Evidence of a cumulative effect of cardiometabolic disorders at midlife and subsequent cognitive function

EMMANUELLE KESSE-GUYOT, CHANTAL JULIA, VALENTINA ANDREEVA, LEOPOLD FEZEU, SERGE HERCBERG, PILAR GALAN

Université Paris 13, Sorbonne Paris Cité, Research Unit on Nutritional Epidemiology, U1153 Inserm/Inra/Cnam/Université Paris 13, Centre de Recherche en Epidemiologies et Biostatistiques Sorbonne Paris Cité, UFR SMBH, 74, rue Marcel Cachin, Bobigny Cedex 93017, France

Address correspondence to: E. Kesse-Guyot. Tel: (+33) 148388979; Fax: (+33) 148388931. Email: e.kesse@uren.smbh.univ-paris13.fr

Abstract

Background: longitudinal data as regards the link between the cumulative effect of cardiometabolic disorders and cognition are relatively scant and heterogeneous.

Objective: we examined the cross-time associations of MetS status with cognitive performance in ageing adults.

Design and methods: using data from the French SU.VI.MAX cohort, we studied 2,788 adults. The presence of abdominal obesity, hyperglycaemia, dyslipidaemia and elevated blood pressure was clinically evaluated in 1994–96. Cognitive performance was assessed after a mean of 13 years via a battery of six validated instruments. The standardised individual test scores were summed up to provide a composite cognitive performance measure; principal component analysis was performed to define performance scores on verbal memory and executive functioning. Associations between MetS and subsequent cognitive performance were examined via ANCOVA, providing estimates of mean difference and corresponding 95% confidence intervals (CI).

Results: MetS status at midlife was not associated with subsequent cognitive function. However, a 1-unit increase in the number of cardiometabolic disorders present was associated with a decrease in the composite cognitive score (mean difference = −0.36; 95% CI: −0.68, −0.05). Significant associations were also found with several cardiometabolic disorders (hyperglycaemia, central obesity and dyslipidaemia) and specific cognitive domains.

Conclusion: this study supports the existence of a cross-time, cumulative effect of cardiometabolic disorders present at midlife and subsequent cognitive performance. Given the worldwide population ageing and the increase in MetS prevalence, there is an urgent need for recommendations as regards cognitive ageing.

Keywords: metabolic syndrome, cardiometabolic disorders, memory, executive function, glycaemia, cognition, prospective cohort, older people

Introduction

The metabolic syndrome (MetS) represents a combination of several disorders such as abdominal obesity, hyperglycaemia/insulin resistance, dyslipidaemia/hypertriglyceridaemia, low HDL-cholesterol and elevated blood pressure [1]. Lifestyle factors, such as dietary habits, are a primary contributor to the development of MetS [2]. Its prevalence is increasing dramatically worldwide, and particularly in industrialised countries as a result of the growing prevalence of obesity [3]. MetS has been shown to predict diabetes, atherosclerosis, cardiovascular disease (CVD) and mortality [4,5]. In addition, the critical role of individual metabolic and vascular disorders, in particular central adiposity, diabetes and hypertension, has been demonstrated with respect to the development of cognitive impairment [6]. These disorders may exhibit potential synergistic effects [7]. Besides, in a context where the world’s population is ageing rapidly, age-related cognitive decline is a major societal health concern. As no treatment is available for postponing or slowing down cognitive decline, prevention through...
modifiable factors emerges as the only effective short-term strategy to counteract age-related cognitive disorders [7].

Cross-sectional epidemiological research, evaluating the link between various cardiometabolic disorders and cognitive function, is plentiful [8] and supports an inverse association, mainly with regard to executive functioning. However, the design of such studies prevents any inference of causality.

Longitudinal findings are relatively scant and inconsistent [9–15]. In a recent review, authors emphasised common methodological deficiencies, such as inadequate accounting for confounders and disparities in the measurement of cognitive function, which might have led to the inconsistent findings.

Thus, our main objective was to advance knowledge about the long-term role of different cardiometabolic risk factors (taken individually and cumulatively), evaluated at midlife, in cognitive performance in different domains among ageing adults. Our secondary aim was to investigate the potential role of individual cardiometabolic risk factor, apart from a potential synergistic effect.

Materials and methods

Study population

The SU.VI.MAX study (SUPplémentation en VItamines et Minéraux AntioXydants, 1994 – 2002) was initially designed as a randomised double-blind, placebo-controlled primary prevention trial and included a total of 12,741 individuals (women aged 35–60 years and men aged 45–60 years) for a planned follow-up of 8 years. It tested the potential efficacy of daily supplementation with antioxidant vitamins and minerals delivered at nutritional doses (ascorbic acid, vitamin E, β-carotene, selenium and zinc) for the prevention of cancer, ischaemic heart disease and overall mortality [16].

At the end of the trial phase, the participants were invited to enroll in an additional observational follow-up. From the initial sample, 6,850 participants were included on a voluntary basis in the SU.VI.MAX 2 observational study (2007–09).

The SU.VI.MAX and SU.VI.MAX 2 studies were conducted according to the guidelines laid down in the Declaration of Helsinki and were approved by the Ethics Committee for Studies with Human Participants of Paris-Cochin Hospital (CCPPRB n = 706 and n = 2,364, respectively) and the Comité National Informatique et Liberté (CNIL n = 334,641 and n = 907,094, respectively). Written informed consent was obtained from all participants.

Inclusion and exclusion criteria

From the 6,850 participants in the SU.VI.MAX 2 study, we excluded women younger than 45 years at baseline (n = 1,267) (for age comparison purposes across gender), those with missing or incomplete data from the neuropsychological

<table>
<thead>
<tr>
<th>6,850 participants enrolled in the SU.VI.MAX 2 study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,267 participants younger than 45 years at baseline</td>
</tr>
<tr>
<td>5,583 participants older than 45 years in 1994</td>
</tr>
<tr>
<td>1,056 participants did not attend the neuropsychological evaluation</td>
</tr>
<tr>
<td>4,527 participants undergoing the neuropsychological evaluation (2007-2009)</td>
</tr>
<tr>
<td>80 participants with at least one missing neuropsychological test score</td>
</tr>
<tr>
<td>4,447 participants with no missing neuropsychological test data</td>
</tr>
<tr>
<td>1,419 participants with at least one missing variable for vascular and metabolic status</td>
</tr>
<tr>
<td>3,028 participants with all vascular and metabolic data available</td>
</tr>
<tr>
<td>240 participants with at least one missing covariate value</td>
</tr>
<tr>
<td>2,788 participants with no missing data on covariates</td>
</tr>
</tbody>
</table>

Figure 1. Flowchart.
evaluation \( (n = 1,136) \), from the MetS evaluation \( (n = 1,419) \), or regarding any of the covariates \( (n = 240) \) (Figure 1).

Among all SUVIMAX participants older than 45 years at baseline \( (n = 5,583) \), the ones included in the present study \( (n = 2,788) \), compared with those who were excluded, were more likely to have a higher educational attainment, fewer depressive symptoms, lower body mass index (BMI), a better metabolic profile and better cognitive performance (data not tabulated).

**Cognitive assessment**

Self-reported memory troubles (‘Do you have any memory complaints?’ [yes/no]) were recorded at baseline (1994).

In 2007–09, all participants were invited to undergo a check-up that included an overall clinical examination and an evaluation of cognitive performance carried out by trained neuropsychologists. Episodic memory was evaluated using the R-I-48 test, which is a delayed cued recall test based on a list of 48 words belonging to 12 different categories. This test was designed to limit ‘ceiling effects’ encountered in some list-learning instruments. The total score was the number of words retrieved (maximum score of 48) [17]. Lexical-semantic memory was assessed by verbal fluency tasks, including a semantic fluency task, which consisted of naming as many animals as possible, and a phonemic fluency task consisting of citing words beginning with the letter P. The total score was the number of correct words produced during a 2-min period for each task [18]. Working memory was assessed with the forward and backward digit span. Participants were asked to repeat two sequences of digits, forwards and backwards. The number of digits increased by one until the participant failed two consecutive trials of the same digit span. One point was scored for each correct sequence repeated, with a maximum score of 14 points for digit span forward as well as backward [19]. Mental flexibility was assessed through the Delis–Kaplan trail-making test (TMT) consisting of connecting numbers and letters alternating between the two series. The score was the time in seconds needed to complete the task [20]; thus, a lower value corresponded to better performance. For our analyses, we used the inverse of the TMT score, such that a higher score corresponded to a better result. The inverse of the TMT score was log-transformed to improve normality. Cognitive test scores were converted into \( T \) scores (mean = 50, \( SD = 10 \)). Principal component analysis (PCA) was performed to yield summary measures accounting for the correlations among the cognitive tests, thereby maximising the explained variance. Factors were rotated through an orthogonal transformation. In addition, a composite cognitive score was defined as the mean of the 6 standardised test scores. Finally, the extracted factors as well as the composite cognitive score were rescaled to an \( SD = 10 \).

**Identification of cardiometabolic disorders and MetS**

Health status data were collected at baseline and at the end of the follow-up. Use of antidiabetic (oral hypoglycaemic agents or insulin), antihypertensive or lipid-lowering medications was self-reported on the baseline questionnaire. Also at baseline (1994–96), weight was measured to the nearest 0.5 kg using an electronic scale (Seca, Hamburg, Germany), with participants wearing indoor clothing and no shoes. Height was measured to the nearest 0.5 cm with a wall-mounted stadiometer under the same conditions. Blood pressure measurements were recorded by a trained investigator using a standard mercury sphygmomanometer. Measurements were taken after a 10-min rest. Waist circumference was measured as the circumference (to the nearest 0.5 cm) midway between the lower rib and the iliac crest, with participants in a standing position and wearing underwear. Next, baseline and follow-up blood samples were collected after a 12-h fast; all biochemical measurements were centralised at a single laboratory. Fasting blood glucose and serum triglycerides (at each follow-up visit), baseline serum total cholesterol (Advia 1650, Bayer Diagnostics), baseline serum apolipoprotein B (nephelometric assay; BNA Behring) and serum HDL-cholesterol at follow-up (Advia 1650, Bayer Diagnostic) were measured. HDL-cholesterol was not measured at baseline; thus, Planella’s equation and the Friedewald formula were used to calculate HDL-cholesterol from total cholesterol and apolipoprotein B values [21, 22]. MetS was defined using the 2009 interim consensus statement [1] as meeting at least three of the following criteria: abdominal obesity (waist circumference \( \geq 94 \) cm for men and \( \geq 80 \) cm for women), high blood pressure (systolic blood pressure (SBP)/diastolic blood pressure (DBP) \( \geq 130/85 \) mmHg or antihypertensive medication use), raised triglycerides (\( \geq 1.7 \) mmol/l or fibrate medication use), low HDL-cholesterolaelaemia (<1.03 mmol/l for men or <1.29 mmol/l for women) and raised fasting glucose (glycaemia \( \geq 5.6 \) mmol/ or antidiabetic medication use).

**Covariates**

Upon enrollment, information on gender, date of birth, smoking status (never-smoked, former or current smoker), physical activity (irregular, equivalent to <1 h of walking per day, equivalent to at least 1 h of walking per day), alcohol use (g/day), occupation (homemakers, blue-collar workers, white-collar workers, managerial/professional staff), education (primary, secondary or university level) was collected via self-administered questionnaires. Concomitant with the cognitive evaluation, depressive symptoms were assessed via the validated French version of the Center for Epidemiologic Studies Depression Scale (CES-D) [23].

**Statistical analysis**

Included participants and those who were excluded due to missing data were compared using the \( \chi^2 \) test or the Wilcoxon rank test, as appropriate. Descriptive baseline characteristics are reported as mean (SD) or percentage, by sex. Reported \( P \) values refer to the Wilcoxon rank test or to the \( \chi^2 \) test, as appropriate.

Covariance analyses were used to estimate the difference in mean cognitive scores (95% confidence interval, CI) according
to the presence of midlife cardiometabolic disorders, the number of cardiometabolic disorders (modelled as categories and on a continuous scale), MetS status at midlife (i.e. baseline) and MetS status persistence over the follow-up.

The initial ANCOVA model was adjusted for age, gender, education and follow-up time between baseline and cognitive evaluation. Model 2 was further adjusted for occupational status, intervention group during the SU.VI.MAX trial phase (1994–2002), tobacco use status, physical activity, alcohol consumption, depressive symptoms and baseline memory troubles.

Regarding the individual cardiometabolic disorders, a third set of models was mutually adjusted for the remaining disorders. Effect modification by gender was also tested.

We used inverse probability weighting to correct the estimates for potential selection bias [24, 25]. All tests of statistical significance were two-sided, and the type I error was set at 5%. Statistical analyses were performed using the SAS software (version 9.3, SAS Institute Inc., Cary, NC, USA).

**Results**

Two core cognitive factors were extracted through PCA, accounting for 61% of the total initial variance in cognitive performance. The first factor reflected language and lexical-semantic memory. The highest factor loadings were for semantic (0.79) and phonemic fluency (0.67) and the RI-48 cued recall test (0.76). The second factor reflected executive functioning. Its highest factor loadings were for the forward (0.84) and backward (0.83) digit span tasks and, to a lesser extent, the TMT (0.51).

Baseline characteristics by gender are given in Table 1. Age at cognitive evaluation was 65.5 ± 4.6 years, and the duration of follow-up was 13.4 ± 0.6 years. Depressive symptoms were higher among women than among men. Men exhibited poorer cardiometabolic profiles; they were more educated, more often current smokers and more physically active than women, and also were less likely to report memory troubles at baseline. MetS prevalence at baseline was 31.1% in men and 13.3% in women.

Results of the analyses regarding the link between each individual disorder modelled as a continuous variable and cognitive function are presented in Supplementary data, Table S2, available in *Age and Ageing* online. Glycerinaemia as a continuous variable was negatively associated with the composite cognitive score and with executive functioning; a CI: −0.68, −0.05). In turn, no significant association was detected between MetS status overall and cognitive function, irrespective of the cognitive domain.

Results of the analyses regarding the link between each individual disorder modelled as a continuous variable and cognitive function are presented in Supplementary data, Table S2, available in *Age and Ageing* online. Glycerinaemia as a continuous variable was negatively associated with the composite cognitive score and with executive functioning; a CI: −0.68, −0.05). In turn, no significant association was detected between MetS status overall and cognitive function, irrespective of the cognitive domain.

**Table 1. Baseline characteristics of the sample, SU.VI.MAX study N = 2,788 (except when otherwise specified)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men</th>
<th>Women</th>
<th>Pr</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1,480</td>
<td>1,308</td>
<td></td>
</tr>
<tr>
<td>Age at cognitive evaluation, years</td>
<td>66.0 ± 4.5</td>
<td>65.1 ± 4.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Follow-up duration</td>
<td>13.4 ± 0.6</td>
<td>13.4 ± 0.6</td>
<td>0.93</td>
</tr>
<tr>
<td>Alcohol use, g/day</td>
<td>25.2 ± 19.1</td>
<td>8.5 ± 9.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.4 ± 3.0</td>
<td>23.6 ± 3.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Depressive symptoms at follow-up (CES-D score)</td>
<td>7.4 ± 6.6</td>
<td>10.4 ± 8.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>91.0 ± 9.0</td>
<td>76.8 ± 9.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)b</td>
<td>127.95</td>
<td>120.88</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)b</td>
<td>6.07 (6.02–6.12)</td>
<td>5.95 (5.89–6.00)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)b</td>
<td>5.89 (5.85–5.92)</td>
<td>5.51 (5.47–5.54)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)b</td>
<td>1.70 (1.68–1.72)</td>
<td>1.89 (1.87–1.91)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Intervention group, %</td>
<td>53.1</td>
<td>53.8</td>
<td>0.7058</td>
</tr>
<tr>
<td>Education, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>22.2</td>
<td>20.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Secondary</td>
<td>36.1</td>
<td>45.0</td>
<td></td>
</tr>
<tr>
<td>Post-secondary</td>
<td>41.8</td>
<td>34.3</td>
<td></td>
</tr>
<tr>
<td>Occupation, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>0.5</td>
<td>15.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Blue collar</td>
<td>7.7</td>
<td>3.4</td>
<td></td>
</tr>
<tr>
<td>White collar</td>
<td>48.2</td>
<td>65.7</td>
<td></td>
</tr>
<tr>
<td>Managerial staff</td>
<td>43.5</td>
<td>15.8</td>
<td></td>
</tr>
<tr>
<td>Smoking status, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smokers</td>
<td>37.1</td>
<td>66.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Former smokers</td>
<td>52.1</td>
<td>24.6</td>
<td></td>
</tr>
<tr>
<td>Current smokers</td>
<td>10.8</td>
<td>8.6</td>
<td></td>
</tr>
<tr>
<td>Physical activity, %</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Irregular</td>
<td>22.0</td>
<td>24.4</td>
<td></td>
</tr>
<tr>
<td>&lt;1 h/day</td>
<td>25.9</td>
<td>35.6</td>
<td></td>
</tr>
<tr>
<td>≥1 h/day</td>
<td>52.2</td>
<td>40.1</td>
<td></td>
</tr>
<tr>
<td>Memory troubles, %</td>
<td>26.9</td>
<td>44.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Metabolic syndrome, %</td>
<td>31.1</td>
<td>13.3</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

BP, blood pressure; BMI, body mass index; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol.

aValues are mean ± SD or %, except when otherwise specified.

bGeometric mean (95% confidence interval).

1Defined as meeting at least three of the following criteria: abdominal obesity (waist circumference ≥94 cm for men and ≥80 cm for women), high blood pressure (systolic blood pressure (SBP)/diastolic blood pressure (DBP) ≥130/85 mmHg or antihypertensive medication use), raised triglycerides (≥1.7 mmol/l or fibrate medication use), low HDL-cholesterol (≤1.03 mmol/l for men or ≤1.29 mmol/l for women) and raised fasting glucose (glycemia ≥5.6 mmol/l or anti diabetic medication use).

1P values based on Wilcoxon rank test or χ² trend test.
Table 2. Association between metabolic syndrome, its individual components and subsequent cognitive function, weighted for selection bias

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Model 1</th>
<th>Composite cognitive score</th>
<th>P</th>
<th>Verbal memory</th>
<th>P</th>
<th>Executive functioning</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated waist circumference</td>
<td>Model 1</td>
<td>-0.09 (-0.83 to 0.66)</td>
<td>0.82</td>
<td>0.58 (-0.18 to 1.33)</td>
<td>0.13</td>
<td>-0.72 (-1.49 to 0.06)</td>
<td>0.07</td>
</tr>
<tr>
<td>Model 2</td>
<td>-0.44 (-1.18 to 0.29)</td>
<td>0.24</td>
<td>0.40 (-0.36 to 1.16)</td>
<td>0.30</td>
<td>-1.04 (-1.82 to 0.27)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>-0.31 (-1.08 to 0.46)</td>
<td>0.43</td>
<td>0.71 (-0.08 to 1.50)</td>
<td>0.08</td>
<td>-1.18 (-1.99 to -0.37)</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Elevated triglycerides or treatment</td>
<td>Model 1</td>
<td>-0.11 (-1.08 to 0.86)</td>
<td>0.83</td>
<td>-1.19 (-2.17 to -0.21)</td>
<td>0.02</td>
<td>1.05 (0.04 to 2.06)</td>
<td>0.04</td>
</tr>
<tr>
<td>Model 2</td>
<td>-0.29 (-1.25 to 0.67)</td>
<td>0.55</td>
<td>-1.26 (-2.24 to -0.28)</td>
<td>0.01</td>
<td>0.85 (-0.16 to 1.86)</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>-0.01 (-1.00 to 0.98)</td>
<td>0.98</td>
<td>-1.35 (-2.36 to -0.34)</td>
<td>0.01</td>
<td>1.34 (0.30 to 2.37)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Low HDL</td>
<td>Model 1</td>
<td>-1.57 (-4.21 to 1.07)</td>
<td>0.24</td>
<td>-0.34 (-3.02 to 2.34)</td>
<td>0.80</td>
<td>-2.01 (-4.76 to 0.75)</td>
<td>0.15</td>
</tr>
<tr>
<td>Model 2</td>
<td>-1.97 (-4.58 to 0.64)</td>
<td>0.14</td>
<td>-0.40 (-3.08 to 2.27)</td>
<td>0.77</td>
<td>-2.55 (-5.29 to 0.18)</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>-1.85 (-4.47 to 0.78)</td>
<td>0.17</td>
<td>-0.10 (-2.79 to 2.59)</td>
<td>0.94</td>
<td>-2.70 (-5.45 to 0.05)</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>Elevated BP or treatment</td>
<td>Model 1</td>
<td>0.21 (-0.50 to 0.93)</td>
<td>0.56</td>
<td>0.07 (-0.66 to 0.80)</td>
<td>0.85</td>
<td>0.29 (-0.46 to 1.04)</td>
<td>0.45</td>
</tr>
<tr>
<td>Model 2</td>
<td>-0.11 (-0.82 to 0.61)</td>
<td>0.77</td>
<td>-0.14 (-0.87 to 0.59)</td>
<td>0.71</td>
<td>0.05 (-0.70 to 0.80)</td>
<td>0.90</td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>0.13 (-0.61 to 0.87)</td>
<td>0.73</td>
<td>-0.10 (-0.86 to 0.65)</td>
<td>0.79</td>
<td>0.36 (-0.42 to 1.13)</td>
<td>0.37</td>
<td></td>
</tr>
<tr>
<td>Elevated blood glucose or treatment</td>
<td>Model 1</td>
<td>-1.06 (-1.80 to -0.33)</td>
<td>0.01</td>
<td>-0.64 (-1.38 to 0.11)</td>
<td>0.09</td>
<td>-0.86 (-1.63 to -0.09)</td>
<td>0.03</td>
</tr>
<tr>
<td>Model 2</td>
<td>-1.10 (-1.83 to -0.37)</td>
<td>0.003</td>
<td>-0.63 (-1.38 to 0.12)</td>
<td>0.10</td>
<td>-0.92 (-1.68 to -0.15)</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>-1.07 (-1.81 to -0.33)</td>
<td>0.01</td>
<td>-0.59 (-1.35 to 0.17)</td>
<td>0.13</td>
<td>-0.91 (-1.69 to -0.13)</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

*Values are adjusted mean difference in cognitive performance (95% confidence interval).
**Model 1 is adjusted for age, gender, education and follow-up time between baseline and cognitive evaluation.
***Model 2: model 1 + adjustment occupational status, intervention group during the SU.VI.MAX trial phase (1994–2002), tobacco use status, physical activity, alcohol consumption, depressive symptoms, baseline memory troubles.
****Model 3: Model 2 + adjustment for other MetS components.

Bold value signifies P < 0.05.

(borderline significant negative association was observed with verbal memory.

Finally, MetS persistence over the follow-up was not associated with cognitive function (Supplementary data, Table S3, available in Age and Ageing online).

**Discussion**

Utilising a large sample of ageing adults recruited from the general French population, this study provided compelling evidence of a detrimental long-term role of cardiometabolic disorders in cognition, especially executive functioning, whereas MetS status per se was not associated with cognition. Our findings further support the inverse linear association between the number of cardiometabolic disorders and cognitive function. That relationship remained significant after extensive adjustment for potential confounding factors. In particular, we observed a negative association between elevated glycaemia and waist circumference, respectively, and cognitive function.

Longitudinal research focussing on the link between MetS status and cognitive function is scant [9–15] and rather inconsistent. Indeed, while some studies reported an overall association between MetS and cognitive decline for at least one cognitive ability [10, 12–14], others have reported associations in specific subgroups or substantial attenuation of the associations after accounting for confounders [11, 14, 15]. Evidence of an association between MetS and specific cognitive domains is even more inconsistent, possibly because of the wide range of neuropsychological measures used. As highlighted recently, performance in individual cognitive domains should be summarised using PCA or factor analysis, as in the present study, to focus on the overall domain rather than on performance on a specific test [26]. Overall, our findings are not in line with the scant existing evidence supporting an association between MetS and cognitive ageing, as we did not observe a clear association between midlife MetS and cognitive function.

Our study sheds new light on the relationship between MetS and various domains of cognition, suggesting that rather than the MetS status per se, the number of cardiometabolic disorders present at midlife is associated with poorer cognitive function, and in particular executive functioning. Other research has also documented a link between cumulating cardiometabolic disorders and cognitive ageing, but that association pertained only to memory performance [13].

The fact that cumulating cardiometabolic disorder was associated with poorer executive functioning may be explained by the underlying physiopathological pathways since this particular cognitive domain is predominantly affected in vascular cognitive impairment.

Considering the individual cardiometabolic disorders, our findings are consistent with evidence regarding the critical, detrimental role of elevated glycaemia on cognitive ageing, especially in the domains of attention and executive functioning [26, 27]. Indeed, it is now well recognised that multiple mechanisms associated with glucose or insulin dysregulation, including production of reactive oxygen species and glycation end-products, endothelial proliferation, amyloid-oligomerisation and tau phosphorylation, can lead to vascular and neuronal damage [28].

Moreover, the negative association between waist circumference and executive functioning is in line with epidemiological
data supporting a detrimental impact of midlife adiposity on cognitive ageing [29, 30].

Finally, as previously reported [9, 12, 13], we observed a link between high triglyceride levels and poorer cognitive function, whereas a borderline association close to statistical significance was detected as regards elevated blood pressure.

Some limitations of our study should be noted. One limitation pertains to the evaluation of cognitive performance only at follow-up. We cannot rule out the possibility of pre-existing baseline differences in cognition according to cardiometabolic profiles, limiting the potential for causal inference and preventing the assessment of cognitive decline. However, the relatively young baseline age of our population and the ability to follow the complex study protocol (filing out many questionnaires over a long period of time) argues for the likely absence of cognitive impairment at baseline. Second, caution is needed when generalising the present findings, as participants were relatively healthy volunteers involved in a long-term nutrition-focussed study. The absence of an association between high blood pressure and cognitive function is somewhat unexpected. This might be partly attributed to measurement error in blood pressure measurement (or to lack of sufficient level of variability). When performing analyses using antihypertensive treatment to define high blood pressure, no association was detected, probably due to insufficient statistical power or to a survival artefact.

Another issue pertains to potential bias due to non-participation and death, in particular because of differential attrition due to midlife cardiometabolic co-morbidity or mortality. Among SU.VI.MAX participants >45 years at baseline (N = 10,090), subjects excluded from the current study were more likely to be women, younger, more often smokers, with lower levels of education and less physically active. They also more frequently exhibited dyslipidaemia and high blood pressure. To partly correct for selection bias, we used inverse probability weighting. Finally, despite the extensive adjustment for confounders, residual confounding, especially related to co-morbid conditions related to cognitive functioning, cannot be excluded.

Strengths and original aspects of our study include its cross-time design and long-term follow-up allowing consideration of midlife exposure. In addition, standardised cognitive evaluation was completed in a relatively young population, and a neuropsychological battery of sensitive tests (limiting ceiling and/or floor effects) was used. Finally, following recent recommendations [26], we used PCA to focus on cognitive domains as well as extensive statistical adjustment using good-quality data.

In conclusion, apart from the critical role of MetS on risk of diabetes and CVD, our study supports the existence of deleterious consequences of cumulating cardiometabolic disorders regarding specific cognitive domains, such as executive functioning, with a particular impact of elevated glucose. Overall, cardiometabolic disorders are potentially preventable through public health action targeting nutrition and physical activity.

**Metabolic syndrome and cognitive function**

**Key points**

- Epidemiological evidence based on longitudinal data as regards the link between MetS and cognition is scant.
- A cumulative effect of cardiometabolic disorders in midlife on subsequent cognitive performance is observed.
- Some cardiometabolic disorders (elevated glycaemia, adiposity and dyslipidaemia) were associated with specific cognitive domains.

**Conflicts of interest**

None declared.

**Supplementary data**

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

**References**

11. Akbaraly TN, Kivimaki M, Shipley MJ et al. Metabolic syn-
drome over 10 years and cognitive functioning in late midlife:
12. Raffaitin C, Feart C, Le GM et al. Metabolic syndrome and cog-
nitive decline in French elders: the Three-City Study.
13. Komulainen P, Lakka TA, Kivipelto M et al. Metabolic syn-
drome and cognitive function: a population-based follow-up
study in elderly women. Dement Geriatr Cogn Disord 2007;
23: 29–34.
14. Yaffe K, Haan M, Blackwell T, Cherkasova E, Whitmer RA,
West N. Metabolic syndrome and cognitive decline in elderly
Latinos: findings from the Sacramento Area Latino Study of
15. Yaffe K, Kanaya A, Lindquist K et al. The metabolic syndrome,
inflammation, and risk of cognitive decline. JAMA 2004; 292:
2237–42.
randomized, placebo-controlled trial of the health effects of
antioxidant vitamins and minerals. Arch Intern Med 2004;
164: 2335–42.
17. Ivanou A, Adam S, Van der LM et al. Memory evaluation
with a new cued recall test in patients with mild cognitive
impairment and Alzheimer’s disease. J Neurol 2005; 252:
47–55.
18. Lezak MD, Howieson DB, Loring DW. Neuropsychological
20. Delis DC, Kaplan E, Kramer JH. Delis-Kaplan Executive
Function System (D-KEFS) Examiner’s Manual. San Antonio,
21. Planella T, Cortes M, Martinez-Bru C, Gonzalez-Sastre F,
Ordonez-Llanos J. Calculation of LDL-cholesterol by using
apolipoprotein B for classification of nonchylomicronemic dys-
22. Friedewald WT, Levy RI, Fredrickson DS. Estimation of
the concentration of low-density lipoprotein cholesterol in plasma,
without use of the preparative ultracentrifuge. Clin Chem
23. Radloff L. The CES-D scale: a self-report depression scale for
research in the general population. Appl Psychol Meas 1977;
1: 385–401.
24. Seaman SR, White IR. Review of inverse probability weighting
for dealing with missing data. Stat Methods Med Res 2013; 22:
278–95.
25. Hernan MA, Robins JM. Estimating causal effects from epidemi-
ological data. J Epidemiol Community Health 2006; 60: 578–86.
26. Crichton GE, Elias MF, Buckley JD, Murphy KJ, Bryan J,
Frisardi V. Metabolic syndrome, cognitive performance, and
27. McCrimmon RJ, Ryan CM, Frier BM. Diabetes and cognitive
28. Panza F, Solfrizzi V, Logroscino G et al. Current epidemi-
ological approaches to the metabolic-cognitive syndrome.
29. Dahl AK, Hassing IB. Obesity and Cognitive Aging.
30. Elias MF, Goodell AL, Waldstein SR. Obesity, cognitive func-
tioning and dementia: back to the future. J Alzheimers Dis

Received 28 July 2014; accepted in revised form 14 January
2015