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ORIGINAL ARTICLE

Arthralgia in midlife Singaporean women: the Integrated Women's Health Program (IWHP)

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ABSTRACT

Objective: Arthralgia is a common menopausal complaint in midlife women, and its causes remain unclear. We examined the prevalence of menopausal arthralgia with various factors including sleep quality, depression/anxiety, muscle strength and physical performance among midlife Singaporean women.

Methods: The Integrated Women's Health Program (IWHP) comprised 1120 healthy, community-dwelling women of Chinese, Malay or Indian ethnicities (aged 45–69 years) attending well-women clinics at the National University Hospital, Singapore. Sociodemographic, menopausal, reproductive and health data were obtained with validated questionnaires. Muscle strength, physical performance and dual-energy X-ray absorptiometry were measured. Women with moderate to very severe symptoms using the Menopause Rating Scale were classified as having arthralgia. Multivariable logistic regression analyses examined risk factors for arthralgia.

Results: One-third of the participants reported arthralgia, and 12.7%, 16.2% and 71.2% were in the premenopausal, perimenopausal and postmenopausal period, respectively. Menopausal symptoms, such as vaginal dryness (adjusted odds ratio [aOR]: 2.64, 95% confidence interval [CI]: 1.64, 4.24) and physical/mental exhaustion (aOR: 2.83, 95% CI: 1.79, 4.47), were independent risk factors for arthralgia. Poor muscle strength (aOR: 2.20, 95% CI: 1.29, 3.76), obesity (aOR: 1.94, 95% CI: 1.13, 3.32) and rheumatoid arthritis (aOR: 7.73, 95% CI: 4.47, 13.36) were also independently associated with arthralgia after adjustment for confounders.

Conclusions: Arthralgia in midlife Singaporean women was associated with menopausal symptoms of vaginal dryness and physical and mental exhaustion. Women with poor muscle strength were more likely to experience menopausal arthralgia.

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Arthralgia; joint and muscular pain; menopause; muscle strength; Integrated Women's Health Program

Introduction

The menopausal transition has been linked to a variety of symptoms, such as hot flushes, a depressed mood, poor sleep, genito-urinary complaints, joint pain and muscular stiffness [1,2]. In particular, joint and muscular pain have been reported frequently among midlife women, ranging from 16.7% in the USA [3] to 77% in Ecuador [4]. In a previous study from Singapore, joint and muscular pain, collectively referred to as arthralgia, was ranked as the top menopausal complaint, with 12.7% of midlife women reporting moderate to severe symptoms [5].

The term 'arthralgia' is commonly used among breast cancer survivors as a side effect of aromatase-inhibitor treatment drugs, which reduces estrogen levels drastically [6]. Arthralgia affects approximately one in two patients (46%) [7], resulting in premature therapy discontinuation and high non-compliance rates [8]. Aromatase-induced arthralgia has been previously correlated with insomnia [9] and depression [10]. Even though prior studies have been conducted among breast cancer survivors, studies examining risk factors of arthralgia among healthy midlife women undergoing natural menopause are few to none.

Among healthy midlife women, arthralgia is an important cause of disability and decline in quality of life [11]. The abrupt reduction of estrogens during the perimenopause has been associated with increased arthralgia [12]. Nevertheless, surprisingly few studies have reported on menopausal arthralgia among healthy midlife women, in contrast to other extensively studied menopausal conditions such as vasomotor symptoms, sleep and mental health issues [13]. The Australian Longitudinal Study of Women's Health reported that increased bodily pain during the perimenopausal period was associated with poor physical functioning [14,15], while the Study of Women's Health Across the Nation (SWAN) also reported increased pain symptoms among women in the perimenopausal and postmenopausal periods compared to premenopausal women [3].

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The causes of menopausal arthralgia are unclear. The Melbourne Women's Midlife Health Project demonstrated that 51.7% of their women have joint pains, a portion of whom had arthritis, suggesting a distinction between arthritis and arthralgia [16]. A recent cross-sectional study of Japanese women reported that low handgrip strength (HGS) and insomnia symptom scores were independent risk factors for arthralgia, although comorbidities such as rheumatoid arthritis and osteoarthritis were not evaluated in the study [17]. Knowledge gaps in the prevalence and associated risk factors for such a common and debilitating condition among healthy midlife women prompted this study. Filling these gaps will help understand the burden of arthralgia and its associated factors among a healthy population of midlife women and may shed understanding on improving its management.

Methods

Study cohort and design

The Integrated Women's Health Program (IWHP) was planned as a prospective cohort study examining important health issues affecting midlife Singaporean women [18]. The current report is a cross-sectional analysis based on information of the cohort collected at baseline. Participants were recruited from well-women clinics at the National University Hospital between September 2014 and October 2016 through flyers, posters and word of mouth. They were healthy, community-dwelling women 45–69 years of age; of Chinese, Malay or Indian ethnicity; and had no terminal illness or life-threatening condition. Of the 2191 eligible participants, 1201 were enrolled in the study (54.8% participation rate), while 880 declined and 110 were non-contactable. Details of the cohort have been previously been described [18]. The IWHP study was approved by the National Healthcare Group's Domain Specific Review Board (DSRB Reference number: 2014/00356). All participants provided written informed consent.

Definition of arthralgia

The Menopause Rating Scale (MRS) was designed to evaluate menopausal symptoms and their severity [19]. The MRS is a self-administered questionnaire comprising 11 symptoms or complaints, with a severity score from 0 (no symptoms) to 4 (very severe symptoms). The statement used to evaluate arthralgia was 'stiffness or soreness in joints, neck, or shoulder'. Women were characterized as having arthralgia if they indicated a score of 2 (moderate), 3 (severe) or 4 (very severe). Those with none (0 points) or mild (1 point) symptoms were considered not to have arthralgia. The MRS scale has been used extensively and demonstrated to have good reliability and validity [19].

Potential risk factors

Age at baseline (45–54 years, 55–64 years, ≥65 years), ethnicity (Chinese, Malay, Indian), highest education level attained (no formal education or primary level, secondary or pre-university, university), current smoking status (yes, no) and current alcohol consumption (yes, no) were obtained from a questionnaire. Physical activity level (measured by metabolic equivalents [METs] per week) was determined using the Global Physical Activity Questionnaire, which accounts for moderate and vigorous physical activity during work and recreation, as well as physical activity exerted during transport [20]. Low physical activity levels were denoted by <600 MET-min/week [20].

Besides joint pain, other symptoms from the MRS comprised somatic complaints (hot flushes, heart discomfort, sleep problems), psychological complaints (depressive mood, irritability, anxiety, physical and mental exhaustion), and genito-urinary complaints (sexual problems, bladder problems, vaginal dryness) [19]. Menopausal status was defined based on menstrual cycle frequency and time since last menstrual period [18].

Sleep quality was determined using the 19-item Pittsburgh Sleep Quality Index (PSQI), which measures sleep disturbances and self-rated quality of sleep over the past month [21]. A score >5 points out of 21 indicates poor sleep quality. Other sleep variables of interest include usual bedtime (before 22:00, 22:00–23:59, after 23:59), time taken to fall asleep (>15 min, ≤15 min), wake time (before 06:00, 06:00–08:00, after 08:00), and sleep duration (≤6 h, 7–8 h, >8 h).

Diabetes was considered present if the fasting blood glucose level was ≥7.0 mmol/l, antidiabetic medication was used or the condition was physician-diagnosed. Hypertension was characterized as present if systolic blood pressure was ≥140 mmHg and/or diastolic blood pressure was ≥90 mmHg, anti-hypertensive medication was used or the condition was reported as physician diagnosed. Depression and/or anxiety was based on two criteria: a cut-off score of ≥16 on the Centre for Epidemiological Studies for Depression Scale [22] and/or ≥10 using the General Anxiety Disorder scale [23], or the use of anti-depressants. Urinary incontinence was assessed using a subscale of the Pelvic Floor Disability Index [24]; the index classifies different types of incontinence (stress, urge, mixed, leakage). Participants were classified as having the condition when they had any type of incontinence present. Rheumatoid arthritis (yes, no), osteoarthritis (yes, no) and asthma (yes, no) were self-reported within a disease questionnaire. Participants were asked to rate their health status (poor/fair, good/very good/excellent). All administered questionnaires were returned. Osteoporosis at the lumber spine and/or femoral neck were determined based on a *T*-score of ≤–2.5 using dual-energy X-ray absorptiometry.

Height was measured twice and weight once using an electronic measuring station (SECA 769) by trained study coordinators. Body mass index (BMI) was calculated as weight (kilograms) divided by the square of average height (meters), and participants were grouped into normal/underweight (<23.0 kg/m^2), overweight (23.0–24.49 kg/m^2) or obese (≥27.5 kg/m^2) categories. Visceral adipose tissue (VAT) was assessed using dual-energy X-ray absorptiometry, and participants were categorized into tertiles (<88.6 cm^2, 88.6–131.0 cm^2, >131 cm^2). Upper body muscle strength was assessed using a Jamar dynamometer, with the maximum

grip strength value out of four tries (two on each hand) taken for analysis. A maximum HGS value <18 kg was considered weak upper body strength [25]. Lower extremity performance was assessed by trained study coordinators who adhered strictly to a standardized protocol described by Simonsick et al., comprising five repeated chair stands (≥12 s denoting poor lower body muscle strength [25]), standing balance tests (semi-tandem, tandem, one-leg stands for 30 s), and usual and narrow 6-m walks [26]. A cut-off of <1 m/s on the 6-m walks was used [25], and the combination of both poor lower and upper body strength was classified as a low muscle strength index (MSI), as described previously [27].

Total serum 25-hydroxyvitamin D was assessed using liquid chromatography–tandem mass spectrometry; a vitamin D level ≤20 ng/ml was considered deficient.

Statistical analysis

Demographic and lifestyle factors, menopausal and reproductive symptoms, sleep factors, health conditions, and anthropometric and dual-energy X-ray absorptiometry measures in women with and without arthralgia were compared using Pearson's chi-square test. Crude (unadjusted) results were expressed as frequency (*n*) and percentage (%).

Factors significantly associated with arthralgia in our crude analyses ($p < 0.10$), such as ethnicity, education level, hot flushes, heart discomfort, physical and mental exhaustion, sexual problems, vaginal dryness, poor sleep quality, bedtime, time taken to fall asleep, sleep duration, urinary incontinence, rheumatoid arthritis, asthma, self-rated health, BMI and MSI, were included in the stepwise multivariable logistic regression model. VAT, HGS and the repeated chair stand test were not included as these variables are closely related to BMI and the MSI.

Additionally, factors associated with joint pain in previous studies, such as age, smoking, alcohol consumption, physical activity, menopausal status, diabetes, hypertension, depression and/or anxiety, and vitamin D were a priori selected as potential confounding factors in our multivariable logistic regression analyses. Interactions between each predictor in the multivariable logistic regression model with both rheumatoid arthritis and osteoarthritis were checked, but none of these interactions were statistically significant. Hence, only the main effects model is presented. Results of the binary logistic regression analyses are presented as the adjusted odds ratio (aOR) with the respective 95% confidence interval (CI). Menopausal symptoms such as sleep problems, anxiety, irritability, depressive mood and bladder problems were excluded from the unadjusted and adjusted analyses, as they overlap with other variables examined, such as the PSQI, depression and/or anxiety, and urinary incontinence. Model fit was examined using Nagelkerke's R^2 and Hosmer and Lemeshow's goodness-of-fit test.

Sensitivity analyses were conducted using multivariable binary logistic regression analysis after excluding women with osteoarthritis, rheumatoid arthritis or missing arthritis data ($n = 325$). All results were analyzed using SPSS Statistics version 28.0 (IBM Corp, Armonk, NY, USA).

Results

Out of 1201 women, we excluded 81 women with missing arthralgia data, leaving a total of 1120 participants with a mean age of 56.2 ± 6.3 years for this study. The majority were Chinese (81.4%), with Indian and Malay forming the minority ethnic groups (Table 1). Most participants (84.3%) had secondary or higher levels of education. Only a small minority smoked (2.2%) or consumed alcohol (6.9%). Most were postmenopausal (71.2%), and one-quarter of the participants reported low physical activity levels of <600 MET-min/week. Participants who reported moderate to very severe joint muscle discomfort (arthralgia) comprised 33.5% (Table 1), while 464 participants (41.4%) reported mild joint muscle discomfort.

Crude analysis of risk factors associated with arthralgia

Arthralgia was more prevalent among Indian and Malay women compared to Chinese women, and among women with secondary or pre-university education levels compared to their university-educated counterparts (Table 1). All menopausal symptoms, including hot flushes, heart discomfort, physical and mental exhaustion, sexual problems and vaginal dryness, were significantly associated with arthralgia. Arthralgia tended to be higher in those with poor sleep quality (PSQI >5), with bedtime after 23:59, requiring >15 min to fall asleep and a short (≤6 h) or long (>8 h) sleep duration.

Women with urinary incontinence, rheumatoid arthritis, asthma or self-rated poor/fair health were more likely to report arthralgia. Overweight or obese women and women with VAT levels in the middle and highest tertiles were more likely to report arthralgia compared to underweight or normal-weight women and women with VAT levels in the lowest tertile. Women with poor muscle strength (HGS <18 kg, repeated chair stand performance time ≥12 s, poor or intermediate MSI) were more likely to report arthralgia compared to women with better muscle strength (HGS ≥18 kg, repeated chair stand performance <12 s, normal MSI). Tandem stands, one-leg stand and gait speed were not significantly associated with arthralgia.

Adjusted analysis of risk factors associated with arthralgia

Adjusted analyses indicated that secondary or pre-university education level (aOR: 1.91, 95% CI: 1.19, 3.08) was positively associated with arthralgia compared to university-educated women (Table 2). Amongst menopausal symptoms, physical and mental exhaustion (aOR: 2.83, 95% CI: 1.79, 4.47) and vaginal dryness (aOR: 2.64, 95% CI: 1.64, 4.24) were independently associated with arthralgia. Women with rheumatoid arthritis were 7.73 times (95% CI: 4.47, 13.36) more likely to report arthralgia compared to women without rheumatoid complaints. Poor to fair self-rated health was associated with 1.46 higher odds (95% CI: 1.02, 2.08) of arthralgia. Being overweight (aOR: 1.59, 95% CI: 1.08, 2.34) or obese (aOR: 1.94, 95% CI: 1.13, 3.32) was also associated with higher risks. Among physical performance measures, weak whole body muscle strength as denoted by poor MSI (aOR: 2.20, 95% CI:

Table 1. Crude (unadjusted) associations between participant characteristics and menopausal arthralgia (moderate or very severe joint muscle discomfort) ($n = 1120$).

Characteristic	*Total* (n)	*Arthralgia* (n = *375, 33.5%*)	*No arthralgia* (n = *745, 66.5%*)	p-*Value*
Demographic and lifestyle factors, *n* (%)				
Age (years)				0.433
45–54	480	170 (35.4)	310 (64.6)	
55–64	495	156 (31.5)	339 (68.5)	
≥65	145	49 (33.8)	96 (66.2)	
Ethnicity				0.031
Chinese	912	287 (31.5)	625 (68.5)	
Malay	65	27 (41.5)	38 (58.5)	
Indian	110	46 (41.8)	64 (58.2)	
Highest education level attained				0.006
No formal or primary	169	42 (24.9)	127 (75.1)	
Secondary or pre-university	722	264 (36.6)	458 (63.4)	
University	222	66 (29.7)	156 (70.3)	
Smoking				0.151
Yes	25	5 (20.0)	20 (80.0)	
No	1092	368 (33.7)	724 (66.3)	
Alcohol consumption				
Yes	77	24 (31.2)	53 (68.8)	
No	1040	350 (33.7)	690 (66.3)	
Physical activity (MET-min/week)				0.670
<600	281	90 (32.0)	191 (68.0)	
≥600	829	277 (33.4)	552 (66.6)	
Menopausal and reproductive symptoms, *n* (%)				
Hot flushes				<0.001
Yes	217	113 (52.1)	104 (47.9)	
No	902	261 (28.9)	641 (71.1)	
Heart discomfort				<0.001
Yes	70	47 (67.1)	23 (32.9)	
No	1050	328 (31.2)	722 (68.8)	
Physical and mental exhaustion				<0.001
Yes	222	142 (64.0)	80 (36.0)	
No	896	232 (25.9)	664 (74.1)	
Sexual problems				<0.001
Yes	178	111 (62.4)	67 (37.6)	
No	936	262 (28.0)	674 (72.0)	
Vaginal dryness				<0.001
Yes	232	138 (59.5)	94 (40.5)	
No	885	235 (26.6)	650 (73.4)	
Menopausal status				0.199
Premenopausal	142	45 (31.7)	97 (68.3)	
Perimenopausal	181	71 (39.2)	110 (60.8)	
Postmenopausal	797	259 (32.5)	538 (67.5)	
Sleep factors, *n* (%)				
Pittsburgh Sleep Quality Index (PSQI)				<0.001
>5	473	203 (42.9)	270 (57.1)	
≤5	638	168 (26.3)	470 (73.7)	
Bedtime				0.027
Before 22:00	44	11 (25.0)	33 (75.0)	
22:00–23:59	714	224 (31.4)	490 (68.6)	
After 23:59	348	135 (38.8)	213 (61.2)	
Time taken to fall asleep (min)				<0.001
>15	436	182 (41.7)	254 (58.3)	
≤15	677	191 (28.2)	486 (71.8)	
Wake time				0.591
Before 06:00	366	129 (35.2)	237 (64.8)	
06:00–08:00	648	210 (32.4)	438 (67.6)	
After 08:00	98	35 (35.7)	63 (64.3)	
Sleep duration (h)				0.017
≤6	666	242 (36.3)	424 (63.7)	
7–8	354	98 (27.7)	256 (72.3)	
>8	28	11 (39.3)	17 (60.7)	
Health conditions, *n* (%)				
Diabetes				0.968
Yes	135	45 (33.3)	90 (66.7)	
No	967	324 (33.5)	643 (66.5)	
Hypertension				0.883
Yes	492	163 (33.1)	329 (66.9)	
No	608	204 (33.6)	404 (66.4)	
Depression and/or anxiety				0.114
Yes	198	76 (38.4)	122 (61.6)	
No	913	297 (32.5)	616 (67.5)	
Urinary incontinence				<0.001
Yes	585	240 (41.0)	345 (59.0)	

(*Continued*)

Table 1. Continued.

Characteristic	*Total (n)*	*Arthralgia (n = 375, 33.5%)*	*No arthralgia (n = 745, 66.5%)*	p-*Value*
No	534	134 (25.1)	400 (74.9)	
Osteoporosis				0.473
Yes	124	38 (30.6)	86 (69.4)	
No	995	337 (33.9	658 (66.1)	
Rheumatoid arthritis				<0.001
Yes	120	89 (74.2)	31 (25.8)	
No	957	263 (27.5)	694 (72.5)	
Osteoarthritis				0.177
Yes	210	79 (37.6)	131 (62.4)	
No	859	281 (32.7)	578 (67.3)	
Asthma				0.006
Yes	90	42 (46.7)	48 (53.3)	
No	1029	333 (32.4)	696 (67.6)	
Poor to fair self-rated health				<0.001
Yes	421	187 (44.4)	234 (55.6)	
No	688	185 (26.9)	503 (73.1)	
Anthropometric and DXA measures, *n* (%)				
Body mass index (BMI) (kg/m^2)				<0.001
Normal or underweight, <23.0	526	147 (27.9)	379 (72.1)	
Overweight, 23.0–27.49	380	138 (36.3)	242 (63.7)	
Obese, ≥27.5	214	90 (42.1)	124 (57.9)	
Visceral adipose tissue (VAT) (cm^2)				0.036
Lowest tertile	380	111 (29.2)	269 (70.8)	
Middle tertile	365	122 (33.4)	243 (66.6)	
Highest tertile	370	141 (38.1)	229 (61.9)	
Physical performance measures, *n* (%)				
Handgrip strength (HGS) (kg)				0.025
<18	260	102 (39.2)	158 (60.8)	
≥18	860	273 (31.7)	587 (68.3)	
Repeated chair stand test (s)				<0.001
≥12	488	196 (40.2)	292 (59.8)	
<12	617	172 (27.9)	445 (72.1)	
Muscle strength index (MSI)[a]				<0.001
Poor	150	65 (43.3)	85 (56.7)	
Intermediate	443	167 (37.7)	276 (62.3)	
Normal	522	142 (27.2)	380 (72.8)	
Semi-tandem stand (s)				0.863
<30	22	7 (31.8)	15 (68.2)	
30	1087	365 (33.6)	722 (66.4)	
Tandem stand (s)				0.822
<30	202	69 (34.2)	133 (65.8)	
30	918	306 (33.3)	612 (66.7)	
One-leg stand (s)				0.125
<15	205	78 (38.0)	127 (62.0)	
≥15	915	297 (32.5)	618 (67.5)	
Usual walk gait speed (m/s)				0.343
<1.0	166	61 (36.7)	105 (63.3)	
≥1.0	949	313 (33.0)	636 (67.0)	
Narrow walk gait speed (m/s)				0.108
<1.0	209	129 (61.7)	80 (38.3)	
≥1.0	906	294 (32.5)	612 (67.5)	
Blood parameters, *n* (%)				
Vitamin D (ng/ml)				0.382
<20	225	81 (36.0)	144 (64.0)	
≥20	887	292 (32.9)	595 (67.1)	

[a]Poor MSI comprises HGS <18 kg and repeated chair stands ≥12 s; intermediate MSI comprises HGS <18 kg or repeated chair stands ≥12 seconds; normal MSI comprises HGS ≥18 kg and repeated chair stands <12 s.
Values presented as row percentages. Results analyzed using Pearson's chi-square test. Missing data accounted for 0.1–6.4% of the overall data. DXA, dual-energy X-ray absorptiometry; MET, metabolic equivalent.

1.29, 3.76) or intermediate MSI (aOR: 1.69, 95% CI: 1.16, 2.45) was significantly associated with arthralgia. Nagelkerke's R^2 is 37.2%, and the Hosmer and Lemeshow's test yielded a *p*-value of 0.899 ($p > 0.05$), indicating good model fit.

Sensitivity analyses excluding women with osteoarthritis or rheumatoid arthritis

Multivariable logistic regression analyses among women without osteoarthritis or rheumatoid arthritis ($n = 795$) showed that physical and mental exhaustion (aOR: 2.58, 95% CI: 1.46, 4.57), vaginal dryness (aOR: 2.15, 95% CI: 1.18, 3.91), being overweight (aOR: 1.77, 95% CI: 1.11, 2.84) or obese (aOR: 2.24, 95% CI: 1.17, 4.30) and having a poor MSI (aOR: 2.35, 95% CI: 1.47, 3.75) or intermediate MSI (aOR: 2.01, 95% CI: 1.04, 3.88) increased risks for arthralgia, that is, findings similar to those observed in the main analyses (Supplementary Table 1). Education level, smoking and self-rated health were not significantly associated with arthralgia in adjusted analyses. Nagelkerke's R^2 is 28.6%,

Table 2. Adjusted associations of studied risk factors with menopausal arthralgia (moderate or very severe joint muscle discomfort) ($n = 1120$).

Characteristic	*aOR (95% CI)*
Demographic and lifestyle factors	
Age (years)	
45–54	Reference
55–64	0.92 (0.58, 1.45)
≥65	1.65 (0.89, 3.03)
Ethnicity	
Chinese	Reference
Malay	1.15 (0.63, 2.08)
Indian	1.38 (0.68, 2.81)
Highest education level attained	
No formal or primary	1.06 (0.54, 2.05)
Secondary or pre-university	1.91 (1.19, 3.08)
University	Reference
Smoking	0.18 (0.04, 0.83)
Alcohol consumption	0.58 (0.19, 1.79)
Physical activity, <600 MET-min/week	0.88 (0.59, 1.32)
Menopausal and reproductive symptoms	
Hot flushes	1.34 (0.87, 2.08)
Heart discomfort	2.07 (0.98, 4.39)
Physical and mental exhaustion	2.83 (1.79, 4.47)
Sexual problems	1.62 (0.96, 2.72)
Vaginal dryness	2.64 (1.64, 4.24)
Menopausal status	
Premenopausal	1.08 (0.58, 2.00)
Perimenopausal	1.10 (0.64, 1.89)
Postmenopausal	Reference
Sleep factors	
Poor sleep quality, PSQI > 5	1.14 (0.71, 1.81)
Bedtime	
Before 22:00	Reference
22:00–23:59	1.28 (0.51, 3.19)
After 23:59	1.68 (0.65, 4.35)
Time taken to fall asleep, >15 min	1.30 (0.87, 1.95)
Sleep duration (h)	
≤6	1.15 (0.74, 1.77)
7–8	Reference
>8	2.18 (0.73, 6.47)
Health conditions	
Diabetes	0.87 (0.51, 1.48)
Hypertension	0.72 (0.50, 1.04)
Depression and/or anxiety	0.82 (0.50, 1.34)
Urinary incontinence	1.27 (0.90, 1.80)
Rheumatoid arthritis	7.73 (4.47, 13.36)
Asthma	1.31 (0.67, 2.57)
Poor to fair self-rated health	1.46 (1.02, 2.08)
Anthropometric and DXA measures	
Body mass index (BMI) (kg/m^2)	
Normal or underweight, <23.0	Reference
Overweight, 23.0–27.49	1.59 (1.08, 2.34)
Obese, ≥27.5	1.94 (1.13, 3.32)
Physical performance measures	
Muscle strength index (MSI)[a]	
Poor	2.20 (1.29, 3.76)
Intermediate	1.69 (1.16, 2.45)
Normal	Reference
Blood parameters	
Vitamin D, <20 ng/ml	1.13 (0.74, 1.72)

[a]Poor MSI comprises handgrip strength (HGS) <18 kg and repeated chair stands ≥12 s; intermediate MSI comprises HGS <18 kg or repeated chair stands ≥12 s; normal MSI comprises HGS ≥18 kg and repeated chair stands <12 s.

Factors mutually adjusted for were age, ethnicity, education level, smoking, alcohol consumption, physical activity, hot flushes, heart discomfort, physical and mental exhaustion, sexual problems, vaginal dryness, menopausal status, poor sleep quality, bedtime, time taken to fall asleep, sleep duration, diabetes, hypertension, depression and/or anxiety, urinary incontinence, rheumatoid arthritis, asthma, self-rated health, BMI, MSI and vitamin D. Nagelkerke's R^2 = 37.2%. Hosmer and Lemeshow's test yielded a p-value of 0.899 ($p > 0.05$), indicating good model fit. aOR, adjusted odds ratio; CI, confidence interval; DXA, dual-energy X-ray absorptiometry; MET, metabolic equivalent; PSQI, Pittsburgh Sleep Quality Index.

and the Hosmer and Lemeshow's test yielded a p-value of 0.956 ($p > 0.05$), indicating good model fit.

Discussion

Our study identified menopausal symptoms and weak muscle strength as independent risk factors for arthralgia in midlife women. Participants who reported physical and mental exhaustion and vaginal dryness had a 2.6-fold to 2.8-fold higher risk of moderate or very severe joint pains. A low MSI, denoting both weak upper and lower body strength, doubled the risk for arthralgia compared to women with normal muscle strength.

We found that 33.5% of our women experienced moderate to very severe joint pain, while 74.9% reported any degree of arthralgia (mild to very severe), which was higher than the prevalence of 53.6% reported by Loh et al. in a nationwide Singapore study in 2005 ($n = 1000$ women, aged 45–60 years) [5]. This difference in prevalence might be due to a true increase in moderate to very severe joint pain, or might be due to artefactual reasons, such as differences in the questionnaires used or study populations recruited. Nonetheless, our observed prevalence of 74.9% is congruent with the 73.3% reported in Oman ($n = 472$, age 40–60 years) [28] and the 77% reported in Ecuador ($n = 300$, mean age: 45.1 years) [4], both of which were based on the MRS.

Our finding that poor muscle strength is a risk factor for arthralgia adds to existing literature. Besides a relatively small study linking weak HGS with muscle and joint pains in middle-aged Japanese women [17], few studies have identified weak muscle strength as a risk factor for arthralgia in midlife women. One randomized controlled trial reported that a stronger knee extensor can increase thresholds of pain [29], suggesting that good muscle strength may reduce pain perception. In another study, high self-efficacy in pain management was associated with reduced pain levels and increased physical activity among patients with hip or knee osteoarthritis [30], and hence increasing patients' self-efficacy for pain management might be beneficial for those experiencing arthralgia. The reverse is also true, whereby joint pain might contribute to muscle weakness. Pain can serve as a barrier to physical activity, leading to reduced muscle mass and strength, and increased risk of sarcopenia [31]. A recent systematic review indicated that hip muscle strengthening exercises can result in pain reduction among patients with patellofemoral pain syndrome [32]. The role of resistance exercise to improve muscle strength and reduce menopausal arthralgia should be explored in future studies.

Arthralgia was independently associated with vaginal dryness, suggesting the possibility of declining estrogen levels in its pathophysiology. Low estradiol levels were previously associated with a higher prevalence of vaginal dryness symptoms in longitudinal modelling of menopausal hormone changes [33]. Plasma estrogen levels fall to pre-pubertal levels during the time of menopause [34], and it is plausible that this decline in estrogen levels could have contributed to joint and muscular complaints. Menopausal arthralgia resembles the severe arthralgia experienced by up to 46% of

women consuming aromatase inhibitors to reduce estrogen levels as part of breast cancer therapy [7]. Estrogen deprivation may also lead to localized inflammatory responses around the joints, resulting in pain [12]. We observed no association of arthralgia with menopausal status, possibly owing to the low numbers of premenopausal women in our cohort. However, menopausal stage was previously associated with aches and joint pain in the longitudinal Penn Ovarian Aging Study [1].

In our study, the number of participants on menopause hormone therapy (MHT) was negligible (1.7%), and hence its relationship with arthralgia could not be elucidated in our study population. However, the use of MHT in alleviating joint and muscular aches has proved efficacious in several studies [35,36]. The Women's Health Initiative (WHI) study reported a lower incidence of new musculoskeletal symptoms among women treated with MHT [36], while discontinuation of MHT resulted in greater pain and stiffness compared to women on placebo [35]. On the contrary, previous MHT use was found to be a major risk factor for developing joint symptoms among postmenopausal breast cancer survivors [37]. Given that current literature presents conflicting findings between MHT use and arthralgia, more studies should be conducted to better understand this relationship.

Women with rheumatoid arthritis complaints were around seven times more likely to report moderate to severe joint and muscular pain. Conditions such as arthritis, osteoporosis and fibromyalgia might co-exist among menopausal women due to aging [38], and this might have resulted in the exacerbation of pain. It is paramount for midlife women to be educated in distinguishing between different types of joint pain to seek appropriate treatment early. We also observed that a higher BMI almost doubled the risk of arthralgia, concurring with findings from the Seattle Midlife Women's Health Study [39]. A higher BMI might result in the upregulation of pro-inflammatory adipokines such as leptin, which has been previously associated with joint pain [40].

Chronic pain syndromes such as fibromyalgia are strongly associated with poor sleep, anxiety and depressive states [41,42]. Although arthralgia in midlife Singaporean women was associated with physical and mental exhaustion, it is surprising that we did not detect any relationship to poor sleep, anxiety and/or depressive states. If confirmed in other studies, it would be interesting to determine whether hitherto unsuspected socio-cultural, psychological or physical factors have a role in this positive adaptive response to menopausal arthralgia [43].

Strengths of our study include its relevance and usefulness for midlife women, since a huge proportion (74.9%) suffered from mild, moderate, severe or very severe forms of arthralgia in our cohort and in a previous nationwide-based Singaporean cohort (53.6%) [5]. Arthralgia is the top menopausal compliant among midlife Singaporean women, and our findings would give clinicians, public health policymakers and researchers a heightened awareness of this condition. Existing literature on joint pain rarely distinguishes between arthralgia and arthritis [44]. The two conditions have different mechanisms, management and treatment. In our study, we distinguished the effects of rheumatoid arthritis and osteoarthritis from arthralgia, and we were able to identify risk factors for arthralgia, independent of arthritis as seen from our sensitivity analyses.

Our study findings should be interpreted in the light of several limitations. Firstly, as our study is based on a cross-sectional analysis of our cohort at baseline, we are unable to ascertain whether studied risk factors temporally preceded the development of arthralgia and thus are unable to ensure their causal nature. Longitudinal follow-up visits are well underway in our cohort, and we should soon be able to study baseline risk factors in relation to new cases of arthralgia that develop during follow-up. Next, our participants were recruited from one hospital, and hence our findings might not be generalizable to other Singapore midlife women. However, the demographics of our women closely resemble those of the Singapore population in terms of ethnicity, marital status and education level. The participation rate of 54.8% might seem relatively low, but it is comparable with participant rates in other midlife women cohorts [45,46]. Lastly, no single 'gold standard' exists to measure arthralgia, and the prevalence of and associated risk factors for arthralgia might depend on the diagnostic criteria and instrument used.

Conclusion

In summary, although arthralgia is one of the most frequent complaints among midlife women, few studies have examined the risk factors associated with this condition. We have found physical and mental exhaustion, vaginal dryness, as well as low muscle strength and high BMI to be positively associated with arthralgia. Interventions, such as exercises to increase muscle strength and reduce obesity, and proper management of other menopausal symptoms, should be developed and tested for relieving joint pains and aches in premenopausal, perimenopausal and postmenopausal women.

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