Early Adult to Mid-Life Cardiovascular Risk Factors and Cognitive Function

Running title: Yaffe et al.; Cardiovascular risk factors and cognitive function

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Abstract

Background—Studies have linked mid- and late-life cardiovascular risk factors (CVRFs) to cognitive function, yet little is known about CVRF exposure in early adulthood and subsequent cognitive function. In addition, most studies rely on single assessments of CVRFs which may not accurately reflect long-term exposure. We sought to determine the association between cumulative exposure to CVRFs from early to mid-adulthood and cognitive function at mid-life.

Methods and Results—In a prospective study of 3,381 adults (ages 18 to 30 at baseline) with 25 years of follow-up, we assessed cognitive function at Year 25 (2010-11) with the Digit Symbol Substitution Test (DSST), Stroop Test, and Rey Auditory Verbal Learning Test (RAVLT) analyzed with standardized z-scores. The primary predictor was 25 year cumulative exposure estimated by areas under the curve (AUCs) for resting systolic and diastolic blood pressure (SBP, DBP), fasting blood glucose (FBG), and total cholesterol. Higher cumulative SBP, DBP, and FBG were consistently associated with worse cognition on all three tests. These associations were primarily significant for exposures above recommended guidelines; cognitive test z scores were between 0.06 to 0.30 points less, on average, for each SD increase in risk factor AUC, after adjusting for age, race, gender, and education, p<0.05 for all. Fewer significant associations were observed for cholesterol.

Conclusions—Cumulative exposure to CVRFs from early to mid-adulthood, especially above recommended guidelines, was associated with worse cognition in mid-life. The meaning of this association and whether it warrants more aggressive treatment of CVRFs earlier in life requires further investigation.

Key words: blood pressure, cholesterol, glucose, risk factor, cognition
Background

Exposure to cardiovascular risk factors (CVRFs) including elevated levels of blood pressure, lipids, and fasting blood glucose (FBG), during early adulthood is associated with adverse cardiovascular outcomes in later life.1-4 The longitudinal relationships of these early adult risk factors with cognitive function are unknown despite a robust body of evidence linking mid and late-life CVRFs to late-life cognitive function.5

While accumulating data from observational studies suggest that CVRFs may be modifiable risk factors for cognitive impairment,6, 7 randomized controlled trials targeting treatment of these conditions including hypertension, dyslipidemia, and diabetes, have reported mixed results.8-10 Most studies (both trials and observational) have focused on risk relationships during mid-adult to late-life periods,11-13 and the nature of this association during earlier life stages has not been defined. Because the neuropathology associated with cognitive impairment and dementia often develops over decades,14 determination of CVRF effects over the life course, starting in early adulthood, could inform the design of more targeted and effective interventions for healthy cognitive aging.

Since individual profiles of CVRFs vary throughout the life course,15, 16 single measures of exposure (often many years prior) may not reflect the longitudinal variation and cumulative burden associated with elevated CVRF level. Summary measures of cumulative exposure that capture both duration and intensity could more accurately estimate the effects of these risk factors over several decades. In order to determine the association between CVRFs early over the life course and cognitive function in mid-life, we investigated the cumulative effects of systolic and diastolic blood pressure (SBP and DBP), fasting blood glucose levels (FBG), and total cholesterol levels measured from early adulthood to mid-life. We hypothesize that greater
cumulative exposure to CVRFs will be associated with worse cognitive performance in mid-life.

Methods

Study population

We studied participants enrolled in the Coronary Artery Risk Development in Young Adults (CARDIA) Study, an investigation of the development of and risk factors for cardiovascular disease. Young adults between the ages of 18 and 30 were recruited from population-based samples of four US cities (Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California). A total of 5,115 participants were enrolled between 1985 and 1986, with roughly equal sample sizes by sex, age (18-24 years and 25-30 years), race (white, black), and education (≤high school, >high school) at each site. Participants completed follow-up examinations every two to five years for 25 years, 1987-1988 (Year 2), 1990-1991 (Year 5), 1992-1993 (Year 7), 1995-1996 (Year 10), 2000-2001 (Year 15), 2005-2006 (Year 20), and 2010-2011 (Year 25, n=3,499). At each exam, participants provided written informed consent, and study protocols were reviewed by institutional review boards at each study site, the CARDIA coordinating center at the University of Alabama, Birmingham, and the University of California, San Francisco. Further details of study recruitment and design are available.17, 18

For this study, we assessed the 3,381 participants who completed the Year 25 visit with evaluation of CVRFs over time (at least two time points required, 98% of the cohort had both baseline and year 25 measures of CVRFs and 93% had at least 2/3rd of possible CVRF measures over time) and at least one of the three cognitive assessments at Year 25. Compared to those in this analytic cohort, the participants without a cognitive assessment were younger, more likely to be male and black, less educated, and more likely to smoke (p<0.01 for all).
Cardiovascular Risk Factor Measurement

Before each clinic exam, participants were asked to fast and abstain from smoking or heavy physical activity for at least 12 hours prior to the visit. Certified technicians collected three measures of resting blood pressure at one minute intervals, using a Hawksley random zero sphygmomanometer (WA Baum Company, Copaigue, NY) at baseline, Years 2, 5, 7, 10, and 15, and at Years 20 and 25, a digital blood pressure monitor (Omron HEM-907XL; Online Fitness, Santa Monica, CA) was used. The oscillometric values were calibrated to the random zero values following a study of both devices at Year 20. In this analysis, SBP and DBP measures were calculated as the average of the second and third measurements.

Fasting total cholesterol was measured enzymatically on the Abbot Spectrum (using Hitachi 917 – R1 cholesterol reagent) at baseline, Years 5, 7, 10, 15, 20, and 25 by the Northwest Lipid Research Laboratory at the University of Washington (Seattle, WA) as previously described.19 At baseline, FBG was measured using the hexokinase ultraviolet method by American Bio-Science Laboratories (Van Nuys, CA), and at subsequent clinic exams, Years 7, 10, 15, 20, and 25, using hexokinase coupled to glucose-6-phosphate dehydrogenase by Linco Research (St. Louis, MO).

Cognitive function assessment

CARDIA technicians who underwent formal training and certification administered a battery of three cognitive tests at the Year 25 exam that included the Digit Symbol Substitution Test (DSST), the Stroop Test, and the Rey Auditory Verbal Learning Test (RAVLT). DSST assesses attention, working memory, psychomotor speed, and executive function with higher scores indicating better performance with a range of 0 to 133.20 The Stroop Test of executive function uses three subtests. We calculated an interference score by subtracting the score on subtest II
from subtest III with a higher interference score indicating worse performance. RAVLT is a test of verbal memory with a range of 0 to 15. Scores on the delayed test were used with higher scores indicating better performance. For ease of interpretation, all cognitive test scores were transformed into standardized z scores with positive values indicating better performance and negative values indicating worse performance.

**Covariates**

At each exam, weight and height were measured, and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Demographic characteristics, cigarette smoking (in years), and alcohol use were based on self-report. Diabetes at year 25 was defined as fasting plasma glucose \( \geq 126 \text{ mg/dL} \), oral glucose tolerance test \( \geq 200 \text{ mg/dL} \), glycosylated hemoglobin \( \geq 6.5\% \), or use of diabetes medications. Incident cardiovascular events over 25 years of follow-up were defined by patient self-report and adjudicated review of hospitalization records.

**Statistical analysis**

Our primary predictors were areas under the curve (AUCs) for four CVRFs. We estimated the mean curve for each CVRF using linear mixed models for each race and sex group, using a linear spline in age with knots at ages 30 and 40 corresponding to decades of the life span, for face validity and to ensure adequate numbers of observations in each of the three age ranges defined by the knots. We then calculated participant-specific CVRF curves as best linear unbiased predictions (BLUPs), based on the mixed models. Next, we calculated areas under the resulting curves (AUCs) over the interval from baseline to the Year 25 visit. Additionally, in order to determine differences between early adult vs early mid-life effects, we also calculated AUCs as subsets of the follow-up interval before and after age 35.
We then used linear regression to assess the independent associations of the AUCs with cognitive function assessed at the Year 25 visit. For each test, we first estimated the unadjusted association, and then estimated the association controlling for age at Year 25, race/ethnicity, sex, and education. In additional models, we also controlled for Year 25 BMI, diabetes, and smoking as well as baseline CVRF level. In a sensitivity analysis, we adjusted for incident cardiovascular events including myocardial infarction, coronary revascularization, stroke, peripheral artery disease, and congestive heart failure. We also estimated associations for models excluding participants with incident cardiovascular events.

In order to distinguish whether any association with cognitive function was attributable to CVRF level above or below recommended guidelines, we divided the overall AUC for each participant and CVRF into two regions, separated by a horizontal line at the recommended (normal) guidelines defined by American Heart Association (AHA) criteria for ideal cardiovascular health: SBP <120 mmHg, DBP <80 mmHg, FBG <100 mg/dL, and total cholesterol<200 mg/dL\(^2\)). We then calculated the area in each of these regions. For curves always remaining below the guideline value, the area in the upper region is zero.

All analyses were completed using SAS version 9.3, and significance testing was 2-sided with significance level set at \(p<0.05\).

**Results**

At Year 25, participant mean age was 50.2 ±3.6, 46.4% were Black, 43.6% were male, and 83.9% had greater than a high school education (Table 1). At Year 25, mean CVRF level was SBP (mean ±SD) = 119.7 ±16.2 mmHg, DBP = 74.8 ±11.2 mmHg, FBG = 99.5 ±28.7 mg/dL, total cholesterol = 192.1 ±36.7 mg/dL. Mean Year 25 cognitive score was 8.3 ±3.3 for RAVLT,
69.9 ±16.2 for DSST, and 22.7 ±10.9 for the Stroop interference score (Table 1). Over the follow up period, 92 participants had an incident cardiovascular event including myocardial infarction (n=32), coronary revascularization (n=32), stroke (n=31), peripheral artery disease (n=4), and congestive heart failure (n=18).

The overall cumulative CVRF AUCs were associated, in most cases, with worse cognitive function (Figure 1). Cumulative levels of both SBP and DBP (per SD increase of AUC) over follow-up were significantly associated with worse performance on all three cognitive tests in unadjusted models (Table 2). In models adjusted for age, sex, race, and education, the cumulative effects of SBP remained negatively associated with cognitive function (RAVLT = -0.09, 95% CI -0.15 to -0.03; DSST = -0.12, 95% CI -0.18 to -0.06; Stroop = -0.11, 95% CI -0.17 to -0.05), and cumulative level of DBP were significantly associated with worse performance on DSST and Stroop (DSST = -0.07, 95% CI -0.12 to -0.02; Stroop = -0.09, 95% CI -0.14 to -0.03) but not RAVLT (RAVLT= -0.05, 95% CI 0.11 to 0.0). Additional adjustment for diabetes, smoking and BMI led to similar results.

The cumulative effects of FBG followed a similar pattern as blood pressure level, with AUC associated with worse performance on RAVLT, Stroop, and DSST in unadjusted models (Table 2). These associations remained significant adjusting for age, sex, race, and education (RAVLT = -0.07, 95% CI -0.11 to -0.02; DSST = -0.08, 95% CI -0.12 to -0.04; Stroop = -0.07, 95% CI -0.12 to -0.03). When we excluded those participants with diabetes (at Year 25, n=462), this association was no longer significant (RAVLT = -0.10, 95% CI -0.21 to 0.01; DSST = 0.03, 95% CI -0.08 to 0.14; Stroop = 0.0, 95% CI -0.12 to 0.11). For total cholesterol, the pattern was not as consistent. Cumulative exposure to cholesterol was associated with worse performance on DSST but not RAVLT or Stroop (Table 2). After multivariable adjustment, the overall effects of
cholesterol remained statistically significantly associated with worse performance on RAVLT (RAVLT = -0.06, 95% CI -0.10 to -0.02; DSST= 0.0, 95% CI -0.04 to 0.04; Stroop= -0.02, 95% CI -0.07 to 0.02) and additional adjustment for diabetes, smoking and BMI did not appreciably alter the findings.

For each risk factor, further adjustment for baseline CVRF level did not appreciably change the association between AUC effects and cognition. We also investigated interactions between race, CVRF AUC, and cognitive function and found no consistent pattern of effects (p-values for interactions between CVRFs and race: p≥0.27 for all on RAVLT, p≥0.05 for all on DSST, p≥0.16 for all on Stroop). In an additional sensitivity analysis, we adjusted for incident cardiovascular events, the associations between CVRF AUCs and cognitive function remained statistically significant but effect sizes were reduced (Supplemental Table). The associations were similar for models which excluded participants with incident cardiovascular events.

To determine whether the cumulative effects of cardiovascular risk factors differed in early adulthood (age<35) compared to early middle age (age ≥35), we evaluated models that separately assessed the contribution of each cumulative risk factor before age 35 and after age 35. In most cases, if the 25-year cumulative effect of a CVRF was significant, then cumulative effects of the risk factor both before age 35 and after age 35 were significant (p<0.05 for all). For example, the 25-year cumulative effect of FBG contributed significantly to the variance of each cognitive test, and both the effects of FBG before 35 and after 35 were significant. For DBP, only the cumulative effects after age 35 were significant.

We next investigated whether the association between CVRFs and cognitive function were attributable to exposure levels above recommended guidelines by estimating the effects of normal (below AHA guidelines) and elevated (above AHA guidelines) cumulative CVRF
exposures. Between 30% to 48% of participants had elevated, cumulative CVRF exposures (SBP = 1635 (48.4%), DBP = 1013 (30.0%), FBG = 1026 (30.4%), cholesterol = 1444 (42.7%). Cumulative exposures to CVRFs in both normal and elevated ranges were significantly associated with cognitive function in unadjusted models (Table 2), but after adjusting for age, sex, race, and education, only the effects of cumulative exposures to elevated levels of CVRFs remained significant. Cumulative exposure to SBP level above recommended guidelines was significantly associated with worse cognitive function on DSST and Stroop (DSST = -0.24, 95% CI -0.41 to -0.07; Stroop = -0.24, 95% CI -0.42 to -0.05, Figure 2a) but was borderline significant for RAVLT (-0.17, 95% CI -0.35 to 0.0). The cumulative effect of elevated DBP level was associated with worse performance on RAVLT and Stroop (RAVLT = -0.25, 95% CI -0.48 to -0.03; Stroop = -0.29, 95% CI -0.53 to -0.06, Figure 2b) but was borderline significant for DSST (-0.22, 95% CI -0.44 to 0.0). For elevated FBG level, cumulative exposure was negatively associated with performance on RAVLT, DSST, and Stroop (RAVLT = 0.09, 95% CI -0.16 to -0.02; DSST = -0.15, 95% CI -0.22 to -0.09; Stroop = -0.13, 95% CI -0.20 to -0.06, Figure 2c), and for cholesterol level above recommended guidelines, the cumulative effect was significant for worse performance on RAVLT (-0.06, 95% CI -0.11 to -0.01) and not on DSST or Stroop (DSST= 0.01, 95% CI -0.04 to 0.05; Stroop= -0.01, 95% CI -0.06 to 0.04; Figure 2d).

Discussion

In this study, we found that CVRFs in early to mid-adulthood were associated with worse cognitive performance in mid-life. In particular, greater cumulative exposure to these measures in levels above recommended guidelines over 25 years was consistently associated with worse cognitive performance on executive function, processing speed, and verbal memory.
The observed association between CVRFs and cognitive function in this study is supported by findings from other studies of older adult populations. Previous investigations have focused primarily on the association between CVRF exposures and cognitive function after age 50 without considering the contribution of early adult exposures. The most consistent findings have been between mid-life CVRFs, including elevated blood pressure and FBG, and late-life cognition. A number of studies have also reported associations between late-life exposures and late-life cognitive impairment, but the results have been less consistent. For example, in a large cohort study of older adults, the association between diabetes and dementia was stronger for mid-life diabetes compared to late-life diabetes. In other studies, decreases in levels of cholesterol and blood pressure in late age were associated with an increased risk of cognitive impairment and dementia suggesting that the relationship with some CVRFs closer to the time of dementia onset may reflect metabolic dysregulation resulting from impaired neurodegenerative processes. Our study has important implications for understanding the role of CVRFs across the life course and suggests that even at subclinical levels, the cumulative effects of CVRFs beginning in early adulthood are associated with cognitive function at middle age.

The mechanisms by which CVRFs in early adulthood affect cognitive function are unclear. Cumulative exposure to high level of CVRFs could increase risk of subclinical ischemia and cause cerebrovascular damage, especially of a subcortical nature. Longitudinal MRI studies in older adults have demonstrated that CVRFs may accelerate the risk of structural brain changes including both atrophy and infarcts, and subcortical regions of the brain may be especially affected leading to the impairment in executive function that we observed in this study. Our findings of an association between cardiovascular risk factors and poor cognitive function are
consistent with other studies of cognitively normal populations.\textsuperscript{33, 35} CVRF exposures have been associated with increased markers of inflammation and oxidative stress which in turn can cause neuronal damage.\textsuperscript{36-38} In addition, neuropathological studies suggest a relationship between elevated CVRF levels and amyloidogenic pathology.\textsuperscript{39-41} CVRFs and the vascular damage associated with elevated levels of these risk factors may interact with amyloid pathways disrupting amyloid clearance and production and increasing amyloid deposition and plaques.\textsuperscript{42, 43} Genetic risk factors could also link the effects of CVRFs to risk of cognitive impairment.\textsuperscript{44, 45}

To our knowledge, this study is one of the first to investigate the effects of early life CVRFs on cognitive function in mid-life, and its strengths include a well-characterized cohort with over 25 years of follow up data. In addition, because there were repeated measures of CVRFs, we were able to evaluate the cumulative effect of CVRFs (using AUCs) which could more accurately capture longitudinal exposure. Assessment of AUCs may be especially useful for our cohort, a younger, healthy study population for which clinical outcomes such as hypertension, dyslipidemia, and diabetes may not be as relevant. There are, however, a number of limitations to consider. This was a biracial cohort of black and white adults, and the results may not be as generalizable to other race/ethnic groups. Furthermore, we did not have measures of cognitive function at baseline. Because cognitive function was only measured at one time point, Year 25, we were unable to determine the relationship of these risk factors with change in cognition.

While the association between CVRF AUCs and mid-life cognitive performance was significant in this study, the effect size for each risk factor was small. However, studies that have investigated differences in mid-life cognitive function by other risk factors like APOE genotype report similar modest effects.\textsuperscript{46} It is unclear if the effects observed in this study merit
reconsideration of currently accepted approaches for life course management of CVRFs or direct intervention during early adulthood. Because of the robust connection between cardiovascular health and brain health, the conceptual framework developed for cardiovascular health promotion may provide an apt model for cognitive aging. In particular, the AHA corresponding recommendations for both primordial, primary, and secondary cardiovascular disease prevention at different stages of the life course may be especially relevant for brain health promotion, and a recent study from CARDIA has suggested that, in young adults, a greater number of ideal cardiovascular parameters, which include both lifestyle behaviors and risk factors, may be associated with better mid-life cognitive performance.

Much of the public health debate on cognitive health has focused on early life development or late life dementia prevention. Our results not only support a role for early adult CVRFs, but the findings also suggest that duration of exposure could be an important factor in determining risk of cognitive impairment. Elevated, yet subclinical CVRF levels may be potential modifiable risk factors for accelerated cognitive aging. While it is unclear whether treatment is warranted, this subgroup, particularly those with multiple elevated CVRFs may represent a critical target group for early prevention. Current evidence indicates that reducing mid-life CVRFs could decrease risk of late-life dementia, but if the neuronal damage associated with cumulative CVRF exposure begins even before mid-life, an expanded focus on earlier stages of the life course may be necessary to effectively reduce CVRF levels and impact the public health burden of cognitive impairment. Further understanding of the longitudinal effects of risk factors which take into account both temporality and duration of exposure may help inform the optimal timing and strategies needed to prevent cognitive decline. Additional long-term investigations which examine the effects of CVRFs and their treatment, coupled with
biomarker and MRI imaging data in younger populations are required to fully determine the implications for effective population-based interventions over the life course.

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**Conflict of Interest Disclosures:** Dr. Yaffe has served on data safety monitoring boards for Takeda, Inc and a study sponsored by the NIH and has served as a consultant for Novartis, Inc. The remaining authors report no conflicts.

**References:**


18. Friedman GD, Cutter GR, Donahue RP, Hughes GH, Hulley SB, Jacobs Jr DR, Liu K,


Table 1. Demographic and risk characteristics of the 3381 CARDIA participants

<table>
<thead>
<tr>
<th>Demographics</th>
<th>N (%) or Mean ± SD</th>
</tr>
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<tbody>
<tr>
<td>Age at Baseline, years</td>
<td>25.1 ± 3.6</td>
</tr>
<tr>
<td>Age at Year 25, years</td>
<td>50.2 ± 3.6</td>
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<tr>
<td>Male</td>
<td>1475 (43.6)</td>
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<tr>
<td>Black</td>
<td>1567 (46.4)</td>
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<tr>
<td>Education, years</td>
<td>15.5 ± 2.5</td>
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<td>&gt; High School Education</td>
<td>2837 (83.9)</td>
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**Cardiovascular Risk Factors**

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<tr>
<th>Systolic blood pressure, mmHg</th>
<th>Mean ± SD</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>109.9 ± 10.8</td>
</tr>
<tr>
<td>Year 25</td>
<td>119.7 ± 16.2</td>
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<tr>
<td>Time-weighted average</td>
<td>111.8 ± 9.3</td>
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<table>
<thead>
<tr>
<th>Diastolic blood pressure, mmHg</th>
<th>Mean ± SD</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>68.4 ± 9.4</td>
</tr>
<tr>
<td>Year 25</td>
<td>74.8 ± 11.2</td>
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<tr>
<td>Time-weighted average</td>
<td>71.2 ± 6.7</td>
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<table>
<thead>
<tr>
<th>Fasting blood glucose, mg/dL</th>
<th>Mean ± SD</th>
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</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>82.0 ± 10.9</td>
</tr>
<tr>
<td>Year 25</td>
<td>99.5 ± 28.7</td>
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<tr>
<td>Time-weighted average</td>
<td>88.8 ± 11.1</td>
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<table>
<thead>
<tr>
<th>Total Cholesterol, mg/dL</th>
<th>Mean ± SD</th>
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<tbody>
<tr>
<td>Baseline</td>
<td>177.4 ± 33.1</td>
</tr>
<tr>
<td>Year 25</td>
<td>192.1 ± 36.7</td>
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<tr>
<td>Time-weighted average</td>
<td>182.4 ± 26.1</td>
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**Cognitive test scores at Year 25**

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<th>Test</th>
<th>N</th>
<th>Mean ± SD</th>
<th>Range</th>
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<tbody>
<tr>
<td>Rey Auditory Verbal Learning Test – Delayed, words</td>
<td>3288</td>
<td>8.3 ± 3.3</td>
<td>0.0-15.0</td>
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<tr>
<td>Digit Symbol Substitution Test, symbols</td>
<td>3350</td>
<td>69.9 ± 16.2</td>
<td>8.0-125.0</td>
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<tr>
<td>Stroop Interference, points</td>
<td>3329</td>
<td>22.7 ± 10.9</td>
<td>-23.0-127.0</td>
</tr>
</tbody>
</table>
Table 2. The unadjusted association of cumulative exposure to overall, normal, and elevated cardiovascular risk factors and cognitive function at mid-life among 3381 CARDIA participants

<table>
<thead>
<tr>
<th></th>
<th>Reyauditory Verbal Learning–delayed</th>
<th>Digit Symbol Substitution Test</th>
<th>Stroop Interference</th>
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<tbody>
<tr>
<td></td>
<td>Standardized difference (95% CI)</td>
<td>Standardized difference (95% CI)</td>
<td>Standardized difference (95% CI)</td>
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<tr>
<td><strong>Systolic Blood Pressure</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>-0.14 (-0.17, -0.10)†</td>
<td>-0.21 (-0.24, -0.18)†</td>
<td>-0.13 (-0.16, -0.10)†</td>
</tr>
<tr>
<td>Normal levels</td>
<td>-0.07 (-0.11, -0.03)†</td>
<td>-0.15 (-0.19, -0.11)†</td>
<td>-0.06 (-0.10, -0.02)‡</td>
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<tr>
<td>Elevated levels</td>
<td>-0.74 (-0.92, -0.57)†</td>
<td>-0.77 (-0.94, -0.59)†</td>
<td>-0.73 (-0.91, -0.55)†</td>
</tr>
<tr>
<td><strong>Diastolic Blood Pressure</strong></td>
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<td></td>
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<tr>
<td>Overall</td>
<td>-0.12 (-0.16, -0.09)†</td>
<td>-0.19 (-0.22, -0.16)†</td>
<td>-0.13 (-0.16, -0.09)†</td>
</tr>
<tr>
<td>Normal levels</td>
<td>-0.07 (-0.11, -0.03)†</td>
<td>-0.15 (-0.19, -0.11)†</td>
<td>-0.08 (-0.12, -0.04)†</td>
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<tr>
<td>Elevated levels</td>
<td>-0.78 (-1.01, -0.55)†</td>
<td>-0.71 (-0.94, -0.47)†</td>
<td>-0.75 (-0.98, -0.51)†</td>
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<td><strong>Fasting Blood Glucose</strong></td>
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</tr>
<tr>
<td>Overall</td>
<td>-0.09 (-0.13, -0.06)†</td>
<td>-0.16 (-0.19, -0.12)†</td>
<td>-0.09 (-0.13, -0.06)†</td>
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<tr>
<td>Normal levels</td>
<td>-0.05 (-0.09, 0.00)§</td>
<td>-0.13 (-0.18, -0.09)†</td>
<td>-0.04 (-0.09, 0.01)</td>
</tr>
<tr>
<td>Elevated levels</td>
<td>-0.19 (-0.26, -0.12)†</td>
<td>-0.21 (-0.28, -0.14)†</td>
<td>-0.20 (-0.27, -0.13)†</td>
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<td><strong>Total Cholesterol</strong></td>
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<tr>
<td>Overall</td>
<td>-0.03 (-0.06, 0.01)</td>
<td>-0.05 (-0.09, -0.02)‡</td>
<td>-0.03 (-0.07, 0.00)</td>
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<tr>
<td>Normal levels</td>
<td>-0.02 (-0.03, 0.06)</td>
<td>-0.05 (-0.09, 0.00)§</td>
<td>0.03 (-0.08, 0.01)</td>
</tr>
<tr>
<td>Elevated levels</td>
<td>-0.11 (-0.16, -0.05)†</td>
<td>-0.06 (-0.12, -0.01)§</td>
<td>-0.04 (-0.09, 0.02)</td>
</tr>
</tbody>
</table>

* per SD increase of area under the curve (AUC)
† p<0.01
‡ p<0.001
§ p<0.05

Figure Legends:

Figure 1. Distribution of cardiovascular risk factor area under the curve (AUC) and association with year 25 cognitive function, adjusted for age, sex, race and education

Figure 2. Cumulative linear association of exposure to elevated level of cardiovascular risk factors with cognitive function at mid-life adjusted for age, sex, race, and education. *p<0.05.
Figure 1A
Figure 1B
Figure 1C
Figure 1D
Figure 2A

Systolic Blood Pressure

Standardized Score Difference (per SD of AUC)

-0.6 -0.5 -0.4 -0.3 -0.2 -0.1 -0.0 0.0 0.1

Rey Auditory Verbal Learning - Delayed
Digit Symbol Substitution Test
Stroop Interference

*
Diastolic Blood Pressure

Standardized Score Difference (per SD of AUC)

-0.6 -0.5 -0.4 -0.3 -0.2 -0.1 0.0 0.1

Rey Auditory Verbal
Learning - Delayed

Digit Symbol Substitution Test

Stroop Interference

Figure 2B
Figure 2C

Fasting Blood Glucose

Standardized Score Difference (per SD of AUC)

-0.6 -0.5 -0.4 -0.3 -0.2 -0.1 0.0 0.1

Rey Auditory Verbal Digit Symbol Stroop Learning - Delayed Substitution Test Interference

*
Figure 2D

Cholesterol

Standardized Score Difference (per SD of AUC)

-0.6  -0.5  -0.4  -0.3  -0.2  -0.1  -0.0  0.0  0.1

Rey Auditory Verbal Learning - Delayed  Digit Symbol Substitution Test  Stroop Interference
Supplemental Table. The association of cumulative exposure to overall cardiovascular risk factors and cognitive function at mid-life adjusting for or excluding incident cardiovascular events*

<table>
<thead>
<tr>
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<th>Stroop Interference</th>
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<tr>
<td></td>
<td>Standardized difference *</td>
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<td>(95% CI)</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
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<td>Adjusting for incident cardiovascular events</td>
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<tr>
<td>Systolic Blood Pressure</td>
<td>-0.09 (-0.15, -0.03)‡</td>
<td>-0.11 (-0.16, -0.05)†</td>
<td>-0.10 (-0.16, -0.03)‡</td>
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<tr>
<td>Diastolic Blood Pressure</td>
<td>-0.05 (-0.10, 0.0)</td>
<td>-0.06 (-0.11, -0.01)§</td>
<td>-0.07 (-0.13, -0.02)§</td>
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<tr>
<td>Fasting Blood Glucose</td>
<td>-0.06 (-0.11, -0.02)‡</td>
<td>-0.07 (-0.11, -0.02)‡</td>
<td>-0.06 (-0.10, -0.01)§</td>
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<tr>
<td>Total Cholesterol</td>
<td>-0.05 (-0.10, -0.01)§</td>
<td>0.01 (-0.03, 0.05)</td>
<td>-0.02 (-0.06, 0.02)</td>
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<td>Excluding incident cardiovascular events</td>
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<td></td>
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<tr>
<td>Systolic Blood Pressure</td>
<td>-0.08 (-0.15, -0.02)‡</td>
<td>-0.10 (-0.16, -0.04)†</td>
<td>-0.11 (-0.18, -0.05)†</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>-0.05 (-0.10, 0.1)</td>
<td>-0.06 (-0.12, -0.01)§</td>
<td>-0.09 (-0.15, -0.03)‡</td>
</tr>
<tr>
<td>Fasting Blood Glucose</td>
<td>-0.05 (-0.09, 0.0)</td>
<td>-0.07 (-0.12, -0.03)‡</td>
<td>-0.08 (-0.13, -0.03)‡</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>-0.05 (-0.09, -0.01)§</td>
<td>0.0 (-0.04, 0.04)</td>
<td>-0.03 (-0.07, 0.02)</td>
</tr>
</tbody>
</table>

*Adjusted for age, race, sex and education

† p<0.001
‡ p<0.01
§ p<0.05