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SCIENTIFIC INVESTIGATIONS

Hot flashes, insomnia, and the reproductive stages: a cross-sectional observation of women from the EPISONO study

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Study Objectives: To investigate the association of hot flashes and insomnia in women in premenopause and postmenopause.

Methods: The study was performed using data from the São Paulo Epidemiological Sleep Study. Women in premenopause were classified as having regular menstrual cycles, being anovulatory, or using hormonal contraceptives. Women in menopause were classified as being in perimenopause, early postmenopause, or late postmenopause. Women reporting frequent insomnia symptoms and relevant daytime complaints were classified as having insomnia disorder. Polysomnography alterations suggestive of insomnia were also identified.

Results: The frequency of hot flashes was 42% among women in postmenopause (mainly in early postmenopause) and 9% among women in premenopause (mainly anovulatory; $P < .01$). Approximately 18.7% had insomnia disorder, 48% had isolated insomnia symptoms, and 32.4% had polysomnography alterations. Comparing women in menopause with those in premenopause, the diagnosis of insomnia was similar (premenopause: 18.9% vs menopause: 17.5%), but women in menopause had more frequent isolated insomnia symptoms (premenopause: 43.9% vs menopause: 55.9%; $P = .02$) and polysomnography correlates of insomnia (premenopause: 26.5% vs menopause: 42.6%; $P < .01$). Hot flashes were more frequent among women with insomnia disorders (25.5%) and with isolated insomnia symptoms (23.0%) when compared with good sleepers (12.6%) in the entire sample ($P = .01$). Among women in late menopause, the prevalence of hot flashes was higher in both women with insomnia disorders (42.1%) and with isolated insomnia symptoms (37.5%) when compared with women who were good sleepers (14.3%; $P = .05$).

Conclusions: Hot flashes are associated with insomnia and polysomnography alterations suggestive of insomnia. The prevalence of hot flashes among women with insomnia disorder is especially high among women in late postmenopause.

Keywords: sleep, hot flashes, insomnia, premenopause, postmenopause, polysomnography

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Women self-report more sleep problems than men and are 3 times more likely to present with insomnia and inadequate sleep. Hot flashes increase both sleep fragmentation and dissatisfaction, leading to a worse quality of life and overall poorer health-related outcomes.

Study Impact: In premenopause, hot flashes are more often observed among women who are anovulatory and those with irregular menstrual cycles, whereas in women in menopause they are more common in early postmenopause. In both cases, hot flashes are associated with both self-reported and objective sleep alterations.

INTRODUCTION

Several studies have noted that women self-report more sleep problems than men, and they are almost 3 times more likely to present with insomnia and inadequate sleep.[1–5] One possible reason for this is hormonal fluctuations over the menstrual or estrous cycles, which have been associated with sleep variations in both humans and rodents.[6–9] Moreover, previous findings have shown that women with irregular menstrual cycles were twice as likely to report sleep problems.[7] This may explain why woman are predisposed to hyperarousal and respond to stress differently.[10] All the physiological phenomena associated with menopause are possible predisposing factors for sleep disturbance, and in particular for insomnia. Previous findings showed that both early and late postmenopause are associated with a variety of symptoms but that sleep complaints in particular tend to increase in late postmenopause.[11]

Among menopausal symptoms, hot flashes have been linked in several studies to sleep disturbances, especially sleep fragmentation[12–14] and insomnia.[15,16] The relationship between hot flashes and sleep fragmentation has been shown by experimental models of induced vasomotor symptoms, leading to an increased number of awakenings, time awake after sleep onset, and sleep transitions.[13,14,17] More specifically, objective hot flashes (measured by skin conductance) have been shown to lead to reduced sleep efficiency,[13] whereas self-reported hot flashes (ie, the perception of having them) reduce sleep quality and increase the number of sleep stage transitions,[13,17] especially to wake and N1 sleep stages.[17]

With respect to insomnia, the prevalence of its symptoms increases proportionally with the severity of vasomotor

symptoms, being observed in more than 80% of women in perimenopause and postmenopause with severe hot flashes.[15] This finding was corroborated by studies that observed a higher Insomnia Severity Index score among women experiencing hot flashes.[14,18] The prevalence of clinical insomnia disorder may be as high as 44% among women experiencing severe hot flashes.

The mechanisms linking hot flashes to sleep fragmentation and insomnia are not clear, but there are 2 main hypotheses: The first speculates that estrogen oscillations may be a common cause of both hot flashes and sleep disturbances,[16] and the second, named "the domino hypothesis," proposes that a sequence of events in which nocturnal hot flashes predispose women to sleep fragmentation leads to insomnia and higher vulnerability to behavior and mood disorders.[16,19] It is possible, therefore, that the increased number of sleep transitions and consequent sleep fragmentation caused by perceived nighttime vasomotor symptoms increases the awareness and memory of the awakening throughout the night, thus predisposing to insomnia.

Although the relationship between hot flashes and sleep disturbances has gained support in the literature, more research is still needed to clarify some aspects. Most studies were performed with clinical patient samples, which may overestimate the magnitude of the problem. To date, only 1 population-based study evaluating the relationship between insomnia and hot flashes has been performed, based on phone calls and a self-reported sleep assessment.[15] Thus, it is not clear to what extent these symptoms affect women in the general population. The prevalence of insomnia disorder among women experiencing hot flashes also needs to be better defined. Understanding the actual relationship between hot flashes and insomnia is important not only for epidemiological and etiological reasons, but with respect to clinical and treatment aspects. If hot flashes are confirmed to be associated with or even predisposing to insomnia, then it is possible that the treatment of vasomotor manifestations would also secondarily improve insomnia symptoms.

Our goal was to describe the occurrence of hot flashes among women at different reproductive stages and analyze associations with self-reported and objective measures of insomnia in a large, representative sample of the adult population of São Paulo, Brazil. We thus studied the hormonal profiles and completed sleep evaluations (questionnaires and polysomnography) of all the women who took part in the São Paulo Epidemiologic Sleep Study (EPISONO).[20]

METHODS

Sampling and study design

EPISONO was a population-based cross-sectional study aimed at describing sleep profiles and the prevalence of sleep disturbances and their risk factors in adults living in São Paulo, Brazil. São Paulo is the largest city in the Southern Hemisphere and the fifth largest metropolis in the world. Participants (ages 20–80 years) underwent examinations from July–December 2007. The complete design, methods, and procedures used in the study are described in detail elsewhere.[20] Briefly, the single-center study involved an initial sample of 1,101 individuals, representative of the population of São Paulo and selected using a 3-stage clustering technique. This sample size allowed the calculation of prevalence estimates to a minimum of 3% or higher, with a 5% chance of error. The recruitment involved 2 phases. In the first phase, participants were interviewed in their own home and answered an initial set of questionnaires. In the second phase, participants underwent polysomnography (PSG), biochemical blood tests, additional questionnaires, and complementary examinations at the Sleep Institute of the Universidade Federal de São Paulo. With a refusal rate of 5.4%, 1,042 volunteers (574 women) agreed to undergo PSG. The study protocol was approved by the Research Ethics Committee of the Universidade Federal de São Paulo (CEP 0593/06) and was registered at ClinicalTrials.gov (ClinicalTrials.gov identifier: NCT00596713).

Instruments and procedures

In the EPISONO study,[20] trained interviewers and psychologists applied a set of 28 questionnaires to all participants. These questionnaires were applied either at the volunteers' homes or at the Sleep Institute, before the PSG exam, and included information related to demographic factors, medical history, use of medication, and sleep-related items. The complete list of questionnaires is described elsewhere.[20] In the current study, we used data acquired using the following 8 questionnaires: the Criteria of Economic Classification Brazil,[21] the Universidade Federal de São Paulo Sleep Questionnaire,[22] the Beck Anxiety Inventory,[23] the Beck Depression Inventory,[24] the Pittsburgh Sleep Quality Index,[25] the Insomnia Severity Index,[26] the Epworth Sleepiness Scale,[27] and a gynecological questionnaire.[7]

General physical measurements were taken immediately before the PSG exam and included hip and waist circumferences (cm), blood pressure, body weight (kg), and height (m), which were used to calculate body mass index with the formula weight/height.[2] PSG was scheduled and performed based on the participants' habitual bedtimes and awaking times. The morning after PSG, 12-hour fasting blood samples were collected to measure progesterone, luteinizing hormone (LH), follicle-stimulant hormone (FSH), and estradiol levels, using the acridinium ester-chemiluminescence method (Advia Centaur/Siemens Healthcare Diagnostics, Erlanger, Germany). Plasma glucose levels were also measured using the glucose oxidase method, as were total cholesterol, low-density and high-density lipoprotein cholesterol, and triglycerides using an auto analyzer and the appropriate reagents.

Gynecological evaluation

The date of the previous menstrual cycle was registered twice, initially during the participant's visit to the sleep laboratory (as part of the gynecological questionnaire) and then in a phone call a month later to assess the regularity of the participant's cycle. All information related to menstrual cycles was later compared to hormonal measures. The participants were grouped according to their reproductive aging stages as being in premenopause, perimenopause, or postmenopause. Women in premenopause were those with regular cycles, and they were further categorized according to 3 possible menstrual cycle stages: the follicular phase (first 12 days of menstrual cycle, with the appropriate proper FSH and estrogen levels based on standard reference levels), the periovulatory phase (near the 14th day of menstrual

cycle, with LH concentrations reaching 50 mIU/mL), and the luteal phase (second half of menstrual cycle, with high progesterone concentrations).[28] All women taking hormonal contraceptives and women who were anovulatory (no hormonal contraceptives, amenorrhea with FSH and LH levels < 30 mIU/mL) were included in 2 separate groups. Women in perimenopause were those presenting an irregular menstrual cycle in the last 1 year, with FSH and LH levels > 30 mIU/mL and an estradiol level > 30 pg/mL. Women in postmenopause were those in amenorrhea for more than a year and with FSH and LH levels > 30 mIU/mL and were considered to be in either early (< 5 years) or late (> 5 years) stages.[29] For the analyses, the perimenopause and postmenopause groups were merged into a general menopause group, representing women with menopause-related symptoms.

Reports of hot flashes (yes/no) were registered as part of the gynecological questionnaire, as was the use of any kind of hormonal or alternative therapies to deal with menopausal symptoms.[7]

Sleep evaluation

A full-night PSG was performed using a digital system (EMBLA S7000, Embla Systems, Inc., Broomfield, CO) at the sleep laboratory during the participants' habitual sleep time. The following physiological variables were monitored simultaneously and continuously: electroencephalogram, electrooculogram, surface electromyogram (submentonian region, anterior tibialis muscle, masseter region, and seventh intercostal space), electrocardiogram, airflow detection via thermocouple and nasal pressure, thoracic and abdominal respiratory effort using inductance plethysmography, snoring, body position, oxyhemoglobin saturation, and pulse rate. Four trained technicians visually scored all of the PSG data according to the standard criteria for investigating sleep.[30] Electroencephalogram arousals, sleep-related respiratory events, and leg movements were scored in accordance with the criteria outlined in *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications* (first edition).[31]

Insomnia evaluation

Insomnia was evaluated in three ways: the severity of insomnia symptoms, a self-reported insomnia diagnosis, and objective sleep alterations suggestive of insomnia.

The severity of insomnia symptoms was evaluated using the Insomnia Severity Index.[26] A self-reported insomnia diagnosis was made based on previous studies,[32] and the participants were classified as good sleepers, as having isolated insomnia symptoms, or as having insomnia disorder. Individuals without frequent or persistent insomnia complaints were classified as good sleepers. Individuals reporting regular insomnia symptoms (difficulties initiating sleep or sleep onset latency > 30 minutes, difficulty maintaining sleep, and/or early morning awakenings, occurring at least 3 times per week) that had little or no effect on daytime activities were classified as having insomnia symptoms. Individual reporting frequent and persistent insomnia symptoms that interfered "considerably" or "extremely" with daily functioning were classified with insomnia disorder, according to *Diagnostic and Statistical Manual of Mental Disorders*-4 criteria.

Objective sleep alterations suggestive of insomnia were also analyzed, based on the methodology previously proposed as an objective insomnia correlate.[32] These alterations were diagnosed whenever participants met 1 of the following criteria: sleep initiating insomnia (sleep onset latency > 30 minutes), sleep maintenance insomnia (wake time after sleep onset > 30 minutes), insomnia with early awakening (total sleep time < 360 minutes and terminal wakefulness > 30 minutes), or mixed disorder (combination of the previous criteria).[32]

Comorbidities

The standard overweight and obesity cutoff points were used: a body mass index of ≥ 25 kg/m^2 and ≥ 30 kg/m^2, respectively. Metabolic syndrome was defined as the presence of at least 3 of the following: (1) waist circumference > 88 cm, (2) systolic blood pressure > 140 mm Hg and/or diastolic BP > 90 mm Hg, (3) fasting glucose ≥ 100 mg/dL, (4) triglycerides ≥ 150 mg/dL, and (5) high-density lipoprotein < 50 mg/dL. Hypertension was defined by the use of antihypertensive medication and/or elevated blood pressure (as for metabolic syndrome). Diabetes was defined by a glucose level ≥ 126 mg/dL, the use of antidiabetic medication, or a previous diagnosis. Anxiety and depression were defined by scores of ≥ 20 in the Beck Anxiety Inventory and Beck Depression Inventory, respectively.

Statistical analysis

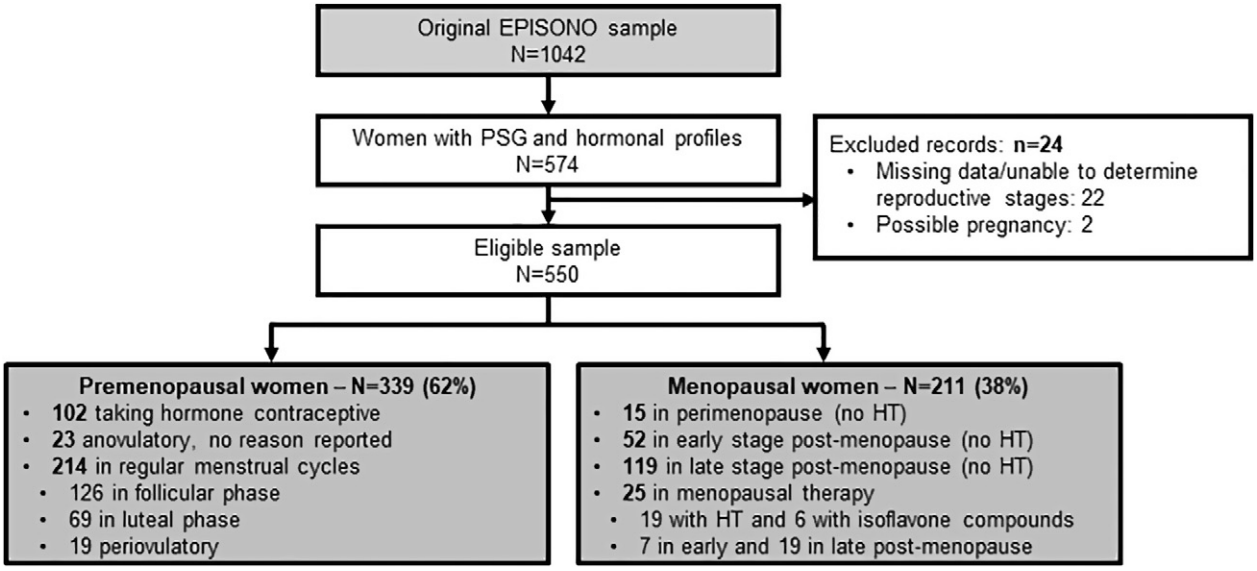
Data analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL). All data that did not meet the assumptions of normality and homogeneity were *z* score–transformed for suitable parametric evaluation. The statistical analysis for the description of the sample group was carried out by 1-way analysis of variance. For the analysis of associations, chi-square testing was performed. The significance level was set at < 5%.

RESULTS

Sample descriptive characteristics

The demographic and clinical characteristics of the study population have been previously described elsewhere.[20] The initial sample of this study comprised 574 women. Two women reported being pregnant after visiting the Sleep Institute and were excluded from the analyses. Another 22 women who did not remember the date of their cycles or were not reachable by phone and whose cycles or menopausal status could not be determined were also excluded. The final sample included 550 women: 339 women in premenopause at different phases of the menstrual cycle and 211 women in menopausal stages (either perimenopause or postmenopause). Twenty-five women in menopause were receiving hormone therapy (n = 19) or isoflavone (n = 6) and were also excluded from the analysis. Smoking, alcohol use, and sedentarism were more frequent among women in premenopause, whereas obesity, metabolic syndrome, hypertension, and diabetes were more frequent in women in postmenopause women. A flowchart of the sample selection is shown in **Figure 1**, the descriptive characteristics of the sample are presented in

Figure 1—Flowchart outlining sample selection.



The menopausal groups do not include women using menopausal therapy (HT or isoflavone). Of the 25 participants in therapy for menopausal symptoms, 7 were in the early stage and 18 were in the late stage. EPISONO = São Paulo Epidemiologic Sleep Study, HT = hormone therapy, PSG = polysomnography.

Table 1, and the clinical characteristics of the sample according to their reproductive stages are presented in **Table 2**.

Frequency of hot flashes

Of all women, 22% reported hot flashes. The frequency of hot flashes was 42% among women in postmenopause and 9% among women in premenopause (χ^2, 83.2; degrees of freedom [*df*], 1; $P <$ .01). Among women in premenopause, those in anovulatory stages had a higher frequency of hot flashes (26%) and were more overweight and older, whereas those taking hormonal contraceptives had a lower frequency of hot flashes (6%) and were younger and more eutrophic. Half of the women in early postmenopause and a third of the women in late postmenopause reported hot flashes.

Frequency of insomnia

Of all women, 18.7% had a diagnosis of insomnia disorder and 48% had isolated symptoms of insomnia. Regarding PSG alterations suggestive of insomnia, 32.4% had at least 1 PSG alteration.

In comparing women in menopause with women in premenopause, we found that the diagnosis of insomnia was slightly more frequent among women in premenopause (premenopause: 18.9% vs menopause: 17.5%), whereas the prevalence of isolated insomnia symptoms was higher among women in menopause (premenopause: 43.9% vs menopause: 55.9%; χ^2, 7.5; *df,* 2; $P =$ .02). PSG correlates of insomnia were more frequent among women in menopause (premenopause: 26.5% vs menopause: 42.6%; χ^2, 14.86; *df,* 1; $P <$ .01).

Among women in menopause, there were no significant associations between stages and insomnia diagnosis (χ^2, 3.6; *df,* 4; $P =$ .46), and the prevalence of insomnia disorder ranged from 16.65% (in late postmenopause) to 25.0% (in early postmenopause). The prevalence of PSG correlates of insomnia ranged from 26.7% (in perimenopause) to 55.5% (in late postmenopause; χ^2, 5.9; *df,* 2; $P =$ .05). Among women in premenopause, insomnia disorder was more frequent among those who were anovulatory (30.4%), isolated symptoms of insomnia were more frequent among those with regular cycles (49.5%), and good sleepers were more frequent among those using contraceptives (50.0%; χ^2, 12.6; *df,* 4; $P =$ .01). PSG alterations suggestive of insomnia were more frequent among women who were anovulatory (34.8%; χ^2, 6.1; *df,* 2; $P =$ .46).

Frequencies of insomnia symptoms, insomnia diagnosis, and objective sleep alterations are presented in **Table 3**. Histograms showing the frequency of each reproductive stage and the presence of hot flashes and insomnia are presented in **Figure 2**.

Association between insomnia and hot flashes

Hot flashes were more frequent among women with insomnia disorders (25.5%) and women with isolated insomnia symptoms (23.0%) compared with good sleepers (12.6%; χ^2, 9.32; *df,* 2; $P =$ .01), when considering the entire sample. Similar results were also observed among women in late menopause, in whom the prevalence of hot flashes was higher in those with insomnia disorders (42.1%) and those with isolated insomnia symptoms (37.5%) than in good sleepers (14.3%; χ^2, 5.8; *df,* 2; $P =$ .05). No significant results were seen in other reproductive life stages. Regarding PSG alterations suggestive of insomnia, the only significant result was observed among women in premenopause, in whom hot flashes were more frequent among those with PSG alterations (15.6%) than among those without any alterations (7.2%; χ^2, 5.3; *df,* 1; $P =$ .03). The associations between hot flashes and insomnia for all reproductive life stages are presented

Table 1—Sample description.

	Total (n = 550)		Hot Flashes (n = 120)	
	n	%	n	%
Age groups, y				
20–29	109	19.8	3	2.7
30–39	120	21.8	9	7.5
40–49	137	24.9	39	28.5
50–59	98	17.8	46	46.9
60–69	54	9.8	16	29.6
70–80	32	5.8	7	21.9
Family income < R$1,520*	251	46.7	63	54.3
Education < 9 y	211	38.6	66	55.5
Premenopause	339	61.6	31	9.1
Anovulatory	23	4.2	6	26.1
Hormonal contraceptive	102	18.5	6	5.9
Regular menstrual cycle	214	38.9	19	8.9
Follicular	126	22.9	11	8.7
Luteal	69	12.5	8	11.6
Periovulatory	19	3.5	0	0
Menopause	211	38.4	89	42.2
Perimenopause	15	2.7	10	66.7
Early stage	59	10.7	32	54.2
Hormone therapy	4	0.7	4	100.0
Isoflavone	3	0.5	3	100.0
Late stage	137	24.9	47	34.3
Hormone therapy	15	2.7	6	40.0
Isoflavone	3	0.5	3	100.0
Health-related behaviors				
Current smoker	127	25.1	31	29.0
Alcohol, weekly	132	30.3	26	29.5
Sedentary	383	69.6	87	72.5
Weekly sleeping pill use	38	6.9	19	15.8
Mental health				
Depression (BDI)	70	13.90	21	19.80
Anxiety (BAI)	62	12.1	22	20.6
Clinical characteristics				
Overweight or obese	336	61.1	93	77.5
BMI 25–30 kg/m^2	208	37.8	53	44.2
BMI ≥ 30 kg/m^2	127	23.1	39	32.5
Metabolic syndrome	131	23.8	42	35.0
Hypertension	205	37.3	62	51.7
Previous diagnosis	145	26.4	50	41.7
BP > 140/90 mm Hg	179	33.1	53	44.9
Using antihypertensive	104	18.9	37	30.8
Diabetes mellitus	32	5.8	13	10.8

Percentages were calculated based on valid participants, excluding missing responses. *Monthly family income, in Brazilian Reais (R$ / BRL). BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, BMI = body mass index, BP = blood pressure.

Table 2—Clinical characteristics among women in different reproductive stages.

	Premenopause (n = 339)								Menopause (n = 211)								*P*
	n	%	Contraceptive Use (n = 102)		Regular Cycles (n = 214)		Anovulatory (n = 23)		n	%	Perimenopause (n = 15)		Early Postmenopause (n = 52)*		Late Postmenopause (n = 119)*		
			n	%	n	%	n	%			n	%	n	%	n	%	
Smoking	85	25.07	25	24.51	58	27.10	2	8.70	42	19.91	4	26.67	16	30.77	22	18.49	.137
Alcohol, weekly	90	26.55	32	31.37	54	25.23	4	17.39	42	19.91	4	26.67	12	23.08	26	21.85	.335
Sedentary	257	75.81	76	74.51	165	77.10	16	69.57	126	59.72	10	66.67	40	76.92	76	63.87	.001
Depression	43	12.68	12	11.76	29	13.55	2	8.70	24	11.37	3	20.00	8	15.38	13	10.92	.824
Anxiety	41	12.09	13	12.75	27	12.62	1	4.35	19	9.00	4	26.67	6	11.54	9	7.56	.144
Weight																	
Overweight	114	33.63	32	31.37	72	33.64	10	43.48	94	44.55	6	40.00	26	50.00	62	52.10	< .001
Obese	54	15.93	14	13.73	33	15.42	7	30.43	73	34.60	7	46.67	21	40.38	45	37.82	—
Metabolic syndrome	50	14.75	9	8.82	38	17.76	3	13.04	81	38.39	5	33.33	20	38.46	56	47.06	< .001
Hypertension	75	22.12	17	16.67	49	22.90	9	39.13	130	61.61	9	60.00	27	51.92	94	78.99	< .001
Diabetes	6	1.77	2	1.96	2	0.93	2	8.70	26	12.32	2	13.33	6	11.54	18	15.13	< .001

*Women in menopause receiving hormone therapy are not presented (7 in early menopause and 19 in late postmenopause). *P* values calculated based on χ^2 test.

in **Figure 3** (insomnia diagnosis) and **Figure 4** (PSG alterations suggestive of insomnia).

DISCUSSION

Women experience a greater number of hormonal changes across the lifespan (associated with events such as pregnancy and the climacteric) than men, and therefore hormonal imbalance has greater overall consequences in women, particularly in relation to sleep duration and quality. A previous observed that among women with sleep complaints in an outpatient sample, those with irregular menstrual cycles were more likely to report insomnia-related sleep difficulties than those with regular cycles.[7]

One of the most common consequences of these hormonal changes are hot flashes. Independent from specific conditions leading to irregularities in menstrual cycles or aging, hot flashes are linked to sleep fragmentation even among healthy younger women of reproductive age, as shown by Joffe, Crawford, Freeman, and colleagues.[33] In this study, the authors described an experimental model using a GnRH agonist to induce hot flashes in healthy young women. They observed that the absence of estrogen led to sleep disruption, particularly when in combination with reports of nighttime hot flashes.

In the current study, hot flashes were observed in 42% of women in menopause. Hot flashes were more frequent among women in perimenopause (67%) and among those using hormonal therapy (60%), and they tended to decrease in later stages (34%). It is not clear why we observed such a high percentage of women reporting hot flashes while using hormonal therapy,[34] but because it was a simple yes or no question in our study, not specifying any time frame, their answers could be referring to a history of having hot flashes rather than having them currently.

In our study, hot flashes were most common in women who were anovulatory and who were found to have an increased risk for insomnia disorder, potentially explained by the occurrence of hot flashes. Possible reasons for becoming anovulatory are polycystic ovary syndrome, hyperprolactinemia, or other hormonal disorders. Polycystic ovary syndrome is the most common cause for anovulatory menstrual cycles in women. Recent studies have associated polycystic ovary syndrome with sleep disturbances such as obstructive sleep apnea[35,36] and insomnia, with the latter having an estimated prevalence of 12.6%.[37] Although many studies have investigated hot flashes among women near the menopausal transition, the only study to investigate this relationship in women in premenopause women was a study that examined polycystic ovary syndrome (based on the Rotterdam criteria) and hot flashes and found no association.[38]

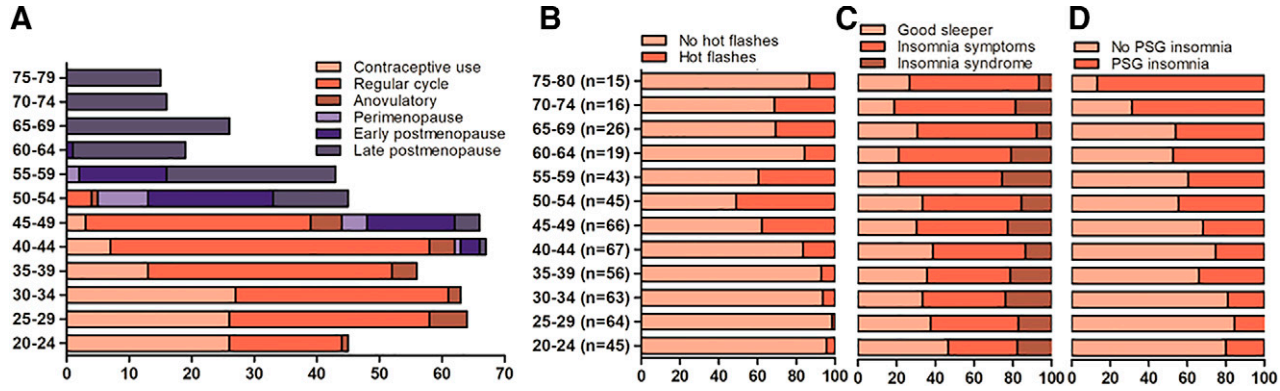
Previous findings examining data from the EPISONO study[20] to evaluate the objective sleep of women in postmenopause indicated that menopause in itself exerts a modest but significant independent effect on some objective sleep parameters, in particular respiratory-related ones such as the apnea-hypopnea index and oxyhemoglobin saturation.[39] In another study that analyzed self-reported sleep problems in a clinical sample of women in menopause from a gynecological outpatient setting, although early menopause was associated with a complex

Table 3—Self-reported and objective insomnia according to reproductive stage.

	Premenopause (n = 339)								Menopause (n = 211)								*P*
	n	%	Contraceptive Use (n = 102)		Regular Cycles (n = 214)		Anovulatory (n = 23)		n	%	Perimenopause (n = 15)		Early Postmenopause (n = 52)*		Late Postmenopause (n = 119)*		
			n	%	n	%	n	%			n	%	n	%	n	%	
Insomnia ≥ 3 d/w in past 6 mo (UNIFESP Sleep Questionnaire)																	
DIS	101	29.79	24	23.53	69	32.24	8	34.78	75	35.55	5	33.33	20	38.46	50	42.02	.465
DMS	122	35.99	28	27.45	88	41.12	6	26.09	115	54.50	8	53.33	27	51.92	80	67.23	< .001
EMA	94	27.73	18	17.65	71	33.18	5	21.74	71	33.65	4	26.67	19	36.54	48	40.34	.053
Insomnia ≥ 3 d/w in past mo (PSQI)																	
SOL > 30 min	127	37.46	30	29.41	86	40.19	11	47.83	82	38.86	8	53.33	22	42.31	52	43.70	.299
Awakenings	143	42.18	30	29.41	98	45.79	15	65.22	113	53.55	8	53.33	27	51.92	78	65.55	< .001
ISI (in past 2 wks)																	
Daytime impairment	85	25.07	28	27.45	50	23.36	7	30.43	43	20.38	3	20.00	16	30.77	24	20.17	.461
Self-reported insomnia diagnosis																	
Good sleeper	126	37.17	51	50.00	68	31.78	7	30.43	56	26.54	5	33.33	20	38.46	31	26.05	.002
Symptoms	149	43.95	34	33.33	106	49.53	9	39.13	118	55.92	7	46.67	26	50.00	85	71.43	
Disorder	64	18.88	17	16.67	40	18.69	7	30.43	37	17.54	3	20.00	13	25.00	21	17.65	
PSG alterations suggestive of insomnia																	
SOL > 30 min	44	12.98	9	8.82	32	14.95	3	13.04	43	20.38	2	13.33	11	21.15	30	25.21	.144
WT > 60 min	94	27.73	21	20.59	66	30.84	7	30.43	123	58.29	7	46.67	30	57.69	86	72.27	< .001
TST < 6 h	178	52.51	45	44.12	117	54.67	16	69.57	145	68.72	9	60.00	37	71.15	99	83.19	< .001
PSG insomnia	90	26.55	18	17.65	64	29.91	8	34.78	90	42.65	4	26.67	20	38.46	66	55.46	< .001

*Women in menopause receiving hormone therapy are not presented (7 in early menopause and 19 in late postmenopause). *P* values calculated based on χ^2 test, comparing women in premenopause and menopause. DIS = difficulty initiating sleep, DMS = difficulty maintaining sleep, EMA = early morning awakening, ISI = Insomnia Severity Index, PSG = polysomnography, PSQI = Pittsburgh Sleep Quality Index, SOL = sleep onset latency, TST = total sleep time, UNIFESP = Universidade Federal de São Paulo, WT = total wake time.

Figure 2—Histograms associating age groups with reproductive stages, hot flashes, and insomnia.



(A) Absolute numbers of women in each reproductive stage (red shade refers to premenopausal stages and blue shade refers to menopausal stages). **(B, C, D)** Histograms (%) relating age groups to hot flashes, self-reported insomnia, and PSG insomnia symptoms, respectively. PSG = polysomnography.

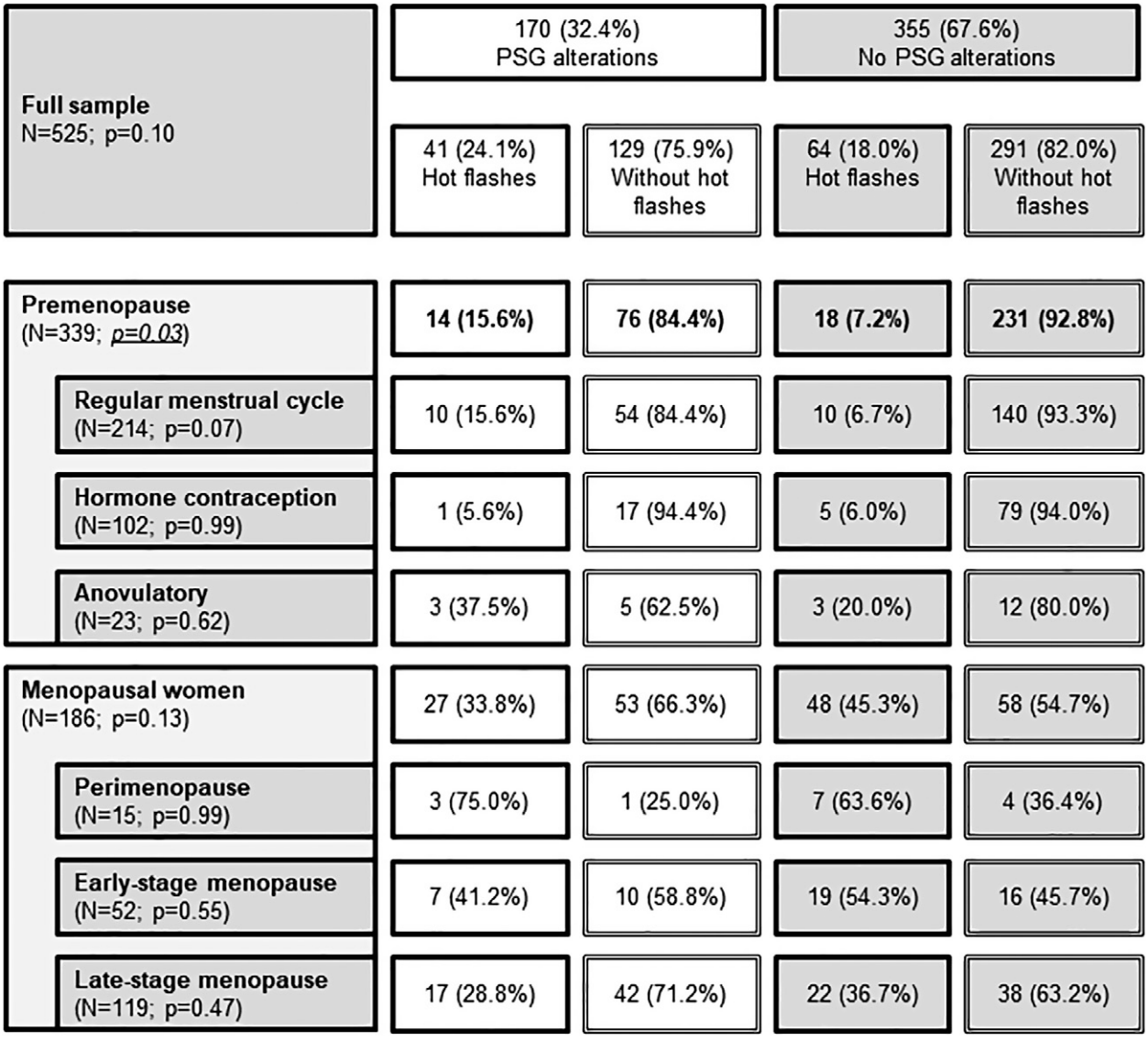
Figure 3—Prevalence of insomnia disorder and association with hot flashes in all reproductive life stages.

	98 (18.7%) Insomnia disorder		252 (48.0%) Isolated symptoms of insomnia		175 (33.3%) Good sleepers	
Full sample N=525; *p=0.01*	**25 (25.5%)** Hot flashes	**73 (74.5%)** Without hot flashes	**58 (23.0%)** Hot flashes	**194 (77.0%)** Without hot flashes	**22 (12.6%)** Hot flashes	**153 (87.4%)** Without hot flashes
Premenopause (N=339; p=0.38)	7 (10.9%)	57 (89.1%)	16 (10.7%)	133 (89.3%)	8 (6.3%)	118 (93.7%)
Regular menstrual cycle (N=214; p=0.44)	3 (7.5%)	37 (92.5%)	12 (11.2%)	94 (88.7%)	4 (5.9%)	64 (94.1%)
Hormone contraception (N=102; p=0.45)	2 (11.8%)	15 (88.2%)	1 (2.9%)	33 (97.1%)	3 (5.9%)	48 (94.1%)
Anovulatory (N=23; p=0.68)	2 (28.6%)	5 (71.4%)	3 (33.3%)	6 (66.7%)	1 (14.3%)	6 (85.7%)
Menopausal women (N=186; p=0.08)	18 (52.9%)	16 (47.1%)	42 (40.8%)	61 (59.2%)	14 (28.6%)	35 (71.4%)
Perimenopause (N=15; p=0.20)	3 (100%)	0 (0%)	5 (71.4%)	2 (28.6%)	2 (40.0%)	3 (60.0%)
Early-stage menopause (N=52; p=0.63)	7 (58.3%)	5 (41.7%)	10 (41.7%)	14 (58.3%)	8 (50.0%)	8 (50.0%)
Late-stage menopause (N=119; *p=0.05*)	**8 (42.1%)**	**11 (57.9%)**	**27 (37.5%)**	**45 (62.5%)**	**4 (14.3%)**	**24 (85.7%)**

combination of symptoms, the sleep-related symptoms were more frequently observed among women in late postmenopause and independent of age.[11] In the current study, in which we are specifically analyzing the association between insomnia disorder or symptoms with hot flashes, we found that women in the later stage of menopause tend to get used to sleep fragmentation, report it less, and experience daytime impairment or distress less often.

In a recent longitudinal study with a 12-year follow-up,[40] Matthews et al also evaluated self-reported and objective sleep measures in women as they traversed menopause, using questionnaires and actigraphy instead of PSG. They observed some key factors covarying with sleep duration regardless of menopausal status or the occurrence of vasomotor symptoms: race/ethnicity and working status. In contrast with our findings,

Figure 4—Prevalence of PSG alterations suggestive of insomnia and association with hot flashes in all reproductive life stages. PSG = polysomnography.



the authors concluded that the sleep characteristics seen among midlife women may not necessarily get worse with aging. They observed that women generally experienced an increase in sleep duration with aging, tied to a decrease in wake after sleep onset. Perhaps this discrepancy with what we observed could be explained by our different objective methods for measuring sleep: As compared to PSG, actigraphy tends to overestimate sleep duration, particularly among people with insomnia, who often spend more time in bed inactive, and older retired individuals, who tend to experience polyphasic sleep or develop more breathing-related sleep disorders.

The use of hormonal contraception seems to protect women against both self-reported and objective insomnia symptoms. The reasons for this effect are unclear, but there are 3 possible explanations: a direct effect of contraceptives on sleep-regulating mechanisms;[41] an indirect effect, in which contraceptives prevent symptoms that could lead to insomnia (eg, hot flashes); or a sampling bias, because women using hormonal contraception are usually younger and more eutrophic, thus being less prone to insomnia.

A previous study analyzing the EPISONO sample showed better objective sleep parameters among women using hormonal contraception, because of both better sleep architecture and fewer sleep-breathing disorders,[42] but the current study is the first to analyze insomnia among them. Other studies have examined the association between sleep disorders and hormonal contraception; the first, using a convenience clinical sample with PSG recordings, found that women using oral contraceptives had better respiratory patterns (reduced apnea-hypopnea index and less time with an arterial oxygenation < 90%), fewer arousals, and shorter sleep onset latency.[7] A second study, based on a nonclinical online survey, found that hormonal contraceptive users reported a worse sleep pattern, with increased daytime sleepiness and more

insomnia symptoms.[43] The reasons for these discrepancies remain unclear, but possible explanations may be related to contraceptive formulation (combined vs progestogen) and route of administration (oral pills vs hormonal intrauterine delivery systems). In addition, the characteristics of the samples and the different methodological approaches used to assess sleep may have affected the results. There are still no randomized controlled trials testing whether hormonal contraception protects both objective and self-reported sleep or exploring whether different contraceptive formulations impact sleep differently.

Finally, the association between hot flashes and insomnia corroborated previous literature.[15] The prevalence of hot flashes among women with insomnia was 25.5%, reaching 58.3% in early menopause and 42.1% in late menopause. In a similar study with a representative sample, Ohayon[15] described a 37.3% prevalence of hot flashes among women in postmenopause. Despite the prevalence in our sample being higher, both studies agree with respect to the high association of hot flashes among women in postmenopause with insomnia.

Although our study has significant strengths, it also has some limitations. First, this was a cross-sectional study (rather than a randomized trial or a longitudinal study), which did not allow us to establish true causal relationships. Second, we did not analyze respiratory data in this study, because it would only have indirect effects, and we also wanted to avoid the duplicate use of data because this study is based on data from the EPISONO study,[20] and the relationship between the apnea-hypopnea index and menopause has already been evaluated in previous articles.[7,39,44] Third, we did not perform an adaptation night in this study, which might have predisposed our results to a first-night effect (ie, the results would be dependent on the participants being in an unfamiliar environment). Although this is an important methodological point, it is not usual for large epidemiological sleep studies to include an adaptation night.[45,46] Moreover, this possibility relates only to the PSG-derived data and not to the main insomnia diagnosis and symptoms. Fourth, current diagnostic guides do not recommend PSG as a diagnostic tool for insomnia disorder, and the PSG insomnia symptoms evaluated in this study cannot be taken as diagnostic criteria for insomnia but rather as isolated objective sleep manifestations that may or may not be suggestive of insomnia. Although these symptoms are in accordance with major insomnia concerns and phenotype, PSG does not provide information regarding symptom frequency (a major diagnostic criterion for insomnia disorder) and may reflect the circumstances in which the exam was performed (ie, a first-night effect). Fifth, hot flashes were assessed using a single yes or no question, without further information on severity, frequency, or onset. Because the EPISONO study[20] is a population-based sleep study based on multiple questionnaire-based assessments, the number of questions related to gynecological data were limited. However, although it was a broad population-based study, blood samples were obtained, which allowed menopause status to be confirmed according to hormonal profile. Although we acknowledge these limitations, we believe that the representativeness of the sample provides a unique analysis of data in a population-based framework, with our study design and coverage overriding the limitations of these screening questions. Note also that we worked with the population of São Paulo, a cosmopolitan urban city with more than 11 million inhabitants. Therefore, although similar data could be collected in cities all over the world, the external validity would be reduced when comparing our data with data from smaller cities or rural populations.

CONCLUSIONS

Our current findings suggest that hot flashes are associated with both self-reported and objective sleep alterations. In general, women reporting hot flashes have a higher likelihood of also having insomnia disorder or isolated symptoms, especially during late postmenopause. Among women in premenopause, reporting hot flashes was associated with PSG alterations suggestive of insomnia. Because an association between hot flashes and insomnia was established, and a high prevalence was observed, further longitudinal studies should be undertaken to evaluate a possible causal relationship between hot flashes and insomnia.

ABBREVIATIONS

EPISONO, São Paulo Epidemiologic Sleep Study
FSH, follicle-stimulant hormone
LH, luteinizing hormone
PSG, polysomnography

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