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ORIGINAL RESEARCH

Arterial Health Markers in Relation to Behavior and Cognitive Outcomes at School Age

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BACKGROUND: Impaired arterial health is associated with a decline in cognitive function and psychopathology in adults. We hypothesized that these associations originate in early life. We examined the associations of blood pressure, common carotid artery intima media thickness, and carotid distensibility with behavior and cognitive outcomes during adolescence.

METHODS AND RESULTS: This study was embedded in the Dutch Generation R Study, a population-based prospective cohort study from early fetal life onwards. Blood pressure, carotid intima media thickness, and carotid distensibility were measured at the age of 10 years. At the age of 13 years, total, internalizing and externalizing problems and attention-deficit hyperactivity disorder symptoms were measured using the parent-reported Child Behavior Checklist (CBCL/6–18), autistic traits were assessed by the Social Responsiveness Scale, and IQ was assessed using the Wechsler Intelligence Scale for Children-Fifth Edition. A 1-SD score higher mean arterial pressure was associated with lower odds of internalizing problems (odds ratio [OR], 0.92 [95% CI, 0.85–0.99]). However, this association was nonsignificant after correction for multiple testing. Carotid intima media thickness and carotid distensibility were not associated with behavior and cognitive outcomes at 13 years old.

CONCLUSIONS: From our results, we cannot conclude that the associations of blood pressure, carotid intima media thickness, and carotid distensibility at age 10 years with behavior and cognitive outcomes are present in early adolescence. Further follow-up studies are needed to identify the critical ages for arterial health in relation to behavior and cognitive outcomes at older ages.

Key Words: attention-deficit hyperactivity disorder ■ autism spectrum disorder ■ behavior ■ blood pressure ■ carotid distensibility ■ carotid intima media thickness ■ IQ

With normal development and aging, the human vasculature is subject to many alterations and changes in structure and function.[1] Arteries stiffen with age, resulting in higher systolic blood pressure and activating a pathway in which the formation of atherosclerosis and thickening of the intima media wall of the artery is accelerated.[2] These structural and functional changes to arteries negatively influence cerebral blood flow, microvascular remodeling and oxygen delivery.[3,4] In adults, hypertension is associated with cognitive dysfunction, which might be explained by disruption of the intra-cerebral vasculature and subsequent ischemic white matter damage.[5] Increased carotid intima media thickness (cIMT), a marker of atherosclerosis and impaired arterial health, also seems to be associated with a higher risk of cognitive impairment.[6] Already in adolescence arterial stiffness seems to precede elevated blood pressure and

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CLINICAL PERSPECTIVE

What Is New?

- This study, embedded in the large Generation R population-based prospective cohort study, examined the associations of blood pressure, carotid intima media thickness, and carotid distensibility at 10 years old with cognitive and behavior outcomes in 13-year-old adolescents.
- In this study no associations of blood pressure, carotid intima media thickness, and carotid distensibility with mental health outcomes were observed in adolescence.

What Are the Clinical Implications?

- Further studies using repeated data during childhood and adolescence assessing the full scope of arterial health markers in relation to cognitive and behavior outcomes are needed to identify critical ages for these associations, which could pose an opportunity for early intervention in preventing disease.

Nonstandard Abbreviations and Acronyms

1-SDS	1 SD score
CBCL/6–18	Child Behavior Checklist for Ages 6 to 18
cIMT	carotid intima media thickness
SRS	Social Responsiveness Scale

hypertension.[7] The associations of arterial health with outcomes related to mental health and cognition might therefore originate in childhood. Results from a systematic review on the association of hypertension and cognitive function in children and adolescents, showed that children with hypertension had lower cognitive test performance scores as compared with normotensive children.[8] Also, hypertension in childhood and early adulthood is associated with steeper cognitive decline in midlife, suggesting the long-term effects track from childhood to adulthood.[8] Previous results from the prospective Generation R Study reported that higher diastolic blood pressure across the normotensive range was associated with lower nonverbal IQ at the age of 6 years.[9] Results from a previous study among 32 hypertensive children, and matched controls, suggest that hypertension in children is associated with decreased cognitive functioning and increased risks of higher internalizing problems, attention-deficit hyperactivity disorder (ADHD) depression and anxiety.[10] Previous studies have also suggested positive associations of cIMT with the risks of ADHD and depression in children.[11,12]

We hypothesized that the associations of arterial health with cognitive and mental health outcomes originate in early life and are present across the full range of blood pressure, cIMT, and carotid distensibility. In this population-based prospective cohort study among 4533 children, we examined the prospective associations of blood pressure, cIMT, and carotid distensibility at the age of 10 years with behavior and cognitive outcomes at the age of 13 years. Main outcomes include total, internalizing and externalizing problems, ADHD symptoms, autism spectrum disorder (ASD) traits, and full-scale IQ.

METHODS

Data Availability Statement

Data from the Generation R study are available upon request to the director (generationr@erasmusmc.nl), subject to local rules and regulations. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Design

This study was embedded in the Generation R Study, a population-based prospective cohort study from early fetal life onward.[13] Children born between April 2002 and January 2006 and living in Rotterdam, the Netherlands were eligible for participation. Details on response and follow-up have been described previously.[13] We had information on carotid and blood pressure measurements in 5420 singleton births. Included in the data collection were questionnaires, physical and ultrasound examinations, biological samples and behavioral observations, which were performed in mothers, fathers, and children. Analyses were restricted to a subgroup of (n=4533) children for whom we had follow-up information at 13 years. A flowchart is provided in Figure S1. Written informed consent was provided by all parents and children. The Medical Ethics Committee of Erasmus Medical Center approved the study (MEC-2012-165). This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline.[14]

Childhood Blood Pressure, Common Carotid Artery Intima Media Thickness, and Common Carotid Distensibility

Children visited the research facility at the median age of 9.7 years (95% range, 9.4–10.5 years). Blood pressure measurement was repeated 4 times in supine position at the right brachial artery with a 1-minute interval using an automated sphygomanometer Datascope Accutorr Plus (Paramus, NJ).[15] Mean systolic, diastolic and mean arterial blood pressure were calculated using the last 3 measurements. We used the age-, sex-, and height-adjusted 95th percentile cutoff for mean systolic and diastolic blood pressure values from the Fourth report on the diagnosis, evaluation and treatment of high blood pressure in children and adolescents from the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents to classify children as hypertensive.[16]

As previously described, at the same visit, cIMT and distensibility were measured 3 times at both common carotid arteries using the Logiq E9 device (GE Medical Systems, Wauwatosa, WI).[17] Children were in the supine position, with the head tilted slightly away from the transducer. The common carotid artery was identified in a longitudinal plane, ~10 mm proximal from the carotid bifurcation. We obtained 6 recordings that ideally included multiple heart cycles. The analyses were performed offline and semi-automatically, using the application Carotid Studio (Cardiovascular Suite, Quipu srl, Pisa, Italy). For each recording, at all R-waves of the simultaneous ECG, cIMT was computed at the far wall as the average distance between lumen-intima and media-adventitia borders. The average cIMT in all frozen end-diastolic frames of the acquired image sequence, was computed. Distensibility was defined as the relative change in lumen area during systole for a given pressure change. Lumen diameter was computed as the average distance between the far and near media-adventitia interfaces, for each frame of the acquired image sequence. Distension was calculated as the difference between the maximal (diastolic) and minimal (systolic) lumen diameter. Per recording, the average distension and diameter values were used to compute average distensibility. Further data processing was performed in R. Children with at least 1 successful cIMT or distensibility measurement were included. The overall mean cIMT (mm) and distensibility ($kPa^{-1}\times10^{-3}$) were used as main outcomes of interest. For the final analyses, distensibility was log-transformed to deal with a skewed distribution. We constructed standard deviation score (SDS) values as [observed value−mean]/SD for the childhood outcome measures to enable comparison of effect estimates. In a reproducibility study performed among 47 subjects, the interobserver and intraobserver intraclass correlation coefficient were greater than 0.85.

Behavioral and Cognitive Outcomes

At the median age of 13.5 years (95% range, 13.1–14.6 years), the primary caregiver (91.4% mothers) was asked to complete the Child Behavior Checklist (CBCL)/6–18.[18,19] The CBCL measures emotional and behavioral problems on a continuous severity scale. Based on the behavior of the child in the preceding 6 months, each of the total 99 items is rated on a 3-point scale: 0 (not true), 1 (somewhat true), 2 (very true or often true). Together the 99 items result in the total problems sum score, a higher score indicating more emotional and behavioral problems. This total problems sum score can be subdivided into internalizing and externalizing problems. Internalizing problems consist of emotionally reactive and anxious/depressed symptoms, as well as somatic complaints and symptoms of being withdrawn. Externalizing problems consist of rule breaking and aggressive behavior.[20] From the CBCL, we used the weighted sum score of total problems, internalizing problems, externalizing problems, and the Diagnostic and Statistical Manual of Mental Disorders-oriented ADHD symptoms. We used both dichotomous cut-off scores and continuous scores. As in previous studies, we used the CBCL validated subclinical score defined as the highest 20%.[21,22] For the final analyses, scores on the total problems, internalizing problems, externalizing problems and ADHD symptoms subscales were natural log-transformed to deal with a skewed distribution.

The primary caregiver completed an adapted version of the Social Responsiveness Scale (SRS), consisting of 18 items. This abbreviated version shows high correlations with the full scale.[23,24] The SRS is a quantitative measure of autistic traits for children aged between 4 and 18 years.[23,25,26] Scoring is on a 4-point Likert scale. The shortened 18-item SRS contained items from 3 subscales: social cognition, social communication, and autistic mannerisms. The Cronbach alpha indicated high inter-item reliability for the SRS (α=0.92). We used, the recommended cutoffs for screening in population-based settings of weighted scores consistent with 1.078 for boys and 1.000 for girls.[27] The total sum score of autistic traits was natural log-transformed to deal with a skewed distribution.

Children's IQ was assessed using a subset of the Wechsler Intelligence Scale for Children-Fifth Edition (WISC-V) also at the age of 13 years old. The WISC-V is an instrument assessing individual cognitive functioning in 6 to 16-year-olds. In collaboration with Pearson (Pearson Clinical Assessment, San Antonio, TX), 4 core subtests from the WISC-V were selected to assess specific cognitive domains and to derive an estimated full scale IQ.[28] The 4 subsets consisted of vocabulary, matrix reasoning, digit span and coding.[20] We used IQ estimates as continuous and dichotomous outcomes, using a cut-off of <80, as defined in the WISC-V manual, to distinguish borderline low IQ scores.[28] For all outcomes, we constructed standard deviation scores as [observed value−mean]/SD within the population to enable comparison of effect estimates.

Covariates

We used directed acyclic graphs to identify potential covariates (Figure S2). We obtained information on sex, birth weight, gestational age at birth, ethnicity, maternal educational level, childhood daily physical activity and tv watching habits using questionnaires and registries.[13] At median age of 9.7 years, children were invited to visit the research facility and their height and weight were measured. We calculated sex- and gestational age–adjusted body mass index (BMI) (kg/m^2) SDS. At the same visit, a venous blood sample was collected and serum glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides, and C-reactive protein concentrations were measured.[13,29]

Statistical Analysis

First, we described maternal and childhood characteristics. We performed a nonresponse analysis by comparing characteristics of children with and without outcome assessments by using independent Student *t* test, Mann–Whitney *U* and χ^2 tests. We tested for nonlinearity but did not observe nonlinear associations. Second, we used logistic regression models to assess the associations of systolic, diastolic and mean blood pressure, cIMT, and carotid distensibility with cut-off scores of the total problems, internalizing and externalizing problems, ADHD symptoms, autism traits, and IQ at age 13 years. Third, we used linear regression models to assess the associations of blood pressure, cIMT, and carotid distensibility with continuous scores for the same behavior and cognitive outcomes. As additional analyses, we used linear regression models to assess the association of age-, sex-, and height-adjusted systolic and diastolic blood pressure >95th percentile as cut-off for hypertension with the same behavior and cognitive outcomes.[16] We tested for statistical interaction of maternal educational level and ethnicity of the child in these associations but no statistically significant interactions were observed (P>0.05). For all analyses, the basic models were adjusted for child's sex and age at outcome assessment. The confounder-adjusted model, which we considered the main model, was additionally adjusted for age at exposure assessment, birth weight, gestational age at birth, ethnicity of the child, BMI, and maternal educational level. The additional cardiometabolic and lifestyle model was similar as the confounder model with additional adjustment for glucose, total cholesterol, high-density lipoprotein cholesterol, triglycerides, and C-reactive protein concentrations, daily physical activity and daily television-watching habits, all at the age of 9 years. Potential confounders were identified based on previous literature, and we selected those that fulfilled the graphical criteria for confounding in a directed acyclic graph and changed the effect estimates >10% after addition to the crude model. We considered 3 groups of outcomes, namely CBCL derivatives, SRS scores, and IQ. We corrected for multiple testing by using the Bonferroni Method and specified significant P values as P<0.003. Missing data in covariates (ranging from 0.1% to 7.0%) were multiple imputed using the Markov Chain Monte Carlo method. Ten imputed data sets were created and analyzed together.[30] Statistical analyses were performed using the Statistical Package of Social Sciences version 25.0 for Windows (SPSS Inc., Chicago, IL).

RESULTS

Participant Characteristics

Follow-up measurements were available for 4533 children with a median age of 13.5 (95% range, 13.1–14.5) years, of whom 2300 (50.7%) were girls, and 2832 (62.5%) were of Dutch ethnicity. cIMT was normally distributed (mean, 0.5 [SD, 0.04] mm) (Table 1). Table S1 shows subjects characteristics from the observed nonimputed data. Table S2 shows parental characteristics of the study population. Table S3 shows that compared with the study population (n=4533), children without outcome measurements (n=866), had lower birth weights, were more often of non-Dutch ethnicity, and had higher BMI and blood pressure at the 9-year follow-up measurement. Mothers of children without outcome measurements less frequently had a high education level.

Arterial Health Markers and Total, Internalizing, and Externalizing Problems

Table 2 shows the associations of blood pressure, cIMT, and carotid distensibility with cut-off scores for total, internalizing, and externalizing problems at 13 years of age. A 1-SD score (1-SDS) higher mean arterial pressure was associated with lower odds of internalizing problems (odds ratio [OR], 0.92 [95% CI, 0.85–0.99]) but was nonsignificant after correction for multiple testing. Diastolic blood pressure, cIMT, and carotid distensibility were not associated with behavioral outcomes at 13 years old. The results from the basic and cardiometabolic lifestyle models were largely similar as from the main-confounder models (Tables S4 and S5). Table S6 shows that arterial health markers were not associated with continuous scores for total, internalizing, and externalizing problems at 13 years of age. Table S7 shows that hypertension was not associated with continuous scores for total, internalizing, and externalizing problems at 13 years of age.

Table 1. Descriptive Statistics of the Study Population*

Characteristics	N=4533
Maternal education level, n (%)	
Primary education	332 (7.3)
Secondary education	1817 (40.0)
Higher education	2384 (52.7)
Birth	
Child sex, female n (%)	2300 (50.7)
Gestational age at birth, median (95% range), wk	40.1 (35.7–42.3)
Birth weight, median (95% range), g	3470 (2250–4503)
Ethnicity, n (%)	
Dutch	2832 (62.5)
Non-Dutch, Western country origin	390 (8.6)
Non-Dutch, Non-Western country origin	1310 (28.9)
Childhood	
Age at exposure assessment, median (95% range), y	9.7 (9.4–10.5)
Body mass index, median (95% range), kg/m^2	16.9 (14.0–24.2)
Systolic blood pressure, mean (SD), mm Hg	102.9 (7.8)
Diastolic blood pressure, mean (SD), mm Hg	58.4 (6.3)
Mean arterial pressure, mean (SD), mm Hg	73.2 (6.2)
Carotid intima media thickness, mean (SD), mm	0.5 (0.04)
Carotid distensibility, median (95% range), kPa^{-1}×10^{-3}	55.9 (37.4–85.2)
Glucose, mean (SD), mmol/L	5.2 (0.9)
Total cholesterol, mean (SD), mmol/L	4.3 (0.7)
HDL cholesterol, mean (SD), mmol/L	1.5 (0.3)
Triglycerides, median (95% range), mmol/L	1.0 (0.7–2.6)
Serum level CRP, median (95% range) mmol/L	0.4 (0.3–5.7)
Age at outcome assessment, median (95% range), y	13.5 (13.1–14.5)
CBCL total problems score, median (95% range)	14.0 (0.0–62.1)
CBCL internalizing problems score, median (95% range)	4.0 (0.0–21.3)
CBCL externalizing problems score, median (95% range)	2.0 (0.0–18.0)
CBCL ADHD symptoms score, median (95% range)	2.0 (0.0–10.0)
SRS autism traits score, median (95% range)	4.0 (0.0–15.8)
Estimated WISC-V IQ, mean (SD)	102.2 (13.6)
Weekly physical activity, n (%)	
<3 h per day	2893 (63.8)
>3 h per day	1640 (36.2)
Daily television watching, n (%)	
No television watching	742 (16.4)
0 to 2 h per day	3114 (68.7)
>2 h per day	677 (14.9)

Values are mean (SD), median (95% range), or number (valid %). ADHD indicates attention-deficit hyperactivity disorder; CBCL, Child Behavior Checklist; CRP, C-reactive protein; HDL, high-density lipoprotein; SRS, Social Responsiveness Scale; and WISC-V, Wechsler Intelligence Scale for Children-Fifth Edition.

*Characteristics are based on the pooled data sets after multiple imputations.

Arterial Health Markers and ADHD Symptoms, ASD Traits, and IQ

Table 3 shows the associations of blood pressure, cIMT, and carotid distensibility with cut-off scores for ADHD symptoms, ASD traits, and IQ at 13 years of age. cIMT and carotid distensibility were not associated with ADHD symptoms, ASD traits, and IQ. A 1-SDS higher systolic, diastolic, and mean arterial pressure was associated with higher odds of a low IQ (OR, 1.22 [95% CI, 1.06–1.39]; OR, 1.19 [95% CI, 1.05–1.36]; and OR, 1.23 [95% CI, 1.07–1.40], respectively) in the basic models (Table S8). These associations attenuated into nonsignificance in the confounder model. The difference between the basic and confounder model was mainly explained by maternal education level. Results from the cardiometabolic lifestyle models are shown in Table S9. Table S10 shows that arterial health markers were not associated with continuous scores for ADHD symptoms, ASD traits, and IQ at 13 years of age in the confounder models. Table S11 shows that hypertension was not associated with continuous scores for ADHD symptoms, ASD traits, and IQ at 13 years of age.

DISCUSSION

In this population-based cohort study, we observed that children with higher mean arterial pressure had lower odds of high internalizing problems. However, this association attenuated into nonsignificance after correction for multiple testing. The association of higher blood pressure with a higher odds of low IQ was fully explained by maternal education level. We observed no associations of diastolic blood pressure, cIMT, or carotid distensibility with behavior and cognitive outcome at 13 years of age.

Hypertension is associated with cognitive dysfunction in adults.[5] Hypertension has a destructive impact on cerebral blood vessels and results in disruption of the functional and structural intracerebral vasculature.[5] These alterations are responsible for micro infarcts, brain atrophy, and subsequent ischemic white matter damage.[5]

Table 2. Associations of Arterial Health Markers With Total, Internalizing, and Externalizing Problems Scores at School Age

Markers of arterial health in SDS	n	Total problems >20th percentile (n=805)†	Internalizing problems >20th percentile (n=892)‡	Externalizing problems >20th percentile (n=935)§
		Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Systolic blood pressure (1 SDS=7.83 mm Hg)	4470	0.92 (0.84–1.00)	0.93 (0.86–1.01)	0.94 (0.87–1.02)
Diastolic blood pressure (1 SDS=6.33 mm Hg)	4470	0.95 (0.88–1.03)	0.93 (0.86–1.00)	0.96 (0.89–1.04)
Mean arterial pressure (1 SDS=6.15 mm Hg)	4469	0.93 (0.86–1.02)	0.92 (0.85–0.99)*	0.95 (0.88–1.03)
Carotid intima media thickness (1 SDS=0.04 mm)	4174	1.02 (0.94–1.10)	0.93 (0.96–1.01)	1.04 (0.97–1.13)
Carotid distensibility (1 SDS=0.09 kPa^{-1}×10^{-3})	4010	1.07 (0.98–1.17)	1.05 (0.97–1.14)	1.04 (0.96–1.13)

Values are odds ratios (95% CI) obtained from multivariable logistic regression models and reflect the differences in parent-reported behavioral problems, total problems (SD score), internalizing problems (SD score), and externalizing problems (SD score) for arterial health markers. The top 20% of the total problems, internalizing problems, and externalizing problems were used. Total number of available cases: †n=4015, ‡n=4018, §n=4008. Pooled estimates are from multiple imputed data sets. The confounder model is adjusted for age at time of exposure measurement, age at outcome measurement, sex of the child, birth weight, gestational age at birth, ethnicity of the child, body mass index measured at the follow-up visit at 9 years old, and maternal education level.

*P value<0.05.

Optimal arterial function leads to adequate blood pressure and brain circulation and subsequent brain development and function. Childhood is a critical period for brain development. Therefore, we hypothesized that a higher blood pressure and cIMT and a lower carotid distensibility are associated with impaired cognitive and mental health outcomes already from childhood onwards.

A previous study, a prospective observational cohort study conducted in North America, among 845 children 2 to 18 years of age with chronic kidney disease, reported associations of persistent hypertension with more attention, adaptive and behavioral symptoms.[31] In the same study, hypertension attributable to glomerular diagnosis was related to fewer internalizing problems.[31] According to the authors, this finding might be explained by the short disease course at the study entry and therefore reduced parental stress in comparison with parents of children with other diagnoses.[31] In a study among 1126 young adults from Finland, men with higher scores for depressive symptoms also had higher cIMT, but this association was not observed in women.[12] In 2 large cohort studies among more than 2900 children, with a 25- to 30-year follow-up, elevated blood pressure was associated with poorer performance on cognitive tests.[32,33] Thus, these previous studies suggest associations of hypertension with behavior and cognitive outcomes, but the associations are not consistent and seem to be influenced by a great number of factors.

In the current study in a general pediatric population, we observed that higher systolic and mean arterial pressure were associated with lower odds of high total and internalizing problem scores, but these associations were nonsignificant after correction for multiple testing. We did not observe associations of diastolic blood pressure, cIMT, and carotid distensibility with behavior and cognitive outcomes. These findings are in contrast to our hypothesis. The difference in our findings and the previous clinical studies presented might be attributable to the population differences. Unlike the previously presented studies, we adjusted for childhood BMI at the age of arterial health measurement. Blood pressure and BMI are highly correlated.[34] Also, maternal educational level at birth has an influence on

Table 3. Associations of Arterial Health Markers With ADHD Symptoms, Autism Traits, and IQ at School Age

Markers of arterial health in SDS	n	ADHD symptoms score >20th percentile (n=968)*	Autistic traits score cutoff (n=336)†	IQ score <80 (n=229)‡
		Odds ratio (95% CI)	Odds ratio (95% CI)	Odds ratio (95% CI)
Systolic blood pressure (1 SDS=7.83 mm Hg)	4470	0.98 (0.90–1.06)	1.03 (0.91–1.17)	1.04 (0.89–1.20)
Diastolic blood pressure (1 SDS=6.33 mm Hg)	4470	0.97 (0.90–1.05)	1.05 (0.93–1.18)	1.07 (0.93–1.23)
Mean arterial pressure (1 SDS=6.15 mm Hg)	4469	0.97 (0.90–1.05)	1.05 (0.93–1.18)	1.06 (0.92–1.23)
Carotid intima media thickness (1 SDS=0.04 mm)	4174	1.07 (0.99–1.15)	1.02 (0.91–1.14)	1.06 (0.92–1.22)
Carotid distensibility (1 SDS=0.09 kPa^{-1}×10^{-3})	4010	1.00 (0.92–1.08)	1.01 (0.89–1.14)	1.07 (0.92–1.24)

Values are odds ratios (95% CI) obtained from multivariable logistic regression models and reflect the differences in parent-reported behavioral problems, attention-deficit hyperactivity disorder symptoms score (SD score), autistic traits score (SD score), and IQ (SD score) for arterial health markers. The top 20% of the attention-deficit hyperactivity disorder symptoms score, autistic traits score (weighted scores >1.078 for boys and >1.000 for girls), and IQ score (<80) were used. Total number of available cases: *n=3999, †n=4007, ‡n=4244. Pooled estimates are from multiple imputed data sets. The confounder model is adjusted for age at time of exposure measurement, age at outcome measurement, sex of the child, birth weight, gestational age at birth, ethnicity of the child, body mass index measured at the follow-up visit at 9 years old, and maternal educational level. ADHD indicates attention-deficit hyperactivity disorder; and SDS, SD score.

both childhood cognitive development and on arterial health.[35–37] Maternal education level most likely works as a proxy for socioeconomic status and is associated with a wide range of health, cognitive, behavioral and socio-emotional outcomes in children.[38] Since the direction of the effect estimates were similar in the basic and final models, adjustment for covariates does not explain the difference in effect estimate direction as compared with previous studies. Additional analyses in a subgroup of children who met the criteria for hypertension showed similar results as for the full range of blood pressure, but we had low numbers of children with hypertension. Parent-reported outcome assessments might be influenced by mood of the parent, since parental stress is found to be higher in families dealing with sickness of a child and might influence the parents perception of childhood behavioral problems.[39] In our study this potential effect might not be present because of the general healthy population. Thus, our results may differ from previous studies in hypertensive populations, because of population difference and the adjustment for confounders in the association of arterial health and behavior and cognitive outcomes.

Previously, cIMT has been associated with ADHD and depression.[11] The relations of carotid stiffness or distensibility with behavior and cognition have rarely been examined. One study among 85, 10- to 14-year-old children receiving treatment for ADHD and 53 siblings without ADHD, showed that children being treated with a stimulant medication for ADHD had higher arterial stiffness.[40] Another study among 51 children and adolescents with ADHD and 51 healthy controls, showed that cIMT was significantly higher in the ADHD group compared with the control group. No correlation was found between cIMT and the duration of ADHD.[41] We did not observe any association of cIMT or carotid distensibility with behavior and cognitive outcomes. In contrast to the previous studies among individuals with ADHD and or depressive symptoms, our study was performed among a general population. Previous research has shown that in healthy adolescents cIMT deviates at the age of 17 years, whereas cIMT deviates around the age of 12 years in children with familial hypercholesterolemia.[42,43] Our general population of 13-year-old children might therefore be slightly too young with regard to variance in the cIMT.

The results from our study suggest that within the normal range of blood pressure, cIMT, and carotid distensibility at 10 years old, no associations are present for behavior and cognitive outcomes at 13 years of age. The adolescent brain matures in a dynamic fashion. White matter is increased and formed synapses are selectively eliminated, causing reorganization of the brain. This brain reorganization goes accompanied by profound emotional and cognitive changes.[44] Cerebral blood flow has been shown to reduce significantly from childhood with the biggest decline in early adolescence.[45] Moreover, in children with untreated hypertension cerebral vascular reactivity is stunted, but this is not the case for elevated blood pressure or whitecoat hypertension.[46] This might be indicative for a relation in which there is a blood pressure threshold that needs to be exceeded before alteration of cerebral function occurs, though this is speculative. Longitudinal studies using repeated measurements are necessary to identify the critical ages for arterial health in relation to behavior and cognitive outcomes at older ages.

Strengths of this study include the study design, large number of participants, and extensive report on behavioral and cognitive outcomes. This study also has limitations. Blood pressure measurements were conducted in the supine position instead of the sitting position recommended by the 2020 International Society of Hypertension Global Hypertension Practice Guidelines.[47] Blood pressure measurements and the prevalence of high blood pressure have been shown to be significantly lower in the supine position compared with the sitting position.[48] Therefore, in our study blood pressure and the prevalence of hypertension could be underestimated. However, we do not expect that this effect influences our associations of interest. Carotid femoral pulse wave velocity is an important marker of arterial health and arterial stiffness.[7,49] As carotid femoral pulse wave velocity precedes hypertension and in adult studies has been associated with cerebral damage, this marker is of great interest.[4,7] In this study carotid femoral pulse wave velocity and the associations with cognition and behavior were not assessed, which poses a limitation on the complete assessment of arterial health. We did however measure and research carotid distensibility. Though carotid distensibility represents elasticity, this can be used as a surrogate for local arterial stiffness, as it too represents a vascular wall or pressure-related arterial wall property.[49] Also, of the 9503 singleton live births only 4533 children had data on arterial health and behavior and cognitive outcome measurements. Children not included in our analyses had lower birth weights, were more often of non-Dutch ethnicity, had higher BMI and blood pressure measurements. Also, their mothers were less often highly educated. This seems to suggest bias to a relatively healthier population and might affect the generalizability of our results. We repeated the analysis among Dutch children only as the largest ethnic subgroup and observed similar results (data not shown). Recent literature suggests an association between urban environment, including exposure to air pollutants, with both cardiovascular disease and alterations in neurodevelopment.[50,51] Since, the Generation R Study population is an urban population, the difference between rural and urban environment could not be considered. This study was embedded in an ongoing population-based prospective cohort study, but with a short follow-up. We have adjusted our analyses for childhood BMI. However recent studies suggest that directly assessed body fat measures are stronger related to body composition in the associations under review than BMI.[52,53] We repeated the analysis adjusting for childhood cardiometabolic and lifestyle factors. The results of these analyses were largely similar as the main results. Although we adjusted for many potential confounders, residual confounding might still be a possibility also attributable to the observational nature of the study.

CONCLUSIONS

From our results, we cannot conclude that the associations of blood pressure, cIMT, and carotid distensibility at age 10 years with cognitive and mental health outcomes are present in adolescence and across the full range of these arterial health markers. Further studies investigating the relationship of arterial health markers with behavior and cognitive outcomes and using repeated measurements across childhood are needed to identify the critical ages for arterial health in relation to behavior and cognitive outcomes at older ages.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S11
Figures S1–S2

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