

Towards Engineering Early Vascular Aging as the Biomarker of Metabolic Dysregulations in Complex Posttraumatic Stress Disorder Due to Childhood Sexual Abuse: A Lyfas Study

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Abstract

Background and Objective: Repetitive Childhood sexual abuse (CSA) often predisposes CPTSD which affects mental and cardiometabolic health. Early vascular aging (EVA) is the hallmark sign of adverse cardiometabolic health. Smartphone-based cardiovascular optical biomarker (COB) instrument Lyfas captures such risk non-invasively. This study aims to examine two EVA-related COBs such as Arterial stiffness index (ASI) and Vascular aging (VA) in CPTSD and CPTSD with CSA in adults.

Method: An IoT-enabled platform is created for the study. Interested visitors enroll and take the CPTSD Check List – Civilian type (PCL-C) self-tests and also fill out an online form related to CSA. The cohorts scoring high for PCL-C encompass Case-I (males and females 189 and 188, respectively) while those having a positive history of CSA comprise Case-II (males and females 11 and 12, respectively). An equal number of control groups are also considered for each case. All the four groups take Lyfas tests and the COBs are captured from their index finger capillaries using the smartphone's camera sensor, light, and the technique called arterial photoplethysmography. The EVA-COBs are validated against the ultrasound Doppler and then correlated with the PCL-C scores statistically.

Results: The study observes (i) higher anxiety levels in both the genders with the mean SD2/SD1 (anxiety biomarker) in males and females (p -values < 0.05), (ii) Lyfas ASI and Doppler's Acceleration index (AI%) are yielding to each other in males and females, respectively, (iii) High VA in both the genders (p -values < 0.05), which are > 20 , (iv) Mean PCL-C scores of 32.06 and 38 in males and females refer to moderately high CPTSD (p -values < 0.05) in the population, (v) risk of EVA in females is twice of males.

Conclusions: Lyfas is an assistive biomedical application that can screen and monitor mental health-related cardiometabolic health in the vulnerable population. The VA and ASI are two useful biomarkers. Authors also have linked the biological disorders leading to social aberrations in the CPTSD cases with or without the history of CSA and inferred that CSA further deteriorates the natural coping mechanism of CPTSD.

Keywords: Lyfas, Posttraumatic stress disorder, Complex posttraumatic stress disorder, Childhood sexual abuse, Early vascular aging, Complex posttraumatic stress disorder Check List – Civilian type

Introduction

Posttraumatic Stress Disorder (PTSD) is enlisted in the Diagnostics and Statistical Manual – Vth version (DSM-V). There, the criteria described, are applied to anyone who has ever suffered from it and must be above 6 years of age [1]. It has usually been referred to as the war veterans who have witnessed psychologically shocking incidences, such as severance of the body parts of their fellow soldiers, brutal murders, gang rapes, genocide, etc. Suddenly witness-

ing an extreme form of human brutality or a shocking accident, live ghastly animal sacrifices, and many such similar incidences are the principal cause of the hyperarousal, as noted in PTSD.

Complex Posttraumatic Stress Disorder (CPTSD) is a form of repetitive psychological trauma as a result of continued or repetitive abuse, kidnapping, sexual manipulations, domestic violence, and so forth during childhood [2]. It also causes hyperarousal and flash-

backs in the affected person like PTSD. Childhood sexual abuse (CSA) contributes to a high percentage of CPTSD cases across the world.

The population statistics according to the International Classification of Diseases (ICD)-11, about 3.4% and 3.8% of the population suffer from PTSD and CPTSD, respectively and women are the worse sufferers[3]. Epidemiological surveys show that at least one in ten children suffers from CSA, where female children (1:7) are more vulnerable compared to males (1:25)[4]. Repetitive sexual abuse and manipulations, which are the contact e.g. ranging from inappropriate touch to the completed intercourse) or non-contact e.g., showing pornography to sex organs happens in millions of children and adolescents irrespective of cultural, socioeconomic, relational, educational, and demographic differences. It leads to an array of long-lasting adverse psychological consequences which lasts for the entire life[5].

The neurobiology of CPTSD shows that it harms the primary brain areas such as (i) the ventromedial prefrontal cortex which regulates the fear perception, (ii) the amygdala which reacts to the threat, and (iii) the hippocampus which is responsible for memory[6]. As a result, uncontrollable fear, hyperactive response to threat perceptions, and long-lasting sudden flashbacks of memories are the three hallmark features of CPTSD. The neurohormones also play a significant role in CPTSD. Dysregulations of catecholamines, such as dopamine and norepinephrine that control fear and threat perceptions, serotonin which maintains sleep and sexual behavior, glutamate that helps in-memory store, and gamma-aminobutyric acid (GABA) which prevents hyper anxiety states, play significant roles in CPTSD[7]. The CSA augments such hyperactive/hypervigilant threat perceptions, uncontrollable response to stressors, severe degrees of apprehension, high level of anxiety, chronic sleeplessness, lack of appetite, relationship issues, suicidal thoughts, behavioral shifts such as the early onset of cigarette smoking, gambling, uncontrolled impulse, and many others in the affected population[8].

CSA-led CPTSD also results in adverse metabolic health outcomes (AMHO)[9]. Long-term mental stress in CPTSD is responsible for it in the vulnerable population by altering the Hypothalamus-Pituitary-Adrenal (HPA) axis, where sympathetic overdrive is the principal pathophysiology. As a result, enhanced vascular aging (EVA) is one of the hallmark features of AMHO. Currently, the risk of EVA can be checked by the pulse-Doppler Ultrasound study that assesses the vascular wall motion[10].

Lyfas is a biomedical application[11]. It runs on smartphones and does not require any additional hardware support. On installation, it converts the smartphone into a health instrument that assesses the autonomic homeostasis of the body by capturing the heart rate variability (HRV) and its correlates together called cardiovascular optical biomarkers (COBs) as the physiological surrogates of such homeostasis, among which Arterial stiffness index (ASI) and Endothelial scores or vascular aging (VA) are the two key biomarkers

of EVA [11]. *Lyfas* captures the COBs from the index finger capillary using the phone camera and light. It obtains the pulse rate variability and pulse wave velocity of the arterioles using the techniques like arterial photoplethysmography (APPG)[12]. Further, the HRV data thus captured, are engineered using digital signal processing. Its proprietary AI algorithm provides the mind-body analytics of the test-takers[11].

The *objectives* of this paper are to examine the behavioral patterns of the *Lyfas* COBs, especially the ASI and VA in the cohorts of CPTSD with and without the history of CSA, and to study the risk of EVA in the population at risk.

Method

Clinical Trial Registration and Consent to Participate

a. The study protocol was approved by the *Vagas Institutional Ethics Committee* review board (No. ECR/1181/Inst/KA 2019, dated 30-01-2020).

b. *Signed informed consents* of all participants' have been taken according to the declaration of Helsinki by the research team prior test.

Study Design

In this section, the design (methods, processes, and techniques) of the study is elaborated. *The online metadata capturing and storing method* is the mainstay of the study. An online platform has been created enabling IoT for visitors[11]. The platform consists of (a) questionnaire-based instruments, namely CPTSD Check List – Civilian type (PCL-C), (b) an awareness page about the topic with necessary scientific literature, (c) a framework to take PCL-C tests online, (d) interpretation of the PCL-C scores, and (e) in case the scores are abnormal, necessary health tips are provided. The emphasis of the platform is on providing a ubiquitous and personalized solution for the visitors by contributing to their health literacy visitors with the standard disclaimers for online health information[13]. The epidemiological metadata of the test population is kept anonymous and private on the server for research purposes.

The participation process is online and is exclusively made for adults in this purposive, cross-sectional-retrospective trial. A total of 400 Indian adult males and females (200 each) participated. All participants are drug-naïve, normotensives, without any positive history of substance abuse including alcoholism, and are non-smokers. Both the genders have a history of CPTSD over the accumulated mean period of 16.5 years (males: 17.77 years and females: 15.23 years). Appropriate ethical committee clearance and consent to participate as per Helsinki guidelines have been obtained as per the pre-requisite of the trial. Males with a median age of 36 years, minimum age of 18 years, and maximum age of 85 years and females with a median age of 32 years, minimum age of 18 years, and maximum age of 76 years, respectively took the PCL-C self-test online[13]. PCL-C is a 5-point 17-item questionnaire that captures the problem that has bothered the test-taker in the last month[14]. A PCL-C score of 17-29 is regarded as *negligible/mild*, 30-44 as *moderate*, and 45-85 as *severe*[14]. The

cohort consisting of CPTSD-positive subjects is referred to as the 'Case-I' group. For a controlled study, an equal number of 'healthy control-I (HC-I)' is considered who do not have CPTSD.

With in the total population who took the test, 5.5% percent of males, i. e., 11 and 6% of females, i. e., 12 have a positive history of CSA. This cohort i.e., CPTSD+CSA comprises the 'Case-II' group. Similarly, a 'healthy control – II (HC-II)' is taken for a controlled trial who have a positive history of CSA but developed CPTSD.

The Lyfas test (the method) is taken thrice daily (7 am, 2 pm, and 10 pm) for a month (the whole of January 2022). The COBs considered are as follows:

- *HRVScore* (a parasympathetic mood biomarker, desired healthy value >75),
- *RMSSD* (a parasympathetic biomarker of sympathovagal balance, the desired healthy score is >40) (16),
- *LF-HRV* (the biomarker of sympathetic drive)
- *HF-HRV* (the biomarker of parasympathetic drive)
- *LF/HF* (the marker of sympathovagal balance with the healthy value <1.8,
- *pNN50* (a parasympathetic biomarker of sleep, desired healthy value should be >35),
- *VO₂Max* (a biomarker of cardiopulmonary coherence, in the case of males and females the desired values, are more than or equal to 50.42±8.37 and 36.80±5.59 ml/Kg/min, respectively),
- *Energy* (a biomarker of metabolism, the value must be 35-70 ml/Kg2) (15),
- *SD2/SD1* (a biomarker of sympathovagal balance and here measures anxiety with the desired healthy value between 1 and 1.8). The EVA COBs (the principal focus of the study):
- *ASI* (the biomarker of arterial aging, a healthy score must be between -0.2 to 0.5),
- *Vascular aging* (a biomarker of endothelial health with a healthy score of age + value ≤ 20 and normal heart rate) is considered in this study [15-20].

ASI can be captured from arterial pulse wave velocity [20]. It is important to note that the EVA COBs (ASI and VA) are validated against Doppler ultrasound studies and the observations can be found in the *result* section. As mental and cardiometabolic health are closely linked, the authors propose that the aberrations in ASI and VA optical biomarkers signify the risk of AMHO in the vulnerable population[21].

Statistical Techniques

The statistical techniques are used step-wise as per the flow of the study as follows:

A) *Internal consistency (Cronbach's alpha)* of the data has been computed at first as garbage data would produce garbage results[22].

B) Parameter-wise *Descriptive statistics* of the data are measured to note the central tendency, which can be obtained by computing

the mean and the median and its dispersion which is evaluated by calculating the standard deviation.

C) *Data normality distribution check* is the third step which can be visualized by histogram plots (parameter-wise) of the population. Distribution type guides whether to use parametric tests (in case of normally distributed data) or non-parametric tests otherwise.

D) *Kruskal-Wallis testis* used for one-way analysis of variance as there are >2 groups (Case-I, II, and HC-I and II) in this experiment, followed by *Dunn's posthoc test* to examine the statistically significant median differences between any two groups at a time [23,24]. The null hypothesis (H0) is that there is no inter-group median difference. The p-values <0.05 indicates that the H0 is rejected.

E) *Spearman's rank correlation* is then performed to note the significant correlations among the COBs in Case-I (CPTSD) and Case-II (CPTSD+CSA) [25]. The key focus is to observe the correlations between PCL-C scores and COBs of EVA, i.e., the ASI and VA, case and gender-wise. The correlation score is denoted by 'ρ' which varies from -1 to +1. Values close to 1.0 indicate a high positive correlation, while those close to -1 refer to high negative correlations and those which are close to '0' either from the positive or negative sides are considered to have negligible or non-correlations, respectively. In this study, the correlation scores (in %) are arbitrarily classified on the (a) Low (1-5%), (b) low-moderate (6-10%), (c) moderate (11-15%), (d) high-moderate (16-20%), (e) high (21-25%), and finally (f) >25% as very high. The classification is made with a rationale that even a low correlation score is often significant concerning EVA across the genders.

F) Finally, the *relative risk (RR)* and *absolute risk (AR)* are computed to evaluate the hazard of EVA in PTSD cases with and without CSA. An RR value of '1' states an identical risk of EVA between the cases and the control groups, while values >1.0 and <1.0 refers to the higher and lower risk of EVA, respectively [26]. AR has been measured as the number of positive cases by the total number of cases.

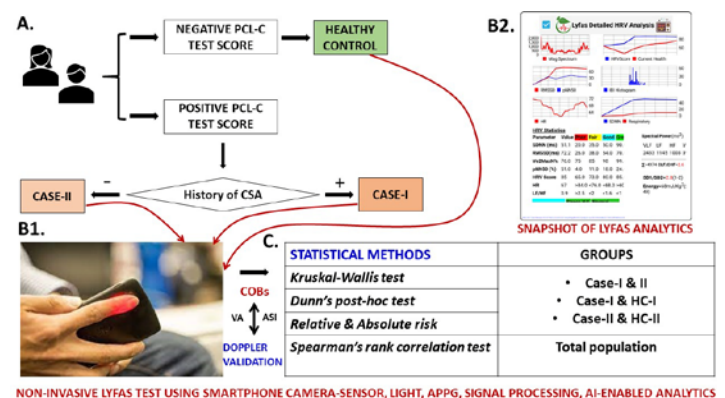


Figure 1: The Study Methodology.

Figure 1 displays the study methodology. It has been described in three parts – A, B1, B2, and C. Part A describes how Case-I and II and the Healthy Controls (HC) are obtained. Part B is all about the Lyfas test and a sample Lyfas analytics snapshot showing the COB scores and plots. Part C describes the key statistical techniques,

used in this study and the population cohorts (groups) involved.

Results

Data internal consistency (*Cronbach's alpha*) for the study population is 0.83, which is indicative of good internal consistency in the data[27].

The *population statistics* show the percentage of male and female populations affected (see Table 1). From this table, it can be noted that the exposure/experience of the CSA (5.75% of the total population, 5.5% of males and 6% of females) shifts the CPTSD population from mild (61.37 and 61.78%, respectively in males and females) to severe grades in both the genders (81.81 and 75.01%, respectively in males and females). Both the genders suffered from the mixture of 'contact' and 'non-contact' type of CSA. In the interview, it has been noted that males with mild CPTSD encountered continued incidences of *incestuous exhibitionism or IE* (87%) in the family leading to a pang of guilt on one side of their minds

coupled with a cyclical obsession with voyeurism (peeping into the washroom to see naked women bathing) on the other side (92% of the IE population). *Exposure to pornography (EP)* by peers and cousins further flared the guilt-induced trauma in 80% of those who suffer from moderate CPTSD. *Fondling of genitalia (FG)* including *forced masturbation* coupled with *IE* and *EP* is found in 85% of severe CPTSD cases as a matter of severe guilt.

In the case of females, *inappropriate sexual gestures (ISG)*, and *bad/disgusting touch (BT)* have been the most common cause of mild CPTSD (96%). *An ignorant/overlooking approach (AIA)* of their parents towards the act and the perpetrator(s) further flares the trauma into moderate (94%) and severe (90%) degrees of CPTSD over the period. Exposures to CSA have caused CPTSD as the victims/sufferers grow up with the repetitively induced psychological trauma.

It is important to mention that 'M' and 'F' refers to males and females, respectively in all the tables.

Table 1: Affected population statistics

Grade	CPTSD (N=377)		CPTSD with CSA (N=23)		Significant CSA type and %	
	M (N=189)	F (N=188)	M (N=11)	F (N=12)	M	F
Mild	61.37	61.78	0	8.33	IE (87%)	ISG+BT (96%)
Moderate	20.12	7.91	18.19	16.66	IE+EP (80%)	BT+AIA (94%)
Severe	18.51	30.31	81.81	75.01	IE+EP+FG (85%)	BT+AIA (90%)

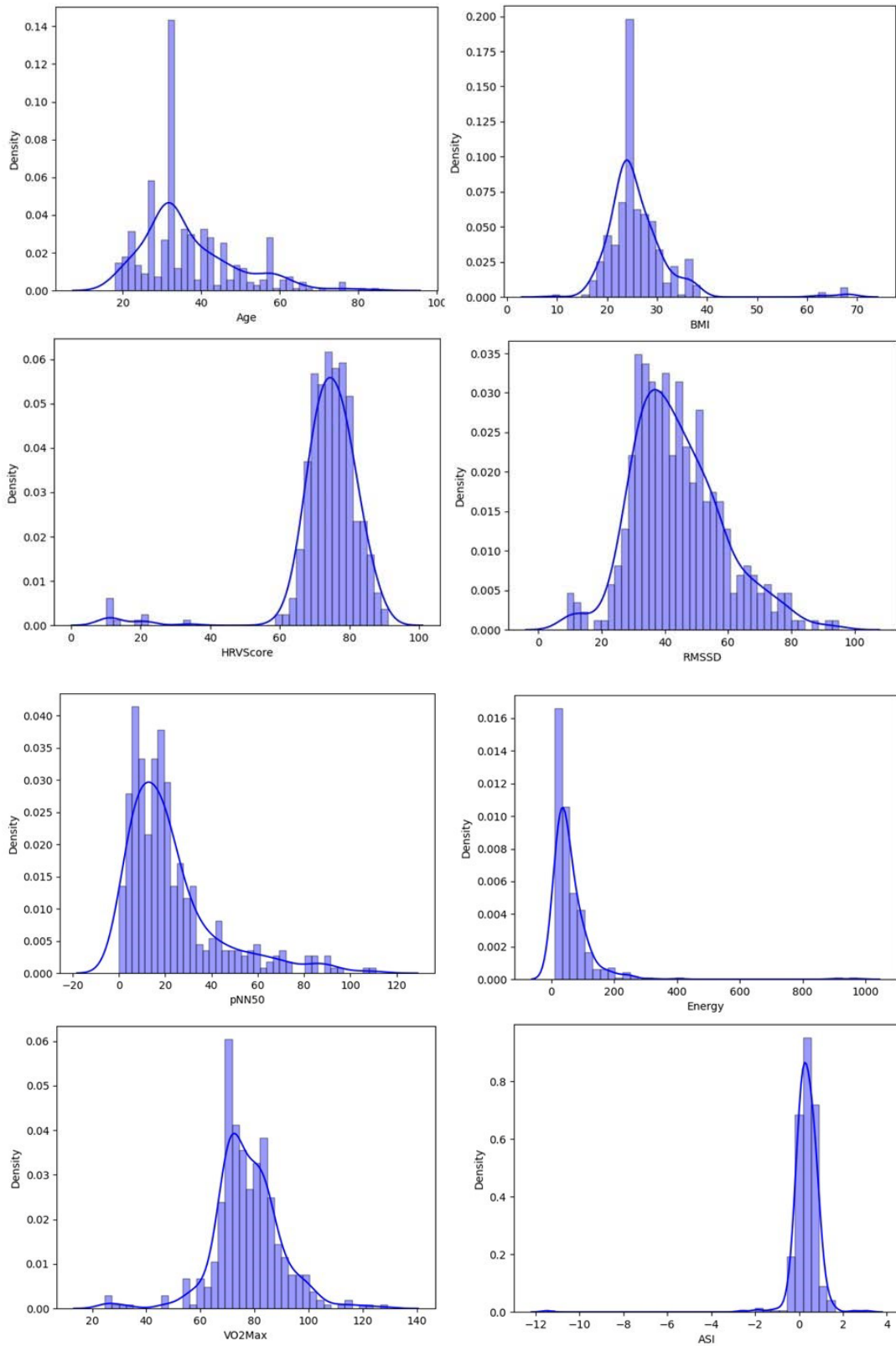
Descriptive statistics of the study population can be found in Table 2, gender and parameter-wise. The table shows a trend of higher anxiety levels in both the genders (mean SD2/SD1 (anxiety biomarker of sympathovagal balance) in males and females are 1.94 and 2.1, respectively (p-values <0.05), which is greater than the

cutoff value of 1.8. High vascular ages are evident in both the genders (mean scores for males and females are 23.2 and 25.04, respectively, which are >20, which is the cutoff value). Mean PCL-C scores (see CPTSD Score in row-16) of 32.06 and 38 in males and females refer to moderately high CPTSD.

Table 2: Parameter and gender-wise descriptive statistics

No.	Parameter	Mean				Stdev		Max		Min	
		M	F	M	F	M	F	M	F	M	F
1	Age	37.09	36.27	36	32	12.85	10.89	85	76	18	18
2	BMI	26.65	23.38	25.5	23.8	8.52	4.54	68.1	37	9	16.6
3	RMSSD	45.45	42.27	43.7	39.45	14.28	14.62	95	90	9	10
4	HRV Score	74	73.4	75	73.5	12.4	9.18	91	90	10	10
5	LF	728	543	511	392	642	522	4342	4193	117	60.89
6	HF	443	359	339	301	328	242	2085	1515	75	74
8	LF/H	1.68	1.38	1.5	1.23	0.71	0.59	4.8	3.79	0.48	0.47
9	ASI	0.32	0.3	0.4	0.31	0.94	0.51	2.5	3.1	-11.6	-2.6
10	pNN50	23.58	21.56	16	18	21.77	18.14	106	111	0	2
11	VO2Max	81.36	73	82	71	14	9.57	129	111	24.7	46.6
12	Energy	65.47	56.53	42.65	43.04	98.33	50.96	973	403	10	9.53
13	SD2/SD1	1.94	2.1	1.35	1.4	1.87	2.6	14.96	30	0.41	0.46
14	VA	23.20	25.04	25.87	28.66	23.9	23.23	54.21	55.2	-174.42	-165
15	CPTSD Score	32.06	38	26	30	10.73	14.7	69	63	14	20

Figure 2 shows the parameter-wise histogram plots of the population as evidence of the not-normal distribution of the data.



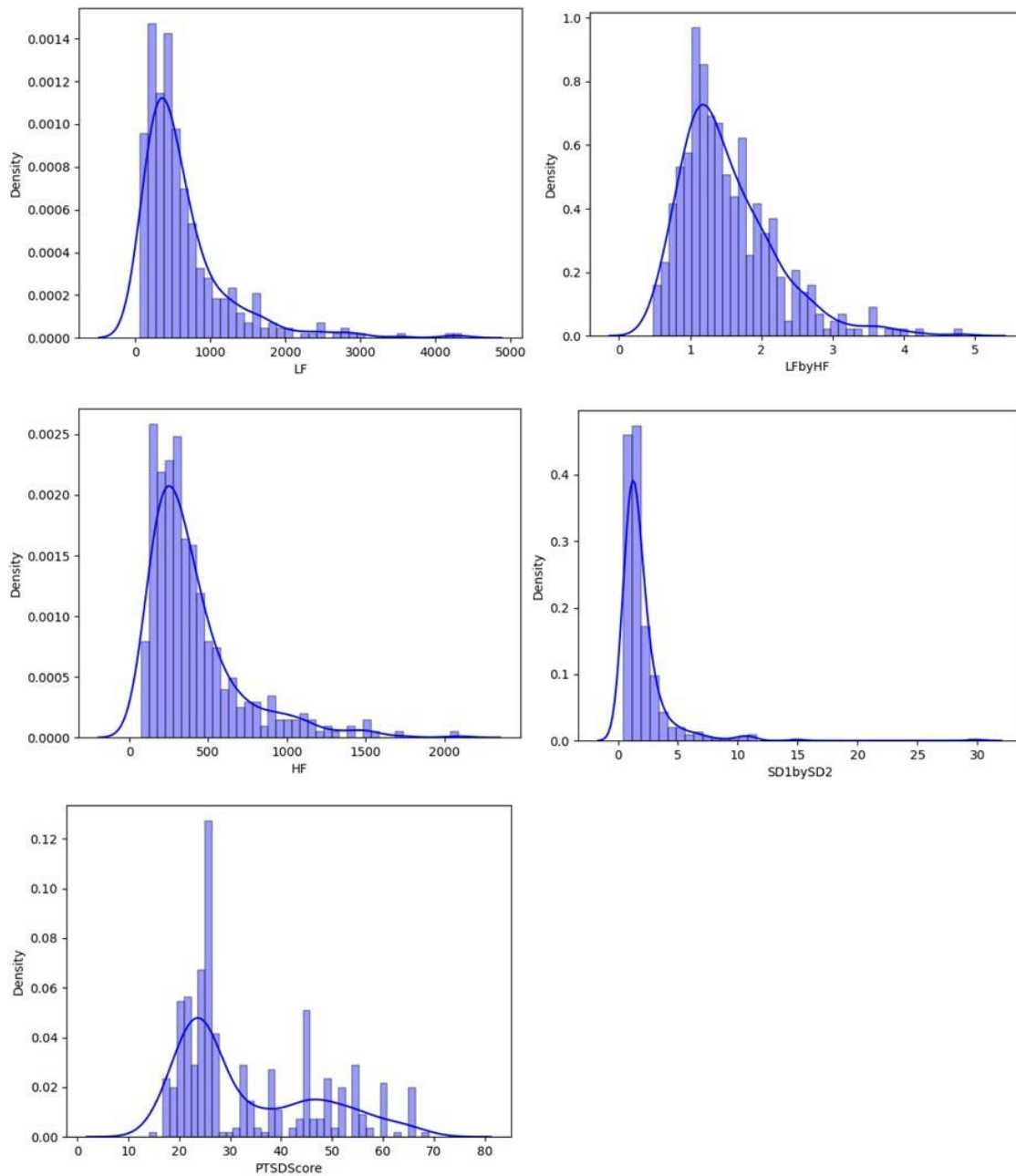


Figure 2: Histogram plots of the parameters.

In Fig. 2, the x and the y-axis represent the scores of the parameters and the corresponding density scores. The line plots across the histograms are the probability distribution curves which should be bell-shaped for normally distributed data. In these plots, none of the plots has a bell-shaped line curve which proves that the population data is not normally distributed.

In the next step, the heterogeneity of the data needs to be checked gender-wise where the null hypothesis states there is no intergroup difference between the Case-I, Case-II, and the HC in the data. The Kruskal-Wallis test shows the p-values are <0.05 rejecting the H_0 , which means that there exist inter-group median differences. Dunn's posthoc tests among the groups corroborate the k-statistics

results (p-values <0.05) showing the statistically significant median differences.

Lyfas EVA COB parameter ASI (normalized) is tested against the in-principle synonymous term called early systolic peak Acceleration index (AI %, here it is normalized). ASI scores beyond -0.5 to 0.2 (here, these are normalized) need arterial evaluation, while AI when slows down due to higher adjustment of the upstroke of the systolic peak to the transmitted frequency) predicts for impending arterial stiffness/stenosis of a standard Doppler ultrasound [28,29]. Table 3 shows a sample of 20 cases comprised of an equal number of adult males and females. Mean squared error or MSE and Root

mean squared error or RMSE is calculated and found 94.98 and 98.04% between 'Lyfas ASI' and 'Doppler AI'. Figures 3a and 3b show the sample of Lyfas and Doppler studies of one male and female each.

Table 3: Lyfas COBs and Doppler ultrasound data (both normalized)

Lyfas mean ASI		Doppler mean AI		MSE		RMSE		Accuracy (%)	
M	F	M	F	M	F	M	F	M	F
0.26	0.32	26	32.8	2.12	6.04	1.45	2.45	98.55	97.55

Male, Age:45, BMI:27.1

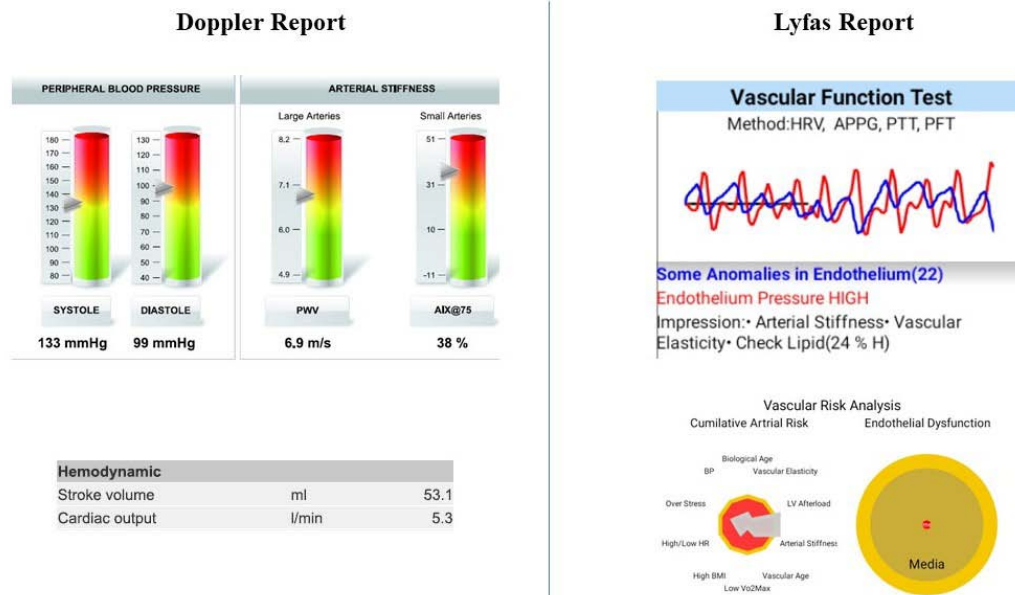


Figure 3a: Lyfas and Doppler marker status in a male.

Female, Age:61, BMI:39.5

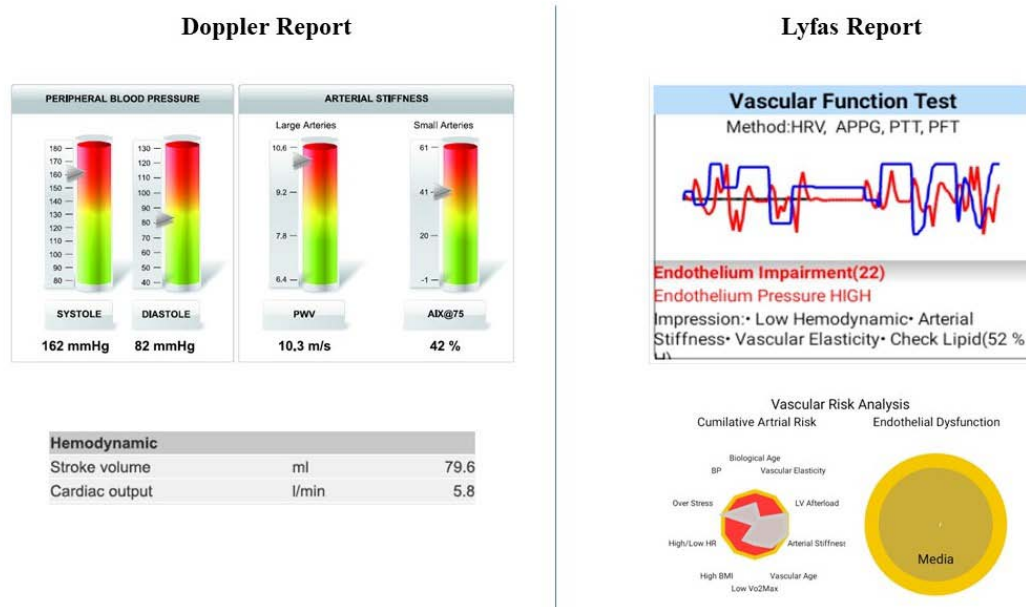


Figure 3b: Lyfas and Doppler marker status in a female.

In these figures, the Doppler report (on the left side) and Lyfas arterial analysis (on the left side) can be visualized. As mentioned, the AI of Doppler could be considered synonymous with the ASI of Lyfas. In this sample, Lyfas visual analytics shows thickening of the smooth muscle layer of the artery to such an extent, that its lumen (refer to the red dot in Fig 3a) is almost closed. In Fig. 3b even the dot is invisible indicating closure of the lumen in the virtually presented arterial cross-section pictures. In the adjacent polygon, Lyfas also shows the important biological markers as the arms of the polygon. These are hypertension, vascular elasticity, left ventricular afterload, arterial stiffness, high BMI, low VO2Max, and autonomic stress or AS (causing adrenergic overdrive) causes accelerated biological aging by enhancing premature arterial aging. As the contribution of the above factors increases the grey arrow within the polygon touches or becomes close to the respective arm. In the case of the male, two contributing factors are LV afterload

and arterial stiffness. For the female subject, increased autonomic stress and arterial stiffness are the two most significant markers. Hence, arterial stiffness is a common occurrence in both cases and can help estimate the risk of EVA in the vulnerable population.

The study further examines the correlations. To pursue it, Spearman's rank correlation has been performed on this population to see how the COBs such as ASI and VA are correlated with other parameters in Case-I and II male and female-wise. The correlations can be visualized in figures 4(a-d), respectively. The focus of the study is to explore the risk of adverse metabolic health outcomes in PTSD (Case-I) and PTSD-CSA-affected (Case-II) male and female populations. Therefore, the figures are evaluated based on the relevant findings, i.e., the correlations between PCL-C scores and the vascular COBs (ASI and VA).

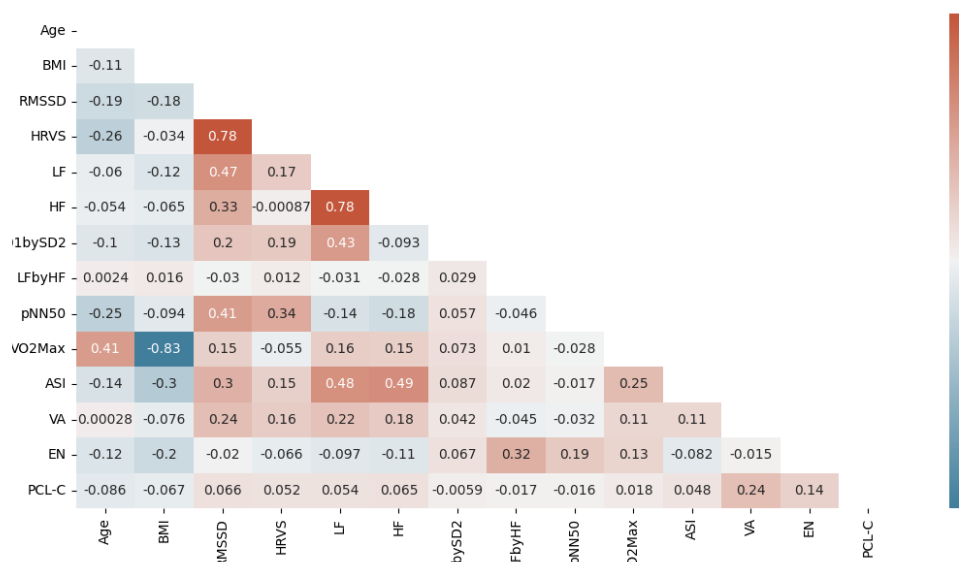


Figure 4a: Spearman's correlation in Case-I (Males).

In this heatmap, the correlations between PCL-C score and VA ($\rho = 0.24$) and PCL-C score and ASI ($\rho = 0.04$) are found *high* and *low*, respectively.

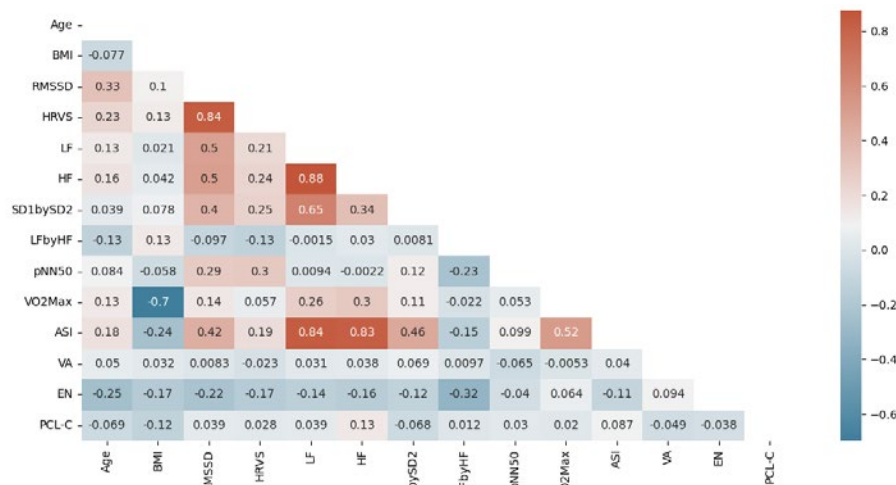


Figure 4b: Spearman's correlation in Case-I (Females).

In this heatmap, the correlation between PCL-C score and ASI is *low-moderate* ($\rho = 0.08$).

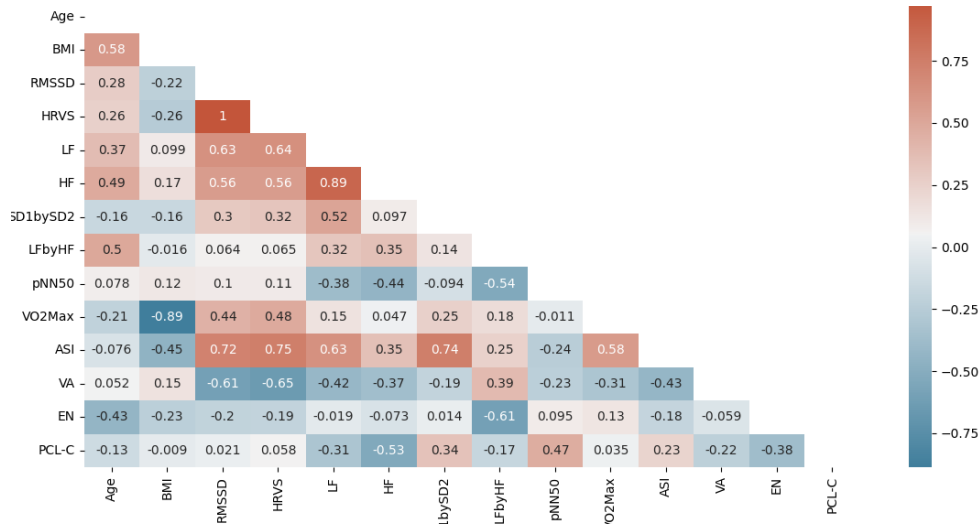


Figure 4c: Spearman's correlation in Case-II (Males).

In this heatmap, the correlation between PCL-C score and ASI is *high* ($\rho = 0.23$).

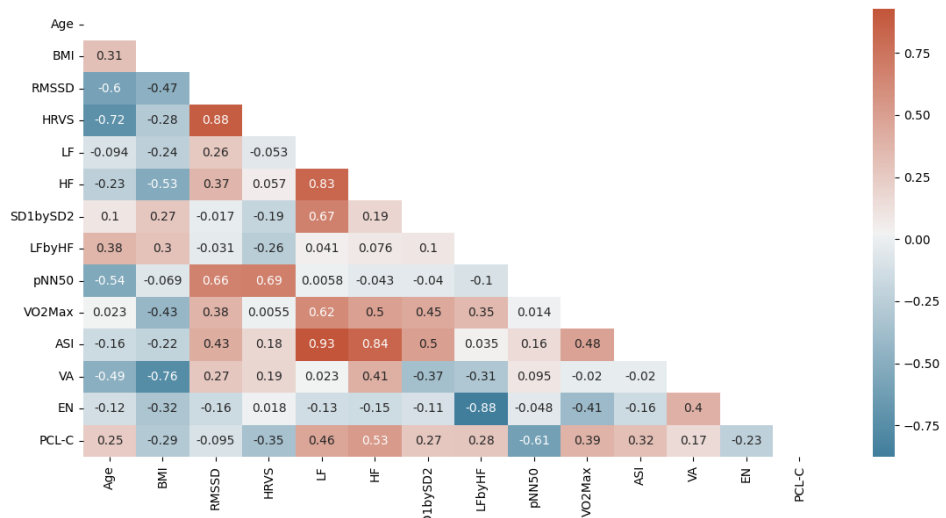


Figure 4d: Spearman's correlation in Case-II (Females).

In this heatmap, the correlations between PCL-C score and VA are *high-moderate* ($\rho = 0.17$) and PCL-C score and ASI are *very high* ($\rho = 0.32$).

Table 4 shows the summary of the correlation findings.

Table 4: Correlation findings in males and females

M	F	ρ	Interpretation
-	VA	0.17	High moderate
-	ASI	0.32	Very high
ASI	-	0.23	High
-	ASI	0.08	Low-moderate
VA	-	0.24	High
ASI	-	0.04	Low

In table 4, *Very high* ASI is seen in females, while *high* VA can be seen in both males and females. Therefore, females are at more risk of EVA. Recent studies also have found an increasing trend of AMHO and psychiatric illnesses in females, which could be two significant precursors to the EVA [30,31].

Finally, the results of RR and AR can be seen in Table 5.

Table 5: Results of AR and RR calculations gender and case-wise

Risk(%)	Case-I				Case-II				Increment (%)			
	M		F		M		F					
	VA	ASI	VA	ASI	VA	ASI	VA	ASI				
AR	57	53	65	77	82	91	66	91	41	70	1	18
RR	1.62	1.93	1.08	1.37	1.68	1	2	2.14				

AR statistics show female dominance in EVA scores by 13% and 44% respectively for VA and ASI in case-I, while in case-II it is 22% and a trivial amount, respectively. Under the ‘Increment (%)’ column, how CSA enhances the EVA has been mentioned. Males exposed to CSA are more at risk of developing EVA compared to females.

RR statistics show that exposure to CSA increases the vulnerability of EVA in both males and females. A more prevalence of the risk is noted in females compared to males which are 2-times of males.

Discussion

The study finally proposes the “CSA-CPTSD-EVA” model (see Fig. 5), which states that brain-body-heart are tightly interlinked to society. Hence, the discussion is made in two major events: Biological and Societal.

Biological Events

EVA happens physiologically as the age advances in males and females as a natural process. Because hypertension, diabetes, and substance abusers including smokers are already excluded in choosing the study population, gonadal and mental conditions and their influence on vascular health have been discussed here.

Baroreceptor Sensitivity Dysregulation

Baroreceptors are a type of mechanoreceptors sensitive to pressure and can be found in the carotid sinus and aortic arch and also on the heart walls[32]. Its afferent components project into the central nervous system via the 9th (glossopharyngeal) and 10th (vagus) cranial nerves further terminating into the nucleus tractus solitarius (NTS) in the brain stem and then further to central neural pathways connecting the NTS to the preganglionic sympathetic vasomotor neurons in the intermediolateral and vagal cardiomotor system[33]. The nerve endings are then terminated in the medial-adventitial junction of the arteries causing them to dilate and contract[34]. The voltage-gated calcium (Ca⁺⁺) channel is the principal transducer of membrane potential changes by allowing Ca⁺⁺ to enter the cells and raise the potential for successful mechano-electrical transduction[35]. Gamma-aminobutyric acid (GABA) and glutamate play an important role in baroreflex sensitivity, which also play important role in PTSD-CPTSD[36]. Baroreceptor dysregulations lead to sympathetic overactivity causing increased blood pressure and the heart rate, which is evident during mental and metabolic stress; if prolonged, may be responsible for arterial stiffening, hypertension, abnormal cardiac activity, and even sudden cardiac death. As mentioned above, PTSD and CPTSD may cause cardiometabolic disorders. Here, the cause of EVA could be either PTSD-CPTSD or cardiometabolic disorders or both.

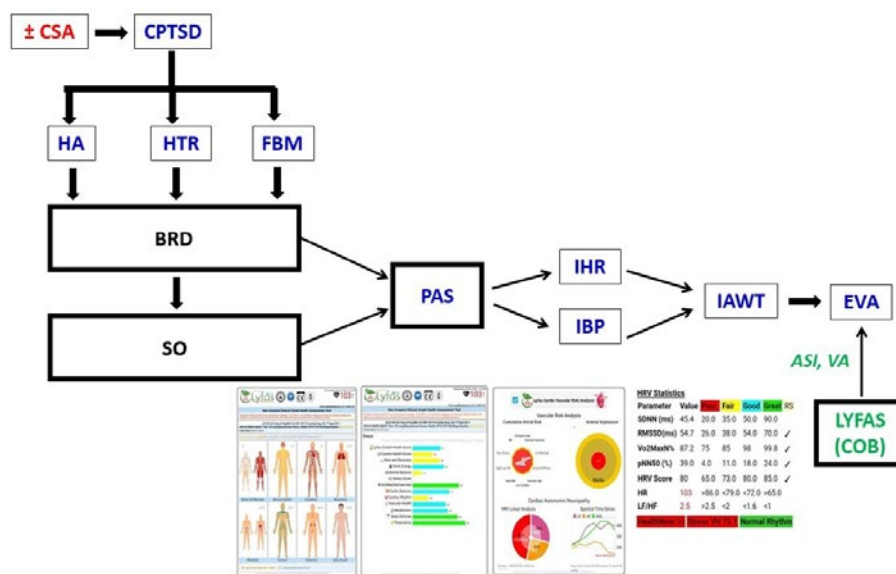


Figure 5: The proposed CSA-CPTSD-EVA model.

Abbreviations: CSA, Childhood Sexual Abuse; CPTSD, Complex Posttraumatic Stress Disorder; HA, Hyperarousal; HTR, Hyperactive Threat Response; FBM, Flashback Memories; BRD, Baroreceptor Dysregulation; SO, Sympathetic Overdrive; PAS, Persistent Autonomic Stress; IHR, Increased Heart Rate; IBP, Increased Blood Pressure; IAWT, Increased Arterial Wall Thickness; EVA, Early Vascular Aging

The HPA Axis

HPA axis dysregulations leading to persistent sympathetic overdrive due to the parasympathetic dampening in the body results in an AS which affects the arteries and the heart. The authors hypothesize that the random bursts of norepinephrine in the blood during the hyperarousal and traumatic flashbacks over a prolonged period cause EVA in a progressive manner.

The Role of Gonadal Hormones in the Female

Fig. 5 explains the CSA-CPTSD-EVA model where the outcome is BRD-led AS at the backdrop of the occurrence of EVA. The reason why the female population is more affected could be due

to three factors – (i) a drop in estrogen and follicular stimulating hormone in the perimenopausal period makes the arteries more susceptible to AS, (ii) dampened efferent (i.e., the parasympathetic branch) baroreflex due to natural estrogen depletion, and (iii) onset of vasomotor symptoms due to temperature dysregulations and oxidative stress [37-39]. Mood dysregulation is a hallmark feature of menopause and perimenopause[40]. The intensity of CPTSD is often coupled with the perimenopausal or menopausal ages when the estrogen receptors are depleted[41].

The role of gonadal hormones in the male

In the case of males, testosterone plays a similar role. A fall in testosterone could be the key cause of EVA in them[42].

In this paper, the average increments of ASI and VA with age in females are 32.44% and 30.71%, which are 26.55% and 32% in males, respectively in Case-II when compared to Case-I (12.11% and 10.09% in females and 8.65% and 11.07% in males) and HCs (2.48% and 4.09% in females and 1.65% and 1.07% in males). Fig. 6 shows how VA and ASI are increased with aging in Case-II.

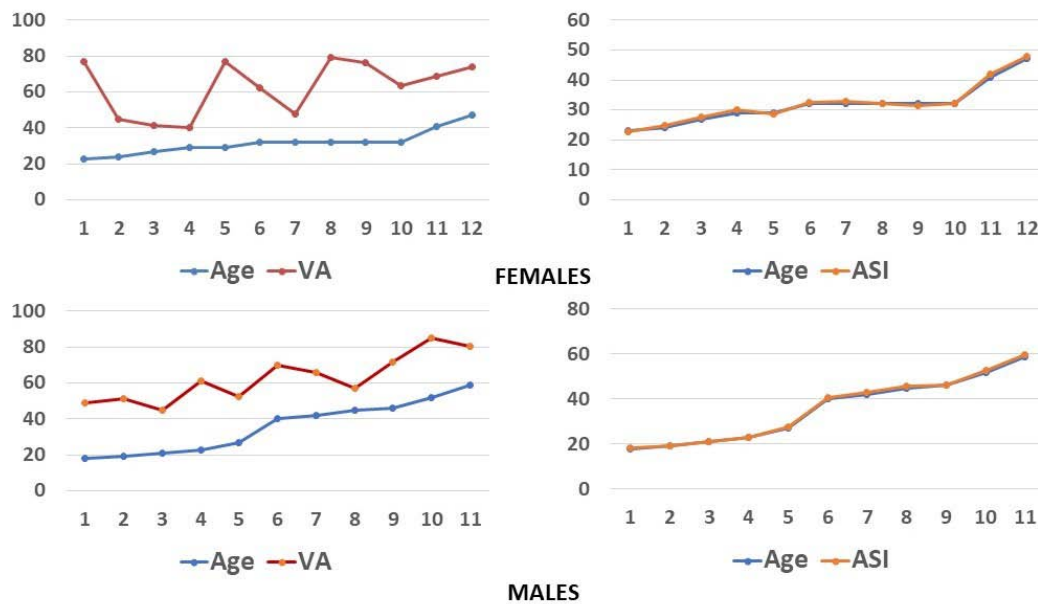


Figure 6: Age vs ASI and VA Scores in Case-II.

Fig. 6 shows the trend of EVA-Age line plots for both genders. The x and y-axes represent the population size and the values of VA and ASI. The VAs in males and females are non-linear while ASI scores are linear. The probable reason could be that the body naturally tries to compensate aging process through the parasympathetic activity; however, when the arterial wall starts depleting the elastin and laminin due to turbulent flow of the blood instead of normal laminar due to sympathetic overdrive, collagen deposition becomes a regular process that causes the arterial walls stiff and non-malleable due to fibrosis with or without narrowing of its lumen.

Societal Events

The societal consequences of CPTSD with or without CSA are

nothing but how the brain behaves to it.

The Outcome of CPTSD with or without CSA

The adverse societal outcomes of CPTSD are due to the pathophysiological aberrations in the brain, neurotransmitters, and dampening of the parasympathetic system in the body of the sufferer. Hence, its hostile societal consequences might be due to the persistent AS and hyperarousal. The dead mother syndrome, coined by Andre Green may be one flashing example of the origin and outcome of having an unemotionally attached mother leading to CPTSD and destructive narcissism[43].

Authors postulate that symptomatic CSA-positive CPTSD sufferers are at high risk of cardiovascular metabolic syndromes. They

state that such syndromes occur as a natural mechanism to eliminate the impending life risk in society.

The contribution of the work is as follows:

- a) Novel and holistic method of combining the IoT, Biomedical application-based screening and monitoring tool of CPTSD with or without the history of CSA, and correlating it with the risk of cardiometabolic syndrome
- b) Associated societal risks such as extreme forms of mental illnesses leading to suicide and other crimes due to hyperarousal-based aggression, and
- c) The provides light on the completely messed-up biological and societal life of a CPTSD victim with or without CSA.

The limitation of the work lies with:

- a) Senile EVA needs to be filtered as it can add to the noise in the study population, and
- b) The findings in males and females can be corroborated by noting the changes in the gonadal hormones as natural aging happens.

Conclusions

The study has demonstrated an end-to-end holistic and ubiquitous platform for screening and monitoring CPTSD with or without CSA. The study shows both males and females in Case-I and II have EVA which is corroborated by the Lyfas COBs (e.g., ASI and VA). A higher average rise of ASI and VA in males and females in Case-I and II are noticed even below 30 years of age which supports the specific effect of CPTSD and CPTSD plus CSA on the arterial stiffness that is different from senile stiffness.

CPTSD is still poorly understood by the researchers as the trauma might affect the cellular mechanisms by elevating more oxidative stress and thereby reducing the release of the nitric oxide (NO) that causes vasodilatation. Lyfas studies to assess oxidative stress could be useful to understand the cellular mechanism of CPTSD in the population. A longitudinal meta-analysis of CPTSD with or without the history of CSA using Lyfas could give a better picture of EVA in the population.

Conflicts of Interest: The authors declare that there are no conflicts of interest.

Author Contributions: SC designed the study, performed the experimental work, and drafted the manuscript. RD analyzed the data, conceived the work, and gave valuable insights to enrich the scientific content.

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