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The cortisol awakening response and the metabolic syndrome in a population-based sample of middle-aged men and women

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Abstract

The objective was to explore the relationship between the cortisol awakening response (CAR) and the metabolic syndrome (MetS) as defined by the National Cholesterol Education Program criteria. The final study sample consisted of 91 women (14 with MetS) and 84 men (15 with MetS), aged 45 to 70 years, from a general population sample. The only exclusion criteria were no consent, pregnancy, or insufficient cortisol testing. On the day of measurement (weekday), salivary cortisol was sampled at awakening and 15 minutes after awakening. Relative CAR (CAR%) and the MetS were the main variables studied. Results showed that, in women with the MetS, cortisol at awakening was significantly lower (mean, 8.92 vs 12.33 nmol/L; $P = .05$) and the CAR was significantly higher (91.4% vs 36.5%, $P < .001$) than in women without the syndrome. Significant difference in the relative CAR was also present between men and women with MetS (38.5% and 91.4%, respectively; $P = .02$). No difference was seen in the awakening response comparing men with and without the MetS. In a regression model, the response to awakening was dependent on the MetS in women ($F_{1,89} = 13.19$, $P < .001$); but the model was not significant in men. Furthermore, the awakening response was associated with more depressive symptoms in women ($F_{1,80} = 8.12$, $P = .01$) and with weekday/weekend cortisol sampling in men ($F_{1,82} = 4.63$, $P = .03$). The association between the relative CAR and the MetS remained significant but somewhat attenuated after adjusting for depressive symptoms ($P = .01$). Results indicate a sex difference in the CAR% in the presence of the MetS independent of depressive symptoms, a known correlate of the MetS.

1. Introduction

The cortisol awakening response (CAR) is a frequently used biological marker in stress research and has been applied extensively both in experimental and in field research [1]. However, there are still issues to be resolved; and comparisons between different studies are complex because of different approaches used [2,3]. There are moderate inter- and intraindividual variations in cortisol levels, and norm values are yet to be established. Cortisol awakening response is considered a distinct and separate part of the circadian cortisol rhythm.

A recent meta-analysis has confirmed that psychosocial factors, such as work and life stress, are associated with an increased CAR; and fatigue, burnout and exhaustion are associated with a reduced CAR [4]. Contradictory results for depression have been reported, where both increased and reduced CARs have been found [5-7]. Cortisol patterns have also been linked to mixed disorders, hypertension, cardiovascular disease, and abdominal obesity [8-13]. Few studies have explored potential sex differences in the CAR in relation to the metabolic syndrome (MetS) as an entity.

The aim of this study was to explore, in an ambulatory setting, the CAR in a population-based sample of middle-

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Institutional approval: All study subjects gave written informed consent before participation. The University of Göteborg Ethics Committee (Ö 044-03) approved the study.

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aged individuals. The presence of the MetS was defined according to the National Cholesterol Education Program (NCEP) [14].

2. Materials and methods

2.1. Subjects

The study was based on a specifically recruited subsample from the INTERGENE, a randomly sampled population-based cohort of Swedish adults [15] INTERGENE is a population-based research program that assesses the INTERplay between GENEtic susceptibility and environmental factors for the risk of chronic diseases in Western Sweden. The protocol used consisted of questionnaires and a health checkup including anthropometric measurements (weight, length, waist and hip circumference), electrocardiogram, heart rate, blood pressure, and a blood sample for analysis of plasma glucose, serum triglycerides, and high-density lipoprotein cholesterol (HDL-C). Furthermore, blood samples were also taken for later analysis and stored at −70°C.

In addition to the health checkup, 194 men and women aged between 45 and 70 years were asked to perform salivary cortisol testing at awakening on an ordinary weekday. The participants were recruited consecutively, from a mixture of rural and suburban populations, from April 1, 2003, to April 30, 2004, at 5 different municipalities in Western Sweden. There were no participants from the main city of Göteborg. The exclusion criteria were no consent, pregnancy, and insufficient cortisol testing. Twelve subjects declined participation (mean age, 52.6 ± 6.7 years). There were no pregnancies. Of the remaining 182 study subjects, 7 had insufficient cortisol testing (too little saliva, discolored sample, or high values [>75 nmol/L] indicating contamination with blood). They were therefore excluded, giving a final participation rate of 90%.

Thus, 175 participants—91 women and 84 men—with a mean age of 56.9 ± 7.0 years were included in the final analysis. Responses to the main questionnaire were complete in 99% of cases with the exception of cigarette smoking (3.4% missing), alcohol consumption (15.4% missing), still menstruating (15.4% missing), and 9.1% missing from the Zung self-rating depression scale. Tables 1 and 2 present the characteristics of the participants.

2.2. Questionnaires

Along with the invitation to the INTERGENE, participants were mailed written information about the study and a questionnaire on background factors, lifestyle, and questions on health problems. These data were checked at the examination. As depression was not formally diagnosed according to *Diagnostic and Statistical Manual of Mental Disorders* criteria, but based on the Zung [16] self-rating depression scale, the term *depressive symptoms* will be used. Furthermore, data on marital status, education, employment, cigarette and alcohol use, and physical activity were obtained. For women, 3 specific questions were asked: "Are you pregnant?" "Are you still menstruating?" and "Do you use any hormone treatments?" For the purpose of this study, 2 groups were formed with and without systemic hormone therapy.

2.3. Anthropometry and hemodynamic measurements

Height and weight were measured to the nearest centimeter and 0.1 kg, respectively. Subjects wore light clothing and no

Table 1
Participant characteristics according to sex and the MetS (NCEP criteria) in men and women aged 45 to 70 years

	Men			Women		
	Non-MetS	MetS	*P*	Non-MetS	MetS	*P*
n	69	15		77	14	
Age (y)	57.0 (7.4)	58.6 (6.7)	NS	55.9 (6.5)	59.9 (7.2)	.04
Education (%)						
Low (compulsory)	29.4	60.0	.04	10.5	35.7	.03
Medium/high (university)	70.6	40.0	NS	89.5	64.3	NS
Marital status (%)						
Married/cohabiting	85.3	73.3	NS	78.9	85.7	NS
Work status (%						
Working full/part time	67.6	53.3	NS	63.2	50.0	NS
Old age pensioner	20.6	20.0	NS	13.2	28.6	NS
Early retirement/other	11.8	26.7	NS	23.7	21.4	NS
Postmenopausal (%)				81.5	83.3	NS
Hormones used (%)				22.2	7.7	NS
Depressive symptoms (%)[a]	17.5	42.9	NS	20.3	61.5	.01
Regular leisure activity (%)	36.8	20.0	NS	18.2	7.1	NS
Smoker (%)[b]	21.5	6.7	NS	16.0	35.7	NS
Alcohol (grams/d)[c]	9.8 (11.4)	2.8 (6.9)	.01	4.0 (6.3)	0.5 (2.8)	.01

Data are percentages of subjects or means (SD) except for "Alcohol," where data are median (interquartile range). NS indicates not significant.

[a] n = 159 (9.1% missing data).

[b] n = 169 (3.4% missing data).

[c] n = 148 (15.4% missing data).

Table 2
Metabolic, hemodynamic, and anthropometric variables according to sex and the MetS (NCEP criteria) in men and women aged 45 to 70 years

	Men			Women		
	Non-MetS	MetS	*P*	Non-MetS	MetS	*P*
n	69	15		77	14	
P-glucose (mmol/L)	5.04 (0.46)	6.24 (2.01)	.01	5.11 (0.95)	6.09 (1.70)	.03
S-triglycerides (mmol/L)	1.52 (0.96)	2.96 (1.14)	<.001	1.20 (0.60)	1.94 (0.61)	<.001
S-HDL-C (mmol/L)	1.68 (0.47)	1.06 (0.17)	<.001	1.84 (0.33)	1.31 (0.24)	<.001
Systolic blood pressure (mm Hg)	144.3 (22.6)	144.2 (11.5)	NS	134.1 (21.0)	145.7 (12.3)	.02
Diastolic blood pressure (mm Hg)	87.0 (11.2)	88.5 (10.4)	NS	83.0 (9.3)	90.0 (10.4)	.01
Hypertension (%)	76.8	100	.06	63.6	100	.004
Waist (cm)	93.1 (8.0)	107.4 (8.8)	<.001	81.5 (8.6)	98.0 (9.7)	<.001
BMI ≥30 (%)	7.2	53.3	<.001	7.8	50.0	<.001
Elevated WHR (%)	11.6	53.3	.001	22.1	85.7	<.001

Data are means (SD) or percentage of subjects. BMI indicates body mass index; WHR, waist-to-hip ratio.

shoes and had fasted for at least 4 hours. The waist was measured in centimeters midway between the inferior rib margin and the iliac crest; and hip circumference, as the maximum measure over the buttocks. Body mass index was calculated as body weight divided by height^2 (kilograms per square meter). Using an automatic device (OMRON 711, Omron Healthcare Europe B.V., Hoofddorp, The Netherlands), pulse rate (beats per minute) and blood pressure (millimeters of Hg) were measured in the sitting position after 2 minutes of rest. Measurements were made in duplicate.

2.4. Cortisol measurements

Salivary cortisol was sampled twice in the morning. The subjects were instructed, orally and in writing, to chew on a cotton swab (Salivette; Sarstedt, Landskrona, Sweden) for 30 to 60 seconds. The first measurement was at awakening irrespective of clock time, and the second measurement was made after 15 minutes [12,17,18]. The participants were instructed to perform the test on a weekday and not to brush their teeth, smoke, have breakfast, or put anything in their mouths before or during the sampling period. Marked with time of day and date, the swabs were replaced in their containers and returned by post to the laboratory. Salivary cortisol was determined by radioimmunoassay technique (Orion Diagnostica Oy, Espoo, Finland). Intra- and interassay coefficients of variation (CVs) were less than 10%.

2.5. Metabolic measurements

Analyses of *P*-glucose (enzymatic hexakinase method with 4% CV at 5 and 15 mmol/L), *S*-triglycerides (enzymatic method with 4% CV at 1 and 2 mmol/L), and *S*-HDL-C (homogeneous enzymatic method with 5% CV at 1 and 2 mmol/L) were performed according to standard laboratory procedures at the Department of Clinical Chemistry and Transfusion Medicine, Sahlgrenska University Hospital, Göteborg, Sweden.

2.6. Definitions

The MetS was defined according to NCEP criteria as 3 or more of the following: plasma glucose of at least 6.1 mmol/L, HDL-C less than 1.04 mmol/L for men and less than 1.29 mmol/L for women, serum triglycerides of at least 1.7 mmol/L, hypertension = systolic blood pressure of at least 130 mm Hg or diastolic blood pressure of at least 85 mm Hg or treatment, waist circumference greater than 102 cm for men and greater than 88 cm for women.

Waist to hip ratio (WHR) was classified according to World Health Organization guidelines [19]. The WHR cutoffs were greater than 1.0 for men and greater than 0.85 for women. A transformed Zung depression score of at least 50 was used as index for the presence of depressive symptoms.

2.7. Statistics

For descriptive statistics (Tables 1-3), standard statistical tests were used. Student *t* test was used for normally distributed data; nonparametric test (Mann-Whitney), for nonnormally distributed data, and χ^2, for categorical data. For the change from awakening to 15 minutes, paired-samples *t* tests were carried out on logarithmically transformed data. Results are presented using the original linear scale (Fig. 1). As the CAR is highly dependent on the cortisol level at awakening, the relative CAR (CAR%) was calculated. *Relative CAR* was defined as ([cortisol at 15 minutes minus cortisol at awakening] divided by cortisol at awakening) × 100. The CAR% was normally distributed and used as the outcome variable throughout. Simple regression analyses were performed. Variables significantly associated

Table 3
Salivary cortisol (nanomoles per liter) at awakening and 15 minutes later and the calculated relative awakening response by sex in men and women aged 45 to 70 years

	Men	Women	*P*
n	84	91	
At awakening	12.88 (0.88)	11.81 (0.62)	NS
+15 min	15.84 (0.84)	15.29 (0.59)	NS
CAR%	36.4 (0.1)	45.0 (0.1)	NS

Data are means (SE).

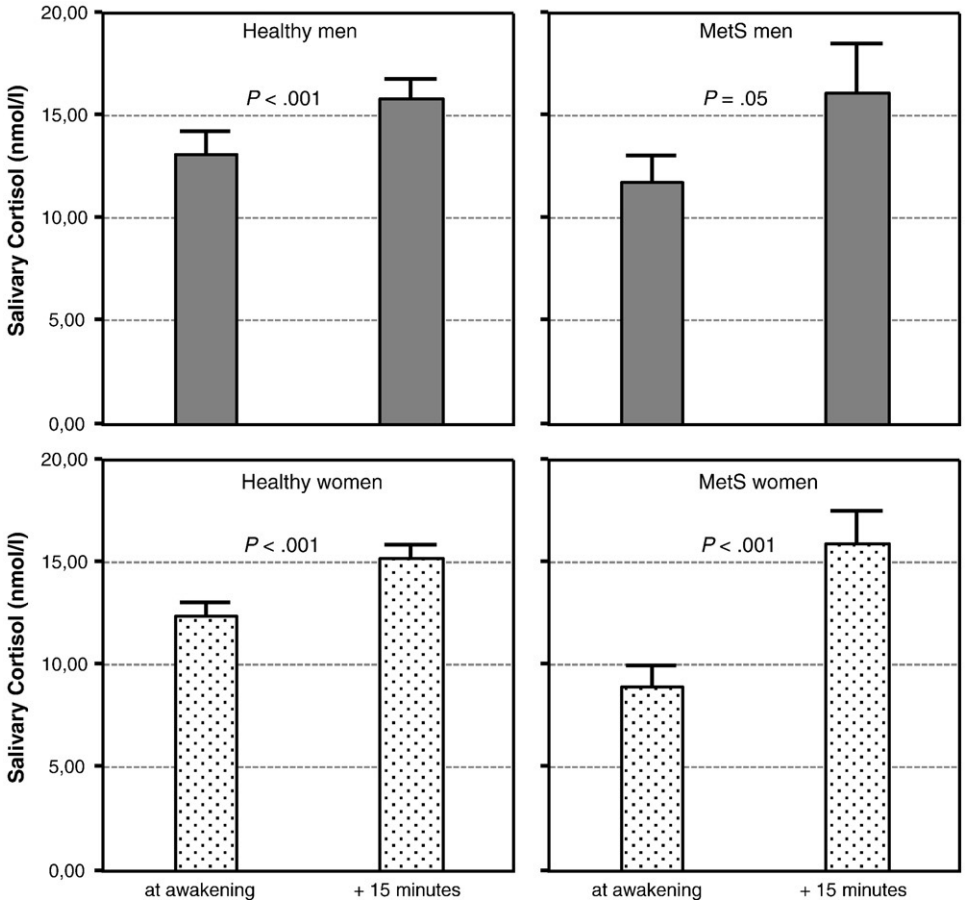

Fig. 1. Salivary cortisol (nanomoles per liter) at awakening and 15 minutes later by sex and the MetS in men and women aged 45 to 70 years. Data are mean and SE. Solid bars = men; checked bars = women. Statistical testing on logarithmically transformed data.

with CAR% were then entered into a regression model. Analyses were done for each sex separately.

For components making up the MetS, waist measurements were missing for 1 man and 4 women; blood pressure measurements were missing in 1 woman; and glucose, triglyceride, and HDL-C were missing in 1 man. The expectation-maximization imputation method was used to fill in missing values for the MetS. All tests were 2-sided, and a P value $\leq .05$ was considered statistically significant. Analyses were made using the SPSS (Chicago, IL) version 15.0 computer package.

3. Results

The prevalence of the MetS was 17.9% in men and 15.4% in women. Characteristics are found in Table 1. Women with the MetS were significantly older than women without the syndrome (P = .04), but there were no significant differences with respect to menopausal status or hormone replacement therapy/oral contraceptives used. Women with MetS also reported significantly more depressive symptoms than women without MetS (P = .01). Women and men with MetS were less formally educated and reported significantly less alcohol consumption than women and men without MetS. All components of MetS, except systolic and diastolic blood pressure in men, differed significantly between men and women with MetS compared with those without (Table 2). The participants did not differ from the population-based INTERGENE cohort in any of the MetS components except for systolic blood pressure, which was somewhat lower (P = .03) in the entire male cohort (139 mm Hg) compared with the male participants (144 mm Hg) in this study.

All study subjects were instructed to perform the cortisol testing on a weekday. However, 14 men and 5 women with a mean age of 57.8 ± 7.8 years performed the cortisol sampling on a weekend. Furthermore, 21.7% (20 men and 18 women) with a mean age of 57.1 ± 8.3 years did not have a cortisol increase (sample 2 ≤ sample 1) from awakening to 15 minutes later. These subjects did not differ from participants with increased CAR% in awakening time, social or demographic variables, MetS components, MetS, or WHR (data not shown). Of the 38 nonresponders, 10 had an awakening cortisol less than or equal to the mean awakening cortisol value for responders of 10.7 nmol/L. The remaining 28 nonresponders had a mean awakening cortisol of 21.4 nmol/L.

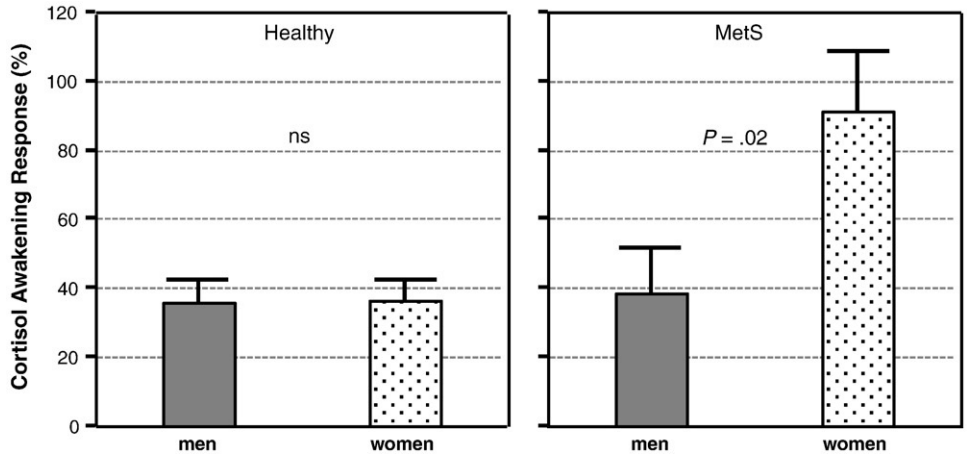

Fig. 2. The CAR% in men and women aged 45 to 70 years, with and without the MetS. Data are means and SE. Solid bars = men; checked bars = women.

3.1. Salivary cortisol results

Findings on salivary cortisol values by sex are presented in Table 3 and by sex and MetS in Fig. 1. Average first cortisol sample time was 6:26 (±19 minutes) AM for men and 6:48 (±14 minutes) AM for women (P = .05). A significant difference in CAR% was found between men and women with MetS (mean [SE] CAR%, 38.5 [13.1] and 91.4 [17.0], respectively; P = .02). Women with the MetS awoke with a significantly lower mean (SE) cortisol level (8.92 [0.96] nmol/L) than women without the syndrome (12.33 [0.69] nmol/L, P = .05). They reached the same salivary cortisol level after 15 minutes. Women with MetS had a mean (SE) CAR% of 91.4 (17.0), and women without MetS had a mean (SE) CAR% of 36.5 (5.7) (P < .001). The corresponding values for men were 38.5% (13.1) and 36.0% (6.1) (Fig. 2). The main results did not change when nonresponders were excluded from the analysis (data not shown).

Associations were found for CAR% and MetS ($F_{1,89}$ = 13.19, P < .001), for CAR% and depressive symptoms in women ($F_{1,80}$ = 8.12, P = .01), and also for CAR% and type of day the test was performed, that is, weekday/weekend, in men ($F_{1,82}$ = 4.63, P = .03). There were no significant associations between CAR% and age, awakening time, alcohol, smoking status, marital status, education, work status, or physical activity for either sex. Furthermore, there were no significant associations between CAR% and the factors of the individual MetS components (data not shown).

Table 4
Regression of relative change in the CAR on MetS, depressive symptoms, and weekday or weekend cortisol sampling for women aged 45 to 70 years

	Coefficient b	Standard error (b)	t	P
Constant	32.3	7.0	4.61	<.001
MetS	49.8	17.9	2.78	.01
Depressive symptoms	23.9	14.1	1.70	.09
Weekday/weekend	−30.8	25.7	−1.20	.24

The significant variables in univariate analyses, MetS, depressive symptoms, and weekday/weekend coded 0/1, respectively, were simultaneously entered into a linear regression model. The overall model was significant only for women (R^2 = 18%, $F_{3,78}$ = 5.50, P = .002) but not for men ($F_{3,73}$ = 1.94, not significant). Table 4 shows the coefficients for women.

4. Discussion

4.1. Main finding

This study explored the CAR and NCEP-defined MetS in a population sample of middle-aged men and women. Our results showed a salivary cortisol pattern in women with MetS characterized by a low awakening level. Furthermore, they showed an enhanced—on average, 90%—awakening response already in the first 15 minutes after waking up. The result remained significant even after adjusting for depressive symptoms. Furthermore, a significant difference in CAR% was seen between men and women with MetS. The awakening responses in men were comparable to the response found in women without MetS.

4.2. The awakening response

Generally, there seems to be little difference between sexes in basal cortisol levels and in the awakening response in healthy individuals under everyday conditions. Under acute or experimental conditions, however, men tend to react more vigorously to stress than women [20,21]. In chronic stress, women have been shown to have larger increases in cortisol than men; that is, a different cortisol pattern has been found in high-stress women compared with high-stress men and low-stress men and women [22]. The finding in the present study of different CARs in men and women when the MetS is present is another example of a sex-specific cortisol regulation. Possible mechanisms behind reported sex

differences in CAR are hypothalamic-pituitary-adrenal (HPA) axis interactions with the gonadal axis [20,21] and/or psychologic or psychosocial factors; for instance, some stressors have been shown to affect men and women differently [23,24]. However, the exact mechanisms underlying these sex differences are still to be revealed. There are also indications that higher age may increase the stress response to challenge, more so in women than in men [25,26]. In this study, we did not find CAR% to be associated with age. Furthermore, we found no association between the awakening response and time of awakening. Again, published results are inconsistent.

A nonresponse to awakening has been reported to occur in 26% of cases [27]. In this study, we found 22% nonresponders. Repeatedly, it has been shown that noncompliance with the cortisol protocol might distort results [28]. Of the 38 nonresponders in this study, three fourths showed high awakening levels with subsequent decline at 15 minutes. Indirectly, it might be suspected that these subjects have had a delay between waking up and taking the first sample. The remaining nonresponders had low awakening levels and minimal change in cortisol levels at 15 minutes; and again indirectly, it might be suspected that these subjects would be true nonresponders. This study was an ambulatory study, and it was not possible to check compliance with the study protocol objectively. Excluding nonresponders in analyses did not change the main result.

As has been reported previously, we found the awakening response to be associated with depressive symptoms and weekday/weekend [29,30]. In this study, these associations were sex dependent, with depressive symptoms significantly associated with CAR% in women and weekday/weekend significantly associated with CAR% in men only. Hyperactivity of the HPA axis has been seen in major depression, although there may be different responses in subtypes of depression as have been suggested [31]. The participants in this study came from a randomly sampled population-based cohort. Therefore, it seems unlikely that our finding should be due to subtypes of depressive disorders among our participants. When adjusting for depressive symptoms, the main finding was still significant, indicating MetS to contribute independently to the awakening response in women.

As mentioned before, previous studies have shown the awakening response to be blunted on weekends. This has been attributed to less anticipatory stress on weekends compared with weekdays. We found the expected lower response on weekends to be present in men. However, women showed a response on weekends similar to that found on weekdays, indicating the presence of more anticipated demands in this group. Yet, work status did not differ significantly between men and women.

4.3. The MetS

The prevalence of the MetS varies and is dependent on the definition of the syndrome, age, lifestyle, and ethnic background. Using a modified World Health Organization definition of MetS, an overall prevalence of 15% in a European population has been reported, which is in line with what was found in this study [32]. We found women with MetS to show a low awakening cortisol. Low cortisol levels have been reported in disease states particularly characterized by stress sensitivity, pain, and fatigue. Low awakening cortisol has also been found in insomnia, in subjects with abdominal obesity, in cancer patients, and in healthy individuals under stress [17,33,34]. Low awakening levels have been suggested to be adaptive as well as maladaptive [35]. The mechanism behind the low levels at awakening is not clear but could be due to disturbances at several levels of the HPA axis both centrally and peripherally [36,37].

Previous studies focusing on abdominal obesity and salivary cortisol patterns have found that associations in men and women are not consistent. For instance, abdominal obesity as measured by WHR has been found to be associated with increased CAR in men [11,12]. Steptoe et al [11] studied both men and women; and although the awakening response was somewhat greater in women than in men, they found no significant association between WHR and CAR in women. Therrien et al [38] reported an enhanced CAR% in centrally obese men, whereas there were no difference between lean and obese women. However, signs of altered HPA axis function in nondepressed women with abdominal obesity has been reported as well as increased cortisol secretion in women with central fat [39-41]. All 3 studies were experimental, and participants were younger. Our results support findings of a link between MetS and altered HPA function. Moreover, the result indicates a possible pathophysiologic sex difference behind the development of the MetS.

4.4. Strengths and limitations

Contrary to several other studies, we used the MetS as an entity, not substituted for WHR or individual features of the MetS. Our participants were not patients but came from a population-based random sample. Except for systolic blood pressure in men, our participants were representative of the main cohort in MetS components and anthropometric variables; and the prevalence of MetS was the expected. Furthermore, we adjusted for depressive symptoms. However, few exclusion criteria do open up for more concern regarding confounding variables. As there were nearly 200 participants and these were recruited out of a random sampled population, potential confounders might be assumed to be equally distributed across study groups. Linear regression modeling was also used, and we adjusted for the variables found to be associated with CAR%. These measures were applied in an attempt to reduce confounding; but of course, it does not with certainty exclude such influence. For instance, data on cortisone and antidepressant medication among participants might have improved the regression model. Although the participation rate was high, a

low primary participation rate in the whole INTERGENE study (53%) will somewhat lessen the generalizability of results. In addition, because of the comparatively low prevalence of MetS and the size of the study, the MetS group was small, restricting further analyses.

In different studies, number of days for cortisol sampling have varied [11,30,42,43]; and different sampling times have also been in use (awakening and/or 15, 20, 30, and 45 minutes) [2]. The reason we chose awakening and 15 minutes was to ensure that the cortisol sampling would be firmly on the upward slope of the morning cortisol response [12]. Peak cortisol levels have been reported at variable times postawakening. Whether the expected further increase in cortisol levels would have been equal across groups in this study or would have differed between groups cannot be answered because of the sampling protocol used. Lasikiewicz et al [44] have reported the awakening response to be relatively stable across days; but today, repeated measures over several days are recommended [45], as is repeated sampling postawakening, all to achieve more stable results. Further studies using extended protocols and specifically designed to address possible sex differences in the awakening response are needed.

5. Conclusion

Our results indicate a sex difference in awakening cortisol level and in the relative CAR in the presence of the MetS (NCEP defined), independent of depressive symptoms.

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