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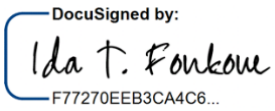
Signature: 


Ida Tchuisseu Fonkoue 3/24/2023

PTSD Symptoms Severity and Sleep Quality Predict Vascular Dysfunction in Young, Trauma-Exposed Women

By

Ida Tchuisseu Fonkoue
M.D., Ph.D.

Clinical Research

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Vasiliki Michopoulos
*Advisor*

---

Jordan Kempker
*Committee Member*

---

Abigail Powers Lott
*Committee Member*

Accepted:

Kimberly Jacob Arriola, Ph.D, MPH
Dean of the James T. Laney School of Graduate Studies

3/24/2023

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# Abstract

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**By** Ida Tchuisseu Fonkoue

Posttraumatic stress disorder (PTSD) is linked to sleep disturbances and significantly higher risk of developing cardiovascular disease (CVD). Further, vascular dysfunction and sleep are independently associated with CVD. Uncovering the link between PTSD symptom severity, sleep disturbances and vascular function could shine a light on mechanisms of CVD risk in trauma-exposed young women. Therefore, the purpose of the present study was to investigate the individual and combined effects of sleep efficiency and PTSD symptom severity on vascular function. We recruited 60 otherwise healthy women (age, 26±7 years and BMI, 27.7±6.5 kg/m$^2$) who had been exposed to trauma. We objectively quantified sleep efficiency (SE) using actigraphy, endothelial function via Framingham reactive hyperemia index (fRHI), and arterial stiffness via pulse wave velocity (PWV). PTSD symptom severity was assessed using the PTSD checklist for DSM-5 (PCL5). PWV was correlated with age (r =.490, $p$<.001) and BMI (r =.484, $p$<.001). Additionally, fRHI was positively correlated with SE (r=.409, $p$=.001) and negatively correlated with PTSD symptoms (r=-.382, p=.002). Next, to explore the predictive value of SE and PTSD symptoms on PWV and fRHI, we conducted two separate multiple linear regression models. The model predicting PWV was significant ($R^2$=.49, p<.001), with age, BMI and SE emerging as predictors. Likewise, the model predicting fRHI was significant ($R^2$=.36, p<.001), with both PTSD symptoms and SE as significant predictors. Our results suggests that while PTSD symptom severity impacts endothelial function, sleep efficiency influences overall vascular function in young trauma-exposed women, after controlling for age and BMI.

# PTSD Symptoms Severity and Sleep Quality Predict Vascular Dysfunction in Young, Trauma-Exposed Women

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# 1. Introduction

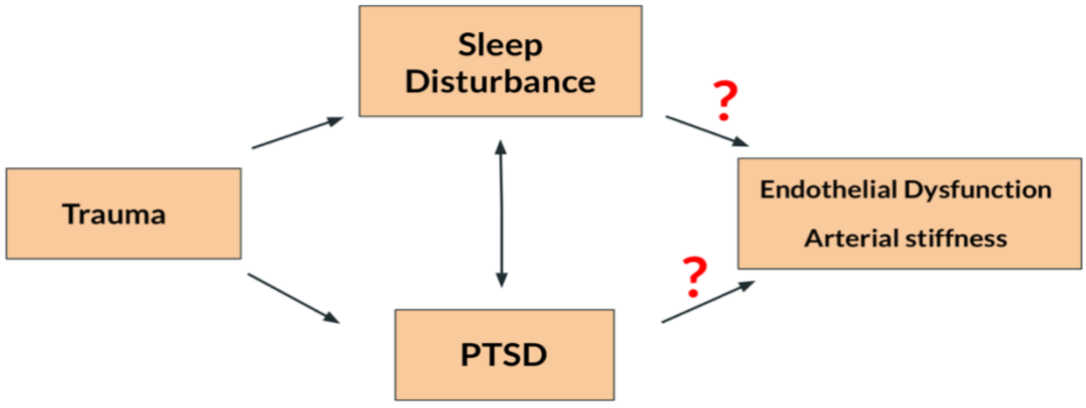
Posttraumatic stress disorder (PTSD) is a debilitating disorder that can develop in individuals after either witnessing or experiencing a traumatic event and is often complicated by the co-occurrence of conditions such as depression, drug and alcohol use, and eating disorders (1–3). Recent evident suggests individuals who have been exposed to trauma and/or developed posttraumatic stress disorder (PTSD) are at increased risk for cardiometabolic complications including CVD and type-2 diabetes mellitus (4, 5). Cardiovascular diseases (CVD) such as coronary artery disease or heart attack remain the leading cause of death among women in the United States, starting as early as 20 years old (6). Further, women are more likely to suffer from interpersonal trauma and are two to three times more likely to develop PTSD than men (7–9). However, the underlying mechanisms linking trauma and PTSD in women to CVD remain unclear.

Sleep disturbances (i.e. disruptive nighttime behaviors), which are a frequent complaint among adults who have experienced trauma and develop PTSD (10), have emerged as a modifiable risk factor for CVD (11). In 2022, the American Heart Association added sleep to its cardiovascular checklist "Life's Essential 8", highlighting the central role of sleep in cardiovascular health (12). In the last decade, multiple studies have revealed that total sleep deprivation increases systolic and diastolic BP in both men and women (13, 14). Moreover, there is strong evidence that short sleep durations are associated with hypertension in women, but not men (15, 16). Low sleep efficiency indicated by actigraphy is associated with greater arterial stiffness (17) and a significant predictor of future cardiovascular risk. Further, endothelial dysfunction, an initiating step in atherosclerosis, is a marker of future CVD (18, 19) and might also be influenced by sleep quality (20, 21). This association between sleep and vascular

dysfunction may be driven by lack of nocturnal dipping of blood pressure, which is a strong independent predictor of CVD risk (22). Sustained elevated blood pressure (allostatic load) at night may increase atherosclerotic plaques and stiffness of large arteries leading to greater risk for CVD (23). Thus, it is likely that the association of PTSD with CVD risk may emerge through interacting physiological and behavioral mechanisms that relate to both PTSD symptoms and CVD, such as sleep. While the evidence is accumulating to support that insufficient sleep and vascular dysfunction independently contribute to adverse cardiovascular conditions, uncovering the associations between sleep and vascular dysfunction could shine a light on mechanisms of CVD risk in otherwise healthy, trauma-exposed women. This could serve to identify at-risk women who may benefit from targeted interventions, with the ultimate goal of lowering CVD risk.

Therefore, the purpose of the present study was to investigate the individual and combined effects of sleep quality and PTSD symptom severity on two markers of vascular dysfunction: arterial stiffness and endothelial function. We hypothesized that both PTSD symptom severity and objective sleep measures, particularly low sleep efficiency, would both be associated with greater arterial stiffness and endothelial dysfunction. Due to the comorbidity of depression and anxiety with PTSD, we also investigated their contributions to theses associations.

**Figure 1. The gap in knowledge**



## 2. Materials and methods

***Ethical Oversight:*** All procedures in this study were approved by the Institutional Review Board of the University of Minnesota.

***Study Sample:*** Female participants were recruited from the University of Minnesota Twin Cities (Minneapolis and St. Paul) campus, the surrounding community, women's shelters and through the University of Minnesota Medical Center, Fairview Hospital. Eligibility requirements for all phases of the study included a history of trauma, age (18 – 40 years old), premenopausal women, free from any known CVD and the ability to give informed consent. Exclusion criteria included trans women and men and non-binary individuals, pregnant, breastfeeding, or unwilling to practice birth control during participation in the study, medical conditions such as hypertension, diabetes, heart disease, vascular disease, ongoing illicit drug use, excessive alcohol use (>2 drinks per day), hyperlipidemia, autonomic dysfunction, any serious systemic disease, medications for PTSD or other cardiovascular diseases, psychiatric comorbidities such as ongoing substance abuse, severe traumatic brain injury and the inability or unwillingness to abstain from nicotine use for at least 12 hours prior to physiologic studies (visit 2). The goal of theses exclusion criteria was to limit heterogeneity in circulating estrogen level as well as comorbid conditions that could have an effect on our exposures and outcome variables. Eligibility criteria were assessed via screening survey and phone interviews. Trauma exposure was self-reported and stated in writing by the participants. Although participants were asked to report the trauma that currently affects them the most, they were welcome to list more than one traumatic event if applicable.

***Experimental Design*** (see ***Figure 2***)***:*** We used a cross-sectional study design for the current study. After completing the screening survey online, participants who met the inclusion criteria were invited to the lab for the first of their two visits. All visits (visit 1 and 2) occurred between

8:00 AM and 1:00 PM. During visit 1, after obtaining written informed consent, we administered interviews and surveys, measured vital signs, collected anthropomorphic data, and configured the Actiwatch to record participants' sleep/wake patterns for seven days. Participants were also instructed to maintain a sleep diary. Prior to visit 2 (vascular visit), all subjects were instructed to abstain from smoking, exercise, alcohol, caffeine and over-the-counter medication affecting blood pressure for 12 h before laboratory testing and a minimum of 6 h for food. Visit 2 was scheduled within 1-5 days after the onset of menstruation, to ensure that vascular measurements are recorded during the early follicular phase of the menstrual cycle. For each participant, a urine pregnancy test was performed to exclude pregnancy. During this visit, after 10 min of rest upon arrival, participants were fitted for endothelial function measurement (reactive hyperemia index; RHI) using endothelial Peripheral Arterial Tone (EndoPAT) by forearm occlusion technique. Following EndoPAT, we waited 30 min to ensure that the participant was back to baseline conditions. Next, we performed pulse wave velocity (PWV) measurement using Applanation Tonometry for assessment of arterial stiffness (described below as well). Participants were compensated for the two visits.

**Figure 2. Experimental Design**

***Measures:***

Exposure variables:

**PTSD checklist for DSM-5 (PCL5) with criterion A (traumatic event).** The PTSD checklist is a 20-item self-reported questionnaire based on the *fifth edition of the Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) symptoms of PTSD (24). Participants reported how much they were bothered by a symptom over the past month using a 5-point Likert scale (0 = 'Not at all', 1 = 'A little bit', 2 = 'Moderately', 3 = 'Quite a bit', 4 = 'Extremely'), with a total score ranging from 0 to 80. Participants were asked to complete the PCL5 in relation to the traumatic experience that troubled them the most. It was updated to the PTSD Checklist for DSM-5 with criterion A (24). PCL is one of the most widely used screening measures for PTSD and findings support PCL5 as a psychometrically sound measure of PTSD in individuals at high risk for exposure to trauma (25) .

**Spielberger State-Trait Anxiety Inventory for Adults.** The STAI ("Form Y") assesses self-reported anxiety (both state and trait anxiety) using a validated 40-item four-point Likert scale questionnaire (26). State anxiety reflects transient (i.e., current moment) emotional anxiety due to situational stress. Trait anxiety assesses an individual's predisposition to react with anxiety in any stressful event. Together, the STAI allows quantification of personal characteristic anxiety reactivity, as well as transient fluctuations dependent on the situation. Both subscales have been shown to have good internal reliability and test-retest reliability (27).

**Beck Depression Inventory-II (BDI-II).** The BDI-II is a well-validated 21-item self-report measure, scored from 0 to 3, of current depressive symptoms (28). In the first portion of the test, psychological symptoms are assessed whereas the second portion assesses physical symptoms. In this study, items were summed to create an overall, continuous depression severity score and to

compute a categorical diagnostic of current depression where a cut-off score greater than 18 suggests probable depression (28).

Outcome variables:

**Objective sleep quality measured by wrist actigraphy.** We quantified sleep quality using 24-hour actigraphy and sleep surveys. Wrist actigraphy is a measure of 24-hour sleep/wake cycles using Actiwatch Spectrum Plus (Philips Respironics, Bend, OR). Participants wore the Actiwatch for seven consecutive nights and days to include weekdays and weekends (i.e., Monday – Sunday). A sleep diary was kept simultaneously and used to adjudicate the start and the end of the primary sleep period. The Actiwatch records activity counts each second (sampling rate: 32 Hz) with the mean of each second summed for each 30-second epoch. Data were averaged over the seven-day wear period. 24-hour actigraphy allowed objective measurement of sleep variables of interest including total sleep time (TST), sleep efficiency (ratio of TST to total time in bed), sleep latency, and wakefulness after sleep onset (WASO) time spent awake in bed after falling asleep. Sleep efficiency was our primary sleep measure of interest.

**Subjective sleep quality.** Participants also completed three validated questionnaires for evaluating subjective sleep, including (1) Pittsburgh Sleep Quality Index (PSQI) (29), (2) Insomnia Severity Index (ISI) (30), and (3) Epworth Sleepiness Scale (ESS) (31).

**Endothelial function.** Endothelial function was assessed via peripheral arterial tonometry using the EndoPAT2000 device (Itamar Medical Ltd., Caesarea, Israel). Reactive Hyperemia Index (RHI) obtained via peripheral arterial tonometry provides a validated estimation of microvascular endothelial function that correlates closely with direct angiographic measurements of coronary endothelial function (32, 33) as previously described (34–36). While FMD assesses the health of conduit vessels, Endo-PAT is a good measure of microvasculature function (33). Inflatable

pressure cuffs were attached to the index fingers of both hands while the participants rested in the supine position in a quiet laboratory. A blood pressure cuff was placed in the participant's non-dominant forearm. After a 6 min resting baseline, the blood pressure cuff was inflated to a suprasystolic pressure (>220 mmHg) for a period of 5 min, followed by rapid cuff deflation and data collection (recovery) for another 5 mins. RHI was calculated as follows: the ratio of the occluded arm's mean pulse wave amplitude 90–150 seconds post occlusion to the mean PWA from baseline readings of the same arm. The result was further divided by the same ratio from the control arm, which allows the device to account for non-endothelium-dependent vascular changes during testing (37). The final ratio is then multiplied by a proprietary baseline correction factor (Itamar Medical Ltd). An alternative reactive hyperemia score, proposed by Framingham Heart Study researchers, uses the natural logarithmic transformation of the RHI ratio (fRHI), does not include the baseline correction factor, and utilizes only the readings from 90 to 120 seconds for post occlusion (37). fRHI has been shown to be more reproducible than RHI in young individuals (38), is reliable using day-to-day measurements in healthy and diseased population (32), and is more highly associated with several cardio-metabolic risk factors; including obesity (38).

**Aortic arterial stiffness.** We quantified arterial stiffness via applanation tonometry (SphygmoCor XCEL, Atcor Medical, Sydney, Australia) with the participant lying in the supine position. Pulse wave velocity (PWV) measurements were performed non-invasively using a tonometer placed over the carotid artery and a blood pressure cuff over the femoral artery. The distance from the carotid to femoral artery measurement sites was measured and PWV was calculated as the quotient of the distance and the time delay between the carotid and femoral pressure waveforms (m/s). The SphygmoCor method uses the foot of the waveform as an onset point for calculating the time

differences between the R wave and the pulse waveforms at each site (39). We collected 2-3 measures of PWV per participant and calculated the average value.

***Data analysis:*** The overall analytic approach was to examine the predictive value of sleep efficiency and PTSD severity on vascular function using both self-report measures and objective measures. We ran descriptive analysis for baseline characteristics of the overall sample. To minimize the likelihood of making a type-II error with multiple testing, bivariate Pearson product correlations were used next to determine which anthropometric, psychological and sleep measures (i.e., PCL5 score, BDI, PSQI, and SE%) were associated with vascular function (fRHI, PWV). Due to the role they could have in these associations, depression, anxiety, age and BMI were included in initial correlation analyses. Next, a series of linear regression models were fit to examine the individual and combined predictive values of PTSD symptom severity (PCL5 score) and SE on fRHI and PWV, while controlling for participants' age, BMI, depression symptom severity (BDI score) and trait anxiety (STAI score). Specifically, we conducted two multiple linear regression models predicting fRHI and PWV separately. All analyses were conducted using SPSS v.28 with a significance level of $p < .05$. A listwise deletion (complete-case analysis) approach was used to handle missing data for the linear regression.

## 3. Results

Descriptive statistics and average vascular measures for the women included in our study are presented in ***Table 1***. The study included 60 young trauma-exposed women with a mean age of 26.0 years (SD = 7 years, range =18 – 40) and BMI of 27.7 kg/m$^2$ (SD=6.5 kg/m$^2$, range=17.0 – 43.1). Overall, the participants were normotensive (mean±SD) (SBP=105.6±9.0, DBP=68.5±9.0 mmHg) but resting heart rate (76±11 beats/min; bpm) tended to be high for some participants

ranging from 55 to 120 bpm. PTSD symptom severity (35.53±15.9 a.u.) and depression severity (18.4±10 a.u.) were mild to moderate in our sample while anxiety severity was moderate on average for trait (45.7±12.2 a.u.) and high for state (51.6±12.3 a.u.). On average, the women in our study had poor objective sleep as evidenced by an average sleep efficiency of 81.7±5.5%. Likewise, subjective sleep was poor with a PSQI score of 8.8±3.9 a.u., ISI score 11.2±5.9 a.u. and ESS score of 8.6±4.0 a.u. Endothelial function is reported as RHI, LnRHI and fRHI. Arterial stiffness is reported as PWV and augmentation index. From the overall sample of 60, a subset of 57 women had available vascular data.

**Table 1. Descriptive characteristics of participants**

| Variables (n=60) | Mean±SD | Minimum | Maximum |
|---|---|---|---|
| ***Participant's characteristics:*** | | | |
| Age (years) | 26.0±7 | 18 | 40 |
| Weight (lb) | 166.7±46.8 | 109.6 | 309.0 |
| BMI ($Kg/m^2$) | 27.7±6.5 | 17.0 | 43.1 |
| Abdominal circumference (cm) | 82.2±20.8 | 27.0 | 126.0 |
| ***Hemodynamic:*** | | | |
| Systolic Blood Pressure (mmHg) | 105.7±9.0 | 88 | 125.0 |
| Diastolic Blood Pressure (mmHg) | 68.5±9.0 | 48.3 | 88.0 |
| Mean Arterial Pressure (mmHg) | 80.3±8.2 | 62.5 | 99.7 |
| Heart rate (beats/min) | 76.3±11.5 | 55.3 | 120.7 |
| Respiratory rate (breaths/min) | 15.6±2.8 | 7 | 24 |
| ***Mental Health:*** | | | |
| Beck's Depression Inventory-II | 18.4±10 | 0 | 44 |
| PTSD checklist for DSM-5 criterion A (PCL5) | 35.53±15.9 | 5 | 62 |
| State-Trait Anxiety Inventory Trait (STAI-T) | 45.7±12.2 | 20 | 71 |
| State-Trait Anxiety Inventory State (STAI-S) | 51.6±12.3 | 24 | 71 |

| | | | |
|---|---|---|---|
| ***Sleep Measures:*** | | | |
| *Subjective:* | | | |
| Pittsburgh Sleep Quality Index (PSQI) | 8.8±3.9 | 2 | 17 |
| Insomnia Severity Index (ISI) | 11.2±5.9 | 0 | 26 |
| Epworth Sleepiness Scale (ESS) | 8.6±4.0 | 1 | 18 |
| *Objective:* | | | |
| Sleep Efficiency (%) | 81.7±5.5 | 64.4 | 92.3 |
| Onset latency (min) | 31.5±22.1 | 0.5 | 127.4 |
| Wake After Sleep Onset (min) | 45.9±15.4 | 20.4 | 90.5 |
| Total Sleep Time (min) | 436.2±57.3 | 305.4 | 614 |
| ***Vascular Measures:*** | | | |
| *Endothelial function:* | | | |
| Reactive hyperemia index (RHI) | 1.98±0.69 | 1.12 | 3.88 |
| Natural logarithm of reactive hyperemia index (LnRHI) | 0.61±0.33 | 0.11 | 1.22 |
| Framingham reactive hyperemia index (fRHI) | 0.44 ±0.43 | -0.17 | 1.33 |
| *Arterial stiffness:* | | | |
| Pulse wave velocity (PWV) (m/s) | 5.83±0.82 | 4.35 | 8 |
| Augmentation Index (AI) (unit) | 123.08±8.7 | 106.0 | 151.5 |

BMI= Body Mass Index;

***Table 2*** depicts correlations among the different mental health assessments collected in the study, as well as with age and BMI. PTSD (PCL5), depression (BDI) and state anxiety (STAI) symptom severity were highly correlated with each other ($p<.001$). Additionally, BMI was correlated with BDI, PCL5 and STAI trait ($p<.05$).

**Table 2. Bivariate correlations among mental health surveys**

| | Age (years) | BMI ($kg/m^2$) | BDI-II score | PCL5 Score | STAI-Trait | STAI-State |
|---|---|---|---|---|---|---|
| **Age (years)** | -- | | | | | |
| **BMI ($kg/m^2$)** | .22 | -- | | | | |
| **BDI-II score** | -.05 | .36** | -- | | | |
| **PCL5** | .09 | .27* | .67*** | -- | | |
| **STAI-Trait** | .17 | .30* | .38** | .38** | -- | |
| **STAI-State** | -.04 | .17 | .64*** | .48*** | .63*** | -- |

*Note. *p < .05; **p < .01; ***p < .001; **N=60**; BMI= Body mass index; BDI-II= Beck's depression inventory II; PCL5= PTSD checklist for DSM5 criterion A; STAI-Trait= State-trait anxiety inventory for adults-trait; STAI-State= State-trait anxiety inventory for adults-state.* These are bivariate correlations results using Pearson correlation coefficient.

***Figure 3*** are scatterplots depicting the bivariate correlations between PWV and the predictors which are age, BMI, sleep efficiency and STAI-trait. These were included in the linear regression model later. There were significant positive correlations between PWV and age (r =.490, *p*<.001), BMI (r =.484, *p*<.001), and STAI-trait (r =.344, *p*=.004) as seen in panels **A**, **B** and **D**. Sleep efficiency (panel **C**) showed no association with PWV (r=-.168, *p*=.112). Additionally, although not depicted here, age and BMI were moderately correlated (r=.242, *p*=.026).

**Figure 3. Correlations with pulse wave velocity (PWV)**

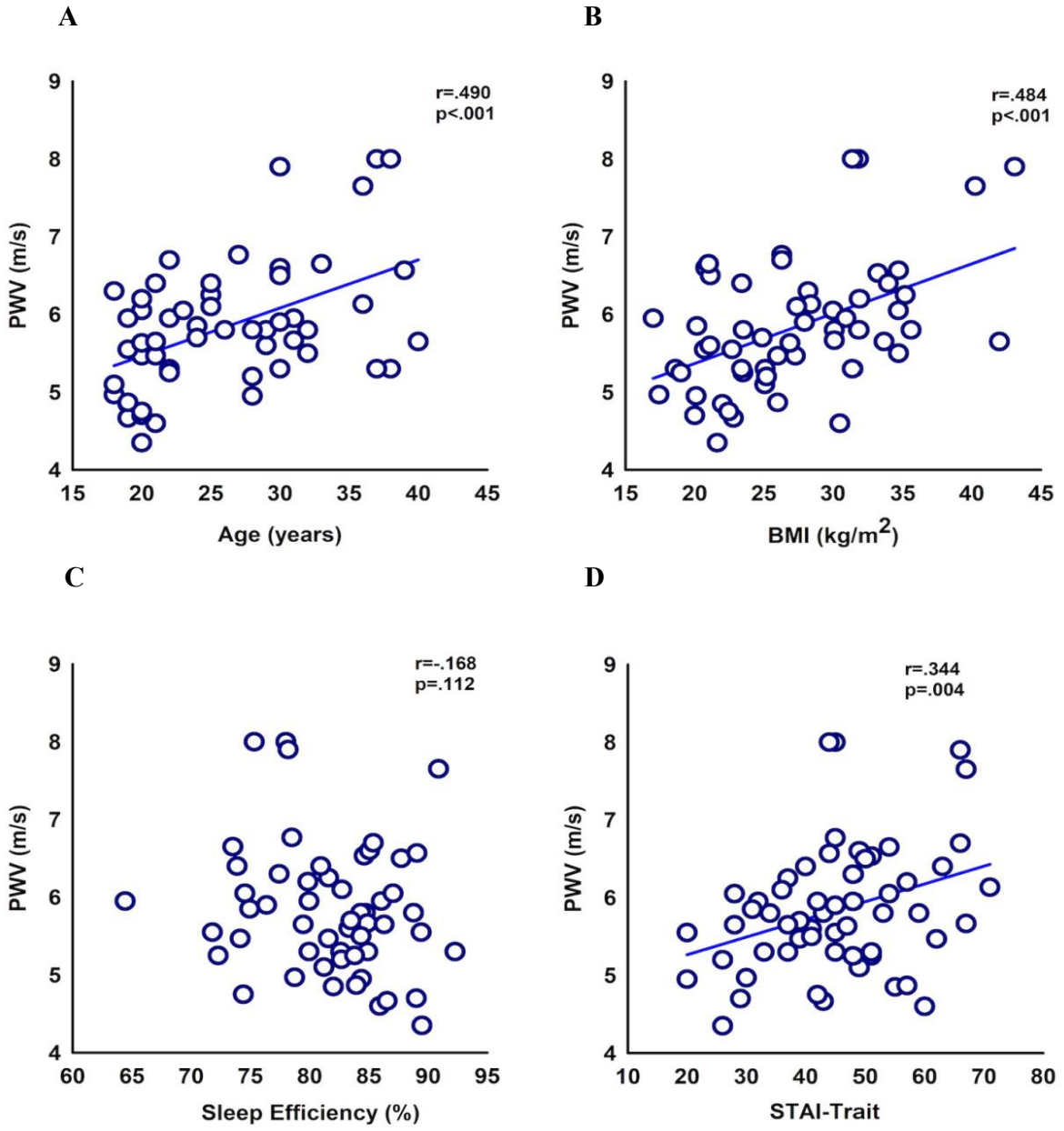



**Figure 3.** The association between PWV and age **(A)**, BMI **(B)**, sleep efficiency (n=54) **(C)**, and STAI-trait **(D)** in 57 young healthy trauma exposed women (age range 18–40 yr). A Pearson product correlation coefficient and *p*-value <.05 as was considered as significant. Strong correlations were observed between PWV and age (r =.490, *p*<.001), BMI (r =.484, *p*<.001), STAI-trait (r =.344, *p*=.004). However, there was no relationship between PWV and sleep efficiency (r=-.168, *p*=.112). PWV= Pulse wave velocity (m/s); BMI= Body Mass Index (kg/m$^2$); STAI-trait= State-Trait Anxiety Inventory for Adults-Trait.

**Figure 4. Correlations with reactive hyperemia index (RHI)**

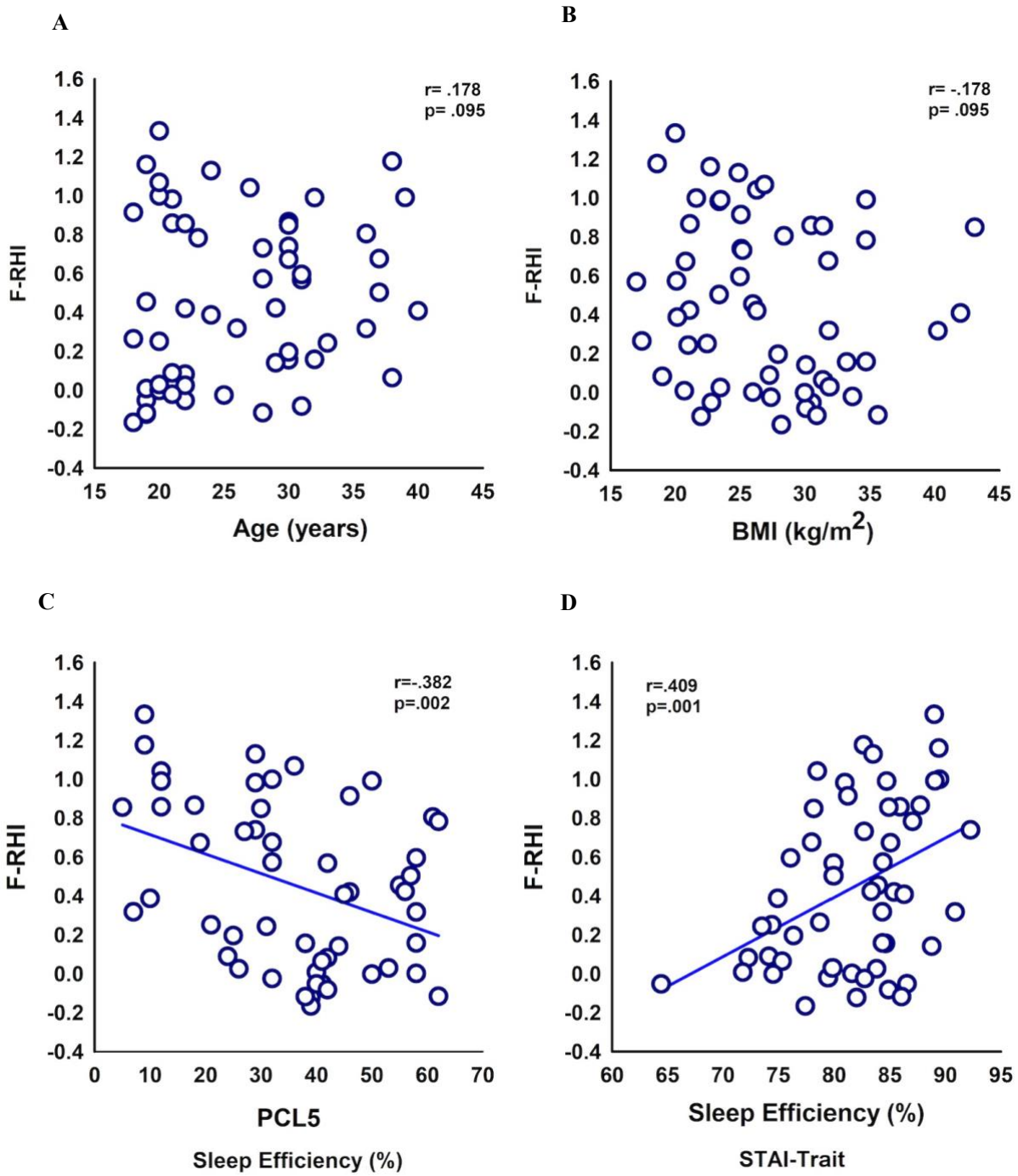



**Figure 4.** The association between fRHI and age **(A)**, BMI **(B)**, PCL5 (n=53) **(C)**, and sleep efficiency (n=53) **(D)** in 57 young healthy trauma-exposed women (age range 18–40 yr). A Pearson product correlation coefficient was used to assess the relationship and p-value <.05 was considered as significant. Strong correlations were observed between fRHI and PCL5 (r=-.382, *p*=.002) and sleep efficiency (r=.409, *p*=.001). Age (r=.178, *p*=.095) and BMI (r=-.178, *p*=.095) were not associated with fRHI. fRHI= Framingham Reactive Hyperemia Index; BMI= Body Mass Index; PCL5= PTSD checklist for DSM-5 criterion A.

The result of the first multiple linear regression model predicting PWV is shown in ***Table 3***. The final model with age, BMI, STAI trait and sleep efficiency accounted for nearly 50% of the variance in PWV in this population of trauma-exposed young women ($R^2$=.490, *p*<.001). In this model, sleep efficiency (β =-.268, *p*=.013) but not PCL5 was associated with PWV. In contrast, as shown in ***Table 4***, both PCL5 (β =-.373, *p*=.005) and sleep efficiency (β =.358, *p*=.005) were significant predictors of fRHI in the final model ($R^2$=.360, *p*<.001) which included age, BMI, PCL5 and sleep efficiency. Although age (β =.233, *p*=.068) and BMI (β =-.148, *p*=.261) was not associated with fRHI.

**Table 3. Multiple linear regression for pulse wave velocity**

| ***Predictor variables*** | ***β coefficient*** | ***t statistic*** | ***95% CI*** | ***p-value*** |
|---|---|---|---|---|
| (Constant) | | 4.501 | 3.220, 8.414 | <.001* |
| Age (years) | **.416** | **3.865** | **.026, .082** | **<.001*** |
| BMI (kg/m$^2$) | **.341** | **3.058** | **.016, .076** | **.004*** |
| State-Trait Anxiety (STAI-trait) | .201 | 1.873 | -.001, .029 | .067 |
| *Sleep efficiency (%)* | ***-.268*** | ***-2.587*** | ***-.071, -.009*** | ***.013**** |

***$R^2$= 0.49, p<0.001, n= 54;*** *BMI= Body mass index*

**Table 4. Multiple linear regression for fRHI**

| ***Predictor variables*** | ***β coefficient*** | ***t statistic*** | ***95% CI*** | ***p-value*** |
|---|---|---|---|---|
| (Constant) | | -2.005 | -2.945, 0.006 | .051 |
| Age (years) | 233 | 1.867 | -.001, 0.031 | .068 |
| BMI (kg/m$^2$) | -.148 | -1.138 | -.028, 0.008 | .261 |
| PCL5 | **-.373** | **-2.988** | **-.016, -0.003** | **.005*** |
| *Sleep efficiency (%)* | **.358** | **2.935** | **0.008, 0.044** | **.005*** |

***$R^2$= 0.36, p<0.001, n=50;*** *BMI= Body mass index; PCL5= PTSD checklist for DSM5 criterion A*

# 4. Discussion

In this cross-sectional study, we investigated the predictive value of PTSD symptoms and sleep on vascular function in young trauma-exposed women. Our goal was to determine if PTSD symptom severity and/or sleep disturbances influenced vascular function in this community sample. Our main finding is that PTSD symptoms have a greater impact on endothelial function, while sleep efficiency impacts both arterial stiffness and endothelial function. Second, we found that age and BMI predicted arterial stiffness, but not endothelial function. The close link between PTSD symptom severity, sleep and endothelial function in these young and otherwise healthy women suggest that endothelial dysfunction may be a key component of early vascular dysfunction in women exposed to trauma, and can serve to identify at-risk women who may benefit from targeted interventions, with the ultimate goal of lowering CVD risk.

Accumulating evidence suggests that vascular dysfunction is independently associated with CVD (18, 19, 40). The current study revealed that arterial stiffness in trauma-exposed women increases with age and BMI, with age as the main predictor. These findings are consistent with well-established age- and obesity-related risks of CVD (41–44). However, we did not anticipate such a strong association of arterial stiffness with age in this sample of premenopausal women when circulating levels of estrogen are expected to be higher overall; especially given prior minimal changes in PWV reported between the ages of 20 and 40 years in a cohort of 987 healthy individuals (45). A recent paper with 891 resistant hypertensive patients revealed that increased aortic stiffness predicts adverse cardiovascular outcomes and mortality (46). Therefore, in young otherwise healthy women, the significant change in aortic stiffness already present between the ages of 18 and 40 years old could be increasing the cardiovascular risk profile of women after menopause, when the beneficial effects of estrogen on vascular function is lost. Estrogen is a

vasodilator and hypotensive agent, inducing vascular relaxation by acting directly on the vascular smooth muscle to stimulate the release of endothelium-derived vasodilatory substances like nitric oxide (47). Prior research has found that trauma-exposed women diagnosed with PTSD who display lower level of estrogen have a higher psychophysiological response to hyperarousal stimulus than those with normal levels, suggesting a possible mediating effect of estrogen in trauma-associated cardiovascular dysfunction (48).

Endothelial dysfunction, an early marker of atherosclerosis (19) which is associated with a decline in the production of the vasodilator agent nitric oxide, was also examined in the current study using fRHI. The Framingham Heart Study previously reported that fRHI is inversely correlated with various cardiovascular risk factors (49). Although age and increased BMI significantly contributed to arterial stiffness in our sample, they did not have a comparable effect on endothelial function. Instead, PTSD symptom severity and low sleep efficiency, two direct consequences of trauma exposure, predicted endothelial function, such that a higher PTSD symptoms and lower objective sleep efficiency are associated with a low fRHI. At the 2022 North American Menopause Society Annual Meeting in Atlanta, GA, researchers from the University of Pittsburgh presented data highlighting that in 260 postmenopausal women, those with a history of trauma also had lower levels of estrogen, compared to women without trauma (50). Thus, it is possible that trauma may promote lower estrogen levels, thereby inhibiting the vasoprotective effects of estrogen via regulation of eNOS/NO production on endothelial function. PTSD symptoms are associated with low-grade inflammation that is linked to atherosclerosis development (51). We previously reported elevated levels of systemic (TNF-α, CRP, IL-1β, IL-6) and vascular markers of inflammation such as cell adhesion molecule (ICAM-1) in patients with high PTSD symptoms (52). In addition to contributing to vascular remodeling by promoting cell

growth and proliferation of vascular smooth muscles, vascular inflammation could be impairing endothelial function by reducing vascular NO bioavailability and increasing oxidative stress (53, 54). Endothelial dysfunction could be the acute marker of vascular dysfunction in this population, while arterial stiffness might appear over time with chronic sleep disturbances.

Low sleep efficiency may contribute to both aspects of vascular dysfunction in trauma, regardless of age and BMI. Poor sleep – a CVD risk factor – is common after trauma exposure (10, 11). A recent community-based cohort study of 3810 participants (55) from the SHHS (Sleep Heart Health Study) investigated the role of sleep efficiency in CVD based on polysomnography records and reported that sleep efficiency was associated with the incidence of primary (major adverse cardiovascular event) and secondary composite cardiovascular outcomes. In general, the women in our study had poor sleep. Objective sleep efficiency of 82% was lower in our sample than the recommended 85% (56). Several studies suggest that women may be at heightened risk for sleep insufficiency-related CVD (57). In a non-PTSD population, Carter et al. found that sleep deprivation elicited sympathetic arousal in post-menopausal women but not men (13). Moreover, Holwerda et al. highlighted the acute effect of sympathetic activity on central artery stiffness (58). The chronic increase in sympathetic arousal might exert an allostatic load on the vascular wall leading to smooth muscle remodeling and stiffening of the arterial wall over time. This might explain why sleep efficiency predicted both endothelial function and arterial stiffness.

Of note, PTSD and depression severity was mild to moderate in our sample. On the other hand, anxiety severity in our sample ranged from moderate to severe and was a significant predictor of arterial stiffness in the current study. A negative association between anxiety and sleep have been reported (59). Excess anxiety can make it harder to fall asleep and stay asleep through the night, and sleep disturbances can worsen anxiety. The current results show that while

endothelial dysfunction is more related to PTSD symptom severity, there is some association between trait anxiety and resting arterial stiffness in young trauma-exposed women. However, that association was dampened when we controlled for BMI due to the correlation between trait anxiety and BMI in our sample. Studies support a link between anxiety and the development of HTN and CVD (60–62). Increased sympathetic reactivity and vasoconstriction to a laboratory mental stress task was found in individuals with chronic anxiety compared to controls (63). Moreover, augmented sympathetic reactivity to a physical stressor has been found to increase carotid artery pulse wave velocity without modulation in blood pressure and heart rate (64).

There are important limitations to note about the present study. First, we had a relatively small sample size for multiple linear regression analyses. A larger sample size including objective sleep indicators such as our actigraphy measure or polysomnography could yield more powerful results. Second, the current study is cross-sectional and correlational, and therefore neither causal nor temporally oriented conclusions can be drawn. Future prospective studies with controlled comparisons are necessary to inform etiology and focused conclusions and implications. Third, the current study did not assess trauma load or examine how the associations and predictions may vary by traumatic event type. Future research should investigate if different types of traumatic event exposures are differentially related to sleep problems and vascular markers of CVD risk. Fourth, given the biological sex and age group of our participants, the results may not generalize to other populations. Of note, we excluded trans people who are likely to have high rates of trauma and CVD risks. However, given that young women are also underrepresented in research and are increasingly at risk for PTSD and its related complications, including CVD, the value of studying this population far outweighs any limitations of generalizability. Finally, we did not measure circulating levels of estrogen.

Findings from the current study have important clinical implications. Specifically, sleep could be a useful tool to assess future risk of cardiovascular disease in individuals with PTSD, as sleep deprivation is known to be associated with increased risk of hypertension and cardiovascular events (57). Therefore, identifying trauma-exposed women with poor sleep can serve to identify at-risk individuals who may benefit from targeted sleep interventions, with the ultimate goal of lowering cardiovascular risk. Future clinical trials aimed at reducing CVD risk in individuals with PTSD would benefit from examining the intersection of sleep, low estrogen and vascular health.

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## 7. Disclosures

None

# 8. References


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