Vanished Gender Differences of Cardiometabolic Risk Factors After Matching the Apnea Hypopnea Index at Postmenopausal Age

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ABSTRACT

Background: Sleep-disordered breathing (SDB) and cardiometabolic risk factors are male prevalent.

Objective: This study investigated whether gender differences remained prominent after matching for the apnea hypopnea index (AHI) and postmenopause.

Methods: In a retrospective analysis of 350 eligible SDB patients, female patients were matched with male patients of the same age and body mass index (BMI) (age-BMI-matched [nAHImt]; n = 102 pairs) or were matched with male patients of the same age, BMI, and AHI (age-BMI-AHI-matched [AHImt]; n = 66 pairs). The nAHImt or AHImt patients were further separated into junior and senior subgroups.

Results: In the nAHImt/junior group, women had shorter neck circumferences, better sleep architecture, and lower AHI, Epworth Sleepiness Scale (ESS) score, blood pressure (BP), total cholesterol (TC), triglyceride (TG), and uric acid (UA) than nAHImt/junior men. In the AHImt/junior group, women had shorter neck circumferences, lower waist/hip ratios, ESS, BP, TG, and UA than AHImt junior men. In the nAHImt/senior group, women had lower AHI, neck circumferences, waist/hip ratios, diastolic BP, and UA than men. In contrast, in the AHImt/senior group, most cardiometabolic parameters were similar between women and men. After further matching for the AHI, many elements of gender differences disappeared.

Conclusions: Compared with AHImt men, women had lower UA, TG, BP, and daytime sleepiness before menopause, but gender differences became indistinguishable postmenopause. We suggested that matching sleep quality or adjusting AHI would be noteworthy and required for studying gender differences. (*Gend Med*. 2012;9:9–20)

Key words: cardiovascular, gender differences, metabolic syndrome, sleep apnea.

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INTRODUCTION

Sleep-disordered breathing (SDB), characterized by repetitive apneas or hypopneas, arterial oxygen desaturation, and repetitive arousals during sleep, has been shown to elevate serum C-reactive protein (CRP),[1] blood pressure (BP),[2] hyperglycemia, and dyslipidemia.[3] In other words, SDB appears to be an independent risk for cardiovascular disease[4] through cascades of neurohormonal and hemodynamic mechanisms.

Across a variety of samples[5,6] and races,[7,8] men appear to be more vulnerable to SDB than women. However, a few studies focused on whether cardiovascular impacts of SDB were gender variant. Although sexual hormonal status during the premenopausal stage may protect women from respiratory dysfunction and upper-airway narrowing during sleep, the lack of sexual hormones after menopause increases the risk of SDB incidence.[9,10] Thus, it is rational to assume that menopausal age may be a key factor in investigating gender differences in SDB severities and cardiometabolic risks. Furthermore, it is not clear whether previously reported gender differences will be potentially co-affected by the severity of SDB or SDB consequences, such as sleep quality and daytime alertness.

Therefore, we hypothesized that women with similar SDB severities (apnea hypopnea index [AHI]) to men might lose preferences in sleep features, daytime alertness, BP, proinflammatory status, and metabolism, reflecting the independent effects of sex hormones on these variables. Accordingly, we retrospectively examined these parameters between recruited eligible male and female pairs from our sleep clinic. Pairs were either matched for age and body mass index (BMI) (nAHImt), or matched for age, BMI, and AHI (AHImt) in junior and senior patients.

METHODS

Patients

All patients who were diagnosed with SDB were recruited for the study. However, those with serious medical or psychological problems, receiving hormone replacement therapy, who could not complete at least a 3-hour longpolysomnographic study, or were unwilling to join this study were excluded. All patients received an explanation of the research and signed informed consent forms with approval from Institutional Review Board of the China Medical University Hospital (CSMUH No: CS07161) before their participation. This study was under retrospective analysis.

Questionnaire, Anthropometry, Blood Pressure, and Biochemical Analysis

Anthropometric parameters (weight, height, neck circumference, waist circumference, hip circumference, BMI, waist/hip ratio), Epworth Sleep Scale (ESS) score,[11] life style questionnaire, and blood biochemical analysis for fasting glucose, triglyceride (TG), total cholesterol (TC), HDL, LDL, uric acid (UA), and high sensitivity CRP (hs-CRP) were completed in all patients as in a previous study.[12]

Polysomnography

Overnight laboratory-based polysomnographic studies were completed in all SDB patients, and sleep parameters were defined and quantified in a manner identical to a previous report.[12] Data on sleep polysomnographic parameters, including total sleep time, AHI, arousal index, lowest oxygen saturation, and duration of <90% oxygen saturation (SaO_2), as well as the percentages of total sleep time in non-rapid eye movement sleep (REM) stages I and II (NREM I+II%), NREM III+IV%, and REM sleep (REM%), were collected.

Matching of Male and Female Pairs

Four hundred sixty patients diagnosed with SDB who underwent polysomnography and consecutive anthropometric and biochemical measurements in the sleep clinic were recruited between 2008 and 2009. After screening for the exclusion criteria, 350 patients were eligible for gender-pair matching. All male and female pairs were randomly selected and stepwise matched for age and BMI (nAHImt) as in most previous studies, or once more matched for age, BMI, and AHI (AHImt), from this 350 patient database. According to previous cutoff settings for Asian-Pacific obesity,[13] there were 4 BMI cutoffs for normal, overweight (>23 kg/m^2), obesity (>25 kg/m^2), and severe obe-

sity (>30 kg/m^2). Four levels SDB severity were defined as none (AHI <5), mild (5 ≤ AHI <15), moderate (15 ≤ AHI <30), and severe (AHI ≥30). For more precise matching, each 10-year age span, 4 stratified BMI ranges, and 4 levels of SDB severity were used (**Table I**).

Menopause is a continuous process of declining female sexual hormones,[14] with an onset age of around 50 years in Taiwan.[15] Therefore, to investigate female menopause associated gender differences, we separated all patients into junior (<50 years old) and senior (>50 years old) groups and compared their corresponding variables.

Statistical Analysis

Data are expressed as mean (SD). A log transformation was used if variables were not normally distributed. Pearson's correlation was used to examine the relationship between each of the 2 parameters. Statistical analysis was performed with paired Student *t* tests for each variable. A *P* value < 0.05 was considered significant.

RESULTS

The paired numbers in nAHImt/junior, nAHImt/senior, AHImt/junior, and AHImt/senior groups were 51, 51, 33, and 33 (**Table I**), respectively. In the nAHImt/junior group, women had significantly lower AHI values and shorter neck circumferences, but had waist/hip ratios similar to men (**Table II**). By polysomnographic study, women had a significantly shorter stage I+II%, a longer stage III+IV%, a lower desaturation index, a higher value of lowest oxygen saturation, and a lower ESS score compared with men. No differences were found in values of total sleep time, sleep efficiency, REM%, arousal index, and SaO_2 <90%. Furthermore, women had significantly lower systolic and mean BP, and lower serum levels of TC, TG, and UA (**Table III**). However, their gender counterparts had similar values of diastolic BP, serum levels of fasting glucose, HDL, LDL, and CRP and its log transformed value.

In the nAHImt/senior group, women had significantly lower values of AHI, neck circumference, and waist/hip ratios, and higher stage III+IV%, lower arousal index, less frequent oxy-

Table I. Distribution of matched male and female pairs

Parameter	Age, y	20–29				30–39				40–49				50–60			
	BMI, kg/m^2	18.5–22.9	23–24.9	25–29.9	≥30	18.5–22.9	23–24.9	25–29.9	≥30	18.5–22.9	23–24.9	25–29.9	≥30	18.5–22.9	23–24.9	25–29.9	≥30
nAHImt		Junior (pn = 51)												Senior (pn = 51)			
		9	5	3	0	5	0	7	0	6	3	9	4	20	10	17	4
AHImt AHI, events/h		Junior (pn = 33)												Senior (pn = 33)			
0–4.9		1	0	0	0	0	0	1	0	1	1	2	0	1	2	1	0
5.0–14.9		2	1	0	0	1	0	2	0	3	1	2	0	1	2	2	1
15.0–29.9		0	0	0	0	0	0	2	0	2	0	3	0	3	2	5	1
≥30		0	2	0	0	1	0	0	0	2	1	1	1	4	4	2	2

AHI = apnea hypopnea index; AHImt = pairs matched for age, BMI, and AHI; BMI = body mass index; nAHImt = pairs matched for age and BMI; pn = paired number of subjects. Distributions of the male and female pairs matched for nAHImt or matched for AHImt in junior (<50 yrs old) and senior (≥50 yrs old) groups.

Table II. Anthropometric and sleep polysomnographic parameters

	nAHImt				AHImt			
	Junior (pn = 51)		Senior (pn = 51)		Junior (pn = 33)		Senior (pn = 33)	
Parameter	Men	Women	Men	Women	Men	Women	Men	Women
Age, y	35.7 (8.3)	35.5 (8.1)	56.5 (5.7)	56.3 (5.1)	38.9 (8.5)	38.6 (7.9)	57.5 (5.8)	56.9 (5.1)
BMI, kg/m^2	24.4 (3.4)	24.1 (3.7)	24.7 (3.2)	24.5 (3.6)	24.3 (2.8)	23.9 (2.9)	25.6 (3.6)	25.4 (4.4)
AHI, events/h	30.3 (24.3)	16.2 (17.5)‡	39.2 (25.8)	22.6 (21.2)***	23.2 (22.6)	22.1 (24.6)	26.6 (19.5)	28.9 (23.5)
Neck circumference, cm	38.1 (2.9)	34.0 (2.8)‡	38.7 (2.6)	34.5 (2.1)‡	37.9 (3.2)	34.1 (2.8)‡	39.7 (2.4)	35.3 (1.9)‡
WHR	0.87 (0.09)	0.84 (0.07)	0.94 (0.04)	0.87 (0.10)*	0.91 (0.06)	0.85 (0.07)*	0.86 (0.27)	0.87 (0.09)
Total sleep time, min	289 (52)	278 (51)	251 (67)	270 (59)	282 (49)	292 (36)	250 (82)	268 (67)
Sleep efficiency, %	80.7 (14.4)	79.9 (13.2)	71.4 (18.9)	75.8 (15.8)	79.5 (14.3)	82.9 (9.56)	70.0 (21.9)	74.5 (18)
NREM I and II, %	69.4 (12.5)	64.0 (12.1)*	66.7 (14.4)	66.1 (13.9)	68.4 (16.6)	66.2 (12.2)	63.1 (16.1)	63.9 (14.6)
NREM III and IV, %	4.4 (6.4)	9.7 (9.3)‡	1.4 (3.7)	4.4 (6.4)‡	6.1 (7.4)	8.4 (9.7)	3.4 (7.9)	4.4 (7.0)
REM sleep, %	10.3 (6.9)	11.4 (6.2)	9.4 (13.7)	11.0 (6.3)	10.2 (6.8)	12.2 (6.1)	11.1 (16.2)	10.7 (6.7)
Arousal index, events/h	34.1 (17.5)	33.1 (17.1)	44.6 (19.3)	36.2 (16.6)†	36.2 (18.7)	35.3 (19.2)	43.4 (18.7)	36.6 (16.9)
Desaturation index, events/h	16.3 (21.2)	6.8 (9.5)‡	27.9 (22.8)	11.2 (14.9)‡	10.2 (15.4)	6.0 (9.5)	19.2 (19.2)	15.4 (17.2)
Lowest oxygen saturation, %	82 (13)	88 (7)‡	79 (13)	86 (8)‡	86 (6)	88 (8)	81 (9)	85 (7)*
SaO_2 <90%, min	17 (43)	4 (16)	26 (49)	5 (13)‡	5 (17)	5 (20)	27 (56)	6 (10)*
ESS	7.8 (4.1)	6.4 (4.6)*	6.8 (5.0)	6.3 (3.8)	8.4 (3.8)	6.4 (4.9)*	6.7 (4.3)	6.5 (4.1)

AHI = apnea hypopnea index; AHImt = pairs matched for age, BMI, and AHI; BMI = body mass index; ESS = Epworth Sleep Scale score; nAHImt = pairs matched for age and BMI; NREM = non-rapid eye movement sleep; pn = paired number of subjects; SaO_2 = oxygen saturation; WHR = waist/hip ratio.
Values are means (SD).
The parameters were presented from male and female pairs, matched for nAHImt or matched for AHImt in junior (<50 yrs old) and senior (≥50 yrs old) patients.
*$P < 0.05$.
†$P < 0.01$.
‡$P < 0.001$ significance of difference in females from matched males.

Table III. Blood pressures and biochemical parameters

	nAHImt				AHImt			
	Junior (pn = 51)		Senior (pn = 51)		Junior (pn = 33)		Senior (pn = 33)	
Parameter	Men	Women	Men	Women	Men	Women	Men	Women
Systolic BP, mm Hg	125 (16)	116 (14)*	135 (20)	132 (21)	128 (17)	117 (13)†	136 (16)	139 (20)
Diastolic BP, mm Hg	86 (14)	80 (12)	90 (12)	86 (12)*	89 (12)	80 (13)‡	90 (10)	88 (13)
Mean BP, mm Hg	99 (14)	90 (18)*	105 (14)	100 (13)	102 (13)	92 (12)†	105 (11)	105 (14)
TC, mg/dL	190 (37)	174 (38)*	194 (35)	194 (38)	185 (35)	177 (38)	190 (42)	201 (35)
TG, mg/dL	147 (142)	97 (51)*	128 (73)	128 (73)	142 (115)	95 (43)*	151 (118)	151 (87)
HDL, mg/dL	42.9 (11.5)	47.3 (10.8)	43.3 (12.7)	47.1 (13.5)	46.3 (13.1)	47.8 (12.0)	43.8 (13.5)	44.3 (14.0)
LDL, mg/dL	130 (40)	117 (37)	132 (35)	127 (33)	125 (39)	121 (34)	129 (40)	131 (25)
Glucose, mg/dL	100 (19)	99 (22)	115 (37)	107 (30)	100 (13)	106 (29)	116 (50)	109 (36)
UA, mg/dL	6.30 (1.46)	5.09 (1.39)‡	6.4 (1.7)	5.44 (1.95)*	6.41 (1.62)	4.73 (1.40)‡	6.14 (1.37)	5.78 (2.09)
CRP, mg/dL	0.23 (0.38)	0.30 (0.60)	0.31 (0.70)	0.18 (0.18)	0.21 (0.37)	0.26 (0.71)	0.20 (0.30)	0.19 (0.19)
Log CRP, mg/dL	–1.00 (0.57)	–0.90 (0.58)	–0.93 (0.53)	–0.98 (0.47)	–1.00 (0.50)	–1.12 (0.48)	–0.99 (0.46)	–0.92 (0.45)

AHI = apnea hypopnea index; AHImt = pairs matched for age, body mass index, and AHI; BP = blood pressure; CRP = C-reactive protein; nAHImt = pairs matched for age and body mass index; pn = paired number of patients; TC = total cholesterol; TG = triglycerides; UA = uric acid.
Values are means (SD).
The parameters were reported from male and female pairs, matched for nAHImt or matched for AHImt in junior (<50 yrs old) and senior (≥50 yrsold) patients.
*P <0.05, † P <0.01.
‡P <0.001 significance of difference in females from matched males.

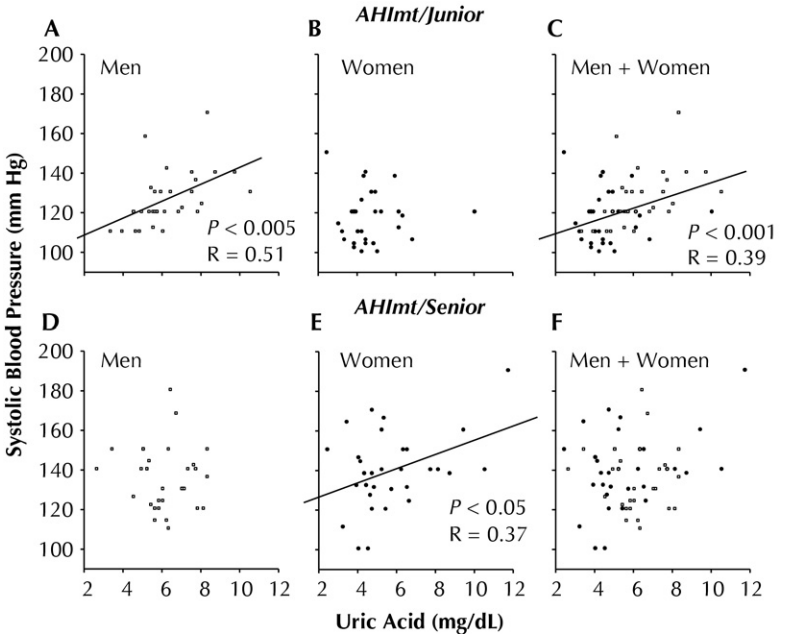

Figure 1. Pearson's correlation between plasma uric acid levels and systolic blood pressure in men (A, D), women (B, E), and both genders together (C, F) in age-body mass index-Apnea Hypopnea Index (AHI) matched (AHImt)/junior (A–C) and AHImt/senior (D–F) groups.

gen desaturation, higher lower oxygen saturation, and shorter durations of SaO_2 <90% than men, although both genders had similar values in total sleep time, sleep efficiency, NREM I+II%, REM%, and ESS scores. In variables of BP (**Table III**) and metabolic and proinflammatory states, all the previously mentioned variables were similar, except diastolic BP, with women having lower measurements than men.

In the AHImt/junior group (**Table II**), women still had significantly lower values of neck circumference, waist/hip ratios, and ESS score than men, whereas no differences in polysomnographic variables were observed. Moreover, women had significantly lower systolic, diastolic, and mean BPs, and lower serum values of TG and UA than junior AHImt men (**Table III**). No differences were observed among the values of fasting glucose, TC, HDL, LDL, and CRP and its log transformed value.

In the AHImt/senior group, women had less differences, but significantly shorter neck circumferences, higher lowest oxygen saturation, and a shorter period of SaO_2 <90% (**Table II**). Interestingly, all other parameters and parameters related to BP and metabolic and proinflammatory states were similar between senior AHImt men and women (**Table III**).

In the junior group, UA was positively correlated with systolic BP (**Figure 1A**) and with TG (**Figure 2**) in men and in men+women, whereas in the senior group, UA was found to be positively correlated with systolic BP (**Figure 1E**) in women and with TG (**Figures 2E** and **2F**) in women and men+women. Further, waist/hip ratio was positively correlated with UA in women and men+women of the junior group as well as in women of the senior group (**Figures 3B**, **3C**, and **3E**), although this correlated trend was still found in men+women of the senior group (P = 0.057) (**Figure 3F**). Paradoxically, in the senior group, waist/hip ratio (**Figure 3D**) was negatively correlated with UA in men.

DISCUSSION

Being a physiologic watershed in female life, menopause might be reasonably assumed to be a confounding factor in epidemiologic studies involving gender issues.[14] However, to our knowledge, few cardiometabolic studies of AHI matching or adjusting risk factors have taken gender-related

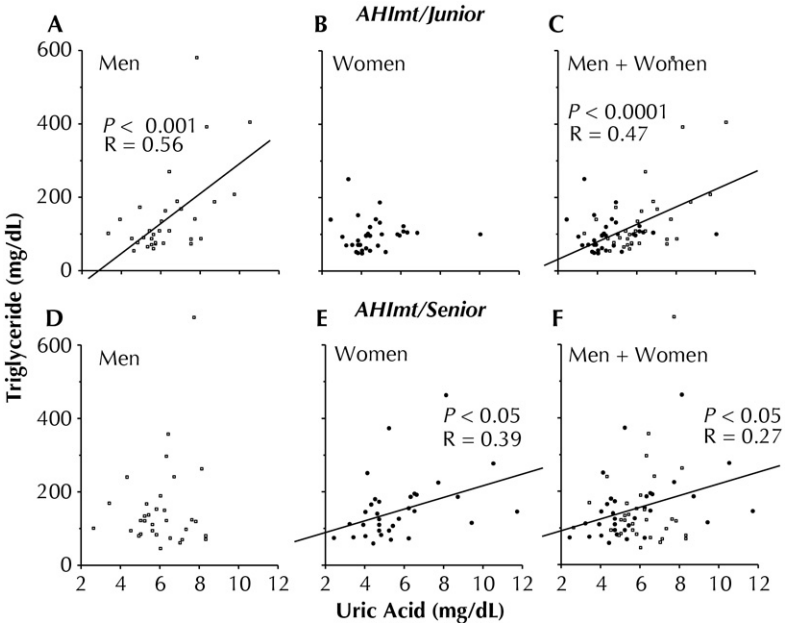

Figure 2. Pearson's correlation between plasma uric acid levels and plasma triglyceride levels in men (A, D), women (B, E), and both genders together (C, F) in age-body mass index-Apnea Hypopnea Index (AHI) matched (AHImt)/junior (A–C) and AHImt/senior (D–F) groups.

SDB and female menopause into consideration. This study appeared to be the first to examine gender differences in sleep architecture, systemic inflammation, hypertension, self-reported daytime sleepiness, and metabolic aberration in gender pairs by further matching for AHI, accounting

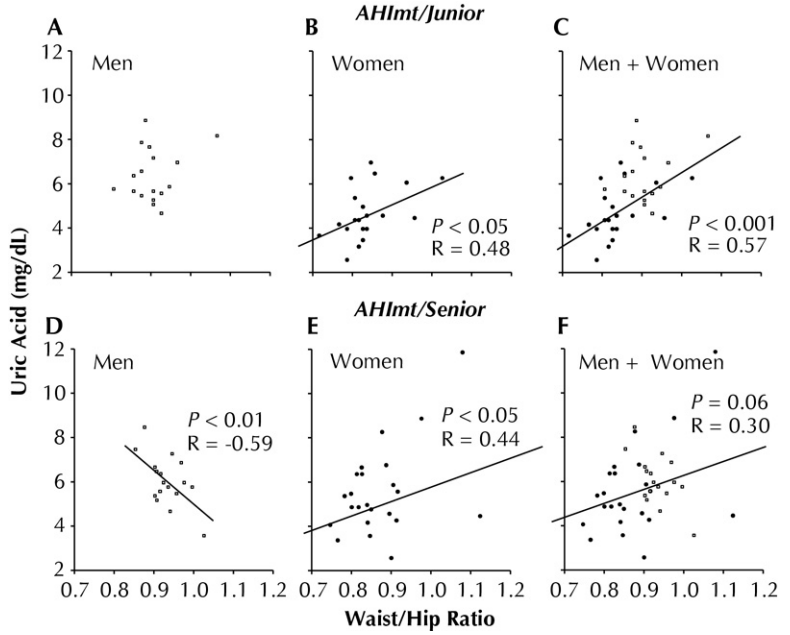

Figure 3. Pearson's correlation between waist/hip ratio and plasma uric acid level in men (A, D), women (B, E) and both genders together (C, F) in age-body mass index-Apnea Hypopnea Index (AHI) matched (AHImt)/junior (A–C) and AHImt/senior (D–F) groups.

for menopausal effects, and considering various potential biases.[16] A recent prospective community-based cohort study that recruited patients of ≥40 years of age (median follow-up of 8.7 years) showed that SDB was a significant predictor of incident coronary heart disease in men ≤70 years old as well as of incident heart failure in men, but not in women.[17] Although no direct evidence was available, the authors attributed these differences between the sexes to the lower prevalence of severe SDB and less cumulative exposure to SDB, possible better physiologic response, and better unmeasured health behaviors, such as diet, exercise, and obesity in women than in men, even with a similar AHI. Although our data were not observed longitudinally, our results might imply that gender effects modulated cardiometabolic risk factors independently of age, BMI, and AHI, particularly for younger than quasi-menopausal age groups, leading to different incident coronary and heart failure.

Interestingly, in a study of women compared with age- and either AHI- or BMI-matched men, Yukawa et al[18] reported that, irrespective of menopausal state, AHI levels were lower in women than in men; this was associated with lower values of ESS scores, BMI, and BP for women. We believed that it was too early to conclude whether gender affected hypertension, when multiple potential biases such as BMI, AHI, smoking, alcohol, exercise habits, and diabetes mellitus might be present.[16]

Female hormones, or estradiol, have been known to play an important role in cardiovascular protection.[19] Moreover, estrogen depletion coincides with androgen increases, which in postmenopausal status lead to increases in peripheral resistance and BP.[19] The present finding that women had lower BP exclusively at premenopausal ages independent of BMI and AHI might indicate that female sexual hormones have a "self-reliant effect" in lowering BP beyond their concomitant preventive effects on SDB.

In animal studies, intermittent hypoxia increased liver TG and phospholipids by upregulating genes of lipid biosynthesis.[20] Furthermore, SDB patients were found to have poorer serum lipid profiles.[21,22] Women in premenopausal or postmenopausal states who are receiving estrogen have a less atherogenic lipid profile, potentially accounted for by sex hormones and body fat distribution, despite the effects of gender-related SDB.[23–25] In the AHImt groups, TG, but not HDL, LDL, or TC levels, was significantly lower in the junior/women group, whereas all of the aforementioned lipid profiles showed no gender differences in the senior group. These findings might imply that TG was more affected than other lipids by sex hormones, independent of age, BMI, and SDB severity.

Visceral fat, an important determinant of hepatic lipase activity content, was shown to be reduced by continuous positive airway pressure therapy in SDB patients.[26,27] Furthermore, with less visceral fat,[28] premenopausal women were found to be more insulin sensitive than men. Moreover, the waist/hip ratio, which is well correlated with visceral fat,[29] was found to be a good predictor for metabolic disorders in men and women.[30] Again, these gender issue studies of visceral fat distribution did not explore SDB concerns until recently. By using energy x-ray absorptiometry, Simpson et al[31] found that percentages of neck fat in women and abdominal fat in men were significant predictors of AHI values. Unfortunately, menopausal impact was not considered. In AHImt groups, men had higher values of the waist/hip ratio, BP, TG, and UA in the junior group, but not in the senior one. This might suggest that beyond SDB, effects of gender and sex hormones were still essential to visceral fat accumulation, in the sequential order of BP, UA, and a certain lipid profile.

Tissue hypoxia will degrade adenosine triphosphate into UA, which might be reflected in SDB patients with increases in the urinary UA/creatinine ratio during nighttime sleep.[32] Further, hyperuricemia was found to be associated with hypertension, menopause, and metabolic syndrome.[33–36] Meanwhile, the visceral fat in elderly[37,38] women proved to correlate positively with their serum UA levels, and this gender gap narrowed with age.[39,40] The findings of these studies were consistent with our findings, suggesting that the waist/hip ratio was positively

correlated with UA values in AHImt/junior and senior/women or women+men (**Figure 3**).

Furthermore, in nonobese, hypertensive, and alcoholic men, Collantes et al[41] found asymptomatic hyperuricemia to be associated with mixed hyperlipidemia or hypertriglyceridemia; it has been speculated that purine metabolism flows through these TG pathways. Interestingly, this phenomenon was consistent with our findings that UA correlated positively with TG in the junior/men, junior/men+women, senior/women, and senior/men+women (**Figure 2**) tri-matching groups. This gender effect on the UA–TG relationship appeared substantially dependent on chronologic menopausal age. In other words, the high-androgen/low-estrogen related UA–TG association in young men might shift to older women as the result of postmenopausal hormonal changes, which is possibly similar to the mechanisms of the UA–systolic BP association (**Figure**). Conversely, the linkages of systolic BP or TG to UA were absent in junior/women and senior/men of the tri-matching groups. We assumed that some unclear compensatory or confounding mechanisms might counteract or attenuate these associated relationships.

Paradoxically, in AHImt/senior/men, waist/hip ratio was negatively correlated with serum UA levels. The explanations of these phenomena were complicated. We hypothesized that among these senior men, the effect of long-term central obesity on an increase of cardiac output,[42] even during sleep, might mitigate the tissue hypoxia impact from SDB, meaning the greater the waist/hip ratio, the lower the serum UA levels. However, their visceral fat (waist/hip ratio) might have affected their BP and lipid profiles and, in turn, diminished the systolic BP–UA and TG–UA associations in the AHImt/senior/men group. Further studies are required to confirm these assumptions.

SDB women were observed to have more insomnia, hypothyroidism, and treatment for depression than men matched for age, BMI, AHI, and ESS score.[43] In the general population, the presence of excessive daytime sleepiness was strongly associated with depression, obesity, diabetes and SDB, age, exercise habits, and other covariates.[16] The predictors of sleepiness (ESS score $\cong$ 13.5)[33] for obese subjects (BMI 35–40 kg/m^2) were depressive mood and log AHI values. However, gender differences in excessive daytime sleepiness, after controlling for age, BMI, AHI, and exercise, remained obscure. The results of our study might indicate that among slim patients in a sleep clinic, the premenopausal women had lower ESS scores than the men.

The serum CRP level, a potential marker of cardiovascular disease,[44] could be elevated by aging, smoking, obesity/visceral obesity, insulin resistance, hypertension,[45] or total/partial sleep deprivation.[46] Among clinical SDB patients, although Guilleminault et al[47] reported that only BMI was significantly associated with high CRP values without gender differences, Lui et al[45] showed that in men, the CRP levels were significantly predicted by each value of AHI, waist circumference, and serum TG level. In our study, after age-BMI-matching, no gender difference of serum CRP levels was found in either the junior or senior groups, independent of AHI values. Our results appeared to be supported by the findings of Guilleminault et al[47] while not conflicting with the findings of Lui et al's.[45]

Further AHI matching in our study was meaningful in attenuating gender discrepancies in sleep architecture. This result suggested that the gender impact disappeared with old age. In contrast, age and BMI matching potentially diminished gender differences in a major portion of the lipid profile and the CRP-related proinflammatory state. From the clinical perspective, our study might have underscored the different weightings of impacts of gender, BMI, SDB, and menopause on various cardiometabolic risk factors.

There were still several limitations to the present study. Transactional rather than longitudinal, this research could not offer cause and effect models, nor could it explore the dynamic changes among the variables. Different prevalences of SDB in women, especially at younger ages, and gender-different body features meant that case number matches for age, BMI, and AHI were lower and not evenly distributed. A huge

community-based rather than clinical based cohort study might offer more complete information on gender issues.

CONCLUSIONS

Women of premenopausal age had observable preferences over age- and BMI-matched men in daytime alertness, BP, and serum levels of TG and UA. Furthermore, matching for AHI values beyond age and BMI attenuated gender discrepancies in sleep architecture and TC serum levels in premenopausal ages.Most differences disappeared in postmenopausal age groups. After further matching AHI, much of the gender difference disappeared. We suggest that researchers should be cautious in interpreting gender difference findings without considering sleep quality or the AHI. Our findings imply that AHI matching or AHI adjusting would be noteworthy and should be required in studies of gender differences.

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CONFLICTS OF INTEREST

The authors have indicated that they have no other conflicts of interest regarding the content of this article.

REFERENCES

1. Yokoe T, Minoguchi K, Matsuo H, et al. Elevated levels of C-reactive protein and interleukin-6 in patients with obstructive sleep apnea syndrome are decreased by nasal continuous positive airway pressure. *Circulation*. 2003;107:1129–1134.
2. Narkiewicz K, Somers VK. Chronic orthostatic intolerance: part of a spectrum of dysfunction in orthostatic cardiovascular homeostasis? *Circulation*. 1998;98:2105–2107.
3. Vgontzas AN, Papanicolaou DA, Bixler EO, et al. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. *J Clin Endocrinol Metab*. 2000; 85:1151–1158.
4. Phillips BG, Somers VK. Sleep disordered breathing and risk factors for cardiovascular disease. *Curr Opin Pulm Med*. 2002;8:516–520.
5. Block AJ, Boysen PG, Wynne JW, Hunt LA. Sleep apnea, hypopnea and oxygen desaturation in normal subjects. A strong male predominance. *N Engl J Med*. 1979;300:513–517.
6. Young T, Palta M, Dempsey J, et al. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med*. 1993;328:1230–1235.
7. Young T, Hutton R, Finn L, et al. The gender bias in sleep apnea diagnosis. Are women missed because they have different symptoms? *Arch Intern Med*. 1996;156:2445–2451.
8. Ip MS, Lam B, Lauder IJ, et al. A community study of sleep-disordered breathing in middle-aged Chinese men in Hong Kong. *Chest*. 2001;119:62–69.
9. Popovic RM, White DP. Influence of gender on waking genioglossal electromyogram and upper airway resistance. *Am J Respir Crit Care Med*. 1995; 152:725–731.
10. Bixler EO, Vgontzas AN, Lin HM, et al. Prevalence of sleep-disordered breathing in women: effects of gender. *Am J Respir Crit Care Med*. 2001;163: 608–613.
11. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14:540–545.
12. Ting H, Lo HS, Chang SY, et al. Post- to pre-overnight sleep systolic blood pressures are associated with sleep respiratory disturbance, pro-inflammatory state and metabolic situation

in patients with sleep-disordered breathing. *Sleep Med*. 2009;10:720–725.
13. Chang CJ, Wu CH, Chang CS, et al. Low body mass index but high percent body fat in Taiwanese subjects: implications of obesity cutoffs. *Int J Obes Relat Metab Disord*. 2003;27:253–259.
14. Al-Azzawi F, Palacios S. Hormonal changes during menopause. *Maturitas*. 2009;63:135–137.
15. Torng PL, Su TC, Sung FC, et al. Effects of menopause and obesity on lipid profiles in middle-aged Taiwanese women: the Chin-Shan Community Cardiovascular Cohort Study. *Atherosclerosis*. 2000;153:413–421.
16. Basta M, Lin HM, Pejovic S, et al. Lack of regular exercise, depression, and degree of apnea are predictors of excessive daytime sleepiness in patients with sleep apnea: sex differences. *J Clin Sleep Med*. 2008;4:19–25.
17. Gottlieb DJ, Yenokyan G, Newman AB, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the Sleep Heart Health Study. *Circulation*. 2010; 122:352–360.
18. Yukawa K, Inoue Y, Yagyu H, et al. Gender differences in the clinical characteristics among Japanese patients with obstructive sleep apnea syndrome. *Chest*. 2009;135:337–343.
19. Miller VM, Duckles SP. Vascular actions of estrogens: functional implications. *Pharmacol Rev*. 2008;60:210–241.
20. Li J, Grigoryev DN, Ye SQ, et al. Chronic intermittent hypoxia upregulates genes of lipid biosynthesis in obese mice. *J Appl Physiol*. 2005;99:1643–1648.
21. Coughlin SR, Mawdsley L, Mugarza JA, et al. Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome. *Eur Heart J*. 2004;25:735–741.
22. Tan KC, Chow WS, Lam JC, et al. HDL dysfunction in obstructive sleep apnea. *Atherosclerosis*. 2006; 184:377–82.
23. St-Amand J, Despres JP, Lemieux S, et al. Does lipoprotein or hepatic lipase activity explain the protective lipoprotein profile of premenopausal women? *Metabolism*. 1995;44:491–498.
24. Applebaum DM, Goldberg AP, Pykalisto OJ, et al. Effect of estrogen on post-heparin lipolytic activity. Selective decline in hepatic triglyceride lipase. *J Clin Invest*. 1977;59:601–608.
25. Tikkanen MJ, Nikkila EA. Regulation of hepatic lipase and serum lipoproteins by sex steroids. *Am Heart J*. 1987;113:562–567.
26. Carr MC, Hokanson JE, Deeb SS, et al. A hepatic lipase gene promoter polymorphism attenuates the increase in hepatic lipase activity with increasing intra-abdominal fat in women. *Arterioscler Thromb Vasc Biol*. 1999;19:2701–2707.
27. Chin K, Shimizu K, Nakamura T, et al. Changes in intra-abdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome following nasal continuous positive airway pressure therapy. *Circulation*. 1999;100:706–712.
28. Ruderman N, Chisholm D, Pi-Sunyer X, Schneider S. The metabolically obese, normal-weight individual revisited. *Diabetes*. 1998;47:699–713.
29. Brook RD, Bard RL, Rubenfire M, et al. Usefulness of visceral obesity (waist/hip ratio) in predicting vascular endothelial function in healthy overweight adults. *Am J Cardiol*. 2001;88:1264–1269.
30. Chen CC, Wang WS, Chang HY, et al. Heterogeneity of body mass index, waist circumference, and waist-to-hip ratio in predicting obesity-related metabolic disorders for Taiwanese aged 35-64 y. *Clin Nutr*. 2009;28:543–548.
31. Simpson L, Mukherjee S, Cooper MN, et al. Sex differences in the association of regional fat distribution with the severity of obstructive sleep apnea. *Sleep*. 2010;33:467–474.
32. Saito H, Nishimura M, Shibuya E, et al. Tissue hypoxia in sleep apnea syndrome assessed by uric acid and adenosine. *Chest*. 2002;122:1686–1694.
33. Beard JT, 2nd.Serum uric acid and coronary heart disease. *Am Heart J*. 1983;106:397–400.
34. Cook DG, Shaper AG, Thelle DS, Whitehead TP. Serum uric acid, serum glucose and diabetes: relationships in a population study. *Postgrad Med J*. 1986;62:1001–1006.
35. Chu NF, Wang DJ, Liou SH, Shieh SM. Relationship between hyperuricemia and other cardiovascular disease risk factors among adult males in Taiwan. *Eur J Epidemiol*. 2000;16:13–17.
36. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality, the NHANES I epidemiologic follow-up study, 1971-1992. National

Health and Nutrition Examination Survey. *JAMA*. 2000;283:2404–2410.
37. Lee MS, Lin SC, Chang HY, et al. High prevalence of hyperuricemia in elderly Taiwanese. *Asia Pac J Clin Nutr*. 2005;14:285–292.
38. Takahashi S, Yamamoto T, Tsutsumi Z, et al. Close correlation between visceral fat accumulation and uric acid metabolism in healthy men. *Metabolism*. 1997;46:1162–1165.
39. Pan WH, Chang YH, Chen JY, et al. Nutrition and Health Survey in Taiwan (NAHSIT) 1993-1996: Dietary Nutrient Intakes Assessed by 24-Hour Recall. *Nutr Sci J*. 1999;24:11–39.
40. Chang HY, Pan WH, Yeh WT, Tsai KS. Hyperuricemia and gout in Taiwan: results from the Nutritional and Health Survey in Taiwan (1993-96). *J Rheumatol*. 2001;28:1640–1646.
41. Collantes Estevez E, Pineda Priego M, Anon Barbudo J, Sanchez Guijo P. Hyperuricemia-hyperlipemia association in the absence of obesity and alcohol abuse. *Clin Rheumatol*. 1990;9:28–31.
42. Kopelman PG. Obesity as a medical problem. *Nature*. 2000;404:635–643.
43. Shepertycky MR, Banno K, Kryger MH. Differences between men and women in the clinical presentation of patients diagnosed with obstructive sleep apnea syndrome. *Sleep*. 2005;28:309–314.
44. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*. 2003;107:499–511.
45. Lui MM, Lam JC, Mak HK, et al. C-reactive protein is associated with obstructive sleep apnea independent of visceral obesity. *Chest*. 2009;135:950–956.
46. Meier-Ewert HK, Ridker PM, Rifai N, et al. Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. *J Am Coll Cardiol*. 2004;43:678–683.
47. Guilleminault C, Kirisoglu C, Ohayon MM. C-reactive protein and sleep-disordered breathing. *Sleep*. 2004;27:1507–1511.

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