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Cardiovascular Risk Factors From Childhood and Midlife Cognitive Performance

The Young Finns Study

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ABSTRACT

BACKGROUND In adults, high blood pressure (BP), adverse serum lipids, and smoking associate with cognitive deficits. The effects of these risk factors from childhood on midlife cognitive performance are unknown.

OBJECTIVES This study sought to investigate the associations between childhood/adolescence cardiovascular risk factors and midlife cognitive performance.

METHODS From 1980, a population-based cohort of 3,596 children (baseline age: 3 to 18 years) have been followed for 31 years in 3- to 9-year intervals. BP, serum lipids, body mass index, and smoking were assessed in all follow-ups. Cumulative exposure as the area under the curve for each risk factor was determined in childhood (6 to 12 years), adolescence (12 to 18 years), and young adulthood (18 to 24 years). In 2011, cognitive testing was performed in 2,026 participants aged 34 to 49 years.

RESULTS High systolic BP, elevated serum total-cholesterol, and smoking from childhood were independently associated with worse midlife cognitive performance, especially memory and learning. The number of early life risk factors, including high levels (extreme 75th percentile for cumulative risk exposure between ages 6 and 24 years) of systolic BP, total-cholesterol, and smoking associated inversely with midlife visual and episodic memory and visuospatial associative learning (-0.140 standard deviations per risk factor, $p < 0.0001$) and remained significant after adjustment for contemporaneous risk factors. Individuals with all risk factors within recommended levels between ages 6 and 24 years performed 0.29 standard deviations better ($p = 0.006$) on this cognitive domain than those exceeding all risk factor guidelines at least twice. This difference corresponds to the effect of 6 years aging on this cognitive domain.

CONCLUSIONS Cumulative burden of cardiovascular risk factors from childhood/adolescence associate with worse midlife cognitive performance independent of adulthood exposure. (J Am Coll Cardiol 2017;69:2279-89)
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ABBREVIATIONS AND ACRONYMS

ApoE = apolipoprotein E

AUC = area under the curve

BMI = body mass index

BP = blood pressure

LDL = low-density lipoprotein

PAL = paired-associates learning test

RVP = rapid visual information processing test

SD = standard deviation

SE = standard error

Epidemiological evidence indicates that exposure to midlife high blood pressure (BP), adverse serum lipids, and smoking are associated with cognitive decline later in life (1–4). Studies in animal models have observed associations between these risk factors and cognitive performance. Spontaneously hypertensive rats show cognitive decline compared with normotensive strains (5). In rodents (6,7), the high-fat diet-induced hypercholesterolemia leads to memory deficits. In addition, adolescent rats exposed to nicotine show long-lasting cognitive deficits (8). Although the mechanisms underlying these associations are largely unclear, experimental studies have suggested that cardiovascular risk factors may damage both neuronal and vascular tissues of the brain. Studies in rodents have shown that hypertension may alter cerebral vasculature and eventually lead to restrained function of the blood-brain barrier (9). Moreover, experiments on rodents have indicated that diet-induced hypercholesterolemia may influence the expression of genes in the brain relevant for cellular mechanisms for learning, memory, and neurodegeneration (10). Simultaneously, experiments on rodent and rabbit brains have shown evidence that hypercholesterolemia may induce inflammatory changes (6,7,11) that are associated with disturbed beta-amyloid metabolism (6,7,11). Furthermore, experimental evidence on rodent brains has suggested that smoking exposure may induce oxidative stress (12–14), which may trigger cerebral inflammatory changes (12) and lead to neuropathological changes, such as accumulation of beta-amyloid peptide and phosphorylation of tau protein, related to cognitive decline (13).

SEE PAGE 2290

It is therefore plausible that exposure to cardiovascular risk factors in early life may affect later cognitive performance. In support of this hypothesis, a link between cumulative burden of young adulthood cardiovascular risk factors and cognitive performance was shown in young and middle-age adults in the CARDIA (Coronary Artery Risk Development in Young Adults) cohort (15). Whether a similar link exists between early life risk exposure and adulthood cognitive function is unknown. We sought to address this knowledge gap in the YFS (Cardiovascular Risk in Young Finns Study), which has followed a population-based sample of individuals from childhood to adulthood. As a part of the 31-year follow-up study, cognitive testing was performed using a test battery focusing on several cognitive domains that are related to brain structures typically affected in the early stages of cognitive decline (16). We hypothesized that a greater burden of cardiovascular risk factors in childhood, adolescence, and young adulthood, including repeatedly assessed BP, serum lipids, and smoking, are associated with worse cognitive performance in midlife.

METHODS

POPULATION. This analysis is a part of the YFS, which is an ongoing longitudinal population-based study on cardiovascular risk factors from childhood to adulthood. The first cross-sectional study included 3,596 randomly selected children and adolescents (boys and girls; ages 3, 6, 9, 12, 15, and 18 years) and was performed in 1980. The cohort has been followed in regular intervals in 1983, 1986, 1989, 2001, and 2007; the latest follow-up study was conducted in 2011. Detailed information on the population and protocol is reported elsewhere (17).

PROCEDURES AND MEASUREMENTS. Outcome measure cognition. In 2011, a computerized cognitive testing battery (CANTAB, Cambridge Cognition, Cambridge, United Kingdom) was used to assess cognitive performance in 2,026 participants. The YFS test battery included: 1) motor screening test used as a training/screening tool to indicate difficulties in test execution; 2) paired-associates learning (PAL) test measured visual and episodic memory and visuospatial associative learning; 3) spatial working memory test measured short-term and spatial working memory and problem solving; 4) reaction time test measured reaction and movement speed and attention; and 5) rapid visual information test (RVP) measured visual processing, recognition, and sustained attention.

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Each test produced several variables. Principal component analysis was conducted to identify components accounting for the majority of the variation within the dataset. Principal components were created for each test for performance in specific cognitive domains. The motor screening test component was excluded from further analyses because of the ceiling effect (i.e., all participants had the maximum score in this test). Other components were normalized using a rank order normalization procedure resulting in 4 variables, each with mean 0 and standard deviation (SD) 1. All available data for each cognitive test were used in the analyses; therefore, the number of participants varies between the models (n = 177 were excluded because of technical reasons in some of the test domains and n = 51 refused to participate in all or some of the tests). Detailed description and validation of the cognitive data have been reported previously (18).

Exposure variables BP, serum lipids, body mass index, and smoking. Standard methods were used for measuring BP, serum total-cholesterol, high-density lipoprotein cholesterol, and triglycerides at baseline and all follow-up studies. Low-density lipoprotein (LDL) cholesterol was calculated according to Friedewald (19). Details of these methods have been described previously (20). At all study phases, the participants' weight and height were measured and body mass index (BMI) was calculated. To use all available repeatedly measured exposure data for continuous variables, we estimated subject-specific curves for cardiovascular risk factors by mixed model regression splines (21). The area under the curve (AUC) for continuous risk variables was evaluated to indicate a long-term burden of each measured attribute (22). The AUC variables were defined separately for childhood (6 to 12 years), adolescence (12 to 18 years), young adulthood (18 to 24 years), and early life (6 to 24 years). For interpretability, the AUC variables were standardized resulting in variables with mean 0 and SD 1. Smoking exposure was queried throughout the follow-up time. Smoking status was dichotomized into daily smokers and nonsmokers, defined as current daily smoking (yes/no) at the baseline or at any of follow-up studies when the participants were age 12 to 24 years.

In addition to studying the associations using continuous AUC variables and the dichotomized smoking variable, the combined effect of several risk factors from childhood to young adulthood on midlife cognitive performance was analyzed. For that purpose, a 3-level variable indicating the number of cardiovascular risk factors during early life (6 to 24 years) was created (1 = no risk factors, 2 = 1 risk factor, 3 = 2 or 3 risk factors) including the variables that showed significant association with cognitive performance in the multivariate analyses (i.e., systolic BP, serum total-cholesterol, and smoking). To define risk factors using the continuous AUC variables, the distributions of BP and serum total-cholesterol were dichotomized into high (≥75th percentile) and low (<75th percentile) risk factor levels (sensitivity analyses were additionally performed by using cutpoints of 70th, 80th, and 85th percentiles). Such dichotomized variables and the binary smoking variable were summed to create the variable indicating the number of risk factors (range: 0 to 3) during early life. The age- and sex-specific mean values of systolic BP, total- and LDL-cholesterol corresponding to the highest 75th percentile of the AUC variables between ages 6 and 24 years are presented in Online Table 1. A similar variable indicating the number of midlife risk factors at the time of cognitive testing was constructed. Current midlife daily smoking was queried at the time of cognitive testing and categorized as nonsmokers versus daily smokers.

In addition to the arbitrarily selected risk factor cutpoints, we examined whether the effect of early life risk exposure is attributable to levels of risk factors repeatedly exceeding the recommended guidelines. The age- and sex-specific cutpoints were considered for variables showing significant effect for cognitive performance in the multivariate analyses (i.e., systolic BP (23), LDL-cholesterol (24), and smoking (25). The exact cutpoints for these risk factors are presented in Online Table 2. The participants were classified into: 1) no risk factor levels exceeding guidelines or levels exceeding at most once per risk factor; 2) risk factor levels exceeding guidelines on 1 risk factor at least twice; 3) risk factor levels exceeding guidelines at least twice on 2 risk factors; 4) risk factor levels exceeding guidelines at least twice on all risk factors.

Covariates. The following primary covariates were used in the analyses: age, sex, baseline household income, antihypertensive and dyslipidemia medication, and diagnoses of cardiovascular diseases and type 1 and 2 diabetes mellitus. Altogether, 1,901 individuals with cognitive test data had complete data on exposure variables and primary covariates. Age was defined in full years at the end of the year 2011. Baseline household income, use of antihypertensive (n = 192) or dyslipidemia (n = 72) medication, and type 1 diabetes diagnoses (n = 12) were queried. Participants were classified as having type 2 diabetes based on self-reported and register-confirmed diagnosis, self-reported glucose-lowering medication, or abnormal

plasma glucose or hemoglobin A1c values (n = 75). Diagnoses of cardiovascular diseases (n = 13) were adjudicated from the National Hospital Discharge register. Additionally, data on the following covariates were available for restricted numbers of participants, and were therefore used in additional analyses: childhood academic performance (n = 1,684), adulthood education (n = 1,894), apolipoprotein E (apoE) genotype (n = 1,803), and adulthood physical activity (n = 1,884). Childhood academic performance expressed as grade point average (i.e., mean of grades in all individual school subjects at baseline or either of the 2 subsequent follow-ups for those participants who were not of school age at baseline) was queried and used as a proxy for childhood cognitive ability. Adulthood education was assessed with questionnaires at the follow-up studies in 2001, 2007, and 2011. The maximum years of education was determined as a continuous variable from self-reported data concerning total years of education. ApoE genotypes were analyzed with standard methods, and individuals were divided into apoEε4 carriers (≥1 ε4 allele) and noncarriers (no ε4 alleles). Physical activity was queried and the level of physical activity was calculated as the mean of the adulthood (ages 24 to 49 years) physical activity indexes (range: 5 to 15). Detailed description of the covariates is presented in the Online Appendix.

STATISTICAL ANALYSES. Student *t* test was applied for continuous variables and chi-square test for categorical variables. Linear regression analyses were conducted to examine the associations between childhood/adolescence/young adulthood cardiovascular risk factors and midlife cognitive performance. First, age- and sex-adjusted regression analyses were conducted separately for cumulative burden of each cardiovascular risk factor in childhood, adolescence, and young adulthood using each cognitive domain as outcome. After that, family income, antihypertension and dyslipidemia medication, and diagnoses of cardiovascular diseases and diabetes mellitus were entered as covariates in these analyses.

Second, further analyses were conducted for visual and episodic memory and visuospatial associative learning (PAL test), which was the cognitive domain showing most consistent results in the analyses separately for each early life cardiovascular risk factors. These analyses were conducted first unadjusted, and then entering age and sex as covariates. After that, all early life cardiovascular risk factors were entered in the same age- and sex-adjusted model. Then, the analyses were additionally adjusted for family income, antihypertension and dyslipidemia medication, and diagnoses of cardiovascular diseases and diabetes mellitus. Because of high intercorrelation (r = 0.94) between total- and LDL-cholesterol, these variables showed essentially similar relations with the cognitive domains and were not considered simultaneously in the multivariable models. Finally, all analyses were further adjusted for childhood academic performance, adulthood education, apoEε4, and adulthood physical activity. Additionally, we tested the possible effect modification caused by sex or age on the associations between cardiovascular risk factors and performance on those cognitive domains that showed significant results in the multivariate models. The possible effect modification was analyzed by adding interaction terms in the fully adjusted multivariate models. No significant interactions were found (data not shown). All statistical analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, North Carolina) and $p < 0.05$ as the level of significance. Detailed description of all statistical methods is presented in the Online Appendix.

RESULTS

CHARACTERISTICS OF THE POPULATION. The characteristics of the study population and numbers of participants in each separate cognitive test are shown in Online Table 3. The representativeness of the study population participating in the cognitive testing was examined by comparing the baseline differences between participants and nonparticipants (Online Table 4). Participants were more often women and older than nonparticipants. In addition, they originated from families with higher income and had better childhood academic performance. No differences were observed in the exposure variables.

Cardiovascular risk factors in childhood, adolescence, and young adulthood. Associations between childhood (age 6 to 12 years), adolescence (age 12 to 18 years), and young adulthood (age 18 to 24 years) cardiovascular risk factors and midlife cognitive performance are shown in Online Table 5. The consistent finding was that elevated systolic BP and adverse lipids (high total- or LDL-cholesterol) in childhood, adolescence, and young adulthood, as well as cigarette smoking in adolescence and young adulthood, associated systematically with lower midlife visual and episodic memory and visuospatial associative learning (PAL test) (Online Table 5). In general, the effect estimates of cardiovascular risk factors for the PAL test were similar across all exposure age categories. Additionally, we found some links of serum total-cholesterol, triglycerides,

TABLE 1 Performance in the PAL Test, Estimated Difference in Cognitive Age, and Mean Values of Risk Factor Variables Across the Early Life Cumulative Cardiovascular Risk Factor Burden

Early Life Risk Factor Burden (Between Ages 6 and 24 yrs)	N	PAL Test	Difference in *Cognitive Age**	Age 6–9 yrs	Age 12–15 yrs	Age 18–24 yrs
					Systolic BP	
The AUC variable for systolic BP						
First quartile	462	0.21 ± 1.00	Ref.	101.8 ± 6.1	102.9 ± 6.3	107.1 ± 7.4
Second quartile	461	0.09 ± 0.99	+2.4 yrs	108.3 ± 6.0	110.0 ± 5.4	114.9 ± 6.1
Third quartile	462	-0.09 ± 0.98	+6.0 yrs	111.1 ± 6.3	115.3 ± 5.5	122.6 ± 5.9
Fourth quartile	463	-0.21 ± 0.98	+8.4 yrs	117.5 ± 6.8	124.3 ± 8.1	132.6 ± 8.4
					Serum Total-Cholesterol	
The AUC variable for serum total-cholesterol						
First quartile	462	0.16 ± 0.96	Ref.	4.7 ± 0.5	4.1 ± 0.5	3.9 ± 0.5
Second quartile	461	-0.02 ± 0.98	+3.6 yrs	5.3 ± 0.4	4.8 ± 0.4	4.6 ± 0.4
Third quartile	462	0.03 ± 0.98	+2.6 yrs	5.8 ± 0.4	5.2 ± 0.4	5.1 ± 0.5
Fourth quartile	463	-0.17 ± 1.04	+6.6 yrs	6.6 ± 0.6	6.1 ± 0.7	6.0 ± 0.7
					Daily Smoking	
Daily smoking (between ages 12 and 24 yrs)						
No	1,306	0.04 ± 1.00	Ref.	*All participants were nonsmokers*	0%	0%
Yes	491	-0.13 ± 0.97	+3.4 yrs		71.3%	94.5%

Values are mean ± SD of the performance in the PAL test indicating learning and memory and of the cardiovascular risk factor values in the quartiles of the AUC variables for early life systolic BP and serum total-cholesterol (age 6 to 24 years) and for dichotomized (age 12 to 24 years) smoking. For the PAL test, the values are mean ± SD of the rank order normalized principal component for the PAL test where the higher values indicate better performance. *The difference in *cognitive age* has been calculated comparing the difference in the PAL test performance between the risk factor quartiles to our previous finding on the effect of age (-0.05 SD per year) on the PAL test (18). The lowest quartile has been used as the reference category for all comparisons for *cognitive age*.

AUC = area under the curve; BP = blood pressure; PAL = paired-associates learning; Ref. = reference.

smoking, and BMI to the test measuring sustained attention and visual processing (RVP test). However, only the results for the PAL test remained consistently unchanged after further adjustments for family income, antihypertension and dyslipidemia medication, and diagnoses of cardiovascular diseases and diabetes mellitus. Detailed results are therefore presented to examine the independent effects of early life cumulative burden of systolic BP, serum total-cholesterol, BMI, and smoking on PAL test performance: First, we calculated the mean values of the midlife PAL test performance and each cardiovascular risk factor in childhood (age 6 to 9 years), adolescence (age 12 to 15 years), and early adulthood (age 18 to 24 years) within the quartiles of the early life AUC variables for the same risk factors (**Table 1**). We also calculated the difference in *cognitive age* across the quartiles in the PAL test performance on the basis of our previous study that showed a -0.05 SD decline per year in the YFS population (18). For example, the table shows a 0.42 SD difference between the extreme systolic BP quartiles. This corresponds to 8.4 years' difference in *cognitive age*. Similarly, we see a 0.33 SD difference between the extreme serum total-cholesterol quartiles (6.6 years) and a 0.17 SD difference between smokers and nonsmokers (3.4 years).

Second, analyses were conducted to examine the independent effects of early life (between ages 6 and 24 years) cumulative burden of systolic BP, serum total-cholesterol, BMI, and smoking on midlife visual and episodic memory and visuospatial learning (PAL test) (**Table 2**). In the unadjusted bivariate analyses (**Table 2**, row A), early life exposure to elevated systolic BP, serum total-cholesterol, and smoking were inversely related with the PAL test performance. These associations were attenuated but remained significant when the effects of age and sex were taken into account (**Table 2**, row B) when mutually adjusted for in a multivariate model (**Table 2**, row C) and when additionally adjusted for family income, antihypertension and dyslipidemia medications, and diagnoses of cardiovascular disease and diabetes mellitus (**Table 2**, row D). This indicates that all 3 risk factors were independently associated with the PAL test performance and that none of the other covariates had significant confounding effects.

Further multivariate analyses were conducted including childhood academic performance, adulthood education, apoEε4 genotype, and adulthood physical activity level as covariates in the model. In this sample, the results for BP and serum total-cholesterol remained essentially similar for visual and episodic memory and visuospatial associative learning (PAL test; n = 1,450; systolic BP: β = -0.065, standard error [SE] = 0.031, p = 0.034; serum total-cholesterol: β = -0.076, SE = 0.028, p = 0.006), but

TABLE 2 Associations Between Cumulative Burden of Early Life Vascular Risk Factors (Age 6 to 24 Years) and Midlife Visual and Episodic Memory and Visuospatial Associative Learning (PAL Test) in 1,733 YFS Participants

Row	Model	β Coefficient (SE)	p Value
A	Unadjusted bivariate models		
	Systolic BP	**−0.152 (0.023)**	**<0.0001**
	Serum total-cholesterol	**−0.122 (0.024)**	**<0.0001**
	BMI	0.018 (0.026)	0.490
	Smoking	**−0.182 (0.054)**	**0.001**
B	Age- and sex-adjusted models		
	Systolic BP	**−0.067 (0.026)**	**0.010**
	Serum total-cholesterol	**−0.064 (0.025)**	**0.010**
	BMI	−0.004 (0.025)	0.870
	Smoking	**−0.123 (0.053)**	**0.001**
C	Multivariate model 1		
	Systolic BP	**−0.076 (0.028)**	**0.006**
	Serum total-cholesterol	**−0.059 (0.025)**	**0.018**
	BMI	0.026 (0.026)	0.315
	Smoking	**−0.140 (0.053)**	**0.008**
D	Multivariate model 2		
	Systolic BP	**−0.064 (0.028)**	**0.023**
	Serum total-cholesterol	**−0.053 (0.025)**	**0.037**
	BMI	0.029 (0.026)	0.281
	Smoking	**−0.140 (0.053)**	**0.008**

Values are β coefficients (SE) and p values from linear models. Unadjusted models are conducted separately for variables indicating cumulative burden of early life (6 to 24 years) cardiovascular risk factors (i.e., systolic BP, serum total-cholesterol and BMI, adolescence and young adulthood smoking at the ages of 12 to 24 years) without covariates. Age- and sex-adjusted models are conducted separately for each early life cardiovascular risk factor. In the multivariate model 1, all variables indicating cumulative burden of early life (6 to 24 years) and cardiovascular risk factors are entered simultaneously in an age- and sex-adjusted model. The multivariate model 2 is adjusted additionally for childhood family income, adulthood antihypertension and dyslipidemia medications, and diagnoses of cardiovascular diseases and diabetes mellitus. Variables for visual and episodic memory and visuospatial associative learning (PAL test) and cardiovascular risk factors are standardized (mean 0, SD 1), thus the β coefficients indicate the amount of change in the PAL test performance in standard deviations when the cumulative burden (6 to 24 years) of an early life risk factor increases by 1 SD. One SD unit is equivalent to ∼6 mm Hg for systolic BP, ∼0.7 mmol/l (∼27 mg/dl) for total-cholesterol, and ∼2.4 kg/m^2 for BMI. For smoking, the β coefficient estimates the effect of daily smoking between ages 12 to 24 years. For the PAL test, lower values indicate lower cognitive performance. In all models, the participants with missing data on any of the variables in the fully adjusted model were excluded from the analyses. Statistically significant results are presented in **bold**.

BMI = body mass index; SD = standard deviation; SE = standard error; YFS = Young Finns Study; other abbreviations as in Table 1.

the additional adjustments diluted the effects of smoking for visual and episodic memory and visuospatial associative learning (PAL test, n = 1,450; smoking: β = −0.032, SE = 0.060, p = 0.60) and for recognition, visual processing, and sustained attention (RVP test, n = 1,545; smoking: β = −0.033, SE = 0.057, p = 0.568). The covariate that was mainly responsible for the dilution of the effect of smoking was childhood academic performance, which was directly and highly significantly (p value always <0.008) associated with all midlife cognitive domains.

MULTIPLE CARDIOVASCULAR RISK FACTORS. Because early life cardiovascular risk factors associated systematically with visual and episodic memory and visuospatial associative learning (PAL test), the effects on that cognitive domain were investigated in relation to: 1) the number of early and midlife cardiovascular risk factors; and 2) the number of early life risk factors exceeding the recommended guidelines.

NUMBER OF EARLY AND MIDLIFE CARDIOVASCULAR RISK FACTORS. Persons with none or 1 risk factor (defined as continuous AUC values exceeding the 75th percentile and frequent smoking) during their early life (ages 6 to 24 years) performed better in the PAL test than participants with 2 to 3 early life cardiovascular risk factors. After adjusting for age, sex, family income, antihypertension and dyslipidemia medications, and diagnoses of cardiovascular diseases and diabetes mellitus, the association between the number of early life cardiovascular risk factors and midlife cognitive performance was highly significant (n = 1,733; β = −0.135, SE = 0.034, p < 0.0001). Similar but weaker association between the number of risk factors and PAL test was found for current midlife cardiovascular risk factors (n = 1,662; β = −0.080, SE = 0.035, p = 0.020).

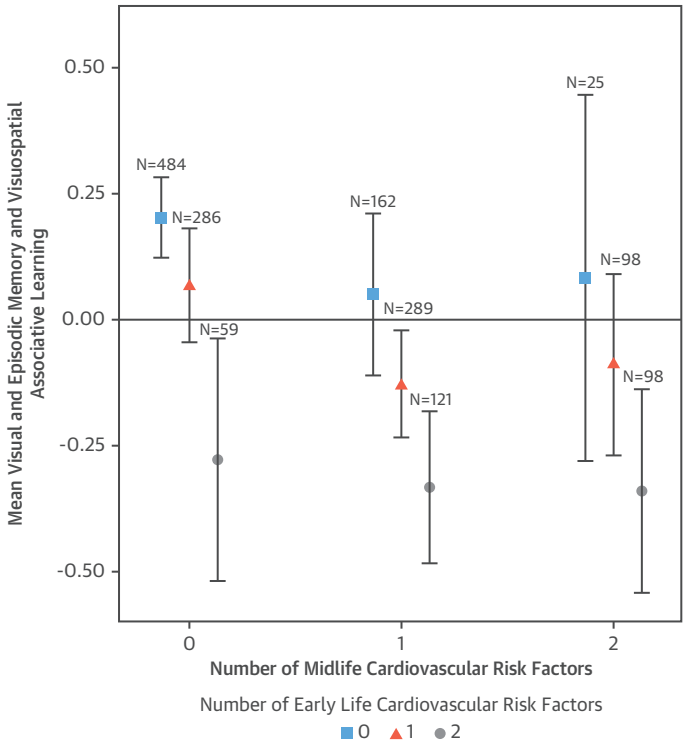
To examine whether the effect of early life risk factors on PAL test were independent of the effect of contemporaneous risk factors, we stratified the cohort into groups according to the number of early and midlife risk factors (Figure 1). When simultaneously entered in a multivariable model, the effect of early life risk factors remained significant (n = 1,622; β = −0.102, SE = 0.037, p = 0.006), but the effect of the midlife risk factors was diluted (β = −0.052, SE = 0.038, p = 0.166). The "independent" effect of early risk exposure is illustrated in Figure 1. For example, individuals who have been exposed to several risk factors in early life have consistently of about 0.25 SDs lower memory and learning compared with the population mean regardless of the number of contemporary risk factors (gray dots in Figure 1). This corresponds to about 5 years in *cognitive aging* in our population. These results remained essentially similar after further adjustments with childhood academic performance, adulthood education, apoEε4 genotype, and physical activity level (N = 1,450; early life risk factors: β = −0.116, SE = 0.040, p = 0.004; midlife risk factors: β = 0.004, SE = 0.040, p = 0.916).

In addition to the 75th percentile cutpoint used in the main analyses, we performed sensitivity analyses for the association between the number of risk factors and cognitive performance using cutpoints of 70th, 80th, and 85th percentiles for determining the risk factor levels. The associations between the number of early and midlife cardiovascular risk

factors and midlife cognitive performance remained virtually unchanged regardless of the cutpoint used (Online Table 6). Thus, by using several risk factor percentile cutpoints, the number of early life risk factors remained robustly associated with midlife memory and learning. When the models were simultaneously controlled for the midlife risk factors, the effect of early life risk factors remained significant, but the effects of the midlife risk factors were always diluted. Furthermore, all models gave identical results if high total-cholesterol was replaced with high LDL-cholesterol in the risk scores.

EARLY LIFE RISK FACTORS EXCEEDING THE RECOMMENDED GUIDELINES. In addition to the risk factor levels based on percentile cutpoints, we examined whether the effect of early life risk exposure is attributable to levels of risk factors repeatedly exceeding the recommended guidelines for pediatric atherosclerosis prevention using cutpoints shown in Online Table 2. The analyses that considered risk factors exceeding recommended guidelines indicated that the persons with early life risk factors within the recommended guidelines had a 0.29 SD better visual and episodic memory and visuospatial associative learning (PAL test) than those exceeding the guidelines at least twice on all risk factors (model adjusted for age, sex, family income, antihypertension and dyslipidemia medications, and diagnoses of cardiovascular diseases and diabetes mellitus: n = 1,568; β = -0.088, SE = 0.032, p = 0.007) (**Central Illustration**). This effect remained identical after further adjustments with childhood academic performance, adulthood education, apoEε4 genotype, and physical activity level (n = 1,341; β = -0.077, SE = 0.035, p = 0.029).

FIGURE 1 Midlife Performance on Episodic Memory and Visual Associative Learning According to the Number of Early Life and Midlife Cardiovascular Risk Factors (N = 1,622)



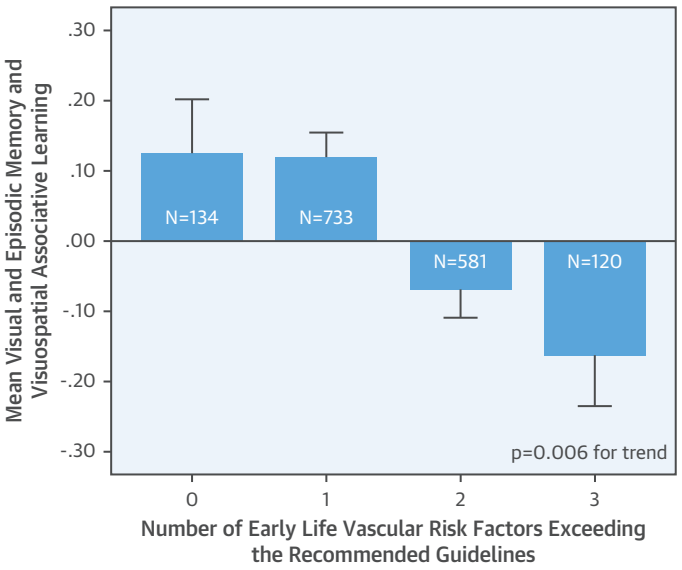
The values represent means and 95% confidence intervals indicating cognitive performance on visual and episodic memory and visuospatial associative learning in subgroups classified according to the number of risk factors in early and midlife. The variables showing significant association for cognitive performance in the multivariate analyses (i.e., systolic blood pressure [BP], serum total-cholesterol, and smoking) were included in the variable for the cardiovascular risk factor clustering. In a multivariable model, the association between the number of early life cardiovascular risk factors and midlife cognitive performance was significant (p = 0.003) after adjustments for age, sex, family income, and the number of midlife cardiovascular risk factors. The reference line is set on the population mean. A 3-level variable indicating the number of risk factors during early life was created from the area under the curve (AUC) variables for each cardiovascular risk factor (1 = no risk factors, 2 = 1 risk factor, 3 = 2 or 3 risk factors), and the categories are indicated with colors in the figure. The AUC variables for BP and serum total-cholesterol were dichotomized into high-risk factor level (≥75th percentile) and low-risk factor level (<75th percentile). Smoking status was dichotomized into smokers and nonsmokers. The dichotomical variables were summed to create the variable indicating the number of risk factors (range: 0 to 3) during early life (6 to 24 years). A similar variable indicating the number of cardiovascular risk factors at the time of cognitive testing was formed and placed in the x-axis in the figure.

DISCUSSION

We found that increasing cumulative burden of systolic BP, serum total- and LDL-cholesterol, and smoking in childhood/adolescence associated with worse visual and episodic memory and visuospatial associative learning at midlife (PAL test). Importantly, the associations were independent of midlife exposures to the same risk factors. These findings suggest that the associations between early life cardiovascular risk factors and midlife cognitive performance do not only reflect tracking of risk factor levels from childhood to adulthood, but that the risk factors potentially start to exert their influence on cognitive performance already in childhood.

Previous studies have observed inverse associations between adulthood systolic BP, serum cholesterol, BMI, and smoking and midlife cognitive performance (15) or risk of late-life cognitive deficits (1-4). To the best of our knowledge, this is the first study examining the cumulative burden of cardiovascular risk factors from childhood in relation to cognitive performance in midlife. Of the risk factors examined, we were able to demonstrate the independent effects of early life systolic BP, serum total- and

CENTRAL ILLUSTRATION Childhood Vascular Factors and Midlife Cognition: Midlife Performance on Episodic Memory and Visual Associative Learning



Rovio, S.P. et al. J Am Coll Cardiol. 2017;69(18):2279–89.

These data are based on the number of risk factors (high low-density lipoprotein [LDL]-cholesterol, elevated systolic blood pressure [BP], and cigarette smoking) with levels exceeding the recommended guidelines (16-18). The variables showing significant association for cognitive performance with guideline recommendations for children/adolescence (i.e., LDL-cholesterol, systolic BP, and smoking) were included in the variable for the cardiovascular risk factor clustering. The **bars** indicate the mean values of the principal component for visual and episodic memory and visuospatial associative learning and the **whiskers** are standard errors. The individuals were classified as: 0 = no risk factor levels exceeding guidelines or levels exceeding at most once per risk factor; 1 = risk factor levels exceeding guidelines twice or more on 1 risk factor; 2 = risk factor levels exceeding guidelines twice or more on 2 risk factors; or 3 = risk factor levels exceeding guidelines twice or more on all risk factors. The inverse dose-response relation with cognitive performance was significant ($\beta = -0.088$; $p = 0.007$), adjusted for age, sex, family income, antihypertension and dyslipidemia medications, and diagnoses of cardiovascular diseases and diabetes mellitus. The reference line is set on the population mean.

LDL-cholesterol, and smoking. Participants with these early life risk factors, factored as continuous or binary variables, defined either by using several arbitrary cutpoints or by using current guidelines for atherosclerosis prevention, had worse midlife cognitive performance than those with low risk factor levels. Although the observational nature of our study precludes making clinical recommendations, it provides evidence on cognitive benefits gained by maintenance of cardiovascular risk factors at low levels already from early life. If this hypothesis is correct, adopting active monitoring and treatment strategies against cardiovascular risk factors from childhood would be needed to turn the focus of cognitive deficits prevention from secondary and tertiary prevention to primordial prevention. With the future YFS follow-up data on cognitive performance, we will be able to estimate using observational data whether changes in risk factor levels from childhood to adulthood are associated with the deterioration of cognitive function between mid- to old adulthood.

The 4 cognitive domains were selected as outcomes to obtain a comprehensive outlook to cognitive performance. Based on previous experimental studies in animals, we especially expected to see links between cardiovascular risk factors and tests indicating memory and learning. Indeed, we found that the effects of early life risk exposure were strongly and robustly associated with the visual and episodic memory and visuospatial associative learning (PAL test). Similarly, the CARDIA study found strong associations between serum total-cholesterol, BP, and verbal memory (15). Additionally, we found weak links of smoking and BMI to the test measuring sustained attention and visual processing (RVP test) that were of borderline significance or did not survive adjustments. The CARDIA study used the Stroop test, which resembled the RVP test used in our study, and found some associations with systolic BP (15). We did not find associations between risk exposures and working memory (spatial working memory test) or reaction time (reaction time test). Effects on the reaction time were not expected based on previous animal data. Additionally, the lack of effects of risk factor exposure on working memory in midlife is perhaps also not surprising because difficulties in encoding and recall might become visible before difficulties in other type of memory functions (e.g., working memory, recognition) (26). Thus, our results are consistent with studies in animal models that have observed associations between cardiovascular risk factors and memory and learning.

The neural networks related to the PAL test localize mainly to medial temporal lobes, specifically to the hippocampus and parahippocampal gyrus (16). These anatomical structures are responsible for learning and memory (27). Imaging studies have reported that exposure to cardiovascular risk factors is associated with increased amount of cerebral white matter alterations and structural brain changes in the elderly (28-31) and augment the effect of age on volume loss in the hippocampus, entorhinal cortex, and medial temporal lobes in healthy adults (32). These findings may offer insights into the associations between early cardiovascular risk factors and medial temporal lobe-related brain functions. Furthermore, in elderly

patients with mild cognitive impairment, deficits in the PAL test have been linked to preclinical Alzheimer's disease pathology (33-36).

The main neuropathological mechanisms underlying associations between cardiovascular risk factors and old age cognitive deficits are suggested to be subclinical ischemia causing cerebrovascular damage (27,37), structural brain changes, and atrophy (28-31). Additionally, risk factors may influence cerebral β-amyloid protein metabolism (38,39). In young populations, however, the mechanisms remain unknown. Cardiovascular risk factors cause systemic atherosclerosis, loss of distensibility in the vasculature, vessel fibrosis, plasma protein leakage, and accumulation of lipid-containing macrophages in the vessels (40-42). In the brain, these changes may lead to cerebral hypoperfusion and local inflammation, which disrupt the vulnerable surrounding neuronal milieu (37). Additionally, by inducing cerebral hypoperfusion atherosclerotic changes may initiate and/or accelerate neurodegenerative changes (e.g., β-amyloid deposition and clearance, synaptic and neuronal dysfunction/loss) that ultimately lead to alterations in cognitive performance (38,39).

We found that the participants with several early life cardiovascular risk factors, including elevated BP, high LDL-cholesterol, and smoking, exceeding the recommended guidelines had an ~0.3 SDs lower performance in the PAL test than those participants whose risk factors remained always within the guidelines. When using arbitrary cutpoints for BP and total-cholesterol (exceeding 75th percentiles), we similarly found that individuals who had been exposed to all 3 risk factors in early life had an ~0.4 SDs lower performance in the PAL test than individuals without any early life risk factor exposures. In the YFS population, we see a linear decline in the PAL test performance that equals 0.05 SDs per year between ages 34 and 49 years (18). Therefore, the present study suggests that the effect of early life risk factor clustering on the PAL test performance corresponds to a 6- to 8-year difference in *cognitive age*. Furthermore, we found that the cumulative effect of the early life risk exposure on the PAL test performance was stronger and independent of the effect of current midlife risk exposure. This observation emphasizes the role of early life risk exposure on later cognitive performance, and may be in line with the existence of differential sensitive periods and age windows of vulnerability to environmental factors and conditions during brain maturation (43).

STUDY LIMITATIONS. Limitations of this study include that cognitive performance was measured once. This prevented us from studying the role of early life cardiovascular risk factors on changes in midlife cognitive performance. Furthermore, we were unable to examine the role of glucose levels as an early life risk factor because we did not have data to construct a cumulative exposure variable similarly to systolic BP and serum total-cholesterol. However, the CARDIA study found no association between young adulthood/midlife cumulative blood glucose burden and midlife cognitive performance among normoglycemic population (15). Another limitation is the possibility of residual confounding resulting from unmeasured factors, which is always possible in observational studies such as the YFS. Our results remained unchanged after controlling the analyses for a wide array of possible confounding factors including the adulthood levels of cardiovascular risk factors. It remains possible, however, that some unmeasured factors contribute to the association between cardiovascular risk factors and cognitive performance. Furthermore, computerized cognitive tests are not routinely used in clinical settings to diagnose cognitive performance. In this study, the test battery was not used for clinical decision making but as a tool to evaluate cognitive performance among healthy young and middle-age adults on a population level. Previous studies have shown that these tests are useful in capturing variation in cognitive performance in healthy populations (44-46). Therefore, the tests used in the YFS may be considered adequate in discriminating the cognitive variation among the participants. Another potential limitation is a possible selection in the follow-up study; the participants were more often women and older than nonparticipants, and they originated from families with higher income and had better childhood academic performance. However, no differences were observed in the levels of early life exposure variables. Furthermore, we conducted several statistical tests in our study, which may increase the probability of false positive findings; however, because the main analyses were based on a priori hypotheses, we did not apply multiple testing correction. Moreover, with respect to the establishment of causality, observational studies are prone to bias caused by reverse causation. Nevertheless, the use of existing population cohorts from childhood to adulthood is the only realistic approach to test the hypothesis that early life risk exposure is causally linked with adult cognitive performance because it is not possible to perform life-long randomized control trials to test causal relations between childhood risk factors and adult outcomes. The most important competing explanation for these associations is that cognitive function in

early life might determine (or might be associated with other factors determining) the emergence of vascular risk factors. If that hypothesis was true, midlife cognitive performance would simply be a marker of tracked early life cognitive function. We were able to test this hypothesis in a restricted number of the YFS participants by using available data on academic performance as a proxy for their childhood cognitive performance. Academic performance was defined as grade point average, which indicates the mean of all school grades during 1 school year. As an overall measure of academic performance, it may be considered as an indicator of the participants' cognitive ability at baseline. Indeed, when introduced as a covariate, the effect of smoking was diluted. This suggests that the association between early life smoking and midlife cognitive performance might be confounded by baseline cognitive performance; however, the effects of other risk factors as well as the effect of the early life risk factor clustering remained essentially similar after taking account the childhood academic performance. Nevertheless, because the possibility of residual confounding remains, the results in YFS should be replicated in other longitudinal cohorts with follow-up from childhood to adulthood.

CONCLUSIONS

In summary, these data indicate that the cumulative burden of BP, serum total- and LDL-cholesterol, and smoking from childhood and adolescence associate independently and combined with midlife cognitive performance. The findings give support to active monitoring/treatment strategies against cardiovascular risk factors from childhood to turn the focus of cognitive deficits prevention to primary and primordial prevention.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Systolic BP, serum cholesterol levels, and smoking in childhood and adolescence are associated with worse cognitive performance, especially memory and learning, by midlife, independent of later exposure to these risk factors. These findings point to the importance of implementing primordial prevention strategies directed against cardiovascular risk factors earlier in life to promote cognitive health in adulthood.

TRANSLATIONAL OUTLOOK: The mechanisms by which cardiovascular risk factors present in childhood and adolescence promote the cognitive decline associated with aging require further investigation.

REFERENCES

1. Knopman D, Boland LL, Mosley T, et al. Cardiovascular risk factors and cognitive decline in middle-aged adults. Neurology 2001;56:42–8.

2. Tolppanen A-M, Solomon A, Soininen H, Kivipelto M. Midlife vascular risk factors and Alzheimer's disease: evidence from epidemiological studies. J Alzheimers Dis 2012;32:531–40.

3. Rusanen M, Rovio S, Ngandu T, et al. Midlife smoking, apolipoprotein E and risk of dementia and Alzheimer's disease: a population-based cardiovascular risk factors, aging and dementia study. Dement Geriatr Cogn Disord 2010;30:277–84.

4. Gorelick PB, Scuteri A, Black SE, et al. Vascular contributions to cognitive impairment and dementia: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2011;42:2672–713.

5. Grünblatt E, Bartl J, Iuhos D-I, et al. Characterization of cognitive deficits in spontaneously hypertensive rats, accompanied by brain insulin receptor dysfunction. J Mol Psychiatry 2015;3:6.

6. Ullrich C, Pirchl M, Humpel C. Hypercholesterolemia in rats impairs the cholinergic system and leads to memory deficits. Mol Cell Neurosci 2010;45:408–17.

7. Thirumangalakudi L, Prakasam A, Zhang R, et al. High cholesterol-induced neuroinflammation and amyloid precursor protein processing correlate with loss of working memory in mice. J Neurochem 2008;106:475–85.

8. Counotte DS, Spijker S, Van de Burgwal LH, et al. Long-lasting cognitive deficits resulting from adolescent nicotine exposure in rats. Neuropsychopharmacology 2009;34:299–306.

9. Ueno M, Sakamoto H, Tomimoto H, et al. Blood-brain barrier is impaired in the hippocampus of young adult spontaneously hypertensive rats. Acta Neuropathol 2004;107:532–8.

10. Mateos L, Akterin S, Gil-Bea F-J, et al. Activity-regulated cytoskeleton-associated protein in rodent brain is down-regulated by high fat diet in vivo and by 27-hydroxycholesterol in vitro. Brain Pathol 2009;19:69–80.

11. Sparks DL, Kuo YM, Roher A, Martin T, Lukas RJ. Alterations of Alzheimer's disease in the cholesterol-fed rabbit, including vascular inflammation. Preliminary observations. Ann N Y Acad Sci 2000;903:335–44.

12. Khanna A, Guo M, Mehra M, Royal W. Inflammation and oxidative stress induced by cigarette smoke in Lewis rat brains. J Neuroimmunol 2013;254:69–75.

13. Ho Y-S, Yang X, Yeung S-C, et al. Cigarette smoking accelerated brain aging and induced pre-Alzheimer-like neuropathology in rats. PLoS One 2012;7:e36752.

14. Rueff-Barroso CR, Trajano ETL, Alves JN, et al. Organ-related cigarette smoke-induced oxidative stress is strain-dependent. Med Sci Monit 2010;16:BR218–26.

15. Yaffe K, Vittinghoff E, Pletcher MJ, et al. Early adult to midlife cardiovascular risk factors and cognitive function. Circulation 2014;129:1560–7.

16. de Rover M, Pironti VA, McCabe JA, et al. Hippocampal dysfunction in patients with mild cognitive impairment: a functional neuroimaging study of a visuospatial paired associates learning task. Neuropsychologia 2011;49:2060–70.

17. Raitakari OT, Juonala M, Rönnemaa T, et al. Cohort profile: the cardiovascular risk in Young Finns Study. Int J Epidemiol 2008;37:1220–6.

18. Rovio SP, Pahkala K, Nevalainen J, et al. Cognitive performance in young adulthood and midlife: relations with age, sex, and education-The Cardiovascular Risk in Young Finns Study. Neuropsychology 2016;30:532–42.

19. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499–502.

20. Porkka KV, Raitakari OT, Leino A, et al. Trends in serum lipid levels during 1980-1992 in children and young adults. The Cardiovascular Risk in Young Finns Study. Am J Epidemiol 1997;146:64–77.

21. Welham S. Longitudinal data analysis. In: Fitzmaurice G, Davidian M, Verbeke G, Molenberghs G, editors. Longitudinal Data Analysis. Boca Raton, Florida: Chapman & Hall/CRC, 2009:253–89.

22. Lai C-C, Sun D, Cen R, et al. Impact of long-term burden of excessive adiposity and elevated blood pressure from childhood on adulthood left ventricular remodeling patterns: the Bogalusa Heart Study. J Am Coll Cardiol 2014;64:1580–7.

23. Kaelber DC, Pickett F. Simple table to identify children and adolescents needing further evaluation of blood pressure. Pediatrics 2009;123:e972–4.

24. Jolliffe CJ, Janssen I. Distribution of lipoproteins by age and gender in adolescents. Circulation 2006;114:1056–62.

25. Kavey R-EW, Daniels SR, Lauer RM, Atkins DL, Hayman LL, Taubert K. American Heart Association guidelines for primary prevention of atherosclerotic cardiovascular disease beginning in childhood. Circulation 2003;107:1562–6.

26. Drag LL, Bieliauskas LA. Contemporary review 2009: cognitive aging. J Geriatr Psychiatry Neurol 2010;23:75–93.

27. Blennow K, de Leon MJ, Zetterberg H. Alzheimer's disease. Lancet 2006;368:387–403.

28. Vuorinen M, Solomon A, Rovio S, et al. Changes in vascular risk factors from midlife to late life and white matter lesions: a 20-year follow-up study. Dement Geriatr Cogn Disord 2011;31:119–25.

29. Knopman DS, Penman AD, Catellier DJ, et al. Vascular risk factors and longitudinal changes on brain MRI: the ARIC study. Neurology 2011;76:1879–85.

30. Debette S, Seshadri S, Beiser A, et al. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. Neurology 2011;77:461–8.

31. Launer LJ, Lewis CE, Schreiner PJ, et al. Vascular factors and multiple measures of early brain health: CARDIA brain MRI study. PLoS One 2015;10:e0122138.

32. Raz N, Lindenberger U, Rodrigue KM, et al. Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cereb Cortex 2005;15:1676–89.

33. Blackwell AD, Sahakian BJ, Vesey R, Semple JM, Robbins TW, Hodges JR. Detecting dementia: novel neuropsychological markers of preclinical Alzheimer's disease. Dement Geriatr Cogn Disord 2004;17:42–8.

34. Swainson R, Hodges JR, Galton CJ, et al. Early detection and differential diagnosis of Alzheimer's disease and depression with neuropsychological tasks. Dement Geriatr Cogn Disord 2001;12:265–80.

35. Fowler KS, Saling MM, Conway EL, Semple JM, Louis WJ. Computerized neuropsychological tests in the early detection of dementia: prospective findings. J Int Neuropsychol Soc 1997;3:139–46.

36. Fowler KS, Saling MM, Conway EL, Semple JM, Louis WJ. Paired associate performance in the early detection of DAT. J Int Neuropsychol Soc 2002;8:58–71.

37. Kalaria RN. Vascular basis for brain degeneration: faltering controls and risk factors for dementia. Nutr Rev 2010;68 Suppl 2:S74–87.

38. Reed BR, Marchant NL, Jagust WJ, DeCarli CC, Mack W, Chui HC. Coronary risk correlates with cerebral amyloid deposition. Neurobiol Aging 2012;33:1979–87.

39. Rodrigue KM, Rieck JR, Kennedy KM, Devous MD, Diaz-Arrastia R, Park DC. Risk factors for β-amyloid deposition in healthy aging: vascular and genetic effects. JAMA Neurol 2013;70:600–6.

40. Altman R, Rutledge JC. The vascular contribution to Alzheimer's disease. Clin Sci (Lond) 2010;119:407–21.

41. Grinberg LT, Thal DR. Vascular pathology in the aged human brain. Acta Neuropathol 2010;119:277–90.

42. Vasilevko V, Passos GF, Quiring D, et al. Aging and cerebrovascular dysfunction: contribution of hypertension, cerebral amyloid angiopathy, and immunotherapy. Ann N Y Acad Sci 2010;1207:58–70.

43. Marco EM, Macrì S, Laviola G. Critical age windows for neurodevelopmental psychiatric disorders: evidence from animal models. Neurotox Res 2011;19:286–307.

44. Koepsell TD, Kurland BF, Harel O, Johnson EA, Zhou X-H, Kukull WA. Education, cognitive function, and severity of neuropathology in Alzheimer disease. Neurology 2008;70:1732–9.

45. Robbins TW, James M, Owen AM, Sahakian BJ, McInnes L, Rabbitt P. Cambridge Neuropsychological Test Automated Battery (CANTAB): a factor analytic study of a large sample of normal elderly volunteers. Dementia 1994;5:266–81.

46. De Luca CR, Wood SJ, Anderson V, et al. Normative data from the CANTAB. I: development of executive function over the lifespan. J Clin Exp Neuropsychol 2003;25:242–54.

KEY WORDS blood pressure, body mass index, cognitive performance, serum cholesterol, smoking

APPENDIX For a supplemental Methods section as well as tables, please see the online version of this article.