# Cardiovascular Risk Factor Trajectories Since Childhood and Cognitive Performance in Midlife The Cardiovascular Risk in Young Finns Study

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# Cardiovascular Risk Factor Trajectories Since Childhood and Cognitive Performance in Midlife

## The Cardiovascular Risk in Young Finns Study

**BACKGROUND:** Cardiovascular risk factors, such as high blood pressure, adverse serum lipids, and elevated body mass index in midlife, may harm cognitive performance. It is important to note that longitudinal accumulation of cardiovascular risk factors since childhood may be associated with cognitive performance already since childhood, but the previous evidence is scarce. We studied the associations of cardiovascular risk factors from childhood to midlife, their accumulation, and midlife cognitive performance.

**METHODS:** From 1980, a population-based cohort of 3596 children (3–18 years of age) have been repeatedly followed up for 31 years. Blood pressure, serum lipids, and body mass index were assessed in all follow-ups. Cardiovascular risk factor trajectories from childhood to midlife were identified using latent class growth mixture modeling. Cognitive testing was performed in 2026 participants 34 to 49 years of age using a computerized test. The associations of the cardiovascular risk factor trajectories and cognitive performance were studied for individual cardiovascular risk factors and cardiovascular risk factor accumulation.

**RESULTS:** Consistently high systolic blood pressure (β=–0.262 SD [95% CI, –0.520 to –0.005]) and serum total cholesterol (β=–0.214 SD [95% CI, –0.365 to –0.064]) were associated with worse midlife episodic memory and associative learning compared with consistently low values. Obesity since childhood was associated with worse visual processing and sustained attention (β=–0.407 SD [95% CI, –0.708 to –0.105]) compared with normal weight. An inverse association was observed for the cardiovascular risk factor accumulation with episodic memory and associative learning (*P* for trend=0.008; 3 cardiovascular risk factors: β=–0.390 SD [95% CI, –0.691 to –0.088]), with visual processing and sustained attention (*P* for trend<0.0001; 3 cardiovascular risk factors: β=–0.443 SD [95% CI, –0.730 to –0.157]), and with reaction and movement time (*P* for trend=0.048; 2 cardiovascular risk factors: β=–0.164 SD [95% CI, –0.318 to –0.010]).

**CONCLUSIONS:** Longitudinal elevated systolic blood pressure, high serum total cholesterol, and obesity from childhood to midlife were inversely associated with midlife cognitive performance. It is important to note that the higher the number of cardiovascular risk factors, the worse was the observed cognitive performance. Therefore, launching preventive strategies against cardiovascular risk factors beginning from childhood might benefit primordial promotion of cognitive health in adulthood.

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## Clinical Perspective

### What Is New?

- This study provides a novel long-term and comprehensive outlook on blood pressure, serum lipids, and body mass index trajectories from childhood to midlife and on their associations with cognitive performance in midlife.
- This is the first study to highlight the link between longitudinal cardiovascular risk factor accumulation from childhood to midlife and poor cognitive performance in midlife.

### What Are the Clinical Implications?

- This study highlights the inverse association of longitudinal accumulation of cardiovascular risk factors from childhood to midlife on cognitive performance in midlife.
- The results give support to active monitoring of systolic blood pressure, serum total cholesterol, and obesity since childhood to promote adulthood cognitive health. In addition, emphasis on reducing the number of risk factors may be beneficial.
- The findings from this study elucidate possibilities to move the focus of cognitive decline prevention from secondary and tertiary prevention to primary and even primordial prevention by controlling for cardiovascular risk factors from childhood.

The aging population highlights the need for primordial prevention of cognitive deficits.[1] Subclinical deficiencies, for example, in memory, learning, and decision making, precede cognitive deficits plausibly even decades before they become clinically detectable.[2] Incidence of cognitive deficits is influenced by well-established risk factors including, for example, low education, hypertension, obesity, type 2 diabetes, smoking, physical inactivity, poor diet, and depression.[1] Results from previous observational studies on cardiovascular risk factors (CVRFs) have been focused on late life[3–5] or middle age,[4–10] whereas there are only a few studies from earlier adulthood.[5,11,12] These studies have reported inverse associations of hypertension or high blood pressure (BP),[3,5–7,10–12] adverse serum lipids,[6,10–12] and obesity[3,7,10,12,13] on cognitive performance.

It is notable that even if CVRFs often tend to accumulate,[14] previous studies have mainly focused on the effects of individual CVRF exposures,[11,13] whereas few studies have focused on the association between CVRF accumulation and cognitive performance[3–5,7–10,12] or the risk of dementia.[6] It is important to note that instead of using data from a single measurement point, only a few previous studies with data from adulthood have focused on the associations between longitudinally measured adulthood CVRF accumulation[3,4,9,12] and cognitive performance. To our knowledge, CARDIA (Coronary Artery Risk Development in Young Adults) is the only previous study with data from young adulthood to midlife (baseline, 18–30 years of age) and with results suggesting an adverse association between longitudinally assessed CVRF accumulation and cognitive performance.[12] Moreover, no previous study has been able to demonstrate these associations since childhood.

Leveraging the data from the YFS (Cardiovascular Risk in Young Finns Study), we have previously shown that elevated systolic BP (SBP), high serum total cholesterol, and smoking from childhood to early adulthood may exert their influence on midlife cognitive performance independent of the same risk factor levels in adulthood.[15] Therefore, this study aimed to close the existing knowledge gap on the associations of CVRFs from childhood to midlife and CVRF accumulation with cognitive performance measured in midlife.

## METHODS

### Participants

Anonymized data are available on request from the YFS research group (https://youngfinnsstudy.utu.fi/). The YFS is a national, longitudinal, population-based study that focuses on CVRFs from childhood to adulthood. The baseline study was conducted in 1980, when 3596 randomly selected individuals (boys and girls, all White) 3, 6, 9, 12, 15, and 18 years of age participated in clinical examinations. Follow-up studies were conducted for the whole study population in 1983, 1986, 2001, 2007, and 2011 and for a subsample also in 1989 and 1992. The study was approved by local ethics committees. All participants provided written informed consent. The design, population, and protocol of the YFS have been thoroughly reported elsewhere.[16]

### Cognitive Performance

Cognitive performance was assessed in 2026 participants 34 to 49 years of age (in 2011) with the Cambridge Neuropsychological Test Automated Battery (CANTAB, Cambridge Cognition, Cambridge, United Kingdom). The battery included 4 tests that reflect different cognitive domains: (1) the Paired Associates Learning test assessed episodic memory and associative learning, (2) the Spatial Working Memory test measured short-term working memory, (3) the Reaction Time test measured reaction and movement time, and (4) the Rapid Visual Information Processing test assessed visual processing and sustained attention. Each of the 4 tests produced several variables. Test-specific principal component analyses were conducted, and the first components resulting from these analyses were considered to represent performance in each studied cognitive domain. The principal components were normalized using a rank-order normalization procedure, resulting in 4 normally distributed components (mean=0 and SD=1) and transformed so that a greater value in the component indicates better cognitive performance. All available data for each cognitive test were used. Therefore, the number of participants varies between the components (177 were

excluded because of technical reasons; 51 refused to participate in all or some of the tests). A detailed description of the cognitive testing is presented in the Expanded Methods in the Data Supplement. The validation of the cognitive data are presented elsewhere.[17]

## Cardiovascular Risk Factors

In all study phases, standard methods were used for measuring SBP and diastolic BP (DBP).[18] Venous blood samples were taken after an overnight fast. Serum total cholesterol and triglyceride concentration were determined enzymatically with standard methods.[18] High-density lipoprotein (HDL) cholesterol was analyzed after precipitation of very-low-density lipoprotein cholesterol and low-density lipoprotein (LDL) cholesterol. The concentration of LDL cholesterol was calculated using the Friedewald formula for participants with triglycerides <4 mmol/L. Data on antihypertensive and dyslipidemia medications were obtained from the questionnaires in all adulthood follow-up studies (in 2001, 2007, and 2011). Weight (in kilograms) and height (in meters) were measured, and body mass index (BMI) was calculated as weight (in kilograms)/height (in meters squared).[16]

## Covariates

Age was defined in full years at the end of 2011. Genotyping was performed for 2443 samples using a custom-built Illumina Human 670k BeadChip at the Welcome Trust Sanger Institute. Genotypes were called using an Illuminus clustering algorithm.[19] Genotype imputation was performed using Beagle software[20] and the Sequencing Initiative Suomi as reference data. A polygenic risk score for cognitive performance (hereafter "polygenic risk score") was calculated using LDpred, a Bayesian method that estimates posterior mean causal effect sizes from genome-wide association study summary statistics from genome-wide association study summary statistics using prior assumptions for the genetic architecture and linkage disequilibrium information from a reference panel[21]: an infinitesimal fraction of causal variants was assumed, and summary statistics were from Savage et al.[22] Genome-wide association studies for intelligence were used. The linkage disequilibrium between markers was estimated from the Sequencing Initiative Suomi data. The polygenic risk score was used as a proxy for childhood cognitive performance. The analyses for individual CVRF trajectories were adjusted for other adulthood CVRFs. Serum glucose concentrations were analyzed using standard enzymatic methods.[18] Smoking was queried, and smoking status was dichotomized into daily smokers (daily smoking in any of the adulthood follow-up studies) and nonsmokers. Physical activity was assessed with a standardized questionnaire in all study phases, and a physical activity index was calculated as performed previously.[23] A diet score in adulthood was calculated[24] on the basis of the American Heart Association's definition,[25] which included recommended ideal intake levels of fruits and vegetables, fish, whole grains, sodium, and sugar-sweetened beverages. The mean values of the CVRF measurements, physical activity indices, and diet scores in adulthood follow-up studies were calculated. Childhood school performance expressed as grade point average (ie, 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. The maximum years of education until the cognitive testing was queried. Socioeconomic status (SES) in childhood was determined as an annual income of the family in 1980.[26] Four annual family income strata at the time of baseline were determined: (1) <17 000 euros, (2) 17 000 to 27 000 euros, (3) 27 001 to 34 000 euros, and (4) >34 000 euros. A detailed description of the covariates is presented in the Expanded Methods in the Data Supplement.

## Statistical Analysis

Heterogeneity in the longitudinal development of SBP, DBP, serum lipids, and BMI was investigated using group-based trajectory modeling performed with the SAS PROC TRAJ procedure[27] to identify subgroups of YFS participants who shared similar underlying trajectories between 9 and 49 years of age. Participants who used antihypertensive (N=273) or dyslipidemia medication (N=100) in adulthood follow-ups were excluded from the CVRF-specific trajectory modeling analyses. The BMI measurements obtained during participants' pregnancies were excluded from the BMI trajectory modeling analyses. All other participants were included in trajectory analyses but, for reliability, a minimum of 3 measurements was required with at least 1 being from childhood and adolescence (9–18 years of age) and at least 1 from adulthood (21–49 years of age). For each CVRF, the decision on the number and shape of the trajectory groups (Tables I through VIII in the Data Supplement) was based on clinical plausibility and standard criteria,[28,29] which are the Bayesian information criterion indicating the goodness of fit of the models and the posterior probability indicating internal reliability of each participant belonging to a specific trajectory group. Participants were assigned to the trajectory group where they had the highest posterior probability to belong (Tables IX through XV in the Data Supplement). For meaningful statistical analyses linking CVRF trajectories and cognitive performance, a frequency of >5% was preferred for the trajectory groups (not applicable for BMI because of clinical and statistical aspects). Last, 7 individual trajectory models for SBP, DBP, serum lipids, and BMI were formed (Figure for SBP, serum total cholesterol, and BMI; and Figures I through IV in the Data Supplement for DBP, LDL cholesterol, HDL cholesterol, and serum triglycerides) with adequate fit to data, good classification accuracy, and a strong clinical interpretability (Tables XVI through XXII in the Data Supplement). For DBP, LDL cholesterol, HDL cholesterol, and triglycerides, a detailed description of creation of the trajectory groups is presented in Expanded Methods in the Data Supplement. Sex-specific trajectory modeling was performed for each CVRF (Figures I through V in the Data Supplement), and the results were similar to the analyses for all participants. Therefore, to increase the statistical power, the analyses for cognitive performance were conducted among all participants.

For SBP (N=2361), a 5-group trajectory solution was considered optimal (Figure A): (1) low-stable SBP (N=415, 17.6%) with a consistently low SBP level, (2) normal-stable SBP (N=935, 39.6%) with consistently normal (<120 mm Hg) SBP level, (3) moderate-stable SBP (N=399, 16.9%) with SBP level consistently close to ideal (120 mm Hg),[25] (4) moderate-increasing SBP (N=471, 20.0%) with normal SBP in childhood

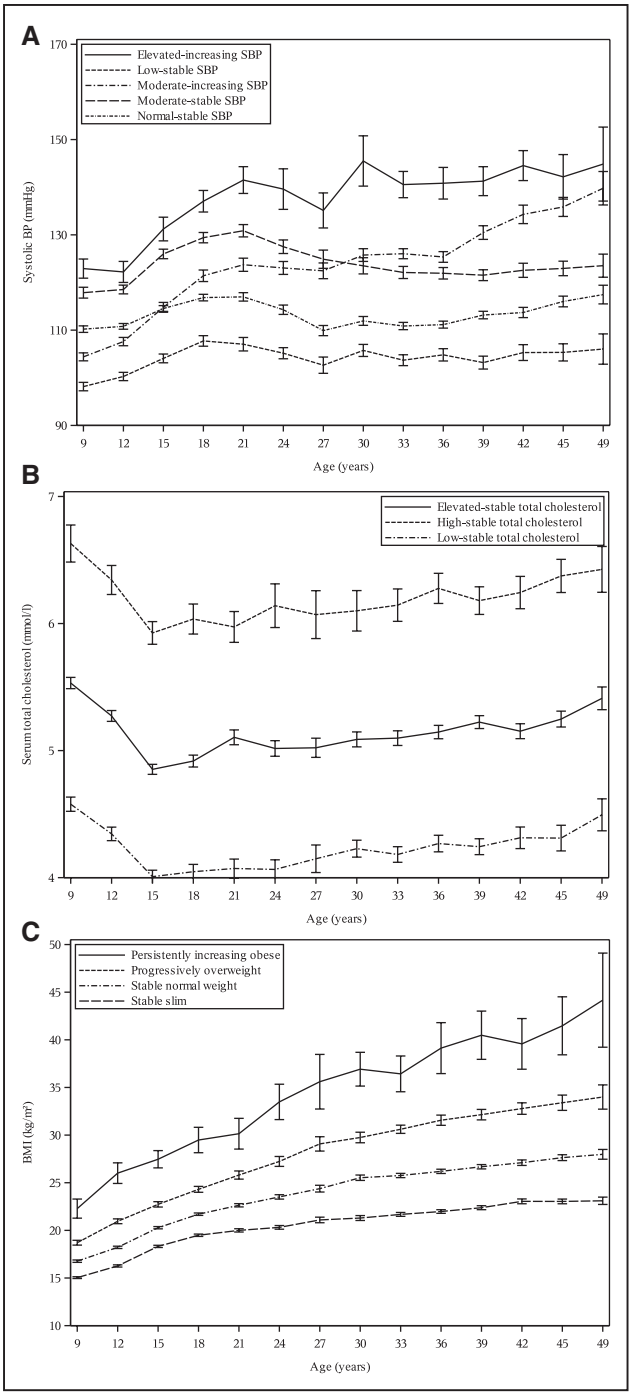


**Figure. Trajectories from childhood to midlife for SBP (A), serum total cholesterol (B), and BMI (C).**
Cardiovascular risk factor trajectories since childhood were identified using latent class growth mixture modeling. Values are means and 95% CIs for each cardiovascular risk factor. Five trajectory groups for SBP (**A**), 3 trajectory groups for serum total cholesterol (**B**), and 4 trajectory groups for BMI (**C**) were identified. Participants who had antihypertensive medication in any adulthood follow-up year (2001, 2007, or 2011) were excluded from the SBP trajectory modeling. Participants who had dyslipidemia medication in any adulthood follow-up year were excluded from the serum total cholesterol trajectory modeling. BMI measurements obtained during participants' pregnancies were excluded from the BMI trajectory modeling. BMI indicates body mass index; and SBP, systolic blood pressure.

but continuously increasing BP level from youth to midlife, and (5) elevated-increasing SBP (N=141, 6.0%) with elevated SBP in childhood and continuously increasing BP level throughout adulthood. For serum total cholesterol (N=2562), a 3-group trajectory solution was considered optimal (Figure B): (1) low-stable total cholesterol (N=690, 26.9%) with consistently low serum total cholesterol, (2) elevated-stable total cholesterol (N=1409, 55.0%) with serum total cholesterol levels consistently close to ideal (<5.172 mmol/L),[25] and (3) high-stable total cholesterol (N=463, 18.1%) with consistently high serum total cholesterol. For BMI (N=2588), a 4-group trajectory solution was considered optimal (Figure C): (1) stable slim (N=994, 38.4%) with consistently low body weight, (2) stable normal weight (N=1104, 42.7%) with body weight consistently close to normal (25 kg/m$^2$), (3) progressively overweight (N=412, 15.9%) reaching overweight in childhood or adolescence and gaining weight throughout adulthood, and (4) persistently increasing obese (N=78, 3.0%) reaching obesity in childhood or adolescence and gaining weight throughout adulthood. A detailed description of the creation of the CVRF trajectories is presented in the Expanded Methods in the Data Supplement.

Linear regression analyses were conducted to investigate the associations of CVRF trajectory groups and midlife cognitive performance. All regression analyses were conducted as multivariable models using the standardized principal components for cognitive performance as outcome variables and adjusting for age, sex, and polygenic risk score. Furthermore, a fully adjusted model additionally included other adulthood CVRFs (SBP, serum total cholesterol, BMI, fasting serum glucose, smoking, physical activity, and diet). In addition, all analyses were further adjusted for childhood school performance, childhood SES, and adulthood education. $P<0.05$ was considered the level of statistical significance. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, NC).

# RESULTS

## Characteristics and Representativeness of the Study Population

The background characteristics of the study population and number of participants in the cognitive tests are presented in the Table 1. This study leveraged the data on the YFS participants with cognitive data (1104 women and 922 men; age 10.8 years at baseline and 41.8 years at cognitive testing). The descriptive characteristics individually for each SBP, serum total cholesterol, and BMI trajectory groups in the 21- and 31-year follow-ups are presented in Table 2. For DBP, LDL cholesterol, HDL cholesterol, and triglyceride trajectory groups, the descriptive characteristics are presented in Table XXIII in the Data Supplement. Representativeness of the study population participating in the cognitive testing was examined by comparing the baseline and 21-year follow-up data between the participants and nonparticipants (Table XXIV in the Data Supplement).

## CVRF Trajectories From Childhood to Midlife and Cognitive Performance

SBP was inversely associated with episodic memory and associative learning; the elevated-increased SBP group

**Table 1. Background Characteristics of the Study Population**

| Background characteristics | Data |
|---|---|
| Sex | |
| Women, n (%) | 1104 (54.5) |
| Men, n (%) | 922 (45.5) |
| Age, y (N=2026) | |
| At baseline | 10.8 (5.0) |
| At cognitive testing | 41.8 (5.0) |
| Years of education (N=1928) | 14.9 (2.8) |
| Adulthood smoking, n (%) yes (N=2017) | 494 (24.4) |
| Antihypertensive medication, n (%) yes (N=2018) | 221 (11.0) |
| Dyslipidemia medication, n (%) yes (N= 2018) | 87 (4.3) |
| Cognitive components, mean (SD)* | |
| Women | |
| Paired Associates Learning test (N=1848) | 0.05 (0.99) |
| Rapid Visual Information Processing test (N=1975) | –0.06 (0.97) |
| Reaction Time test (N=1822) | –0.18 (0.94) |
| Spatial Working Memory test (N=2011) | –0.16 (0.96) |
| Men | |
| Paired Associates Learning text (N=1848) | –0.06 (1.01) |
| Rapid Visual Information Processing text (N=1975) | 0.07 (1.03) |
| Reaction Time test (N=1822) | 0.22 (1.03) |
| Spatial Working Memory test (N=2011) | –0.20 (1.01) |

Values are mean (SD) for continuous variables and n (%) for categorical variables. Adulthood smoking status was dichotomized into smokers and nonsmokers where "active smoking" was defined if the participant reported smoking daily in any of the adulthood follow-up time points (2001, 2007, or 2011). The use of antihypertensive medication in any adulthood follow-up survey was defined as "antihypertensive medication use." The use of dyslipidemia medication in any adulthood follow-up survey was defined as "dyslipidemia medication use." For cognitive components, we used a principal component analysis to calculate components indicating episodic memory and associative learning (Paired Associates Learning test), visual processing and sustained attention (Rapid Visual Information Processing test), reaction and movement time (Reaction Time test), and short-term working memory (Spatial Working Memory test) in the Cambridge Neuropsychological Test Automated Battery.

*Cognitive components were standardized; mean=0, SD=1.

had worse episodic memory and associative learning compared with the normal-stable SBP group (Paired Associates Learning test; β=–0.256 SD [95% CI, –0.510 to –0.002]; age, sex, and polygenic risk score adjusted). In addition, the moderate-increasing SBP group had worse visual processing and sustained attention compared with the normal-stable SBP group (Rapid Visual Information Processing test; β=–0.201 SD [95% CI, –0.343 to –0.060]; age, sex, and polygenic risk score adjusted). After adding adulthood CVRFs (BMI, serum total cholesterol, fasting serum glucose, smoking, physical activity, and diet) into the multivariable model, the associations for SBP remained essentially similar (Table 3A for episodic memory and associative learning, Table 3B for visual processing and sustained attention). In addition, in the fully adjusted model, a better performance in the reaction and movement time test was observed for the moderate-stable SBP group compared with the normal-stable SBP group (Reaction Time test; Table 3C). No associations were found between SBP trajectory groups and short-term working memory (Spatial Working Memory test; Table 3D). Furthermore, no associations were found between DBP trajectory groups and any cognitive domains (Table XXVA in the Data Supplement).

Serum total cholesterol was inversely associated with episodic memory and associative learning; the high-stable total cholesterol group had worse episodic memory and associative learning compared with the low-stable total cholesterol group (Paired Associates Learning test; β=–0.238 SD [95% CI, –0.386 to –0.090]; age, sex, and polygenic risk score adjusted). After additional adjustments for adulthood CVRFs (SBP, BMI, fasting serum glucose, smoking, physical activity, and diet), the association for episodic memory and associative learning remained essentially similar (Table 3A). No associations were found for serum total cholesterol trajectories on other cognitive domains (Table 3B through 3D). For serum LDL cholesterol trajectories, a similar inverse association was found for episodic memory and associative learning compared with serum total cholesterol trajectory analysis (Table XXVB in the Data Supplement). Furthermore, no associations were found for HDL cholesterol or triglyceride trajectory groups and any cognitive domain (Table XXVC and D in the Data Supplement).

BMI showed an inverse graded association with visual processing and sustained attention; the progressively overweight (β=–0.213 SD [95% CI, –0.350 to –0.075]) and persistently increasing obese (β=–0.540 SD [95% CI, –0.835 to –0.246]) groups had worse visual processing and sustained attention (Rapid Visual Information Processing test) compared with the stable normal weight group after adjusting for age, sex, and polygenic risk score. After adding adulthood CVRFs (SBP, serum total cholesterol, fasting serum glucose, smoking, physical activity, and diet) into the multivariable model, the associations remained essentially similar (Table 3B). No associations were found for the BMI trajectory groups for other cognitive domains (Table 3A, 3C, and 3D).

## CVRF Accumulation From Childhood to Midlife and Cognitive Performance

To study the possible association of the CVRF accumulation since childhood, a risk score was calculated on the basis of the CVRF trajectories (Table XXVI in the Data Supplement). Risk points were given to participants belonging to (1) moderate-increasing SBP or elevated-increasing SBP groups, (2) high-stable total cholesterol group, (3) progressively overweight or persistently increasing obese groups, and (4) those having antihypertensive or dyslipidemia medication in adulthood. The risk points were summed to form the risk score indicating the longitudinal CVRF accumulation. The descriptive

**Table 2. Descriptive Characteristics for the Cardiovascular Risk Factor Trajectory Groups**

| Variable | N (%) | | SBP, mm Hg (SD) | | Total cholesterol, mmol/L (SD) | | Body mass index, kg/m$^2$ (SD) | |
|---|---|---|---|---|---|---|---|---|
| | Total* | Women† | In year 2001 | In year 2011 | In year 2001 | In year 2011 | In year 2001 | In year 2011 |
| Systolic blood pressure (N=2634) | | | | | | | | |
| Low-stable SBP | 415 (15.8) | 314 (75.7) | 102.56 (7.47) | 105.23 (8.16) | 4.95 (0.92) | 4.99 (0.95) | 22.82 (3.41) | 24.16 (3.90) |
| Normal-stable SBP | 935 (35.5) | 621 (66.4) | 110.44 (7.17) | 113.41 (9.06) | 5.07 (0.91) | 5.13 (0.89) | 24.36 (3.84) | 25.70 (4.61) |
| Moderate-stable SBP | 399 (15.0) | 155 (38.8) | 122.01 (7.85) | 122.17 (8.06) | 5.22 (0.92) | 5.22 (1.00) | 25.88 (4.04) | 27.13 (4.62) |
| Moderate-increasing SBP | 471 (17.9) | 150 (31.8) | 124.30 (7.95) | 130.20 (11.25) | 5.28 (1.05) | 5.33 (0.99) | 25.53 (3.98) | 27.21 (4.76) |
| Elevated-increasing SBP | 141 (5.4) | 36 (25.5) | 137.97 (11.31) | 143.07 (12.71) | 5.54 (0.98) | 5.50 (0.95) | 27.69 (4.82) | 27.77 (4.27) |
| Antihypertensive medication‡ | 273 (10.4) | 145 (53.1) | 127.96 (14.30) | 125.56 (14.74) | 5.43 (1.11) | 5.20 (0.93) | 28.11 (5.82) | 30.16 (6.56) |
| Total cholesterol (N=2662) | | | | | | | | |
| Low-stable total cholesterol | 690 (25.9) | 362 (52.5) | 114.47 (12.62) | 116.21 (12.95) | 4.23 (0.55) | 4.29 (0.54) | 24.27 (3.96) | 25.80 (4.81) |
| Elevated-stable total cholesterol | 1409 (52.9) | 788 (55.9) | 116.32 (12.85) | 118.80 (14.04) | 5.17 (0.64) | 5.23 (0.65) | 25.00 (4.45) | 26.35 (4.88) |
| High-stable total cholesterol | 463 (17.4) | 253 (54.6) | 118.15 (12.78) | 122.81 (14.91) | 6.25 (0.81) | 6.31 (0.84) | 25.96 (4.51) | 27.14 (4.99) |
| Dyslipidemia medication‡ | 100 (3.8) | 32 (32.0) | 127.89 (15.40) | 123.84 (13.46) | 6.32 (1.30) | 5.23 (1.22) | 27.64 (4.80) | 30.46 (6.57) |
| Body mass index (N=2588) | | | | | | | | |
| Stable slim | 994 (38.4) | 611 (61.5) | 113.39 (12.09) | 116.16 (14.23) | 5.02 (0.93) | 5.07 (0.94) | 21.62 (1.99) | 22.64 (2.31) |
| Stable normal weight | 1104 (42.7) | 530 (48.0) | 116.82 (12.49) | 119.32 (13.29) | 5.23 (1.01) | 5.27 (0.95) | 25.61 (2.46) | 27.01 (2.86) |
| Progressively overweight | 412 (15.9) | 214 (51.9) | 121.76 (14.07) | 124.30 (13.87) | 5.34 (0.98) | 5.21 (0.95) | 30.06 (3.31) | 32.64 (3.92) |
| Persistently increasing obese | 78 (3.0) | 41 (52.6) | 128.55 (15.57) | 126.69 (15.04) | 5.37 (1.01) | 5.06 (0.98) | 37.52 (4.67) | 39.70 (7.23) |

Values are mean (SD) for continuous variables and n (%) for categorical variables. Year 2001 indicates follow-up year 21 and year 2011 indicates follow-up year 31. SBP indicates systolic blood pressure.

*Percentages are calculated against the total population.

†Percentages are calculated against the participants within each trajectory group.

‡If participants had antihypertensive or dyslipidemia medication in any adulthood follow-up year 2001, 2007, or 2011, they were defined to belong to medication group and were excluded from the trajectory modeling.



characteristics for the risk score groups are presented in the Table 4.

For the CVRF score, inverse linear trends were found for episodic memory and associative learning (Paired Associates Learning test; β=–0.068, *P*=0.026 for trend), visual processing and sustained attention (Rapid Visual Information Processing test; β=–0.139, *P*<0.0001 for trend), and reaction and movement time (Reaction Time test; β=–0.078, *P*=0.015 for trend) in the age, sex, and polygenic risk score–adjusted analyses. After additional adjustments for fasting serum glucose, smoking, physical activity, and diet score, the association remained essentially similar (Table 5). In the multivariable model analyses for the increasing number of CVRFs, the group without any CVRFs was used as the reference. An inverse association was found on episodic memory and associative learning for 3 CVRFs, on visual processing and sustained attention for 2 CVRFs and with 3 CVRFs, and with 2 CVRFs on reaction and movement time (Table 5); adjusted for age, sex, and polygenic risk score. After additional adjustments for fasting serum glucose, smoking, physical activity, and diet, the association diluted only marginally (Table 5). No associations were found for short-term working memory (Spatial Working Memory test).

To increase the clinical interpretability of our findings, we transformed the association of longitudinal CVRF accumulation to correspond with cognitive aging; we compared the β estimates of the CVRF score with the β estimates of age in the test-specific fully adjusted multivariable models (estimates for age: Paired Associates Learning test β=–0.056 SD; Rapid Visual Information Processing test β=–0.022 SD; Reaction Time test β=–0.009 SD; Table 5). For example, for episodic memory and associative learning, the β estimate for the participants having 3 CVRFs corresponded with a 6.9-year difference in cognitive age. For visual processing and sustained attention, the β estimate for those with 3 CVRFs corresponded with a 20.6-year effect of cognitive aging, whereas the β estimate for those with 2 CVRFs corresponded with a 17.9-year difference in cognitive age for reaction and movement time.

## Additional Analyses

We conducted additional multivariable analyses where the fully adjusted models (age, sex, polygenic risk score, adulthood SBP, serum total cholesterol, BMI, fasting serum glucose, smoking, physical activity, and diet) were further adjusted with childhood school performance,

**Table 3. Associations Between Cardiovascular Risk Factor Trajectories From Childhood to Midlife and Cognitive Performance in Midlife**

| Test | β Estimate | 95% CI | *P* value |
|---|---|---|---|
| A. Paired Associates Learning test | | | |
| Systolic blood pressure (N=1389) | | | |
| Normal stable | Reference | | |
| Low stable | 0.075 | –0.070 to 0.220 | 0.309 |
| Moderate stable | –0.047 | –0.196 to 0.102 | 0.535 |
| Moderate increasing | –0.063 | –0.211 to 0.084 | 0.399 |
| Elevated increasing | –0.262* | –0.520 to –0.005* | 0.046* |
| Serum total cholesterol (N=1489) | | | |
| Low stable | Reference | | |
| Elevated stable | –0.040 | –0.153 to 0.074 | 0.494 |
| High stable | –0.214* | –0.365 to –0.064* | 0.005* |
| Body mass index (N=1557) | | | |
| Stable normal weight | Reference | | |
| Stable slim | –0.055 | –0.162 to 0.052 | 0.311 |
| Progressively overweight | 0.027 | –0.116 to 0.170 | 0.712 |
| Persistently increasing obese | –0.207 | –0.520 to 0.107 | 0.197 |
| B. Rapid Visual Information Processing test | | | |
| Systolic blood pressure (N=1476) | | | |
| Normal stable | Reference | | |
| Low stable | –0.115 | –0.260 to 0.029 | 0.118 |
| Moderate stable | –0.003 | –0.148 to 0.143 | 0.970 |
| Moderate increasing | –0.185* | –0.327 to –0.043* | 0.011* |
| Elevated increasing | –0.157 | –0.396 to 0.082 | 0.197 |
| Serum total cholesterol (N=1585) | | | |
| Low stable | Reference | | |
| Elevated stable | 0.011 | –0.098 to 0.121 | 0.838 |
| High stable | –0.049 | –0.195 to 0.097 | 0.513 |
| Body mass index (N=1662) | | | |
| Stable normal weight | Reference | | |
| Stable slim | –0.067 | –0.171 to 0.038 | 0.210 |
| Progressively overweight | –0.165* | –0.304 to –0.025* | 0.021* |
| Persistently increasing obese | –0.407* | –0.708 to –0.105* | 0.008* |
| C. Reaction Time test | | | |
| Systolic blood pressure (N=1369) | | | |
| Normal stable | Reference | | |
| Low stable | 0.021 | –0.126 to 0.168 | 0.780 |
| Moderate stable | 0.155* | 0.003 to 0.306* | 0.045* |
| Moderate increasing | –0.020 | –0.169 to 0.129 | 0.795 |
| Elevated increasing | 0.197 | –0.064 to 0.459 | 0.139 |
| Serum total cholesterol (N=1466) | | | |
| Low stable | Reference | | |
| Elevated stable | –0.026 | –0.143 to 0.090 | 0.658 |
| High stable | –0.065 | –0.221 to 0.092 | 0.418 |
| Body mass index (N=1533) | | | |
| Stable normal weight | Reference | | |

(*Continued*)

**Table 3. Continued**

| Test | β Estimate | 95% CI | *P* value |
|---|---|---|---|
| Stable slim | –0.020 | –0.130 to 0.090 | 0.717 |
| Progressively overweight | –0.016 | –0.164 to 0.132 | 0.836 |
| Persistently increasing obese | –0.305 | –0.630 to 0.020 | 0.065 |
| D. Spatial Working Memory test | | | |
| Systolic blood pressure (N=1502) | | | |
| Normal stable | Reference | | |
| Low stable | 0.030 | –0.112 to 0.171 | 0.679 |
| Moderate stable | –0.085 | –0.229 to 0.058 | 0.245 |
| Moderate increasing | –0.061 | –0.201 to 0.079 | 0.396 |
| Elevated increasing | –0.165 | –0.401 to 0.071 | 0.170 |
| Serum total cholesterol (N=1613) | | | |
| Low stable | Reference | | |
| Elevated stable | –0.091 | –0.200 to 0.019 | 0.104 |
| High stable | –0.068 | –0.213 to 0.077 | 0.358 |
| Body mass index (N=1693) | | | |
| Stable normal weight | Reference | | |
| Stable slim | –0.064 | –0.167 to 0.039 | 0.224 |
| Progressively overweight | 0.029 | –0.109 to 0.166 | 0.683 |
| Persistently increasing obese | 0.151 | –0.146 to 0.448 | 0.318 |

Values are β estimates, 95% CIs, and *P* values from linear regression models. All models were adjusted for age, sex, polygenic risk score, and adulthood cardiovascular risk factors (fasting serum glucose, smoking, physical activity, and diet). For systolic blood pressure, models were further adjusted with adulthood body mass index and adulthood serum total cholesterol. For serum total cholesterol, models were further adjusted with adulthood body mass index and adulthood systolic blood pressure. For body mass index, models were further adjusted with adulthood systolic blood pressure and adulthood serum total cholesterol. Cognitive tests measured episodic memory and associative learning (Paired Associates Learning test), visual processing and sustained attention (Rapid Visual Information Processing test), reaction and movement time (Reaction Time test), and short-term working memory (Spatial Working Memory test); and the Cambridge Neuropsychological Test Automated Battery was used for cognitive testing. SBP indicates systolic blood pressure.

*Data are significant.

adulthood education, and childhood SES (Tables XXVII and XXVIII in the Data Supplement). Because of missing data on the additional covariates, the number of participants was lower in these additional models. The analyses for SBP and episodic memory and associative learning showed that the β estimate for the elevated-increasing SBP group remained similar after the additional adjustments, but the *P* value was slightly diluted (model without additional adjustments: β=–0.262 SD, *P*=0.046 versus model with additional adjustments: β=–0.221 SD, *P*=0.127). For visual processing and sustained attention, the association for the moderate-increasing SBP group remained substantially similar as in the model without the additional adjustments (β=–0.185 SD, *P*=0.011 versus β=–0.179 SD, *P*=0.020). In the analyses for serum total cholesterol and episodic memory and associative learning, the β estimate for the high-stable total cholesterol strengthened after the additional adjustments (β=–0.214 SD, *P*=0.005 versus β=–0.259 SD, *P*=0.002). In relation to the association between BMI and visual processing and sustained attention, an inverse graded association was observed similar to the analyses without the additional adjustments (progressively overweight: β=–0.165 SD, *P*=0.021 versus β=–0.170 SD, *P*=0.022 and persistently increasing obese: β=–0.407 SD, *P*=0.008 versus β=–0.377 SD, *P*=0.018). Furthermore, for the CVRF score, an inverse association for episodic memory and associative learning was observed similar to the analyses without the additional adjustments (3 CVRFs: β=–0.390 SD, *P*=0.011 versus β=–0.345 SD, *P*=0.041). For visual processing and sustained attention, β estimates were marginally lower in the analyses with the additional adjustments (2 CVRFs: β=–0.241 SD, *P*=0.001 versus β=–0.213 SD, *P*=0.007; 3 CVRFs: β=–0.443 SD, *P*=0.003 versus β=–0.404 SD, *P*=0.008). For reaction and movement time, the β estimate was similar but the *P* value was diluted in the analyses with the additional adjustments (2 CVRFs: β=–0.164 SD, *P*=0.037 versus β=–0.167 SD, *P*=0.059).

## DISCUSSION

We observed that longitudinal exposure to high SBP and serum total cholesterol since childhood are associated

**Table 4. Descriptive Characteristics for Cardiovascular Risk Factor Score Groups**

| Score | N (%) | | In year 2011 | | |
|---|---|---|---|---|---|
| | Total* | Women† | Systolic blood pressure, mm Hg (SD) | Total cholesterol, mmol/L (SD) | Body mass index, kg/m² (SD) |
| 0 | 826 (48.1) | 523 (63.3) | 112.24 (10.12) | 4.89 (0.75) | 24.36 (3.30) |
| 1 | 598 (34.8) | 303 (50.7) | 122.87 (13.41) | 5.29 (0.98) | 27.01 (4.66) |
| 2 | 244 (14.2) | 98 (40.2) | 129.74 (13.75) | 5.64 (1.00) | 30.68 (5.71) |
| 3 | 50 (2.9) | 17 (34.0) | 134.35 (16.56) | 5.66 (1.27) | 34.98 (5.64) |

Values are means (SDs) for continuous variables and n (%) for categorical variables. Year 2011 indicates 31-year follow-up study. Risk points were given to participants belonging to adverse trajectory groups: (1) in systolic blood pressure, moderate-increasing systolic blood pressure or elevated-increasing systolic blood pressure groups; (2) in serum total cholesterol, high-stable total cholesterol group; (3) in body mass index, progressively overweight or persistently increasing obese groups; and (4) if participants had antihypertensive or dyslipidemia medication in any adulthood follow-up year (2001, 2007, or 2011), they were given a risk point for that specific risk factor. The analyses were conducted among Cardiovascular Risk in Young Finns Study participants with data on cognitive performance and polygenic risk score for cognitive performance (N=1718).

*Percentages are calculated against the total population.

†Percentages are calculated against the participants within each trajectory group.

with poorer midlife episodic memory and associative learning and that overweight and obesity from childhood to midlife associate with worse visual processing and sustained attention in midlife. It is important to note that we found that longitudinal accumulation of CVRFs since childhood associates with poorer episodic memory and associative learning, longer reaction and movement time, as well as worse visual processing and sustained attention in an additive graded manner.

Our present results complement the previous findings from the YFS,[15] where SBP, serum total and LDL cholesterol, and smoking in childhood and adolescence were associated with poor episodic memory and associative learning independent of the adulthood CVRFs. In the present study, similar associations were observed for SBP, serum total cholesterol, and serum LDL cholesterol in relation to episodic memory and associative learning, because the trajectory groups with consistently elevated SBP, high serum total cholesterol, and high serum LDL cholesterol level had worse performance in the Paired Associates Learning test. Adverse association for serum total cholesterol might mainly be mediated via serum LDL cholesterol, because there were no associations for serum HDL cholesterol or serum triglycerides. Furthermore, our previous study indicated weak adverse associations of BMI, serum lipids, and smoking for visual processing and sustained attention, that is, cognitive domains localized in the frontal areas of the brain. In the present study, the longitudinal approach was gained through applying the CVRF trajectories, which brought up the clear inverse association between obesity since childhood and visual processing and sustained attention in midlife. These observations are supported by previous findings on the associations between CVRFs and frontal lobe–related cognitive domains.[9,11–13] The present study also brings new evidence on the graded association of CVRF accumulation on visual processing and sustained attention, on reaction and movement time, and on episodic memory and associative learning. These novel findings underline the importance of early identification of CVRFs already beginning from childhood. Primary prevention of cognitive deficits and dementia by treating CVRFs in midlife is acknowledged by the Lancet Commission.[1] Noticeably, the only early life (<45 years of age) risk factor pointed out in the Commission's statement is low education. Together with our previous findings on the independent role of childhood CVRFs on adulthood cognitive performance,[15] the present findings support the view that CVRFs are potentially relevant in dementia risk prevention already earlier than believed. In addition, our findings indicate that the guidelines on the CVRF levels established for cardiovascular disease prevention[25] could also be applied in relation to cognitive performance outcomes.

To our knowledge, this is the first longitudinal population-based study examining the association between CVRF accumulation from childhood to midlife and cognitive performance in midlife. Previous evidence on the effects of CVRF accumulation is mainly based on elderly cohorts in which the CVRFs and cognitive performance have been assessed among participants >50,[5,8,10,12] 60,[3,5] or even 70 years of age.[4,5,7] The neuropathological processes causing cognitive deficits are known to be ongoing already years or decades before manifesting as clinical cognitive deficits.[2] Therefore, middle-aged or elderly cohorts are not necessarily the optimal target populations when aiming to find means for primary or primordial prevention for cognitive deficits. Furthermore, in the previous longitudinal studies on CVRF accumulation, the CVRF measurements have usually been performed only at a single time point.[5,7–10] Nevertheless, our findings are supported by previous longitudinal studies on older cohorts. The CARDIA study has shown adverse associations of longitudinally measured SBP and DBP, fasting blood glucose and serum total cholesterol

**Table 5. Association Between Cardiovascular Risk Factor Score and Cognitive Performance in Midlife**

| Cardiovascular risk factor score | Model 1 | | | Model 2 | | | Difference in cognitive aging* |
|---|---|---|---|---|---|---|---|
| | β estimate | 95% CI | *P* value | β estimate | 95% CI | *P* value | |
| Episodic memory and associative learning (Paired Associates Learning test; N=1551) | | | | | | | |
| 0 | Reference | | | Reference | | | |
| 1 | –0.062 | –0.169 to 0.045 | 0.256 | –0.069 | –0.176 to 0.038 | 0.207 | |
| 2 | –0.104 | –0.250 to 0.043 | 0.166 | –0.128 | –0.277 to 0.020 | 0.090 | |
| 3 | –0.305† | –0.600 to –0.010† | 0.043* | –0.390† | –0.691 to –0.088† | 0.011† | 6.9 |
| Visual processing and sustained attention (Rapid Visual Information Processing test; N=1656) | | | | | | | |
| 0 | Reference | | | Reference | | | |
| 1 | –0.104 | –0.208 to 0.001 | 0.051 | –0.097 | –0.202 to 0.007 | 0.068 | |
| 2 | –0.271† | –0.414 to –0.127† | 0.0002† | –0.241† | –0.386 to –0.095† | 0.001† | 11.2 |
| 3 | –0.488† | –0.768 to –0.208† | 0.001† | –0.443† | –0.730 to –0.157† | 0.003† | 20.6 |
| Reaction and movement time (Reaction Time test; N=1527) | | | | | | | |
| 0 | Reference | | | Reference | | | |
| 1 | –0.053 | –0.163 to 0.058 | 0.351 | –0.046 | –0.156 to 0.064 | 0.411 | |
| 2 | –0.199† | –0.353 to –0.046† | 0.011† | –0.164† | –0.318 to –0.010† | 0.037† | 17.9 |
| 3 | –0.152 | –0.459 to 0.154 | 0.331 | –0.122 | –0.434 to 0.190 | 0.442 | |
| Short-term working memory (Spatial Working Memory test; N=1687) | | | | | | | |
| 0 | Reference | | | Reference | | | |
| 1 | 0.067 | –0.035 to 0.170 | 0.198 | 0.066 | –0.036 to 0.169 | 0.205 | |
| 2 | –0.016 | –0.156 to 0.125 | 0.827 | –0.014 | –0.156 to 0.128 | 0.846 | |
| 3 | 0.082 | –0.195 to 0.359 | 0.560 | 0.081 | –0.204 to 0.365 | 0.578 | |

Values are β estimates, and 95% CIs and *P* values are from linear regression models. Model 1 was adjusted for age, sex, and polygenic risk score. Model 2 was also adjusted for adulthood cardiovascular risk factors (fasting serum glucose, smoking, physical activity, and diet). The Cambridge Neuropsychological Test Automated Battery for (1) episodic memory visuospatial associative learning (Paired Associates Learning test), (2) visual processing and sustained attention (Rapid Visual Information Processing test), (3) reaction and movement time (Reaction Time test), and (4) short-term working memory (Spatial Working Memory test) was used for cognitive testing. A significant inverse trend between increasing number of cardiovascular risk factors and cognitive performance was found for (1) episodic memory and associative learning (*P* value for trend: *P*=0.026 in model 1 and *P*=0.008 in model 2), (2) visual processing and sustained attention (*P* value for trend: *P*<0.0001 in models 1 and 2), and (3) reaction and movement time (*P* value for trend: *P*=0.015 in model 1 and *P*=0.048 in model 2), whereas the trend was nonsignificant for short-term working memory (*P* value for trend: *P*=0.638 in model 1 and *P*=0.636 in model 2).

*For the statistically significant results, the association of the cardiovascular risk factor accumulation was compared with the effect of age on the same cognitive domain to increase the clinical interpretation of the findings. For that, the difference in cognitive aging was estimated dividing the β estimates for the cardiovascular risk factor accumulation score by the β estimate for age from the same statistical model (β estimates for age for the separate cognitive domains: Paired Associates Learning test β=–0.056 SD; Rapid Visual Information Processing test β=–0.022 SD; Reaction Time test β=–0.009 SD).

†Data are significant.

with executive function, and processing speed and verbal memory measured in adulthood and midlife.[11] The CARDIA study also found that the number of ideal cardiovascular health components, defined by the American Heart Association,[25] was longitudinally and directly associated with all studied cognitive domains.[12] Further supporting our results, the PATH (Personality and Total Health) Through Life Project has pointed out that CVRF accumulation may be associated with decline in reaction time during 8 years of follow-up in participants aged 43 years at baseline.[9] In addition, in the ELSA (English Longitudinal Study of Ageing) cohort, midlife accumulation of CVRFs (eg, diabetes, hypertension, smoking, physical inactivity, and obesity) was associated with accelerated memory decline during 10 years of follow-up,[4] whereas in the Framingham Heart Study, longitudinal exposure to both obesity and hypertension in midlife has been found to inversely associate with memory in men.[3]

There are some previous studies applying the latent class growth mixture modeling for longitudinally measured CVRFs. A previous study on the YFS cohort reported a model with 6 trajectory groups for BMI.[30] The differences between the previous and the present BMI trajectory models were mainly in the separate trajectories for overweight and obese participants in the previous study and for consistently slim and normal weight participants in the present study. Eventually, the aim of the present study was to examine the association of longitudinal trajectories since childhood with effective clinical classification accuracy and cognitive performance. Therefore, a model with fewer BMI groups was selected to ensure reliable classification accuracy for meaningful analyses on cognitive performance. In relation to SBP, the trajectory model in the present study is in line with the BP trajectory model reported from the CARDIA

study.[31] Furthermore, similarly to our trajectory model for serum total cholesterol, 3 trajectory groups were identified for non-HDL cholesterol between young adulthood and midlife in the Framingham Offspring study[32] and 3 trajectory groups for HDL cholesterol on a subsample of the YFS cohort using cholesterol measurements until young adulthood (24 years of age).[33] Therefore, these previous findings support our longitudinal CVRF trajectory models.

To date, there are no studies in animal models examining the association between accumulation of the applied CVRFs and cognitive performance. Nevertheless, the animal data have shown inverse associations of hypercholesterolemia and obesity on cognitive performance, mainly learning and long-term memory, via neuroinflammatory changes,[34] cholinergic dysfunction, enhanced cortical β-amyloid and τ, and microbleedings,[35] as well as via regulation of cerebral blood flow by causing progressive dysfunction of the vascular endothelium-dependent relaxation.[36] Furthermore, the harmful association of hypertension for brain structures has been observed in rodents, because high BP has been linked to the leakage of serum components from small vessels into hippocampus through impaired blood–brain barrier possibly leading to neuronal and glial damage.[37] Furthermore, in human studies applying imaging methods, midlife hypertension has been suggested to accelerate the occurrence of white matter lesions, whereas increased midlife waist:hip ratio may associate with decreased total brain volume.[13] Furthermore, hypertension[13] has been suggested to associate with the disturbances in white matter perfusion and ischemia, which, at the same time, often manifests as deep white matter lesions.[38] In addition, periventricular white matter lesions in old age may originate from blood–brain barrier dysfunction or disturbance in cerebrospinal fluid production[38] and, interestingly, to associate with reduced processing speed.[39]

## Limitations and Strengths

Some limitations need to be addressed. First, cognitive performance was measured once in midlife. Therefore, there were no data on baseline cognitive performance, and, thus, we were unable to study the role of CVRFs on the changes in cognitive performance. However, we adjusted all analyses for polygenic risk score indicating genetic cognitive capacity. In addition to polygenic risk score, the analyses were adjusted for childhood school performance as a proxy for childhood cognitive performance and for childhood SES and adulthood education as an indicators of life-course SES. Second, acknowledging the lack of data after midlife, we were unable to study the role of CVRFs on cognitive performance with a whole life-course perspective. Third, with respect to the establishment of causality, all observational studies are prone to bias caused by reverse causation. Therefore, we are not able to draw firm conclusions on the causal relations between CVRFs and cognitive performance. Nevertheless, because it is impossible to perform randomized control trials to test life-course causal relations between CVRFs and cognitive performance in humans, the use of existing population cohorts with follow-up data from childhood to adulthood is the only realistic approach to study this topic. Fourth, several statistical tests were conducted, which increase the probability for false-positive findings. However, because the main analyses were based on strict a priori hypotheses, we did not apply multiple testing correction. Fifth, in observational studies such as the YFS, residual confounding might interrupt the interpretation of the results. For example, because of the lack of longitudinal childhood data on serum glucose levels, we were unable to conduct the trajectory analyses for serum glucose similarly as for other CVRFs. Nonetheless, our results remained robust to adjustment for a wide array of possible confounding factors including adulthood glucose levels. It remains possible, however, that some unmeasured factors contribute to the associations between CVRFs and cognitive performance. Sixth, the participants using antihypertensive and dyslipidemia medications were excluded from the CVRF trajectory analyses, and, therefore, the results for SBP and serum lipids may be underestimations of the true associations. However, in the analyses for the CVRF accumulation the participants using these medications were given risk points, which means that underestimation is not plausible considering our results for the CVRF accumulation. Last, latent class growth analysis offers a data-driven longitudinal method to model CVRFs. Because the method bases merely on the data and applies no a priori hypothesis for the groups, it allows for analysis of the lifelong natural history of CVRFs. Because of the lack of a priori hypothesis, the criticisms may point out that latent class growth analyses result in groups that do not exist or produce an oversimplification of the true variability of the CVRFs. However, if the diagnostic criteria related to the analyses are amply followed, as in our study, latent class growth analysis comprises an adequate method to model longitudinally measured CVRFs and to effectively differentiate participants into clinically meaningful groups.

The key strength of our study is the unique, large, randomly selected population-based cohort, which is representative of the general Finnish population. With a follow-up time over 30 years, it allows us to study the longitudinal associations between multiple CVRFs since childhood in healthy adults. We used computerized cognitive test with, for example, better accuracy, standardization, and reliability compared with traditional noncomputerized tests. Hence, even if not

applied in clinical practice, the YFS cognitive test is adequate and accurate in assessing different cognitive domains and, importantly, sensitive to detect differences in healthy adults.

## CONCLUSIONS

Our results show that SBP, serum total cholesterol, and BMI measured longitudinally from childhood to midlife associate with cognitive performance in midlife. It is important to note that the more adverse CVRFs were accumulated from childhood to midlife, the worse association for cognitive performance was observed in midlife. Given the current lack of cure for the major causes of dementia, delaying the onset of clinical cognitive deficits should be in the key focus of cognitive health promotion. If the associations found in the present study are causal, early interventions on CVRFs could offer an opportunity for primordial promotion of cognitive health.

## ARTICLE INFORMATION

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### Disclosures

None.

### Supplemental Materials

Expanded Methods
Expanded Results
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