Original Research Article

Statistical Validation of LENS: A Smartphone-based Empty Nest Syndrome Screening and Monitoring Biomarker Tool

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ABSTRACT

Background: Empty Nest Syndrome (ENS) is a complex grief state, observed in the affected parents when their children leave home. Studies show ENS may progress to clinical-grade depression and anxiety if left uncared for.
Methodology: In this double-blind case-control cross-sectional study, 80 subjects are recruited by a panel of psychologists and psychiatrists. Subjects are divided into two equal groups – case (with ENS symptoms) and control (without symptoms). Three instruments are applied – a) ENS interpretation by the psychologists based on the symptoms, b) Lyfas smartphone-based biomedical application to capture the cardiovascular optical biomarkers (COB) from the index finger non-invasively with the help of arterial photoplethysmography technique, and c) Hamilton's depression scales (HAM-D), which psychiatrists have used to check the mental health of the subjects. The COB (e.g., SD1/SD2, LF/HF, HRVScore, and ENERGY) and a set of physical parameters (e.g., Body mass index or BMI, Heart rate or HR, Systolic blood pressure or SBP, Diastolic blood pressure or DBP, Glycosylated hemoglobin or HbA1c, Cholesterol, Triglyceride, Thyroid-stimulating hormone or TSH, Estradiol or E2, and Testosterone or TST) consist the independent variables, while ENS scores interpreted by the psychologists and HAM-D scores interpreted by the psychiatrists are the dependent variables. Spearman's rank correlation and Bland Altman's reliability tests are performed to mine the significant independent variables and reliability of Lyfas ENS (LENS) application.
Results: The study observes that SD1/SD2, LF/HF, HRVScore, ENERGY, DBP, BMI, HR, HbA1c, TSH, and Estradiol have significant roles in ENS. Bland Altman's reliability measure shows that LENS (novel instrument under trial) has a high agreement of 92.85% and 93.86%, respectively with ENS scoring done by senior psychologists (champion instrument1) and HAM-D grading performed by psychiatrists (champion instrument2).
Conclusions: LENS can be used as a clinical-graded pocket application for screening and monitoring ENS.

Keywords: Lyfas; Empty Nest Syndrome; Cardiovascular Optical Biomarkers; Hamilton Depression Scale

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INTRODUCTION

ENS is not a clinical entity under the Diagnostic and Statistical Manual – V (DSM-V), however, it is listed in the International Classification of Diseases (ICD)-11 under "Other Associated Problems with Social or Cultural Environment" (Code: QE0Y) [1]. However, it is a well-observed psychological phenomenon among the parents in society for five decades, mostly in the developing nations [2], when their children leave home for a job or higher educational purposes or marriage [3]. In recent days, offices and institutions are opening in India and overseas, causing children to move out to chase their dreams. It is a sudden disjoint in the family that enjoyed the togetherness during working from home, attending online classes, and so forth. The sudden news of the expectant departure of the children poses to be psychologically shocking to the parents. Some are trapped within the ENS, a term applicable for the parent birds' mental grief when their grown-up chicks leave the nest [4]. The grief is mostly distributed around the loneliness due to the

disassociation with the children. Middle-aged parents in our society also face a similar grief state, which usually lasts for 2 weeks [5] following the departure of the children, especially when the youngest one departs [2]. Indians prefer joint families, where middle-aged parents cohabitate with their grown-up adult children. These parents are stuck within the intergenerational gap and their generations are called the sandwich generation [2]. Given a situation, when these children leave, the jolt is even higher on them. However, the duration of the symptoms and signs can be extended, even for months instead of the conventional 2 weeks duration as the duration is not specified in the available literature. It could pose a subtle risk of developing depression unless intervened [6] [7] [8].

The QBIs are used to screen and monitor ENS in various sociocultural setups to measure the love bonding in the families. ENS screening is currently made with Questionnaire-based instruments (QBIs) having variable reliabilities [9]. Mothers, being the primary caregivers since birth, are mostly disturbed psychologically as they are no longer been gratified by serving or taking care of their children, known as the 'shrinking circle stage' [10]. The psychological impact is even worse in the case of widows and divorced women as they are devoid of any partner-led emotional support [11]. Cumulative or sequential comorbidities, such as diabetes mellitus [12], cardiovascular diseases [13], malnutrition [14], dyslipidemia [15], etc., menopausal or perimenopausal syndrome due to persistent estrogen (E2) depletion in the body [16], loss of jobs [17], lack of sexual intimacy [18], and so forth are related indicators to that of the ENS and its severity. Studies have found that fathers too are affected by the departure [19]. This is one side of the issue. While, on the other side, increased personal spaces, restored conjugal intimacies, elevated mood as a result of positive thinking of the prosperity of the children, enriched societal mingling, and so forth try to compensate for that disassociation-induced psychological trauma, as the authors of this work have noted while speaking to the participants. The QBIs, therefore, bring holistic psychological snapshots of the test-takers. However, an inherent issue of QBI is that the answers to the questions can be falsified as per the wish of the test-takers or under any unwanted influence.

Mobile health (mHealth) is gaining popularity due to its non-invasive and pervasive nature. Optical sensors in the smartphone camera capture the Heart rate variability (HRV) and its correlated optical biomarkers to evaluate the cardiac autonomic modulation (CAM) from the index finger capillary circulation using the method of arterial photoplethysmography and various signal processing/filtering techniques. HRV correlates are much influenced by the state of mental health, as related research has already shown [20]. Lyfas is a smartphone-based cardiovascular optical biomarker (COB) instrument that is commercially available. Its proprietary heuristics classifies the biomarkers as per their physiological significance [21]. Hence, the physiological data captured by Lyfas can not be tampered with or falsified as per the wish of the test-takers. This is an inherent advantage of Lyfas as a research instrument over QBI and is hence used in this study.

The rationale of the study

Depression in the elderly population is gaining the number steadily in India. Hopelessness, suicidality, organic mental illnesses are increasing in number as well. Post COVID-19 3rd wave (Omicron), the Indian families are suddenly experiencing that children are leaving homes due to employment, education, and marital causes. The parents suddenly do not see them around and start suffering from 'low' feelings.

Over 85 such cases have reached Acculi Labs Pvt. Ltd. Which is an m-healthcare organization situated in Bangalore India for assistance. Some of them have clinical symptoms of depression. The lab with the help of its clinically validated product namely Lyfas, two psychologists and psychiatrists each has therefore pursued this study to examine the concept of ENS in the suspected population.

Hypothesis

- Cardiovascular biomarkers alongside the physical parameters can unfold the subtle depression risk in ENS, and
- Lyfas ENS (LENS) can be a reliable ENS monitoring tool for early assessment of the mental and metabolic risks in the vulnerable population.

Objective: Identifying meaningful COB and physical biomarkers as a screening process of ENS in the vulnerable groups.

METHODOLOGY

In this section, the study protocol, population selection, and statistical analysis are discussed.

Study protocol

Ethical committee clearance

The study protocol is submitted by Acculi Labs Pvt. Ltd., Bangalore, Karnataka, India has been approved by the Vagus 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).
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.

Place and Type of study

It is an online double-blind case-control cross-sectional study conducted at Acculi Labs Pvt. Ltd. Bangalore India that has developed a clinically validated smartphone-based optical healthcare biomarker instrument, called Lyfas [21]. Lyfas is a CE and ISO certified commercially available instrument that provides a holistic snapshot of the mind-body homeostasis in the test takers.

ENS symptoms

There are different types of symptoms that exist; however, in this work, the following three are the most occurring symptoms [22],

1. Sadness or grief reaction
2. Worries or fear, and
3. Emptiness.

Subjects having at least two symptoms are considered as 'having ENS' designated as '1' in the data matrix otherwise '0' in this study as per the advice of two senior psychologists.

Solitary symptom	**%**
1	30
2	30
3	40
Symptom combination	**%**
1, 2	25
1, 3	68
2, 3	07

Therefore, emptiness is the major attribute at the backdrop of ENS.

Population distribution

Case (N = 40)

The case group consists of those whose children left home and are suffering from the above-mentioned ENS symptoms for a month or even more. Their distributions are as follows:
Males: 50 – 60 years – 13 (65%); Females: 50 – 60 years – 10 (50%);
Males: 61 – 70 years – 07 (35%); Females: 61 – 70 years – 10 (50%).

Control (N = 40)

The Control group consists of those whose children moved out before a month but they are not suffering from any ENS type of symptoms.
Their distributions are as follows:
Males: 50 – 60 years – 07 (35%); Females: 50 – 60 years – 10 (50%);
Males: 61 – 70 years – 13 (65%); Females: 61 – 70 years – 10 (50%).

Duration of study and the team

Two months – 1st November 2021 till 31st December 2021.

The team consists of two data operators, psychologists, psychiatrists, and one data scientist.

Instruments used

- **Lyfas Non-invasive Optical Biomarker Instrument (Lyfas) [21]**

Lyfas is a clinically validated optical biomarker healthcare (mobile health or m-health) instrument, which works based on the principle of reflectant arterial photoplethysmography and photochromatography. It works on the Android OS version 7 or over. In India, the number of Android smartphone users is the highest and hence, the technology has much higher coverage among the test-takers. Its' multilingual voice-assisted technical support has made it user-friendly. Post-test, Lyfas provides the mind-body analytics report to the test-taker. The report is created using its AI/ML and heuristics-based analytics.

Recently, Lyfas has been successfully trialed in screening and monitoring sub-clinical depression and its other adverse consequences on mental health, hypertension-anger-anxiety triad, perimenopausal anger traits, and pandemic-related mental health issues. Starting the test to the generation of the report takes on an average of 5 minutes. It can be applied to all age groups above toddlers. Lyfas is commercially available as a screening and monitoring instrument for mind-body homeostasis. It is important to note that the clinical efficacy of Lyfas has been tested in screening and monitoring the sub-clinical state of depression during the COVID-19 period [20] and Stress Anxiety Depression (SAD) state during the COVID-19 pandemic period [23], mapping the triad of hypertension-anxiety-anger [24], anger in perimenopausal women [25], and cardiac risk screening [26] [27] and found reliable. Lyfas has also been found as a reliable biofeedback instrument when compared to the gold standard biofeedback instrument, namely the Polar H10 sensor and Kubios software [28]. Lyfas has also been successful in estimating arterial stiffness in the vulnerable population [29]. Hence, it is a versatile m-health instrument, which could be envisioned as the future generation of digital healthcare.

In this study, an attempt has been made to develop a Lyfas optical biomarker-based ENS estimation tool or *LENS*.

- **Hamilton Depression Scale as the QBI (HAM-D) [30]**

It is a gold standard 17-item 5-point scale (score 0, 1, 2, 3, and 4 as absent, mild, moderate, severe, and incapacitating, respectively) to assess and monitor the severity of depression in adults. Assessment has been conducted every two weeks. The average administration time is about 20-30 minutes. Rating is done by the clinicians and not by the test-takers. The minimum HAM-D score is '0', while the maximum is '68'. Scores between 10 – 13, 14 – 17, and >17 are considered to be 'mild', 'mild-to-moderate', and 'moderate-to-severe' depressions, respectively.

In this paper, Lyfas is a novel optical biomarker healthcare instrument, which is hypothesized as having a good or strong agreement with psychologists-envisioned ENS probability (Instrument – 1) and wisdom of psychiatrists in HAM-D scorecard (Instrument – 2).

Data collection

An online questionnaire is posted on the web. Participants' age, gender, and answers to the questions are noted. Their identities are kept confidential throughout the study. After informed consent is obtained, all participants are subjected to Lyfas tests, HAM-D tests, and relevant laboratory tests. Those who are under anti-depressive, anti-psychotic, and or anti-anxiety medications are excluded from the study. Also, those with serious comorbidities, such as cancers, cardiovascular diseases, are excluded.

Timing of the tests

- Lyfas tests: taken thrice daily at 7 am, 2 pm, and 10 pm in a relaxed position for three days per week for eight weeks (total 72 tests per participant)
- HAM-D tests: performed on the day of the second Lyfas test for better correlations of optical biomarkers that Lyfas captures and analyses with that of the HAM-D scores (total 4 tests)
- Laboratory tests are performed on the same day when HAM-D tests are taken once a month (total 2 tests).

It is important to mention that the average of all scores is considered to construct the data matrix (row x column), a sample of which can be viewed in Table 2.

Parameter selection

Table 1 shows the biomarker parameters, selected in this work. It is worth noting that social constructs, such as attachment, education level, financial conditions, etc. are not considered in this work. The authors would consider these parameters as the future extension of this work.

Table 1: Parameters were chosen to study ENS

No.	Physical parameters	Range	No.	Optical biomarkers	Range
1	Body mass index (BMI)	18.5-24.9	**1**	SD1/SD2 (anxiety biomarker)	0.9-3.3
2	Heart Rate (HR)	60-100 bpm	**2**	LF/HF (anger biomarker)	0.7-1.8
3	Systolic Blood Pressure (SBP)	<120 mmHg	**3**	HRVScore or HRVS (mood biomarker)	>75
4	Diastolic Blood Pressure (DBP)	<80 mmHg	**4**	ENERGY or EN (mood biomarker)	40-90 mJ/Kg^2
5	Glycosylated Hemoglobin (HbA1c)	<6.1-<6.5%			
6	Cholesterol (CH)	<200 mg%			
7	Triglycerides (TG)	<150 mg%			
8	Thyroid Stimulating Hormone (TSH)	0.4-4mIU/L			
9	Estrogen (E2)	Premenopausal: 30-400 pg/ml; ERT-naïve Postmenopausal: 0-30 pg/ml Males: 10-40 pg/ml			
10	Testosterone (TST)	Males in their 50s: 215-878 ng/dl Males in their 60s: 196-859 ng/dl Males in their 70s: 156-819 ng/dl Females 15-70 ng/dl			

Table 2: A sample data of ten cases

No	BMI	HR	SBP	DBP	HbA1c	CH	TG	E2	TST	TSH	SD1/SD2	LF/HF	HRVS	EN	ENS	HAM-D
1	27.5	90	160	85	9	220	284	27	370	4	3.27	1.5	90.2	57.74	1	6
2	19.9	121	146	80	8	187	187	47	687	4	2.78	0.9	87.7	43.65	1	12
3	26.2	53	100	96	5	246	299	13	909	1	1.12	0.4	85.8	39.94	1	9
4	26.5	74	146	124	10	216	161	17	596	4	0.97	0.5	88.9	99.04	0	11
5	16.9	69	132	84	5	153	171	46	525	1	4.85	1.7	83.3	137.23	1	6
6	28.6	58	123	69	5	204	178	27	860	1	1.13	0.7	77.8	58.13	1	8
7	22.9	97	137	104	6	153	207	38	344	1	1.46	1.4	89.7	113.08	0	12
8	25.6	49	168	71	7	205	132	33	680	3	0.81	1.2	87.8	30.83	1	7
9	23.9	71	149	84	12	201	235	51	496	2	0.81	1.4	88.9	96.88	1	5
10	23.7	75	155	106	8	273	147	34	353	3	11.53	0.8	80.7	51.8	0	4

Statistical analysis

Following statistical analysis is performed gender (male and female) and age-group-wise (50 – 60 years and 61 – 70 years).

Basic statistics

- Descriptive statistics is performed to note the data distribution by examining minimum values (min), maximum values (max), mean, median, standard deviation (stdev), and quartile values, i.e., Q1 (25%), Q2 (50%) or median, Q3 (75%) distributions [31]
- Data distribution (normality check by Shapiro-Wilk test) [32]
- Data fidelity/internal consistency check (Cronbach's alpha test) [33].

Significance tests to mine the statistically significant biomarkers to gain insight in assessing the occult state of depression as in ENS or overt clinical state of depression as evident in HAM-D scores by

- Spearman's correlations measures, where the correlation coefficient values are positive (>0.0) or negative (<0.0), or non-correlated (close to 0.0) [34].

Bland-Altman reliability test [35] to examine the degree of agreement between the Lyfas optical biomarkers (novel instrument) to ENS (assessed by two psychologists, i.e., human wisdom-based champion instrument-1) and HAM-D (assessed by two psychiatrists, i.e., human wisdom-based champion instrument-2). A strong agreement is referred to as minimum proportional bias.

RESULTS

In this section, results are displayed which are obtained by performing the analysis. In section 4, elaborations of the results are made.

Descriptive statistics

Table 3a-d showcases the descriptive statistics gender and age-group-wise.

Table 3a: Results of descriptive statistics of male 50 – 60 years age group

	count	mean	Std	min	25%	50%	75%	max
BMI	20	25.055	3.55	16.9	23.425	25	26.75	32.7
HR		72.6	24.30	0	64	74.5	87.25	121
SBP		140.8	24.26	100	124.5	146	161.5	174
DBP		91.35	17.41	67	77.75	92.5	104.5	124
HbA1c		7.85	2.25	5	6	7.5	9.25	12
Chol		217.25	34.41	153	203.25	214.5	235.5	295
TG		195.4	51.44	132	159.75	180	223	299
E2		32.8	12.79	13	21.75	33.5	44.5	52
TST		695.6	236.23	344	491.75	687.5	904.5	1072
TSH		2.85	1.46	1	1	3	4	5
SD1BYSD2		2.919	2.45	0.81	1.1275	2.5	3.7475	11.53
LFBYHF		1.155	0.48	0.4	0.8	1.05	1.425	2.4
HRVSCORE		85.56	4.27	77.8	82.975	86.75	88.9	91.5
ENERGY		73.658	43.81	20.51	38.645	54.77	107.5375	157.84
ENS		0.65	0.49	0	0	1	1	1
HAM-D		8.3	2.64	4	6	8	10.25	12

Table 3b: Results of descriptive statistics of female 50 – 60 years age group

	count	mean	Std	min	25%	50%	75%	max
BMI	20	27.42	5.09	19.90	24.30	27.45	28.95	41.80
HR		85.15	11.69	63.00	76.25	86.00	93.25	107.00
SBP		137.10	24.28	104.00	117.25	133.50	156.25	176.00

DBP		97.40	17.88	60.00	88.50	95.50	111.50	123.00
HbA1c		8.60	2.09	5.00	7.00	8.50	10.00	12.00
Chol		227.65	41.85	156.00	203.00	234.00	253.75	296.00
TG		216.70	57.66	133.00	163.00	210.00	270.50	297.00
E2		179.75	107.34	41.00	84.75	163.50	249.25	401.00
TST		50.05	18.54	18.00	35.00	52.00	70.25	72.00
TSH		2.90	1.21	1.00	2.00	3.00	4.00	5.00
SD1BYSD2		2.32	2.20	0.43	1.00	1.48	2.65	8.71
LFBYHF		1.32	0.92	0.60	0.90	1.10	1.43	5.00
HRVSCORE		82.52	7.29	63.10	79.10	83.60	87.58	93.20
ENERGY		68.04	43.69	17.59	38.91	58.36	84.99	198.70
ENS		0.50	0.51	0.00	0.00	0.50	1.00	1.00
HAM-D		7.90	2.55	4.00	6.00	8.50	10.00	12.00

Table 3c: Results of descriptive statistics of male 61 – 70 years age group

	count	**mean**	**Std**	**min**	**25%**	**50%**	**75%**	**max**
BMI	20	25.27	2.78	22.00	22.85	24.65	27.35	30.40
HR		71.90	14.75	33.00	65.00	72.00	82.00	97.00
SBP		138.35	28.73	101.00	113.00	138.00	165.50	179.00
DBP		101.40	15.02	66.00	94.00	105.50	112.75	122.00
HbA1c		8.15	2.01	5.00	7.00	7.50	10.00	12.00
Chol		216.65	48.99	150.00	172.00	211.50	245.50	299.00
TG		205.70	47.78	133.00	179.25	195.00	244.25	290.00
E2		31.05	14.90	11.00	19.50	30.50	43.00	53.00
TST		703.90	297.07	285.00	427.25	759.00	993.75	1097.00
TSH		2.60	1.39	1.00	1.00	2.50	4.00	5.00
SD1BYSD2		4.00	5.07	0.52	1.39	2.13	4.06	22.46
LFBYHF		1.17	0.56	0.40	0.90	1.00	1.20	2.50
HRVSCORE		83.23	4.98	71.40	81.08	83.10	84.40	97.40
ENERGY		80.57	44.45	22.10	48.32	70.46	104.04	191.77
ENS		0.35	0.49	0.00	0.00	0.00	1.00	1.00
HAM-D		7.20	2.75	4.00	5.00	6.50	10.00	12.00

Table 3d: Results of descriptive statistics of female 61 – 70 years age group

	count	**mean**	**std**	**min**	**25%**	**50%**	**75%**	**max**
BMI	20	26.60	4.96	18.00	21.90	26.65	29.00	37.90
HR	20	70.85	26.60	0.00	68.75	78.50	82.00	106.00
SBP	20	141.20	24.57	103.00	120.75	140.00	166.25	179.00
DBP	20	94.75	19.92	61.00	80.75	95.00	114.00	121.00
HbA1c	20	8.75	2.15	5.00	7.00	9.00	10.25	12.00
Chol	20	230.75	45.29	155.00	199.25	224.00	271.00	297.00
TG	20	214.05	51.91	131.00	172.00	222.50	256.00	285.00
E2	20	14.80	10.10	0.00	6.75	16.50	23.50	29.00

TST	20	41.70	16.50	17.00	26.00	40.00	51.25	72.00
TSH	20	3.10	1.45	1.00	2.00	3.00	4.00	5.00
SD1BYSD2	20	3.74	5.62	0.73	0.96	1.23	2.78	23.80
LFBYHF	20	1.34	0.43	0.70	0.98	1.35	1.63	2.00
HRVSCORE	20	82.54	4.36	72.90	79.30	84.00	85.65	89.50
ENERGY	20	92.42	52.11	19.41	56.07	82.76	127.82	193.47
ENS	20	0.50	0.51	0.00	0.00	0.50	1.00	1.00
HAM-D	20	7.20	2.44	4.00	5.00	7.00	9.00	12.00

In the above tables, higher values are indicated by red-filled cells.

3.2. Normality check (Shapiro-Wilk test)

Table 4 shows the statistic and p-values gender and age-group-wise. For normally distributed data, the expected statistics score is less than the critical value of the significance level and p-values over 0.05 (CI 95%).

Table 4: Shapiro-Wilk Test

	Statistics score	**p-value**	**Interpretation**
Male 50-60 years	0.578	0.00001	Not normal
Female 50-60 years	0.833	0.00002	Not normal
Male 61-70 years	0.557	0.0003	Not normal
Female 61-70 years	0.807	0.0001	Not normal
Average for the population:	0.69375	0.000108	Not normal

3.3. Internal consistency check (Cronbach's alpha test)

Table 5 shows the alpha-values gender and age-group-wise for the study population. For judging the internal consistency of the data, the expected alpha value is expected to be close to 1.0 [36]. For this population, the average alpha value is moderately good (>0.6) [36].

Table 5: Cronbach's alpha Test

	Alpha
Male 50-60 years	0.637
Female 50-60 years	0.733
Male 61-70 years	0.557
Female 61-70 years	0.807
Average for the population:	**0.6835**

3.4. Spearman's correlation measure

Fig. 1a-d. Shows the item-wise correlation and its heatmap for visualization, gender, and age-group-wise. Table 5 mentions the respective p-values. The correlations having p-values <0.05 are said to be statistically significant. High correlation values i.e., values close to 0.5 and above (whether it is positive or negative) are considered in this study.

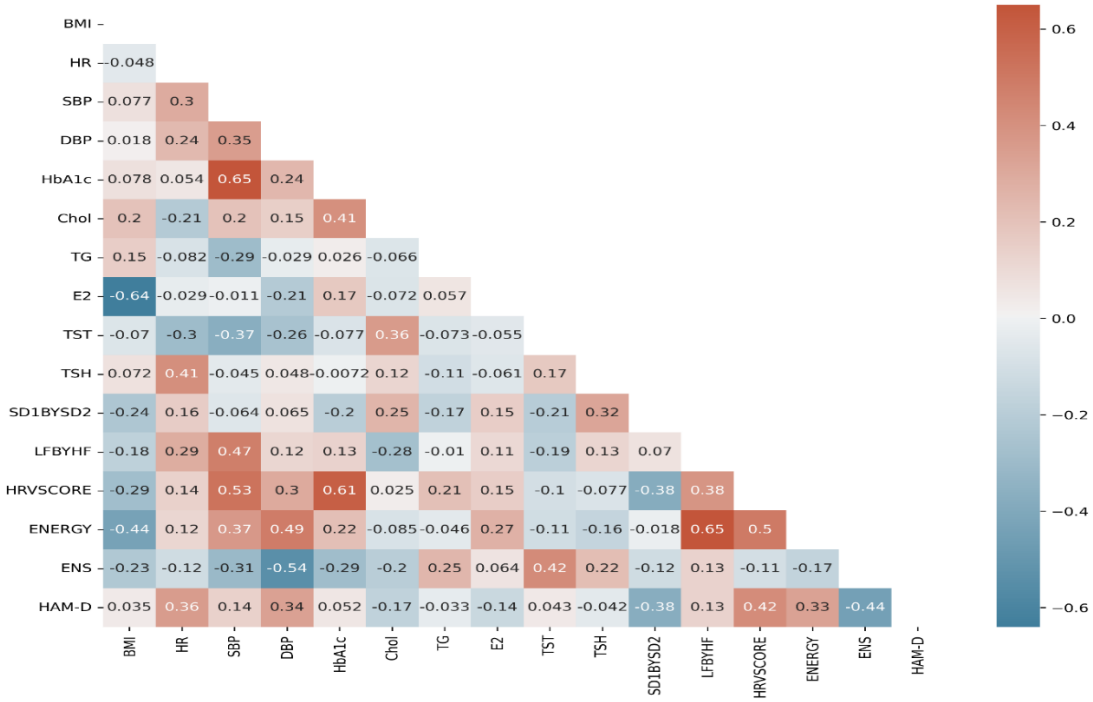


Fig. 1a: Correlation heatmap in males within the age group of 50-60 years.

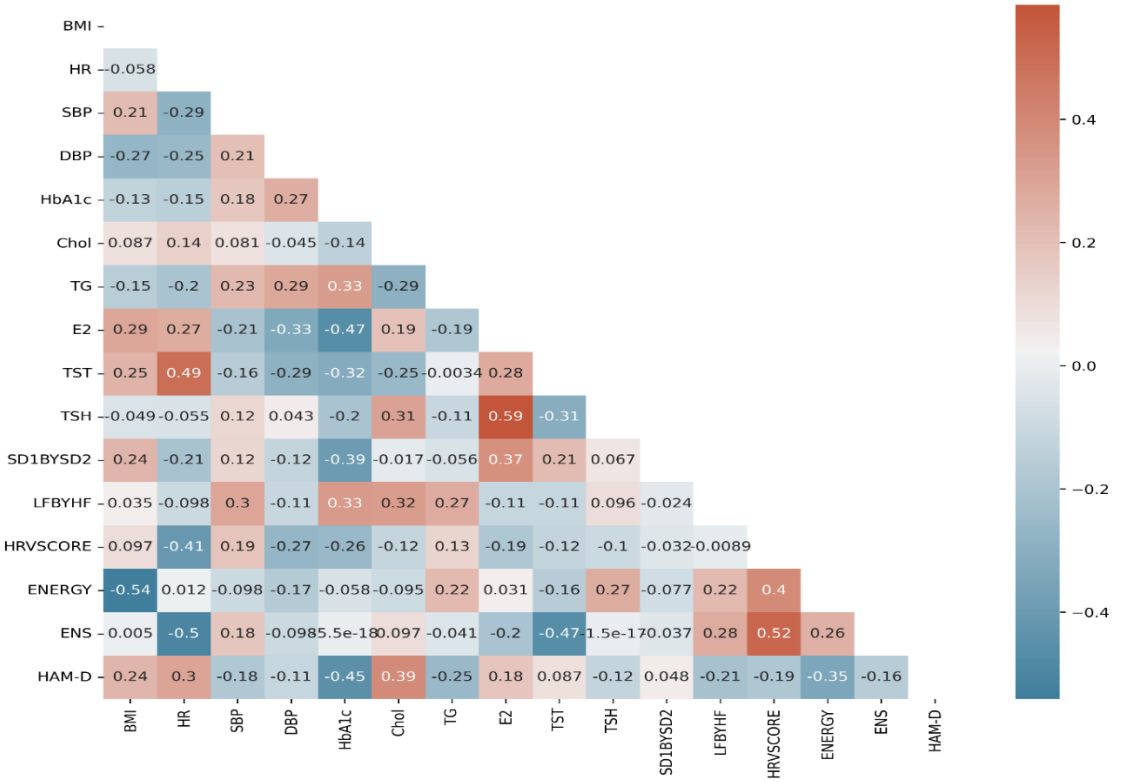


Fig. 1b: Correlation heatmap in females within the age group of 50-60 years.

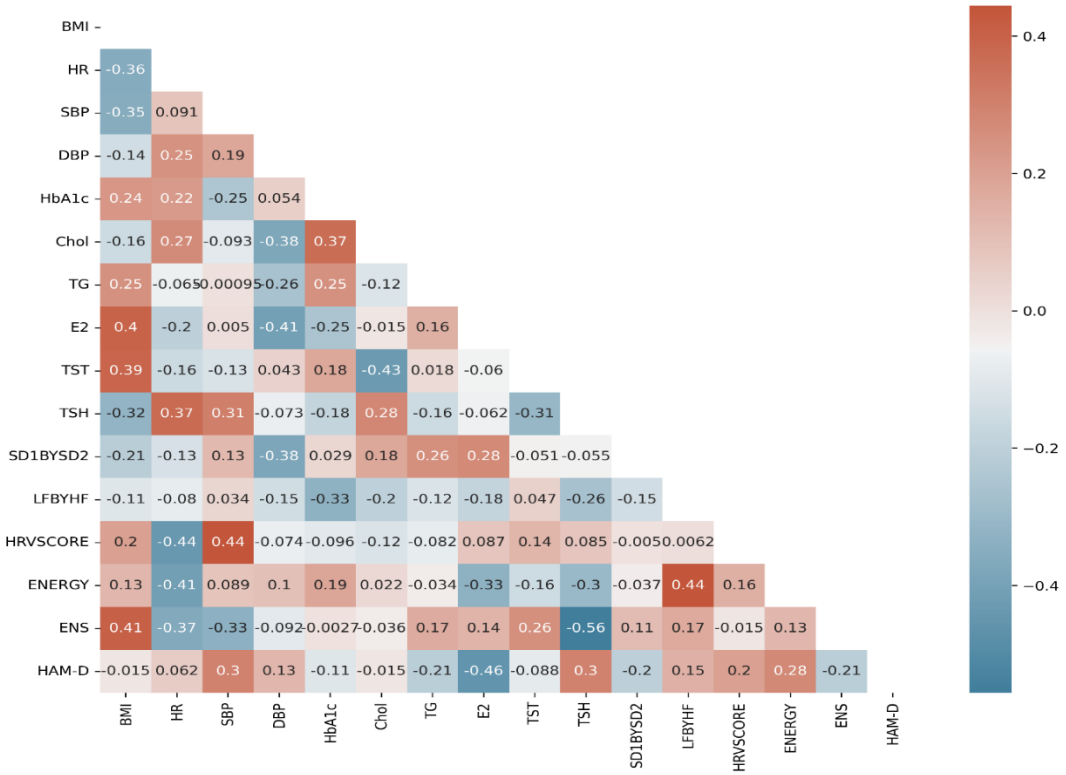


Fig. 1c: Correlation heatmap in males within the age group of 61-70 years.

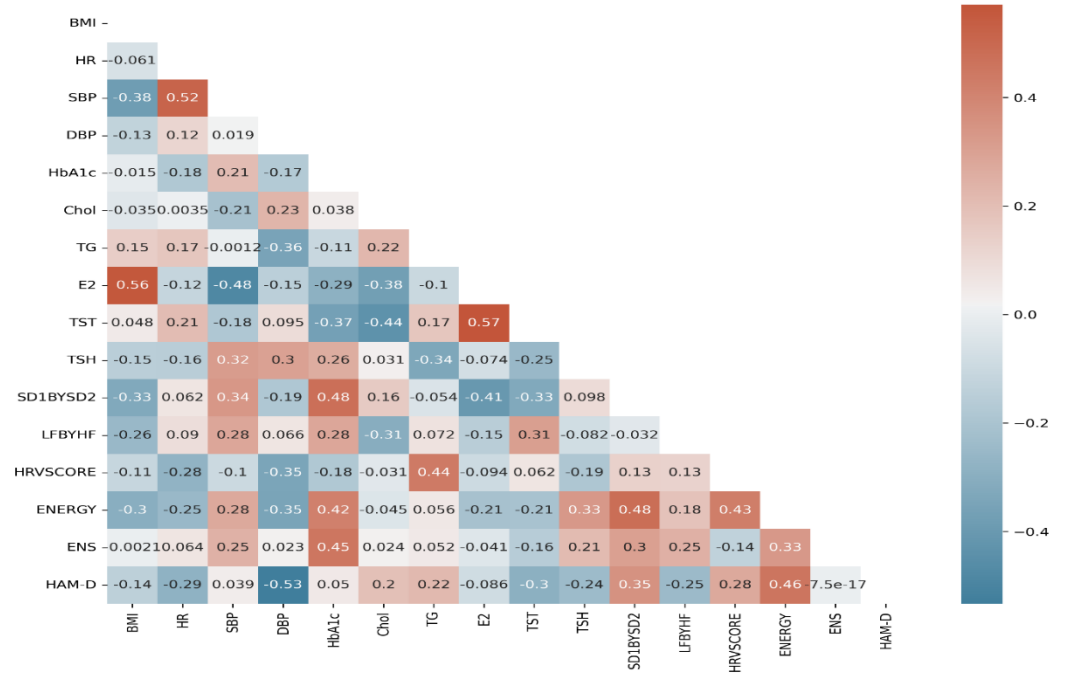


Fig. 1d. Correlation heatmap in females within the age group of 61-70 years.

Table 5 shows the snapshot of the biomarkers, which have high inter-correlation coefficient values and are statistically significant (p-value <0.05).

Table 6: Pairwise statistically significant correlations (p-values <0.05)

No	Parameter-1	Biomarker type	Parameter-2	Biomarker type	Correlation-score	p-values
1	LF/HF	Lyfas	ENERGY	Lyfas	0.65	0.0025
2	HRVScore	Lyfas	HbA1c	Physical	0.61	0.0201
3	BMI	Physical	E2	Physical	*-0.64*	0.0014
4	HRVScore	Lyfas	ENS	NA	0.52	0.0142
5	HR	Physical	ENS	NA	*-0.5*	0.0401
6	E2	Physical	HAM-D	NA	*-0.44*	0.0319
7	ENS	NA	TSH	Physical	*-0.56*	0.1008
8	HbA1c	Physical	ENS	NA	0.45	0.4501
9	ENERGY	Lyfas	HAM-D	NA	0.46	0.4911
10	DBP	Physical	HAM-D	NA	*-0.53*	0.1109
11	SD1/SD2	Lyfas	ENERGY	Lyfas	048	0.0029

From Table 5, the following observations are made:

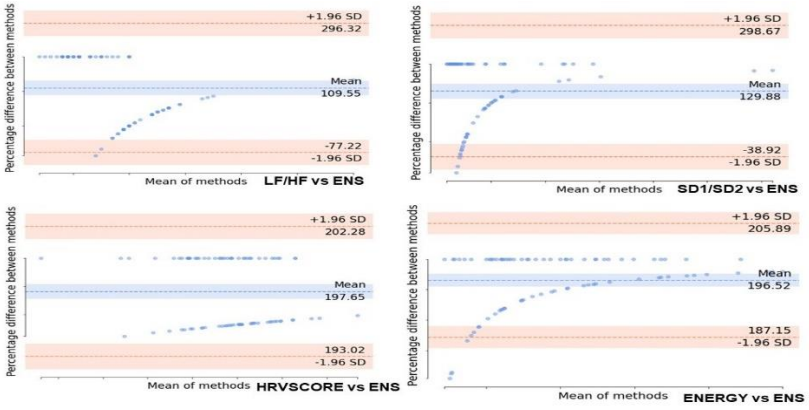
- High correlating statistically significant optical biomarkers are LF/HF, ENERGY, HRVScore, and SD1/SD2, i.e., 100% of all considered in this study
- High correlating statistically significant optical biomarkers are BMI, HR, E2, HbA1c, DBP, and TSH i.e., 60% of all considered in this study
- With 100% optical biomarkers and 60% physical biomarkers, ENS state to depression (HAM-D) can be studied, and further, it has been estimated that
    - Significant correlations within the optical biomarker group are 1 (**LF/HF** and **ENERGY**), 11 (**SD1/SD2** and **ENERGY**) **(18%)**
    - Significant correlation within the physical biomarker group is 3, i.e., **BMI (9%)**
    - A significant correlation between optical and physical biomarker groups is 2 (**HRVScore** and **HbA1c**) **(9%)**
    - Significant correlations between optical biomarkers and ENS and HAM-D: 4 (**HRVScore** and ENS), 5 (**HR** and HAM-D), 9 (**ENERGY** and HAM-D) **(27%)**
    - Significant correlations between physical biomarkers and ENS and HAM-D: 6 (**E2** and HAM-D), 7 (**TSH** and ENS), 8 (**HbA1c** and ENS), and 10 (**DBP** and HAM-D) **(36%)**.

Therefore, cumulatively, 54% (18 + 9 + 27)% of significant statistical correlations are contributed by optical biomarkers, obtained from Lyfas. In the next section, the inter-rated reliabilities (degrees of agreement) among the ENS (given by a pair of psychologists), HAM-D scores (obtained from three senior psychiatrists), and Lyfas as a clinical m-heath instrument are measured.

3.5. Bland-Altman reliability assessment Lyfas biomarkers (novel m-health instrument) vs. HAM-D and ENS (two champion human instruments), ENS vs. HAM-D for the whole population

Fig. 2 displays the reliability assessment as follows:

Lyfas biomarkers vs. ENS



2a: Lyfas optical biomarkers (novel instrument under reliability study) vs. ENS (Instrument – 1, scoring done by psychologists).

The study shows that the proportional bias between Lyfas optical biomarkers and ENS probability is 7.15 with the Stdev of 2.71, which means the limit of agreement between Lyfas optical biomarkers and ENS probability, estimated by the experienced psychologists is **92.85%** that is appreciable for a 'novel' instrument against psychologists (expert human instrument – 1), which is the 'champion' instrument.

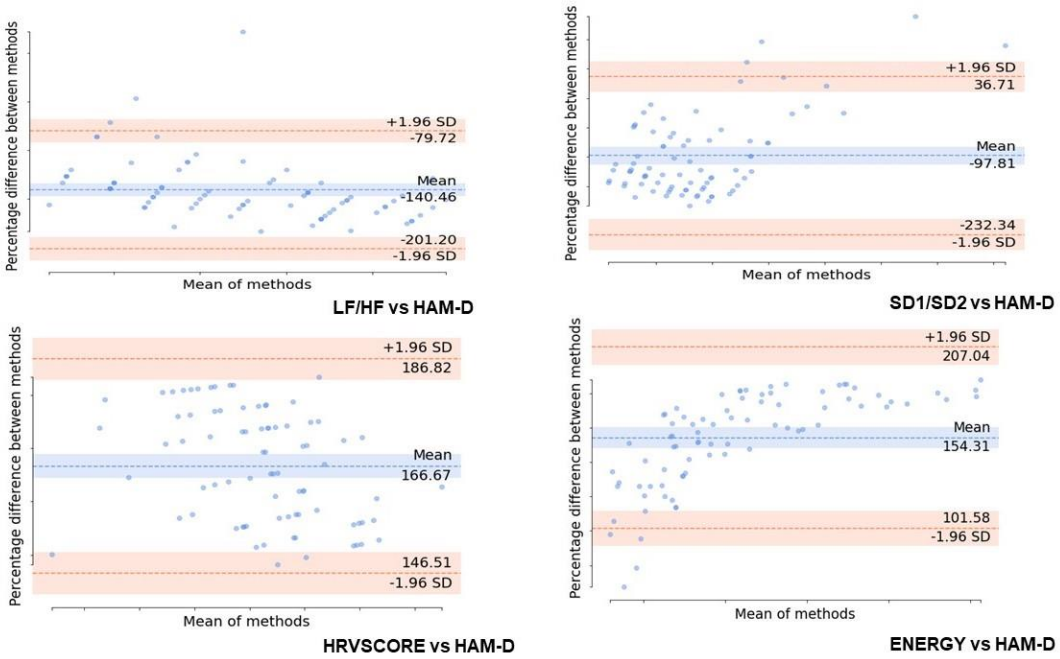


Fig. 2b. Lyfas optical biomarkers (novel instrument under reliability study) vs. HAM-D (Instrument – 2, scoring by psychiatrists).

The study shows that the proportional bias between Lyfas optical biomarkers and ENS probability is 6.14 with the Stdev of 2.77, which means the limit of agreement between Lyfas optical biomarkers and ENS probability, estimated by the experienced psychiatrists is **93.86%** that is appreciable for a 'novel' instrument against psychiatrists (expert human instrument – 2), which is another 'champion' instrument. Thereover, the overall agreement between Lyfas optical biomarkers and the human expertise is **93.86%**, which is quite encouraging for a novel m-health instrument.

DISCUSSION

The present study has been designed to examine the (a) existence of ENS (assessed by psychologists based on the designated sign-symptoms), (b) its progression into clinical depression (assessed by psychiatrists by using HAM-D QBI), (c) significant biomarkers such as (i) optical (obtained through the Lyfas tests) and (ii) physical biomarkers (obtained through laboratory tests and physical examination) as the assessors at the backdrop of ENS and its progression into depression among middle-aged Indian parents. The study observes that ENS does exist in Indian society, especially in the current state of the pandemic when children are leaving homes to join jobs and colleges, getting married and moving out, and so on. Based on this population size, the prevalence of ENS is around 50%, where 80% of the ENS cases may progress into clinically 'mild' depression as assessed by psychiatrists using HAM-D QBI. Mothers and fathers both are equally affected, which refutes the claim that mothers being the primary caregivers are affected more than their male counterparts.

From the descriptive statistics, it is noted that Indian middle-aged parents suffer from comorbidities such as hypertension, T2DM, Hypothyroidism, and dyslipidemia. It raises queries on poor health awareness, adoption of alternative medications instead of researched modern western medicines, sedentary lifestyles, affinity towards junk foods and processed sweets, and so forth.

From the correlation test, statistically significant biomarkers – both optical and physical can be mapped to understand the ENS-to-Depression transition and as shown in Fig. 3.

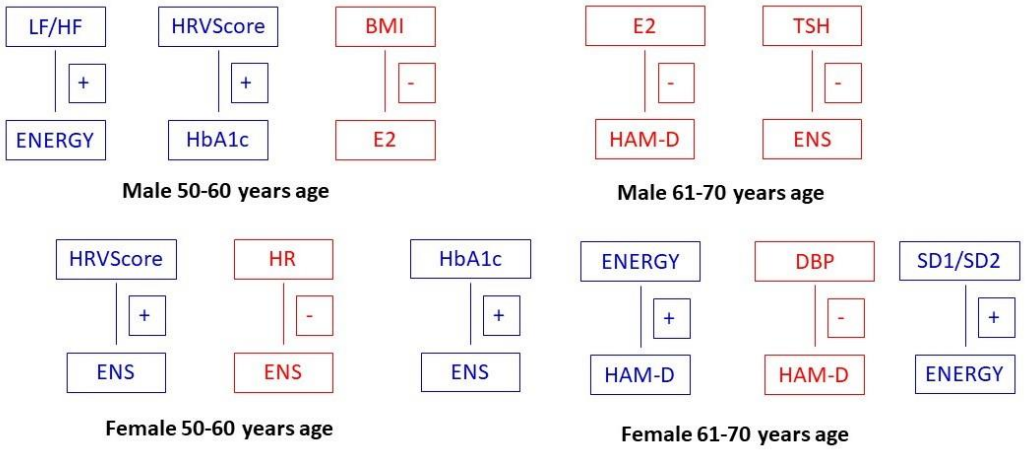


Fig. 3. Gender and age-group-wise biomarker-ENS-HAM-D correlation mapping.

LF/HF attributes to sympathovagal balance. A high ratio determines sympathetic overdrive or parasympathetic dampening [26]. *ENERGY* is the outcome of the quality of such balance, where high LF/HF refers to high ENERGY [37]. In middle-aged fathers (50-60 years group), from the data, it can be evident that the sympathetic drives are reduced as there is no motivation left in their life to rear the children and as a result, less amount of ENERGY is produced. The motivation was there previously when they were staying together. Another important reason could be that the fathers are all socioeconomically stable or established by the age of 50s and above; however, the utilization of such a state towards their children has suddenly become limited as they have left the home. This population group presents mostly with the combination of *worry* and *emptiness* (50%), where emptiness is more than the feeling of worry. In this age group, *HRVScore* is high due to more time to socialize, be with old friends, meet relatives, and so forth. These activities work as a compensatory mechanism for emptiness and worry. A high HRVScore indicates a good mood and thus reduces vulnerability to depression [38]. It is important to state that Indian middle-aged males suffer from premature old-age syndrome. They fall into more sedentary lifestyles, such as watching television, no physical activities, spending time in temples and worshipping praying for the children to God, and eating carbohydrate-rich food as most of them are vegetarian. A constant worry activates the hypothalamus-pituitary-adrenal axis causing flooding of cortisol from the adrenal cortex, which leads to neo-glucogenesis-induced hyperglycemia that eventually is reflected by higher *HbA1c*. In elderly males, the study shows that the *E2* level and *HAM-D*-based depression severity are negatively correlated. It is worth noting here that, this group mostly suffers from the combination of *emptiness* and *grief reaction* or *sadness* (62%). In this age group, andropause is nature's rule in most cases. E2 level decreases as andropause approaches in both sexes. In males, testosterone (TST) is decreased as andropause approaches with the progression of age. E2 is produced by TST by the aromatase enzyme [39]. As TST is diminishing with the progression of the chronological age, it may be presumed that the E2 conversion is also less. E2 is a proven biological neuroleptic [16] and therefore its fall increases the vulnerability towards clinical depression as the extension of ENS, in middle-aged and elderly males. High BMI indicates metabolic slowdown [40]. Low E2 dysregulates mood. To elevate the mood, the craving for junk foods and processed sweets is evident in middle-aged Indian males that are reflected through the elevated HRVScore [41]. It is another interesting finding of this research. Worry increases the metabolic demand due to higher sympathetic activities. Worry when co-associated with dysmetabolic syndromes such as diabetes mellitus, cardiovascular disorders, polycystic ovary syndrome, obesity, dyslipidemia, etc. causes thyroid dysfunctions [42]. As a result, to maintain homeostasis, the body requires more thyroxin and the demand needs to be fulfilled by the pituitary gland by secreting more TSH from its anterior lobe, provided the thyroid gland functions insufficiently, which is evident in the above-mentioned dyslipidemic syndromes. The researchers have also shown a higher tendency of hypothyroidism in middle-aged males with traits of depressive episodes [43]. In the case of

males, the authors feel that depressive episodes are mostly the outcome of a lack of any further motivation in life, either from the family front or from a professional career perspective. Reduction of TST is one important factor behind the loss of motivation, which is much more common in middle-aged and elderly fathers of moved-out children. On the contrary, middle-aged and elderly mothers who suffer from entangled recursive negative thoughts may develop clinical depression [44]. In this study, for both the 50-60-year-old and elderly mothers, the chief symptom combination is *worry* and *emptiness* (90%). The authors have observed that worry brings cascading negative thoughts leading to low HRVScore at the beginning. Later, they succumb to continuous thrusts of negative emotion and do not have the energy left even to further worry. As a compensatory mechanism, going forward, they withdraw their emotions. It leads to increased HRVScore although chances of developing ENS prevail within them as emptiness has not been corrected and only the worry part has been corrected. The authors have found that the HR is reduced in emptiness could be due to the lower basal metabolic rate. Emptiness shows reduced HR, while worry increases it, but the latter eventually gets balanced. On contrary, emptiness in them is a constant attribute and does not get corrected in most cases. Hence, ENS vulnerability remains high although the HR is decreased. In Indian societies, in both the parents, emptiness prevails until they are taken away by their children to stay with them. Diabetes is also a predisposing factor for ENS, as evident from this work. Negative energy is the key driver of emotional entanglement in depression. Therefore, in this work, high HAM-D scores are correlated with high negative energy. In depression, as the metabolism reduces, BP falls due to emotional exhaustion. SD1/SD2, as mentioned earlier, is the optical biomarker of anxiety. When anxiety level raises, the body needs more energy and hence Lyfas analytics shows higher energy levels in anxious elderly females.

CONCLUSION

Based on the findings of the research, the study concludes that,

- ENS exists very much in India due to its joint type family structure
- Subjects with 'emptiness' feelings have a high propensity towards developing clinical depression as a lingering construct, while sadness and worry can be compensated with time in both the fathers and mothers
- In Indian societies, both parents are equally affected by ENS as fathers are also emotionally engaged in Indian society as the primary caregiver (source of earning, safety, and security for the family), as seen in the study of [2] have demonstrated that both genders suffer equally due to ENS.
- The study confirms that LENS can correlate with ENS state and its transition into clinical-grade mild depression in 80% of cases, and
- Lyfas as a non-invasive optical biomarker instrument is reliable as closely as mental healthcare experts by 92.85% (psychologists) and 93.86% (psychiatrists) and thus Lyfas can be used in ENS cases to screen and monitor the risk of developing clinical-grade depression.

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