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Authors: Lyngdoh T, Viswanathan B, Kobrosly R, van Wijngaarden E, Huber B, Davidson PW, Cory-Slechta DA, Strain JJ, Myers GJ, Bovet P
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Blood pressure and cognitive function: a prospective analysis among adolescents in the Seychelles

Tanica Lyngdoh[a], **Bharathi Viswanathan**[b], **Roni Kobrosly**[c], **Edwin van Wijngaarden**[c], **Brittany Huber**[d], **Philip W. Davidson**[d], **Deborah A. Cory-Slechta**[e], **JJ Strain**[f], **Gary J. Myers**[d,e], and **Pascal Bovet**[a,b]

[a]Institute of Social and Preventive Medicine, Lausanne University Hospital, Lausanne, Switzerland [b]Ministry of Health, Section of Noncommunicable Diseases, Victoria, Republic of Seychelles [c]Department of Community and Preventive Medicine, University of Rochester Medical Center, Rochester, NY, USA [d]Department of Pediatrics, University of Rochester Medical Center, Rochester, NY, USA [e]Department of Environmental Medicine, University of Rochester Medical Center, Rochester, NY, USA [f]Northern Ireland Centre for Food and Health, University of Ulster, Coleraine, Northern Ireland, UK

Abstract

Objective—An inverse relationship between blood pressure and cognitive function has been found in adults, but limited data are available in adolescents and young adults. We examined the prospective relation between blood pressure and cognitive function in adolescence.

Methods—We examined the association between BP measured at the ages of 12–15 years in school surveys and cognitive endpoints measured in the Seychelles Child Development Study at ages 17 (n=407) and 19 (n=429) years, respectively. We evaluated multiple domains of cognition based on subtests of the Cambridge Neurological Test Automated Battery (CANTAB), the Woodcock Johnson Test of Scholastic Achievement (WJTA), the Finger Tapping test (FT) and the Kaufman Brief Intelligence Test (K-BIT). We used age-, sex- and height-specific z-scores of systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP).

Results—Six out of the 21 cognitive endpoints tested were associated with BP. However, none of these associations were found to hold for both males and females or for different subtests within the same neurodevelopmental domain or for both SBP and DBP. Most of these associations disappeared when analyses were adjusted for selected potential confounding factors such as socio-economic status, birth weight, gestational age, body mass index, alcohol consumption, blood glucose, and total n-3 and n-6 polyunsaturated fats.

Conclusions—Our findings do not support a consistent association between BP and subsequent performance on tests assessing various cognitive domains in adolescents.

Keywords

blood pressure; cognitive function; adolescents; Seychelles and prospective

CONFLICT OF INTEREST
The authors declare that they have no competing interests.

INTRODUCTION

Hypertension in adolescence is increasingly recognized as a health problem, which may affect long-term health and development. A recent narrative review mainly based on evidence from adult studies concluded that chronic hypertension in children could result in learning disabilities and deficiencies in executive function [1]. However, we are aware of only a few observational studies on the association between blood pressure (BP) and cognitive function in young persons that support this possibility [2–5]. Therefore, the relationship between cognitive function and BP in adolescence is still unclear.

As shown in a recent review [6], the association between hypertension and cognition has been well recognized and investigated for decades in adults. While the overall consensus based on cross-sectional and prospective studies is that there is a clinically significant cognitive decline with hypertension, the shape of the association has been described as linear[7–9], J-shaped [10] or U-shaped [11] in middle-aged and elderly adults. . Data from randomized controlled trials could provide convincing evidence. However, only a few trials have examined cognitive function in response to BP reduction and none was conducted among youth. While cognitive function improved in response to blood pressure lowering medication in a trial among adults over 69 years [12], a recent meta-analysis of nine placebo-controlled trials among middle-aged and elderly individuals showed no reduction in the overall risk of dementia and some differences in further sub-group analysis according to medication type [13]. Although the mechanisms relating BP to cognitive function in both adolescence and young adults are still largely unclear, in older adults both hypotension and hypertension are known to be associated with disruption in neurovascular coupling leading to decreased vascular reserve capacity, cognitive decline, and dementia [15].

Given that the association between BP and cognitive function may be modified by age, further evaluation of this relationship is needed at all ages, especially in young persons. Studying the association between BP and cognitive function in youth has the advantage of being less biased by concurrent effects of age-related co-morbid conditions and medications, which typically occur at older ages. In this study, we examined whether BP, measured at the ages of 12 and 15 years in school surveys, was associated with cognitive function assessed by a broad battery of cognitive outcomes measured at ages 17 and 19 years in the Seychelles Child Development Study (SCDS).

METHODS

Study population

The SCDS is a prospective cohort study initiated in 1989–90 to assess the association between prenatal exposure to mercury from fish consumption during pregnancy and subsequent child development. Details of this study have been previously described [16] and data showed no consistent association between pre-natal exposure to mercury and the later development in childhood of either cognitive function [17] or blood pressure [18]. The cohort represents about 50% of all births during the enrollment period. All children who were 3±1 month of age were invited to participate and those who accepted were enrolled. Of the 779 Seychellois infants originally enrolled, 705 subjects were eligible for evaluation after exclusion of 74 participants because of lack of prenatal exposure data, the presence of medical conditions that might affect development, or withdrawal from the study. Since cognitive test requires color vision, another 7 participants (total n= 698) were excluded from the analysis.

As part of the study design, the participants completed a comprehensive battery of cognitive tests assessing learning, memory, attention and academic performance at age 17 years and of

motor speed and control, verbal and non-verbal intelligence at age 19 years. Informed consent was obtained from the parents or caregivers of the participants until age 17 years and from the participants at age 19 years.

Data on BP were available from a routine school-based surveillance program of all students in the 7th and 10th grades aged 12 and 15 years respectively. The survey was conducted in all public and private schools in Seychelles under the auspices of the Ministry of Health and the Ministry of Education. We linked these school-based BP data with the cognitive outcomes assessed within the SCDS based on the national identification number that is available for all Seychelles citizens. The study protocol was approved by the human subjects review boards at both the University of Rochester, USA, and in the Republic of Seychelles.

Study procedures and measurements

Cognitive measures—At age 17 years, participants in the SCDS were evaluated using a battery of neuropsychological tests (Supplementary Table 1). These tests included the Cambridge Neurological Test Automated Battery (CANTAB), which assessed learning, attention and memory, and the Woodcock Johnson Tests of Achievement (WJTA), which assessed academic performance. At age 19 years, participants completed the Finger Tapping (FT) test which assessed motor speed and control, and the Kaufman Brief Intelligence Test (K-BIT), which assessed verbal and non-verbal intelligence. These tests have been well validated and have been used extensively in previous epidemiological studies [20, 21] and in the Seychelles participants [22, 23]. The tests were translated into the Creole language and used after having been carefully piloted [16].

Blood pressure measurements—Methods used for BP measurement within the school screening program and selected results have been described previously [24]. Briefly, BP was measured by trained school nurses in all students of all schools at ages 12 and 15 years. Readings were performed using a validated oscillometric automated device (Omron M5, Omron Healthcare Europe BV, The Netherlands). The children were in the sitting position, after a rest of at least 5 minutes, and cuff size was adapted to the arm circumference. Two BP readings were taken one minute apart at each visit and the average of the two values was computed at both 12 and 15 years of age. Z scores of both systolic BP (SBP) and diastolic BP (DBP) specific for age, sex and height were generated using standard guidelines [25]. We also generated an index for mean arterial BP (MAP) using the formula: DBP + 1/3 × (SBP-DBP)) [26].

Covariates—We adjusted analyses for variables known or presumed to be associated with BP and/or cognitive function [4, 27–30]. Covariates included birth weight, gestational age, socio-economic status, alcohol consumption (measured at age 19 years), body mass index (BMI, derived from the average of measurements made at the ages of 12 and 15 years), blood glucose (measured at age 19 years), and total n-3 and n-6 polyunsaturated fats (PUFA) (measured at age 19 years).

Information on birth weight and gestational age was available from birth records. Socioeconomic status was measured as maternal Hollingshead score obtained at age 17 years [31]. This score is based on maternal occupational and educational characteristics. The subjects alcohol consumption was determined based on the self-reported number of days with one or more drinks in the past month (none, 1–2 days and 3 days and above). Body mass index (BMI) was calculated as weight (kg) divided by height (meters) squared. Weight was measured using a precision electronic scale (Seca 870, Hamburg, Germany) and height was measured with a fixed stadiometer (Seca 208). Fasting blood glucose (FBG) was measured on venous plasma using a Glycotronic® C reflectometer (Macherey-Nagel, Düren,

Germany). We used total *n-3* (combining docosahexaenoic acid + eicosapentaenoic acid + alpha-linolenic acid) and total *n-6* (combining arachidonic acid + linoleic acid) as measures of polyunsaturated fatty acid concentration in plasma; the details of measurements have been previously described [32].

Statistical analysis

With regards to baseline variables, we calculated the mean and standard deviation (SD) for continuous variables and percentages for categorical variables. Because BP and cognitive function differ by sex, analyses were performed separately in males and in females. We used the t-test to test for differences in continuous variables between males and females and the chi-square test for categorical covariates. We used Spearman rank correlation coefficients to describe the correlations between the different subtests of cognitive function.

The main aim of this study was to examine whether BP (SBP, DBP and MAP) at aged 12–15 years was associated with i) CANTAB and WJTA outcomes at 17 years and ii) FT and K-BIT at 19 years as the dependent variables. We used z-scores for BP because normal values of BP vary by age, height and sex in children and adolescents. Hence the "crude" associations between BP and cognitive function tests are inherently adjusted for sex, age and height. Of the 698 participants of the SCDS examined around birth, data were available for 580 (83%) participants for BP at age 12–15 years; for 518(74%) /453 (65%) participants for CANTAB/WJTA at age 17 years; and for 451 (65%) participants for FT/KBIT at age 19 years. Hence, for the present analysis complete data on BP and relevant cognitive tests were available for 407 participants at age 17 years and 429 participants at age 19 years. We also carried out multivariable analyses controlling for socio-economic status, birth weight, gestational age, BMI (at age 12–15 years), alcohol consumption (at age 19 years), blood glucose (at age 19 years), total *n-3* and *n-6* (at age19 years). The proportion of missing data for the covariates ranged from 0.25% for alcohol consumption to 26.7% for socioeconomic status. The multivariable analyses utilize data on available cases. Since sex differences in the association between BP and cognition have been observed earlier [33], we included a multiplicative interaction term between sex and BP indexes in the overall models. We report the standardized regression coefficients (which express the change in the cognitive outcome corresponding to a 1 SD increase in the respective BP index) to allow direct comparison of the associations of BP indexes with different cognition tests. Regression diagnostics were performed for all the analyses and appropriate transformation was made whenever the residuals were not normally distributed. Transformations included: log transformation for intra-extra dimensional shift (IED) total trials, IED pre-ED errors, paired associate learning (PAL) total errors+1, RTI simple reaction time and rapid visual information processing (RVP) total false alarms+1; square-root transformation for spatial working memory (SWM) within errors and SWM total errors; and square transformation for letter-word identification. Further, we split the sample into participants with values above and below the 75^{th} percentile both for BP indexes and cognitive functions and ran multiple logistic regression analyses adjusting for the same co-variates. We used cutoffs of 75^{th} percentile to ensure that we had sufficient numbers in both the groups. Statistical tests were performed using Stata 11 (StataCorp, College Station, TX, USA). The significance level used for two-sided tests was $P < 0.05$. The current study involved secondary analysis of data but the selection of co-variates and the analytical models used were decided before running the analyses to minimize spurious findings when examining a large number of associations. Nonetheless, we also interpreted the findings after using the Bonferroni correction procedure to adjust for multiple hypothesis testing (i.e. by setting statistical significance of the P value at 0.001 (0.05/21 endpoints).

RESULTS

Table 1 summarizes selected demographic and clinical characteristics of the participants. Differences between males and females were observed for some of the characteristics including socio-economic status, alcohol consumption, birth weight, BMI and fasting glucose.

The distribution of BP and cognitive outcomes in the participants is presented in Table 2. Females had higher mean DBP while males had higher levels of SBP. With regards to the cognitive outcomes, very few (7 out of 21 tested) of the test scores were different between males and females. There was, however, no consistent difference between males and females in their test scores across the remaining subtests within the same cognitive domains except for FT (which only had 2 subtests).

Correlation coefficients between the different subtests of cognition ranged from 0.01 (between FT dominant hand and paired associate learning (PAL) total errors, WJTA letter-word identification and math fluency) to moderately high correlation of 0.57 (between K-BIT verbal scaled score and WJTA passage comprehension) and 0.79 (between WJTA applied problems and calculation) (Supplementary Table 2). These correlations suggest some degree of overlap between tests within and between domains of cognitive function.

The crude associations between BP z-scores and various domains of the CANTAB and WJTA subtests at 17 years of age are presented in Table 3a. On the CANTAB we found associations of paired associate learning (PAL) stages with SBP and MAP in females, rapid visual information processing (RVP) total misses with DBP, spatial working memory (SWM) with DBP and MAP in the overall sample. We did not observe any associations with the other cognitive outcomes including the academic achievement indicators.

At age 19 years, we found FT test scores in the dominant hand to be inversely associated with DBP while those in non-dominant hand to be positively associated with SBP in all participants (Table 3b).

Results were not altered after adjusting for socio-economic status, birth weight, gestational age, BMI, alcohol consumption, blood glucose, or total *n-3* and *n-6*. (Supplementary Tables 3a and 3b). There were no significant sex interactions with any model. Similarly, using logistic regression including those above and below 75th percentile (Supplementary Tables 4a and 4b) did not produce any consistent associations of BP with cognitive function and the few significant associations present were not the same as those in the linear regressions. On adjusting for multiple testing, the few significant associations that we observed in the univariate and multi-variate regressions were no longer significant.

DISCUSSION

We found no consistent evidence of an association between BP measured in early adolescence and cognitive outcomes measured in late adolescence. BP was associated with 3 of the 21 endpoints in the primary analysis, but after accounting for multiple testing there were no associations present. These associations could have been due to chance, particularly when one considers that the limited associations present were not consistent for both systolic and diastolic BP, or for both males and females, or for different subtests measuring the same neurodevelopmental domain. Therefore, our findings do not support a substantial and consistent association of BP with cognitive function in adolescence.

In older adults, several physiologic mechanisms, including atherosclerotic and hemodynamic processes, have been postulated to link BP to diminished cognitive function.

Small vessel disease is associated with impairment of cerebral blood flow and breakdown of the blood-brain barrier [34]. These hemodynamic conditions related to hypertension or even hypotension (e.g. excessive BP reduction) may induce cerebral hypoperfusion and result in disruption of neuronal activity and subsequent neurodegenerative processes characterized by white matter lesions visible with magnetic resonance imaging [35]. Studies have shown that white matter lesions are closely correlated with both hypertension [36] and poorer cognitive functions [37].

Although a role of BP on cognitive function was hypothesized in young persons [1], few studies have examined the association between BP and cognitive function in this age group. This question is relevant in view of adverse associations found among middle aged adults [38] and considering that cognitive function improved with antihypertensive treatment in middle-aged hypertensive adults [39]. A cross-sectional study conducted in a nationally-representative sample of 5077 children aged 6–16 years in the US (NHANES III) found that cognitive function (based on block design and digit span test scores of the Wechsler Intelligence Scale for Children (WISC) and the Revised-WISC) decreased as SBP (but not DBP) increased [4]. Similarly, a higher prevalence of learning disabilities (defined as a subject having a current individualized education plan) was observed among hypertensive (18%) as compared to non-hypertensive children (9%) in a small cross-sectional study of 201 children [2]. In contrast, Wharton and colleagues demonstrated that BP was associated with enhanced cognition, as measured by two visuospatial attention tasks. However, high BP was not associated with recognition memory performance in another smaller cross-sectional study of 105 participants with a mean age of 19.3 years [5]. Of note, results of cross-sectional studies may not distinguish if hypertension precedes or follows the measured outcomes. For example, emotional stress or anxiety, as a result of impaired learning skills due to cognitive impairment, could be a cause of elevated BP rather than elevated BP being a cause of cognitive impairment [40].

Hence, our findings are partly in agreement with the study of Wharton and coworkers (who observed no association between BP and memory performance) but contrast with results in the NHANES III (which found an inverse association between an intelligence test and BP). Although the NHANES III had a large sample, it assessed only intellectual function and academic performance. It is important to note that the three studies showing either positive or negative associations in youth used a cross-sectional design, while our findings are based on longitudinal data. A possible explanation for the lack of association between BP and cognition in adolescents in our study can be that some anticipated underlying mechanisms (e.g. atherosclerotic changes and other age-related co-morbidities related to hypertension) are unlikely to occur at this young age. As noted in a review, BP has to be severely elevated for end-organ damages to occur in the central nervous system of hypertensive children [41]. It is also possible that mild to moderate elevation in BP may not be enough to trigger manifestations of cognitive decline. Finally, duration of follow-up is an equally important consideration. A recent review by Elias and colleague found that relations between hypertension and cognition are more likely to be observed when the exposure to hypertension precedes the outcome by as many as 10 to 20 years [6].

The presence of an association between BP and cognition in young subjects in earlier studies may suggest that other mechanisms could underlie the development of cognitive impairment in young adults or that associations are confounded by variables other than those considered in our analyses. Increased cardiovascular or neuroendocrine reactivity and anxiety are some of the hypotheses proposed to explain the putative associations between cognition and hypertension in adolescents [42]. BP is a complex parameter and it is possible that associations between BP and intelligence could be influenced by an accumulation of experiences throughout life including birth history, dietary habits, family disruption etc. It

could follow that these factors would need to be identified and considered in analytical models. It is often difficult to assess whether BP is an independent risk factor or simply a marker of other cardio-metabolic conditions. Hence, the association between BP and cognition observed in some studies (as well as in our study) could be driven by other factors which tend to co-exist with BP. For example, BP tends to interact with type 2 diabetes with regards to cognitive function and hypertensive adults with diabetes are at greatest risk for poor cognitive performance [43]. In our study, adjusting for a number of important covariates did not alter the results.

Our study has several strengths including a fairly large sample size relative to most previous studies in adolescents and adults, a detailed assessment of cognitive and academic tests, a prospective design and information on a number of covariates known to influence the associations. Our study also has some limitations. Firstly, the precision of our BP measurements is limited since we relied on only 2 readings of BP at each of two visits at age 12 years and age 15 years (hence a total of 4 readings). However, the correlation between BP at age 12 years and age 15 years (r=0.35 and 0.31 for SBP and DBP respectively) was good and similar to other studies with the same length of follow-up [44], suggesting that BP was adequately assessed in our study. Secondly, we used US references to assess age-, sex- and height-adjusted BP. While these z-scores may need to be calibrated before they are used in other populations, the ranking of BP among children is likely to be unaffected and the associations we found with outcomes are likely to be valid. Thirdly, there has been some attrition in the SCDS cohort with participation of 58% at age 17 and 61% at age 19 from the initial cohort examined at birth. The reduction in the sample size is mainly due to two reasons. Firstly, attrition could have arisen due to the long follow up of the SCDS cohort (at age 17–19 years), possibly limited motivation of adolescents to participate in follow up examinations (which could last up to two consecutive days), and possible unwillingness to give blood (at age 19 years). Secondly, we used data on BP from a school-based surveillance program conducted at age 12–15 years. In this routine school-based screening program, students who were not present on the survey day were generally not traced and the screening may not have been performed in some classes due to limited manpower. However, there was no significant difference in baseline characteristics including birth weight, gestational age, socio-economic status and clinical characteristics including BMI, glucose, total *n-3* and *n-6* measured at 19 years between subjects included and not included in the analysis (data not shown), which suggests that our estimates are not biased because of missing data. Future studies with a larger sample size, larger number of BP measurements including ambulatory BP monitoring and more covariates assessed through the life course may be needed to unravel the contribution and combinations of the many complex parameters that impact cognitive function. Similarly, further analysis based on changes of both exposure and outcome over time could provide additional insight to disentangle the effect of BP on cognitive outcomes while analysis of changes in cognitive outcomes in relation to BP lowering treatment in youth would provide more definite answers.

In conclusion, our findings do not support a consistent association between BP and cognitive function during adolescence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Reference List

1. Sharma M, Kupferman JC, Brosgol Y, Paterno K, Goodman S, Prohovnik I, et al. The effects of hypertension on the paediatric brain: a justifiable concern. Lancet neurology. 2010 Sep; 9(9):933–940. [PubMed: 20675195]
2. Adams HR, Szilagyi PG, Gebhardt L, Lande MB. Learning and attention problems among children with pediatric primary hypertension. Pediatrics. 2010 Dec; 126(6):e1425–e1429. [PubMed: 21059718]
3. Lande MB, Adams H, Falkner B, Waldstein SR, Schwartz GJ, Szilagyi PG, et al. Parental assessments of internalizing and externalizing behavior and executive function in children with primary hypertension. The Journal of pediatrics. 2009 Feb; 154(2):207–212. [PubMed: 18823913]
4. Lande MB, Kaczorowski JM, Auinger P, Schwartz GJ, Weitzman M. Elevated blood pressure and decreased cognitive function among school-age children and adolescents in the United States. The Journal of pediatrics. 2003 Dec; 143(6):720–724. [PubMed: 14657815]
5. Wharton W, Hirshman E, Merritt P, Stangl B, Scanlin K, Krieger L. Lower blood pressure correlates with poorer performance on visuospatial attention tasks in younger individuals. Biological psychology. 2006 Oct; 73(3):227–234. [PubMed: 16701935]
6. Elias MF, Goodell AL, Dore GA. Hypertension and cognitive functioning: a perspective in historical context. Hypertension. 2012 Aug; 60(2):260–268. [PubMed: 22753214]
7. Knopman DS, Mosley TH, Catellier DJ, Coker LH. Atherosclerosis Risk in Communities Study Brain MRIS. Fourteen-year longitudinal study of vascular risk factors, APOE genotype, and cognition: the ARIC MRI Study. Alzheimer's & dementia : the journal of the Alzheimer's Association. 2009 May; 5(3):207–214.
8. Starr JM, Whalley LJ, Inch S, Shering PA. Blood pressure and cognitive function in healthy old people. Journal of the American Geriatrics Society. 1993 Jul; 41(7):753–756. [PubMed: 8315187]
9. Swan GE, Carmelli D, Larue A. Systolic blood pressure tracking over 25 to 30 years and cognitive performance in older adults. Stroke; a journal of cerebral circulation. 1998 Nov; 29(11):2334–2340.
10. Waldstein SR, Giggey PP, Thayer JF, Zonderman AB. Nonlinear relations of blood pressure to cognitive function: the Baltimore Longitudinal Study of Aging. Hypertension. 2005 Mar; 45(3): 374–379. [PubMed: 15699446]
11. Bohannon AD, Fillenbaum GG, Pieper CF, Hanlon JT, Blazer DG. Relationship of race/ethnicity and blood pressure to change in cognitive function. Journal of the American Geriatrics Society. 2002 Mar; 50(3):424–429. [PubMed: 11943035]
12. Starr JM, Whalley LJ, Deary IJ. The effects of antihypertensive treatment on cognitive function: results from the HOPE study. Journal of the American Geriatrics Society. 1996 Apr; 44(4):411–415. [PubMed: 8636587]
13. Staessen JA, Thijs L, Richart T, Odili AN, Birkenhager WH. Placebo-controlled trials of blood pressure-lowering therapies for primary prevention of dementia. Hypertension. 2011 Feb; 57(2):e6–e7. [PubMed: 21189407]
14. Arvanitakis Z, Leurgans SE, Barnes LL, Bennett DA, Schneider JA. Microinfarct pathology, dementia, and cognitive systems. Stroke; a journal of cerebral circulation. 2011 Mar; 42(3):722–727.
15. Novak V, Hajjar I. The relationship between blood pressure and cognitive function. Nature reviews Cardiology. 2010 Dec; 7(12):686–698.
16. Marsh DO, Clarkson TW, Myers GJ, Davidson PW, Cox C, Cernichiari E, et al. The Seychelles study of fetal methylmercury exposure and child development: introduction. Neurotoxicology. 1995 Winter;16(4):583–596. [PubMed: 8714865]
17. Davidson PW, Cory-Slechta DA, Thurston SW, Huang LS, Shamlaye CF, Gunzler D, et al. Fish consumption and prenatal methylmercury exposure: cognitive and behavioral outcomes in the main cohort at 17 years from the Seychelles child development study. Neurotoxicology. 2011 Dec; 32(6):711–717. [PubMed: 21889535]

18. Thurston SW, Bovet P, Myers GJ, Davidson PW, Georger LA, Shamlaye C, et al. Does prenatal methylmercury exposure from fish consumption affect blood pressure in childhood? Neurotoxicology. 2007 Sep; 28(5):924–930. [PubMed: 17659343]
19. Davidson PW, Strain JJ, Myers GJ, Thurston SW, Bonham MP, Shamlaye CF, et al. Neurodevelopmental effects of maternal nutritional status and exposure to methylmercury from eating fish during pregnancy. Neurotoxicology. 2008 Sep; 29(5):767–775. [PubMed: 18590763]
20. Luciana M. Practitioner review: computerized assessment of neuropsychological function in children: clinical and research applications of the Cambridge Neuropsychological Testing Automated Battery (CANTAB). Journal of child psychology and psychiatry, and allied disciplines. 2003 Jul; 44(5):649–663.
21. Woodcock RW, McGrew KS, Mather N. Woodcock-Johnson III Tests of Achievement Itasca. 2001
22. Kobrosly RW, van Wijngaarden E, Galea S, Cory-Slechta DA, Love T, Hong C, et al. Socioeconomic position and cognitive function in the Seychelles: a life course analysis. Neuroepidemiology. 2011; 36(3):162–168. [PubMed: 21508650]
23. Myers GJ, Davidson PW, Cox C, Shamlaye CF, Palumbo D, Cernichiari E, et al. Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study. Lancet. 2003 May 17; 361(9370):1686–1692. [PubMed: 12767734]
24. Chiolero A, Paradis G, Madeleine G, Hanley JA, Paccaud F, Bovet P. Birth weight, weight change, and blood pressure during childhood and adolescence: a school-based multiple cohort study. Journal of hypertension. 2011 Oct; 29(10):1871–1879. [PubMed: 21881523]
25. National High Blood Pressure Education Program Working Group on High Blood Pressure in C, Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics. 2004 Aug; 114(2 Suppl 4th Report):555–576. [PubMed: 15286277]
26. Vander, AJ. Human Physiology: The Mechanisms of Body Function. 5th ed.. New York: McGraw-Hill, Inc.; 1990.
27. Johnson KC, Margolis KL, Espeland MA, Colenda CC, Fillit H, Manson JE, et al. A prospective study of the effect of hypertension and baseline blood pressure on cognitive decline and dementia in postmenopausal women: the Women's Health Initiative Memory Study. Journal of the American Geriatrics Society. 2008 Aug; 56(8):1449–1458. [PubMed: 18637980]
28. Molander L, Gustafson Y, Lovheim H. Low blood pressure is associated with cognitive impairment in very old people. Dementia and geriatric cognitive disorders. 2010; 29(4):335–341. [PubMed: 20389075]
29. Tsivgoulis G, Alexandrov AV, Wadley VG, Unverzagt FW, Go RC, Moy CS, et al. Association of higher diastolic blood pressure levels with cognitive impairment. Neurology. 2009 Aug 25; 73(8): 589–595. [PubMed: 19704077]
30. Strain JJ, Davidson PW, Thurston SW, Harrington D, Mulhern MS, McAfee AJ, et al. Maternal PUFA Status but Not Prenatal Methylmercury Exposure Is Associated with Children's Language Functions at Age Five Years in the Seychelles. The Journal of nutrition. 2012 Nov; 142(11):1943–1949. [PubMed: 23014496]
31. Hollingshead, AB. Four factor index of social status. New Haven: Department of Sociology, Yale University; 1975.
32. Strain JJ, Davidson PW, Bonham MP, Duffy EM, Stokes-Riner A, Thurston SW, et al. Associations of maternal long-chain polyunsaturated fatty acids, methyl mercury, and infant development in the Seychelles Child Development Nutrition Study. Neurotoxicology. 2008 Sep; 29(5):776–782. [PubMed: 18590765]
33. Waldstein SR, Katzel LI. Gender differences in the relation of hypertension to cognitive function in older adults. Neurological research. 2004 Jul; 26(5):502–506. [PubMed: 15265267]
34. Manolio TA, Olson J, Longstreth WT. Hypertension and cognitive function: pathophysiologic effects of hypertension on the brain. Current hypertension reports. 2003 Jun; 5(3):255–261. [PubMed: 12724059]

35. van Dijk EJ, Breteler MM, Schmidt R, Berger K, Nilsson LG, Oudkerk M, et al. The association between blood pressure, hypertension, and cerebral white matter lesions: cardiovascular determinants of dementia study. Hypertension. 2004 Nov; 44(5):625–630. [PubMed: 15466662]

36. Liao D, Cooper L, Cai J, Toole J, Bryan N, Burke G, et al. The prevalence and severity of white matter lesions, their relationship with age, ethnicity, gender, and cardiovascular disease risk factors: the ARIC Study. Neuroepidemiology. 1997; 16(3):149–162. [PubMed: 9159770]

37. Breteler MM, van Swieten JC, Bots ML, Grobbee DE, Claus JJ, van den Hout JH, et al. Cerebral white matter lesions, vascular risk factors, and cognitive function in a population-based study: the Rotterdam Study. Neurology. 1994 Jul; 44(7):1246–1252. [PubMed: 8035924]

38. Launer LJ, Masaki K, Petrovitch H, Foley D, Havlik RJ. The association between midlife blood pressure levels and late-life cognitive function. The Honolulu-Asia Aging Study. JAMA : the journal of the American Medical Association. 1995 Dec 20; 274(23):1846–1851. [PubMed: 7500533]

39. Miller RE, Shapiro AP, King HE, Ginchereau EH, Hosutt JA. Effect of antihypertensive treatment on the behavioral consequences of elevated blood pressure. Hypertension. 1984 Mar-Apr;6(2 Pt 1):202–208. [PubMed: 6724662]

40. Waldstein SR, Manuck SB, Ryan CM, Muldoon MF. Neuropsychological correlates of hypertension: review and methodologic considerations. Psychological bulletin. 1991 Nov; 110(3): 451–468. [PubMed: 1758919]

41. Belsha CW. Ambulatory blood pressure monitoring and hypertensive target-organ damage in children. Blood pressure monitoring. 1999 Jun-Aug;4(3–4):161–164. [PubMed: 10610241]

42. Elias MF, Elias PK. Hypertension affects neurobehavioral functioning: so what's new? Psychosomatic medicine. 1993 Jan-Feb;55(1):51–54. [PubMed: 8446741]

43. Elias PK, Elias MF, D'Agostino RB, Cupples LA, Wilson PW, Silbershatz H, et al. NIDDM and blood pressure as risk factors for poor cognitive performance. The Framingham Study. Diabetes care. 1997 Sep; 20(9):1388–1395. [PubMed: 9283785]

44. Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. Circulation. 2008 Jun 24; 117(25):3171–3180. [PubMed: 18559702]

Table 1

Distribution of selected characteristics among participants

	Overall (N=407)		Male (N=187)		Female (N=220)		P-value
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Socio-economic status[§]	29.72	16.08	31.99	15.10	27.72	16.69	**0.022**
Alcohol intake (days per month)[*]							
None	27.33		14.94		37.37		**<0.001**
1–2	35.76		31.17		39.47		
≥3	36.92		53.90		23.16		
Birth weight (kg)	3.17	0.49	3.24	0.50	3.10	0.47	**0.004**
Gestational age (weeks)	39.68	1.08	39.76	1.17	39.61	0.99	0.163
BMI [at 12 years](kg/m^2)	19.14	3.86	18.81	3.70	19.41	3.97	0.116
BMI [at 15 years](kg/m^2)	20.64	3.71	20.05	2.94	21.14	4.20	**0.003**
Fasting glucose (mmol/L)	5.04	0.55	5.19	0.57	4.93	0.50	**<0.001**
n-3 (DHA,EPA,ALA mg/ml)	0.05	0.02	0.05	0.01	0.04	0.02	0.732
n-6 (AA,LA mg/ml)	0.15	0.05	0.16	0.05	0.15	0.04	0.195

BMI=body mass index; *n*-3= omega-3 fatty acids; DHA= docosahexaenoic acid; EPA= eicosapentaenoic acid; ALA= alpha-linolenic acid; *n*-6=omega-6 fatty acids; AA= arachidonic acid; and LA= linoleic acid.

[§]Socio-economic status based on maternal Hollingshead score.

[*]Results presented as percentages.

Between-group comparisons by t-test or chi-square test.

Table 2

Summary statistics for blood pressure indexes and cognitive outcomes

	Overall		Male		Female		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Blood pressure (mmHg)							
			Age 12–15 years				
N	566		262		304		
SBP	107.67	9.60	108.99	10.12	106.55	9.00	**0.011**
DBP	66.98	6.99	65.64	7.10	68.12	6.71	**<0.001**
MAP	80.55	7.10	80.09	7.40	80.93	6.83	0.238
			Age 17 years				
N	407		187		220		
CANTAB learning/reverse learning							
IED total trials* ↓	125.61	48.49	120.10	41.89	130.29	53.11	**0.039**
IED pre-ED errors* ↓	10.23	6.77	9.75	6.05	10.65	7.32	0.277
PAL total errors + 1* ↓	11.38	13.35	11.73	16.58	11.09	9.84	0.627
PAL stages completed ↑	5.99	0.91	6.00	0.92	5.98	0.90	0.802
CANTAB attention							
RTI simple reaction time*§	177.54	103.26	163.72	104.80	189.28	100.69	**0.004**
RVP total misses ↓	14.15	5.06	13.87	5.29	14.39	4.86	0.307
RVP total false alarms + 1* ↓	3.99	5.91	3.50	3.57	4.40	7.32	0.197
CANTAB memory							
DMS, % correct (12,000-ms delay) ↑	77.52	15.46	78.18	15.45	76.95	15.48	0.425
PRM, % correct ↑	85.96	10.81	87.68	10.09	84.51	11.19	**0.003**
SRM, % correct ↑	81.20	10.39	82.03	9.79	80.50	10.85	0.139
SWM within errors* ↓	2.00	3.52	1.91	3.42	2.08	3.61	0.426
SWM total errors* ↓	27.13	16.46	26.20	16.70	27.92	16.25	0.262
WJTA							
Passage comprehension ↑	76.62	17.78	75.02	19.51	77.98	16.09	0.094
Calculation ↑	85.28	14.85	84.48	15.72	85.96	14.06	0.316

	Overall		Male		Female		
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Letter-word identification* ↑	101.68	23.96	98.47	26.68	104.41	21.07	**0.025**
Applied problems ↑	85.92	12.94	86.19	13.82	85.69	12.17	0.695
Math fluency ↑	74.03	11.49	71.39	10.55	76.27	11.80	**<0.001**
			Age 19 years				
N	429		182		247		
Finger Tapping(FT)							
Dominant hand ↑	46.12	6.20	48.72	6.14	44.20	5.52	**<0.001**
Non-dominant hand ↑	40.95	5.67	43.74	5.17	38.89	5.12	**<0.001**
K-BIT							
Verbal scaled score ↑	12.83	2.42	12.77	2.43	12.87	2.41	0.699
Matrices standard score ↑	103.31	17.19	102.87	19.01	103.64	15.75	0.645

SBP=systolic blood pressure; DBP= diastolic blood pressure; MAP= mean arterial pressure; IED= intra-extra dimensional shift; PAL= paired associate learning; RTI=simple reaction time; RVP= rapid visual information processing; DMS= delayed match to sample; PRM=pattern recognition memory; SRM=spatial recognition memory; SWM= spatial working memory; CANTAB=Cambridge Neurological Test Automated Battery; and WJTA= Woodcock Johnson Tests of Achievement; K-BIT= Kaufman Brief Intelligence Test.

*t-test performed after appropriate transformation.

Arrows indicate direction of better performance

§RTI scores indicate response speed and not necessarily better or worse

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Table 3

a: Univariate associations between blood pressure indexes z-scores and Cambridge Neurological Test Automated Battery (CANTAB) and Woodcock Johnson Tests of Achievement (WJTA) outcomes

	SBP			DBP			MAP		
	Overall	***Male***	***Female***	***Overall***	***Male***	***Female***	***Overall***	***Male***	***Female***
CANTAB									
CANTAB learning/reverse learning									
log (IED total trials)	−0.05	−0.06	−0.03	0.02	−0.05	0.05	−0.01	−0.06	0.02
log (IED pre-ED errors)	−0.09	−0.08	−0.10	−0.09	−0.13	−0.06	−0.10	−0.12	−0.08
log (PAL total errors + 1)	0.09	0.05	0.12	0.09	0.09	0.09	0.10	0.08	0.11
PAL stages completed	−0.07	0.01	**−0.14***	−0.08	−0.04	−0.12	−0.08	−0.02	**−0.14***
CANTAB attention									
log (RTI simple reaction time)	0.04	0.05	0.03	0.04	0.01	0.05	0.05	0.04	0.04
RVP total misses	0.04	−0.01	0.09	**0.11***	0.08	0.13	0.09	0.05	0.12
log (RVP total false alarms + 1)	−0.09	−0.09	−0.09	0.02	0.05	−0.01	−0.03	−0.01	−0.05
CANTAB memory									
DMS, % correct (12,000-ms delay)	0.04	0.02	0.06	−0.08	−0.09	−0.07	−0.03	−0.05	−0.02
PRM, % correct	0.03	0.00	0.04	−0.02	−0.01	−0.01	0.00	−0.01	0.01
SRM, % correct	0.01	0.04	−0.02	−0.04	−0.06	−0.01	−0.02	−0.02	−0.02
Sqrt (SWM within errors)	0.09	0.13	0.05	**0.12***	0.14	0.09	**0.11***	**0.15***	0.08
Sqrt (SWM total errors)	0.04	0.06	0.02	0.10	**0.16***	0.03	0.08	0.13	0.03
WJTA									
Passage comprehension	0.02	0.03	0.01	−0.01	0.00	−0.03	0.00	0.01	−0.01
Calculation	0.00	0.04	−0.03	−0.04	−0.03	−0.06	−0.02	0.00	−0.05
Square(Letter-word identification)	−0.01	0.02	−0.03	0.03	0.04	0.00	0.02	0.03	−0.02
Applied problems	0.01	0.04	−0.03	−0.07	−0.04	−0.11	−0.04	0.00	−0.08
Math fluency	0.08	0.13	0.06	0.02	0.02	−0.01	0.05	0.08	0.02

b: Univariate associations between blood pressure indexes and Finger Tapping (FT) and Kaufman Brief Intelligence Test (K-BIT) outcomes

	SBP			DBP			MAP		
	Overall	***Male***	***Female***	***Overall***	***Male***	***Female***	***Overall***	***Male***	***Female***
Finger Tapping(FT)									
Dominant hand	0.07	0.12	0.01	**−0.10***	−0.01	−0.12	−0.03	0.05	−0.07
Non-dominant hand	**0.14****	0.10	**0.15***	−0.02	−0.01	0.04	0.05	0.05	0.10
K-BIT									
Verbal scaled score	0.05	0.01	0.09	0.02	0.08	−0.01	0.04	0.05	0.03
Matrices standard score	0.01	0.01	0.02	0.00	0.02	−0.02	0.01	0.02	0.00

Abbreviations as in Table 2. Results are expressed as standardized regression coefficients. Tot=total (N=407), M=males (N=187) & F=females (N=220).

* $P < 0.05$;

** $P < 0.01$

Results are expressed as standardized regression coefficients. Tot=total (N=407), M=males (N=187) & F=females (N=220).

* $P < 0.05$;

** $P < 0.01$