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Associations of fat mass index with hot flashes and lean mass index with insomnia in middle-aged women

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ABSTRACT

Objective: This cross-sectional study examined the relationship between body composition and physical and mental symptom severity in middle-aged women.

Methods: The first-visit records of 554 women aged 40–64 years were examined. The fat mass index (FMI) and lean mass index (LMI) were defined as fat mass and lean mass divided by the height squared, respectively. The participants were divided into two groups according to their median values.

Results: The only menopausal symptom with significantly different severity between the high and low FMI groups was hot flashes (HF) on the Menopausal Health-Related Quality of Life Questionnaire. The factors associated with severe HF were investigated using multiple logistic regression analysis. After adjusting, the FMI (kg/m²) was independently positively associated with severe HF (odds ratio, 1.08; 95% confidence interval, 1.02–1.15). Insomnia was the only menopausal symptom with significantly different severity between the LMI groups (defined as Athens Insomnia Scale score ≥ 10 points). The factors associated with moderate-to-severe insomnia were investigated using multiple logistic regression analysis. After adjusting, the LMI (kg/m²) was independently negatively associated with moderate-to-severe insomnia (odds ratio, 0.72; 95% confidence interval, 0.55–0.94).

Conclusions: The FMI was positively associated with severe HF, whereas the LMI was negatively associated with moderate-to-severe insomnia in middle-aged women.

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Introduction

Women in menopausal transition experience various issues, such as vasomotor symptoms (VMS), urogenital atrophy, sexual dysfunction, somatic symptoms, cognitive impairment, sleep disturbances and psychological distress. VMS and urogenital atrophy are primarily attributable to estrogen fluctuations or deficiency induced by ovarian dysfunction. However, the factors that exacerbate or alleviate other menopausal symptoms are not fully characterized.

Regarding the relationship between body composition and menopausal symptoms, obesity is a risk factor for VMS, especially during perimenopause and immediately postmenopause [1]. In a meta-analysis of 4219 individuals, obesity (body mass index [BMI] > 30 kg/m²) was independently associated with hot flashes (HF) [2]. In addition, a cross-sectional study of 461 individuals in the USA revealed a relationship between abdominal fat, particularly abdominal subcutaneous fat, and HF [3]. A plausible hypothesis for this association is that the adipose tissue is an insulator, interfering with the normal thermoregulatory mechanism of heat dissipation [1]. In contrast, the 'lean hypothesis' suggests that women with more adipose tissues might have increased circulating

estrogen levels due to the aromatization of androgen in peripheral fat and are at a lower risk for HF. An American study of 1546 participants (the Study of Women's Health Across the Nation [SWAN]) observed that the BMI was positively associated with VMS in premenopausal and early perimenopausal women and was negatively associated with VMS in late perimenopausal and postmenopausal women [4]. The study suggests that the 'thermoregulatory hypothesis' might be valid for premenopausal and early perimenopausal women, and the 'lean hypothesis' might be valid for late perimenopausal and postmenopausal women, whose serum estrogen levels significantly decrease. Obesity might also be associated with HF as leptin impairs thermoregulation and increases core body temperature. Furthermore, serum leptin concentrations were associated with the occurrence and duration of HF in 201 women aged 45–54 years, irrespective of the estradiol serum level [5].

Regarding the relationship between body composition other than obesity and menopausal symptoms, a study of 758 perimenopausal women in China revealed an independent negative relationship between the lean body mass and moderate-to-severe menopausal symptoms (Kupperman's index > 15). Muscle or joint pains and sexual problems were

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predeterminants for lean body mass, while HF or sweating and muscle or joint pains were predeterminants for fat mass [6].

Combining all the previous studies, the relationships between height-adjusted fat lean mass and menopausal symptoms have not been fully clarified. Therefore, we conducted this study to identify the relationships between body composition parameters, as explanatory variables, and physical and mental symptoms, as objective variables, in middle-aged women.

Materials and methods

Study population

This cross-sectional study reviewed the first-visit records of 722 Japanese women who participated in the Systematic Health and Nutrition Education Program at the Menopause Clinic of Tokyo Medical and Dental University, Tokyo, Japan, between March 2007 and January 2021. All of the participants in the program visited or were referred to our clinic for menopausal symptom treatment. The final analysis was performed on 554 women, excluding 77 with unknown menopausal status or primary ovarian insufficiency, 55 on hormone replacement therapy, four without the menopausal quality of life questionnaire and 32 aged <40 or >64 years.

The Tokyo Medical and Dental University Review Board reviewed and approved the research protocol (approval number: 774, on 23 March 2010). Written informed consent was obtained from all participants. This study was conducted in accordance with the Declaration of Helsinki.

Menopausal status

We distinguished three menopausal statuses: premenopausal, perimenopausal and postmenopausal. The participants in the premenopausal group had regular menstrual periods for the past 3 months; those in the perimenopausal group had experienced menstruation in the past 12 months but no menstruation or irregular menstrual cycles in the last 3 months; and those in the postmenopausal group had no menstruation in the past 12 months.

Physical assessment

Height, weight, and waist and hip circumference were measured. In addition, body composition data were evaluated using a bioimpedance analyzer (MC190-EM; Tanita, Tokyo, Japan) for fat, lean and muscle mass. Weight, fat mass and lean mass were divided by the height squared to generate the BMI, fat mass index (FMI) and lean mass index (LMI).

Lifestyle characteristics

Lifestyle factors were assessed, including smoking habits (none, <20 and >20 cigarettes daily), alcohol consumption (none, sometimes, daily), caffeine consumption (none, 1–2 and ≥ 3 times daily) and regular exercise habits (yes, no).

Questionnaire

The Menopausal Health-Related Quality of Life Questionnaire (MHR-QOL) [7], developed and validated at our clinic, is a modified version of the Women's Health Questionnaire and other questionnaires [8–10]. Physical and psychological symptoms were scored using a 4-point Likert scale based on symptom frequency. In this analysis, the scores were reversed to gain as the frequency of each symptom increased (0, none or one time monthly; 1, one or two times weekly; 2, three or four times weekly; 3, almost daily).

The Hospital Anxiety and Depression Scale (HADS) is a reliable screening test widely used for mental health in patients with somatic symptoms [11]. The HADS consists of seven items covering two subscales, depression and anxiety symptoms, in which participants respond to each item on a 4-point Likert scale. Patients rated 8–10 points were likely to suffer from anxiety or depression, while those rated 11–21 points were suffering from anxiety or depression.

The Athens Insomnia Scale (AIS) was developed as a brief, easy-to-administer, self-assessment questionnaire to determine insomnia severity according to the International Classification of Diseases, 10th Edition. It consists of eight items, and participants responded to a 4-point Likert scale regarding their insomnia in the last month. The scoring range for the AIS is 0–24 points, with higher scores indicating severe insomnia. The internal consistency and test-retest reliability of the AIS have been previously confirmed [12]. We employed 10 points as a cut-off value for the AIS, instead of 6 points for the English version [13], as a recent study revealed that insomnia could be classified as no insomnia (0–5 points), mild insomnia (6–9 points), moderate insomnia (10–15 points) and severe insomnia (16–24 points) using the Japanese version of the AIS (74% sensitivity and 83% specificity for moderate insomnia) [14].

Statistical analysis

Continuous variables were described as the mean \pm standard deviation. The required sample size of 267 was calculated by multiplying the number of independent variables by 10 and dividing the product by the prevalence of moderate-to-severe insomnia (4 and 0.15, respectively) [15]. The 554 participants were divided into two groups using the median FMI and LMI values, respectively. Both groups were compared using the Mann-Whitney test, chi-square test and Fisher's exact probability test for age, menopausal status, lifestyle and each menopausal symptom on the MHR-QOL, HADS and AIS. Subsequently, multivariate logistic regression analysis was performed with variables that significantly differed between the high and low FMI and LMI groups, respectively, as the objective variables. Multicollinearity between variables was determined using the cut-off points for Pearson or Spearman's correlation coefficients of $|R| > 0.9$. In Model 1, FMI/LMI were explanatory variables, and in Model 2 the analysis was adjusted for background factors. We used analysis of deviance as a measure to test the models. Statistical significance was set at $p < 0.05$. All statistical analyses were

performed using GraphPad Prism version 9.1.2 (GraphPad Software, San Diego, CA, USA) and JMP version 14.0.2 (SAS Institute Inc., Cary, NC, USA).

Results

The participants' average age was 51.1 ± 4.7 years (mean \pm standard deviation). The median BMI, FMI and LMI values were 20.92, 15.44 and 5.69 kg/m^2 , respectively. Background characteristics of the high and low BMI, FMI and LMI groups are presented in [Table 1](#). Regular exercise habits were the only background item that differed significantly between the BMI and FMI groups. Conversely, there was no statistical difference in any characteristic between the LMI groups. Menopausal symptoms that differed significantly between the high and low BMI, FMI and LMI groups are presented in [Table 2](#). The menopausal symptoms that differed significantly between the BMI, FMI and LMI groups were HF and night sweats, HF and insomnia, respectively.

Multiple logistic regression analysis was conducted to identify independent associations between the FMI, LMI and menopausal symptoms identified. In the following analysis, the participants who answered '3 (almost every day)' to HF on the MHR-QOL questionnaire were defined as having severe HF (27.4%). Multivariate logistic regression analysis was performed with severe HF as the objective variable and FMI (kg/m^2) as the explanatory variable (Model 1-1), and FMI was positively associated with the presence of severe HF (adjusted odds ratio [OR] [kg/m^2], 1.07; 95% confidence interval [CI], 1.01–1.14, $p = 0.027$). Then, background factors, such as age, menopausal status and regular exercise habits, were adjusted and significantly differed between the high and low FMI groups (Model 1-2). Furthermore, multivariate logistic regression analysis revealed that FMI was independently positively associated with severe HF (OR, 1.08; 95% CI, 1.02–1.15; $p = 0.016$). Regarding perimenopausal and postmenopausal background factors, they were positively associated with severe HF compared to premenopausal ([Table 3](#)). Likewise, patients rated 10–24 points on the AIS had moderate-to-severe insomnia (31.0%). Multivariate logistic regression analysis was performed with moderate-to-severe insomnia as the objective variable and LMI (kg/m^2) as the explanatory variable (Model 2-1), and LMI was negatively associated with moderate-to-severe insomnia (OR, 0.77; 95% CI, 0.61–0.97; $p = 0.028$). Then, we adjusted for background characteristics, such as age, menopausal status, HADS depression and anxiety, which were associated with insomnia in perimenopausal and postmenopausal women in our previous study [[16](#)] (Model 2-2). Multivariate logistic regression analysis revealed that the LMI was independently negatively associated with insomnia (OR, 0.72; 95% CI, 0.55–0.94; $p = 0.015$). Depression and anxiety (background factors) were also positively associated with insomnia ([Table 4](#)).

Discussion

This cross-sectional study revealed that FMI (kg/m^2) was positively associated with severe HF, and LMI (kg/m^2) was negatively associated with moderate-to-severe insomnia in

middle-aged women after adjusting for background characteristics.

Considering the body composition changes in middle-aged women, decreased estrogen levels after menopause are associated with obesity, as estrogen and estrogen receptors regulate various aspects of glucose and lipid metabolism. Therefore, obesity is a major public health issue in postmenopausal women as being overweight and obese were reportedly associated with hypertension, cardiovascular diseases and various cancers, including breast cancer [[17,18](#)].

The association between HF and obesity has been well reported. This study also observed an independent relationship between HF and height-adjusted fat mass, which supports the thermoregulatory model. It had been suggested that the 'thermoregulatory hypothesis' might be valid for premenopause and perimenopause; however, when serum estrogen levels significantly decrease, the 'lean hypothesis' may be valid in postmenopausal women [[4](#)]. This study revealed that the thermoregulatory mechanism could be effective through all menopausal stages, as severe HF and FMI remained positively related even after adjusting for menopausal status.

Sarcopenia is the loss of skeletal muscle mass and strength with aging [[19](#)]. Muscle mass decreases with age after 27 years, with a notable decrease starting at 50 years [[20](#)]. There are sex-independent mechanisms, such as increased inflammation, satellite cell senescence, decreased muscle cell regeneration and protein synthesis. Most sex-reported studies observed no significant association between sex and sarcopenia prevalence [[21](#)]; nonetheless, a study of 1851 Japanese residents aged ≥ 65 years (50.5% women; mean age 72.0 ± 5.9 years) revealed that the sarcopenia prevalence was 11.5% in men and 16.7% in women [[22](#)]. The inability of lower estrogen, which inhibits inflammation and protects skeletal muscle, to control the aforementioned mechanisms could be a reason for the postmenopausal loss of muscle mass, unique to women [[23](#)].

Previous studies have reported an association between menopausal insomnia and muscle mass. A cross-sectional study (BASE-II) of 1196 older participants reported an association between low appendicular lean mass and poor sleep quality in women [[24](#)]. Moreover, a meta-analysis involving 19,677 participants revealed that sarcopenia prevalence was associated with poor sleep quality [[25](#)]. Myokines and other substances produced by skeletal muscle also affect sleep [[26](#)]. With exercise, peroxisome proliferator-activated receptor gamma-coupled factor 1- α (PGC1- α) increases the expression of fibronectin type III domain-containing protein 5 (FNDC5) in skeletal muscle, which can release irisin into circulation after proteolysis [[26](#)]. In addition, myokine promotes the expression of brain-derived neurotrophic factor in the brain, which increases slow wave activity in non-rapid eye movement sleep. Moreover, lactate produced by the skeletal muscle after exercise stimulates irisin production in the brain in a PGC-1 α -dependent manner [[26](#)]. Moreover, Bmal1, a core clock protein whose expression increases PGC-1 α dependently, might influence sleep regulation [[26](#)]. These combined mechanisms could underlie the negative

Table 1. Comparison of background characteristics between the high and low BMI, LMI and FMI groups.

Characteristic	BMI			LMI			FMI		
	High (n = 277)	Low (n = 277)	p-Value	High (n = 277)	Low (n = 277)	p-Value	High (n = 277)	Low (n = 277)	p-Value
Age and menopausal status									
Age (years), mean (standard deviation)	51.0 (4.5)	51.2 (5.0)	0.825 ^a	51.0 (4.7)	51.2 (4.8)	0.541 ^a	51.1 (4.5)	51.1 (5.0)	0.819 ^a
Menopausal status, premenopausal/perimenopausal/postmenopausal (%)	32.1/49.1/18.8	24.9/50.5/24.5	0.094 ^b	31.0/48.4/20.6	26.0/51.3/22.7	0.412 ^b	31.0/50.9/18.1	26.0/48.7/25.3	0.095 ^b
Lifestyle characteristics (%)									
Frequency of alcohol consumption, daily/sometimes/never	10.3/25.3/64.5	12.0/32.0/56.0	0.124 ^b	11.6/24.0/64.4	10.6/33.3/56.0	0.053 ^b	8.5/27.2/64.3	13.8/30.1/56.2	0.068 ^b
Smoking habit, more than 20 cigarettes per day/1–20 cigarettes per day/none	4.4/7.3/88.3	1.8/8.7/89.5	0.193 ^b	3.6/7.3/89.1	2.6/8.8/88.6	0.636 ^b	3.7/7.7/88.6	2.5/8.3/89.1	0.725 ^b
Amount of daily tea/coffee consumption, more than three cups/1–3 cups/none	54.6/35.5/9.9	62.5/28.7/8.7	0.161 ^b	55.3/36.4/8.4	61.9/27.8/10.3	0.098 ^b	57.0/33.5/9.6	60.1/30.8/9.1	0.751 ^b
Regular exercise habit, yes/no	35.9/64.1	46.5/53.5	0.012 ^c	40.6/59.4	41.8/58.2	0.795 ^c	34.1/65.9	48.4/51.6	0.001 ^c

^aMann–Whitney test.^bChi-squared test.^cFisher's exact test.

BMI, body mass index; FMI, fat mass index; LMI, lean mass index.

Table 2. Comparison of menopausal symptom scores between the high and low BMI, LMI and FMI groups.

Characteristic	BMI			LMI			FMI		
	High (n = 160)	Low (n = 149)	p-Value	High (n = 158)	Low (n = 151)	p-Value	High (n = 159)	Low (n = 150)	p-Value
MHR-QOL physical and psychological symptom									
Nausea	0.4 (0.8)	0.5 (0.9)	0.764 ^a	0.4 (0.8)	0.4 (0.9)	0.645 ^a	0.4 (0.8)	0.5 (0.9)	0.200 ^a
Dizziness	0.7 (1.0)	0.6 (0.9)	0.131 ^a	0.6 (0.9)	0.7 (1.0)	0.862 ^a	0.7 (1.0)	0.6 (0.9)	0.096 ^a
Numbness	0.9 (1.2)	0.9 (1.2)	0.636 ^a	0.9 (1.2)	0.8 (1.2)	0.860 ^a	0.8 (1.2)	0.9 (1.2)	0.474 ^a
Muscle and joint pain	2.3 (1.0)	2.2 (1.1)	0.400 ^a	2.2 (1.0)	2.2 (1.1)	0.868 ^a	2.3 (1.1)	2.2 (1.1)	0.480 ^a
Tiredness	2.1 (1.1)	2.1 (1.1)	0.622 ^a	2.1 (1.1)	2.0 (1.1)	0.401 ^a	2.1 (1.1)	2.1 (1.1)	0.467 ^a
Headaches	1.0 (1.1)	0.9 (1.1)	0.091 ^a	1.0 (1.0)	0.9 (1.1)	0.110 ^a	1.0 (1.1)	0.9 (1.1)	0.298 ^a
Frequent urination	1.1 (1.3)	1.1 (1.3)	0.795 ^a	1.1 (1.3)	1.1 (1.3)	0.957 ^a	1.1 (1.3)	1.1 (1.3)	0.795 ^a
Hot flashes	1.4 (1.2)	1.2 (1.2)	0.034 ^a	1.3 (1.2)	1.3 (1.3)	0.423 ^a	1.4 (1.2)	1.2 (1.2)	0.013 ^a
Night sweats	1.2 (1.2)	1.0 (1.1)	0.031 ^a	1.1 (1.2)	1.0 (1.2)	0.237 ^a	1.1 (1.2)	1.0 (1.2)	0.107 ^a
Difficulty in initiating sleep	1.0 (1.2)	1.1 (1.2)	0.368 ^a	1.0 (1.2)	1.1 (1.2)	0.365 ^a	1.0 (1.2)	1.1 (1.2)	0.266 ^a
Non-restorative sleep	1.4 (1.2)	1.5 (1.2)	0.315 ^a	1.5 (1.2)	1.4 (1.2)	0.801 ^a	1.4 (1.2)	1.5 (1.3)	0.575 ^a
HADS									
Anxiety subscale score	7.9 (3.7)	8.3 (3.8)	0.260 ^a	7.9 (3.6)	8.3 (4.0)	0.411 ^a	7.9 (3.9)	8.3 (3.9)	0.232 ^a
Depression subscale score	7.6 (3.8)	7.5 (4.0)	0.681 ^a	7.4 (3.7)	7.6 (4.1)	0.781 ^a	7.7 (3.8)	7.4 (4.0)	0.354 ^a
AIS									
Total score	7.5 (4.1)	8.0 (4.5)	0.271 ^a	7.1 (3.6)	8.5 (4.8)	0.011 ^a	7.5 (4.0)	8.1 (4.5)	0.325 ^a
Sleep induction	0.8 (0.9)	0.9 (1.0)	0.583 ^a	0.7 (0.9)	1.0 (1.0)	0.008 ^a	0.8 (0.9)	0.9 (1.0)	0.486 ^a
Awakenings during the night	0.6 (0.8)	0.7 (0.8)	0.218 ^a	0.5 (0.7)	0.8 (0.9)	0.002 ^a	0.6 (0.8)	0.7 (0.8)	0.250 ^a
Final awakening	0.8 (0.8)	0.9 (0.8)	0.192 ^a	0.7 (0.7)	1.0 (0.8)	0.002 ^a	0.8 (0.8)	0.9 (0.8)	0.209 ^a
Total sleep duration	1.0 (0.7)	1.0 (0.8)	0.884 ^a	1.0 (0.7)	1.1 (0.9)	0.707 ^a	1.0 (0.7)	1.0 (0.8)	0.644 ^a
Sleep quality	1.0 (0.8)	1.2 (0.8)	0.042 ^a	1.0 (0.7)	1.3 (0.9)	0.002 ^a	1.1 (0.8)	1.2 (0.8)	0.120 ^a
Well-being during the day	1.0 (1.0)	1.1 (1.0)	0.322 ^a	1.0 (0.9)	1.1 (1.0)	0.250 ^a	1.0 (0.9)	1.1 (1.0)	0.264 ^a
Functioning capacity during the day	1.1 (1.0)	1.2 (1.0)	0.300 ^a	1.1 (0.9)	1.3 (1.0)	0.071 ^a	1.1 (1.0)	1.2 (0.9)	0.621 ^a
Sleepiness during the day	1.2 (0.7)	1.0 (0.6)	0.006 ^a	1.2 (0.7)	1.0 (0.6)	0.015 ^a	1.1 (0.7)	1.0 (0.6)	0.047 ^a

^aMann–Whitney test.

Data presented as mean (standard deviation). AIS, Athens Insomnia Scale; BMI, body mass index; FMI, fat mass index; HADS, Hospital Anxiety and Depression Scale; LMI, lean mass index; MHR-QOL, Menopausal Health-Related Quality of Life Questionnaire.

association between moderate-to-severe insomnia and LMI observed in this study.

Contrarily, sleep deprivation decreases blood concentrations of IGF-1 and testosterone, anabolic hormones vital to protein synthesis, and increases blood concentrations of protein catabolic hormones, such as cortisol, affecting muscle mass maintenance [27,28]. In addition, insulin resistance associated with sleep deficiency is a major risk factor for

declining muscle mass and muscle function in old age [29]. Thus, the loss of muscle mass could be caused by insomnia.

Insomnia scores differed between the LMI groups, with the lower LMI group scoring worse on the total insomnia scores and most sub-domains but having better scores only on the characteristic 'Sleepiness during the day' for some unknown reasons. A longitudinal study of individuals in the Penn State adult cohort found a significantly associated relationship

Table 3. Associations between the FMI (kg/m²) and severe hot flashes.

Model	Explanatory variable	OR	95% CI	p-Value
1-1	FMI (kg/m ²)	1.07	1.01–1.14	0.027
1-2	FMI (kg/m ²)	1.08	1.02–1.15	0.016
	Age (years)	0.88	0.29–2.67	0.820
	Regular exercise (yes/no)	1.01	0.68–1.49	0.960
	Menopausal status			
	Perimenopausal/premenopausal	1.87	1.09–3.22	0.023
	Postmenopausal/premenopausal	2.26	1.28–3.99	0.005

Model 1-1: association between FMI (kg/m²) and severe hot flashes, $p = 0.027$. Model 1-2: multivariate logistic regression model, adjusted for age, regular exercise and menopausal status, $p = 0.014$. CI, confidence interval; FMI, fat mass index; OR, odds ratio.

Table 4. Associations between the LMI (kg/m²) and moderate-to-severe insomnia.

Model	Explanatory variable	OR	95% CI	p-Value
2-1	LMI (kg/m ²)	0.77	0.61–0.97	0.028
2-2	LMI (kg/m ²)	0.72	0.55–0.94	0.015
	HADS anxiety subscale score	1.20	1.09–1.32	<0.001
	HADS depression subscale score	1.15	1.05–1.26	0.003
	Age (years)	1.02	0.95–1.11	0.535
	Menopausal status			
	Perimenopausal/premenopausal	0.58	0.27–1.19	0.135
	Postmenopausal/premenopausal	0.94	0.45–1.97	0.865

Model 2-1: association between LMI (kg/m²) and moderate-to-severe insomnia, $p = 0.025$. Model 2-2: multivariate logistic regression model, adjusted for anxiety, depression, age and menopausal status, $p < 0.001$. CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; LMI, lean mass index; OR, odds ratio.

between obesity and weight gain and the onset and persistence of excessive daytime sleepiness [30]. The result of the present study was not consistent with that report.

This study also found an association between the BMI and FMI and regular exercise habit. Nevertheless, no significant association between the LMI and regular exercise habit was observed. This could be attributed to the fact that this study did not investigate the type and intensity of exercise, including aerobic exercise and strength training.

A major limitation of this study was the possibility of selection bias. The participants in this experiment were referred to the clinic for management of menopausal symptoms, which suggests that they tended to have sufficient symptoms to warrant treatment for them. Possible demographic or other differences between the women included in this analysis and those excluded from the analysis make it difficult to generalize the results to the broader population.

In conclusion, FMI was positively associated with severe HF, and LMI was negatively associated with moderate-to-severe insomnia in perimenopausal and postmenopausal women. Weight loss could improve HF, while the contribution of increasing muscle mass to the improvement of moderate-to-severe insomnia warrants further investigation.

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