Objective: Vasomotor symptoms affect 60-80% of women during the menopausal transition. Anxiety, depression, and anxiety sensitivity can have an important role in the distressful experience of vasomotor symptoms. Our aim was to evaluate the prevalence and association of vasomotor and negative affect symptoms.

Methods: A cross-sectional study was conducted with 89 perimenopausal women aged 45-55 years. Broad psychiatric and clinical evaluations were carried out. The primary outcome was the vasomotor symptom problem rating and the main study factor was anxiety sensitivity. Linear regression analyses were conducted to examine the associations between the study factors and the primary outcome, and a multiple regression model was created to assess which variables were independently associated with vasomotor symptom problem rating.

Results: The prevalence of anxiety, depression, and vasomotor symptoms were 58, 62, and 73%, respectively. Negative affect symptoms were positively associated with vasomotor symptom problem rating. The association of anxiety sensitivity and vasomotor symptom problem rating remained significant after controlling for perimenopausal stage, thyrotropin, follicle-stimulating hormone levels, and psychotropic medication use ($b = 0.314, p = 0.002$).

Conclusion: A better understanding of the experience of vasomotor symptoms is needed, especially the role of negative affect symptoms and anxiety sensitivity. New strategies focusing on related thoughts and behaviors could improve the quality of life of perimenopausal women.

Keywords: Anxiety; depression; perimenopause

Introduction

Vasomotor symptoms (VMS) are characterized by hot flashes and night sweats (HF/NS) and are considered a major symptom of menopause, affecting 60-80% of women during the menopausal transition, especially in the late perimenopause and early postmenopausal years. Perimenopause is a period with a high prevalence of negative affect symptoms: 46.9 and 56.3% of perimenopausal Brazilian women reported depression and anxiety symptoms, respectively. Although the relationship between negative affect and VMS is not fully understood, these two factors have consistently been associated across investigations. This association suggests that women with more depression, anxiety, and general negative mood are at increased risk for reporting VMS and are also more bothered by symptoms, regardless of their frequency. Alternatively, VMS may also have a negative impact on mood. Regarding depression, a bidirectional association with VMS is largely supported by the literature. However, the association between anxiety and VMS is still controversial, since there have been different results about the presence of a direct relationship between VMS severity and anxiety symptoms. Two main questions remain unclear: whether anxiety precedes or is a consequence of HF, and whether anxiety can influence the perception or number of HF events.

One possible explanation for the lack of consensus about the association between anxiety and VMS is the heterogeneity of anxiety and vasomotor measures. Moreover, measures that confound physical and psychological symptoms cannot distinguish between the somatic aspects of anxiety and VMS. A study by Gibson et al. evaluated the temporal associations between VMS and negative affect in the multi-site Study of Women’s Health Across the Nation (SWAN). In their sample, negative affect symptoms, anxiety sensitivity, and vasomotor symptoms during perimenopause.
affect, adjusted by same-day VMS, was not associated with next-day VMS. In contrast, VMS, adjusted by same-day negative mood, was associated with next-day negative mood. In another longitudinal analysis from the SWAN study, Bromberger et al. reported that although the association of frequent VMS with high levels of anxiety was significant for all women over a 10-year follow-up period, the odds were greater among those with high baseline anxiety. On the other hand, for women who did not have high baseline anxiety levels, VMS increased the odds of having high anxiety across the stages of the menopause transition. Moreover, the Penn Ovarian Aging cohort explored the differences between affective and somatic anxiety symptoms and found that the somatic symptom dimension increased the risk of HF more than 300% during the menopausal transition. These findings could indicate the importance of concepts such as anxiety sensitivity (AS) in the relationship between anxiety-related sensations and the experience of HF.

AS is the personal tendency to react with fear to anxiety-related symptoms. It results from the belief that these symptoms and sensations have harmful somatic, social, or psychological consequences. Empirically, AS is distinguishable from the tendency to experience more frequent anxiety symptoms (e.g., trait anxiety) and the propensity to negative affect (e.g., neuroticism). Although AS was initially conceptualized as a specific vulnerability factor for panic disorder, due to the prominence of fears in that disorder, it has since been established more broadly as an index of distress intolerance.

Individuals with high AS are hypervigilant regarding internal stimuli and are more likely to misinterpret benign physical sensations as having harmful consequences: they worry that something might be seriously wrong when they have palpitations or when they blush or sweat in front of people. Women with high levels of AS report greater levels of anxiety, depression, and menstrual distress across the menstrual cycle than women with low levels of AS. Although it has been determined that AS plays an important role in the heightened reactions to hormonal changes exhibited by some women in menstrual distress, few studies have evaluated the specific association between AS and VMS.

The aim of this study was to explore the association between negative affect (mainly anxiety and its components) and HF/NS in perimenopausal women. The primary objective was to evaluate the association between AS symptoms and the bothersomeness of VMS. Our hypothesis was that perimenopausal women with more negative affect symptoms, specifically AS symptoms, would have higher VMS problem ratings.

Methods

Procedures and participants

In this cross-sectional investigation, women between 45 and 55 years old in the menopausal transition were invited to participate in this study through Internet and newspaper announcements made between March and September, 2017. Menopausal transition was defined according to the Stages of Reproductive Aging Workshop criteria: menstruation within the past 12 months but a persistent difference of 7 days or more in the length of consecutive cycles or an interval of amenorrhea of 60 days or more. The exclusion criteria were comorbid diagnosis of substance abuse or psychotic episode (past or present), untreated clinical diseases, menopause after surgery or chemotherapy, hormone replacement therapy, or oral contraceptive use.

Upon their visit to the hospital clinical research center, the participants had an extensive clinical, gynecological, and psychiatric evaluation. They also completed self-reported questionnaires regarding AS and their physical activity. Blood samples were collected by convenience for a complete blood count and to determine follicle-stimulating hormone (FSH) and thyrotropin (TSH) levels.

Measurements

Information on sociodemographic, clinical, and gynecological variables were collected using a structured questionnaire by trained psychiatrist and psychologist. The evaluated sociodemographic characteristics were age, self-reported race, educational level, employment, and socioeconomic class (according to 2016 Associação Brasileira de Empresas de Pesquisas criteria). Clinical variables, smoking, weight profile, chronic disease, psychotropic medication use (antidepressants, antipsychotics, mood stabilizers, or anxiolytics), and family history of psychiatric disorders were assessed by the researchers. Gynecological information included the presence of premenstrual symptoms prior to perimenopause, family history of VMS, and perimenopausal stage (according to the date of the last period). Physical activity was evaluated using the International Physical Activity Questionnaire-Short Form, which assesses the intensity of different activities, including planned exercise and housework. This questionnaire was translated and validated for use in Brazil and has good reliability.

Psychiatric disorders were assessed with the Mini-International Neuropsychiatric Interview (MINI), which consists of a structured and validated diagnosis interview based on DSM-IV and CID-10 psychiatric diagnostic criteria (adapted by the researchers to DSM-5 criteria). The instrument has been translated and validated for use in Brazil.

The severity of anxiety and depression symptoms were evaluated using the Hamilton Anxiety Rating Scale (HAMA) and the Hamilton Depression Scale (HAM-D), respectively. The HAM-A is a widely used 14-item clinical scale that measures somatic and psychic anxiety symptoms. Scores range from 0 to 56 and were classified as mild anxiety (14 to 17), moderate anxiety (18 to 24), and moderate to severe anxiety (> 25 points). It was translated and validated for use in Brazil, showing good psychometric properties.

The HAM-D investigates how the patient has been feeling in the last seven days. We used the validated version of the scale. Scores range from 0 to 52 and are classified as follows: severe depression (> 25), moderate depression (18-24), and mild depression (7-17).
HF/NS frequency was measured with the Hot Flush Rating Scale, which records the number of HF/NS experienced in the previous week. The scale has good test-retest reliability ($r = 0.8$) and validity, with significant correlations based on daily diary recordings of HF ($r = 0.97$, $p < 0.001$) and NS ($r = 0.94$, $p < 0.001$). Scores were derived using factor analysis with good internal consistency ($\chi^2 = 0.9$) and test-retest reliability ($r = 0.8$). The scale was translated and adapted for use in Brazil with good internal consistency (frequency-Cronbach’s $\chi = 0.739$; problem-rating-Cronbach’s $\chi = 0.912$). Problem rating, the primary outcome of this study, is determined by the mean of three items: To what extent do you regard your flashes/sweating as a problem?; How distressed do you feel about your HF?; and How much do your HF interfere with your daily routine? Each item is measured on a 10-point scale, with higher scores indicating more problematic HF.20

The Anxiety Sensitivity Index-Revised (ASI-R) was used to evaluate the level of AS, which was our main study factor. It consists of a Likert scale from 0 (agree very little) to 4 (agree very much). The sum of the responses for the 36 items represent the AS level, with higher scores indicating a more intense AS level.21 The ASI-R has adequate criterion validity and excellent internal consistency ($\chi = 0.95$), with all 36 items showing adequate item-total correlations.

### Data analysis

Frequencies and percentages were used to describe categorical variables. Median and percentiles (25 and 75) or means and standard deviation (SD) were used to describe numeric variables. According to the Shapiro-Wilk test, VMS problem rating did not have normal distribution. SPSS version 25.0 was used for all analyses.

The presence of any anxiety disorder (panic disorder, agoraphobia, social anxiety disorder, or generalized anxiety disorder) was an independent measure. To compare characteristics between patients with and without a diagnosis, the $\chi^2$ test was used for sociodemographic, gynecological, and clinical factors, while an independent-sample Mann-Whitney U test was used to compare factors related to VMS.

We used simple regressions to test the association between the dependent variable (VMS problem rating) and the independent variables. To assess which variables were independently associated with VMS problem rating, we constructed a multiple regression model, using the variance inflation factor to evaluate multicollinearity. Variables were chosen for the multiple regression model according to multicollinearity and clinical relevance.

The sample size calculation considered the probability of a type I error of 0.05 (bilateral) and a type II error of 0.2. Based on Freeman et al.,22 a correlation coefficient of 0.3 was expected between anxiety and VMS regarding depressive symptoms, and a sample size of 85 women was considered to have sufficient power to detect differences. A significance level of 5% was accepted in all analyses and all tests were two-tailed.

### Ethics statement

This study was approved by the ethics committee of Hospital de Clínicas de Porto Alegre, state of Rio Grande do Sul, Brazil. Written informed consent was obtained from all participants.

### Results

Of the 240 women who sought enrollment in the study by e-mail, 92 were interviewed and 89 were considered eligible for participation (one was not perimenopausal, one could not finish the interview, and one was taking hormonal contraceptives). The sociodemographic, clinical, and gynecological characteristics of the sample are described in Table 1.

The results of the complete psychiatric evaluation are shown in Table 2. The prevalence of anxiety symptoms in our sample was 58.43%, and 39.3% were diagnosed with any anxiety disorder. A total of 61.79% of the women reported depressive symptoms.

Seventy-three percent of women reported VMS: 66.3% had HF and 52.8% had NS. The median frequency of VMS was 10 per week and the mean problem rating was 4.33 (Table 3). Women diagnosed with any anxiety disorder had more premenstrual symptoms ($p = 0.046$) and higher psychotropic medication use ($p = 0.032$), as well as higher scores in all components of the VMS problem rating scale (extent as a problem, distress, and interference with daily routine) compared to those without anxiety disorders.

Perimenopausal stage, complete blood count, AS Index, FSH and TSH levels, HAM-A and HAM-D scores, and number of diagnosed disorders (MINI) were significantly associated with VMS problem rating in the unadjusted analysis (Table 4). The frequency of VMS was also associated with problem rating ($\beta = 0.505$, $p < 0.001$), predicting 25.5% of the variance. Regarding the association between VMS problem rating and AS, the $\beta = 0.254$ and the $p$-value = 0.018. The association between AS and frequency of VMS was not statistically significant ($\beta = -0.032$, $p = 0.768$).

For the multivariate analysis, we excluded the HAM-A and HAM-D results and the number of diagnosed disorders (MINI) due to their collinearity with the AS Index, the main study factor. Since the literature indicates that psychotropic medications can interfere with both anxiety symptoms and VMS, we chose to include them, despite their non-significant correlation with VMS problem rating in our sample.23 After adjustment, the association between VMS problem rating and AS symptoms remained statistically significant ($\beta = 0.314$, $p = 0.002$) after controlling for perimenopausal stage, psychotropic medication use, and FSH and TSH levels (Table 5). This model explained 26.9% of the VMS problem rating variance.

### Discussion

In this sample of 89 perimenopausal women, the majority reported having VMS with HF/NS and considered the
symptoms to be dysfunctional. In addition, more than half of the sample had depressive and anxiety symptoms. Furthermore, 39.3% were diagnosed with any anxiety disorder. Women with anxiety disorders described their VMS as more bothersome, more dysfunctional and distressful, and as having greater interference in their daily routine than women not diagnosed with any anxiety disorder. Higher VMS problem ratings were associated with perimenopausal stage, FSH and TSH values, depressive and anxious symptoms, number of diagnosed...

| Characteristics                                      | Total       | With anxiety diagnosis | Without anxiety diagnosis | p-value |
|-------------------------------------------------------|-------------|------------------------|---------------------------|---------|
| Race                                                  |             |                        |                           | 1.0     |
| White                                                 | 77 (86.5)   | 31 (40.3)              | 46 (59.7)                 |         |
| Nonwhite                                              | 12 (13.5)   | 4 (33.3)               | 8 (66.7)                  |         |
| Marital status                                        |             |                        |                           | 1.0     |
| With a partner                                        | 62 (69.7)   | 24 (38.7)              | 38 (61.3)                 |         |
| Without a partner                                     | 27 (30.3)   | 11 (40.7)              | 16 (59.3)                 |         |
| Education, years                                      |             |                        |                           | 0.692   |
| 0-8                                                   | 6 (6.7)     | 2 (33.3)               | 4 (66.7)                  |         |
| 9-11                                                  | 33 (37.1)   | 15 (45.4)              | 18 (54.6)                 |         |
| 12 or more                                            | 50 (56.2)   | 18 (36.0)              | 32 (64.0)                 |         |
| Paid employment                                       |             |                        |                           | 0.339   |
| Yes                                                   | 64 (71.9)   | 23 (35.9)              | 41 (64.1)                 |         |
| No                                                    | 25 (28.1)   | 12 (48.0)              | 13 (52.0)                 |         |
| Sociodemographic class                                |             |                        |                           | 0.367   |
| A                                                     | 13 (14.6)   | 3 (23.1)               | 10 (76.9)                 |         |
| B1                                                    | 18 (20.2)   | 10 (55.5)              | 8 (44.5)                  |         |
| B2                                                    | 27 (30.5)   | 10 (37.0)              | 17 (63.0)                 |         |
| C1                                                    | 21 (23.6)   | 7 (33.3)               | 14 (66.7)                 |         |
| C2                                                    | 9 (10.1)    | 5 (55.6)               | 4 (44.4)                  |         |
| D-E                                                   | 1 (1.1)     | 0 (0.0)                | 1 (10.0)                  |         |
| Smoker                                                |             |                        |                           | 1.0     |
| Yes                                                   | 83 (93.3)   | 33 (39.8)              | 50 (60.2)                 |         |
| No                                                    | 6 (6.7)     | 2 (33.3)               | 4 (66.7)                  |         |
| Physical activity (IPAQ) (n=83)                       |             |                        |                           | 1.0     |
| Active                                                | 69 (83.1)   | 27 (39.1)              | 42 (60.9)                 |         |
| Sedentary                                             | 14 (16.9)   | 6 (42.9)               | 8 (57.1)                  |         |
| Weight profile                                        |             |                        |                           | 0.290   |
| Normal weight (BMI 18.5-24.9 kg/m²)                   | 24 (26.9)   | 9 (37.5)               | 15 (62.5)                 |         |
| Overweight (BMI 25-29.9 kg/m²)                        | 33 (37.1)   | 10 (30.3)              | 23 (69.7)                 |         |
| Obese (BMI ≥ 30)                                      | 32 (36.0)   | 16 (50.0)              | 16 (50.0)                 |         |
| Chronic disease                                       |             |                        |                           | 0.829   |
| Yes                                                   | 50 (56.2)   | 19 (38.0)              | 31 (62.0)                 |         |
| No                                                    | 39 (43.8)   | 16 (41.0)              | 23 (59.0)                 |         |
| Use of psychotropic medication                        |             |                        |                           | 0.032   |
| Yes                                                   | 19 (21.3)   | 12 (63.2)              | 7 (38.8)                  |         |
| No                                                    | 70 (78.7)   | 23 (32.9)              | 47 (67.1)                 |         |
| Premenstrual symptoms                                 |             |                        |                           | 0.046   |
| Yes                                                   | 54 (60.7)   | 26 (48.1)              | 28 (51.9)                 |         |
| No                                                    | 35 (39.3)   | 9 (25.7)               | 26 (74.3)                 |         |
| Family history of vasomotor symptoms                  |             |                        |                           | 0.368   |
| Yes                                                   | 58 (65.2)   | 25 (43.1)              | 33 (56.9)                 |         |
| No                                                    | 31 (34.8)   | 10 (32.3)              | 21 (67.7)                 |         |
| Family history of psychiatric disorders                |             |                        |                           | 0.829   |
| Yes                                                   | 40 (44.9)   | 15 (37.5)              | 25 (62.5)                 |         |
| No                                                    | 49 (55.1)   | 20 (40.8)              | 29 (59.2)                 |         |
| Perimenopausal stage                                  |             |                        |                           | 0.521   |
| Early                                                 | 39 (44.3)   | 14 (35.9)              | 25 (64.1)                 |         |
| Late                                                  | 49 (55.7)   | 21 (42.9)              | 28 (57.1)                 |         |

Data presented as n (%). BMI = body mass index; IPAQ = International Physical Activity Questionnaire.
psychiatric disorders, and AS symptoms. An important finding was that the association of AS and VMS problem rating remained significant even when adjusted for peri-menopausal stage, FSH, TSH, and psychotropic medication use. To our knowledge, few studies have explored the relationship between negative affect and VMS problem rating, focusing specifically on the role of AS. Although the prevalence of major depression disorder and depressive symptoms in our sample was high, it is in agreement with the literature. In Brazilian studies with perimenopausal women, the prevalence of anxiety disorders and symptoms in our study resemble the rates found by other studies. Veras et al.24 found that 33.3% of peri- and postmenopausal Brazilian women were diagnosed with anxiety disorders according to the MINI, and the prevalence of anxiety symptoms reported by Polisseni et al.2 was 56.3%. Other studies, however,

### Table 2 Assessment of psychiatric characteristics

| Measurement                                      | n (%) |
|--------------------------------------------------|-------|
| Mini-International Neuropsychiatric Interview (n=89) |       |
| Major depressive episode – current               | 22 (24.7) |
| Major depressive episode – previous              | 27 (30.3) |
| Persistent depression                            | 9 (10.1) |
| Suicide risk                                     | 1 (1.1) |
| Bipolar disorder type I                          | 2 (2.2) |
| Bipolar disorder type II                         | 1 (1.1) |
| Panic disorder                                    | 5 (5.6) |
| Agoraphobia                                       | 14 (15.7) |
| Social anxiety disorder                          | 17 (19.1) |
| Obsessive-compulsive disorder                     | 2 (2.2) |
| Post-traumatic stress disorder                    | 1 (1.1) |
| Compulsive eating disorder                       | 3 (3.4) |
| Generalized anxiety disorder                      | 32 (36.0) |
| Any anxiety disorder                              | 35 (39.3) |
| Hamilton Anxiety Scale (n=89)                    |       |
| No anxiety                                       | 37 (41.6) |
| Mild anxiety                                     | 14 (15.7) |
| Moderate anxiety                                 | 15 (16.9) |
| Moderate-severe anxiety                          | 23 (25.8) |
| Hamilton Depression Scale (n=89)                 |       |
| No depression                                    | 34 (38.2) |
| Mild depression                                  | 40 (44.9) |
| Moderate depression                              | 12 (13.5) |
| Severe depression                                | 3 (3.4) |
| Anxiety Sensitivity Index-Revised (n=86), median (percentiles 25/75) | 14.0 (5.0/46.0) |
| Penn State Worry Questionnaire (n=85)            |       |
| Low worry                                         | 15 (17.6) |
| Moderate worry                                    | 49 (57.6) |
| Severe worry                                      | 21 (24.7) |

### Table 3 Vasomotor symptoms

|                                | Total     | With anxiety disorder | Without anxiety disorder | p-value |
|--------------------------------|-----------|-----------------------|--------------------------|---------|
| Hot flashes and night sweats   | 65 (73.0) | 27 (41.5)             | 38 (58.5)                | 0.626   |
| Hot flashes                     | 59 (66.3) | 24 (40.7)             | 35 (59.3)                | 0.820   |
| Night sweats                    | 47 (52.8) | 21 (44.7)             | 26 (55.3)                | 0.288   |
| Hot Flush Rating Scale, median (percentiles 25/75) |             |                       |                          |         |
| Hot flash frequency (per week)  | 6.0 (0.0/21.0) | 6.0 (0.0/21.0) | 6.0 (0.0/21.0) | 0.668   |
| Night sweat frequency (per week)| 1.0 (0.0/13.0) | 3.0 (0.0/15.0) | 0.0 (0.0/7.5) | 0.202   |
| Hot flash or night sweat frequency (per week) | 10.0 (0.0/35.0) | 10.0 (1.0/35.0) | 10.0 (0.0/35.8) | 0.983   |
| Rating of distress              | 5.0 (1.0/8.0) | 8.0 (1.0/9.0) | 4.5 (1.0/8.0) | 0.041   |
| Rating of interference with daily routine | 2.0 (1.0/7.0) | 5.0 (1.0/8.0) | 1.0 (1.0/5.0) | 0.019   |
| Problem rating                  | 4.3 (1.0/7.3) | 6.3 (1.0/8.0) | 3.7 (1.0/6.4) | 0.016   |

Data presented as n (%), unless otherwise specified.
reported frequencies ranging from 9 to 21%, and these lower rates may be associated with broader inclusion criteria and the rating scales used.\textsuperscript{26,27}

The women in our sample presented slightly higher AS levels than a nonclinical sample of undergraduate American and Canadian women (ASI-R = 12.8; SD = 10.5), but a lower mean total score than a sample of patients diagnosed with primary anxiety (ASI-R = 30.8; SD = 15.3).\textsuperscript{21,28} Although we found no studies that applied the ASI-R to perimenopausal women, it can be inferred that our results are similar to nonclinical samples.

The prevalence of VMS in our sample was similar to that found by a cross-sectional Brazilian study.\textsuperscript{29} In the SWAN cohort, 60-80% of women experienced VMS during the menopausal transition,\textsuperscript{1} and in a cross-sectional study of women from Chile, Ecuador, Panama, and Spain, 58.5% of the sample reported VMS.\textsuperscript{30} More than half of our sample reported HF and 52.8% complained of NS, rates similar to those found in a study of perimenopausal women from southern Brazil.\textsuperscript{29} The frequency of HF/NS in our study was lower than that found by a large study with a sample of women from different countries, although the results are similar in terms of problem rating scores.\textsuperscript{30} Several studies have also reported an association between depressive symptoms and VMS, but few have focused on HF/NS.\textsuperscript{29-31} On the other hand, many anxiety studies have found an association with VMS severity and bothersomeness.\textsuperscript{20,32-33} Our study showed high prevalence rates of generalized anxiety disorder and social anxiety disorder. The former is characterized by worry and fear of different situations, catastrophic thoughts, and body sensations, while the latter is characterized by hypervigilance to social and somatic clues. Both disorders are associated with higher AS, and thus with the bothersomeness of VMS.

In our sample, the VMS problem rating was associated with perimenopausal stage, FSH, and TSH. Longitudinal studies have also found an association between perimenopausal stage and VMS, reporting increased frequency and severity in the late perimenopausal stage.\textsuperscript{32,34} In the adjusted analysis, however, perimenopausal stage was not associated with VMS problem rating, which was also reported by Freeman et al.\textsuperscript{6} Several other studies have also reported an association between the frequency and severity of VMS and FSH levels.\textsuperscript{1,34} Since VMS occur in the context of the reproductive hormone changes in the menopausal transition (declining estrogen levels and rising FSH levels, which stabilize in the late transition and postmenopause), it can be inferred that women with higher FSH levels would have more frequent and bothersome VMS.\textsuperscript{35} Interestingly, we found a negative association between TSH and VMS problem rating. Very few studies have explored this association, and most reported that symptoms of thyroid function abnormalities could be very similar to those of menopause, including VMS.\textsuperscript{36} Because of the numerous interactions between thyroid hormones and most body systems, as well as their major role in metabolism, the relationship between thyroid hormones and VMS requires further investigation.\textsuperscript{34}

The hypothesis that women with higher levels of negative affect and, specifically, higher rates of AS, would be more bothered by VMS was confirmed in our study. Moreover, adjusting for biological variables (FSH and TSH),

| Table 4 Results of the simple regression of study factors and the primary outcome* |
|---------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                           | Unstandardized coefficients | Standardized coefficients |
|                                           | B     | SE   | b     | t    | p-value |
| Perimenopausal stage                     | 1.305 | 0.631| 0.218 | 2.068| 0.042  |
| Complete blood count                     | 2.050 | 0.912| 0.235 | 2.247| 0.027  |
| Anxiety Sensitivity Index                | 0.025 | 0.011| 0.254 | 2.406| 0.018  |
| Follicle-stimulating hormone             | 0.026 | 0.009| 0.296 | 2.888| 0.005  |
| Thyrotropin                               | -0.972| 0.302| -0.326| -3.216| 0.002  |
| Hamilton Anxiety Scale                   | 0.141 | 0.028| 0.480 | 5.109| 0.000  |
| Hamilton Depression Scale                | 0.145 | 0.045| 0.325 | 3.211| 0.002  |
| Number of diagnoses – MINI               | 0.606 | 0.200| 0.310 | 3.037| 0.003  |
| Penn State Worry Questionnaire           | 0.039 | 0.028| 0.153 | 1.409| 0.163  |
| Psychotropic medication use              | 0.493 | 0.779| 0.068 | 0.633| 0.528  |

MINI = Mini-International Neuropsychiatric Interview; SE = standard error.
* Problem-rating of vasomotor symptoms.

| Table 5 Results from the multiple regression of the study factors and the primary outcome* |
|---------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                           | Unstandardized coefficients | Standardized coefficients |
|                                           | B     | SE   | b     | t    | p-value |
| (Constant)                                | 3.563 | 1.140| 3.126 | 0.002 |
| Perimenopausal stage                      | 0.803 | 0.621| 0.134 | 1.292| 0.200  |
| Follicle-stimulating hormone              | 0.021 | 0.009| 0.242 | 2.328| 0.022  |
| Thyrotropin                               | -0.993| 0.299| -0.328| -3.325| 0.001  |
| Anxiety Sensitivity Index                 | 0.031 | 0.010| 0.314 | 3.185| 0.002  |
| Psychotropic medication use               | -0.286| 0.701| -0.040| -0.407| 0.685  |

SE = standard error.
*Vasomotor symptom problem rating.
perimenopausal stage, and psychotropic medication use, the association with AS remained significant. One possible explanation for our findings is that women with higher AS are more vigilant to symptoms such as palpitations, sweating, and blushing, which are common VMS, and are prone to interpret them as signs of a more serious condition. Also, women with higher AS might interpret VMS as having an extremely harmful social impact, since women have little control over the appearance and duration of HF.

These findings are consistent with Musicl et al., who showed that AS plays an important role in perimenopausal distress. Focusing on VMS, Hunter & Chilcot37 developed and tested a cognitive behavioral model, and their study suggested that the level of symptom perception and somatic amplification could increase the likelihood of symptom detection, but could also increase the reporting of HF/NS due to a higher sensitivity and selective attention to small variations in thermoregulatory sensations.

Our findings must be interpreted in light of certain limitations. The cross-sectional design provides no information on the causal relationship between the factors. Furthermore, although our sample size had sufficient power to detect differences, it was not a large selection. Bias secondary to the means of enrollment could have determined that women with higher education and more concerned about their health were interviewed. In addition, the rate of psychiatric comorbidity was high, which might have interfered with the perception of VMS, possibly inflating the association between AS and VMS problem rating. However, our study also has a number of strengths. We conducted a broad psychiatric evaluation using trained clinicians, instead of using only self-report questionnaires. Not only was the severity of anxiety and depression symptoms evaluated, but depressive and anxiety disorders were diagnosed as well. Exploring the factors related to VMS problem rating provides important information for clinical purposes, making it possible to develop cost-effective non-pharmacological strategies, such as protocols for interventions based on psychoeducation and cognitive-behavioral techniques. Few studies have focused on the association between AS and VMS. Further studies with larger samples and longitudinal designs are needed to explore the relationship between negative affect and the bothersomeness of VMS, with a view to understanding the role of AS.

In short, based on our findings, it can be concluded that the evaluation of women seeking treatment for VMS should include assessment of negative affect symptoms. Moreover, the early identification of women with higher levels of AS and VMS would allow the development of new strategies targeting these symptoms, reducing the burden of psychological and somatic changes brought about by the menopausal transition.

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Disclosure

The authors report no conflicts of interest.

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