RESEARCH ARTICLE

Validating Lyfas as a reliable mental health screening and monitoring instrument: a step towards mobile health application during COVID-19 Pandemic

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Abstract:

COVID-19 has disturbed mental health to a great extent. Lockdowns, re-infections in fully vaccinated people, frequent mutations of the virus, working from home, shutting of school colleges, contradictory information flying in the air, and so on are some serious predisposing factors in deteriorating the mental health. The Indian Govt. has granted the telemedicine model of healthcare in the country. Mobile health (mHealth) adds to it effectively and Lyfas is such a smartphone-based instrument that works using the principle of arterial photoplethysmography and photochromatography. It captures short (120 sec) heart rate variability (HRV) and the allied optical biomarkers that surrogate for the cardiovascular autonomic modulation, which is influenced by mental health issues. The study aims to validate Lyfas optical biomarkers (SD1/SD2, LF/HF, pNN50, and HRVscores) and a set of physical parameters e.g., age, HR, BP – systolic and diastolic, and serum cortisol in addressing the mental health state. A total of RTPCR positive 1130 adults (Male 541, Female 589) within the age group of 27-68 yrs. participated in the study. Till the participants became RTPCR negative (average time of 14 days), the Depression-Anxiety-Stress Screening-21 (DASS-21) and Covid Screening Scale (CSS)-based monitoring is done once daily to note the distress levels, and Lyfas tests are taken thrice daily simultaneously. The average of all scores constructs the experimental data. Internal consistency (Cronbach's α), normality test (Shapiro Wilkis test), and Spearman's correlations (ρ) and their respective statistical significance ($p<0.05$, CI: 95%) are computed. The study concludes that Lyfas biomarkers show strong correlations with that of the DASS-21 and CSS scores. Physical parameters are also corroborative to the result.

Keywords: COVID-19; Lyfas; Optical biomarkers; Depression Anxiety Stress Scale-21; COVID Stress Scale (CSS); Shapiro Wilkis test; Cronbach's alpha; Spearman's correlation; Bland Altman's reliability assessment

1. Introduction

Constant mental health issues are predominant in today's pandemic population. Too many socioeconomic and health-related worries are internally affecting many causing anxiety, depression, and stress.[1] The advent of vaccines in the market might reduce the health worries, however, frequent infections and re-infections of the fully vaccinated population by new COVID mutants have retained or even increased it to a great extent.[2] Immobilities, such as working from home, shutting down of the schools and colleges, restricted weekends due to imposed administrative decisions have set a new normal of an isolated feeling in people at large. It has hindered socialization-based emotional buffering of the pending stress.[3] Hypochondriasis in the form of psychosomatic illnesses and phobia of catching the virus as well as thanatophobia (fear of death) is frequently noted in society.[4] As a result, the need for low-cost affordable healthcare has been increased but accessing it physically has been hindered. Apprehending such a dilemma, the Ministry of Health, Govt. of India granted the Telemedicine model of healthcare in the country as a wisely foresighted step in 2020, much before the COVID-19 situation in the country became havoc.[5] There is a clear guideline published as of its standard operational process.[5] Mobile health (mHealth) is a novel extension to the Telemedicine mode of healthcare, where

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smartphones are used to evaluate the psychophysiological state of the body by capturing the short term (120 sec) Heart rate variability (HRV) and its allied optical biomarkers that surrogate for the cardiovascular autonomic modulation, which is influenced by the aberrations in the state of mind and body especially the brain and the heart and its related organs in the body. The popularity of mHealth is growing steadily proportional to the number of smartphone users and the increasing demand for healthcare as this pandemic is causing various comorbidities, e.g., hypertension, diabetes, endocrinal and reproductive issues, mental health disorders, cardiac health problems, and so forth. Lyfas is a smartphone-based novel biomarker instrument that uses the principle of arterial photoplethysmography and photochromatography to assess the cardiac autonomic response from the peripheral capillary of the index finger when it is gently pressed on the rear camera of the smartphone and the LED torchlight is 'ON'.[6] Lyfas is a multilingual voice-assisted instrument and hence it is much user-friendly. It essentially works in three layers – A. Data capturing layer: where the raw optical biomarkers (HRV and its associates) are captured from the index finger capillary, B. Signal processing layer: a low-pass filtering technique is used to remove the noise in the signals thus captured, C. Analytical layer: here, using its proprietary heuristics, Lyfas gives a snapshot of the mind-body homeostasis of the test-takers, and D. Therapeutic layer: that gives the psychophysiological insight to the medical doctors, especially related to the 'health risk' of their patients. Figure 1 shows the standard operating process (SOP) of Lyfas mental health risk screening and monitoring.

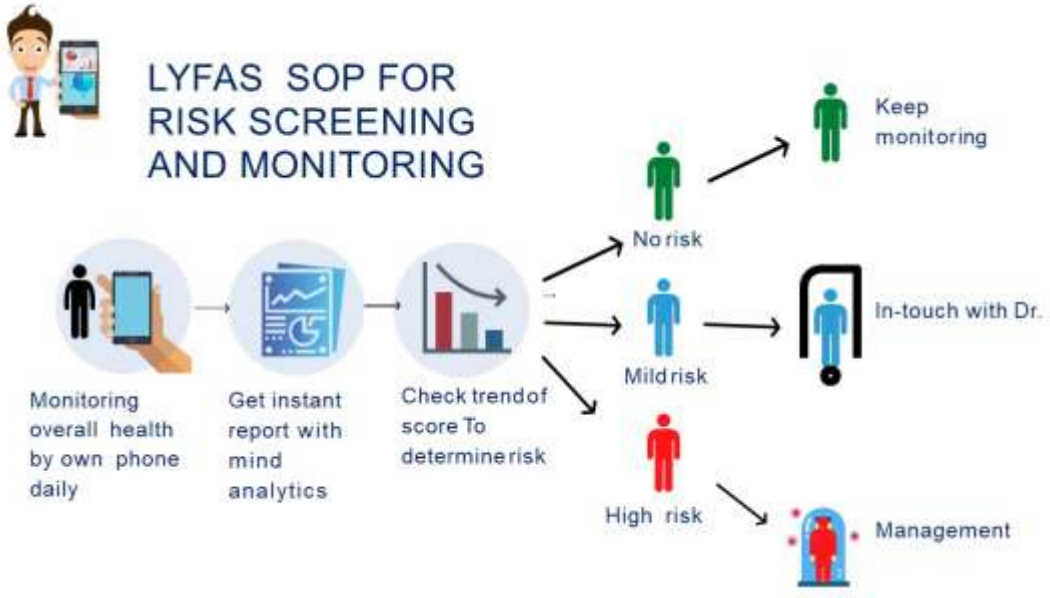

Figure 1. The SOP of Lyfas mental health risk screening.

Objective: In this study, an attempt has been made to validate Lyfas as a mental health screening and monitoring instrument using optical biomarkers: HRVScore, pNN50, LF/HF, and SD1/SD2) with the reference to two published and well-acclaimed questionnaire-based instruments – (i) Depression Anxiety Stress Scale-21 (DASS-21), [7] and (ii) Covid Stress Scale (CSS).[8]

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2. Methods

2.1. Ethical committee clearance

a) The study protocol is submitted by the *Acculi Labs Pvt. Ltd., Bangalore, Karnataka, India* has been approved by the *Vagas Institutional Ethics Committee, Bengaluru, Malleswaram, Karnataka, India* review board, registered with the *Central Drugs Standard Control Organization, Ministry of Health and Family Welfare, Govt. of India (No. ECR/1181/Inst/KA/2019, dated 30-01-2020).*[9]
b) Signed informed consents of all participants' have been taken on the organization letterhead according to the *declaration of Helsinki* by the research team prior test.[10]

2.2. Coding and computation

Computations are done using Python 3.9.7 (64 bits) on IDLE editor in Windows 10 OS.

2.3. Instruments used in the study

A. Depression Anxiety Stress Scale-21 (DASS-21)[7]

This is a 21-items, 4-point scale i.e., having a score of 0 to 3 to measure the emotional state during the past one week in three attributes - depressions, anxiety, and stress, each having 7 items, divided into subscales of similar content. The *depression scale* measures hopelessness (loss of hope in life), dysphoria (generalized dissatisfaction with life), devaluation of life, self-deprecation (frequent self-criticism), lack of interest or involvement in the activities that were previously enjoyable or anhedonia, and inertia (resistive to any form of change). The *anxiety scale* assesses autonomic arousal e.g. hyperventilation, nausea, palpitation, and so forth, skeletal muscle effects such as hypermobility, situational anxiety, i.e., too much apprehension, and subjective experience of anxious affect, e.g., sleeplessness, thirst, sweating, and so on. The *stress scale* is a measure to assess the sensitivity levels of chronic nonspecific arousal, such as difficulty in relaxing, nervous arousal, and easily being upset, agitated, being irritable, over-reactive, and becoming impatient of moderate to high degrees. By summing up the scores for the relevant items, scores of the attributes are calculated. It is worth noting that the DASS-21 is based on a dimensional rather than a categorical conception of psychological disorder. The differences in depression, anxiety, and stress experienced by normal subjects and clinical populations are essentially differences of degree, by which DASS-21 has been assumed in the test-takers. Hence, there are no direct correlations between DASS-21-based diagnosis to that of the classification system of ICD and DSM. Recommended cut-off scores for conventional severity labels as normal, mild, moderate, severe, and extremely severe in depression, anxiety, and stress are 0-9, 10-13, 14-20, 21-27, 28+; 0-7, 8-9, 10-14, 15-19, and 20+; 0-14, 15-18, 19-25, 26-33, 34+ respectively.

B. COVID Stress Scale (CSS)[8]

CSS assesses three attributes, such as the *worries*, their *frequency*, and *actions* taken to alleviate the worries over the past seven days. It is a 36-item questionnaire, where each item has a 5-point scale i.e., the score of 0 to 4. The whole questionnaire is broken into three parts as per the attributes. Under 'worries', there are 24 questions or items, while under the 'frequency of worries' and 'actions taken to alleviate the worries' there are 6 questions each. Final scoring is performed into six subscales – 'Danger', 'Socioeconomic consequences', 'Xenophobia', 'Contamination', 'Traumatic stress', and 'Compulsive checking' with the cumulative scores by adding the scores of items 1-6, 7-12, 13-18, 19-24, 25-30, 31-36, respectively. The

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final score is obtained by adding all subscale scores.

C. Lyfas[6]

It is a commercially available non-invasive and pervasive optical biomarker smartphone instrument for home health care full body check for making differential diagnoses based on cardiovascular biomarker scores, captured from the index finger capillaries when the finger is gently placed on the rear main camera of the phone using the phone's LED torchlight. From the capillary arterioles, with the help of the principle of arterial photoplethysmography and pulse wave signal processing, it evaluates the pulse rate variability that is physiologically synonymous to the heart rate variability (HRV), i.e., beat-by-beat variations of heart, which is a non-invasive metric of autonomic nervous system (ANS) activity. HRV and its correlates surrogate for cardiovascular autonomic modulation due to the alterations in mental health conditions, such as anxiety, depression, and mental stress.[11] Lyfas has recently been tested in subclinical depression tracing during the COIVD-19 pandemic period and found as an effective instrument also in detecting the cascade of it in the form of insomnia and negative thoughts.[12] Lyfas is also a reliable instrument for assessing cardiopulmonary coherence as a biofeedback instrument with an average accuracy, precision, and j-statistic of 81%, 75%, and 80%, respectively.[13] The key focus of its AI-enabled algorithm is to forecast cardiovascular risks and mental healthcare in the test-takers

2.4. Recruitment of the study population

A total of 1130 adults (Male 541, Female 589) within the age group of 27-68 years who are RTPCR positive participated in the study. The study is performed till they become RTPCR negative with an average time of 14 days. The distribution of age and gender can be seen in the following pie chart (Figure 2). It is important to note that none of the subjects has any comorb conditions, such as diabetes, thyroid diseases, previous history of mental illnesses, hypertension, other cardiovascular illnesses, neurological disorders, and so on.

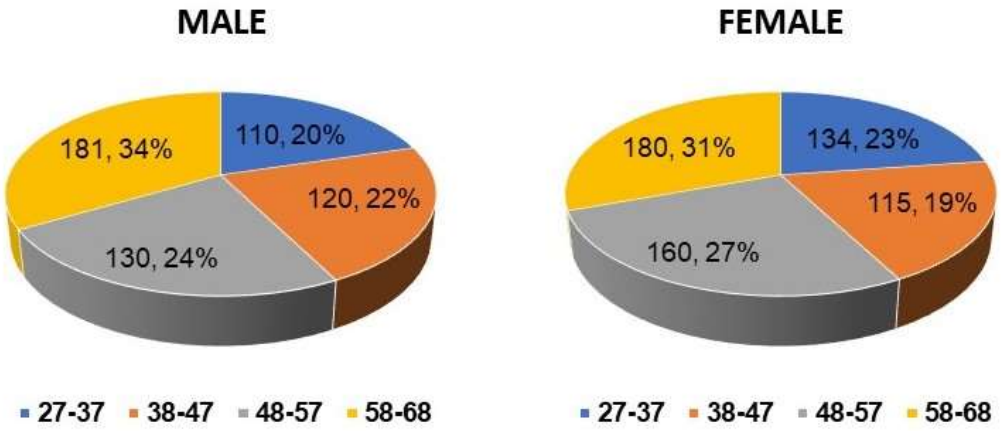

Figure 2. Age distribution in male and female participants.

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2.5. Rationale behind the parameter selection

Parameters are divided into three categories – A. Physical, B. Biomarkers obtained with Lyfas tests, and C. Questionnaire-based instruments (DASS-21 and CSS). A and B construct the independent parameters, while C constructs dependent parameter. Based on this information, finally, the data matrix is constructed for further analysis.

A. Physical parameters

- *Age* has appreciable correlations in coping with mental stress.[14] Studies have found that with increasing age, the incidence of mental health decreases although in the middle-age the intensity is maximum.[14] In women, the intensity of mental illness is more than in men with a prevalence rate of 1 in 3.[15]

- Uncontrolled *Blood pressure* (*systolic and diastolic*) has been linked with mental illnesses as the comorbid conditions and vice versa.[16] In this study, BP has been measured two times in a day – 7 am and 7 pm.

- *HR* has been linked to mental issues such as anxiety, mood disorders, and depression. Palpitation (tachycardia) and arrhythmias are the commonest symptoms of severe anxiety disorders and panic attacks due to sympathetic overdrive.[17] HR has been measured alongside the BP, daily.

- *Cortisol* is secreted from the adrenal cortex as a protective hormone in combating the imminent stress of the body, followed by epinephrine to increase the HR, respiration rate, and blood glucose to meet the metabolic demand of the body. In mental illnesses, such as depression, memory issues, and psychotic disorders, cortisol is found to be decreased in amount, while a long-lasting rise of cortisol refers to prolonged stress.[18] The key axis called Hypothalamus-Pituitary-Adrenal (HPA) axis is responsible for such control. Cortisol is measured two times a day – (i) between 6-7 am and (ii) 4-5 pm and the average values are considered for further analysis.

B. Optical biomarkers from Lyfas (13)*, taken thrice/day (7 am, 2 pm, and 10 pm)*

- *HRVscore* describes the quality of the mood.[19] A score over 80 is considered to be of a high-quality stress-free mood, while scores below 75 refer to emotional derangements, such as dejection, disassociation, and risk of depression.[12]

- Low frequency (*LF*)/High Frequency (*HF*) of R-R intervals.[20] A value around and over 2.5 refers to definitive sympathetic overdrive (normal range 1-1.8), such as anger.

- *pNN50* which is a pair of R-R intervals that differs more than 50 milliseconds,[21] where scores of 10-20% indicate low parasympathetic drive and a healthy score is considered to be >35. The pNN50 also refers to the quality of sleep that is directly correlated with mental health, where too much sleep refers to depression and insomnia in anxiety and some psychotic disorders,[22] *and*

- *SD1/SD2* is a ratio of short and long HRV,[23] where a value below 0.9 and over 3 refers to sympathetic impairment and dominance, respectively. SD1/SD2 refers to anxiety biomarkers.

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C. DASS-21 and CSS scores

- The data obtained are random as the questionnaire sheets are filled up by the subjets daily whenever they feel depressed, anxious and stressed.

Construction of the sample matrix

It is important to note that the trends of the daily average of all parameters for 14 days are taken into developing the sample dataset, which looks like a matrix of 'N'sample-size or rows, where 'i' varies from 1 to 'N' (total population); 'M' columns, where 'j' varies from 1 to 'M'(all independent variables). Dependent variables are denoted as 'O' and its size/number i.e., 'k' varies from 1 to 'O' as seen in equation 1. The values of parameters in the matrix are the daily average of the total readings as mentioned before.

$$N_i \times M_j \rightarrow O_k \ldots (1)$$

2.6. Statistical analysis such as Descriptive statistics**,** Internal consistency check (Cronbach's alpha), Shapiro Wilk normality test, and Spearman's correlation coefficient measures and factor-wise corresponding statistical significance tests are performed. Results obtained by using each have been elaborated in the following section.

3. Results

This section showcases the results as follows.

3.1. Descriptive statistics

Descriptive statistics gives the data spread both horizontally (standard deviations or std and longitudinally through mean and median (50% quartile). It also provides information about the data range by computing the minimum (min) and maximum (max) values. By computing the 25% (first) and 75% (third) quartiles, it also gives information about the data in the lower and upper quartiles and their distribution. Below, Table 1 gives comprehensive information of the male and female samples, where the cell values, which are italicized and of red fonts, denote high average values of the independent and dependent parameters. According to the mean scores, the sample shows the trend of *high* mean BP (SBP >120 mmHg and DBP>80 mmHg), cortisol (>20 mcg/dL), HR (>82 bpm), LF/HF (>3.0), low HRVScore (<40), depression-anxiety-stress as per the DASS-21 and CSS scores supporting a *high* degree of mental turmoil among the participants.

Table 1. Descriptive statistics of the average readings of 14 days (a) Males and (b) Females

MALE	count	mean	std	min	25%	50%	75%	max
Age	541	47.16	12.16	27	36	47	58	68
SBP		*134.71*	14.54	110	121	*136*	146	160
DBP		*95.33*	21.02	60	77	*95*	113	130
Cortisol		*23.90*	3.73	18	21	*24*	27	30
HR		*96.75*	17.22	68	82	*96*	113	125
SD1bySD2		2.44	1.13	1	1	2	3	4
LFbyHF		*6.59*	3.58	1	4	*7*	10	12
pNN50		50.65	30.45	0	23	50	79	100
HRVScore		*39.86*	23.44	1	20	*41*	59	80
Depression		*35.25*	14.66	10	22	*35*	48	60
Anxiety		*34.87*	14.90	8	23	*34*	48	60
Stress		*37.37*	13.08	15	26	*37*	49	60

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CSS		*73.50*	39.90	1	42	*73*	106	144

(a)

FEMALE	**count**	**mean**	**std**	**min**	**25%**	**50%**	**75%**	**max**
Age	589	47.68	12.39	27	37	49	58	68
SBP		*134.81*	15.02	110	121	*135*	149	160
DBP		*94.46*	20.40	60	77	*93*	112	130
Cortisol		*23.77*	3.70	18	21	*24*	27	30
HR		*96.41*	17.11	68	81	*96*	110	125
SD1bySD2		2.49	1.13	1	1	3	3	4
LFbyHF		*6.48*	3.42	1	3	*6*	9	12
pNN50		48.66	28.20	0	24	49	72	100
HRVScore		*38.61*	22.81	1	20	*37*	58	80
Depression		*35.43*	15.06	10	22	*36*	49	60
Anxiety		*33.99*	15.37	8	20	*35*	47	60
Stress		*36.92*	13.18	15	26	*37*	48	60
CSS		*70.14*	42.57	1	32	*68*	108	144

(b)

3.2. Parameter trend analytics

Trends of the parameters have been observed during the 14 days of the study to obtain a more comprehensive view of the data in both genders. Figure 3 shows the daily average trends of the independent and dependent parameters in each of one (a) male and (b) female participant. Similarly, trend analysis has been performed on the rest of the participants, and from that information results of descriptive statistics are obtained.

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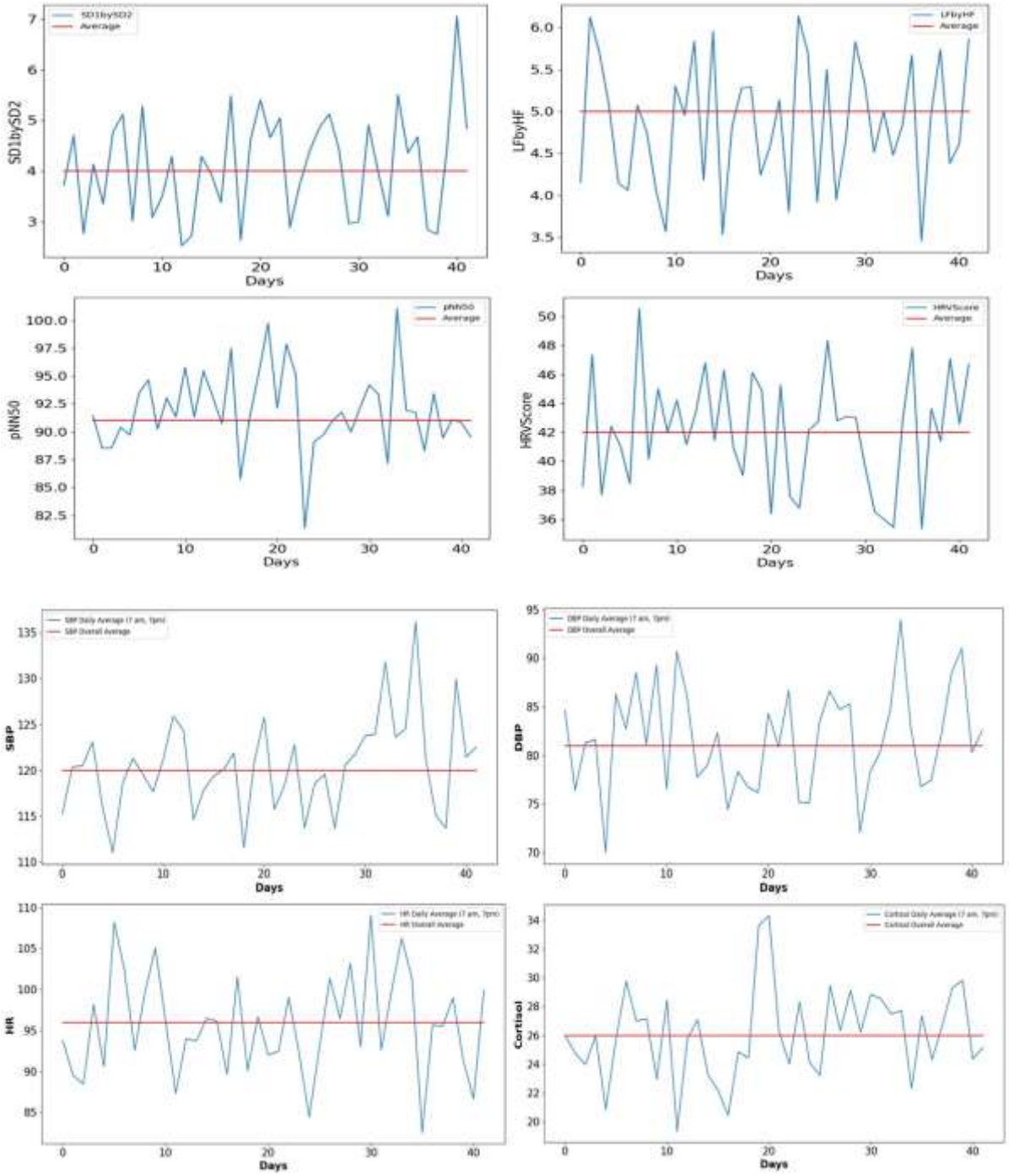

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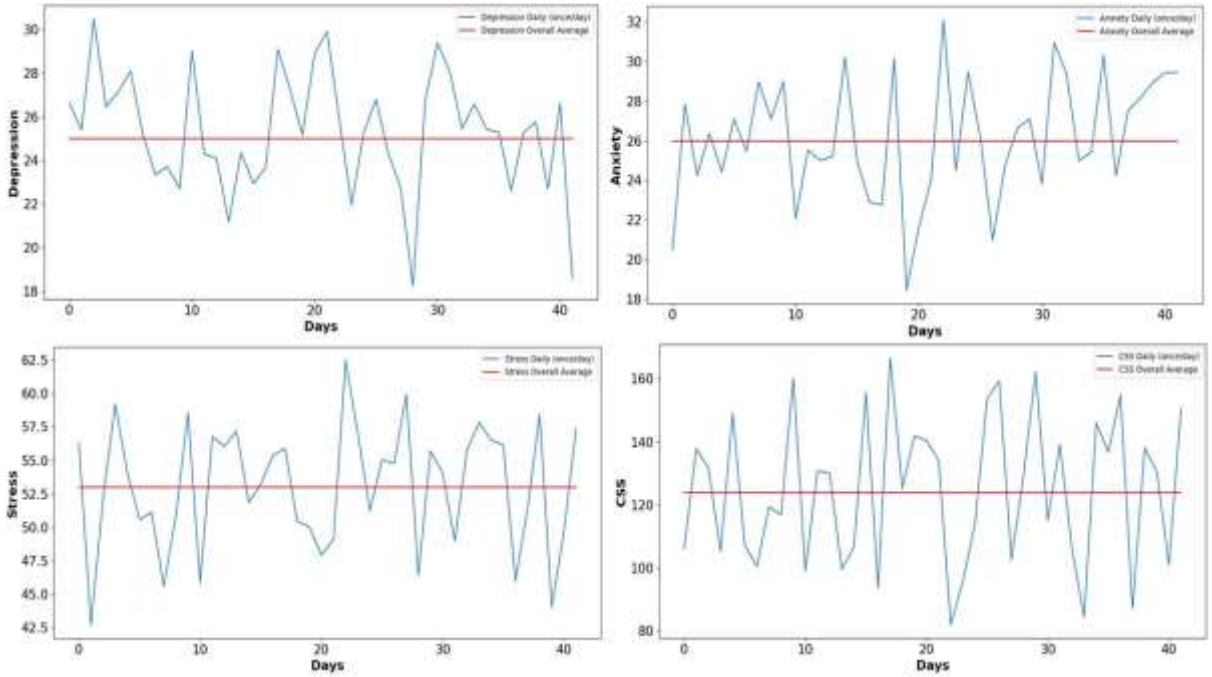
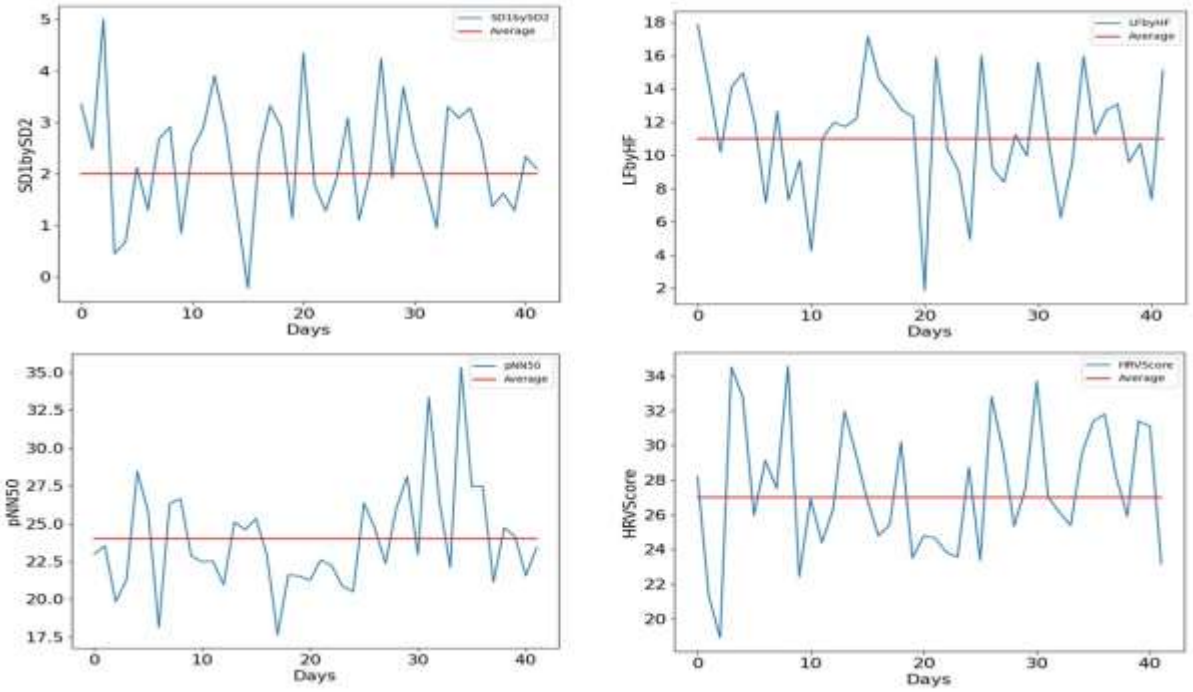


(a)



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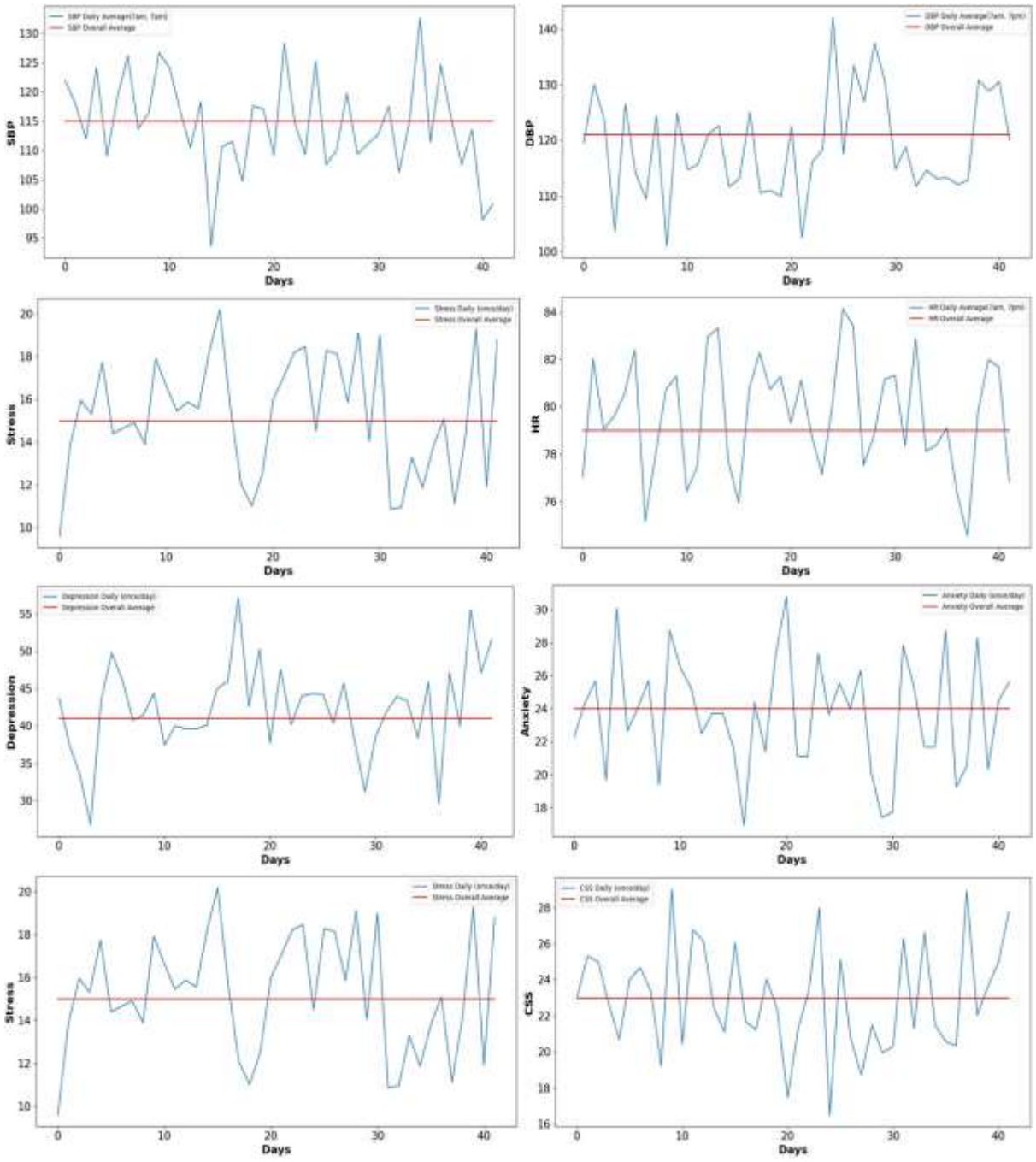

(b)

Figure 3. A sample snapshot of the trend analytics of a male and female subject.

The above Figure 3 is depicting the trend of each one male and female as the sample subject, where the *male* participant shows high anxiety levels (SD1/SD2) with an average score of 4.0, where the normal range is 1-3.3, whereas the *females'* does not show any anxiety trait (average 2). The *male* and *female* both show a high anger scale (LF/HF) with an average score of 5 and 11, respectively (normal range 1-1.8). The trend data also shows that the

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female participant suffers from chronic insomnia (pNN50 of 24, while the healthy score is expected to be over 35), while the sleep of the *male* counterpart is not affected (average score of 91). Finally, the HRVScore of *both* genders is below normal (male: 42, female: 27, while the healthy score is expected to be over 80), reflecting signs of depression.

3.3. Internal consistency check (Cronbach's α)

Data fidelity/reliability/internal consistency check is an important data mining method.[24] It shows how closely related sets of items are lying as a group. It is also a scale-reliability assessment method. Alpha (α, see equation 2) increases when the inter-item correlations increase holding the number of items constant. An α value greater than or equal to 0.8 is considered to be very good.[25] It is advisable that before putting the data into statistical experiments, its internal consistency must be checked as too similar data skews the results.[26-27] In equation 2, N refers to the number of items, ρ_{ij} and ρ_N^2 denotes the covariance between two items i and j and item variances and inter-item covariances, respectively.

The α value of the sample data is found to be *0.8012*, which states that the data within is internally consistent and hence appreciable for further analysis.

$$\alpha = \frac{N^2 \rho_{ij}}{\rho_N^2} \ldots (2)$$

3.4. Shapiro-Wilk normality test[28]

It is a reliable measure of normality or Gaussian distribution of a continuous variable. The Null hypothesis (H_0) states that the variable is normally distributed when the p-value is greater than 0.05. The Alternative hypothesis (H_1)states it is not normally distributed and the p-values are less than 0.05.

Shapiro-Wilk normality results show test statistics = *0.9238* and p-values = *0.00011* and therefore, it rejects H_0 for the sample, which means that the sample data is not normally distributed.

3.5. Spearman's correlation coefficient measures[29]

It is a measure of the strength of association/correlation (correlation coefficient or ρ between two parameters and its statistical significance (p-value <0.05; CI 95%). In this work ρ and p-values are measured between each independent parameter with that of each dependent parameter, mentioned in section 2.5. The values of ρ are set between -0.1 to 0.1 to initially accommodate even the lowest possible correlations, where positive i.e., 0.0 to 0.1, negative i.e., 0.0 to -0.1, and closer to '0.0' values indicate 'positive', 'negative', and 'non-correlations'. It is important to mention here that *70% cut-off values* have been considered for each positive and negative side, i.e., any value below 70% cut-off (i.e., below 0.07 or above -0.07) has not been considered for the study. Figure 4 (a) and (b) show the correlation (ρ) values. Table 2 shows the correlation ranking. All respective p-values are found <0.05, i.e., all correlations are found to be statistically significant, and hence each of these is not mentioned separately.

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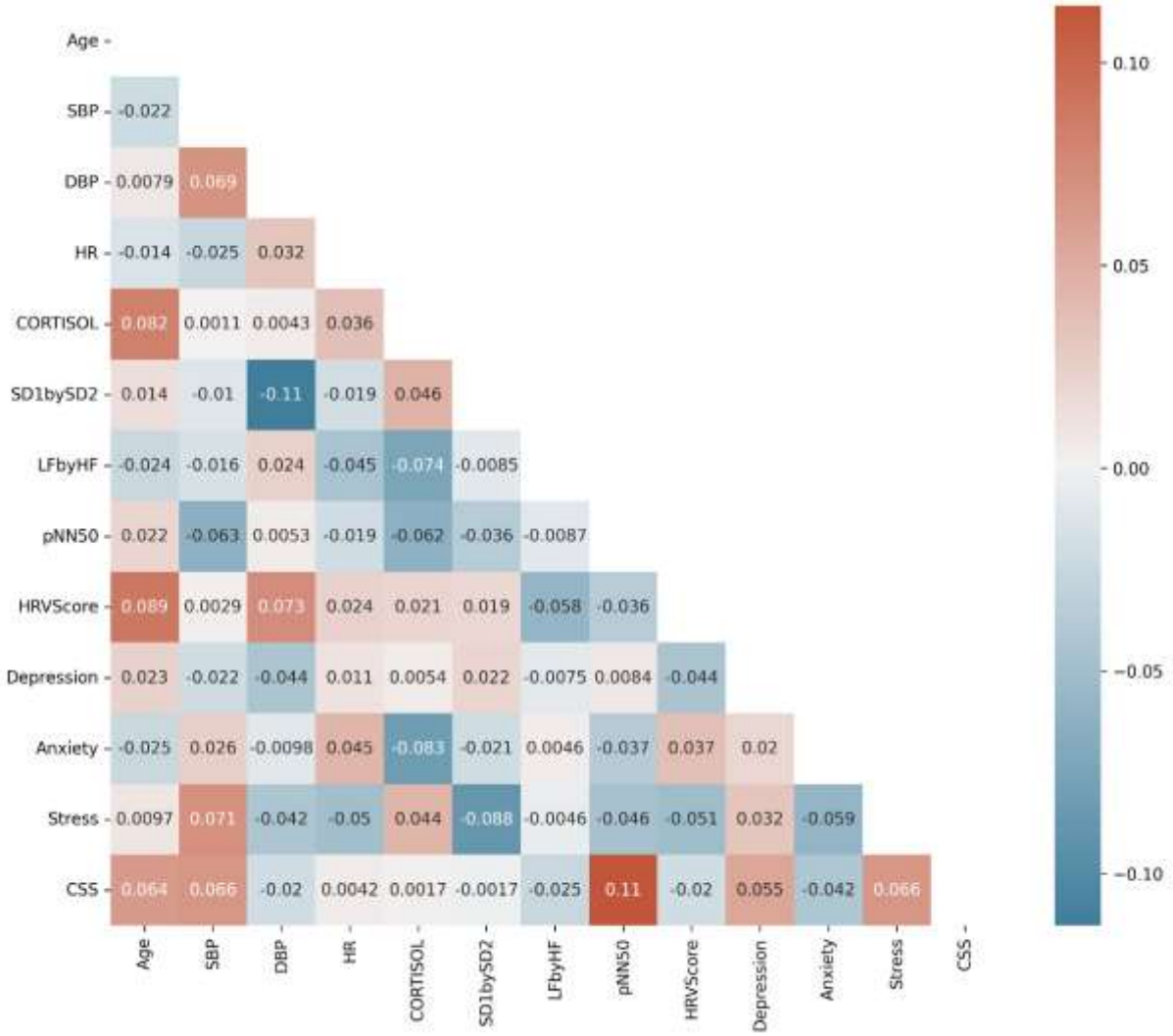

(a) Male

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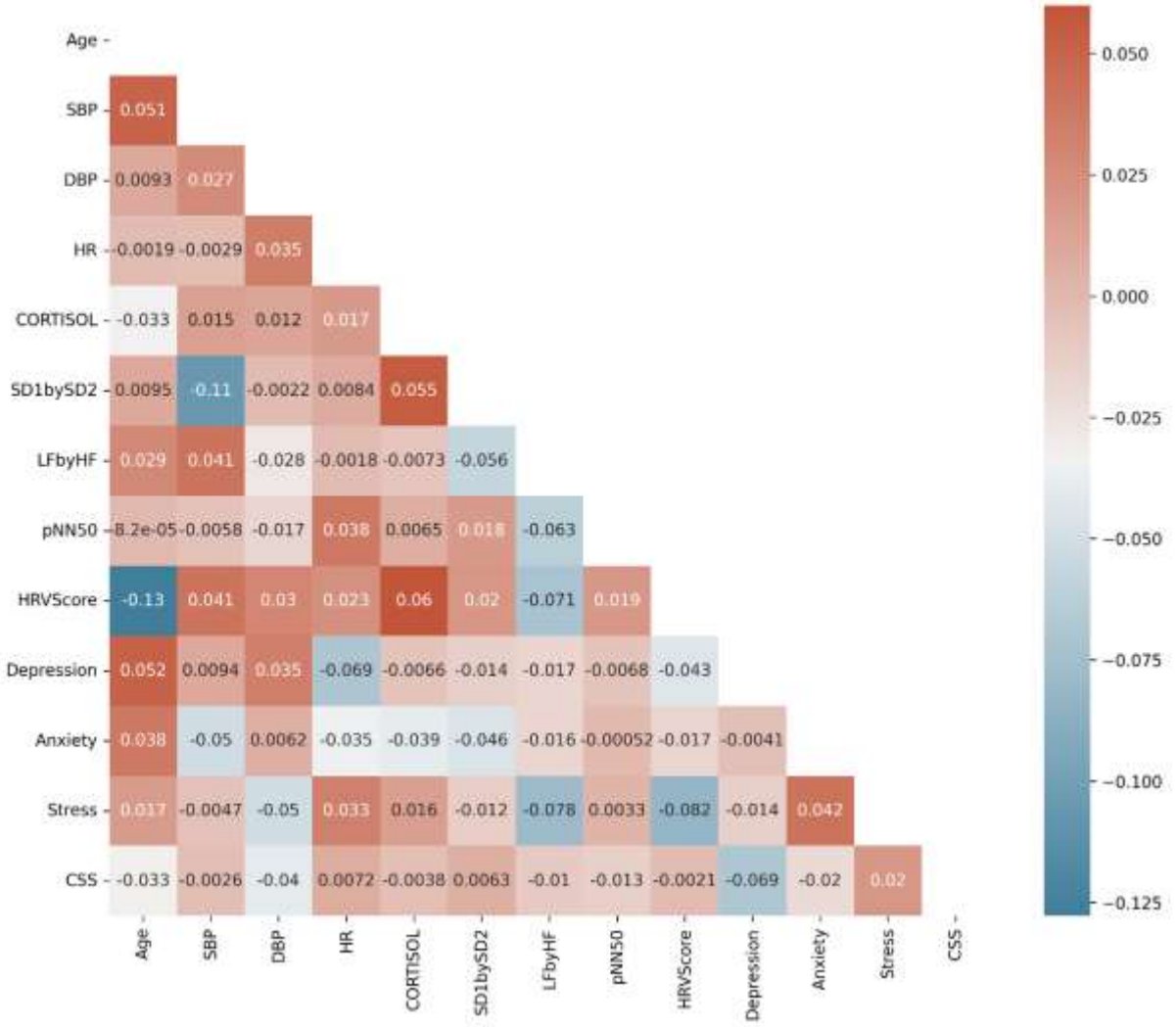

(b) Female

Figure 4. Correlation heatmaps of males and females.

Table 2. Correlation ranking (P1 and P2 are Parmeter1 and 2)

MALE	**P1**	**P2**	**ρ**	**Rank**
1	Age	HRVScore	0.09	**2**
2	Age	CORTISOL	0.08	**2**
3	SBP	DBP	0.07	**3**
4	SBP	Stress	0.07	**3**
5	*DBP*	*SD1/SD2*	*-0.1*	**1**
6	DBP	HRVScore	0.07	**3**
7	*CORTISOL*	*Anxiety*	*-0.08*	**2**
8	*CORTISOL*	*LF/HF*	*-0.07*	**3**
9	*SD1/SD2*	*Stress*	*-0.08*	**2**
10	pNN50	CSS	0.1	**1**

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FEMALE	P1	P2	ρ	Rank
1	*Age*	*HRVScore*	*-0.1*	**1**
2	*SBP*	*SD1/SD2*	*-0.1*	**1**
3	*HR*	*Depression*	*-0.07*	**3**
4	*LF/HF*	*Stress*	*-0.08*	**2**
5	*LF/HF*	*HRVScore*	*-0.07*	**3**
6	*HRVScore*	*Stress*	*-0.08*	**2**

From Table 2, the summary *significant* parameters are as follows:

A. Physical parameters:

In **Males**-

1. *Age* and *DBP* has high positive correlations with HRVScore,
2. *DBP* is negatively correlated SD1/SD2,
3. *SBP* is positively correlated with stress, and
4. *Cortisol* is negatively correlated to LF/HF and Anxiety.

In **Females**-

1. *Age* has a negative correlation with HRVScore,
2. *SBP* has a negative correlation with SD1/SD2, and
3. *HR* is negatively correlated with depression.

B. Optical biomarkers:

1. *pNN50* has the highest positive correlation with '*CSS*' in **males**, while, *SD1/SD2* has high negative correlations with '*stress*', and
2. *LF/HF* and *HRVScore* have a very high negative correlation with '*stress*' in **females**.

A combined association can be found in Figure 5.

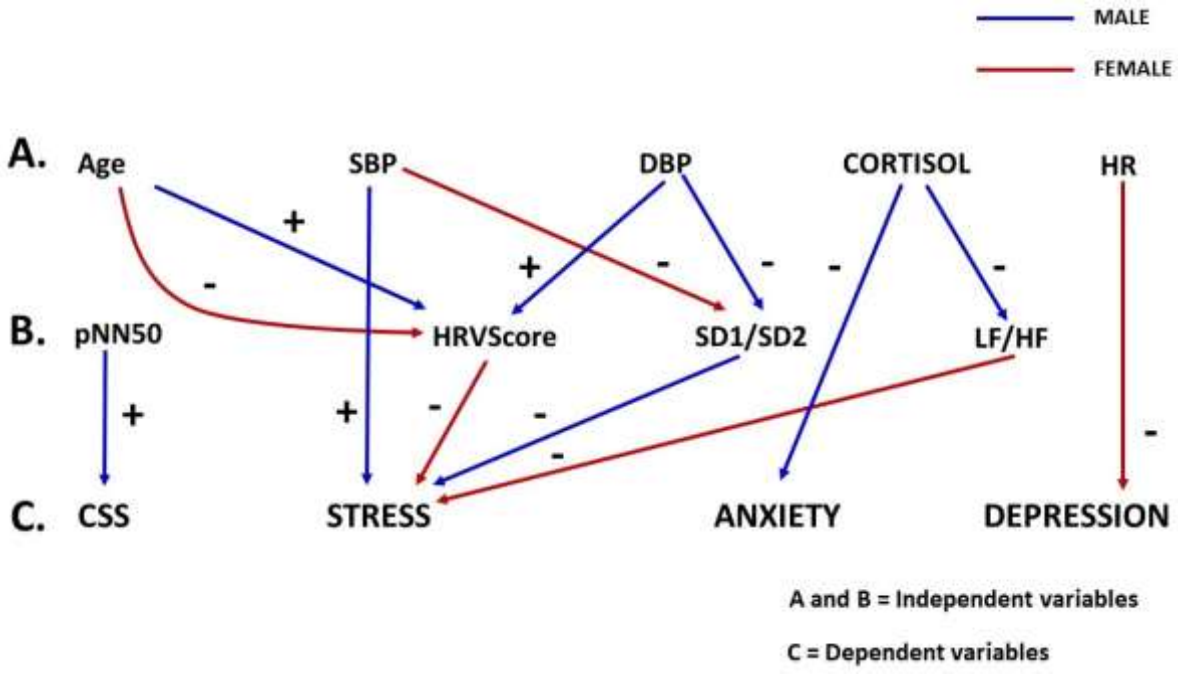

Figure 5. Intertwined associations among the significant independent variables with that of the dependent variables.

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4. Discussions

This section essentially explains the flow chart in Figure 5 with respect to COVID-19 pandemic situations. Under 'A', 'B', and 'C', the correlations among the significant physical (A) and optical biomarkers (B), which are the independent parameters, and dependent parameters (C) are mentioned. Increased HRVScore is a representation of happiness and vice versa.[30] The happiness state of females is directly correlated to their mood (emotional stability), which again biologically depends upon the estrogen (E2) level.[31] At an earlier age, females have better hormonal regulation and hence the HRVScores are usually better. On contrary to that when they grow older, the HRVScores are reduced due to the depletion of E2 in the brain. In the case of males, their happiness comes from social skills channelized through verbal and non-verbal behavior that help stabilize their thought processes.[32] Therefore, it can be postulated that gathering of social recognition and wisdom with age advancement leads to higher mood stabilization that is reflected through the high HRVScores.

The pNN50 is a snapshot of the parasympathetic system.[33] Usually, any form of stress leads to sympathetic dominance that raises HR and BP. Stress compensation through positive self-esteem[34] happens through the stimulation of the hypothalamic-pituitary-adrenal axis resulting in the release of cortisol from the zona fasciculata cells of the adrenal cortex in the blood,[35] abreast increments of the vagal tone (by releasing abundant acetylcholine from the presynaptic vesicles as the neurotransmitter) to dampen norepinephrine that is secreted by the chromaffin cells of the adrenal medulla. Thus, a higher pNN50 score during stress is a usual occurrence and argues in favor of parasympathetic compensation to stress-induced sympathetic overdrive.

Since females have higher parasympathetic activation than their male counterparts their bodies compensate for the stress by raising the parasympathetic activation even further.[36] Overthinking and crying are two complex emotional mechanisms in females, popularly termed as 'sympathy crying', where the parasympathetic activities are predominant over its sympathetic counterpart to reduce high HR i.e., the palpitations and as a result, their anxiety levels are reduced.[37] E2 plays a critical role in such a compensatory mechanism as mentioned before. In males, any stressful situation (e.g., loss of job during the COVID-19 pandemic) leads to increased testosterone secretion from the adrenal gland to combat the situation.[38] As an outcome of this process, brain signals skews towards positivity (e.g., refurbishing resume and submitting for new job search) that is reflected through the high HRVScores and reduced SD1/SD2, which is the anxiety biomarker. High levels of stress, low HRVScore, increased serum cortisol, and decreased E2 are the typical physiological snapshots in females in their middle ages. They compensate through crying. In the case of males, during the stress/fear perception, they go to the fight-or-flight mode (amygdala dominance over prefrontal cortex) immediately. However, to maintain physiological homeostasis, the body releases cortisol from the adrenal cortex. Cortisol, in turn, stimulates the cognitive ability (positive thoughts and optimism) in the prefrontal cortex by processing the fear-response that in turn, slows down the amygdala-based reactive response to stress.[39] Cortisol, later, stimulates the cardio-renal axis and thereby reduces the cardiac autonomic neuropathy, induced by stress-related sympathetic overdrive,[40] which is reflected through the low level of LF/HF. In the case of females, LF/HF is reduced due to more expressed emotions than males through their parasympathetic predominance as described above.

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In the case of depression which can be better termed as the 'self-disassociation syndrome' in this study because of the ongoing pandemic period, resulting in low self-esteem and negative thoughts. Consequently, the body goes into a slower metabolic state, and thus the sympathetic activity is reduced while the parasympathetic drive remains unaltered or increased.

Another interesting observation of the study is that cortisol exhaustion (<3 mcg/dL) due to random waves of panicky situations and thanatophobia has caused adrenal fatigue in many, especially in the elderlies could be the major cause of COVID-19 deaths as seen in one case.

5. Conclusions

Two questionnaire-based mental health instruments (DASS-21 and CSS) and a novel biomarker instrument Lyfas are used to screen and monitor the mental health of 1130 Indian adults during the COVID-19 pandemic. The key objective is to validate the clinical efficacy of Lyfas to these questionnaire-based instruments, which are already validated. The study observes that the strength of the interplay, measured by the correlation scores of physical parameters, optical biomarkers obtained from Lyfas, and DASS-21 and CSS, are statistically significant ($p<0.05$; CI 95%). The average correlation of Lyfas in physiologically predicting the DASS-21 and CSS is 0.082, i.e., 82% as per the chosen scale of -0.1 to +0.1. The pNN50 (biomarker for the parasympathetic system) shows the highest (100%) correlation with CSS; while, SD1/SD2, LF/HF, and HRVScore show a high correlation (80%) with the stress under the DASS-21. Cortisol, as the primary hormone in stressful situations, plays a significant role in reducing the sympathetic overdrive, which is expressed by a high LF/HF and the anxiety level that is expressed by a high SD1/SD2 in the study group. Therefore, the authors argue in favor of using Lyfas in screening and monitoring the mental health state of adults, and pNN50, HRVscore, SD1/SD2, and LF/HF could provide a useful insight into the mental health of the population at risk.

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