JOURNAL OF NATURAL REMEDIES
DOI: 10.18311/jnr/2023/30310
RESEARCH ARTICLE

Association of Family History, Life-Style Related Factors, Dietary Patterns, and Psychological Status with *Amavata* (~Rheumatoid Arthritis) among the Population of Jamnagar, India: A Matched Case-Control Study

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Abstract

Background: The modern medical community now recognises *Amavata* as a condition that can lead to Rheumatoid Arthritis (RA) due to a combination of genetic predisposition, poor dietary habits, altered lifestyle, disturbed sleep, disturbed psychological condition, etc. *Amavata's* origins are said to be two thousand years old, but there is no rigid evidence to support this. **Aim:** To evaluate the association of family history, different dietary patterns and lifestyle related risk factors such as *Vyayama*, improper bowel movements, disturbed/irregular sleep patterns, psychological stress, etc., in the pathology of *Amavata* (~RA). **Materials and Methods:** A matched case-control study was conducted from 18 April 2018 to 09 January 2020, containing 150 cases (patients of *Amavata*), and 150 controls (healthy volunteers), matching in age (between 18-50 years), and both the sexes (1:1 ratio) selected from Jamnagar district. After receiving written informed permission, data were obtained using CRF (Case Record Form). An open-ended questionnaire through the one-to-one interview was used to obtain data on eating habits, psychological and emotional circumstances previous to sickness, lifestyle features such as sleep, *Vyayama* (physical activity), and bowel patterns. Chi-square tests and Odds Ratios (OR) were computed. **Results:** The statistical analysis revealed that positive family history (χ^2 = 63.021, p<0.001), *Avyayama* (lack of physical activity) (OR = 7.43, χ^2 = 79.95, p<0.001), *Diwaswapna* (day time sleep) (OR = 12.86, χ^2 = 93.048, p<0.001), disturbed night sleep (OR = 44.25, χ^2 = 159.61, p<0.001), constipation (OR = 85.17, χ^2 = 144.10, p<0.001), *Atishrama* (occupational stress)(OR = 22.86, χ^2 = 96.989, p<0.001), disturbed psychological status (p<0.001) and faulty dietary patterns (p<0.001) were found to have statistically significant association with *Amavata* (~RA). **Conclusion:** Strong positive associations were found between positive family history, *Avyayama* (lack of physical activity), *Diwaswapna* (daytime sleep), disturbed night sleep, constipation, disturbed psychological status, *Atishrama* (occupational stress), and faulty dietary patterns (*Adhyashana*, *Vishamashana*, *Viruddhashana*) with *Amavata* which are statistically significant and they can be considered as the potential risk factors for the incidence of *Amavata* (~RA).

Keywords: *Amavata*, Constipation, Dietary Patterns, Disturbed Sleep, Family History, Psychological Status, Rheumatoid Arthritis

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Article Received on: 20.05.2022 Revised on: 09.05.2023 Accepted on: 25.05.2023

1. Introduction

In the contemporary age, there has been a significant shift in dietary habits from traditional to modern eating patterns all across the world. Because of the globalization and modernity of food and eating, this nutritional change may lead to several metabolic illnesses. The etiology of several metabolic illnesses is influenced by such improper eating habits[1]. Aside from the dietary shift, irregular sleep patterns, physical, and psychological stress may also promote metabolic illnesses, resulting in an increase of morbidity in community health on a day-to-day basis[2,3]. *Amavata* is one such condition that has been linked to Rheumatoid Arthritis in contemporary medicine. It's important to know that Rheumatoid Arthritis (RA) is an inflammatory illness that causes pain, disability and early death if left untreated. Recent studies on RA revealed that everyone lakh people, between 0.5 and 1 per cent of the world's population, are infected[4].

Ayurved literature advocates that faulty dietary habits like *Samashana* (consumption of wholesome as well as unwholesome food substances together), *Vishamashana* (consumption of food in either irregular quantity or at irregular/inappropriate time), *Viruddhashana* (consumption of incompatible diet), *Adhyashana* (consumption of food prior to the digestion of previous meal) are the causative factors for the *Amotpatti* (the genesis of *Ama*-undigested food material), which is an integral part of various diseases, *Amavata* is one of them[5,6]. Furthermore, the Charaka Samhita and Sushruta Samhita, the other compendiums for the general medical practitioners of Ayurveda, claim that an individual who is consuming *Matravat Ahara* (prescribed quantity of food), if his/her *Manas* (mind) is afflicted with *Chinta* (anxiety), *Bhaya* (fear), *Shoka* (grief), *Krodha* (anger), etc., and if he or she follows irregular sleep patterns including *Ratrijagarana* (night awakening), *Diwaswapna* (day sleep), the consumed food could not get digested and eventually leads to the formation of *Ama*[7,8].

It is also claimed that the ascertainment of *Jatharagni* (digestive fire) aids in the assessment of the *Agnibala* (digestive capacity) of an individual. The *Jaranashakti* (ability to digest food) of an individual reveals the status of gut flora qualitatively and quantitatively. The condition of bowels (constipation-present/absent) indicates *Jatharagni* or *Agni* or *Koshtha* (gastro-intestine tract). Both *Vishamagni* (irregular digestive capacity) and *Mandagni* (diminished digestive capacity) are the reason for *Amotpatti* (production of *Ama* - an indigested food substances)[9].

All the above-mentioned factors are the etiology of *Amavata*, as stated in ayurvedic literature. However, there is a paucity of scientific data in support. To fulfill this lacuna, the present study was carried out to evaluate the association of different dietary patterns such as *Samashana*, *Viruddhashana*, *Vishamashana*, *Adhyashana*, etc., psychological stress, emotional disturbance, and constipation status (bowel condition) with *Amavata* (~RA). A case-control survey study was carried out with the following aim and objectives. This sort of observational study based on community may facilitates the better prevention of the diseases[10,11].

2. Aim and Objectives

2.1 Aim

To evaluate the association of family history, different dietary patterns and lifestyle related risk factors such as *Vyayama,* improper bowel movements, disturbed/ irregular sleep patterns, psychological stress, etc., in the pathology of *Amavata* (~RA).

2.2 Objectives

- To evaluate the association of *Vyayama* (physical exercise) with *Amavata.*
- To evaluate the association of different dietary patterns, bowel patterns, and constipation with *Amavata* .
- To evaluate the association of different sleep patterns with *Amavata.*
- To evaluate the association of disturbed psychological status with *Amavata.*

3. Materials

3.1 Study Design: Case-Control Study

Case-control studies are useful in determining the relative importance of the disease's etiological causes and their covalent relationship with it. Epidemiological studies can only be applied to the general population if risk factors detected in ill populations are compared with those found in healthy populations. In observational research, the case-control technique helps to identify the most vulnerable, preventative, and therapeutic strategies. Consequently, always, seeks to uncover the

triggering factor in ill individuals and the protective or preventing factor in healthy individuals[12].

3.2 Study Sample and Sample Size Fixation[13]

The following formula has been used to calculate the sample size required for the present study.

Sample Size = $r+1/r \times (p^*) (1-p^*) (Z_{\beta}+Z_{\alpha/2})^2/(P_1-P_2)^2$

where, *r* = Ratio of control to cases, 1 for an equal number of cases and controls, p* is average proportion exposed = proportion of exposed cases + proportion of control exposed/2

Zb = Standard normal variate for power = for 80% power it is 0.84 and for 90% value is 1.28. The researcher has to select power for the study.

Za/2 = Standard normal variate for the level of significance as mentioned in the previous section.

p1 – p2 = Effect size or difference in proportion expected based on previous studies. p1 is the proportion in cases and p2 is proportion in control.

The ratio of cases and controls is 1:1 for the present study. Based on the expected proportion in controls is 0.05, the assumed odds ratio is 4, Confidence level = 0.95, Power = 0.9, considering the design effect as 1, the calculated sample size per group is 131. An additional 10% was added to compensate for the dropout and finally, it was calculated to be 144. Finally, 150 subjects in each group and a total of 300 participants in both groups were covered.

Cases and controls were split equally between the two groups based on age and gender in this investigation. 150 diagnosed patients of *Amavata* (cases) and 150 healthy volunteers (controls) were recruited using the simple random sample approach and interviewed to get information about their medical histories and their involvement in the current research (the detailed study flow is depicted in Figure 1).

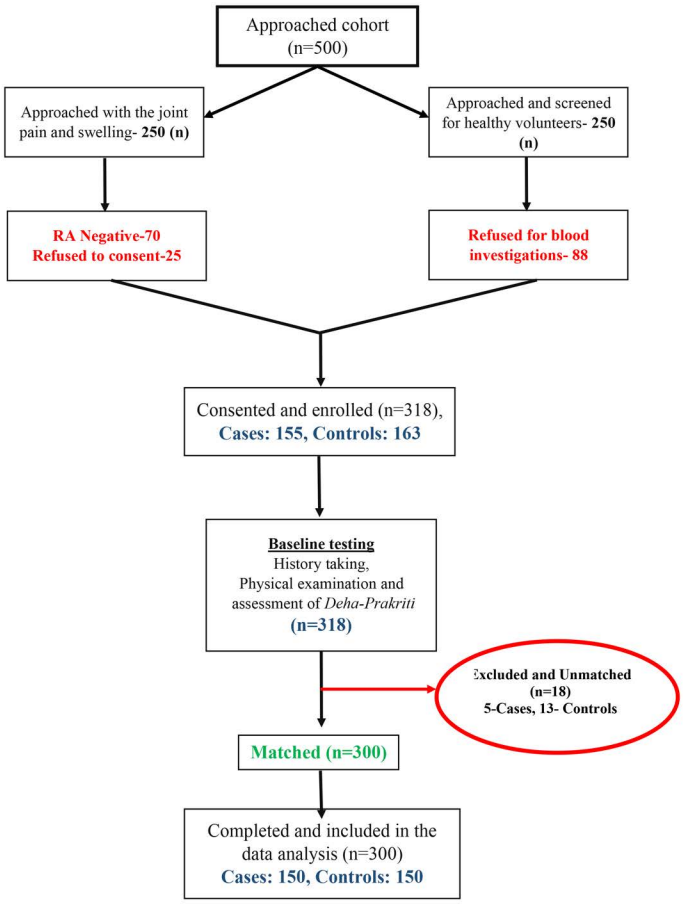

Figure 1. Study flow chart as per the STROBE statement.

4. Methodology

4.1 Criteria for Inclusion of Cases

Those who had the diagnostic features of both the *Amavata*[14] and Rheumatoid Arthritis [met the ACR, 1987 Criteria[15] with positive RA factor (quantitative) and positive CRP (quantitative)] for less than or equal to 5 years of disease onset and were above the age of 18 years and below 50 years were included in the study. The study participants were selected from Institute for Post-graduate Teaching and Research in Ayurveda (IPGT & RA) Hospital, Jamnagar's Out Patient Department (OPD), and In Patient Department (IPD) and those interested in signing a written informed consent form participated in the study, which was conducted from April 18, 2018 to January 9, 2020.

4.2 Criteria for Inclusion of Controls

Controls are people who are free of illness have met the qualifying requirements, and are of the same age and gender as the patients. They were also recruited from the same population as the cases. For the current study, only those healthy persons who had completed a questionnaire created by CSIR-Ayurgenomics unit-TRISUTRA (Translational Research and Innovative Science Through Ayurgenomics), CSIR (Council of Scientific & Industrial Research), IGIB (Institute of Genomics and Integrative Biology), New Delhi and who had given written informed consent were considered for inclusion.

4.3 Exclusion Criteria for Cases

Amavata patients with other co-morbidities such as Diabetes, Hypothyroidism, or any other endocrinal and metabolic disorders, less than 18 and more than 50 years of age, and those who refused to participate in the study were excluded.

4.4 Exclusion Criteria for Controls

Unhealthy individuals, less than 18 and more than 50 years of age, and those who were not willing to participate in the study were excluded.

4.5 Ethical Clearance

The Institutional Ethics Committee of the Gujarat Ayurved University's Institute for Post Graduate Teaching and Research in Ayurveda, Jamnagar, gave their approval; vide letter no. PGT/7-A/Ethics/2017-18/3042 dated 19/02/2018.

4.6 CTRI Registration

The Clinical Trial Registry-India (CTRI) has been notified about this trial and registered prospectively vide CTRI/2018/04/013241 [Registered on 13/04/2018].

4.7 Method of Data Collection

The present study was initiated after IEC approval and CTRI registration. The goal of the study, what is anticipated of them, and the predicted participant benefit of observing and analyzing, were all stated to all the participants before the start of the study. After getting the informed consent the data were collected. Based on the responses of the participant the Case Record Form (CRF) was filled by the Principal Investigator. The method of direct interviews and open-ended questions were employed to collect the data. The questions on the disease's current status were asked first, followed by a pattern, which was established to elicit historical information about their detailed personal history which envelopes dietary patterns, psychological status and emotional status before the onset of the disease, lifestyle-related factors such as sleep, *Vyayama* (physical activity), bowel patterns, and so on. The entire data collection process was completed in 40 minutes for each participant (on an average). CCRAS-PAS scale (available at ccras.res.in) has been used to assess the Deha-Prakriti of all the participants.

4.8 Avoiding Bias

In the present study, the selection bias was avoided by selecting suitable cases and controls and both the groups were matched in terms of age and sex. To counteract recall bias, patients with persistent memory impairment were excluded. By blinding the study participants to their case or control status, observer bias was avoided. Responder bias was addressed by keeping research participants ignorant of the hypothesis under investigation and assuring them that both case and

control groups had the same chances and motivations to recall earlier occurrences.

4.9 Statistical Analysis

The Chi-square analysis was performed to determine the relationship of various socio-demographic variables with *Amavata*; odds ratios were calculated to find out the weightage of involved etiological factors or risk factors. Both these tests were applied using the Statistical Package for Social Sciences (SPSS Inc., Chicago, Illinois, USA) version 20.0 software.

Table 1. Distribution of various demographic variables among cases and controls along with statistical analysis

Sr. No.	Variable	Level code	Label	Cases (N)	Controls (N)	Chi-square	P-value
1.	Age group	1	18-30	30 (20 %)	28 (18.7%)	1.722	0.423
		2	31-40	59 (39.3%)	50 (33.3%)		
		3	41-50	61 (40.7%)	72 (48%)		
2.	Gender	1	Male	21 (14%)	21 (14%)	0.001	0.977
		2	Female	129 (86%)	129 (86%)		
3.	Marital status	0	Unmarried	17 (11.3 %)	34 (22.7%)	7.7	0.021
		1	Married	132 (88%)	116 (77.3%)		
		2	Widow	1 (0.7%)	0		
4.	Education	0	Uneducated	17 (11.3%)	8 (5.3%)	19.746	<0.001
		1	Primary	33 (22%)	16 (10.7%)		
		2	Secondary	54 (36%)	50 (33.3%)		
		3	Higher-secondary	15 (9.68%)	14 (9.3%)		
		4	Graduate	20 (13.3%)	42 (28%)		
		5	Post-graduate	11 (7.3%)	20 (13.3%)		
5.	Socio-economic status	1	BPL*	41 (27.3%)	27 (18%)	8.929	0.03
		2	LMC*	81 (54%)	77 (51.3%)		
		3	UMC*	27 (18%)	46 (30.7%)		
		4	Rich	1 (0.7%)	0		
6.	Occupation	1	Student	13 (8.7%)	26 (17.3%)	32.681	<0.001
		2	House-wife	109 (72.7%)	74 (49.3%)		
		3	Business	3 (2.0%)	0		
		4	Govt. employee	1 (0.7%)	21 (14%)		
		5	Private employee	27 (17.42%)	29 (19.3%)		
7.	Religion	1	Hindu	132 (88%)	135 (90%)	4.660	0.46
		2	Muslim	16 (10.7%)	9 (6%)		
		3	Sikh	0	1 (0.7%)		
		4	Buddha	1 (0.7%)	2 (1.3%)		
		5	Christian	0	1 (0.7%)		
		6	Jain	1 (0.7%)	2 (1.3%)		
8.	Type of diet	1	Vegetarian	111 (74%)	108 (72%)	0.152	0.696
		2	Mixed diet	39 (26%)	42 (28%)		
9.	Type of Family	1	Nuclear	34 (22.7%)	119 (79.3%)	96.372	<0.001
		2	Joint	116 (77.3%)	31 (20.7%)		

*BPL: Below Poverty Line; LMC: Lower Middle Class; UMC: Upper Middle Class.

Table 2. Showing the distribution of various etiological factors among cases and controls along with the statistical analysis

Sr. No.	Etiological Factor	Level code	Label	Cases (N)	Controls (N)	Chi-square	P-value
1.	Family History	0	Negative	92 (61.33 %)	148 (98.67%)	63.021*	<0.001
		1	Positive	58 (38.67 %)	2 (1.33%)		
2.	*Deha-Prakriti* (single predominant)	1	*Vata* (V+VP+VK)**	126 (84%)	27 (18%)	137.281	<0.001
		2	*Pitta* (PV+PK)**	4 (2.7%)	68 (45.3%)		
		3	*Kapha* (K+KP+KV)**	20 (13.3%)	55 (36.7%)		
3.	*Vyayama* (Physical activity)	0	Absent	123 (82%)	57 (38%)	60.5	<0.001
		1	Present	27 (18%)	93 (62%)		
4.	Sound sleep (in night time)	0	Absent	123 (82%)	14 (9.33%)	159.61	<0.001
		1	Present	27 (18%)	136 (90.67%)		
5.	Disturbed sleep (in night time)	0	Absent	27 (18%)	136 (90.67%)	159.61	<0.001
		1	Present	123 (82%)	14 (9.33%)		
6.	*Divaswapna* (Day sleep)	0	Absent	25 (16.67%)	108 (72%)	93.048	<0.001
		1	Present	125 (83.33%)	42 (28%)		
7.	Nature of bowels	1	Regular	48 (32%)	142 (94.67%)	126.833*	<0.001
		2	Irregular	102 (68%)	8 (5.33%)		
8.	Bowel frequency (per day)	1	One time	76 (50.67%)	2 (1.33%)	103.546*	<0.001
		2	Two times	64 (42.67%)	144 (96%)		
		3	More than two times	10 (6.67%)	4 (2.67%)		
9.	Stool consistency	1	Hard	100 (66.67%)	4 (2.67%)	140.109*	<0.001
		2	Semi-solid	50 (33.33%)	146 (97.33%)		
10.	Constipation	0	Absent	45 (30%)	146 (97.33%)	144.10*	<0.001
		1	Present	105 (70%)	4 (2.67%)		
11.	*Atishrama* (occupational stress)	0	Absent	61 (40.67%)	141 (94%)	96.989*	<0.001
		1	Present	89 (59.33%)	9 (6%)		
12.	*Samashana*	0	Absent	125 (83.33%)	10 (6.67%)	178.11	<0.001
		1	Present	25 (16.67%)	140 (93.33%)		
13.	*Adhyashana*	0	Absent	110 (73.33%)	140 (93.33%)	21.06	<0.001
		1	Present	40 (26.67%)	10 (6.67%)		
14.	*Vishamashana*	0	Absent	20 (13.33%)	142 (94.67%)	199.73*	<0.001
		1	Present	130 (86.67%)	8 (5.33%)		
15.	*Viruddhashana*	0	Absent	27 (18 %)	143 (95.33%)	182.66*	<0.001
		1	Present	123 (82%)	7 (4.67%)		
16.	*Chinta* (Anxiety)	0	Absent	104 (69.33%)	148 (98.67%)	45.858*	<0.001
		1	Present	46 (30.67%)	2 (1.33%)		
17.	*Bhaya* (fear)	0	Absent	73 (48.67%)	149 (99.33%)	97.453*	<0.001
		1	Present	77 (51.33%)	1 (0.67%)		
18.	*Shoka* (grief and stress)	0	Absent	64 (42.67%)	145 (96.67%)	114.71*	<0.001
		1	Present	86 (57.33%)	5 (3.33%)		

19.	*Krodha* (anger)	0	Absent	66 (44%)	148 (98.67%)	106.95*	<0.001
		1	Present	84 (56%)	2 (1.33%)		

*with Yates correction

**V: Vataja; VP: Vata-Pittaja; VK: Vata-Kaphaja; PV: Pitta-Vataja; PK: Pitta-Kaphaja; K: Kaphaja; KP: Kapha-Pittaja; KV: Kapha-Vataja.

Table 3. Odds ratio and χ^2 between cases and controls for their exposure to various etiological factors

Sr. No.	Etiological factors	Odds Ratio	CI (95%)	χ^2	*P*	Type of association
1.	Family history (Positive/negative)	46.05	11.13-195.61	60.021*	<0.001	Positive
2.	*Vyayama* (Physical Activity)	0.13	0.08 - 0.23	60.5	<0.001	Negative
3.	*Avyayama* (lack of physical activity)	7.43	4.37 – 12.64	79.95	<0.001	Positive
4.	Sound sleep (in night time)	0.02	0.01 – 12.64	159.61	<0.001	Negative
5.	Disturbed sleep (in night time)	44.25	22.2-88.23	159.61	<0.001	Positive
6.	*Divaswapna* (Day sleep)	12.86	7.36 – 22.46	93.048	<0.001	Positive
7.	Constipation	85.17	29.72 – 244.09	144.10	<0.001	Positive
8.	*Atishrama* (occupational stress)	22.86	10.81 – 48.32	96.989	<0.001	Positive
9.	*Samashana*	0.01	0.01-0.03	178.11	<0.001	Negative
10.	*Adhyashana*	5.09	2.44-10.63	21.6	<0.001	Positive
11.	*Vishamashana*	115.38	49.13 – 270.95	199.73	<0.001	Positive
12.	*Viruddhashana*	93.06	39.16 – 221.14	182.66	<0.001	Positive
13.	*Chinta* (Anxiety)	32.79	7.77-137.84	45.858	<0.001	Positive
14.	*Bhaya* (fear)	157.16	21.43 – 1152.53	97.453	<0.001	Positive
15.	*Shoka* (grief and stress)	38.97	15.09 – 100.6	114.71	<0.001	Positive
16.	*Krodha* (anger)	94.18	22.49 – 393.34	106.95	<0.001	Positive

*with Yates correction

5. Observations and Results

The demographic-related variables of both groups are summarized in Table 1. Age group, gender, marital status, educational status, occupation, and type of family are documented along with their Chi-square values in the table. Age group, gender, religion, and type of diet were found to have non-significant associations (p>0.05). Marital status (p value at 0.021), educational status (p<0.001), socioeconomic status (p value at 0.03), occupation (p<0.001), and type of family (p<0.001) were found to have significant associations. Among them, marital status (p value at 0.021) and socioeconomic status (p value at 0.03) were slightly significant, whereas the educational status, occupation, and type of family were highly significant (p<0.001). The frequencies of various risk factors including family history, different dietary patterns, sleep patterns, disturbed psychological status (p<0.001), and *Atishrama* (occupational stress p<0.001) of both the groups were found significantly different (Table 2). To evaluate the association of etiological factors with *Amavata*, the odds ratio of each factor was calculated and documented along with the values (Table 3).

6. Discussion

A significant association was found between various risk factors including positive family history, dietary patterns, disturbed psychological status, and *Amavata* (Rheumatoid Arthritis). Various other demographic factors were also studied and significant association was found for marital status (p value is 0.021), education status (p<0.001), socio-economic status, occupation (p value is 0.03), and type of family (p<0.001), whereas no association was found with age, gender, religion, and type of diet (p>0.05). There were two groups involved in the present study; one was the case group consisting of *Amavata* patients (N = 150); the other was the control group (N=150) consisting of healthy individuals. Both groups were matched by age and sex. So, the age and gender were found non-significant (p>0.05). The ratio of cases and controls in the present study was 1:1. The mean age of the case group (N = 150) was 39.35 ± 9.115 years. The mean age of the control group (N = 150) was 38.49± 8.937 years. Sex-wise, the majority of the subjects were females (N = 129), covering 86%, as *Amavata* (Rheumatoid Arthritis) mainly affects the women population. According to epidemiological studies, women are disproportionately affected by autoimmune diseases such as Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), and Systemic Sclerosis (SSc) among others. There seem to be two important factors at play, and they may have an influence on other concerns, such as changes in the microbiota, sex hormones and (Epi-)genetics. Women's and men's fluctuating levels of estradiol (and progesterone) and testosterone (and other hormones) reveal the RA hereditary bias. By decreasing cytokine (e.g. Tumor Necrosis Factor (TNF)) communication (high estradiol levels), establishing immunological tolerance, and reducing the intensity of inflammation during pregnancy, estradiol reduces synovial inflammation[16]. Pregnancy-induced anti-inflammatory cytokines like IL-10 may be mitigated by progesterone's induction of Tregs and suppression of Th17 growth[17,18]. If testosterone is present, it could protect against the development of autoantibodies in a RA patient[19]. Both Tissue Inhibitor Metalloproteinase-1 (TIMP-1) and the Interleukin-9 receptor, two X-linked genes previously implicated in RA's gender bias, have recently come to light (IL9R). An association between RA in general (TIMP1) and an anti-Cyclic Citrullinated Peptide antibody (anti-CCP) antibody-positive RA was shown by single nucleotide polymorphisms in both genes (anti-CCP)[20]. For people with a genetic predisposition, such as shared epitope, there is evidence that changes in the gut microbiota may be linked to inflammation, like RA. The Human Leucocyte Antigen (HLA) genotype (DRB1*0401) of females may have a role in altering the makeup of the gut microbiota, leading to increased production of pro-inflammatory cytokines and bacterial translocation[21].

In both the study groups, married subjects occupied a significant portion. As the majorly involved age group belongs to 31-50 (81%) years, the maximum number of subjects were married. Most of the subjects in both groups belonged to the urban type of habitat as the present study has been conducted at Jamnagar and its peripheries[22]. However, as compared to the control group, *Amavata* patients from rural areas had a much higher prevalence of the disease. When compared to the control group, the proportion of housewives (homemakers) was found to be higher in the case group. The fact that workers from both the public and private sectors made up the majority of the study's control group suggests that they are at ease in their jobs. The majority of participants in this research had secondary education. However, the percentage of uneducated was significantly more in the case group (11.3%), whereas, in the control group, only 5.3% were uneducated. It indicates that literacy has a significant role in the manifestation of *Amavata*. Health literacy gives knowledge about a healthy lifestyle and its importance to humankind, helping them prevent disease conditions. The maximum number of subjects were below the poverty line and lower-middle-class categories. However, their percentage was slightly higher in the case group (81.3%) than in the control group (69.3%) which is statistically significant. The socio-economic status and habitat are interlinked factors. Due to their poor economic status, they cannot afford a hygienic and nutritious diet. Moreover, they always strive for day-to-day essentials. It provokes them to consume an unhygienic, incompatible, stale, and less or mal-nutritious diet. This may lead to the formation of *Ama* in the body, which plays a pivotal role in the manifestation of RA[23].

Religion and type of diet were found to have an insignificant association (p>0.05) with *Amavata* as the study has been conducted at Jamnagar and its peripheries

which is a dominant Hindu geographical region and where a majority of them are vegetarians. Hence, there was no much change in their type of diet[22,24]. *Amavata* patients were found to come from joint families (77.3%), while the majority of healthy participants were from nuclear households (79.3%). It suggests that the sort of family a person grows up in has a big impact on whether or not they develop *Amavata*. As a result, *Vata*[25] is aggravated, and *Amavata* is more likely to arise in joint households, where women are subjected to a great deal of physical stress. In joint households, homemakers tend to eat and sleep irregularly, which may contribute to the production of *Ama*, a key factor in the emergence of *Amavata*[23,24].

6.1 Family History (p<0.001)

Among patients of *Amavata*, the positive family history is significantly high (40%) compared with the controls (1.23%). Other contemporary research works also support it[26]. Hence, the persons who had a positive family history were more vulnerable to getting *Amavata*. It suggests the prevalence of genetic predisposition among *Amavata* patients.

6.2 *Deha-Prakriti* (p<0.001)

Samadoshaja or *Tridoshaja Deha-Prakriti* were not detected in either group. The majority of *Amavata* patients (84%) had *Vata* dominating *Deha-Prakriti*, while the majority of healthy volunteers (45.3%) had *Pitta* predominant *Deha-Prakriti* and *Kapha* prominent (36.7%). People were found as Single *Vataja*, *Vata-Kaphaja*, and *Vata-Pittaja Deha-Prakriti* 23.3%, 32%, and 28.7% of the case group, respectively. It denotes the susceptibility of *Vata*-dominated *Deha-Prakriti* and the protective character of *Pitta* and *Kapha*-dominated *Deha-Prakriti*.

6.3 *Vyayama* (Physical Activity) (p<0.001)

In the case group, most subjects had not followed any type of physical exercise (82%). On the contrary, 62% of the healthy volunteers were found as practicing regular *Vyayama,* other than their occupation. It is also clearly stated that the regular practice of *Vyayama* increases *Agni*[26]. Maybe, this is one reason for the manifestation of *Amavata* in the case group, as the absence of *Vyayama* leads to diminution of *Agni*, leading to formation of *Ama*, thereby manifesting *Amavata*.

Regular physical exercise promotes the qualities of *Laghutwa* (lightness), *Karmasamarthya* (the capacity to accomplish any task well), *Kapha-kshaya* (alleviation of *Kapha dosha*), and *Agnivriddhi* (enhances the digestive power) according to Ayurveda[27]. In his commentary on the Charaka samhita, Chakrapani Dutta said that the removal of all the diseased elements of *Tridosha* in *Vyayama* strengthens the digestive ability[28]. *Vyayama* is also said to be one of the ten varieties of *Niragni-sweda* (sweating caused without the aid of the fire) since it raises the body temperature, resulting in sweating[29]. According to this, there is a clear correlation between regular *Vyayama* practice and *Agnibala* (digestive force). It is the digestive system's job to break down food and provide the body with energy. Regular exercise stimulates the gut and increases intestinal function, preventing digestive disorders. As a result, the muscles in the digestive system remain active even while you are resting, helping food to travel through the system more quickly[30].

The most recent research shows that *Vyayama* improves Basal Metabolic Rate (BMR) via using mitochondrial Adenosine triphosphate (ATP) at the cellular level resulting in an increase in caloric intake. To match the rate of ATP decay with the rate of ATP synthesis, skeletal muscle can speed up energy turnover from rest to maximal force/power production. This needs an integrated response from both inside the cell and systemically. In order to sustain ATP generation to support muscular contraction, the metabolic co-ordination necessary to achieve this involves the demands on various substrates. It is also possible to see an increase in sympathetic activity as a result of the brain's motor center activating the sympathetic system, which results in an endocrine response to exercise. A new focus is on the function of skeletal muscle in a systemic endocrine response that seems to be connected to the availability of substrates in the working muscle[31].

6.4 Sleep Patterns

6.4.1 Disturbed Night Sleep (p<0.001)

The majority of the subjects in the case group (82%) were presented to have disturbed night sleep, whereas most controls (90.67%) were having a sound sleep during night-time. It was owing to the predominance of *Laghu* (lightness), *Ruksha* (roughness) attributes of

Vata in the case group. Moreover, *Amavata* patients have the *Rajoguna* predominant, *Alpa Sattva* (possessing psychologically weak strength), and most of them were afflicted with *Chinta* (anxiety), *Bhaya* (fear), *Shoka* (grief), and *Krodha* (anger), etc. On the contrary, due to the predominance of *Gurutwa* (heaviness), *Snigdhatwa* (unctuousness), *Sthiratwa* (stableness) of *Kapha* with a stable mind, the majority of healthy volunteers had a good sleep.

6.4.2 Divaswapna (Day Sleep) (p<0.001)

As the night sleep disturbed, the majority of case group subjects (83.33%) were found to have day sleep, which leads to the formation of *Ama*, thereby it leads to the pathogenesis of *Amavata*. These findings are also supported by the mean duration of night sleep and day sleep in both groups. In the case group, the mean durations of night sleep and day sleep were 6.07 ± 0.95 and 1.25 ± 0.85 hrs per day, respectively. In the control group, the mean durations of night sleep and day sleep were 6.91 ± 0.75 and 0.28 ± 0.51 hrs per day respectively. The mean duration of night sleep was significantly less in the case group; day sleep was significantly more in the case group. It reflects *Ruksha guna* of *Vata* predominance in the case group, *Guru* and *Snigdha Gunas* of *Kapha* in the control group.

6.4.3 Nidra Viparyaya (p<0.001)

It means irregular sleep patterns, which might be due to persistent pain in the affected joints. Despite *Deha-Prakriti*, other reasons may influence sleep, such as emotional disturbances, socio-economic problems, etc. A total of 82% (n = 128) were found to have sleep disturbances. Sleep disturbances, including insomnia, independently contribute to the risk of inflammatory disorders and major depressive disorder[32]. The discovery of reciprocal connections between the central nervous system, sleep, and the immune system has shown that sleep enhances immune defences and that afferent signals from immune cells promote sleep. One mechanism by which sleep is proposed to provide a survival advantage is supporting a naturally integrated immune system that might anticipate injury and infectious threats. However, in modern times, chronic social threats can drive the development of sleep disturbances in humans, contributing to the dysregulation of inflammatory and antiviral responses[33].

Modern research works reported that sleep is hypothesized to be a restorative process that is important for the immune system's proper functioning. The severity of disordered sleep in depressed and alcoholic subjects correlates with declines in natural and cellular immunity and is associated with alterations in the complex cytokine network. Sleep loss has a role in mediating these immune changes as experimentally induced partial night sleep deprivation replicates the kind of sleep loss found in clinical samples and induces a pattern of immune alterations similar to that found in depressed and alcoholic patients. Despite evidence that sleep and sleep loss affect immune processes and nocturnal secretion of cytokines, the clinical significance of these immune changes is unknown[34].

6.5 Bowel Patterns

6.5.1 Bowel Irregularity (p<0.001)

68% of the case group individuals were presented with irregular bowels, whereas 94.67% of the control group individuals were presented with regular bowels. It reflects the usage of digestive aids in case and control groups. It is because of impaired digestive capacity and dominance of *Vata* in the case group. To regularise their bowels, the maximum number of patients, i.e., 70% were using laxatives, 16% were using antacids, 6.67% were using digestives, and 0.67% were using carminatives. On the other hand, 98% of healthy volunteers were not using any digestive aids, 1.33% were using antacids, and 0.67% were using laxatives.

6.5.2 Bowel Frequency(p<0.001)

It was categorized one time of bowels as fewer bowel, two times as moderate or normal, more than 2 times as aggregated bowel frequencies. Less bowel frequency was found majorly in the case group (50.67%), markedly more than the control group (1.33%). In most of the controls (96%), normal bowel frequency was found. It is a result of more prevalence of *Vata* with its *Laghu*, *Ruksha Gunas* and recurrent formation of *Ama* in the case group; more prevalence of *Pitta* and increased digestive capacity, which protects from the formation of *Ama* in the control group.

6.5.3 Stool Consistency (p<0.001)

The majority of the case group (66.67%) was found to have hard stools, whereas the majority of controls (97.33%) were found to have semi-solid stools. It shows more weight of constipation, irregular bowel habits, and less bowel frequency in the case group. Overall, it can be determined that irregular bowel patterns, less bowel frequency, and a hard type of stools cause constipation due to the weightage of *Laghu* and *Ruksha Gunas* of *Vata* in the case group.

6.5.4 Constipation (p<0.001)

70% of *Amavata* patients have had constipation, whereas 97.33% of the controls were presented as not having constipation. It indicates the prevalence of digestive issues in the case group, as there is the predominance of *Laghu*, *Ruksha Gunas* of *Vata*. Any type of digestive issue is not noticed in the control group, as *Pitta* is predominant. Disturbed night sleep, night awakening, and lack of *Vyayama* trigger constipation, which was more prevalent in the case group. It was also confined to the assessment of *Deha-Prakriti* as the majority of the cases (patients of *Amavata*) were found to have *Vata* predominant and their *Krura-Koshtha* (unpredictable digestive system in nature) which produces *Ama*, manifest *Amavata*. It can be correlated with the triggering of the auto-immune mechanism, thereby the manifestation of RA.

6.6 Occupational Stress (p<0.001)

Comparatively, the majority of the *Amavata* subjects (59.33%) had occupational stress. As the majority of subjects of *Amavata* were having *Vataja Pradhana Deha-Prakriti*, and they have *Alpa Bala* (less physical strength), *Alpa Sattva* (less psychological strength), due to the predominance of *Rajoguna*, *Asahishnuta* and they are not able to tolerate work stress and non-adjustment nature. On the other hand, most healthy individuals in the control group were not had any occupational stress as they have *Pittaja*, *Kaphaja Pradhana Deha-Prakritis*. It has been also proved by Baghel, *et al.,*[35] and Goswami, *et al.*[36].

6.7 Type of Meal Consumption (p<0.001)

The majority of *Amavata* patients were found to have non-specific (81.33%) and irregular (79.33%) types of dietary patterns because of the predominance of *Chapalachitta* (fickle mind). Moreover, as a result of Viruddhashana (82.58%) and Vishamashana (87.10%), the chances for the formation of *Ama* were more in the case group. On the contrary, the majority of healthy individuals (95.09%) were found to have healthy dietary habits, which protect them from the formation of *Ama* in the body. Due to the predominance of *Rajoguna*, and *Chapalachitta*, carvings for the food timings may vary or not be fixed. Further studies can be planned with more emphasis on the food ingredients and their preparation patterns will pave a roadmap to prescribe the right food preparatory methods, thereby, it will be easier to prevent the disease causation.

6.8 Psychological Condition (p<0.001)

It is delineated that even though an individual who consumes *Pathya* (wholesome) and *Matravat Ahara* (appropriate quantity of food, i.e., neither less nor excess), if his or her mind is afflicted with *Chinta* (worry), *Bhaya* (fear), *Shoka* (grief), *Krodha* (anger), *Dukha* (irritability), the *Ama* will be formed in their body[37,38]. On the other hand, healthy individuals were found to have sound psychological status. They are less afflicted with these factors. The maximum number of *Amavata* subjects were found to have emotional disturbance which plays a crucial role in the causation and increases the pain. Emotional disturbance envelopes several causes in both the genders, such as poor economic status, joint family, excessive physical work, the sudden demise of dearest ones, financial problems, disturbed marital life, Bad Obstetric History (BOH) including repeated abortions, infertility, etc. As the reason for emotional disturbance or imbalance varies in each individual, the overall emotional disturbance is considered and not the reason behind it. This gives a scope for further studies if a well planned and executed analytical observational study either a case-control or a cohort study, definitely help to explore

the specific reason more prevalent in the diseased individual, thereby, it can be very easy to prevent the disease manifestation by finding the correct solution of the cause.

6.9 Association of Emotional Disturbance in the Immune Dysregulation[39] (p<0.001)

Recent findings indicate that people living with Posttraumatic Stress Disorder (PTSD) have higher circulating T-cell lymphocytes and lower cortisol levels, suggesting that chronic sufferers of PTSD may be at risk for autoimmune diseases like RA. Besides, patients with comorbid PTSD were more likely to have clinically higher T-cell counts, hyper-reactive immune responses on standardized delayed cutaneous hypersensitivity tests, clinically higher immunoglobulin-M levels, and clinically lower dehydroepiandrosterone levels. The latter clinical evidence confirms the presence of biological markers consistent with a broad range of inflammatory disorders, including cardiovascular and autoimmune diseases.

Emotional disturbance is now recognized as an important risk factor in the pathogenesis of autoimmune rheumatic diseases, including RA. The stress response system's activation influences the close relationship between the hypothalamic-pituitary-adrenal axis, the sympathetic nervous system, and the immune system[40]. The quality of the relationship between the patient and his family and other social factors were found to be useful prognostic factors in patients with RA[41]. Hence, RA is an example of a stress-related disease that is induced by emotional disturbance.

Overall, it has been found that the positive family history, joint family, *Avyayama* (lack of physical activity), disturbed sleep, *Diwaswapna* (day sleep), constipation, *Atishrama* (occupational stress), *Adhyashana*, *Vishamashana*, *Viruddhashana*, and altered psychological status were found to have a positive association, whereas, a negative family history, nuclear type of family, sound sleep, *Vyayama*, *Samashana*, and non-afflicted psychological status were found to have a negative association with *Amavata* (~RA). Patient counselling using motivational interviewing has been shown to reduce maladaptive behaviours and promote beneficial health behavioural changes in the long term[42]. Motivational interviewing may be used to help people avoid bad eating habits, a poor lifestyle, and *Prajnaparadha* (intellectual errors). Understanding the significance of the research may be done by looking at how evidence-based epidemiological studies are incorporated into public health policy[43]. In terms of preventing risky behaviour, a population and high-risk strategy should be taken into consideration[10,44].

7. Limitations

The present study covered only a limited population, focusing on a specific regional population (Jamnagar and its peripheries). A multi-centric study covering a large scale of subjects will explore further factors responsible for disease causation. Incorporating genotype analysis of HLA DRβ1, immunity markers, and stress indicators and comparing it with *Deha-Prakriti*, thereby pinpoint prediction of susceptibility can be achieved with robust evidence.

8. Conclusion

Based on the observations and discussion, it can be concluded that positive family history, *Avyayama* (lack of physical activity), *Diwaswapna* (day sleep), disturbed night sleep, constipation, *Atishrama* (occupational stress), faulty dietary patterns viz. *Adhyashana*, *Vishamashana*, *Viruddhashana*, and disturbed emotional status (*Chinta*, *Bhaya*, *Shoka*, and *Krodha*) were found as the risk factors, whereas negative family history, nuclear type of family, sound sleep, *Vyayama*, *Samashana*, and non-afflicted psychological status were found as the protecting factors to the causation of *Amavata* (RA) and both the aspects were found statistically significant. The community-based awareness campaigns to be conducted to educate the people about the importance of healthy dietary patterns and lifestyle regimens to prevent the disease are recommended.

9. References

1. Sproesser G, Ruby MB, Arbit N, Akotia CS, Alvarenga Md, Bhangaokar R, *et al*. Understanding traditional and modern eating: The TEP10 framework. BMC Public Health. 2019; 19:1606(2019). https://doi.org/10.1186/s12889-019-7844-4

2. Huang T, Mariani S, Redline S, *et al*. Sleep irregularity and risk of cardiovascular events. J Am Coll Cardiol. 2020; 75(9):991-9. https://doi.org/10.1016/j.jacc.2019.12.054
3. Stein DJ, Benjet C, Gureje O, Lund C, Scott KM, Poznyak V, van Ommeren M. Integrating mental health with other non-communicable diseases. BMJ (Clinical research ed.). 2019; 364:l295. https://doi.org/10.1136/bmj.l295
4. Uhlig T, Moe RH, Kvien TK. The burden of disease in rheumatoid arthritis. Pharmacoeconomics. 2014; 32(9):841-51. https://doi.org/10.1007/s40273-014-0174-6 PMID: 24859304.
5. Pt. Hari Sadashiva Shastri Paradakara, Ashtangahridayam of Vagbhata, Sarvangasundari commentary by Arunadatta and Ayurvedarasayana commentary by Hemadri, Sharirasthana, Ch. 8, Ver. 13, Varanasi: Chaukhambha Sanskrit Sansthan, Reprint; 2018. p. 150.
6. Acharya YT. Madhavanidana of Sri Madhavakara, Madhukosha Sanskrit Commentary by Srivijayarakshita and Atankadarpana commentary Srikanthadatta, Ch. 6, Ver.7, 1st edition, Bombay:Nirnaya Sagar press; 1932. p. 85.
7. Acharya YT. Sushruta Samhita of Sushruta, Sutra sthana. Ch. 46. Ver. 500-501. Reprint ed. Varanasi:Chaukhambha Surbharati Prakashan; 2014. p. 251.
8. Acharya YT. Charaka Samhita of Agnivesha, Vimana Sthana. Ch. 2. Ver. 9. Reprint ed. Varanasi:Chaukhambha Surbharati Prakashan; 2014. p. 238.
9. Acharya YT. Charaka Samhita of Agnivesha, Chikitsa Sthana. Ch. 15. Ver. 42. Reprint ed. Varanasi: Chaukhambha Surbharati Prakashan; 2014. p. 517.
10. Bishop FL, Lauche R, Cramer H, Pinto JW, Leung B, Hall H, *et al*. Health behavior change and complementary medicine use: National Health Interview Survey 2012. Medicine (Kaunas). 2019; 55(10):632. https://doi.org/10.3390/medicina55100632 PMID: 31554323; PMCID: PMC6843558.
11. David D, Moyses S. Gorddis epidemiology. 6th ed. Philadelphia. Chapter Epidemiological approach to disease and intervention.
12. Bhalerao S, Parab S. Study designs. Int J Ayurveda Res. 2010; 1(2):128. https://doi.org/10.4103/0974-7788.64406
13. Sample size for a case-control study (ausvet.com.au) [Internet]. [cited 2021 Aug 29]. Available from https://epitools.ausvet.com.au/casecontrolss
14. Rastogi S, Singh RH. Development of diagnostic criteria for Amavata: Inferences from a clinical study. J Res Ayurvedic Sci. 2009; XXX(03):1-10.
15. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988; 31(3):315-24. https://doi.org/10.1002/art.1780310302 PMID: 3358796.
16. Straub RH. The complex role of estrogens in inflammation. Endocr Rev. 2007; 28:521-74. https://doi.org/10.1210/er.2007-0001
17. Hughes GC, Choubey D. Modulation of autoimmune rheumatic diseases by oestrogen and progesterone. Nat Rev Rheumatol. 2014; 10:740-51. https://doi.org/10.1038/nrrheum.2014.144
18. Tan IJ, Peeva E, Zandman-Goddard G. Hormonal modulation of the immune system—A spotlight on the role of progestogens. Autoimmun Rev. 2015; 14:536-42. https://doi.org/10.1016/j.autrev.2015.02.004
19. Keith RC, Sokolove J, Edelman BL *et al*. Testosterone is protective in the sexually dimorphic development of arthritis and lung disease in SKG mice. Arthritis Rheum. 2013; 65:1487-93. https://doi.org/10.1002/art.37943
20. Burkhardt J, Petit-Teixeira E, Teixeira VH, *et al*. Association of the X-chromosomal genes TIMP1 and IL9R with rheumatoid arthritis. J Rheumatol. 2009; 36:2149–57. https://doi.org/10.3899/jrheum.090059
21. Gomez A, Luckey D, Yeoman CJ, *et al*. Loss of sex and age driven differences in the gut microbiome characterize arthritis-susceptible 0401 mice but not arthritis-resistant 0402 mice. PLoS One. 2012; 7(4). https://doi.org/10.1371/journal.pone.0036095
22. Available from: https://www.mcjamnagar.com/Home.aspx, accessed on 29.08.2021.
23. Upadhyaya Y. Madhavanidana of Sri Madhavakara, Madhukosha Sanskrit Commentary by Srivijayarakshita and Srikanthadatta with Vidyotini Hindi Commentary, Volume 1, Ch. 25, Ver.1, Varanasi: Chaukhambha Prakashan, Reprint; 2016. p. 508.
24. Acharya YT. Charaka Samhita of Agnivesha, Vimana Sthana., Ch. 2. Ver. 9. Reprint ed. Varanasi: Chaukhambha Surbharati Prakashan; 2014. p. 238-9.
25. Acharya YT. Charaka Samhita of Agnivesha, Chikitsa Sthana., Ch. 28. Ver. 15-18. Reprint ed. Varanasi: Chaukhambha Surbharati Prakashan; 2014. p. 617.
26. Frisell T, Holmqvist M, Källberg H, Klareskog L, Alfredsson L, Askling J. Familial risks and heritability of rheumatoid arthritis: role of rheumatoid factor/anti-citrullinated protein antibody status, number and type of affected relatives, sex, and age. Arthritis and Rheumatism. 2013; 65(11):2773-82. https://doi.org/10.1002/art.38097
27. Acharya YT. Charaka Samhita of Agnivesha, Sutra Sthana. Ch.7. Ver. 32. Reprint ed. Varanasi: Chaukhambha Surbharati Prakashan; 2014. p. 50-1.
28. Acharya YT. Chakrapanidutta's Ayurveda Deepika commentary, Charaka Samhita of Agnivesha, Sutra Sthana. Ch.7. Ver. 32. Reprint ed. Varanasi: Chaukhambha Surbharati Prakashan; 2014. p. 50-1.

29. Acharya YT. Charaka Samhita of Agnivesha, Sutra Sthana. Ch.14. Ver. 64. Reprint ed. Varanasi: Chaukhambha Surbharati Prakashan; 2014. p. 92.
30. Owen L, Sunram-Lea SI. Metabolic agents that enhance ATP can improve cognitive functioning: A review of the evidence for glucose, oxygen, pyruvate, creatine, and L-carnitine. Nutrients. 2011; 3(8):735-55. https://doi.org/10.3390/nu3080735
31. Codella R, Luzi L, Terruzzi I. Exercise has the guts: How physical activity may positively modulate gut microbiota in chronic and immune-based diseases. Dig Liver Dis. 2017; 50(4):331-41. https://doi.org/10.1016/j.dld.2017.11.016
32. Irwin MR, Opp MR. Sleep health: Reciprocal regulation of sleep and innate immunity. Neuropsychopharmacology. 2017; 42(1):129-55. https://doi.org/10.1038/npp.2016.148
33. Irwin MR. Sleep and inflammation: Partners in sickness and in health. Nat Rev Immunol. 2019; 19(11):702-15. https://doi.org/10.1038/s41577-019-0190-z
34. Irwin M. Effects of sleep and sleep loss on immunity and cytokines. Brain Behav Immun. 2002; 16(5):503-12. https://doi.org/10.1016/S0889-1591(02)00003-X
35. Baghel AS, Dwivedi RR. A fundamental and applied study of Prakriti and its influence on profession and vice-versa. Ph.D. Dissertation Submitted to Gujarat Ayurved University, Jamnagar; 2004.
36. Goswami C, Vyas MK, Baghel AS, Hitesh A. Vyas influence of DP on medical profession. PG Dissertation Submitted to Gujarat Ayurved University, Jamnagar; 2016.
37. Acharya YT. Charaka Samhita of Agnivesha, Vimana Sthana. Ch. 2. Ver. 8-9. Reprint ed. Varanasi: Chaukhambha Surbharati Prakashan; 2014. p. 238.
38. Acharya YT. Sushruta Samhita of Sushruta, Sutra sthana. Ch. 46. Ver. 500-501. Reprint ed. Varanasi: Chaukhambha Surbharati Prakashan; 2014. p. 251.
39. Boscarino JA. Posttraumatic stress disorder and physical illness: Results from clinical and epidemiologic studies. Ann N Y Acad Sci. 2004; 1032:141-53. https://doi.org/10.1196/annals.1314.011
40. Cuolo M, Straub RH. Stress as a risk factor in the pathogenesis of rheumatoid arthritis. Neuroimmunomodulation. 2006; 13(5-6):277-82. https://doi.org/10.1159/000104855
41. Hutchins J, Erkan D, Yazici Y, Robbins L. Patients' perspective of autoimmune diseases in Abstract book from 7th Intern Congress of SLE, NY; 2004.
42. Zaccardelli A, Friedlander HM, Ford JA, Sparks JA. Potential of lifestyle changes for reducing the risk of developing rheumatoid arthritis: Is an ounce of prevention worth a pound of cure? Clin Ther. 2019; 41(7):1323-45. https://doi.org/10.1016/j.clinthera.2019.04.021 PMID: 31196646; PMCID: PMC6684958.
43. Davis, FG, Peterson CE, Bandiera F, Carter-Pokras O, Brownson RC. How do we more effectively move epidemiology into policy action? Annals of Epidemiology. 2012; 22(6):413-16. https://doi.org/10.1016/j.annepidem.2012.04.004
44. David D, Moyses S. Gorddis epidemiology. 6th ed. Philadelphia. Chapter Epidemiological approach to disease and intervention.