Cardiovascular Risk Markers and Cognitive Performance in Children

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Markers of cardiovascular risk and cognitive performance were assessed in 347 children. In contrast with body mass index and blood pressure, only retinal microcirculation explained a unique proportion of variance in inhibitory control and information processing, when dependencies between markers of cardiovascular risk were accounted for. *(J Pediatr 2020;224:162-5).*

School children with high inhibitory control (ie, ability to override a dominant/prepotent response) have been found to outperform peers on reading and math skills.[1-3] Inhibitory control is also related to cooperative/prosocial behavior, which in turn may improve peer acceptance and decrease the likeliness of being bullied at school.[4-7] Thus, it is useful to understand the factors that influence children's inhibitory control. Schoolchildren with a high cardiovascular risk owing to obesity and/or hypertension have been found to perform poorly on cognitive tasks involving inhibitory control.[8,9] Obesity-driven inflammation affecting multiple brain areas and processes related to neurogenesis and plasticity have been proposed as one of the mechanisms underlying this effect.[10] In addition, impaired microvascular health, as indexed by narrower retinal arterioles and wider retinal venules, resulting in a lower retinal arteriolar-to-venular diameter ratio, may also affect aspects of executive functions.[11] Because retinal and cerebral vessels share a similar embryological origin as well as functional and structural characteristics, this link may indicate that executive function is influenced by the brain's vascular network.[12]

Different markers of cardiovascular risk have been related to inhibitory control in children. However, previous studies either investigated only a single marker, failed to account for dependencies among multiple markers, or examined only children with a high cardiovascular risk. Thus, evidence on the individual and relative contributions of cardiovascular risk markers to inhibitory control is lacking. This knowledge would be useful to aid the development of inhibitory control by managing pediatric markers of cardiovascular risk. The present study investigated the relative contributions of body mass index, blood pressure, and microcirculation to inhibitory control in children.

Methods

Data were collected as part of a school-based, cross-sectional study in Switzerland (n = 718) and the present investigation is based on a subset of data (n = 347).[13] All primary school children aged 6-8 years were invited to participate. The study was approved by the Ethic committee of the University of Basel (EKBB, Basel, No. 258/12) and data were collected in 2016. Parents were informed about the purpose of this study and written informed consent was obtained to participate. Children were screened for retinal vessel diameters, body mass index, blood pressure, and cognitive function in their respective school setting. Additionally, legal guardians of participants reported their monthly income, the participant's birth status (preterm vs full term) and filled in the Conner attention deficit hyperactivity disorder index to assess hyperactivity. Participants further filled in the Insomnia Severity Index to assess sleep. All assessments were performed under fasting conditions and with no prior engagement in physical activity.

Inhibitory control was assessed with a computer-based version of the Flanker task, which was administered with E-Prime 2.0 (PST, Pittsburgh, Pennsylvania). Visual stimuli were 5 black fish presented on a white background. In congruent trials, the fish were facing the same direction, whereas in incongruent trials the central fish was facing in the opposite direction of the flanking fish. During the task, participants were required to press a button corresponding with the direction of the central fish. Task instructions were given verbally and on the screen. After an intertrial interval of 1100-1500 ms (random variation), visual stimuli were presented for 2000 ms or until a response was collected. Congruent and incongruent trials appeared with equal probability and their order was fully randomized. After participants completed 16 practice trials, 2 test blocks with 40 trials each were administered. As dependent variables, reaction time (on response-correct trials) and accuracy were calculated for congruent and incongruent trials.

A portable wall-mounted stadiometer (Seca 206, Basel, Switzerland) and the InBody device (InBody 170 Biospace device; InBody Co, Seoul, Korea) were used to measure body height and weight, respectively. Body mass index was calculated as weight in kilograms divided by the square of height

AVR	Arteriolar-to-venular ratio

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in meters. Blood pressure was measured 5 times in the sitting position with an automated oscillometric device (Oscillomate, CAS Medical Systems, Branford, Connecticut). The appropriate cuff size was determined based on existing guidelines.[14] For cases, in which the cuff size was difficult to determine, the midarm circumference was used for an accurate determination of the correct cuff size. The mean of the 3 measurements with the smallest variation was used for statistical analysis.

Retinal arteriolar and venular diameters were assessed using a Static Vessel Analyser (SVA-T, Imedos Systems UG, Jena, Germany) with an integrated Topcon fundus camera and an advanced image processing unit. Three valid photographs from the right and left eye were taken at an angle of 45° with the optic disc at the center. Retinal vessels were identified in an area of 0.5-1.0 disc diameter away from the margin of the optic disc (Vesselmap 2, Visualis, Imedos Systems UG). A single experienced examiner differentiated retinal arterioles and venules in the ring zone. The arteriolar-to-venular ratio (AVR) was calculated by dividing the central retinal arteriolar equivalent by the central retinal venular equivalent, which were derived using the Parr-Hubbard formula.[15]

Statistical analysis was performed with SPSS 25.0 (IBM, Armonk, New York) and the AMOS interface. Before the main analyses, zero-order Pearson correlation coefficients were calculated for relations between the predictors (AVR, body mass index, systolic and diastolic blood pressures), dependent variables (reaction time on congruent and incongruent trials), and potential confounders (age, sex, socioeconomic status, sleep, birth status). Additionally, curve fitting was used to test whether associations between individual predictors and outcomes followed a linear or curvilinear trend. Based on the results, main analyses included terms to model curvilinear relations. Path analyses were used to examine the relation between cardiovascular risk markers, information processing and inhibitory control, and covariances were estimated between predictors and outcomes. Based on zero-order correlations, confounders showing a statistically significant ($P < .05$) or at least a weak association with predictors ($r \geq 0.10$) and/or the dependent variables were included in the model. Covariance between reaction time and accuracy on both trial types was estimated to control any relations between the predictors and reaction time for a speed-accuracy trade-off. The null hypothesis suggesting that regression coefficients equal zero was tested and rejected at a P value of less than .05. Missing data (**Table I**; available at www.jpeds.com) were treated by applying the full information maximum likelihood approach as it is suggested to be less biased and more efficient than other approaches.[16] The fits of the models to the data was examined and considered good at root mean square area of 0.08 or less and a χ^2/df of 2 or less.[17,18]

Results

The total sample included 347 participants (n = 172 girls/175 boys), of whom 308 participants were born full term, 49 were hypertensive, and 49 were overweight or obese. Descriptive data (means and standard error) for all variables are shown in **Table II**. Based on zero-order correlations (**Table III**; available at www.jpeds.com), age, sex, socioeconomic status, and sleep were related with 1 or more predictors and outcomes, and were therefore included as potential confounders in the model. Curve estimation supported a linear relation between AVR and reaction time on congruent and incongruent trials (F = 4.94; $P = .027$), whereas no linear or curvilinear relations were found between other predictors and the outcomes.

Table II. Participants' (n = 172 girls/175 boys) characteristics, cardiovascular risk markers, and cognitive performance

Characteristics	Mean	SE	Minimum	Maximum
Age, y	7.20	0.02	6.42	8.95
Body mass index, kg/m^2	15.93	0.13	12.07	26.32
AVR	0.870	0.003	0.73	1.03
Central retinal arteriolar equivalent, μm	198.83	0.86	150.72	237.24
Central retinal venular equivalent, μm	226.68	0.86	189.47	278.46
Systolic blood pressure, mm Hg	104.17	0.47	85.00	134.00
Diastolic blood pressure, mm Hg	63.72	0.41	45.67	87.67
Socioeconomic status based on income*	5.16	0.11	1.00	7.00
Insomnia severity index (sum score)	3.14	0.19	0.00	19.00
ADHD index (sum score)	2.18	0.18	0.00	16.00
Congruent reaction time, ms	1383.08	269.37	442.75	1546.74
Incongruent reaction time, ms	1355.02	326.45	394.00	1647.08
Congruent accuracy, % correct	93.59	0.47	43.00	100.00
Incongruent accuracy, % correct	89.90	0.69	11.00	100.00

ADHD, attention deficit hyperactivity disorder.
*1 = lowest income category; 7 = highest income category.

Path analyses revealed that higher AVR was associated with slower reaction time on congruent ($\beta = -0.18$; $B = -588.5$; $SE = 206.5$; $P = .004$), and incongruent trials ($\beta = -0.13$; $B = -531.9$; $SE = 251.2$; $P = .034$), when covariates and accuracy were accounted for. In contrast, body mass index, as well as systolic and diastolic blood pressure, were not related to reaction time on both trial types (**Figure**). Absolute and parsimony-adjusted fit was good, root mean square area of 0.050 (χ^2/df = 1.8).

Discussion

Even at preclinical stages, children with a higher body mass index and blood pressure are affected by narrowing of retinal arterioles and/or widening of retinal venules.[19] These early microvascular impairments do not only have implications for the pediatric cardiovascular risk, because the present findings indicate higher cognitive performance in children with a higher AVR. This relation does not seem to be domain specific, because associations of similar direction and magnitude were found for information processing and inhibitory control. Among different cardiovascular markers, the AVR seems to be a potential candidate, by which these domains can partly be influenced in children undergoing cognitive

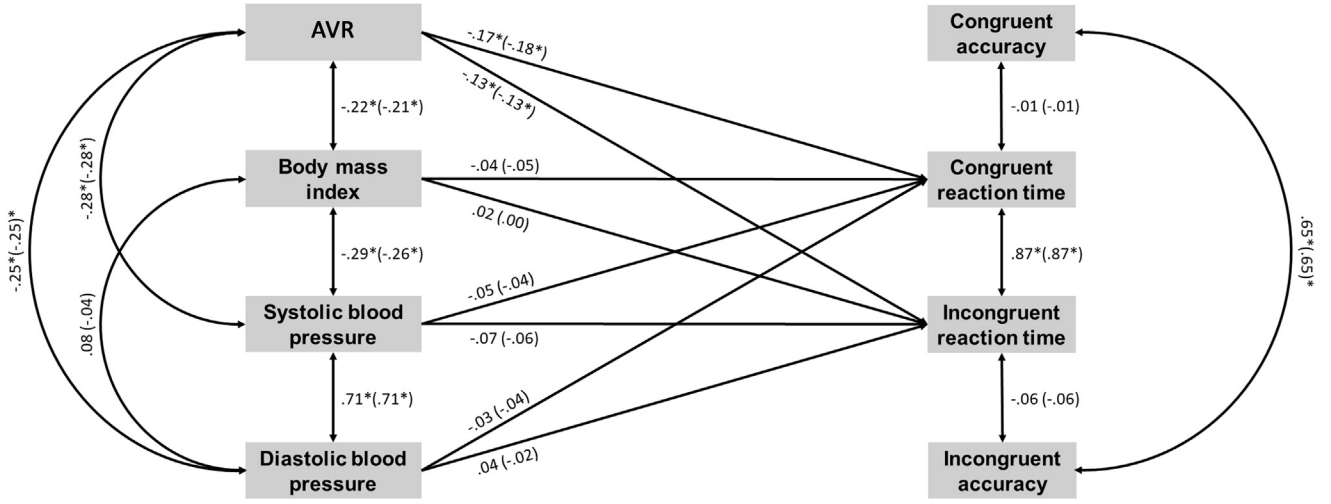

Figure. Standardized regression coefficients for associations between cardiovascular markers (AVR, body mass index, systolic and diastolic blood pressure) and information processing and inhibitory control, while accounting for interrelations. Values in brackets indicate standardized regression coefficients, when the model is controlled for age, sex, socio-economic status, and sleep. *$P < .05$.

development. A possible explanation of this link is based on considering retinal vessel diameters as a proxy of the brain's vascular network.[12] The arterial baroreflex contributes directly and indirectly to the cerebral blood flow by autonomic and systemic blood pressure regulation and the local retinal autoregulation. In turn, cerebral blood flow and metabolism are suggested to influence cognitive performance in many, but not all circumstances.[20,21] Thus, it seems to be likely that a low AVR signals an unfavorable condition of the cerebral microcirculation, which affects 1 or more of these processes. Moreover, decreases in white matter microstructural integrity have been related to narrowing of retinal arterioles, suggesting that such changes are of vascular origin.[22] Owing to the role of white matter integrity for cognitive function in children, the present findings might in part be explained by a favorable facilitation of this structure in children with a high AVR.[23,24]

The lack of associations between body mass index, blood pressure, and reaction time on the Flanker task conflicts with previous studies showing impaired cognitive performance in children with obesity and hypertension.[8,9] Similar to the present findings, no such association was reported in a large cohort including children of different body mass index categories.[25] Consequently, it seems that the link between these markers and cognitive performance may only be observed in children at higher cardiovascular risk. In this case, lower cognitive performance might rather be due to obesity-driven inflammation and accompanied hormonal changes than the direct influence of high body mass index and/or blood pressure.[10] Because the present findings do not support a general association between markers of cardiovascular risk, information processing, and inhibitory control, they indicate that retinal microvascular, and hence cerebrovascular function may be a candidate underlying the improvement of these cognitive domains.

Given the cross-sectional design of the present study, longitudinal and experimental data are needed to test whether cognitive performance can be altered by decreasing the risk for impairments in microcirculation. Some other weaknesses limit the interpretation of our findings. First, the cognitive test tapped information processing and inhibitory control only, so that it is unclear if the present findings can be generalized to other cognitive domains. However, inhibitory control plays an important role for academic skills, and even small improvements can be considered meaningful.[2,3] Second, only body mass index, blood pressure, and retinal vessel diameters were examined. Lipid- and inflammation-related markers could also explain a unique proportion of variance in cognitive performance. It should be noted that the selection of predictors in the models was based on specific markers, which have been linked with aspects of executive function in pediatric populations. However, this does not rule out the possibility that other markers, such as body fat and waist-to-hip ratio, show more pronounced associations with cognitive function. Third, the sample was recruited from primary schools and, therefore, large interindividual differences might have affected the results. Although important confounders, such as age, birth status, symptoms of attention deficit hyperactivity disorder, sleep, and socioeconomic status, were accounted for, the influence of other sources of heterogeneity could not be ruled out.

The present findings indicate that retinal microvascular diameter as a marker for cerebrovascular health is independently associated with inhibitory control and information processing in school-age children. The causal pathway between cerebrovascular functioning and blood flow with neurophysiological and cognitive functioning needs to be elucidated in future prospective, long-term studies. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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Table I. Proportion of missing data for each variable

Categories	Variables	No. (%) with complete data
Outcome	Reaction time and accuracy on Flanker task	347 (100)
Predictors	Retinal AVR	267 (77)
	Body mass index	322 (92)
	Systolic blood pressure	326 (94)
	Diastolic blood pressure	326 (94)
Covariates	Sex	347 (100)
	Age	347 (100)
	Birth status	347 (100)
	Socioeconomic status	299 (86)
	Sleep insomnia	285 (82)

Table III. Zero-order correlations between anthropometric measures, participants' characteristics, cardiovascular risk markers, and cognitive performance

Characteristics		1	2	3	4	5	6	7	8	9	10	11	12
1	Age	–	–	–	–	–	–	–	–	–	–	–	–
2	Sex*	−0.05	–	–	–	–	–	–	–	–	–	–	–
3	Birth status†	−0.07	0.02	–	–	–	–	–	–	–	–	–	–
4	SES	−0.08	−0.11	−0.04	–	–	–	–	–	–	–	–	–
5	ISI	−0.05	−0.09	0.04	−0.04	–	–	–	–	–	–	–	–
6	ADHD-I	−0.06	−0.13‡	0.07	−0.07	0.27‡	–	–	–	–	–	–	–
7	AVR	0.04	−0.11	0.02	0.04	0.02	0.06	–	–	–	–	–	–
8	CRAE	0.02	0.10	0.02	0.03	−0.07	−0.02	0.58‡	–	–	–	–	–
9	CRVE	−0.03	0.22‡	−0.04	0.01	−0.11	−0.05	−0.23‡	0.62‡	–	–	–	–
10	BMI	0.16‡	0.03	−0.02	−0.22‡	−0.01	−0.01	−0.22‡	−0.21‡	−0.05	–	–	–
11	Systolic BP	0.09	−0.06	−0.01	−0.07	0.09	0.08	−0.28‡	−0.35‡	−0.15‡	0.29‡	–	–
12	Diastolic BP	0.13‡	−0.03	0.06	−0.08	0.11	0.09	−0.25‡	−0.31‡	−0.13‡	0.09	0.71‡	–
13	RT_{con}	−0.13‡	0.12‡	−0.08	−0.15‡	0.01	−0.05	−0.14‡	−0.10	−0.02	−0.02	−0.03	−0.02
14	RT_{inc}	−0.10	0.04	−0.06	−0.10	−0.01	−0.06	−0.13‡	−0.09	−0.02	0.03	0.01	0.03

ADHD-I, Conner's attention deficit hyperactivity disorder index (sum score); *BMI*, body mass index; *BP*, blood pressure; *CRAE*, central retinal arteriolar equivalent; *CRVE*, Central retinal venular equivalent; *ISI*, Insomnia Severity Index (sum score); RT_{con}, congruent reaction time; RT_{inc}, incongruent reaction time; *SES*, socioeconomic status based on income.
*Dummy coded (0 = girls; 1 = boys).
†Dummy coded (0 = preterm birth; 1 = full-term birth).
‡$P < .05$.