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# Is There an Association Between Metabolic Syndrome and Cognitive Function in Very Old Adults? The Newcastle 85+ Study

*Stephanie L. Harrison, MSc,* Blossom C. M. Stephan, PhD,* Mario Siervo, PhD,† Antoneta Granic, PhD,* Karen Davies, PhD,* Keith A. Wesnes, PhD,‡§ Thomas B. L. Kirkwood, PhD,† Louise Robinson, MD,* and Carol Jagger, PhD**

**OBJECTIVES:** To determine, using data from the Newcastle 85+ Study, whether there is an association between modern diagnostic criteria for metabolic syndrome (MetS) and cognitive function in very old adults (≥85) and whether inflammation, physical activity, or diabetes mellitus status affects this association.

**DESIGN:** Longitudinal, population-based cohort study.

**SETTING:** Newcastle and North Tyneside, United Kingdom.

**PARTICIPANTS:** Community-dwelling and institutionalized men and women recruited through general practices (N = 845).

**MEASUREMENTS:** MetS was defined according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria. Cross-sectional and prospective (up to 5 years of follow-up) associations between MetS and global cognitive function (assessed using the Mini-Mental State Examination (MMSE)) and between MetS and attention and episodic memory (assessed using the Cognitive Drug Research battery) were performed.

**RESULTS:** MetS was not associated with cognitive function at baseline or cognitive change over time. Lack of association was not because MetS was predictive of subsequent mortality. Of the individual components of the MetS criteria, high blood pressure was associated with better cognitive function at baseline (MMSE: $\beta$ (standard error (SE)) = −0.716 (0.152), $P < .001$), and low high-density lipoprotein cholesterol was associated with poorer global cognitive function at baseline (MMSE: 0.436 (0.131), $P = .001$).

**CONCLUSION:** The association between MetS and cognitive decline, which has been described in younger populations (<75), was not apparent in this population of individuals aged 85 and older at baseline. **J Am Geriatr Soc 2015.**

**Key words: metabolic syndrome; cohort study; very old; cognition; aging**

Metabolic syndrome (MetS) refers to a group of metabolic and vascular disorders that occur simultaneously and is frequently defined as having three or more of the following: high blood pressure, high glucose levels, large waist circumference, low high-density lipoprotein cholesterol (HDL-C) levels, and high triglyceride levels.[1] An association has been observed between MetS and dementia, including preclinical dementia,[2] but few studies have examined the link between MetS and cognitive function more generally, although cross-sectional and longitudinal associations between MetS and poor cognitive function have been found.[3–6] In young-old adults (<75), each of the individual diagnostic components of MetS has also been associated with greater risk of cognitive impairment,[7] although whether the association between poor cognitive function and MetS is greater than the sum of its individual diagnostic components is still unclear.[3,5]

The one other longitudinal study, the Leiden 85+ Study,[8] that has explored the association between MetS and cognitive decline in very old adults (≥85) found that participants with MetS had a slower rate of cognitive decline than those without MetS, but because of data restrictions, that study used a modified version of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria. Body mass index (BMI) was used instead of waist circumference, and nonfasting rather than fasting plasma glucose levels were

From the *Institute of Health and Society, †Institute of Cellular Medicine, Institute of Cell and Molecular Biosciences, Campus for Ageing and Vitality, Newcastle University, Newcastle upon Tyne, ‡Wesnes Cognition Ltd, Streatley on Thames, and §Department of Psychology, Northumbria University, Newcastle upon Tyne, UK.

Address correspondence to Stephanie L. Harrison, Institute of Health and Society, Newcastle University, Baddiley-Clark, Richardson Road, Newcastle upon Tyne NE2 4AX, UK. E-mail: s.harrison@newcastle.ac.uk

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measured.[8] Thus, whether similar results are found when MetS is defined using the specific NCEP ATP III criteria, as originally defined, is not known, so it was explored in another cohort study of individuals aged 85 and older, the Newcastle 85+ Study.

The hypothesis was that MetS was associated with a slower rate of cognitive decline, consistent with the findings from the Leiden 85+ Study, although it was hypothesized that individuals with MetS with high inflammation or diabetes mellitus may have a greater risk of cognitive decline as a result of a greater metabolic and vascular load and accelerated cognitive aging.

The aim of this study was to determine whether there is an association between MetS and cognitive function in the Newcastle 85+ cohort using the full version of the NCEP ATP III criteria. To the knowledge of the authors, this is the first study to test the association between MetS and cognitive function in very old adults when mapping criteria specifically set by NCEP ATP III, without making any adjustments. Whether levels of inflammation, physical activity, or diabetes mellitus modify associations was also examined.

## METHODS

### Study Population

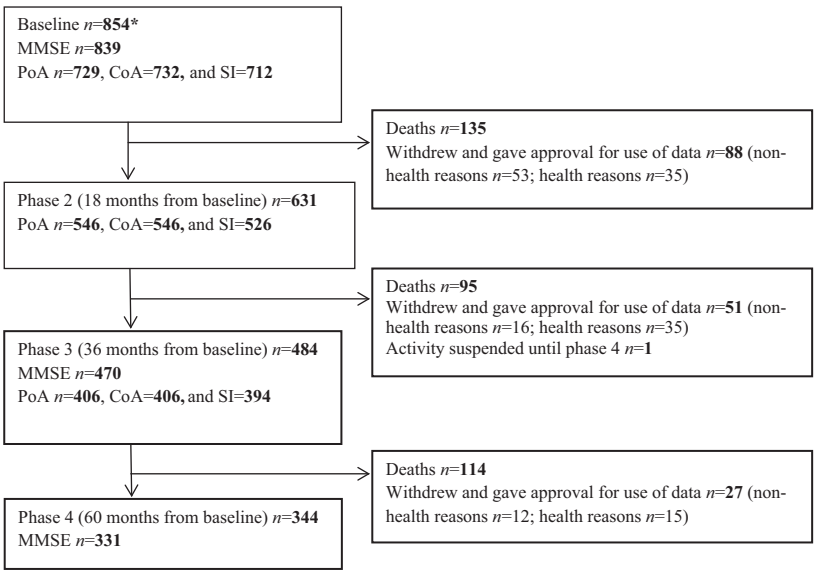
Participants were from the Newcastle 85+ Study, a population-based longitudinal study of health and aging in very old adults; full details of the study have been published previously.[9,10] In brief, all surviving adults born in 1921, regardless of health status and place of residence, who turned 85 in 2006 when the study commenced and were permanently registered with a participating general practice in Newcastle-upon-Tyne and North Tyneside (northeast England) were invited to participate; 845 participants had baseline (2006–2007) data collected, including information from a detailed multidimensional health assessment interview and review of general practice records. Follow-up took place at 18 (Phase 2), 36 (Phase 3), and 60 (Phase 4) months. Figure 1 shows the numbers of participants at each follow-up and how many participants had available cognitive test scores. Further details of retention in the Newcastle 85+ Study have been described elsewhere.[11] A trained research nurse conducted all assessments at the participant's usual residence (home or institution).

### Metabolic Syndrome

MetS was diagnosed using the NCEP ATP III criteria,[1] which require that the participant fulfill three or more of the following five clinical criteria: large waist circumference (≥102 cm in men, ≥88 cm in women), high triglycerides (≥1.7 mmol/L (150 mg/dL) or receiving drug treatment for high triglycerides), low HDL-C (<1.03 mmol/L (40 mg/dL) in men, <1.3 mmol/L (50 mg/dL) in women, or receiving drug treatment for low HDL-C), high blood pressure (≥130 mmHg systolic blood pressure, ≥85 mmHg diastolic blood pressure, or receiving antihypertensive medication), and high fasting glucose (≥5.6 mmol/L (100 mg/dL) or receiving drug treatment for high glucose). MetS status was determined for 92.4% (n = 781) of the 845 participants seen at baseline.

### Cognitive Assessment

Global cognitive function was assessed using the Mini-Mental State Examination (MMSE),[12] which includes questions based on five domains: orientation, registration, attention and calculation, recall, and language, with scores ranging from 0 to 30. The MMSE was administered at baseline and 36 (Phase 3) and 60 (Phase 4) months.




Abbreviations: *The present analysis required data from both the health assessment and review of general practice records which was available for 845 participants. MMSE=Mini-Mental State Examination; PoA=Power of Attention; CoA=Continuity of Attention; SI=Sensitivity Index for Recognition Ability.

**Figure 1.** Flowchart of participants at each phase of the Newcastle 85+ Study.

Attention and episodic memory were measured using the Cognitive Drug Research (CDR) computerized assessment system, conducted at baseline and 18 (Phase 2) and 36 (Phase 3) months. A test administrator explained each task to each participant, the task stimuli were presented on the screen of a laptop computer, and the participant responded using a two-button (NO/YES) response box. Although computer literacy is not a requirement of the CDR, a training session on the CDR battery, with fewer stimuli, was performed before the assessment to demystify the process and ensure that participants were comfortable. The standard time delay between training and assessment was 1 week.[13] Three main tasks measuring response times were used to examine core aspects of attention: Simple Reaction Time, which determines alertness, power of concentration, and ability to respond rapidly; Choice Reaction Time, which is similar to Simple Reaction Time but adds stimulus discrimination and response selection; and the Digit Vigilance Task, which measures sustained attention, attentiveness, and ability to ignore distractions. Two composite variables were used from the CDR test results that were created from the three main attention tasks: power of attention (PoA), measuring focused attention, and continuity of attention (CoA), measuring sustained attention.[14]

Episodic and declarative memory was assessed using a word recognition task.[15] Using the results from the word recognition task, a sensitivity index for recognition ability (SI) (formed by combining correct recognition responses for original words and correct rejections of new words; range 0–1) was calculated to determine memory performance.

### Transformations of Cognitive Test Scores

PoA scores were positively skewed and were therefore logarithmically ($\log_{10}$) transformed; CoA and MMSE scores were negatively skewed and were corrected using the following formula: NEWX = SQRT(K–X), in which K is the maximum score, and X is the participant's score. Lower transformed PoA, CoA, and MMSE scores reflect better cognitive performance.

### Potential Confounding Factors

All multivariable models were adjusted for potential confounding factors previously shown in the literature to be associated with cognitive function or MetS: sociodemographic factors (sex, years of education, marital status), health factors (history of stroke, ischemic heart disease, heart failure), and lifestyle factors (smoking status, current alcohol consumption).

### Inflammatory Marker

C-reactive protein (CRP) was measured from a fasting baseline blood sample drawn between 7:00 a.m. and 10:30 a.m. and delivered to the laboratory (vein to laboratory) in less than 1 hour, where it was analyzed using a high-sensitivity assay, with high inflammation defined as greater than the median (2.6 mg/L) CRP level and low inflammation as the median CRP level or less.

### Statistical Analysis

Baseline characteristics of participants with and without MetS were compared using chi-square tests for categorical variables and Mann–Whitney *U*-tests for nonnormally distributed continuous variables. Nonnormally distributed data were presented as medians and interquartile ranges (IQRs). Participants lost to follow-up were also compared with those still in the study 5 years after baseline using Mann-Whitney *U*-tests for nonnormally distributed continuous data and chi-square tests for categorical data. All reported *P*-values are two-tailed, and statistical significance was set at $P < .05$.

SPSS Statistics 19.0 (IBM Corp., Armonk, NY) mixed models were used with a restricted maximum likelihood method using a first-order autoregressive covariance matrix to examine parameter estimates ($\beta$) with standard errors (SEs). Linear mixed models were used to examine change in attention and episodic memory (CDR cognitive tasks) over 36 months (baseline to Phase 3) and in global cognitive functioning (MMSE) over 60 months (baseline to Phase 4). To compare results with those of the Leiden 85+ Study,[8] the first linear mixed model included MetS status at baseline, time, an interaction between MetS and time, and all potential confounding factors. The parameter estimate for MetS shows the cross-sectional effect of MetS on cognitive function at baseline and is presented as the cross-sectional effect. The parameter estimate for time shows the change in cognition scores over time for the whole population and is presented as change over time (MMSE, 5 years; CDR, 3 years). The parameter estimate for the interaction between MetS and time shows the change in cognition over time attributable to MetS and is presented as change due to MetS. These models were then repeated for the number of MetS components (0–5) and then for each individual MetS component with change in cognitive function over time.

Analyses were also performed after stratifying participants according to level of inflammation (categorized as high (>2.6 mg/L CRP) vs low (≤2.6 mg/L CRP)), physical activity (self-reported, question based on sporting activities, gardening, housework, do it yourself work, and walking, categorized as high (≥3 times per week) vs low to medium (<3 times per week)), and diabetes mellitus status at baseline (with presence of diabetes mellitus defined according to review of general practice health records or as a fasting glucose level ≥7.0 mmol/L, as defined by the World Health Organization classification).[16] Whether greater risk of mortality associated with MetS might mask the relationship between MetS and cognitive decline was examined using Cox proportional hazard models. Hazard ratios (HRs) for mortality were estimated with MetS first adjusted for potential confounding factors (as detailed above) and then further adjusted for baseline cognitive function.

## RESULTS

### Baseline Characteristics of Participants According to MetS Status

The baseline prevalence of MetS was 27.4% (95% confidence interval (CI) = 24.3–30.5%; n = 214). Of those with

**Table 1. Baseline Characteristics of Participants in the Newcastle 85+ Study According to Metabolic Syndrome (MetS) Status**

| Characteristic | All Participants, N = 845 | MetS, n = 214 | No MetS, n = 567 | *P*-Value |
|---|---|---|---|---|
| Female, n (%) | 526 (62.2) | 145 (67.8) | 331 (58.4) | .02 |
| Education, years, n (%) | | | | |
| 0–9 | 534 (64.4) | 139 (66.2) | 354 (63.2) | .41 |
| 10–11 | 189 (22.8) | 50 (23.8) | 130 (23.2) | |
| ≥12 | 106 (12.8) | 21 (10.0) | 76 (13.6) | |
| High blood pressure, n (%)[a] | 781 (94.4) | 212 (99.1) | 519 (93.0) | <.001 |
| High glycemia, n (%)[b] | 232 (29.7) | 141 (65.9) | 90 (15.9) | <.001 |
| High triglycerides, n (%)[c] | 222 (28.5) | 152 (71.4) | 70 (12.4) | <.001 |
| Low high-density lipoprotein cholesterol, n (%)[d] | 60 (8.2) | 51 (26.4) | 9 (1.7) | <.001 |
| High waist circumference, n (%)[e] | 291 (38.3) | 167 (81.1) | 110 (21.1) | <.001 |
| Physical activity, n (%) | | | | |
| Low | 189 (23.3) | 51 (23.9) | 122 (21.7) | .18 |
| Moderate | 349 (43.0) | 99 (46.5) | 234 (41.6) | |
| High | 274 (33.7) | 63 (29.6) | 206 (36.7) | |
| Smoking status, n (%) | | | | |
| Never smoked | 301 (38.0) | 72 (33.6) | 200 (38.1) | .38 |
| Current or former smoker | 491 (62.0) | 136 (65.4) | 325 (61.9) | |
| Current alcohol drinker | 488 (59.5) | 131 (61.5) | 341 (60.5) | .79 |
| Diabetes mellitus, n (%) | 211 (25.0) | 94 (43.9) | 53 (9.4) | <.001 |
| History of stroke, n (%) | 114 (13.5) | 26 (12.1) | 80 (14.1) | .48 |
| History of ischemic heart disease, n (%) | 278 (32.9) | 94 (43.9) | 167 (29.5) | <.001 |
| History of heart failure, n (%) | 100 (11.8) | 34 (15.9) | 58 (10.2) | .03 |
| C-reactive protein, mg/L, median (interquartile range) | 2.6 (4.8) | 3.3 (6.0) | 2.3 (4.5) | <.001 |

[a] Systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, or drug treatment.
[b] Fasting glucose ≥5.6 mmol/L or drug treatment.
[c] ≥1.7 mmol/L or drug treatment.
[d] <1.03 mmol/L in men, <1.3 mmol/L in women, or drug treatment.
[e] ≥102 cm in men, ≥88 cm in women.

MetS, 68.7% (n = 147) met three of the NCEP ATP III criteria, 24.8% (n = 53) met four criteria, and 6.5% (n = 14) met five criteria. The most common MetS criterion met in the whole population was high blood pressure (94.4%), followed by large waist circumference (38.3%), high triglycerides (28.5%), high fasting glucose (29.7%), and low HDL-C (8.2%).

The baseline characteristics of the sample included in this analysis are shown according to MetS status in Table 1. Participants with MetS were significantly more likely to be female ($P = .02$) and to have diabetes mellitus ($P < .001$), higher CRP levels ($P < .001$), and a history of ischemic heart disease ($P < .001$) and heart failure ($P = .03$). There were no significant differences found between participants with and without MetS in level of education, physical activity, smoking status, current alcohol consumption, marital status, living arrangement, depressive symptoms, or history of stroke. Table 2 shows the cognitive scores of participants at baseline and each follow-up phase.

## MetS and Global Cognitive Function: MMSE

There was no cross-sectional association between MetS and global cognitive function (Table 3). When examining the individual components of MetS, individuals with high blood pressure had higher baseline MMSE scores ($\beta$ (SE) = −0.716 (0.152), $P < .001$), and individuals with low HDL-C levels had lower baseline MMSE scores ($\beta$ (SE) = 0.436 (0.131), $P = .001$).

**Table 2. Baseline and Follow-Up Phase Cognitive Test Results for the Newcastle 85+ Participants According to Metabolic Syndrome (MetS) Status**

| Cognitive Test | Baseline | Follow-Up 1 | Follow-Up 2 |
|---|---|---|---|
| | Median (Interquartile Range) | | |
| Global cognition (Mini-Mental State Examination (range 0–30))[a] | | | |
| All participants | 28.0 (4.0) | 27.0 (5.0) | 27.0 (6.0) |
| MetS | 28.0 (4.0) | 27.0 (5.0) | 27.0 (5.0) |
| No MetS | 28.0 (4.0) | 27.0 (5.0) | 27.0 (5.0) |
| Focused attention (power of attention, ms)[b,c] | | | |
| All participants | 1,492.1 (358.8) | 1,535.2 (344.2) | 1,547.1 (354.7) |
| MetS | 1,511.4 (397.4) | 1,603.7 (453.1) | 1,558.2 (387.7) |
| No MetS | 1,479.0 (335.7) | 1,515.7 (330.8) | 1,540.1 (339.2) |
| Sustained attention (continuity of attention, arbitrary units)[b,d] | | | |
| All participants | 54.0 (8.0) | 54.0 (8.0) | 54.0 (8.0) |
| MetS | 54.0 (9.0) | 54.0 (8.0) | 55.0 (10.0) |
| No MetS | 54.0 (7.0) | 54.0 (7.0) | 54.0 (7.0) |
| Episodic memory (sensitivity index for recognition ability (range 0–1))[b] | | | |
| All participants | 0.60 (0.28) | 0.56 (0.33) | 0.60 (0.33) |
| MetS | 0.60 (0.27) | 0.56 (0.29) | 0.60 (0.32) |
| No MetS | 0.60 (0.32) | 0.56 (0.36) | 0.60 (0.33) |

[a] Follow-up 1 was at 36 months; follow-up 2 was at 60 months.
[b] Follow-up 1 was at 18 months; follow-up 2 was at 36 months.
[c] Sum of simple reaction time, choice reaction time, and digit vigilance task (range in this population, 1,061.0–10,892.9).
[d] Choice reaction time accurate responses × 0.30 + digit vigilance task accurate responses × 0.30–digit vigilance task false alarms (range in this population, −13 to 60).

**Table 3. Effect of Metabolic Syndrome (MetS) and MetS Components on Global Cognition over 60 Months and Attention and Episodic Memory over 36 Months**

| | Cross-Sectional Effect[a] | Change over Time[b] | Change Due to MetS[c] |
|---|---|---|---|
| Cognitive Test | | β (SE) P-Value | |
| Global cognition (MMSE) | | | |
| MetS[d] | 0.106 (0.076) .16 | 0.326 (0.048) <.001 | −0.026 (0.093) .78 |
| Per extra MetS component | 0.001 (0.077) .97 | 0.286 (0.090) .001 | 0.016 (0.040) .69 |
| MetS components | | | |
| High BP[e] | −0.716 (0.152) <.001 | 0.323 (0.042) <.001 | 0.077 (0.225) .73 |
| High glycemia[f] | 0.075 (0.073) .31 | 0.287 (0.049) <.001 | 0.104 (0.091) .25 |
| High TG[g] | 0.050 (0.075) .51 | 0.323 (0.049) <.001 | −0.006 (0.090) .94 |
| Low HDL-C[h] | 0.436 (0.131) .001 | 0.320 (0.043) <.001 | −0.019 (0.190) .92 |
| High WC[i] | −0.024 (0.070) .74 | 0.298 (0.053) <.001 | 0.040 (0.083) .63 |
| Focused attention (PoA) | | | |
| MetS[d] | 0.008 (0.007) .24 | 0.026 (0.004) <.001 | −0.001 (0.007) .91 |
| Per extra MetS component | 0.002 (0.002) .41 | 0.028 (0.005) <.001 | −0.001 (0.002) .73 |
| MetS components | | | |
| High BP[e] | −0.025 (0.014) .08 | 0.029 (0.015) .06 | −0.003 (0.016) .83 |
| High glycemia[f] | 0.006 (0.006) .34 | 0.022 (0.004) <.001 | 0.014 (0.007) .05 |
| High TG[g] | 0.005 (0.007) .45 | 0.028 (0.004) <.001 | −0.006 (0.007) .40 |
| Low HDL-C[h] | 0.022 (0.012) .07 | 0.027 (0.003) <.001 | −0.009 (0.014) .54 |
| High WC[i] | 0.012 (0.006) .06 | 0.026 (0.004) <.001 | 0.001 (0.007) .82 |
| Sustained attention (CoA) | | | |
| MetS[d] | 0.049 (0.084) .56 | 0.143 (0.046) .002 | −0.097 (0.089) .27 |
| Per extra MetS component | −0.044 (0.034) .20 | 0.165 (0.069) .002 | −0.025 (0.030) .40 |
| MetS components | | | |
| High BP[e] | −0.417 (0.175) .02 | 0.126 (0.194) .52 | −0.015 (0.198) .94 |
| High glycemia[f] | 0.059 (0.081) .47 | 0.104 (0.047) .03 | 0.045 (0.087) .60 |
| High TG[g] | −0.077 (0.083) .35 | 0.127 (0.047) .01 | −0.036 (0.087) .68 |
| Low HDL-C[h] | 0.153 (0.151) .31 | 0.124 (0.042) .003 | −0.196 (0.176) .27 |
| High WC[i] | −0.013 (0.078) .86 | 0.105 (0.051) .04 | 0.014 (0.081) .87 |
| Episodic memory (SI) | | | |
| MetS[d] | 0.010 (0.015) .52 | −0.018 (0.008) .02 | −0.016 (0.015) .30 |
| Per extra MetS component | 0.006 (0.006) .30 | −0.019 (0.013) .14 | −0.002 (0.006) .79 |
| MetS components | | | |
| High BP[e] | 0.136 (0.031) <.001 | 0.007 (0.337) .81 | −0.032 (0.034) .36 |
| High glycemia[f] | 0.015 (0.015) .30 | −0.018 (0.008) .03 | −0.014 (0.015) .35 |
| High TG[g] | −0.008 (0.015) .61 | −0.027 (0.008) .001 | 0.015 (0.015) .31 |
| Low HDL-C[h] | 0.001 (0.027) .97 | −0.024 (0.007) .001 | −0.013 (0.030) .66 |
| High WC[i] | 0.011 (0.014) .45 | −0.021 (0.009) .02 | −0.004 (0.014) .76 |

Models adjusted for sex; education; smoking status; alcohol consumption; marital status; and history of stroke, ischemic heart disease, and heart failure. For Mini-Mental State Examination (MMSE), power of attention (PoA), and continuity of attention (CoA), scores are transformed, and higher scores reflect worse performance.

[a] Cross-sectional effect of MetS (or number of components or each component) on cognitive function at baseline across the population.

[b] Effect of time across the population over 60 months for MMSE and 36 months for PoA, CoA, and sensitivity index for recognition ability (SI) scores.

[c] Change over time attributable to MetS (or number of components or each component).

[d] Reference is the group without MetS or without the component.

[e] Systolic blood pressure (BP) ≥130 mmHg, diastolic BP ≥85 mm Hg, or drug treatment.

[f] Fasting glucose ≥5.6 mmol/L or drug treatment.

[g] Triglycerides (TG) ≥1.7 mmol/L or drug treatment.

[h] High-density lipoprotein cholesterol (HDL-C) <1.03 mmol/L in men, <1.3 mmol/L in women, or drug treatment.

[i] Waist circumference (WC) ≥102 cm in men, ≥88 cm in women.

Of the 839 participants who completed the MMSE at baseline, 57.0% (n = 478) were reassessed on the MMSE at one or more of the follow-up phases. Participants who were lost to follow-up were more likely to have more depressive symptoms ($P = .01$), to live in an institution ($P < .001$), to have high levels of inflammation ($P = .01$), and to be diagnosed with dementia ($P < .001$) than those with at least one follow-up MMSE assessment. MetS at baseline was not associated with loss to follow-up ($P = .65$). There was also no significant difference in number of MetS components between those lost to follow-up and those included ($P = .10$). Although there was a significant decline in MMSE score over time ($\beta$ (SE) = 0.326 (0.048), $P < .001$), neither MetS nor the individual MetS components were associated with changes in MMSE scores (Table 3).

### Stratification of MMSE Results According to Inflammation, Physical Activity, and Diabetes Mellitus

There was no association between MetS and MMSE score over time when the results were stratified according to

**Table 4. Effect of Metabolic Syndrome (MetS) on Global Cognition over 60 Months and Attention and Episodic Memory over 36 Months According to Level of Inflammation**

| Cognitive Test | Participants with High Inflammation[a] | Participants with Low Inflammation[b] |
|---|---|---|
| | $\beta$ (SE) *P* | |
| Global cognition (Mini-Mental State Examination)[c] | | |
| Cross-sectional effect of MetS on cognitive function at baseline across the population | −0.092 (0.107) .39 | 0.106 (0.759) .16 |
| Effect of time across the population over 60 months | 0.341 (0.079) <.001 | 0.326 (0.048) <.001 |
| Change over time attributable to MetS | −0.154 (0.135) .26 | −0.026 (0.092) .78 |
| Focused attention (power of attention) | | |
| Cross-sectional effect of MetS on cognitive function at baseline across the population | −0.001 (0.009) .87 | 0.019 (0.010) .07 |
| Effect of time across the population over 36 months | 0.212 (0.006) <.001 | 0.029 (0.005) <.001 |
| Change over time attributable to MetS | −0.003 (0.010) .79 | 0.003 (0.107) .78 |
| Sustained attention (continuity of attention) | | |
| Cross-sectional effect of MetS on cognitive function at baseline across the population | −0.070 (0.114) .54 | 0.227 (0.129) .08 |
| Effect of time across the population over 36 months | 0.165 (0.072) .02 | 0.134 (0.059) .03 |
| Change over time attributable to MetS | −0.128 (0.124) .30 | −0.069 (0.132) .60 |
| Memory (sensitivity index for recognition ability) | | |
| Cross-sectional effect of MetS on cognitive function at baseline across the population | 0.029 (0.020) .16 | −0.012 (0.024) .61 |
| Effect of time across the population over 36 months | −0.012 (0.012) .32 | −0.023 (0.011) .03 |
| Change over time attributable to MetS | −0.028 (0.021) .18 | −0.011 (0.023) .66 |

Models adjusted for sex; education; smoking status; alcohol consumption; marital status; and history of stroke, ischemic heart disease, and heart failure.
[a] >Median (2.6 mg/L) C-reactive protein (CRP) level.
[b] ≤Median CRP level.
[c] Lower score indicates better performance.

inflammation level (Table 4) or diabetes mellitus status (data not shown). In contrast, MetS was associated with poorer global cognitive performance at baseline in individuals with low levels of physical activity than in those with high levels ($\beta$ (SE) = 0.223 (0.101), $P = .03$), although this was not replicated in the longitudinal analysis.

### MetS and Attention and Memory: CDR (PoA, CoA, and SI) Measures

The cross-sectional results showed no significant differences between those with and without MetS on any of the CDR scores (Table 3). Examination of each individual MetS component found that higher blood pressure at baseline was associated with better attention (CoA: $\beta$ (SE) = −0.417 (0.175), $P = .02$) and episodic memory performance ($\beta$ (SE) = 0.136 (0.031), $P < .001$) than lower blood pressure.

Over 36 months, there was a significant decline in focused attention (PoA: $\beta$ (SE) = 0.026 (0.004), $P < .001$), sustained attention (CoA: $\beta$ (SE) = 0.143 (0.046), $P = .002$), and episodic memory ($\beta$ (SE) = −0.018 (0.008), $P = .02$) in the whole population. Similar to the MMSE results, there was no evidence of an association between MetS and change in any of the CDR cognitive measures over time. Stratification of CDR results according to inflammation, physical activity, and diabetes mellitus status did not yield any significant results (Table 4).

### Sensitivity Analyses

Because previous studies have found no association between MetS and cognitive decline in healthy older adults and less decline in individuals with Alzheimer's disease,[17] 74 (8.8%) participants with dementia at baseline (defined from review of general practice records) were excluded and the analyses repeated, with little change in the results. Similarly, people with any cognitive impairment at baseline (two sets of analyses: excluding those with MMSE ≤ 25 and then MMSE ≤24) were also excluded, but again this did not affect the results (data not shown).

Further sensitivity analyses were conducted, including changing the definition of hypertension because of the higher proportion (>85%) fulfilling NCEP ATP III criteria for hypertension (e.g., tertiles and new normal blood pressure recommendations from the Eighth Joint National Committee (JNC8) of less than 150/90 mmHg for those aged ≥60[18] instead of ≥130 mmHg systolic blood pressure, ≥85 mmHg diastolic blood pressure, or receiving antihypertensive medication) and using glycosylated hemoglobin (cutoff 7%) instead of fasting glucose to define diabetes mellitus. These adjustments did not change the cross-sectional or longitudinal findings (data not shown).

### MetS and Mortality

Using Cox proportional hazard models with adjustment for sex, education, smoking status, alcohol consumption, marital status, history of stroke, ischemic heart disease, and heart failure, MetS was not found to be associated with mortality (HR = 1.01, 95% CI = 0.82–1.25, $P = .92$). Adding cognitive impairment at baseline to the model did not change this result (HR = 0.99, 95% CI = 0.80–1.23, $P = .95$).

## DISCUSSION

This prospective cohort study of adults aged 85 and older found that MetS was not associated with cognitive performance at baseline or over time, although with regard to

the individual MetS components, high blood pressure was found to be associated with better baseline cognitive performance, and low HDL-C was associated with poorer baseline cognitive performance. Furthermore, MetS was associated with poorer baseline cognitive performance in participants with lower levels of physical activity.

The main strengths of the study include the use of the prospective Newcastle 85+ data and the representativeness of the participants. Only one previous study has examined MetS and longitudinal changes in cognitive function in very old adults,[8] but it did not fulfill the exact NCEP ATP III criteria for MetS (e.g., measurements of fasting glucose levels and waist circumference were not collected), which was achieved in the Newcastle 85+ Study. Tests of whether inflammation level, physical activity, or diabetes mellitus status affected the association between MetS and cognitive performance had not been conducted before in this age group. There are some limitations. A lower prevalence of MetS was found in the Newcastle 85+ sample than in the previous study. This may have reduced the ability of this study to find significant associations between MetS and cognitive function. Furthermore, generalization of the findings may be limited to similar populations (aged ≥85 and white).

In previous longitudinal studies, results have been mixed. A positive association between MetS and poorer cognitive function over time has been observed.[19–29] Generally, where longitudinal associations have been found, participants have been younger (highest mean age 75).[20] Other longitudinal studies have found no association between MetS and cognitive function.[17,30,31] One of these studies was similar in design to this study, being conducted with participants aged 80 and older (mean age 85) and including measures for global cognition, memory and executive function.[30] Furthermore, the Leiden 85+ Study found MetS to be associated with decelerated cognitive function on measures of global cognition function (MMSE), attention and processing speed, but no association was found for memory,[8] although as noted above, that study mapped MetS using modified NCEP ATP III criteria and also recorded a higher prevalence of MetS (42.2%) than in the current study (27.4%). A recent study of Taiwanese men aged 75 and older (mean age 82.4) also found MetS to be significantly associated with lower risk of global cognitive decline over 1 year and found a prevalence of MetS (22.5%) similar to that found in the current study,[32] although this was based on a version of the NCEP ATP III criteria modified for Chinese men. Age differences seen in the risk of cognitive decline associated with MetS may reflect a survivor bias, such that older participants may represent healthy survivors who are not susceptible to the potentially harmful effect of MetS on cognition.[8] Furthermore, the development of cognitive impairment may lead to a lower risk of certain components of MetS and therefore of MetS overall. For example, smaller waist circumference may be due to difficulties eating, or lower blood pressure may be due to underlying dementia pathology.[30]

Methodological differences and heterogeneity of the different populations studied may explain inconsistencies in the results. Studies differ widely in the assessment used for cognitive function, age of participants, and classification criteria for MetS. Furthermore, no previous study has used the CDR assessment system (episodic memory and attention tasks). The CDR assessment system has been well validated in previous studies with older individuals[33] and has been found to have high sensitivity in tracking changes in attention and memory over time.[34]

The current investigation of the individual MetS components identified a cross-sectional association between high blood pressure and better performance on sustained attention, episodic memory, and global cognition at baseline. This conflicts with other studies that have reported a greater risk of cognitive impairment in individuals with hypertension,[3,6,7] although age may be an effect modifier, because these studies were conducted in younger populations. A study examining blood pressure and cognitive function over a wide age range found high blood pressure to be associated with greater risk of cognitive impairment in individuals younger than 75, but high blood pressure was associated with better cognitive function in older participants, and this association was strongest in those aged 85 and older.[35] There was a high prevalence of high blood pressure according to the NCEP ATP III criteria in this cohort (94.4%), which demonstrates the difficulty in discriminating between individuals when applying the current definition of MetS to this age group, but modifying criteria to use less-strict cutoffs[18] did not change the results. In contrast, low HDL-C was associated with lower MMSE scores at baseline, consistent with previous studies that have reported that lower HDL-C is associated with greater risk of cognitive impairment.[3,7,17,23] The Leiden 85+ Study found an association between low HDL-C and lower baseline MMSE scores but, similar to the current study, did not find a longitudinal effect.[8]

The lack of an association between MetS overall and cognitive function may be due to individual components of MetS working in opposing directions (e.g., low HDL-C may be harmful, whereas high blood pressure may be beneficial in this age group). This highlights the importance of examining the individual components of MetS when assessing associations between MetS and cognition, particularly in very old adults. This adds to other evidence that clustering of risk factors in older populations is problematic.[5,8] Furthermore, MetS as a construct is currently under debate and may be replaced by newer integrated risk models of cardiovascular health such as "Life's Simple 7," proposed by the American Heart Association.[36]

The timing of the assessment of MetS is important, and a recent metaanalysis found MetS to be associated with cognitive decline in subjects younger than 70, whereas the association was not significant for older participants.[37] Investigations into this effect are needed to determine whether this is due to a survivor effect or whether MetS or any of the MetS components offer protective biological mechanisms in very old adults. Previous work has suggested that, for very old adults, MetS or certain components of MetS (e.g., obesity) could offer protection against cognitive decline. Obesity has been associated with greater risk of dementia at midlife, but the association appears to be reversed in late life,[38] perhaps through biological mechanisms such as insulin resistance[39,40] or

because, for older adults, being underweight is an indication of poor health, but further research is needed to understand the etiology of the null or potentially reverse effect of MetS on cognitive decline seen in very old adults. Furthermore, the current definition of MetS may not be appropriate for very old adults, and the cutoff values for each of the MetS components may need to be revised in order for a diagnosis of MetS to be meaningful in individuals in this age group.[8]

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