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CARDIOVASCULAR RISK FACTOR TRAJECTORIES SINCE CHILDHOOD AND COGNITIVE PERFORMANCE IN MIDLIFE – THE CARDIOVASCULAR RISK IN YOUNG FINNS STUDY

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ABSTRACT

Background: Cardiovascular risk factors, such as high blood pressure, adverse serum lipids, and elevated body mass index in midlife may harm cognitive performance. Importantly, longitudinal accumulation of cardiovascular risk factors since childhood may associate with cognitive performance already since childhood, but the prior 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 (age 3-18 years) 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 aged 34-49 years 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% confidence interval (CI) -0.520–-0.005) or serum total cholesterol (β=-0.214 SD, 95%CI -0.365–-0.064) associated with worse midlife episodic memory and associative learning compared to consistently low values. Obesity since childhood associated with worse visual processing and sustained attention (β=-0.407 SD, 95%CI -0.708–-0.105) compared to normal weight. An inverse trend association was observed for the cardiovascular risk factor accumulation with episodic memory and associative learning (p for trend 0.008; three cardiovascular risk factors: β=-0.390 SD, 95%CI -0.691–-0.088), with visual processing and sustained attention (p for trend <0.0001; three cardiovascular risk factors: β=-0.443 SD, 95%CI -0.730–-0.157), and with reaction and movement time (p for trend 0.048; two cardiovascular risk factors: β=-0.164 SD, 95%CI -0.318–-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. Importantly, the higher the number of cardiovascular risk factors was, the worse cognitive performance was observed. Therefore, launching preventive strategies against cardiovascular risk factors beginning from childhood might benefit primordial promotion of cognitive health in adulthood.

Key words: cognitive performance, cardiovascular risk, trajectories, childhood, adulthood, midlife, longitudinal, population-based

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 already since childhood in order to promote adulthood cognitive health. Additionally, emphasis on reducing the number of risk factors may be beneficial.

- The findings from the current study elucidate possibilities to move the focus of cognitive decline prevention from secondary and tertiary prevention to primary and even primordial prevention through controlling cardiovascular risk factors already from childhood.

INTRODUCTION

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 34-49 years of age (in 2011) with the Cambridge Neuropsychological Test Automated Battery (CANTAB®, Cambridge Cognition, Cambridge, United Kingdom). The test battery included 4 tests that reflect different cognitive domains: (1) the Paired Associates Learning (PAL) test assessed episodic memory and associative learning, (2) the Spatial Working Memory (SWM) test measured short-term

working memory, (3) the Reaction Time (RTI) test measured reaction and movement time, and (4) Rapid Visual Information Processing (RVP) 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 is 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 <4mmol/l. Data on antihypertensive and dyslipidemia medications were obtained from the questionnaires in all adulthood follow-up studies (in 2001, 2007 and 2011). Weight (kg) and height (m) were measured, and body mass index (BMI) was calculated as weight (kg)/height (m^2)[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 (SISu) 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 (GWAS) summary statistics by assuming a prior for the genetic architecture and linkage disequilibrium (LD) information from a reference panel[21]: an infinitesimal fraction of causal variants were assumed, and summary statistics from Savage et al.[22] GWAS for intelligence were used. The LD between markers was estimated from the SISu 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 (*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. 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) <17000 euros, (2) 17000–27000 euros, (3) 27001–34000 euros, and (4) >34000 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 the 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-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-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 1 for SBP, serum

total cholesterol, and BMI; and Figures I-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-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-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 1/Panel 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 (<120mmHg) SBP level; (3) *moderate-stable SBP* (N=399, 16.9%) with SBP level consistently close to ideal (120mmHg)[25]; (4) *moderate-increasing SBP* (N=471, 20.0%) with normal SBP in childhood but continuously increasing BP level from youth to midlife; (5) *elevated-increasing SBP* (N=141, 6.0%) with elevated SBP in childhood and continuously increasing BP level throughout the adulthood. For serum total cholesterol (N=2562), a 3-group trajectory solution was considered optimal (Figure 1/Panel 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 (<5.172mmol/l)[25]; (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 1/Panel 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 (25kg/m^2); (3) *progressively overweight* (N=412, 15.9%) reaching overweight in childhood or adolescence and gaining weight throughout the adulthood; (4)

persistently increasing obese (N=78, 3.0%), reaching obesity in childhood or adolescence and gaining weight throughout the 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 as the level of statistical significance. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc. Cary, North Carolina, USA).

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 the 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 non-participants (Table XXIV in the Data Supplement).

Cardiovascular Risk Factor Trajectories from Childhood to Midlife and Cognitive Performance

SBP was inversely associated with episodic memory and associative learning; the 'elevated-increased SBP' group had worse episodic memory and associative learning compared with the 'normal-stable SBP' group (PAL-test; β=-0.256 SD, 95% confidence interval (CI) -0.510–-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 (RVP-test; β=-0.201 SD, 95%CI -0.343–-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 3/Panel A for episodic memory and associative learning, Panel B 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 (RTI-test; Table 3/Panel C). No associations were found between SBP trajectory groups and short-term working memory (SWM-test; Table 3/Panel D). Furthermore, no associations were found between DBP trajectory groups and any cognitive domains (Table XXV/Panel A 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 (PAL-test; β=-0.238 SD,

95%CI -0.386–-0.090; age, sex, and polygenic risk score adjusted). Furthermore, a weak inverse association was observed for the 'elevated-stable total cholesterol' group on short-term working memory (SWM-test; β=-0.099 SD, 95%CI -0.207–0.010; 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 3/Panel A), whereas the associations for short-term working memory was diluted (Table 3/Panel D). No associations were found for serum total cholesterol trajectories on other cognitive domains (Table 3/Panels B and C). 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 XXV/Panel B in the Data Supplement). Furthermore, no associations were found for HDL cholesterol or triglyceride trajectory groups and any cognitive domain (Table XXV/Panels C 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–-0.075) and 'persistently increasing obese' (β=-0.540 SD, 95%CI -0.835–-0.246) groups had worse visual processing and sustained attention (RVP-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 3/Panel B). No associations were found for the BMI trajectory groups for other cognitive domains (Table 3/Panels A, C, and D).

Cardiovascular Risk Factor 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 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 (PAL-test; β=-0.068, p=0.026 for trend), visual processing and sustained attention (RVP-test; β=-0.139, p<0.0001 for trend), and reaction and movement time (RTI-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 group. 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 (SWM-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: PAL-test β=-0.056 SD; RVP-test β=-0.022 SD; RTI-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, adulthood education, and childhood SES (Table 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 vs. 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 vs. 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 vs. 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 similarly to the analyses without the additional adjustments ('progressively overweight': β=-0.165 SD, p=0.021 vs. β=-0.170 SD, p=0.022 and 'persistently increasing obese': β=-0.407 SD, p=0.008 vs. β=-0.377 SD, p=0.018). Furthermore, for the CVRF score, an inverse association for episodic memory and associative learning was observed similarly to the analyses without the additional adjustments (3 CVRFs: β=-0.390 SD, p=0.011 vs. 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 vs. β=-0.213 SD, p=0.007; 3 CVRFs: β=-0.443 SD, p=0.003 vs. 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 (two CVRFs: β=-0.164 SD, p=0.037 vs. β=-0.167 SD, p=0.059).

DISCUSSION

We observed that longitudinal exposure to high SBP and serum total cholesterol since childhood are associated 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 poorer 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 PAL-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, *i.e.* 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[4,5,7]of age. 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 systolic and diastolic BP, fasting blood glucose and serum total cholesterol with executive function, processing speed and verbal memory measured in adulthood/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 English Longitudinal Study of Ageing (ELSA) cohort, midlife accumulation of CVRFs (*e.g.* 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 three 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 beta-amyloid and tau, 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 over-simplification of the true variability of the CVRFs. However, taken that 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 non-computerized 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.

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Disclosures

None.

Supplemental Materials

Expanded Methods

Expanded Results

Data Supplement Figures I-V

Data Supplement Tables I-XXVIII

References 40-41

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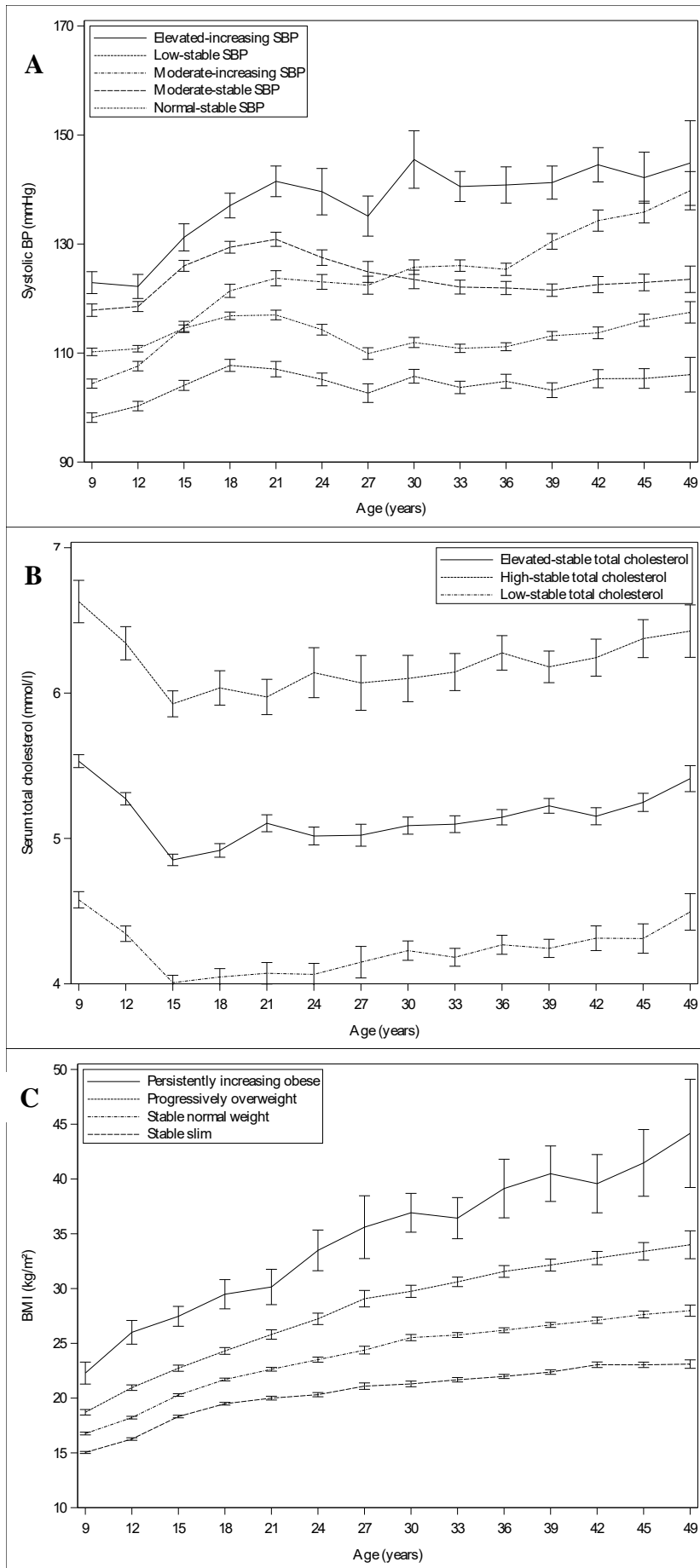
Figure 1. Trajectories from Childhood to Midlife for Systolic Blood Pressure (SBP) (A), Serum Total Cholesterol (B), and Body Mass Index (BMI) (C).

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.

Table 1. Background Characteristics of the Study Population.

Background characteristics			
Sex			
Women, N (%)		1104 (54.5)	
Men, N (%)		922 (45.5)	
Age, years (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**	**Men**
PAL-test (N=1848)	*Cognitive*	0.05 (0.99)	-0.06 (1.01)
RVP-test (N=1975)	*components*	-0.06 (0.97)	0.07 (1.03)
RTI-test (N=1822)	*were*	-0.18 (0.94)	0.22 (1.03)
SWM-test (N=2011)	*standardized;*	-0.16 (0.96)	-0.20 (1.01)
	mean 0, SD 1		

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.

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

	N (%)	N women (%)	SBP in year 2001 mmHg (SD)	SBP in year 2011 mmHg (SD)	Total cholesterol in year 2001 mmol/l (SD)	Total cholesterol in year 2011 mmol/l (SD)	BMI in year 2001 kg/m2 (SD)	BMI in year 2011 kg/m2 (SD)
Systolic blood pressure (SBP) (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 (BMI) (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**.**

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

	β estimate	95% CI	p-value		β estimate	95% CI	p-value
A. PAL-test				**C. RTI-test**			
Systolic blood pressure (N=1389)				**Systolic blood pressure (N=1369)**			
Normal-stable SBP	Reference			Normal-stable SBP	Reference		
Low-stable SBP	0.075	-0.070 – 0.220	0.309	Low-stable SBP	0.021	-0.126 – 0.168	0.780
Moderate-stable SBP	-0.047	-0.196 – 0.102	0.535	Moderate-stable SBP	**0.155**	**0.003 – 0.306**	**0.045**
Moderate-increasing SBP	-0.063	-0.211 – 0.084	0.399	Moderate-increasing SBP	-0.020	-0.169 – 0.129	0.795
Elevated-increasing SBP	**-0.262**	**-0.520 – -0.005**	**0.046**	Elevated-increasing SBP	0.197	-0.064 – 0.459	0.139
Serum total cholesterol (N=1489)				**Serum total cholesterol (N=1466)**			
Low-stable total cholesterol	Reference			Low-stable total cholesterol	Reference		
Elevated-stable total cholesterol	-0.040	-0.153 – 0.074	0.494	Elevated-stable total cholesterol	-0.026	-0.143 – 0.090	0.658
High-stable total cholesterol	**-0.214**	**-0.365 – -0.064**	**0.005**	High-stable total cholesterol	-0.065	-0.221 – 0.092	0.418
Body mass index (N=1557)				**Body mass index (N=1533)**			
Stable normal weight	Reference			Stable normal weight	Reference		
Stable slim	-0.055	-0.162 – 0.052	0.311	Stable slim	-0.020	-0.130 – 0.090	0.717

Progressively overweight	0.027	-0.116 – 0.170	0.712	Progressively overweight	-0.016	-0.164 – 0.132	0.836
Persistently increasing obese	-0.207	-0.520 – 0.107	0.197	Persistently increasing obese	-0.305	-0.630 – 0.020	0.065

B. RVP-test   **D. SWM-test**

Systolic blood pressure (N=1476)   **Systolic blood pressure (N=1502)**

Normal-stable SBP	Reference			Normal-stable SBP	Reference		
Low-stable SBP	-0.115	-0.260 – 0.029	0.118	Low-stable SBP	0.030	-0.112 – 0.171	0.679
Moderate-stable SBP	-0.003	-0.148 – 0.143	0.970	Moderate-stable SBP	-0.085	-0.229 – 0.058	0.245
Moderate-increasing SBP	**-0.185**	**-0.327 – -0.043**	**0.011**	Moderate-increasing SBP	-0.061	-0.201 – 0.079	0.396
Elevated-increasing SBP	-0.157	-0.396 – 0.082	0.197	Elevated-increasing SBP	-0.165	-0.401 – 0.071	0.170

Serum total cholesterol (N=1585)   **Serum total cholesterol (N=1613)**

Low-stable total cholesterol	Reference			Low-stable total cholesterol	Reference		
Elevated-stable total cholesterol	0.011	-0.098 – 0.121	0.838	Elevated-stable total cholesterol	-0.091	-0.200 – 0.019	0.104
High-stable total cholesterol	-0.049	-0.195 – 0.097	0.513	High-stable total cholesterol	-0.068	-0.213 – 0.077	0.358

Body mass index (N=1662)   **Body mass index (N=1693)**

Stable normal weight	Reference			Stable normal weight	Reference		
Stable slim	-0.067	-0.171 – 0.038	0.210	Stable slim	-0.064	-0.167 – 0.039	0.224

Progressively overweight	**-0.165**	**-0.304 – -0.025**	**0.021**	Progressively overweight	0.029	-0.109 – 0.166	0.683
Persistently increasing obese	**-0.407**	**-0.708 – -0.105**	**0.008**	Persistently increasing obese	0.151	-0.146 – 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.

Table 4. Descriptive Characteristics for Cardiovascular Risk Factor (CVRF) Score Groups.

Score	N (%)	N women (%)	SBP in year 2011 mmHg (SD)	Total cholesterol in year 2011 mmol/l (SD)	BMI in year 2011 kg/m^2 (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.

Table 5. Association between Cardiovascular Risk Factor (CVRF) Score and Cognitive Performance in Midlife.

Cardiovascular risk factor score	Model 1 β estimate	95% CI	p-value	Model 2 β estimate	95% CI	p-value	Difference in cognitive aging*
Episodic memory and associative learning (PAL-test; N=1551)							
0	*Reference group*			*Reference group*			
1	-0.062	-0.169 – 0.045	0.256	-0.069	-0.176 – 0.038	0.207	
2	-0.104	-0.250 – 0.043	0.166	-0.128	-0.277 – 0.020	0.090	
3	**-0.305**	**-0.600 – -0.010**	**0.043**	**-0.390**	**-0.691 – -0.088**	**0.011**	6.9
Visual processing and sustained attention (RVP-test; N=1656)							
0	*Reference group*			*Reference group*			
1	-0.104	-0.208 – 0.001	0.051	-0.097	-0.202 – 0.007	0.068	
2	**-0.271**	**-0.414 – -0.127**	**0.0002**	**-0.241**	**-0.386 – -0.095**	**0.001**	11.2
3	**-0.488**	**-0.768 – -0.208**	**0.001**	**-0.443**	**-0.730 – -0.157**	**0.003**	20.6
Reaction and movement time (RTI-test; N=1527)							
0	*Reference group*			*Reference group*			
1	-0.053	-0.163 – 0.058	0.351	-0.046	-0.156 – 0.064	0.411	
2	**-0.199**	**-0.353 – -0.046**	**0.011**	**-0.164**	**-0.318 – -0.010**	**0.037**	17.9
3	-0.152	-0.459 – 0.154	0.331	-0.122	-0.434 – 0.190	0.442	
Short-term working memory (SWM-test; N=1687)							
0	*Reference group*			*Reference group*			
1	0.067	-0.035 – 0.170	0.198	0.066	-0.036 – 0.169	0.205	

2	-0.016	-0.156 – 0.125	0.827	-0.014	-0.156 – 0.128	0.846
3	0.082	-0.195 – 0.359	0.560	0.081	-0.204 – 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.

SUPPLEMENTAL MATERIAL

CARDIOVASCULAR RISK FACTOR TRAJECTORIES SINCE CHILDHOOD AND

COGNITIVE PERFORMANCE IN MIDLIFE

–

THE CARDIOVASCULAR RISK IN YOUNG FINNS STUDY

by Hakala JO et al. 2021

EXPANDED METHODS

Participants

The Cardiovascular Risk in Young Finns Study (YFS) is a national ongoing longitudinal population-based study focusing on cardiovascular risk factors from childhood to adulthood. The first cross-sectional study was conducted in five Finnish university cities and their rural surroundings in 1980, when 3596 randomly selected individuals (boys and girls) aged 3, 6, 9, 12, 15, and 18 years participated in clinical examinations. All participants were white Caucasian. 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 design, population, and protocol of the YFS have been thoroughly reported elsewhere[16].

Ethics approval and consent to participate

The study protocol was reviewed and approved by Ethics Committees of each of the five participating universities (medical schools of Helsinki, Turku, Tampere, Kuopio, and Oulu). The written informed consent was obtained from all participants in accordance with the Helsinki Declaration[18].

Cognitive performance

Detailed description and validation of the cognitive data in YFS population have been reported previously[17]. During the latest follow-up examination in 2011, the Cambridge Neuropsychological Test Automated Battery (CANTAB®, Cambridge Cognition, Cambridge, UK) was used to assess cognitive performance among the participants aged 34-49 years, N=2026. The CANTAB® is a computerized, predominantly nonlinguistic, and culturally neutral test focusing on a wide range of cognitive domains. The test is performed using a validated touchscreen computer system. The full test battery includes 24 individual tests from which a suitable test battery for each particular study may be selected. In the YFS, the test battery was selected so that it could be accomplished in 20–30 minutes and included tests that are sensitive to aging[40,41]. The tests in YFS measured several cognitive domains: (a) short-term memory, (b) spatial working memory, (c) problem solving, (d) reaction time, (e) attention, (f) rapid visual processing, (g) visual memory, (h) episodic memory, and (i) visuospatial learning.

Cognitive testing was performed during clinical examination. Due to the blood sampling included in the study protocol, the subjects came to the examinations after fasting at least 12 hours. They were instructed to avoid smoking and heavy physical activity as well as to avoid drinking alcohol and coffee during the previous evening and the morning before the examinations. Before the cognitive testing, the subjects were provided with a light snack,

including a whole grain oat-based snack biscuit, a small portion of fruit or berry oatmeal, and weak fruit or berry juice.

During cognitive testing, the participants first conducted a motor screening test (MOT) measuring psychomotor speed and accuracy. In this study, the MOT was considered a training procedure where the participants were introduced to the equipment used in the testing and a screening tool to point out any difficulties in vision, movement, comprehension, or ability to follow simple instructions. During the MOT, a series of red crosses were shown in different locations on the screen, and the participants were advised to touch, as quickly as possible, the center of the cross every time it appeared. **Paired Associates Learning (PAL) test** was used to assess visual and episodic memory as well as visuospatial associative learning, containing aspects of both delayed-response procedure and conditional learning. During the PAL-test, one, two, three, six, or eight patterns were displayed sequentially in boxes placed on the screen. After that, the patterns were presented in the center of the screen, and the participants were supposed to point to the box in which the particular pattern was previously seen. The test moves on to the next stage if all the patterns are placed to the right boxes. In the case of an incorrect response, all the patterns are redisplayed in their original locations and another recall phase is followed. The test terminated if the patterns were still incorrectly placed after 10 presentation and recall phases. **Spatial Working Memory (SWM) test** was used to measure ability to retain spatial information and to manipulate items stored in the working memory, problem solving, and the ability to conduct a self-organized search strategy. During this test, the participants were presented with randomly distributed colored boxes ranging in number from four to eight. After that, the participants were supposed to search for tokens hidden in the boxes. When a token was found, it was supposed to be moved to fill an empty panel on the right-hand side of the screen. Once the token had been moved from the box, the participant had to recall that the

computer would never hide a new token in a box that previously contained one; therefore, the participants were not supposed to revisit the same boxes again. **Reaction Time (RTI) test** assessed speed of response and movement on tasks where the stimulus was either predictable (simple location task) or unpredictable (five-choice location task). In the first part of this test, a large circle was presented in the center of the screen. The participant was supposed to press a button on a press pad until a small yellow spot appeared in the large circle. When the yellow spot appeared, the participant was supposed to touch the spot as soon as possible with the same hand that was pressing the button on the press pad. In the second part of the test, the same task was performed, except that in this part, five large circles were presented on the screen, and the small yellow spot could appear in any of the five circles. Again, the participant was supposed to touch, as soon as possible, the yellow spot with the hand pressing the button on the press pad. **Rapid Visual Information (RVP) test** was used to assess visual processing, recognition, and sustained attention. In this test, the participant was presented with a number sequence (e.g. 3, 5, 7) next to a large box where numbers appeared in a random order. Whenever the particular sequence was presented, the participant was supposed to press a button on a press pad. At the beginning, the participant was given visual cues (*i.e.* colored or underlined numbers) to help the participant recognize the particular sequence. When the test proceeded, the cues were removed.

Each of the CANTAB® tests produced several variables. Principal component analysis was conducted to reduce the number of variables and to identify components accounting for the majority of the variation within the cognition dataset. Principal component analysis was selected since it allows the identification of the main sources of variation in multidimensional data without losing important information and without introducing inherent bias due to subjectivity. Principal component analyses were performed separately for all individual tests.

The first components resulting from these analyses were considered to represent cognitive performance related to the particular domain. After creating the overall and testwise principal components, their distributions were analyzed. The component for the motor screening test was excluded from further analyses because it did not discriminate the subjects, indicating a ceiling effect. All other components were normalized based on the rank order normalization procedure, resulting in four separate variables, each with a mean value of 0 and a standard deviation of 1. After that, the principal components were transformed so that a greater value in the principal component indicates better cognitive performance (for example, higher value in the component for reaction time indicates better performance, not a longer reaction time). All available data for each cognitive test were used in the analyses, and therefore, the number of participants varies between the models (N=177 excluded due to technical reasons; N=51 refused to participate in all or some of the tests).

Cardiovascular risk factors

Blood pressure was measured from the right-side brachial artery with a standard mercury sphygmomanometer in 1980, and 1983 and a random zero sphygmomanometer (Hawksley & Sons Ltd.; Lancing, U.K.) in 1986, 2001, 2007, and 2011 follow-ups in sitting position after 5 minutes rest. Korotkoff's fifth phase was used as the sign of diastolic blood pressure (DBP) and first phase as the sign of systolic blood pressure (SBP). Readings to the nearest even number of millimeters of mercury were performed at least three times on each subject. Average of these measurements was used in the analysis[18]. Venous samples were drawn from the right antecubital vein after a 12-h overnight fast. Serum total cholesterol and triglyceride concentrations were determined enzymatically (Olympus System Reagent; Olympus Diagnostica GmbH, Hamburg, Germany) in a clinical chemistry analyzer (AU400; Olympus Optical Ltd, Mishima, Japan)[18]. High-density lipoprotein (HDL) cholesterol was analyzed after

precipitation of very low-density lipoprotein (VLDL) cholesterol and low-density lipoprotein (LDL) cholesterol with dextrane sulphate-Mg^{2+}. The concentration of LDL-cholesterol was calculated using the Friedewald-formula for participants with triglycerides < 4mmol/l. Height and weight were measured at all examinations[16]. Weight was measured in light clothes without shoes with a digital scale, with an accuracy of 0.1 kg, and height was measured by a wall-mounted stadiometer (Karhu, Finland) with 0.5 cm accuracy. Body mass index (BMI) was calculated as weight (kg)/height (m^2)[18]. Data on antihypertensive and dyslipidemia medications were obtained from the questionnaires in the follow-up studies in 2001, 2007, and 2011. There were no participants using antihypertensive or dyslipidemia medications in childhood but not in adulthood.

Covariates

Age was defined in full years at the end of 2011. Genotyping was performed for 2443 samples using custom build Illumina Human 670k BeadChip at Welcome Trust Sanger Institute. Genotypes were called using Illuminus clustering algorithm[19]. Genotype imputation was done using Beagle software[20] and The Sequencing Initiative Suomi (SISu) 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 (GWAS) summary statistics by assuming a prior for the genetic architecture and linkage disequilibrium (LD) information from a reference panel[21]: an infinitesimal fraction of causal variants was assumed and summary statistics from Savage et al.[22] GWAS for intelligence were used. The LD between markers was estimated from the SISu data. The polygenic risk score was used as a proxy for childhood cognitive performance. Serum glucose concentrations were determined by the enzymatic hexokinase method (Glucose System Reagent, Beckman Coulter Biomedical O'Callaghan's Mills, Ireland) on an automatic analyzer

(AU400, Olympus, Tokyo, Japan)[18]. Cigarette smoking was ascertained as a part of a self-administered questionnaire throughout the follow-up studies among participants aged 12 years and older. Adulthood smoking status was dichotomized into smokers and nonsmokers where active smoking was defined if participant reported smoking daily in any of the adulthood follow-up studies (2001, 2007 or 2011). Furthermore, subjects who reported current smoking at any of the follow-up phases at the ages between 12 and 24 years were classified as early-life smokers. The analyses for individual cardiovascular risk factor (CVRF) trajectories were adjusted for other CVRFs, and therefore a mean value of the measurements in adulthood follow-up studies (follow-up years 2001, 2007, and 2011) was calculated for cardiovascular risk covariates to indicate longitudinal exposure to SBP, serum total cholesterol, BMI, and serum glucose. Physical activity was assessed with a standardized self-administered questionnaire in all study phases and a physical activity index was calculated as previously[23]. The index (range 5–15 points) combines information on frequency and intensity of leisure-time physical activity, participation in sports club training, participation in competitive sport events, and the habitual way of spending leisure time. To evaluate physical activity exposure in adulthood, an average value of the physical activity index was calculated over the adulthood follow-up period. Dietary habit was assessed in adulthood follow-up studies with detailed quantitative food frequency questionnaire that provided an estimate of food consumption in grams per day[24]. Intake goals defined by the AHA[25] was used and are expressed for a 2000-kcal diet. Therefore, the intake goals according to subjects' total energy intake was scaled. Then, achievement of the 5 AHA ideal dietary goals was dichotomized: ≥4.5 cups per day of fruits and vegetables (approximated as 450 g/d), ≥two 3.5-oz servings per week of fish (approximated as 1 oz/d), ≥three 1-oz servings per day of whole grains (approximated as 3 oz/d), sodium <1500 mg/d, and ≤450 kcal (36 oz) of sugar-sweetened beverages per week (approximated as 5 oz/d). A diet score (range 0–5 points) was calculated based on number of

ideal dietary goal achieved. A mean value of the diet scores was calculated from the measurements in adulthood follow-up studies. Childhood school performance expressed as grade point average (*i.e.* mean of grades in all individual school subjects at baseline or either of the two subsequent follow-ups for those participants who were not of school age at baseline) was queried. Adulthood education was queried in follow-up studies in 2001, 2007, and 2011. Maximum years of education was determined as a continuous variable from self-reported data concerning total years of education attained until the year 2011. 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) <17000 Euros; 2) 17000–27000 Euros; 3) 27001–34000 Euros; 4) >34000 Euros.

Statistical Analysis

Heterogeneity in the longitudinal development of SBP, DBP, serum lipids, and BMI were investigated using group-based trajectory modeling performed with SAS PROC TRAJ procedure[27] to identify subgroups of YFS participants who shared similar underlying trajectories between ages 9 and 49 years. The PROC TRAJ procedure uses maximum likelihood estimation method, which handles incomplete data without listwise deletion. Diagnostics of model accuracy for each CVRF was based on standard criteria[28,29] which are the Bayesian Information Criteria (BIC) indicating goodness-of-fit of the models and the posterior probability indicating internal reliability. The BIC values were compared to preceding simpler models (fewer amount of trajectory groups or lower term) and 2*ΔBIC > 10 was considered as a significant change indicating better goodness-of-fit. Trajectory analysis produces each participant a posterior probability (from 0 to 1) of belonging to a specific trajectory group. Based on posterior probabilities, the participants were assigned to the trajectory group where they had the highest posterior probability to belong. Mean average

posterior probability of 0.70 has been set as a cut-off point to indicate that the trajectory encompasses participants with similar CVRF patterns and discriminates the participants with different pattern[28,29].

For reliability, minimum of three measurements were required with at least one being from childhood/adolescence (ages 9-18 years) and at least one from adulthood (ages 21-49 years). None of the three CVRF were normally distributed within the age group, and therefore the CVRFs were first normalized using rank order normalization procedure within the age groups resulting in normally distributed components each with mean 0 and SD 1. At first step in trajectory modeling, the number of trajectories was decided by using quadratic model (Supplemental Table I). The choice of the number of trajectory groups were based on goodness-of-fit (2*ΔBIC), proportion of subjects classified in each group with a posterior probability >0.70 (Supplemental Tables IX-XV), and values of mean posterior class membership probabilities as well as clinical plausibility. For meaningful statistical analyses linking CVRF trajectories and cognitive performance, frequency of >5% was preferred for the trajectory groups (not applicable for BMI due to clinical and statistical aspects). Finally, the shape of each trajectory group was decided by comparing goodness-of-fit (2*ΔBIC) between quadratic and cubic order term (Supplemental Tables II-VIII). These steps resulted in seven individual trajectory models for SBP, DBP serum lipids, and BMI (Figure 1 for SBP, serum total cholesterol, and BMI and Supplemental Figures I-IV for DBP, LDL-cholesterol, HDL-cholesterol, and serum triglycerides) with adequate fit to data, good classification accuracy and a strong clinical interpretability (Supplemental Tables XVI-XXII). Sex specific trajectory modeling was performed for each CVRF (Supplemental Figures I-V), 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.

After excluding participants using antihypertensive medication in 2001, 2007 or 2011 (N=273) from the trajectory modeling analyses, N=2361 participants had at least three and 84.8% participants had at least four SBP measurements (median 5 measurements) with at least one being from childhood and at least one from adulthood. In trajectory modeling, indicator for better goodness-of-fit, $2*\Delta BIC > 10$, was significant for the highest amount of trajectory groups (Supplemental Table I). Also, posterior probabilities were above the 0.70 limit in every solution (Supplemental Table IX), but in addition, group sizes were >5% for five-group or less trajectory solutions. Therefore, five-trajectory solution was considered optimal number for trajectory groups. After assessing goodness-of-fit ($2*\Delta BIC > 10$) for five-trajectory solution shapes (Supplemental Table II), a final trajectory solution was chosen (Supplemental Table XVI): (1) *low-stable SBP* (N=415, 17.6%) with consistently low SBP level; (2) *normal-stable SBP* (N=935, 39.6%) with consistently normal (<120mmHg) SBP level; (3) *moderate-stable SBP* (N=399, 16.9%) with SBP level consistently close to ideal (120mmHg)[25]; (4) *moderate-increasing SBP* (N=471, 20.0%) with normal SBP in childhood but continuously increasing BP level from youth to midlife; (5) *elevated-increasing SBP* (N=141, 6.0%) persons had elevated SBP in childhood and the BP level increased throughout the adulthood (Figure 1/Panel A). Sex specific trajectory modeling was performed for DBP, and the results were similar compared to the analyses for all participants (Supplemental Figure V/Panels A and D).

After excluding participants using antihypertensive medication in 2001, 2007 or 2011 (N=273) from the trajectory modeling analyses, N=2339 participants had at least three and 84.9% participants had at least four DBP measurements (median 5 measurements) with at least one being from childhood and at least one from adulthood. In trajectory modeling, indicator for better goodness-of-fit, $2*\Delta BIC > 10$, was significant for the highest amount of trajectory groups

(Supplemental Table I). Posterior probabilities were above the 0.70 limit only for three or less trajectory solutions (Supplemental Table X). Therefore, three-group trajectory solution was considered optimal. After assessing goodness-of-fit (2*ΔBIC >10) for three-trajectory solution shapes (Supplemental Table III), a final trajectory solution was chosen (Supplemental Table XVII): (1) *low-stable DBP* (N=326, 13.9%) with consistently low DBP level; (2) *normal-stable DBP* (N=1517, 64.9%) with consistently close to ideal (<80mmHg) DBP level; (3) *moderate-increasing DBP* (N=496, 21.2%) with normal DBP in childhood but continuously increasing DBP level from youth to midlife (Supplemental Figure I/Panel A). Sex specific trajectory modeling was performed for DBP, and the results were similar compared to the analyses for all participants (Supplemental Figure I/Panel B and C).

After excluding the participants using dyslipidemia medication in 2001, 2007 or 2011 (N=100) from the serum total cholesterol trajectory modeling analyses, N=2562 participants had at least three and 85.3% participants had at least four serum total cholesterol measurements (median 5 measurements) of which at least one measurement was from childhood and at least one from adulthood. In trajectory modeling, indicator for better goodness-of-fit, 2*ΔBIC >10, was significant for the highest amount of trajectory groups (Supplemental Table I). Posterior probabilities were above the 0.70 limit only for six or less trajectory solutions (Supplemental Table XI), but in addition, group sizes were >5% for three-group or two-group trajectory solutions. Therefore, three-group trajectory solution was considered optimal number for trajectory groups. After assessing goodness-of-fit (2*ΔBIC >10) for three-trajectory solution shapes (Supplemental Table IV), a final trajectory solution was chosen (Supplemental Table XVIII): (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 (<5.172mmol/l)[25]; (3) *high-stable total cholesterol* (N=463,

18.1%) with consistently high serum total cholesterol (Figure 1/Panel B). Sex specific trajectory modeling was performed for serum total cholesterol, and the results were similar compared to the analyses for all participants (Supplemental Figure V/Panels B and E).

After excluding the participants using dyslipidemia medication in 2001, 2007 or 2011 (N=100) from the serum LDL-cholesterol trajectory modeling analyses, N=2541 participants had at least three and 84.8% participants had at least four serum LDL-cholesterol measurements (median 5 measurements) of which at least one measurement was from childhood and at least one from adulthood. In trajectory modeling, indicator for better goodness-of-fit, 2*ΔBIC >10, was significant for the highest amount of trajectory groups (Supplemental Table I). Posterior probabilities were above the 0.70 limit for six or less trajectory solutions (Supplemental Table XII), but in addition, group sizes were >5% for three-group or two-group trajectory solutions. Therefore, three-group trajectory solution was considered optimal. After assessing goodness-of-fit (2*ΔBIC >10) for three-trajectory solution shapes (Supplemental Table V), a final trajectory solution was chosen (Supplemental Table XIX): (1) *low-stable LDL-cholesterol* (N=977, 38.4%) with consistently low serum LDL-cholesterol; (2) *elevated-stable LDL-cholesterol* (N=1259, 49.6%) with serum LDL-cholesterol levels consistently close to 3.5mmol/l; (3) *high-stable LDL-cholesterol* (N=305, 12.0%) with consistently high serum LDL-cholesterol (Supplemental Figure II/Panel A). Sex specific trajectory modeling was performed for serum LDL-cholesterol, and the results were similar compared to the analyses for all participants (Supplemental Figure II/Panel B and C).

After excluding the participants using dyslipidemia medication in 2001, 2007 or 2011 (N=100) from the serum HDL-cholesterol trajectory modeling analyses, N=2561 participants had at least three and 85.3% participants had at least four serum HDL-cholesterol measurements

(median 5 measurements) of which at least one measurement was from childhood and at least one from adulthood. In trajectory modeling, indicator for better goodness-of-fit, $2*\Delta BIC > 10$, was significant for the highest amount of trajectory groups (Supplemental Table I). Posterior probabilities were above the 0.70 limit for seven or less trajectory solutions (Supplemental Table XIII). The group sizes were >5% for five or less trajectory solutions. In addition, in five-group trajectory solutions, average posterior probability in one group was 0.71 as in four-group trajectory solutions all average posterior probabilities were above 0.84. Furthermore, the lowest minimum posterior probabilities were in five-group trajectory solution only 0.35 in two groups as in four-group trajectory solution all minimum posterior probabilities were above 0.50. Therefore, lower average and minimum posterior probabilities as well as clinically less meaningful analyses linking HDL-cholesterol and cognitive performance, five-trajectory solution was abandoned, and four-group trajectory solution was considered optimal. After assessing goodness-of-fit ($2*\Delta BIC > 10$) for four-trajectory solution shapes (Supplemental Table VI), a final trajectory solution was chosen (Supplemental Table XX): (1) *low-stable HDL-cholesterol* (N=531, 20.7%) with consistently low serum HDL-cholesterol; (2) *normal-stable HDL-cholesterol* (N=1169, 45.7%) with serum HDL-cholesterol levels consistently close to ideal (>1.2mmol/l)[21]; (3) *elevated-stable HDL-cholesterol* (N=690, 26.9%) with consistently elevated serum total cholesterol; (4) *high-stable HDL-cholesterol* (171, 6.7%) with consistently high serum HDL-cholesterol levels (close to 2mmol/l) (Supplemental Figure III/Panel A). Sex specific trajectory modeling was performed for serum HDL-cholesterol, and the results were similar compared to the analyses for all participants (Supplemental Figure III/Panel B and C).

After excluding the participants using dyslipidemia medication in 2001, 2007 or 2011 (N=100) and triglyceride measurements above 10mmol/l from the serum triglyceride trajectory

modeling analyses, N=2561 participants had at least three and 85.2% participants had at least four serum total cholesterol measurements (median 5 measurements) of which at least one measurement was from childhood and at least one from adulthood. In trajectory modeling, indicator for better goodness-of-fit, $2*\Delta BIC >10$, was significant for the highest amount of trajectory groups (Supplemental Table I). Posterior probabilities were above the 0.70 limit in all trajectory solutions (Supplemental Table XIV), but in addition, group sizes were >5% for three-group or two-group trajectory solutions. Therefore, three-group trajectory solution was considered optimal. After assessing goodness-of-fit ($2*\Delta BIC >10$) for three-trajectory solution shapes (Supplemental Table VII), a final trajectory solution was chosen (Supplemental Table XXI): (1) *low-stable triglycerides* (N=2076, 81.1%) with consistently low serum triglycerides; (2) *normal-increasing triglycerides* (N=349, 13.6%) with normal serum triglyceride levels in childhood but increasing triglyceride levels in midlife; (3) *normal-rapidly increasing triglycerides* (N=136, 5.3%) with normal triglyceride levels in childhood but rapidly increasing triglyceride levels from youth to midlife (Supplemental Figure IV/Panel A). Sex specific trajectory modeling was performed for serum triglycerides, and the amount of trajectory groups lowered in two in both women and men (Supplemental Figure IV/Panel B and C).

In total, 2588 participants had at least three and 83.8% participants had at least four BMI measurements (median 5 measurements) including at least one measurement from childhood and at least one from adulthood. The BMI measurements obtained during the participant's pregnancy were excluded from the BMI trajectory modeling analyses. In trajectory modeling, indicator for better goodness-of-fit, $2*\Delta BIC >10$, was significant for the highest amount of trajectory groups (Supplemental Table I). Also, posterior probabilities were above the 0.70 limit in every solution (Supplemental Table XV), but trajectory group size was already in three-trajectory solution 6.14% for group 3 and in four-trajectory solution 3.05% for group four.

Three-trajectory solution was not considered clinically appropriated. Therefore, four-group trajectory solution was considered optimal number for trajectory groups. After assessing goodness-of-fit ($2*\Delta BIC > 10$) for four-trajectory solution shapes (Supplemental Table VIII), a final trajectory solution was chosen (Supplemental Table XXII): (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 ($25kg/m^2$); (3) *progressively overweight* (N=412, 15.9%) reached overweight in childhood/adolescence and gained weight throughout the adulthood; (4) *persistently increasing obese* (N=78, 3.0%) reached obesity in childhood/adolescence and gained weight throughout the adulthood (Figure 1/Panel C). Sex specific trajectory modeling was performed for BMI, and the results were similar compared to the analyses for all participants (Supplemental Figure V/Panels C and F).

Student's t-test or the Wilcoxon rank sum test was applied for analyses for continuous variables. Associations between categorical variables were studied with the chi-square test. Linear regression analyses were conducted to investigate the associations for 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, fully adjusted model included additionally other adulthood CVRFs (SBP, serum total cholesterol, BMI, fasting serum glucose, smoking, physical activity, and diet). Additionally, all analyses were further adjusted for childhood school performance, childhood SES, and adulthood education. $P<0.05$ was considered as the level of statistical significance. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc. Cary, North Carolina, USA).

Supplemental Table I: Characteristics for Trajectory Modeling for Each Cardiovascular Risk Factor Trajectory on Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Serum Total Cholesterol, Serum LDL-cholesterol, Serum HDL-cholesterol, Serum Triglycerides, and Body Mass Index (BMI).

SBP	LOGLIK	BIC	AIC	2*ΔBIC
2 traj – x^2	-15385.54	-15416.60	-15393.54	.
3 traj – x^2	-15062.77	-15109.37	-15074.77	614.47
4 traj – x^2	-14933.32	-14995.34	-14949.32	227.83
5 traj – x^2	-14831.74	-14909.40	-14851.74	172.11
6 traj – x^2	-14765.39	-14858.59	-14789.40	101.62
7 traj – x^2	-14724.38	-14833.12	-14752.38	50.96
DBP	**LOGLIK**	**BIC**	**AIC**	**2* ΔBIC**
2 traj – x^2	-15566.14	-15597.17	-15574.14	.
3 traj – x^2	-15419.42	-15465.96	-15431.42	262.41
4 traj – x^2	-15304.20	-15381.77	-15324.20	168.38
5 traj – x^2	-15236.17	-15313.75	-15256.17	136.05
6 traj – x^2	-15197.42	-15290.51	-15221.42	46.47
7 traj – x^2	-15174.23	-15282.83	-15202.23	15.36
Serum total cholesterol	**LOGLIK**	**BIC**	**AIC**	**2*ΔBIC**
2 traj – x^2	-16552.53	-16583.93	-16560.53	.
3 traj – x^2	-16025.89	-16072.98	-16037.89	1021.90
4 traj – x^2	-15737.14	-15799.93	-15753.14	546.09
5 traj – x^2	-15608.78	-15687.26	-15628.78	225.34
6 traj – x^2	-15474.23	-15568.41	-15498.23	237.71
7 traj – x^2	-15434.57	-15544.45	-15462.57	47.92
Serum LDL-cholesterol	**LOGLIK**	**BIC**	**AIC**	**2*ΔBIC**
2 traj – x^2	-16229.46	-16260.82	-16237.46	.
3 traj – x^2	-15602.62	-15649.66	-15614.62	1222.32
4 traj – x^2	-15288.00	-15350.72	-15304.00	597.88
5 traj – x^2	-15156.35	-15234.75	-15176.35	231.94
6 traj – x^2	-15033.52	-15127.61	-15057.52	214.30
7 traj – x^2	-14966.05	-15075.82	-14994.05	103.58
Serum HDL-cholesterol	**LOGLIK**	**BIC**	**AIC**	**2*ΔBIC**
2 traj – x^2	-16457.78	-16489.17	-16465.78	.
3 traj – x^2	-15828.42	-15875.50	-15840.42	1227.33
4 traj – x^2	-15614.39	-15677.18	-15630.39	396.65

	LOGLIK	BIC	AIC	2*ΔBIC
5 traj – x^2	-15501.82	-15580.30	-15521.82	193.75
6 traj – x^2	-15392.91	-15487.09	-15416.91	186.42
7 traj – x^2	-15312.72	-15422.60	-15340.72	128.99
Serum triglycerides	**LOGLIK**	**BIC**	**AIC**	**2*ΔBIC**
2 traj – x^2	-17035.42	-17066.81	-17043.42	.
3 traj – x^2	-16654.60	-16701.68	-16666.60	730.26
4 traj – x^2	-16407.29	-16470.08	-16423.29	463.22
5 traj – x^2	-16230.50	-16308.98	-16250.50	322.19
6 traj – x^2	-16118.05	-16212.23	-16142.05	193.51
7 traj – x^2	-16069.05	-16178.92	-16097.05	66.61
BMI	**LOGLIK**	**BIC**	**AIC**	**2*ΔBIC**
2 traj – x^2	-15114.08	-15145.51	-15122.08	.
3 traj – x^2	-14129.14	-14176.30	-14141.14	1938.44
4 traj – x^2	-13614.06	-13676.93	-13630.06	998.73
5 traj – x^2	-13278.72	-13357.31	-13298.72	639.25
6 traj – x^2	-13035.34	-13129.64	-13059.34	455.32
7 traj – x^2	-12823.59	-12933.61	-12851.59	392.06

Values are log-likelihood (LOGLIK), the Bayesian Information Criteria (BIC), the Akaike Information Criteria (AIC), and the change of the BIC (compared to the preceding BIC) multiplied two (2*Δ BIC).

Supplemental Table II: Comparison of Five Group Trajectory Model Shapes in Systolic Blood Pressure.

	LOGLIK	BIC	AIC	2*ΔBIC
5 traj – (2,2,2,2,2)	-14831.7	-14909.4	-14851.7	Ref.
5 traj – (2,2,2,2,3)	-14828.2	-14909.8	-14849.2	0.8
5 traj – (2,2,2,3,2)	-14829.1	-14910.7	-14850.1	2.5
5 traj – (2,2,3,2,2)	-14831.7	-14913.3	-14852.7	7.8
5 traj – (2,3,2,2,2)	-14831.7	-14913.3	-14852.7	7.8
5 traj – (3,2,2,2,2)	-14827.5	-14909.1	-14848.5	0.7
5 traj – (2,2,2,3,3)	-14828.2	-14913.7	-14850.2	8.5
5 traj – (2,2,3,3,2)	-14829.1	-14914.5	-14851.1	10.2
5 traj – (2,3,3,2,2)	-14831.7	-14917.2	-14853.7	15.5
5 traj – (3,3,2,2,2)	-14825.2	-14910.6	-14847.2	2.4
5 traj – (2,2,3,2,3)	-14828.2	-14913.7	-14850.2	8.5
5 traj – (2,3,2,2,3)	-14828.2	-14913.7	-14850.2	8.5
5 traj – (3,2,2,2,3)	-14824.0	-14909.4	-14846.0	0.04
5 traj – (3,3,3,2,2)	-14827.5	-14916.8	-14850.5	14.9
5 traj – (3,3,2,2,3)	-14824.0	-14913.3	-14847.0	7.8
5 traj – (3,2,2,3,3)	-14821.7	-14911.0	-14844.7	3.1
5 traj – (2,2,3,3,3)	-14828.2	-14917.5	-14851.2	16.3
5 traj – (3,3,2,3,2)	-14825.2	-14914.5	-14848.2	10.1
5 traj – (3,2,3,3,2)	-14827.5	-14916.8	-14850.5	14.9
5 traj – (2,3,3,3,2)	-14829.0	-14918.3	-14852.0	17.9
5 traj – (3,3,3,3,2)	-14825.1	-14918.3	-14849.1	17.8
5 traj – (3,3,3,2,3)	-14821.5	-14914.8	-14845.6	10.8
5 traj – (3,3,2,3,3)	-14821.6	-14914.8	-14845.6	10.8
5 traj – (3,2,3,3,3)	-14821.6	-14914.8	-14845.6	10.8
5 traj – (2,3,3,3,3)	**-14825.5**	**-14918.7**	**-14849.5**	**18.5**
5 traj – (3,3,3,3,3)	-14821.5	-14918.6	-14846.5	18.4

Values are log-likelihood (LOGLIK), the Bayesian Information Criteria (BIC), the Akaike Information Criteria (AIC), and the change of the BIC (compared to the preceding BIC) multiplied two (2Δ* BIC).

Supplemental Table III: Comparison of Three Group Trajectory Model Shapes in Diastolic Blood Pressure.

	LOGLIK	BIC	AIC	2*ΔBIC
3 traj – (2,2,2)	-15419.4	-15466.0	-15431.4	.
3 traj – (2,2,3)	-15419.4	-15469.8	-15432.4	7.7
3 traj – (2,3,2)	-15419.4	-15469.8	-15432.4	7.8
3 traj – (3,2,2)	-15418.7	-15469.1	-15431.7	6.2
3 traj – (2,3,3)	-15419.4	-15473.7	-15433.4	15.5
3 traj – (3,3,2)	-15418.6	-15472.9	-15432.6	13.9
3 traj – (3,2,3)	-15418.6	-15472.9	-15432.6	14.0
3 traj – (3,3,3)	**-15418.6**	**-15476.8**	**-15433.6**	**21.7**

Values are log-likelihood (LOGLIK), the Bayesian Information Criteria (BIC), the Akaike Information Criteria (AIC), and the change of the BIC (compared to the preceding BIC) multiplied two (2Δ* BIC).

Supplemental Table IV: Comparison of Three Group Trajectory Model Shapes in Serum Total Cholesterol.

	LOGLIK	BIC	AIC	2*ΔBIC
3 traj – (2,2,2)	**-16025.9**	**-16073.0**	**-16037.9**	**.**
3 traj – (2,2,3)	-16022.8	-16073.8	-16035.8	1.6
3 traj – (2,3,2)	-16019.7	-16070.7	-16032.7	4.5
3 traj – (3,2,2)	-16023.5	-16074.6	-16036.5	3.2
3 traj – (2,3,3)	-16016.7	-16071.6	-16030.7	2.8
3 traj – (3,3,2)	-16017.3	-16072.3	-16031.3	1.4
3 traj – (3,2,3)	-16020.4	-16075.3	-16034.4	4.7
3 traj – (3,3,3)	-16014.2	-16073.1	-16029.2	0.2

Values are log-likelihood (LOGLIK), the Bayesian Information Criteria (BIC), the Akaike Information Criteria (AIC), and the change of the BIC (compared to the preceding BIC) multiplied two (2Δ* BIC).

Supplemental Table V: Comparison of Three Group Trajectory Model Shapes in LDL-cholesterol.

	LOGLIK	BIC	AIC	2*ΔBIC
3 traj – (2,2,2)	-15602.6	-15649.7	-15614.6	.
3 traj – (2,2,3)	-15599.0	-15650.0	-15612.0	0.6
3 traj – (2,3,2)	-15593.0	-15644.0	-15606.0	11.4
3 traj – (3,2,2)	-15599.5	-15650.5	-15612.5	1.6
3 traj – (2,3,3)	**-15589.0**	**-15643.9**	**15603.0**	**11.5**
3 traj – (3,3,2)	-15589.8	-15644.6	-15603.8	10.1
3 traj – (3,2,3)	-15595.8	-15650.7	-15609.8	2.1
3 traj – (3,3,3)	-15585.7	-15644.5	-15600.7	10.3

Values are log-likelihood (LOGLIK), the Bayesian Information Criteria (BIC), the Akaike Information Criteria (AIC), and the change of the BIC (compared to the preceding BIC) multiplied two (2Δ* BIC).

Supplemental Table VI: Comparison of Four Group Trajectory Model Shapes in HDL-cholesterol.

	LOGLIK	BIC	AIC	2*ΔBIC
4 traj – (2,2,2,2)	-15614.4	-15677.2	-15630.4	0.0
4 traj – (2,2,2,3)	-15612.6	-15679.3	-15629.6	4.3
4 traj – (2,2,3,2)	-15600.1	-15666.8	-15617.1	20.7
4 traj – (2,3,2,2)	-15600.1	-15666.8	-15617.1	20.7
4 traj – (3,2,2,2)	-15606.4	-15673.1	-15623.4	8.2
4 traj – (2,2,3,3)	-15611.5	-15682.2	-15629.6	10.0
4 traj – (2,3,3,2)	-15599.5	-15670.1	-15617.5	14.2
4 traj – (3,3,2,2)	**-15592.8**	**-15663.5**	**-15610.8**	**27.4**
4 traj – (3,2,2,3)	-15604.6	-15675.2	-15622.6	3.9
4 traj – (2,3,3,2)	-15599.5	-15670.1	-15617.5	14.2
4 traj – (3,2,3,2)	-15605.3	-15675.9	-15623.3	2.5
4 traj – (2,3,2,3)	-15611.6	-15682.2	-15629.6	10.0
4 traj – (2,3,3,3)	-15597.6	-15672.1	-15616.6	10.1
4 traj – (3,3,3,2)	-15592.1	-15666.7	-15611.1	21.0
4 traj – (3,2,3,3)	-15603.5	-15678.1	-15622.5	1.7
4 traj – (3,3,2,3)	-15603.5	-15678.1	-15622.5	1.7

4 traj – (3,3,3,3)	-15590.2	-15668.7	-15610.2	16.9

Values are log-likelihood (LOGLIK), the Bayesian Information Criteria (BIC), the Akaike Information Criteria (AIC), and the change of the BIC (compared to the preceding BIC) multiplied two (2Δ* BIC).

Supplemental Table VII: Comparison of Three Group Trajectory Model Shapes in Triglycerides.

	LOGLIK	BIC	AIC	2*ΔBIC
3 traj – (2,2,2)	-16654.6	-16701.7	-16666.6	0
3 traj – (2,2,3)	-16654.5	-16705.5	-16667.5	7.7
3 traj – (2,3,2)	**-16623.8**	**-16674.8**	**-16636.8**	**53.8**
3 traj – (3,2,2)	-16654.4	-16705.4	-16667.4	7.4
3 traj – (2,3,3)	-16622.3	-16677.2	-16636.3	49
3 traj – (3,3,2)	-16623.7	-16678.7	-16637.7	46
3 traj – (3,2,3)	-16654.3	-16709.2	-16668.3	15
3 traj – (3,3,3)	-16622.2	-16681.1	-16637.2	41.2

Values are log-likelihood (LOGLIK), the Bayesian Information Criteria (BIC), the Akaike Information Criteria (AIC), and the change of the BIC (compared to the preceding BIC) multiplied two (2Δ* BIC).

Supplemental Table VIII: Comparison of Four Group Trajectory Model Shapes in Body Mass Index.

BMI	LOGLIK	BIC	AIC	2*ΔBIC
4 traj – (2,2,2,2)	-13614.1	-13676.9	-13630.1	Ref.
4 traj – (2,2,2,3)	-13608.2	-13675.0	-13625.2	3.9
4 traj – (2,2,3,2)	-13613.4	-13680.2	-13630.4	6.6
4 traj – (2,3,2,2)	-13613.4	-13680.2	-13630.4	6.6
4 traj – (3,2,2,2)	-13612.2	-13679.0	-13629.2	4.2
4 traj – (2,2,3,3)	-13607.4	-13678.1	-13625.4	2.4
4 traj – (2,3,3,2)	-13611.9	-13682.6	-13629.9	11.3
4 traj – (3,3,2,2)	-13611.6	-13682.3	-13629.6	10.8

4 traj – (3,2,2,3)	-13606.4	-13677.1	-13624.4	0.4
4 traj – (2,3,3,2)	-13611.9	-13682.6	-13629.9	11.3
4 traj – (3,2,3,2)	-13611.6	-13682.3	-13629.6	10.8
4 traj – (2,3,2,3)	-13606.7	-13677.4	-13624.7	0.9
4 traj – (2,3,3,3)	-13605.8	-13680.5	-13624.8	7.1
4 traj – (3,3,3,2)	**-13609.9**	**-13684.6**	**-13628.9**	**15.3**
4 traj – (3,2,3,3)	-13605.6	-13680.2	-13624.6	6.6
4 traj – (3,3,2,3)	-13605.6	-13680.2	-13624.6	6.6
4 traj – (3,3,3,3)	-13603.9	-13682.5	-13623.9	11.1

Values are log-likelihood (LOGLIK), the Bayesian Information Criteria (BIC), the Akaike Information Criteria (AIC), and the change of the BIC (compared to the preceding BIC) multiplied two ($2\Delta^*$ BIC).

Supplemental Table IX: Comparison of Systolic Blood Pressure Trajectory Model Posterior Probabilities.

	N (%)	Mean (SD)	Min	Max
Posterior probabilities using **two** trajectory model (x^2-term for each trajectory)				
Group 1	1360 (57.60)	0.92 (0.12)	0.50	1.00
Group 2	1001 (42.40)	0.90 (0.14)	0.50	1.00
Posterior probabilities using **three** trajectory model (x^2-term for each trajectory)				
Group 1	889 (37.65)	0.87 (0.15)	0.50	1.00
Group 2	1235 (52.31)	0.87 (0.14)	0.50	1.00
Group 3	237 (10.04)	0.87 (0.15)	0.51	1.00
Posterior probabilities using **four** trajectory model (x^2-term for each trajectory)				
Group 1	777 (32.91)	0.85 (0.17)	0.34	1.00
Group 2	510 (21.60)	0.75 (0.17	0.34	1.00
Group 3	845 (35.79)	0.76 (0.16)	0.35	1.00
Group 4	229 (9.70)	0.86 (0.16)	0.38	1.00
Posterior probabilities using **five** trajectory model (x^2-term for each trajectory)				
Group 1	408 (17.28)	0.83 (0.16)	0.40	1.00
Group 2	475 (20.12)	0.74 (0.18)	0.35	1.00
Group 3	406 (17.20)	0.73 (0.18)	0.36	1.00
Group 4	935 (39.60)	0.76 (0.16)	0.36	1.00
Group 5	137 (5.80)	0.87 (0.17)	0.34	1.00
Posterior probabilities using **six** trajectory model (x^2-term for each trajectory)				

Group 1	403 (17.07)	0.83 (0.16)	0.41	1.00
Group 2	176 (7.45)	0.74 (0.20)	0.32	1.00
Group 3	504 (21.35)	0.72 (0.18)	0.35	1.00
Group 4	398 (16.86)	0.72 (0.19)	0.33	1.00
Group 5	833 (35.28)	0.75 (0.16)	0.34	1.00
Group 6	47 (1.99)	0.86 (0.18)	0.43	1.00
Posterior probabilities using **seven** trajectory model (x^2-term for each trajectory)				
Group 1	347 (14.70)	0.82 (0.16)	0.37	1.00
Group 2	470 (19.91)	0.71 (0.18)	0.33	1.00
Group 3	152 (6.44)	0.73 (0.19)	0.32	1.00
Group 4	740 (31.34)	0.72 (0.16)	0.34	1.00
Group 5	510 (21.60)	0.70 (0.17)	0.34	0.99
Group 6	122 (5.17)	0.76 (0.17)	0.41	1.00
Group 7	20 (0.85)	0.86 (0.18)	0.47	1.00

Values are means (standard deviations) for posterior probabilities, minimum and maximum posterior probabilities, and numbers (percentages) for categorical variables.

Supplemental Table X: Comparison of Diastolic Blood Pressure Trajectory Model Posterior Probabilities.

	N (%)	Mean (SD)	Min	Max
Posterior probabilities using **two** trajectory model (x^2-term for each trajectory)				
Group 1	1533 (65.54)	0.91 (0.13)	0.50	1.00
Group 2	806 (34.46)	0.86 (0.15)	0.50	1.00
Posterior probabilities using **three** trajectory model (x^2-term for each trajectory)				
Group 1	341 (14.58)	0.79 (0.16)	0.50	1.00
Group 2	1517 (64.86)	0.83 (0.13)	0.50	1.00
Group 3	481 (20.56)	0.84 (0.16)	0.50	1.00
Posterior probabilities using **four** trajectory model (x^2-term for each trajectory)				
Group 1	401 (17.14)	0.77 (0.19)	0.34	1.00
Group 2	569 (24.33)	0.68 (0.16)	0.36	1.00
Group 3	954 (40.79)	0.74 (0.18)	0.36	1.00
Group 4	415 (17.74)	0.82 (0.18)	0.37	1.00
Posterior probabilities using **five** trajectory model (x^2-term for each trajectory)				
Group 1	223 (9.53)	0.78 (0.18)	0.37	1.00
Group 2	597 (25.52)	0.69 (0.17)	0.34	1.00

Group 3	423 (18.09)	0.69 (0.18)	0.33	0.99
Group 4	922 (39.42)	0.74 (0.17)	0.36	1.00
Group 5	174 (7.44)	0.8 (0.18)	0.38	1.00
Posterior probabilities using **six** trajectory model (x^2-term for each trajectory)				
Group 1	214 (9.15)	0.76 (0.19)	0.39	1.00
Group 2	255 (10.90)	0.72 (0.18)	0.34	1.00
Group 3	667 (28.52)	0.68 (0.17)	0.30	1.00
Group 4	790 (33.78)	0.73 (0.17)	0.29	1.00
Group 5	381 (16.29)	0.68 (0.18)	0.27	0.99
Group 6	32 (1.37)	0.82 (0.17)	0.53	1.00
Posterior probabilities using **seven** trajectory model (x^2-term for each trajectory)				
Group 1	210 (8.98)	0.77 (0.19)	0.33	1.00
Group 2	69 (2.95)	0.68 (0.18)	0.38	0.99
Group 3	58 (2.48)	0.82 (0.17)	0.37	1.00
Group 4	920 (39.33)	0.67 (0.15)	0.28	0.95
Group 5	450 (19.24)	0.69 (0.17)	0.32	1.00
Group 6	270 (11.54)	0.64 (0.18)	0.27	0.99
Group 7	362 (15.48)	0.66 (0.17)	0.27	0.98

Values are means (standard deviations) for posterior probabilities, minimum and maximum posterior probabilities, and numbers (percentages) for categorical variables.

Supplemental Table XI: Comparison of Serum Total Cholesterol Trajectory Model Posterior Probabilities.

	N (%)	Mean (SD)	Min	Max
Posterior probabilities using **two** trajectory model (x^2-term for each trajectory)				
Group 1	1601 (62.49)	0.94 (0.11)	0.50	1.00
Group 2	961 (37.51)	0.92 (0.13)	0.50	1.00
Posterior probabilities using **three** trajectory model (x^2-term for each trajectory)				
Group 1	690 (26.93)	0.89 (0.14)	0.51	1.00
Group 2	1409 (55.00)	0.88 (0.13)	0.50	1.00
Group 3	463 (18.07)	0.91 (0.13)	0.50	1.00
Posterior probabilities using **four** trajectory model (x^2-term for each trajectory)				
Group 1	524 (20.45)	0.89 (0.13)	0.51	1.00
Group 2	1316 (51.37)	0.87 (0.14)	0.50	1.00
Group 3	667 (26.03)	0.89 (0.14)	0.50	1.00

	N (%)	Mean (SD)	Min	Max
Group 4	55 (2.15)	0.91 (0.15)	0.56	1.00
Posterior probabilities using **five** trajectory model (x^2-term for each trajectory)				
Group 1	527 (20.57)	0.89 (0.13)	0.50	1.00
Group 2	287 (11.20)	0.76 (0.18)	0.37	1.00
Group 3	1304 (50.90)	0.86 (0.14)	0.34	1.00
Group 4	402 (15.69)	0.81 (0.17)	0.35	1.00
Group 5	42 (1.64)	0.94 (0.13)	0.48	1.00
Posterior probabilities using **six** trajectory model (x^2-term for each trajectory)				
Group 1	494 (19.28)	0.88 (0.14)	0.50	1.00
Group 2	1243 (48.52)	0.85 (0.15)	0.36	1.00
Group 3	317 (12.37)	0.75 (0.17)	0.38	1.00
Group 4	100 (3.90)	0.86 (0.16)	0.45	1.00
Group 5	403 (15.73)	0.79 (0.18)	0.36	1.00
Group 6	5 (0.20)	0.99 (0.02)	0.95	1.00
Posterior probabilities using **seven** trajectory model (x^2-term for each trajectory)				
Group 1	356 (13.90)	0.84 (0.16)	0.47	1.00
Group 2	1007 (39.31)	0.79 (0.15)	0.37	1.00
Group 3	376 (14.68)	0.72 (0.19)	0.35	1.00
Group 4	430 (16.78)	0.66 (0.16)	0.35	0.99
Group 5	91 (3.55)	0.80 (0.18)	0.34	1.00
Group 6	288 (11.24)	0.80 (0.18)	0.36	1.00
Group 7	14 (0.55)	0.96 (0.07)	0.79	1.00

Values are means (standard deviations) for posterior probabilities, minimum and maximum

posterior probabilities, and numbers (percentages) for categorical variables.

Supplemental Table XII: Comparison of LDL-cholesterol Trajectory Model Posterior Probabilities.

	N (%)	Mean (SD)	Min	Max
Posterior probabilities using **two** trajectory model (x^2-term for each trajectory)				
Group 1	1630 (64.15)	0.95 (0.10)	0.51	1.00
Group 2	911 (35.85)	0.92 (0.13)	0.50	1.00
Posterior probabilities using **three** trajectory model (x^2-term for each trajectory)				
Group 1	949 (37.35)	0.90 (0.14)	0.50	1.00
Group 2	1270 (49.98)	0.89 (0.14)	0.50	1.00
Group 3	322 (12.67)	0.90 (0.14)	0.50	1.00

Posterior probabilities using **four** trajectory model (x^2-term for each trajectory)			
Group 1	635 (24.99)	0.89 (0.14)	0.50	1.00
Group 2	1309 (51.52)	0.87 (0.14)	0.50	1.00
Group 3	553 (21.76)	0.90 (0.13)	0.50	1.00
Group 4	44 (1.73)	0.94 (0.10)	0.62	1.00
Posterior probabilities using **five** trajectory model (x^2-term for each trajectory)			
Group 1	413 (16.25)	0.85 (0.16)	0.50	1.00
Group 2	1120 (44.08)	0.83 (0.13)	0.50	1.00
Group 3	740 (29.12)	0.82 (0.14)	0.50	1.00
Group 4	244 (9.60)	0.86 (0.16)	0.50	1.00
Group 5	24 (0.94)	0.97 (0.09)	0.56	1.00
Posterior probabilities using **six** trajectory model (x^2-term for each trajectory)			
Group 1	228 (8.97)	0.84 (0.16)	0.50	1.00
Group 2	951 (37.43)	0.82 (0.13)	0.50	0.99
Group 3	223 (8.78)	0.80 (0.17)	0.37	1.00
Group 4	902 (35.50)	0.80 (0.15)	0.36	1.00
Group 5	207 (8.15)	0.82 (0.18)	0.37	1.00
Group 6	30 (1.18)	0.98 (0.06)	0.78	1.00
Posterior probabilities using **seven** trajectory model (x^2-term for each trajectory)			
Group 1	209 (8.23)	0.85 (0.15)	0.50	1.00
Group 2	908 (35.73)	0.79 (0.14)	0.37	0.99
Group 3	473 (18.61)	0.66 (0.17)	0.34	0.99
Group 4	506 (19.91)	0.70 (0.18)	0.32	1.00
Group 5	264 (10.39)	0.79 (0.19)	0.34	1.00
Group 6	151 (5.94)	0.82 (0.19)	0.32	1.00
Group 7	30 (1.18)	0.96 (0.09)	0.64	1.00

Values are means (standard deviations) for posterior probabilities, minimum and maximum posterior probabilities, and numbers (percentages) for categorical variables.

Supplemental Table XIII: Comparison of HDL-cholesterol Trajectory Model Posterior Probabilities.

	N (%)	Mean (SD)	Min	Max
Posterior probabilities using **two** trajectory model (x^2-term for each trajectory)				
Group 1	1626 (63.49)	0.95 (0.11)	0.50	1.00
Group 2	935 (36.51)	0.92 (0.13)	0.50	1.00

Posterior probabilities using three trajectory model (x^2-term for each trajectory)				
Group 1	942 (36.78)	0.91 (0.13)	0.50	1.00
Group 2	1287 (50.25)	0.89 (0.13)	0.50	1.00
Group 3	332 (12.96)	0.91 (0.15)	0.50	1.00
Posterior probabilities using four trajectory model (x^2-term for each trajectory)				
Group 1	546 (21.32)	0.86 (0.15)	0.50	1.00
Group 2	1186 (46.31)	0.84 (0.13)	0.50	1.00
Group 3	665 (25.97)	0.85 (0.15)	0.50	1.00
Group 4	164 (6.40)	0.89 (0.15)	0.50	1.00
Posterior probabilities using five trajectory model (x^2-term for each trajectory)				
Group 1	589 (23.00)	0.86 (0.17)	0.39	1.00
Group 2	369 (14.41)	0.71 (0.18)	0.35	1.00
Group 3	587 (22.92)	0.82 (0.16)	0.37	1.00
Group 4	873 (34.09)	0.76 (0.16)	0.35	1.00
Group 5	143 (5.58)	0.89 (0.14)	0.51	1.00
Posterior probabilities using six trajectory model (x^2-term for each trajectory)				
Group 1	483 (18.86)	0.85 (0.16)	0.37	1.00
Group 2	411 (16.05)	0.73 (0.17)	0.34	1.00
Group 3	245 (9.57)	0.8 (0.16)	0.38	1.00
Group 4	880 (34.36)	0.78 (0.15)	0.37	1.00
Group 5	462 (18.04)	0.73 (0.18)	0.35	1.00
Group 6	80 (3.12)	0.89 (0.16)	0.49	1.00
Posterior probabilities using seven trajectory model (x^2-term for each trajectory)				
Group 1	422 (16.48)	0.85 (0.16)	0.43	1.00
Group 2	336 (13.12)	0.72 (0.18)	0.33	1.00
Group 3	878 (34.28)	0.77 (0.16)	0.35	1.00
Group 4	251 (9.80)	0.78 (0.17)	0.38	1.00
Group 5	117 (4.57)	0.79 (0.18)	0.40	1.00
Group 6	509 (19.88)	0.73 (0.17)	0.31	1.00
Group 7	48 (1.87)	0.89 (0.16)	0.42	1.00

Values are means (standard deviations) for posterior probabilities, minimum and maximum

posterior probabilities, and numbers (percentages) for categorical variables.

Supplemental Table XIV: Comparison of Triglyceride Trajectory Model Posterior Probabilities.

	N (%)	Mean (SD)	Min	Max
Posterior probabilities using **two** trajectory model (x^2-term for each trajectory)				
Group 1	2319 (90.55)	0.99 (0.06)	0.50	1.00
Group 2	242 (9.45)	0.93 (0.12)	0.51	1.00
Posterior probabilities using **three** trajectory model (x^2-term for each trajectory)				
Group 1	2020 (78.88)	0.95 (0.10)	0.50	1.00
Group 2	402 (15.70)	0.83 (0.15)	0.45	1.00
Group 3	139 (5.43)	0.92 (0.13)	0.43	1.00
Posterior probabilities using **four** trajectory model (x^2-term for each trajectory)				
Group 1	1995 (77.90)	0.95 (0.11)	0.39	1.00
Group 2	250 (9.76)	0.84 (0.16)	0.38	1.00
Group 3	249 (9.72)	0.83 (0.17)	0.37	1.00
Group 4	67 (2.62)	0.93 (0.13)	0.43	1.00
Posterior probabilities using **five** trajectory model (x^2-term for each trajectory)				
Group 1	1883 (73.53)	0.93 (0.12)	0.35	1.00
Group 2	292 (11.40)	0.76 (0.18)	0.36	1.00
Group 3	117 (4.57)	0.91 (0.14)	0.44	1.00
Group 4	252 (9.84)	0.82 (0.18)	0.35	1.00
Group 5	17 (0.66)	0.97 (0.06)	0.76	1.00
Posterior probabilities using **six** trajectory model (x^2-term for each trajectory)				
Group 1	1806 (70.52)	0.92 (0.12)	0.39	1.00
Group 2	341 (13.32)	0.79 (0.17)	0.41	1.00
Group 3	244 (9.53)	0.76 (0.18)	0.35	1.00
Group 4	115 (4.49)	0.89 (0.16)	0.44	1.00
Group 5	37 (1.44)	0.88 (0.16)	0.49	1.00
Group 6	18 (0.70)	0.95 (0.11)	0.56	1.00
Posterior probabilities using **seven** trajectory model (x^2-term for each trajectory)				
Group 1	1813 (70.79)	0.91 (0.14)	0.34	1.00
Group 2	156 (6.09)	0.77 (0.19)	0.38	1.00
Group 3	314 (12.26)	0.65 (0.17)	0.32	1.00
Group 4	107 (4.18)	0.78 (0.19)	0.40	1.00
Group 5	111 (4.33)	0.90 (0.14)	0.47	1.00
Group 6	46 (1.80)	0.86 (0.16)	0.49	1.00
Group 7	14 (0.55)	0.99 (0.03)	0.92	1.00

Values are means (standard deviations) for posterior probabilities, minimum and maximum posterior probabilities, and numbers (percentages) for categorical variables.

Supplemental Table XV: Comparison of Body Mass Index Trajectory Model Posterior Probabilities.

	N (%)	Mean (SD)	Min	Max
Posterior probabilities using **two** trajectory model (x^2-term for each trajectory)				
Group 1	2051 (79.25)	0.98 (0.07)	0.50	1.00
Group 2	537 (20.75)	0.94 (0.12)	0.51	1.00
Posterior probabilities using **three** trajectory model (x^2-term for each trajectory)				
Group 1	1511 (58.38)	0.95 (0.11)	0.51	1.00
Group 2	918 (35.47)	0.92 (0.13)	0.50	1.00
Group 3	159 (6.14)	0.95 (0.12)	0.52	1.00
Posterior probabilities using **four** trajectory model (x^2-term for each trajectory)				
Group 1	993 (38.37)	0.90 (0.13)	0.50	1.00
Group 2	1103 (42.62)	0.89 (0.13)	0.50	1.00
Group 3	413 (15.96)	0.92 (0.13)	0.51	1.00
Group 4	79 (3.05)	0.97 (0.08)	0.53	1.00
Posterior probabilities using **five** trajectory model (x^2-term for each trajectory)				
Group 1	928 (35.86)	0.90 (0.13)	0.50	1.00
Group 2	286 (11.05)	0.86 (0.17)	0.40	1.00
Group 3	1086 (41.96)	0.88 (0.14)	0.43	1.00
Group 4	214 (8.27)	0.86 (0.16)	0.40	1.00
Group 5	74 (2.86)	0.97 (0.07)	0.71	1.00
Posterior probabilities using **six** trajectory model (x^2-term for each trajectory)				
Group 1	820 (31.68)	0.89 (0.14)	0.43	1.00
Group 2	324 (12.52)	0.86 (0.16)	0.40	1.00
Group 3	133 (5.14)	0.91 (0.14)	0.46	1.00
Group 4	1026 (39.64)	0.85 (0.14)	0.35	1.00
Group 5	242 (9.35)	0.83 (0.18)	0.42	1.00
Group 6	43 (1.66)	0.96 (0.10)	0.54	1.00
Posterior probabilities using **seven** trajectory model (x^2-term for each trajectory)				
Group 1	552 (21.33)	0.88 (0.14)	0.50	1.00
Group 2	479 (18.51)	0.83 (0.16)	0.41	1.00
Group 3	1016 (39.26)	0.83 (0.14)	0.40	1.00
Group 4	131 (5.06)	0.86 (0.17)	0.38	1.00
Group 5	131 (5.06)	0.90 (0.14)	0.50	1.00

	N (%)	Mean (SD)	Min	Max
Group 6	240 (9.27)	0.82 (0.18)	0.38	1.00
Group 7	39 (1.51)	0.98 (0.07)	0.62	1.00

Values are means (standard deviations) for posterior probabilities, minimum and maximum

posterior probabilities, and numbers (percentages) for categorical variables.

Supplemental Table XVI: Posterior Probabilities for Systolic Blood Pressure (SBP)

Trajectories Using Five Trajectory Model ("2,3,3,3,3" model).

	N (%)	Mean (SD)	Min	Max
Group 1 = Low-stable SBP	415 (17.58)	0.83 (0.16)	0.36	1.00
Group 2 = Normal-stable SBP	935 (39.60)	0.76 (0.16)	0.36	1.00
Group 3 = Moderate-stable SBP	399 (16.90)	0.73 (0.18)	0.35	1.00
Group 4 = Moderate-increasing SBP	471 (19.95)	0.74 (0.18)	0.36	1.00
Group 5 = Elevated-increasing SBP	141 (5.97)	0.87 0.17)	0.40	1.00

Values are means (standard deviations) for posterior probabilities, minimum and maximum

posterior probabilities, and numbers (percentages) for categorical variables.

Supplemental Table XVII: Posterior Probabilities for Diastolic Blood Pressure (DBP)

Trajectories Using Three Trajectory Model ("3,3,3" model).

	N (%)	Mean (SD)	Min	Max
Group 1 = Low-stable DBP	326 (13.94)	0.79 (0.16)	0.50	1.00
Group 2 = Normal-stable DBP	1517 (64.86)	0.83 (0.13)	0.50	1.00
Group 3 = Moderate-increasing DBP	496 (21.21)	0.84 (0.16)	0.50	1.00

Values are means (standard deviations) for posterior probabilities, minimum and maximum

posterior probabilities, and numbers (percentages) for categorical variables.

Supplemental Table XVIII: Posterior Probabilities for Serum Total Cholesterol Trajectories Using Three Trajectory Model ("2,2,2" model).

	N (%)	Mean (SD)	Min	Max
Group 1 = Low-stable total cholesterol	690 (26.93)	0.89 (0.14)	0.51	1.00
Group 2 = Elevated-stable total cholesterol	1409 (55.00)	0.88 (0.13)	0.50	1.00
Group 3 = High-stable total cholesterol	463 (18.07)	0.91 (0.13)	0.50	1.00

Values are means (standard deviations) for posterior probabilities, minimum and maximum posterior probabilities, and numbers (percentages) for categorical variables.

Supplemental Table XIX: Posterior Probabilities for LDL-cholesterol Trajectories Using Three Trajectory Model ("3,3,3" model).

	N (%)	Mean (SD)	Min	Max
Group 1 = Low-stable LDL-cholesterol	977 (38.44)	0.90 (0.14)	0.50 €	1.00 €
Group 2 = Elevated-stable LDL-cholesterol	1259 (49.55)	0.90 (0.13)	0.50 €	1.00 €
Group 3 = High-stable LDL-cholesterol	305 (12.00)	0.91 (0.13)	0.50 €	1.00 €

Values are means (standard deviations) for posterior probabilities, minimum and maximum posterior probabilities, and numbers (percentages) for categorical variables.

Supplemental Table XX: Posterior Probabilities for HDL-cholesterol Trajectories Using Four Trajectory Model ("3,3,2,2" model).

	N (%)	Mean (SD)	Min	Max
Group 1 = Low-stable HDL-cholesterol	531 (20.73)	0.86 (0.15)	0.50	1.00
Group 2 = Normal-stable HDL-cholesterol	1169 (45.65)	0.84 (0.14)	0.50	1.00
Group 3 = Elevated-stable HDL-cholesterol	690 (26.94)	0.85 (0.15)	0.50	1.00
Group 4 = High-stable HDL-cholesterol	171 (6.68)	0.90 (0.14)	0.50	1.00

Values are means (standard deviations) for posterior probabilities, minimum and maximum posterior probabilities, and numbers (percentages) for categorical variables.

Supplemental Table XXI: Posterior Probabilities for Triglyceride Trajectories Using Three Trajectory Model ("2,3,2" model).

	N (%)	Mean (SD)	Min	Max
Group 1 = Low-stable triglycerides	2076 (81.06)	0.95 (0.10)	0.49	1.00
Group 2 = Normal-increasing triglycerides	349 (13.63)	0.84 (0.16)	0.48	1.00
Group 3 = Normal-rapidly increasing triglycerides	136 (5.31)	0.94 (0.12)	0.41	1.00

Values are means (standard deviations) for posterior probabilities, minimum and maximum posterior probabilities, and numbers (percentages) for categorical variables.

Supplemental Table XXII: Posterior probabilities for Body Mass Index Trajectories Using Four Trajectory Model ("3,3,3,2" model).

	N (%)	Mean (SD)	Min	Max
Group 1 = Stable slim	994 (38.41)	0.90 (0.13)	0.50	1.00
Group 2 = Stable normal weight	1104 (42.66)	0.89 (0.13)	0.50	1.00
Group 3 = Progressively overweight	412 (15.92)	0.92 (0.13)	0.50	1.00
Group 4 = Persistently increasing obese	78 (3.01)	0.98 (0.06)	0.72	1.00

Values are means (standard deviations) for posterior probabilities, minimum and maximum posterior probabilities, and numbers (percentages) for categorical variables.
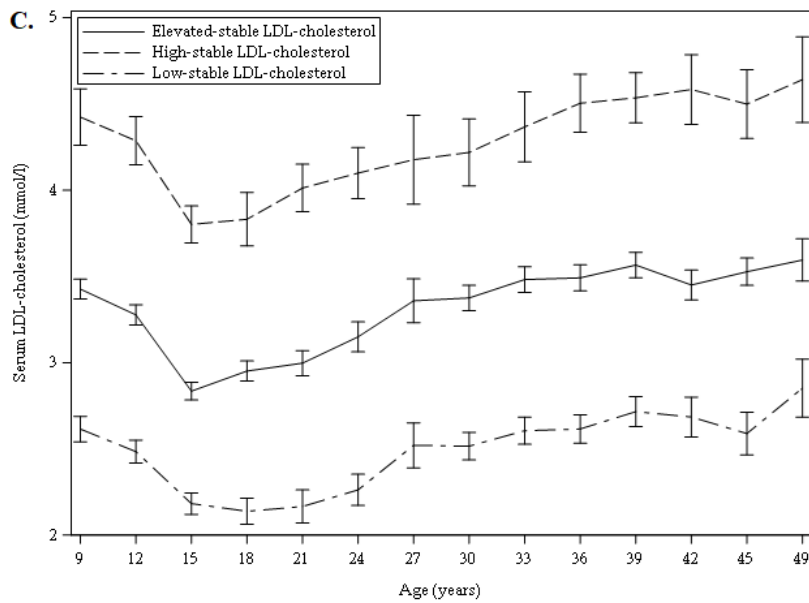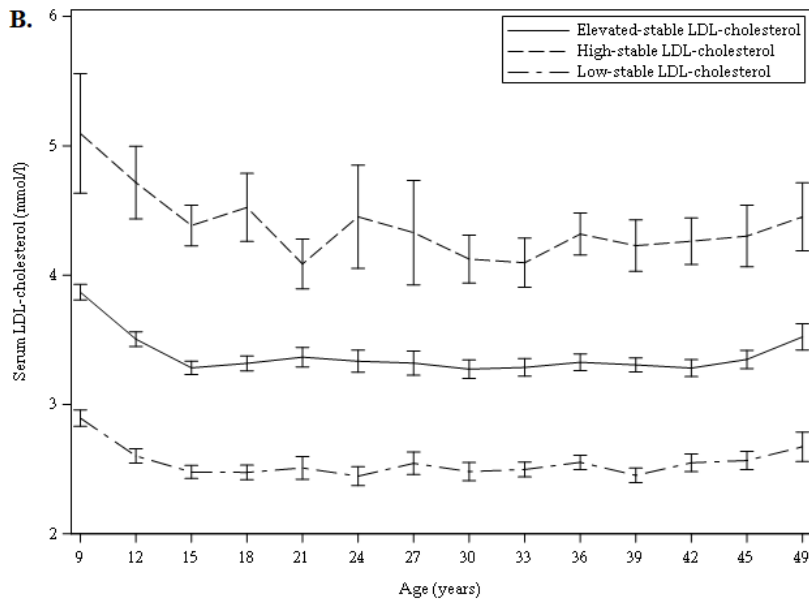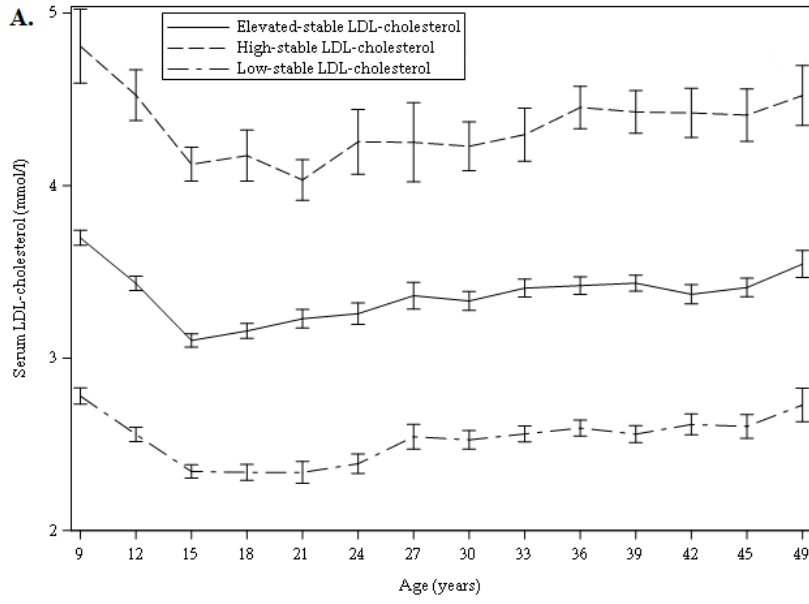
Supplemental Figure I: Trajectories from Childhood to Midlife for Diastolic Blood Pressure (DBP) for Both Sexes (A), and Sex Specific Trajectories for Women (B) and Men (C).

DBP trajectories since childhood were identified using latent class growth mixture modeling. Values are means and 95% confidence intervals. Three trajectory groups for DBP were identified. Participants who had antihypertensive medication in any adulthood follow-up year (2001, 2007 or 2011) were excluded from the DBP trajectory modeling.
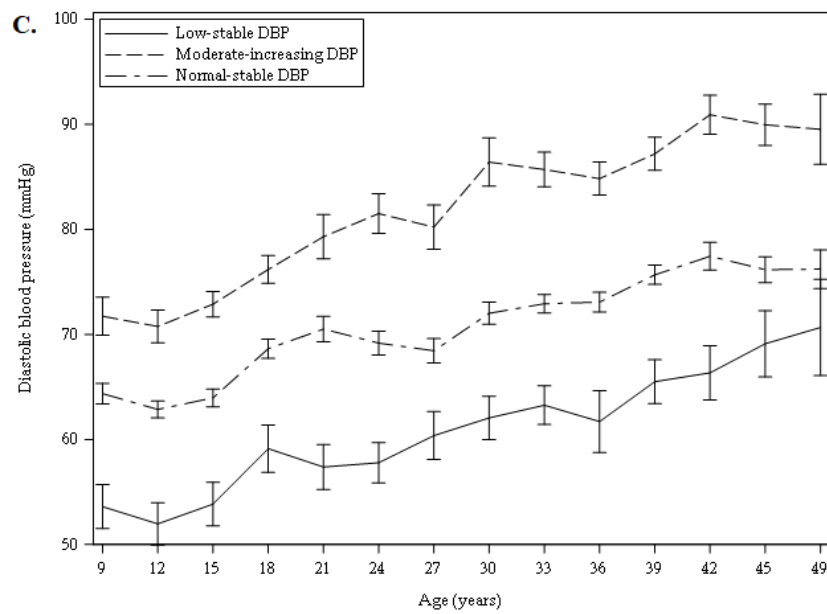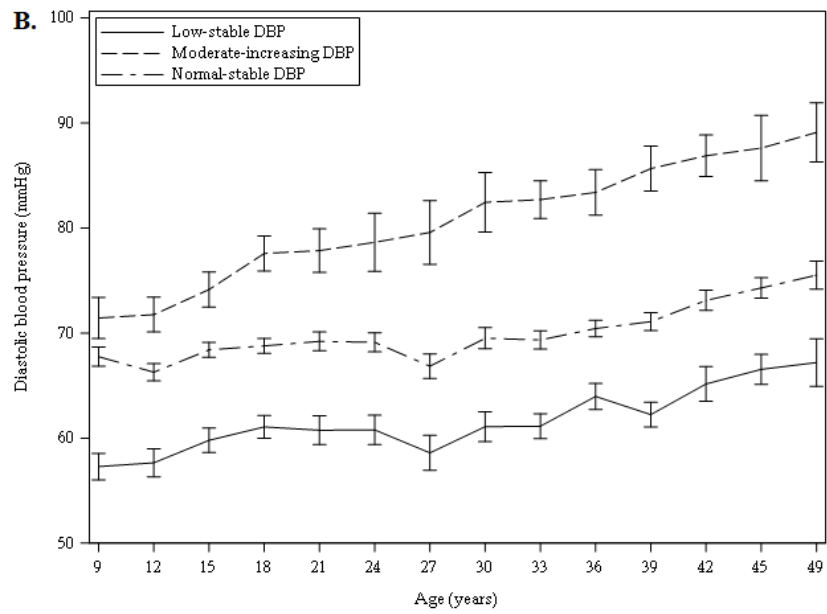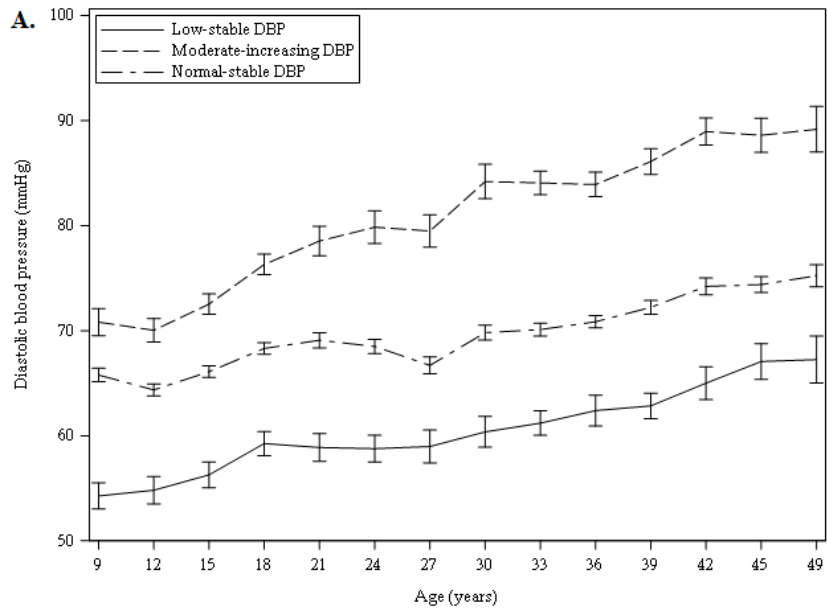
Supplemental Figure II: Trajectories from Childhood to Midlife for Serum LDL-cholesterol for Both Sexes (A), and Sex Specific Trajectories for Women (B) and Men (C).
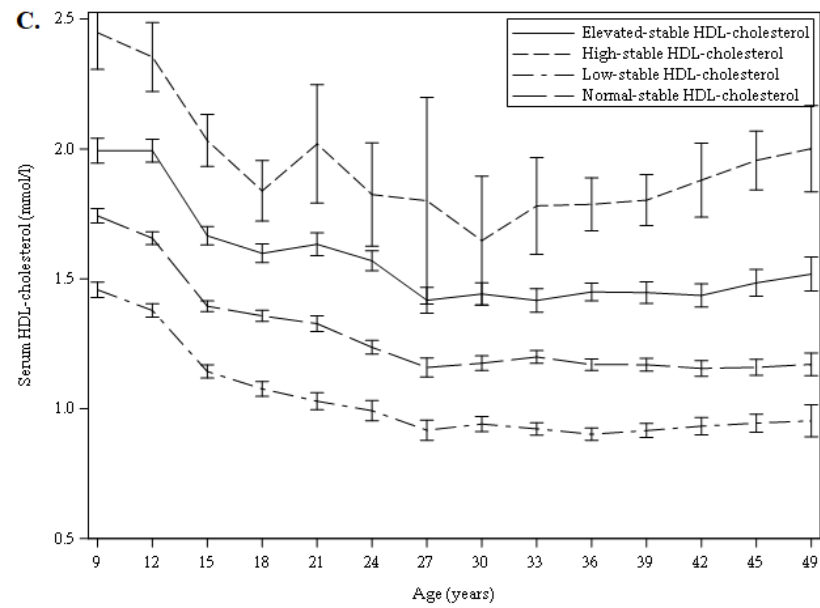
LDL-cholesterol trajectories since childhood were identified using latent class growth mixture modeling. Values are means and 95% confidence intervals. Three trajectory groups for LDL-cholesterol were identified. Participants who had dyslipidemia medication in any adulthood follow-up year (2001, 2007 or 2011) were excluded from the LDL-cholesterol trajectory modeling.

Supplemental Figure III: Trajectories from Childhood to Midlife for Serum HDL-cholesterol for Both Sexes (A), and Sex Specific Trajectories for Women (B) and Men (C).
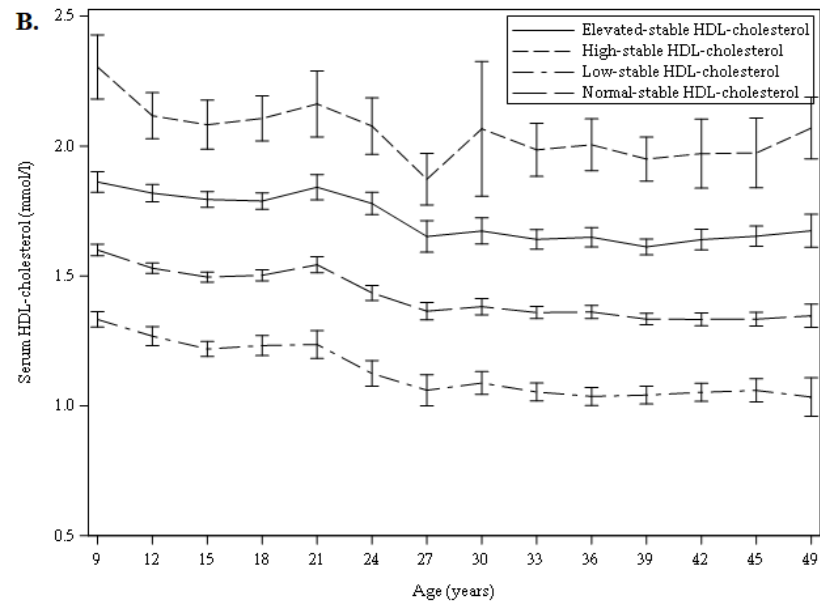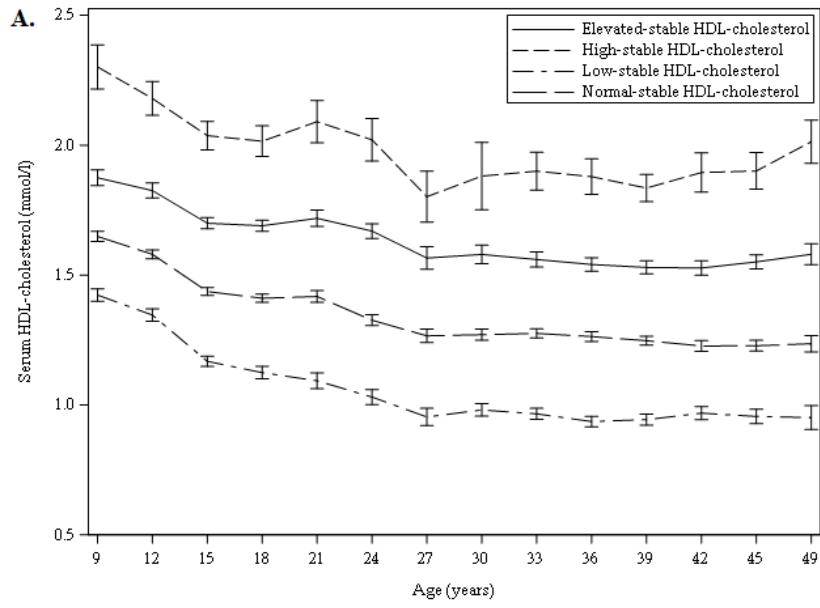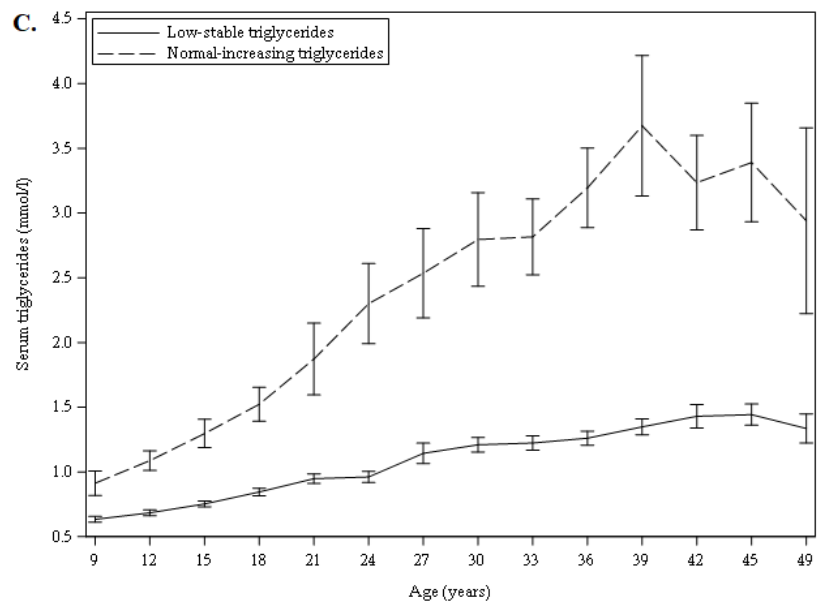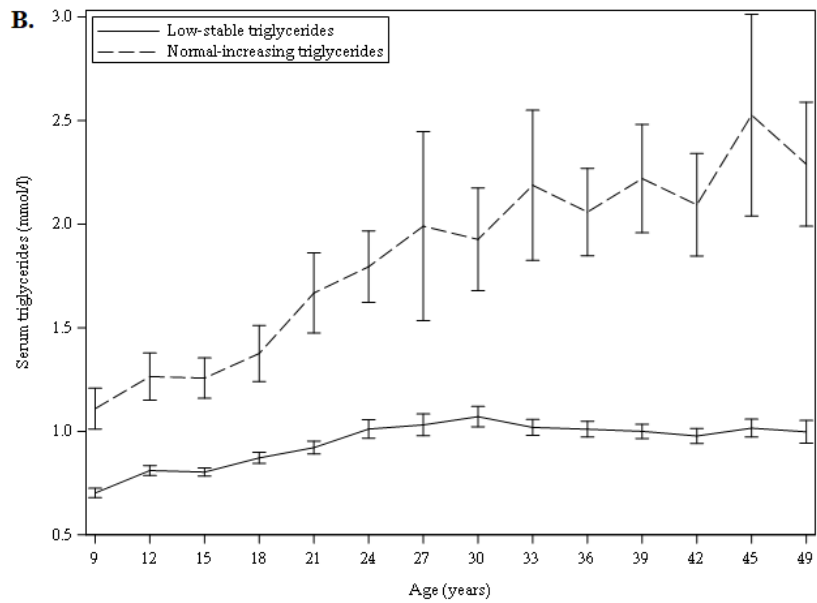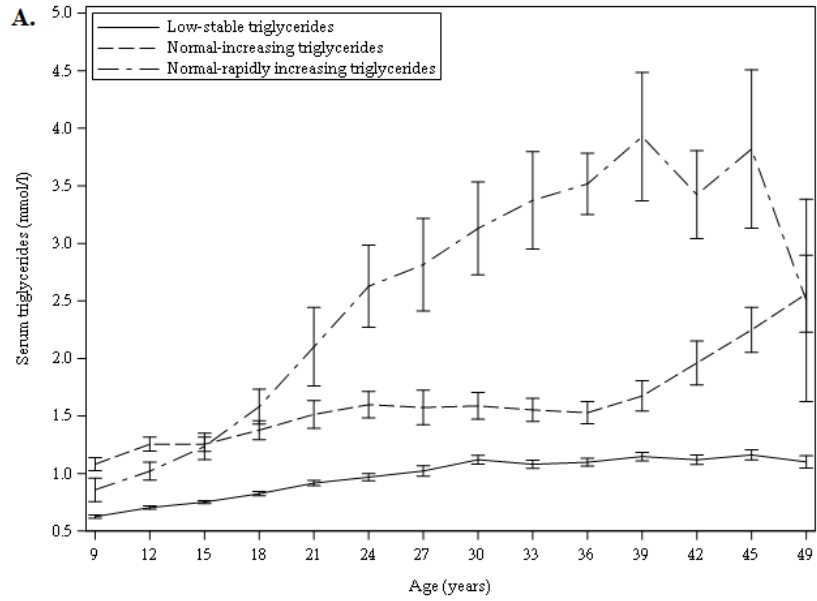
HDL-cholesterol trajectories since childhood were identified using latent class growth mixture modeling. Values are means and 95% confidence intervals. Four trajectory groups for HDL-cholesterol were identified. Participants who had dyslipidemia medication in any adulthood follow-up year (2001, 2007 or 2011) were excluded from the HDL-cholesterol trajectory modeling.

A.

B.

C.

Supplemental Figure IV: Trajectories from Childhood to Midlife for Serum Triglycerides for Both Sexes (A), and Sex Specific Trajectories for Women (B) and Men (C).

Trajectories since childhood for triglycerides were identified using latent class growth mixture modeling. Values are means and 95% confidence intervals. Three trajectory groups were identified for triglycerides in the model with both sexes. Two trajectory groups were identified for triglycerides in the sex specific models. Participants who had dyslipidemia medication in any adulthood follow-up year (2001, 2007 or 2011) were excluded from the triglyceride trajectory modeling. Serum triglyceride measurements above 10mmol/l were excluded from the triglyceride trajectory modeling.

Supplemental Figure V: Sex Specific Trajectories for Women in Systolic Blood Pressure (SBP) (A), Serum Total Cholesterol (B), and Body Mass Index (BMI) (C); for Men in SBP (D), Serum Total Cholesterol (E), and BMI (F).

Sex specific cardiovascular risk factor trajectories since childhood were identified using latent class growth mixture modeling. Values are means and 95% confidence intervals for each cardiovascular risk factor. Five trajectory groups for SBP (A and C), three trajectory groups for serum total cholesterol (B and D), and four trajectory groups for BMI (E and F) 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 participant's pregnancy were excluded from the BMI trajectory modeling.
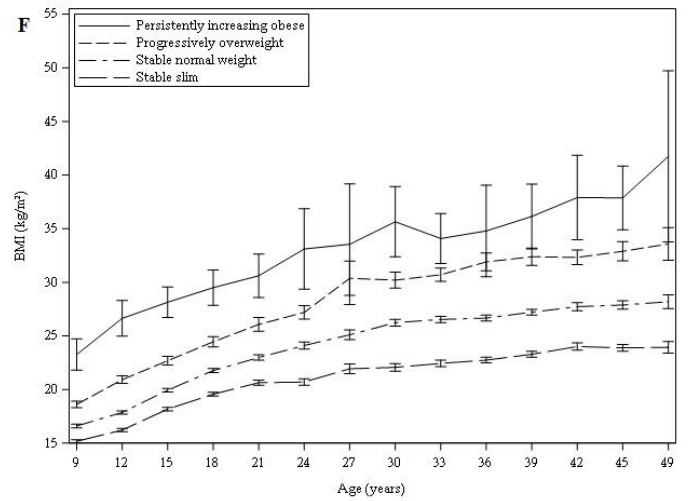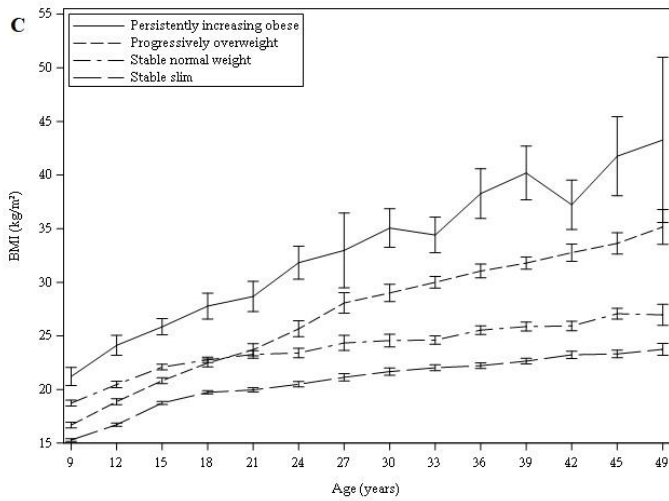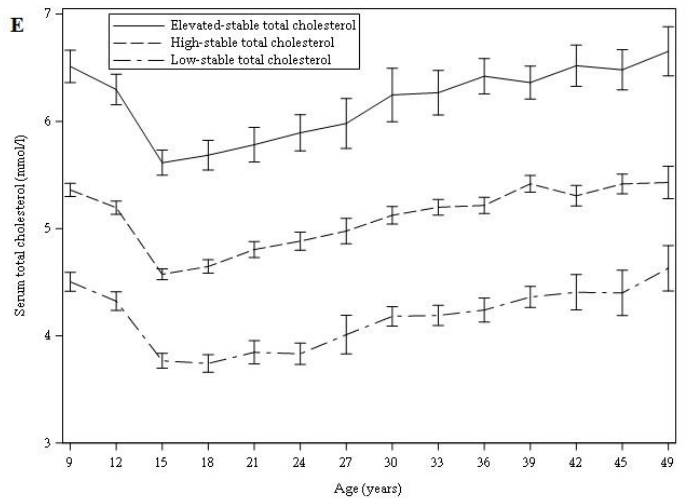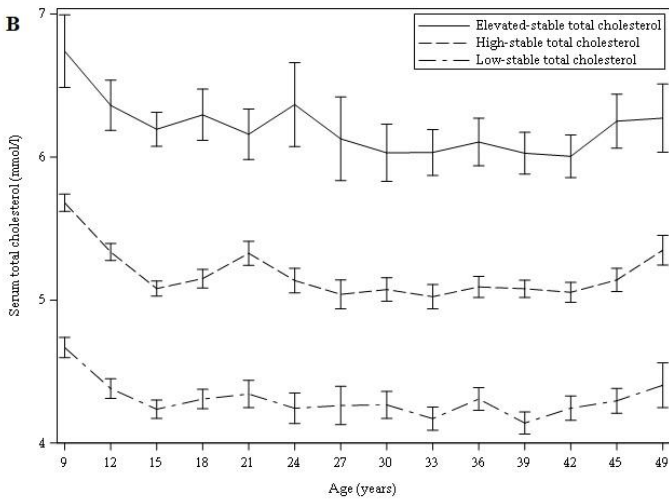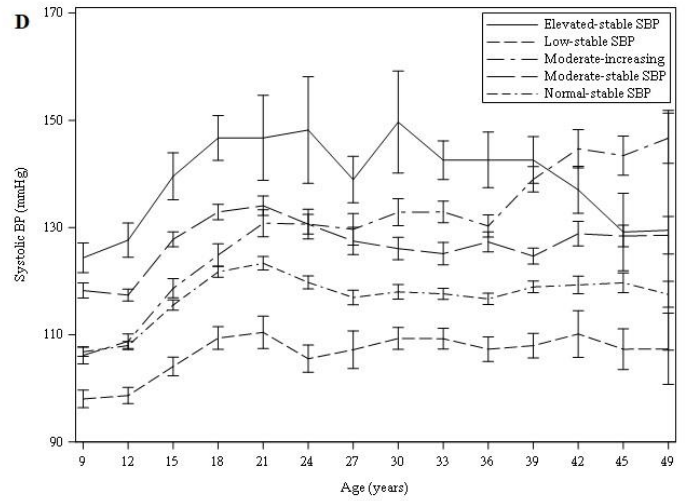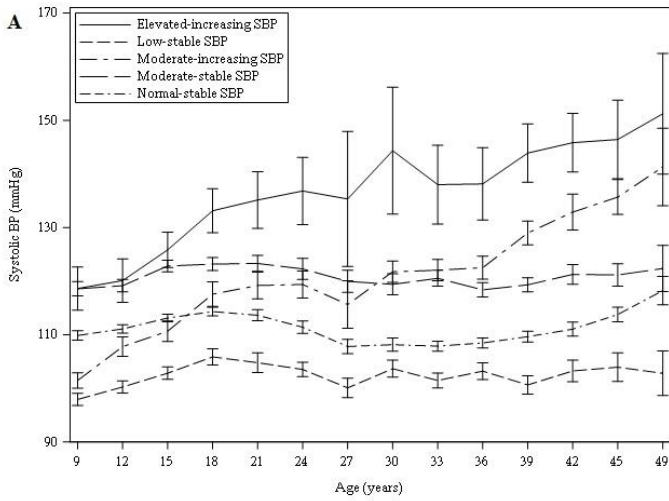
EXPANDED RESULTS

Characteristics and Representativeness of the Study Population

The background characteristics of the study population and numbers 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 / 922 men; age 10.8 years at baseline / 41.8 years at cognitive testing). The descriptive characteristics individually for SBP, serum total cholesterol, and BMI trajectory groups in the 21-year and 31-year follow-ups are presented in the Table 2. For DBP, LDL-cholesterol, HDL-cholesterol, and triglyceride trajectory groups, the descriptive characteristics are presented in the Supplemental Table XXIII. Representativeness of the study population participating in the cognitive testing was examined by comparing the baseline and 21-year-follow-up data of the participants and non-participants (Supplemental Table XXIV). The participants were more often women, older and adulthood non-smokers compared to the non-participants. Additionally, they originated from families with higher income (20.71% vs. 7.85%, p=0.003) and had better school performance in childhood compared to the non-participants (7.77 vs. 7.65, p<0.0001). There were small differences in the CVRFs between participants and non-participants; the participants had higher baseline BMI (18.0 kg/m^2 vs. 17.7 kg/m^2, p=0.004), lower adulthood BP (SBP: 116.2 mmHg vs. 118.0 mmHg, p=0.003; diastolic BP: 70.4 mmHg vs 71.7 mmHg, p=0.017), and lower adulthood triglycerides (1.33 mmol/L vs. 1.36 mmol/L, p=0.044). There were no significant differences between the participants and non-participants in any other CVRFs or in the covariates.

Diastolic Blood Pressure and Serum Lipid Trajectories from Childhood to Midlife and Cognitive Performance

No associations were found for DBP, HDL-cholesterol or triglyceride trajectory groups and cognitive performance (Supplemental Table XXV/Panels A, C, and D). Serum LDL-cholesterol was inversely associated with episodic memory and associative learning; the 'high-stable LDL-cholesterol' group had worse episodic memory and associative learning compared to the 'low-stable total cholesterol' group (adjusted for age, sex, polygenic risk score, and adulthood SBP, BMI, fasting serum glucose, smoking, physical activity, and diet) (Supplemental Table XXV/Panel B). No associations were found for serum LDL-cholesterol trajectories on other cognitive domains.

Supplemental Table XXIII: Descriptive Characteristics for the Diastolic Blood Pressure and Serum Lipid Trajectory Groups.

Cardiovascular risk factor trajectories		
DBP trajectory groups	**N (%)**	**N, women (%)**
Low-stable DBP	326 (13.9)	204 (62.6)
Normal-stable DBP	1517 (64.9)	871 (57.4)
Moderate-increasing DBP	496 (21.2)	191 (38.5)
Follow-up year	**2001**	**2011**
SBP / DBP, mmHg (SD)		
Low-stable DBP	107.6 / 59.5 (10.1 / 7.1)	109.3 / 64.4 (11.1 / 7.4)
Normal-stable DBP	113.1 / 68.0 (10.6 / 7.3)	116.4 / 72.8 (11.8 / 7.7)
Moderate-increasing DBP	126.7 / 81.5 (11.1 / 7.9)	131.2 / 86.9 (13.4 / 8.3)
Total cholesterol, mmol/l		
Low-stable DBP	4.97 (0.89)	5.05 (0.93)
Normal-stable DBP	5.11 (0.95)	5.15 (0.96)
Moderate-increasing DBP	5.35 (0.99)	5.37 (0.93)
BMI, kg/m^2 (SD)		
Low-stable DBP	23.0 (3.4)	24.5 (4.1)
Normal-stable DBP	24.5 (3.8)	25.8 (4.4)
Moderate-increasing DBP	26.6 (4.6)	28.2 (5.3)
LDL-cholesterol trajectory groups	**N (%)**	**N, women (%)**
Low-stable LDL-cholesterol	977 (38.5)	552 (56.5)
Elevated-stable LDL-cholesterol	1259 (49.6)	698 (55.4)
High-stable LDL-cholesterol	305 (12.0)	151 (49.5)
Follow-up year	**2001**	**2011**
SBP / DBP, mmHg (SD)		
Low-stable LDL-cholesterol	114.9 / 69.0 (12.7 / 10.2)	116.9 / 73.6 (13.2 / 10.1)
Elevated-stable LDL-cholesterol	116.7 / 71.2 (12.8 / 10.5)	119.4 / 75.1 (14.2 / 10.3)
High-stable LDL-cholesterol	117.7 / 71.6 (13.0 / 11.4)	122.2 / 76.8 (15.2 / 11.6)
Total cholesterol, mmol/l		
Low-stable LDL-cholesterol	4.41 (0.61)	4.51 (0.67)
Elevated-stable LDL-cholesterol	5.36 (0.71	5.39 (0.70)
High-stable LDL-cholesterol	6.30 (0.80)	6.45 (0.82)
LDL-cholesterol, mmol/l		
Low-stable LDL-cholesterol	2.60 (0.49)	2.65 (0.49)
Elevated-stable LDL-cholesterol	3.46 (0.56)	3.48 (0.56)
High-stable LDL-cholesterol	4.38 (0.70)	4.51 (0.74)
BMI, kg/m^2 (SD)		
Low-stable LDL-cholesterol	24.3 (4.1)	25.8 (4.8)
Elevated-stable LDL-cholesterol	25.2 (4.5)	26.6 (4.9)
High-stable LDL-cholesterol	26.0 (4.6)	27.1 (4.9)
HDL-cholesterol trajectory groups	**N (%)**	**N, women (%)**

Low-stable HDL-cholesterol	531 (20.7)	161 (30.3)
Normal-stable HDL-cholesterol	1169 (45.7)	631 (54.0)
Elevated-stable HDL-cholesterol	690 (26.9)	484 (70.1)
High-stable HDL-cholesterol	171 (6.7)	128 (74.9)
Follow-up year	**2001**	**2011**
SBP / DBP, mmHg (SD)		
Low-stable HDL-cholesterol	118.4 / 71.9 (13.6 / 11.9)	120.3 / 76.7 (13.6 / 10.8)
Normal-stable HDL-cholesterol	116.0 / 70.4 (12.8 / 10.5)	118.9 / 74.8 (14.7/ 10.7)
Elevated-stable HDL-cholesterol	115.4 / 70.1 (12.2 / 9.8)	117.8 / 73.5 (13.2 / 9.5)
High-stable HDL-cholesterol	113.4 / 68.2 (11.8 / 9.9)	118.2 / 73.7 (14.9 / 10.1)
Total cholesterol, mmol/l		
Low-stable HDL-cholesterol	5.05 (1.00)	5.11 (1.02)
Normal-stable HDL-cholesterol	5.03 (0.93)	5.13 (0.95)
Elevated-stable HDL-cholesterol	5.23 (0.88)	5.19 (0.83)
High-stable HDL-cholesterol	5.46 (0.82)	5.63 (0.93)
HDL-cholesterol, mmol/l		
Low-stable HDL-cholesterol	0.94 (0.16)	0.97 (0.15)
Normal-stable HDL-cholesterol	1.23 (0.20)	1.26 (0.20)
Elevated-stable HDL-cholesterol	1.52 (0.22)	1.56 (0.22)
High-stable HDL-cholesterol	1.83 (0.25)	1.93 (0.28)
BMI, kg/m^2 (SD)		
Low-stable HDL-cholesterol	26.5 (4.6)	28.1 (4.9)
Normal-stable HDL-cholesterol	25.0 (4.5)	26.5 (4.9)
Elevated-stable HDL-cholesterol	24.0 (3.9)	25.3 (4.7)
High-stable HDL-cholesterol	23.9 (3.3)	24.5 (4.0)
Triglyceride trajectory groups	**N (%)**	**N, women (%)**
Low-stable triglycerides	2076 (81.0)	1162 (56.0)
Normal-increasing triglycerides	349 (13.6)	211 (60.5)
Normal-rapidly increasing triglycerides	137 (5.4)	30 (21.9)
Follow-up year	**2001**	**2011**
SBP / DBP, mmHg (SD)		
Low-stable triglycerides	115.2 / 69.7 (12.2 / 10.1)	118.1 / 71.8 (13.8 / 10.1)
Normal-increasing triglycerides	118.3 / 72.0 (14.2 / 11.6)	119.9 / 76.6 (15.0 / 11.0)
Normal-rapidly increasing triglycerides	124.7 / 77.8 (14.1 / 12.2)	127.4 / 81.3 (13.6 / 10.3)
Total cholesterol, mmol/l		
Low-stable triglycerides	5.03 (0.89)	5.09 (0.89)
Normal-increasing triglycerides	5.38 (1.00)	5.43 (0.97)
Normal-rapidly increasing triglycerides	5.83 (1.05)	5.91 (1.15)
Triglycerides, mmol/l		
Low-stable triglycerides	1.11 (0.47)	1.07 (0.49)
Normal-increasing triglycerides	1.66 (0.63)	1.71 (0.83)
Normal-rapidly increasing triglycerides	3.25 (1.29)	3.83 (3.59)
BMI, kg/m^2 (SD)		

Low-stable triglycerides	24.6 (4.1)	26.0 (4.8)
Normal-increasing triglycerides	26.0 (5.0)	27.3 (4.8)
Normal-rapidly increasing triglycerides	28.3 (4.1)	29.9 (4.8)

Values are means (standard deviations, SD) for continuous variables and numbers, N (percentages) for categorical variables. Year 2001 indicates follow-up year 21 and year 2011 indicates follow-up year 31. BMI = body mass index; LDL = low density lipoprotein; HDL = high density lipoprotein. If participant 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.

Supplemental Table XXIV: Comparison of the Participants and Non-Participants in the Cognitive Testing.

	Participants (N=2026)	Non-participants (N=1570)	p-value
Sex (N=3596)			**<0.0001**
Women N (%) (N=1832)	1104 (60.3)	728 (39.7)	
Men N (%) (N=1764)	922 (52.3)	842 (47.7)	
Age, years (N=3596)			**<0.0001**
At baseline (1980)	10.8 (5.0)	9.9 (4.9)	
At adulthood (follow-up year 21, 2001)	31.8 (5.0)	30.9 (4.9)	
Childhood school performance (N=3596)	7.77 (0.73)	7.65 (0.74)	**<0.0001**
Years of education (follow-up year 21, 2001) (N=2604)	14.7 (3.1)	14.0 (3.1)	**<0.0001**
Family income at baseline, N (%), (N=3453)			**0.003**
<17000 euros/year (N=950)	512 (14.83)	438 (12.68)	
17000–27000 euros/year (N=1054)	575 (16.65)	479 (13.87)	
27000–37000 euros/year (N=734)	575 (16.65)	309 (8.95)	
>37000 euros/year (N=715)	715 (20.71)	271 (7.85)	
Polygenic risk score (N=2442)	0.01 (1.00)	-0.04 (0.99)	0.27
Cardiovascular risk factors at baseline (1980)			
Systolic blood pressure, mmHg (N=3549)	112.8 (11.9)	112.2 (12.5)	0.17
Diastolic blood pressure, mmHg (N=3000)	68.6 (9.4)	69.0 (9.8)	0.22
Total cholesterol, mmol/l (N=3554)	5.29 (0.90)	5.31 (0.93)	0.77
LDL-cholesterol, mmol/l (N=3551)	3.42 (0.82)	3.45 (0.86)	0.54
HDL-cholesterol, mmol/l (N=3551)	1.56 (0.31)	1.56 (0.31)	0.94
Triglycerides, mmol/L (N=3554)	0.67 (0.31)	0.66 (0.32)	0.38
Body mass index, kg/m^2 (N=3567)	18.0 (3.1)	17.7 (3.1)	**0.004**
Early life smoking, N (%), yes (N=3379)	544 (16.1)	397 (11.8)	0.76
Physical activity index (N=2351)	9.0 (1.8)	9.1 (1.8)	0.33
Cardiovascular risk factors in follow-up year 21 (2001)			
Systolic blood pressure, mmHg (N=2270)	116.2 (13.0)	118.0 (13.3)	**0.003**
Diastolic blood pressure, mmHg (N=2270)	70.4 (10.6)	71.7 (11.3)	**0.017**
Total cholesterol, mmol/l (N=2283)	5.16 (0.97)	5.16 (1.01)	0.83
LDL-cholesterol, mmol/l (N=2251)	3.28 (0.85)	3.27 (0.84)	0.64
HDL-cholesterol, mmol/l (N=2281)	1.29 (0.32)	1.29 (0.33)	0.70
Triglycerides, mmol/L (N=2283)	1.33 (0.88)	1.36 (0.78)	**0.044**
Body mass index, kg/m^2 (N=2276)	25.0 (4.4)	25.2 (4.5)	0.30
Fasting serum glucose, mmol/l (N=2274)	5.02 (0.55)	5.03 (0.79)	0.64

Smoking, N (%) yes (N=2547)	380 (10.3)	261 (15.0)	**<0.0001**
Physical activity index (N=2453)	8.9 (2.0)	8.8 (1.9)	0.76
Diet score (N=2463)	1.18 (0.66)	1.23 (0.66)	0.06
Antihypertensive medication, N (%) yes (N=2620)	43 (2.4)	22 (2.7)	0.69
Dyslipidemia medication, N (%) yes (N=2620)	7 (0.4)	1 (0.1)	0.45

Values are means (standard deviations) for the continuous variables and percentages for categorical variables. Student's t-test, the Wilcoxon rank sum test and χ^2-test were used to study the differences between the participants and non-participants. Age was defined in full years at the end of 2011; Childhood school performance was defined as grade point average (*i.e.* mean of grades in all individual school subjects at baseline or either of the two subsequent follow-ups for those participants who were not of school age at baseline); Years of education was determined as a continuous variable from self-reported data concerning total years of education attained in adulthood until the year 2011; Socioeconomic status in childhood was defined as in four different strata that were dependent on an annual income of the family; LDL = low-density lipoprotein; HDL = high-density lipoprotein; Subjects who reported current smoking at any of the follow-up phases at the ages between 12 and 24 years were classified as early-life smokers; Subjects who were smoking daily in adulthood were classified as smokers. Those with current use of insulin medication were excluded from serum glucose analysis. Physical activity index (range 5 – 15) was measured with a standardized self-administered questionnaire. The ideal diet score in adulthood was based on intake levels of ideal 5 dietary metrics (range 0 – 5): fruits and vegetables, fish, whole grains, sodium, and sugar-sweetened beverages.

Supplemental Table XXV: Associations Between Diastolic Blood Pressure and Serum Lipids from Childhood to Midlife and Cognitive Performance in Midlife.

A. Diastolic Blood Pressure	β estimate	95% CI	p-value	B. LDL-cholesterol	β estimate	95% CI	p-value
PAL-test (N=1385)				**PAL-test (N=1481)**			
Low-stable DBP	Reference			Low-stable LDL-cholesterol	Reference		
Normal-stable DBP	-0.049	-0.197 – 0.100	0.517	Elevated-stable LDL-cholesterol	-0.019	-0.124 – 0.086	0.728
Moderate-increasing DBP	-0.115	-0.302 – 0.072	0.227	High-stable LDL-cholesterol	**-0.175**	**-0.342 – -0.009**	**0.039**
RVP-test (N=1471)				**RVP-test (N=1577)**			
Low-stable DBP	Reference			Low-stable LDL-cholesterol	Reference		
Normal-stable DBP	0.068	-0.080 – 0.217	0.369	Elevated-stable LDL-cholesterol	0.004	-0.098 – 0.105	0.939
Moderate-increasing DBP	-0.067	-0.251 – 0.116	0.472	High-stable LDL-cholesterol	0.036	-0.126 – 0.198	0.660
RTI-test (N=1365)				**RTI-test (N=1458)**			
Low-stable DBP	Reference			Low-stable LDL-cholesterol	Reference		
Normal-stable DBP	0.024	-0.124 – 0.173	0.748	Elevated-stable LDL-cholesterol	0.025	-0.082 – 0.133	0.644
Moderate-increasing DBP	0.165	-0.023 – 0.354	0.085	High-stable LDL-cholesterol	-0.008	-0.181 – 0.165	0.924
SWM-test (N=1497)				**SWM-test (N=1605)**			
Low-stable DBP	Reference			Low-stable LDL-cholesterol	Reference		
Normal-stable DBP	0.120	-0.025 – 0.265	0.103	Elevated-stable LDL-cholesterol	-0.026	-0.127 – 0.075	0.610
Moderate-increasing DBP	0.026	-0.153 – 0.206	0.774	High-stable LDL-cholesterol	-0.017	-0.178 – 0.144	0.836
C. HDL-cholesterol	**β estimate**	**95% CI**	**p-value**	**D. Triglycerides**	**β estimate**	**95% CI**	**p-value**
PAL-test (N=1489)				**PAL-test (N=1489)**			
Low-stable HDL-cholesterol	Reference			Low-stable triglycerides	Reference		
Normal-stable HDL-cholesterol	-0.087	-0.222 – 0.048	0.206	Normal-increasing triglycerides	-0.065	-0.206 – 0.075	0.361
Elevated-stable HDL-cholesterol	-0.048	-0.205 – 0.109	0.548	Normal-rapidly increasing triglycerides	0.057	-0.178 – 0.292	0.634
High-stable HDL-cholesterol	-0.093	-0.331 – 0.145	0.443				
RVP-test (N=1585)				**RVP-test (N=1585)**			

	β	95% CI	p		β	95% CI	p
Low-stable HDL-cholesterol	Reference			Low-stable triglycerides	Reference		
Normal-stable HDL-cholesterol	-0.020	-0.150 – 0.111	0.768	Normal-increasing triglycerides	-0.010	-0.236 – 0.036	0.149
Elevated-stable HDL-cholesterol	0.023	-0.127 – 0.174	0.763	Normal-rapidly increasing triglycerides	0.052	-0.174 – 0.279	0.652
High-stable HDL-cholesterol	-0.149	-0.378 – 0.081	0.203				
RTI-test (N=1466)				**RTI-test (N=1466)**			
Low-stable HDL-cholesterol	Reference			Low-stable triglycerides	Reference		
Normal-stable HDL-cholesterol	-0.090	-0.229 – 0.049	0.204	Normal-increasing triglycerides	-0.073	-0.218 – 0.072	0.326
Elevated-stable HDL-cholesterol	-0.065	-0.226 – 0.097	0.431	Normal-rapidly increasing triglycerides	-0.056	-0.301 – 0.188	0.652
High-stable HDL-cholesterol	0.014	-0.232 – 0.260	0.910				
SWM-test (N=1613)				**SWM-test (N=1613)**			
Low-stable HDL-cholesterol	Reference			Low-stable triglycerides	Reference		
Normal-stable HDL-cholesterol	0.003	-0.127 – 0.133	0.962	Normal-increasing triglycerides	-0.007	-0.142 – 0.129	0.924
Elevated-stable HDL-cholesterol	-0.029	-0.179 – 0.121	0.707	Normal-rapidly increasing triglycerides	-0.012	-0.237 – 0.214	0.919
High-stable HDL-cholesterol	-0.124	-0.353 – 0.104	0.285				

Values are β estimates, 95% confidence intervals (CI), and p-values from linear regression models. All models were adjusted for age, sex, polygenic risk score, and adulthood CVRFs (body mass index, fasting serum glucose, smoking, physical activity, and diet). For diastolic blood pressure (DBP), models were further adjusted with adulthood serum total cholesterol. For lipids, models were further adjusted with adulthood systolic blood pressure. LDL = low density lipoprotein; HDL = high density lipoprotein. Cognitive tests measured episodic memory and associative learning (PAL-test); visual processing and sustained attention (RVP-test); reaction and movement time (RTI-test); and short-term working memory (SWM-test) and CANTAB® cognitive test battery was used for cognitive testing.

Supplemental Table XXVI: Creation of the Cardiovascular Risk Factor (CVRF) Score.

	Risk score points
Systolic blood pressure (SBP)	
Low-stable SBP	0
Normal-stable SBP	0
Moderate-stable SBP	0
Moderate-increasing SBP	1
Elevated-increasing SBP	1
Antihypertensive medication [*]	1
Serum total cholesterol	
Low-stable total cholesterol	0
Elevated-stable total cholesterol	0
High-stable total cholesterol	1
Dyslipidemia medication [*]	1
Body mass index	
Stable slim	0
Stable normal weight	0
Progressively overweight	1
Persistently increasing obese	1
Total risk score, range	0-3

[*] If participant 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 trajectory modeling.

Supplemental Table XXVII: Associations Between Cardiovascular Risk Factor Trajectories from Childhood to Midlife and Cognitive Performance in Midlife.

	β estimate	95% CI	p-value	β estimate	95% CI	p-value
	Model 1			**Model 2**		
A. PAL-test						
Systolic blood pressure	**N=1389**			**N=1156**		
Normal-stable SBP	Reference			Reference		
Low-stable SBP	0.075	-0.070 – 0.220	0.309	0.076	-0.082 – 0.234	0.345
Moderate-stable SBP	-0.047	-0.196 – 0.102	0.535	-0.01	-0.170 – 0.151	0.905
Moderate-increasing SBP	-0.063	-0.211 – 0.084	0.399	-0.037	-0.199 – 0.126	0.657
Elevated-increasing SBP	**-0.262**	**-0.520 – -0.005**	**0.046**	-0.221	-0.505 – 0.063	0.127
Serum total cholesterol	**N=1489**			**N=1255**		
Low-stable total cholesterol	Reference			Reference		
Elevated-stable total cholesterol	-0.040	-0.153 – 0.074	0.494	-0.071	-0.196 – 0.053	0.261
High-stable total cholesterol	**-0.214**	**-0.365 – -0.064**	**0.005**	**-0.259**	**-0.427 – -0.092**	**0.002**
Body mass index	**N=1557**			**N=1285**		
Stable normal weight	Reference			Reference		
Stable slim	-0.055	-0.162 – 0.052	0.311	-0.049	-0.166 – 0.067	0.408
Progressively overweight	0.027	-0.116 – 0.170	0.712	0.06	-0.095 – 0.216	0.446
Persistently increasing obese	-0.207	-0.520 – 0.107	0.197	-0.19	-0.529 – 0.149	0.271
B. RVP-test						
Systolic blood pressure	**N=1476**			**N=1232**		
Normal-stable SBP	Reference			Reference		
Low-stable SBP	-0.115	-0.260 – 0.029	0.118	-0.113	-0.264 – 0.039	0.146
Moderate-stable SBP	-0.003	-0.148 – 0.143	0.970	0.054	-0.097 – 0.204	0.486
Moderate-increasing SBP	**-0.185**	**-0.327 – -0.043**	**0.011**	**-0.179**	**-0.329 – -0.028**	**0.020**
Elevated-increasing SBP	-0.157	-0.396 – 0.082	0.197	-0.119	-0.371 – 0.134	0.356
Serum total cholesterol	**N=1585**			**N=1306**		
Low-stable total cholesterol	Reference			Reference		
Elevated-stable total cholesterol	0.011	-0.098 – 0.121	0.838	-0.004	-0.12 – 0.112	0.949
High-stable total cholesterol	-0.049	-0.195 – 0.097	0.513	-0.046	-0.202 – 0.110	0.563
Body mass index	**N=1662**			**N=1373**		
Stable normal weight	Reference			Reference		
Stable slim	-0.067	-0.171 – 0.038	0.210	-0.086	-0.196 – 0.024	0.126
Progressively overweight	**-0.165**	**-0.304 – -0.025**	**0.021**	**-0.17**	**-0.316 – -0.024**	**0.022**
Persistently increasing obese	**-0.407**	**-0.708 – -0.105**	**0.008**	**-0.377**	**-0.688 – -0.066**	**0.018**
C. RTI-test						
Systolic blood pressure	**N=1369**			**N=1140**		
Normal-stable SBP	Reference			Reference		
Low-stable SBP	0.021	-0.126 – 0.168	0.780	0.042	-0.122 – 0.207	0.613
Moderate-stable SBP	**0.155**	**0.003 – 0.306**	**0.045**	**0.179**	**0.013 – 0.346**	**0.035**
Moderate-increasing SBP	-0.02	-0.169 – 0.129	0.795	0.022	-0.147 – 0.190	0.802
Elevated-increasing SBP	0.197	-0.064 – 0.459	0.139	0.141	-0.154 – 0.437	0.349

Serum total cholesterol	**N=1466**			**N=1206**		
Low-stable total cholesterol	Reference			Reference		
Elevated-stable total cholesterol	-0.026	-0.143 – 0.090	0.658	-0.035	-0.165 – 0.095	0.597
High-stable total cholesterol	-0.065	-0.221 – 0.092	0.418	-0.064	-0.240 – 0.113	0.480
Body mass index	**N=1533**			**N=1265**		
Stable normal weight	Reference			Reference		
Stable slim	-0.020	-0.130 – 0.090	0.717	-0.008	-0.130 – 0.114	0.901
Progressively overweight	-0.016	-0.164 – 0.132	0.836	0.016	-0.148 – 0.180	0.848
Persistently increasing obese	-0.305	-0.630 – 0.020	0.065	**-0.488**	**-0.845 – -0.131**	**0.007**
D. SWM-test						
Systolic blood pressure	**N=1502**			**N=1256**		
Normal-stable SBP	Reference			Reference		
Low-stable SBP	0.030	-0.112 – 0.171	0.679	0.011	-0.143 – 0.164	0.893
Moderate-stable SBP	-0.085	-0.229 – 0.058	0.245	-0.04	-0.194 – 0.115	0.615
Moderate-increasing SBP	-0.061	-0.201 – 0.079	0.396	-0.06	-0.215 – 0.094	0.442
Elevated-increasing SBP	-0.165	-0.401 – 0.071	0.170	-0.122	-0.381 – 0.137	0.355
Serum total cholesterol	**N=1613**			**N=1331**		
Low-stable total cholesterol	Reference			Reference		
Elevated-stable total cholesterol	-0.091	-0.200 – 0.019	0.104	**-0.163**	**-0.282 – -0.044**	**0.007**
High-stable total cholesterol	-0.068	-0.213 – 0.077	0.358	-0.094	-0.254 – 0.067	0.252
Body mass index	**N=1693**			**N=1401**		
Stable normal weight	Reference			Reference		
Stable slim	-0.064	-0.167 – 0.039	0.224	-0.047	-0.160 – 0.065	0.408
Progressively overweight	0.029	-0.109 – 0.166	0.683	0.018	-0.131 – 0.167	0.817
Persistently increasing obese	0.151	-0.146 – 0.448	0.318	0.197	-0.121 – 0.515	0.224

Values are β estimates, 95% confidence intervals (CI), and p-values from linear regression models. Model 1 and model 2 were adjusted for age, sex, polygenic risk score, and adulthood CVRFs (fasting serum glucose, smoking, physical activity, and diet). Model 2 was further adjusted with childhood school performance, adulthood education, and childhood socioeconomic status. For systolic blood pressure (SBP), models were further adjusted with adulthood body mass index (BMI) and adulthood serum total cholesterol. For serum total cholesterol, models were further adjusted with adulthood BMI and adulthood SBP. For BMI, models were further adjusted with adulthood SBP and adulthood serum total cholesterol. Cognitive tests measured episodic memory and associative learning (PAL-test); visual processing and sustained attention (RVP-test); reaction and movement time (RTI-test); and

short-term working memory (SWM-test) and CANTAB® cognitive test battery was used for cognitive testing.

Supplemental Table XXVIII: Association between Cardiovascular Risk Factor (CVRF) Score and Cognitive Performance in Midlife.

	β estimate	95% CI	p-value	β estimate	95% CI	p-value
	Model 1			**Model 2**		
PAL-test	**N=1551**			**N=1282**		
0 CVRF	Reference			Reference		
1 CVRF	-0.069	-0.176 – 0.038	0.207	-0.044	-0.161 – 0.073	0.457
2 CVRFs	-0.128	-0.277 – 0.020	0.090	-0.097	-0.260 – 0.066	0.243
3 CVRFs	**-0.390**	**-0.691 – -0.088**	**0.011**	**-0.345**	**-0.677 – -0.014**	**0.041**
RVP-test	**N=1656**			**N=1370**		
0 CVRF	Reference			Reference		
1 CVRF	-0.097	-0.202 – 0.007	0.068	-0.087	-0.197 – 0.022	0.118
2 CVRFs	**-0.241**	**-0.386 – -0.095**	**0.001**	-0.213	**-0.367 – -0.059**	**0.007**
3 CVRFs	**-0.443**	**-0.730 – -0.157**	**0.003**	-0.404	**-0.704 – -0.105**	**0.008**
RTI-test	**N=1527**			**N=1262**		
0 CVRF	Reference			Reference		
1 CVRF	-0.046	-0.156 – 0.064	0.411	-0.053	-0.175 – 0.070	0.398
2 CVRFs	**-0.164**	**-0.318 – -0.010**	**0.037**	-0.167	-0.340 – 0.006	0.059
3 CVRFs	-0.122	-0.434 – 0.190	0.442	-0.068	-0.418 – 0.282	0.704
SWM-test	**N=1687**			**N=1398**		
0 CVRF	Reference			Reference		
1 CVRF	0.066	-0.036 – 0.169	0.205	0.086	-0.026 – 0.199	0.131
2 CVRFs	-0.014	-0.156 – 0.128	0.846	-0.020	-0.177 – 0.136	0.801
3 CVRFs	0.081	-0.204 – 0.365	0.578	0.105	-0.203 – 0.414	0.504

Values are β estimates, 95% confidence intervals (CI) and p-values from linear regression models. Model 1 and Model 2 models were adjusted for age, sex, polygenic risk score, and adulthood CVRFs (fasting serum glucose, smoking, physical activity, and diet). Model 2 was further adjusted with childhood school performance, adulthood education, and childhood socioeconomic status. Cognitive tests measured episodic memory visuospatial associative learning (PAL-test); visual processing and sustained attention (RVP-test); reaction and movement time (RTI-test); and short-term working memory (SWM-test) and CANTAB® cognitive test battery was used for cognitive testing.