Open Access Research Journal of
Life Sciences
Journals home page: https://oarjpublication/journals/oarjls/
ISSN: 2783-025X (Online)

OARJ OPEN ACCESS RESEARCH JOURNALS

(RESEARCH ARTICLE)

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Modeling the risk of insulin resistance in borderline personality disorder with romantic pathological jealousy in females: A Lyfas empirical study

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Open Access Research Journal of Life Sciences, 2022, 03(02), 063–076

Publication history: Received on 28 April 2022; revised on 13 June 2022; accepted on 15 June 2022

Article DOI: https://doi.org/10.53022/oarjls.2022.3.2.0046

Abstract

Borderline Personality Disorder (BPD) with Romantic pathological jealousy (rPAJ) influences the heart rate variability (HRV) and its cardiovascular optical biomarkers (COBs), which the Lyfas mobile application captures through smartphones. The COBs surrogate insulin resistance (IR), a marker of cardiometabolic risks. The paper aims to non-invasively study the IR risk in BPD-rPAJ affected females. Personality-based Questionnaire (PBQ) and the Multidimensional jealousy scale (MDJS) and Lyfas tests were taken by the participants under psychologists' supervision. The VO2Max (COB of heart-lung coherence after stressful exercise), LF/HF (COB of IR), and Arterial stiffness index (ASI), a marker of early vascular aging, are chosen as the IR biomarkers. HRVScore, SD1/SD2, and pNN50 are chosen as the mood, anxiety, and sleep (MAS) biomarkers. Finally, each of the MAS-IR COBs is regressed to examine the causality. The R2 value >= 25 is considered the significant causative. Furthermore, the relative risk (RR) is computed between significant MAS-IR COBs. The study observes that HRVScore and pNN50 possess high causal relationships with ASI (R2 = 47% and 25%, respectively). The RR shows an increased risk of premature arterial stiffness (PAS) with mood dysregulations (RR = 10.5, p 0.02) and sleep issues (RR = 135, p 0.19) when compared to the baseline population. The study concludes that mood dysregulations and poor sleep quality are associated with a high risk of IR in females suffering from BPD-rPAJ disorder. The onset of the deterioration of their arterial health starts as early as an average of five-and-a-half years.

Keywords: Borderline Personality Disorder; Lyfas; Romantic Pathological Jealousy; Insulin Resistance; Cardiovascular Optical Biomarkers; Premature Arterial Stiffness

1. Introduction

The 5th Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) enlists ten personality disorders divided into three clusters – 'A', 'B', and 'C' (1). *Borderline personality disorder (BPD)* falls under 'B' and the patients are characterized by extreme sensitivity toward apprehended rejections or abandonment (1). This emotion, in turn, pushes their interpersonal relationships to collapse and distortion of their self-image, social behavior, and affect (the external expression of the emotion). Extreme possessiveness and *romantic pathological jealousy* (rPAJ) also called delusional or obsessive jealousy or Othello syndrome is one of the hallmark traits of a worsened BPD. It is also enlisted in ICD-10 (code: F60.3) as an acclaimed mental disorder (2). The incidence rate of BPD and romantic PAJ are 1.6% (1) and 0.5 – 1% (3) respectively in the general population with a female to male ratio of 3:1 (4). The incidence of BPD-rPAJ is however unknown. The obsessive type of rPAJ is also much more common in females compared to males who suffer more from the delusional type, but both are initiated by an abrupt and intense autonomic arousal, termed 'jealous flash' (5). Hence, BPD-rPAJ could be a disastrous combination in females.

Although the number of reported research does not score much, certain areas of the *brain*, that process impulsivity, emotions, mentalizing, interoception (internal sense of the body – both conscious and subconscious), and dopaminergic

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and serotonergic signaling play pivotal roles in emotion processing and converting it into one progressive behavior, found in the BPD-rPAJ combination (6). These are the ventromedial prefrontal cortex, frontostriatal circuitry, thalamus, amygdala, and insula show aberrations in functioning (6). The generation of rPAJ is guided by the ventromedial prefrontal cortex, while rPAJ becomes a habit by the influence of it coupled with basal ganglia. The progression of habit into behavior is more complex and here, dorsal striatal-prefrontal cortex connections along with dopaminergic-serotonin signaling disturbances play crucial roles (6). BPD has a strong gene-environment basis like many other mental illnesses. The heritability of BPD is around 46% in the population (7).

Mental illnesses are known causes of *metabolic syndrome* (MS), characterized by *insulin resistance* (IR) and vice versa. One key feature of IR is sympathetic overdrive or parasympathetic underdrive or a relative overdrive or underdrive of both leading to a high sympathovagal ratio, which is tangible proof of a robust mind-body connection (8). Therefore, these must not be seen separately in the clinical practice, by a clinician, which, unfortunately, still is the current day's practice. Vasculopathy in the form of *premature vascular aging* is a common occurrence in the mental-metabolic syndrome and is often overlooked by clinicians. Early arterial stiffness due to endothelial dysfunctions, gradual loss of elastin that is replaced by tight collagen networks encroaching into the myocytes in the media (the smooth muscle layer), and the associated inflammation-induced calcification and platelet aggregation are found to be the key pathogenesis (9). A few key consequences of early vascular aging are gradual blockade of the vessels leading to ischemia and infarction of the supplying tissue and rupture of the vessels due to excessive stiffening, especially where vessels pass through critical tracks such as hairpin bends and axial twists and it has to accommodate high-speed high-volume blood column for a long time. Hence, in all mental and MS, the chances of developing vasculopathy must not be overlooked.

Lyfas is a clinically-validated biomedical application that runs on a smartphone (10). It captures the short (2-minutes) heart rate variability (HRV) and its correlates (called *cardiovascular optical biomarkers* or COBs) from the index finger capillaries with the help of arterial photoplethysmography (APPG) using the phone's camera sensor and light (10). Its proprietary signal processing layer and the AI algorithm then process the signal into a psychophysiological analytics report (10). Lyfas has been well-tested in mental illnesses (11) (12) (13) and IR (9) (14).

The paper *aims* to (a) examine the behavior of COBs in BPD-rPAJ combination in the population online for the first time, and (b) screen their subsequent risk of developing MS/IR.

2. Material and methods

2.1. Study design

An online platform containing mental health instruments is created (15) (16) where among other test questionnaires, the *Personality Based Questionnaire (PBQ)* (17) and the *Multidimensional Jealousy Scale (MDJS)* (18) are also available (19) for use in this study. A cohort of females is invited to take the PBQ tests online according to the non-probability sampling design and shared their scores with the research team via email. Except for their IP addresses and age, the other personal metadata has not been captured. High-scoring test-takers are counseled by a panel of each of three experienced psychologists (median experience 10 years) to confirm BPD cases, who then are encouraged to take MDJS tests (according to the principle of purposive sampling). The test-takers, who score high for rPAJ, are counseled by psychologists for clinical confirmation. The final 'BPD-rPAJ' combination 'cases' and an equal number of 'healthy controls' took the *Lyfas tests*, thrice daily (7 am, 2 pm, and 10 pm) for three weeks of their menstrual cycles. The final week of the cycle and the days of menstruation (median 10 days) has not been considered, as the premenstrual dysphoria and blood loss are accompanied by physical discomforts, such as pain and weakness which could influence the psychophysiological homeostasis, reflected through altered COB scores that Lyfas captures by the help of a smartphone from index finger capillaries. The COBs are then studied into two groups – (A) COBs of mood (HRVScore or HRVS) (11), anxiety (SD1/SD2) (13), and sleep (pNN50) (11), together called MAS and (B) COBs (VO_2Max (20), LF/HF (14), and Arterial stiffness index (ASI) (9), surrogates of cardiopulmonary coherence, IR, and vascular stiffness, respectively) as the marker of MS/IR. COBs of MAS are then regressed on IR COBs to note the significant associations, which in turn, throws light on the risk of IR for given MAS COB scores. Furthermore, the relative risk (RR) is estimated of developing IR given MAS COBs. Fig. 1 shows the flowchart of the study design. It is worth mentioning here that the research team follows the directions of the psychologists throughout the study.

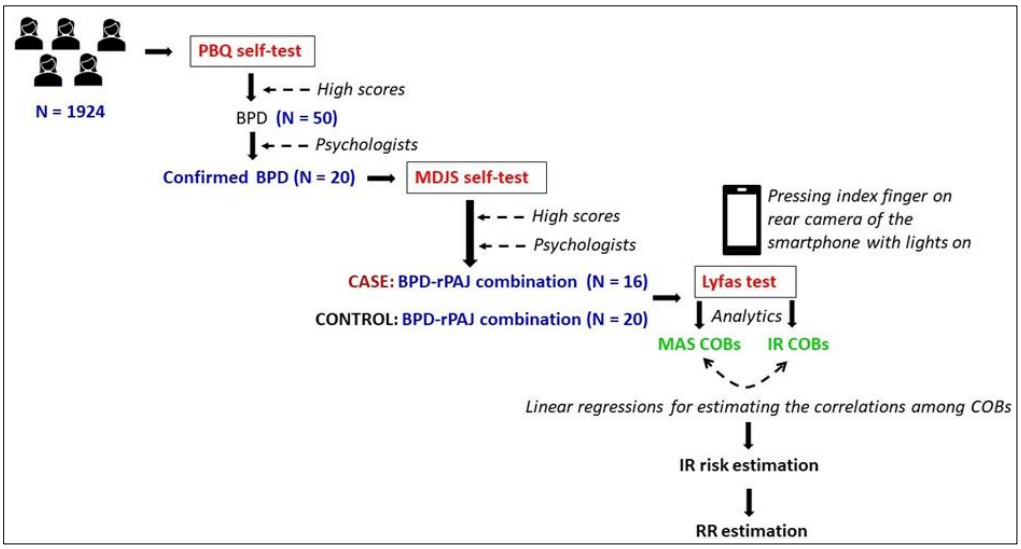


Figure 1 The flowchart of the study design

2.1.1. Exclusion criteria

- History of any substance abuse, the habit of tobacco consumption in any form
- History of other mental illnesses
- Premenstrual syndrome, and
- Positive criminal history.

2.2. Summary of the instruments and their purpose

- PBQ questionnaire: to screen BPD cases
- MDJS questionnaires: to screen rPAJ cases, and
- Lyfas: to capture COBs using the smartphone's in-built camera sensor, light, and APPG. Lyfas desired level and ranges of the COBs are as follows,

A. MAS COBs	B. IR COBs
i) HRVS: >80	i) LF/HF: <2
ii) pNN50: >30	ii) ASI: -0.2 to 0.49
iii) SD1/SD2: 1-2	iii) VO_2Max: >85

The detailed discussion of the Lyfas COBs, PBQ, and MDJS is skipped due to the space constraint.

2.3. Statistical methods

All methods are carried out with IDLE (Python 3.9 64 bits) (21) on Windows 10 Pro OS. Below are the statistical methods carried out sequentially.

2.3.1. Internal consistency test

Checking the internal consistency of the data is an important step to examine its degree of fidelity before analyzing it. *Cronbach's alpha (α)* is a measure of such fidelity (22). Its values of 0.8-0.9 are considered to be of good consistency (23).

2.3.2. Descriptive statistics

It provides the central tendency (mean and median) and the range of dispersion (standard deviation and skewness) of the data for each variable. Table 1 shows the descriptive statistics of cases and healthy controls.

2.3.3. Normality test

Data distribution whether it is normal or not is the next important step to deciding on choosing statistical methods. For normally distributed data parametric tests are used, else non-parametric tests are considered. In this study, histogram plots are used for the normality visualization (see Fig.2). For normally distributed data, the plots follow the normal distribution graph.

2.3.4. Mann-Whitney rank U-test (24)

The U-test is a non-parametric version of the unpaired t-test. It tests the median difference between the case and healthy control. The null hypothesis (H_0) is accepted when no difference is noted, else the alternate hypothesis (H_1) is accepted. The calculated U-statistics less than the critical value (obtained from the U-table) rejects H_0 which means that the difference has occurred by chance. In this study, each of the case and healthy control possesses six parameters, such as Age, HRVS, pNN50, SD1/SD2, LF/HF, ASI, and VO_2Max. U-tests are conducted for each parameter alongside estimation of individual z-score.

2.3.5. Multiple Linear Regressions (MLR) (25)

Here, the regression analysis estimates the causal relationships between independent (factors) and dependent variables (responses) at a grade between 0 (no relation) and 1 (maximum relation). The hyperplane (a unique line) is calculated using the ordinary least squares. It minimizes the sum of squared differences between the data and that line so that the degrees of the factor-response relationships become statistically significant. In this study, MAS and IR Cobs construct the independent and dependent variables to examine their causal relationships to assess the IR risk for the given MAS dysregulations, which is the principal objective of the study. The R-squared (R^2) values are calculated to find out the strength of such relationships between 0 (i.e., nil relationship) and 1 (i.e., maximum relationship), expressed in %. It explains the proportion of the variance for a dependent variable (here each of the IR COBs) that is explained by the independent variables (here the MAS COBs). It is important to mention that R^2 values >=25% are considered significant in this study.

2.3.6. Relative risk (RR) (26)

The RR is a measure of the risk of any event in one group (given MAS disorders) vs. another group (occurrence of IR).

Further to note statistically significant relationships, CI upper and lower bound and the respective p-values of HRVS-ASI and pNN50-ASI are computed (27)

3. Results and discussion

3.1. Population statistics

A total of 1924 females took the PBQ self-tests. Based on the captured IP address, the traffic is assessed separately for PBQ and MDJS tests. Region-wise, most traffic is from the USA (64%), followed by the UK (23%), while 12% is from India in the case of the PBQ self-tests. While, for the MDJS self-tests, these are 51%, 17%, and 18%, respectively for the above regions. The study shows that 84% of females (30-48 years, mean age 41.45 years) took PBQ self-tests, while MDJS was taken by 73% in the age group of 22-30 years mean age 26.72 years). The expertise-confirmed BPD-rPAJ combination is found to be 16 out of 1924, i.e., 0.83% in this study.

3.2. PBQ self-test results

Fig. 2. is the screenshot of the online PBQ self-test analytics (28), where the disorders are seen along the x-axis and the population size across the y-axis where 52% of 1924 test-takers i.e., 1000 fall under BPD as per the test results. Out of a total of 1000 suspected BPD of variable grades, 95% score 30-49, 3% score 50-70, and the remaining 2% score >70. This (2+3=5)% of high-scoring cases, i.e., 50 cases with a strong suspicion of BPD are sent to psychologists for confirmation. Out of these 50 cases, 40%, i.e., 20 are diagnosed with confirmed BPD and later took MDJS tests.

Figure 2 The online PBQ-analytics

3.3. MDJS self-test results

Fig. 3 is the screenshot of the overall method of having the MDJS self-test analytics (29). A cohort of 80% of 20 confirmed BPD cases, i.e., 16 has confirmed rPAJ as per the self-test scores and counseling of psychologists. This is the final cohort (the BPD-rPAJ combination as the case). After discussion with the psychologists, 20 healthy controls are also selected for comparative analysis. In both Fig. 2 and 3, the x-axis represents the 'disorder type' and the y-axis refers to the '% of the population.

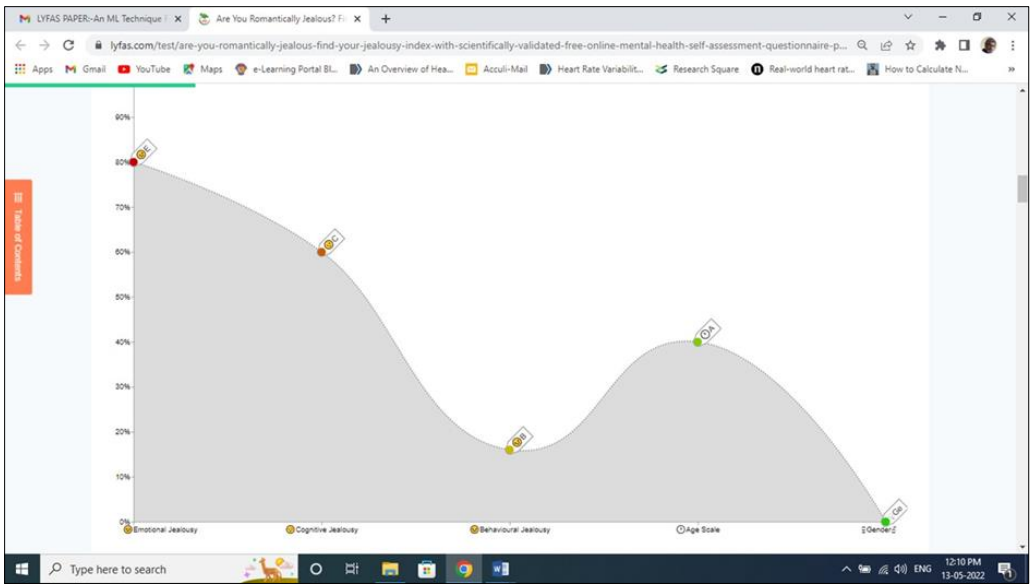


Figure 3 The online MDJS-analytics

3.4. Descriptive statistics of the Lyfas tests and α test results

Finally, 16 BPD-rPAJ combination cases and 20 healthy controls take lyfas tests to capture the HRV-COBs, as mentioned before. The COBs are grouped into MAS (HRVS, SD1/SD2, and pNN50) and IR (VO_2Max, LF/HF, and ASI). Table 1 shows the descriptive statistics of the COBs.

Table 1 Descriptive statistics of Lyfas COBs in the case and healthy control

Parameters		Mean		Median		Stdev		Min		Max	
		Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
Age		29.93	31.65	30.02	32	5.56	8.13	22	22	39	46
MAS	HRVS	75.75	81.85	72	81.5	6.96	5.15	62	65	77	89
	pNN50	19.79	33.17	14.43	35.95	12.88	14.45	6.57	30.66	24.67	54.13
	SD1/SD2	5.07	3.14	2.7	2.53	6.14	1.77	1.62	1.62	26.59	6.10
IR	LF/HF	2.54	1.40	2.46	1.46	0.48	0.11	1.02	1.24	3.17	1.6
	ASI	1.45	1.17	0.46	0.35	0.15	0.45	1.20	0.20	1.68	1.68
	VO_2Max	80.59	86.64	80.69	88.92	7.76	8.19	72.55	82.55	92.31	95.16

The α value of the final study cohort is 0.82, which indicates appreciable internal consistency within the data (23). Fig. 4 shows the *Lyfas analytics* of one BPD-rPAJ case and healthy control, each.

In figure 4, the sample BPD-rPAJ case presents with abnormal COB scores (high LF/HF, ASI, and SD1/SD2). On the other hand, the healthy control sample shows high SD1/SD2 but normal LF/HF and ASI scores. It is important to mention here that SD1/SD2 is persistently high in the population, especially during the running pandemic period, as our study has observed (13). In the sample of BPD-rPAJ, ASI is -0.9, which is abnormal compared to healthy control. In the population, abnormal ASI is found in 100% of cases, compared to 4% in the healthy control.

Abnormal scores are marked red, shown by *descriptive statistics*. Parameter-wise histogram plots measure the normality (see Fig. 5), followed by computation of the U-statistics to examine the median difference between the groups, parameter-wise (see Table 2).

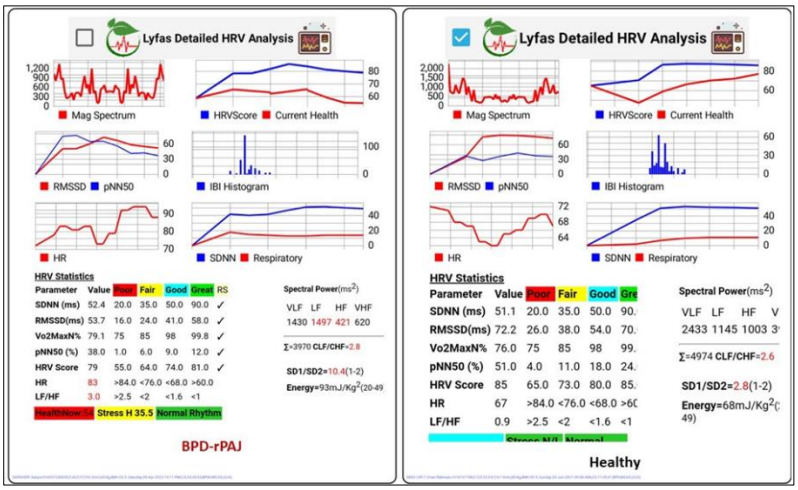
The *histogram* with *density plot* shows that the data is not following the normal distribution.

The *U-stat* and *z-scores* show that there is a significant median difference between the case and control groups. For the medians of BPD-rPAJ and healthy control, to be statistically significant to accept H_0, the U values must be <98, i.e., the critical value of U at $p<0.05$. the corresponding p-values must be <0.05 for supporting H_0.

Finally, the *MLR* between each MAS and IR COBs for the case and control are performed. Fig. 6 shows the results. The aim is to estimate the causal relationships among these and how well each of the MAS COBs can explain each of the IR COBs by calculating the respective R-squared values.

Table 2 U-statistics (2-tailed) parameter-wise between the case and the control (CI: 95%, p=0.05)

Parameter	Calc_U	Crit_val_U <0.05	z-score	p-value	Interpretation
Age	150	98	0.302	0.7614	Not significant at p<0.05
HRVS	151.5		-0.25	0.8025	
SD1/SD2	129		-0.97	0.3324	
pNN50	132		0.3786	0.8754	
LF/HF	146.5		-0.4136	0.6818	
ASI	109		-1.6077	0.1074	
VO_2Max	127		-1.034	0.3030	



Parameters	Value	Interpretation
Cardiac Cycle Stress	0.1	•High value needs thorough cardio vascular assesment. • Ideal is less than 0.3
LeftVentricular Afterload	0.6	• More than .75 may represent unregulated BP
Vascular Stiffness	35.0	• |Age± Value|>20 with high heart rate for adults may represent Arterial or CV anomaliesAge
Arterial Index	-0.9	• Value<-.2 or >=.5 needs arterial investigation

Always seek advise from your physician about the interpretation. **BPD-rPAJ**

Parameters	Value	Interpretation
Cardiac Cycle Stress	0.2	•High value needs thorough cardio vascular assesment. • Ideal is less than 0.3
LeftVentricular Afterload	0.4	• More than .75 may represent unregulated BP
Vascular Stiffness	39.2	• |Age± Value|>20 with high heart rate for adults may represent Arterial or CV anomaliesAge
Arterial Index	0.3	• Value<-.2 or >=.5 needs arterial investigation.

Always seek advise from your physician about the interpretation. **Healthy**

Figure 4 Lyfas analytics show a sample BPD-rPAJ and one healthy control each

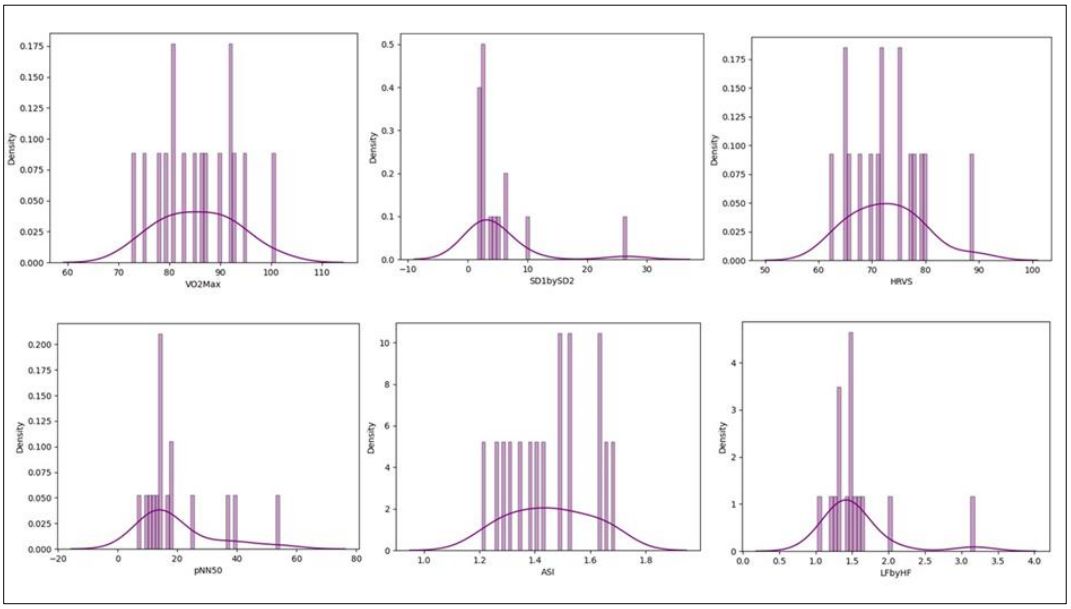


Figure 5 Histogram plots of Lyfas COBs

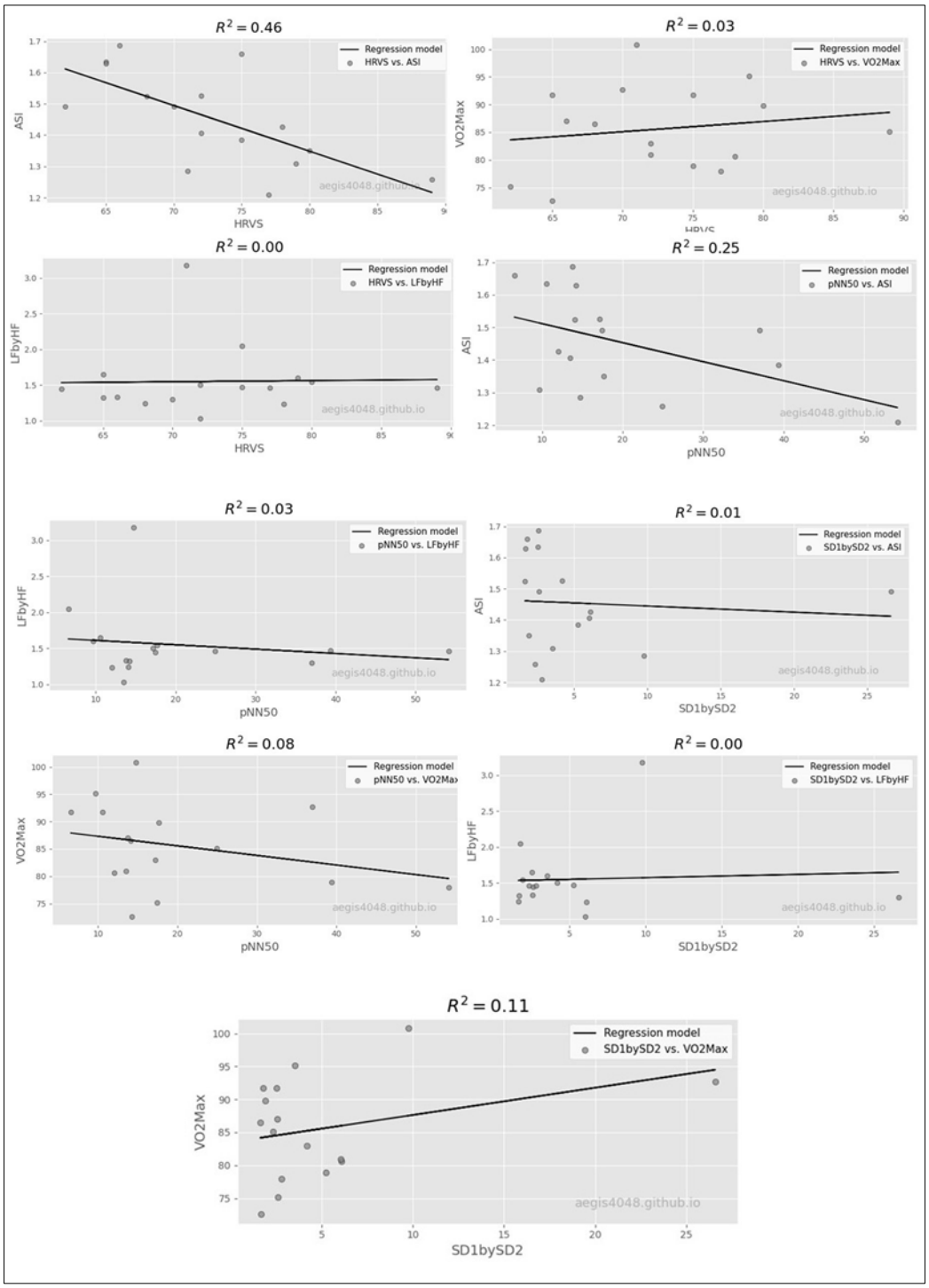


Figure 6 MLR plots

From Fig. 6, it can be noted that (a) HRVS and (b) pNN50 are related to ASI as the IR biomarker with 47% and 25% of strength, respectively. High ASI scores are associated with low values of HRVS (a biomarker of mood) and pNN50 (a biomarker of sleep), which means that frequent dysregulated mood and insomnia are two statistically significant biomarkers of arterial stiffness. Studies have shown that untreated insomnia worsens BPD through negative mood (30).

RR results signify that with mood dysregulations and sleep disorders in the BPD-rPAJ cases, the chances of risk of PAS are 10.5 and 135 higher given the baseline risk of PAS incidences in the study population (see Table 3). To calculate the statistical significance of these two observations, the upper and lower bound of CI (95%, p-value <0.05) and the respective p-values are computed (31). For the HRVS, these are 59.24 and 1.85, while for pNN50, these are 167.44 and

11.11 with the p-values of 0.02 and 0.19, respectively. Therefore, HRVS and ASI have statistically significant relationships, while pNN50 and ASI do not (p-value 0.19 that is >0.05).

Table 3 RR calculations

	ASI_A	ASI_N	RR	CI_upper	CI_lower	*p-value*
HRVS_A	14	2	10.5	59.24	1.85	0.02
HRVS_N	8	12				
pNN50_A	15	1	135	167.44	11.11	0.19
pNN50_N	2	18				

Abbreviations

ASI_A, Abnormal ASI; ASI_N, Normal ASI; HRVS_A, Abnormal HRVS, HRVS_N, Normal HRVS; pNN50_A, Abnormal pNN50; and pNN50_N, Normal pNN50.

The following x-y scatter plots (see Fig. 7) show the overall picture of BPD-rPAJ and the healthy control group concerning the age-normalized (ASI/Age) *risk of PAS*.

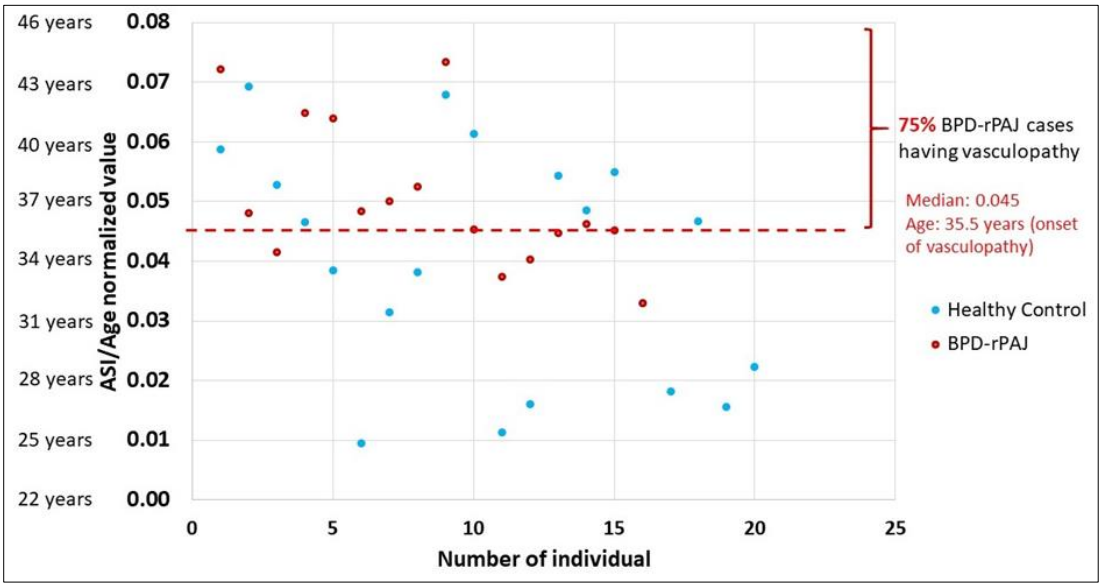


Figure 7 Parametric age-normalized scatter plots of BPD-rPAJ and Healthy control

Figure 7 shows a comprehensive picture of the risk of PAS as age advances in BPD-rPAJ cases when compared to the control. The median age of the onset of risk of PAS in this population is around 35.5 years. The mean age of BPD-rPAJ, in this study, is 30 years. Therefore, the authors, based on the observation, state that after five and a half years of the onset of BPD-rPAJ combinatorial disorder, the risk of PAS starts in the population, and mood dysregulations alongside insomnia are two significant causative parameters.

The paper projects an elaborated referential understanding of the results of the study. Currently, a large and growing body of research shows a high correlation between mental illnesses and cardiovascular diseases (CVD), which arise due to the precipitation of IR biologically or behaviorally shortening the life expectancy (32). The *hypothalamic-pituitary-adrenal axis (HPA-axis)* dysregulation (overactivity) is thought to be the key contributor to IR in neuropsychiatric illnesses (33). The primary role of the HPA axis is to react to stress, where norepinephrine plays the key role followed by cortisol (the stress hormone), secreted from the medulla and cortex of the adrenal glands, respectively. Cortisol, therefore, is the biomarker to measure the severity of mental health (34). Under stressful situations, HPA-axis overactivity causes mood dysregulations, anxiety, sleep disorders, post-traumatic stress disorders, anger, and delusional disorders, and as a result, norepinephrine is secreted in the bloodstream. It increases the heart and respiratory rate to fulfill the elevated oxygen demand by the cells, and blood pressure increases to accommodate extra

blood volume moving at a high speed (measured as pulse wave velocity (35)). The hypothalamus above the brain stem is then triggered and secretes a corticotropic releasing hormone or corticotrophin, which signals the pituitary gland to secrete an adrenocorticotrophic hormone that stimulates the adrenal cortex to secrete cortisol, the stress hormone. To combat/cope with the chronic stressors, the body requires more energy, which is obtained by increasing more sugar in the blood through glycogenolysis and gluconeogenesis in the liver cells (36). Cortisol plays the key role here as the end product of the HPA-axis hyperactivation. In the event of frequent mood dysregulations (swings) due to several external and internal stressors, sympathetic overdrive takes place at a random rate in the BPD, while rPAJ maintains the continuity of such randomness, as the authors of this paper postulate. As a result to it, the arteries need to accommodate the fast-flowing high volume of blood columns off and on, which after a time erodes the internal and then the external elastic lamina and stimulates collagen fiber synthesis and its tight interconnectivity (35). As a result, arteries become stiffer and age faster as the underlying pathogenesis advances further leading to the risk of arteriosclerosis (9). Arteritis (inflammation of the arterial wall leading to calcifications) and platelet-cholesterol aggregations (atherogenesis) then sets over time (9). Such vasculopathy is commonly noted in IR due to neuropsychiatric disorders. The PAS in the coronary arteries causes atherogenic blockades along with hypertrophic cardiomyopathies due to longstanding hypertension are the major precipitating factors of sudden early cardiac deaths, which are as early as in the 35-54 years of age group and increasing when compared to older females (37). However, other than mental illnesses, several other factors such as cigarette smoking, diabetes, obesity, and family history of CVDs also need to be inquired about to assess the cumulative risk (37).

Disturbances in the *circadian rhythm (CR)* lead to sleep phase shifts as the disorders often found in mental illnesses. Disturbed endogenous and exogeneous CR is noted in BPD (38) and r-PAJ, especially the delusional type (39). Together, there might be an emerging circadian phenotype of phase-delayed and misaligned rest-activity patterns in the affected population. As a result, the patients suffer from insomnia in the course of morbidity, primarily characterized by an exacerbated maladaptive personality, such as rage and episodes of frequent delusions. It is worth noting that during the non-rapid eye movement (NREM) sleep, BP falls by 10-20% (40), popularly known as the 'nocturnal dipping', which is essential for maintaining good cardiovascular health by giving the heart to recover from the strain it underwent when the person was awake in day-time (41). No such fall sustains night-time high BP that contributes to the development of essential hypertension and PAS, obesity, diabetes, atherogenesis, and sudden cardiac death as the sequels.

Reproductive hormones, such as estrogen, progesterone, and testosterone play significant roles in the occurrence of endothelial dysfunction and large elastic arterial stiffening due to decreased elastin-to-collagen ratio, a salient phenotype of the risk of CVD (42). Low testosterone and estrogen play a significant role in PAS as the studies have reported (42). It has been noted that the steepest drop of testosterone in females happens in their early reproductive age and stayed constantly low throughout their life (42). Estrogen also plays a vasoprotective role and a fall of it may also be responsible for premature arterial stiffening (43). Females with low estrogen-progesterone and testosterone are therefore at risk of arterial vasculopathy. There is also another side of the testosterone theory. In females with r-PAJ, it has been observed that the 'competitive' testosterone levels are increased when their partners flirt with another woman but no change in its level when their partners are engaged in passionate kissing or having a casual dialogue with another woman (44). The researchers have also observed that erotic intimacy increases testosterone while nurturant intimacy reduces it (44). Therefore, based on these findings, the authors hypothesize that nurturant females are at more risk of premature arterial stiffening, compared to erotic types. Indian females by nature are more nurturant (possess high motherly feelings) in nature and as a result, they are more at risk of premature arterial aging, though it needs to be studied. A large body of research shows that BPD is worsened a week before the onset of menstruation due to fluctuations of 17β-estradiol (estrogen) and progesterone (P4) although the finding is not consistent for all females (44). The study shows that a high level of P4 in the luteal phase and intense fluctuations in the estradiol during the ovulation worsen the emotional expression (the affect) in the BPD cases (44). Now, when compounded with r-PAJ, the authors hypothesize that reproductive hormones play a significant role in modulating and worsening the expressed emotions in these females and thereby affecting their arterial health.

In the *neuropsychiatry* of BPD-rPAJ, the impulsivity seen in BPD is often amygdala-based, where amygdala hyperactivation to negative emotions is coupled with inhibited frontal regulation (45). *Testosterone* plays a significant role in stimulating amygdala-based aggression repetitively. Together, it causes PAS due to the randomly flowing of the rage-induced high volume of blood at a high velocity, as mentioned before. The rPAJ involves several areas of the brain as imaging studies have shown. One of the most important areas is the ventromedial frontal cortex (6). Connective dysregulations in it result in the generation of affective meaning, and habit formation when mingled with basal ganglia. In this context, the aberrated dopaminergic and serotonergic signals due to erratic prefrontal and dorsal striatal connections play a significant role in transforming jealousy into habitual behavior in the affected population (6). Jealousy is the other form of competitional stress leading to fluctuating testosterone and estrogen in the blood causing arterial stiffness in females (46).

The *key points*, discussed above, are as follows:

- BPD-rPAJ cases show a higher risk of developing MS/IR (e.g., CVD), marked by an early arterial wall stiffening and enhancing faster vascular aging.
- HPA-axis dysregulations poorly influence their body's physiology of handling stress in the early reproductive age group and affect vascular health early.
- Disturbances in the CR, affect the mood and thereby as a consequence, affects vascular health.
- Fluctuations, in the reproductive hormones, especially too high and too low levels, play crucial roles in the psyche as well as in the vascular health adversely, and
- The erratic interconnections between the ventromedial prefrontal cortex with the prefrontal cortex and striatum, and strong connections with the basal ganglia characterized by disturbances in the dopaminergic and serotonergic signals, transform jealousy into habitual behavior that, if remains uncontrolled, leads to PAS in the vulnerable population.

Therefore, using the non-invasive, ubiquitous, and user-friendly Lyfas biomarker instrument, COBs that surrogate the mood (HRVS) and sleep quality (pNN50), could be much useful in screening the vascular health (ASI) of the psychiatric cases. For a clinician, it could be an advantage. However, parameters, such as obesity, diabetes, hormonal disorders, hypertension, substance abuse, cigarette smoking, family history of CVD, and when possible, brain scans may be considered for getting a holistic view to diagnose the deadly triad of *mental illness-IR-PAS* in the population at risk.

4. Conclusion

BPD-rPAJ combination is risky to develop CVD through PAS in females. The onset of PAS is about 5.5 years from the onset of BPD-rPAJ, as evident in this study. Lyfas COBs could be useful to screen it early just by smartphones in a non-invasive and pervasive manner. The method can be used for the epidemiological survey of the dreaded combination of *mental illness-IR-PAS* in the global population. Medical professionals such as doctors and nurses could be trained in Lyfas application and interpretations for early screening of IR in mental health in broader ways.

Compliance with ethical standards

Acknowledgments

The authors gratefully acknowledge the guidance of the psychologists.

Disclosure of conflict of interest

The authors declare no potential conflict of interest concerning the research, authorship, and/or publication of this article.

Statement of ethical approval

The study protocol has been approved by the review board of Vagus Institutional Ethics Committee, Bengaluru, Karnataka, India, Approval number: ECR/1181/Inst/KA/2019, dated 30-01-2020. It is registered with the Central Drugs Standard Control Organization, Ministry of Health and Family Welfare, Govt. of India.

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.

Author contribution

RD has created the Lyfas application, designed the study, and conducted data collection and preprocessing. SC has analyzed the data in-depth, correlated it clinically, and written the paper. Both authors have reviewed the final manuscript.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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