

Sexual Assault and White Matter Hyperintensities Among Midlife Women

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Abstract

Background

Traumatic experiences have been linked to poor mental and physical health. However, there has been little examination of their relationship to neuroimaging markers of cerebrovascular risk. White matter hyperintensities (WMHs) are markers of brain small vessel disease. WMHs can be detected decades before the onset of dementia and other disorders and can serve as early markers for these brain disorders. We tested whether traumatic experiences were associated with brain WMH volume among midlife women.

Methods

In the MsBrain study, 145 women (mean age = 59 years) without cardiovascular disease, stroke, or dementia were recruited. Women completed questionnaires [trauma checklist, depression, post-traumatic stress measures]; physical measures [body mass index (BMI), blood pressure (BP)]; phlebotomy; actigraphy sleep measurement, and 3 Tesla magnetic resonance brain imaging for WMHs. Cross-sectional associations between traumatic experiences and WMH volume were assessed in linear regression models. Covariates were age, race/ethnicity, education, BMI, BP, lipids, preeclampsia, sleep, and additionally depressive and post-traumatic stress disorder symptoms.

Results

68% of women endorsed at least one of the traumas assessed. The most common trauma was sexual assault (23% of women). Women with trauma exposure had greater WMH volume than women without trauma [B(SE) = .24 (.09), $p = .01$, multivariable]. The single trauma most associated with WMH was sexual assault [B(SE) = .25 (.11), $p = .02$, multivariable]. Results persisted adjusting for depressive or post-traumatic stress symptoms.

Conclusions

A trauma history, particularly sexual assault, was associated with greater WMH volume controlling for covariates, including depressive and post-traumatic symptoms. Sexual assault may place women at risk for poor brain health.

Introduction

A burgeoning literature points to the importance of psychosocial stress and trauma to the development of mental health disorders (Bacchus, Ranganathan, Watts, & Devries, 2018; Felitti et al., 1998; Kessler et al., 2017; Liu et al., 2017) and to poor physical health outcomes such as cardiovascular disease (CVD)

(Breiding, Black, & Ryan, 2008; Liu, Logan, & Alhusen, 2020; Santaularia et al., 2014; Suglia, Sapra, & Koenen, 2015). A more limited body of work links major stressors in adulthood (Kershaw et al., 2014; Kornerup et al., 2010) or childhood to risk for brain diseases such as stroke (Kornerup et al., 2010; Merrick et al., 2019; Rich-Edwards et al., 2012) or dementia (Radford et al., 2017). However, findings are inconsistent and require further investigation (Gallo et al., 2014; Goodwin & Stein, 2004; Radford et al., 2017; Sumner et al., 2015; Yaffe et al., 2010).

Neuroimaging can detect subclinical changes in the brain before the onset of clinical disease and thereby can be useful for understanding brain health at earlier in life. Lesions in the white matter that appear as white matter hyperintensities (WMHs) on T2-weighted magnetic resonance imaging (MRI) are a subclinical marker of cerebral small vessel damage thought to develop due to small vessel disease (Debette & Markus, 2010). WMHs are linked to subsequent cognitive decline, dementia, and mortality (Debette & Markus, 2010). WMHs can be detected decades before the onset of these brain disorders that typically emerge later in life (Benjamin et al., 2019; Lambert et al., 2014) and thus can serve as an early marker of risk for the development of these brain disorders.

We tested the hypothesis that midlife women with a trauma history would have a greater volume of WMHs. We focused on women, as women are at particular risk of major traumatic events such as sexual assault, as well as brain diseases such as dementia (Benjet et al., 2016). We examined these associations controlling for a range of potential confounders, including demographics, risk factors for WMHs, sleep, and in additional models, depression or post-traumatic stress symptoms.

Methods

Sample

Women (N = 159) aged 45–67 underwent neuroimaging as part of the MsBrain Study, a study of menopause and brain aging. Women were recruited between 2017 and 2020 from the Pittsburgh, PA community and from the MsHeart study, a study of non-smoking women free of clinical CVD who were previously studied for menopause and cardiovascular health (Thurston et al., 2016). Exclusion criteria included a reported history of stroke or cerebrovascular accident; dementia; seizure disorder; brain tumor; Parkinson's Disease; a history of head trauma with loss of consciousness; contraindications to MRI; current chemotherapy; active substance use (established via urine toxicology screen and interview); pregnancy; and current use of select medications including hormone therapy (oral or transdermal estrogen and/or progesterone), selective estrogen receptor modulators, aromatase inhibitors, selective serotonin reuptake inhibitors, or serotonin norepinephrine reuptake inhibitors. Of the 159 women, seven women were excluded due to detected or suspected brain tumor, stroke, or seizure disorder; three women were excluded due to missing trauma data; and four women were excluded from multivariable models due to missing data on key covariates [high density lipoprotein (HDL) cholesterol: N = 3; sleep actigraphy: N = 1], yielding a final sample of 145 women.

Design and Procedures

Participants underwent telephone and in-person screening procedures (including a urine toxicology screen), physical measurements, a medical history interview, completion of questionnaires, three days of sleep actigraphy measurement, and brain MRI.

Measures

Trauma exposure

Trauma was assessed via the Brief Trauma Questionnaire which was developed for the Nurses Health Study II (Koenen et al., 2009) and adapted from the Brief Trauma Interview (Schnurr, Lunney, Sengupta, & Spiro III, 2005; Schnurr, Spiro, Vielhauer, Findler, & Hamblen, 2002). This self-report questionnaire assesses traumatic events, including car accidents, natural disasters, life threatening illness, being beaten or mugged, sexual assault, death of a child, sexual harassment, threat of injury or violence, or witnessing a severe injury or death. Interrater reliability for the presence of Criterion A1 trauma exposure according to the DSM-IV was high [average kappa = .70 (range .74–1.00) for all events except illness (.60)] (Koenen et al., 2009).

WMH

MRI scanning was performed at the MR Research Center of the University of Pittsburgh an average of 12 days (standard deviation = 4.9; range 4–30) from the trauma measurements. A 3T Siemens Tim Trio MR scanner was used, with a Siemens 64-channel head coil. Two series of MR images were analyzed for the current study: A magnetization-prepared rapid gradient echo (MPRAGE) T1-weighted sequence and T2-weighted (T_2w) Fluid-attenuated inversion recovery (FLAIR) sequence. MPRAGE images were acquired in the axial plane using the following parameters: TR = 2400 ms; TE = 2.22 ms; TI = 1000 ms; flip angle = 8°; FOV = 256*240 mm; slice thickness = 0.8mm; voxel size = 0.8 mm*0.8mm; matrix size = 320*300; and number of slices = 208. FLAIR images were acquired in the axial plane using the following parameters: TR = 9690 or 10000 ms; TE = 91 ms; TI = 2500 ms; flip angle = 135°; FOV = 256 x 256 mm; matrix = 320 x 320; slice thickness = 1.6 mm; voxel size = 0.8mm*0.8mm; and number of slices = 104. The small change in TR from 9690 to 10000 was performed one year into the study to meet Specific Absorption Rate (SAR) human safety guidelines for participants with a higher BMI. This change slightly increased the time of acquisition but had minimal effect on image contrast.

An automated pipeline was used to segment WMHs on the T_2w FLAIR images using previously documented and validated methods (Wu et al., 2018; Wu et al., 2006). Cerebral and cerebellar white matter were segmented in individual T_2w FLAIR image space using SPM12 (Wellcome Trust Centre for Neuroimaging, <http://www.fil.ion.ucl.ac.uk/spm/>). Manual inspection of each image was performed to rule out cerebellar WMHs. As no lesions in the cerebellum were observed in our participants, the mean and standard deviation of the cerebellar white matter on the FLAIR image was used to Z-transform the

FLAIR image (Z-T_{2w} FLAIR). On the Z-transformed FLAIR images, voxels ≥ 2 and within the cerebral white matter mask were identified as WMHs. This method uses individual mean and standard deviation from normal cerebellar white matter to standardize individual FLAIR images, which avoids systematic bias in seed selection between participants with significant cerebral WMHs versus those with few WMHs. Z-transformation also reduces intensity variations across individual FLAIR images. For additional models considering regional WMHs, FreeSurfer (Athinoula A. Martinos Center for Biomedical Imaging, <https://surfer.nmr.mgh.harvard.edu/v7.1.1>) processing was performed on individual T1w MPRAGE images. Based on white matter segmentation and cortical white matter labeling from FreeSurfer, cortical white matter masks for the frontal, temporal, parietal, and occipital lobes, and white matter masks for periventricular were generated for the localization of WMHs. The total WMH and regional volumes (in cubic centimeters) were normalized by intracranial volumes (ICV) [$n\text{WMHs} = \text{WMHs}/\text{ICV}$] and log transformed for analysis.

Additional measures

Height was measured via fixed stadiometer and weight via balance beam scale. BMI was calculated [$\text{weight (kg)}/\text{height}^2 \text{ (m)}$]. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) was the average of three seated measurements taken via a Dinamap v100. Demographics; medical, reproductive, and current and past psychiatric history (including addictions); medication use; and health behaviors, including smoking, alcohol use, and current and prior substance use (e.g., marijuana, heroin and opiates, benzodiazepines, cocaine/crack/amphetamines, methamphetamines, other substances) were assessed by questionnaires and interview. Race/ethnicity was self-reported. Educational attainment was assessed as years of completed education (classified as high school/vocational, college graduate, >college). Preeclampsia was assessed via reproductive history questionnaire (scored as yes = preeclampsia at any pregnancy; no = preeclampsia at no pregnancy or never pregnant). Depressive symptoms and post-traumatic stress disorder (PTSD) symptoms were assessed via the widely-used and well-validated Center for Epidemiologic Studies Depression Survey (Radloff, 1977) and the PTSD civilian symptom checklist (PCLC) (Marshall, 2004), respectively. Childhood abuse/neglect was assessed via the 28-item short form of the Child Trauma Questionnaire (CTQ), a validated multi-dimensional scale of childhood abuse and neglect experienced at or before age 18 (Bernstein et al., 1994) and categorized according to clinical cutpoints (Walker et al., 1999).

Assessment of glucose, insulin, and lipids from a fasting blood sample was determined using an enzymatic assay or immunoturbidimetric assay. LDL was calculated using the Friedewald equation (Friedewald, Levy, & Fredrickson, 1972). Homeostatic model assessment, an index reflecting insulin resistance, was calculated [$(\text{fasting insulin} * \text{fasting glucose})/22.5$] (Matthews et al., 1985).

Women wore an Actiwatch 2 wrist actigraph unit on the wrist of the non-dominant hand (Respironics, Inc., Murrysville, PA) (Ancoli-Israel et al., 2003) and completed a sleep diary (Monk et al., 1994) for three days. Actigraphy data were collected in 1-min epochs and analyzed with Philips Actiware v6.0.0 software, with a wake threshold of 40 and number of epochs of sleep/wake for sleep onset/offset of 10. Wake after

sleep onset (WASO; minutes of wakefulness between actigraphy-defined sleep onset time and actigraphy-defined final wake time) was our sleep measure of interest given its relations to WMH in this sample (Thurston et al., 2020).

Statistical analysis

Variables were examined for distributions, outliers, and cell sizes. WMHs, BMI, and WASO were log transformed to conform to model assumptions of normality. Bivariate relations between study variables and WMHs were examined via Pearson and Spearman correlation coefficients. We tested the relation of any trauma exposure to WMH and each trauma exposure separately in relation to WMH in linear regression models. Select covariates (age, race, education) were *a priori* selected for inclusion in models, and all other covariates were included based upon their relationship with the outcome at $p < .10$. In additional analyses, we considered the number of trauma exposures (none, one, two or more) in relation to WMH as well as PTSD symptoms, depressive symptoms, childhood abuse (CTQ), and substance use as additional covariates in models testing relationships of trauma to WMH. In additional models, we considered trauma in relation to regional WMHs (frontal, temporal, parietal, occipital lobes; note: the few periventricular WMHs precluded analyses of this region). All tests were two tailed with an alpha set to 0.05. Analyses were conducted using SAS v9.4 (SAS Institute, Cary, NC).

Results

Participants were on average 59 years old, overweight, and normotensive (Table 1). Most of the women (67%, $N = 98$) reported a history of trauma. Study covariates did not vary by trauma exposure. The most common trauma was sexual assault, reported by 23% ($N = 33$) of the women, followed by witnessing serious injury or death (22% of women, $N = 32$; Table 2)

Table 1
Sample characteristics

N	145
Age, M (SD)*	59.12 (4.08)
Race/ethnicity, N (%)	115 (79.31)
White	30 (20.69)
Black / Other	
Education, N (%)	51 (35.17)
High school/some college/vocational	46 (31.72)
College graduate	48 (33.10)
>College	
Body mass index, Median (IQR)	27.83 (24.50, 32.73)
Systolic blood pressure, mmHg, M (SD)	116.76 (12.49)
Diastolic blood pressure, mmHg, M (SD)	67.42 (8.56)
Low density lipoprotein cholesterol, mg/dL, M (SD)	116.99 (34.88)
High density lipoprotein cholesterol, mg/dL, M (SD)	63.99 (16.99)
Triglycerides, mg/dL, Median (IQR)	95.00 (69.00, 123.00)
Homeostatic model assessment, Median (IQR)	3.50 (2.31, 4.95)
Depressive symptoms, high (≥ 16 CESD), N (%)	19 (13.10)
Post-traumatic stress symptoms (PCLC), M (SD)	24.12 (7.87)
White matter hyperintensity volume, Median (IQR)†	0.0035 (19.00–28.00)
† Normalized to intracranial volume	
SD = standard deviation, IQR = interquartile range, CESD = Center for Epidemiologic Studies of Depression Scale, PCLC = Post Traumatic Stress Disorder Checklist, Civilian Version	

Table 2
Prevalence of traumatic experiences

	N (%) yes
Any trauma	98 (67.69)
Serious accident	31 (21.38)
Natural or human made disaster	16 (11.03)
Serious illness	8 (5.52)
Attacked, beaten, or mugged	24 (16.55)
Sexual assault	33 (22.92)
Death of one's child	10 (6.90)
Workplace sexual harassment	30 (20.83)
Serious injury	18 (12.50)
Witness serious injury/death	32 (22.38)

In multivariable models, women who had a traumatic experience had higher volume of WMHs than women who had not experienced trauma (Table 3). When individual traumas were considered in additional models, the single trauma significantly associated with greater volume of WMHs was sexual assault (Table 3, Fig. 1).

Table 3
Relation of traumatic experiences to WMH volume

	WMH volume	
	Model 1	Model 2
	B(SE)	B(SE)
Any trauma	0.23 (0.09)*	0.24 (0.09)*
Serious accident	0.08 (0.11)	0.07 (0.11)
Natural or human disaster	0.13 (0.14)	0.10 (0.14)
Serious illness	0.13 (0.19)	0.12 (0.19)
Attacked, beaten, or mugged	0.22 (0.12)†	0.20 (0.12)†
Sexual assault	0.23 (0.11)*	0.25 (0.11)*
Death of child	-0.11 (0.18)	-0.10 (0.18)
Workplace sexual harassment	0.01 (0.11)	0.03 (0.11)
Serious injury	0.10 (0.13)	0.10 (0.13)
Witness serious injury/death	0.04 (0.11)	0.02 (0.11)
†p < .10, *p < .05		
Note: WMH, body mass index log transformed		
WMH = white matter hyperintensity, SE = standard error		
Model 1: Age, race, education, body mass index, diastolic blood pressure, high density lipoprotein cholesterol, preeclampsia		
Model 2: Age, race, education, body mass index, diastolic blood pressure, high density lipoprotein cholesterol, preeclampsia + sleep (wake after sleep onset)		

In additional models, we considered the number of traumas in relation to WMHs. We found that women experiencing two or more traumas had particularly greater WMHs [one trauma: B(SE) = 0.20 (0.11), p = 0.08; two or more traumas: B(SE) = 0.23 (0.11), p = 0.03; relative to no trauma, adjusted for age, race, education, BMI, DBP, HDL cholesterol, and preeclampsia]. We further considered trauma in relation to regional WMHs, finding that trauma exposure was associated with significantly greater WMHs in the left frontal lobe and left and right parietal lobes; of the individual traumas, findings were pronounced for sexual assault in relation to parietal lobe WMHs (Supplemental Table 1). We also considered depressive symptoms and PTSD symptoms each as additional covariates in primary models; they were not associated with WMHs nor they did explain these relations (Supplemental Table 2). We further considered a history of childhood abuse, which was assessed on a subset of women (N = 123). Childhood abuse/neglect history was not associated with WMHs and when additionally controlling for a history of childhood abuse/neglect in primary models, associations persisted between trauma and WMHs [B(SE)

= .30 (.11), $p = .006$, multivariable with childhood abuse/neglect] and sexual assault and WMHs [B(SE) = B(SE) = .37 (.13), $p = .005$, multivariable with childhood abuse/neglect]. We also considered a role for smoking (only three women were smokers in the sample), current alcohol use, current and prior substance use, and a history of addiction in trauma – WMHs associations, but these factors were not associated with WMHs and did not explain associations (data not shown).

Discussion

Midlife women who had experienced a traumatic event had higher WMH volumes than women who had not experienced such an event. Of the traumatic experiences assessed, sexual assault was the single trauma significantly related to WMHs. These associations persisted with adjustment for multiple covariates, including key cardiovascular risk factors, objectively-assessed sleep, depressive or post-traumatic symptoms, and even a history of childhood abuse or neglect. Findings point to potential adverse impact of trauma, particularly sexual assault, on women's brain health.

This study is the first to demonstrate that traumatic events are associated with greater WMHs. Select prior literature has linked traumatic experiences to stroke or dementia, but these studies largely focused on childhood abuse and self-reported outcomes (Kershaw et al., 2014; Kornerup et al., 2010; Merrick et al., 2019; Radford et al., 2017; Rich-Edwards et al., 2012; Scott et al., 2013). This study advances this literature in its use of neuroimaging as well as examination of a broader range of traumatic experiences throughout life. Use of neuroimaging allows for investigation of these relationships among women earlier in life, which supports the identification of at-risk women for early detection and intervention.

A highly novel finding is that sexual assault was the single trauma associated with WMHs. Notably, sexual violence is highly prevalent in the United States (US), with 44% of women having experienced sexual assault in their lifetime (Smith et al., 2018). A limited literature has linked sexual assault to cerebrovascular health, with one study finding a history of sexual assault was associated with increased risk of self-reported stroke (Santaularia et al., 2014), and another finding military sexual assault (sexual assault or repeated, threatening sexual harassment in the context of military service) linked to medical record-documented cerebrovascular disease (Gibson et al., 2020). However, no prior literature has examined sexual assault in relation to WMHs. These data underscore the importance of sexual violence to women's brain health.

Several mechanisms may link trauma and sexual assault to WMHs. Trauma and sexual assault in particular have been associated with adverse cardiovascular disease (CVD) risk factor profiles (Breiding et al., 2008; Santaularia et al., 2014) that have been linked to WMHs (Debette et al., 2011). However, the associations between trauma and WMHs remained when we controlled for these risk factors. Trauma exposure is often associated with poor sleep, and we and others have found poorer sleep continuity associated with greater volume of WMHs (Thurston et al., 2020). However, control for objectively-assessed sleep did not attenuate these associations. Trauma exposure is a major stressor, which increases the risk for psychiatric disorders such as depression and PTSD (Kessler, Davis, & Kendler, 1997;

Liu et al., 2017), yet our associations were not explained by depressive or PTSD symptoms assessed via validated instruments. Further, our findings were not explained by a history of childhood abuse, which has been linked to stroke later in life (Kornerup et al., 2010; Merrick et al., 2019; Rich-Edwards et al., 2012), and can set individuals on a trajectory of increased trauma exposure throughout life (Ullman, Najdowski, & Filipas, 2009). We carefully considered key behavioral factors, particularly alcohol and substance use, as well as an addiction history, which did not explain our associations here. Other mechanisms, such as the hypothalamic pituitary adrenal axis, inflammatory pathways, or epigenetic changes warrant investigation in these relationships.

In additional exploratory analyses, we also considered regional WMHs. We found that trauma was related to significantly greater WMHs in the left and right parietal lobe as well as in the left frontal lobe. When considering individual traumas, findings were most consistent for sexual assault and parietal WMHs. These associations are notable given findings that parietal lobe WMHs in particular predict later incident Alzheimer Disease (Brickman et al., 2012).

It is notable that although sexual assault was the most common trauma reported in this study (23%), the sexual assault prevalence found here is lower than that reported from national surveys (Smith et al., 2018). Reasons for our lower rate may have included our more constrained definition of sexual assault (contact with private parts) as compared to many national surveys which often include additional experiences such as forced kissing (Smith et al., 2018). Further, in light of our exclusion criteria (CVD-free, largely nonsmoking, no SSRI/SNRI antidepressant use), our sample was likely lower risk than the general population.

This work has limitations. Our trauma measure was a checklist that assessed if the trauma occurred but not its timing or chronicity. We also did not have information on the perpetrator of any violence; and thus, intimate partner violence could not be distinguished from other forms of physical or sexual assault. The next steps of this work should include investigating these questions with more detailed multidimensional trauma measures that also include information on the timing, frequency of occurrence, and the relationship of any perpetrators of interpersonal violence to the respondent. Further, statistical power for addressing the impact of traumas that had a low base rate here was limited (e.g., death of child); future work should select populations with level rates of these traumas to ascertain their links to health. We assessed PTSD and depression via validated symptom measures, but not via clinical diagnostic interview, which can be implemented in the next steps of this work. This work only included women; whether results can be extended to those of other genders requires investigation.

This study has key strengths. Considering traumatic experiences and sexual assault in particular in relation to WMH is novel. We considered a range of potential confounders in this work, including key risk factors and psychiatric symptoms. As women are at particular risk for poor brain health as they age, our focus on women adds important information to the growing body of work that investigates midlife women's brain health.

Conclusions

This study found that midlife women with a history of trauma and higher WMH volume than women without this history. Associations were particularly notable for sexual assault. These relationships were not explained by key CVD risk factors nor by psychological symptoms. Future work should investigate whether preventing or treating the sequelae of sexual assault can enhance women's cerebrovascular health as they age.

Declarations

Acknowledgments

Not applicable.

Author Contributions

Author contributions included conception and study design (RCT, PM), data collection or acquisition (KJ, MW), statistical analysis (RCT, PM, YC), interpretation of results (All authors), drafting the manuscript work or revising it critically for important intellectual content (All authors), and approval of final version to be published and agreement to be accountable for the integrity and accuracy of all aspects of the work (All authors).

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Compliance with Ethical Standards

Procedures were approved by the University of Pittsburgh Institutional Review Board. Participants provided written informed consent.

Conflict of Interest

Dr. Maki receives consultant fees from Pfizer, Abbvie, and Balchem.

Dr. Thurston receives consultant fees from Astellas, Pfizer, Procter & Gamble, and Virtue Health.

Drs. Aizenstein, Chang, Jakubowski, Derby, Koenen, Barinas-Mitchell and Wu report no financial interests or potential conflicts of interest.

Consent for publication

Not applicable.

Availability of data and materials: Anonymized data are shared upon request from qualified investigators consistent with National Institutes of Health guidelines.

Code availability

Not applicable.

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