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# Changes in metabolic risk factors over 10 years and their associations with late-life cognitive performance: The Multi-Ethnic Study of Atherosclerosis

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**Abstract**

**Background:** We examined whether changes in metabolic factors over 10 years were associated with cognitive performance.

**Methods:** Participants from the Multi-Ethnic Study of Atherosclerosis were followed since baseline (2000–2002) with five clinical examinations. At exam 5 (2010–2012), they received a short cognitive battery (Cognitive Abilities Screening Instrument [CASI], Digit Symbol Coding [DSC], and Digit Span [DS]). We examined associations between baseline metabolic factors and their changes over time before cognitive testing.

**Results:** Among 4392 participants, baseline metabolic disorders (fasting glucose, systolic and diastolic blood pressures) were significantly associated with poorer CASI, DSC, and DS scores measured 10 years later. Increases in blood pressure were associated with lower cognitive performance. Results did not differ by race/ethnicity and were stronger among those without the *APOE* ε4 allele.

**Conclusions:** Cognitive performance was associated with antecedent abnormalities in glucose metabolism and blood pressure increases. Findings appeared stronger among *APOE* ε4-negative participants.



*Keywords:* Metabolism; Metabolic disorders; Cognitive function; Brain

## 1. Introduction

Metabolic and vascular risk factors are important modifiable risk factors for dementia [1–3], especially when present in midlife. These processes are interrelated to the extent that they facilitate each other's progression and frequently

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co-occur in the elderly, making it difficult, if not impossible to disentangle their individual contributions to cognitive impairment [4]. The combination of metabolic (obesity, dyslipidemia, insulin resistance, and hyperglycemia) and vascular (hypertension) conditions can be described as a metabolic syndrome, which is defined by the Harmonized Definition [5]. When present in midlife, these conditions increase the risk for cognitive deficits later in life [2,6–9].

As comorbid conditions, metabolic and vascular conditions are thought to accelerate the trajectory of cognitive decline preceding a diagnosis of dementia [4]. These potential metabolic pathways to dementia are proposed to be independent of the apolipoprotein E (*APOE*) ε4 allele [10]. Few studies in older adults have sufficient longitudinal data to examine in detail, the independent and joint effects of midlife metabolic and vascular conditions on cognitive function in later life. The Multi-Ethnic Study of Atherosclerosis (MESA) has collected detailed observations of participants' metabolic and vascular health since 2000–2002 and offers a unique opportunity to assess changes in metabolic and vascular risk factors over time and their effects on cognitive health. In the present study, we examine how baseline metabolic factors and their changes over time are associated with aspects of cognitive performance 10 years later. Furthermore, we investigate how race/ethnicity, baseline hypertension, diabetes, and *APOE* ε4 carriage may modify these associations.

## 2. Methods

### 2.1. Participants

MESA is a prospective observational cohort comprising 6814 adults aged 45–84 years at baseline examination in 2000–2002 who self-reported their race/ethnicity as non-Hispanic white, non-Hispanic black, Hispanic, or Chinese [11]. Adults between the ages of 45 and 84 years who were free of clinically apparent cardiovascular disease (CVD) were recruited from six US communities: Baltimore City and Baltimore County, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; Northern Manhattan and the Bronx, New York; and St. Paul, Minnesota. The primary objective of MESA is to determine the characteristics related to the prevalence and progression of subclinical to clinical CVD [11]. The present study focuses on the subset of participants who returned for MESA exam 5 (2010–2012) and completed cognitive testing. All participants provided informed consent, and institutional review board approval was received at all MESA sites and reading centers.

### 2.2. Measurements

At baseline and each follow-up examination, data were collected using standardized questionnaires to assess demographics and medication usage for high blood pressure, high cholesterol, or diabetes. Participants were interviewed in the language of their choice, including English, Spanish, or Chinese (Mandarin or Cantonese). Waist circumference at the umbilicus was measured to the nearest 0.1 cm using a measuring tape. Resting brachial systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements were obtained using the Dinamap® automated blood pressure device (Dinamap Monitor Pro 100®). Three sequential measures were obtained, and the average of the second and third measurements was recorded. Total and high-density lipoprotein (HDL) cholesterol, triglycerides, glucose and insulin, and hemoglobin $A_{1c}$ (HbA1c, exam 2 and exam 5 only) levels were measured from blood samples obtained after a 12-hour fast. Low-density lipoprotein cholesterol was calculated with the Friedewald equation among those with triglycerides less than 400 mg/dL [12]. Metabolic syndrome was defined using the Harmonized Definition [5], requiring three or more of the following: large waist circumference (women $>$ 88 cm and men $>$ 102 cm); elevated triglycerides ($\geq$8.33 mmol/L [150 mg/dL]); low HDL-cholesterol (men $<$ 40 and women $<$ 50 mg/dL); impaired fasting glucose (6.11–7.0 mmol/L); and elevated blood pressure (BP $\geq$ 130/85 mm Hg or self-reported use of medications for hypertension). Diabetes was defined as fasting glucose $\geq$7 mmol/L (126 mg/dL) or use of hypoglycemic medication. Impaired fasting glucose was defined as a fasting glucose of 6.11–7 mmol/L ($\geq$100 mg/dL to $<$126 mg/dL) or use of diabetes medication. Incident cases of metabolic dysfunction (metabolic syndrome, impaired fasting glucose, and diabetes) met these criteria at each of the follow-up examinations, and noncases did not meet these criteria at any of the available follow-up examinations.

### 2.3. Assessment of cognition

Cognitive function was evaluated during the fifth MESA follow-up exam 5 (2010–2012, $n$ = 4591) using three standardized and validated tests including the following: Cognitive Abilities Screening Instrument (CASI, version 2), a measure of global cognitive functioning; Digit Symbol Coding (DSC), a test of processing speed; and Digit Span (DS, forwards and backwards), a test of working memory, which were previously described in detail [13]. Briefly, the CASI (range 0–100) was selected to measure global cognitive function because it was explicitly developed for cross-cultural use. The DSC (range 0–133) and DS (range 0–28) are subtests of the Wechsler Adult Intelligence Scale-III [14], with lower scores representing poorer performance. The CASI, DSC, and DS tests were completed by 4591 participants across the six centers, resulting in a completion rate of 96.8% of those returning for exam 5. Removing incomplete examinations and clinically recognized dementia resulted in the elimination of 199 (4%) CASI tests: 99 participants with CASI scores deemed invalid by the test administrator, 26 participants with technically invalid CASI scores $<$5, and 74 individuals with an ICD-9 code documented history of dementia or taking memory

medications at or before cognitive testing. The remaining 4392 (96%) individuals were free from clinical dementia with valid and complete cognitive testing data.

### 2.4. Estimation of the APOE ε4 allele

The ε4 allele of the *APOE* gene is a strong risk factor for Alzheimer's disease and is associated with cognitive decline [15]. *APOE* isoforms were estimated from single nucleotide polymorphisms rs429358 and rs7412 from the genotyping conducted in all MESA participants.

### 2.5. Statistical analyses

Descriptive statistics were calculated as the number and percent or mean (standard deviation [SD]) for categorical and continuous variables, respectively. Chi-square tests or analysis of variance (ANOVA) determined differences by race/ethnicity. Means and SDs of each cognitive test were analyzed and presented for all demographic variables with corresponding tests of differences applied using ANOVA. *APOE* isoforms were dichotomized into *APOE* ε4 negative (ε4−) or positive (ε4+) to define *APOE* ε4 carriage when entered into models as a covariate or interaction term. *APOE ε4* status was missing for 6% of the cohort, but was included as a missing category. General linear models were used to examine the associations between metabolic factors and their components and each cognitive test adjusted for age, sex, race/ethnicity, education, and *APOE* ε4 carriage. Continuous variables were standardized with a mean of zero and an SD of one to compare the magnitude

Table 1
Participant characteristics by metabolic syndrome status at baseline (2000–2002) in the MESA cohort ($n$ = 4392)

| Baseline (exam 1) measures (2000–2002) | Metabolic syndrome defined by NCEP guidelines[§] | | | | Unadjusted $P$ value | Adjusted $P$ value |
|---|---|---|---|---|---|---|
| | No ($n$ = 2950) | | Yes ($n$ = 1432) | | | |
| Age, years | 59 | ±9 | 61 | ±9 | <.0001 | <.0001 |
| Women | 1512 | 51% | 863 | 58% | <.0001 | .0062 |
| Race/ethnicity | | | | | <.0001 | <.0001 |
| Chinese | 358 | 12% | 123 | 9% | | |
| African American | 749 | 25% | 509 | 36% | | |
| Hispanic | 557 | 19% | 375 | 26% | | |
| Height (cm) | 167 | ±10 | 166 | ±10 | .0014 | <.0001 |
| Weight (kg) | 167 | ±35 | 192 | ±38 | <.0001 | <.0001 |
| BMI categories | | | | | <.0001 | <.0001 |
| Normal | 1140 | 39% | 118 | 8% | | |
| Overweight or obese | 1810 | 61% | 1313 | 92% | | |
| Education | | | | | | |
| College degree or higher | 1310 | 44% | 426 | 30% | <.0001 | <.0001 |
| Systolic BP (mm Hg) | 120 | ±19 | 132 | ±20 | <.0001 | <.0001 |
| Diastolic BP (mm Hg) | 71 | ±10 | 74 | ±10 | <.0001 | <.0001 |
| Total cholesterol (mg/dL) | 194 | ±34 | 195 | ±38 | .2353 | .8300 |
| Diabetes | | | | | <.0001 | <.0001 |
| Normal | 2694 | 91% | 683 | 48% | | |
| Impaired fasting glucose | 150 | 5% | 405 | 28% | | |
| Untreated diabetes | 29 | 1% | 62 | 4% | | |
| Treated diabetes | 74 | 3% | 281 | 20% | | |
| Diabetes medication | 73 | 2% | 275 | 19% | <.0001 | <.0001 |
| Cholesterol medication | 376 | 13% | 315 | 22% | <.0001 | <.0001 |
| BP medication | 603 | 20% | 712 | 50% | <.0001 | <.0001 |
| *APOE* ε4* | | | | | .3910 | .7692 |
| 1 copy | 676 | 24% | 321 | 24% | | |
| 2 copies | 70 | 3% | 26 | 2% | | |
| Exam 5 cognitive measures (2010–2012) | | | | | | |
| CASI score[†] | 90.0 | 84.0–94.5 | 88.0 | 81.9–93.5 | <.0001 | .1962 |
| Digit Symbol Coding[†] | 53.0 | 40.0–65.0 | 46.0 | 33.0–58.0 | <.0001 | <.0001 |
| Digit Span[†] | | | | | | |
| Forwards | 10.0 | 8.0–12.0 | 9.0 | 7.0–11.0 | <.0001 | <.0001 |
| Backwards | 6.0 | 4.0–7.0 | 5.0 | 4.0–6.0 | <.0001 | .0072 |

Abbreviations: MESA, Multi-Ethnic Study of Atherosclerosis; BMI, body mass index; BP, blood pressure; CASI, Cognitive Abilities Screening Instrument; NCEP, National Cholesterol Education Program.

NOTE. Unadjusted $P$ value uses Mantel-Haenszel chi-Square for categorical variables and Wilcoxon rank sum for continuous variables. Adjusted $P$ value presents results from logistic regression models adjusted for age, sex, race/ethnicity, and education.

**APOE* genotyping available for 4123 with 269 included as a missing category.

[†]Distributions represented by median and interquartile range.

[§]Ten participants were missing exam 1 NCEP defined insulin resistance.

of potential risk factors. Changes in continuous metabolic factors between baseline and exam 5 were also adjusted for corresponding medication use and baseline levels.

DS tests (forward and backward) were summed to create a DS total score. There is no accepted threshold for global cognitive impairment based on the CASI, and CASI scores distributions may differ among racial/ethnic groups [13]; therefore, we defined a threshold for low cognitive function (LCF) as the bottom 10th percentile of each race-specific CASI score distribution. Based on the normal distribution, this corresponds to the approximately one SD below the standardized mean which others have used to identify mild cognitive impairment in studies using nonstandardized tests [16]. We used logistic regression to determine associations between cardiometabolic risk factors and LCF adjusted for covariates. We investigated a priori hypotheses that associations between metabolic risk factors and cognitive performance would differ by race/ethnicity, *APOE*-4 carriage, and baseline diabetes and hypertension status. Resulting main effect *P* values were considered significant at $\alpha < 0.05$ and the threshold used for interactions at $\alpha < 0.15$.

## 3. Results

The baseline characteristics of the study sample free from a clinical dementia diagnosis ($n = 4392$) are presented by Metabolic Syndrome status in Table 1 and by LCF status in Supplementary Table 1. At baseline, individuals with metabolic syndrome tended to be older, were more likely to be women, less likely to have a college degree, have higher baseline BP, impaired fasting glucose or diabetes, and were more likely to be treated for hypertension and diabetes (Table 1). At time of cognitive testing (2010–2012), the mean age of the sample ($n = 4392$) was 70.3 (±9.5) years and 53.1% were women.

Table 1 shows that baseline metabolic syndrome was significantly associated with lower raw scores on tests of global cognition (CASI score, $P < .001$), speed of processing (DSC, $P < .001$), and working memory (DS total, $P < .001$). After adjustment for age, sex, education, race/ethnicity, and *APOE* ε4, baseline metabolic syndrome was associated with lower scores on DSC, DS total, but not with CASI scores (Table 2). Higher baseline levels of fasting glucose levels, SBP, and DBP were associated with lower CASI scores ($\beta = -0.28$, $P = .021$; $\beta = -0.31$, $P = .019$; $\beta = -0.38$, $P = .002$) as well as lower scores on the other cognitive measures (DSC, DS total; see Table 2). The other components of metabolic syndrome measured at baseline, waist circumference, and HDL-cholesterol were only associated with DSC; Triglycerides were only associated with DS total (Table 2).

### 3.1. Changes in metabolic factors over time

Changes in metabolic factors over 10 years are presented in the Supplementary Table 2. In general, mean insulin, glucose, and HbA1c increased in the cohort over time, while average lipid and BP levels declined. Other measures tended to be more stable over time. Increases in SBP and DBP over 10 years were associated with performance on the CASI ($\beta = -0.33$, $P = .007$ and $\beta = -0.41$, $P = .008$, respectively)

Table 2
The associations between changes in components of metabolic syndrome over 10 years and cognitive test scores assessed at exam 5 ($n = 4392$)

| | CASI score | | | Digit Symbol coding | | | Digit Span total | | |
|---|---|---|---|---|---|---|---|---|---|
| Measures | β | SE | *P* value | β | SE | *P* value | β | SE | *P* value |
| Metabolic syndrome | | | | | | | | | |
| Exam 1 | −0.45 | 0.25 | .0703 | −2.68 | 0.53 | <.0001 | −0.63 | 0.14 | <.0001 |
| By exam 5 | −0.30 | 0.27 | .2724 | −1.61 | 0.58 | .0052 | −0.35 | 0.15 | .0222 |
| Glucose (mg/dL) | | | | | | | | | |
| Exam 1 | −0.28 | 0.12 | .0207 | −1.61 | 0.25 | <.0001 | −0.20 | 0.07 | .0028 |
| Change | −0.05 | 0.12 | .6533 | −0.59 | 0.25 | .0192 | −0.11 | 0.07 | .1048 |
| Waist circumference (cm) | | | | | | | | | |
| Exam 1 | 0.02 | 0.11 | .8691 | −0.87 | 0.24 | .0004 | −0.12 | 0.06 | .0540 |
| Change | 0.17 | 0.11 | .1341 | 0.08 | 0.24 | .7487 | −0.04 | 0.06 | .5409 |
| Systolic BP (mm Hg) | | | | | | | | | |
| Exam 1 | −0.31 | 0.13 | .0194 | −1.42 | 0.28 | <.0001 | −0.39 | 0.07 | <.0001 |
| Change | −0.33 | 0.12 | .0068 | −0.71 | 0.26 | .0072 | −0.02 | 0.07 | .7986 |
| Diastolic BP (mm Hg) | | | | | | | | | |
| Exam 1 | −0.38 | 0.12 | .0023 | −1.35 | 0.26 | <.0001 | −0.18 | 0.07 | .0085 |
| Change | −0.41 | 0.12 | .0008 | −0.40 | 0.26 | .1272 | 0.09 | 0.07 | .1932 |
| Triglycerides (mg/dL) | | | | | | | | | |
| Exam 1 | −0.02 | 0.15 | .8968 | −0.62 | 0.32 | .0569 | −0.22 | 0.09 | .0104 |
| Change | −0.17 | 0.15 | .2480 | −0.14 | 0.32 | .6668 | −0.11 | 0.08 | .1690 |
| HDL-c (mg/dL) | | | | | | | | | |
| Exam 1 | −0.06 | 0.11 | .5545 | 1.43 | 0.23 | <.0001 | 0.08 | 0.06 | .2061 |
| Change | −0.20 | 0.11 | .0595 | −0.04 | 0.23 | .8621 | 0.02 | 0.06 | .7215 |

Abbreviations: CASI, Cognitive Abilities Screening Instrument; SE, standard error; BP, blood pressure; HDL-c, high-density lipoprotein cholesterol.

NOTE. All model adjusted for age, sex, race/ethnicity, education, and *APOE* ε4. Change models adjusted for baseline. Coefficients for the continuous measures are compared per standardized z-scores.

as well as the DSC and DS tests, whereas changes in other metabolic factors were not associated with global cognition (Table 2). Metabolic syndrome (DSC $\beta = -1.61$, $P = .005$; DS $\beta = -0.35$, $P = .02$), glucose change (DSC $\beta = -0.59$, $P = .019$), and SBP change (DSC $\beta = -0.71$ $P = .007$) were associated with slower processing speed.

### 3.2. Low global cognitive function

Race-specific LCF (scoring in the lowest 10% of CASI) was significantly associated with older age and having the *APOE* ε4 allele, baseline SBP, and hypertension treatment (data not shown). Participants with metabolic syndrome at any examination had a 41% increase in the odds of LCF on CASI 10 years later (Table 3). A higher fasting glucose level at baseline was associated with the increased odds of having LCF (Table 3). Elevated SBP at both baseline and exam 5 were associated with a 10%–15% increase in the odds of LCF (Table 3).

### 3.3. Effect modification by age, race, diabetes, hypertension, and APOE

The relationships between metabolic factors and the odds of having LCF at exam 5 did not appear to be modified by race/ethnicity as indicated by a lack of statistically significant interactions (all $P > .15$). Significant interactions between *APOE* ε4 status and metabolic markers as they related to LCF included metabolic syndrome at baseline, insulin at exam 5 and changes in insulin over time, glucose at exam 5 and changes in BP (Table 3). The associations between LCF and metabolic factors were primarily driven by *APOE* ε4− individuals (Table 3) and generally did not approach significance among *APOE* ε4+ individuals. Having clinical hypertension and diabetes at baseline modified the associations between metabolic factors and cognitive function; specifically, fasting glucose ($\beta = -0.22$, $P = .044$), SBP ($\beta = -0.30$, $P = .009$), and DBP ($\beta = -0.35$, $P = .002$) were significant predictors of lower

Table 3
The odds ratios for having low cognitive function based on CASI scores (the lowest 10% of racial distributions) in the total sample and by *APOE* ε4 status

| | Total ($n = 4392$) | *APOE* ε4 positive ($n = 1093$) | *APOE* ε4 negative ($n = 3030$) | Interaction |
|---|---|---|---|---|
| Measures | OR (95% CI) | OR (95% CI) | OR (95% CI) | *P* value |
| Metabolic syndrome | | | | |
| Exam 1 | 1.35 (1.09–1.66) | 0.98 (0.65–1.47) | 1.33 (1.02–1.72) | .129 |
| Exam 5 | 1.29 (1.04–1.59) | 1.01 (0.68–1.51) | 1.27 (0.98–1.64) | .253 |
| Both versus neither | 1.41 (1.10–1.80) | 0.92 (0.56–1.49) | 1.52 (1.12–2.07) | .089 |
| Insulin (mU/L) | | | | |
| Exam 1 | 0.99 (0.88–1.10) | 0.95 (0.73–1.25) | 1.00 (0.87–1.14) | .597 |
| Exam 5 | 1.04 (0.94–1.16) | 0.83 (0.63–1.09) | 1.16 (1.01–1.33) | .012 |
| Change | 1.06 (0.96–1.18) | 0.80 (0.61–1.04) | 1.19 (1.04–1.35) | .003 |
| Glucose (mg/dL) | | | | |
| Exam 1 | 1.09 (1.00–1.20) | 1.04 (0.85–1.28) | 1.11 (1.00–1.24) | .326 |
| Exam 5 | 1.04 (0.94–1.15) | 0.90 (0.71–1.15) | 1.10 (0.98–1.25) | .075 |
| Change | 0.95 (0.85–1.05) | 0.87 (0.72–1.06) | 0.99 (0.87–1.13) | .373 |
| HOMA-IR | | | | |
| Exam 1 | 0.98 (0.85–1.12) | 0.89 (0.51–1.57) | 0.99 (0.83–1.18) | .619 |
| Exam 5 | 1.08 (0.97–1.20) | 0.79 (0.59–1.06) | 1.18 (1.04–1.33) | .014 |
| Change | 1.10 (0.98–1.23) | 0.92 (0.78–1.08) | 1.20 (1.06–1.36) | .008 |
| Systolic BP (mm Hg) | | | | |
| Exam 1 | 1.13 (1.02–1.26) | 1.24 (1.02–1.51) | 1.10 (0.97–1.25) | .237 |
| Exam 5 | 1.13 (1.02–1.25) | 1.04 (0.85–1.26) | 1.20 (1.06–1.35) | .221 |
| Change | 1.01 (0.92–1.11) | 0.87 (0.72–1.04) | 1.09 (0.97–1.22) | .023 |
| Diastolic BP (mm Hg) | | | | |
| Exam 1 | 1.09 (0.98–1.21) | 1.24 (1.02–1.51) | 1.06 (0.93–1.20) | .317 |
| Exam 5 | 1.15 (1.04–1.28) | 1.14 (0.94–1.40) | 1.18 (1.04–1.34) | .487 |
| Change | 1.05 (0.95–1.16) | 0.91 (0.75–1.10) | 1.11 (0.98–1.25) | .076 |
| Triglycerides (mg/dL) | | | | |
| Exam 1 | 1.06 (0.96–1.17) | 0.98 (0.79–1.22) | 1.08 (0.96–1.21) | .413 |
| Exam 5 | 1.09 (0.99–1.21) | 1.10 (0.92–1.31) | 1.11 (0.98–1.25) | .153 |
| Change | 1.02 (0.91–1.14) | 1.10 (0.89–1.36) | 1.02 (0.88–1.17) | .337 |
| HDL-c (mg/dL) | | | | |
| Exam 1 | 1.00 (0.90–1.11) | 1.12 (0.92–1.36) | 0.95 (0.83–1.08) | .151 |
| Exam 5 | 1.03 (0.93–1.14) | 1.11 (0.91–1.35) | 1.00 (0.88–1.14) | .335 |
| Change | 1.03 (0.93–1.14) | 1.01 (0.83–1.22) | 1.04 (0.91–1.18) | .980 |

Abbreviations: CASI, Cognitive Abilities Screening Instrument; BP, blood pressure; HOMA-IR, Homeostatic Model Assessment-Insulin Resistance; HDL-c, high-density lipoprotein cholesterol.

NOTE. Total model adjusted for age, sex, race/ethnicity, education, and *APOE* ε4. Stratified models adjusted for age, sex, race/ethnicity, and education. Coefficients for the continuous measures are compared per standardized z-scores.

CASI scores among individuals free from diabetes at exam 1 and not among those with diabetes at baseline. In addition, higher fasting glucose ($\beta = -0.02$, $P < .001$) and diabetes ($\beta = -1.91$, $P = .003$) at baseline were significantly associated with lower CASI scores among individuals free from hypertension at baseline but not among those with hypertension at baseline ($P = .390$ and $P = .769$, respectively) (data not shown).

## 4. Discussion

In the MESA study, baseline metabolic factors were associated with cognitive function 10 years later. Fasting insulin, glucose, and BP were significantly associated with poorer global cognition, speed of processing, and working memory tested 10 years later, suggesting that metabolic factors in the middle-to-late-life transition period may have long-term effects on multiple domains of cognitive function. Although aggregate metabolic syndrome was itself not associated with global cognitive performance, higher levels of fasting plasma glucose at baseline were significantly associated with performance on all tests of cognitive performance 10 years later, in both the total sample and among participants free from baseline diabetes, hypertension, or carriage of the *APOE* ε4 allele. Taken together, these data suggest that subclinical abnormalities in fasting glucose in middle-age may contribute to poorer cognitive performance later in life by a pathway that is not driven by the *APOE* ε4 allele, the primary genetic risk factor for Alzheimer's disease.

Changes in metabolic risk factors over time had little effect on global cognitive performance or risk for cognitive dysfunction aside from small effects on speed of processing. The results presented herein show that elevated metabolic factors and not their changes over the mid-to-late-life transition period are predictors of cognitive performance in older adults. These findings add to a growing literature relating insulin resistance and prediabetes with poorer cognitive performance in both middle-age [17,18] and late-life [8,9,19], especially in those at high risk for cardiovascular disease [20]. Other studies have reported that trajectories of insulin and HbA1c are associated lower cognitive performance [21]. In contrast to these findings, associations between diabetes and rate of cognitive change are less consistent [22] and suggest intensive glycemic control in diabetics may not provide additional benefit [23].

As previously reported, the MESA study has shown that race/ethnicity and the presence of the *APOE* ε4 allele were significantly associated with performance on the cognitive tests [13]. In these analyses, race/ethnicity did not have significant effects on the observed relationships between metabolic factors and cognitive performance, suggesting common effects across groups. However, baseline diabetes, hypertension, age and carriage of the *APOE* ε4 allele significantly modified associations between CASI and the metabolic factors. These findings suggest that metabolic risk factors for dementia may have greater effects on cognition among those with chronic metabolic diseases and among *APOE* ε4− individuals, which is consistent with our previous findings in trials of intranasal insulin [24,25] and other large cohort studies [19,26].

Although BP remained relatively stable for the entire cohort over 10 years, individuals with increases in SBP and declines in DBP over time demonstrated poorer performance on CASI and DS. These data provide further support that better control of excess pulsatility in the mid-to-late-life transition period as a key factor that may preserve global cognitive function and working memory, as shown by several studies [27–29] and reviews [30,31].

There are several important limitations to this study. First, cognitive performance was assessed at a single time point (exam 5); therefore, we have no knowledge of baseline cognition or cognitive change over the 10 years when risk factors were assessed. Second, cognition was assessed with a brief battery of cognitive tests and does not include sufficient detail to permit the adjudication of mild cognitive impairment or dementia. MESA used standardized cognitive tests that are valid for assessing cognition in a racially/ethnically diverse cohort. Given the differences in CASI scores between racial/ethnic groups, we aimed to address these biases by creating conservative thresholds for cognitive impairment using LCF among each racial/ethnic group. Third, the syndromic nature of metabolic syndrome presents interesting challenges for examining its components in isolation. The emphasis on clinically defined thresholds may promote unnecessary burden on the accuracy of these thresholds when applied to other conditions; these data show that subclinical metabolic dysfunction in midlife maybe important for brain health. Examining the individual components promotes multiple testing and increases the likelihood of type-1 statistical error. The results presented here are consistent with previous reports in the literature; yet, results should be interpreted with caution.

## 5. Conclusions

Fasting plasma glucose and BP were the only baseline metabolic factors to significantly predict lower performance on all tests (CASI, DSC, and DS) 10 years later. This underscores the importance of subclinical metabolic dysfunction in the middle-to-late-life transition period as an early risk factor for late-life cognitive impairment. The observed relationships between antecedent metabolic dysfunction and late-life cognitive performance were not affected by race/ethnic differences, remained significant among individuals free from diabetes and hypertension at baseline, and were stronger among individuals who did not carry the primary genetic risk factor for Alzheimer's disease, the *APOE* ε4 allele. These data provide further support that early and aggressive multidomain treatment strategies to prevent diabetes and hypertension in midlife may have important, albeit indirect effects on preserving cognitive function in aging.

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## Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.dadm.2017.03.003.

## RESEARCH IN CONTEXT

1. Systematic review: We searched the literature for relevant studies on the association between cardiometabolic risk factors and cognitive performance or impairment. Cardiometabolic disorders may be important modifiable risk factors for cognitive decline and dementia; however, few studies have detailed cardiometabolic phenotypes in midlife, a time when these risk factors are thought to have their greatest impact.
2. Interpretation: Our findings suggest that metabolic syndrome and specifically the elements of higher fasting glucose along with increasing blood pressure over time were significant predictors of poorer cognitive performance 10 years later. These associations appeared to be stronger among those without *APOE* ε4.
3. Future directions: Further studies should take advantage of detailed cardiovascular and cardiometabolic phenotyping to better characterize the association between midlife risk and cognition in later life.

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