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Subclinical Metabolic and Cardiovascular Factors and Brain White Matter Microstructural Integrity in Young Women

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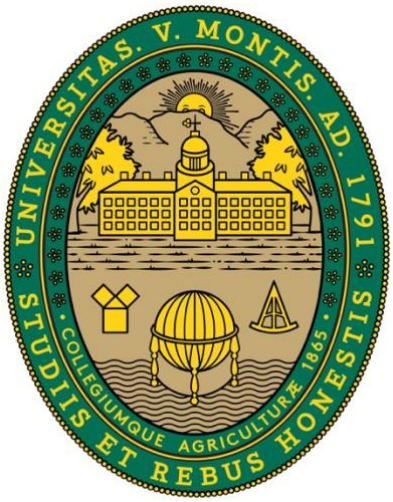

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Abstract

Pregnancy places women in a state of metabolic change that can exacerbate underlying risk factors for disease. Prior studies note physiological risk factors for pregnancy-induced hypertensive disorders, but few have focused on whether these cardiovascular and metabolic risk factors affect brain structure in early adulthood prior to pregnancy. Therefore, more research is needed to assess how subclinical cardiovascular and metabolic risk factors may affect brain health or be exacerbated by the hormonal and metabolic imbalances caused by pregnancy. This study examined how specific cardiovascular and metabolic risk factors assessed prior to pregnancy affected brain white matter microstructural integrity. This study examined 62 participants, all young (31 ± 5 years), healthy women, who received both metabolic and cardiovascular assessments as well as multi-modality MRI imaging including acquisition of T2 Fluid-Attenuated Inversion Recovery (FLAIR) sequencing and Diffusion Tensor Imaging (DTI). The hypotheses were that abnormal cardiovascular and metabolic profiles would be associated with increased white matter hyperintensities (WMH), and abnormal cardiovascular and metabolic findings would be related to lower Fractional Anisotropy (FA) and increased Mean Diffusivity (MD) in posterior cortical areas. The results showed that the presence of WMH was related to increased MD in bilateral white matter tracts and altered measures of cardiac function. FA and MD in numerous posterior and occipital tracts, commissural fibers and subcortical structures correlated with age, BMI, and measures of cardiovascular and metabolic function such as pulse wave velocity (PWV), cholesterol and insulin resistance (HOMA-IR). These relationships shed light on women's cerebrovascular health as it relates to subclinical risk factors at a young age, prior to pregnancy. More research must be done to examine how subclinical risk factors may impact potentially dangerous pregnancy outcomes in the form of hypertensive

disorders such as pre-eclampsia and how these early life influences on brain structure impact brain functioning in late age.

Introduction

Currently, there is a gap in the scientific community's understanding of how metabolic and cardiovascular risk factors relate to pregnancy and brain health. Though this study focuses on white matter integrity in young women prior to pregnancy, it is important to understand how pregnancy exacerbates cardiovascular and metabolic risk factors in women and how such risk factors affect post-pregnancy outcomes. First, this literature review will describe pregnancy as the ultimate 'stress test for life' (see below). It will then describe relevant risk factors for disordered cardiovascular and metabolic functioning and their relationship with brain structure and function. Examining the relationship between cardiovascular and metabolic measures and brain structure allows for the identification of biomarkers that are predictive of not just microstructural damage, but also the development of age-related brain deterioration that have not yet been observed in healthy young women. Identifying such relationships may improve clinical focus upon the health of young women that have implications for healthy or pathological aging later in life.

Pregnancy-Induced Metabolic Disorder

An influential 2003 review proposed that pregnancy will transiently place a woman in metabolic syndrome (Williams 2003). During this period, women who are *predisposed* by existing risk factors developed hypertensive disorders during pregnancy as well as at later timepoints when their metabolic syndrome returned (Williams 2003). Therefore, pre-existing subclinical risk factors may be exacerbated by pregnancy and already sensitive vascular conditions. While it is not known how risk factors may affect brain structural integrity in young healthy women, the foundational ideas of this review support the hypothesis that brain health

may also be exacerbated by a subclinical cardiovascular and metabolic dysfunction phenotype existing before pregnancy.

Over half a million women each year die from pregnancy-related causes (Duley, 2009). Pre-eclampsia (PE) is a common hypertensive disorder and the precursor to eclampsia, which is characterized by the addition of grand mal seizures (Phipps et al., 2019). PE and eclampsia directly contribute to 10-15% of global pregnancy deaths (Duley, 2009) and include symptoms such as proteinuria and hemorrhage within sensitive organ beds (Phipps et al., 2019). While 99% of PE deaths occur in low- and middle-income countries (Duley, 2009), the United States has growing numbers of women with PE during pregnancy. Based on hospital discharge survey datasets from 1980-2010, the U.S. has seen a mild increase in all forms of pre-eclampsia, and a 322% increase in severe pre-eclampsia during those years (Ananth et al., 2013). Such statistics reinforce our interest in understanding how PE develops and how it affects health of other organ systems. Future research can examine alternative mechanisms and treatments to slow this growth in cases.

Risk Factors for Hypertension and Cerebral Impairment

Risk factors for cardiovascular and metabolic impairment previously assessed by the Bernstein group include pules wave velocity (PWV), insulin, cholesterol, and body mass index (BMI). PWV is a measure of arterial stiffness and is generally regarded as an independent predictor of cardiovascular disease (Jannasz et al., 2019). Cardiovascular disease presents in the brain as cerebral small vessel disease (CSVD). One study of arterial stiffness and cognitive impairment found that elderly patients with a higher PWV showed damaged cerebral microcirculations, which was associated with WMH and microbleeds in later life (Li et al.,

2017). This study reveals important findings of PWV as a possible biomarker for CSVD in the brain, with WMH as a comorbidity.

WMH are age-related lesions that are associated with various dementias in later life (Prins & Scheltens, 2015). In young adults, WMH are rare and fall usually within the range of 0-1 on the Fazekas scale which indicates none to small punctate lesions, respectively. Large confluent WMH fall within a 2-3 on the Fazekas Scale (Fazekas et al., 1987; Wahlund et al., 2001). WMH are exacerbated by cardiovascular risk factors like small vessel disease in older adults. In a 2016 longitudinal study of hypertensive elderly adults, WMH nearly doubled in volume over the course of four years (Abraham et al., 2016). These dramatic structural changes were associated with cognitive deficits. These data focus on the natural brain changes associated with late age but support our hypothesis that hypertensive risk factors may cause small vessel disease in the brain of younger individuals, increasing their WMH count and risk for pathological brain aging in the future. These relationships have not yet been demonstrated in younger women; however, in a pathology series of maternal death during the period of 2003-2006, perivascular edema lesions were found within 68.4% of patients' brains, a further 36.8% showed evidence of hemorrhage (Hecht et al., 2017).

Perhaps even less understood is the relationship between insulin and cortical microstructure. It is known that insulin is an important regulator of feeding and cognition and plays an active role within the central nervous system (CNS). During pregnancy, a mother will undergo anabolic/catabolic phases (first storing nutrients, later preparing for birth) characterized by changes in insulin sensitivity: disruptions in a mother's metabolic physiology can cause hormone imbalances, reduced insulin sensitivity and even induce gestational diabetes mellitus (Meo & Hassain, 2016). One review found that insulin plays a key role in oxidative balance

within the brain. Specifically, insulin increases neurotransmitter turnover, ensures proper neuron formation, and even combats the development of certain dementias such as Alzheimer's Disease (Kellar & Craft, 2020). While there is currently little understanding of how insulin plays a direct role in holistic brain health, insulin regulation is severely altered during pregnancy, and this may disrupt processes within the brain.

Cholesterol plays a vital part in structure and hormone metabolism within every human cell. While cholesterol rises in pregnancy, it is not fully known how this plays a role in the mother's health or fetal development (Bartels & O'Donoghue, 2011). In the brain, excess cholesterol is associated with the development of WMH and CVSD in later life, as is a BMI of greater than 25 (Williamson et al., 2018). Again, these studies yield findings relevant to our work, but in an entirely different group of older men and women. Future studies should address the presence of these biomarkers in young women and the possible microstructural damage they suggest.

The current study analyzed data gathered by Ira Bernstein, M.D. and colleagues from their research in women before pregnancy that examined cardiovascular and metabolic functioning. A subset of women in these original studies participated in an MRI session where they underwent fluid attenuated inversion recovery (FLAIR) scans and diffusion tensor imaging (DTI) to assess white matter integrity. While these data were collected 10-15 years ago and to date the brain structural measures had not been examined. Dr. Dumas' lab examines brain structure and function in women, and she has recently begun working with the Bernstein group. This project examined associations between the cardiovascular and metabolic measures obtained previously such as pulse wave velocity (PWV), insulin, cholesterol, and body mass index (BMI) and white matter structure to understand the relationship between cardiovascular and metabolic

functioning and brain structure in women before pregnancy. These measures will be further described below.

White Matter Assessment

Fluid-Attenuated Inversion Recovery (FLAIR) T2 Images

White matter structure can be examined from FLAIR T2 MRI sequences for presence of white matter hyperintensities (WMH) in the brain. FLAIR T2 scans alter the rate of radio pulses used to capture an image, lengthening the effective echo time and inversion time. This causes fat molecules to become brightened, and fluids and gray and white matter to appear dark. T2 scans are commonly used to visualize areas of hemorrhage or lesion within the brain, which are usually areas of concentrated demyelination and axonal loss. WMH are common in older people and people with hypertension (Sharma et al., 2021). WMH are relatively uncommon in young healthy adults (Sachdev et al., 2008). A common method for assessing T2 FLAIR scans for damage is the Fazekas scale (Fazekas et al., 1987; Wahlund et al., 2001)—a conventional scoring procedure used to judge cortical abnormalities. The clinical relevance of WMH will be further discussed in the Previous Works section.

The Fazekas Scale

The Fazekas Scale is an ordinal ranking method that is used to compare or quantify periventricular and deep white matter lesions. It was developed by Fazekas in 1987 (Fazekas et al., 1987) and remains the most widely used scale to determine confluence and severity of WMH in research settings. The Fazekas scale is best practiced with transverse T2-weighted or FLAIR MRI and ranks WMH presence ordinally from 0 (healthy), 1 (punctiform), 2 (early confluent),

and 3 (diffuse confluent). Grade 2 is deemed pathological in patients under seventy years old, while grade 3 is always pathological (From the Imaging Cognitive Impairment Network (ICINET) et al., 2017).

Diffusion Tensor Imaging (DTI)

DTI is another MRI method that measures the translational movement of water throughout the brain. Specifically, this process is termed anisotropy, and occurs maximally within white matter tracts in healthy subjects, where inter-structural communication occurs (Lope-Piedrafita, 2018). Fractional Anisotropy (FA) is a measure that shows how severely disrupted white matter tracts are in the presence of degraded neurons or axons. FA therefore can be used to quantify connectivity between various cortical structures. Low FA values are indicative of microstructural damage in white matter tracts and studies have found that this may contribute to the onset of dementia in older adults (Prins & Scheltens, 2015). In addition to FA, this study examined mean diffusivity (MD), a nonspecific measure of water movement restriction caused by cellular membranes (Clark et al., 2011). Together, these data will allow for the examination of white matter structural integrity as it relates to the diffusion and movement of water throughout the brain.

Fractional Anisotropy (FA) & Mean Diffusivity (MD)

FA is a measure of directional diffusion and is represented by a scalar value ranging from zero to one. Unrestricted water molecules will diffuse freely in space—this movement can be restricted by the presence of cellular membranes, certain molecules, or white matter tracts, for example. This is the founding principle of DTI: that white matter microstructure can be assessed

by tracking water diffusion that is dependent on its orientation and integrity (Beulieu, 2002). A FA value of zero represents unbound water molecules such as CSF which flow essentially unrestricted throughout the ventricles, known as isotropic movement, while a fiber bundle will represent FA values closer to one, deemed anisotropic movement (Morgan et al., 2013). FA may decrease in the event of membrane deterioration such as demyelination or axonal degradation. MD is another measure of microstructural integrity and describes the average mobility of water molecules independent of tissue directionality. Therefore, MD is a nonspecific measure that is sensitive to changes in barriers which restrict the motion of water. MD increases with increased water content, which may result from cerebral edema or inflammation. Thus, FA and MD have an inverse relationship, where inflammation or degradation caused by neurodegeneration result in decreased FA and increased MD (Ibrahim et al., 2011).

Hypotheses

First, I hypothesized that abnormal cardiovascular and metabolic findings would be related to lower FA and increased MD in posterior cortical areas. Secondarily, I hypothesized that abnormal cardiovascular and metabolic profiles would be associated with increased Fazekas scores. The specific regions where white matter integrity may be impacted are cortical white matter projection, commissural, and association fibers in occipital-posterior regions of the brain (Bastin et al., 2009).

Significance

This study examined how metabolic and cardiovascular data assessed in women pre-pregnancy including PWV, insulin, cholesterol, and BMI were associated with measures of brain

white matter structure (WMH, FA, MD) to examine whether cardiovascular and metabolic profiles were related to brain structural integrity. These relationships have been observed in older adults and are thought to be diseases of aging. This will be the first study to examine these relationships in young women of childbearing age.

Methods

Participants

This analysis included 62 women who completed the pre-pregnancy component of the study during the examination period from 2010 – 2014. Mean subject age was 31 ± 5 years, with body mass index 26 ± 6 kg/m^2. Women were majority Caucasian (88%). 50% (N=31) of the women had a prior pregnancy with preterm preeclampsia and 50% did not.

Procedures

Study Visits

The study consisted of two visits at the UVM Clinical Research Center (CRC). Subjects were assessed in early morning beginning from 0700 and 0800 to control for post-absorptive, or fasting states. Study Visit 1 consisted of cardiovascular and metabolic testing, while Study Visit 2 had an MRI session. Subjects were assessed during the follicular phase—or pre-ovulatory phase—of the menstrual cycle after a three-day sodium/potassium-controlled diet to provide a cardiac control for menstrual or dietary hormonal changes. Other requirements for participation included participants refraining from consuming caffeine or alcohol for 24 hours prior to each study day, as well as the use of nonsteroidal anti-inflammatory or decongestant medication 48 hours prior to each study day.

Metabolic and Cardiovascular Assessments Protocol

Cardiovascular and metabolic measures were assessed during the pre-ovulatory period for each woman. Patients were all assessed in the dorsal supine position for at least 15 minutes prior to measures of cardiac function. Blood pressure was obtained using a noninvasive and continuous monitoring device during Valsalva techniques to record alpha- and beta-adrenergic responsiveness. Subjects forcefully exhaled against a non-fixed low resistance 40 mmHg pressure. The calculated difference between peak MAP measured at the end of the late phase II of the Valsalva technique and trough MAP at the end of the early phase II reflects baroreceptor activity reflected by vascular alpha-adrenergic receptors. The calculated difference between baseline MAP and the top of phase IV reports beta-adrenergic activity. Cardiac ejection and pulse wave velocity of the brachial artery were assessed using dual echocardiography with Doppler ultrasound.

Pulse wave velocity is considered the gold standard for measuring arterial stiffness and was obtained by measuring time from EKG R wave to peak systolic flow in the brachial and popliteal arteries. Volume loading with tonometric blood pressure monitoring was used to assess vascular compliance. Blood was drawn to assess inflammatory markers such as cholesterol, insulin, and low-density lipoproteins (LDL).

MRI Assessment

MRI images were obtained using a 3-Tesla Philips research magnet within the MRI Research Facility at the University of Vermont Medical Center (UVMMC). Relevant MRI modalities include T2 fluid-attenuated inversion recovery (FLAIR) images and diffusion tensor imaging (DTI). T2 Sagittal Flair Images were obtained to assess white matter lesions and

consisted of 240 contiguous 1.1-mm interleaved slices with no interslice gap, field of view = 25 cm, matrix = 252 × 252, obtained with the following sequence: echo time = 373.1 ms, inversion time = 1600 ms, repetition time = 4.8 seconds, bandwidth = +/- 789 Hz, one signal average. The 2D DTI MR images which were used to assess white matter structural integrity consisted of 150 single shot spin-echo contiguous 2-mm interleaved slices with no interslice gap, field of view = 24 cm, matrix = 120 × 120, obtained with the following sequence: echo time = 55 ms, repetition time = 9.4 s, bandwidth = +/- 2.745 kHz, in 7 gradient directions (x, y, z, x+y, x+z, y+z, x+y+z) with a maximum b value of 820 sec/mm^2 per gradient axis. The total acquisition time was around 40 seconds.

Imaging Analysis

White Matter: Number of WMH and Classification of Subjects

T2-weighted FLAIR imaging was used to visually assess the presence of white matter hyperintensities. Two investigators visually rated WMH in accordance with the Fazekas Scale (Fazekas et. Al, 1987)—ranking WMH presence ordinally from 0 (healthy), 1 (punctiform), 2 (early confluent), and 3 (diffuse confluent). Two trained raters were blind to pregnancy history and cardiovascular assessments. A third experienced MRI technologist adjudicated and discrepancies between the raters (Initial agreement at ~80%) reviewed the images to remove visual discrepancies. 17 women showed evidence of white matter hyperintensities (WMH), and 45 women had normal white matter structure.

White Matter: Microstructural Integrity

Raw dicom data from the DTI scan were converted to nifti format to accommodate for b-value and gradient vectors—indicating the magnitude of the diffusion gradient and the directions the gradients were applied—as was recommended by Stanford's Wandell Laboratory. All images first underwent correction for eddy induced spatial distortions, which are caused by loops of electrical current that induced by a changing magnetic field, using FSL's Probabilistic Tracking to Eddy Current Correction, or "eddy_correct". Binary brain masks were generated for each subject using FSL's Brain Extraction Tool (BET) for skull-stripping. Diffusion tensors were reconstructed at each voxel from which fractional anisotropy (FA) and mean diffusivity (MD) maps were taken, as well as the first, second and third eigenvectors and eigenvalues. A series of tract-based spatial statistics were performed on respective FA and MD directories. These steps registered all images to a FMRIB_FA template, merged all subjects into 1x1x1mm standard space upon an MNI152 image, and projected pre-aligned data onto a white matter skeleton. Pre-registered mean skeletonized files were then returned to an individual registered format (fslsplit). Atlases were assessed for relevant white matter and subcortical structures for ROI analysis. The Johns Hopkins University (JHU) DTI-based white matter atlas was used for posterior occipital white matter tracts and the Harvard-Oxford cortical and subcortical structural atlas was used for exploratory analysis of subcortical structures, including the thalamus and basal ganglia. ROIs were extracted from atlases, binarized and FA/MD values were extracted from the binarized ROI masks.

Statistical Analysis

Voxelwise statistical analysis was performed using the randomize tool within the General Linear Model (GLM) program in FSL, after manually generating design matrix and contrast files. This was accomplished using Threshold-Free Cluster Enhancement (TFCE) method to generate raw t-statistics from 5,000 random permutations to reduce uncertainty. Independent samples t-tests were done using the Wizard GLM to observe areas of significance in whole-brain comparisons of two subject groups. FSLeyes was used to visualize areas of difference for further ROI analysis. ROI statistical analysis was completed using SPSS Version 28 (IBM, Armonk, NY). Independent samples t-tests were used to delineate differences between two groups of interest (Fazekas score, pregnancies with pre-eclampsia) while Pearson correlation was used to model association between continuous metabolic measures and ROI FA/MD values.

Results

Participant Characteristics

Of the 62 women who underwent the initial testing phase, 17 were nulliparous (27.4%), 26 had one prior pregnancy (41.9%), 13 had two prior pregnancies (21%), and 6 had three or more prior pregnancies (9.7%). Among the 34 total women who returned for the third-trimester portion of the study, 6 had developed pre-term pre-eclampsia (17.6%). 17 women were found to evidence white matter hyperintensities of Fazekas score 1, and no women were found to evidence WMH greater than Fazekas score 1.

Statistical Hypothesis Testing

The multiple comparisons problem states that if many hypotheses are tested, such as in the large-scale correlational analysis done in this study, the chance of observing a significant

result increases. Thus, the chance of incorrectly rejecting the null hypotheses increases. This mistake is known as a Type 1 Error. Several corrections for multiple comparisons have been proposed, such as the Bonferroni Correction (Bonferroni, 1936), which includes dividing the standard alpha level of .05 by the number of comparisons that are made. The Bonferroni Method has been criticized because it can increase the possibility of falsely accepting the null hypothesis, known as Type 2 Error. Therefore, the Bonferroni can reduce statistical power (Nakagawa, 2004). The Bonferroni Correction is not preferred in this study, which is an exploratory analysis; however, a correction factor is required. We propose to discuss the significance of results which are found to be significant at the .01 alpha level to provide more stringent critical values.

Fractional Anisotropy Metabolic Measures

Negative correlations were observed between fractional anisotropy in posterior-occipital white matter tracts, as well as major commissural fibers in subcortical structures. FA was negatively correlated with age in the genu ($r = -.421$, $p < .001$) of the corpus callosum. FA in left ($r = -.415$, $p < .001$) superior longitudinal fasciculus was negatively correlated with age. FA in the left posterior thalamic radiation ($r = -.490$, $p < .001$) was negatively correlated with age. FA correlated with BMI in right putamen ($r = .459$, $p < .001$). FA negatively correlated with android tissue percent in the right putamen ($r = .373$, $p = .003$). FA negatively correlated with LDL in the fornix ($r = -.371$, $p = .007$). FA correlated with HOMA-IR in the right putamen ($r = .520$, $p < .001$). Similarly, FA negatively correlated with cholesterol in the fornix ($r = -.366$, $p = .008$) (Table 1).

Fractional Anisotropy and Cardiovascular Measures

FA correlated with mean arterial pressure in the right posterior corona radiata (r = .343, p = .008). FA negatively correlated with popliteal PWV in the fornix (r = -.351, p = .005) (Table 2).

Mean Diffusivity and Metabolic Measures

MD was negatively correlated with BMI in the right corticospinal tract (r = -.378, p = .002). MD negatively correlated with android tissue percent in the right corticospinal tract (r = -.331, p = .009). MD was positively associated with calculated LDL in the splenium of the corpus callosum (r = .355, p = .010). MD was positively associated with HOMA-IR in the fornix (r = .384, p = .005). MD was positively associated with cholesterol in the splenium of the corpus callosum (r = .391, p = .004) (Table 3).

Mean Diffusivity and Cardiovascular Measures

MD was positively correlated with supine MAP in the fornix (r = .329, p = .009). MD was negatively correlated with mean arterial pressure in the left anterior internal capsule (r = -.351, p = .006) and right putamen (r = -.405, p = .001). MD was correlated with brachial PWV, time to start in the fornix (r = .357, p = .004). MD was associated with popliteal PWV in the fornix (r = .378, p = .002) (Table 4).

White Matter Hyperintensities and Mean Diffusivity

Group analyses among women with Fazekas score 0 vs 1 showed significant differences in MD between groups. The Fazekas score 1 group MD appeared to be significantly higher than

the Fazekas score 0 group in the following white matter tracts: right (t = -2.682, p = .011) and left (t = -2.073, p = .045) anterior internal capsule, right (t = -2.234, p = .033) external capsule, right (t = -2.457, p = .021) and left (t = -2.375, p = .023) posterior corona radiata, right (t = -2.682, p = .011) posterior thalamic radiation (t = -2.446, p = .020), and the right (t = -2.394, p = .023) and left (t = -2.248, p = .034) superior longitudinal fasciculi (Table 5).

White Matter Hyperintensities and Cardiovascular and Metabolic Factors

The Fazekas score 1 group demonstrated higher AUC cardiac output (t = -2.265, p = .032) and increased time from R to peak systolic flow (t = -2.173, p = .038) (Table 6).

Discussion

The aim of this study was to examine relationships between subclinical cardiovascular and metabolic factors and white matter structure in women prior to pregnancy. I hypothesized that posterior-occipital tracts would be particularly vulnerable to subclinical cardiovascular and metabolic processes because of their demonstrated interaction with hypertensive disorders of pregnancy such as pre-eclampsia (Siepmann et al., 2017) and even mid and late-life risk factors for atherosclerosis (Power et al., 2017). Significant relationships observed in women prior to pregnancy may be consequential to brain health through the lens of pregnancy as an exacerbation of such cardiovascular and metabolic risk factors. Further, this study aimed to compare white matter microstructural integrity between various groups: specifically, FA and MD in those who had a history of pre-eclampsia and those who did not, as well as subjects with a Fazekas score of 1 versus subjects with a Fazekas score of 0. Such differences may support the hypothesis that observable low-grade hyperintensities in early life impact the diffusion of water through

surrounding white matter tracts. Therefore, this study seeks to understand how biomarkers for vascular disease in early life may impact microstructural integrity.

Metabolic Profiles and White Matter Integrity

Age

Subject age was inversely related to FA in the genu of the corpus callosum, a large body of commissural nerve fibers that allows for communication between the right and left hemispheres. Age was inversely related with FA in the left posterior thalamic radiation—a nerve fiber that enables communication between caudal sections of the thalamus and the parietal and occipital cerebral cortex (George & Das, 2021), as well as the left superior longitudinal fasciculus, which is a bidirectional nerve bundle that relays information between anterior and posterior structures. This follows relationships that have been long known between age and FA—age is a predictor of decreased fractional anisotropy throughout the brain, on the scale of 3% per decade within the frontal lobe according to one study (Grieve et al., 2007).

Body Mass Index (BMI) and Android Tissue Fat Percentage

BMI was associated with FA in the right putamen, a subcortical structure belonging to the basal ganglia. Though the putamen does not belong to a posterior-occipital white matter tract, this finding demonstrates the opposite relationship that was expected. According to prior studies (Verstynen et al., 2012), increased BMI was associated with a global decrease in white matter microstructural integrity. One study on metabolic measures in obese young men found that BMI was positively associated with increased volumes of basal ganglia structures and white matter atrophy including the bilateral putamen (Lou et al., 2014). It is unclear how such enlargement of

the putamen could contribute to increased FA, but this relationship has been observed in patients with neurodegenerative disease and in the current study (described below in greater detail, see HOMA-IR). Android tissue fat percentage was associated with FA in the right putamen. Though this relationship was not hypothesized in this study, it is consistent with research that has focused on the relationship between obesity and white matter integrity: a 2019 cross-sectional study found that total body fat percentage was associated with FA globally in both men and women, and negatively associated with mean diffusivity globally in women (Dekkers et al., 2019). The same study concluded that obesity specifically contributed to greater coherence of water movement through white matter tracts represented by the association with FA, but a lower magnitude of white matter structure represented by the negative association with MD. These relationships were supported in this study (see "Metabolic Profiles and Mean Diffusivity" below).

BMI was negatively associated with MD in the right corticospinal tract. Further, android tissue fat percentage was negatively associated with MD in the right corticospinal tract, demonstrating the opposite result from the initial hypothesis. The relationship between BMI and mean diffusivity remains unclear even in prior research: a 2020 study found that overweight or obese subjects showed both increases and decreases in white matter integrity in certain aspects of the left corticospinal tract (Carbine et al., 2020). Another study that focused on white matter integrity in older women found decreased fractional anisotropy in women with increased BMI, but this was also associated with lower axial diffusivity and increased radial diffusivity in frontal, temporal, and parietal white matter (Ryan and Walther, 2014). Despite puzzling relationships between BMI and MD, the negative association between android tissue percentage and MD is consistent with results outlined above: Dekkers et al. showed that both BMI and total

body fat percentage were associated with a decrease in MD but increase in FA—the opposite relationship to previously described findings in normal aging, and those authors propose that perhaps other factors such as the neuronal influence on body weight regulation and eating behavior could play a role (Dekkers et al., 2019).

Low Density Lipoproteins (LDL) and Cholesterol

LDL and cholesterol were inversely related to FA in the fornix. This relationship supports the hypothesis that abnormal cardiovascular profiles would be associated with adverse microstructural integrity measures, though the fornix is a fiber bundle that is located in the medial aspect of the cerebral hemispheres. LDL is a cholesterol-carrier that is considered a risk factor for atherosclerosis, leading to cardiovascular events such as myocardial infarction, stroke, and heart attack (Khatana et al., 2020). The fornix is a C-shaped fiber bundle that is part of the limbic circuit, most notably as an output for the hippocampus. It is implicated in the development and recall of episodic memories (Senova et al., 2020). One study found negative associations between plasma LDL levels and FA in frontal corticospinal tracts in young obese males (Lou et al., 2014), but no studies have observed such relationships in the subcortical limbic circuitry of young healthy women.

Calculated LDL was also associated with MD in the splenium of the corpus callosum. While the splenium was not originally implicated in the original hypotheses, it showed similar relationships to what was expected. Further, cholesterol was associated with MD in the splenium of the corpus callosum. Both findings support the hypothesis that adverse metabolic profiles were associated with altered diffusion in the brain, though some studies have shown that increases in cholesterol offer protective effects: one previous study on cholesterol and white

matter integrity found that high levels of serum cholesterol were associated with increased FA and decreased MD (Warstadt et al., 2014). Another study found the same protective effect between cholesterol and FA and no relationship with MD (Power et al., 2014). The current relationship between LDL, cholesterol, and MD is not well understood and more research is necessary.

Despite past literature, this study of young women prior to pregnancy indicates that increases in cholesterol and its carriers such as LDL result in decreased directional movement of water through white matter tracts and increased overall diffusion, indicating possible alterations in these subjects' axon density, myelination, or axon diameter within the fornix. These effects have not yet been observed in prior literature but could possibly be caused by a lack of neuroprotective effects that are mentioned in populations with comorbidities such as obesity. It is astounding that these relationships are seen in young healthy women with no obvious comorbidities.

Homeostatic Model of Insulin Resistance (HOMA-IR)

HOMA-IR was inversely related with FA in the fornix and associated with FA in the right putamen. Increased insulin resistance is considered abnormal and is associated with global decreases in axial diffusivity and decreased FA in the body and genu of the corpus callosum, according to one previous study (Ryu et al., 2014). Therefore, the alterations in integrity in the fornix are consistent with previous discoveries. However, the strong relationship between FA in the right putamen was unexpected. Though this study focused on healthy young women, one explanation is that increased insulin resistance has been observed as a biomarker for alterations in basal ganglia associated neurodegenerative disease such as Parkinson's, Alzheimer's, and

Huntington's diseases (Akhtar & Sah, 2020). Parkinson's disease, for example, has been implicated in alteration in volumetric alterations of the right putamen (Sigirli et al., 2021), and increased HOMA-IR is associated with enlarged perivascular space in the basal ganglia, according to one study (Wu et al., 2020). Increased FA within the putamen has been observed in early-onset Huntington's disease patients and patients with certain epilepsies (Gerdes et al., 2012, Singh et al., 2013). While decreased FA was indicative of microstructural damage, increased FA may indicate neurodegeneration. Despite these findings, current relationships between insulin resistance, fractional anisotropy in the basal ganglia, and resulting neurodegenerative disease are unclear in younger women.

HOMA-IR was associated with MD in the fornix, while MD in the remaining white matter tracts was negatively associated with HOMA-IR. It is known that increased MD reveals white matter microstructural damage and understanding of the relationship between HOMA-IR and MD is unclear. As is mentioned above, one previous study found that insulin resistance was associated with decreased FA and decreased axial diffusivity (Ryu et al., 2014), but other studies and reviews have found that increased insulin resistance and fasting insulin levels were significantly associated with WMH (Wang et al., 2020), as was diabetes itself (Weinstein et al., 2015). Since the presence of WMH was commonly observed with decreased FA and increased MD (Liu et al., 2021), more work must be done to reveal these relationships in young women.

The literature on individuals with neurodegenerative disease may explain how extreme pathologies result in microstructural changes in white matter integrity, but do not explain how similar changes are observed in healthy young women. In the context of this study, women who displayed increased insulin resistance showed altered directional movement and increased total diffusion of water in the fornix, and a strengthened or further restriction of water movement in

the right putamen. These observations are unprecedented in this demographic and may be exacerbated by gestational diabetes, which may impart severe consequences onto a mother's cerebrovascular health and exacerbate the risk of preterm pre-eclampsia (Trivett et al., 2021).

Cardiovascular Profiles and White Matter Integrity

Area Under the Curve (AUC) Mean Arterial Pressure (AUC MAP) and Supine Mean Arterial Pressure (MAP)

AUC MAP was associated with FA in the right posterior corona radiata. This pattern does not support the original hypothesis that increased arterial pressure would be related to decreased FA in the brain as is proposed in prior publications. One 2021 study found strong correlations between high pulse pressure and restricted isotropic diffusion in global white matter in populations that had been corrected for age and sex, however these relationships only strengthened for subgroups of women over the age of 75 (Reas et al., 2021). More work must be done to reveal the relationship between AUC MAP and FA in posterior-occipital tracts in young women.

MAP was related to MD in the fornix while again displaying negative relationships with other white matter tracts. This relationship supported the hypothesis that increased arterial stiffness had adverse consequences on white matter integrity; however, the inverse relationships in this specific white matter bundle did not. It is well known that arterial stiffness is a biomarker for hypertensive disorders which may exacerbate the risk for stroke (Veglio et al., 2009), and that on the microstructural scale, any breakdown to barriers that prevent the free movement of hydrogen such as neurodegeneration will increase MD (Stebbins, 2010). Therefore, increased MD in the fornix with increased arterial pressure was anticipated. Further, negative associations

were observed between AUC MAP and MD in the left anterior internal capsule and in the right putamen. As observed in the relationship above between FA and AUC MAP, increased anisotropic movement and decreased free diffusion suggested that prior to breakdown in vascular structure, restricted perfusion may account for these changes in FA and MD.

This study found increased restrictive directional movement of water in the right posterior corona radiata and increased total diffusion in the fornix. Such relationships have only been observed in elderly or diseased populations and therefore the prior work may not be completely applicable to this demographic of healthy young women. Possible explanations for the directions of these relationships lie in the fact that these women are healthy: it is possible that the increased anisotropy observed in the posterior corona radiata is caused by healthy axonal integrity despite increased mean arterial pressure, therefore strengthening directional water movement prior to neurodegeneration that is observed in later life. However, these relationships should not prevent discussion of the mother's cerebrovascular health, as it is not known how these relationships may be altered or exacerbated by the cardiovascular load placed on the mother during pregnancy. These factors likely contribute to the degeneration of axonal and vascular membranes that contribute to white matter integrity.

Popliteal and Brachial Pulse Wave Velocity (PWV)

Popliteal PWV was negatively associated with FA in the fornix. This supports the initial hypothesis that impaired cardiac measures resulted in more isotropic water movement in the brain. Previous studies also supported this hypothesis: one study focused on patients with major depressive disorder found significantly reduced FA in the posterior thalamic radiations, and this relationship was partially mediated by PWV in older patients (Hermesdorf et al., 2017). A

longitudinal 2013 study noted associations between aortic PWV and the presence of white matter lesions in a group of biracial elderly men and women (Rosano et al., 2013). While the relationship between PWV and white matter hyperintensities and disrupted FA is sparse, these results are consistent with current knowledge of white matter integrity in elderly populations but are not anticipated in young healthy women.

Both brachial and popliteal PWV were associated with MD in the fornix. This aligned with the hypothesis that increased PWV has adverse effects on white matter integrity, but not in posterior occipital tracts, and is supported by previous research on elderly populations: one cross sectional study focusing on aortic stiffness found that increases in carotid femoral PWV were associated with decreases in FA and increases in MD (Wei et al., 2020), while another meta-analysis on individuals over the age of 30 years found that increases in PWV were associated with the presence of WMH and cerebral small vessel disease (Li et al., 2017). These relationships have been observed in older subject populations, and these relationships were similarly observed in young women, prior to pregnancy.

Cardiac measures like brachial and popliteal PWV were related to isotropic water movement and decreased total water diffusion in the fornix. It is known that increased PWV contributes to arterial stiffening, increasing systolic blood pressure and myocardial oxygen consumption (London et al., 2004). These changes likely alter cerebral perfusion and increase the risk of cerebral edema. These results are unprecedented in young women and therefore represent a challenge that must be addressed through further investigation—particularly in the context of pregnancy-induced hypertensive disorder which develops from adverse cardiac events, such as pre-eclampsia, which will exacerbate consequences on white matter integrity, leading to changes in cognition and neurodegenerative or psychiatric disorder in later life.

White Matter Hyperintensities and White Mater Integrity

Significant relationships were not observed in comparisons between subjects with Fazekas score 1 and 0 (indicating the presence of WMH or not) and FA. However, global differences in MD were observed between women who had WMH and those who did not, indicating that the presence of WMH was associated with increased MD in posterior-occipital white matter tracts. These findings supported the original hypothesis that WMH indicated microstructural damage, potentially caused by underlying inflammation, cerebral edema, and neurodegeneration: resulting in more open hydrogen diffusion in young women. A 2021 study on elderly populations who have WMH similarly found global decreases in MD (Liu et al., 2021), but these relationships have not yet been observed in young women.

These findings are consistent with current literature on WMH but are unique to this demographic of young women prior to pregnancy. It is recommended that the presence of WMH be taken into consideration both prior to and post-pregnancy as a measure of cerebrovascular and cognitive health, and in assessing the integrity of white matter tracts. These results are particularly consequential because global differences are observed in MD even for low-grade hyperintensities—none of the women in this sample were graded above a Fazekas score of 1, indicating the lowest level of observable cortical damage above healthy subjects. Therefore, this study shows that even Fazekas grade 1 hyperintensities in young women will affect global water diffusion and potentially have implications for brain and vascular health in later life.

Cardiovascular and Metabolic Factors and White Matter Hyperintensities

No relationships between metabolic factors and the presences of WMH were observed; however, there were significant differences observed between individuals with WMH and their

respective cardiac output and aortic PWV, indicating that these cardiac factors may serve as biomarkers for WMH. This relationship supported the hypothesis that adverse cardiac measures altered cerebrovascular health. Data from this study indicated that individuals with increased cardiac output had more WMH, which conflicted with published data that showed reduced cardiac output contributed to WMH development (Jefferson et al., 2011). This prior study was in elderly subjects, the majority being male. Yet, the results from young women are corroborated by another study which showed that increased aortic PWV was associated with WMH: a 2021 study found that aortic PWV was associated with decreased gray matter volume and the development of WMH (Bown et al., 2021). These findings were similarly observed in this study in a younger female sample, despite the obvious differences in age and possible comorbidities.

It is well known that adverse cardiovascular profiles are associated with arterial stiffening, cerebral small vessel disease, hypertension, and associated disorders. Further, it is known that white matter lesions may present as a symptom of cardiovascular deficits. This study revealed that cardiac output and aortic PWV were associated with the presence of low grade WMH in young women. These results are significant because previous observations had only been made in elderly or diseased populations, and these results illustrate that these biomarkers may exist far before any obvious cognitive alterations or the presentation of neurodegenerative disease. It is proposed that certain cardiac measures such as cardiac output or PWV be used as biomarkers for pathological WMH.

Summary

This study reports relationships between cardiovascular and metabolic factors and white matter integrity observed in young women prior to pregnancy. While similar studies have been

conducted in elderly or diseased populations, no studies have been done on this demographic, which yielded surprising results. The current examination of cardiovascular and metabolic risk factors and their relationship to brain health is critical to understanding how certain biomarkers may be exacerbated by cardiac and metabolic changes induced by pregnancy to influence metabolic, cardiovascular, and cognitive pathologies. Therefore, this study is particularly important in the context of both pre-pregnancy brain health and as an exploratory analysis of biomarkers that may contribute to fatal diseases such as hypertensive pre-eclampsia. There is far more work to be done in discovering how these biomarkers may alter white matter integrity post-pregnancy, how such adverse cardiovascular and metabolic measures propagate into various pathologies, and whether these changes impart cognitive alterations on to the mother or child.

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Tables

Table 1

Pearson Correlations between Metabolic Measures and Fractional Anisotropy of White Matter Tracts

	Age	BMI	Android, tissue fat %	Calculated Low Density Lipoproteins, mg/dL	HOMA-IR	Cholesterol, mg/dl
Body Corpus Callosum	-0.178	0.076	0.006	-0.189	0.061	-0.194
Genu Corpus Callosum	-0.421**	0.068	0.058	-0.183	0.142	-0.157
Splenium Corpus Callosum	-0.316*	0.071	-0.004	-0.174	0.142	-0.057
Fornix	-0.189	-0.041	0.011	-0.371**	-0.398**	-0.366**
Right Anterior Internal Capsule	-0.013	0.05	-0.05	-0.07	0.003	-0.089
Left Anterior Internal Capsule	-0.163	0.154	0.04	-0.118	0.101	-0.02
Right External Capsule	-0.033	0.304*	0.214	0.14	0.2	0.199
Right Posterior Corona Radiata	-0.067	0.172	0.051	0.198	0.183	0.206
Left Posterior Thalamic Radiation	-0.490**	0.266*	0.078	0.046	0.143	0.184
Right Superior Longitudinal Fasciculus	-0.279*	0.277*	0.23	-0.022	0.286	0.06
Left Superior Longitudinal Fasciculus	-0.415*	0.205	0.145	-0.034	0.186	0.064
Right Thalamus	-0.036	0.186	0.026	-0.136	0.059	-0.142
Left Thalamus	0.101	0.244	0.122	-0.055	0.158	-0.063
Right Putamen	-0.009	0.450**	0.373*	0.232	0.520**	0.241
Left Putamen	-0.013	0.3*	0.173	-0.013	0.301	0.093

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

Table 2

Pearson Correlations between Cardiovascular Measures and Fractional Anisotropy of White Matter Tracts

	Supine MAP	AUC Mean Arterial Pressure	Brachial PWV time to start, corrected for cardiac ejection	Popliteal PWV, time to start, corrected for cardiac ejection
Body Corpus Callosum	0.028	.266*	-0.229	-0.249
Genu Corpus Callosum	-0.004	0.246	-0.165	-0.250*
Splenium Corpus Callosum	0.241	0.056	-0.022	-0.031
Fornix	-0.316*	-0.061	-0.295*	-0.351**
Right Anterior Internal Capsule	0.208	0.299*	0.024	0.091
Left Anterior Internal Capsule	0.073	0.282*	-0.097	-0.132
Right External Capsule	0.134	0.153	-0.007	0.011
Right Posterior Corona Radiata	0.270*	0.343**	0.063	0.086
Left Posterior Thalamic Radiation	0.191	0.103	-0.039	-0.189
Right Superior Longitudinal Fasciculus	0.268*	0.154	0.044	0.01
Left Superior Longitudinal Fasciculus	0.207	0.141	0.042	-0.25
Right Thalamus	0.123	0.310*	-0.1	-0.175
Left Thalamus	0.095	0.263*	-0.047	-0.093
Right Putamen	0.257*	0.268*	0.132	0.265*
Left Putamen	0.105	0.24	0.089	0.189

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

Table 3

Pearson Correlations between Metabolic Measures and Mean Diffusivity of White matter Tracts

	Age	BMI	Android, tissue fat %	Calculated Low Density Lipoproteins, mg/dL	HOMA-IR	Cholesterol, mg/dl
Genu Corpus Callosum	0.212	-0.002	-0.018	0.280*	-0.121	0.312*
Splenium Corpus Callosum	0.03	-0.215	-0.139	0.355**	-0.121	0.391**
Fornix	0.173	0.054	-0.049	0.341*	0.384**	0.327*
Right Corticospinal	-0.168	-.378**	-.0331**	-0.238	-0.323*	-0.245
Left Corticospinal	-0.229	-0.217	-.0275*	-0.296*	-0.182	-0.265
Right Anterior Internal Capsule	0.093	0.009	-0.008	0.045	-0.182	0.03
Left Anterior Internal Capsule	0.069	0.037	-0.021	-0.002	-0.145	-0.018
Right External Capsule	0.187	-0.054	-0.013	0.004	-0.164	-0.026
Right Posterior Corona Radiata	0.181	-0.320*	-0.226	0.118	-0.311*	0.144
Left Posterior Corona Radiata	0.092	-.0255*	-0.223	-0.012	-0.188	0.005
Right Posterior Thalamic Radiation	0.271*	-0.21	-0.205	-0.167	-0.266	-0.113
Left Posterior Thalamic Radiation	0.270*	-0.183	-0.197	-0.238	-0.24	-0.192
Right Superior Longitudinal Fasciculus	0.218	-0.028	0.007	0.12	-0.244	0.111
Right Thalamus	0.084	-0.213	-.0257*	0.032	0.011	0.037
Right Putamen	0.03	-0.114	-0.11	-0.177	-0.262	-0.188
Right Caudate	0.102	0.061	-0.006	0.334*	0.131	0.321*

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Table 4
Pearson Correlations between Cardiovascular Measures and Mean Diffusivity of White matter Tracts (Continued)

	Supine MAP	AUC Mean Arterial Pressure	Brachial PWV time to start, corrected for cardiac ejection	Popliteal PWV, time to start, corrected for cardiac ejection
Genu Corpus Callosum	0.029	-0.273*	0.155	0.102
Splenium Corpus Callosum	-0.011	0.078	0.048	0.002
Fornix	0.329**	0.084	0.357**	0.378**
Right Corticospinal	-0.229	-0.046	-0.031	-0.17
Left Corticospinal	-0.207	-0.037	-0.122	-0.191
Right Anterior Internal Capsule	-0.083	-0.310*	0.07	-0.239
Left Anterior Internal Capsule	-0.026	-0.351**	0.134	-0.097
Right External Capsule	-0.086	-0.326*	0.044	-0.179
Right Posterior Corona Radiata	-0.321*	-0.141	-0.012	-0.215
Left Posterior Corona Radiata	-0.213	0.02	-0.036	-0.072
Right Posterior Thalamic Radiation	-0.298*	-0.186	0.063	-0.186
Left Posterior Thalamic Radiation	-0.280*	-0.195	-0.076	0.052
Right Superior Longitudinal Fasciculus	-0.309*	-0.317*	-0.075	-0.271*
Right Thalamus	-0.022	-0.068	0.245	0.275*
Right Putamen	-0.208	-0.405**	0.034	-0.147
Right Caudate	0.274*	-0.151	0.305*	0.154

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

Table 5

Independent Samples t-Test: Mean Diffusivity in Women with Fazekas Score 0 vs. 1

N(0) = 45 N(1) = 17	Fazekas Score	Mean	t-value	p-value
Body Corpus Callosum	0	0.00077651	-1.193	0.243
	1	0.000787		
Genu Corpus Callosum	0	0.0007478	-1.75	0.089
	1	0.00076406		
Splenium Corpus Callosum	0	0.00074564	-0.677	0.504
	1	0.00075135		
Fornix	0	0.00119907	-1.896	0.066
	1	0.00130582		
Right Corticospinal	0	0.00069736	1.771	0.086
	1	0.00068224		
Left Corticospinal	0	0.00070369	1.64	0.108
	1	0.00069059		
Right Anterior Internal Capsule	0	0.00065829	-2.682	0.011*
	1	0.00067947		
Left Anterior Internal Capsule	0	0.00065991	-2.073	0.045*
	1	0.00067		
Right External Capsule	0	0.00071222	-2.234	0.033*
	1	0.00072935		
Left External Capsule	0	0.00071933	-1.23	0.226
	1	0.00072418		
Right Posterior Corona Radiata	0	0.000756	-2.457	0.021*
	1	0.000777		
Left Posterior Corona Radiata	0	0.00075296	-2.375	0.023*
	1	0.00077071		
Right Posterior Thalamic Radiation	0	0.00077542	-2.446	0.02*
	1	0.00079371		
Left Posterior Thalamic Radiation	0	0.00077816	-0.757	0.454
	1	0.00078359		
Right Superior Longitudinal Fasciculus	0	0.00072762	-2.394	0.023*
	1	0.00074418		
Left Superior Longitudinal Fasciculus	0	0.00072324	-2.248	0.034*
	1	0.00073629		
Right Thalamus	0	0.00077764	-0.895	0.379
	1	0.00078612		
Left Thalamus	0	0.00078833	-0.605	0.549
	1	0.00079447		
Right Putamen	0	0.00069022	-1.861	0.071
	1	0.00071112		

Left Putamen	0	0.00073373	-0.602	0.551
	1	0.00073794		
Right Caudate	0	0.00074111	-1.776	0.084
	1	0.00077194		
Left Caudate	0	0.0006826	-0.892	0.377
	1	0.00068782		

* Correlation is significant at the 0.05 level (2-tailed).

(Table 6)

Independent Samples t-Test: White Matter Hyperintensities and Cardiovascular, Metabolic Factors

	Fazekas Score	N	Mean	t-value	p-value
BMI	0	45	25.708	-0.195	0.847
	1	17	27.126		
Supine MAP	0	45	90.341	-0.924	0.366
	1	17	90.868		
HOMA-IR	0	36	1.355	-0.757	0.456
	1	16	1.706		
Cholesterol, mg/dl	0	36	158.610	-0.637	0.53
	1	16	164.630		
triglycerides, mg/dL	0	36	84.610	-1.049	0.308
	1	16	111.750		
Calculated Low Density Lipoproteins, mg/dL	0	36	92.110	-0.161	0.873
	1	16	93.250		
A-II	0	32	42.781	0.109	0.914
	1	13	42.325		
CRP, ng/mL	0	41	5993.802	0.21	0.836
	1	14	5544.570		
AUC Mean Arterial Pressure	0	42	113.321	0.675	0.504
	1	17	91.325		
AUC Pulse	0	40	9.673	-0.32	0.752
	1	17	19.379		
AUC Pulse Pressure	0	40	67.168	-1.58	0.125
	1	17	114.426		
AUC Cardiac Output	0	40	6.564	-2.265	0.032*
	1	17	15.706		
Aortic PWV, time from beginning systolic flow to R, seconds	0	45	0.062	-0.279	0.783
	1	17	0.063		
Aortic PWV, time from R to peak systolic flow (time to peak)	0	45	0.147	-2.173	0.038*
	1	17	0.160		
Brachial PWV time to start, corrected for cardiac ejection	0	45	8.060	0.148	0.883
	1	17	7.996		

Popliteal PWV, time to start, corrected for cardiac ejection	0	45	3.884	1.296	0.205
	1	17	3.674		
Cardiac Output (L/min)	0	45	4.609	0.169	0.867
	1	17	4.563		

* Correlation is significant at the 0.05 level (2-tailed).

Figures

Figure 1 Fazekas Scale (Michaeu, lmaios)

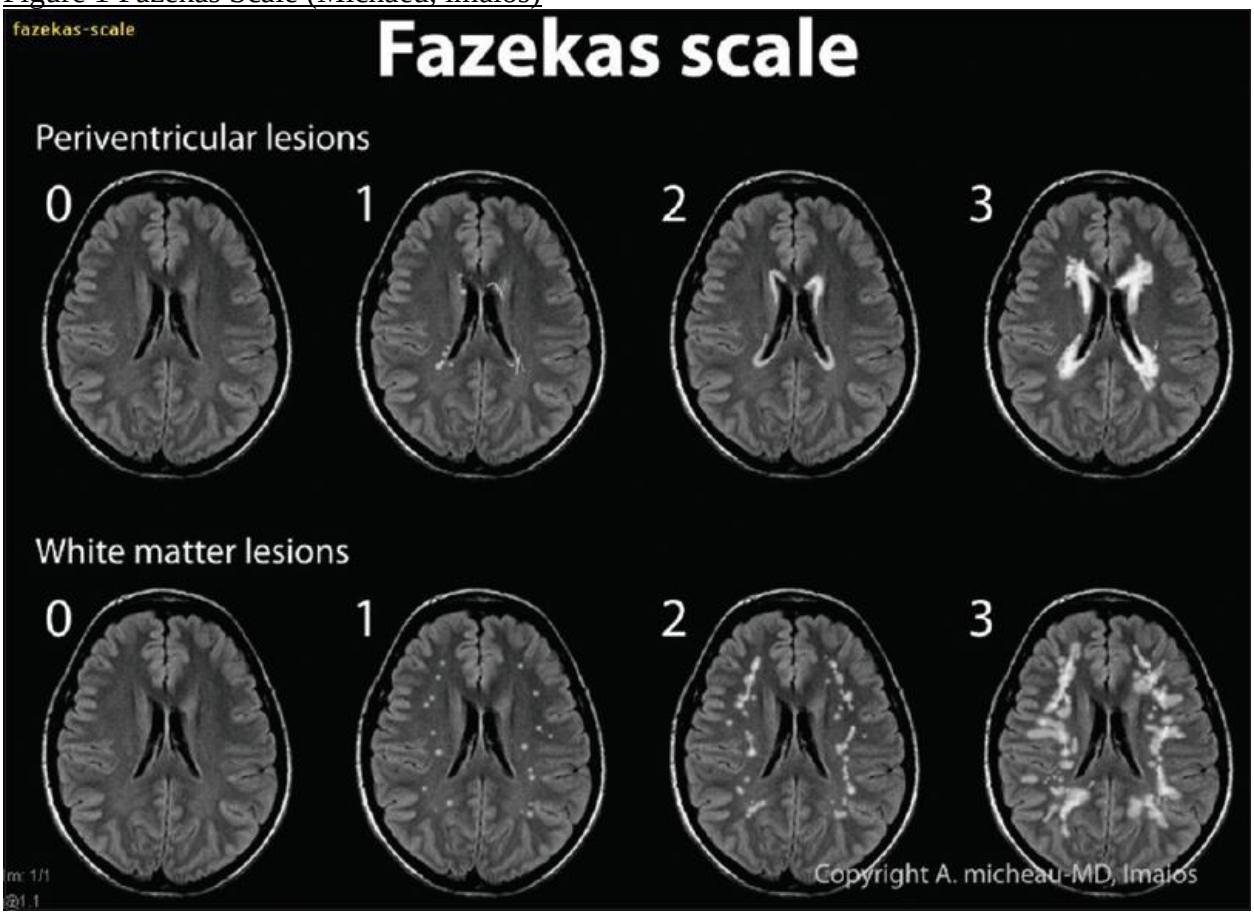

Figure 2 Healthy Brain

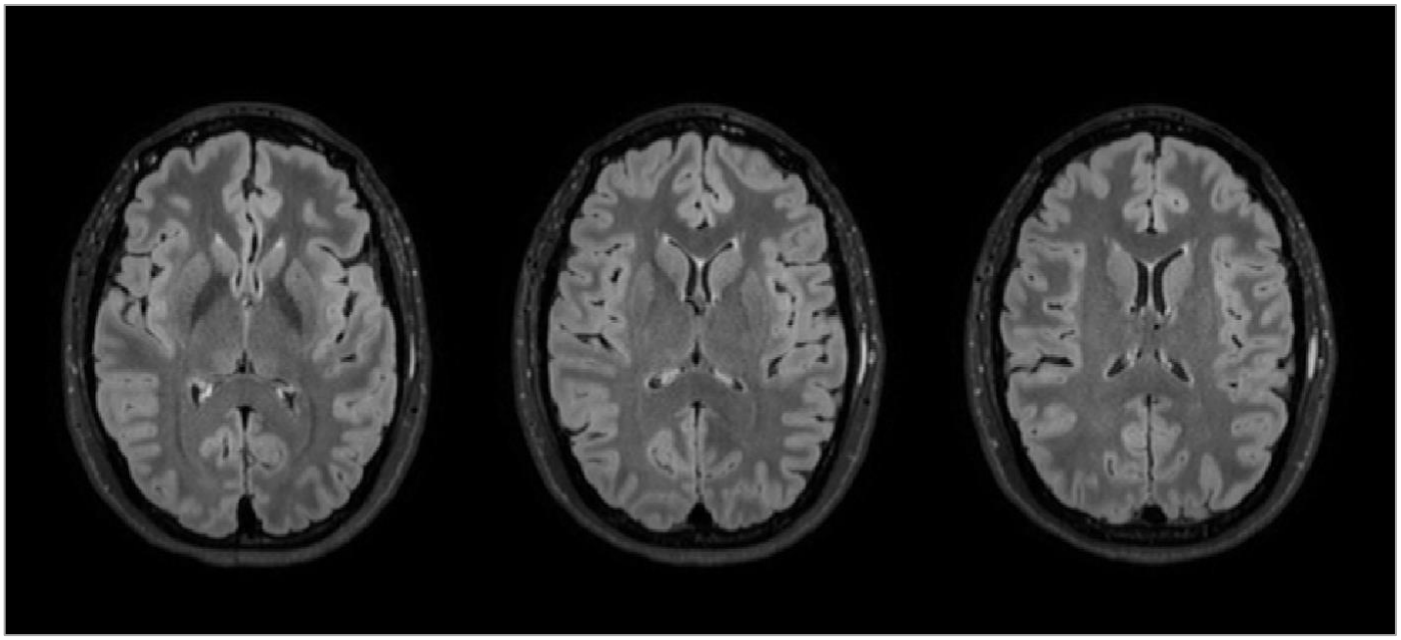

Figure 3 Brain with WMH

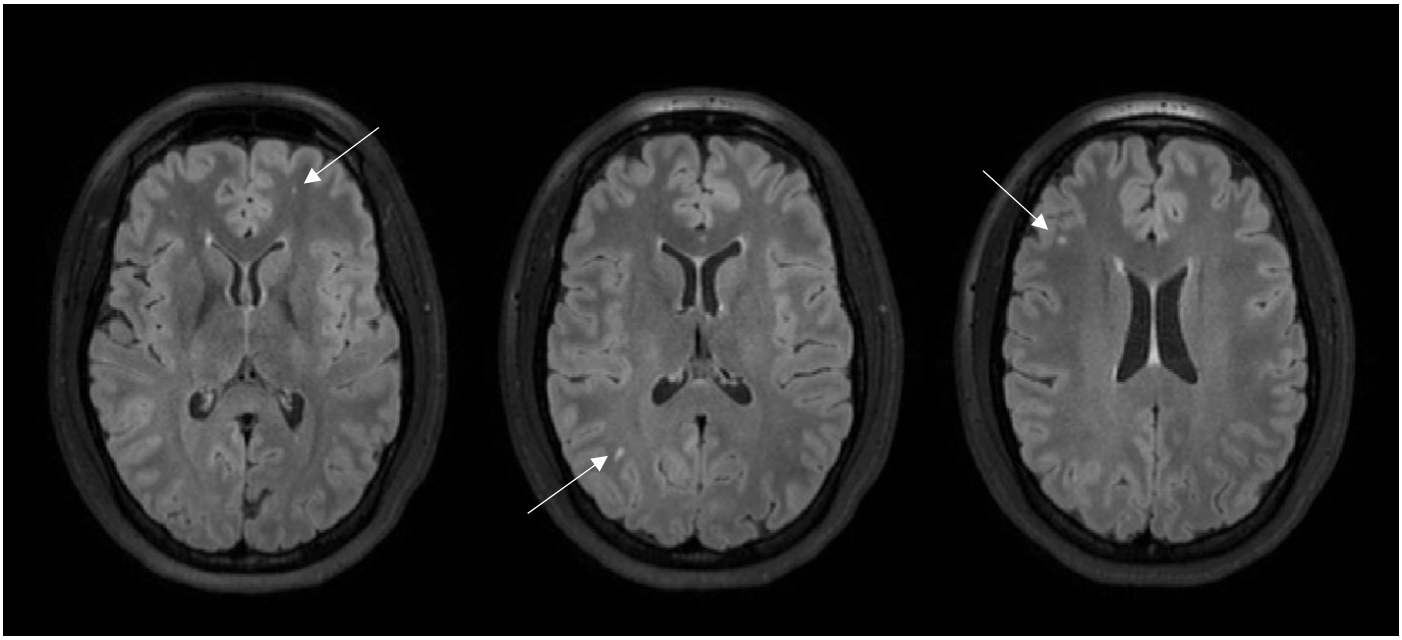

Figure 4 Voxelwise Independent Samples t-Test: Fazekas Score and Mean Diffusivity of White Matter Tracts

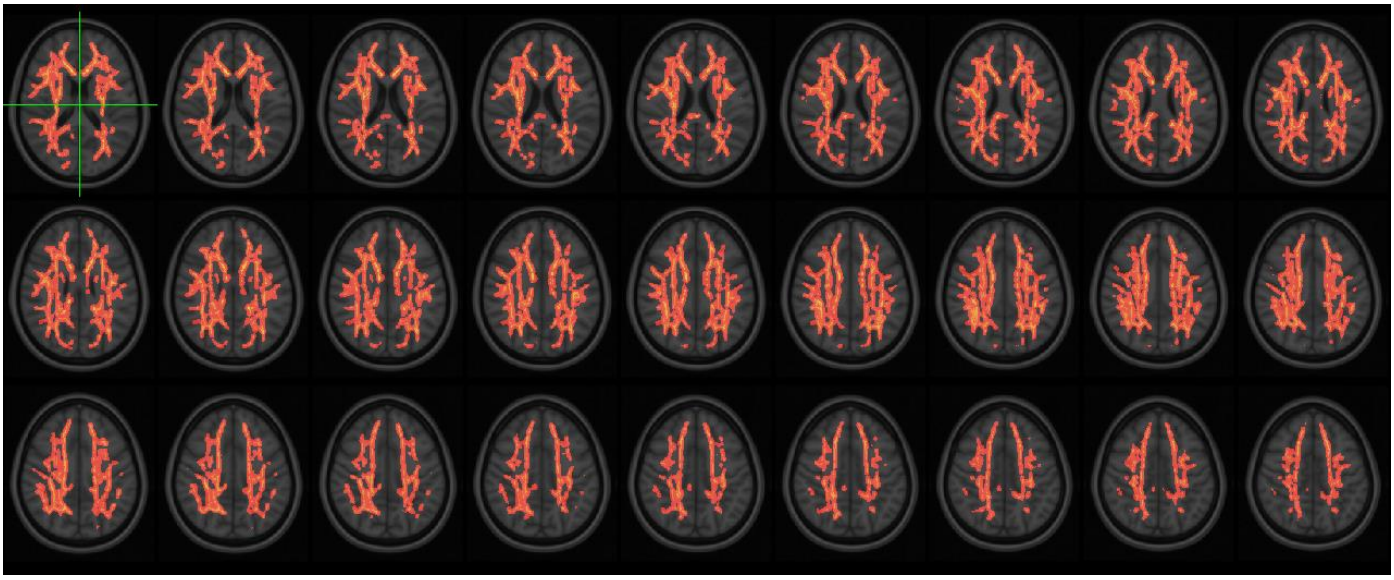

Figure 4 represents global p-statistics which have been thresholded at p = .949, giving alpha = .05 (FSLeyes takes 1-p for statistical thresholding). The remaining significant white matter tract differences were then fattened to provide realistic visual results. Ultimately, it shows areas where the Fazekas group displays higher mean diffusivity scores than the healthy subject group.

There appear to be global differences between individuals with low-grade WMH and those who do not, with the WMH group displaying an overall increase in the magnitude of diffusion compared to the healthy group.

Figure 5 Voxelwise Independent Samples t-Test: History of Pre-Eclampsia and Mean Diffusivity

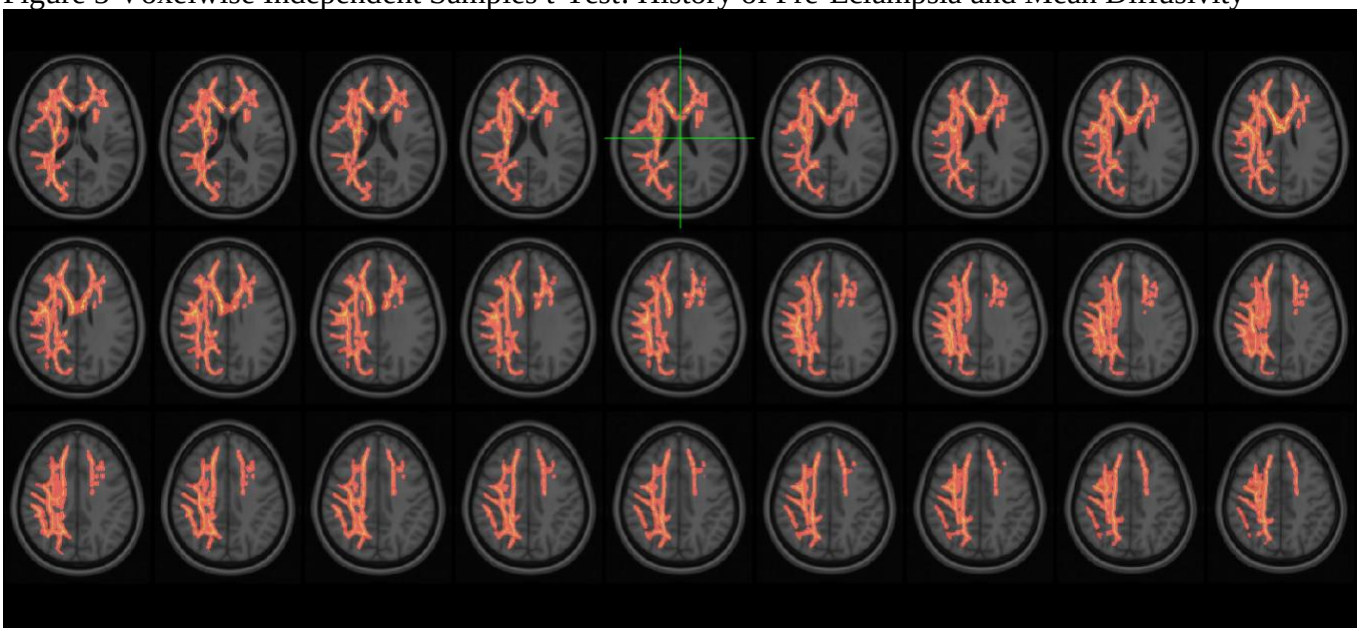

Figure 5 shows right-hemisphere localized differences between subjects with a history of pre-eclampsia (n = 31) and healthy subjects (n = 31) in prior pregnancy and current mean diffusivity scores. These scores represent areas where healthy subjects had higher mean diffusivity than affected subjects. Highlighted areas represent differences that are thresholded as significant at the alpha = .05 level or less.

This was an exploratory analysis on the impact of pre-eclampsia on white matter integrity. Such relationships were not observed between pre-eclampsia and FA, but right-hemisphere increases in total diffusion were observed in women who had pre-eclampsia before. It is unclear why these changes are limited to the right hemisphere, but it is known that vascular morphologies such as increased blood pressure or arterial stiffening contribute to fluid leakage and cerebral edema associated with increased MD.