essential 8 includes eight components of the cardiovascular health (Lloyd-Jones, Allen, et al., 2022): healthy diet, participation in physical activity, avoidance of nicotine, restorative sleep, healthy weight, and healthy levels of blood lipids, glycated blood hemoglobin, and blood pressure. Each metric has a scoring algorithm ranging from 0 to 100 points, allowing the generation of a composite cardiovascular health score (CVH) (the unweighted average of all components) that also varies from 0 to 100 points (Supplementary file 3). Binary categorizations of LE8 were employed to characterize overall CVH. Scores of 50–100 were considered moderate-to-high CVH, and 0 to 49 points were considered low CVH (Lloyd-Jones, Allen, et al., 2022).

2.3.1. *LE8® health indicators domain*

Blood biomarkers (Uban et al., 2018) were collected using the Vacutainer system (Becton Dickinson, UK) between 8:30 and 9:30 a.m. postprandial. Non-HDL cholesterol (mg/dL) and glycated hemoglobin (HbA1c) were measured using commercial enzymatic kits running on autoanalyzer platforms (Corvalán et al., 2017) Systolic (SBP) and diastolic (DBP) blood pressure (mmHg) were measured twice at 2-min intervals, using the Omron HEM-7200, in line with Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents of the American Academic of Pediatrics (Flynn et al., 2017). Height was measured with a portable stadiometer to the nearest 0.1 cm, with the patient in bare feet and nothing on their head. Weight was measured to the nearest 0.1 kg using a digital scale. Body Mass Index (BMI) was calculated using the following formula: weight (kg)/height(M)^2 according to IOTF cutoff points (Cole et al., 2000, 2007).

Non–HDL cholesterol metric - Points (Levels): 100(<100 mg/dL), 60 (100–119 mg/dL), 40 (120–144 mg/dL), 20 (145–189 mg/dL),0 (≥190 mg/dL). If participant is treated with medications for cholesterol, then 20 points were deducted from the score.

Glycated hemoglobin (HbA1c) metric - Points (HbA1c (%) Level): 100 (No history of diabetes or HbA1c < 5.7); 60 (No diabetes and HbA1c 5.7–6.4); 40 (Diabetes with HbA1c < 7.0); 30 (Diabetes with HbA1c 7.0–7.9); 20 (Diabetes with HbA1c 8.0–8.9); 10 (Diabetes with Hb A1c 9.0–9.9); 0 (Diabetes with HbA1c ≥ 10.0).

Systolic and diastolic BP metric - Points (mm Hg percentiles for age/sex): 100 (Optimal: <90th percentile); 75 (Elevated: ≥90th–<95th percentile or ≥120/80 mm Hg); 50 (Stage 1 hypertension: ≥95th–<95th percentile or 130/80 to 139/89 mm Hg); 25 (Stage 2 hypertension (≥95th percentile or ≥140/90 mm Hg); 0 (SBP ≥160 or ≥95th percentile or 30 mm Hg SBP, and DBP ≥100 or ≥95th percentile). If participant is treated with medications for high blood pressure, then 20 points were deducted from the score.

Body Mass Index metric - Points (BMI percentile for age and sex): 100 (5th–<85th percentile); 70 (85th–<95th percentile); 30 (95th–<120% of the 95th percentile); 15 (120%–<140% of the 95th percentile); 0 (≥140% of the 95th percentile).

2.3.2. *LE8® health behaviors domain*

Data for calculating physical activity, sleep duration and diet scores were collected via self-report questionnaires developed and validated within the study population. Parents or other guardians completed the questionnaires for adolescents ages 11 to 12.

Physical activity was assessed using a single item question derived from the Youth Risk Behavior Survey (Brener et al., 2002). The question asks respondents to report the number of days, within the past 7-days, they were active at a moderate intensity level for at least 60-min per day. This questionnaire demonstrated consistent reliability and moderate validity in adolescents and higher reliability and validity in adolescents (Nascimento-Ferreira et al., 2018). Average daily PA was calculated as (Weekly Leisure PA + Weekly PA During School + Weekly Commuting PA)/7. PA Minutes of intensity activity per week metric - Points (Minutes): 100 (≥420), 90 (360–419), 80 (300–359), 60 (240–299), 40 (120–239), 20 (1–119), 0 (0).

Sleep duration was assessed using the Parent Sleep Disturbance Scale for Children (Bruni et al., 1996). This scale asks the respondent to report the average number of sleep hours a child receives nightly over the past six months. The question 'How many hours of sleep does your child get on most nights?' determined the 'typical' total sleep time; possible responses were: 1) 9–11 h, 2) 8–9 h, 3) 7–8 h, 4) 5–7 h, 5) Less than 5 h. Points assigned based on optimal range = 9–12 h: 100 (Age-appropriate optimal range), (90 < 1 h above optimal range), 70(<1 h below optimal range), 40 (1–<2 h below or ≥1 h above optimal range), 20 (2–<3 h below optimal range), 0 (≥3 h below optimal range) (Nagata et al., 2023).

Dietary habits were assessed using the Block Kids Food Screener (Hunsberger, O'Malley, Block, & Norris, 2015). It is a 41-item instrument designed to assess foods consumed over the past week to evaluate dietary intake of nutrients and food groups for measurement using the Mediterranean Eating Pattern for Americans (MEPA) diet score (Cerwinske, Rasmussen, Lipson, Volgman, & Tangney, 2017; Mellen, Gao, Vitolins, & Goff, 2008) **(Supplementary File).** Diet score range was 0–16 based on the MEPA diet adherence score – Points: 100 (15–16 points (top/ideal diet)), 80 (12–14 points), 50 (8–11 points), 25 (4–7 points), 0 (0–3 points).

Nicotine use. Respondents were asked whether the participant was living with an active indoor smoker (tobacco products, such as cigarettes, smokeless tobacco, cigars, hookah, or e-cigarettes) at home. Those who reported yes were further asked whether they have ever tried any tobacco products in their life with separate questions for each type of product (i.e., e-cigarette, cigarette, cigar, smokeless tobacco, hookah, pipe, and nicotine replacement). Those who reported yes were classified as ever users of tobacco (Dai et al., 2022). Points (Status): 100 (Never tried), 50 (Tried any nicotine product, but >30 days ago), 25 (Currently using inhaled nicotine delivery systems-e-cigarettes), 0 (Current combustible use (within 30 days). Those reporting that the participant resides with an active indoor smoker had 20 points deducted from their points unless the score was 0.

2.4. *Covariates*

Covariate data of interest included biologic sex (male; female), age (in years), ethnicity, socioeconomic indicators (parent education; household income), and city population density to account for relevant environmental factors (Fan et al., 2021).

Ethnicity: was self-reported, and according to the American Community Survey, the participants were grouped into five categories: Asian, Black, Hispanic, Other, or White (Garavan et al., 2018). The Other category included adolescents identified as multiracial and/or who belonged to an ethnicity that was too small to create a separate category.

Parent education was categorized as follows: a high school diploma or less, a college or technical diploma, a Bachelor's degree, and a Graduate degree.

Household income was organized into the following categories: less than $50,000, $50,000–100,000, and greater than $100,000.

2.5. *Statistical analysis*

Descriptive analyses are presented as mean or median (quantitative variables) and percentages (qualitative variables), and 95% confidence intervals (95%CI). We assessed the association between exposures and outcomes using multilevel linear regression. The magnitude of these associations was subsequently expressed as unadjusted (not shown) and adjusted β-coefficients and their respective 95%CI. Multilevel linear regression models using random effects intercept were fitted to analyze the relationship between each cognitive measure, brain morphometric measures, and LE8® variables (Snijders & Bosker, 1999). Homoscedasticity was graphically assessed in all regression models to meet the criteria of this analysis.

The multilevel adjusted analysis was conducted following a hierarchical conceptual framework model (Victora, Huttly, Fuchs, & Olinto, 1997) (Supplementary **File 2**) that had been previously formulated in four levels (the association of the first two levels not shown): ***1)*** contextual variable (city population density was used based previously established relations between urbanization on cardiovascular health (Shah et al., 2023) and brain outcomes (Xiao et al., 2023)***; 2)*** socioeconomic indicators (parent education and household income); 3***)*** demographic indicators (sex, age, and ethnicity); and ***4)*** LE8® variables. The LE8® were divided into four groups: ***I)*** individual components score (Physical activity LE8 score; Nicotine exposure LE8 score; Diet LE8 score; Sleep health LE8 score; Body Mass Index LE8 score; Blood Lipids LE8 score; Glycated hemoglobin LE8 score; Blood Pressure LE8 score); ***II)*** Life's Essential 8 – Health behaviors; ***III)*** Life's Essential 8 – Health factors; and ***IV)*** Life's Essential 8 – Overall Score. In this model, the variables were controlled for those in the same level and those in higher order levels (Victora et al., 1997). Variables with P-values ≤0.20 in the univariate analysis (Victora et al., 1997) were indicated as necessary to include in the hierarchical multivariable analysis and then entered through the levels of the theoretical conceptual model described above. Significance in the final models was identified with p-values <0.05 or when there was more than 10% modification in the beta coefficient of any variable already in the model. Before performing the adjusted analyses, possible interactions between the covariates were identified. Following Rothman's guidance, no adjustments are needed for multiple comparisons (Rothman, 1990). It is recognized that cardiovascular health behaviors and cardiovascular health factors have a strong collinearity. Therefore, to analyze the association of cardiovascular health behaviors independently of cardiovascular health factors on executive function and MRI measures, we performed a multilevel linear regression model of cardiovascular health factors (independent variable) on executive function and MRI measures score (dependent variable), adjusting by the residuals of a previous regression of cardiovascular health behaviors on cardiovascular health factors. Similarly, to analyze the association of cardiovascular health factors independently of cardiovascular health behaviors on executive function and MRI measures, we performed a multilevel linear regression model of cardiovascular health behaviors (independent variable) on executive function and MRI measures score (dependent variable), adjusting by the residual of a previous regression of cardiovascular health factors on cardiovascular health behaviors (Kirkwood, Kirkwood, & Jonathan, 2014). The statistical software package Stata version 17.0 (Stata Corp., College Station, TX, USA) was used for all statistical calculations.

Table 1

Sociodemographic, behavioral, and clinical characteristics by biological sex, ABCD Study baseline (2018).

VARIABLES	Female n = 439			Male n = 539		
	mean or %	(CI 95%)		mean or %	(CI 95%)	
Age (years)	11.9	(11.8;	12.0)	12.0	(11.8;	12.1)
Household Income						
less than $50,000	25.4	(20.4;	31.2)	23.7	(19.3;	28.8)
$50,000 – $99,999	27.8	(22.6;	33.7)	25.3	(20.8;	30.5)
≥ $100 000	46.8	(40.6;	53.0)	51.0	(45.4;	56.5)
Ethnicity						
White Caucasian	50.9	(44.9;	56.9)	55.5	(50.0;	60.9)
African American	13.2	(9.6;	17.9)	11.0	(8.0;	14.9)
Hispanic	11.7	(8.3;	16.2)	11.3	(8.2;	15.3)
Don't Know	8.7	(5.8;	12.7)	11.0	(8.0;	14.9)
[a] Mixed or Other Ethnicity	15.5	(11.6;	20.4)	11.2	(8.2;	15.3)
Maternal education						
High school or less degree	11.3	(8.0;	15.7)	12.0	(8.9;	16.1)
Some college degree	26.3	(21.4;	31.9)	25.9	(21.4;	31.0)
Bachelor degree	39.1	(33.4;	45.1)	39.2	(34.0;	44.6)
Graduate degree	23.3	(18.6;	28.8)	22.8	(18.6;	27.7)
Physical activity (≥ 60 min of moderate or vigorous per week)	17.5	(14.3;	21.4)	19.3	(16.2;	22.9)
Never smoker (%)	99.8	(98.3;	100.0)	99.0	(97.7;	99.6)
Mediterranean Eating Pattern for Americans (0–16 points)	**4.9**	**(4.7**	**5.1)**	**5.3**	**(5.2**	**5.5)**
Sleep health (9–11 h per night)	49.4	(44.8;	54.1)	49.2	(45.0;	53.3)
Body Mass Index (BMI) (kg/m^2)	18.70	(18.30;	19.11)	18.57	(18.26;	18.87)
Non–HDL cholesterol (mg/dL)	158.68	(155.75;	161.62)	156.58	(154.16;	159.00)
Glycated hemoglobin (HbA1c) (%)	5.15	(5.12;	5.18)	5.16	(5.12;	5.19)
Systolic Blood Pressure (mm Hg)	**102.4**	**(101.4;**	**103.3)**	**103.8**	**(102.8;**	**104.7)**
Diastolic Blood Pressure (mm Hg)	60.4	(59.5;	61.1)	60.0	(59.3;	60.7)
Life's Essential 8 – Health behaviors [1]	**65.1**	**(63.3**	**66.8)**	**67.5**	**(66.1**	**68.9)**
Life's Essential 8 – Health factors [2]	**73.7**	**(72.6**	**74.8)**	**76.1**	**(75.3**	**76.9)**
Life's Essential 8 – Overall Score [3]	**71.0**	**(70.0**	**72.0)**	**73.6**	**(72.8**	**74.4)**
Cardiovascular Health (CVH) Categories						
Low CVH (0–49)	2.7	(1.6;	4.8)	1.1	(0.5;	2.5)
Moderate CVH (50–79)	70.6	(66.2;	74.7)	64.9	(60.8;	68.9)
High CVH (Score 80 to 100)	**26.7**	**(22.7;**	**31.0)**	**34.0**	**(30.1;**	**38.1)**
Executive function (raw score)	**83.92**	**(83.17;**	**84.66)**	**85.13**	**(84.47;**	**85.79)**
Executive function (age-corrected)	**105.66**	**(104.14;**	**107.18)**	**107.76**	**(106.43;**	**109.09)**
Total whole brain cortical volume in mmˆ3	**571393.7**	**(566798.1;**	**575989.4)**	**625788.0**	**(621248.5;**	**630327.4)**
Total whole brain cortical area in mmˆ2	**180707.4**	**(179293.9;**	**182120.9)**	**199458.0**	**(198005.2;**	**200910.9)**
Mean cortical thickness in mm for whole brain	2.729	(2.721;	2.737)	2.720	(2.712;	2.727)

1 = Healthy diet, participation in physical activity, avoidance of nicotine, healthy sleep.

2 = Healthy weight (BMI), and healthy levels of blood lipids, HbA1c, and blood pressure.

3 = Summarize 1 and 2.

In bold, the significant difference (p-value <0.05) between sexes.

[a] Mixed or Other Ethnicity (Afro-Caribbean/Indo-Caribbean; East Asian (China); South Asian (i.e. India); Southeast Asian (i.e. Philippines); American Native; Pacific Islander; Other Ethnicity). 87 individuals refuse to answer the ethnicity. 17 individuals refuse to answer the household income level.

3. Results

This ABCD ancillary study included 978 US adolescents (55.1% boys). Most were white race/ethnicity (53.4%), and almost 40% of the participant's parents reported having bachelor's degrees. Boys scored significantly higher than girls on the Mediterranean eating pattern for Americans, had higher systolic blood pressure levels and Life's Essential 8 (health behaviors; health factors and overall score). Also, boys presented a higher proportion of high CVH, executive function (raw score and age-corrected), total whole brain cortical volume (mm^3) and total whole brain cortical area (mm^2). The baseline sociodemographic, behavioral, and clinical characteristics by biological sex are shown in Table 1.

The associations between Life's Essential 8 metrics score of cardiovascular health and executive function measured by the NIH Toolbox (raw score and age-corrected) are shown in Table 2. Physical activity score showed a positive association with executive function (raw score and age-corrected). There was a significant direct association between the LE8 health behaviors domain and LE8 overall score with both executive function outcomes, with a greater magnitude of association for age-corrected executive function.

Table 3 presents the association between LE8 metrics score of cardiovascular health and brain development outcomes. Sleep health LE8 score, LE8 health behaviors, LE8 health factors, and LE8 overall score showed significant positive associations with total whole brain cortical area in mm^3 and mm^2. LE8 health factors score was positively associated with the total whole brain cortical area in mm^2. The BMI health LE8 score, LE8 health factors score domain and LE8 overall score were positively associated with mean cortical thickness in mm for the whole brain.

Table 2
Beta coefficients* (CI 95%) evaluating the association between Life's Essential 8 (LE8) metrics score of cardiovascular health and executive and cognitive function outcomes, ABCD Study (2020).

	Executive and Cognitive function (raw score)			Executive and Cognitive function (age-corrected)		
	β	(CI 95%)		β	(CI 95%)	
Physical activity LE8 score	**0.024**	**0.004**	**0.044**	**0.046**	**0.007**	**0.085**
Nicotine exposure LE8 score	0.073	−0.076	0.222	0.169	−0.111	0.449
Diet LE8 score	−0.002	−0.023	0.019	−0.002	−0.043	0.039
Sleep health LE8 score	0.009	−0.022	0.040	0.018	−0.043	0.078
Body Mass Index LE8 score	0.006	−0.023	0.034	−0.013	−0.068	0.043
Blood Lipids LE8 score	0.009	−0.029	0.047	−0.004	−0.077	0.070
Glycated hemoglobin LE8 score	−0.026	−0.101	0.048	−0.015	−0.160	0.130
Blood Pressure LE8 score	−0.009	−0.041	0.023	−0.007	−0.069	0.056
Life's Essential 8 – Health behaviors 1	**0.094**	**0.048**	**0.141**	**0.156**	**0.067**	**0.246**
Life's Essential 8 – Health factors 2	0.003	−0.055	0.061	0.001	−0.110	0.112
Life's Essential 8 – Overall Score 3	**0.111**	**0.041**	**0.182**	**0.173**	**0.037**	**0.309**

Beta coefficients multilevel mixed models their respective confidence intervals 95% (95% CI) adjusted for potential confounders: ex, age ethnicity, and household income.
Significant associations are in bold.
1 = Healthy diet, participation in physical activity, avoidance of nicotine, healthy sleep.
2 = Healthy weight (BMI), and healthy levels of blood lipids, HbA1c, and blood pressure.
3 = Summarize 1 and 2.

When we analyzed the association between CVH categories and the executive function and brain development, we observed the adolescents categorized as low CVH had significantly lower mean cortical thickness in mm for whole brain compared with the adolescents categorized as high CVH (Table 4).

4. Discussion

Our geographically diverse study of 978 adolescents observed a positive association between overall cardiovascular health, healthy behaviors, and executive function. This suggests that better cardiovascular health is correlated with an increased cortical area in the adolescent brain. Importantly, our analysis includes city density and other context-level variables, underscoring the significant role that environmental factors play in the impact of physical activity on cognitive and mental health outcomes (Pesce et al., 2023). This acknowledgment helps deepen our understanding of how physical activity can influence cognition and mental health in various urban settings. Additionally, our findings indicate that adequate sleep, normal weight, and robust cardiovascular health each positively correlate with cortical area, aligning with previous research such as (Gui et al., 2021), which found a similar correlation in Chinese adolescents. Our study is the first to show that better cardiovascular health, assessed through eight different components, is associated with increased total whole brain cortical area.

Our findings indicate a positive correlation between physical activity and enhanced executive function, including cognitive abilities. Previous research suggests that regular exercise supports healthy brain development, crucial during adolescence—a key period of healthy brain growth. (Walsh, Smith, Northey, Rattray, & Cherbuin, 2020). Additionally, other studies have demonstrated how negative factors such as poor diet (Costello, Geiser, & Schneider, 2021), physical inactivity (Donnelly et al., 2016), insufficient sleep (Hehr, Huntley, & Marusak, 2023), and obesity (Kulisch, Arumäe, Briley, & Vainik, 2023), can adversely affect these cognitive functions in adolescents. These lifestyle behaviors contribute to anti-inflammatory effects, crucially countering chronic inflammation known to be associated with cognitive decline. Therefore, integrating these healthy behaviors offers a significant strategy for bolstering brain health and cognitive functions during the pivotal developmental stage of adolescence (Wilhite et al., 2023).

Our research demonstrates that the link between cardiovascular health and executive function emerges in childhood, with adolescents showing superior executive function correlating with better cardiovascular health, as indicated by BMI, blood pressure, blood lipids, and glycated hemoglobin levels. These findings underscore the importance of public health interventions to enhance cardiovascular health in adolescents. Improved cardiovascular health is associated with lower cortisol levels, contributing to enhanced stress management and, consequently, better executive function (Flores-Reséndiz et al., 2019). In addition to the well-established benefits for physical health, improving cardiovascular health may also positively affect cognitive development and academic achievement (Rodriguez-Ayllon et al., 2023).

Our study revealed a positive association between adequate sleep and the total cortical area of the whole brain in mm^2 among adolescents. Sleep plays a crucial role in memory consolidation and brain function restoration, with insufficient sleep being associated with cognitive deficits (Durmer & Dinges, 2005). Sleep deprivation is thought to impair the prefrontal cortex, which is vital for executive functions, through reduced glucose metabolism and disrupted neural connectivity (Chee & Chuah, 2008).

Our results, demonstrating a positive correlation between cardiovascular health and cortical volume, align with prior studies indicating that cardiovascular risk factors like hypertension and obesity contribute to decreased brain volume and cortical thinning (Debette & Markus,

Table 3

Beta coefficients[a] (CI 95%) evaluating the association between Life's Essential 8 (LE8) metrics score of cardiovascular health and brain development outcomes, ABCD Study (2020).

	Total whole brain cortical volume in mmˆ3			Total whole brain cortical area in mmˆ2			Mean cortical thickness in mm for whole brain		
	β	(CI 95%)		β	(CI 95%)		β	(CI 95%)	
Physical activity LE8 score	85.1	−52.3	222.6	26.0	−19.3	71.2	0.0000	−0.0002	0.0003
Nicotine exposure LE8 score	−62.3	−929.7	805.1	−142.3	−437.5	152.9	0.0010	−0.0005	0.0024
Diet LE8 score	−22.9	−170.6	124.7	−12.0	−60.5	36.5	0.0000	−0.0003	0.0002
Sleep health LE8 score	**294.9**	**82.8**	**506.9**	**94.2**	**24.7**	**163.7**	0.0000	−0.0003	0.0004
Body Mass Index LE8 score	152.4	−44.3	349.2	−7.1	−71.8	57.5	**0.0008**	**0.0004**	**0.0011**
Blood Lipids LE8 score	−47.6	−304.0	208.7	−4.5	−89.4	80.3	−0.0001	−0.0005	0.0003
Glycated hemoglobin LE8 score	26.9	−464.6	518.4	−19.4	−180.6	141.8	0.0005	−0.0003	0.0013
Blood Pressure LE8 score	82.8	−133.3	299.0	12.7	−58.7	84.0	0.0001	−0.0003	0.0005
Life's Essential 8 – Health behaviors 1	**365.0**	**36.6**	**693.4**	103.1	−3.6	209.9	0.0001	−0.0005	0.0006
Life's Essential 8 – Health factors 2	**460.3**	**61.1**	**859.5**	11.1	−119.8	142.0	**0.0018**	**0.0012**	**0.0025**
Life's Essential 8 – Overall Score 3	**738.5**	**247.9**	**1229.2**	119.0	−40.2	278.2	**0.0015**	**0.0006**	**0.0023**

Significant associations are in bold.

1 = Healthy diet, participation in physical activity, avoidance of nicotine, healthy sleep.

2 = Healthy weight (BMI), and healthy levels of blood lipids, HbA1c, and blood pressure.

3 = Summarize 1 and 2.

[a] Beta coefficients multilevel mixed models their respective confidence intervals 95% (95% CI) adjusted for potential confounders: ex, age ethnicity, and household income.

Table 4

Adjusted[a] means and 95% CIs of neurocognitive outcomes in each category of the cardiovascular health (CVH) categories ABCD Study (2020).

	Low CVH (0–49)			Moderate CVH (50–79)			High CVH (Score 80 to 100)		
Neurocognitive Outcomes	mean	(CI 95%)		mean	(CI 95%)		mean	(CI 95%)	
Executive function (raw score)	87.6	81.0	94.2	89.0	88.3	89.8	90.9	89.3	92.6
Executive function (age-corrected)	102.4	89.7	115.1	102.8	101.3	104.2	107.1	103.9	110.3
Total whole brain cortical volume in mmˆ3	595195.1	553666.2	636724.0	591213.1	585747.8	596678.4	600977.6	588808.8	613146.5
Total whole brain cortical area in mmˆ2	198936.1	185543.6	212328.6	191743.1	189993.2	193493.1	193533.7	189617.8	197449.5
Mean cortical thickness in mm for whole brain	**2.63**	**2.56**	**2.69**	2.68	2.68	2.69	**2.70**	**2.68**	**2.72**

[a] Adjusted means were estimated by potential confounders: population density, sex, ethnicity, age, family income.

2010). Our findings add to this body of research by identifying the whole brain, where cardiovascular health is most strongly associated with the cortical area. The exact mechanisms linking cardiovascular health to cortical area remain to be fully elucidated. Nonetheless, it is proposed that prolonged exposure to cardiovascular risk factors may affect the brain's structure and functionality via changes in cerebral blood flow, neuroinflammation, and oxidative stress (Ye et al., 2023). Neurovascular coupling links neural activity to changes in cerebral blood flow (Talbot et al., 2023), benefits from a healthy cardiovascular system, enhancing brain efficiency (Iadecola et al., 2023).

4.1. Strengths and limitations

This study has numerous strengths. First, this is a large ethnically diverse study to investigate the associations between the AHA construct of ideal cardiovascular health metrics and executive function and cortical-brain volume in US adolescents. Second, the executive function and cortical-brain volume assessment were conducted using a validated questionnaire (NIH Toolbox) and magnetic resonance imaging. Moreover, we found that overall CVH is most strongly associated with the whole brain cortical volume. However, our findings should be considered in light of study limitations. This study is a cross-sectional design, and therefore causality cannot be established. Also, despite our multilevel analysis with many of the established potential confounders, it was not possible to adjust the analysis for other potentially brain-associated factors such as genetics or intrauterine development.

5. Conclusions

Cardiovascular health behaviors and overall cardiovascular health were directly associated with brain and executive function. These findings have important implications for public health interventions aimed at promoting healthy behaviors in adolescents, which may positively impact cognitive development and academic achievement. Our findings add to this body of research by identifying the whole brain (mean cortical thickness and total brain cortical volume), where cardiovascular health is most strongly associated with the cortical area. In addition to the well-established benefits for physical health, improving cardiovascular health may also positively affect brain structure and executive function. Further research is needed to understand better the underlying mechanisms of the association between cardiovascular health and cortical development, as well as to investigate the potential for interventions aimed at improving cardiovascular health to promote brain health and executive function.

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CRediT authorship contribution statement

Augusto César F. De Moraes: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. **Marcus V. Nascimento-Ferreira:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis. **Ethan H. Hunt:** Writing – review & editing, Writing – original draft. **Gregory Knell:** Writing – review & editing, Writing – original draft, Formal analysis. **John Virostko:** Writing – review & editing, Writing – original draft, Formal

analysis, Data curation. **Susan S. Tapert:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Funding acquisition. **Harold W. Kohl:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mhpa.2024.100611.

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