Association of cardiovascular risk factors with MRI indices of cerebrovascular structure and function and white matter hyperintensities in young adults

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Key Points

Questions: Are cardiovascular risk factors associated with early changes in brain blood vessel density, size and curvature, brain blood flow, and brain white matter integrity in young adults?

Results: In individuals with average age of 25, vascular risk factors, including higher blood pressures and body mass index, were correlated with reduced blood vessel density, and, reduced brain blood vessel density was associated with reduced cerebral blood flow and early injury to brain cell connections.

Meaning: In young adults, the structure of brain blood vessels, as well as cerebral blood flow and lesions of brain white matter, were correlated with risk factors for vascular disease, suggesting the young adult period may be a target for primordial prevention of cerebrovascular disease.

Abstract

Importance: Risk of stroke and brain atrophy in later life relate to levels of cardiovascular risk in early adulthood. However, it is unknown whether cerebrovascular changes are already present in young adults.

Objective: To examine relationships between modifiable cardiovascular risk factors and cerebrovascular structure, function and white matter integrity in young adults.

Design, Setting, and Participants: A cross-sectional observational study completed between August 2014 and May 2016 at the University of Oxford, United Kingdom. Participants recruited through active and passive recruitment from the local community, including invitation from the Oxford University Hospitals Hypertension Service.

Exposures: Clinic and ambulatory blood pressure (mmHg), body mass index (kg/m^2), objective physical activity (hours/week), alcohol intake (drinks/week), smoking (pack years), peak oxygen uptake (ml/kg/min), peak exercise blood pressure (mmHg), lipid profile (mg/dL), insulin resistance and use of anti-hypertension medication.

Main Outcomes and Measures: Cerebral vessel density ($vessels/cm^3$), caliber (μm) and tortuosity, brain white matter hyperintensity lesion count (number), and in a subgroup (n=52) brain blood arrival time (seconds) and cerebral blood flow (ml/100g/min) assessed by brain magnetic resonance.

Results 125 participants (mean age 25±5 years, 49% female) were recruited. Cerebrovascular morphology and white matter hyperintensity count correlated with cardiovascular risk factors in univariable and multivariable models. In a risk score, for each healthier modifiable risk factor, characterised as: ambulatory blood pressure

<130/80mmHg; BMI < 25kg/m^2; top tertile of cardiovascular fitness; non-smoker; <8 alcoholic drinks/week; normotensive exercise blood pressure response; cholesterol <200mg/dL; and fasting glucose <100mg/dL, vessel density increased by 0.3 vessels/cm^3 (95%CI 0.1 to 0.5, p=0.003), vessel caliber by 8μm (95%CI 3 to 13, p=0.01) and white matter hyperintensity lesions reduced by 1.6 lesions (95%CI 0.6 to 2.8, p=0.006). In subgroup analysis, cerebral blood flow varied with vessel density and increased by 2.5ml/min/100g per risk score (95%CI 0.05 to 4.98, p=0.05).

Conclusions and Relevance In this preliminary study, involving young adults without clinical evidence of cerebrovascular disease, modifiable cardiovascular risk factors were associated with MR indices of cerebral vessel structure and function, and white matter hyperintensities. Further research is needed to determine the clinical importance of these findings for the primordial prevention of cerebrovascular disease.

Key words: brain health, cardiovascular risk factors, young adults,

Introduction

A life-course approach to understand risk of cardiovascular disease is well established[1, 2] and it is accepted that changes in cardiac and vascular structure that underlie this risk emerge very early in life[3, 4]. Whether modifiable cardiovascular risk factors, and novel early life exposures such as birth complications, influence the early cerebrovasculature is less well studied.

Cardiovascular risk closely relates to cerebrovascular injury and cognitive decline in older adults[5, 6]. Markers of cerebral injury in mid-life, including white matter hyperintensity lesions, predict future stroke, dementia and all-cause mortality[7, 8]. Progression of white matter hyperintensity lesions is faster in association with metabolic dysfunction and hypertension [9]. Experimental studies demonstrate cardiovascular risk factors result in remodelling of the brain vasculature, including vessel rarefaction, reduced vessel caliber and cerebral blood flow [10]. Elevated blood pressure, dyslipidemia and low fitness in early adulthood are known to predict brain health in older adult life[2, 11, 12]. Whether cerebrovascular morphological changes are already evident in young adults, and correlate with white matter hyperintensity lesions and risk factors at this age, is unclear.

Advances in brain MRI allow automated segmentation and analysis of vessel morphology, white matter hyperintensity lesions[13, 14] and blood flow[15]; thus making it possible to build a robust and sensitive quantification of brain health for an individual[13, 14]. Therefore, the objective of the current study was to use multi-modality brain imaging to test the hypothesis that cardiovascular risk profiles are already correlated with variation in vessel morphology and white matter hyperintensity lesions in young adulthood.

Methods

Study design and participants

This was a cross-sectional observational study completed between August 2014 and May 2016. The South Central Research Ethics Committee for the National Health Service Health Research Authority (NHS HRA) approved the study (14/SC/0275). All participants gave written informed consent. Measurements were completed at the Oxford Cardiovascular Clinical Research Facility and Oxford Centre of Clinical Magnetic Resonance Research, John Radcliffe Hospital, University of Oxford, United Kingdom. Image analysis performed using pipelines developed at the Hotchkiss Brain Institute, University of Calgary and Wellcome Centre for Integrative Neuroimaging, University of Oxford[14-18]. Final data collection was completed on the 31st of May 2016.

Participants aged 18 to 40 years were recruited through active and passive recruitment[19] including local advertising, invitation from local birth cohort studies and invitation from the Oxford University Hospital Hypertension Service. Strategies were designed to recruit adults with a heterogeneity in risk factors known to be present in young adult populations including traditional risk factors such as hypertension and more novel factors such as gestational age. Participants were excluded if they had previous cardiovascular or cerebrovascular events, renal dysfunction or metabolic disease including diagnosis of hyperlipidaemia. Participants with secondary causes of hypertension such as renal vascular disease, vascular anomalies or adrenal dysfunction were excluded following assessment in Oxford University Hospital Hypertension Service. Recruitment was continued to 125 participants to ensure over 90% power at P=0.05 to identify a 0.70-SD difference in vessel density, vessel caliber and white matter lesion count between lowest and highest cardiovascular risk tertile groups. The subgroup of 52 participants with ASL measures provides 80% power to detect 10% difference in perfusion[20].

Procedures

Cardiovascular Risk Assessment

Participants attended a research clinic in the morning after a 12-hour fast to complete a detailed cardiovascular risk assessment (Supplementary Data eMethods 1). Measurements included: body size, fasting blood samples, clinic and 24-hour blood pressure, as well as peak oxygen uptake and exercise blood pressure (from cardiopulmonary exercise testing). In addition, participants completed a detailed lifestyle questionnaire and had seven complete days of objectively measured physical activity.

Brain Imaging and Analysis

Individuals underwent multimodality brain MRI scanning (3.0T Trio Tim, Siemens, Munich, Germany). The MRI protocol included T1-weighted structural, T2-weighted Fluid-Attenuated Inversion Recovery (FLAIR), Diffusion Tensor Imaging (DTI) and Time-of-Flight (TOF) MR Arteriogram (MRA) (Supplementary Data eMethods 2). MR imaging was completed fasted and prior to exercise testing. Complete acquisition and analysis methods are presented in the on-line supplement.

T1-weighted images were processed using FMRIB Software Library (FSL) tools[21]. Brain vessel segmentation was completed on TOF MRA using previously described automated segmentation tools (Figure 1)[14, 18]. Binary segmentations were used to determine vessel density, caliber and tortuosity.

White matter hyperintensity (WMH) lesions were segmented using the Brain Intensity AbNormality Classification Algorithm (BIANCA) a fully-automated, supervised method for WMH detection[13, 22]. BIANCA classifies image voxels based on their intensity and spatial features, where the intensity features were extracted from T2-weighted FLAIR, T1-weighted and DTI fractional anisotropy (FA) images, FA images

were generated using DTI tools, FSL topup, FSL eddy and DTIFit[21, 23-25]. WMH masks were manually segmented from 10 images to use as the training set for BIANCA, these were independently verified by a neurologist (TS) and radiologist (DM) blinded to participant risk profile. Lesion count was selected as the most sensitive outcome of white matter change in young adults in whom a single lesion, independent of volume, could be considered abnormal[26]. Minimum lesion size used in analysis was 1 mm^3.

A subgroup of 52 participants also had multi-delay vessel-encoded pseudocontinuous Arterial Spin Labelling (ASL), identical to a previously published protocol[15]. Cerebral blood flow and blood arrival time were estimated from ASL images using a previously described analysis pipeline[15, 17]. Gray matter masks were used to calculate the average cerebral blood flow after linear registration of the ASL MRI to the T1-weighted MRI dataset.

Statistical Analysis

Existing literature on risk predictors of brain health was used to define an a priori set of potential correlates of MRI brain health in young adults[5, 6, 12, 27-29]. These were grouped as: 1) non-modifiable, including age, sex, gestational age, and 2) modifiable, including systolic blood pressure, body mass index (BMI), peak exercise capacity (oxygen uptake ml/min/kg), peak exercise diastolic blood pressure, weekly vigorous activity, alcohol consumption, smoking history, lipid profile, glucose and insulin resistance, and current hypertension medication.

Univariable analysis was completed to investigate correlation between the defined cardiovascular risk markers and brain outcomes. Multivariable analysis was completed using a forced entry linear regression model. To reduce multiple testing and potential interaction between the variables, the prediction model was restricted

to a subset of variables (resting systolic blood pressure, body mass index, vigorous physical activity, alcohol consumption and smoking). This model was adjusted for non-modifiable factors including age, sex and gestational age.

To investigate correlation between risk markers and brain outcomes, participants were scored for positive traits in modifiable risk profiles: BMI <25 kg/m^2; highest tertile cardiovascular fitness and/or physical activity; alcohol <8 drinks/week; non-smoker for > 6 months; blood pressure on awake ambulatory monitoring <130/80 mmHg; a non-hypertensive diastolic response to exercise (peak diastolic blood pressure <90 mmHg), total cholesterol <200mg/dL; and fasting glucose <100mg/dL[5, 6, 12, 27-29]. Two models were created to represent: 1) simple modifiable health score determined from lifestyle measures recorded in clinic (physical activity, BMI, smoking, alcohol), and 2) detailed modifiable health score that additionally included clinical investigations (exercise testing, blood samples and ambulatory blood pressure). Relationships between scores and brain outcomes were studied using linear regression adjusted for age and sex. Secondary sensitivity analysis assessed minimum number and combinations of factors required to maintain model significance.

In addition, univariable analysis was completed to investigate correlation between vessel morphology and white matter hyperintensity lesion count and in a subgroup (n=52), blood arrival time and cerebral blood flow. These relationships were further investigated with fixed entry linear regression models adjusted for modifiable and non-modifiable factors used in the models above (Supplementary data eTable 2-4).

Statistical analysis was undertaken using Statistical Product and Service Solutions (SPSS) Version 22 (Armonk, New York, U.S). Normality of variables was assessed by visual assessment of curves. If normally distributed, results are presented as

mean ± standard deviation for continuous variables, otherwise median and interquartile range. For categorical variables, number and percentage are presented. Comparison between groups for continuous variables was performed with a 2-sided, independent-sample Student's *t* test. Multivariable analysis was completed using forced entry linear regression. All multivariable analyses were adjusted for age and sex. P-values <0.05 were considered statistically significant and all results were considered exploratory. Results are presented as point estimate and 95% confidence intervals stated in units appropriate to the risk factor and brain outcome being reported. Graphpad Prism 7 software was used for statistical figures and mean with 95% confidence intervals presented.

Results

125 participants completed the brain MRI protocol and cardiovascular risk assessment study measures. The mean age of participants was 24.7±5.0 years, 61 participants were female (49%), the mean gestational age was 36.6±4.3 weeks, educational attainment was high with 86 completing University level education (68.8%), 29 participants had prior history of hypertension of which 21 were on anti-hypertension medications (16.8%) (Table 1).

Modifiable risk factors and association with brain vessel structure and white matter hyperintensity lesions

Univariable correlations between risk factors (SBP, BMI, smoking pack years, Ex DBP, Cholesterol/HDL ratio, Hypertension treatment) and brain vessel density and caliber are presented in Table 2. Vessel tortuosity only varied with gestational age in both univariable and multivariable models (0.005 unit tortuosity change/gestational week, 95%CI 0.001 to 0.009, p=0.007) (Supplementary Data, eTable 1). In the multivariable models, systolic blood pressure (-0.2 vessels/cm^3 per 10mmHg, 95%CI -0.004 to -0.4, p=0.04), smoking (2 vessels/cm^3 per 10 pack years, 95%CI 0.6 to 3.0,

p=0.04) and Body Mass Index (-0.1 vessels/cm^3 per 1kg/m^2, 95%CI -0.01 to -0.15, p=0.02) remained independent correlates of vessel density, while vessel caliber was independently correlated with systolic blood pressure (-6µm per 10mmHg, 95%CI -0.5 to -10.0, p=0.03) and smoking (40µm per 10 pack years, 95%CI 2.0 to 80.0, p=0.04). In univariable models, white matter hyperintensities also correlated with smoking, exercise diastolic blood pressure and, in addition, alcohol intake (Supplementary Data, eTable 2).

Modifiable behavioural risk scores provide an overall assessment of risk profile based on: high physical activity; not smoking in the last 6 months; body mass index <25 kg/m^2; and alcohol consumption <8 drinks/week demonstrated that vessel density increased by 0.5 vessels/cm^3 for each additional score point (95%CI 0.2 to 0.8, p=0.002) and vessel caliber by 10µm (95%CI 2.0 to 17.0, p=0.01) (Table 3). The more complex cardiovascular risk model based on a cumulative score across 8 parameters also correlated with vessel morphology. Each increase in score associated with a 0.3 vessels/cm^3 higher vessel density (95%CI 0.1 to 0.5, p=0.003) and 8µm greater vessel caliber (95%CI 3.0 to 13.0, p=0.01). Similarly, white matter hyperintensity lesion count correlated with scores in Model 1 and 2, reducing by 2.2 lesions per additional positive score on the simple grading (95%CI -0.5 to 4.0, p=0.01), and 1.6 fewer white matter hyperintensity lesions per unit of the complex score (95%CI -0.5 to 3.0, p=0.006). Differences in vessel morphology and white matter hyperintensity lesions between tertiles of the study group, divided based on the complex score, are presented in Figure 2.

In exploratory secondary analysis, a sensitivity analysis was performed removing individual components from the modifiable health scores. The minimum combination of components required to maintain significant correlations were 3 factors, with alcohol consumption and body mass index being essential in each score (data not

presented). Models 1 and 2 also correlated with the total volume of white matter hyperintensity adjusted for brain size with a 61 mm^3 reduction in white matter hyperintensity lesion volume for each additional score on model 1 (95%CI -5 to -117 mm^3, p=0.03) and a 51 mm^3 lower white matter hyperintensity lesion volume per additional score on model 2 (95%CI -15 to -87 mm^3 p=0.006).

Vessel Morphology and brain MRI biomarkers of cerebral blood flow, arrival time and white matter lesion count

To explore whether cerebral blood flow also varied with cardiovascular risk factors, a subgroup (n=52) analysis was performed in those with cerebral blood flow measures (mean cerebral blood flow 60 ml/100g/min (SD 11.5) and mean blood arrival time 1.01 seconds (SD 0.08)). In univariable analysis, slower blood arrival time and reduced cerebral blood flow were correlated with increased BMI (Supplementary Data, eTable 2). Cerebral blood flow was also lower in correlation with anti-hypertensive medication 11 ml/100g/min (95%CI -3 to -18, p=0.007). When cerebral blood flow and blood arrival time was modelled using the simple modifiable risk score, blood arrival time was 0.03 second faster for each additional point (95%CI -0.007 to -0.05,p=0.009) and cerebral blood flow 4 ml/100g/min higher (95%CI 0.5 to 7.6, p=0.03) (Table 3).

In multivariable analysis, controlling for modifiable risk factors (SBP, BMI, VPA, smoking, alcohol intake) blood arrival time and cerebral blood flow varied with cerebral vessel density, with each additional vessel per cm^3 correlating with a 0.015 seconds faster blood arrival time (95%CI -0.002 to -0.03, p=0.02) and 3 ml/100g/min increase in cerebral blood flow (95%CI 0.7 to 5.4, p=0.01). Vessel density was inversely correlated with white matter hyperintensitivity count with a reduction of 1.5 lesions per unit increase in vessel density per cm^3 (95%CI -0.4 to -2.7, p=0.01). (Supplementary Data eTables 3-4).

Discussion

This study demonstrates adverse modifiable cardiovascular risk profiles in young people are associated with differences in brain vessel structure and function as well as an increased number of white matter hyperintensity lesions. This suggests cerebrovascular pathology may be accumulating earlier than previously anticipated.

Modifiable risk factors such as blood pressure, BMI, smoking and lipid profile are known to drive systemic vascular disease in young people in part through biological vascular disorders including endothelial dysfunction and oxidative stress[30-32]. The current study suggests the cerebrovasculature may be similarly affected. Novel early life factors, such as preterm birth, have also been linked with early vascular disease[33] as the third trimester and early neonatal period are hypothesized to be times of significant vascular remodelling. Gestational age did predict vessel tortuosity, consistent with previous reports in infants[34], but not other cerebrovascular measures. Further work is needed to understand whether this was because participants were largely born late preterm or because cardiovascular risk profile overwhelms this early exposure.

To capture the complete risk profile of each participant, ideal modifiable cardiovascular risk scores were developed. Such scores are established prediction tools for future cardiovascular and cerebrovascular disease in older populations[5, 27, 35]. In this study, the simple risk score correlated with variation in all of the cerebrovascular measures including vascular structure, brain blood flow and white matter hyperintensities. The difference in white matter lesion burden between lowest and highest modifiable risk scores was around 20%. No longitudinal outcome studies have tracked white matter hyperintensities from similar age groups but the typical rate of progression of white matter hyperintensity lesions per year in older populations is 10 to 20%[36, 37]. Adverse modifiable cardiovascular risk factors are

major determinants of this progression[38] with small lesions increasing in size or clustering into confluent lesions[39, 40]. Accumulation of lesions from an early age might explain why, by mid-life, white matter hyperintensity lesion volume is an established predictor of future stroke risk[7]. If a 20% difference between groups were maintained into older adult life, this would be associated with a 2 to 3-fold increased risk of stroke, dementia and all-cause mortality[7].

However, it has been proposed that early small lesions, as observed in this study, may be reversible[41, 42]. Reducing multiple risk factors can change risk trajectories and reduce vascular disease burden[43]. Individuals with higher cardiovascular fitness have a greater number of small vessels[44] and exercise interventions are associated with beneficial effects on cerebral perfusion[45-48] as well as short-term benefits for brain volume [49, 50]. In addition, sustained lifestyle intervention and active blood pressure lowering in patients with diabetes, or following a stroke, significantly reduces the burden of white matter hypertensities and prevents accumulation of new lesions[51-54]. These interventions typically achieve 25% improvements in cardiovascular fitness and 10 mmHg reductions in blood pressure, comparable to differences between high and low risk groups in this study.

However, lifestyle-based primary cardiovascular prevention in young people requires complex intervention design. Recent systematic review of interventions in young hypertensives demonstrated that the optimal way to intervene is poorly understood with lack of sustained effect[55]. The alternative to lifestyle interventions would be pharmacological treatment. Anti-hypertensive use in this study group was associated with a trend towards increased brain vessel density[17, 18]. However, there was not a proportional increases in cerebral blood flow; a phenomenon previously described in hypertensives and proposed to be a ‘brain protective’ response, as cerebral vessel rarefaction drives an increase in blood pressure to maintain cerebral blood flow[56].

Further work to identify optimal interventions in young adults to maintain autoregulation of cerebral blood flow, while reducing risk, may be required.

Limitations

This study has several limitations. First, a small sample recruited at a single site increases risk of bias and the study may be underpowered to identify subtle correlations with some risk factors. Second, mixed passive and active recruitment strategies mean the sample is not population-based and could be considered similar to a convenience sample. Therefore, it is not possible to generalise expected prevalence of cerebrovascular changes to the wider population. Third, the study is cross-sectional and causality of the observed relationships cannot be inferred. Fourth, cerebral blood flow was only available in a subgroup so ability to understand interactive effects of modifiable risk factors, vascular remodelling and perfusion on white matter integrity is limited. Fifth, longitudinal follow up will be required to comment on the clinical significance of the observed findings. As such, this study should be considered preliminary and exploratory but does support a need for future work. The complexity of the imaging protocol and associated financial costs may limit its widespread use but large multi-centre studies with more focused protocols, and extended follow up, will allow tracking of vascular remodelling and assessment of impact on white matter and later disease. Randomised control trials will also allow effects of both lifestyle and pharmacological intervention to be properly evaluated.

Conclusion

In this preliminary study involving young adults without clinical evidence of cerebrovascular disease, modifiable cardiovascular risk factors were associated with MRI indices of cerebral vessel structure and function, and white matter hyperintensities. Further research is needed to determine the clinical importance of these findings for the primordial prevention of cerebrovascular disease.

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Authorship

All authors meet criteria for authorship: WW, AL, HB, CF, HD, PL contributed to the design of the study, secured funding and refined the overall study protocol and lead the project delivery, NF, LG, TO, MJ, CM contributed to the development of the Brain MRI protocol and related pipelines, AL, WW, OH, JF, SN contributed to image acquisition and quality control, WW, NF, LG, TO, MJ, CM, JB, HB, TS, DM, RP contributed to brain MRI image processing and analysis, AD advised on accelerometer protocol for objective physical activity measurement and compressed analysis of raw data, WW, AL, HB, OH, completed cardiovascular risk assessment and analysis of measures, WW, CF, PL and EF contributed to the statistical analysis, WW wrote the manuscript with support from LG, OH, AL, CF, NF, HD, PL. All authors contributed to revision of the manuscript. PL completed the final edit of the manuscript.

Disclosures

Dr. Okell reports grants from The Royal Academy of Engineering, during the conduct of the study; In addition, Dr. Okell has a patent (US Patent 9,757,047) with royalties paid from Siemens Healthcare. All other authors declare no competing interests.

Role of the funding source

The funders of the study had no role design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis

Access to data

Dr. Williamson and Professor Leeson had full access to all of the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis

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654 Table **1. Age, demographics and cardiovascular risk profile of study group.**

	Study Group (n=125)
Demographics	
Age, mean (SD), years	24.7 (5.0)
Female, n, (%)	61 (49%)
Gestational Age, mean (SD), weeks	36.6 (4.3)
Smoking, n, (%)	19 (15.2)
Smokers' median pack years (IQR)	2.7 (6.7)
Alcohol, n, (%)	97 (77.6)
Alcohol consumers' median drinks per week (IQR)	4.0 (4.0)
Hypertension Diagnosis, n, (%)	29 (23.0)
FHx Stroke or CHD, n, (%)	10 (8)
Education Level	
Completed University, n, (%)	86 (68.8)
Anthropometrics	
Height, mean (SD), m	1.73 (0.1)
Weight, mean (SD), kg	70.9 (13.8)
BMI, mean (SD), kg/m^2	23.6 (3.7)
Blood pressure, mean (SD), mmHg	
Resting Systolic	122.0 (11.6)
Resting Diastolic	71.3 (9.55)
Ambulatory Awake Systolic	129.6 (11.8)
Ambulatory Awake Diastolic	76.9 (8.0)
Peak Exercise Systolic	174.8 (25.4)
Peak Exercise Diastolic	87.1 (12.4)
Fitness	
Peak VO_2, mean (SD), ml/kg/min	37.9 (9.6)
Peak Respiratory Exchange Ratio, mean (SD)	1.2 (0.06)
VPA, median (IQR), hours per week	0.74 (1.25)
MVPA, median (IQR), hours per week	14.73 (6.09)
Biochemistry	
Total Cholesterol, mean (SD), mg/dL	170.15 (29.0)
LDL, mean (SD), mg/dL	97.45 (25.9)
HDL, mean (SD), mg/dL	55.68 (11.2)
TChol:HDL ratio, mean (SD)	3.18 (0.85)
Triglyceride, median (IQR), mg/dL	74.4 (54.0)
Blood Glucose, mean (SD), mg/dL	88.2 (7)
HOMA-IR, mean (SD)	0.77 (0.46)
HsCRP, median (IQR), mg/L	0.57 (1.16)
Brain MRI Outcomes	
Brain vessel density, mean (SD), $vessels/cm^3$	8.3 (1.41)
Brain vessel calibre, mean (SD), μm	531 (36)
Brain vessel tortuosity, mean (SD)	1.49 (0.088)
Brain white matter hyperintensity lesion count, mean (SD)	20.9 (7.9)

655 Abbreviations: FHx, Family History, BMI, body mass index; SBP, systolic blood
656 pressure; DBP, diastolic blood pressure; Alcohol (1 drink per week = 2 units of
657 alcohol), Peak VO_2, Peak Oxygen Uptake; VPA, Vigorous Physical Activity; MVPA,
658 Moderate to Vigorous Physical Activity; LDL, low density lipoprotein; HDL, high
659 density lipoprotein; T Chol: total cholesterol; HsCRP, highly sensitive C reactive
660 protein; HOMA-IR, homeostatic model assessment of insulin resistance.
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Table 2. Univariable correlations and regression models for modifiable risk factors and brain vessel density and vessel caliber

	Brain Vessel Density (vessels/cm^3)				**Brain Vessel Caliber (µm)**			
	Univariable		Adjusted		Univariable		Adjusted	
	Point Estimate (95 %CI)	P value	Point Estimate (95 %CI))	P value	Point Estimate (95 %CI)	P value	Point Estimate (95 %CI)	P Value
Gestational Age, weeks	-0.001 (-0.06 to 0.06)	.98	-0.02 (-0.08 to 0.03)	.42	-0.1 (-2.0 to 1.0)	.88	-1.0 (-3.0 to 0.5)	.16
Resting SBP, mmHg	-0.03 (-0.004 to -0.05)	**.02**	-0.02 (-0.0004 to -0.04)	**.046**	-0.4 (-1.0 to 2.0)	.15	-0.6 (-0.05 to -1.0)	**.03**
BMI, kg/m^2	-0.10 (-0.02 to -0.16)	**.01**	-0.08 (-0.01 to -0.15)	**.02**	-1.0 (-3.0 to 1.0)	.33	-1.0 (-3.0 to 1.0)	.42
VPA, hours per week	0.10 (-0.17 to 0.39)	.42	-0.04 (-0.28 to 0.20)	.75	1.0 (-6.0 to 8.0)	.73	-2.0 (-9.0 to 4.0)	.49
Alcoholic drinks per week	-0.10 (-0.008 to -0.025)	.31	-0.01 (-0.04 to 0.02)	.41	-0.1 (-1.0 to 1.0)	.70	-1.0 (-2.0 to 0.1)	.09
Smoking pack years	0.20 (0.06 to 0.30)	**.004**	0.17 (0.06 to 0.28)	**.004**	3.0 (-0.2 to 6.0)	.06	4.0 (0.2 to 8.0)	**.04**
Peak VO_2, ml/kg/min	0.01 (-0.02 to 0.04)	.5			0.4 (-0.2 to 1.0)	.19		
Peak Ex DBP, mmHg	-0.02 (-0.003 to -0.04)	**.047**			-1.0 (-0.4 to -1.0)	**<.001**		
Cholesterol/HDL Ratio	-0.40 (-0.06 to -0.69)	**.02**			-3.0 (-10.0 to 5.0)	.52		
HOMA IR	-0.56 (0.04 to -1.17)	.07			-14.0 (-30 to 1.0)	.08		
Hypertension Rx	0.75 (-0.01 to 1.5)	.05			10 (-9.0 to 31.0)	.27		
Model Statistics			**R^2=0.20 p=.009**				**R^2=0.24 p=.001**	

The adjusted multivariable models are restricted to simple modifiable factors that can be assessed during a clinical consultation (resting systolic blood pressure, body mass index, participation in vigorous physical activity, alcohol consumption and smoking). The models were controlled for age, sex and gestational age. Abbreviations and units: SBP, systolic blood pressure (mmHg); BMI, body mass index (kg/m^2); VPA, Vigorous Physical Activity (hours per week); Alcohol (1 drink per week = 2 units of alcohol); Smoking (pack years); Peak VO_2, Peak Oxygen Uptake (ml/kg/min); Ex DBP, Peak exercise diastolic blood pressure (mmHg), Cholesterol/HDL ratio, ratio total cholesterol/high density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance, Hypertension Rx participant taking prescription medications for hypertension (yes/no)**.**

Table 3. Modifiable health scores and correlation with brain vessel density, vessel caliber, brain blood flow and white matter hyperintensity lesion count

	Model 1 Simple Modifiable Health Score		**Model 2 Detailed Modifiable Health Score**	
	Change in point estimate per unit increase in score (95%CI)	P Value	Change in point estimate per unit increase in score (95%CI)	P Value
Brain Vessel Density, vessels/cm^3	0.50 (0.19 to 0.81)	**.002**	0.31 (0.112 to 0.514)	**.003**
Brain Vessel Caliber, µm	10 (2.0 to 17.0)	**.014**	8.0 (3.0 to 13.0)	**.002**
Brain Vessel Tortuosity	0.004 (-0.02 to 0.02)	.97	0.005 (-0.008 to 0.18)	.44
Brain Blood Flow, ml/min/100g	4.0 (0.5 to 7.6)	**.027**	2.47 (-0.05 to 4.98)	.05
Brain Blood Arrival Time, seconds	-0.03 (-0.007 to -0.05)	**.009**	-0.014 (-0.03 to 0.001	.07
Brain white matter hyperintensity lesion count, number	-2.16 (-0.46 to -3.86)	**.013**	-1.58 (-0.47 to -2.79)	**.006**

Model 1 uses a cumulative score for modifiable risk factors that can be assessed in a single consultation based on 4 factors, given equal weight, with a positive score assigned for: alcohol consumption <8 drinks/week; participating in >=75 minutes vigorous physical activity or high moderate to vigorous activity; not smoking in last 6 months; and body mass index <25 kg/m^2. Model 2 uses a cumulative score across a comprehensive assessment of modifiable risk factors including a score for: high cardiovascular fitness and/or physical activity (measured as being in the top tertile of peak oxygen uptake (110% predicted peak oxygen uptake or higher) or participating in >=75 minutes vigorous physical activity); not smoking in last 6 months; ambulatory awake blood pressure <130/80 mmHg; body mass index <25kg/m$^{2;}$ fasting total cholesterol <200 mg/dL; fasting blood glucose <100 mg/dL; and diastolic blood pressure at peak exercise <=90 mmHg. Models are adjusted for age and sex.

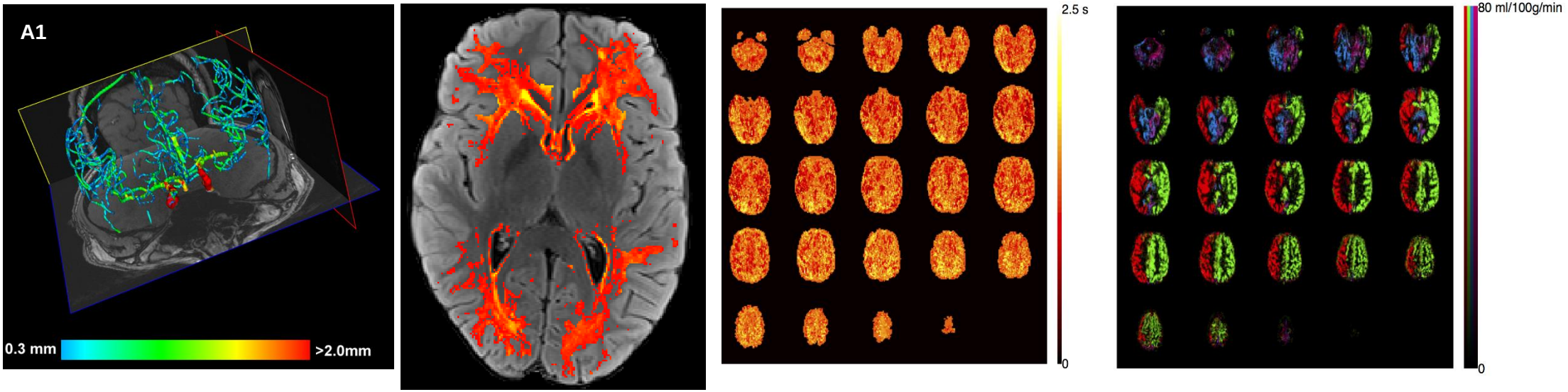
Figure 1. Panels A1 and A2 provide a case comparison of the MRI imaging modalities and analysis tools used to assess brain vessel morphology, white matter lesion count, cerebral perfusion and blood arrival time

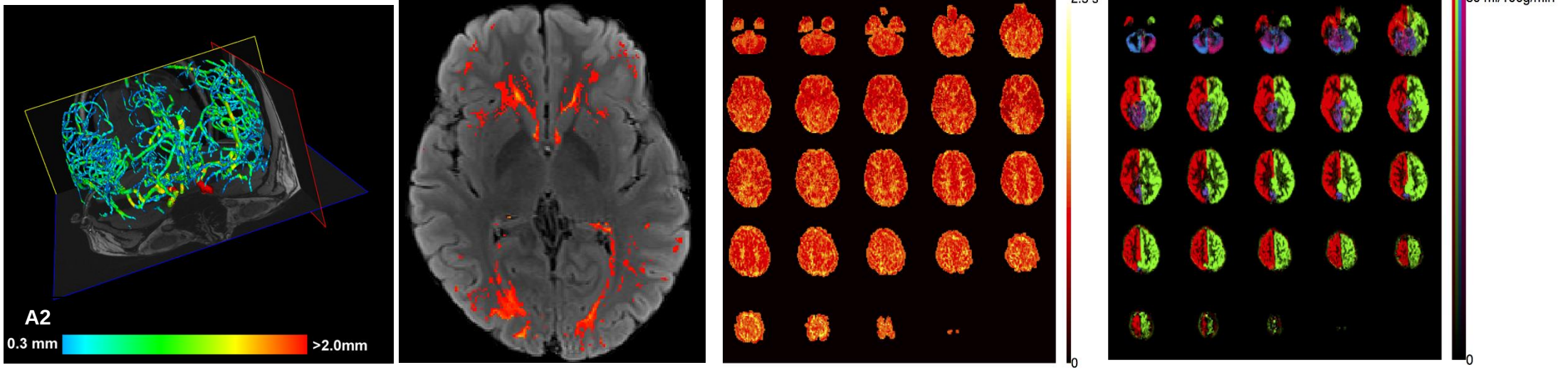
3D Reconstruction of Brain Vessels segmented from Time of Flight MRI arteriogram

Probability map of white matter hyperintensity lesions overlayed on Axial FLAIR image

Axial arterial spin labeled images demonstrating brain blood flow

Axial arterial spin labeled images demonstrating brain blood arrival time

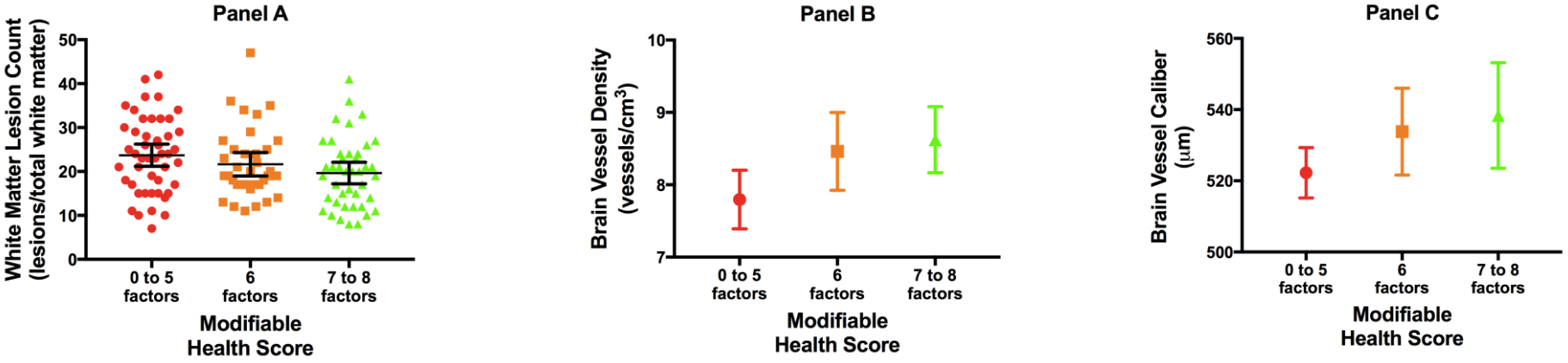




Time of Flight (TOF) magnetic resonance arteriogram was used to acquire images of the brain vessels, this was analyzed using automated tools generating binary segmentations to determine overall vessel density, caliber and tortuosity. 3D reconstructions of segmented brain vessels are provided in column one of Panels A1 and A2. Three image modalities T2 weighted Fluid Attenuated Inversion Recovery (FLAIR), Diffusion Tensor Imaging (DTI) and T1 weighted structural images were used to optimise white matter segmentation and white matter hyperintensity lesion quantification using analysis tools from the Brain Intensity AbNormality Classification Algorithm (BIANCA). BIANCA is a fully automated, supervised method for white matter hyperintensity detection, based on the k-nearest neighbour (*k*-NN) algorithm. The BIANCA output is a probability map of the likelihood that the voxel being classified is a lesion. The probability map is displayed in column 2 of panels A1 and A2, on a spectrum of orange to yellow, and overlaid on an axial FLAIR image for comparison. Voxels likely to be white matter hyperintensity lesions are demonstrated as bright yellow. A threshold of 0.9 was applied to define the voxel as lesion or not which was then fed into cluster analysis to identify individual lesions and quantify white matter hyperintensity volumes. White matter hyperintensity lesions are demonstrated as bright yellow. In a subgroup of the study population (n=52) pseudocontinuous vessel selective arterial spin labelling (ASL) was acquired to allow the assessment of blood flow to the brain. This provides two outputs, a measure of blood arrival time (seconds), demonstrated in column 3 and a measure of volume of blood flow (ml/100g/min) demonstrated in column 4, of Panels A1 and A2.

Panel A1 and A2 provide a comparison between two cases with visible differences in vessel morphology and white matter intensity lesion count that may be associated with observed differences in optimal risk profiles. Case A1 is a 21 year old male with BMI 26 kg/m^3, resting blood pressure 144/81 mmHg, awake ambulatory blood pressure 135/74 mmHg, 40 minutes of vigorous activity and 14 hours of moderate to vigorous activity per week measured on trixial accelerometer, non-smoker with alcohol intake greater than 8 drinks per week, blood pressure at peak exercise measured 200/70 mmHg, total cholesterol 178 mg/dl and fasting blood glucose 77 mg/dl. Case A1 vessel density measures 6.4 $vessels/cm^3$, he has 30 white matter hyperintensity lesions measuring 1mm or more, cerebral blood flow measuring 62ml/100g/min (lower intensity on colour scale in column 4) and blood arrival time of 1.26 second (more yellow on the colour scale in column 3). Case A2 is a 24 year old female with BMI 23 kg/m^3, resting blood pressure 134/81 mmHg, awake ambulatory blood pressure 122/77 mmHg, recording 20 minutes of vigorous activity and 21 hours of moderate to vigorous activity per week measured on trixial accelerometer, non-smoker with alcohol intake less than 2 drinks per week, blood pressure at peak exercise measured 180/90 mmHg, total cholesterol 127 mg/dl and fasting blood glucose 84 mg/dl. Case A1 vessel density measures 12.6 $vessels/cm^3$, she has 8 white matter hyperintensity lesions, cerebral blood flow measuring 83ml/100g/min (brighter intensity on colour scale) and blood arrival time of 1.07 second (more orange on the colour scale in column 3).

Figure 2. Comparison of white matter lesion count and vessel morphology between groups of participants based on their modifiable health score.



Model 2 modifiable health score provided a comprehensive assessment of modifiable risk factors based on a cumulative score for each of the following factors: high cardiovascular fitness (defined as physical activity measured in the top tertile of peak oxygen uptake (>=110% predicted peak oxygen uptake) or participating in >=75 minutes vigorous physical activity per week); not smoking in last 6 months; ambulatory awake blood pressure <130/80mmHg; body mass index <25kg/m^2; fasting total cholesterol <200 mg/d;, fasting blood glucose <100 mg/dL; and diastolic blood pressure at peak exercise <= 90mmHg. The panels in figure 2 present comparisons between groups of participants who in Model 2 score 0 to 5 positive factors (n=47), 6 factors (n=36) and >7 positive factors (n=42). Participants with >7 factors have a mean vessel density 11% higher than participants with 0 to 5 positive traits (Panel B, 8.6 vessels/cm^3 (SD 1.39) vs 7.8 vessels/cm^3 (SD 1.21) p=0.007), a mean vessel caliber 3% higher (Panel C, 538μm (SD 21) vs 522μm (SD 45) p=0.02) and on average 20% lower white matter hyperintensity lesion counts (Panel A, 19.6 lesions (SD 7.8) vs 23.5 lesions (SD 8.6) p=0.03). Panels present group means and 95%CI and reported group differences are adjusted for age and sex.