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2 **Glycaemia but not the metabolic syndrome is associated with cognitive**  
3 **decline: Findings from the European Male Ageing Study**

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health”, “Multicentre study”

75 **ABSTRACT**

76 **Objectives:** Previous research has indicated that components of the metabolic syndrome (MetS), such  
77 as hyperglycaemia and hypertension, are negatively associated with cognition. However, evidence that  
78 MetS itself is related to cognitive performance has been inconsistent. In this longitudinal study, we  
79 aimed to investigate whether MetS or its components affect cognitive decline in ageing men and whether  
80 any interaction with inflammation existed.

81 **Design:** Longitudinal study over a mean of 4.4 (SD  $\pm$  0.3) years.

82 **Setting:** Multi-centre European male Ageing Study (EMAS).

83 **Participants:** Men aged 40-79 years.

84 **Measurements:** Cognitive functioning was assessed using the Rey-Osterrieth Complex Figure (ROCF),  
85 the Camden Topographical Recognition Memory (CTRM) task, and the Digit Symbol Substitution Test  
86 (DSST). High-sensitivity C-reactive protein (hs-CRP) levels were measured using a chemiluminescent  
87 immunometric assay.

88 **Results:** Overall, 1,913 participants contributed data to the ROCF analyses and 1,965 subjects  
89 contributed to the CTRM and DSST analyses. In multiple regression models, the presence of baseline  
90 MetS was not associated with cognitive decline over time ( $p>0.05$ ). However, logistic ordinal  
91 regressions indicated that high glucose levels were related to a greater risk of decline on the ROCF Copy  
92 ( $\beta=-0.42$ ,  $p<0.05$ ) and the DSST ( $\beta=-0.39$ ,  $p<0.001$ ). There was neither a main effect of hs-CRP levels  
93 nor an interaction effect of hs-CRP and MetS at baseline on cognitive decline.

94 **Conclusions:** We found no evidence for a relationship between MetS or inflammation and cognitive  
95 decline in this sample of ageing men. However, glycaemia was negatively associated with visuo-  
96 constructional abilities and processing speed.

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101 **OBJECTIVE**

102 The metabolic syndrome (MetS) is a cluster of cardiovascular risk factors which includes abdominal  
103 obesity, hypertension, hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-c), and  
104 elevated blood glucose levels[1], affecting 20-30% of adults suffering from MetS worldwide[2]. MetS  
105 and its components are associated with a range of negative cardiovascular health outcomes[3]. Emerging  
106 evidence suggests that MetS may also present an increased risk of dementia[4-7] and accelerated decline  
107 of cognitive abilities such as visual working memory[8] and executive functioning[9,10]. However,  
108 while some studies indicate that MetS affects cognition over and above the sum of its individual  
109 components[11,12], not all research has confirmed a synergistic effect of MetS criteria on cognitive  
110 decline. The longitudinal Atherosclerosis Risk in Communities Study found that hypertension and  
111 diabetes mellitus were associated with greater declines in processing speed, verbal memory, and  
112 executive functioning in middle-aged men, whereas MetS as a whole was not[13]. Similarly, prospective  
113 data of 2,476 older adults indicated that risk factors such as hyperinsulinemia and diabetes but not MetS  
114 were associated with an increased risk of developing dementia[14]. Moreover, a large multi-centre study  
115 of 7,087 community-dwelling older adults suggested that MetS does not predict development of  
116 dementia any better than its' separate components[15]. It is therefore not yet clear whether MetS is a  
117 better predictor of cognitive ageing than its individual components. The relationship between MetS and  
118 cognition may be further complicated by concurrent inflammatory processes, with the first increasing  
119 the latter and vice versa[11]. In people with MetS, some cross-sectional and longitudinal studies have  
120 primarily observed poor cognitive performance[16-18] and mild cognitive impairment[19] in  
121 individuals who present with high serum markers of inflammation. The inflammatory response should  
122 therefore be considered when examining the association between MetS and cognitive ageing. We  
123 present longitudinal findings from the European Male Ageing Study (EMAS), a multi-centre cohort  
124 study of middle-aged and older men[20]. The main objective was to investigate whether baseline MetS  
125 was associated with cognitive decline over time in ageing men. Furthermore, we aimed to examine the  
126 impact of individual MetS components on cognitive ageing. Lastly, we explored potential interaction  
127 effects of MetS and hs-CRP levels, a biomarker of inflammation, on the rate of cognitive decline.

## 128 **METHODS**

### 129 **Study participants**

130 Recruitment and assessment of participants of the European Male Ageing Study have been described in  
131 detail elsewhere[20]. Briefly, 3,369 community-dwelling men aged 40 to 79 years were recruited from  
132 population and health registers in centres based in Leuven, Belgium; Manchester, UK; Florence, Italy;  
133 Łódź, Poland; Malmö, Sweden; Santiago de Compostela, Spain; Szeged, Hungary; and Tartu, Estonia.  
134 A letter of invitation including a postal questionnaire was sent to gather information about education,  
135 general health, and physical activity. The mean adjusted response rate across the eight centres was 43%.  
136 Men who agreed to partake were invited to attend for physical and cognitive performance measures, an  
137 interviewer-assisted questionnaire, and a fasting blood test. Follow-up assessments took place at a mean  
138 of 4.4 (SD  $\pm$  0.3) years after the baseline measurements. Ethical approval was obtained in accordance  
139 with local practice and institutional requirements in each centre. All participants gave their written  
140 informed consent.

### 141 **Interviewer-assisted questionnaire and anthropometry**

142 The interviewer-assisted questionnaire included the Beck Depression Inventory-II (BDI) for subjective  
143 depressive symptoms[21], the Physical Activity Scale for the Elderly (PASE)[22], and questions  
144 regarding smoking habits, alcohol consumption, and health. Height and weight were measured using  
145 standard, calibrated instruments[20]. Current prescription and non-prescription medication use was self-  
146 reported by the participants.

### 147 **Cardiovascular risk factors**

148 Seated pulse and blood pressure was recorded following a rest period of 5 minutes using an automated  
149 sphygmomanometer (Omron 500I, Omron Healthcare (UK), Ltd Milton Keynes, UK). Waist  
150 circumference was measured three times using anthropometric tape, with the median value being used  
151 for analyses. Morning phlebotomy was performed before 10am to obtain a fasting blood sample.  
152 Analyses of triglyceride and HDL-c levels were performed in local centres with commercially available  
153 enzymatic assays. The presence of metabolic syndrome was determined according to the National  
154 Cholesterol Education Program Adult Treatment Panel-III (ATP-III) definition[1]. Participants were

155 classified as having MetS if three or more of the following criteria were met: waist circumference >102  
156 cm, fasting triglyceride >1.7 mmol/l, fasting HDL-c <1.03 mmol/l, blood pressure >130/85 mmHg or  
157 current use of anti-hypertensive medication, and fasting glucose >5.6 mmol/l or current use of anti-  
158 diabetic medication. Levels of hs-CRP were measured using a solid-phase chemiluminescent  
159 immunometric assay (Immulite 2000 hs-CRP assay; Diagnostics Products Corporation, Siemens,  
160 Deerfield, IL, USA) with a sensitivity of 0.1 g/l. The intra- and inter-assay coefficients of variation were  
161 2.8% and 3.1%, respectively.

### 162 **Cognitive performance**

163 The EMAS cognitive test battery consisted of four tasks: the Rey-Osterrieth Complex Figure (ROCF)  
164 Copy and Recall, the Camden Topographical Recognition Memory (CTRM) task, and the Digit Symbol  
165 Substitution Test (DSST). The ROCF tasks provide an indication of visuo-constructional abilities and  
166 memory recall[23]. In the Copy component, participants were instructed to copy an abstract figure as  
167 accurately as possible within a 5-minute time limit. In the Recall task, participants were asked without  
168 previous warning to draw the figure from memory thirty minutes after completing the copy. Scoring  
169 criteria were based on the original procedure, with a maximum score of 36 points. The CTRM assesses  
170 visual recognition memory[24] and involves the sequential presentation of photographs of urban scenes  
171 followed by a forced-choice recognition component. One point was given for each correctly identified  
172 image, with a maximum score of 30. Finally, the DSST is a paper-and-pencil subtest from the Wechsler  
173 Adult Intelligence Scale used to measure psychomotor speed and visual scanning[25]. Participants had  
174 to substitute as many symbols for digits as possible within 60 seconds using a coding table.

### 175 **Statistical analysis**

176 Participants with incomplete cognitive or MetS data at baseline or follow-up were excluded from the  
177 analyses. Characteristics of the study sample at baseline were compared by MetS status using Mann-  
178 Whitney *U* tests for continuous variables and  $\chi^2$  tests for dichotomous variables. Continuous cognitive  
179 change was calculated by subtracting the baseline score from the follow-up score. In order to specifically  
180 compare participants with significant cognitive decline to those who did not demonstrate cognitive  
181 decline, cognitive change was also investigated as a categorical variable. Participants were divided into

182 the categories “Decline” (>1 SD decrease from baseline), “No change” (<1 SD change from baseline),  
183 and “Improvement” (>1 SD increase from baseline). Furthermore, we examined the effect of persistent  
184 MetS over time, defined as the presence of MetS at both baseline and follow-up measurements.  
185 Dichotomous variables (absent vs. present) were created for baseline MetS status as well as for the  
186 individual MetS criteria based on the ATP-III definition.

187 Age-adjusted linear regressions were performed to examine the relationship between continuous  
188 cognitive decline and MetS. Categorical cognitive decline was investigated using age-adjusted ordinal  
189 logistic regressions. Predictors were baseline MetS status, number of MetS criteria present (0-5), and  
190 individual dichotomised MetS criteria. Subsequently, further adjustments were made for education  
191 (years), BDI score, smoking (non-smoker vs. currently smoking), alcohol consumption (<1 day/week  
192 vs.  $\geq$ 1 day/week), PASE score, and centre. Finally, analyses were adjusted for the presence of heart  
193 disease and stroke. An interaction term between BDI score and baseline MetS was included to assess  
194 potential moderation effects of depressive symptoms on the relationship between MetS and cognitive  
195 decline, as previous research has indicated that MetS is associated with an increased risk of  
196 depression[26] which can negatively affect cognition[27]. Furthermore, an interaction term between hs-  
197 CRP and baseline MetS status was used as a predictor variable to examine the effect of inflammation  
198 on MetS and cognitive decline. Results are expressed as unstandardized beta coefficients ( $\beta$ ) and 95%  
199 confidence intervals. Statistical analyses were undertaken using Stata version 13.1 (StataCorp, College  
200 Station, TX, USA).

## 201 **RESULTS**

### 202 **Cohort characteristics**

203 Of the men who participated in baseline assessments, 2,738 (86.1% of survivors) returned for follow-  
204 up measurements. A total of 698 participants was excluded from the analyses due to incomplete MetS  
205 data, resulting in a final cohort of 1,913 participants for the ROCF tests and 1,965 participants for the  
206 CTRM and DSST. Baseline characteristics of the sample by MetS status are shown in Table 1. On  
207 average, participants with MetS at baseline were older, showed more subjective depressive symptoms,  
208 were less physically active, had higher levels of hs-CRP, consumed less alcohol, and were more likely

209 to have a history of heart disease or diabetes. The prevalence of MetS was 28.8% at baseline and 32.6%  
210 at follow-up. A  $\chi^2$  test revealed that baseline MetS incidence differed significantly by centre ( $p < 0.001$ ),  
211 ranging from 18.3% in Leuven to 44.2% in Szeged. The most common MetS criterion met was  
212 hypertension (85%), followed by abdominal obesity (35%), hyperglycaemia (33%),  
213 hypertriglyceridaemia (28%), and high HDL-c levels (13%). Mean cognitive scores on the ROCF Recall  
214 and CTRM tasks improved slightly over time, while a decline was observed for the DSST (see Table 2).  
215 A decline of 1SD or more from baseline occurred in 9.0% of participants on the ROCF Copy, 16.0% on  
216 the ROCF Recall, 15.8% on the CTRM, and 20.8% on the DSST. Mann-Whitney tests showed that  
217 participants who were lost to follow-up had lower baseline scores on the ROCF Copy ( $U = -9.01$ ,  $p$   
218  $< 0.001$ ), ROCF Recall ( $U = -8.87$ ,  $p < 0.001$ ), CTRM ( $U = 6.85$ ,  $p < 0.001$ ), and DSST ( $U = -11.21$ ,  $p$   
219  $< 0.001$ ) than those who returned for follow-up. Furthermore, a  $\chi^2$  test indicated that participants with  
220 MetS at baseline were more likely to be lost to follow-up than those who did not have MetS ( $p < 0.001$ ).

### 221 **Metabolic syndrome and cognitive decline**

222 Linear regression models of baseline MetS status, MetS components, and continuous cognitive decline  
223 are summarised in Table 3. In age-adjusted models, MetS, large waist circumference, and high blood  
224 pressure were related to a better performance on the ROCF Recall. Furthermore, hypertriglyceridemia  
225 was associated with a greater decline on the DSST. None of the associations were maintained after  
226 adjusting for confounders such as education, physical activity, and centre. Furthermore, interaction  
227 terms between age or BDI score and MetS or MetS components were not significant for any of the  
228 cognitive tasks (all  $p > 0.05$ ). An increasing number of MetS components was related to better ROCF  
229 and poorer DSST performance in age-adjusted but not fully-adjusted models (see Table 3).

230 When cognitive scores were investigated as categorical variables, there was a significant  
231 negative association between baseline MetS and performance on the ROCF Copy and DSST in age-  
232 adjusted models (see Table 4). In addition, an increasing number of MetS components was related to a  
233 worsening performance on the ROCF Copy, the CTRM, and the DSST. Of the individual components,  
234 large waist circumference was related to poor performance on the DSST, high glucose levels correlated  
235 with decline on the ROCF Copy, CTRM, and DSST, and high HDL-c was associated with decline on

236 the ROCF Recall. After adjusting for additional confounders, logistic regressions indicated that the  
237 relationship between glucose levels and decline on the ROCF Copy and DSST remained significant.  
238 When these associations were analysed separately for participants <65 years and participants ≥65 years  
239 at baseline, only the correlation between ROCF Copy change remained significant for older ( $\beta = -0.74$ ,  
240  $p < 0.01$ ) but not younger participants ( $\beta = -0.19$ ,  $p = 0.541$ ). Finally, persistent MetS was associated  
241 with greater decline on the DSST in age-adjusted ( $\beta = -1.02$ ,  $p < 0.01$ ) but not fully adjusted models ( $\beta$   
242  $= -0.81$ ,  $p = 0.225$ ). There were no significant associations between persistent MetS and decline on the  
243 ROCF or CTRM tasks (data not shown).

#### 244 **Cognitive decline and hs-CRP**

245 Baseline hs-CRP levels were not independently associated with decline on any of the four tasks in either  
246 age- or fully-adjusted linear regression models (all  $p > 0.05$ ). Furthermore, there were no significant  
247 interaction effects of hs-CRP and MetS on cognitive performance on either the ROCF Copy ( $\beta = -0.37$ ,  
248  $p = 0.220$ ), the ROCF Recall ( $\beta = -0.32$ ,  $p = 0.501$ ), the CTRM ( $\beta = -0.32$ ,  $p = 0.317$ ), or the DSST ( $\beta =$   
249  $0.12$ ,  $p = 0.750$ ).

#### 250 **CONCLUSIONS**

251 In this cohort of ageing European men, we found no evidence for a longitudinal association between  
252 baseline MetS status or the cumulative effect of its components and cognitive decline over a mean period  
253 of 4.4 years. However, hyperglycaemia was associated with an increased risk of decline in visuo-  
254 constructional abilities and processing speed. These results are consistent with cross-sectional findings  
255 from the EMAS study that glucose level but not MetS was related to cognitive performance[28]. In  
256 accordance with the present findings, several prospective studies reported no significant correlations in  
257 either middle-aged[13] or older populations[15,29,30]. Although a number of longitudinal studies found  
258 a correlation between MetS and memory[8,10], executive function[10,31], and processing speed[17,30],  
259 effect sizes are generally small[32]. Disparate outcomes in prior studies may in part be caused by  
260 differences in methodology and samples. A meta-analysis of 13 longitudinal studies found that, across  
261 investigations, 17 different tasks were employed to assess cognitive functioning[32], complicating direct  
262 comparisons. In addition, several studies opted for an alternative definition instead of the commonly

263 used ATP-III guidelines. However, longitudinal studies using the World Health Organisation[33] or  
264 American Heart Association[34] guidelines also reported non-significant associations between MetS  
265 and cognition. Nevertheless, use of alternative diagnostic criteria might yield different results. Finally,  
266 it has been suggested that MetS affects cognition more strongly in women than in men[5,10,15,35,36],  
267 although the reverse pattern has also been observed[18]. Genetic dissimilarities may make women more  
268 vulnerable to the influence of vascular risk factor on the brain than men[15], which could explain the  
269 null findings in our all-male cohort. However, little is known about possible biomechanisms which could  
270 account for a gender-dependent association between MetS and cognition and additional research is  
271 needed.

272         While there is thus no conclusive evidence for a relationship between MetS and cognitive  
273 ageing, prior research has frequently reported associations between the individual MetS components  
274 and cognition. While the majority of studies indicates that hyperglycaemia or diabetes[18,20,33,37] and  
275 hypertension[13,18,33,37] in particular are detrimental to cognitive functions, others suggest that HDL-  
276 c levels[38] or hypertriglyceridemia[9] are most strongly related to cognitive ageing. The present study  
277 supports previous findings that hyperglycaemia presents a risk factor of cognitive decline, with raised  
278 glucose levels correlating with declines in visuoconstructional abilities and processing speed. Therefore,  
279 hyperglycaemia and/or diabetes may be driving associations between MetS and cognitive decline.  
280 Possible mechanisms by which hyperglycaemia could affect cognitive functions include increases in  
281 early pre-programmed cell death[37] and microvascular disease[38]. Although we found that waist  
282 circumference, blood pressure, and hypertriglyceridemia were also related to ROCF Recall and DSST  
283 performance, these associations were mainly explained by confounding factors. Previous studies which  
284 did not correct for the influence of these confounders may have overestimated the effect of these risk  
285 factors on cognition. Variance in age of the participants from different studies may also explain some  
286 of the conflicting findings, as it has been proposed that the influence of MetS components changes with  
287 age[39]. The present findings suggested that high glucose levels may be particularly detrimental to  
288 cognitive functioning in individuals aged 65 and over. However, we found no other age-related effects  
289 of MetS components on cognition in any of our regression models when including an interaction term  
290 between age and the individual components. Nevertheless, as our sample was relatively young, our

291 findings may not be comparable to those studies investigating people aged 85 years and over.

292 Finally, some studies have indicated that the relationship between MetS and cognition is  
293 modified by inflammation, with the combined presence of MetS and high hs-CRP levels being  
294 associated with greater declines in global cognition[11,18,40] and non-amnesic mild cognitive  
295 impairment[19]. However, we found no evidence of an association between hs-CRP levels, MetS, and  
296 cognitive decline. Once again, this may be due to differences in population characteristics and cognitive  
297 assessments. For example, the longitudinal Sacramento Area Latino Study of Aging (SALSA), which  
298 found that high CRP levels were associated with greater cognitive decline in older adults with MetS  
299 than low CRP levels, used measures of global cognition and verbal abilities to examine cognitive  
300 decline[41]. It is possible that the cognitive tasks used in the present study, which focused on  
301 visuospatial functioning and processing speed, were unable to capture potential interaction effects of  
302 MetS and inflammation. In addition, studies investigating the relationship between CRP, the metabolic  
303 syndrome, and cognition tend to define high and low inflammation based on distributions within the  
304 participant sample [16,42] rather than using a pre-specified value. A wide variety of values has therefore  
305 been used to define 'high' inflammation, making it difficult to establish how CRP levels relate to MetS  
306 and cognition. Other biomarkers such as interleukin-6 (IL-6), homocysteine, and  $\alpha$ 1-antichymotrypsin  
307 may be more strongly correlated with cognitive decline[43]. Alternatively, some studies have used a  
308 combination of inflammatory markers, such as CRP and IL-6 measures, to define high inflammation  
309 rather than investigating the biomarkers in isolation[16]. Future research including or combining other  
310 inflammation biomarkers may contribute to our understanding of the role of inflammation in the  
311 relationship between MetS and cognition.

312 Major strengths of EMAS are its prospective and multi-centre design and the broad range of  
313 physiological and performance measures collected. One limitation is that our assessment of cognitive  
314 domains was constrained by the necessary use of culture- and language-fair instruments. We therefore  
315 cannot draw conclusions about the effects of MetS on semantic abilities in men. In addition, performance  
316 on the ROCF and CTRM tasks may be influenced by a practice effect, as underscored by an average  
317 improvement in scores over time, resulting in an underestimation of cognitive decline in our cohort.  
318 However, when we investigated the participants with the greatest cognitive decline in a sub-analysis,

319 we also did not find a significant association with MetS. As we did not have information about the  
320 presence of MetS prior to our baseline measurements, we were not able to investigate the influence of  
321 any long-term duration of MetS on cognition. However, we found no association between persistent  
322 MetS over 4.4 years and cognitive function. We cannot exclude that a longer duration could be an  
323 important factor in predicting cognitive decline, as a study of middle-aged adults indicated that MetS  
324 was only related to decline in verbal abilities if the syndrome persisted over 10 years[44]. However, the  
325 Caerphilly Prospective Study also found no association between length of MetS exposure and cognitive  
326 performance in a group of middle-aged men over 14 years[35]. It is therefore not yet clear whether the  
327 duration of MetS is related to cognitive decline. As we conducted multiple tests to investigate the  
328 relationship between metabolic syndrome and cognitive decline, there was an increased risk of Type I  
329 errors. Although the results therefore need to be interpreted with caution, the absence of an association  
330 between MetS and cognition in any of our analyses reinforces our conclusion that the syndrome may be  
331 unrelated to cognitive decline. Another limitation to our study is that participants lost to follow-up on  
332 average had lower cognitive scores and were more likely to have MetS. It is therefore possible that  
333 individuals with MetS showing the greatest cognitive impairments were not included in this study.  
334 Moreover, we acknowledge that a relatively small number of participants showed significant cognitive  
335 decline on several of the tasks used. Although we cannot exclude the possibility that the present study  
336 lacked power to investigate associations with cognitive decline, the significant relationships between  
337 cognition and hyperglycaemia suggest that this is not the case. Moreover, several larger prospective  
338 studies have similarly failed to find a relationship between MetS and cognition, providing further  
339 support for our results[13,15,16]. It should be noted that our results are based on a relatively healthy  
340 cohort of European men. As significant associations between MetS and cognitive decline have  
341 previously been reported in other ethnic groups, including Latino [41], Chinese [45], and Korean  
342 participants [46], the present findings should be extrapolated to other populations with care. In addition,  
343 as we did not include measures of mild cognitive impairment or dementia, it is unclear whether the  
344 metabolic syndrome might be associated with more severe cognitive impairments. Finally, although we  
345 adjusted for the influence of alternative factors which may be associated with cognitive decline and  
346 dementia independent of MetS, there are a number of potential predictors which were not investigated

347 here. For example, risk factors and biomarkers such as the APOE4 allele[47], amyloid load[48], and  
348 hippocampal volume[49] have been related to cognitive decline and risk of dementia in healthy older  
349 adults. We cannot exclude the possibility that factors such as these affected our results. Further research  
350 is needed to clarify the relationship between MetS and dementia syndromes.

## 351 **CONCLUSION**

352 In view of the large percentage of the population affected by metabolic syndrome, it is important to  
353 understand the consequences of the MetS on general health. Although some previous research suggests  
354 that MetS negatively affects cognition over and above individual cardiovascular risk factors, we did not  
355 find evidence that MetS is related to cognitive decline with age in a large sample of middle-aged and  
356 older European men. Additionally, there was no indication that inflammatory processes worsened  
357 cognitive performance. However, our findings indicate that hyperglycaemia may have a significant  
358 negative effect on several domains of cognitive decline with age. Further research is needed to explore  
359 whether the findings from the EMAS cohort extend to other populations.

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1 **Table 1** Baseline characteristics of the EMAS cohort by baseline MetS status (N = 1,965)

	<b>No MetS</b> <b>(n = 1,399</b> <b>71.2%)</b>	<b>MetS</b> <b>(n = 566</b> <b>28.8%)</b>	<b>p-value</b>
	<b>Mean (SD) or %</b>		
Age (years)	58.5 (10.7)	60.0 (10.3)	0.005
Age left education (years)	21.4 (7.1)	21.9 (8.2)	0.915
BDI score	6.2 (6.0)	7.2 (6.2)	<0.001
PASE score	212.3 (86.8)	198.6 (92.0)	0.002
Waist circumference (cm)	94.4 (9.0)	107.0 (9.3)	<0.001
Triglycerides (mmol/l)	1.2 (0.6)	2.0 (0.8)	<0.001
Glucose (mmol/l)	5.3 (0.9)	6.3 (1.5)	<0.001
HDL-c (mmol/l)	1.5 (0.3)	1.2 (0.3)	<0.001
Systolic blood pressure (mmHg)	143.3 (20.2)	151.4 (19.4)	<0.001
Diastolic blood pressure (mmHg)	86.0 (11.7)	90.6 (11.8)	<0.001
Hs-CRP (mg/l)	0.3 (0.7)	0.5 (0.7)	<0.001
Current smoker (%)	19.6	20.1	0.208
Alcohol consumption ≥1 day/week (%)	59.3	54.3	0.044
Heart condition (%)	14.0	18.4	0.017
Diabetes (%)	2.8	14.6	<0.001
Stroke (%)	2.5	4.1	0.064

- 2 Abbreviations: BDI, Beck Depression Inventory; PASE, Physical Activity Scale for the Elderly; hs-
- 3 CRP, high-sensitivity C-reactive protein.

1 **Table 2** Paired *t*-tests comparing mean (SD) cognitive performance scores at baseline and follow-up in  
2 EMAS

	<b>N</b>	<b>Baseline</b>	<b>Follow-up</b>	<b><i>p</i>-value</b>
ROCF Copy	1,913	34.0 (3.8)	34.0 (4.0)	0.778
ROCF Recall	1,913	17.8 (6.4)	18.5 (7.0)	<0.001
CTRM	1,965	23.2 (4.5)	23.5 (4.7)	0.002
DSST	1,965	29.1 (8.3)	28.2 (8.9)	<0.001

3 Abbreviations: ROCF, Rey-Osterrieth Complex Figure; CTRM, Camden Topographical Recognition  
4 Memory; DSST, Digit Symbol Substitution Test.

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**Table 3**  $\beta$ -coefficients (95% CI) of linear regressions for baseline MetS, number of MetS components, individual criteria, and continuous cognitive decline in EMAS

	ROCF Copy	ROCF Recall	CTRM	DSST
<b>Model 1<sup>a</sup></b>				
Metabolic syndrome	0.13 (-0.23; 0.50)	0.67 (0.10; 1.24)*	0.06 (-0.32; 0.44)	-0.29 (-0.74; 0.17)
Number of MetS components (0 – 5)	0.07 (-0.07; 0.21)	0.32 (0.09; 0.54)**	0.04 (-0.11; 0.18)	-0.23 (-0.41; -0.05)*
Individual criteria				
Waist circumference >102 cm	0.08 (-0.27; 0.43)	0.61 (0.06; 1.16)*	-0.18 (-0.54; 0.18)	-0.16 (-0.60; 0.28)
Blood pressure >130/85 and/or using anti-hypertensive medication	0.13 (-0.34; 0.60)	0.98 (0.24; 1.73)*	-0.00 (-0.49; 0.48)	-0.29 (-0.89; 0.31)
Blood glucose >5.6 mmol/l and/or using anti-diabetic medication	0.28 (-0.08; 0.63)	0.22 (-0.34; 0.78)	0.17 (-0.19; 0.53)	0.39 (-0.83; 0.06)
HDL-c <1.03 mmol/l	0.02 (-0.47; 0.50)	0.27 (-0.50; 1.04)	0.35 (-0.16; 0.85)	-0.38 (-1.01; 0.24)
Triglycerides > 1.5 mmol/l	-0.03 (-0.39; 0.34)	0.45 (-0.13; 1.03)	0.08 (-0.30; 0.46)	-0.54 (-1.01; -0.08)*
<b>Model 2<sup>b</sup></b>				
Metabolic syndrome	0.05 (-0.33; 0.44)	0.48 (-0.12; 1.07)	0.24 (-0.16; 0.64)	0.04 (-0.43; 0.52)
Number of MetS components (0 – 5)	0.05 (-0.10; 0.21)	0.16 (-0.07; 0.40)	0.12 (-0.03; 0.28)	-0.07 (-0.26; 0.12)

<b>Individual criteria</b>				
Waist circumference >102 cm	0.06 (-0.31; 0.42)	0.55 (-0.01; 1.12)	-0.01 (-0.39; 0.37)	0.03 (-0.43; 0.49)
Blood pressure >130/85 and/or using anti-hypertensive medication	0.17 (-0.33; 0.67)	0.28 (-0.49; 1.06)	0.12 (-0.40; 0.64)	-0.23 (-0.85; 0.39)
Blood glucose >5.6 mmol/l and/or using anti-diabetic medication	0.36 (-0.02; 0.73)	0.08 (-0.50; 0.66)	0.28 (-0.11; 0.67)	0.15 (-0.31; 0.62)
HDL-c <1.03 mmol/l	-0.24 (-0.77; 0.29)	0.21 (-0.60; 1.03)	0.51 (-0.05; 1.06)	-0.10 (-0.76; 0.57)
Triglycerides > 1.5 mmol/l	-0.07 (-0.46; 0.31)	0.07 (-0.52; 0.67)	0.17 (-0.23; 0.57)	-0.43 (-0.91; 0.05)
<b>Model 3<sup>c</sup></b>				
Metabolic syndrome	0.06 (-0.33; 0.45)	0.47 (-0.13; 1.07)	0.24 (-0.16; 0.65)	0.06 (-0.43; 0.54)
Number of MetS components (0 – 5)	0.06 (-0.09; 0.22)	0.17 (-0.07; 0.40)	0.13 (-0.03; 0.29)	-0.06 (-0.25; 0.13)
<b>Individual criteria</b>				
Waist circumference >102 cm	0.08 (-0.29; 0.45)	0.56 (-0.01; 1.13)	-0.02 (-0.41; 0.37)	0.04 (-0.42; 0.50)
Blood pressure ≥130/85 and/or using anti-hypertensive medication	0.18 (-0.33; 0.68)	0.25 (-0.53; 1.03)	0.16 (-0.36; 0.69)	-0.15 (-0.78; 0.47)
Blood glucose ≥5.6 mmol/l and/or using anti-diabetic medication	0.35 (-0.03; 0.72)	0.06 (-0.52; 0.65)	0.29 (-0.10; 0.69)	0.13 (-0.34; 0.60)

HDL-c <1.03 mmol/l	-0.19 (-0.72; 0.34)	0.22 (-0.60; 1.04)	0.51 (-0.05; 1.07)	-0.10 (-0.77; 0.57)
Triglycerides ≥ 1.5 mmol/l	-0.06 (-0.45; 0.33)	0.11 (-0.49; 0.71)	0.18 (-0.22; 0.59)	-0.42 (-0.90; 0.06)

\*  $p < 0.05$  \*\*  $p < 0.01$

<sup>a</sup>Adjusted for age

<sup>b</sup>Adjusted for age, education, BDI score, physical activity, smoking, alcohol consumption, and centre

<sup>c</sup>Adjusted for age, education, BDI score, physical activity, smoking, alcohol consumption, centre, and co-morbidities

Abbreviations: ROCF, Rey-Osterrieth Complex Figure; CTRM, Camden Topographical Recognition Memory; DSST, Digit Symbol Substitution Test; HDL-c, high-density lipoprotein cholesterol.

**Table 4**  $\beta$ -coefficients (95% CI) of ordinal logistic regressions of baseline MetS, number of MetS components, individual criteria, and categorical cognitive change in EMAS

	ROCF Copy	ROCF Recall	CTRM	DSST
<b>Model 1<sup>a</sup></b>				
Metabolic syndrome	-0.34 (-0.64; -0.03)*	-0.06 (-0.26; 0.14)	-0.16 (-0.36; 0.04)	-0.22 (-0.43; -0.009)*
Number of MetS components (0 – 5)	-0.13 (-0.25; -0.01)*	-0.04 (-0.11; 0.04)	-0.13 (-0.21; -0.05)**	-0.17 (-0.25; -0.09)***
Individual criteria				
Waist circumference >102 cm	-0.20 (-0.49; 0.09)	-0.02 (-0.21; 0.17)	-0.18 (-0.37; 0.01)	-0.31 (-0.51; -0.11)**
Blood pressure >130/85 and/or using anti-hypertensive medication	0.34 (-0.07; 0.76)	0.05 (-0.20; 0.31)	-0.18 (-0.45; 0.08)	-0.14 (-0.41; 0.13)
Blood glucose >5.6 mmol/l and/or using anti-diabetic medication	-0.48 (-0.77; 0.18)**	-0.14 (-0.34; 0.05)	-0.34 (-0.53; -0.14)**	-0.44 (-0.64; -0.24)***
HDL-c <1.03 mmol/l	-0.40 (-0.79; 0.00)	-0.28 (-0.54; -0.02)*	-0.04 (-0.31; 0.23)	-0.23 (-0.51; 0.05)
Triglycerides >1.5 mmol/l	-0.02 (-0.34; 0.30)	0.07 (-0.13; 0.27)	-0.17 (-0.37; 0.03)	-0.10 (-0.31; 0.11)
<b>Model 2<sup>b</sup></b>				
Metabolic syndrome	-0.26 (-0.61; 0.10)	-0.02 (-0.23; 0.19)	-0.07 (-0.29; 0.14)	-0.14 (-0.38; 0.09)
Number of MetS components (0 – 5)	-0.12 (-0.29; 0.05)	-0.03 (-0.11; 0.06)	-0.03 (-0.12; 0.06)	-0.08 (-0.18; 0.01)

<b>Individual criteria</b>				
Waist circumference >102 cm	-0.18 (-0.58; 0.21)	0.09 (-0.12; 0.30)	-0.03 (-0.24; 0.19)	-0.16 (-0.40; 0.07)
Blood pressure >130/85 and/or using anti-hypertensive medication	0.56 (0.06; 1.05)*	0.06 (-0.22; 0.33)	-0.10 (-0.38; 0.18)	-0.05 (-0.35; 0.24)
Blood glucose >5.6 mmol/l and/or using anti-diabetic medication	-0.42 (-0.76; -0.07)*	-0.14 (-0.34; 0.07)	-0.31 (-0.52; -0.10)**	-0.40 (-0.62; -0.17)**
HDL-c <1.03 mmol/l	-0.30 (-0.88; 0.27)	-0.11 (-0.41; 0.20)	0.03 (-0.29; 0.35)	-0.10 (-0.44; 0.24)
Triglycerides >1.5 mmol/l	0.13 (-0.23; 0.50)	0.09 (-0.12; 0.31)	-0.07 (-0.29; 0.15)	-0.14 (-0.37; 0.09)
<b>Model 3<sup>c</sup></b>				
Metabolic syndrome	-0.25 (-0.61; 0.10)	0.00 (-0.21; 0.22)	-0.06 (-0.28; 0.15)	-0.13 (-0.36; 0.10)
Number of MetS components (0 – 5)	-0.12 (-0.29; 0.05)	-0.02 (-0.11; 0.07)	-0.02 (-0.11; 0.07)	-0.08 (-0.17; 0.02)
<b>Individual criteria</b>				
Waist circumference >102 cm	-0.16 (-0.56; 0.24)	0.10 (-0.12; 0.31)	-0.02 (-0.23; 0.20)	-0.15 (-0.39; 0.08)
Blood pressure >130/85 and/or using anti-hypertensive medication	0.20 (-0.43; 0.83)	-0.09 (-0.38; 0.20)	0.01 (-0.28; 0.31)	0.03 (-0.29; 0.34)
Blood glucose >5.6 mmol/l and/or using anti-diabetic medication	-0.42 (-0.77; -0.07)*	-0.12 (-0.33; 0.09)	-0.31 (-0.52; -0.10)	-0.39 (-0.62; -0.17)***

HDL-c <1.03 mmol/l	-0.28 (-0.86; 0.29)	-0.09 (-0.40; 0.21)	0.04 (-0.28; 0.36)	-0.10 (-0.44; 0.24)
Triglycerides >1.5 mmol/l	0.11 (-0.25; 0.48)	0.09 (-0.12; 0.31)	-0.06 (-0.28; 0.16)	-0.13 (-0.36; 0.10)

\*  $p < 0.05$  \*\*  $p < 0.01$  \*\*\*  $p < 0.001$

<sup>a</sup>Adjusted for age

<sup>b</sup>Adjusted for age, education, BDI score, physical activity, smoking, alcohol consumption, and centre

<sup>c</sup>Adjusted for age, education, BDI score, physical activity, smoking, alcohol consumption, co-morbidities, and centre

Abbreviations: ROCF, Rey-Osterrieth Complex Figure; CTRM, Camden Topographical Recognition Memory; DSST, Digit Symbol Substitution Test; HDL-c, high-density lipoprotein cholesterol.