

Washington University School of Medicine

Digital Commons@Becker

---

2020-Current year OA Pubs

Open Access Publications

---

8-1-2023

## Cardiovascular and metabolic health is associated with functional brain connectivity in middle-aged and older adults: Results from the Human Connectome Project-Aging study

Barnaly Rashid  
*Harvard University*

Matthew F Glasser  
*Washington University School of Medicine in St. Louis*

Thomas Nichols  
*University of Oxford*

David Van Essen  
*Washington University School of Medicine in St. Louis*

Meher R Juttukonda  
*Harvard University*

*See next page for additional authors*

Follow this and additional works at: [https://digitalcommons.wustl.edu/oa\\_4](https://digitalcommons.wustl.edu/oa_4)



Part of the [Medicine and Health Sciences Commons](#)

Please let us know how this document benefits you.

---

### Recommended Citation

Rashid, Barnaly; Glasser, Matthew F; Nichols, Thomas; Van Essen, David; Juttukonda, Meher R; Schwab, Nadine A; Greve, Douglas N; Yacoub, Essa; Lovely, Allison; Terpstra, Melissa; Harms, Michael P; Bookheimer, Susan Y; Ances, Beau M; Salat, David H; and Arnold, Steven E, "Cardiovascular and metabolic health is associated with functional brain connectivity in middle-aged and older adults: Results from the Human Connectome Project-Aging study." *NeuroImage*. 276, 120192 (2023).  
[https://digitalcommons.wustl.edu/oa\\_4/2408](https://digitalcommons.wustl.edu/oa_4/2408)

This Open Access Publication is brought to you for free and open access by the Open Access Publications at Digital Commons@Becker. It has been accepted for inclusion in 2020-Current year OA Pubs by an authorized administrator of Digital Commons@Becker. For more information, please contact [vanam@wustl.edu](mailto:vanam@wustl.edu).

---

## Authors

Barnaly Rashid, Matthew F Glasser, Thomas Nichols, David Van Essen, Meher R Juttukonda, Nadine A Schwab, Douglas N Greve, Essa Yacoub, Allison Lovely, Melissa Terpstra, Michael P Harms, Susan Y Bookheimer, Beau M Ances, David H Salat, and Steven E Arnold



# Cardiovascular and metabolic health is associated with functional brain connectivity in middle-aged and older adults: Results from the Human Connectome Project-Aging study

Barnaly Rashid<sup>a,b,\*</sup>, Matthew F. Glasser<sup>c</sup>, Thomas Nichols<sup>d</sup>, David Van Essen<sup>c</sup>, Meher R. Juttukonda<sup>a,b</sup>, Nadine A. Schwab<sup>a,b</sup>, Douglas N Greve<sup>a,b</sup>, Essa Yacoub<sup>e</sup>, Allison Lovely<sup>a,b</sup>, Melissa Terpstra<sup>f</sup>, Michael P. Harms<sup>g</sup>, Susan Y. Bookheimer<sup>h</sup>, Beau M. Ances<sup>c,g</sup>, David H. Salat<sup>a,b,\*</sup>, Steven E. Arnold<sup>a,b,\*</sup>

<sup>a</sup> Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, 149 13th St., Charlestown, MA 02129, United States

<sup>b</sup> Harvard Medical School, Boston, MA, United States

<sup>c</sup> Washington University School of Medicine, St. Louis, MO, United States

<sup>d</sup> University of Oxford, Oxford, United Kingdom

<sup>e</sup> Center for Magnetic Resonance Research, University of Minnesota, Minneapolis, MN, United States

<sup>f</sup> University of Minnesota, Minneapolis, MN, United States

<sup>g</sup> Washington University in St. Louis, St. Louis, MO, United States

<sup>h</sup> University of California, Los Angeles, Los Angeles, CA, United States

## ARTICLE INFO

### Keywords:

Resting-state fMRI  
Cardiovascular risk  
Functional connectivity  
Aging  
Alzheimer's disease

## ABSTRACT

Several cardiovascular and metabolic indicators, such as cholesterol and blood pressure have been associated with altered neural and cognitive health as well as increased risk of dementia and Alzheimer's disease in later life. In this cross-sectional study, we examined how an aggregate index of cardiovascular and metabolic risk factor measures was associated with correlation-based estimates of resting-state functional connectivity (FC) across a broad adult age-span (36–90+ years) from 930 volunteers in the Human Connectome Project Aging (HCP-A). Increased (i.e., worse) aggregate cardiometabolic scores were associated with reduced FC globally, with especially strong effects in insular, medial frontal, medial parietal, and superior temporal regions. Additionally, at the network-level, FC between core brain networks, such as default-mode and cingulo-opercular, as well as dorsal attention networks, showed strong effects of cardiometabolic risk. These findings highlight the lifespan impact of cardiovascular and metabolic health on whole-brain functional integrity and how these conditions may disrupt higher-order network integrity.

## 1. Introduction

Abnormalities in cardiovascular and metabolic (CVM) status in adulthood are associated with greater cognitive decline and risk for dementia due to Alzheimer's disease and related disorders (including cerebrovascular, Lewy body and frontotemporal dementia diseases) in later life (Chakrabarti et al., 2015; Duron and Hanon, 2008; Luchsinger and Mayeux, 2004; Sahathevan et al., 2012). Such CVM abnormalities, reflected in diverse physiological malfunctions such as dyslipidemia and insulin resistance, being overweight or obese, hypertension, and inflammation, commonly travel together, albeit to varying degrees among individuals. Because of their coincidence and interactions, it is useful to consider these abnormalities together. Various terms and definitions

for clusters of CVM factors have been described, e.g., metabolic syndrome, dysmetabolic syndrome, syndrome X and insulin resistance syndrome (Eckel et al., 2005; Groop and Orho-Melander, 2001; Rao, 2001; Reaven, 2004; Timar et al., 2000).

There are many gaps in knowledge about how these complex and interactive CVM factors contribute to cognitive decline and Alzheimer's disease and related disorders in later life. It is unknown whether CVM factors affect the brain only when parameters are clinically abnormal (e.g., hypertension or diabetes diagnosis as defined by clinical criteria) in later life when Alzheimer's disease and related disorders emerge or whether any atyp in subclinical CVM physiology might affect brain function over the lifespan. It is possible that CVM abnormalities in midlife lead to cumulative neural effects,

\* Corresponding authors.

E-mail addresses: [brashid@mgh.harvard.edu](mailto:brashid@mgh.harvard.edu) (B. Rashid), [dsalat@mgh.harvard.edu](mailto:dsalat@mgh.harvard.edu) (D.H. Salat), [searnold@mgh.harvard.edu](mailto:searnold@mgh.harvard.edu) (S.E. Arnold).

<https://doi.org/10.1016/j.neuroimage.2023.120192>.

Received 28 March 2023; Received in revised form 15 May 2023; Accepted 24 May 2023

Available online 27 May 2023.

1053-8119/© 2023 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

increasing vulnerability and accelerating cognitive decline in later life.

While the mechanisms linking CVM status to cognitive impairment and dementia in later life are not yet clear, their effects may be due to various factors. CVM-associated cerebrovascular disease may produce low level chronic ischemia and blood brain barrier dysfunction. Systemic and blood-borne lipid and oxidative biochemicals may promote protein misfolding of amyloid, tau and other Alzheimer's disease and related disorders' pathologies. High circulating levels of insulin or other diabetes-associated factors may induce a state of insulin resistance in the brain (Arnold et al., 2018) and CVM-associated immune dysregulation and "inflammaging" may affect the brain's ability to clear Alzheimer's disease and related disorders' pathologies and otherwise affect synaptic and neuronal survival and plasticity. For example, misfolded  $\alpha$ -synuclein protein (M Ashraf et al., 2014) pathologies via ischemia may have deleterious effects on the cerebrovascular neural systems subserving cognition, thus decreasing the reserve or resilience capacity of the brain to withstand various stresses to the system. Since these risk factors (RFs) rarely occur in isolation (Luchsinger et al., 2005), the combined effects of the RFs on aging and diseases should be fully examined. Studies have suggested that exposure to cardiometabolic RFs in mid-life and younger-old life further increases the risk for dementia in late-life (Malik et al., 2021; Whitmer et al., 2005), although minimal to no associations between RFs and dementia risk were reported in the oldest old population (i.e., 85+ years (Beydoun et al., 2008; Harrison et al., 2015)). Moreover, since dementia-related pathologies may begin to accumulate decades before the onset of clinical symptoms (Jack Jr et al., 2013), understanding how these cardiometabolic RFs impact brain integrity should aid in elucidating the underlying neurophysiology of cardiometabolic-related late-life dementia risk.

CVM factors have previously been associated with gray and white matter changes (Coutinho et al., 2017; Friedman et al., 2014; Leritz et al., 2011; Rao, 2001; Ryu et al., 2017; Salat et al., 2012; Williams et al., 2013). These studies additionally demonstrate that *sub-clinical* variation in CVM status (e.g., variation in blood pressure) is associated with cognitive changes in older adults. In other words, clinically defined 'risk' states (e.g., hypertension) are not necessary to see an impact on neural health. However, functional brain alterations associated with CVM status across the age-span are yet to be fully understood. In addition, while the relationship between isolated RFs and neural integrity have been previously examined (Kim and Feldman, 2015; Park et al., 2018), little is known about how the shared contribution of cumulative RFs disrupts the functional organization and temporal dependency (i.e., covariation or correlation between functional activations over time) across brain regions. A better understanding of the association between co-occurring CVM factors and functional brain integrity across the lifespan may inform early detection and intervention, particularly since many of these are modifiable (Blazer et al., 2015; Livingston et al., 2017; Qiu and Fratiglioni, 2015).

Here, we used cross-sectional functional magnetic resonance imaging across the adult lifespan in the Human Connectome Project in Aging (Bookheimer et al., 2019; Harms et al., 2018) (HCP-A) to elucidate the role of CVM factors on brain health, particularly cortical and sub-cortical brain functional connectivity (FC). We used a surface-based cortical parcellation (Glasser et al., 2016; Ji et al., 2019) developed with multimodal neuroimaging data in order to relate any effects to well-defined, functionally relevant regions. We aimed to answer two primary questions: 1) *How is CMV health associated with whole-brain functional connectivity?*; and 2) *How does cumulative CVM risk affect the network-level functional connectivity?*. To do so, we estimated the associations between CVM factors and whole-brain FC and further implemented a novel quantitative connectivity metric and visualization framework that highlights cumulative CVM-related disruption within each cortical area or subcortical structure relative to all other cortical areas or subcortical structures. We explored the 'strengthening' and 'weakening' associations of CVM factors. In this context, we refer to 'strengthening' and 'weakening'

**Table 1**  
Demographic information and participant characteristics.

	Participants (N = 930)
<b>Age</b>	Mean $\pm$ SD: 61.6 $\pm$ 16 Range: 36 - 90+ years Below 65 years: 59% 65+ years: 41%
<b>Sex</b>	Female: 55.6%
<b>Race</b>	Caucasian: 72.8% African American: 13.44% Asian: 6.34% More than one: 4.4% Native American: less than 1% Unknown or not reported: 2.8%
<b>Ethnicity</b>	Hispanic or Latino: 10.97% Not Hispanic or Latino: 87.74% Unknown or not reported: 1.29%

ening' in terms of how the CVM measures covary with the correlation value (e.g., increased metabolic risk is associated with a weakening of the correlation); however, this terminology is not used here as an index of functional integrity. Additionally, we explored CVM associations with between-network FC measures. We hypothesized that elevated CVM factors would be associated with overall dysregulated FC patterns, and that these weakening association patterns would be evident at the network-level.

## 2. Materials and methods

### 2.1. Participants

The Human Connectome Project in Aging (HCP-A) study has recruited over 1200 healthy adults aged 36 to 90+ years old across four acquisition sites using matched MRI scanning protocols as well as centralized data analysis pipelines (Bookheimer et al., 2019; Harms et al., 2018). All participants in the HCP-A study exhibited typical health for their age without stroke, clinical dementia, or other identified causes of cognitive decline. Of these 1200 healthy participants, the current study processed and analyzed all 930 individuals for whom their multi-modal neuroimaging data including resting fMRI neuroimaging was currently available and had passed quality control. The study was approved and monitored by the Institutional Review Board. All participants provided informed, written consent for this Institutional Review Board-approved study. After obtaining written consent, the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005) was administered, and participants meeting the determined normal threshold for their age bracket were considered eligible for the study. No participants were excluded based on medication use, although self-reported medication use was recorded during the study visit in order to investigate or avoid specific medication confounds. Essential health assessments for HCP-A study include measurements of vital signs, and blood laboratory tests including complete blood counts, metabolic, lipid and endocrine panels, vascular health/burden factors, genetic testing for Alzheimer's disease risk, gonadal hormones, and health and other environmental factors that are known to show associations to brain circuitry during typical aging, as well as in dementia and other diseases (Iturria-Medina and Evans, 2015), as previously described (Bookheimer et al., 2019).

Data from participants aged 90+ years were lumped together while reporting due to privacy concerns. Additional details on the inclusion and exclusion criteria for HCP-A can be found in a previous publication (Bookheimer et al., 2019). Table 1 presents the demographic information of the participants processed and analyzed for the current study.

### 2.2. CVM health assessment

A composite index of CVM health factors or "CVMi" of averaged z-transformed measures was calculated from 12 available variables,

each of which have been established to increase risk for, or correlate with CVM status (Ahn et al., 2017; Chien et al., 2017; Ettehad et al., 2016; Koliaki et al., 2019; Kubota et al., 2017; Levin et al., 2001; Sandesara et al., 2019; Skaaby et al., 2017; Sozen and Ozer, 2017; Vasan et al., 2001; Wang et al., 2017). These encompassed: cardiac-autonomic (heart rate, heart rate variability), vascular (blood pressure [systolic and diastolic] adjusted for medication, creatinine clearance), metabolic (BMI, hemoglobin A1c, total LDL and HDL cholesterol, triglycerides, and vitamin D), and immune (C-reactive protein [CRP], albumin) systems. For participants who were taking blood pressure medication, the raw blood pressure values were adjusted by adding 10 points, prior to z-scoring and averaging the measures (Law et al., 2003a; Wald et al., 2009). Similarly, measures of hemoglobin A1c (Sherifali et al., 2010) and cholesterol (Law et al., 2003b; Weir and Moser, 2000) were adjusted for medication by following existing approaches from the literature. Higher values of CVMI indicate poorer cumulative CVM status, even within the subclinical range for disease for any individual measure.

To fully eliminate the shared variance between age and CVMI, we incorporated a more stringent approach for the regression analyses by first orthogonalizing CVMI with respect to age prior to using it as a regressor in the models. The orthogonalized CVMI measures were obtained using the Gram-Schmidt process (Björck, 1994; Gerstorfer et al., 2023; Omidikia and Kompany-Zareh, 2013) to produce uncorrelated variables by removing the projection of age from CVMI.

Figure S1 presents additional information on the orthogonalization of CVMI with age. Moreover, Figure S2 highlights the Pearson's correlation between measures used for the CVMI estimation, and Table S1 presents the Group-wise mean, standard deviation (SD) and range (minimum, min; maximum, max) for each age group, as well as the Cohen's D effect size and p-values highlighting the group difference in the variables used for CVMI estimation.

### 2.3. Image acquisition

Structural MRI images were acquired across sites using a 3.0 Tesla Prisma scanner (Siemens; Erlangen, Germany) utilizing a 32-channel head coil. T1-weighted imaging was performed using multi-echo MPRAGE (van der Kouwe et al., 2008) at 0.8 mm isotropic resolution with TR = 2500 ms, TI = 1000 ms, TE = 1.8/3.6/5.4/7.2 ms, and flip angle = 8 deg. T2-weighted imaging was performed using SPACE (Mugler et al., 2000) at 0.8 mm isotropic resolution with TR = 3200 ms and TE = 564 ms. Both sequences used embedded volumetric navigators for prospective motion correction and selective reacquisition of the lines in k-space corrupted by motion (Hess et al., 2011). As explained (Elam et al., 2021), the mean image of just the first two echoes from the MPRAGE acquisition was used as the input to subsequent processing.

The resting-state functional MRI (fMRI) scans were acquired with a 2D multiband (MB) gradient-recalled echo (GRE) echoplanar imaging (EPI) sequence (eight-fold slice acceleration [MB8], TR/TE = 800/37 ms, flip angle = 52°) and 2.0 mm isotropic voxels covering the whole brain. fMRI scans were acquired in pairs of two runs, with opposite phase encoding polarity (anterior-to-posterior [AP] and posterior-to-anterior [PA]) so that the fMRI data in aggregate is not biased toward a particular phase encoding polarity. Each run of the resting-state fMRI scans was 6.5 min in length. Matched, phase encoding direction reversed spin echo images were also obtained for distortion correction. During the scan, participants viewed a small white fixation crosshair on a black background. Participants were instructed to stay still, stay awake, and blink normally while looking at the fixation crosshair.

### 2.4. Imaging data preprocessing

The HCP-A structural and functional data were analyzed using an HCP-Style approach (Glasser et al., 2016) to maximize the spatial lo-

calization of high-resolution functional signals (Coalson et al., 2018). The data were processed using the publicly released HCP minimal preprocessing pipelines (Glasser et al., 2013; Smith et al., 2013), as well as pipelines for cross-subject registration (Robinson et al., 2014), and fMRI denoising (Glasser et al., 2018, 2019). These methods are described in detail in the cited publications; in brief: All structural and functional images were corrected for distortions, including gradient nonlinearity distortions and b0 distortions in the EPI images (Andersson et al., 2003). All images were aligned within and across modalities to account for subject head motion, with cross-modal alignment being performed using boundary-based registration (Greve and Fischl, 2009). Cortical surface meshes and subcortical structure segmentations were reconstructed and performed using FreeSurfer version 6.0 (Fischl, 2012). All datasets were converted to NIFTI, GIFTI, and CIFTI file formats to aid in cross-software compatibility. All data were aligned to MNI space in the volume using FNIRT (Andersson et al., 2007) and initially on the cortical surface using a gentle folding-based registration ('MSMSulc' (Robinson et al., 2018)). Spatially specific artifacts (e.g., from subject head motion, vascular physiology, or the MRI scanner) were removed from each subject's fMRI using multi-run spatial ICA+FIX with linear detrending and without movement regressors (Glasser et al., 2018, 2019). Cortical "areal-feature-based" cross-subject alignment was performed using 'MSMAll' registration with T1w/T2w myelin maps, resting state networks, and resting state visuotopy driving the alignment (Robinson et al., 2018), which removes most but not all cross-subject variability in cortical areas (Glasser et al., 2016). Global artifacts (e.g., from subject respiration) were removed from each subject's fMRI with temporal ICA (Glasser et al., 2018, 2019) using weighted regression (Glasser et al., 2016) of a previously computed (on HCP 'Young Adult' data) combined spatial ICA and temporal ICA decomposition onto the HCA data (as native temporal ICA has not yet been run on the HCA data (Lamichhane et al., 2021)). Resting state fMRI timeseries were concatenated across runs after demeaning and normalization of unstructured noise variance and averaged within 180 atlas-defined cortical areas per cerebral hemisphere (Glasser et al., 2016) and 16 FreeSurfer subcortical structures (Fischl et al., 2002) to reduce the effects of random noise.

### 2.5. Resting-state functional connectivity modeling

As the optimal approach for modeling functional connectivity that best corresponds to invasive (tracer-based) measures of anatomical connectivity is not yet known (Hayashi et al., 2021), we choose a standard approach. Functional connectivity was modeled using "full" Pearson correlation with a Fisher z transformation. Thus, a FC matrix for N regions is defined as the  $N \times N$  matrix M, where  $M(i,j)$  contains the full correlation of the time courses between region i and region j. In this way, a  $376 \times 376$  FC matrix was formed for each subject. The cortical areas were also grouped using a pre-defined assignment to one of 12 functional networks (Ji et al., 2019) and connectivity values were averaged within and between networks for some analyses. The 12 functional networks included primary visual (VIS1), secondary visual (VIS2), auditory (AUD), somatomotor (SMN), cingulo-opercular (CON), default-mode (DMN), dorsal attention (DAN), frontoparietal (FPN), language (LAN), posterior multimodal (pMM), ventral multimodal (vMM), and orbito-affective (OA) networks.

#### 2.5.1. Analysis of CVMI and age associations with functional connectivity

To understand how CVMI is associated with FC measures, we explored 2 separate linear regression models: whole-brain ROI-to-ROI and between-network models.

#### 2.5.2. Whole-brain ROI degrees

To evaluate the associations between whole-brain, pairwise ROI-to-ROI FC and clinical/demographic covariates, we developed a simplified 'ROI degree' estimation scheme that would allow us to examine CVMI-

**Table 2**  
Criteria to determine strengthening or weakening association.

Strengthening Association	Mean-FC <sup>ROI</sup> = '+' ve Effect <sup>ROI</sup> = '+' ve	Mean-FC <sup>ROI</sup> = '-' ve Effect <sup>ROI</sup> = '-' ve
Weakening Association	Mean-FC <sup>ROI</sup> = '+' ve Effect <sup>ROI</sup> = '-' ve	Mean-FC <sup>ROI</sup> = '-' ve Effect <sup>ROI</sup> = '+' ve

and age-related associations at a global (whole-brain) level and also providing a novel metric of the degree of ‘disruption’ for each individual region relative to all other regions. For each of 376 × 375/2 = 70,500 pairs of ROIs, we fit the following three linear regression models:

$$\left\{ \begin{array}{l} \text{Model}_1^{CVMI} : FC \approx \beta_0 + \beta_1 \times CVMI \\ \text{Model}_2^{Age} : FC \approx \beta_0 + \beta_1 \times Age \\ \text{Model}_3^{CVMI+Age} : FC \approx \beta_0 + \beta_1 \times CVMI + \beta_2 \times Age \\ \text{Inference 3a. CVMI - adjusted - for - age} \\ \text{Inference 3b. Age - adjusted - for - CVMI} \end{array} \right.$$

Note that, for Model 3, as indicated by the *Inferences 3a* and *3b*, we used both CVMI and age as regressors (independent variables), estimating the (i) CVMI effect adjusted for age, and (ii) age effect adjusted for CVMI.

After thresholding the CVMI regression coefficients at each edge (pair of cortical areas) at  $p < 0.05$  (uncorrected), the degree (i.e., each uncorrected  $p < 0.05$  association was assigned a value of 1, and their sum reflects the degree or the total number of edges per region) of each ROI was used as a test statistic to summarize the strength of FC–CVMI associations. Additionally, we divided the significant CVMI associations into “strengthening” and “weakening” associations. If both association and underlying FC of the ROI had the same ‘sign/direction’, that is, if an association was positive (or negative) and the underlying FC was also positive (or negative), then we defined it as a *strengthening* association. Associations and FC measures showing opposite sign/direction were denoted as *weakening* associations. The relationships between association and FC measures presented in **Table 2** were considered when identifying whether it’s an “strengthening” or “weakening” association.

Finally, a permutation test (see section 5.7) was implemented and was corrected for multiple comparisons using both false discovery rate (FDR; Benjamini and Hochberg procedure (Benjamini and Hochberg, 1995)) and family-wise error rate (FWER; Hochberg-Bonferroni procedure (Hochberg, 1988; Holland and Copenhaver, 1987)), leading to final estimates of strengthening and weakening association degrees per ROI. Figure S3 provides an illustration of the methodological pipeline for the “whole-brain ROI degrees” estimation. Moreover, a detailed description of the strengthening and weakening association estimation is provided in supplementary section S2 and Figures S4 and S5.

### 2.5.3. Z-scoring of ROI degrees

To remove the effect of chance, we further estimated the z-values of each ROI weakening degree using the following equation.

$$Z - score = \frac{\text{Actual Weakening Degree} - \text{Mean(Permutation Weakening Degrees)}}{\text{Standard Deviation(Permutation Weakening Degrees)}}$$

Here, for each ROI, the actual weakening degree is obtained as described in the previous section. For each ROI, the mean and standard deviation of the permutation weakening degrees were computed using the null distribution of that ROI resulted from the permutation test. The resulting z-scores indicate how likely or unlikely the ROI degrees are to occur under chance. Higher z-score value suggests that the underlying ROI degree is more unlikely under chance, while lower z-score value highlights that the ROI degree is more likely to occur due to chance.

### 2.5.4. Whole-brain FC and CVMI association

In addition to ROI degree estimation, to understand how CVMI impacts the raw FC scores, we have also explored the associations between the full FC matrix and age-adjusted CVMI (orthogonalized to age). The full FC matrix contains 360 cortical areas, which were modularized into underlying 12 brain networks for better visualization. **Figure S6 (c)** presents the uncorrected, FDR-corrected, and FWER-corrected results for the associations between full FC matrix and CVMI. Also, CVMI-adjusted (CVMI orthogonalized to age) age effects on full FC matrix are presented in **Figure S6 (d)**.

The proportion of CVMI effects within the cortical and subcortical networks are also highlighted in **Table S2**, showing the percentage of CVMI- (age-adjusted) and age- (CVMI-adjusted) effects across the networks. For each network, the proportion of effect was computed using the following equation:

$$\text{Proportion of Effect} = \frac{\text{number of ROIs pairs affected within a network}}{\text{Total number of ROIs pairs within a network}} \times 100\%$$

### 2.5.5. Network-level degrees

In addition to the whole-brain association models, we further assessed CVMI associations with between-network FC, after adjusting for age. The FC measures were first modularized into specific brain networks. To examine the associations between orthogonalized CVMI and modularized network FC, we first applied the following linear regression model on the FC between all ROIs within each pair of networks, adjusting for age-effect.

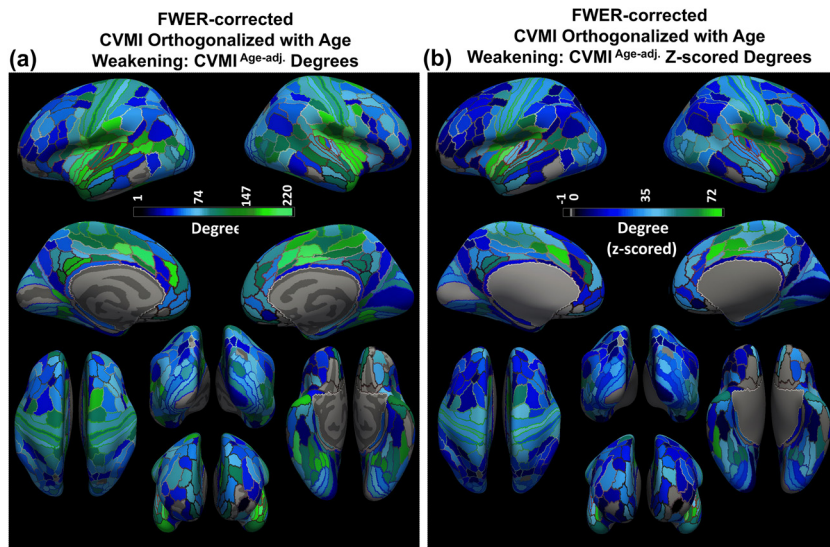
$$\{ \text{Model}_1^{CVMI-adjusted-for-Age} : FC^{\text{pairwise-network}} \approx \beta_0 + \beta_1 \times CVMI + \beta_2 \times Age \}$$

For instance, to estimate the effect of CVMI on the FC between the DMN and CON networks, we estimated the effect of CVMI on the FC between all ROIs within the DMN network and all ROIs within the CON network. Similar to the whole-brain ROI degree approach, we separated the network-level associations as strengthening and weakening. Here, we only report the weakening associations at the network-level as most of the network-level associations were weakening associations (~98%). We defined the network-level degrees as the total number of connections (i.e., ROIs or nodes) between a pair of networks showing CVMI weakening associations, after accounting for age and correcting for multiple comparisons using FWER at  $p < 0.05$ .

### 2.6. Permutation testing

We used Manly’s method (Manly, 1986; Winkler et al., 2014) to obtain permutation-based parameter estimates and construct a reference distribution, and applied FDR correction using Benjamini and Hochberg procedure (at  $\alpha$ -level=0.05, two-sided) (Benjamini and Hochberg, 1995) and FWER correction using Hochberg-Bonferroni procedure (at  $\alpha$ -level=0.05, two-sided) for multiple comparison testing (Hochberg, 1988; Holland and Copenhaver, 1987).

To evaluate the statistical significance of the association, we used a permutation testing procedure to first create a null distribution of the *measure* that quantifies the association (**Figure S7**). The randomization performed to construct the null distribution was done for each pair of ROIs separately. Briefly, for each ROI, we held the connectivity measures constant and shuffled the rows of the independent variable (e.g., CVMI, age) to break the linkage of the participants’ brain features and demographic/clinical features. Then, we performed linear regression analysis using the same dependent and independent (but shuffled) variables to generate a null distribution of the *measure* that quantifies the association (i.e., ROI degrees for whole-brain regression model) after permuting the input data 1000 times ( $N$ ). The  $P_{\text{permutation}}$  value was estimated as the number of null ‘quantifying measure of interest’ (i.e.,



whole-brain FC weakening degrees in the subcortical regions are provided in **Figure S9**. **Figure S10** presents the FDR-corrected results of the association between CVMI and whole-brain FC.

null ROI degrees ( $\omega^*$ ) for whole-brain model) that exceeded the observed measures (i.e., ROI degrees [ $\omega$ ] estimated on the original, unshuffled dataset. Correction for multiple comparisons (across ROIs) was then done on  $p_{\text{permutation}}$  values using FDR and FWER correction ( $\alpha$ -level=0.05, two-sided) unless otherwise stated.

$$\text{Whole - brainmodel} : p_{\text{permutation}} = \frac{1 + \sum_{i=1}^N \begin{cases} 1, & \text{if } \omega_i^* \geq \omega \\ 0, & \text{if } \omega_i^* < \omega \end{cases}}{1 + N}$$

**Figure S8** provides an example of the shuffled independent variable (CVMI, orthogonalized to age) during a run of the permutation test.

### 2.7. Data availability

The Lifespan Human Connectome Project (HCP) consortia for HCP-Aging have done the Lifespan 2.0 Release of imaging and behavioral data on the NIMH Data Archive (NDA), which included cross-sectional visit 1 preprocessed structural and functional imaging data, unprocessed visit 1 imaging data for all included modalities (structural and resting state fMRI), and non-imaging demographic and behavioral assessment data from 725 HCP-Aging (HCP-A, ages 36–100+). Additional participants' data utilized in this work will be publicly available at the next phase of data release.

## 3. Results

### 3.1. CVM factors are associated with whole-brain FC across the adult lifespan

We first examined how a composite index of CVM factors (“CVMI”) encompassing heart rate and heart rate variability, systolic and diastolic blood pressures, kidney function using creatinine clearance, body mass index (BMI), glycemia (hemoglobin A1c), lipids (total LDL and HDL cholesterols) and inflammation (C-reactive protein or CRP) associated with whole-brain functional connectivity (FC) as measured with BOLD fMRI at rest (see Methods for details). We separated the ‘strengthening’ and ‘weakening’ associations of the CVMI on FC, and then estimated the sum of each cortical area’s strengthening and weakening associations, defined as those with a statistically significant association between FC and CVMI. 98.33% of all significant associations between connectivity and CVMI were weakening associations. Because nearly all significant associations were ‘weakening’ associations, we henceforth focus on ‘weakening’ associations only. **Fig. 1** presents the total number of

**Fig. 1. Association between CVMI and whole-brain FC.** (a) FWER-corrected (at  $\alpha$ -level=0.05) CVMI-related weakening association degrees after adjusting for age. (b) FWER-corrected (at  $\alpha$ -level=0.05) CVMI-related z-scores of weakening association degrees after adjusting for age. CVMI measures were orthogonalized to age prior to the regression analyses. Results are depicted on inflated cortical surfaces and separated into left and right hemispheres. The color bar for ROI degree indicates: light green = greater weakening association degrees and darker blue = lesser weakening association degrees. Color bar reflects sum of degrees associated with an ROI (permutation test; FWER-corrected at  $\alpha$ -level=0.05). The color bar for z-scored degree indicates: light green = ROI degree is less likely to occur under chance and darker blue = ROI degree is more likely to occur under chance. Color bar reflects z-scores associated with an ROI, computed by subtracting the mean of that ROI null distribution from actual ROI weakening degree, and then dividing it by the standard deviation of the null distribution (permutation test; FWER-corrected at  $\alpha$ -level=0.05). Each of the ROIs is outlined on the labeled surface maps based on the HCP’s multi-modal cortical parcellation as presented in **Figure S13**. Bar plots showing association between CVMI and

connections (i.e., sum of areas’ degrees) across each area that exhibited a decrease in whole-brain FC (positive and negative correlations closer to zero) with increasing CVMI after adjusting for age; **Figure S9** shows bar charts for the analogous results for subcortical ROIs. Note that, all weakening degrees (both cortical and subcortical) represent associations with the whole brain (i.e., 360 cortical areas across both hemispheres, and 16 subcortical areas). Associations with CVMI were especially prominent in insular, lateral somato-motor, medial frontal, medial parietal, lateral occipital, superior temporal and temporal pole, and inferior lateral fronto-parietal regions. Although age adjustment reduced the overall effects measured, strong regional associations remained even after this adjustment.

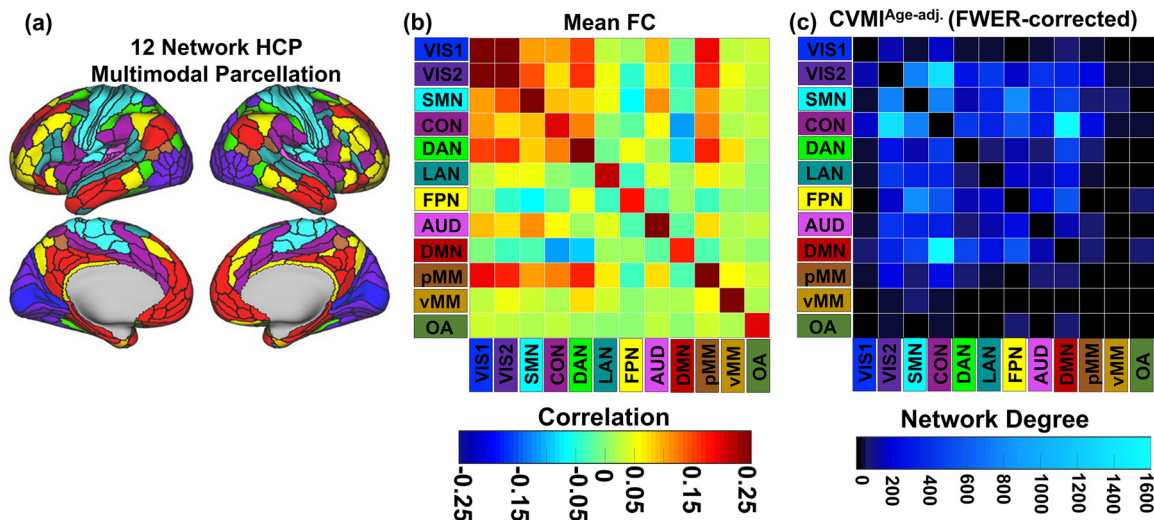
Importantly, the patterns in **Fig. 1** show strong bilateral symmetry, with a correlation between left and right hemisphere values of 0.83 in **Fig. 1a**. Also, several areas stand out as having notably more weakening association degrees than their neighbors (**Figs. 1 and S10**). These include areas FEF and PEF in frontal cortex, area PPop in lateral parietal cortex, area V6 in occipital cortex, and areas d32, p32pr, and a24pr of medial prefrontal and cingulate cortex. Area STSdp is one of the few with a pronounced asymmetry (relatively higher weakening association degrees on the right but not the left).

### 3.2. Between-network weakening associations

In addition to whole-brain associations, we also examined the network-level CVMI associations. **Fig. 2** shows the heatmaps for mean FC between the brain networks and their CVMI associations, after adjusting for age (FWER-corrected,  $p < 0.05$ ). As evident from **Fig. 2**, network-level FC measures between core brain networks showed greater weakening associations with CVMI, for example between the DMN and CON, as well as DMN and DAN, suggesting that integration among higher-level functional brain networks are significantly weakened due to increased CVMI.

### 3.3. Age- and sex-associations

We examined the age- and sex-related associations with FC measures, with and without adjusting for CVMI association. **Figure S11** presents the association between age and whole-brain. Note that age-related associations show regional overlap with CVMI associations, suggesting that these overlapping regions might be generally vulnerable. The associations between CVMI and whole-brain FC in male and female participants



**Fig. 2. Association between CVMI and network-level FC.** (a) The 12-network HCP multimodal parcellation showing color-coded brain networks (Ji et al., 2019). (b) Heatmap of mean FC (i.e., correlation) between brain networks are shown. Color bar for mean FC indicate: dark red=greater correlation and dark blue= greater anti-correlation between brain networks color-coded according to the multimodal parcellation as shown in (a). (c) The FWER-corrected heatmaps for age-adjusted CVMI-related associations between brain networks. The color bar for CVMI- and age-related associations represents *Network Degree* and indicates: light blue = greater weakening network degree and dark blue= lesser weakening network degree. CVMI measures were orthogonalized to age prior to the regression analyses. VIS1: primary visual; VIS2: secondary visual; AUD: auditory; SMN: somatomotor; CON: cingulo-opercular; DMN: default-mode; DAN: dorsal attention; FPN: frontoparietal; LAN: language; PMM: posterior multimodal; VMM: ventral multimodal; and ORA: orbito-affective networks.

(also with age-adjustment) are presented in **Figure S12(a, b)**. The weakening degrees for association between CVMI and whole-brain FC exhibited similar patterns in males and females on average. Moreover, **Figure S12(c)** highlights the weakening degrees from the association between CVMI and whole-brain FC, after adjusting for both age and sex, exhibiting a similar spatial weakening pattern as seen in **Fig. 1**.

#### 4. Discussion

We examined the associations of a composite index of cardiovascular, metabolic, and inflammatory factors that confer risk for dementia in later life with whole-brain and regional FC across the adult lifespan in generally healthy volunteers with normal cognition. We found that increased CVMI index scores, irrespective of any particular clinical CVM diagnoses (e.g., hypertension, hyperlipidemia, diabetes) are associated with reduced FC globally and regionally, emphasizing the importance of even subclinical inter-individual variation. Of particular interest, this effect was strongest among younger and middle-aged adults and was still significant, albeit less strong in the older adults.

Traditionally, the effects of age or other variables of interest on whole-brain FC are analyzed and evaluated only on the raw FC scores and visualized as heatmaps (Vaidya et al., 2019) (or connectograms (Zhang et al., 2017) depending on the number of significant connections). However, while this standard approach provides important patterns of disrupted connectivity, it does not provide how each brain region is affected in a straightforward manner (i.e., is there a set of regions that are more affected than others?). Further, the standard effect estimation using FC measures does not account for strengthening or weakening effects. Rather, it estimates whether it is a positive or negative effect. To more thoroughly understand the results from the standard approach, the mean FC needs to be taken into consideration as the effect of the variable of interest could have four outcomes: (i) the mean FC is positive and the effect is positive; (ii) the mean FC is negative and the effect is negative; (iii) the mean FC is positive and the effect is negative; and (iv) the mean FC is negative and the effect is positive. This complexity is highlighted in **Figure S6**, where we present the heatmaps of age and CVMI effects on full FC scores. Our proposed strengthening/weakening approach takes this into account by computing the effects as strengthening or weaken-

ing and summarizes these effects across individual ROI. The weakening degree estimation highlights how much an ROI is affected by the variable of interest (i.e., age or CVMI). Our surface map representation of the ROI degrees further simplifies the visualization and interpretation of such complex matrix, and highlights hub-like region that are most impacted by CVMI.

Our findings revealed widespread associations between CVMI and FC throughout the brain, particularly highlighting weakened FC patterns with increased level of CVMI. These findings are consistent with previous studies demonstrating brain alteration in the context of one or more cardiovascular and metabolic risk factor diagnoses. For example, in a recent study examining 42 patients with type-2 diabetes, Cui et al. (2015) reported reduced DMN connectivity, which was also associated with worse performance on tasks of memory and executive functioning. Also, Park et al. (2018) reported disrupted frontoparietal network FC based on degree centrality values from 274 individuals with abdominal obesity. In 27 patients with metabolic syndrome (i.e., clustering of 3 or more diagnoses), Rashid et al. identified disrupted FC among the DMN, DAN, ECN and several other brain region (Rashid et al., 2019, 2021). Another study by Xia et al. (2015) revealed associations between Type 2 diabetes mellitus and reduced attentional state across the dorsal and ventral attention networks. Further, Cui et al. (2016) determined association between occipital hypoconnectivity and impaired visual memory and executive function performance in 40 patients with diabetes. Using graph-theory analysis, Baek et al. (2017) reported altered network topological structures in obesity in both whole-brain network and regional levels. However, except for our previous work (Rashid et al., 2019, 2021), these studies did not investigate the diverse and highly interactive CVM factors that collectively are thought to interact and impact brain function and lead to vulnerability to cognitive decline. While CVM factors may individually impact the cerebrovascular system to differing degrees (i.e., blood pressure impacting more than others), they are mechanistically so intertwined that individual contributions are difficult to disaggregate. Here, we demonstrate a simple composite of multiple co-occurring CVM physiological factors are associated with widespread alterations in brain FC. While recent studies on the associations between post-traumatic stress disorder (Jagger-Rickels et al., 2021) (PTSD) and suicide attempt (Stumps et al., 2021), and brain FC have presented simi-



lar quantification of hyper- and hypo-connectivity measures, the current work has extended the FC estimation into ‘strengthening’ and ‘weakening’ estimations along with a novel visualization framework that highlights cumulative CVM-related disruption.

As shown in the previous studies, exposure to cardiovascular risk factors during mid-life are associated with cognitive decline and dementia risks in old-age (Debette et al., 2011; Lamar et al., 2020), with minimal to no associations suggested between these risk factors and dementia risk in the oldest old population (Beydoun et al., 2008; Harrison et al., 2015). Our preliminary findings on age-stratified group-level associations (supplementary section S3), imply that brain alterations due to these classic RFs may occur even earlier than previously reported, emphasizing the importance of recognizing CVM factors early to allowing the greatest opportunity for dietary, lifestyle or medical interventions to preserve FC, maximize cerebral reserve and resilience, and prevent common neurocognitive disorders of aging. However, further investigation is required to fully understand the CVM-related associations at different ages.

Our network-level findings further confirm and expand on prior evidence of CVM-related disruptions in brain FC by demonstrating that the higher-order brain networks that are vital to everyday cognitive function, including DMN, DAN, and CON, have altered FC among themselves, as well as with other brain networks as CVM factors increase. Previously, the domains of executive function and attention that are especially important for higher order cognitive processing (e.g., reasoning, planning and cognitive flexibility), have been associated with different CVM risk factors in isolation (Bucur and Madden, 2010; Gorelick et al., 2012; Leritz et al., 2016; Vincent and Hall, 2015). Further, a recent study showed that the FC measures across multiple networks (DMN, DAN, VIS and SM) are disrupted more globally in patients with a diagnosis of metabolic syndrome, whereas the FC measures across others (ECN, VAN and LIMBIC) exhibit more localized alteration patterns (Rashid et al., 2021). Interestingly, our present findings demonstrate a global alteration in network-level FC with CVMI across most of the core networks, including DMN, DAN, FPN, VIS and SM.

At the whole-brain level, the CVMI associations exhibit greater primary sensory and motor involvement which is thought to be less vulnerable to neurodegenerative disease processes (e.g., Alzheimer’s disease) (Resnick et al., 2003; Thompson et al., 2001) and reduced DMN involvement, deviating from the expected pattern of brain regions typically showing “aging” effects. However, when we examined DMN at the seed-level (results are not shown), more CVMI associations were observed. This general pattern observed at the whole-brain level has alternatively been associated with traveling waves of arousal (Raut et al., 2021) and respiration (Lynch et al., 2020), though perfusion effects of respiration were removed from this data and it was hypothesized that less healthy individuals would have stronger apparent “connectivity” due to respiration, not weaker as we see here.

The mechanistic basis for the associations between CVMI and FC is uncertain. One obvious possibility is that an increased association between CVMI and FC for a given pair of parcels or networks reflects stronger anatomical connectivity that would be evident if tracer-based methods were feasible in humans. Because this is only one of many plausible explanations, we have avoided using the terms ‘connectivity’ and ‘connections’ in describing our FC measures even though these terms are widely used. Alternative explanations for altered FC include diverse direct and/or downstream physical and biochemical effects of CVM factors on a) cerebrovascular functioning, b) neuronal and glial functioning and/or c) promotion of neurodegenerative disease pathologies, ultimately leading to impaired neurosynaptic functioning. Atherosclerosis, lipohyalinosis, endothelial dysfunction and disruption of the blood brain barrier can be mechanistically linked to all of the CVM factors included in our composite index (Berenson et al., 1998; Dessein et al., 2005; Knoflach et al., 2009; Kovacic and Fuster, 2012). Associated changes in cerebral blood flow (CBF) would disrupt resting state signals within

and across functional networks throughout the brain. Indeed, a previous study had linked advancing Alzheimer’s disease and stage and reduced CBF in the temporal and parietal region (Binnewijzend et al., 2016), indicating regional overlap with our current findings highlighting greater ‘whole-brain’ weakening degrees across these regions due to CVMI. Direct or secondary effects on neuronal and glial function may also occur from increased CVMI factors. For instance, high hemoglobin A1c in people with obesity, type 2 diabetes or pre-diabetes reflects insulin resistance of muscle, blood, liver and other cells throughout the body. Neuronal insulin resistance is also a feature of current interest in neurocognitive disorders of aging (Arnold et al., 2018), and may be one factor reflected in weakened FC. Lower levels of vitamin D, frequently co-occurring in people with metabolic syndrome, can have significant direct effects on neurons and glial cells via its roles as a neuroactive steroid and immunomodulator, among others (Talaie et al., 2013). Another example is elevated CRP, which has been described as another risk factor for cerebral vulnerability in people experiencing delirium after medical or surgical stress and injury (Vasunilashorn et al., 2017). Finally, animal models have described mechanistic links between multiple CVM factors and the promotion of neurodegenerative diseases pathologies (De Bem et al., 2021) including amyloid- $\beta$  and tau (Hardy and Selkoe, 2002),  $\alpha$ -synuclein (Spillantini et al., 1998) and TDP-43 (Huang et al., 2020).

Several experimental and methodological limitations must be considered while interpreting this study’s findings. The cross-sectional design of the study limits the interpretation of our findings from a time-varying perspective. Further, there are known and unknown biases inherent in such a nonrandomly accrued cohort of generally healthy research volunteers, especially education, lifestyle, and healthcare. Also, lack of information on participants’ arousal levels during the fMRI recordings limits us to evaluate the association between age and arousal level which might potentially be a confounding factor for the study. Also, our CVMI estimation represents a summary index which weighted a number of CVM RFs in a somewhat agnostic approach. To optimally compute the CVMI, future work should include other constructs of the summary index, such as using principal component analysis (PCA) or factor analysis. Strengths of the present study include the large and exceptionally well-characterized cohort, including a greater representation of under-represented groups (31.4%, data not presented) than is typical in such studies. The current study had a sample size of 930 adults spanning a wide age range (36–90+ years), thereby enabling examination of CVM and age associations with resting FC while providing a sufficient sample for age-based stratification to compare CVMI and FC associations in different age strata. Additional strengths include the HCP-style (Glasser et al., 2016) multi-modal MRI data acquisition and analysis approach, including high spatial and temporal resolution fMRI (Harms et al., 2018), surface-based processing (Glasser et al., 2013) with functional cross-subject alignment (Robinson et al., 2014) and without substantial spatial smoothing for markedly better spatial localization (Coalson et al., 2018), advanced spatial and temporal ICA-based denoising to selectively remove both spatially specific and global fMRI artifacts without changing the neural signal of interest (Glasser et al., 2018, 2019), and use of a multi-modal neurobiologically validated map of human cortical areas for better interpretability and to reduce multiple comparisons while increasing signal to noise ratio (Glasser et al., 2016).

## Summary

The findings presented in the current study demonstrate that CVM factors are associated with functional connectivity of the brain in a large cohort of generally healthy volunteers, and that the CVM effects are stronger in FC among core brain networks. This provides further imperative to the need for early attention to CVM factors in adults for optimal brain health and functioning.

The degree to which CVM-related weakening of functional connectivity in the brain explains the greater vulnerability of people with

CVM disease for emergent dementia will be a natural extension of research in this HCP-A cohort with longitudinal assessment. It is estimated that almost 14 million people in the USA will have dementia by 2050 (Hebert et al., 2013; Matthews et al., 2019) unless progress is made in preventing, delaying and ameliorating cognitive failure in the elderly. Future directions will include determining age-stratified effects of CVMI as well as how these findings relate to change cognition and behavior, as the longitudinal HCP-A cohort is followed into subsequent assessment cycles.

### Authors' contributions

Barnaly Rashid: Study conceptualization, plan of analysis, statistical analysis, data visualization, literature search and review, result interpretation, writing and editing the manuscript, revision of the manuscript.

Matthew F. Glasser: Plan of analysis, data preprocessing, assistance with statistical methods and data visualization, result interpretation, write-up parts of the manuscript, revision of the manuscript.

Thomas Nichols: Plan of analysis, assistance with statistical methods and data visualization, result interpretation, write-up parts of the manuscript, revision of the manuscript.

David Van Essen: Literature search and review, assistance with result interpretation, data visualization, manuscript editing, revision of the manuscript.

Meher R. Juttukonda: Literature search and review, assistance with statistical methods, manuscript editing and revision.

Nadine A. Schwab: Literature search and review, plan of analysis, writing and editing the manuscript, revision of the manuscript.

Douglas N Greve: Plan of analysis, assistance with statistical methods, revision of the manuscript.

Essa Yacoub: Assistance with result interpretation, review, editing and revision of the manuscript.

Allison Lovely: Data collection and management, manuscript editing and revision.

Melissa Terpstra: Assistance with result interpretation, writing and editing the manuscript, revision of the manuscript.

Michael P. Harms: Data preprocessing, assistance with statistical methods, result interpretation, manuscript review, editing and revision.

Susan Y. Bookheimer: Assistance with result interpretation, review, editing and revision of the manuscript.

Beau M. Ances: Plan of analysis, assistance with statistical analysis, data visualization, literature search and review, result interpretation, writing and editing the manuscript, revision of the manuscript.

David H. Salat: Study conceptualization, plan of analysis, assistance with statistical analysis, data visualization, literature search and review, result interpretation, writing and editing the manuscript, revision of the manuscript.

Steven E. Arnold: Study conceptualization, plan of analysis, assistance with statistical analysis, data visualization, literature search and review, result interpretation, writing and editing the manuscript, revision of the manuscript.

### Code availability

The code and pipeline for data processing are available through the publicly released HCP minimal preprocessing pipelines, as well as pipelines for cross-subject registration, and fMRI denoising. Custom MATLAB script used for statistical modeling will be available on request from the corresponding author.

### Funding

This work was supported by the National Institute on Aging (NIA; AG062421), National Institutes of Health (NIH; U19AG073585, U01AG052564 and U01AG052564-S1), and the Challenger Foundation.

### Declaration of Competing Interest

The authors report no competing interests.

### Data availability

The Lifespan Human Connectome Project (HCP) consortia for HCP-Aging have done the Lifespan 2.0 Release of imaging and behavioral data on the NIMH Data Archive (NDA), which included cross-sectional visit 1 preprocessed structural and functional imaging data, unprocessed visit 1 imaging data for all included modalities (structural and resting state fMRI), and non-imaging demographic and behavioral assessment data from 725 HCP-Aging (HCP-A, ages 36–100+). Additional participants' data utilized in this work will be publicly available at the next phase of data release.

### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2023.120192.

### References

- Ahn, C.H., Min, S.H., Lee, D.-H., Oh, T.J., Kim, K.M., Moon, J.H., Choi, S.H., Park, K.S., Jang, H.C., Ha, J., 2017. Hemoglobin glycation index is associated with cardiovascular diseases in people with impaired glucose metabolism. *J. Clin. Endocrinol. Metab.* 102, 2905–2913.
- Andersson, J.L., Jenkinson, M., Smith, S., 2007. In: Non-linear registration, Aka Spatial Normalisation FMRIB Technical Report TR07JA2, 2. FMRIB Analysis Group of the University of Oxford, p. e21.
- Andersson, J.L., Skare, S., Ashburner, J., 2003. How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. *Neuroimage* 20, 870–888.
- Arnold, S.E., Arvanitakis, Z., Macauley-Rambach, S.L., Koenig, A.M., Wang, H.-Y., Ahima, R.S., Craft, S., Gandy, S., Buettner, C., Stoeckel, L.E., 2018. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. *Nat. Rev. Neurol.* 14, 168.
- Baek, K., Morris, L.S., Kundu, P., Voon, V., 2017. Disrupted resting-state brain network properties in obesity: decreased global and putaminal cortico-striatal network efficiency. *Psychol. Med.* 47, 585–596.
- Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J. R. Stat. Soc. Series B Stat. Methodol.* 57, 289–300.
- Berenson, G.S., Srinivasan, S.R., Bao, W., Newman, W.P., Tracy, R.E., Wattigney, W.A., 1998. Association between multiple cardiovascular risk factors and atherosclerosis in children and young adults. *N. Engl. J. Med.* 338, 1650–1656.
- Beydoun, M.A., Beydoun, H., Wang, Y., 2008. Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis. *Obes. Rev.* 9, 204–218.
- Binnewijzend, M.A., Benedictus, M.R., Kuijer, J.P., van der Flier, W.M., Teunissen, C.E., Prins, N.D., Wattjes, M.P., van Berckel, B.N., Scheltens, P., Barkhof, F., 2016. Cerebral perfusion in the prodementia stages of Alzheimer's disease. *Eur. Radiol.* 26, 506–514.
- Björck, Å., 1994. Numerics of gram-schmidt orthogonalization. *Linear Algebra Appl.* 197, 297–316.
- Blazer, D.G., Yaffe, K., Liverman, C.T., 2015. Cognitive aging: progress in understanding and opportunities for action.
- Bookheimer, S.Y., Salat, D.H., Terpstra, M., Ances, B.M., Barch, D.M., Buckner, R.L., Burgess, G.C., Curtiss, S.W., Diaz-Santos, M., Elam, J.S., 2019. The lifespan human connectome project in aging: an overview. *Neuroimage* 185, 335–348.
- Bucur, B., Madden, D.J., 2010. Effects of adult age and blood pressure on executive function and speed of processing. *Exp. Aging Res.* 36, 153–168.
- Chakrabarti, S., Khemka, V.K., Banerjee, A., Chatterjee, G., Ganguly, A., Biswas, A., 2015. Metabolic risk factors of sporadic Alzheimer's disease: implications in the pathology, pathogenesis and treatment. *Aging Dis.* 6, 282.
- Chien, S.-C., Chen, C.-Y., Lin, C.-F., Yeh, H.-I., 2017. Critical appraisal of the role of serum albumin in cardiovascular disease. *Biomark. Res.* 5, 1–9.
- Coalson, T.S., Van Essen, D.C., Glasser, M.F., 2018. The impact of traditional neuroimaging methods on the spatial localization of cortical areas. *Proc. Natl Acad. Sci.* 115, E6356–E6365.
- Coutinho, A.M., Coutu, J.-P., Lindemer, E.R., Rosas, H.D., Rosen, B.R., Salat, D.H., 2017. Differential associations between systemic markers of disease and cortical thickness in healthy middle-aged and older adults. *Neuroimage* 146, 19–27.
- Cui, Y., Jiao, Y., Chen, H.-J., Ding, J., Luo, B., Peng, C.-Y., Ju, S.-H., Teng, G.-J., 2015. Aberrant functional connectivity of default-mode network in type 2 diabetes patients. *Eur. Radiol.* 25, 3238–3246.
- Cui, Y., Li, S.-F., Gu, H., Hu, Y.-Z., Liang, X., Lu, C.-Q., Cai, Y., Wang, C.-X., Yang, Y., Teng, G.-J., 2016. Disrupted brain connectivity patterns in patients with type 2 diabetes. *Am. J. Neuroradiol.* 37, 2115–2122.

- De Bem, A.F., Krolow, R., Farias, H.R., De Rezende, V.L., Gelain, D.P., Moreira, J.C.F., Duarte, J.M.d.N., De Oliveira, J., 2021. Animal models of metabolic disorders in the study of neurodegenerative diseases: an overview. *Front. Neurosci.* 14, 1457.
- DeBette, S., Seshadri, S., Beiser, A., Au, R., Himali, J., Palumbo, C., Wolf, P., DeCarli, C., 2011. Midlife vascular risk factor exposure accelerates structural brain aging and cognitive decline. *Neurology* 77, 461–468.
- Dessein, P.H., Joffe, B.L., Singh, S., 2005. Biomarkers of endothelial dysfunction, cardiovascular risk factors and atherosclerosis in rheumatoid arthritis. *Arthritis Res. Ther.* 7, 1–10.
- Duron, E., Hanon, O., 2008. Vascular risk factors, cognitive decline, and dementia. *Vasc. Health Risk Manag.* 4, 363.
- Eckel, R.H., Grundy, S.M., Zimmet, P.Z., 2005. The metabolic syndrome. *Lancet North Am. Ed.* 365, 1415–1428.
- Elam, J.S., Glasser, M.F., Harms, M.P., Sotiropoulos, S.N., Andersson, J.L., Burgess, G.C., Curtiss, S.W., Oostenveld, R., Larson-Prior, L.J., Schoffelen, J.-M., 2021. The Human Connectome Project: a retrospective. *Neuroimage* 244, 118543.
- Ettehad, D., Emdin, C.A., Kiran, A., Anderson, S.G., Callender, T., Emberson, J., Chalmers, J., Rodgers, A., Rahimi, K., 2016. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet* 387, 957–967.
- Fischl, B., 2012. FreeSurfer. *Neuroimage* 62, 774–781.
- Fischl, B., Salat, D.H., Busa, E., Albert, M., Dieterich, M., Haselgrove, C., Van Der Kouwe, A., Killiany, R., Kennedy, D., Klaveness, S., 2002. Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron* 33, 341–355.
- Friedman, J.I., Tang, C.Y., de Haas, H.J., Changchien, L., Goliash, G., Dabas, P., Wang, V., Fayad, Z.A., Fuster, V., Narula, J., 2014. Brain imaging changes associated with risk factors for cardiovascular and cerebrovascular disease in asymptomatic patients. *JACC: Cardiovasc. Imaging* 7, 1039–1053.
- Gerstorfer, Y., Krieg, L., Hahn-Klimroth, M., 2023. A notion of feature importance by decorrelation and detection of trends by random forest regression. *arXiv preprint arXiv:2303.01156*.
- Glasser, M.F., Coalson, T.S., Bijsterbosch, J.D., Harrison, S.J., Harms, M.P., Anticevic, A., Van Essen, D.C., Smith, S.M., 2018. Using temporal ICA to selectively remove global noise while preserving global signal in functional MRI data. *Neuroimage* 181, 692–717.
- Glasser, M.F., Coalson, T.S., Bijsterbosch, J.D., Harrison, S.J., Harms, M.P., Anticevic, A., Van Essen, D.C., Smith, S.M., 2019. Classification of temporal ICA components for separating global noise from fMRI data: reply to Power. *Neuroimage* 197, 435–438.
- Glasser, M.F., Coalson, T.S., Robinson, E.C., Hacker, C.D., Harwell, J., Yacoub, E., Ugurbil, K., Andersson, J., Beckmann, C.F., Jenkinson, M., 2016. A multi-modal parcellation of human cerebral cortex. *Nature* 536, 171–178.
- Glasser, M.F., Sotiropoulos, S.N., Wilson, J.A., Coalson, T.S., Fischl, B., Andersson, J.L., Xu, J., Jbabdi, S., Webster, M., Polimeni, J.R., 2013. The minimal preprocessing pipelines for the Human Connectome Project. *Neuroimage* 80, 105–124.
- Gorelick, P.B., Nyenhuis, D., Materson, B.J., Calhoun, D.A., Elliott, W.J., Phillips, R.A., Taler, S.J., Townsend, R.R., Group, A.S.o.H.W., 2012. Blood pressure and treatment of persons with hypertension as it relates to cognitive outcomes including executive function. *J. Am. Soc. Hypertens.: JASH* 6, 309–315.
- Greve, D.N., Fischl, B., 2009. Accurate and robust brain image alignment using boundary-based registration. *Neuroimage* 48, 63–72.
- Groop, L., Orho-Melander, M., 2001. The dysmetabolic syndrome. *J. Intern. Med.* 250, 105–120.
- Hardy, J., Selkoe, D.J., 2002. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science* 297, 353–356.
- Harms, M.P., Somerville, L.H., Ances, B.M., Andersson, J., Barch, D.M., Bastiani, M., Bookheimer, S.Y., Brown, T.B., Buckner, R.L., Burgess, G.C., 2018. Extending the Human Connectome Project across ages: imaging protocols for the Lifespan Development and Aging projects. *Neuroimage* 183, 972–984.
- Harrison, S.L., Stephan, B.C., Siervo, M., Granic, A., Davies, K., Wesnes, K.A., Kirkwood, T.B., Robinson, L., Jagger, C., 2015. Is there an association between metabolic syndrome and cognitive function in very old adults? The Newcastle 85+ Study. *J. Am. Geriatr. Soc.* 63, 667–675.
- Hayashi, T., Hou, Y., Glasser, M.F., Autio, J.A., Knoblauch, K., Inoue-Murayama, M., Coalson, T., Yacoub, E., Smith, S., Kennedy, H., 2021. The nonhuman primate neuroimaging and neuroanatomy project. *Neuroimage* 229, 117726.
- Hebert, L.E., Weuve, J., Scherr, P.A., Evans, D.A., 2013. Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. *Neurology* 80, 1778–1783.
- Hess, A.T., Dylan Tisdall, M., Andronesi, O.C., Meintjes, E.M., van der Kouwe, A.J., 2011. Real-time motion and B0 corrected single voxel spectroscopy using volumetric navigators. *Magn. Reson. Med.* 66, 314–323.
- Hochberg, Y., 1988. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika* 75, 800–802.
- Holland, B.S., Copenhaver, M.D., 1987. An improved sequentially rejective Bonferroni test procedure. *Biometrics* 417–423.
- Huang, W., Zhou, Y., Tu, L., Ba, Z., Huang, J., Huang, N., Luo, Y., 2020. Tdp-43: from alzheimer's disease to limbic-predominant age-related tdp-43 encephalopathy. *Front. Mol. Neurosci.* 13, 26.
- Iturria-Medina, Y., Evans, A.C., 2015. On the central role of brain connectivity in neurodegenerative disease progression. *Front. Aging Neurosci.* 7, 90.
- Jack Jr, C.R., Knopman, D.S., Jagust, W.J., Petersen, R.C., Weiner, M.W., Aisen, P.S., Shaw, L.M., Vemuri, P., Wiste, H.J., Weigand, S.D., 2013. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol.* 12, 207–216.
- Jagger-Rickels, A., Stumps, A., Rothlein, D., Park, H., Fortenbaugh, F., Zuberer, A., Fonda, J.R., Fortier, C.B., DeGutis, J., Milberg, W., 2021. Impaired executive function exacerbates neural markers of posttraumatic stress disorder. *Psychol. Med.* 1–14.
- Ji, J.L., Spronk, M., Kulkarni, K., Repovš, G., Anticevic, A., Cole, M.W., 2019. Mapping the human brain's cortical-subcortical functional network organization. *Neuroimage* 185, 35–57.
- Kim, B., Feldman, E.L., 2015. Insulin resistance as a key link for the increased risk of cognitive impairment in the metabolic syndrome. *Exp. Mol. Med.* 47, e149.
- Knoflach, M., Kiechl, S., Penz, D., Zangerle, A., Schmidauer, C., Rossmann, A., Shingh, M., Spallek, R., Griesmacher, A., Bernhard, D., 2009. Cardiovascular risk factors and atherosclerosis in young women: atherosclerosis risk factors in female youngsters (ARFY study). *Stroke* 40, 1063–1069.
- Koliaki, C., Liatis, S., Kokkinos, A., 2019. Obesity and cardiovascular disease: revisiting an old relationship. *Metabolism* 92, 98–107.
- Kovacic, J.C., Fuster, V., 2012. Atherosclerotic risk factors, vascular cognitive impairment, and Alzheimer disease. *Mount Sinai J. Med.: J. Transl. Personal. Med.* 79, 664–673.
- Kubota, Y., Chen, L.Y., Whitsel, E.A., Folsom, A.R., 2017. Heart rate variability and lifetime risk of cardiovascular disease: the atherosclerosis risk in communities study. *Ann. Epidemiol.* 27, 619–625 e612.
- Lamar, M., Boots, E.A., Arfanakis, K., Barnes, L.L., Schneider, J.A., 2020. Brain structural alterations common to cardiovascular disease risk factors and Alzheimer's dementia. *Vasc. Dis., Alzheimer's Dis. Mild Cognit. Impairment: Adv. Integr. Approach* 241.
- Lamichhane, B., Jayasekera, D., Jakes, R., Glasser, M.F., Zhang, J., Yang, C., Grimes, D., Frank, T.L., Ray, W.Z., Leuthardt, E.C., 2021. Multi-modal biomarkers of low back pain: a machine learning approach. *NeuroImage: Clin.* 29, 102530.
- Law, M., Wald, N., Morris, J., Jordan, R., 2003a. Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. *BMJ* 326, 1427.
- Law, M.R., Wald, N.J., Rudnicka, A., 2003b. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ* 326, 1423.
- Leritz, E.C., McGlinchey, R.E., Salat, D.H., Milberg, W.P., 2016. Elevated levels of serum cholesterol are associated with better performance on tasks of episodic memory. *Metab. Brain Dis.* 31, 465–473.
- Leritz, E.C., Salat, D.H., Williams, V.J., Schnyer, D.M., Rudolph, J.L., Lipsitz, L., Fischl, B., McGlinchey, R.E., Milberg, W.P., 2011. Thickness of the human cerebral cortex is associated with metrics of cerebrovascular health in a normative sample of community dwelling older adults. *Neuroimage* 54, 2659–2671.
- Levin, A., Djurdjev, O., Barrett, B., Burgess, E., Carlisle, E., Ethier, J., Jindal, K., Mendelsohn, D., Tobe, S., Singer, J., 2001. Cardiovascular disease in patients with chronic kidney disease: getting to the heart of the matter. *Am. J. Kidney Dis.* 38, 1398–1407.
- Livingston, G., Sommerlad, A., Orgeta, V., Costafreda, S.G., Huntley, J., Ames, D., Ballard, C., Banerjee, S., Burns, A., Cohen-Mansfield, J., 2017. Dementia prevention, intervention, and care. *Lancet North Am. Ed.* 390, 2673–2734.
- Luchsinger, J., Reitz, C., Honig, L.S., Tang, M.-X., Shea, S., Mayeux, R., 2005. Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology* 65, 545–551.
- Luchsinger, J.A., Mayeux, R., 2004. Cardiovascular risk factors and Alzheimer's disease. *Curr. Atheroscler. Rep.* 6, 261–266.
- Lynch, C.J., Silver, B.M., Dubin, M.J., Martin, A., Voss, H.U., Jones, R.M., Power, J.D., 2020. Prevalent and sex-biased breathing patterns modify functional connectivity MRI in young adults. *Nat. Commun.* 11, 1–14.
- M Ashraf, G., H Greig, N., A Khan, T., Hassan, I., Tabrez, S., Shakil, S., A Sheikh, I., K Zaidi, S., Akram, M., R Jabir, N., 2014. Protein misfolding and aggregation in Alzheimer's disease and type 2 diabetes mellitus. *CNS Neurol. Disord.-Drug Targets (Formerly Curr. Drug Targets-CNS Neurol. Disord.)* 13, 1280–1293.
- Malik, R., Georgakis, M.K., Neitzel, J., Rannikmäe, K., Ewers, M., Seshadri, S., Sudlow, C.L., Dichgans, M., 2021. Midlife vascular risk factors and risk of incident dementia: longitudinal cohort and Mendelian randomization analyses in the UK Biobank. *Alzheimer's & Dementia*.
- Manly, B.F., 1986. Randomization and regression methods for testing for associations with geographical, environmental and biological distances between populations. *Res. Popul. Ecol. (Kyoto)* 28, 201–218.
- Matthews, K.A., Xu, W., Gaglioti, A.H., Holt, J.B., Croft, J.B., Mack, D., McGuire, L.C., 2019. Racial and ethnic estimates of Alzheimer's disease and related dementias in the United States (2015–2060) in adults aged  $\geq 65$  years. *Alzheimer's Dementia* 15, 17–24.
- Mugler, J.P., Kiefer, B., Brookeman, J.R., 2000. Three-dimensional T2-weighted imaging of the brain using very long spin-echo trains. In: *Proceedings of the 8th Annual Meeting of ISMRM*.
- Nasreddine, Z.S., Phillips, N.A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J.L., Chertkow, H., 2005. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J. Am. Geriatr. Soc.* 53, 695–699.
- Omidikia, N., Kompany-Zareh, M., 2013. Uninformative variable elimination assisted by gram-Schmidt orthogonalization/successive projection algorithm for descriptor selection in QSAR. *Chemom. Intell. Lab. Syst.* 128, 56–65.
- Park, B.-y., Lee, M.J., Kim, M., Kim, S.-H., Park, H., 2018. Structural and functional brain connectivity changes between people with abdominal and non-abdominal obesity and their association with behaviors of eating disorders. *Front. Neurosci.* 12, 741.
- Qiu, C., Fratiglioni, L., 2015. A major role for cardiovascular burden in age-related cognitive decline. *Nat. Rev. Cardiol.* 12, 267.
- Rao, G., 2001. Insulin resistance syndrome. *Am. Fam. Phys.* 63, 1159.
- Rashid, B., Dev, S.I., Esterman, M., Schwarz, N.F., Ferland, T., Fortenbaugh, F.C., Milberg, W.P., McGlinchey, R.E., Salat, D.H., Leritz, E.C., 2019. Aberrant patterns of

- default-mode network functional connectivity associated with metabolic syndrome: a resting-state study. *Brain Behav.* 9, e01333.
- Rashid, B., Poole, V.N., Fortenbaugh, F.C., Esterman, M., Milberg, W.P., McGlinchey, R.E., Salat, D.H., Leritz, E.C., 2021. Association between metabolic syndrome and resting-state functional brain connectivity. *Neurobiol. Aging* 104, 1–9.
- Raut, R.V., Snyder, A.Z., Mitra, A., Yellin, D., Fujii, N., Malach, R., Raichle, M.E., 2021. Global waves synchronize the brain's functional systems with fluctuating arousal. *Sci Adv* 7, eabf2709.
- Reaven, G., 2004. The metabolic syndrome or the insulin resistance syndrome? Different names, different concepts, and different goals. *Endocrinol. Metab. Clin.* 33, 283–303.
- Resnick, S.M., Pham, D.L., Kraut, M.A., Zonderman, A.B., Davatzikos, C., 2003. Longitudinal magnetic resonance imaging studies of older adults: a shrinking brain. *J. Neurosci.* 23, 3295–3301.
- Robinson, E.C., Garcia, K., Glasser, M.F., Chen, Z., Coalson, T.S., Makropoulos, A., Bozek, J., Wright, R., Schuh, A., Webster, M., 2018. Multimodal surface matching with higher-order smoothness constraints. *Neuroimage* 167, 453–465.
- Robinson, E.C., Jbabdi, S., Glasser, M.F., Andersson, J., Burgess, G.C., Harms, M.P., Smith, S.M., Van Essen, D.C., Jenkinson, M., 2014. MSM: a new flexible framework for multimodal surface matching. *Neuroimage* 100, 414–426.
- Ryu, C.-W., Coutu, J.-P., Greka, A., Rosas, H.D., Jahng, G.-H., Rosen, B.R., Salat, D.H., 2017. Differential associations between systemic markers of disease and white matter tissue health in middle-aged and older adults. *J. Cereb. Blood Flow Metab.* 37, 3568–3579.
- Sahathevan, R., Brodtmann, A., Donnan, G.A., 2012. Dementia, stroke, and vascular risk factors; a review. *Int. J. Stroke* 7, 61–73.
- Salat, D.H., Williams, V.J., Leritz, E.C., Schnyer, D.M., Rudolph, J.L., Lipsitz, L.A., McGlinchey, R.E., Milberg, W.P., 2012. Inter-individual variation in blood pressure is associated with regional white matter integrity in generally healthy older adults. *Neuroimage* 59, 181–192.
- Sandesara, P.B., Virani, S.S., Fazio, S., Shapiro, M.D., 2019. The forgotten lipids: triglycerides, remnant cholesterol, and atherosclerotic cardiovascular disease risk. *Endocr. Rev.* 40, 537–557.
- Sherifali, D., Nerenberg, K., Pullenayegum, E., Cheng, J.E., Gerstein, H.C., 2010. The effect of oral antidiabetic agents on A1C levels: a systematic review and meta-analysis. *Diabetes Care* 33, 1859–1864.
- Skaaby, T., Thuesen, B.H., Linneberg, A., 2017. Vitamin D, cardiovascular disease and risk factors. *Ultraviolet light in human health. Dis. Environ.* 221–230.
- Smith, S.M., Beckmann, C.F., Andersson, J., Auerbach, E.J., Bijsterbosch, J., Douaud, G., Duff, E., Feinberg, D.A., Griffanti, L., Harms, M.P., 2013. Resting-state fMRI in the human connectome project. *Neuroimage* 80, 144–168.
- Sozen, E., Ozer, N.K., 2017. Impact of high cholesterol and endoplasmic reticulum stress on metabolic diseases: an updated mini-review. *Redox Biol.* 12, 456–461.
- Spillantini, M.G., Crowther, R.A., Jakes, R., Hasegawa, M., Goedert, M., 1998.  $\alpha$ -Synuclein in filamentous inclusions of Lewy bodies from Parkinson's disease and dementia with Lewy bodies. *Proc. Natl Acad. Sci.* 95, 6469–6473.
- Stumps, A., Jagger-Rickels, A., Rothlein, D., Amick, M., Park, H., Evans, T., Fortenbaugh, F.C., Fortier, C.B., Fonda, J.R., Lee, D., 2021. Connectome-based functional connectivity markers of suicide attempt. *J. Affect. Disord.* 283, 430–440.
- Talaei, A., Mohamadi, M., Adgi, Z., 2013. The effect of vitamin D on insulin resistance in patients with type 2 diabetes. *Diabetol. Metab. Syndr.* 5, 1–5.
- Thompson, P.M., Mega, M.S., Woods, R.P., Zoumalan, C.I., Lindshield, C.J., Blanton, R.E., Moussai, J., Holmes, C.J., Cummings, J.L., Toga, A.W., 2001. Cortical change in Alzheimer's disease detected with a disease-specific population-based brain atlas. *Cereb. Cortex* 11, 1–16.
- Timar, O., Sestier, F., Levy, E., 2000. Metabolic syndrome X: a review. *Can. J. Cardiol.* 16, 779–789.
- Vaidya, J.G., Elmore, A.L., Wallace, A.L., Langbehn, D.R., Kramer, J.R., Kuperman, S., O'Leary, D.S., 2019. Association between age and familial risk for alcoholism on functional connectivity in adolescence. *J. Am. Acad. Child Adolesc. Psychiatry* 58, 692–701.
- van der Kouwe, A.J., Benner, T., Salat, D.H., Fischl, B., 2008. Brain morphometry with multiecho MPRAGE. *Neuroimage* 40, 559–569.
- Vasan, R.S., Larson, M.G., Leip, E.P., Evans, J.C., O'Donnell, C.J., Kannel, W.B., Levy, D., 2001. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N. Engl. J. Med.* 345, 1291–1297.
- Vasunilashorn, S.M., Dillon, S.T., Inouye, S.K., Ngo, L.H., Fong, T.G., Jones, R.N., Trivison, T.G., Schmitt, E.M., Alsup, D.C., Freedman, S.D., 2017. High C-reactive protein predicts delirium incidence, duration, and feature severity after major noncardiac surgery. *J. Am. Geriatr. Soc.* 65, e109–e116.
- Vincent, C., Hall, P.A., 2015. Executive function in adults with type 2 diabetes: a meta-analytic review. *Psychosom. Med.* 77, 631–642.
- Wald, D.S., Law, M., Morris, J.K., Bestwick, J.P., Wald, N.J., 2009. Combination therapy versus monotherapy in reducing blood pressure: meta-analysis on 11,000 participants from 42 trials. *Am. J. Med.* 122, 290–300.
- Wang, A., Liu, J., Li, C., Gao, J., Li, X., Chen, S., Wu, S., Ding, H., Fan, H., Hou, S., 2017. Cumulative exposure to high-sensitivity c-reactive protein predicts the risk of cardiovascular disease. *J. Am. Heart Assoc.* 6, e005610.
- Weir, M.R., Moser, M., 2000. Diuretics and  $\beta$ -blockers: is there a risk for dyslipidemia? *Am. Heart J.* 139, 174–184.
- Whitmer, R.A., Sidney, S., Selby, J., Johnston, S.C., Yaffe, K., 2005. Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology* 64, 277–281.
- Williams, V.J., Leritz, E.C., Shepel, J., McGlinchey, R.E., Milberg, W.P., Rudolph, J.L., Lipsitz, L.A., Salat, D.H., 2013. Interindividual variation in serum cholesterol is associated with regional white matter tissue integrity in older adults. *Hum. Brain Mapp.* 34, 1826–1841.
- Winkler, A.M., Ridgway, G.R., Webster, M.A., Smith, S.M., Nichols, T.E., 2014. Permutation inference for the general linear model. *Neuroimage* 92, 381–397.
- Xia, W., Wang, S., Rao, H., Spaeth, A.M., Wang, P., Yang, Y., Huang, R., Cai, R., Sun, H., 2015. Disrupted resting-state attentional networks in T2DM patients. *Sci. Rep.* 5, 1–10.
- Zhang, H., Lee, A., Qiu, A., 2017. A posterior-to-anterior shift of brain functional dynamics in aging. *Brain Struct. Funct.* 222, 3665–3676.