Neurovascular Mechanisms of Cognitive Aging:

Arteriosclerosis Precipitates Demyelination and Cognitive Decline

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Abstract

Cerebrovascular support is critical for healthy cognitive aging—arterial stiffness (arteriosclerosis) has been linked to heightened risks for cognitive decline, and ultimately for Alzheimer's disease and other forms of dementia. Conversely, neurovascular health is supported by lifestyle factors, including cardiorespiratory fitness. Here, capitalizing on a relatively large sample of participants with neuroimaging and behavioral data (*N* = 173, age range = 18-87 years), we aimed to provide support for a hierarchical model of neurocognitive aging, which links age-related declines in cerebrovascular health to the rate of cognitive decline via a series of intervening variables, such as cardiorespiratory fitness and white matter integrity. By applying a novel piecewise regression approach to our cross-sectional sample to support Granger-like causality inferences, we show that, on average, a precipitous decline in cerebral arterial elasticity (measured with diffuse optical imaging of the cerebral arterial pulse; pulse-DOT) *temporally precedes* an acceleration in the development of white matter lesions (T1-weighted MRI white matter hypointensities) by nearly a decade. And by employing serial mediation analyses, we show that age may impair cognition via the sequential indirect effect of arteriosclerosis and demyelination on fluid, but not crystallized, abilities. Importantly, we replicate these results using pulse pressure, an independent index of arterial health, thereby providing converging evidence for the central role of arteriosclerosis as an accelerating factor in normal and pathological aging. Enhanced cardiorespiratory fitness may also confer neuroprotective benefits by slowing the rate of arteriosclerosis.

Keywords: aging, cerebrovascular health, cerebral arterial pulse based on diffused optical tomography (pulse-DOT), diffuse optical tomography (DOT), arteriosclerosis, white matter hypointensities (WMHs), cardiorespiratory fitness

1. INTRODUCTION

Cerebrovascular health declines during aging due, in part, to the gradual stiffening of cerebral arteries, or loss of arterial elasticity (arteriosclerosis), and consequent decreases in perfusion of oxygenated blood to neural tissue (Fabiani et al., 2022; Zimmerman et al., 2021). It is believed that vascular risk factors including hypertension and diabetes contribute to both an increased risk of Alzheimer's disease (AD) pathology, such as increased amyloid beta burden, and non-AD cerebrovascular pathologies, such as white matter lesions and cerebral infarcts (Villeneuve & Jagust, 2015), albeit via largely independent pathways. Independent or not, the most common form of dementia during aging remains mixed dementia, involving both AD and cerebrovascular pathologies (Schneider et al., 2007). Therefore, it is crucial to conduct careful and thorough investigations of the neurovascular mechanisms implicated in "normal" and "pathological" cognitive aging, thereby permitting identification of potential points for intervention. The present study, utilizing a multimodal neuroimaging approach, provides multiple sources of converging evidence for the deleterious role that age-related declines in cerebrovascular health play in overall brain health and, ultimately, cognition. The positive effects of cardiorespiratory fitness on cerebrovascular health are also investigated, as they may provide a possible means of intervention to limit arteriosclerosis in aging (Bowie & Clements et al., 2021)

Arteriosclerosis contributes to the development of cerebral small vessel disease (CSVD; see Chojdak-Łukasiewicz et al., 2021 for a review). CSVD, a chronic and progressive neurovascular disease, primarily affects smaller cerebral blood vessels (< 400 µm in diameter) such as smaller arteries and arterioles, which supply blood to the brain's white matter and subcortical gray matter. In its acute form, CSVD accounts for 25% of all strokes, including 25% of all ischemic strokes. However, even in the absence of a symptomatic cerebrovascular accident, the presence of CSVD can be estimated on the basis of hallmark neuroimaging findings, such as recent small subcortical infarcts, "silent" lacunar

infarcts, enlarged perivascular spaces, cerebral microbleeds, cerebral atrophy, and, of particular interest here, white matter hypointensities (WMHs; hypointense regions on T1-weighted MRI images). It is believed that arteriosclerosis and atherosclerosis (the partial blockage or narrowing of arteries due to cholesterol plaque accumulation) ultimately result in partial ischemia and contribute to chronic cerebral hypoperfusion, which manifests as WMHs (Li et al., 2018). These WMHs largely reflect the loss of myelin sheath, due to loss of myelin-forming oligodendrocytes. The loss of electrically insulating myelin around neuronal axons decreases the velocity at which action potentials are conducted, which ultimately limits rates of neuronal firing and information exchange between neurons.

Cerebrovascular health can be measured noninvasively by examining indices of cerebral blood flow derived from magnetic resonance imaging (e.g., arterial spin labeling; Calamante et al., 1999) or Transcranial Doppler ultrasound (Purkayastha & Sorond, 2012). Near-infrared spectroscopy (NIRS), an optical imaging technique, can also provide noninvasive estimates of cerebrovascular health based on analyses of the pulse waveform, which represents oxygenation-dependent changes in near-infrared light absorption. Prior research utilizing this technique, known as diffuse optical tomography of the cerebral arterial pulse (pulse-DOT), has demonstrated that various parameters of the optical cerebral pulse are reliably associated with age, cardiorespiratory fitness, neuroanatomy (globally and regionally), and brain function (Chiarelli et al., 2017; Fabiani et al., 2014; Gratton et al., 2017; Kong et al., 2020; Tan et al., 2017, 2019). By examining the optical pulse waveform, which is time-locked to the EKG R wave (indicating peak ventricular depolarization), one can extract several indices of cerebrovascular health, including, but not limited to, the pulse relaxation function (PReFx) and pulse transit time (the inverse of pulse wave velocity; Fabiani et al, 2014). PReFx describes the temporal overlap between the forward and backward waves generated during each cardiac cycle. A greater overlap between these two waves is associated with low PReFx values and indexes arteriosclerosis, whereas a small overlap is associated with high PReFx values and higher arterial elasticity. Also, importantly, PReFx refers to cerebral arterial

elasticity in the arterial tract connecting the point of measurement with the place where peripheral resistance occurs, and the backward (reflected) wave is generated. This wave's formation occurs downstream from the measurement point. Therefore, despite being superficially measured, PReFx exhibits sensitivity not only to surface-level arterial stiffening but also to stiffness occurring in deeper regions, including those prone to white matter abnormalities. Furthermore, the cerebral pulse-DOT wave, synchronized with the EKG R wave, determines the temporal interval between this time-locking event and the initial diastolic peak of the cerebral pulse wave, which is termed the pulse transit time. Pulse transit time, contingent on the anchoring point's location, reflects both the health of upstream arteries from the measurement site and the condition of the local cerebral vasculature from which the measurement is acquired (Gratton et al., 2017). Longer pulse transit times indicate more compliant arteries, while shorter times indicate less elastic ones. To attain a highly reliable estimate of cerebrovascular health, the present paper employs a composite measure that is based on both aforementioned indices.

Based on prior evidence, Kong and colleagues (2020) proposed a hierarchical model of neurocognitive aging that positions impaired cerebrovascular integrity as one of the early cascading factors that detrimentally impact brain structure, function, and ultimately cognitive and emotional well-being (see **Figure 1** for an expanded diagram of this model). Specifically, to provide preliminary support for this model, they examined pairwise correlations among observed variables representing links in the hypothesized causal chain from aging to cognitive decline and dementia. While this model is not exhaustive or fully representative of all possible causal relations or pathways to cognitive decline, it emphasizes the role of cerebrovascular health, whose decline with age can be mitigated, or possibly even reversed in some cases, with regular aerobic exercise, thereby providing a potential target for readily available interventions to prevent or slow down age-related neurocognitive decline. To briefly summarize their findings, Kong et al. (2020) generally observed stronger correlations among variables

representing adjacent links in the model than those among variables representing non-adjacent links (e.g., $|r_{\text{structure-to-function}}| > |r_{\text{stucture-to-cognition}}|$). Although their findings were generally consistent with the proposed model, the cross-sectional correlational analysis and modest sample size (N = 48) precluded strong inferences regarding the postulated causal role of cerebrovascular mechanisms in accelerating cognitive aging.

The present study intended to address some of these shortcomings, and expand upon the preliminary findings of Kong et al. (2020) by increasing the sample size more than three-fold (N = 173) and conducting piecewise regression and multiple-mediator path analyses (i.e., mediation analyses involving more than one mediator/intervening variable), thereby warranting stronger Granger-like causal inferences. To accomplish this, we *pooled* and *harmonized* data from several in-lab studies, in which key measures of interest were obtained, including participants' age, cerebral arterial elasticity (here, a composite measure based on two indices derived from pulse DOT; Fabiani et al., 2014; Tan et al., 2017; Gratton et al., 2017), neuroanatomical integrity (WMH volume), and fluid cognition (a composite measure based on multiple neuropsychological tests), which is particularly susceptible to age-related decline. In addition, based on a validated equation accounting for age, gender, body mass index (BMI), resting heart rate, and self-report levels of activity (Jurca et al., 2005; Mailey et al., 2010), we calculated estimates of cardiorespiratory fitness, which is improved by regularly performing low-to-moderate intensity aerobic exercise. Given supporting evidence for the beneficial effect of aerobic exercise on brain health and cognition and its potential as a target for lifestyle interventions (Voss, Erickson, et al., 2013; Voss, Vivar, et al., 2013), we investigated the role of cardiorespiratory fitness level as a potential mediator of the relationship between aging and cerebrovascular health (see **Figure 1**). We also sought to replicate the results of all analyses by replacing pulse-DOT with a systemic index of arterial health, pulse pressure (Franklin, 2006; Izzo & Shykoff, 2001; Steppan et al., 2011), which is the

difference between systolic and diastolic blood pressure and generally increases with age. These additional analyses provide an external validation for the pulse-DOT approach.

Large cross-sectional epidemiological studies (Burt & Harris, 1994; Mahmood et al., 2014; Staessen et al., 2000; Stamler & Neaton, 2008) indicate that the effects of arteriosclerosis on vascular function do not typically become evident until middle age (50-60 years old). Therefore, we hypothesized that those brain and cognitive phenomena believed to be caused by the ill effects of arteriosclerosis on vascular function should be relatively spared until then, but should exhibit obvious declines after this age, with variable lags depending on the time required for damage to accumulate and disrupt brain tissue. To test this hypothesis, we performed piecewise (or segmented) regressions to model the expected relationships between age and arteriosclerosis (as indexed by pulse-DOT and pulse pressure), and age and WMHs. Using this analytic approach, we aimed to identify ages (or approximate age ranges) during which declines in cerebral arterial and white matter health begin or accelerate. Specifically, this approach allows us to identify "breakpoints" or "knees" joining two linear regression functions of significantly different slopes. The results of such analyses may justify stronger Granger-like causal inferences regarding the relationship between age-related declines in cerebrovascular health and the development of white matter lesions. For example, if the breakpoint estimates for age vs. pulse-DOT, and age vs. WMHs are separated by a theoretically "plausible" number of years (e.g., ~10 years, with non-overlapping 95% confidence intervals for the estimates) such that the development of arteriosclerosis temporally precedes the development or accelerated development of white matter lesions, thereby allowing ample time for the downstream effects of arteriosclerosis (among other vascular risk factors) to manifest as demyelination (among other structural pathologies), this would provide support for losses in cerebral arterial elasticity as a causal factor in demyelination. Of course, the employment of a cross-sectional design, as always, should caution readers against drawing unjustifiably strong conclusions, as confounding cohort effects are ever-present. Nonetheless, given the

difficulties and costs inherent to performing long-term longitudinal studies, this approach allows us to model these complex relationships in a cross-sectional sample.

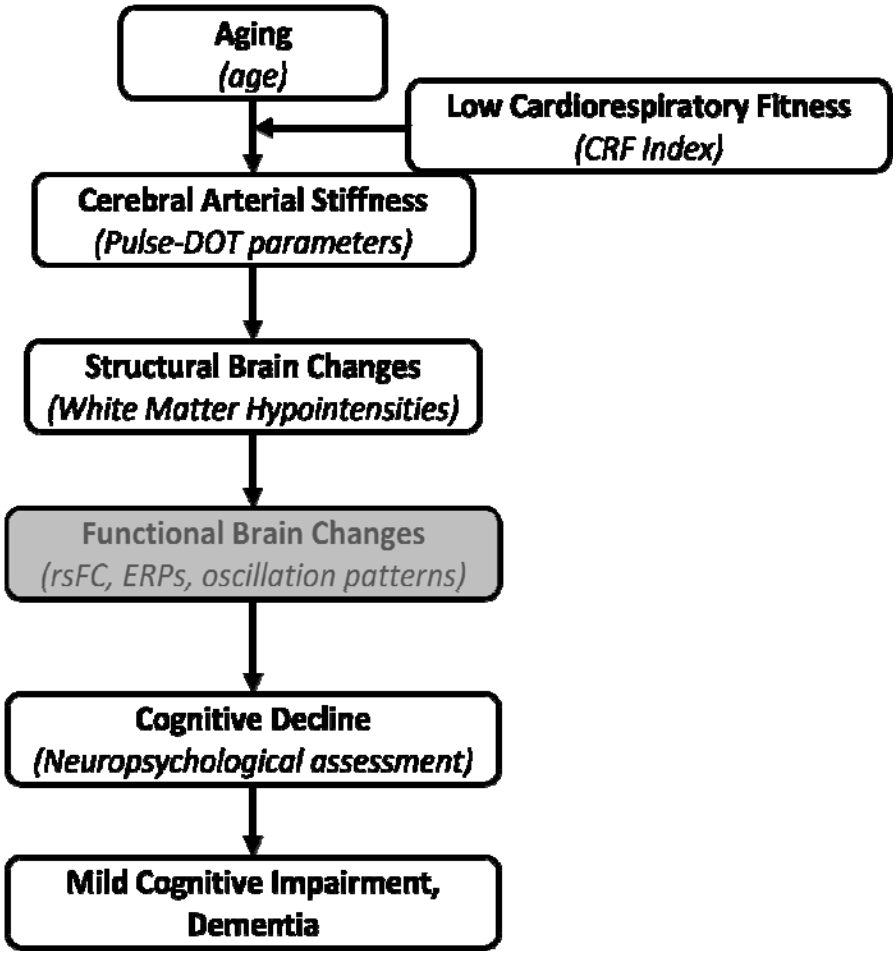

Figure 1: Hypothesized arterial dysfunction pathway to cognitive decline (*measures*). Evidence suggests that CRF may moderate the relationship between age and arterial health, thereby providing a point of intervention (via regular aerobic exercise) to prevent or slow the age-related progression of arteriosclerosis. The panel labelled 'Functional Brain Changes' is greyed out to indicate that the present paper's analyses do not include a marker of functional brain integrity, as traditionally defined.

CRF = cardiorespiratory fitness; pulse-DOT = diffuse optical tomography of the cerebral arterial pulse; rsFC = resting-state fMRI functional connectivity; ERPs = event-related brain potentials; MCI = mild cognitive impairment

2. METHOD

2.1 Participants

Neuroimaging and behavioral data from four studies conducted in our lab (two concluded, two ongoing) were *pooled* and *harmonized* in order to increase statistical power for a cross-sectional investigation of some of the relationships amongst variables in the hypothesized cascade model of neurocognitive aging depicted in **Figure 1**. *Despite the use of pooled data, please note that all the analyses presented here are previously unpublished*. The pooled sample included ***N* = 173 unique participants** (see **Table 1** for sample size, self-reported gender and age-related statistics sorted by study).

Descriptive Characteristics of the Sample					
	Study 1	**Study 2**	**Study 3**	**Study 4**	**All Studies**
N	45 (22 females)	44 (22 females)	60 (39 females)	24 (17 females)	173 (100 females)
Mean **Age** in years (*SD*) [Range]	70.74 (*8.85*) [55.75-87.95]	46.55 (*17.51*) [18.98-75.11]	61.58 (*5.54*) [50.77-70.73]	47.66 (*13.33*) [25.22-71.29]	58.21 (*15.03*) [18.98-87.95]

Table 1: Descriptive characteristics of the sample arranged by study. The rightmost column includes statistics for all participants across all studies.

Participants in studies 1 and 2 reported no history of neurological or psychiatric disorders and had no signs of dementia (as assessed by a score > 51 on the modified Mini-Mental Status Examination (MMSE; Mayeux et al., 1981)) or depression (as assessed by the Beck's Depression Inventory; (Beck et al., 1996)). Participants in studies 3 and 4 were administered the Montreal Cognitive Assessment and were included if they scored > 20 points[1] (Nasreddine et al., 2005). Informed consent was provided by each participant. All procedures were approved by the Institutional Review Board of the University of Illinois.

[1] Nasreddine et al. (2005) suggest that cognitively intact participants score 26-30 points, while participants scoring 18-25 possibly suffer from mild cognitive impairment (MCI). Therefore, studies 3 and 4 may include some participants who may have suffered from MCI during assessments and neuroimaging sessions, although variability in SES and education can also affect the score range.

2.2 Data Acquisition

2.2.1 Cardiorespiratory Fitness Assessment

VO_2max is the gold standard measure for cardiorespiratory fitness (CRF). It represents an individual's maximum oxygen consumption during a high-intensity exercise test. However, older and less fit individuals may be unable to participate in such rigorous exercises due to health conditions. Because studying the relationship between cardiorespiratory fitness, aging, and cerebrovascular health in these individuals is vital, we estimated CRF using an equation based on easily obtainable parameters that reliably predict VO_2max. This equation involves a linear combination of weighted variables such as gender, age, BMI, resting heart rate, physical activity score, and a numerical constant (Jurca et al., 2005; Stamatakis et al., 2013). The resulting CRF index (eCRF), expressed in metabolic equivalents, has shown strong accuracy in approximating VO_2max in a large sample of over 40,000 individuals, with correlations of approximately .7 or higher. Mailey and colleagues (2010) extended the validity of eCRF specifically to 172 older adults, ranging in ages from 60–80 (see also McAuley et al., 2011).

2.2.2 Neuropsychological Assessment

	Fluid Ability			Crystallized Ability
	PROCESSING SPEED	**WORKING MEMORY**	**REASONING/FLEXIBILITY**	**VERBAL**
STUDY 1	-Trail Making Task A	-OSPAN -Forward Digit Span -Backward Digit Span	-Wisconsin Card Sorting Test (accuracy) -Trail Making Task A minus B -KBIT-2 Matrices	-Shipley Vocabulary Subtest -KBIT-2 Verbal Scores
STUDY 2	-Trail Making Task A	-OSPAN -Forward Digit Span -Backward Digit Span	-Wisconsin Card Sorting Test (accuracy) -Trail Making Task A minus B -KBIT-2 Matrices -Raven's Progressive Matrices	-Shipley Vocabulary Subtest -KBIT-2 Verbal Scores
STUDY 3	-Pattern Comparison (NIH Toolbox) -Oral Symbol Digit Test (NIH Toolbox)	-OSPAN -List Sorting WM (NIH Toolbox) -Backward Digit Span	-Flanker (NIH Toolbox) -Dimensional Change Card Sorting (NIH Toolbox)	-Picture Vocabulary (NIH Toolbox) -Oral Reading Recognition (NIH Toolbox)
STUDY 4	-Pattern Comparison (NIH Toolbox) -Oral Symbol Digit Test (NIH Toolbox)	-WM Span Tasks (rotation, symmetry, operation) -List Sorting WM (NIH Toolbox) -Backward Digit Span	-Flanker (NIH Toolbox) -Dimensional Change Card Sorting (NIH Toolbox)	-Picture Vocabulary (NIH Toolbox) -Oral Reading Recognition (NIH Toolbox)

Table 2: Neuropsychological tests (listed by study) administered to assess various cognitive constructs (each column). All assessments under the 'Fluid Ability' heading (processing speed, working memory, reasoning/flexibility) were statistically harmonized and used to compute a composite fluid ability score. The same was done for tests under the 'Crystallized Ability' heading (verbal), comprising tests that assess crystallized ability.

Across all four studies, participants were administered an array of neuropsychological tests, including the Trail Making Tests A and B (Corrigan & Hinkeldey, 1987) to assess processing speed and working memory, the OSPAN task (Unsworth et al., 2005) to assess working memory capacity, and other tests of fluid and crystallized abilities. Given that different, non-overlapping tests of the same cognitive construct were sometimes administered across studies (e.g., Wisconsin Card Sorting Test vs. Dimensional Change Card Sort Test—NIH Toolbox, both of which assess cognitive flexibility), statistical harmonization of these data was required to ensure that scores were comparable. We employed a procedure that allowed us to compute standardized scores based on a multitude of tests (some of which overlapped and some of which did not) assessing crystallized ability and fluid abilities. This procedure is summarized in section 2.3.1, with a more detailed explanation and validation of the procedure in **supplementary materials**. The tests administered and statistically harmonized are listed in **Table 1.**

2.2.3 Structural MRI Acquisition

For participants in studies 1 and 2 identical high-resolution structural scans were collected in a 3-Tesla Siemens Trio MR scanner, using a 12-channel head coil. The 3D T1-weighted anatomical scan for each participant was acquired using an MPRAGE sequence with the following parameters: TR = 1,900 ms; TE = 2.32 ms; 192 sagittal slices; slice thickness = 0.90 mm; FA = 9°; voxel sizes = 0.9 × 0.9 × 0.9 mm, field-of-view (FOV) = 172.8 × 230 × 230 mm.

Participants' T1-weighted images in studies 3 and 4 were acquired in a 3-Tesla Siemens Prisma MR scanner, using a 20-channel head coil. The MPRAGE sequence utilized the following pulse parameters: TR = 2,400 ms; TE = 2.31 ms; 224 sagittal slices; slice thickness = 0.80 mm; FA = 8°; voxel sizes = 0.8 × 0.8 × 0.8 mm, field-of-view (FOV) = 179.2 × 256 × 256 mm. Acceleration factor = 2.

2.2.4 Diffuse Optical Imaging data acquisition

Cerebral arterial elasticity (pulse-DOT) data were obtained during a resting-state optical imaging session, in which seated participants fixated on a cross in the center of a screen. Optical data were acquired with a multichannel frequency-domain oximeter (ISS Imagent, Champaign, Illinois) equipped with 128 laser diodes (64 emitting light at 690 nm and 64 at 830 nm) and 24 photomultiplier tubes. Time-division multiplexing was employed so that each detector picked up light from 16 different sources at different times within a multiplexing cycle at a sampling rate of 39.0625 Hz. The light was transmitted to the scalp by using single-optic fibers (0.4-mm core) and from the scalp back to the photomultiplier tubes by using fiber bundles (3-mm diameter). The fibers were held in place using soft, but semirigid, custom-built helmets, fitted to participants based on their head circumference.

After the helmet was set up, the locations of the optodes were marked digitally to improve spatial accuracy during later data processing, including anatomical coregistration with each participant's structural MRI. Fiducial markers were placed on each participant's left and right preauricular points and on the nasion. These fiducial points, optode locations, and other scalp locations were digitized with a Polhemus FastTrak 3D digitizer (accuracy: 0.8 mm; Colchester, VT) by using a recording stylus and three

head-mounted receivers, which allowed for small movements of the head in between measurements. Optode locations and structural MRI data were then coregistered using the fiducials and a surface-fitting Levenberg and Marquardt algorithm (Chiarelli et al., 2015).

Concurrently, an electrocardiogram (EKG) was recorded using a Brain-Vision recorder and a Brain Products V-Amp 16 integrated amplifier system (Brain Products, Germany). Specifically, lead 1 of the EKG (left wrist referenced to right wrist) was recorded with a sampling rate of 500 Hz and a band-pass filter of 0.1–100 Hz. The exact timing of each R-wave peak was determined by searching for peak points exceeding a voltage threshold (scaled for each participant) and dismissing any peak points outside the normal range of interbeat intervals. The identification of each peak was verified by visual inspection, and false detections, usually misidentifying the T-wave as the R-wave, were eliminated. Concurrent acquisition of EKG and optical pulse data allowed us to time-lock the optical pulse data to the R wave of the EKG, thereby ensuring that the same pulse was analyzed irrespective of its location within the brain. Optical pulse data were acquired from most of the scalp surface but with varying degrees of density (indexed by the number of channels) depending on the specific study. Optical data from study 1 were acquired via one montage (i.e., a single source-detector configuration) comprising 384 channels. Study 2 utilized four montages, each containing 384 channels, which when aggregated for analyses totaled 1,536 channels. Study 3 utilized two montages, each containing 768 channels, for a total of 1,536 channels. Lastly, data for study 4 were acquired for one montage containing 768 channels.

2.2.5 Systemic Pulse Pressure

Participants' blood pressure was taken at the brachial artery of the upper arm at three time points across the experiment and averaged to provide reliable measures of systolic and diastolic blood pressure. Systemic pulse pressure was computed by taking the difference between systolic and diastolic blood pressure. This served as a methodologically independent index of systemic arterial elasticity that provided us the opportunity to validate the results observed when using pulse-DOT as an index of cerebrovascular health, thereby potentially strengthening our conclusions.

2.3 Data Processing and Statistical Harmonization

For all variables (except age), values greater or less than three standard deviations from the sample mean were excluded as outliers. Subsequently, any variables exhibiting positively skewed distributions were log-transformed to be approximately normal.

2.3.1 Neuropsychological Data

To statistically harmonize measures tapping into overlapping constructs across studies, we computed standardized scores of crystallized and fluid abilities for each participant. Fluid ability consists of scores on tests assessing abilities such as processing speed, working memory, cognitive flexibility, and reasoning, which are highly susceptible to age-related decline (see **Table 1** for the complete list of tests

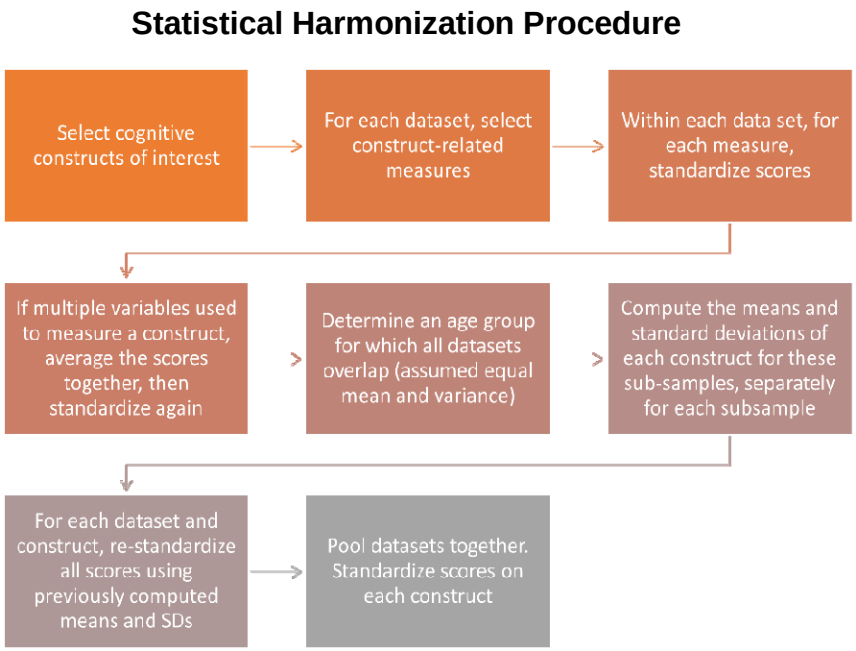

Figure 2: Diagram summarizing the steps involved in statistically harmonizing non-overlapping tests of the same underlying psychological construct across multiple studies. See supplementary material for additional details and validation of this procedure.

used to compute composite fluid and crystallized ability scores). The steps of this procedure are summarized in **Figure 2**. Please view the **supplementary materials** for a more detailed description and validation of the procedure, in which we demonstrate that the age-related trends for the harmonized fluid and crystallized composite scores replicate those observed in prior cognitive aging research.

2.3.2 Structural MRI Data

The FreeSurfer 6.0 image analysis suite (http://surfer.nmr.mgh.harvard.edu/; Fischl & Dale, 2000) was used for cortical reconstruction and volumetric segmentation of all the structural MPRAGE images for all four studies. Estimated total intracranial volume was also extracted from the structural

images derived from the same automated procedures in FreeSurfer (Buckner et al., 2004). WMHs were labeled automatically, based on FreeSurfer 6.0's probabilistic procedure (Fischl et al., 2002). Prior to any analyses, WMH volume was adjusted for estimated total intracranial volume and log-transformed due to its positive skewness.

2.3.3 Optical Measures of Cerebral Arterial Elasticity

Cerebral arterial elasticity was quantified using a composite of two estimates derived from pulse-DOT(Chiarelli et al., 2017; Fabiani et al., 2014). As reviewed in the introduction, the first measure, PReFx, describes the temporal overlap between the forward and backward waves generated during each cardiac cycle. A greater overlap between these two waves is associated with low PReFx values and indexes arteriosclerosis, whereas a small overlap is associated with high PReFx values and higher arterial elasticity. The second measure, pulse transit time is the inverse of pulse wave velocity (as distances cannot be calculated for cerebral arteries). Longer pulse transit times (i.e., slower PWVs) indicate more elastic arteries, and shorter pulse transit times (i.e., faster PWVs) indicate less elastic arteries. To attain a more reliable estimate of cerebral arterial elasticity, we computed factor scores for all participants based on PReFx and pulse transit time by standardizing each measure, computing their sum, and re-standardizing the sum. This estimate, which is a composite pulse-DOT measure, will generally be referred to as simply 'pulse-DOT' throughout the remainder of this paper.

To derive the PReFx and pulse transit time, optical AC intensity data (i.e., the average measures of the amount of light produced by a specific source and reaching a specific detector during a multiplexed 1.6-ms interval) at 830 nm were normalized, movement corrected (Chiarelli et al., 2015), and band-pass filtered between 0.5 and 10 Hz by using a Butterworth filter. The arterial pulse waveform for each channel was obtained by averaging the AC light intensity time-locked to the peak of the R wave of the EKG, ensuring that the same pulse cycle was measured at all locations. Only source-detector distances between 2 and 6 cm were used in the analysis, allowing us to image phenomena occurring

approximately between 1 and 3 cm in depth, thereby providing coverage of most of the cerebral cortex. Here, we employed a global measure of cerebral arterial elasticity, which is the average pulse-DOT across all voxels.

2.3.4 Statistical Analyses

2.3.4.1 Pulse-DOT—Pulse Pressure Correlations.

To ensure that our relatively independent indices of vascular health were correlated to some extent, we conducted bivariate and partial correlations between pulse-DOT and pulse pressure, partialling out age. Note, however, that pulse-DOT may be more sensitive to the status of the *cerebrovasculature*, whose health may differ from that of the aorta, coronary arteries, and arteries throughout the periphery. A significant, moderate correlation would suggest that these indices are measuring similar underlying phenomena, although pulse pressure may be less sensitive to cerebral arterial health, as its point of measurement is peripheral. However, given that systemic pulse pressure is one of the strongest predictors of cerebrovascular accidents (Glynn et al., 2000; Panagiotakos et al., 2005), we expect to observe some covariance between these central and peripheral indices of vascular health, which will provide an external validation for the more novel pulse-DOT estimates.

2.3.4.2 Piecewise Regression

We conducted two piecewise linear regression analyses in which two lines joined by a single breakpoint were fit to the data, allowing us to estimate the 'best' age at which the pre- and post-breakpoint slopes significantly differ. This was done using the *segmented* package (Muggeo, 2008) in R (R Core Team, 2022) and RStudio (RStudio Team, 2020). As a reminder, these analyses were used to estimate a single breakpoint and to test the significance of the difference in slopes between the two fitted lines (i.e., whether the breakpoint did exist) for the relationships between age and pulse-DOT, pulse pressure, and WMHs. High similarity between the breakpoint estimates for age vs. pulse-DOT and age vs. pulse pressure would provide converging evidence from two independent indices of vascular health, thereby instilling additional confidence in the estimated age range during which vascular

problems may accelerate. Conversely, a large difference in the breakpoint estimates for age vs. pulse-DOT/pulse pressure and age vs. WMHs, with non-overlapping confidence intervals, may suggest that precipitous declines in arterial elasticity (arteriosclerosis) temporally precede an acceleration in white matter lesion burden (demyelination), suggesting that these two phenomena may be causally related.

To briefly summarize this analytic approach, via an iterative process, an optimal breakpoint is estimated that minimizes the difference in slope between the two linear regression lines (see Muggeo, 2008 for a detailed explanation of the model and estimation process). We employed the (pseudo) Score statistic (Muggeo, 2016) via the 'pscore.test()' function to test for a non-zero difference-in-slope parameter of the bilinear relationship. Simulation studies have shown that this test is more statistically powerful than the alternative Davies test (Davies, 1987) when the existence of only one breakpoint is being tested (Muggeo, 2016), as is done in the present paper.

2.3.4.3 ***Multiple-Mediator Path Analyses***

Based on previous work in which preliminary correlational evidence was presented for a hierarchical cascade model of neurocognitive aging (Kong et al., 2020), we formed *a priori* hypotheses regarding the relationships among measures representing links in the hypothetical causal chain (**Figure 1**). Specifically, we aimed to test a serial multiple mediator model with four mediators (X = age, M_1 = Pulse-DOT or Pulse Pressure (Vascular Index), M_2 = WMH Volume (Structural Index), Y = cognitive ability, fluid or crystallized ability). Consequently, we performed several multiple-mediator mediation analyses with two intervening variables. Using the PROCESS macro (Hayes, 2017) in R, we conducted four *two-mediator* path analyses. Missing data was handled via listwise deletion, such that if a given subject has a missing value for at least one measure in a model, it is excluded from all tests of that model. Ultimately, we tested the following relationships:

1) Age → Pulse-DOT → WMH Volume → Fluid Cognition
2) Age → Pulse Pressure → WMH Volume → Fluid Cognition

3) Age → Pulse-DOT → WMH Volume → Crystallized Cognition

4) Age → Pulse Pressure → WMH Volume → Crystallized Cognition

We did not predict a significant relation between Pulse-DOT and crystallized ability or a significant indirect effect with WMHs as the mediator of this relationship, because crystallized abilities are largely invulnerable to normal neurocognitive decline (until ~70 years of age, see **Figure S2** of **supplementary materials**), and continue to increase throughout adulthood. Therefore, this model was included to demonstrate a dissociation between the effects of age-related changes in our two intervening variables on fluid abilities versus crystallized abilities.

It should be noted that, because we had *a priori* hypotheses regarding the sequence of events involved in our hypothesized cascade model, an age-related loss of cerebral arterial elasticity may *indirectly* affect cognition via its deleterious impact on white matter integrity, manifesting as demyelination (WMHs). This has obvious consequences for brain function, as the efficiency of communication between brain regions is disrupted due to these lesions, which ultimately impact cognition, possibly manifesting as age-related slowing and reduced working memory capacity, for example.

As the distribution of an indirect effect, the product of the relevant path coefficients ($a_1 \times b_1$, $a_2 \times b_2$, or $a_1 \times d_{21} \times b_2$), is typically non-normal and asymmetric (Hayes, 2009), a bias-corrected bootstrap approach was implemented for significance testing of the indirect effects in each model based on 5,000 bootstrap samples (Preacher & Kelley, 2011). To clarify, in a two-mediator model, path d_{21} corresponds to the effect of *M1* on *M2* when controlling for *X.* We also report coefficient estimates for the total effect, *c* (*Y* regressed on *X* without covariates), and direct effect, *c'*, which is the effect of *X* on *Y* when statistically controlling for the effect of both mediators, M_1 and M_2 on *Y* (paths b_1 and b_2).

2.3.4.4 Relationship between Age, Cardiorespiratory Fitness, and Cerebrovascular Health

Initially, we were primarily interested in the potentially moderating role of eCRF on the relationship between age and vascular health. That is, would eCRF moderate the relationship between age and vascular health such that higher fit participants' vascular health declines more slowly with age, while lower fit participants exhibit a steeper age-related decline? However, given that eCRF is confounded with age such that higher fit participants are largely younger (< 50 years), while lower fit participants are predominantly older (> 50 years), this precluded proper usage of a moderation analysis to discern an interaction between age and cardiorespiratory fitness effects on vascular health. Alternatively, we attempted to assess whether the relation between age and eCRF was additive (i.e., exerting independent effects on the outcome) by conducting bivariate and partial correlations between eCRF and pulse-DOT or pulse pressure while controlling for age. Significant bivariate and partial correlations would indicate that there is an independent, or additive, effect of cardiorespiratory fitness on vascular health, beyond that of one's age. The absence of evidence for an additive relationship, especially in the absence of a properly conducted moderation analysis, leaves open the possibility that the effect of age and cardiorespiratory fitness on arterial health is synergistic.

3. RESULTS

3.1 Correlations between Pulse-DOT and Systemic Pulse Pressure

Systemic pulse pressure and pulse-DOT were moderately negatively correlated ($r(163) = -.28$, $p < .001$) such that increases in pulse pressure were generally associated with declines in pulse-DOT (**Figure 3a**). Importantly, when controlling for age (**Figure 3b**), we still observed a statistically significant negative

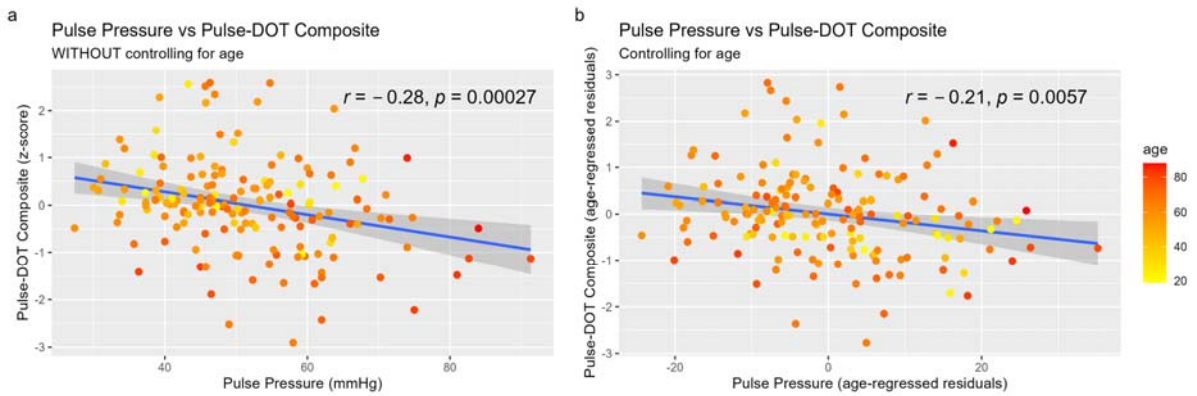

Figure 3: Scatterplots of systemic pulse pressure (systolic blood pressure – diastolic blood pressure) and pulse-DOT (a composite measure of cerebral arterial elasticity based on two optical measures of the pulse: PReFx and pulse transit time). The bivariate **(a)** and partial correlation **(b)** plots both demonstrate significant linear relationships between these two indices of vascular health, but the strength of the correlations is low enough to indicate there is an appreciable amount of unshared variance. Therefore, if the results of subsequent analyses (piecewise regression, mediation) utilizing either index generally converge, this strengthens our inferences regarding the effects of age-related declines in arterial health on brain structure and cognition.

partial correlation ($r(162) = -.21$, $p < .01$). These analyses establish that, while methodologically and spatially distinct indices of arterial elasticity, pulse pressure and pulse-DOT account for overlapping variance, allowing us to validate results in subsequent analyses (e.g., piecewise regression, serial mediation). This may permit stronger causal inferences regarding the mechanisms implicated in neurocognitive aging, especially as it pertains to the role of vascular health.

3.2 Piecewise Regression Analyses

As predicted, the relationships between age and arterial health, and age and white matter lesions exhibited non-linear relationships, leading to suboptimal fits when fitting single ordinary least squares regression functions to these data (**Figure 4**).

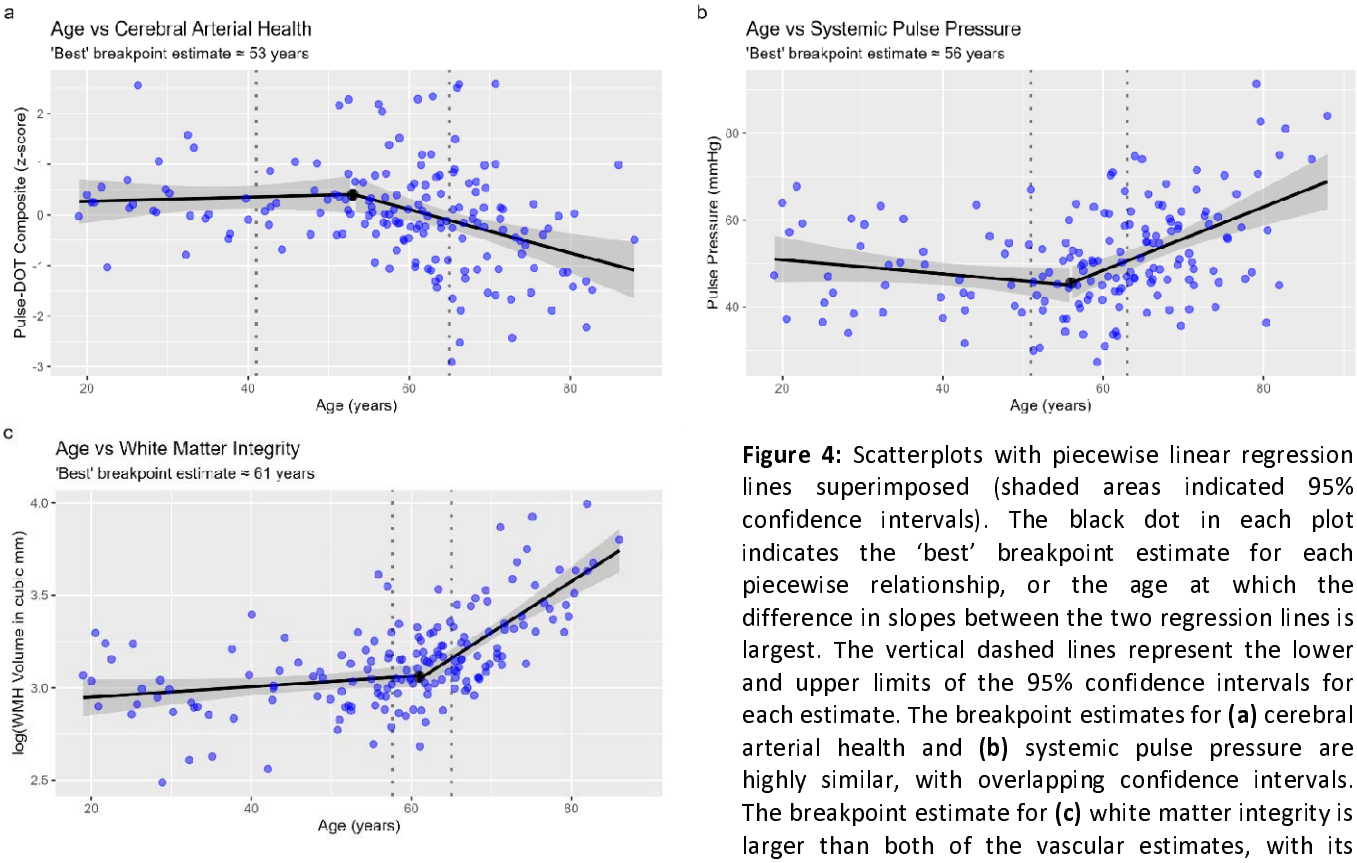

Figure 4: Scatterplots with piecewise linear regression lines superimposed (shaded areas indicated 95% confidence intervals). The black dot in each plot indicates the 'best' breakpoint estimate for each piecewise relationship, or the age at which the difference in slopes between the two regression lines is largest. The vertical dashed lines represent the lower and upper limits of the 95% confidence intervals for each estimate. The breakpoint estimates for **(a)** cerebral arterial health and **(b)** systemic pulse pressure are highly similar, with overlapping confidence intervals. The breakpoint estimate for **(c)** white matter integrity is larger than both of the vascular estimates, with its confidence interval only partially overlapping that of the vascular estimates, suggesting that declines in vascular health precede the accelerated development of white matter lesions.

3.2.1 Age vs. Pulse-DOT Composite

Piecewise linear regression analyses of the association between age and pulse-DOT (n = 171) yielded a single breakpoint estimate (age = 53.11 years, SE = 6.04, p < .01; 95% CI [41.12, 65.04]), indicating that the difference in slopes was statistically significant before and after this point (β_1 = .06, 95% CI [-.31, .43]; β_2 = -.65, 95% CI [-.98, -.31]; standardized regression coefficients reported), with only the post-breakpoint slope (β_2) indicating a significant relationship (**Figure 4a**). As such, our data suggest that a reliable, precipitous decline in cerebral arterial elasticity may not occur until late middle age.

3.2.2 Age vs. Systemic Pulse Pressure

Piecewise linear regression analyses of the association between age and systemic pulse pressure (n = 167) yielded a single breakpoint estimate (age = 57.45 years, SE = 3.05, p < .001; 95% CI [51.42 63.47]), indicating that the difference in slopes was statistically significant before and after this point (β_1 = -.15, 95% CI [-.43, .12]; β_2 = 1.00, 95% CI [0.63, 1.38]; standardized regression coefficients reported), with only the post-breakpoint slope (β_2) indicating a significant relationship (**Figure 4b**). The breakpoint estimate only differs from the pulse-DOT estimate by a few years and is also consistent with prior research examining age-related changes in pulse pressure (Izzo & Shykoff, 2001).

3.2.3 *Age vs. White Matter Hypointensity Volume*

Piecewise linear regression analyses of age and white matter hypointensity volume (n = 171) yielded a single breakpoint estimate (age = 61.30 years, SE = 1.86, p < .001; 95% CI [57.62, 64.97]), indicating that slopes were reliably different before and after this point (β_1 = .16, 95% CI [-.03 .34]; β_2 = 1.60, 95% CI [1.20, 2.00]; standardized regression coefficients reported), with only β_2 yielding a significant relationship (**Figure 4c**). Note that this breakpoint estimate is larger than that of both vascular estimates, and its confidence interval only partially overlaps that of the vascular estimates, suggesting that declines in vascular health generally precede the accelerated development of white matter lesions.

3.3 Multiple-Mediator Path Analyses

3.3.1 Age → Pulse-DOT → WMH Volume → Fluid Cognition

To complement the prior analyses, we conducted several multiple-mediator path analyses to test the hypothesized relationships among age, arterial health (pulse-DOT or systemic pulse pressure), white matter lesions (WMH volume), and cognition (fluid or crystallized). Firstly, we tested the two-mediator indirect effect of age on fluid cognition via pulse-DOT and WMH volume (**Figure 5;** n = 162). Based on a bias-corrected bootstrapped 95% confidence interval, the two-mediator serial indirect effect ($a_1 \times d_{21} \times b_2$) was significant, suggesting that age-related declines in cerebral arterial health impact fluid

abilities *via* their deleterious effects on white matter integrity. Importantly, we observed a significant indirect effect of age on fluid cognition *via* white matter lesions ($a_2 \times b_2$), but *not via* cerebral arterial health ($a_1 \times b_1$), suggesting, once again, that age-related declines in cerebral health largely manifest as degraded white matter, which negatively impacts fluid abilities such as processing speed, working memory, and reasoning. Lastly, no significant indirect effects were observed when crystallized cognition was the final outcome (see **Figure S3** in **supplementary materials** for results).

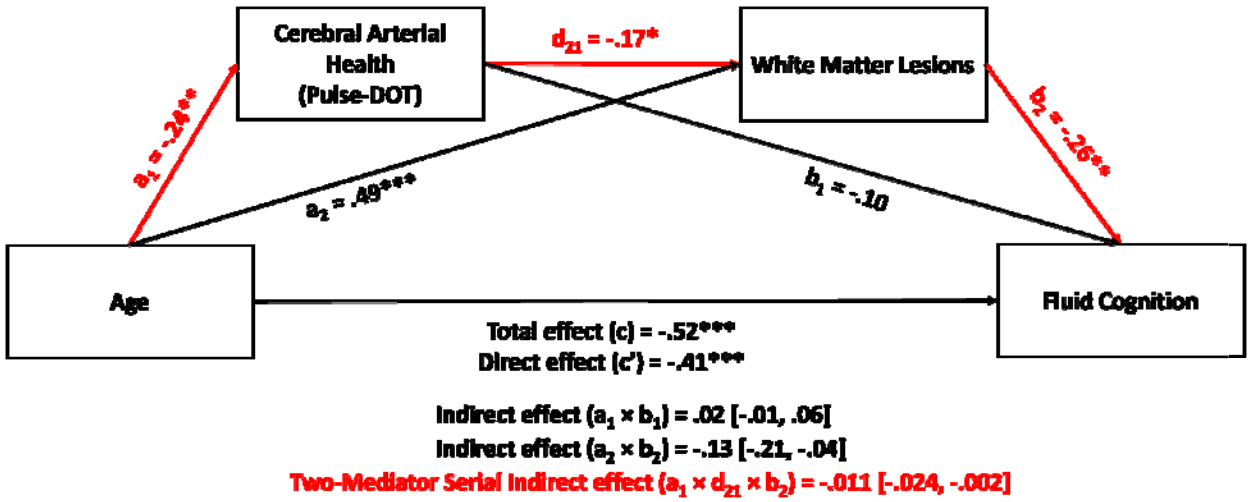

Figure 5: Serial mediation diagram examining the effect of age on fluid cognition via two intervening variables, pulse-DOT (an index of cerebral arteriosclerosis) and white matter hypointensities (an index of white matter lesions). A bootstrapped 95% confidence interval not including zero indicates a significant indirect effect at $p < .05$. Red font/arrows indicate paths implicated in the multiple-mediator indirect effect. *$p < .05$, **$p < .01$, ***$p < .001$

3.3.2 Age → Pulse Pressure → WMH Volume → Fluid Cognition

We sought to replicate the pulse-DOT analyses using pulse pressure as a separate index of arterial health (which is presumably less sensitive to the status of cerebral arteries, as it is measured peripherally at the brachial artery). We re-ran the two-mediator analyses (n = 159) (**Figure 6)**, and successfully replicated the pattern of results observed in **Figure 5**. This indicates that the results of our initial pulse-DOT analyses are reliable and consistent with a cascade model of neurocognitive aging in which age-related declines in cerebral arterial health contribute to demyelination, which ultimately detrimentally impact fluid cognition. Lastly, as with the pulse-DOT mediation analyses, no significant

indirect effects were observed when crystallized cognition served as the final outcome (see **Figure S4** in **supplementary materials** for details).

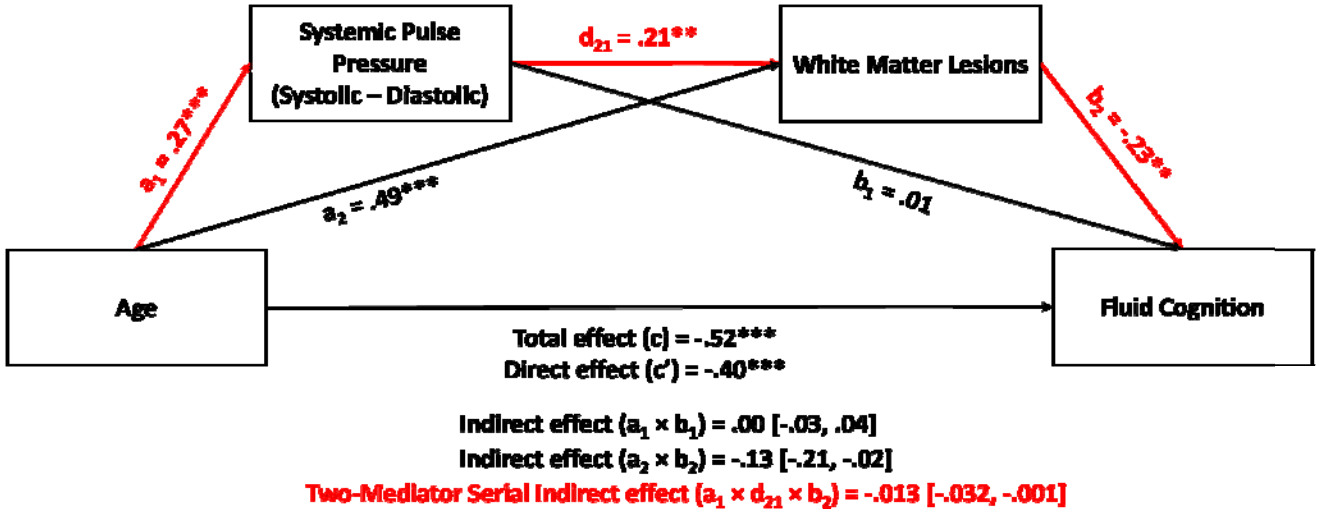

Figure 6: Serial mediation diagram examining the effect of age on fluid cognition via two intervening variables, systemic pulse pressure (an index of arteriosclerosis) and white matter hypointensities (an index of white matter lesions).
A bootstrapped 95% confidence interval not including zero indicates a significant indirect effect at $p < .05$.
Red font/arrows indicate paths implicated in the multiple-mediator indirect effect. *$p < .05$, **$p < .01$, ***$p < .001$

3.4 Effects of Age and Cardiorespiratory Fitness on Vascular Health

The well-known strong negative correlation between age and eCRF, indicating multicollinearity ($r(171) = -.64$, $p < .001$; also see **Figure 7a and 7d**) precluded a proper moderation analysis in which we could examine a potential interaction between age and estimated cardiorespiratory fitness on indices of arterial health. Although we cannot formally test for a significant interaction and, therefore, moderation by eCRF of the relationship between age and arterial health, we attempted to rule out whether the effects of age and eCRF are additive.

The bivariate relationships between eCRF and pulse-DOT ($r(169) = .29$, $p < .001$; **Figure 7b**) and eCRF and systemic pulse pressure ($r(165) = -.21$, $p < .01$; **Figure 7e**) were statistically significant. However, when controlling for age, neither the partial correlation between eCRF and pulse-DOT ($r(168) = .13$, $p = .07$; **Figure 7c**) nor the one between eCRF and systemic pulse pressure ($r(164) = -.02$, $p = .70$;

Figure 7f) remained significant, suggesting that if there is an effect of cardiorespiratory fitness on

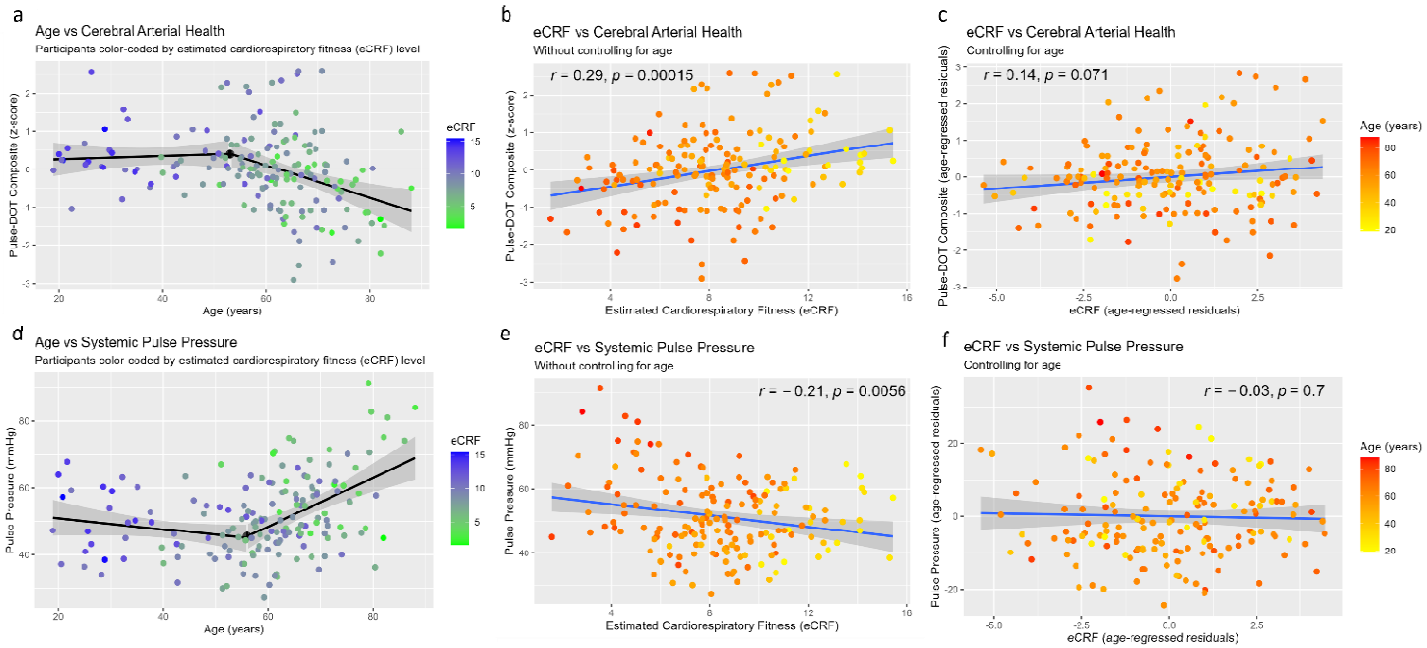

Figure 7: Because age was confounded with eCRF (as seen in plots **(a)** and **(d)**), a moderation analysis to test for an interactio between age and eCRF on arterial health (pulse-DOT or systemic pulse pressure) was deemed inappropriate. Therefore, we teste whether there were independent, additive effects of age and eCRF on either index of arterial health by conducting bivariate an partial correlations, partialling out the effect of age. Plot **(b)** indicates that there is a significant bivariate correlation between eCR and Pulse-DOT, but when age is partialled out of this relationship as seen in plot **(c)**, the correlation is no longer significant (p = .07 Similarly, plot **(e)** demonstrates a significant bivariate correlation between eCRF and pulse pressure, which disappears in plot **(f** when age is partialled out. These results do not support the claim that age and eCRF exert independent effects on arterial health.

vascular health, it is not independent of age. This hints at the possibility that the relationship between age and eCRF on vascular health is interactive and antagonistic.

4. DISCUSSION

We have employed a novel approach to test a cascade model of the role of arteriosclerosis in cognitive aging and ultimately dementia (**Figure 1**). This approach includes the use of piecewise correlations to establish the relative timing of emergence of phenomena in the cascade, to enable Granger-like causal inferences in an otherwise cross-sectional sample. Based on two largely independent

measures of cerebral and systemic arterial health, we have provided converging evidence that age-related declines in arterial elasticity may precede accelerated demyelination by 5-10 years and therefore potentially contribute to increases in white matter lesions, which, in turn, negatively impact fluid , but not crystallized abilities. Specifically, we observed a significant two-mediator indirect effect of age on fluid cognition via cerebral arterial health (measured via pulse-DOT) and WMHs such that age-related declines in cerebral arterial health lead to increases in white matter lesions that negatively impact performance on tests of fluid abilities, which is consistent with the temporal ordering of mechanisms posited in the hierarchical model (see **Figure 1**). Also, as expected, crystallized abilities remained relatively intact despite these age-related neurovascular declines, which is consistent with evidence showing that such abilities do not decline until even older age (~70 years). Similarly, piecewise linear regression analyses yielded breakpoint estimates of age that were separated by approximately eight years for cerebral arterial health (~53 years) and WMHs (~61 years), although the 95% confidence intervals for the two estimates partially overlapped. Importantly, however, we replicated the results of all analyses using an independent and readily accessible index of arterial health, systemic pulse pressure, thereby providing converging evidence for the mediating role of cerebrovascular mechanisms in cognitive aging.

The role of cardiorespiratory fitness in cognitive aging, which is of both theoretical and practical significance, proved more difficult to discern. Although prior research has established that age-related changes in cardiorespiratory fitness are linked to alterations in indices of cerebrovascular health (Johnson et al., 2020; Zimmerman et al., 2014), the precise nature of the relationship remains undetermined. We initially sought to conduct a traditional moderation analysis in which we regress an arterial health index (pulse-DOT or pulse pressure) on age and eCRF, and test for significance of the interaction term, followed by simple slopes analyses if necessary. However, this was deemed statistically inappropriate, as we observed a strong correlation between age and eCRF, thereby confounding

interpretation of the interaction and any follow-up analyses. In lieu of these preferred analyses, we conducted bivariate correlations between eCRF and vascular health (pulse-DOT and pulse pressure), without controlling for age, and partial correlations between eCRF and vascular health while controlling for age. After partialling out the effect of age, the relationships between eCRF and vascular health were no longer significant, possibly indicating that cardiorespiratory fitness exerts its effects on arterial health via an interaction with age or that cardiorespiratory fitness does not reliably affect vascular health at all—the latter of which seems highly unlikely. That is, it may be the case that age-related changes in cerebral arterial health are moderated by cardiorespiratory fitness such that the rate (or slope) of age-related arterial stiffening varies with cardiorespiratory fitness levels—lesser fit participants exhibit steep declines, while more fit participants exhibit shallower declines in arterial health. The present analyses leave open the possibility that the relationship between age and cardiorespiratory fitness on arterial health is multiplicative, not additive. In other words, fitness may delay and/or reduce the effects of age on the brain, perhaps by preventing or reducing the development of arteriosclerosis.

Some limitations of the current analytic approach remain. Firstly, because regression-based mediation analyses assume linear relationships between predictors and outcomes, when including age and pulse-DOT/pulse pressure or white matter hypointensities in a mediation model, statistical power is likely reduced, as these relationships are not best described by a linear function. Therefore, it is arguable that the statistical power of our mediation analyses suffers, suggesting that the mediating roles of arteriosclerosis and demyelination are actually more robust than that reported here. Secondly, due to possible cohort effects, the utilization of a cross-sectional design, as opposed to a longitudinal design, limits the strength of our causal inferences.

To conclude, a relatively large sample allowed us to investigate the putative mechanisms of neurocognitive aging (**Figure 1**) that often result in mild cognitive impairment or even dementia, dramatically impairing a person's quality of life and ability to function in the world. We expanded upon

preliminary correlational analyses presented by Kong et al. (2020) by ***a)*** employing piecewise regression analyses to estimate ages at which arteriosclerosis (cerebral arterial stiffening) and demyelination (white matter lesions) accelerate, ***b)*** conducting several multiple-mediator path analyses to further substantiate the hypothesized causal links proposed in the hierarchical model of neurocognitive aging, and ***c)*** replicating all analyses involving pulse-DOT (providing direct measures of cerebrovascular health) using an independent, peripheral index of vascular health, pulse pressure. Findings were consistent with the proposed sequence of events leading to cognitive decline such that age-related declines in vascular health (using either vascular index) preceded the acceleration in appearance of white matter lesions. Similarly, results of mediation analyses (once again, using either vascular index) were consistent with the proposed sequence of events in neurocognitive aging. Additional analyses suggested that the effects of age and cardiorespiratory fitness on vascular health are not independent and may be interactive. Cardiorespiratory fitness, which can be improved by regularly performing low-to-moderate intensity aerobic exercise, may decelerate the age-related progression of arteriosclerosis, thereby decreasing the rate at which declines in brain structure, brain function, and fluid cognition occur. To bolster these findings, future studies should employ even larger sample sizes and, ideally, longitudinal designs, thereby permitting stronger causal inferences. Also, other significant outcomes, such as BOLD signal-based measures of cerebrovascular reactivity that capture the integrity of neurovascular coupling (Tarantini et al., 2017), may serve as complementary indices of cerebrovascular health when formally testing the hierarchical model. Moreover, the inclusion of latent variables via structural equation modeling, estimated based on multiple indices (i.e., observed variables) representing each link or latent construct in the casual chain, may provide a more comprehensive and accurate characterization of neurocognitive aging.

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