ORIGINAL RESEARCH

Association of Blood Pressure and Arterial Stiffness With Cognition in 2 Population-Based Child and Adult Cohorts

Sander Lamballais, MSc;* Ayesha Sajjad, MD, MPhil, PhD;* Maarten J. G. Leening, MD, PhD; Romy Gaillard, PhD; Oscar H. Franco, MD, PhD; Francesco U. S. Mattace-Raso, MD, PhD; Vincent W. V. Jaddoe, MD, PhD; Sabine J. Roza, MD, PhD; Henning Tiemeier, MD, PhD; M. Arfan Ikram, MD, PhD

***Background*—**High blood pressure levels and higher arterial stiffness have been shown to be associated with lower cognition during adulthood, possibly by accumulative changes over time. However, vascular factors may already affect the brain during early life.

***Methods and Results*—**We examined the relation between cognition and vascular factors within 5853 children from the Generation R Study (mean age 6.2 years) and 5187 adults from the Rotterdam Study (mean age 61.8 years). Diastolic and systolic blood pressure and arterial stiffness were assessed, the latter by measuring pulse-wave velocity and pulse pressure. For cognition, the Generation R Study relied on nonverbal intelligence, whereas the Rotterdam Study relied on a cognitive test battery to calculate the g-factor, a measure of global cognition. In the Generation R Study, standardized diastolic blood pressure showed a significant association with standardized nonverbal intelligence (β=−0.030, 95% confidence interval=[−0.054; −0.005]) after full adjustment. This association held up after excluding the top diastolic blood pressure decile (β=−0.042 [−0.075; −0.009]), suggesting that the relation holds in normotensives. Within the Rotterdam Study, standardized cognition associated linearly with standardized systolic blood pressure (β=−0.036 [−0.060; −0.012]), standardized pulse-wave velocity (β=−0.064 [−0.095; −0.033]), and standardized pulse pressure (β=−0.044 [−0.069; −0.020], and nonlinearly with standardized diastolic blood pressure (quadratic term β=−0.032 [−0.049; −0.015]) after full adjustment.

***Conclusions*—**Blood pressure and cognition may already be related in the general population during early childhood, albeit differently than during adulthood. **(*J Am Heart Assoc*. 2018;7:e009847. DOI: 10.1161/JAHA.118.009847)**

Key Words: adulthood • arterial stiffness • blood pressure • cognition • pediatric

Dementia is a disease posing a huge burden on societies worldwide, and the number of cases is predicted to double by 2040.[1] It is a multifactorial disease, with the role of cardiovascular risk factors increasingly recognized.[2] Blood pressure and arterial stiffness have been of particular interest since these are easily measured and amenable to standard and inexpensive treatments. Interestingly, the effect of high blood pressure may accumulate over time, as midlife,[2–4] persistent hypertension into late life,[5] and longer exposure to hypertension[6] have been shown to associate with dementia. Furthermore, midlife blood pressure and arterial stiffness are also inversely associated with cognition among healthy individuals during later life,[7,8] implying that vascular factors and cognitive functioning relate on a clinical as well as a preclinical level.

The previously described studies have focused on mid- and late-life populations, but the relevance of the associations during early life remains to be elucidated. Given that blood pressure and arterial stiffness in individuals follow stable trajectories,[9–12] partly determined through genetic predisposition,[13,14] it is conceivable that the earliest adverse associations between the vascular factors and cognition may be discernable already at a young age.[15] Previous studies

From the Generation R Study Group (S.L., R.G., V.W.V.J.) and Departments of Epidemiology (S.L., A.S., M.J.G.L., R.G., O.H.F., F.U.S.M.-R., V.W.V.J., H.T., M.A.I.), Cardiology (M.J.G.L.), Internal Medicine (F.U.S.M.-R.), Pediatrics (V.W.V.J.), Psychiatry (S.J.R., H.T.), Child and Adolescent Psychiatry and Psychology (H.T.), Radiology (M.A.I.) and Neurology (M.A.I.), Erasmus MC University Medical Center Rotterdam, Rotterdam, The Netherlands; Departments of Clinical Epidemiology (M.J.G.L.) and Social & Behavioral Sciences (H.T.), Harvard T. H. Chan School of Public Health, Boston, MA.

*Dr Lamballais and Dr Sajjad contributed equally to this work.

Correspondence to: M. Arfan Ikram, MD, PhD, Department of Epidemiology, Erasmus MC University Medical Center Rotterdam, Rotterdam, PO Box 2040, 3000 CA Rotterdam, The Netherlands. E-mail: m.a.ikram@erasmusmc.nl

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Clinical Perspective

What Is New?

- Blood pressure levels are related to cognition in both children and adults from the general population, although the effect sizes were relatively small.
- Diastolic blood pressure associated linearly with cognition in children and nonlinearly in adults.
- Pulse-wave velocity, pulse pressure, and systolic blood pressure are associated with cognition in adults, but not in children.

What Are the Clinical Implications?

- Hemodynamics and adverse vascular risk factors play a role in cognitive function, possibly already exerting their effect in early life.

investigating the link between blood pressure and cognition during childhood and adolescence have primarily focused on hypertensive versus normotensive populations.[16–18] We therefore hypothesize that the associations between vascular factors and cognitive functioning may already be present during childhood as well as within the normal ranges of blood pressure. Finally, given the cumulative effects of vascular risk factors during life, we also hypothesize that the magnitude of the association increases with age.

Hence, we aimed to evaluate whether higher levels of systolic (SBP) and diastolic blood pressure (DBP) and arterial stiffness associated with worse cognition during childhood and mid- to late adulthood. Arterial stiffness was measured directly via carotid–femoral pulse-wave velocity (PWV) and indirectly using pulse pressure (PP).[19] We studied the early life relation in the pediatric Generation R birth cohort, and used data from the Rotterdam Study cohort with individuals aged 45 years and over to establish a benchmark for comparison.

Methods

The data, analytic methods, and study materials will not be made available readily to other researchers for purposes of reproducing the results or replicating the procedure because of legal and informed-consent restrictions. Specific requests for consideration can be made to the respective studies. The first and the corresponding authors had full access to all data sets within this study.

Study Population

The Generation R Study is a population-based birth cohort in Rotterdam, The Netherlands.[20] In short, 9745 children were born between April 2002 and January 2006 from mothers who were enrolled during pregnancy or immediately after birth of the child. Of those, 6690 children visited the research center at the age of 5 to 8 years for follow-up data collection. For this study, we selected 5853 (mean age is 6.2±0.5 years) children with available data on the intelligence quotient (IQ) measure and at least 1 of the vascular measures, including carotid–femoral PWV, SBP, and DBP (Figure 1). The study was conducted in accordance with the guidelines as proposed in the World Medical Association Declaration of Helsinki and was approved by the Medical Ethical Committee of the Erasmus MC University Medical Center in Rotterdam. Written informed consent was obtained from all primary caregivers of the participants.

The Rotterdam Study is a prospective population-based cohort that started in the Ommoord District of The Netherlands.[21] The first 3 cohorts—RS-I, RS-II, and RS-III—started in 1990, 2000, and 2006 and included 7983, 3011, and 3932 participants, respectively. SBP, DBP, and PWV were measured during the third visit of RS-I (RS-I-3), the first visit of RS-II (RS-II-1), and the first visit of RS-III (RS-III-1). Cognitive testing was introduced in 2002, and therefore cognition in the first 2 cohorts was assessed in a later research phase than the vascular measures, namely, in the fourth visit of RS-I (RS-I-4, mean time lag=4.5 years) and the second visit of RS-II (RS-II-2, mean time lag=4.1 years). After exclusion of 527 participants with a history of dementia at the time of the vascular measures, the final population consisted of 5187 individuals (Figure 2). The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC University Medical Center in Rotterdam and by the Dutch Ministry of Health, Welfare and Sport. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians.

Measurement of Blood Pressure and Carotid–Femoral PWV

In Generation R we measured blood pressure 4 times at the right brachial artery, in supine position, with 1-minute intervals using the validated automatic sphygmomanometer Accutorr Plus (Datascope, Paramus, NJ).[22] SBP and DBP were determined by excluding the first measurement and averaging the other measurements. In the Rotterdam Study, blood pressure was measured twice before measurement of PWV. Blood pressure was measured twice with a sphygmomanometer after 5 minutes of rest, and the mean was taken as the participant's reading.

In both studies we assessed carotid–femoral PWV, the reference method to assess aortic stiffness,[23] using an automatic device (Complior; Artech Medical, Pantin, France) with participants in the supine position. Piezoelectric sensors

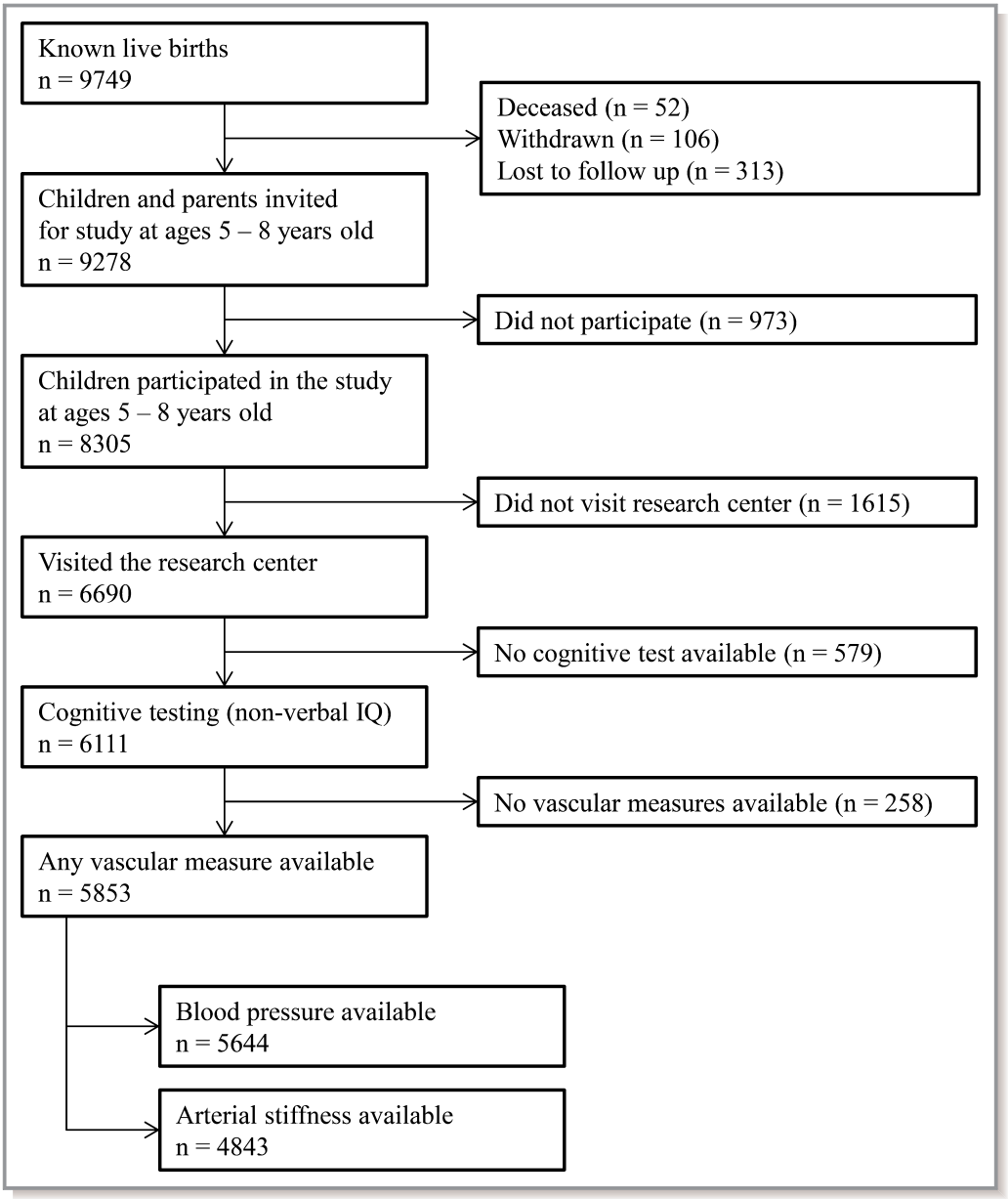

Figure 1. Flow chart of inclusion for the Generation R study.

were placed on the skin close to the carotid (proximal) and femoral (distal) artery. PWV was defined as the ratio between the distance traveled by the pulse wave and the time delay between the carotid and femoral pressure waveforms, as expressed in meters per second.[24] To cover a complete respiratory cycle, the mean of at least 10 consecutive pressure waveforms was used in the analyses. PWV can be measured reliably with good reproducibility in pediatric populations.[25] Finally, we calculated the PP by subtracting DBP from SBP.

Cognitive Function

The ethnic profiles of the studies differ significantly. The Rotterdam Study consists of ≈96% ethnically Dutch participants, whereas the Generation R Study only consists of ≈57% such participants. For Generation R we therefore focused on 2 subtests of the Snijders-Oomen Non-verbal Intelligence Test–Revised (SON-R 2½-7)[26]: "Mosaics," which tapped into spatial visualization abilities, and "Categories," which assessed abstract reasoning abilities. The raw scores were converted to nonverbal IQ using age and sex-specific norms. These scores correlated well with IQ scores derived from the total test (r=0.86)[27] and with the distribution of IQ in the general population.[26]

In the Rotterdam Study, we focused on a much broader range of cognitive domains in order to gain a comprehensive understanding of cognitive function in nondemented elderly.[28] We were interested in the general underlying structure of

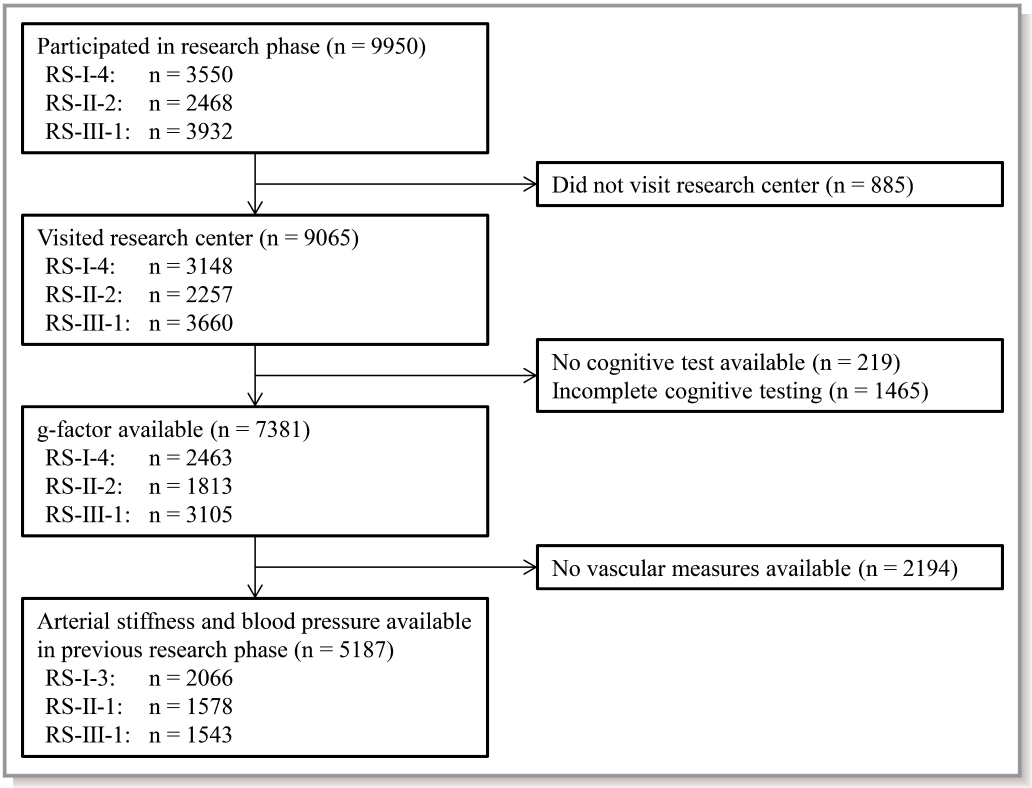

Figure 2. Flow chart of inclusion for the Rotterdam study.

cognition,[29] generally known as the g-factor, a stable concept related to intelligence. For the Rotterdam Study we calculated the g-factor by applying principal component analysis to scores from 5 cognitive tests: Color-word interference Stroop task, letter digit substitution test, verbal fluency test, delayed recall score of the 15-word learning test, and the Purdue pegboard test.[28] The g-factor was defined as the first principal component as returned by the analysis and explained 54.3% of the variance, which is similar to other studies in the literature.[30]

As the 2 studies do not have overlapping scales and as the Rotterdam Study only has 1 nonverbal nonmotor cognitive test, we decided to focus the analyses on general cognition (ie, nonverbal IQ in Generation R and the g-factor in the Rotterdam Study), rather than the subscales.

Measurement of Covariates

For Generation R we included information obtained from midwives and hospital registries on child sex, birth weight (in grams), gestational age at birth, and complications during delivery. Body mass index of the child was based on height and weight as measured during the visit. Child ethnicity was based on parental countries of birth. Maternal age, maternal smoking during pregnancy, and maternal education were assessed by questionnaires. Diet quality was determined by a food frequency questionnaire sent to the children at the age of 8 (median age=8.1 years). The algorithm to score adherence to Dutch dietary guideline has been previously described[31] and is based on sufficient intake of vegetables, fruit, whole grains, fish, legumes, nuts, dairy, oils and soft fats, low intake of sugar-containing beverages, and high-fat and processed meat. The average hours of physical activity per week was based on a parent-reported questionnaire describing time spent on walking, cycling, physical education, swimming, playing outside, and sports participation.[32]

In the Rotterdam Study the covariates were measured during the same examination phases as the vascular measures. Smoking status and education were obtained during home interviews. Body mass index was based on height and weight during the research center visit. Diabetes mellitus was defined as having a fasting glucose level of ≥7.0 mmol/L, or ≥11.1 mmol/L if only nonfasting serum samples were available, or using blood glucose–lowering medication. Fasting glucose levels were available for >97% of the study population. Data on indication for use of blood pressure–lowering medication were based on information collected by a physician at the research center. Adherence to Dutch dietary guidelines was determined via food frequency questionnaires with a similar algorithm as in Generation R.[33] The food frequency questionnaire was not administered for RS-I-3, so the data from RS-I-1 were used, which were collected 4 to 10 years

earlier. Alcohol use was assessed during home interviews with questions based on beer, wine, liquor, and moderately strong alcohol types such as sherry and port. The algorithm to calculate alcohol in grams per day is provided elsewhere.[34] For RS-I-3 and RS-II-1, physical activity was assessed using a validated adapted version of Zutphen Physical Activity Questionnaire[35] and expressed in metabolic equivalent of task hours per week.[36] For RS-III-1, physical activity was assessed using the LASA Physical Activity Questionnaire, and expressed in metabolic equivalent of task hours per week.[37] Because of the difference between the questionnaires, we standardized the metabolic equivalent of task hours per cohort. Finally, the time interval between the 2 visits was included in the models because it represents the aging between the visits, and cognition generally declines with age.

Statistical Analysis

Initially, both ordinary linear regression and iteratively reweighted least squares were used to analyze the data, the latter using Huber-White standard errors. Because the models did not noticeably differ in their estimates and standard errors, we decided to report the results from the iteratively reweighted least-squares models. In order to increase the comparability between studies, we standardized the determinants and outcomes. All levels of associations are presented with their 95% confidence intervals (CIs).

Generation R used 4 models:

1. Model 1: adjusted for sex of the child and age of the child during the visit.
2. Model 2: model 1 further adjusted for birth weight, body mass index of the child during visit, ethnicity of the child, gestational age at birth, diet quality score, and physical activity.
3. Model 3: model 2 further adjusted for prenatal or perinatal maternal variables (ie, education level at birth of the child, age at birth of the child, parity, and smoking during pregnancy).
4. Model 4: model 3 further adjusted for maternal diabetes mellitus and hypertension during the pregnancy.

Additionally, pre-eclampsia has been consistently associated with elevated blood pressure in the offspring[38]; thus, we ran a sensitivity analysis excluding children with mothers experiencing pre-eclampsia during pregnancy in order to ensure that the association was not accounted for by this population.

The Rotterdam Study used 2 models:

1. Model 1: adjusted for age, sex, cohort, and time interval between the measures.
2. Model 2: model 1 further adjusted for education level, body mass index, smoking status, diabetes mellitus status, use of blood pressure–lowering medication, diet quality score, alcohol intake, and physical activity standardized per cohort.

For both studies, we additionally adjusted the models with PWV as the determinant for heart rate and mean arterial pressure (DBP+1/3×(SBP−DBP)).

Several studies have found nonlinear associations between blood pressure and measures of cognition.[39] We therefore performed sensitivity analyses with quadratic terms for DBP and SBP in both the Generation R and the Rotterdam Study cohorts. In addition, stratification for antihypertensive drug use has shown that the association between blood pressure and cognition is diminished in those who use antihypertensive drugs,[40] so we stratified for it in our final sensitivity analysis.

All adjustment variables had <5% missing values except for maternal smoking, diabetes mellitus, and hypertension during pregnancy, with 13.4%, 14.6%, and 14.7% missingness, respectively. This pattern is because of the questions being part of a prenatal questionnaire, which was not filled out by all participants who were included postpartum. Missing values were imputed 100 times using chained equations, and the model fits for each imputed data set were subsequently pooled.[41] Statistical analyses were performed in R 3.3.3.[42] The package mice 2.30[43] was used for multiple imputation, and MASS 7.3 to 45,[44] sandwich 2.3 to 4,[45] and lmtest 0.9 to 35[46] to create the iteratively reweighted least-squares models.

Results

Generation R

Characteristics of the Generation R study population stratified by ethnicity are provided in Table 1. The mean carotid–femoral PWV was 5.5 (0.9) m/s, and the mean SBP, DBP, and PP were 103 (8), 61 (7), and 42 (7) mm Hg, respectively. The average nonverbal IQ score was 101 (15) points. Excluded participants (ie, those who took part in the research phase but did not have data on cognition) had younger mothers at birth (29.4 versus 30.6 years, $P<0.05$) who were less likely to have obtained higher education (40.4% versus 46.9%, $P<0.05$) and were less likely to be of Dutch ethnicity (53.8% versus 57.4%, $P<0.05$).

Table 2 shows the associations between standardized PWV, SBP, DBP, and PP with standardized nonverbal IQ in 6-year-old children. When corrected for sex and age of the child, all 3 vascular measures were negatively associated with the nonverbal IQ score. However, only DBP remained statistically significantly associated after adjusting for all child and maternal covariates (β=−0.030, 95% CI=[−0.054; −0.005]). This relationship was not modified by sex and ethnicity. After

Table 1. Characteristics of the Generation R Study Participants

Characteristics (N=5853)	Dutch (n=3350)	Other Western (n=510)	Non-Western (n=1993)
IQ score	104±15	101±15	96±15
Systolic blood pressure, mm Hg	102±8	103±9	104±9
Diastolic blood pressure, mm Hg	60±7	61±7	62±7
PP, mm Hg	42±6	42±7	42±7
PWV, m/s	5.5±0.9	5.5±0.9	5.6±0.9
Male, %	49.4	45.0	51.8
Age, y	6.1±0.4	6.1±0.5	6.3±0.6
Birth weight, g	3451±584	3406±562	3316±556
Body mass index, kg/m^2	15.9±1.5	16.2±1.8	16.7±2.2
Gestational age at birth, w	39.8±1.9	39.8±2.0	39.6±1.8
Diet quality score	4.5±1.2	4.5±1.2	4.4±1.3
Physical activity, h/wk	2.2±1.2	2.2±1.3	1.9±1.2
Characteristics of mothers at partum			
Education, %			
Low	2.8	7.4	22.1
Intermediate	39.6	34.7	55.2
High	57.6	57.9	22.7
Age, y	31.4±4.7	31.0±4.9	29.1±5.6
Nulliparous, %	61.1	56.0	47.6
Pregnancy smoking, %			
Never	74.8	75.1	74.9
Until aware	10.0	10.9	6.2
Continued	15.2	14.0	18.9
Diabetes mellitus, %	0.2	0.0	0.9
Hypertension, %	1.0	1.1	1.9

PP indicates pulse pressure; PWV, pulse wave velocity.

Table 2. Associations Between Standardized Blood Pressure, Standardized PP, Standardized PWV, and Standardized Child Nonverbal IQ Scores Within the Generation R Study

Nonverbal IQ	Model	β	95% CI	
			Lower	Upper
SBP	1*	−0.059	−0.084	−0.033
	2†	−0.027	−0.053	−0.002
	3‡	−0.018	−0.043	0.008
	4§	−0.018	−0.043	0.007
DBP	1*	−0.068	−0.094	−0.043
	2†	−0.040	−0.065	−0.015
	3‡	−0.030	−0.055	−0.006
	4§	−0.030	−0.054	−0.005
PP	1*	−0.001	−0.028	0.026
	2†	0.009	−0.016	0.035
	3‡	0.011	−0.015	0.036
	4§	0.010	−0.015	0.036
PWV	1*	−0.036	−0.061	−0.010
	2†	−0.017	−0.043	0.008
	3‡	−0.015	−0.039	0.009
	4§	−0.015	−0.039	0.009

Table shows the results from the iteratively reweighted least-squares models. All β values represent the change in the outcome when increasing the value of a determinant by 1 SD. CI indicates confidence interval; DBP, diastolic blood pressure; PP, pulse pressure; PWV, pulse wave velocity; SBP, systolic blood pressure.
*Model 1 consisted of age (y) and sex. The models for PWV were additionally corrected for pulse rate before measurement (beats/min) and mean arterial pressure (mm Hg).
†Model 2 consisted of all variables from model 1, birth weight (g), body mass index (kg/m^2), ethnicity of the child, gestational age at birth, diet quality score, and physical activity (h/wk).
‡Model 3 consisted of all variables from model 2, education of the mother at birth of the child, age of the mother at birth of the child, and parity.
§Model 4 consisted of all variables from model 3, smoking status, diabetes mellitus during pregnancy, and hypertension during pregnancy.

exclusion of 114 children (2.2%) whose mothers experienced preeclampsia during pregnancy, the association remained statistically significant and the effect size was not affected (β=−0.032, 95% CI=[−0.059; −0.005]). To ensure that the association held up in a normotensive population, we excluded the top decile for DBP, and the effect size seemed to be unaffected (β=−0.42, 95% CI=[−0.075; −0.009]).

Rotterdam Study

Characteristics of the Rotterdam Study participants stratified by cohort are provided in Table 3. The carotid–femoral PWV had a mean of 11.6 (3.0) m/s, and SBP, DBP, and PP averaged at 144 (22), 84 (10), and 60 (16) mm Hg, respectively. For participants from RS-I and RS-II, the median interval between the measurements of exposures and the outcome was 4.4 years (interquartile range=4.1–4.7 years). Excluded participants (ie, those with incomplete data on cognition and the vascular measures) were more likely to use blood pressure–lowering medication (35.4% versus 29.3%, $P<0.05$), meet the criteria for diabetes mellitus (14.1% versus 9.8%, $P<0.05$), and were more likely to have obtained lower levels of education (42.5% versus 33.0%, $P<0.05$).

Table 4 shows the associations between standardized carotid–femoral PWV, PP, and blood pressure with the standardized g-factor. For DBP, no significant associations were shown in model 1 and 2 (β=−0.006, 95% CI=[−0.028; 0.017]). In contrast, carotid–femoral PWV (β=−0.064, 95% CI=[−0.095; −0.033]), SBP (β=−0.036, 95% CI=[−0.060;

Table 3. Characteristics of the Rotterdam Study Participants

Characteristics (N=5187)	RS-I Cohort (n=2066)	RS-II Cohort (n=1578)	RS-III Cohort (n=1543)
Cognitive function g-factor	−0.52±0.93	−0.08±0.88	0.47±0.86
SBP, mm Hg	149±20	150±20	130±18
DBP, mm Hg	84±10	86±10	80±10
PP, mm Hg	64±16	64±16	50±11
PWV, m/s	13.0±2.8	12.2±2.8	9.1±1.6
Age, y	63.6±5.7	63.1±6.6	58.0±7.3
Sex (male), %	42.0	44.0	42.7
Time interval between measurements, y	4.5±0.4	4.1±0.5	0.0±0.0
Education, %			
Low	43.3	30.1	26.0
Medium	44.7	51.6	46.2
High	12.0	18.3	27.8
Body mass index, kg/m^2	26.8±3.8	27.1±3.9	27.4±4.3
Smoking, %			
Never	33.0	30.1	33.3
Past	51.7	51.4	46.3
Current	15.3	18.5	20.4
Diabetes mellitus, %	10.0	10.8	8.5
Blood pressure–lowering medication, %	36.5	24.4	27.7
Diet quality score	6.9±1.8	6.2±1.9	6.9±1.9
Alcohol, g/d	11.2±15.4	11.0±14.3	8.8±9.5

DBP, diastolic blood pressure; PP indicates pulse pressure; PWV, pulse wave velocity; RS, Rotterdam Study; SBP, systolic blood pressure.

−0.012]), and PP (β=−0.044, 95% CI=[−0.069; −0.020]) showed statistically significant negative associations with the g-factor. These relationships were not modified by sex. For comparison, a year increase in age led to a 0.062 SD decrease of the g-factor (95% CI=[−0.065; −0.058]).

Nonlinear Associations

Within Generation R, the quadratic terms for DBP and SBP did not reach statistical significance (P>0.05). Within the Rotterdam Study, the quadratic term for DBP (β=−0.032, CI 95%=[−0.048; −0.015]) but not SBP (β=−0.013, CI 95%=[−0.029; 0.002]) reached statistical significance. This suggests the presence of a nonlinear relationship between DBP and the g-factor where more extreme values of DBP (ie, both at the lower and higher ends) were associated with a quadratic decrease in the g-factor.

Table 4. Associations Between Standardized Blood Pressure, Standardized PP, Standardized PWV, and the Standardized g-Factor Within the Rotterdam Study

g-Factor	Model	β	95% CI	
			Lower	Upper
SBP	1*	−0.059	−0.084	−0.033
	2†	−0.036	−0.060	−0.012
DBP	1*	−0.021	−0.045	0.001
	2†	−0.006	−0.028	0.017
PP	1*	−0.065	−0.091	−0.039
	2†	−0.044	−0.069	−0.020
PWV	1*	−0.080	−0.112	−0.047
	2†	−0.064	−0.095	−0.033

Table shows the results from the iteratively reweighted least-squares models. All β values represent the change in the outcome when increasing the value of a determinant by 1 SD. CI indicates confidence interval; DBP, diastolic blood pressure; PP, pulse pressure; PWV, carotid–femoral pulse wave velocity; SBP, systolic blood pressure.
*Model 1 consisted of age (y), sex, cohort, and time difference between exposure and outcome measurements (y). The models for PWV were additionally corrected for pulse rate before measurement (beats/min) and mean arterial pressure (mm Hg).
†Model 2 consisted of all variables from model 1, education, body mass index (kg/m^2), smoking status, diabetes mellitus, blood pressure–lowering medication use, diet quality score, alcohol intake (g/d), and physical activity standardized per cohort (metabolic equivalent of task h/wk).

Antihypertensive Drug Use

Within those who did not use antihypertensive drugs, we found similar associations as described above (ie, linear associations for PWV (β=−0.082, 95% CI=[−0.119; −0.046]) and SBP (β=−0.031, 95% CI=[−0.060; −0.002]) with cognition, and a statistically significant quadratic term for DBP (β=−0.022, 95% CI=[−0.038; −0.005])). In those using antihypertensive drugs, none of the linear terms reached statistical significance. However, the coefficient for the quadratic DBP term remained statistically significant (β=−0.055, 95% CI=[−0.078; −0.031]).

Discussion

In both the pediatric and elderly cohorts, vascular measures were associated with cognition. In particular, DBP but not SBP, PP, or PWV was negatively associated with nonverbal IQ among 6-year-old children. In middle-aged and elderly, both arterial stiffness and SBP were negatively associated with the g-factor, while DBP showed an inverted nonlinear relation. Thus, the exact nature of the vascular–cognitive relation might depend on the life phase.

Cognition in elderly has been previously linked to blood pressure.[7,39] However, most studies dichotomized blood pressure measures into presence or absence of hypertension, and the cut-offs used varied among the studies. In addition,

most of those studies also did not adjust for antihypertensive drug use, which has been suggested to modify the cognitive–vascular relationship.[40] In the current study, we showed that the associations were statistically significant for continuous blood pressure measures and when adjusting for use of antihypertensive drugs.

The findings within the Generation R cohort suggest that the vascular–cognitive relation may extend to earlier life phases as well. The association between DBP and nonverbal IQ in the pediatric cohort showed a similar effect size as the SBP and arterial stiffness associations with the g-factor within the Rotterdam Study. While blood pressure and cognition have been studied in pediatric populations, those studies have generally focused on hypertensive cases.[16–18,47] Lande and colleagues[16] showed among 5077 children aged 6 to 16 years that elevated blood pressure levels seem to relate to a digit-span test, although this effect disappeared after multiple testing correction. In addition, Adams and colleagues[17] showed in 201 children that those with sustained primary hypertension were more likely to have learning disabilities. While the effect sizes cannot be directly compared because of differing determinants and outcomes, the current study does show that the association holds for normotensive populations. It also bolsters the idea that the association between the vascular and cognitive performance may have its roots in childhood.

Different mechanisms have been proposed to link hypertension and arterial stiffness to cognition. Cerebrovascular disease burden is a likely mechanism during adulthood. For example, brain plaque and tangle burden seemingly mediate the effect of diastolic blood pressure on cognition.[48] Additionally, the relation between arterial stiffness and memory may be mediated by cerebrovascular resistance and white matter hyperintensities.[49] However, such pathways may depend on aging[50] and could thus not be relevant for explaining the findings in our pediatric sample.

A more likely mechanism is cerebrovascular reactivity, which encompasses the vasodilatory and vasoconstrictive ability of cerebral vessels. Indeed, Settakis and colleagues showed that hypertensive adolescents (aged 14–18 years) had reduced cerebrovascular reactivity compared with normotensives after a 30-s breath hold.[51] The most profound difference was found for the diastolic blood flow velocity. Another study by Wong and colleagues in hypertensive and normotensive children (aged 7–20 years) showed that diastolic blood pressure related more strongly to cerebrovascular reactivity than systolic blood pressure after a CO_2 challenge test.[52] Hypertensive status has also been linked to reduced cerebrovascular reactivity in regions related to the default mode network,[53] which in turn plays a role in cognitive functioning.[54] The association between DBP and nonverbal IQ in our pediatric sample may thus be mediated by cerebrovascular reactivity.

Lower DBP seemed to be associated with lower levels of cognitive function in the adults but not the children. Several mechanisms can underlie this difference. First, blood pressure in children may be more tightly controlled, especially at lower values, than in adults.[55,56] As such, the lower end of the blood pressure distribution in children does not reach levels at which they become detrimental to the brain. Second, brains of children may better withstand low blood pressure, for instance, because of better compensatory mechanisms of the small peripheral vessels. Third, perhaps prolonged exposure to hypotension is necessary for it to impair cognitive function. Further studies are needed to confirm and explain this finding.

The association between arterial stiffness and the g-factor in elderly could be related to the SBP findings. Interestingly, the relation between SBP and arterial stiffness may in fact be bidirectional.[57,58] The former increases pulsatile aortic wall stress, leading to stretching and thus stiffening of elastic lamellae of the large arteries. Conversely, arterial stiffness has been shown to predict hypertension in mid- to late adulthood.[59–61]

The findings show statistical significance, but the question remains whether they warrant clinical implications since 1 SD change in DBP within the Generation R pediatric sample roughly translated to half of a nonverbal IQ point change. It remains to be seen whether treatment of high blood pressure in childhood would have beneficial effects on cognition later in life. Our study does underscore that the detrimental effects of blood pressure, however small those may be, might have an origin already in early life. The findings therefore give causation insights into the interplay between the vascular system and cognition during the life course. Effect sizes found in the Rotterdam Study adult sample can be interpreted more clearly, with 1 SD increase in SBP and PWV having about the same effect on the g-factor as aging half a year and 1 year, respectively. Such findings do warrant further investigation of any causal benefit of blood pressure–lowering medication and lifestyle changes on cognition.

Several limitations should be taken into account. First, the comparability of results between the cohorts is hampered because of the difference in measures of cognition. The children were tested for nonverbal IQ because of the diverse ethnic background of the children, while the g-factor did include a verbal component. In addition, the g-factor may capture other aspects of cognition that were not assessed in the children. Second, both cohorts were studied cross-sectionally, which increased the comparability between the cohorts but did not allow a clearer, developmental narrative, and also prevented any causal interpretations. In particular, the hypothesized relationship could actually be reversed, with higher levels of cognition being associated with healthier diets and lower levels of sedentary behavior.[62,63] Fourth, the determinants and

outcome were not measured in the same visit for the majority of the Rotterdam Study population. This may have led to survivor bias because of selective attrition between the visits, and potentially residual confounding because of time-dependent covariates. Finally, our cohorts do not cover the age ranges of 6 to 45 years, and the exact life course relation between the vascular and cognitive systems remains to be elucidated. However, both cohorts were recruited in the same study area and rely on similar methodologies, strengthening the comparability of the findings.

We found that blood pressure and arterial stiffness showed significant associations with cognition during mid- and late adulthood. In addition, we showed that DBP during childhood also associates with nonverbal cognition, even after excluding the top DBP decile. Thus, we have provided evidence that the associations between cognition and vascular factors hold for the general population and across the age spectrum, warranting further investigation into the exact mechanisms that govern the associations over the whole life course.

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Disclosures

None.

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