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RESEARCH

Anatomic analysis of etiology and incidence of melasma development in women

Kadınlarda melazma gelişim sıklığı ve etiyolojisinin anatomik analizi

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Abstract

Purpose: Melasma is a condition originating from facial hyperpigmentation, significantly affecting quality of life. While its etiology is multifactorial, lifestyle and external factors are crucial in its manifestation. The main objective of this study was to unveil the relationship between environmental factors and melasma incidence numerically. Also, optimizing the treatment strategies and aiding the development of computerized diagnostic tools were aimed.

Materials and Methods: Data was collected from 100 volunteer women in the Cukurova region of Turkey via questionnaire. Multiple computational approaches and statistical tests were used to analyze associated with melasma and environmental factors such as body mass index, sports status, and smoking.

Results: The relationship between the environmental factors (such as body mass index ($p<0.001$, $r=0.47$), sports status ($p<0.001$, $r=19.3$), and smoking ($p<0.001$, $r=16$)) and melasma was found to be significant. Our findings also highlight the potential role of several features like regular medicine intake ($p<0.001$ $r=14$), chronic diseases ($p=0.001$, $r=10.2$), and water consumption ($p<0.001$, $r=-0.373$) in melasma development.

Conclusion: Our study contributes to the literature on the incidence and etiology of melasma in the Cukurova regional population of Turkey. Moreover, this study provides foundational insights for the future development of a machine learning-based classification mechanism to enhance treatment efficiency and patient satisfaction.

Keywords:. etiology, incidence, facial hyperpigmentation, lifestyle, melisma

Öz

Amaç: Melazma fasiyal hiperpigmentasyondan kaynaklanan, yaşam kalitesini önemli ölçüde etkileyen bir durumdur. Etiyolojisi çok faktörlü olmakla birlikte, ortaya çıkışında yaşam tarzı ve dış faktörler çok önemlidir. Bu çalışmanın temel amacı çevresel faktörler ile melazma görülme sıklığı arasındaki ilişkiyi sayısal olarak ortaya koymaktır. Ayrıca tedavi stratejilerinin optimize edilmesi ve bilgisayarlı tanı araçlarının geliştirilmesine yardımcı olunması da amaçlanmıştır.

Gereç ve Yöntem: Akdeniz bölgesindeki 100 gönüllü kadından anket yoluyla veriler toplandı. Verileri analiz etmek için çoklu hesaplamalı yaklaşımlar ve istatistiksel testler kullanıldı ve vücut kitle indeksi, spor durumu ve sigara içme gibi çevresel faktörlerin melazma ile ilişkisi incelendi.

Bulgular: Çalışmamızda incelediğimiz çevresel faktörler (vücut kitle indeksi ($p<0.001$, $r=0.47$), spor durumu ($p<0.001$, $r=19.3$) ve sigara içme ($p<0.001$, $r=16$) gibi) ve melasma ilişkisi anlamlı bulunmuştur. Bulgularımız aynı zamanda düzenli ilaç alımı ($p<0.001$ $r=14$), kronik hastalıklar ($p=0.001$, $r=10.2$) ve su tüketimi ($p<0.001$, $r=-0.373$) gibi çeşitli özelliklerin melazma gelişimindeki potansiyel rolünü de ortaya koymuştur.

Sonuç: Çalışmamız Akdeniz toplumunda melazmanın görülme sıklığı ve etiyolojisi konusunda literatüre katkı sağlamaktadır. Ayrıca bu çalışma, tedavi verimliliğini ve hasta memnuniyetini artırmak için makine öğrenimine dayalı bir sınıflandırma mekanizmasının gelecekteki gelişimi için temel bilgiler sunmaktadır.

Anahtar kelimeler: etiyoloji, görülme sıklığı, yüz hiperpigmentasyonu, yaşam tarzı, melazma

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INTRODUCTION

The skin is an organ that gives an idea about our general body health, ethnicity, lifestyle, and age. As we progress through time, our skin undergoes various changes, manifesting as wrinkles, roughness, laxity, and uneven pigmentation [1]. Hyperpigmentation, a frequently encountered condition in dermatology clinics, refers to the darkening of the skin color. It is a cosmetic concern that can occur in the epidermis, dermis, or both, and it is particularly prevalent in the Mediterranean region [2]. Melasma, the most common hypermelanosis of the face, significantly affects the quality of life [3]. Also, melasma typically presents as symmetrical, homogenous, irregular patches or macules in shades ranging from light to dark brown. While melasma is more commonly observed in women, it has also been reported in approximately 10% of men [4]. Although melasma is asymptomatic, when it is found on the face, it can become a cosmetic and psychosocial problem that can adversely affect people's social relationships and quality of life.

Melasma treatment can be based on various modalities, such as topical treatments (hydroquinone, azelaic acid, glutathione, n-acetylcysteine, topical corticosteroids, and others), triple combination therapies (Westerhof formula, Kligman formula), dual combination treatments, semi-drugs, traditional medicine systems (Ayurveda and Unani), systemic treatments (vitamins, procyanidin), laser treatments (fractional), and physical modalities (dermabrasion, chemical peeling, TCA(trikarboksilik asit), and more) [5,6]. The multifactorial etiology of melasma necessitates a personalized treatment strategy based on these modalities. Understanding the primary factors that define melasma's etiology can significantly enhance treatment efficiency [1-3]. Furthermore, identifying these key variables is crucial in developing computer-aided planning or diagnostic tools.

The hypothesis of our study was determined as "Melasma formation is affected by environmental factors." So the primary goal of this study was to identify and examine the most impactful lifestyle factors. Moreover, this study aims to lay the groundwork for the future development of a computer-aided system, assisting doctors and patients in treatment planning. It is worth noting that the analysis in this study aims to inform long-term strategies rather than immediate treatment approaches. Addressing the etiological factors of melasma, in conjunction with treatment, will also enhance treatment effectiveness and expedite the healing process.

MATERIALS AND METHODS

Sample

Data is collected from one hundred volunteer women aged 24 to 55 who reside in the Cukurova region of Turkey. Half of the participants were diagnosed with melasma, while the remaining half were classified as healthy.

Inclusion criteria were; being volunteer women aged 24 to 55, diagnosed with facial melisma, patients who applied to the clinic in the last five years (2018-2023). It should be noted that all melasma cases included in the study were diagnosed for the first time. They had not undergone any previous melasma treatment and not initiated any treatment at the time of data collection.

Informed consent was obtained from all subjects involved in the study and the necessary permissions for the research were obtained from the Cukurova University Faculty of Medicine Non-invasive Clinical Research Ethics Board, with number 132/29. In addition, the experimental procedures were conducted in accordance with the Declaration of Helsinki.

Power analysis reveals that with 50 participants in each group (totaling 100 participants), our study design can detect an effect size of Cohen's $d \geq 0.5$ with a power of approximately 0.676 under a two-tailed test with an alpha level of 0.05, using the Mann-Whitney U test. Although the power of 0.676 falls below the standard threshold of 0.80, it is robust enough to identify medium-to-significant effects, which are our main focus as we investigate how lifestyle factors influence melasma.

Data collection and classification

The participants' skin type and melasma classes were classified through photographs with a full face imaging system (Observ 520, InnoFaith Beauty Sciences, Eindhoven, Netherlands). Assessment of the skin type was completed with clinical evaluation of the photographs. Subsequently, a clinical evaluation of the participants' skin type was conducted using photographs and the Fitzpatrick scale, which categorizes skin into five levels, ranging

from "I" (lightest) to "V" (darkest) [7]. Furthermore, the classes of melasma cases were determined based on the melasma-type scale using the photographs [7]. Sample photographs from the dataset representing different melasma cases are presented in Fig. 1.

Figure 1. Centrofacial type (A), malar type (B) and mandibular type (C) of melasma.

Each melasma case was assigned to one of the three classes which are:

Centrofacial: The macules occupying the forehead, cheeks, nose, upper lips, and chin (Fig. 1A).

Malar: The macules are confined to the cheeks and nose (Fig. 1B).

Mandibular: The macules are seen over the ramus of the mandible (Fig. 1C).

The study aimed to uncover the etiology of melasma by gathering data on additional variables through a questionnaire that examined crucial factors related to participants' lifestyle and medical history. Table 1 lists the variables assessed through the questionnaire, providing insights into the factors influencing melasma development.

Survey analysis

This study aims to quantify the relationship between lifestyle and melasma in a specific geographic population. The survey collected information on the following topics; age, body mass index, smoking status, alcohol use, number of pregnancies, frequency of red meat consumption, frequency of sunscreen use, cancer in family history, daily water consumption, level of exercising, sleep duration, frequency of makeup application, hormone therapy status, medicine usage, chronic disease. The survey was applied on paper, and a voluntary consent form was signed beforehand. We explored which factors most influence melasma with several computational approaches. Data was gathered from surveys of individuals with and without melasma and then analyzed using a computer. The survey content was created as a result of literature review, taking into account the etiology of hyperpigmentation. The variables within the data set were categorical or continuous values within defined ranges. The optimal criterion for automated estimation varies based on the data's characteristics and the problem being addressed. Each factor was accepted as a feature that characterize an observation (individual) and several analytical methods were employed within the MATLAB framework to assess feature significance. Detailed explanations of each test are provided in the subsequent sections.

The t-statistic with pooled variance

In our analysis, MATLAB's "rankfeatures" function was utilized for feature ranking, employing the absolute value two-sample t-test with pooled variance estimate. This approach computes the difference in means of each feature between the two populations. Larger values suggest a more substantial discriminatory power between the two classes.

The relative entropy (KL Divergence)

We similarly utilized MATLAB's "rankfeatures" function to rank the features with the Kullback-Leibler (KL) divergence, commonly known as relative entropy. The KL divergence quantifies the dissimilarity between two probability distributions. A higher KL value indicates the distinction of the feature distributions.

Minimum redundancy maximum relevance

We employed MATLAB's "fscmrmr" function for feature selection, which implements the Minimum Redundancy Maximum Relevance (MRMR) algorithm. The MRMR methodology selects features highly correlated with the target variable while being mutually non-redundant. This algorithm ensures that the chosen features have strong predictive power and provide diverse, non-overlapping information.

Statistical analysis

Statistical analysis was conducted using the SPSS v.22 software (IBM SPSS Statistics, Chicago, IL, USA). Pearson's correlation coefficient test was performed for continuous variables, while the categorical variables were evaluated with the Chi-Square Test of Independence to assess the relationship between patients' lifestyle attributes and melasma. It should be noted that binary grouping (melasma, non-melasma)

is applied for both of the tests. A significance level of p=0.05 was deemed statistically significant.

RESULTS

In each test, features were assigned rankings between 1 and 15, where 1 represents the most significant feature and 15 the least. The results can be found in Table 1. The Borda count technique is used to determine an overall ranking based on the test results. In this method, the most significant feature (ranked first) receives 14 points, and the least significant feature (ranked 15th) receives 0 points. The Borda count rank for each feature is determined by the sum of its points from all tests. The results are presented in Fig. 2. In addition to feature importance tests, statistical tests were applied to reveal the effect of external factors on melasma. BMI (body mass index), sports activity, and smoking status are the most significant factors associated with melasma, showing strong statistical correlations and high Borda rankings. Medicine usage, water consumption, and chronic disease also demonstrate notable associations with melasma, backed by significant statistical evidence and moderate to substantial Borda points. It should be noted that a low correlation was found between melasma and sunscreen use, number of pregnancies, and family history of skin cancer. Results, indicating the possible role of evaluated factors presented in Table 3.

Table 1. Descriptions of the analyzed attributes are presented with minimum and maximum values.

No	Feature Description	Minimum	Maximum
1	Age of the participant (Continuous Variable)	24	55
2	Body mass index (Continuous Variable)	20.1	28.2
3	Smoking status (1: Yes, 2: No)	1	2
4	Alcohol Use (1: Regular, 2: Occasional, 3: No)	2	3
5	Number of pregnancies	0	3
6	Frequency of red meat consumption (1: Regular, 2: Occasional, 3: No)	1	3
7	Frequency of sunscreen use (1: Regular, 2: Occasional, 3: No)	1	2
8	Existence of skin cancer in family history (1: Yes, 2: No)	1	2
9	Daily water consumption (Continuous Variable)	1.5	4
10	Level of exercising (1: Regular, 2: Occasional, 3: No)	1	3
11	Sleep Duration	6	9
12	Frequency of makeup application (1: Regular, 2: Occasional, 3: No)	1	3
13	Hormone therapy status (1: Yes, 2: No)	1	2
14	Medicine Usage (1: Yes, 2: No)	1	2
15	Chronic disease (1: Yes, 2: No)	1	2

Table 2. Ranks of the attributes for each test are presented. Each number indicates the order of the feature with respect to its significance. Most significant features are indicated with 1.

Attribute	T-Test	Entropy	MRMR
Age	6	9	8
Body mass index	1	3	1
Smoking status	3	8	2
Alcohol use	9	11	7
Number of pregnancies	13	14	14
Frequency of red meat consumption	10	13	12
Frequency of sunscreen use	15	15	15
Cancer in Family History	14	1	10
Daily water consumption	5	7	3
Level of exercising	2	6	4
Sleep Duration	11	12	13
Frequency of makeup application	8	10	11
Hormone therapy status	12	2	9
Medicine Usage	4	5	6
Chronic Disease	7	4	5

MRMR; Minimum Redundancy Maximum Relevance

Table 3. Statistical test results are given to showcase the degree of relation between evaluated attributes and melasma types.

Continuous Variables		
Attribute	**Pearson's correlation (df=2)**	
	r	p
Age	0.366	< .001
Body mass index	0.47	< .001
Daily water consumption	-0.373	< .001
Categorical Variables		
Attribute	**Chi-Square**	
	H	p
Smoking Status	16	< .001
Alcohol Use	4.89	0.027
Number of pregnancies	2.55	0.466
Frequency of red meat consumption	3.19	0.203
Frequency of sunscreen use	0	1
Cancer in Family History	1.01	0.315
Level of exercising	19.3	< .001
Sleep Duration	6.01	0.111
Frequency of makeup application	5.73	0.057
Hormone therapy status	2.04	0.153
Medicine Usage	14	< .001
Chronic Disease	10.2	0.001

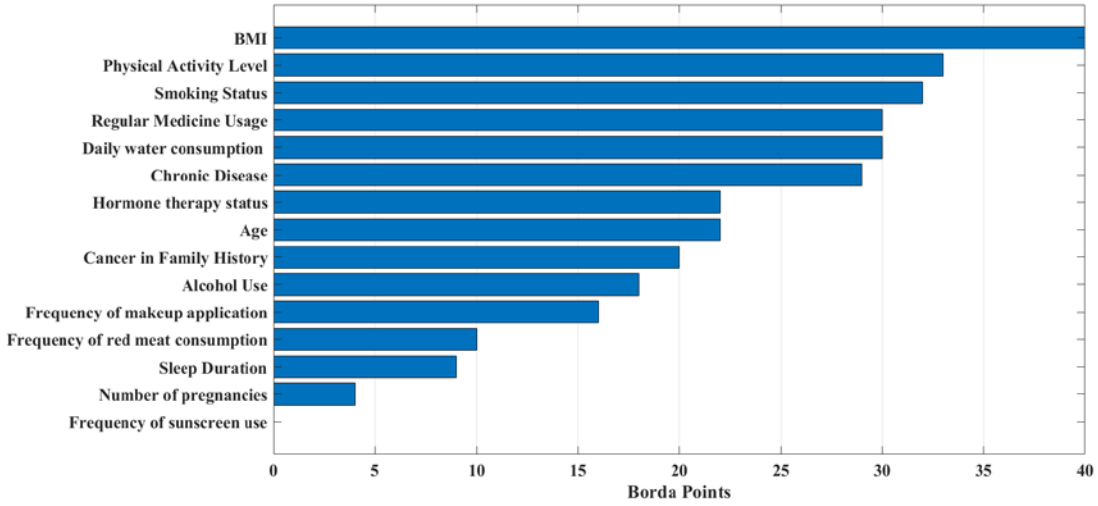

Figure 2. Feature importance based on Borda points.

DISCUSSION

Melasma is hypermelanosis of the skin. It is also the most common form of facial hyperpigmentation [8]. The two most important factors in its etiology are sun exposure and genetic predisposition. Pregnancy, hormone treatments (oral contraceptives), cosmetics, phototoxic drugs, thyroid dysfunction, emotional factors and anticonvulsant drugs are also held responsible. It is also reported in the literature that it is more common in women of reproductive age[9-10]. Age has scored with moderate Borda points, suggesting some relevance, and is also supported by a significant correlation with melasma.

Moreover, BMI received the highest Borda points. Statistical analyses underscored a significant positive correlation, strengthening the case for BMI being an important predictor. This suggests that individuals with a higher body mass index are more susceptible to melasma, raising the hypothesis that not exercising might also make people more likely to get this condition. Our study also explored the sporting habits of participants, which scored high on Borda points, indicating strong relevance to melasma, as supported by the Chi-Square test results. It is plausible to conclude that the susceptibility to melasma increases in those less physically active. Exercising is important not just for overall health but also for keeping the skin healthy. This is because physical exercise affects melatonin secretion, a hormone that plays a key role in treating skin coloration issues[11]. This hormone is crucial for treating skin conditions that affect color, such as melasma.[12].

Moreover, melatonin plays a pivotal role in regulating the sleep cycle. Consequently, we examined the daily sleep hours of our study's participants. Despite this sleep duration exhibited low Borda points and did not demonstrate a significant association with melasma, based on our statistical evaluation.

Regarding smoking status, our study found that 48% of the participants smoked and 34% of smokers had melasma (centrofacial 12%, malar 11%, mandibular 11%). These results show that smoking increases the susceptibility to melasma formation. Tobacco contains a wide range of carcinogenic substances that have toxic and immunosuppressive effects on various organs, including the skin. There are many studies examining the relationship between skin cancer and smoking [13]. However, no study has examined the relationship between smoking and hyperpigmentation. In our study, it has been revealed that smoking has high relevance according to Borda points which is also supported by the statistical test showing a significant relationship with melasma.

Melanogenesis, the process of skin coloration, is influenced by UV radiation, hormones, genetics, pregnancy, thyroid issues, inflammation, cosmetics, certain medications (like oral contraceptives), and

reactive oxygen species, among other factors. Alcohol consumption also promotes reactive oxygen species production, similar to smoking[14]. Studies on the relationship between alcohol consumption and psoriasis and skin disease are widely available in the literature[15, 16]. However, its relationship with hyperpigmentation hasn't been extensively studied. In our research, 55% of participants consumed alcohol; 33% of these had melasma (distributed as 11% centrofacial, 11% malar, and 11% mandibular), compared to 22% without melasma. Among non-drinkers, 29% didn't have melasma, and 16% did (with a distribution of 5% centrofacial, 6% malar, and 5% mandibular). Many studies suggest alcohol impacts various skin diseases and can trigger acne[17]. Although alcohol had fewer Borda points in our study, the significant statistical connection indicates its importance, supporting literature findings.

Dietary habits cause various dermatologic diseases such as increased risk of several cancers. In the literature, it has been reported that especially dermatitis herpetiformis, atopic dermatitis, acne vulgaris, psoriasis vulgaris, pemphigus, urticaria, pruritus and allergic contact dermatitis are related with dietary habits [18]. However, there is no study examining the relationship with hyperpigmentation (melasma). In the studies conducted by Yen et al. and Rothberg et al. it was reported that red meat consumption was among the factors causing skin cancer [19,20]. In our study, we also questioned the degree of relationship between red meat consumption and melasma. However frequency of red meat consumption has fewer Borda points, which corresponds with the lack of statistical significance found in the Chi-Square test.

In addition, the materials applied to human skin for skin cleansing, skin care, and beauty purposes are chemical industrial products. These chemicals cause disruption of the skin barrier function and trigger melasma formation [21]. Among the chemicals to which our skin is exposed, make-up products also negatively affect the skin barrier. Therefore, melanin is synthesized and stored in melanocytes through oxidative reaction and transferred to neighboring keratinocytes through dendritic processes of melanocytes, thus hyperpigmentation occurs on the skin surface [22].

In our research, we looked at makeup use among participants. 26% of women with melasma wore makeup regularly, 19% wore it sometimes, and 2% never wore it. Among women without melasma, 15% never wore makeup. Makeup application received moderate Borda points, hinting at some importance, yet the statistical analysis showed the association was only marginally significant.

Occupational status is another factor affecting make-up application and thus melasma formation. Of the 50 women with melasma, 38 were professionals and 12 were housewives. In some professions, melasma formation increases especially due to sun exposure. Sun protection is also a very important rule in the treatment of melasma. Melanocyte cells that give color to the skin secrete excessive melanin due to factors such as pregnancy, sun exposure, genetic predisposition, use of birth control pills and exposure to cosmetic products (make-up materials, perfumes, soaps and creams) and thus skin staining occurs [23]. However, sun protection factor has the lowest Borda points and was found to have no association with melasma in the statistical analysis. We think that this is due to the fact that all of our participants used sunscreen regularly and occasionally and there were no participants who did not use sunscreen. While 32% of those without melasma used sunscreen regularly, 18% used it occasionally.

Another factor is the number of pregnancies, which scored the second-lowest Borda points, aligning with the statistical analysis that showed no significant association. Considering the pathophysiology of melasma, the changes in estrogen and progesterone levels during pregnancy can increase melanocyte-stimulating hormone levels[24]. The lack of significant difference in our study might be attributed to the absence of pregnant participants. This is because the melasma caused by previous pregnancies might have resolved or never occurred. Hormonal changes during pregnancy lead to hyperpigmentation, and the use of birth control pills and hormone supplements can induce melasma formation[25]. Literature suggests that fluctuations in hormone levels can cause skin hyperpigmentation.

Additionally, regular sleep, another factor influencing melatonin levels, was examined in our study since the melatonin hormone aids in initiating sleep and potentially enhancing sleep quality. We inquired about the daily sleep hours of the women in our study. Research by Harlim et al., Vilar et al., and Gupta et al. indicates that irregular sleep patterns can provoke various dermatological conditions[26-28]. Yet, other studies highlight that the quality of sleep might be more significant than the quantity of sleep. In our analysis, sleep duration received low Borda points

and showed no significant correlation with melasma. However, 12% of the participants with melasma were healthcare professionals, suggesting that night shift work, such as in nursing or medicine, might contribute to melasma due to disrupted melatonin secretion.

Additionally, we asked the study volunteers about their regular medication use. Thirty-one percent of participants reported using medication regularly. Among these, two individuals were on hormone therapy, seventeen used birth control pills, five were on psychiatric medications, two took diabetes medication, one used hypertension medication, one was on epilepsy medication, and one underwent chemotherapy. Notably, all individuals using medications regularly were diagnosed with melasma. Our findings suggest that hormone therapy, birth control pills, and chemotherapy impact melasma, as stated in the literature. Moreover, the study implies that medications for psychiatric conditions, diabetes, hypertension, and epilepsy, as well as the chronic diseases themselves, may influence melasma development. This is supported by the significant number of Borda points attributed to chronic disease, reinforcing its significant association with melasma. The Borda ranking further indicates that regular medication usage is a critical factor, consistent with Chi-Square test results showing a significant association. However, to definitively claim the effect of these medications on melasma incidents, more participants are necessary. Thus, we advocate for additional research to explore the impact of various drugs and chronic conditions on melasma.

In our study, 16 of the participants using medication had centrofacial melasma, while one individual undergoing chemotherapy treatment exhibited mandibular melasma. This same individual, treated with chemotherapy, also has a genetic predisposition, as they were diagnosed with malignant melanoma and have a family history of skin cancer. Literature suggests that individuals with a family history of skin cancer are more prone to hyperpigmentation[29]. Within our study, one patient with a family history of skin cancer showed a lower Borda ranking, which corresponds with the statistical finding of no significant link to melasma. Nonetheless, it appears this patient's melasma was not widespread, potentially due to consistent sunscreen use, abstaining from alcohol and smoking, avoiding red meat, and drinking 3 liters of water daily.

Water, comprising 60-75% of our body, is crucial for cells and tissues. The "Dietary Guidelines for Americans 2010" recommend a daily water intake of 2.7 liters for women and 3.7 liters for men, while the "European Food Safety Authority" advises 2-2.5 liters per day. Although the link between skin health and water consumption is not definitively proven, it is widely acknowledged[30]. Our analysis found a significant negative correlation between water intake and melasma, underlining the importance of hydration. Participants without melasma reported higher water consumption. While specific studies on the relationship between melasma and water intake are lacking, there are studies indicating that water consumption and skin health are important [31].

Melasma treatment often combines laser therapy and cosmetics tailored to the root cause. The primary goal of our study was to reveal the relationship between environmental factors and melasma numerically. Through this, the optimization of the treatment strategy and computerized pathology diagnosis is intended to increase the efficiency of the treatment and patient satisfaction. We have determined the significant associations between melasma and factors like sports and smoking. Moreover, our analysis indicates that an individual's BMI significantly alters the likelihood of melasma incidence. It should be noted that the significant features identified in this study could serve as initial results for the development of a machine learning-based estimation mechanism for melasma.

Limitations of the study; In our study, the demographic characteristics and lifestyle of patients with melasma can be used in a classification mechanism based on machine learning. However, the relationship between melasma and melatonin has been shown at the level of evidence in many current studies, and although it is included in treatment protocols and its hormonal effect is of high evidence level, it is a limitation that the correlation between melatonin and hormones cannot be compared with biochemical findings in this study. We recommend conducting current studies examining the relationship between biochemical findings and lifestyle. We also recommend conducting similar studies that discuss the relationship between genders and include more people and male patients.

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