Vasomotor symptoms, estradiol levels and cardiovascular risk profile in women

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Abstract

Objectives: We investigated whether menopausal vasomotor symptoms (VMS) are related to an adverse cardiovascular risk profile. Furthermore, we examined the association between estradiol levels and VMS, and whether an association between VMS and cardiovascular risk factors can be explained by estradiol levels.

Study design: We used data from a Swedish population-based sample of 5,857 women, aged 50 to 64 years. Data on VMS and potential confounders were collected by questionnaires.

Main outcome measures: Body mass index (BMI), waist hip ratio (WHR), glucose, blood pressure, lipid profile and estradiol levels were measured.

Results: Symptoms of flushing/sweats were reported by 55% and sweats by 31% of all women. Estradiol concentrations were significantly lower in women with VMS. After multivariate adjustment, women with symptoms of sweats had a statistically significantly higher BMI, waist hip ratio, total cholesterol level, LDL level, triglycerides level, glucose level, systolic and diastolic blood pressure. These patterns did not change after correction for estradiol. The associations between flushing/sweats combined and cardiovascular risk factors were less pronounced.

Conclusions: Women with VMS have a less favorable cardiovascular risk profile. Although estradiol levels were significantly lower among women with VMS, the increased cardiovascular risk profile cannot be explained by circulating estradiol levels.

Key words: cardiovascular risk profile; estrogen; vasomotor symptoms; women; menopause

1. Introduction

We previously proposed that women with menopausal vasomotor symptoms (VMS) may differ from those without with respect to cardiovascular risk factors [1]. In a large community-based sample of perimenopausal women, we indeed found that women with symptoms of flushing or night sweats have increased BMI, cholesterol levels, systolic and diastolic blood pressures compared to women without VMS [2]. Recent findings showing that hot flushes are associated with subclinical cardiovascular disease [3], further support the idea that VMS may signal underlying adverse vascular changes.

Because hot flushes accompany the decline of estrogens in the vast majority of peri- and postmenopausal women [4] and because estrogen therapy has shown beneficial treatment effects [5], there is little doubt that estrogens play a role in the genesis of hot flushes. However, the exact mechanism of how estrogen levels are related to VMS is still unknown. Furthermore, the estrogen deficit accompanying menopause is also thought to play a dominant role in the increased cardiovascular disease (CVD) risk after menopause [6]. Therefore, the relationship between VMS and CVD risk factors may reflect the effect of decreasing estradiol levels.

The present study was set up to extend our findings in another population-based sample of perimenopausal women in whom also other markers of CVD risk were measured, such as lipoprotein sub fractions and glucose. Furthermore, we aimed at examining the association between circulating estradiol levels and VMS, and whether a possible association between VMS and cardiovascular risk factors can be explained by estradiol levels.

2. Methods

2.1 Population

The present research was conducted within the population–based "The Women's Health in the Lund Area (WHILA) Study". The aim of the WHILA study is to evaluate women's health status and their lifestyles and analyze the relevant social and/or medical risk factors for current and future diseases. The WHILA study covers all women (N=10,766) born between December 2, 1935, and December 1, 1945, and living in the Lund area, Sweden, by December 1, 1995. Women were invited to a health screening procedure, which took place between 1996 and 2000. Details from the study have been published elsewhere [7]. Informed consent was obtained and the ethics committee at Lund University approved the study.

Of the total population of 10,776 women, 6,917 (64.2%) completed the generic questionnaire and underwent a physical and laboratory assessment, and were therefore eligible for the present study. After exclusion of those with missing VMS data (n=819), blood pressure data (n=15), waist hip ratio (WHR) (n=18), lipid profile (n=104), glucose level (n=5), or prevalent CVD (n=99), 5,857 women were left for analysis. For the glucose analysis we also excluded those with prevalent diabetes (n=107), leaving 5,750 women for analysis of glucose.

2.2 General background questionnaire

At baseline, participants filled in a mailed general questionnaire containing questions on demographics, the presence of chronic diseases, and risk factors for chronic diseases. Physical activities during leisure time were categorized into low (e.g. walk, cycling or gardening for up to 2-4 hours/week) and regular (vigorous training, such as running, swimming, tennis or gymnastics for more than three hours/week). Smoking, OCs use, and HT use were categorized as never, past or current. Education was categorized into primary school,

secondary school, and university degree, according to the highest attained level of education stated by the respondent. Use of anti-hypertensive medication (ATC-code C02) was classified as yes or no. Menopausal status at enrolment was defined as follows: women were 'premenopausal' if they reported having regular natural menses, 'postmenopausal' if they reported not having had menses over the past 12 months, and 'perimenopausal/unknown' if they were inconsistent in their answers regarding regular menses and not having had menses over the past 12 months, therefore assuming they were having irregular cycles. Women with incomplete or missing questionnaire data, or who reported current use of OCs or HT, were classified as perimenopausal/unknown if they were between 46 and 55 years of age, and postmenopausal if they were older than 55 years [8].

2.3 Vasomotor symptoms

To assess the presence of VMS, two questions were asked. The first question was "Do you have problems of sweats/hot flushes?" and was asked in the reproductive history section of the questionnaire and presumably relates to the current situation. The second question was "Did you experience symptoms of sweats during the preceding three months?" and was asked in a general section concerning somatic symptoms. This section also contained questions on other symptoms such as feeling cold, headache, feeling of tiredness, sleeping problems, and depression. Both questions were to be answered with yes or no.

The questionnaire was a composite of several pre-existing and validated questionnaires [9] and some questions were validated in a subset prior to general mailing.

2.4 Other measurements

Body weight and height were measured and BMI was calculated. All women were measured in underwear and bare footed. All instruments were calibrated on a daily basis. WHR was obtained by dividing waist circumference in centimetres by hip circumference in centimetres.

Blood pressure was measured twice at the right arm after 15 minutes rest in seated position using a mercury sphygmomanometer with a cuff size adjusted to the circumference of the arm. The average of two recordings, measured to the nearest 2 mmHg, was the blood pressure used for the statistical analyses.

2.5 Laboratory analysis

Non fasting serum levels of the lipid profile and blood glucose were measured by a Cholestech LDX-instrument (Cholestech Corporation, Hayward, CA, USA) on capillary whole blood. The instrument measured values within a range for serum cholesterol between 2.59 and 12.90 mmol/L, for serum HDL between 0.39 and 2.59 mmol/L and for serum triglycerides between 0.51 and 7.34 mmol/L. Serum LDL was calculated.

KRYPTOR®-Estradiol 17B (BRAHMS Ag, Henningsdorf, Germany) were used for automated immunofluoroscent assays of estradiol in human serum. KRYPTOR® uses TRACE® (Time Resolved Amplified Cryptate Emission) technology, based on a non-radiative transfer of energy. Detection limits and coefficients of variations for estradiol were 3.5 pmol/L and 7.1% respectively. All measurements were carried out in the same laboratory and by the same examiners.

2.6 Data analysis

All statistical analyses were performed using the Statistical Analysis System, version 9.1 (SAS Institute, Inc.). Characteristics of the study population are described for all women and

for women with and without symptoms separately by means and standard deviations for normally distributed continuous variables and frequencies and percentages for categorical variables.

Estradiol concentrations were logarithmically transformed. For women with and without VMS, the geometric means and 95% confidence intervals (CI's) of estradiol levels were calculated. Next, general linear models were used to examine the association between estradiol levels and presence of VMS, adjusted for age and hormone use.

Linear regression analyses was used to estimate the relation of symptoms of flushing/sweats combined or sweats only with BMI, WHR, cholesterol, HDL, LDL, triglycerides, glucose, systolic and diastolic blood pressure. The linear regression coefficients (β) are presented with 95% CI's. The group of women with no symptoms was used as the reference category. Regression models were adjusted for age, smoking, education, physical activity during leisure time and menopausal status (model 2). To elucidate whether and to what extent the observed associations of VMS and cardiovascular risk factors might be explained by intermediates, further analysis also adjusted for estradiol (model 3) and BMI (model 4).

To rule out the influence of the use of antihypertensive medication on blood pressure, we repeated the blood pressure analyses in women not using antihypertensive drugs. Furthermore, we studied a possible modifying effect of type of menopause by restricting our analyses to the subgroup of women with a natural menopause. We also repeated all analyses in the subgroup of women not using HT or OCs to study a potential modifying effect of hormone use.

3. Results

In total, 55% of all women reported symptoms of flushing/sweats and 31% reported symptoms of sweats only. The mean age of the total group was 56.3 ± 3.0 years (range 50 to 64 years) and was lower in women with VMS. Moreover, symptomatic women were less likely to have regular physical activity during leisure time and to be highly educated compared to asymptomatic women. (Table 1)

3.1 Estradiol

After adjustment for age and hormone use, estradiol levels were significantly lower in the women with flushes/sweats as compared to the women without (30.5 [95% CI 29.2, 32.0] vs. 36.7 [95% CI 34.8, 38.6] pmol/L respectively). Estradiol concentrations were also significantly lower in the women with symptoms of sweats only as compared to asymptomatic women (28.1 [95% CI 26.4, 29.8] vs. 35.8 [95% CI 34.4, 37.3] pmol/L respectively). (Table 2)

3.2 BMI & WHR

Symptoms of flushing/sweats were associated with a significantly increased BMI, but not with WHR. Symptoms of sweats were associated with statistically significantly increased BMI as well as WHR. After multivariate adjustment women reporting sweats had a 0.71 kg/m^2 [95% CI 0.48, 0.93] higher BMI and a 0.012 [95% CI 0.008, 0.015] higher WHR compared to women with no sweats. Including estradiol in the models did not change the results. (Table 3)

3.3 Lipids

Women with symptoms of flushing/sweats had statistically higher total cholesterol and LDL levels compared to asymptomatic women. No statistically significant associations were found for flushing/sweats and HDL and triglycerides. Symptoms of sweats only were associated with a 0.03 mmol/L [95% CI -0.05, -0.004] lower HDL level, which was statistically

significant. However, this difference did not remain after multivariate adjustment (-0.02 mmol/L [95% CI -0.04, 0.004]). However, after multivariate adjustment, symptoms of sweats only was associated with a significant 0.14 mmol/L [95% CI 0.08, 0.20] higher total cholesterol level, a 0.10 mmol/L [95% CI 0.05, 0.15] higher LDL level and a 0.12 mmol/L [95% CI 0.08, 0.16] higher triglycerides level. Additionally including estradiol and BMI in the models did not materially change the results. (Table 3)

3.4 Blood pressure

Women reporting symptoms of flushing/sweats had a lower systolic blood pressure, although these results did not reach statistical significance. No association was found for flushing/sweats and diastolic blood pressure. However, women with symptoms of sweats only had a 1.68 mm/Hg [95% CI 0.74, 2.62] significantly higher systolic blood pressure and a 0.79 mm/Hg [95% CI 0.27, 1.31] significantly higher diastolic blood pressure compared to asymptomatic women. Results were not altered after including estradiol in the models. Inclusion of BMI in the adjustments attenuated the differences between women with and without sweats but remained significant for sweats only and systolic blood pressure (1.51 mm/Hg [95% CI 0.55, 2.47]). Results were similar in the subgroup of 5,304 women who did not use antihypertensive drugs. (Table 3)

3.5 Glucose

We did not find an association for symptoms of flushing/sweats and glucose level. Symptoms of sweats only were associated with a 0.07 mmol/L [95% CI 0.01, 0.14] significantly higher glucose level. Including confounders or estradiol level in the regression model did not change these results. After including BMI to the model the estimate for sweats only was still in the same direction, but the CI became wider (0.06 mmol/L [95% CI -0.01, 0.13]).

All results were essentially similar in the subgroup of women with a natural menopause, and in the subgroup of women not using OCs or HT (data not shown).

4. Discussion

This large population-based cross-sectional study of postmenopausal women shows that symptoms of sweats only were associated with increased BMI, WHR, systolic and diastolic blood pressures, glucose-, total cholesterol-, LDL-, and triglycerides levels. The associations for combined flushing and sweats with CVD risk factors were less pronounced, but were largely in the same direction of a less favorable risk profile. Although VMS are related to decreased estradiol concentrations, the associations with CHD risk factors could not be explained by the women's circulating estradiol levels.

To appreciate the findings, some aspects of the present study need to be addressed. A possible limitation includes the cross-sectional design of the study. However, we expect that effects of VMS on several risk factors, such as blood pressure, are more acute effects, and therefore this has probably not influenced our results to a large extent. In the present study we found some small changes to be statistically significant. However, even small changes in risk factors may be relevant to vascular events. The overall reduction in ischaemic heart disease (IHD) from a total systolic blood pressure reduction of 22 mm/Hg [10] and cholesterol reduction of 0.6 mmol/L [11] is estimated to be approximately 50% and 39%, respectively. Therefore, the higher systolic blood pressure of 2 mm/Hg and the higher total cholesterol of 0.14 mmol/L among the symptomatic women in our study might be related to about 4% and 10% higher incidence of IHD in these women, respectively. Nevertheless, to gain more insight in the risk of vascular events in women with VMS, it is of importance to extend our findings in longitudinal studies with clinically manifest endpoints of CHD as the outcome. A limitation includes the method of gathering information on VMS. First, VMS were self reported; we asked whether women have problems with sweats/hot flushes by means of a questionnaire. However, any misclassification is most likely to be non-differential with regard to CHD, most likely leading to a dilution of the true effect. Second, it is not entirely clear

whether symptoms of sweats reflect menopausal sweats. However, the prevalence of sweats in WHILA was very similar to that of night sweats in a comparable study [2], and sleep problems were more common among women with (night) sweats than in asymptomatic women. Therefore, it is likely that the women have truly reported menopausal sweats. Finally, the question on sweats only specifically defined the time scale of within the last three months, which was not the case for flushing/sweats. This may have led to a less accurate measure of the combined variable, which reduces the chances of picking up associations. This might be an explanation for our finding that symptoms of sweats only had a stronger effect on cardiovascular risk factors than symptoms of flushing/sweats combined.

In our analyses, we additionally adjusted for estradiol level, which was measured only once. However, as estradiol levels fluctuate dramatically during the menopausal transition, it is likely that a single serum measurement cannot capture these wide fluctuations. Future work should further examine the role of estradiol on the relationship between VMS and cardiovascular risk factors with more detailed hormonal assessments.

Obviously, it is a point of discussion whether or not it is necessary to adjust for BMI in the analyses regarding blood pressure and lipids. In our view, BMI is an essential determinant of blood pressure [12], and also causally related to endocrine and metabolic changes with menopause and factors in the causal pathway should not be included in the regression models. The fact that adding BMI to the models weakened the results supports the view that BMI lies in the causal pathway and that adjustment has led to an overcorrection.

The focus of studies unraveling the etiology of VMS has mainly been on hot flushes and not that much on symptoms of sweating. However, we assume the mechanism of sweating is very similar to what is known about the mechanism of hot flushes. Reasons to believe this include that during a hot flush (1) sweating and skin conductance, an electrical measure of sweating, increase [13], (2) the whole body sweat rate in one subjects is measured to be about

1.3 g/min [14] and (3) measurable sweating has been found to occur during 90% of the hot flushes [13]. In our study, the prevalence of sweats among women with moderate to severe hot flushes was more than 50%, while only 20% of the women with mild hot flushes also had symptoms of sweats.

Briefly, a hot flush is a sensation of heat and flushing that occurs suddenly [15]. Hot flushes arise as a result of a reduced thermoregulatory zone [16], caused by an increased sympathetic nervous system (SNS) activity [13]. Measures of SNS activity, such as epinephrine and norepinephrine, are also possible mediators for various vascular abnormalities [17], such as increased cholesterol levels [18], hypertension [19], and myocardial infarction and stroke [20]. Given that catecholamines are also involved in the etiology of VMS, an increase in SNS activity might be the primary cause for the association of VMS with an adverse CVD risk profile although definitive conclusions can not currently be made.

We found that estradiol concentrations were significantly lower among women with VMS as compared to women without VMS. Nevertheless, since additional adjustment for estradiol levels did not change our found associations, our findings indicate that VMS were still independently associated with an unfavorable CVD risk profile. Furthermore, given that estrogen concentrations remain low throughout menopause and that symptoms usually subside with time after menopause, it is not very likely that estrogen deficiency as such is the only risk factor for symptoms [21]. Recently, it has been suggested that hormonal fluctuations that occur during menopause are involved as well [15,22,23]. More research into this is necessary to fully understand the current findings.

Earlier studies found that thinner women were more likely to report VMS than heavier women [24,25], because of conversion of androgens to estrogens in fat tissue. According to more recent investigations [2,26,27] including the present, women with higher body weight

have an increased risk of VMS. This may be caused by the effect of increased insulation from body fat, resulting in elevated core body temperature, which triggers hot flushes [28].

Previously we reported that women with VMS have increased BMI, cholesterol levels, systolic and diastolic blood pressures compared to women without symptoms [2]. In the present study we were able to replicate this and extend these findings to other markers of CVD risk, such as WHR, glucose, LDL and triglycerides levels. Furthermore, a recent study found that women with hot flushes have more subclinical cardiovascular disease [3]. Another recent study, however, showed no differences in lipids, lipoproteins, sex hormone binding globulin, or high sensitive C-reactive protein between women with and without of mild hot flushes [29]. However, with the small sample size and low number of women with symptoms, the statistical power was only 40% to find an association between VMS and cholesterol levels in that study based on the effect sizes in our study. The conflicting results from the Rancho Bernardo Study, where night sweats were not associated with BMI, lipid levels and blood pressure, could be explained by the much higher age of the study group, suggesting that the study population might not be comparable to ours [30].

Together, our results further support our hypothesis that women with VMS, differ from those without with respect to cardiovascular risk factors. Although estradiol levels were significantly lower among women with VMS, the increased cardiovascular risk profile cannot be explained by circulating estrogen levels.

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Table 1 Characteristics of the study population of 5,857 women according to presence of hot flushes/sweats and sweats only

		Presence of hot flushes/sweats		Presence of sweats	
Characteristics	**All women (N=5,857)**	**Absent (N=2,637)**	**Present (N=3,220)**	**Absent (N=3,979)**	**Present (N=1,878)**
	Mean ± SD*	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**
Age, years	56.3 ± 3.0	56.5 ± 3.1	56.1 ± 2.9[a]	56.5 ± 3.0	55.9 ± 2.9[a]
BMI *, kg/m^2	25.3 ± 4.1	25.2 ± 4.2	25.4 ± 4.1	25.1 ± 4.0	25.8 ± 4.3[a]
WHR	0.78 ± 0.06	0.78 ± 0.06	0.78 ± 0.06	0.77 ± 0.06	0.79 ± 0.07[a]
SBP *, mm/Hg	131.9 ± 17.1	132.4 ± 17.1	131.6 ± 17.0	131.6 ± 16.9	132.7 ± 17.4 [b]
DBP *, mm/Hg	85.0 ± 9.3	85.0 ± 9.2	85.0 ± 9.4	84.8 ± 9.2	85.5 ± 9.4[b]
Total cholesterol, mmol/L	5.9 ± 1.1	5.9 ± 1.1	6.0 ± 1.1[b]	5.9 ± 1.1	6.0 ± 1.07[a]
HDL, mmol/L	1.74 ± 0.43	1.75 ± 0.43	1.74 ± 0.43	1.75 ± 0.42	1.73 ± 0.44[b]
LDL, mmol/L	3.46 ± 0.99	3.44 ± 0.99	3.49 ± 0.97[b]	3.44 ± 0.98	3.53 ± 0.97[b]
Triglycerides, mmol/L	1.62 ± 0.76	1.60 ± 0.75	1.63 ± 0.77	1.57 ± 0.74	1.70 ± 0.80[a]
Glucose, mmol/L	6.15 ± 1.40	6.18 ± 1.50	6.12 ± 1.31	6.12 ± 1.38	6.21 ± 1.44[b]

Table 2 Unadjusted and adjusted geometric mean of estradiol levels (pmol/L) by symptoms of flushing and sweats.

Models	Presence of hot flushes/sweats		Presence of sweats	
	Absent (N=2,637)	Present (N=3,220)	Absent (N=3,979)	Present (N=1,878)
	Geometric mean (95% CI)	Geometric mean (95% CI)	Geometric mean (95% CI)	Geometric mean (95% CI)
Model 1*	34.0 (32.1-36.0)	32.5 (30.9-34.1)	36.4 (34.8-38.2)	27.0 (25.3-28.8)[a]
Model 2†	34.6 (32.7-36.6)	32.0 (30.4-33.6)	37.1 (35.5-38.8)	26.0 (24.3-27.7)[a]
Model 3‡	36.7 (34.8-38.6)	30.5 (29.2-32.0)	35.8 (34.4-37.3)	28.1 (26.4-29.8)[a]

[b]

[a] P-value < 0.0001 [b] P-value 0.02

[*] Model 1 = Univariate (crude) model.

[†] Model 2 = Adjusted for age (continuous).

[‡] Model 3 = Model 2 and OC's (never, past, current) and HT (never, past, current) use.

Table 3 Adjusted estimates for the relationship between presence of vasomotor symptoms and cardiovascular risk factors

Models	Hot flushes/sweats	Sweats	Hot flushes/sweats	Sweats
	BMI β kg/m^2 (95% CI)		WHR β (95% CI)	
Model 1*	0.18 (-0.03, 0.39)	0.71 (0.48, 0.93)[a]	0.002 (-0.001, 0.006)	0.012 (0.008, 0.015)[a]
Model 2†	0.21 (0.00, 0.42)[b]	0.71 (0.48, 0.93)[a]	0.003 (-0.001, 0.006)	0.012 (0.008, 0.015)[a]
Model 3‡	0.21 (-0.01, 0.43)	0.69 (0.46, 0.92)[a]	0.003 (-0.001, 0.006)	0.011 (0.008, 0.015)[a]
	Total cholesterol β mmol/L (95% CI)		HDL β mmol/L (95% CI)	
Model 1*	0.06 (0.01, 0.12)[b]	0.14 (0.08, 0.20)[a]	-0.003 (-0.02, 0.02)	-0.03 (-0.05, -0.004)[b]
Model 2†	0.06 (0.01, 0.12)[b]	0.14 (0.08, 0.20)[a]	0.001 (-0.02, 0.02)	-0.02 (-0.04, 0.004)
Model 3‡	0.05 (-0.01, 0.10)	0.12 (0.06, 0.18)[a]	0.003 (-0.02, 0.03)	-0.02 (-0.04, 0.005)
Model 4§	0.04 (-0.02, 0.10)	0.11 (0.05, 0.17)[b]	0.007 (-0.01, 0.03)	-0.002 (-0.03, 0.02)
	LDL β mmol/L (95% CI)		Triglycerides β mmol/L (95% CI)	
Model 1*	0.05 (0.002, 0.10)[b]	0.10 (0.05, 0.16)[a]	0.03 (-0.01, 0.07)	0.13 (0.09, 0.17)[a]
Model 2†	0.06 (0.004, 0.11)[b]	0.10 (0.05, 0.15)[b]	0.02 (-0.02, 0.06)	0.12 (0.08, 0.16)[a]

Model 3‡	0.04 (-0.01, 0.09)	0.08 (0.03, 0.14)[b]	0.02 (-0.02, 0.06)	0.12 (0.08, 0.17)[a]
Model 4§	0.03 (-0.02, 0.09)	0.07 (0.01, 0.13)[b]	0.01 (-0.03, 0.05)	0.09 (0.05, 0.13)[a]

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