Long-term Variability in Cardiometabolic and Inflammatory Parameters and Cognitive Decline: The English Longitudinal Study of Ageing

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Long-term variability in cardiometabolic and inflammatory parameters and cognitive decline: the English Longitudinal Study of Ageing

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Abstract

Background

The relationship between variability in cardiometabolic and inflammatory parameters and cognitive changes is unknown. We aimed to investigate the association of visit-to-visit variability (VVV) in body mass index (BMI), waist-to-height ratio (WHtR), systolic blood pressure (SBP), total cholesterol (TC), triglycerides, glycated hemoglobin (HbA1c), high-sensitivity C-reactive protein (hs-CRP), ferritin, as well as the composite effect of the VVV in these parameters on cognitive decline.

Methods

We performed a longitudinal study using data from adults aged 50 years and older in the English Longitudinal Study of Ageing (ELSA). Biomarkers were assessed at waves 2 (baseline, 2004/2005), 4 (2008/2009), 6 (2012/2013), 8 (2014-2016) and 9 (2018/2019). Cognitive function, including memory, executive function and orientation, were measured. VVV was expressed as the coefficient of variation (CV), standard deviation (SD), and variability independent of the mean (VIM) across visits conducted at a mean interval of 3.5 years. To explore the composite effect of parameter variability, we generated a variability score (range: 0-24), where 0 points were assigned for Q1, 1 point for Q2, 2 points for Q3, and 3 points for Q4 each for the variability of eight parameters measured as VIM. Participants were divided based on quartiles of variability score. Linear mixed models were used to evaluate longitudinal associations.

Results

A total of 2366 participants (56.1% women, mean age 63.0 ± 7.5 years) with at least three measurements of biomarkers were included, and the mean follow-up duration was 11.2 ± 2.0 years. Higher BMI, SBP, TC, HbA1c and ferritin variability was linearly associated with global and domain-specific cognitive decline irrespective of their mean values over time. Additionally, compared with the lowest quartile, participants in the highest quartile of variability score had a significantly worse global cognitive decline rate (-0.0238, 95% CI -0.0376, -0.0100), memory decline rate (-0.0224, 95% CI -0.0319, -0.0129) and orientation decline rate (-0.0129, 95% CI -0.0245, -0.0012).

Conclusions

Higher variability in cardiometabolic and inflammatory parameters was significantly associated with cognitive decline, and the composite effect of these parameters was evident. Stabilizing these parameters may serve as a target to preserve cognitive function.

Keywords

Cardiometabolic, cognitive decline, longitudinal study, inflammation, variability

Background

Increased lifespan around the world has resulted in a substantial increase in the frequency of age-related diseases, especially dementia, a neurodegenerative disorder occurring in later life that is characterized by progressive deterioration of cognitive function [1,2], resulting in a serious health care-related economic and social burden [3]. Dementia is preceded by a long period of progressively accelerating cognitive decline [4]. To date, there are no effective pharmacologic agents to prevent or treat the disease; hence, identifying risk factors for cognitive decline to prevent dementia is a major public health priority [5].

An increasing amount of attention has been given to the effect of modifiable risk factors, including education, physical activity, lifestyle factors, psychiatric symptoms and cardiometabolic abnormalities, on cognitive performance [2,6,7]. Cardiometabolic abnormalities include cardiovascular risk factors such as obesity, elevated triglycerides, elevated total cholesterol (TC), hypertension, high glycemia, and increased inflammation [8–10]. It was demonstrated that the presence of obesity, hypertension, cardiovascular disease or diabetes was associated with a substantially higher risk for cognitive decline and dementia through multiple causal pathways, including direct effects on neurons, hypoperfusion due to reduced cerebral blood flow, and promotion of the amyloid cascade, emphasizing the importance of managing metabolic and vascular risk factors [2,11,12].

Recently, visit-to-visit or day-to-day variability in biological parameters has emerged as a previously unrecognized residual risk factor that is independently associated with the development of cognitive dysfunction or dementia. Several prospective studies have linked higher blood pressure variability (BPV) to cortical infarcts, lower hippocampal volume, and impaired cognitive function [13,14]. In a Taiwanese study, glycemic variability was demonstrated to be independently associated

with an increased risk of Alzheimer's disease (AD) independent of traditional risk factors in patients with type 2 diabetes [15]. Another study of 382 women reported that greater C-reactive protein (CRP) variability, reflecting persistent residual immune activation, was correlated with poorer cognitive performance [16]. These results indicate that biomarker variability could aid in achieving a better prediction of cognitive dysfunction, suggesting a new avenue of risk modification.

However, the clustering or cooccurrence of cardiometabolic and inflammatory risk factors is the most likely scenario [17]. These factors exert an interactive influence that results in a greater impact on an individual's health status [7,18]. However, there remains a lack of knowledge relating to the composite effect of the variability in cardiometabolic and inflammatory parameters on cognitive functions in general or in a specific domain, which needs to be better understood. In this study, we aimed to 1) examine the association between visit-to-visit variability (VVV) in body mass index (BMI), waist-to-height ratio (WHtR), systolic BP (SBP), TC, triglycerides, glycated hemoglobin (HbA1c), high-sensitivity CRP (hs-CRP) and ferritin and changes in cognitive function and 2) investigate the composite effect of VVV in these parameters on cognitive decline using 11-year follow-up data from a large community-dwelling cohort study of adults aged 50 years and older.

Methods

Study population

We conducted a prospective analysis of data from the English Longitudinal Study of Ageing (ELSA), a prospective and nationally representative cohort of adults over the age of 50 years living in England. The sample was drawn from households that had previously responded to the Health Survey for England (HSE) in 1998, 1999, and 2001 (wave 0) [19]. The first active phase of data collection in ELSA took place in 2002–2003 (wave 1). Details on the ELSA are described elsewhere [20]. The time of the first visit with the nurse was considered the baseline timepoint for all participants. The present analyses used data collected in waves 2 (2004/2005), 4 (2008/2009), 6 (2012/2013), 8 (2014-2016) and 9 (2018/2019) of the ELSA, the five waves in which blood samples were taken during nurse visits. Among 7666 participants who underwent a nurse visit at wave 2, 5133 were excluded because they had fewer than three measurements of biomarkers. An additional 167 individuals were excluded for the following reasons: did not complete cognitive assessment at

baseline (n = 5); had reported memory decline or had a diagnosis of dementia and/or AD at baseline (n = 7); or had data missing for at least one of the eight cardiometabolic and inflammatory parameters (n = 155). Ultimately, the study population consisted of the remaining 2366 participants (1038 men and 1328 women) who had complete study variable data, baseline cognitive assessments and at least one reassessment of cognitive function and were free of cognitive diseases at baseline **(Additional file: Fig S1)**.

The data are available through the UK Data Service, and ethical approval for ELSA was provided by the London Multicentre Research Ethics Committee (MREC/01/2/91). All research was performed in accordance with research and data protection guidelines, and informed consent was obtained from all respondents.

Measurement of cardiometabolic and inflammatory parameters

Six cardiometabolic risk factors were evaluated: BMI (kg/m^2), WHtR, SBP (mmHg), TC (mmol/l), triacylglycerol (mmol/l) and HbA1c (%). Hs-CRP (mg/L) and levels of ferritin (ng/ml) were assessed as inflammation risk factors. These risk factors have been previously used to identify cardiometabolic and inflammation-related abnormalities [21,22].

BMI was calculated as the weight in kilograms divided by the square of the height in meters, and obesity was defined as BMI $\geq$ 30 kg/m^2. WHtR was the waist circumference divided by height. After resting in a seated position for at least 5 minutes, SBP was measured on the participant's right arm by a trained physician with an electronic sphygmomanometer (Omron HEM-7200 Monitor, Batteries, and Stopwatch).

Blood samples were collected at each ELSA nurse visit (available for 71.94% of the participants at wave 2, 64.50% at wave 4, 65.89% at wave 6, 54.84% at wave 8 and 59.82% at wave 9) and were analysed to obtain data on a range of biomarkers. Details of the process have been described elsewhere [23]. TC (cholesterol oxidase assay method) and triacylglycerol (enzymatic method) levels were measured using an Olympus 640 analyser calibrated to the Centers for Disease Control guidelines. Total HbA1c was measured using a Tosoh G7 analyser (Tosoh, Tokyo, Japan) [23]. Hs-CRP was measured using the N Latex CRP monoimmunoassay on the Behring Nephelometer II analyser. Fibrinogen was measured using a modification of the Clauss thrombin clotting method on the Organon Teknika MDA 180 analyzer. All blood samples were analysed and

subjected to regular internal quality control at the Royal Victoria Infirmary laboratory (Newcastle upon Tyne, UK) [23].

Definition of variability indices

The mean value of each parameter was calculated based on the mean of all visits for each participant. We expressed VVV in each parameter as the variability independent of the mean (VIM) of the longitudinal intraindividual measurements across visits in each patient. Two other indices of variability were also used: standard deviation (SD) and coefficient of variation (CV). The VIM was calculated as $100 \times SD / mean^{\beta}$, where β is the regression coefficient based on the natural logarithm of the SD over the natural logarithm of the mean [24].

To investigate the composite effect of VVV in cardiometabolic and inflammatory parameters on cognitive decline, we also generated a variability score where 0 points were assigned for Q1 (lowest quartile of variability), 1 point for Q2, 2 points for Q3, and 3 points for Q4 (highest quartile of variability) each for BMI, WHtR, SBP, TC, triacylglycerol, HbA1c, hs-CRP and ferritin variability measured as VIM. Therefore, the total score ranged from 0 to 24. Participants were divided based on quartiles of variability score.

Cognitive assessments

Cognitive function was assessed at each wave in ELSA using a battery of standard tests covering three cognitive domains: memory, executive function and orientation. *Memory* was measured using immediate and delayed recall of ten unrelated words. We created an overall memory score (ranging from 0 to 20) by summing the scores of the immediate and delayed recall tests (maximum of 10 points for immediate and 10 points for delayed recall; correlation coefficient of 0.70), with higher scores indicating better memory performance. *Executive function* was measured using a verbal fluency task in which participants were asked to name as many animals as they could in one minute. The verbal fluency score was calculated as the total count of words excluding repeated and nonanimal words (ranging from 0 to 60), and higher scores indicated better executive function [25]. Both immediate and delayed word recall tests and verbal fluency tasks have been shown to have good construct validity and consistency [25,26]. *Orientation* was assessed by asking four questions related to the day and date, i.e., the day of the week and month, the month, and the year, and

participants received one point for each correct answer (ranging from 0 to 4). Generally, higher scores indicate better cognitive function, and there was no evidence of floor or ceiling effects.

To enable comparison across cognitive tests, the standardized z score for the cognitive test scores at each wave was calculated by subtracting the mean score at baseline and dividing the value by the SD of the baseline scores. A z score of 1 means that the performance on the particular cognitive test was 1 SD above the mean score at baseline.

Covariates

The following covariates that were demonstrated to be associated with both cardiometabolic and inflammatory risks and cognitive function in previous studies were selected for our analyses: age, sex, cohabitation status (living alone or not), educational level (NVQ3/GCE A level or above), current cigarette smoking, current alcohol consumption (at least 1 day per week), regular exercise (performing at least 1 day per week of moderate physical activity), depressive symptoms, history of hypertension, cardiovascular diseases (absence of angina, heart attack, congestive heart failure, stroke, heart murmur or abnormal heart rhythm), diabetes, chronic lung disease and cancer. Depressive symptoms were measured using an 8-item version of the Center for Epidemiologic Studies Depression Scale (CES-D), and elevated depressive symptoms were indicated by a CES-D-8 score greater than 3 (sensitivity: 70%, specificity: 79%) [27].

Statistical analysis

Baseline characteristics are presented as the mean ± SD for continuous variables or number (percentage) for categorical variables. Participants were classified into quartiles of variability score. Univariate linear regression analysis or chi-square tests for trends were used to test the significance of trends across the quartiles.

Multivariable linear mixed-effect models were used to examine the longitudinal association between VVV in cardiometabolic and inflammatory parameters and cognitive decline. The models take into account both intra- and interindividual variations in response variables (cognitive z score) over time and are particularly appropriate for the analysis of longitudinal data with repeated measurements. Time was defined as the number of years since baseline. The fixed effect of the model included the interaction term between the exposure of interest (cognitive z score) and time.

Random effects included intercept and slope for time to address the interindividual differences at baseline and different rates of change in cognitive function during the follow-up period. In the current study, a negative β value for the interaction item of time and variability score indicated that a 1-unit increment in variability score was associated with a faster cognitive decline rate as time increased. The following two linear mixed-effect models were applied: Model 1 included quartiles of variability score (quartile 1 as the reference), time (years from baseline), time × quartiles of variability score interaction, age (years) and sex (male and female). Model 2 was additionally adjusted for baseline BMI (kg/m^2), WHtR, SBP (mmHg), TC (mmol/l), triacylglycerol (mmol/l), HbA1c (%), hs-CRP (mg/l), ferritin (ng/l), education level (below level 3 National Vocational Qualification [NVQ3]/General Certificate of Education [GCE] A level, or equal to NVQ3/GCE A level or above), cohabitation status (currently living alone or not), hypertension (yes or no), cardiovascular disease (yes or no), diabetes (yes or no), chronic lung disease (yes or no), cancer (yes or no), current smoking (yes or no), current alcohol consumption (drink at least once per week or not), regular exercise (yes or no) and depressive symptoms (yes or no). The *p* for trend was calculated by using the median value in each quartile of the variability score. The effect of each SD increment in the variability score was calculated by modeling the variability score as a continuous variable. The potential effect modification by age, sex, obesity and diabetes was evaluated through stratified analysis and interaction testing using a likelihood ratio test.

The following sensitivity analyses were performed to evaluate the robustness of our main results: 1) The multiple imputation of chained equations (MICEs) method was used to replace missing data for cognitive assessments during follow-up (waves 4, 6, 8 and 9) and using all available data in the sensitivity analyses. Baseline characteristics, including age, sex, education level, cohabitation status, hypertension, cardiovascular disease, diabetes, chronic lung disease, cancer, current smoking, current alcohol consumption, regular exercise, depressive symptoms and baseline cognitive scores, were used to impute the missing values. For each longitudinal analysis, we created 20 imputed data sets and pooled the results using the "mi impute chained" procedure of STATA (version 15; StataCorp, College Station, Texas). The imputation quality was assessed by comparing the imputed data with the original data using density plots. 2) A total of 326 participants (n = 128 at wave 2, n = 122 at wave 4, n = 109 at wave 6, n = 60 at wave 4 and n = 10 at wave 9) with hs-CRP >10 mg/L were removed since this hs-CRP level may indicate the presence of an acute infection

or serious acute illness. 3) SD or CV was modelled instead of VIM as VVV indices of cardiometabolic and inflammatory parameters. 4) In consideration of the possible influence of hypertension, cardiovascular diseases or diabetes status on the variability of cardiometabolic and inflammatory parameters, sensitivity analysis excluding those participants with baseline hypertension, cardiovascular disease or diabetes was also performed.

Statistical analyses were performed using STATA (version 15; StataCorp, College Station, Texas). All analyses were two-sided, and an alpha value of 0.05 was considered the threshold for statistical significance.

Results

Baseline characteristics

The mean age of the 2366 participants was 62.99 ± 7.49 years, and 1328 (56.13%) were female. The mean follow-up duration was 11.15 ± 1.97 years, and the mean number of cognitive assessments was 4.60 ± 0.71. A comparison of baseline characteristics between participants included and not included is shown in **Additional file: Table S1**.

Table 1 describes the distribution of characteristics of the included study participants by quartiles of variability score. Participants in the highest quartile of variability score were more likely to be older, male, single, current smokers and have a lower educational level. The prevalence of comorbid conditions such as diabetes, cardiovascular disease (CVD), chronic lung diseases, cancer and depressive symptoms was also higher in the groups with higher variability scores. As expected, the baseline cognitive function (including memory and executive function score) decreased incrementally as the quartiles of variability score increased (p for trend <0.001). **Additional file: Table S2** also presents the characteristics of clinical parameters according to variability score quartiles.

Variability in individual parameters and cognitive decline

We first examined the longitudinal association between variability in individual cardiometabolic and inflammatory parameters and the rate of change in cognitive scores (**Table 2**). After multivariable adjustment, a 1-SD increment in variability in BMI, HbA1c and ferritin (measured as

VIM) was significantly associated with an increased rate of decline in global cognitive z score (-0.0194 points/year, 95% CI -0.0332, -0.0057; -0.0186 points/year, 95% CI -0.0234, -0.0152 and -0.0150 points/year, 95% CI -0.0095, -0.0005;, respectively); a 1-SD increment in BMI-VIM, SBP-VIM, TC-VIM and ferritin-VIM was significantly associated with an increased rate of decline in memory z score (-0.0153 points/year, 95% CI -0.0249, -0.0057; -0.0050 points/year, 95% CI -0.0080, -0.0019; -0.0061 points/year, 95% CI -0.0092, -0.0030 and -0.0059 points/year, 95% CI -0.0090, -0.0028;, respectively); a 1-SD increment in TC-VIM and HbA1c-VIM was significantly associated with an increased rate of decline in executive function z score (-0.0035 points/year, 95% CI -0.0069, -0.0001 and -0.0058 points/year, 95% CI -0.0095, -0.0022, respectively); and a 13.79 ng/ml increment in ferritin-VIM was significantly associated with an increased rate of decline in orientation z score (-0.0042 points/year, 95% CI -0.0080, -0.0003).

Variability score and rates of cognitive decline

Next, we explored the composite effect of cardiometabolic and inflammatory parameter variability on the rate of cognitive decline. **Fig 1** shows the trajectories of cognitive z scores by quartiles of variability score from waves 2 to 9 (2004–2005 to 2018–2019). Those with the highest variability score (fourth quintile) showed the greatest decline in cognitive z scores over time.

Compared with the lowest quartile of variability score, the rate of global cognitive decline associated with the second, third, and highest quartiles was increased by -0.0076 points/year (95% CI -0.0191, 0.0039), -0.0145 points/year (95% CI -0.0265, -0.0026) and -0.0238 points/year (95% CI -0.0376, -0.0100), respectively (*p* for trend <0.001, **Table 3**) (Model 2). Similarly, memory and orientation also declined faster with increasing quartiles of variability score (*p* for trend <0.05). The rate of memory decline associated with the highest quartile compared with the lowest quartile was -0.0224 points/year faster (95% CI -0.0319, -0.0129), and the same rate of orientation decline was -0.0129 points/year faster (95% CI -0.0245, -0.0012). However, we did not find a significant association between variability score quartiles and executive function decline. These associations were attenuated after further adjustment for covariates in Model 2 but remained significant for global cognitive and memory function. When modeled as a continuous variable, a 1-SD increment in variability score was associated with a higher rate of global cognitive z score decline (-0.0080 points/year, 95% CI -0.0125, -0.0036) and memory z score decline (-0.0061 points/year, 95% CI -

0.0092, -0.0030). We did not find a significant association between variability score and executive function or orientation decline in the fully adjusted models.

We did not observe effect modification by age or presence or absence of obesity or diabetes in the current study (**Fig 2**). However, a faster rate of executive function z score decline was observed among female subgroups (*P* for interaction < 0.05).

Sensitivity analysis

As shown in **Additional file: Table S3**, the results remained similar (even stronger) when 326 participants with hs-CRP >10 mg/L were removed from the main analyses. **Additional file: Fig. S2** shows that the distribution of the imputed data is generally similar to that of the original data, and longitudinal results using imputed data (n = 2371) were similar to those from the main analyses (**Additional file: Table S4**). Thus, the impact of missing data on our main findings was likely to be small. Sensitivity analysis using the variability index with SD and CV was also performed, and the results were generally consistent and even strengthened in the fully adjusted models (**Additional file: Tables S5 and S6**). We also excluded participants with hypertension, diabetes or cardiovascular disease at baseline, and robust results showing positive associations between variability score and cognitive decline were still observed (**Additional file: Table S7**).

Discussion

In this community-based prospective cohort with a mean follow-up period of 11.15 years, we examined the association between variability in cardiometabolic and inflammatory parameters and cognitive decline. Higher variability in each parameter (BMI, SBP, TC, HbA1c or ferritin) was linearly associated with either global or domain-specific cognitive decline independent of their mean values. More importantly, a composite effect of these parameters was evident, showing a linear association between variability scores and global and memory cognitive decline (but not executive function or orientation). The results were materially unchanged in various sensitivity analyses and analyses conducted in different subgroups, confirming that these relationships are widely applicable. Our findings are novel because, to our knowledge, no prior prospective study has assessed cognitive changes in response to the composite effect of variability in cardiometabolic and

313 inflammatory parameters.

314 Cardiovascular diseases, hypertension, metabolic diseases (including type 2 diabetes, obesity,
315 etc.) and inflammation are well-established risk factors for impaired cognitive function, which needs
316 to be properly managed and considered an important therapeutic target [2,28,29]. In addition to the
317 presence of these detrimental conditions, variability in each cardiometabolic and inflammatory
318 parameter (including BMI, SBP, TC, HbA1c and ferritin) has emerged as a novel risk factor for a
319 decline in cognitive functioning. In a prospective cohort study comprising 976 Chinese adults, VVV
320 calculated from BP with a mean measurement interval of 3.2 years was associated with a faster rate
321 of cognitive decline in verbal memory independent of the average BP level [30], which is consistent
322 with our results. The findings of our study are also in line with previous studies suggesting that long-
323 term TC variability may be more informative than mean BP in predicting cognitive function in older
324 adults [31,32]. We provided additional evidence that participants with high TC variability also have
325 cognitive degeneration in another domain, the animal listing tests, which represented abilities in
326 executive function. Individuals' orientation ability, reflected by "date naming", also declined, but
327 the decline was not significant. Together with other studies reporting other adverse effects of TC or
328 low-density lipoprotein cholesterol variability [33–35], there are indications that cholesterol
329 variability and its stabilization could be a target for further research. In addition, we and others
330 demonstrated that glycemic variability was related to faster rates of cognitive decline [36,37]. The
331 association of ferritin variability with various health outcomes has not been well evaluated, and only
332 limited studies have reported that ferritin levels were independently related to cognitive
333 performance [38]. Our study adds new evidence that there is a dose-response relationship between
334 VVV in ferritin and cognitive decline in memory and orientation. Research examining the
335 association between anthropometric parameter variability and cognitive function in the general older
336 population is scarce. Only one prospective study has examined the association between BMI
337 variability and dementia [39], and others are limited to the effect of body weight variability on
338 dementia [40–42]. In our study, we examined the relationship between the variability in two obesity
339 indicators (BMI and WHtR) and cognitive decline. We found a significant relation between long-
340 term BMI variability and accelerated cognitive decline in memory, and the association remained
341 positive after adjusting for mean BMI or after performing several sensitivity analyses. However, no
342 association was observed between WHtR variability and cognitive function. Further investigation

is warranted to explore the relationship between other obesity indicators and cognitive decline. Likewise, variability in other parameters (triglycerides and hs-CRP) was not found to increase the rate of cognitive decline in our study, although it was unknown whether variability in triglycerides and hs-CRP was associated with cognitive function in previous studies. Of note, these above parameters are likely to exert an interactive influence and appear in clusters as a cardiometabolic syndrome [43,44]. Our study is the first to reveal the positive association between the composite effect of variability in cardiometabolic parameters and greater cognitive decline, mainly memory decline.

Although the precise mechanisms underlying the phenomenon remain unclear, several potential explanations can be proposed. First, high BPV might reflect long-term hemodynamic instability in the systemic circulation, which may lead to endothelial dysfunction and microvascular damage with consequent alterations in brain structure and function [17]. Decreased hippocampal volume, cerebral microbleeds, and cortical infarcts caused by repeated episodes of cerebral hypoperfusion are other potential pathogenic mechanisms behind the association between BPV and cognitive impairment [13]. Second, cholesterol variability has been related to instability of atherosclerotic plaques, lower cerebral blood flow and endothelial dysfunction resulting from repeated fluctuations in the atherosclerotic plaque composition, thereby increasing the risk of subclinical cerebrovascular injury [45–47]. Third, glycemic fluctuations are associated with an increased production of reactive oxygen species, which in turn cause glucose-mediated vascular damage in the central nervous system [48,49]. Fourth, elevated ferritin could contribute to tau pathology by causing its aggregation, therefore leading to deteriorated neurodegeneration and the development of impaired cognitive function [50]. Fifth, pathways linking variability in body weight with cognitive function may be mediated by cardiovascular risk factors [51], insulin resistance [52], or personality factors (high neuroticism and low conscientiousness) [53], all of which are associated with both weight cycling and cognitive impairment [54]. Since the majority of cardiometabolic risk factors are interrelated and connected to the general notion of a healthy lifestyle, including smoking, alcohol consumption, regular exercise and a healthy diet, stabilizing these parameters by focusing on these lifestyle or health factors may be a target to reduce an individual's risk of developing cognitive decline and/or dementia [6].

We also found that the combined effect of variability in cardiometabolic and inflammatory

parameters on executive function decline was stronger among females. It is likely that cardiometabolic factors play a larger role in women than in men due to the sex-specific effects of sex hormones and molecular mechanisms on glucose and lipid metabolism, as well as cardiac energy metabolism and function [55,56]. Therefore, compared with men, women with cumulating cardiometabolic risks have poorer executive functioning since this particular cognitive domain is predominantly affected in vascular cognitive impairment [57].

A major strength of the present study is that this is the first general population-based study exploring the relationship between cardiometabolic variability, inflammatory parameters and cognition over a long-term follow-up of 11 years. Our study also has other strengths, including the inclusion of several metrics of VVV, the robust measurement of cognitive function, the appropriate statistical model and adjustment for mean values of these parameters. Nevertheless, the present findings should be considered in the context of some potential limitations. First, we were unable to determine causality in the findings due to the observational nature of the study. However, our findings show that high variability in cardiometabolic and inflammatory parameters was independently related to a greater longitudinal cognitive decline, thus implying that poor cognition is a corollary of high variability in cardiometabolic and inflammatory parameters, not vice versa. We also performed sensitivity analyses to strengthen the causal relationship of the association and confirmed similar results. Second, exclusion of participants with fewer than three clinical measurements, baseline cognitive diseases or missing data might be a source of selection bias since their characteristics were different from the included participants: the excluded participants were older, had a lower education level, were less likely to exercise regularly, included a higher percentage of current smokers and patients with comorbidities, and had lower baseline cognitive scores (**Additional file: Table S1**). Therefore, the association between variability in cardiometabolic and inflammatory parameters and cognitive decline might have been diluted. Third, large intervals between clinical measurements (3.5 years) and relatively few measurements may restrict the generalizability of our findings. Fourth, since ELSA did not include clinical diagnoses of dementia or AD during follow-up, the association between long-term VVV in cardiometabolic and inflammatory parameters and dementia/AD could not be examined. Finally, although we adjusted for several potential confounders to minimize the possibility that some of the unknown factors influencing the variability of cardiometabolic and inflammatory parameters might moderate

the risk of cognitive decline, the effect of other unmeasured variables such as genetic susceptibility still remains to be elucidated.

Conclusion

Our study adds new evidence to support the association of variability in single or multiple cardiometabolic and inflammatory parameters with decline in specific domains of cognitive functioning, irrespective of the effect of mean values, using 11-year follow-up data from a large community-dwelling cohort study of adults aged 50 years and older living in England. Reducing the variability in cardiometabolic and inflammatory parameters may serve as a target for promoting resilience and preserving cognitive reserve, especially in the older population. The effect of control and stabilization of these parameters on the rate of cognitive decline merits further investigation.

Abbreviations

AD, Alzheimer's disease; BMI, body mass index; CI, confidence interval; CV, coefficient of variation; CVD, cardiovascular disease; ELSA, the English Longitudinal Study of Ageing; HbA1c, glycated hemoglobin; hs-CRP, high-sensitivity C-reactive protein; HR, hazard ratio; HSE, the Health Survey for England; SD, standard deviation; SBP, systolic blood pressure; TC, total cholesterol; VIM, variability independent of the mean; VVV, visit-to-visit variability; WHtR, waist-to-height ratio.

Declarations

Ethics approval and consent to participate

The ethical approval for ELSA was provided by the London Multicentre Research Ethics Committee (MREC/01/2/91), and informed consent was obtained from all respondents.

Consent for publication

Not applicable.

Availability of data and materials

The datasets analysed during the current study are available through the UK Data Service (https://beta.ukdataservice.ac.uk/datacatalogue/series/series?id=200011) on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

RZ conceived and designed the project, performed the statistical analysis, interpreted the data and wrote the manuscript. HML conceived the study and substantively revised the manuscript. FRL acquired and managed the data, and revised the manuscript. JRY, YZL and JZZ contributed to discussion. XBW conceived and designed the study, and substantively revised the manuscript.

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Tables

Table 1. Baseline characteristics of participants according to quartiles of variability score.

Characteristic	Total	Quartiles of variability score [a]				*P* for trend [b]
		Q1	Q2	Q3	Q4	
Range of variability score	1-23	≤9	10-12	13-15	≥16	-
No. of participants	2366	607	716	642	401	-
Mean follow-up time, years	11.15 ± 1.97	11.34 ± 1.87	11.24 ± 1.88	11.06 ± 2.03	10.82 ± 2.13	<0.001
Age, years	62.99 ± 7.49	62.46 ± 6.92	62.94 ± 7.68	62.75 ± 7.34	64.27 ± 8.10	0.002
Female, %	1328 (56.13)	311 (23.42)	397 (29.89)	362 (27.26)	258 (19.43)	<0.001
Living alone, %	564 (23.84)	111 (19.68)	170 (30.14)	163 (28.90)	120 (21.28)	<0.001
Education NVQ3/GCE A level or above, %	744 (31.45)	197 (26.48)	234 (31.45)	196 (26.34)	117 (15.73)	0.198
Hypertension, %	600 (25.36)	121 (20.17)	194 (32.33)	177 (29.50)	108 (18.00)	0.007
CVD, %	580 (24.51)	116 (20.00)	167 (28.79)	181 (31.21)	116 (20.00)	<0.001
Diabetes, %	112 (4.73)	10 (8.93)	27 (24.11)	42 (37.50)	33 (29.46)	<0.001
Chronic lung disease, %	69 (2.92)	17 (24.64)	14 (20.29)	19 (27.54)	19 (27.54)	0.067
Cancer, %	121 (5.11)	21 (17.36)	39 (32.23)	31 (125.62)	30 (24.79)	0.015
Depression symptoms, %	406 (17.16)	88 (21.67)	108 (26.60)	123 (30.30)	87 (21.43)	0.001
Current smoking, %	287 (12.13)	54 (18.82)	71 (24.74)	92 (32.06)	70 (24.39)	<0.001
Current alcohol consumption, %	1482 (62.64)	416 (28.07)	431 (29.08)	401 (27.06)	234 (15.79)	0.009
Regular exercise, %	2070 (87.49)	539 (26.04)	648 (31.30)	547 (26.43)	336 (16.23)	0.002

Baseline global cognitive score	36.41 ± 7.89	37.19 ± 8.37	36.59 ± 7.62	36.07 ± 7.81	35.46 ± 7.65	0.004
Baseline memory score	11.04 ± 3.08	11.38 ± 3.19	11.18 ± 3.03	10.86 ± 3.06	10.58 ± 2.99	<0.001
Baseline executive function score	21.55 ± 6.28	22.00 ± 6.49	21.58 ± 6.09	21.40 ± 6.26	20.06 ± 6.26	0.016
Baseline orientation score	3.82 ± 0.43	3.81 ± 0.47	3.84 ± 0.38	3.81 ± 0.43	3.82 ± 0.46	0.533

Values are presented as the mean ± SD for continuous variables and number (%) for categorical variables.

[a] 0 points assigned for Q1 (lowest quartile of variability), 1 point for Q2, 2 points for Q3, and 3 points for Q4 (highest quartile of variability) for BMI, WhtR, SBP, total cholesterol, triacylglycerol, HbA1c, hs-CRP and ferritin variability measured as VIM. Total score ranged from 0 to 24.

[b] Calculated using univariate linear regression for continuous variables and chi-square test for trend for categorical variables.

Abbreviations: VIM, variability independent of the mean; CVD, cardiovascular disease.

627 **Table 2. Longitudinal analysis of the association between variability in cardiometabolic-inflammatory parameters defined as VIM (per SD increment) and**
628 **cognitive decline using linear mixed models.**

	Global cognitive z scores	Memory z score	Executive function z score	Orientation z score
BMI				
Model 1 [a]	**-0.0251 (-0.0387, -0.0114)**	**-0.0173 (-0.0269, -0.0077)**	-0.0094 (-0.0200, 0.0011)	-0.0006 (-0.0123, 0.0110)
Model 2 [b]	**-0.0194 (-0.0332, -0.0057)**	**-0.0153 (-0.0249, -0.0057)**	-0.0080 (-0.0185, 0.0026)	0.0018 (-0.0100, 0.0135)
WHtR				
Model 1	-0.0009 (-0.0051, 0.0033)	-0.0007 (-0.0036, 0.0023)	0.0001 (-0.0032, 0.0032)	0.0006 (-0.0029, 0.0033)
Model 2	0.0025 (-0.0020, 0.0070)	0.0016 (-0.0005, 0.0035)	0.0014 (-0.0019, 0.0047)	0.0028 (-0.0007, 0.0064)
SBP				
Model 1	-0.0032 (-0.0076, 0.0011)	**-0.0055 (-0.0086, -0.0024)**	-0.0028 (-0.0062, 0.0006)	**-0.0041 (-0.0078, -0.0004)**
Model 2	-0.0017 (-0.0061, 0.0026)	**-0.0050 (-0.0080, -0.0019)**	-0.0023 (-0.0057, 0.0011)	-0.0036 (-0.0074, 0.0001)
Total cholesterol				
Model 1	-0.0027 (-0.0071, 0.0016)	**-0.0075 (-0.0105, -0.0044)**	**-0.0042 (-0.0076, -0.0008)**	-0.0027 (-0.0064, 0.0010)
Model 2	-0.0012 (-0.0056, 0.0033)	**-0.0061 (-0.0092, -0.0030)**	**-0.0035 (-0.0069, -0.0001)**	-0.0024 (-0.0062, 0.0014)
Triglycerides				
Model 1	-0.0018 (-0.0062, 0.0026)	0.0001 (-0.0030, 0.0031)	-0.0020 (-0.0054, 0.0014)	-0.0020 (-0.0058, 0.0017)
Model 2	-0.0021 (-0.0065, 0.0023)	-0.0001 (-0.0031, 0.0031)	-0.0021 (-0.0055, 0.0012)	-0.0023 (-0.0061, 0.0014)
HbA1C				
Model 1	**-0.0224 (-0.0269, -0.0179)**	**-0.0040 (-0.0072, -0.0008)**	**-0.0070 (-0.0106, -0.0034)**	-0.0028 (-0.0067, 0.0011)
Model 2	**-0.0186 (-0.0234, -0.0138)**	-0.0016 (-0.0048, 0.0017)	**-0.0058 (-0.0095, -0.0022)**	-0.0015 (-0.0055, 0.0026)

hs-CRP				
Model 1	0.0019 (-0.0024, 0.0062)	-0.0025 (-0.0055, 0.0006)	-0.0002 (-0.0035, 0.0031)	0.0017 (-0.0020, 0.0053)
Model 2	0.0025 (-0.0018, 0.0068)	-0.0022 (-0.0052, 0.0009)	-0.0001 (-0.0034, 0.0032)	0.0022 (-0.0015, 0.0059)
Ferritin				
Model 1	**-0.0074 (-0.0117, -0.0030)**	**-0.0071 (-0.0102, -0.0040)**	-0.0019 (-0.0053, 0.0015)	**-0.0046 (-0.0083, -0.0009)**
Model 2	**-0.0050 (-0.0095, -0.0005)**	**-0.0059 (-0.0090, -0.0028)**	-0.0010 (-0.0044, 0.0024)	**-0.0042 (-0.0080, -0.0003)**

[a] Model 1 was adjusted for age, sex and years from baseline.

[b] Model 2 was adjusted for Model 1 plus cumulative mean BMI, WHtR, SBP, total cholesterol, triacylglycerol, HbA1c, hs-CRP and ferritin; education level; cohabitation status; hypertension; cardiovascular disease; diabetes; chronic lung disease; cancer, current smoking; current alcohol consumption; regular exercise; and depressive symptoms.

Abbreviations: SD, standard deviation; VIM, variability independent of the mean; BMI, body mass index; WHtR, waist-to-height ratio; hs-CRP, high-sensitivity C-reactive protein.

Table 3. The composite effect of visit-to-visit variability in cardiometabolic-inflammatory markers measured as VIM on memory decline using linear mixed models.

	Variability score [a]				*P* for trend	β per SD increment in variability score
	Q1	Q2	Q3	Q4		
Global cognitive z scores						
Model 1[b]	Ref.	-0.0096 (-0.0211, 0.0019)	**-0.0175 (-0.0294, -0.0056)**	**-0.0306 (-0.0440, -0.0172)**	**<0.001**	**-0.0108 (-0.0151, -0.0064)**
Model 2[c]	Ref.	-0.0076 (-0.0191, 0.0039)	**-0.0145 (-0.0265, -0.0026)**	**-0.0238 (-0.0376, -0.0100)**	**<0.001**	**-0.0080 (-0.0125, -0.0036)**
Memory z score						
Model 1	Ref.	**-0.0110 (-0.0191, -0.0029)**	**-0.0102 (-0.0186, -0.0018)**	**-0.0265 (-0.0359, -0.0170)**	**<0.001**	**-0.0075 (-0.0106, -0.0045)**
Model 2	Ref.	**-0.0097 (-0.0178, -0.0017)**	-0.0075 (-0.0159, 0.0009)	**-0.0224 (-0.0319, -0.0129)**	**<0.001**	**-0.0061 (-0.0092, -0.0030)**
Executive function z score						
Model 1	Ref.	0.0011 (-0.0078, 0.0099)	-0.0056 (-0.0148, 0.0036)	-0.0096 (-0.0200, 0.0008)	**0.034**	**-0.0040 (-0.0074, -0.0007)**
Model 2	Ref.	0.0019 (-0.0069, 0.0107)	-0.0039 (-0.0132, 0.0053)	-0.0068 (-0.0172, 0.0037)	0.108	-0.0031 (-0.0065, 0.0003)
Orientation z score						
Model 1	Ref.	-0.0041 (-0.0138, 0.0057)	-0.0058 (-0.0160, 0.0043)	**-0.0139 (-0.0253, -0.0025)**	**0.020**	-0.0035 (-0.0072, 0.0002)
Model 2	Ref.	-0.0045 (-0.0143, 0.0053)	-0.0054 (-0.0156, 0.0048)	**-0.0129 (-0.0245, -0.0012)**	0.087	-0.0024 (-0.0062, 0.0013)

[a] 0 points assigned for Q1 (lowest quartile of variability), 1 point for Q2, 2 points for Q3, and 3 points for Q4 (highest quartile of variability) for BMI, WhtR, SBP, total cholesterol, triacylglycerol, HbA1c, hs-CRP and ferritin variability measured as VIM. Total score ranged from 0 to 24.

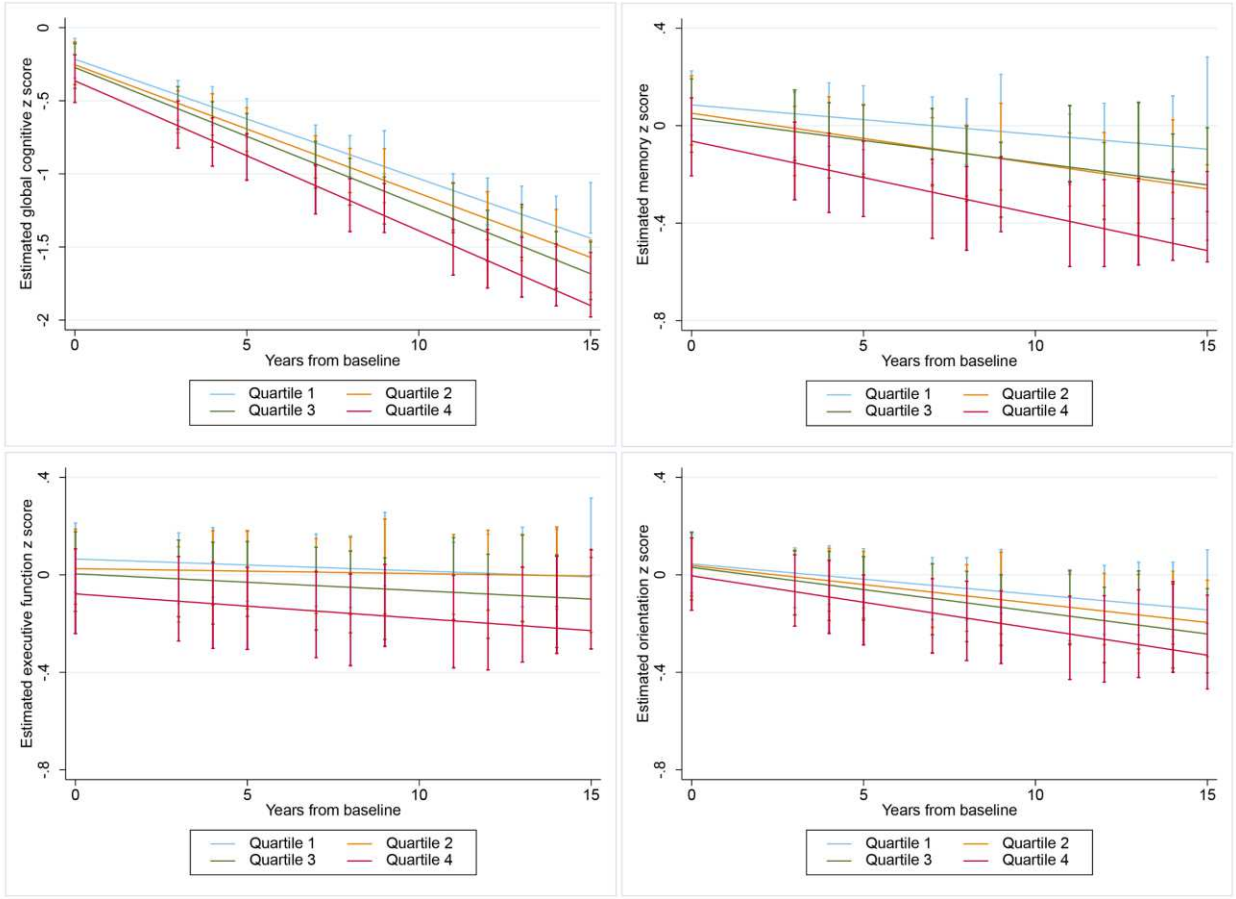
[b] Model 1 was adjusted for age, sex and years from baseline.

[c] Model 2 was adjusted for Model 1 plus cumulative mean BMI, WHtR, SBP, total cholesterol, triacylglycerol, HbA1c, hs-CRP and ferritin; education level; cohabitation status; hypertension; cardiovascular disease; diabetes; chronic lung disease; cancer; current smoking current alcohol consumption; regular exercise; and depressive symptoms.

Abbreviations: SD, standard deviation; VIM, variability independent of the mean.

Figures

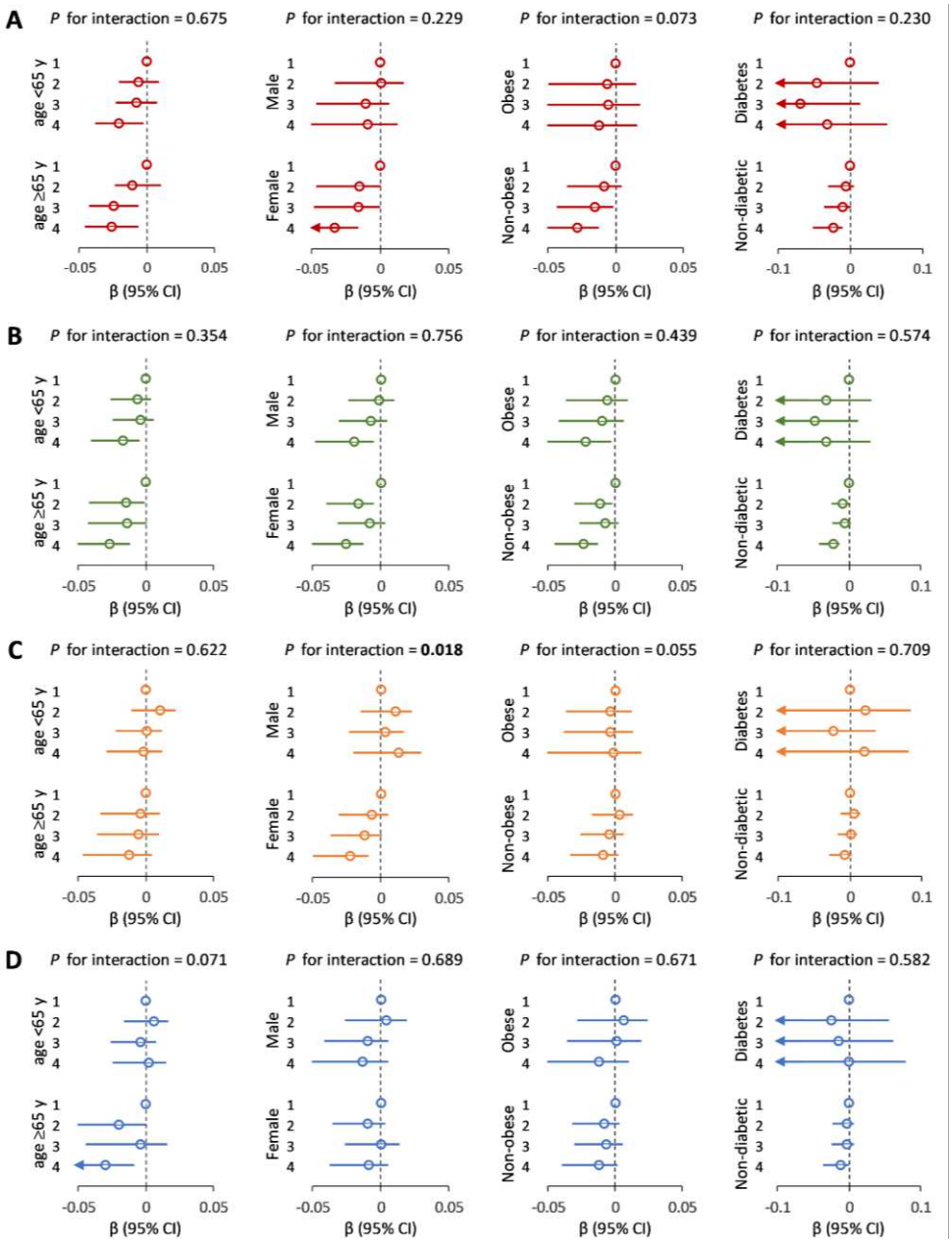
Figure 1. Estimated mean cognitive z score with 95% CIs at follow-up intervals by quartiles of variability score.



The results were adjusted for age; sex; years from baseline; cumulative mean BMI, WHtR, SBP, total cholesterol, triacylglycerol, HbA1c, hs-CRP and ferritin; education level; cohabitation status; hypertension; cardiovascular disease; diabetes; chronic lung disease; cancer; current smoking; current alcohol consumption; regular exercise; and depressive symptoms.

Abbreviations: CI, confidence intervals; BMI, body mass index; WHtR, waist-to-height ratio; hs-CRP, high-sensitivity C-reactive protein.

Figure 2. Subgroup analysis of the association between quartiles of variability score and cognitive decline, stratified by age, sex, baseline obesity and diabetes status.



Coefficient (β) and 95% confidence interval (CI) of global cognitive z score (a), memory z score (b), executive function z score (c) and orientation z score (d) by quartiles of variability score. 0 points assigned for Q1 (lowest quartile of variability), 1 point for Q2, 2 points for Q3, and 3 points for Q4 (highest quartile of variability) for BMI, WHtR, SBP, total cholesterol, triacylglycerol, HbA1c, hs-CRP and ferritin variability measured as VIM. Total score ranged from 0 to 24. Adjusted for age; sex; years from baseline; cumulative mean BMI, WHtR, SBP, total cholesterol, triacylglycerol, HbA1c, hs-CRP and ferritin; education level; cohabitation status; hypertension;

cardiovascular disease; diabetes; chronic lung disease; cancer; current smoking; current alcohol consumption; regular exercise; and depressive symptoms.

Abbreviations: VIM, variability independent of the mean; BMI, body mass index; WHtR, waist-to-height ratio; hs-CRP, high-sensitivity C-reactive protein.

Figures

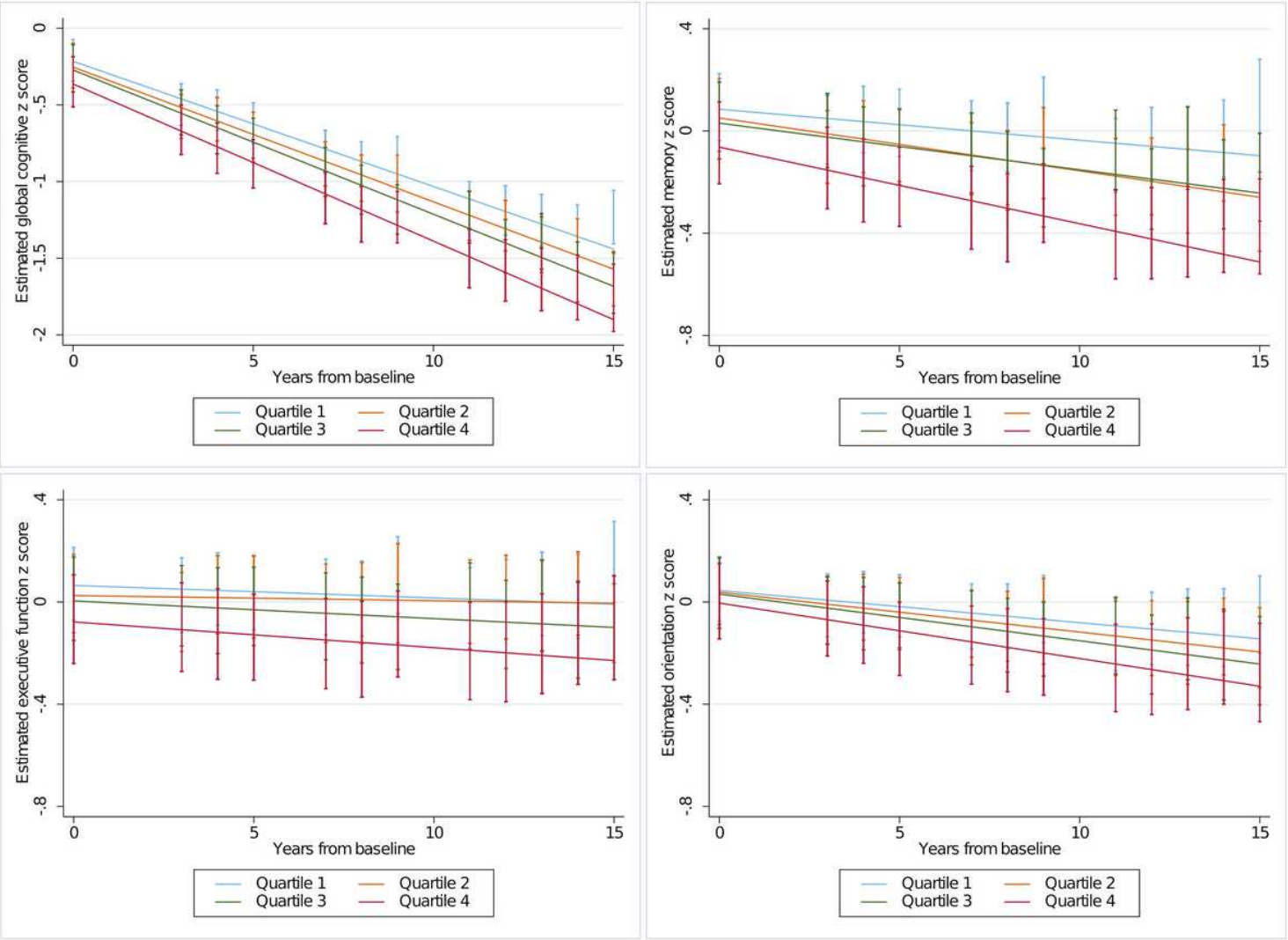


Figure 1

Estimated mean cognitive z score with 95% CIs at follow-up intervals by quartiles of variability score. The results were adjusted for age; sex; years from baseline; cumulative mean BMI, WHtR, SBP, total cholesterol, triacylglycerol, HbA1c, hs-CRP and ferritin; education level; cohabitation status; hypertension; cardiovascular disease; diabetes; chronic lung disease; cancer; current smoking; current alcohol consumption; regular exercise; and depressive symptoms. Abbreviations: CI, confidence intervals; BMI, body mass index; WHtR, waist-to-height ratio; hs-CRP, high-sensitivity C-reactive protein.

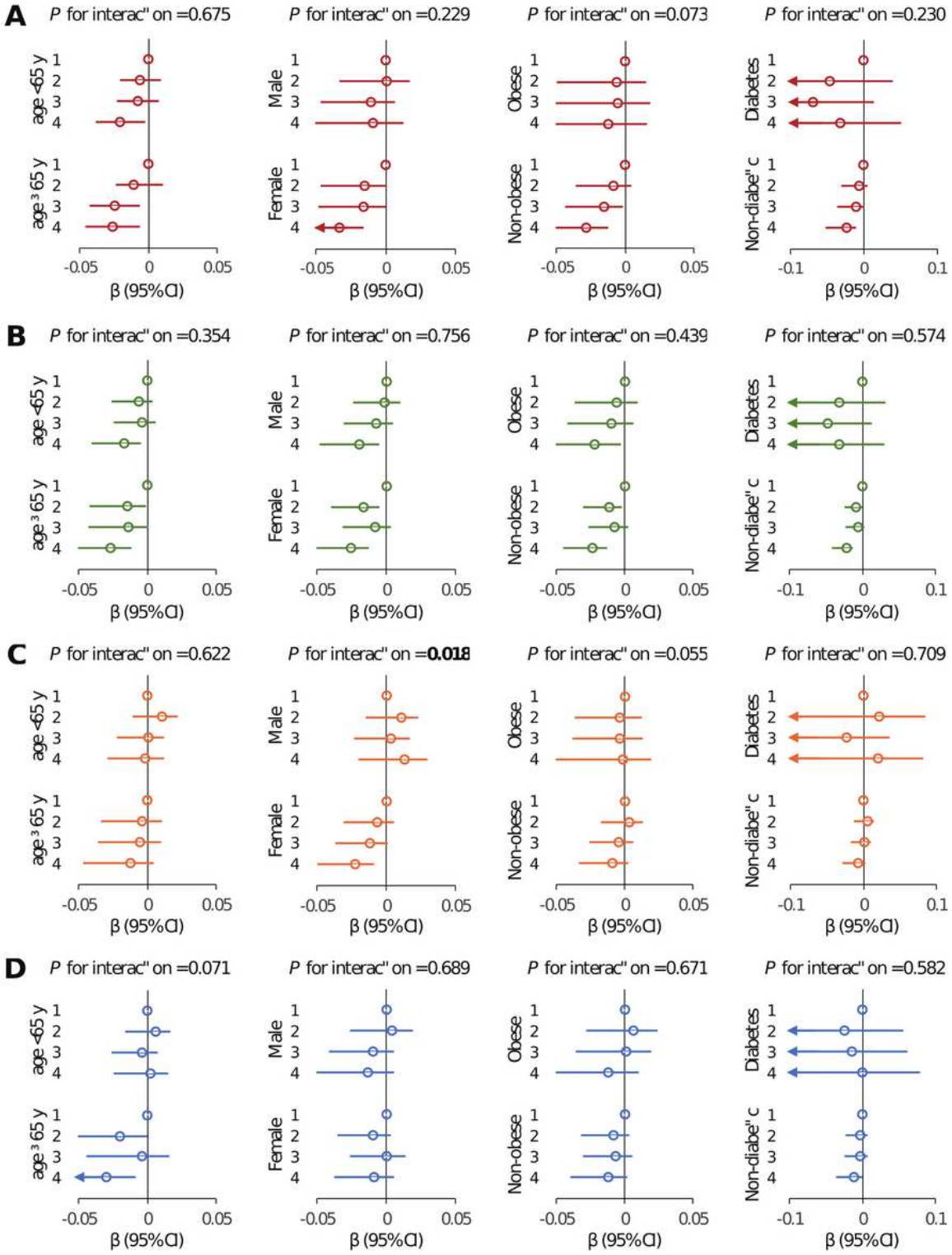


Figure 2

Subgroup analysis of the association between quartiles of variability score and cognitive decline, stratified by age, sex, baseline obesity and diabetes status. Coefficient (β) and 95% confidence interval (CI) of global cognitive z score (a), memory z score (b), executive function z score (c) and orientation z score (d) by quartiles of variability score. 0 points assigned for Q1 (lowest quartile of variability), 1 point for Q2, 2 points for Q3, and 3 points for Q4 (highest quartile of variability) for BMI, WHtR, SBP, total

cholesterol, triacylglycerol, HbA1c, hs-CRP and ferritin variability measured as VIM. Total score ranged from 0 to 24. Adjusted for age; sex; years from baseline; cumulative mean BMI, WHtR, SBP, total cholesterol, triacylglycerol, HbA1c, hs-CRP and ferritin; education level; cohabitation status; hypertension; cardiovascular disease; diabetes; chronic lung disease; cancer; current smoking; current alcohol consumption; regular exercise; and depressive symptoms. Abbreviations: VIM, variability independent of the mean; BMI, body mass index; WHtR, waist-to- height ratio; hs-CRP, high-sensitivity C-reactive protein.

Supplementary Files

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- Supplementarymaterials.docx