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Marital status and variability in cortisol excretion in postmenopausal women

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Abstract

Based on the premise that acute and chronic stresses stimulate and suppress cortisol secretion, respectively, and the hypothesis that marriage provides a buffer to stress, we tested whether extreme values of serum cortisol concentrations would be less likely in married women than in unmarried women. Three hundred women were recruited from two central Connecticut communities. Cortisol was measured in overnight urine samples using liquid chromatography–tandem mass spectrometry. Information on each subject's demographic characteristics, such as income and education level was collected. Mean log urinary cortisol was virtually identical in married and unmarried women, however, as predicted, the variance was significantly larger in the unmarried group ($p = 0.01$). After adjustment for potential confounders, multivariate logistic regression still revealed that absolute deviation of $\log_{10}$ cortisol from the mean was smaller for married versus unmarried women ($p < 0.01$); deviation from the mean cortisol was also higher for non-working than working women. These results support the idea that marriage and employment reduce the extreme levels of cortisol secretion, and by extension, this may reflect differences in levels of stress in married and in working women compared to unmarried and non-working women.

Keywords: Cortisol; Stress; Marriage; Epidemiology

Cortisol is important for normal function of a wide variety of bodily processes (Bartels et al., 2003; Goodyer et al., 2001; Fraser et al., 1999). It is the primary hormonal mediator of the stress response by the hypothalamic-pituitary-adrenalcortical axis (HPA) (Wust et al., 2000; Giese-Davis et al., 2004; Corcoran et al., 2001), and, thus, an informative endocrine marker of stress and HPA axis function.

Sephton and Spiegel (2003) review how psychosocial factors can influence cortisol regulation of the HPA axis. Generally, acute stress raises cortisol production (Schedlowski et al., 1992; Gerra et al., 2001; Prinz et al., 2001), and evidence suggests that chronic stress can suppress morning cortisol levels (Sephton et al., 2000). Miller et al. (2002) and coworkers theorized that with prolonged exposure to chronic stress, glucocorticoid receptors are down-regulated, the body's sensitivity to cortisol declines, and the immune system's response to anti-inflammatory signals is impaired. In addition, Stetler et al. (2004) reported that depression blunts the cortisol response to daily activities that are associated with cortisol changes in non-depressed persons.

Women over 50 years old experience loss in many ways, e.g., the loss of a spouse through death or divorce, children departing from home, declining health status, retirement, and increased risks for many health problems. At this transitional time, women in stable marital relationships are more likely to have access to many different types of social support, which may buffer older women from the negative effects of emotionally stressful life events.

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Studies of overall mortality have shown that married women have lower death rates than unmarried women. Sorlie et al. (1995) analyzed data from the National Longitudinal Mortality Study based on census data and covering over a half million persons over age 25 in the U.S. They reported that married women over age 45 had significantly lower death rates than widowed women (RR = 1.42), divorced women (RR = 1.37), and never married women (RR = 1.31). In addition, a recent CDC study found that across all demographic groups; married adults were the healthiest, and widowed adults were the least healthy (Schoenborn, 2004). Married adults were also less likely to experience severe psychological stress or to engage in risky health behaviors (Schoenborn, 2004). The transition from married to unmarried status is associated with negative health behaviors (Umberson, 1992; Lee et al., 2005; Schone and Weinick, 1998). The association between social support and physical health has been found on diverse health outcomes, such as coronary heart disease, cancer, infectious diseases, efficacy of immunizations, and unipolar depression (Hayes et al., 2001; Hawkley and Cacioppo, 2003, 2004; Uchino et al., 1996; Gallo et al., 2003).

Based on the observations of a marriage benefit to health cited above, we hypothesized that married women are at lower life stress and less likely to suffer from either acute or chronic stress, than unmarried women. Unmarried women would therefore tend to have more extreme urinary cortisol levels than married women. Not all marriage is beneficial and not all single people are unhappy. In particular, marital strain can induce an added burden of anxiety (Robles and Kiecolt-Glaser, 2003). However, in the aggregate, as cited above, married persons tend to have an overall benefit in the major health outcomes compared to unmarried persons. This benefit may be influenced by the effect of stress on risk of coronary heart disease in particular (Kuper et al., 2002).

Before collection of our cortisol data, we formulated the hypothesis that unmarried women would be more likely to have extreme cortisol levels, both higher and lower, than married women. We tested this hypothesis in women over age 50 sampled from two communities in Connecticut by comparing the distribution in cortisol between the two groups. First, we compared the dispersion, as measured by variance, in log urinary cortisol between the two groups with the expectation that it would be significantly higher in unmarried women. We then modeled the deviations from the mean cortisol in order to adjust for possible confounders such as education and income. We used overnight urinary excretion of cortisol as an integrated measure of nocturnal cortisol production; we chose this method, and not plasma nor saliva determinations because we believed it to provide better feasibility in our study population.

1. Materials and methods

1.1. Study subjects

A sample of women was recruited from two communities in Connecticut: the cities of West Hartford (WH) and New Britain (NB). All data were collected between Fall of 2001 and Spring of 2003.

Cluster areas were selected from census block groups within distinct geographically referenced boundaries. We used the 1990 U.S. Census Bureau's Topographically Integrated Encoding and Referencing line file (TIGER), which is a geographically referenced source recording the 214,000 street segments throughout Connecticut. This process generated an inventory of street segments within the selected areas from which a random sample was drawn. Subsequently, lists of residences' telephone numbers were also selected at random from the street inventory lists. Interviewers contacted area households by phone during daylight hours and early evening Monday through Saturday, to screen women for eligibility.

1.2. Study design

For Phase I of the study, subjects responded by phone to a detailed semi-structured questionnaire that elicited demographic, general health and reproductive history information. A subset of the Phase I participants consented to Phase II of the study and provided a single overnight urine sample. A time was arranged with the Phase II participants for the urine collection technician to drop off materials and provide urine collection instructions.

Materials included an 800 mL urine collection basin, a 250 mL Nalgene urine storage bottle, a small Styroform cooler, ice packs, and urine collection instructions. Participants were instructed to void immediately before going to bed, and then to collect all urine voided during the night, as well as the first morning void. Women were instructed to keep their urine sample refrigerated or chilled in the container provided. The samples were then retrieved within 2 h of the morning void and returned to the University of Connecticut Health Center clinical laboratory. Samples were placed in freezer storage at $-80\ ^{\circ}$ C without preservative.

1.3. Urinary cortisol and creatinine measurements

Cortisol was measured in urine samples using a method previously described (Taylor et al., 2002). In brief, deuterated cortisol (added as internal standard), and cortisol were extracted with methylene chloride. The methylene chloride extract was washed, dried, reconstituted, and analyzed by liquid chromatography–tandem mass spectrometry (LC/MS/MS) using multiple reaction monitoring in positive mode. A calibration curve consisting of five points (0.25–30 ng cortisol/mL) was assayed with each batch of samples. Samples and quality control pools were measured in one to two replicates in each of the two assays. Urinary creatinine concentrations were measured using a Vitros 250 Chemistry Analyzer (Ortho-Clinical Diagnostics).

1.4. Statistical analysis

Cortisol measurements were transformed to $\log_{10}$ because untransformed values were skewed. The log cortisol was normally distributed. Descriptive statistics for the study participants include demographic parameters, work characteristics, family characteristics, and self-reported health status. Summary statistics are presented herein as mean (S.D.) for continuous variables, and percentages for categorical variables. Comparisons between married versus Unmarried women and between West Hartford versus New Britain were made for continuous variables (e.g., age, body mass index (BMI), number of children) using independent samples *t*-test, and for categorical variables (e.g., marital status, prior alcohol consumption or not) using Pearson's chi-square. The unmarried women include divorced, widowed, and never married.

Absolute deviations from mean $\log_{10}$ cortisol were generated by subtracting each woman's log cortisol value from the sample mean of the log cortisol values for each group, married and unmarried. This measure is termed the 'deviation'. We modeled this statistic because we wanted to determine whether the significantly higher variance in the unmarried women might be accounted for by confounders such as income and age. We therefore conducted liner regression. All independent variables that were thought *a priori* to be associated with cortisol, and related to marital status, were considered to be potential confounders of the relationship between marital status and cortisol. The potential covariates included in the analysis were: age at interview, currently working or not, number of children, BMI, education (high school versus college and post-college versus college), exercise or not, self-assessed health status

(excellent versus good and fair/poor versus good), prior day consumption of heart medications or not, prior day consumption of depression medications or not, prior day consumption of alcohol or not, and hormone replacement therapy for menopausal symptoms or not. It has been demonstrated that the dependent variable can be switched with the key independent variable of interest in a binary logistic regression in order to address the association between the two (Prentice, 1976). The association between absolute deviations in mean $\log_{10}$ cortisol and marital status, adjusting for potential confounders, was examined using a binary logistic regression, by reversing the dependent variable; absolute deviations of mean $\log_{10}$ cortisol, with the independent variable marital status (yes/no). Both univariate and multivariate logistic regressions were performed to determine the association between marital status and absolute deviations of $\log_{10}$ cortisol. In the multivariate model, the first of two blocks entered into the model applied a Wald forward selection with potential covariates with a 0.05 cut-off value. The second block entered in absolute deviations of $\log_{10}$ cortisol. Although income, race and smoking status were thought to be potential confounders, these variables were not included in the forward selection because of missing data or lack of variation between the groups within these variables.

After analyzing the combined study sample, analyses were stratified by town cluster. All statistical analyses were performed using SPSS, Version 12.0.1 (SPSS Inc., Chicago, Illinois).

2. Results

There were 732 eligible women recruited who completed an interview: 52% were from NB and 48% were from WH. Of these 732 women, 300 also provided a urine sample for cortisol analysis: 44% from NB and 56% from WH. Those women agreeing to Phase II did not differ appreciably from those who declined on age, weight, age at menarche and menopause, or smoking. Percentages of Phase II participants and non-participants who were married were 56 and 48.

The women in our study from West Hartford ($N = 168$) and from New Britain ($N = 132$) were similar ($p > 0.10$) for age, prior day consumption of heart medications or depression medications, employment status, cortisol, % non-white, and marital status (data not shown). West Hartford had a significantly ($p < 0.001$) higher proportion of post-college educated participants, as well as a higher self-reported ($p < 0.001$) excellent health status than New Britain. Participants in West Hartford also had a significantly higher ($p < 0.05$) proportion of participants who reported in a food diary that they had consumed alcohol the day before and had significantly higher income. There was a trend ($p < 0.10$) toward significance for West Hartford participants to have lower BMI and fewer children.

Table 1 shows the clinical and demographic characteristics of the 300 study participants, grouped by married ($N = 168$) and unmarried ($N = 132$). (It is a coincidence that these numbers are identical to the numbers of women in West Hartford and New Britain.) The two groups were comparable ($p > 0.1$) for BMI, race, education, working status, prior day consumption of depression medications, heart medications, alcohol, and $\log_{10}$ cortisol levels; however, the variances in log cortisol are significantly different. Married women had more children, higher income, and better self-reported health status, and were significantly younger.

Fig. 1 shows the distributions of $\log_{10}$ transformed cortisol for married and unmarried women. Levene's test for equality of variances for these two distributions is significant ($p = 0.012$),

Table 1
Assessment of baseline characteristics by marital status

Variable	Unmarried ($N = 132$)	Married ($N = 168$)
Age, mean (S.D.) (years)**	69.1 (10.4)	65.5 (9.9)
BMI, mean (S.D.)	26 (5.6)	26 (4.5)
Number of children, mean (S.D.)*	2.2 (1.87)	2.7 (1.55)
Non-Hispanic White (%)	93.2	97.0
Education (%)		
High school or less	44.7	40.5
College (referent group)	37.9	34.5
Post-college	17.4	25.0
Income*** (%)		
<$30,000	64.2	23.7
$30–49,999	17.4	26.0
$50,000–74,999	12.8	18.3
$75,000 plus	5.5	32.1
Working (%)	24.2	26.2
Self reported health status (%)		
Excellent**	21.2	38.7
Good (referent group)	56.8	47.6
Fair/poor~	22.0	13.7
Cortisol (transformed, $\log_{10}$), mean (S.D.), ng/mg creatinine	1.20 (0.380)	1.20 (0.299)
Prior day consumption (%)		
Depression meds	13.6	11.3
Heart meds	49.2	47.0
Alcohol	19.7	25.6

~ $p < 0.10$.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

showing greater variance in $\log_{10}$ cortisol values in the unmarried women compared to the married women. This seems to be due to a higher percentage of unmarried women at both outer regions of the distribution of transformed cortisol measurements, and more married women with cortisol values in the middle region of the of distribution. The difference between these distributions is more pronounced when viewing the New Britain population separately and less evident for the West Hartford population (not shown).

The means of the cortisol deviations were comparable ($p > 0.1$) on race, education of high school or less versus college education, income levels, self-reported health status, prior day consumption of depression medications, heart medications, and alcohol consumption, hormone replacement therapy status, and smoking status (data not shown). There were significantly higher mean cortisol deviations in those who were unmarried compared to married ($p < 0.05$) and those not working compared to working ($p < 0.05$). Those who had post-college education had marginally ($p < 0.1$) lower cortisol deviations than those with lesser education. Similarly, those who exercised had marginally lower ($p < 0.1$) cortisol deviations than the group that did not exercise.

Table 2 shows the results of the logistic regression results for marital status and absolute deviations from mean log cortisol concentrations. Marital status is significantly associated with

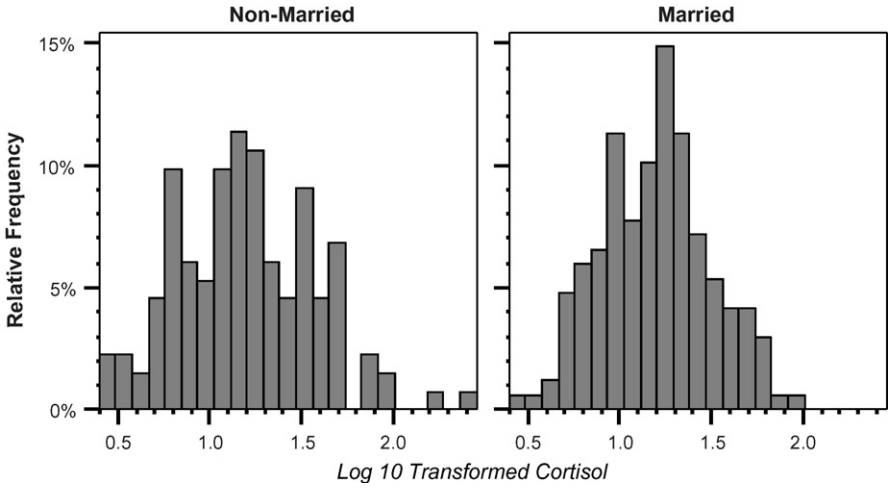

Fig. 1. Transformed cortisol by marital status.

Table 2
Logistic regression analysis of marital status as a function of absolute deviations of mean $\log_{10}$ transformed cortisol concentrations ($N = 300$)

Variables	β	Wald test	Odds	95% confidence interval for odds ratio	
		Z-ratio	Ratio	Lower	Upper
(2a) Main effect model					
Absolute deviations from mean $\log_{10}$ transformed cortisol*	−1.465	6.169	0.23	0.073	0.734
Constant	0.636	10.315			
(2b) Main effect model forward selection on demographic covariates					
Absolute deviations from mean $\log_{10}$ transformed cortisol**	−1.768	8.000	0.17	0.050	0.581
Age**	−0.035	8.036	0.97	0.942	0.989
Number of children**	0.208	7.584	1.23	1.062	1.428
Excellent health status**	0.801	7.544	2.23	1.258	3.947
Fair/poor health status	−0.284	0.712	0.75	0.390	1.456
Constant	2.380	7.536			
(2c) New Britain cluster main effect model					
Absolute deviations from mean $\log_{10}$ transformed cortisol*	−2.074	5.610	0.13	0.023	0.699
Constant	0.651	4.934			
(2d) New Britain cluster main effect model forward selection on demographic covariates					
Absolute deviations from mean $\log_{10}$ transformed cortisol**	−2.533	7.231	0.08	0.013	0.503
High school or less*	1.123	6.558	3.08	1.302	7.267
Post-college	−1.081	1.890	0.34	0.073	1.584
Excellent health status**	1.578	7.454	4.84	1.561	15.032
Fair/poor health status	0.106	0.054	1.11	0.455	2.716
Constant	−0.095	0.045			
(2e) West Hartford cluster main effect model					
Absolute deviations from mean $\log_{10}$ transformed cortisol	−0.887	1.157	0.41	0.082	2.073
Constant	0.598	4.830			
(2f) West Hartford cluster main effect model forward selection on demographic covariates					
Absolute deviations from mean $\log_{10}$ transformed cortisol	−0.278	0.084	0.77	0.116	4.968
Age**	−0.063	11.550	0.94	0.905	0.974
Number of children*	0.309	6.388	1.36	1.072	1.732
High school or less~	−0.683	2.736	0.51	0.225	1.134
Post-college	0.738	2.689	2.09	0.866	5.054
Constant	3.986	9.351			

~ $p < 0.1$.
* $p < 0.05$.
** $p < 0.01$.

cortisol level deviations ($p = 0.013$; variable 2a). After adjusting for significant confounders (age, $p = 0.005$; number of children, $p = 0.006$; health status, $p = 0.005$), the association increased between marital status and absolute deviations from mean cortisol ($p = 0.005$; variable 2b). A likelihood ratio test for the difference between the models is significant ($p < 0.001$), and indicates that adding the confounders yields a better fit to the data. In addition, the estimated coefficient for the absolute deviations from mean $\log_{10}$ transformed cortisol increases by 17% in the adjusted model.

Analyses stratified by town location show that unadjusted New Britain deviations from the mean $\log_{10}$ cortisol levels were significantly associated with marital status ($p = 0.018$; variable 2c). Adjusting for demographics within this sub-sample leads to an increased significant association between marital status and absolute deviations from mean cortisol ($p = .007$; variable 2d). The estimated coefficient for the absolute deviations from mean $\log_{10}$ transformed cortisol increases by 18% in the adjusted model.

The unadjusted West Hartford sub-sample did not have a significant association between marital status and absolute deviations from mean cortisol before ($p = 0.282$; variable 2e) or after ($p = 0.696$; variable 2f) adjusting for demographics.

3. Discussion

In a sample drawn from the general population of central Connecticut, we observed a significantly elevated dispersion in overnight urinary cortisol level in older unmarried compared to married women, as we predicted. There was no difference in mean cortisol between these two groups. The prediction of greater dispersion was based on the idea that acute stress elevates cortisol production, whereas chronic stress tends to suppress cortisol production as an adaptation to the damage that can accumulate from a constant state of arousal from stressors in life. Urinary cortisol is considered a good measure of integrated plasma free cortisol over the period of the urine collection (Levine et al., 2007).

According to one salient theory, elevation of cortisol can result from high ‘‘allostatic load’’, or a chronic wear and tear on the body resulting from stress and manifested as, for example, hypertension and chronic elevation of inflammatory cytokines (McEwen, 2005). In The MacArthur Study of Successful Aging, Seeman et al. (2001) used a measure of ‘‘allostatic load’’ and reported that elevated levels of this index among a cohort of men and women aged 70–79 was associated with subsequent increased mortality. Urinary cortisol was one of 10 parameters constituting this allostatic index. In the same cohort, Karlamangla et al. (2005) reported that elevated cortisol level by itself at baseline predicted future cognitive decline. In this investigation, an overnight urine sample was assayed for cortisol by liquid chromatography and reported after log transformation with creatinine adjustment, as was done in our study. Many other studies of cortisol variations have targeted populations based in clinical or institutional settings. Cushing’s syndrome results from chronic elevation of cortisol caused by adrenal (directly) or pituitary tumors (indirectly by elevation of ACTH); an effective screening test is cortisol concentration in 24-h urine samples (Nieman and Ilias, 2005; Lin et al., 1997). The resulting symptoms include anxiety, depression, uncontrolled diabetes, and obesity.

A response to chronic stress can be a hypocortisolism (Fries et al., 2005), which may be an adaptation to reduce allostatic load designed to alleviate the adverse consequences of a long-term state of elevated physiological arousal. Low cortisol production is also associated with a number of stress-related conditions including chronic fatigue syndrome, post-traumatic stress disorder, irritable bowel syndrome, and others (Fries et al., 2005; McEwen, 2007).

We suggest that the higher variability in urinary cortisol observed among unmarried women in our sample is due to a variable response to an increased level of acute and chronic stress for single women compared to married women. In sum, we propose, unmarried women experience more stress. For some this manifests as elevated cortisol, whereas for others the stress has become chronic and a hypocortisolism has resulted. On a group level, therefore, we observed similar mean cortisol levels but more unmarried women with more extreme than average levels, both higher and lower, than among married women. The adverse health consequences associated with high cortisol have been extensively studied and referred to above. The adverse consequences associated with low cortisol are less clear, but it is associated with stress-related disorders (Fries et al., 2005).

While our results were consistent with prediction, there are limitations of this study which require a cautious interpretation of these results. First is a possible selection bias in which women who are physically and mentally healthier are more likely to marry in the first place, and to remarry if a previous marital relationship is disrupted (Beckett and Elliot, 2002). It could be that women who marry tend to be more adaptive in how they manage stress and are more likely over time to stay married and are less likely to become divorced or widowed than those who have less psychological resiliency (Beckett and Elliot, 2002). Therefore, there could be an element of bias in the composition of the married population sample (Beckett and Elliot, 2002; Kisker and Goldman, 1987; House et al., 1988). If this is true, our interpretation of a marriage ‘buffer’ to stress becomes less likely.

Another limitation is that we compared currently married women to all unmarried women. This latter group includes widowed, divorced, and never married women, each of whom may tend to have different levels of acute and chronic stress. However, aggregating unmarried women in this way should have the effect of reducing the power of our study to detect any difference between the groups. In fact we found a significantly higher variability in unmarried women than married women in cortisol excretion, as predicted. The result of this limitation is that we are unable to disentangle which reasons for being single are most associated with more extreme cortisol levels, and by inference with higher acute or chronic stress.

Finally, we did not have information on feelings of social connectedness, quality of the marriage for the married women,

nor social capitol. This information should be collected in future studies in order to isolate, if possible, which marriages are most beneficial in terms of cortisol excretion, and which unmarried conditions are most strongly associated with extreme cortisol excretion profiles.

Some studies have found that marriage has a deleterious effect on women (Luecken et al., 1997; Light, 1997). However, many of these studies involved the 'role overload' experienced by working mothers, especially with young children at home. For example, Luecken et al. (1997) found that working mothers with at least one child at home excreted significantly more cortisol than working women without children. However, in our study, the ages of the women ranged from 50 to 91 years, so this is not an issue.

Future studies should focus on what aspects of an unmarried life contribute to extreme cortisol levels. There is some clue from our data that the unmarried women from New Britain, a low SES community, had a greater dispersion of cortisol than the unmarried women from West Hartford, a more affluent community. Chronic elevation of cortisol can lead to gradual bone lose and to abdominal obesity (McEwen, 2007), and so future studies of unmarried women with elevated cortisol should examine these endpoints.

If our results are confirmed in future studies, and if the observed greater variance in unmarried women is in fact due to stress, then the question arises what are the factors which tip the hyper-secretion of cortisol to a hypo-secretion, and how long must stress be endured by older unmarried women before it triggers the adaptive response? In addition, there are many different kinds of stress in life (McEwen, 2005); are there classes of stress (e.g., physical threat from living in a dangerous neighborhood) that sustain arousal chronically and others (e.g., precarious income) to which adaptation, and hypo-secretion of cortisol, occurs within a period of time?

Recent evidence indicates that there is considerable variability in the circadian cortisol rhythm, both within and across individuals (Miller et al., 2002). Also, a substantial minority of adults exhibit a flat diurnal rhythm, even in the absence of stress and/or medical problems involving the HPA axis (Miller et al., 2002; Smyth et al., 1997; Stone et al., 2001). In spite of these findings, we found that the absolute deviation of log cortisol from the mean was smaller for married versus unmarried women. Unmarried women were more likely to have extreme levels of urinary cortisol, particularly in New Britain, the lower socioeconomic community.

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