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ORIGINAL RESEARCH

Associations Between Cardiorespiratory Fitness, Cardiovascular Risk, and Cognition Are Mediated by Structural Brain Health in Midlife

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BACKGROUND: Evidence in older adults suggests that higher cardiorespiratory fitness and lower cardiovascular risk are associated with greater cognition. However, given that changes in the brain that lead to cognitive decline begin decades before the onset of symptoms, understanding the mechanisms by which modifiable cardiovascular factors are associated with brain health in midlife is critical and can lead to the development of strategies to promote and maintain brain health as we age.

METHODS AND RESULTS: In 501 middle-aged (aged 40–65 years) adult participants of the BBHI (Barcelona Brain Health Initiative), we found differential associations among cardiorespiratory fitness, cardiovascular risk, and cognition and cortical thickness. Higher cardiorespiratory fitness was significantly associated with better visuospatial abilities and frontal loading abstract problem solving (β=3.16, P=0.049) in the older middle-aged group (aged 55–65 years). In contrast, cardiovascular risk was negatively associated with better visuospatial reasoning and problem-solving abilities (β=−0.046, P=0.002), flexibility (β=−0.054, P<0.001), processing speed (β=−0.115, P<0.001), and memory (β=−0.120, P<0.001). Cortical thickness in frontal regions mediated the relationship between cardiorespiratory fitness and cognition, whereas cortical thickness in a disperse network spanning multiple cortical regions across both hemispheres mediated the relationship between cardiovascular risk and cognition.

CONCLUSIONS: The relationships between modifiable cardiovascular factors, cardiorespiratory fitness, and cardiovascular risk, and cognition are present in healthy middle-aged adults. These relationships are also mediated by brain structure highlighting a potential mechanistic pathway through which higher cardiorespiratory fitness and lower cardiovascular risk can positively impact cognitive function in midlife.

Key Words: cardiorespiratory fitness ■ cardiovascular health ■ cognition ■ exercise ■ mediation ■ midlife ■ structural brain health

Understanding factors associated with maintenance of cognitive brain health in aging is of great clinical and public health interest. An increase in lifespan over the past century has not been accompanied by an increase in health span,[1] and brain-related disorders are projected to account for half of the worldwide economic impact of disability by 2030.[2] Notwithstanding, the development of pathological loss

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CLINICAL PERSPECTIVE

What Is New?

- We extend prior work by demonstrating that some of the well-established relationships between determinants of cardiovascular health and brain health that exist in older age are already present in middle age.
- Cardiorespiratory fitness was associated with frontal cognitive abilities, such as visuospatial problem solving, but only in individuals aged 55 years and older.
- Cardiovascular risk was associated with a wide range of cognitive abilities within the whole sample; these results suggest distinct, but synergistic effects of cardiovascular risk and cardiorespiratory fitness with cognitive brain health in healthy middle-aged adults.

What Are the Clinical Implications?

- Importantly, we advance existing knowledge by revealing that such relationships driven by distinct patterns of cortical thickness, specifically cortical thickness in frontal regions mediated the relationship between cardiorespiratory fitness and visuospatial problem solving, whereas cortical thickness in a disperse network spanning multiple cortical regions across both hemispheres mediated the relationship between cardiovascular risk and multiple domains of cognition.
- The implications of our study lie within the potential importance of engaging in modifiable lifestyle behaviors that can promote heart health, early in midlife, long before the onset of measurable cognitive decline.

Nonstandard Abbreviations and Acronyms

CPET	cardiopulmonary exercise testing
CRF	cardiorespiratory fitness
CVR	cardiovascular risk

of brain health does not appear to be an obligatory consequence of aging.[3] Several lifestyle behaviors have been found to be protective of age-related and pathological brain changes, which are referred to as the concept of cognitive reserve.[4] Cognitive reserve helps to explain why certain individuals can withstand age-related and pathological brain changes while maintaining their cognitive and physical functioning and ultimately their independence with age.[4]

Although cognitive reserve is a theoretical construct and is rarely measured directly, several modifiable sociobehavioral proxies have been found to contribute to the development of cognitive reserve.[4] For instance, maintaining an active lifestyle by engaging in physical exercise,[5,6] promoting cardiovascular health,[7] consuming nutritious foods,[8,9] assuring sufficient good-quality sleep,[10–12] and maintaining motor skills[13] are independently associated with better cognitive brain health across one's lifespan. The exact mechanisms by which modifiable sociobehavioral proxies influence the development of cognitive reserve are not fully elucidated but can be attributed to the interplay between brain reserve and brain maintenance. That is, brain reserve is defined as the neurobiological capital, or structural integrity, of the many components of the nervous system at any given point in time, whereas brain maintenance is defined as the reduced development of age-related changes over time.[4] Brain maintenance reflects the notion that the brain can be modified by experience, and many of the same lifestyle proxies that contribute to cognitive reserve also contribute to brain maintenance.[4] Finally, it is also known that measurable changes in brain structure precede clinically measurable cognitive deficits by many years,[14,15] and therefore examining the relationships between modifiable factors that may contribute to cognitive and brain reserve beginning in midlife may provide evidence to develop and refine lifestyle strategies capable of promoting or maintaining brain health in older age.

There is strong evidence that cardiovascular health in midlife is a strong predictor of cognitive health in later life.[7,16] One important domain of cardiovascular health is cardiorespiratory fitness (CRF). The gold-standard measure of CRF is the maximum rate of oxygen consumption during incremental exercise, or VO_2max, which measures the body's efficiency to intake, circulate, and use oxygen during exercise. CRF has been identified as a critical mechanism implicated in exercise's effect on cognitive function.[5,6,16–18] Furthermore, numerous studies have associated CRF itself with cognitive functions, whereby rather than having a global effect on cognition, high levels of CRF later in life seem to be related to selective enhancement of cognitive abilities more reliant on frontal brain areas such as executive and reasoning abilities.[5,6]

Another important cardiovascular health predictor is the risk of developing a future cardiovascular event, which can be calculated by measuring several factors such as hypertension, cigarette smoking, diabetes, hyperlipidemia, family history, and obesity.[19] Interestingly, cardiovascular risk (CVR) factors overlap with cognitive impairment risk factors,[20–24] further strengthening the link between cardiovascular and cognitive health. Evidence suggests that CVR later in life is associated with more diffuse patterns of gray matter atrophy and white matter lesions, thus potentially affecting cognitive abilities in a more global manner.[25–27] As such, low CVR

burden in middle age might be associated with a more global effect on cognitive health and brain structure.

In this study, our primary objective was to assess the respective relationships between CRF and CVR and cognitive function in midlife in a sample of 501 adults aged 40 to 65 years. We further aimed to examine the mechanistic correlates of these relationships in midlife through measures of brain structure using magnetic resonance imaging (MRI), by testing whether cortical thickness mediated the relationships between each predictor (CVR and CRF) and cognitive function. Although genetic predisposition influences both CRF[28,29] and CVR,[30] these 2 factors are modifiable through lifestyle changes. Therefore, further elucidating the relationships and potential mechanisms of these modifiable cognitive reserve protecting factors in midlife can contribute to the development of more effective and precise lifestyle interventions to maintain or improve cognitive brain health with age.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Participants

This was a cross-sectional study that included data collected on a subset of participants enrolled in the ongoing BBHI (Barcelona Brain Health Initiative) (https://bbhi.cat/en/), who were selected to participate in phase 2 of the initiative, which involved a comprehensive in-person assessment.[31,32] For a detailed description of the cohort and study protocol see Cattaneo et al.[31,32] Inclusion criteria (assessed by a medical doctor) for this study included: (1) age between 40 and 65 years and (2) absence of any neurological or psychiatric disorders. Exclusion criteria included any person presenting with any contraindications for brain MRI and cardiopulmonary exercise testing (CPET) (see details below). We further excluded those participants who did not meet the criteria for a completed CPET evaluation (see CPET section). A cohort consort diagram from the wider BBHI study and selection criteria for this analysis is shown in Figure 1. A total of 501 participants were eligible for this analysis based on having completed a full CPET evaluation. There were incomplete data on a total of 114 subjects (74 subjects did not have full neuropsychological data and 40 subjects did not have sufficient information for the calculation of the Framingham score) and were therefore excluded from the cognitive analyses. All participants gave written informed consent before participation in any study procedures, all of which conformed to the Declaration of Helsinki for research involving human subjects. All procedures were approved by the ethics and education committee of the Institut Guttmann (Badalona, Spain). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist has been used for the reporting of the present study results.[33]

Neuropsychological Exam

Neurocognitive assessments were performed by 2 licensed neuropsychologists. Education in years was assessed via an online questionnaire, and this information was validated and corrected by a neuropsychologist or physician during the in-person assessments. Paper and pencil evaluations consisted of a battery of well-established neuropsychological tests. These included Matrix Reasoning,[34] Cancelation Test,[34] Block Design,[34] Trail Making Test B,[35] Trail Making Test A,[36] Digit Forward, Digit Backward, Letter–Number Sequencing,[37] Rey Auditory Verbal Learning Test,[38] Digit Symbol Substitution,[34] and Corsi Block-Tapping Task.[39] Tests were grouped in cognitive domains using a data-driven approach with principal component analysis. Scores on individual tests were *Z*-score normalized before their inclusion in the principal component analysis with Oblimin rotation, considering the probable correlation between latent factors.[40] Based on the sample size, the acceptable level of factor loading was set at 0.30.[41] Cognitive domains were then created as the composite sum of the *Z* scores for each test per the results from the principal component analysis. The principal component analysis indicated the presence of 5 principal components for the cognitive scores. The first factor included the Digit Symbol Test (0.65), the Cancellation Test (0.76) and the Trail Making Test A (0.80), likely reflecting visual searching, processing speed, and attentional components. The second component comprised all 3 measures of the Rey Auditory Verbal Learning Test (immediate recall=–0.85, delayed recall=–0.89, recognition=–0.81) creating a verbal memory domain. The third component contained the Digit Forward (0.81), Digit Backward (0.66), and Letter–Number Sequencing (0.68), reflecting a working memory domain. Cognitive flexibility and set-shifting abilities were reflected in the fourth component, which included the Trail Making Test B (0.91) and the Trail Making Test B-A (1.02). Finally, a visuospatial reasoning and problem-solving domain was found in the fifth component comprising Wechsler Adult Intelligence Scale Fourth Edition matrix reasoning (0.78), Block Design (0.74), and Corsi cubes (0.46).

Cardiopulmonary Exercise Testing

Before CPET evaluation, participants were assessed for potential absolute and relative contraindications for maximal exhaustive exercise following the Guidelines of

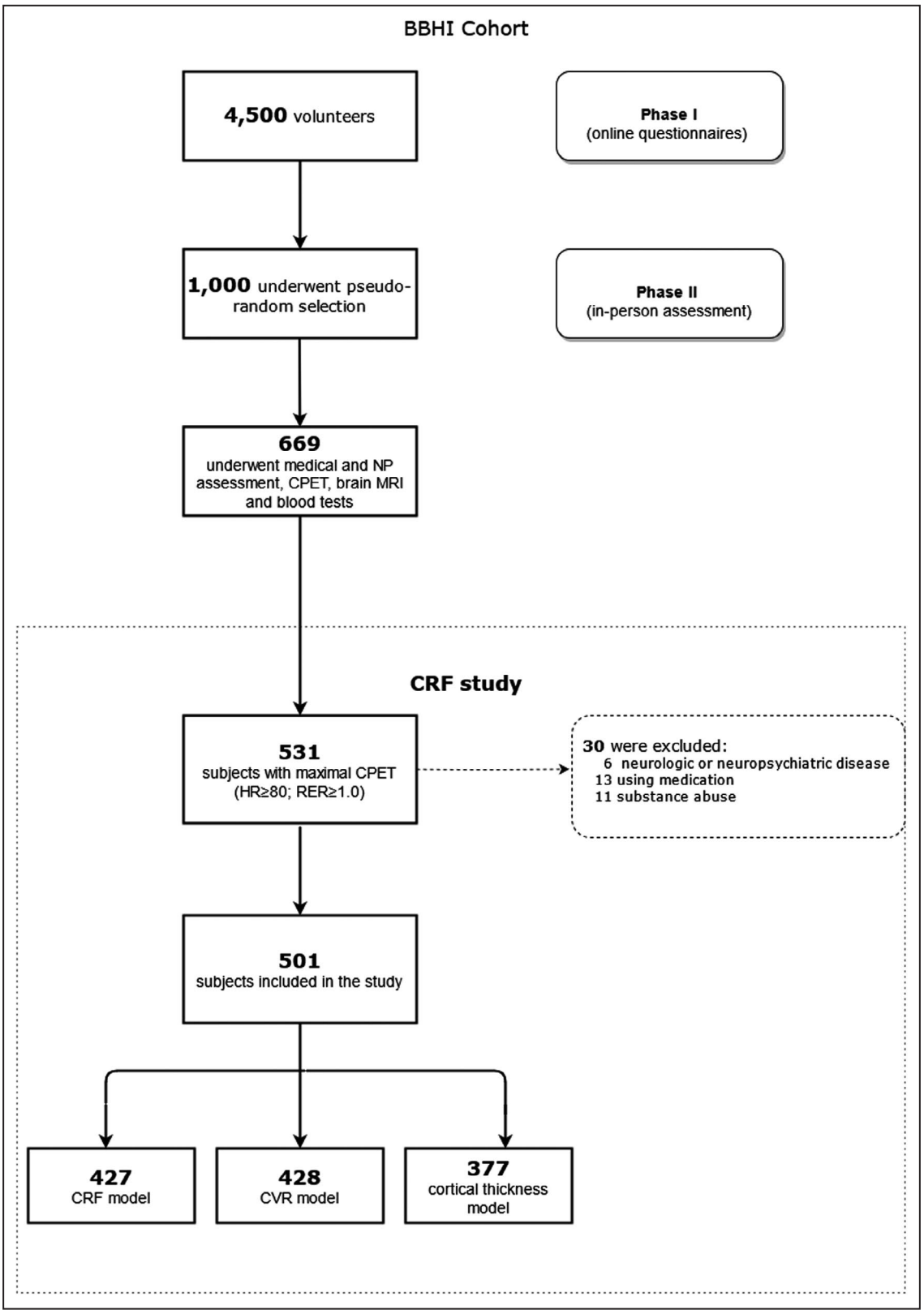

Figure 1. Cohort consort diagram from the wider BBHI (Barcelona Brain Health Initiative) study and selection criteria for the current analysis.

CPET indicates cardiopulmonary exercise testing; CRF, cardiorespiratory fitness; CVR, cardiovascular risk; HR, heart rate; MRI, magnetic resonance imaging; NP, neuropsychology assessment; and RER, respiratory exchange ratio.

the Spanish Society of Cardiology for Clinical Practice in Exercise Testing.[42] The Physical Activity Readiness Questionnaire[43] was administered to assess for safety to participate in the CPET. Additionally, participants performed baseline spirometry (Ergoflow flowsensor; Geratherm Respiratory, Bad Kissingen, Germany) and a baseline 12-lead ECG recording before the test (WAM Wireless Acquisition Module; Mortara, Milwaukee, WI). Individuals who had forced expiratory volume in 1 second of <80%, forced expiratory volume in 1 second/forced vital capacity ratio of >80%, or peak expiratory flow of >75% did not complete the CPET evaluation.

The CPET was performed using a modified Wasserman protocol[44] on a cyclometer (Ergoselect 4 model; Ergoline, Bitz, Germany) with a respiratory gas analysis system (Ergostik; Geratherm Respiratory). The modified Wasserman protocol[44] consisted of a 7-minute warm-up phase (no load), a progressive workload phase, and a 5-minute recovery phase (minimal load). The slope of the progressive increase in workload was calculated individually by dividing the expected maximum workload (calculated automatically by the Bluecherry software [Geratherm Respiratory] from height, weight, age, and sex) by 9, to derive a progressive increase in workload that would result in a maximal exercise test lasting ≈13 minutes.

Gas analysis was conducted using a tight-fitting face mask (Hans Rudolph, Shawnee, KS), and the following measures were recorded continuously: oxygen consumption, oxygen uptake (efficiency slope), and respiratory exchange ratio (VO_2/VCO_2), 12-lead ECG, heart rate (beats per minute, from a 12-lead ECG), and pulse oximetry. Blood pressure, measured manually from the left arm using a blood pressure cuff (Boso Medicus X; Boso, Jungingen, Germany) and a handheld sphygmomanometer (MDF Instruments, Agoura Hills, CA) and perceived effort, measured via the Spanish translation of the Borg scale,[45] were recorded every 2.5 minutes. Ventilatory thresholds (lactate threshold and respiratory compensation point) were calculated using the V-slope method.[44]

A test was considered complete under the following criteria: verbal manifestation of exhaustion, Borg score of ≥9, heart rate of ±10 bpm of heart rate max, or inability to maintain pedal cadence (≈70 rpm). The highest full minute VO_2 uptake (maximal oxygen consumption) value observed during the final minute of the test was accepted as the functional aerobic capacity (VO_2 plateau). Whenever a VO_2max plateau could not be detected, we applied the following 2 metrics to determine the validity of the CPET results: (1) the maximal respiratory exchange ratio (respiratory exchange ratio of ≥1.0, considered to be indicative of true maximal oxygen uptake),[46,47] and (2) the reached target heart rate ≥80% of the maximum theoretical expected heart rate (220−age). We use the term VO_2peak (oxygen uptake during peak exercise) herein because only 20.4% of participants reached a detectable VO_2 plateau. To ensure that scaling VO_2peak by total body mass did not affect the associations with our outcomes, we replicated our results using allometric scaling[48,49] (Data S1, Tables S1 through S3).

Medical Exam and Cardiovascular Risk Assessment

A medical evaluation included a structured interview, which gathered past and present medical history (including diagnosis of diabetes), medication intake (including antihypertensive drugs), alcohol and tobacco consumption, absolute and relative risk factors for the CPET, anthropometric measures (weight, height, body mass index, and waist circumference), and blood pressure. Questionnaires about education history (including number of years of formal higher education) and self-reported physical activity (including the International Physical Activity Questionnaire)[50] were filled out by each participant. A fasting blood draw was performed to measure total cholesterol (millimoles per liter) and high-density lipoprotein (millimoles per liter). The modified Framingham cardiovascular disease risk calculator was then used to calculate the 5-year risk of the development of any cardiovascular disease,[51] including the following variables: age (years), biological sex, total cholesterol, high-density lipoprotein, systolic blood pressure, treatment for hypertension, smoker status, and diabetes status. In addition, we also we calculated the modified Framingham cardiovascular disease risk calculator using a formula that was adapted specifically for the Catalan population (the Registre Gironí del Cor[52,53]). The latter is presented in Data S2, Tables S4 through S6, and Figure S1.

Structural MRI

Participants underwent a high-resolution (0.8×0.8×0.8 mm^3) 3-dimensional magnetization-prepared rapid gradient-echo T1-weighted structural brain MRI session using a 3T Siemens Magnetom Prisma machine. A total of 208 contiguous axial slices were obtained in ascending fashion (sequence parameters of repetition time=2400 ms, echo time=2.22 ms, inversion time=1000 ms, flip angle=8°, slice thickness=0.8 mm, and field of view=256 mm). Additionally, a high-resolution (0.8×0.8×0.8 mm^3) 3-dimensional SPACE T2-weighted structural brain MRI was undertaken, using the same device (sequence parameters of repetition time=3200 ms, echo time=563 ms, flip angle=120°, slice thickness=0.8 mm, and field of view=256 mm). Image quality control measures were implemented manually by a trained MRI technician.

Cortical reconstruction and volumetric segmentation were performed with the Freesurfer image analysis suite, which is documented and freely available for

download online (http://surfer.nmr.mgh.harvard.edu/). A 3-dimensional cortical surface model was created by running the recon-all processing stream with default parameters,[54] except for the addition of the T2 flag for the improvement of pial surfaces reconstruction. Therefore, inputs for this command were T1-w volumes and T2-w volumes. Briefly, automated Talairach transformation[55] and intensity normalization[56] were followed by non–brain tissue removal,[57] tessellation of the gray and white matter boundary, and automated topology correction.[58] Finally, surface deformation enabled the detection of tissue boundaries; gray–white and gray–cerebrospinal fluid (CSF) borders.[54] The cortical surfaces were then inflated and registered to a spherical atlas that used individual cortical folding patterns to match cortical geometry across subjects.[57,59,60]

Cortical Thickness Analyses

Individual cortical thickness maps were calculated as the closest distance from the gray–white matter boundary to the gray–cerebrospinal fluid boundary at each vertex on the tessellated surface.[54] Then, a Gaussian kernel of 10-mm full width at half maximum was applied to these maps. Vertex-wise general linear models were run in FreeSurfer version 6.0, with cortical thickness as the dependent variable and either CVR or CRF as the independent variables, with education, age, body mass index, socioeconomic status, waist perimeter, and biological sex as controlling predictors of no interest. A total of 5 models were fitted: Models 1 and 2 included CVR as the predictor of interest, using the Registre Gironí del Cor and Framingham scores, respectively. Models 3, 4, and 5 addressed CRF (ie, VO_2peak) as the predictor of interest. Whereas Models 1, 2, and 3 were fitted for the whole set of observations; the fitting of Models 4 and 5 were restricted to a dichotomization of the sample according to their age: younger middle-aged (aged 40–54 years) and older middle-aged (aged 55–65 years), respectively. For each model, regions where the predictor of interest significantly predicted cortical thickness were identified using a method provided by FreeSurfer (ie, mri_glmfitsim). Here, multiple comparisons correction of whole-brain vertices was performed by computing *P* values for contiguous clusters of vertices based on Monte-Carlo Null-Z simulations[61] and permutation[62] (with 10 000 iterations per simulation). This method assigns a *P* value to each resulting cluster. Consequently, we used a cluster-forming threshold of $P<0.005$ in cardiovascular risk models (ie, Models 1 and 2), and $P<0.05$ in cardiorespiratory fitness models (ie, Models 3, 4, and 5) and a cluster significance threshold of $P<0.05$ in all models.

Statistical Analysis

All statistical analyses were performed in R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). The associations between predictor variables (VO_2peak, Framingham score) and outcome measures (domain-specific cognitive performance and cortical thickness measures) were analyzed using multiple linear regression, controlling for age, education, socioeconomic status, body mass index, waist perimeter, and biological sex for the VO_2peak models and education and socioeconomic status for the CVR models (age and biological sex are factors used to calculate the Framingham score). Model assumptions were checked using Q-Q plots and fitted versus residual plots in R, and the normality of the residuals was formally checked using Shapiro-Wilk tests of normality. Outlier observations that had influence on the models were removed using Cook's distance (observed using Cook's distance of >0.5) and R's outlier package (upper limit of n=10 in any given model). To conform to the model assumptions, VO_2peak and Framingham scores were $\log^{10}$ transformed before analyses. Model fitness is presented as adjusted R^2 values, and significance was considered at the $P<0.05$ level. We present standardized β coefficients as the strength of the relationship between our predictor and outcome variables. That is, for every 1-unit increase in the predictor, there is an X standard deviation increase in the outcome. Multiple comparisons were corrected for using Bejamini and Hochberg's false discovery rate, at a *q* value of 0.05, after pooling the *P* values from the regression analyses for each predictor model. For the VO_2peak models, the cohort was dichotomized into younger middle-aged (aged 40–54 years) and older middle-aged (aged 55–65 years) groups to gain greater sensitivity to further explore age-related associations.

Mediation analysis using the R mediation package[62] was performed to assess whether cortical thickness mediated the associations between VO_2peak and Framingham and cognitive performance, taking into account all covariates (age, biological sex, socioeconomic status, education, waist perimeter, and body mass index). The total effects (effect of X [predictor variable] on Y [outcome variable]), direct effects (effect of X on Y taking into account M [mediator] [average direct effect]) and indirect effects (or mediation effect, the total effect minus the direct effect [average causal mediation effect]) are reported. The presence of statistical mediation was determined through nonparametric bootstrap confidence intervals via 1000 bootstrap resamples of the estimated indirect effect. The estimated indirect (average causal mediation effect) effect corresponds to the reduction in the independent variable effect on the dependent variable when adjusted for the mediator.

RESULTS

A total of 501 (248 women) participants with a mean±SD age of 53.58±6.96 years (range, 40–65 years)

completed the study. Our sample is generally characterized by White, highly educated, and cognitive and cardiovascularly healthy individuals. Full demographic information is found in Table 1.

Associations Between VO_2peak, Framingham, and Cognitive Functions

At the whole group level, no significant associations between VO_2peak and cognitive functions were found (Table 2). When we dichotomized our sample into younger middle-aged (aged 40–54 years) and older middle-aged (aged 55–65 years) we found no significant correlations between any cognitive domain and VO_2peak in the younger group (Table 2). However, in the older middle-aged adults, we did find a significant and positive association between VO_2peak and visuospatial reasoning and problem solving (β=3.16, *P*=0.049), which remained significant after false discovery rate corrections (false discovery rate *P*=0.0499) (Figure 2).

For CVR, we found a significant negative association between Framingham score and the following cognitive abilities: visuospatial ability (β=−0.046, *P*=0.002), processing speed (β=−0.115, *P*<0.001), flexibility (β=−0.054, *P*<0.001), and verbal memory (β=−0.120, *P*<0.001), but not working memory (β=−0.010, *P*=0.502). Full model results are seen in Table 3 and depicted in Figure 3.

Cortical Thickness

At the whole group level, higher VO_2peak was significantly associated with greater cortical thickness in the left prefrontal cortex (rostral middle frontal gyrus) (cluster-wise corrected with a vertex-wise threshold *P*<0.05, cluster-wise *P*<0.05) (Data S3, Table S7, Figure S2A). In the young middle-aged group (aged 40–54 years) VO_2peak was not associated with any specific gyrus (Data S3, Table S8), whereas in the old middle-aged group (aged ≥55 years), associations with left prefrontal regions (left rostral middle frontal) and left temporal regions (superior temporal gyrus) were seen (Data S3, Table S9, Figure S2B). Moreover, in the older middle-aged group, cortical thickness in the left prefrontal gyrus mediated the relationship between VO_2peak and visuospatial reasoning abilities (Figure 4, Data S3, Table S10).

Higher Framingham risk score was significantly associated with lower cortical thickness across different cortical regions (18 clusters) of both hemispheres including frontal, parietal, temporal, and medial (insula, cuneus) cortices (cluster-wise corrected with a vertex-wise threshold *P*<0.005, cluster-wise *P*<0.05) (Data S4, Table S11 and Figure S3). Cortical thickness significantly mediated the relation between Framingham and visuospatial problem solving, processing speed, flexibility, and memory after controlling for education and monthly incomes. In visuospatial problem solving, the following regions were significantly mediating its relationship with Framingham: left postcentral gyrus, left pars triangularis, left insula, left cuneus, left caudal anterior cingulate gyrus, left transverse temporal gyrus, and right supramarginal region. The relationship between processing speed and Framingham was significantly mediated by right cuneus, whereas flexibility

Table 1. Participant Characteristics

Age	
Age, y, mean±SD	53.58±6.96
Aged 40–54 y, n (%)	288 (54)
Aged ≥55 y, n (%)	243 (46)
Sex, n (%)	
Men	283 (53)
Women	248 (47)
Education, n (%)	
Primary	16 (3)
Secondary	125 (24)
Higher	390 (73)
Cognitive profile, mean±SD (percentile)	
Block design	12.12±3.06 (75)
Matrix reasoning	13.20±2.64 (84)
Direct digits	10.72±3.05 (63)
Indirect digits	11.16±2.62 (63)
Digit symbol	13.67±2.69 (91)
Letter–number sequencing	14.38±2.56 (91)
Cancellation test	11.41±2.76 (63)
TMT-A	11.26±2.77 (63)
TMT-B	8.66±2.16 (37)
Corsi cubes	13.99±2.52 (91)
Fitness evaluation	
VO_2peak, mL/kg per min, mean±SD	24.9±7.18
40–54 y, VO_2peak, mL/kg per min, mean±SD	26.44±7.22
55 y and above VO_2peak, mL/kg per min, mean±SD	23.28±6.57
BMI, kg/m^2, mean±SD	25.40±4.01
IPAQ, METs, min/wk	2558.13±2486.57
Cardiovascular status	
Smoker, n (%)	58 (11)
Diabetes, n (%)	7 (1)
Hypertension, n (%)	40 (8)
Systolic blood pressure, mean±SD	124±16.13
Cholesterol, mg/dL, mean±SD	177.83±75.14
HDL, mm/dL, mean±SD	54.5±24.77
Framingham 5-y risk, %, mean±SD	8.45±6.76

Percentiles extracted from the Wechsler Adult Intelligence Scale Fourth Edition toolbox (Wechsler[63]). BMI indicates body mass index; HDL, high-density lipoprotein; IPAQ, International Physical Activity Questionnaire; METs, metabolic equivalent of task; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B; and VO_2peak, oxygen uptake during peak exercise.

Table 2. Associations Between VO_2peak and Cognitive Domains

	β	SE	*P* value	R^2
Whole population				
Memory	−2.070	1.158	0.074	0.181
Working memory	−1.885	1.117	0.092	0.009
Flexibility	−0.632	0.780	0.418	0.152
Processing speed	<0.001	<0.001	0.715	0.193
Visuospatial problem solving	1.167	1.031	0.258	0.208
40–54 y				
Memory	−1.475	1.336	0.270	0.186
Working memory	−2.229	1.542	0.149	0.007
Flexibility	0.211	0.891	0.813	0.115
Processing speed	−1.035	1.374	0.452	0.164
Visuospatial problem solving	−0.709	1.347	0.598	0.129
55–65 y				
Memory	−3.231	1.971	0.102	0.102
Working memory	−1.284	1.697	0.450	−0.025
Flexibility	−0.667	1.370	0.626	0.094
Processing speed	2.053	1.844	0.267	0.132
Visuospatial problem solving	3.165	1.604	0.049*	0.160

All models are controlling for age, biological sex, body mass index, waist perimeter, socioeconomic status, and education as covariates. R^2 values are adjusted for all predictors. VO_2peak indicates oxygen uptake during peak exercise.
*Survives false discover rate corrections.

had different gyri that mediated its relationship with Framingham, in particular, left postcentral gyrus, left insula, left caudal anterior cingulate gyrus, left transverse temporal gyrus, right inferior parietal gyrus, right cuneus, right supramarginal region, and right superior frontal gyrus. Lastly, left triangularis and left and right cuneus significantly mediated the relationship between Framingham and memory (Figure 4, Data S4, Table S12A through S12D).

DISCUSSION

In the present study, we demonstrate that some of the well-established relationships between determinants of cardiovascular health and brain health that exist in older age are already present in late middle age. In our sample of healthy middle-aged adults, CRF and CVR, 2 independent clinical predictors of cardiovascular health, had distinct associations with neuropsychological metrics of cognitive brain health. CRF had domain-specific associations with cognitive abilities highly reliant on the frontal lobe, but only in individuals aged ≥55 years. In contrast, CVR had domain-general associations with various cognitive abilities within the whole sample. Importantly, mediation analyses strengthened our findings by revealing that the relationships between each predictor and cognition were driven by distinct patterns of cortical thickness. Cortical thickness in frontal regions mediated the relationship between CRF and visuospatial problem solving, whereas cortical thickness in a disperse network spanning multiple cortical regions across both hemispheres mediated the relationship between CVR and multiple domains of cognition.

We found associations between CRF and frontal-loading cognitive abilities (visuospatial reasoning) only in those aged ≥55 years. These results are supported by earlier work in older adults[6,64,65] and more recent work in middle-aged adults.[66] We extend those previous results in 2 important ways. First, although regional specificity of high CRF to the frontal lobe in older adults has been reported,[67–71] the mediating effect of cortical thickness in frontal regions on the relationship between CRF and cognition in midlife is novel, extending previous reports of a similar mediating effect in older adults.[71] Frontal regions are particularly susceptible to age-related cortical thinning,[72] and critical for visuospatial[73] problem solving and executive abilities.[74] High CRF has been shown to decrease small-vessel ischemic disease, which often preferentially affects the frontal/subcortical region of the brain,[75] providing a possible explanation for the reported regional specificity. Furthermore, white matter tracts have been implicated as an indirect path between CRF and better performance of frontal cognitive abilities.[76] Future planned studies will also examine the integrity of white matter tracts in this population.

Second, the age-specific associations between CRF and cognitive abilities can be explained in several ways. It is possible that our neuropsychological test

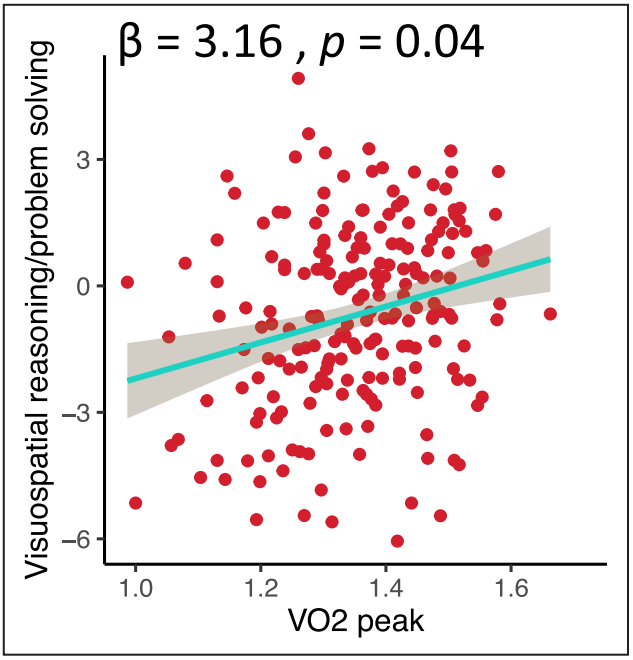

Figure 2. Significant positive relationship between VO_2peak (oxygen uptake during peak exercise) and visuospatial reasoning and problem-solving abilities in the older middle-aged group (aged 55–65 years) after controlling for age and biological sex.
Survives false discovery rate multiple comparison correction (Table 2).

battery may have been insufficiently sensitive for the younger subgroup (aged 40–54 years), and a ceiling effect may have masked potential associations between CRF and cognition. Conversely, and perhaps more likely, the relationship between CRF and neurocognitive function may be stronger in late middle age, when measurable age-related change in neurocognitive performance is more likely to be seen. Our sample of healthy adults scored in the higher percentiles for performance on these cognitive tasks (Table 1). One implication of our findings is the existence of a period from early to late middle age when it becomes particularly critical to maintain CRF to optimize cognitive brain health as we age. Longitudinal studies are needed to explore this possibility further. One potential interpretation for this finding could reflect the growing evidence that variations in brain structure and function precede the onset of behavioral symptoms of cognitive decline by years,[77–79] further strengthening the importance of engaging in modifiable lifestyle behaviors relevant for the promotion and maintenance of brain health in early midlife.

Given our analysis is cross-sectional, we can only speculate about the directionality of these results. Based on our analyses alone, in addition to our interpretations herein, it is just as plausible that higher cognitive resources lead to higher levels of fitness. Although numerous interventional studies have demonstrated that aerobic fitness training can improve cognition,[80,81] other modes of exercise have also been found to positively influence cognition.[13] Furthermore, longitudinal studies have suggested that cognitive resources themselves[82] are predictive of engagement in moderate-intensity physical exercise beyond the age of 50 years (a key modifier of CRF).[83] In addition, in a large longitudinal study, engagement in moderate physical exercise began to decline starting some 8 to 12 years before dementia diagnosis, and in those who did not have an eventual dementia diagnosis, total physical activity continued to increase through older age.[84] As previously mentioned, physical activity is one of many factors found to improve CRF.[85] Taken together, the relationship between CRF and cognition may ultimately be bidirectional, and because we cannot delineate this directionality, the result that these relationships exist in midlife in healthy adults is itself important to know for targeting through longitudinal studies beginning in midlife or earlier.

In contrast to the domain-specific associations with CRF, we found that CVR was associated with performance in many cognitive abilities, including visuospatial reasoning, but also cognitive flexibility, processing speed, and memory. Similar findings have been widely reported both in older adults[86–92] and in middle-aged adults.[7,93–97] We build on these findings by demonstrating that cortical thickness in disperse cortical regions across bihemispheric frontal, cuneus, parietal, temporal, and cingulate areas mediated the relationship between low CVR and better cognitive performance. The overlap between the clusters identified herein and cortical areas considered to be particularly sensitive to the effects of

Table 3. Associations Between Framingham and Cognitive Domains

	β	SE	*P* value	R^2
Memory	−0.120	0.016	<0.001*	0.149
Working memory	−0.010	0.015	0.502	−0.0003
Flexibility	−0.054	0.011	<0.001*	0.094
Processing speed	−0.115	0.016	<0.001*	0.120
Visuospatial problem solving	−0.046	0.015	0.002*	0.072

All models are controlling for socioeconomic status and education as covariates. R^2 values are adjusted for all predictors.
*Survives false discovery rate corrections.

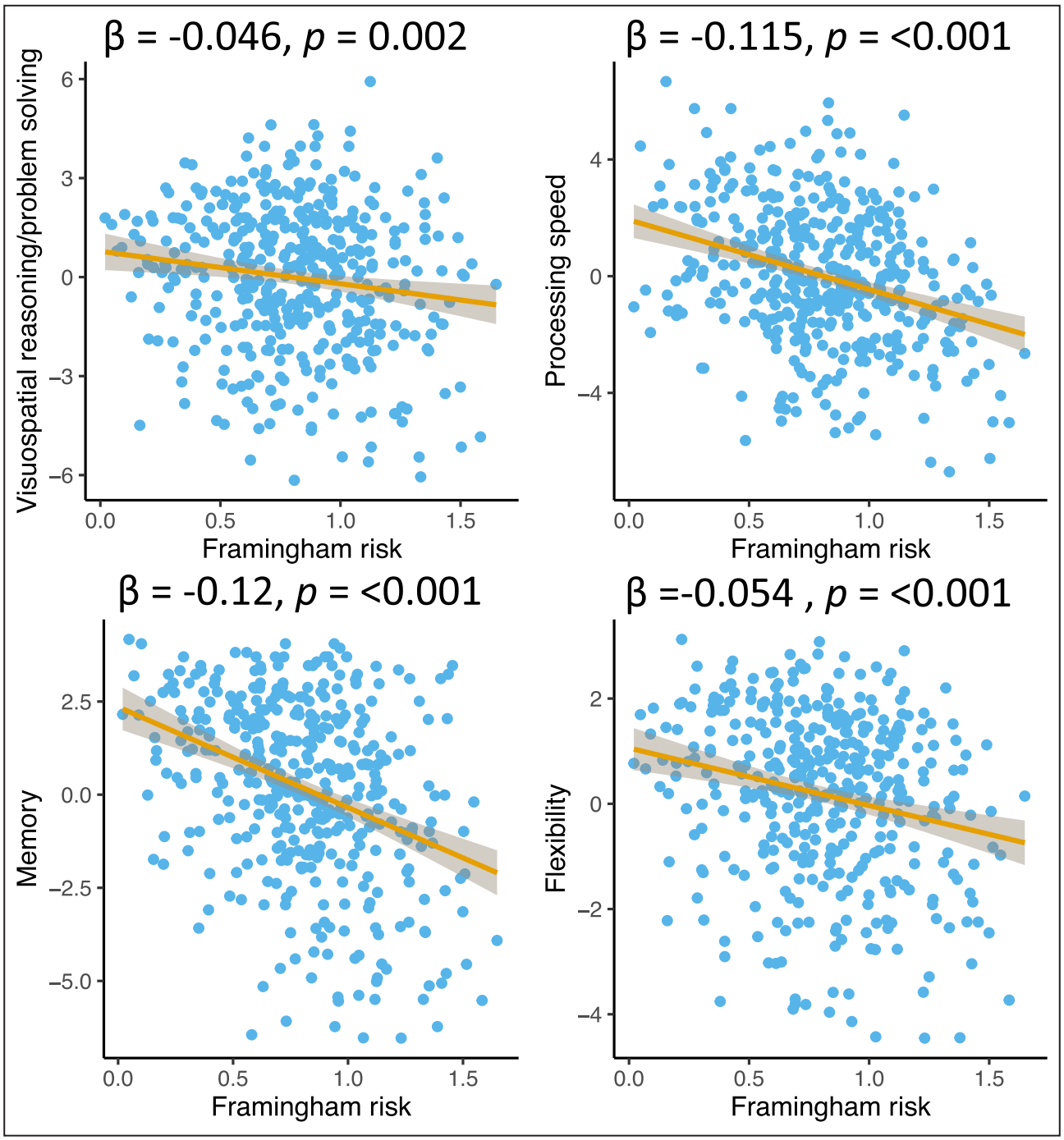

Figure 3. Significant negative relationships between cardiovascular risk (Framingham 5-year risk score) and multiple cognitive domains including flexibility, visuospatial problem-solving abilities, processing speed, and memory, after controlling for education (total number of years) and monthly incomes.
All models survive false discovery rate multiple comparison corrections (Table 3).

early cognitive impairment and Alzheimer's dementia pathology (ie, the inferior and anterior temporal lobe, inferior and superior temporal lobe, and posterior cingulate cortex),[98] supports existing evidence that cardiovascular risk factors are also cognitive risk factors.[21–24]

The region-general pattern of cortical thickness implicated in the relationship between CVR and cognition could be explained by the fact that CVR is mostly associated with small lesions in cerebral white matter that exhibit a more disperse representation over striatal, cortico–cortical, and cortical–subcortical pathways.[90] As mentioned, future studies will additionally assess the integrity of white matter tracts. Importantly, it is noteworthy that management of CVR involves not one but many healthy

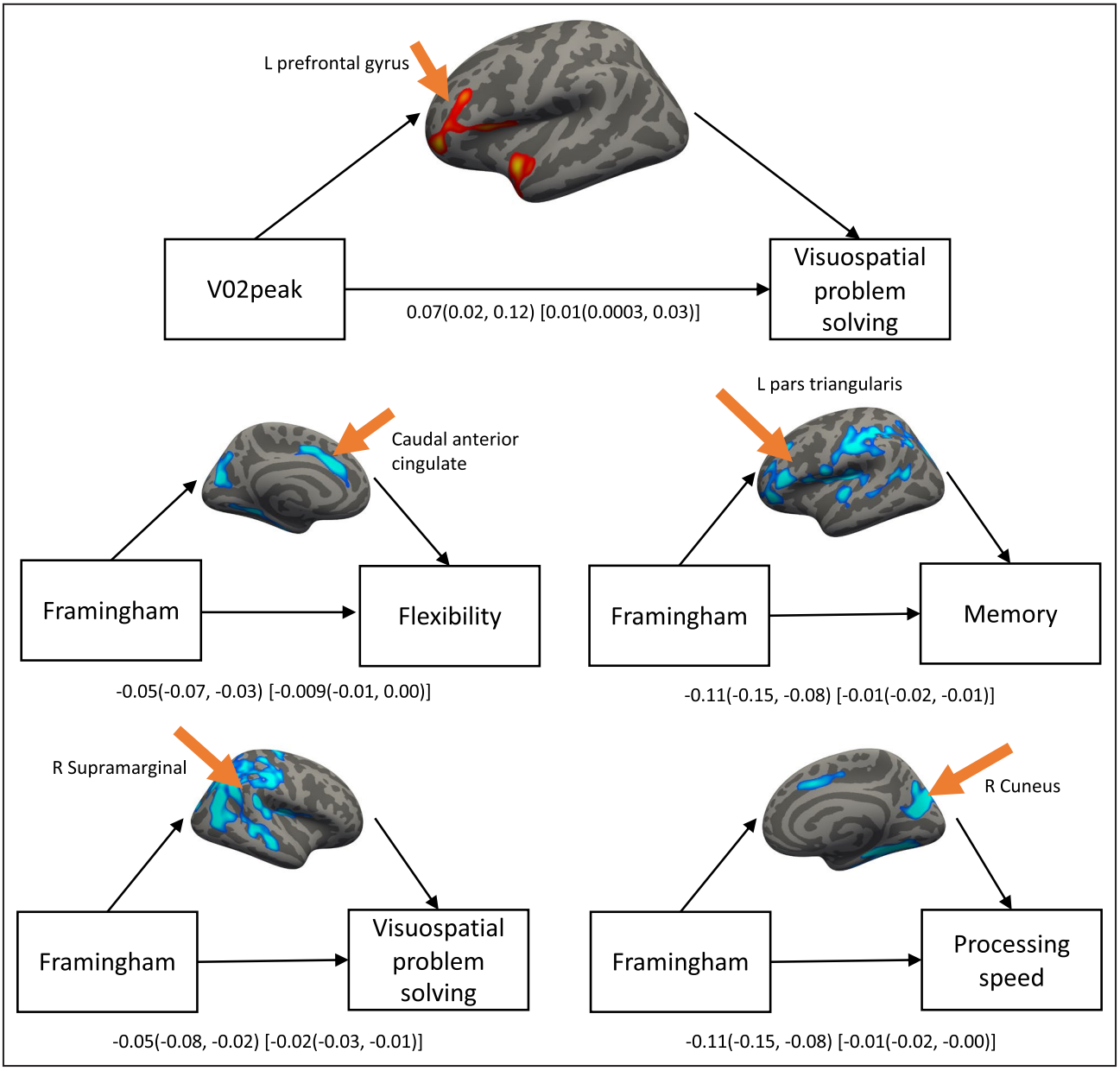

Figure 4. Cortical thickness in various regions mediated relationships between our predictors (VO_2peak and Framingham) and cognitive domains.
The relationship between each predictor and significant cortical thickness clusters (X [predictor variable] on M [mediator]) are found in Tables S7 through S9 along with full mediation model results (Table S10). Orange arrows depict the exact cluster, which mediates the relationship between X (predictor) and Y (cognitive domain outcome). The mediated effect is calculated as the difference between the estimates from the total and direct effects (see Tables S10 and S12A through S12D) which correspond to the reduction in the independent variable (X) effect on the dependent variable (Y) when adjusted for the mediator (M). The total effect (X on Y) is seen under the horizontal arrow representing the β coefficient followed by the 95% CIs in parentheses. The average causal mediation effect (X [predictor variable] on Y [outcome variable] including M [mediator]) is seen between square brackets following the direct effect. In the case of VO_2peak (oxygen uptake during peak exercise) on visuospatial problem solving (top), of the estimated total effect (0.07, note this is the unstandardized β coefficient), an estimated 0.01 is because of the mediator (cortical thickness in the left prefrontal gyrus).

behaviors (avoiding smoking, weight management, and healthy eating habits, to name a few), and we found this collective effort to be manifested by diffuse patterns of brain structure that likely support the wide range of cognitive abilities that were associated with CVR.

One important point that distinguishes our results from previous studies is that our sample was particularly healthy from a heart-health perspective. For instance, our sample had a relatively high group average in CRF (24.9±7.18 mL/kg per minute) (see age

and gender norms for the American population[99]) and a low group average for CVR (estimated to be ≈8% risk of a future cardiovascular event in 5 years). The fact that in this overall healthy sample, individual variations in CRF and CVR were still associated with cognitive behavior, and brain structure demonstrates that these established biomarkers of heart health in older adults may also be sufficiently sensitive for better understanding cognitive trajectories in early and late middle age. It is pertinent to highlight though that these same characteristics of this sample may affect generalizability to other populations. The BBHI sample is by design particularly young and healthy, because our data are cross-sectional samples of this longitudinal cohort study that aims to better understand and characterize neurobiological determinants of cognitive brain health from middle to late life. As such, this sample is exposed to known environmental factors reported to strongly contribute to cognitive brain health, such as adherence to a Mediterranean diet, engagement in physical activity, and leisure activities. It is also important to note that this is a mostly White sample, which is relevant because cardiovascular risk has differential associations with other racial and ethnic groups, particularly in Black and Latino individuals and other minority groups. As such, comprehensive and inclusive brain health strategies must also address this knowledge gap by examining such associations between determinants of cardiovascular health and cognitive brain health in other racial and ethnic groups in midlife.

Importantly, although cognitive brain health is a top health-related priority for people when they reach older age,[100] our findings highlight the relevance of creating a cognitive brain health plan in middle age. Given growing evidence demonstrating changes in the brain related to the onset of neurodegenerative disorders begin some 10 to 20 years before the onset of symptoms,[77–79] it is critical that strategies to mitigate age-related cognitive decline and promote cognitive brain health need to be introduced decades earlier in midlife. CRF and CVR are both modifiable factors, and thus our results could potentially suggest that by adopting lifestyle changes that promote heart health in middle age, it may be possible to actively steer the course of one's cognitive trajectory in later life. Our results (Data S5) also reproduce the ubiquitous association between greater CRF and greater time practicing physical activity (Figure S4). Thus, engagement in a physically active lifestyle is a potential strategy (among many, including diet, sleep, and other cognitively stimulating activities), that are likely to have a positive effect on cognitive brain health even in midlife. Albeit these conclusions need to be supported by longitudinal and interventional studies.

Although our results are complimentary to several previous and large population studies investigating associations between cardiovascular outcomes and cognitive brain health, our study has unique strengths. We add to previous research by examining not just 1 but 2 independent predictors (CRF, CVR), and by using a detailed and comprehensive neuropsychological assessment in over 500 healthy middle-aged adults free from clinically detectable cognitive deficits. Finally, given that the relationship between cardiovascular health and cognition is likely to be underpinned by brain structure, we also advance previous studies by using neuroimaging and analytical methods to demonstrate the mediating effect of brain structure on the relationships between CRF/CVR and cognition.

There are also limitations to our study. Because of the cross-sectional nature of our results, it was not possible to make any kind of inference about casual relationships. In addition, the normalization of VO_2peak to total body mass (referred to as simple ratio standard) can produce confounding results because of individual differences in adiposity levels.[48] We aimed to minimize this source of bias by including waist circumference as a covariate in all analyses. Furthermore, we replicated our results using allometric scaling of VO_2peak to ensure that scaling to total body mass did not confound the associations with cognition.[48,49] Future studies are encouraged to measure adiposity levels and normalize VO_2peak to fat-free mass. Considerations about biological sex interactions are critical in this work given reported differences in CRF,[101–103] CVR,[104] and trajectories of cognitive performance[105] between men and women. We will address biological sex interactions in a future planned study. Finally, we did not assess other potential factors that influence the relationships seen such as diet, physical activity levels, and motor skills.

Taken together, our findings show that even in younger and healthy middle-aged adults with relatively high CRF and low CVR, relationships between these modifiable factors that may contribute to cognitive/brain reserve and cognition exist. Furthermore, we shed light on a potential mechanistic pathway (cortical thickness) that may contribute to this relationship. The implications of our study lie within the potential importance of engaging in modifiable lifestyle behaviors that can promote heart health, early in midlife, long before the onset of measurable cognitive decline, which can be assessed in future longitudinal and interventional study designs.

ARTICLE INFORMATION

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Disclosures

Dr Pascual-Leone is a cofounder of Linus Health and TI Solutions AG; serves on the scientific advisory boards for Starlab Neuroscience, Neuroelectrics, Magstim Inc., and MedRhythms; and is listed as an inventor on several issued and pending patents on the real-time integration of noninvasive brain stimulation with electroencephalography and magnetic resonance imaging. The remaining authors have no disclosures to report.

Supplementary Material

Data S1–S5
Tables S1–S12
Figures S1–S4
References [108–110]

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Supplemental Material

Data S1. CRF allometric scaling models.

VO_2 peak was allometrically scaled using the procedure described by Vanderburgh et al[49,108]and seen in multiple CRF papers.[48,109]Firstly, VO_2 peak and body weight were log-transformed. A log-linear regression model was constructed using log (VO_2 peak) as the dependent and log (body weight) as independent variables. The interaction effect of biological sex was tested and found to significantly modulate the association between body mass and VO_2 peak, justifying the need for biological sex specific exponent. For that reason, regressions were performed separately for men and women to ensure the models were appropriate. Homoscedasticity was assessed by plotting the standardized residuals against the standardized predicted value. The resulting beta coefficients were used as the allometric exponents. Thus, VO_2 peak can then be allometrically scaled using the following equation: [109]

$$\text{allometrically scaled peak } VO_2 = \frac{\text{unscaled peak } VO_2}{\text{body mass}^{\text{exponent}}}$$

In addition, Pearson correlation analysis was used to examine the association of the scaled VO_2 peak with non-scaled VO_2 peak to verify the effectiveness of the allometric scaling approach for controlling for body size within the sample.

There was a very strong correlation between VO_2 peak and allometric VO_2 ($r = .92$, $p < 0.001$), suggesting that total body mass did not strongly affect our VO_2 peak measure and therefore, the results have remained practically stable.

CRF models has been replicated using the new VO_2 scaled value and the results are seen on Table S1, S2 and S3.

Data S2. Cardiovascular risk as measured by the Catalan-adjusted Framingham risk score (REGICOR).

To ensure our results were valid when adjusted for the Catalan population, we repeated our analyses with the REGICOR risk score[53]. The REGICOR (Registre Gironí del Cor) function is an adaptation of the Framingham function to the incidence of ischemic heart disease and prevalence of local risk factors taking into account the different epidemiological characteristics of Spanish population. The Framingham-based REGICOR CV risk function provides a good prediction of the incidence of the coronary events of the general population of a region in the northwest of Spain and having a high long-term follow-up rate[53].

We found similar results both for the cognitive analyses and the cortical thickness analysis.

Data S3. Individual results for the cortical thickness analyses with the VO_2 peak groups and mediation analyses.

We run these models to illustrate the relationship between each significant cluster and VO_2 peak. Significant correlations were seen between VO2 peak and left rostral middle frontal gyrus (r mean=0.118). The older middle age group (55 and above) showed that left rostral middle frontal gyrus (r mean= 0.172) and left superior temporal gyrus (r mean= 0.169) were positively associated to VO_2 peak.

The results also shown that cortical thickness significantly mediated the relationship between CRF 55 and above years old group and visuo-spatial problem solving, after controlling for age, biological sex, monthly incomes, education, waist perimeter and body mass index.

Data S4. Individual plots and table for the cortical thickness analyses with the cardiovascular risk (Framingham) score and mediation analyses.

We run these models to illustrate the relationship between each significant cluster and cardiovascular risk (Framingham score). Distributed clusters across multiple cortical regions were associated with cardiovascular risk (Framingham 5-year risk score). Those specific clusters were left post central (r mean= -0.170), left pars triangularis (r mean= -0.170), left insula (r mean= -0.170), left cuneus gyrus (r mean= -0.172), left lingual (r mean= -0.164), left caudal anterior cingulate gyrus (r mean= -0.184), left superior parietal gyrus (r mean= -0.158), left inferior parietal gyrus (r mean= -0.160), left transverse temporal gyrus (r mean= -0.169). left rostral middle frontal (r mean=-0.161) and left precentral gyrus (r mean= -0.170). On the right hemisphere, the correlations were in right inferior parietal gyrus (r mean= -0.176), para hippocampal region (r mean= -0.184), right cuneus (r mean= -0.192), right supramarginal gyrus (r mean= -0.175), right precentral gyrus (r mean= -0.165), right lateral occipital gyrus (r mean= -0.160), and right superior frontal gyrus (r mean= -0.163).

The results also shown that cortical thickness significantly mediated the relation between CVH and visuo-spatial problem solving, processing speed, flexibility, and memory, after controlling for education and monthly incomes.

Data S5. Self-reported physical activity and its association with cardiorespiratory fitness.

Self-reported physical activity was assessed using the International Physical Activity Questionnaire (IPAQ), validated for the Spanish/Catalan population [50,110]. Data collected from the self-administered IPAQ surveys were summed within each physical activity domain (walking, moderate-intensity and vigorous-intensity activities) to estimate the total metabolic equivalent of task (MET) in minutes/week spent performing physical activity related to occupational, transportation, household, and leisure activities. The questionnaire was scored and analysed using established methods, available on the IPAQ website (www.ipaq.ki.se). Here, data collected with the IPAQ have been reported as a continuous measure. Total scores have been calculated for walking, moderate-intensity activities, and vigorous-intensity activities, for each domain (work, transport, domestic and garden, and leisure) and for overall total physical activity MET-minutes/week score, calculated as: Total physical activity MET-minutes/week = sum of Total (Walking + Moderate + Vigorous) MET-minutes/week scores.

Engagement in physical activity as measured by the total number of METs-min/week including ‘walking’, ‘moderate activity’ and ‘vigorous activity’ explained 46% of the variance in VO_2 peak in our cohort ($\beta = 3.61$, $SE = 0.71$, $p = <.001$, $R^2=0.46$).

Table S1. Associations between CRF whole group allometric scaling values and cognitive domains.

	β	SE	P	R2
Memory	-0.007	0.003	0.023	0.115
Working memory	-0.002	0.002	0.387	0.006
Flexibility	-0.001	0.002	0.487	0.142
Processing speed	-0.0006	0.003	0.839	0.163
Visuo-spatial problem solving	0.005	0.002	0.046	0.198

All CRF allometric scaled models are controlling for age, education and socioeconomic status as a covariate. R2 are adjusted for all predictors.

Table S2. Associations between CRF_40_55 group allometric scaling values and cognitive domains.

	β	SE	P	R2
Memory	-0.007	0.003	0.025	0.115
Working memory	-0.001	0.003	0.062	-0.002
Flexibility	0.0008	0.002	0.704	0.106
Processing speed	-0.006	0.003	0.232	0.103
Visuo-spatial problem solving	0.001	0.003	0.731	0.083

All CRF allometric scaled models are controlling for age, education and socioeconomic status as a covariate. R2 are adjusted for all predictors.

Table S3. Associations between CRF_55 and above group allometric scaling values and cognitive domains

	β	SE	P	R2
Memory	-0.007	0.003	0.022	0.115
Working memory	-0.002	0.004	0.539	0.006
Flexibility	-0.001	0.003	0.706	0.142
Processing speed	0.005	0.005	0.330	0.117

Visuo-spatial problem solving	0.011	0.004	0.007**	0.169

All CRF allometric scaled models are controlling for age, education and socioeconomic status as a covariate. R2 are adjusted for all predictors.

Table S4. Associations between Regicor and cognitive domains.

	β	SE	*P*	R^2
Memory	-2.587	0.392	<0.001	0.128
Working memory	-0.558	0.368	0.130	0.004
Flexibility	-1.105	0.269	<0.001	0.081
Processing speed	-2.331	0.394	<0.001	0.091
Visuo-spatial problem solving	-1.253	0.365	0.0006	0.079

All models are controlling for monthly incomes and education as covariates. R^2 are adjusted for all predictors. *survives false discovery rate (FDR) corrections

Table S5. Regicor Standardized beta coefficients.

	β	*P*
Memory	-0.303	<0.001
Working memory	-0.074	0.130
Flexibility	-0.193	<0.001
Processing speed	-0.274	<0.001
Visuo-spatial problem solving	-0.160	0.0006

All models are controlling for age and education as covariates. R^2 are adjusted for all predictors. *survives FDR corrections

Table S6. Associations between Regicor and anatomical regions of cortical thickness.

Cluster	Hemisphere	Anatomical ROI	Size
1	Left	Postcentral	2525.44
2	Left	Insula	2343.16
3	Left	Pars triangularis	1995.18
4	Left	Superior frontal	1103.54

5	Left	Cuneus	1051.47
6	Left	Inferior parietal	617.95
7	Left	Insula	458.83
8	Left	Superior parietal	436.36
9	Left	Middle temporal	358.97
1	Right	Inferior parietal	9013.89
2	Right	Precuneus	1799.52
3	Right	Superior temporal	1708.11
4	Right	Para hippocampal	1537.87
5	Right	Lateral occipital	935.62
6	Right	Superior frontal	491.33
7	Right	Precentral	401.51

Table S7. Associations between VO_2 peak and anatomical regions of cortical thickness in the whole sample.

Cluster	Hemisphere	Anatomical ROI	Size
1	Left	Rostral middle frontal	1465.59

Table S8. Associations between VO_2 peak and anatomical regions of cortical thickness in the 40-54 years old group.

- No significant results.

Table S9. Associations between VO_2 peak and anatomical regions of cortical thickness in the 55 and above years old group.

Cluster	Hemisphere	Anatomical ROI	Size
1	Left	Rostral middle frontal	1634.39
2	Left	Superior temporal	1168.92

Outcomes	Total effect	ADE	ACME

Visuo-spatial problem solving	**Beta (95%CI)**	**Beta (95%CI)**	**Beta (95%CI)**
Left rostral middle frontal gyrus	0.07(0.02, 0.12)*	0.05(0.006, 0.11)*	0.01(0.0003, 0.03)*
Left superior temporal gyrus	0.07(0.02, 0.12)*	0.06(0.02, 0.11)*	0.007(-0.005, 0.02)

Table S10. Each model was adjusted for age, biological sex, monthly incomes, education, waist perimeter and body mass index. ADE = average direct effect; ACME = average causal mediation effect. Statistical significance at $p < 0.05$ and 95% CI not including 0.

Table S11. Associations between Framingham and anatomical regions of cortical thickness.

Cluster	Hemisphere	Anatomical ROI	Size
1	Left	Post central	3518.9
2	Left	Pars triangularis	1928.37
3	Left	Insula	1428.72
4	Left	Cuneus	1181.96
5	Left	Lingual	845.33
6	Left	Caudal anterior cingulate	833.6
7	Left	Superior parietal	589.08
8	Left	Inferior parietal	587.35
9	Left	Transverse temporal	509.91
10	Left	Rostral middle frontal	376.1
11	Left	Precentral	357.23
1	Right	Inferior parietal	9432.87
2	Right	Parahippocampal	1962.3
3	Right	Cuneus	1806.08
4	Right	Supramarginal	1367.08
5	Right	Precentral	568.03
6	Right	Lateral occipital	462.1
7	Right	Superior frontal	448.49

Outcomes	Total effect	ADE	ACME
	Beta (95%CI)	Beta (95%CI)	Beta (95%CI)
Visuospatial problem solving			
Left postcentral gyrus	-0.05(-0.08, -0.02)*	-0.03(-0.07, 0.00)*	-0.01(-0.02, 0.00)*
Left parstriangularis	-0.05(-0.08, -0.02)*	-0.03(-0.07, 0.00)*	-0.01(-0.02, 0.00)*
Left insula	-0.05(-0.08, -0.02)*	-0.03(-0.07, 0.00)	-0.01(-0.02, -0.01)*
Left cuneus	-0.05(-0.08, -0.02)*	-0.04(-0.07, -0.01)*	-0.01(-0.02, 0.00)*
Left lingual	-0.05(-0.08, -0.02)*	-0.04(-0.08, -0.02)*	-0.002(-0.01, 0.01)
Left caudal anterior cingulate gyrus	-0.05(-0.08, -0.02)*	-0.03(-0.07, 0.00)*	-0.01(-0.02, -0.01)*
Left superior parietal	-0.05(-0.08, -0.01)*	-0.04(-0.08, -0.01)*	-0.006(-0.01, 0.00)
Left inferior parietal	-0.05(-0.08, -0.02)*	-0.04(-0.08, -0.01)*	-0.005(-0.01, 0.01)
Left transverse temporal gyrus	-0.05(-0.08, -0.02)*	-0.04(-0.07, -0.01)*	-0.009(-0.01, 0.00)*
Left rostral middle frontal gyrus	-0.05(-0.08, -0.02)*	-0.04(-0.08, -0.01)*	-0.004(-0.01, 0.00)
Left precentral gyrus	-0.05(-0.08, -0.02)*	-0.04(-0.08, -0.01)*	-0.002(-0.01, 0.01)
Right inferior parietal gyrus	-0.05(-0.08, -0.02)*	-0.04(-0.08, -0.01)*	-0.009(-0.02, 0.00)*
Right parahippocampal region	-0.05(-0.08, -0.02)*	-0.05(-0.08, -0.02)*	-0.0001(-0.011, 0.01)
Right cuneus	-0.05(-0.08, -0.02)*	-0.04(-0.07, -0.01)*	-0.01(-0.02, 0.00)
Right supramarginal gyrus	-0.05(-0.08, -0.02)*	-0.03(-0.07, 0.00)*	-0.01(-0.02, -0.01)*
Right precentral gyrus	-0.05(-0.08, -0.02)*	-0.05(-0.08, -0.01)*	-0.0002(-0.008, 0.01)
Right lateral occipital gyrus	-0.05(-0.08, -0.02)*	-0.05(-0.08, -0.02)*	0.0008(-0.006, 0.01)
Right superior frontal gyrus	-0.05(-0.08, -0.02)*	-0.04(-0.08, -0.02)*	-0.001(-0.10, 0.01)

Table S12A. Each model was adjusted for monthly incomes and education. ADE = average direct effect; ACME = average causal mediation effect. Statistical significance at $p < 0.05$ and 95% CI not including 0.

Outcomes	Total effect	ADE	ACME
	Beta (95%CI)	**Beta (95%CI)**	**Beta (95%CI)**
Processing speed			
Left postcentral gyrus	-0.11(-0.14, -0.08)*	-0.10(-0.14, -0.08)*	-0.005(-0.18, 0.01)
Left parstriangularis	-0.11(-0.14, -0.08)*	-0.10(-0.14, -0.07)*	-0.008(-0.02, 0.00)
Left insula	-0.11(-0.14, -0.08)*	-0.10(-0.14, -0.08)*	-0.004(-0.01, 0.01)
Left cuneus	-0.11(-0.14, -0.08)*	-0.10(-0.14, -0.08)*	-0.003(-0.01, 0.00)
Left lingual	-0.11(-0.14, -0.08)*	-0.11(-0.14, -0.09)*	0.003(-0.005, 0.01)
Left caudal anterior cingulate gyrus	-0.11(-0.14, -0.08)*	-0.10(-0.14, -0.08)*	-0.005(-0.01, 0.00)
Left superior parietal gyrus	-0.11(-0.14, -0.08)*	-0.10(-0.14, -0.08)*	-0.004(-0.01, 0.00)
Left inferior parietal gyrus	-0.11(-0.14, -0.08)*	-0.11(-0.14, -0.08)*	-0.001(-0.01, 0.01)
Left transverse temporal gyrus	-0.11(-0.14, -0.08)*	-0.10(-0.14, -0.07)*	-0.006(-0.01, 0.00)
Left rostral middle frontal gyrus	-0.11(-0.14, -0.08)*	-0.11(-0.14, -0.08)*	-0.001(-0.009, 0.01)
Left precentral gyrus	-0.11(-0.14, -0.08)*	-0.11(-0.15, -0.08)*	0.0009(-0.006, 0.01)
Right inferior parietal gyrus	-0.11(-0.14, -0.08)*	-0.10(-0.13, -0.07)*	-0.01(-0.02, 0.00)
Right parahippocampal region	-0.11(-0.14, -0.08)*	-0.10(-0.14, -0.08)*	-0.005(-0.01, 0.01)
Right cuneus	-0.11(-0.14, -0.08)*	-0.10(-0.13, -0.07)*	-0.01(-0.02, 0.00)*
Right supramarginal gyrus	-0.11(-0.14, -0.08)*	-0.10(-0.14, -0.08)*	-0.006(-0.01, 0.00)
Right precentral gyrus	-0.11(-0.14, -0.08)*	-0.11(-0.14, -0.08)*	-0.001(-0.009, 0.00)

Right lateral occipital gyrus	-0.11(-0.14, -0.08)*	-0.11(-0.14, -0.08)*	0.002(-0.007, 0.01)
Right superior frontal gyrus	-0.11(-0.14, -0.08)*	-0.11(-0.14, -0.08)*	-0.001(-0.01, 0.01)

Table S12B. Each model was adjusted for monthly incomes and education. ADE = average direct effect; ACME = average causal mediation effect. Statistical significance at $p < 0.05$ and 95% CI not including 0.

Outcomes	**Total effect**	**ADE**	**ACME**
	Beta (95%CI)	**Beta (95%CI)**	**Beta (95%CI)**
Flexibility			
Left postcentral gyrus	-0.05(-0.07, -0.03)*	-0.03(-0.06, -0.01)*	-0.01(-0.02, 0.00)*
Left pars triangularis	-0.05(-0.07, -0.03)*	-0.04(-0.07, -0.02)*	-0.007(-0.01, 0.00)
Left insula	-0.05(-0.07, -0.03)*	-0.04(-0.06, -0.02)*	-0.007(-0.01, 0.00)*
Left cuneus	-0.05(-0.07, -0.03)*	-0.04(-0.07, -0.02)*	-0.005(-0.01, 0.00)
Left lingual	-0.05(-0.07, -0.03)*	-0.05(-0.07, -0.03)*	-0.001(-0.008, 0.01)
Left caudal anterior cingulate gyrus	-0.05(-0.07, -0.03)*	-0.04(-0.06, -0.02)*	-0.009(-0.01, 0.00)*
Left superior parietal gyrus	-0.05(-0.07, -0.03)*	-0.05(-0.07, -0.03)*	-0.001(-0.009, 0.00)
Left inferior aprietal gyrus	-0.05(-0.07, -0.03)*	-0.05(-0.07, -0.02)*	-0.001(-0.009, 0.01)
Left transverse temporal gyrus	-0.05(-0.07, -0.03)*	-0.04(-0.06, -0.02)*	-0.008(-0.01, 0.00)*
Left rostral middle frontal gyrus	-0.05(-0.07, -0.03)*	-0.04(-0.07, -0.02)*	-0.003(-0.009, 0.00)
Left precentral gyrus	-0.05(-0.07, -0.03)*	-0.04(-0.07, -0.02)*	-0.002(-0.008, 0.00)
Right inferior parietal gyrus	-0.05(-0.07, -0.03)*	-0.03(-0.06, -0.01)*	-0.01(-0.02,0.00)*

Right parahippocampal region	-0.05(-0.07, -0.03)*	-0.04(-0.06, -0.02)*	-0.007(-0.01, 0.00)
Right cuneus	-0.05(-0.07, -0.03)*	-0.04(-0.06, -0.02)*	-0.009(-0.01, 0.00)*
Right supramarginal gyrus	-0.05(-0.07, -0.03)*	-0.04(-0.06, -0.01)*	-0.01(-0.02,0.00)*
Right precentral gyrus	-<0.001(-<0.001, -0.03)*	-<0.001(-<0.001, -0.03)*	-<0.001(-<0.001, -0.00)
Right lateral occipital gyrus	-0.05(-0.07, -0.03)*	-0.05(-0.07, -0.03)*	-0.0009(-0.00, 0.00)
Right superior frontal gyrus	-0.05(-0.07, -0.03)*	-0.03(-0.06, -0.01)*	-0.01(-0.02, 0.00)

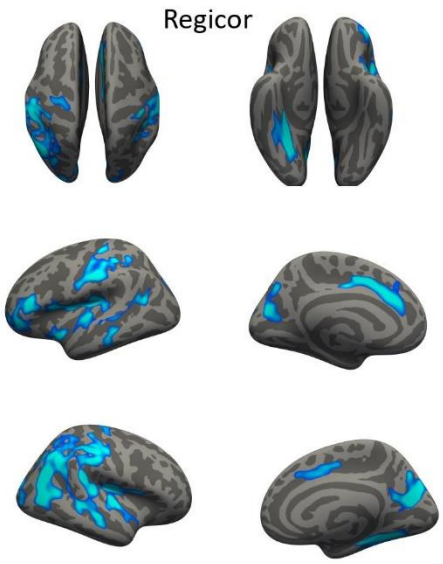
Table S12C. Each model was adjusted for monthly incomes and education. ADE = average direct effect; ACME = average causal mediation effect. Statistical significance at $p < 0.05$ and 95% CI not including 0.

Outcomes	**Total effect**	**ADE**	**ACME**
	Beta (95%CI)	**Beta (95%CI)**	**Beta (95%CI)**
Memory			
Left postcentral gyrus	-0.11(-0.15, -0.08)*	-0.10(-0.14, -0.06)*	-0.01(-0.02, 0.00)
Left pars triangularis	-0.11(-0.15, -0.08)*	-0.10(-0.13, -0.06)*	-0.01(-0.02, -0.01)*
Left insula	-0.11(-0.15, -0.08)*	-0.10(-0.14, -0.07)*	-0.008(-0.01, 0.00)
Left cuneus	-0.11(-0.15, -0.08)*	-0.10(-0.14, -0.07)*	-0.009(-0.02, 0.00)*
Left lingual	-0.11(-0.15, -0.08)*	-0.11(-0.14, -0.08)*	-0.002(-0.01, 0.01)
Left caudal anterior cingulate gyrus	-0.11(-0.15, -0.08)*	-0.11(-0.14, -0.07)*	-0.006(-0.01, 0.00)
Left superior parietal gyrus	-0.11(-0.15, -0.08)*	-0.12(-0.15, -0.08)*	-0.004(-0.00, 0.01)
Left inferior parietal gyrus	-0.11(-0.15, -0.08)*	-0.11(-0.15, -0.07)*	-0.001(-0.01, 0.01)

Left transverse temporal gyrus	-0.11(-0.15, -0.08)*	-0.11(-0.14, -0.07)*	-0.004(-0.01, 0.00)
Left rostral middle frontal gyrus	-0.11(-0.15, -0.08)*	-0.11(-0.14, -0.07)*	-0.004(-0.01, 0.00)
Left precentral gyrus	-0.11(-0.15, -0.08)*	-0.11(-0.15, -0.08)*	-0.0007(-0.00, 0.01)
Right inferior parietal gyrus	-0.11(-0.15, -0.08)*	-0.10(-0.14, -0.06)*	-0.01(-0.02, 0.00)
Right parahippocampal region	-0.11(-0.15, -0.08)*	-0.11(-0.14, -0.07)*	-0.006(-0.01, 0.00)
Right cuneus	-0.11(-0.15, -0.08)*	-0.10(-0.13, -0.06)*	-0.01(-0.02, 0.00)*
Right supramarginal gyrus	-0.11(-0.15, -0.08)*	-0.11(-0.14, -0.07)*	-0.006(-0.01, 0.00)
Right precentral gyrus	-0.11(-0.15, -0.08)*	-0.11(-0.15, -0.08)*	-0.001(-0.01, 0.00)
Right lateral occipital gyrus	-0.11(-0.15, -0.08)*	-0.11(-0.15, -0.08)*	-0.0007(-0.00, 0.01)
Right superior frontal gyrus	-0.11(-0.15, -0.08)*	-0.11(-0.15, -0.08)*	-0.0007(-0.00, 0.01)

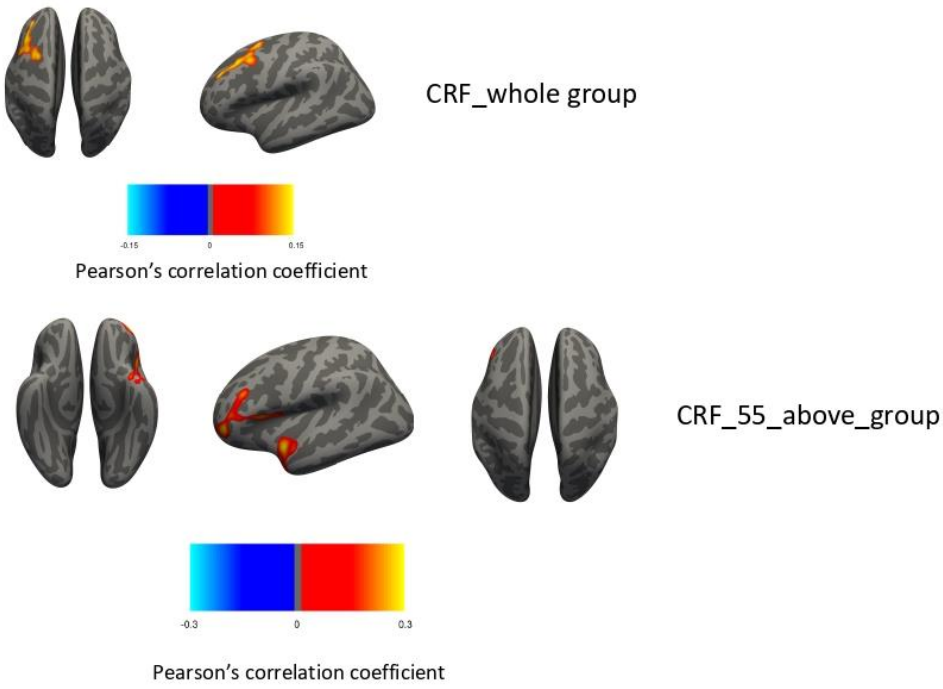
Table S12D. Each model was adjusted for monthly incomes and education. ADE = average direct effect; ACME = average causal mediation effect. Statistical significance at $p < 0.05$ and 95% CI not including 0.

Figure S1. REGICOR and cortical thickness.



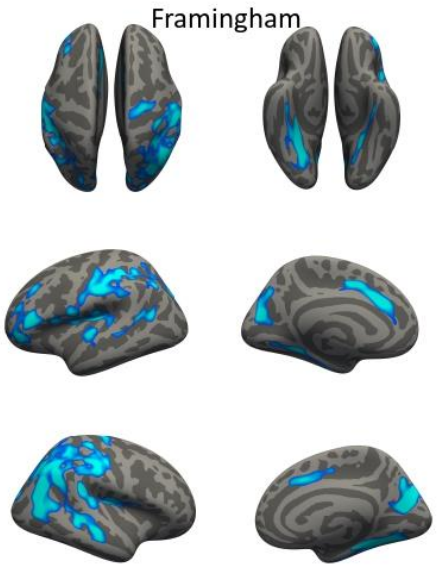
When using the Catalan-population adjusted Framingham risk score, we see similar patterns of associations with cortical thickness compared to those when using Framingham.

Figure S2. CRF and cortical thickness.



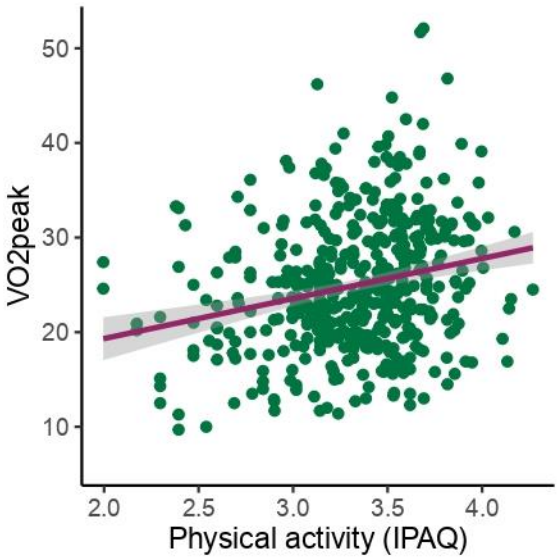
(A). Significant correlations were seen between VO2 peak and left rostral middle frontal gyrus (r mean=0.118). **(B)** The older middle age group (55 and above) showed that left rostral middle frontal gyrus (r mean= 0.172) and left superior temporal gyrus (r mean= 0.169) were positively associated to VO_2 peak.

Figure S3. Framingham and cortical thickness.



All plots illustrating the relationship between each significant cluster and cardiovascular risk (Framingham score). Distributed clusters across multiple cortical regions were associated with cardiovascular risk (Framingham 5-year risk score). Those specific clusters were left post central (r mean= -0.170), left pars triangularis (r mean= -0.170), left insula (r mean= -0.170), left cuneus gyrus (r mean= -0.172), left lingual (r mean= -0.164), left caudal anterior cingulate gyrus (r mean= -0.184), left superior parietal gyrus (r mean= -0.158), left inferior parietal gyrus (r mean= -0.160), left transverse temporal gyrus (r mean= -0.169). left rostral middle frontal (r mean=-0.161) and left precentral gyrus (r mean= -0.170). On the right hemisphere, the correlations were in right inferior parietal gyrus (r mean= -0.176), para hippocampal region (r mean= -0.184), right cuneus (r mean= -0.192), right supramarginal gyrus (r mean= -0.175), right precentral gyrus (r mean= -0.165), right lateral occipital gyrus (r mean= -0.160), and right superior frontal gyrus (r mean= -0.163).

Figure S4. Physical activity and cardiorespiratory fitness.



A significant positive association between physical activity levels (total weekly MET [metabolic equivalent of task]) and $V0_2$ peak, controlling for age, biological sex, education, monthly incomes, BMI (body mass index), and waist was found.