

Examination of associations between personality traits, and polymorphisms of MAO-A and 5-HTT with the severity of menopausal symptoms and depression levels

SEDIGHE ESMAEILZADEH¹, MOULOUD AGAJANI DELAVAR¹, HAMIDREZA NOURI²,
SEPIDEH MASHAYEKH-AMIRI³, NILOUFAR AHMADI³ and REZA NAMDAR⁴

¹Infertility and Reproductive Health Research Center, Health Research Institute;

²Cellular and Molecular Biology Research Center; ³Student Committee Research;

⁴Shahid Yahya Nezhad Hospital, Babol University of Medical Sciences,
Babol, Mazandaran 47135-547, Iran

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Abstract. The aim of the present study was to investigate the association between different personality traits with monoamine oxidase A (MAO-A) and serotonin transporter (5-HTT), and to examine their effects on the severity of menopause symptoms as well as the levels of depression in menopausal women. The study was designed as an analytical cross-sectional study, performed on 132 healthy post-menopausal women in Iran. Personality was assessed using the Revised Edition of the NEO Personality Index (Neuroticism-Extroversion-Openness-Five Factor Inventory). The symptoms score sheet, used for measuring menopausal symptoms, was used to classify the participants according to their menopausal symptoms. Furthermore, Beck Depression Inventory short version was also used to assess depressive symptoms. Examination of blood samples taken from all participants was to identify DNA polymorphisms of 5-HTT using PCR. The results of the present study showed that a high level of neuroticism ($P<0.0001$), low levels of extroversion ($P<0.002$), an openness to experience ($P=0.039$) and conscientiousness ($P=0.001$) were all positively associated with the severity of menopausal symptoms. In addition, a high level of neuroticism ($P<0.0001$), low levels of extroversion ($P<0.0001$), and a low level of agreeableness ($P<0.024$) and conscientiousness ($P<0.0001$) were all positively associated with depressive symptoms. There was no statistically significant association between MAO-A and 5-HTT polymorphisms with menopause and depression scores. Based

on these results, there appears to be a significant association between personality traits with both depression and menopausal symptoms. Identification of homogeneous groups of women who are predisposed to depression and severe menopausal symptoms may allow for the implementation of early prevention programs.

Introduction

A wide range of somatic disorders, psychiatric symptoms, sexual problems and vasomotor symptoms have been reported in menopausal women (1,2). It is also hypothesized that there are numerous clinical menopausal symptoms associated with hormonal changes, particularly estrogen deficiency; however, the physiological mechanisms by which estrogen modulates these symptoms remain unknown (3,4). Furthermore, there appears to be a wide range of menopausal symptoms which remain unknown (4). The personality of individuals is most likely to change between 50-65 years of age, and is supposedly in response to both physical and social circumstances (5). Similarly, several studies have demonstrated that personality traits may intensify menopausal symptoms (6,7).

Personality is an aspect of human life that can predict an individual's reaction to different situations. It is hypothesized that an individual's personality is the combination of traits and patterns, and that both environmental and genetic factors could, to a large extent, contribute to the formation of personality traits; the impact of environmental factors, particularly a deficiency of vitamin D (from living in regions without much sun or overcast regions), tend to affect anxiety, osteoporosis, quality of life and the development of personality (2,8-10). There are five personality traits: Conscientiousness, agreeableness, neuroticism, openness to experience and extroversion. Neuroticism is a tendency to exhibit negative emotions, such as depression, anxiety or anger. Extroversion is associated with socialization, excitement and partaking in activities. Agreeableness, is considered a super trait personality among the five traits, and is characterized as being cooperative, caring, nurturing of others and affectionate (11). An openness

Correspondence to: Professor Mouloud Agajani Delavar, Infertility and Reproductive Health Research Center, Health Research Institute, Babol University of Medical Sciences, Babol-Amol Old Highway, Babol, Mazandaran 47135-547, Iran
E-mail: moloodagajani@yahoo.com

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to experience is the desire of an individual to be curious and sensitive to natural beauty, and is associated with an affinity for art. Conscientiousness is associated with generosity, empathy, cooperation and trust (12). Studies have shown that personality traits tend to be inheritable, and that there may be a genetic basis for personality (13,14).

Numerous studies have demonstrated that serotonin [5-hydroxytryptamine (5-HT)] serves an important role in regulating activity of the central nervous system, and that it can affect a wide range of psychological processes, including individual differences in personality traits (15,16). Additionally, several studies have demonstrated that a reduction in 5-HT levels serves an important role in the onset of depression (17,18). In this regard, polymorphisms in the promoter region of the monoamine oxidase-A (MAO-A) gene may intensify the degree of depression (19). Jurczak *et al* (20) identified that there was a significant correlation between the allele frequency of a 30-bp variable number tandem repeat (VNTR) polymorphism in the promoter region of MAO-A and depression, as well as between the allele frequency of polymorphisms in the 5-HT transporter (5-HTT) gene and the severity of menopausal symptoms in postmenopausal women. However, Grochans *et al* (21) demonstrated that the presence of a 44-bp 5-HTT-LPR polymorphism was significantly more frequently observed in women with severe menopausal symptoms, but there was no significant association between the genotype distribution in the MAO-A promoter region and the severity of menopausal symptoms. Several women experience symptoms for months or even years after their menopause, and this constitutes a major challenge for the social sciences and modern medicine (22-24). Thus, it is imperative to identify personality traits and genes that contribute to the severity of menopausal and depressive symptoms. Although it has been suggested that personality traits and genes are associated with severe menopausal and depressive symptoms, there are inconsistencies between reports on the association between personality traits, genes, depression and the severity of menopausal symptoms (21,25,26). In addition, to the best of our knowledge, there are no such investigations on Iranian patients. The aim of the present study was to investigate the effect of personality traits, and polymorphisms of MAO-A and 5-HTT on the severity of menopausal and depressive symptoms in menopause women.

Patients and methods

Patients. A cross-sectional study was performed on 132 healthy post-menopausal women with a mean age \pm standard deviation of 54.3 ± 4.1 years (range, 45-65) in Babol (Iran). The study was approved by The Ethics Committee of Babol University of Medical Sciences (approval no. MUBABOL.HRI.REC.1395.7; Babol, Iran) and was performed according to guidelines described in the Declaration of Helsinki (27). The sample was selected from primary health care centers in Babol using a cluster sampling method between September 2016 and August 2018. At first, several clusters were randomly selected from primary health care centers and then all eligible individuals in each cluster (based on household records at the clinic) were included in the study.

The inclusion criteria for the study were as follows: Women aged between 45-65 years; able to fill in the questionnaire with

the help of a researcher; final menstruation occurred at least 1 year prior to the study; normal cervical smear test results; and no history of thyroid disease, breast cancer or stroke. The exclusion criteria for the study were: Post-menopausal women with endocrine disorders, chronic diseases or acute disorders; any type of cancer and had to use hormone replacement therapy during the previous 6 months; former and current smokers; those who consumed at least one unit of alcohol per day; those with secondary amenorrhea and who had ovarian surgery; had undergone hysterectomy, chemotherapy or radiotherapy; and those with mental disorders.

Written consent was provided by each participant prior to beginning the study. The participants were free to continue the study or withdraw from it at any point. Participants' weight, height, blood pressure and body mass index (BMI) were assessed. Women's bodyweight was measured with minimal clothing and without shoes using a digital scale. Their height was measured to the nearest cm (28). BMI was calculated using the formula: Weight (kg)/height² (m), which categorized the participants into two groups: BMI <25 and ≥ 25 kg/m² (29). The menopausal status was assessed through a gynecological interview and a questionnaire. The participants were divided into three groups according to their menopausal age: <45, 45-50 and 50-57 (30).

The survey was conducted in two phases. The first phase of the survey was a diagnostic study using a socio-demographic questionnaire and standard research instruments for personality, menopausal symptom and depression diagnosis and the second phase was based on genetic tests.

Socio-demographic questionnaire. The socio-demographic questionnaire sought information on age, marital status, educational level, occupation, the number of parities and the number of abortions. The participants were divided into two groups according to their age: 45-55 and 56-65. The education level of the participants was categorized into two levels: Under diploma and diploma/over diploma. The marital status was classified as: Married, single, divorced or widowed. Occupation was classified as in work or out of work. Women were also categorized into three groups based on the history of abortion: Induced abortion, spontaneous abortion and no history of abortion. The parity of the women was divided into two groups: ≤ 3 and > 3 births.

Symptom score sheet. The symptom score sheet (Modified Greene Scale) (31-33), is a standard measure of menopausal symptoms used in a variety of studies. The sheet includes 20 questions regarding menopausal symptoms and the severity of symptoms, all in a four-point-likert scale for each symptom from 0 (none) to 3 (severe). The women were classified into two categories based on their menopausal symptoms: Minor or no symptoms, 0-15; and severe menopausal symptoms, ≥ 15 . The construct validity and the reliability of the score sheet were assessed based on a number of previous studies (33-35). Additionally, the validity and reliability of the Persian version of the symptoms score sheet has already been assessed (36).

Beck Depression Inventory (BDI-13). BDI-13, which was developed by Beck (1972), was used to assess depressive symptoms (37). Its coefficients were obtained from 0.75 to

Table I. Socio-demographic characteristics, reproductive history and body mass index of participants.

Characteristics	n (%)
Age, years	
45-55	84 (63.6)
56-65	48 (36.4)
Education	
Under diploma	104 (78.8)
Diploma/over diploma	28 (21.2)
Menopause age, years	
<45	17 (12.9)
45-50	75 (56.8)
50-57	40 (30.3)
Marital status	
Married	124 (93.9)
Single/divorced/widowed	8 (6.1)
Occupation	
In work	118 (89.4)
Out work	14 (10.6)
Abortion	
Induced	15 (11.4)
Spontaneous	26 (19.7)
No abortion	91 (68.9)
Body mass index, kg/m ²	
<25	32 (24.2)
≥25	100 (75.8)
Parity	
≤3	71 (53.8)
>3	61 (46.2)

0.83. Items are rated on a 0-3 point scale (0, none; 3, severe symptom manifestation). A possible score on the BDI could range from 0-39; thus, a higher score means a higher severity of depression. An index score of ≤4 indicates none or minimal depression, 5-7 mild, 8-15 moderate, and ≥16 severe (38). The reliability and validity of this questionnaire was verified by Rajabi (39) in Iran.

Neuroticism-Extroversion-Openness-Five Factor Inventory (NEO-FFI). The short form of the NEO questionnaire is comprised of 60 items which evaluates 5 factors including, neuroticism, extraversion, openness to experience, conscientiousness and agreeableness. NEO-FFI is measured based on a 5-point Likert scale from 'strongly disagree' to 'strongly agree'. The questionnaires suitability has been validated is one of the most widely used questionnaires for screening personality (40). Garousi Farshi *et al* (41) verified the reliability and validity of this self-reported personality questionnaire for screening personality with Iranian individuals.

Polymerase chain reaction (PCR). Venous blood samples were obtained from each participant for genetic testing and then transferred to EDTA tubes. Genomic DNA was extracted

using the Miller Salt Out method (42). The DNA was isolated from the whole blood and stored at -20°C. The PCR procedure was used for detecting polymorphisms (43,44). The aim of the analysis was to amplify the 30-bp promoter region VNTR in the MAO gene. PCR was performed separately in 20 µl reaction volume containing 50 ng genomic DNA, 12.5 pmol of each primer, 1.2 µl MgCl₂ (25 mM), 0.8 µl dNTP (10 mM), 2 µl 10x reaction buffer and 1.5 units Taq polymerase (Parstous Biotech). The following primers were used: Forward, 5'-CCC AGGCTGCTCCAGAAA-3' and reverse, 5'-GGACCTGGG CAGTTGTGC-3'. The thermocycling conditions were: Primary denaturation 95°C for 3 min; followed by 34 cycles of denaturing at 94°C for 40 sec, annealing at 57°C for 35 sec, polymerization at 72°C for 50 sec; and a final elongation step of 72°C for 10 min. The amplified fragment sizes were: 239, 209, 226 and 269 bp (45,46). For analysis of the 5-HTT gene, the fragment including the 44-bp insertion/deletion in the regulatory sequence (the presence or the lack of 44-bp) polymorphism was amplified. The sequences of the primers were HTT forward, 5'-GCGCTCCTGCATCCCCCATTA-3' and reverse, 5'-GGGATGCGGGGAATACTGGT-3'. The thermocycling conditions were: Initial denaturation at 95°C for 2 min; followed by 35 cycles of 95°C for 60 sec, 62°C for 60 sec and 72°C for 60 sec; with a final extension step of 72°C for 10 min. The genotype-specific PCR products were analyzed using 3% agarose gel electrophoresis, then visualized under UV light after staining with ethidium bromide, and images were captured using a Gel Imaging system (Vilber Lourmat Deutschland GmbH). Among the PCR products, fragment sizes with lengths of 253 bp (small, S) and 297 bp (long, L) were detected and three genotypes, including S/S, L/S and L/L, were subsequently determined (47).

Statistical analysis. All analyses were performed using SPSS version 16.0 (SPSS, Inc.). Descriptive statistics are presented as the mean ± standard the standard deviation and frequencies (%), and were used to describe the socio demographic characteristics, reproductive history and body mass index of the participants. A χ^2 test was used to verify the null hypothesis, referring to the independence of the analyzed variables. P<0.05 was considered to indicate a statistically significant difference.

Results

Of the patients recruited, 78.8% of patients had completed elementary level only, 10.6% were employed, 94% were married and 18.2% had received hormone therapy. The mean BMI ± standard deviation was 28.7±4.6 kg/m². The majority of women recruited were overweight or obese (70% of the women had a BMI ≥25 kg/m²). The mean age ± standard deviation at menopause was 48.3±4.2 years (Table I).

According to the symptoms score sheet, 59.1% of the participants had severe menopausal symptoms and 40.9% had minor or no symptoms. Personality structure based on NEO-FFI were: Low and medium levels of neuroticism in 77.4% and high levels in 29.5% of the participants; and high levels of extroversion, agreeableness and conscientiousness in ~50% of the participants. Low levels of openness to experience were reported by 75.8% of the respondents and high levels in

Table II. Association of personality traits with menopausal symptoms in Baboli women aged 45-65 years old.

NEO-FFI	Total, n=132	Minor menopausal symptoms, n=54	Severe menopausal symptoms, n=78	χ^2	P-value
Neuroticism, n (%)				25.125	<0.0001 ^b
Low	32 (24.2)	25 (78.1)	7 (21.9)		
Average	61 (46.2)	20 (32.8)	41 (67.2)		
High	39 (29.5)	9 (23.1)	30 (76.9)		
Extroversion, n (%)				12.582	0.002 ^a
Low	29 (22.0)	4 (13.8)	25 (86.2)		
Average	30 (22.7)	12 (40.0)	18 (60.0)		
High	73 (55.3)	38 (52.1)	35 (47.9)		
Openness, n (%)				6.513	0.039 ^a
Low	100 (75.8)	36 (36.5)	64 (64.0)		
Average	23 (17.4)	11 (47.8)	12 (52.2)		
High	9 (6.8)	7 (77.8)	2 (22.2)		
Agreeableness, n (%)				5.118	0.077
Low	33 (25.0)	10 (30.3)	23 (69.7)		
Average	41 (31.1)	14 (34.1)	27 (65.9)		
High	58 (43.9)	30 (51.7)	28 (48.3)		
Conscientiousness, n (%)				14.112	0.001 ^b
Low	10 (7.6)	1 (10.0)	9 (90.0)		
Average	39 (29.5)	9 (23.1)	30 (76.9)		
High	83 (62.9)	44 (53.0)	39 (47.0)		

^aP<0.05, ^bP<0.001. NEO-FFI, Neuroticism-Extroversion-Openness-Five Factor Inventory.

6.8%. A high level of neuroticism ($P<0.0001$), a low level of extroversion ($P<0.002$), openness to experience ($P=0.039$) and conscientiousness ($P=0.001$) were all associated with severe menopausal symptoms, but agreeableness was not significantly associated with symptoms (Table II).

Based on BDI, depressive symptoms were diagnosed in 53.8% and the other 46.2% of the participants had no depressive symptoms at all. A high level of neuroticism ($P<0.0001$), low levels of extroversion ($P<0.0001$), low levels of agreeableness ($P<0.024$) and conscientiousness ($P<0.0001$) were all associated with depressive symptoms, whereas an openness to experience was not significantly associated (Table III).

A statistically significant difference was not observed between the distribution of polymorphisms in the promoter regions of 5-HTT-LPR and MAO-A and the severity of menopausal symptoms (Table IV). In addition, there was no association between 5-HTT-LPR and MAO-A polymorphisms and depression (Table V).

Discussion

In the present study, it was shown that women with a high level of neuroticism had severe menopausal symptoms and depressive symptoms. Additionally, menopausal women with low levels of extroversion, openness to experience or conscientiousness had severe menopausal and depressive symptoms. Menopausal women with low levels of agreeableness had depressive symptoms only with no evidence menopausal symptoms.

These results are in agreement with a previous study where a positive correlation between menopause status and neuroticism was identified (6). The results of the present study are also consistent with the results of a study of Iranian patients that reported a significant relationship between conscientiousness score and the severity of hot flashes and night sweats (48). Depression is frequently observed in menopausal women (49), and several studies have demonstrated the association between personality traits and depression (50,51). Additionally, the relationship between depression and higher scores of neuroticism (51), lower scores of conscientiousness (52), extroversion (53) and openness to experience (53) have been demonstrated. A possible explanation for the relationship between higher levels of neuroticism and depression is that neuroticism is an important contributor for the development of psychological disorders and therefore these patients maybe more prone to depression (6,54).

Exposure to stressful events in everyday life may increase depression, particularly in individuals with high levels of neuroticism, low levels of conscientiousness and openness to experience (55,56). In addition, neuroticism may be associated with polymorphisms in the 5-HTT promoter region. The analysis of 133 healthy elite athletes by Petito *et al* (57) demonstrated that the 5-HTTLPR s/s genotype was associated with an increased neuroticism score. However, another study by Plieger *et al* (58) on 1,075 women found no evidence of an association between 5-HTT polymorphisms and neuroticism.

Table III. Association of personality traits with depression in Baboli women aged 45-65 years old.

NEO-FFI	Total, n=132	No depressive symptoms, n=61	Depressive symptoms, n=71	χ^2	P-value
Neuroticism, n (%)				20.067	<0.0001 ^b
Low	32 (24.2)	25 (78.1)	7 (21.9)		
Average	61 (46.2)	26 (42.6)	35 (57.4)		
High	39 (29.5)	10 (25.6)	29 (74.4)		
Extroversion, n (%)				23.756	<0.0001 ^b
Low	29 (22.0)	3 (10.3)	26 (89.7)		
Average	30 (22.7)	12 (40.0)	18 (60.0)		
High	73 (55.3)	46 (63.0)	27 (37.0)		
Openness, n (%)				1.643	0.440
Low	100 (75.8)	45 (45.0)	55 (55.0)		
Average	23 (17.4)	10 (43.5)	13 (56.5)		
High	9 (6.8)	6 (66.7)	3 (33.3)		
Agreeableness, n (%)				0.024	0.024 ^a
Low	33 (25.0)	9 (27.3)	24 (72.7)		
Average	41 (31.1)	19 (46.3)	22 (53.7)		
High	58 (43.9)	33 (56.9)	25 (43.1)		
Conscientiousness, n (%)				21.422	<0.0001 ^b
Low	10 (7.6)	1 (10.0)	9 (90.0)		
Average	39 (29.5)	9 (23.1)	30 (76.9)		
High	83 (62.9)	51 (61.4)	32 (38.6)		

^aP<0.05, ^bP<0.001. NEO-FFI, Neuroticism-Extroversion-Openness-Five Factor Inventory.

Table IV. Association between 5-HTTLPR genotype and MAO-A promoter region with menopausal symptoms in 132 Baboli women aged 45-65 years old.

Menopausal symptom severity	n (%)	5-HTTLPR, n (%)			MAO A, n (%)		
		S/S	L/L	L/S	3/3	3/4	4/4
Minor	54 (40.9)	7 (46.7)	32 (40.0)	15 (40.5)	10 (45.5)	18 (37.5)	26 (41.9)
Severe	78 (59.1)	8 (53.3)	48 (60.0)	22 (59.5)	12 (54.5)	30 (62.5)	36 (58.1)
χ^2	-	0.235			0.446		
P-value	-	0.889			0.800		

5-HTTLPR, 5-hydroxytryptamine transporter; MAO A, monoamine oxidase A; L, long; S, short.

Table V. Association between the 5-HTTLPR genotype and MAO-A promoter region with the severity of menopausal depression in 132 Baboli women aged 45-65 years old.

Presence/absence of depressive symptoms	n (%)	5-HTTLPR genotype, n (%)			MAO A, n (%)		
		S/S	L/L	L/S	3/3	3/4	4/4
No depressive symptoms	61 (67.2)	8 (11.3)	42 (59.2)	21 (29.6)	8 (13.1)	24 (39.3)	29 (47.5)
Depressive symptoms	71 (53.8)	8 (11.3)	42 (59.2)	21 (29.6)	14 (19.7)	24 (33.8)	33 (46.5)
χ^2	-	0.186			1.143		
P-value	-	0.911			0.562		

5-HTTLPR, 5-hydroxytryptamine transporter; MAO A, monoamine oxidase A; L, long; S, short.

There is a consensus among various researchers that 5-HTT polymorphisms may increase depression in individuals with a stressful life (26,59-61). However, other studies have shown that 5-HTT was not associated with depression (21) and the level of anxiety (62) in menopausal women. Additionally, the MAO-A promoter region was also previously shown to be not associated with depression or menopausal symptoms in menopausal women (21).

The results of these studies are directly in line with our previous findings (63). In the present study, there was no association between 5-HTT polymorphisms, and menopausal symptoms and depression, nor was there an association between polymorphisms of the MAO-A promoter region and menopausal symptoms and depression in menopausal women. In contrast to the results of the present study, Jurczak *et al* (20) showed there was a significant correlation between MAO-A polymorphisms of the promoter region and menopausal symptoms and depression in the post-menopausal women. Additionally in a study with 630 women with menopausal symptoms, 5HTTLPR gene polymorphisms were significantly more common in women with severe menopausal symptoms (21).

The present study had several limitations. First, it used a self-reporting questionnaire to determine the depressive and menopausal symptoms and personality traits, thus the results are not entirely objective. Demographic variables such as educational level and marital status that may be indirectly associated with menopausal symptoms or onset of depression were not assessed. History of amenorrhea for at least 12 months was determined through gynecological interview and was not confirmed by measuring FSH levels, and the small sample size and access to respondents may be another limitation of this study. Therefore, a larger sample size is required to confirm the associations between depressive and menopausal symptoms with personality traits, MAO-A and 5-HTT polymorphisms in menopausal women.

Despite these limitations, the strengths of the present study are: Community-based design, wide inclusion and exclusion criteria, an age group covering the mid-life age (45-65 years), the use of a cluster method for sampling, and the use of valid scale for assessing the menopausal symptoms. The primary strengths of the present study are that only healthy women were included in the study, and women with any other type of chronic disorders were excluded.

In conclusion, a significant relationship between personality traits and the severity of depressive and menopausal symptoms in menopause women was identified. Therefore, it is vital to counsel menopausal women to reduce the severity of depressive and menopausal symptoms, to improve their quality of life. Additionally, health care providers can reduce the severity of depressive and menopausal symptoms based on the personality of women, to identify those at increased risk.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MAD and SMA contributed to interpreting data, and writing the manuscript. MAD contributed to the statistics analyses as well provided study material. SE, NA and RN contributed to data collection and writing the manuscript. HN and NA performed the genetic examination. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Written informed consent was obtained from all subjects before the study. Ethics approval for this study was obtained from Babol University of Medical Science (approval no. MUBABOL,HRI.REC.1395.7).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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