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# Increase in Urinary Cortisol Excretion and Memory Declines: MacArthur Studies of Successful Aging*

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**ABSTRACT**

Cortisol production is increased during stress, and the actions of cortisol on receptors in the brain and other body organs are involved in allostasis, the process of adaptation to stress, as well as in allostatic load, the wear and tear associated with excessive exposure to cortisol. Using data from a community-based longitudinal study of older men and women, aged 70–79 yr, we tested the hypothesis that exposure to increasing levels of cortisol is associated with declines in memory performance. Associations between 12-h urinary free cortisol excretion and performance on tests of memory (delayed verbal recall and spatial recognition), abstraction, and spatial ability were examined. Among the women, greater cortisol excretion was associated with poorer baseline memory performance, independent of socio-demographic, health status, health behavior, and psychosocial characteristics. Moreover, women who exhibited increases in cortisol excretion over a 2.5-yr follow-up period were more likely to show declines in memory performance. By contrast, women who experienced declines in cortisol exhibited improvements in memory performance. No significant associations were found among the men. The results for the women suggest that decrements in memory performance associated with increases in cortisol may not represent irreversible effects, as declines in cortisol were associated with improvements in memory. (*J Clin Endocrinol Metab* **82:** 2458–2465, 1997)

DECLINES in cognitive function with age have sometimes been viewed as an inevitable outcome of the aging process. There is, however, considerable heterogeneity in patterns of cognitive aging, with some individuals experiencing declines in memory and/or other cognitive abilities while others do not (1–3). This heterogeneity in patterns of cognitive aging remains incompletely understood, suggesting the need for examination of additional factors that may contribute to observed differentials in patterns of decline in cognition.

Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis with resultant increased exposure of the hippocampus to elevated glucocorticoid levels has been hypothesized to contribute to declines in memory through the detrimental effects of glucocorticoids on hippocampal neurons (4, 5) and the central role of the hippocampus in aspects of learning and memory in rodents and humans (6–8). Studies with animal models have shown that repeated and prolonged exposure to glucocorticoids causes neurons in the hippocampus to undergo atrophy and to have an increased risk of damage (4, 5, 11, 12). Shorter term exposures have been linked to more reversible patterns of dendritic atrophy of hippocampal neurons (5, 12). This atrophy and/or damage of hippocampal neurons has been related to increased incidence of cognitive deficits (13, 14; for review, see Ref. 5) and to a pattern of decreasing inhibitory feedback to the HPA axis with increased levels of circulating glucocorticoids (11, 15).

In human populations, higher cortisol levels have been associated with poorer memory in both patient and volunteer samples (16–18), including patients with Cushing's disease (19, 20), Alzheimer's disease (AD) (21, 22), and depression (23–25). Case-control studies also indicate higher cortisol in AD patients compared with controls (26–28). Importantly, recent longitudinal research in healthy, cognitively intact, volunteers has provided further evidence for the generalizability of the association between elevated cortisol and poorer memory performance; 24-h cortisol activity was measured annually for 4 yr in 19 healthy volunteers (aged 60–87 yr), and increases in cortisol activity were correlated with poorer memory performance in the fourth year of the study ($r = -0.60$; $P < 0.05$) (29).

Data from the MacArthur Field Study of Successful Aging provide an opportunity to extend these findings. The availability of longitudinal data for both 12-h urinary free cortisol excretion and various aspects of cognition in a sample of older individuals allow us to directly test the hypothesis that increases in cortisol activity are associated with declines in memory performance. In the Lupien *et al.* (29) study, cognitive performance was assessed at only one point in time (the last year of the study), so that it was not possible to evaluate whether those with increasing cortisol levels actually experienced declines in memory coincident with their

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increasing cortisol levels or had simply always had poorer memory performance. In contrast to previous studies using volunteers, the MacArthur Study sample also offers the advantage of a more community-based sampling design.

In the following analyses, we test several hypotheses derived from previous animal and human studies: 1) higher urinary cortisol excretion will be associated with poorer memory performance (cross-sectional association) and 2) patterns of increasing cortisol excretion will be associated with declines in memory (longitudinal association). Urinary free cortisol was employed as a probe of the hypothesized relationship between plasma cortisol levels and memory performance because previous research indicated a high correlation between mean plasma cortisol and 24-h urinary free cortisol (28, 30), and measures of urinary cortisol have been shown to exhibit similar relationships with memory performance as those reported for plasma cortisol (*i.e.* higher urinary cortisol in AD *vs.* normal controls, associated with poorer cognitive performance) (28).

## Subjects and Methods

The general goal of the MacArthur Field Study was to investigate factors associated with "successful aging" (31). As described in detail previously (32), subjects for the MacArthur study were originally subsampled on the basis of age and both physical and cognitive functioning from three community-based cohorts of the NIA's Established Populations for Epidemiologic Studies of the Elderly (EPESE) in Durham, NC; East Boston, MA; and New Haven, CT (33). Age was restricted to 70–79 yr at the time of enrollment to minimize the effects of age differences on subsequent analyses of factors associated with the maintenance of better health and functioning. Age-eligible men and women (n = 4030) were screened on the basis of four criteria of physical functioning and two criteria of cognitive functioning to identify those functioning in the top third of the age group. The selection criteria included 1) no reported disability on the seven-item Activities of Daily Living scale (34), 2) no more than one reported mild disability for eight items testing gross mobility and range of motion (35, 36), 3) ability to hold a semitandem balance for at least 10 s, 4) ability to stand from a seated position five times within 20 s, 5) scores of 6 or more correct on the nine-item Short Portable Mental Status Questionnaire (37), and 6) ability to remember three or more of six elements on a delayed recall of a short story (38).

Of the 4030 age-eligible men and women, a cohort of 1313 subjects met all screening criteria and were eligible for enrollment in the MacArthur study; 1189 (90.6%) agreed to participate and provided informed consent. Baseline data collection was completed between May 1988 and December 1989 and included a 90-min face to face interview covering detailed assessments of cognitive and physical performance, health status, and social and psychological characteristics as well as other lifestyle characteristics. Subjects were also asked to provide 12-h overnight urine samples.

The cohort was reinterviewed beginning in May 1991. A majority of the cohort was reinterviewed between 24–32 months after their baseline interview (mean, 28 months; SD, 4 months). Attrition from the baseline cohort was minimal: 59 (5%) partial or proxy interviews, 47 (4%) refusals at follow-up, and 71 (6%) deaths. At the time of the follow-up interviewing, 12-h urine samples were again collected. Due to funding constraints, assays for urinary cortisol were obtained for 200 of the 900 subjects who provided urine specimens (~20%); specimens were selected for assay based on specimen availability without knowledge of subjects' other characteristics.

### *Urinary free cortisol*

After their interviews, subjects were asked to complete an overnight urine collection from 2000 h that evening until 0800 h the next morning. The 12-h collection period was used to optimize compliance, as the more standard 24-h collection period frequently yields incomplete collections. Our own pilot data also indicated very strong correlations between 12- and 24-h collection schedules (*e.g.* rank-order correlation of 0.81 for cortisol). A primary goal in collecting the urine samples was to obtain integrated estimates of endocrine activity over a defined period of time. The use of an overnight collection protocol minimizes the potential effects of differences in levels of physical activity, providing an estimate of more intrinsic individual differences in basal, nonstimulated cortisol levels, as subjects generally spent this time at home and much of it sleeping. All samples were sent to Nichols Institute for assays of cortisol. Determinations were made by high pressure liquid chromatography (39, 40). Interassay variation was 1% in the low range ($<50$ $\mu$g/dL cortisol) and 8% in the higher range. Results are reported as micrograms of cortisol per g creatinine to adjust for body size as well as any effects of minor incompleteness of the urine collection.

Subjects whose urine specimens were deemed obviously incomplete were excluded from these analyses. At baseline, 768 of the 1016 subjects who provided urine specimens were deemed to have complete specimens (75%). At follow-up, 194 of the 200 for whom 1991 cortisol assays were performed were found to have complete urine specimens (97%). These 194 subjects, with complete urine specimens for both 1988 and 1991, are the focus of the current analyses. As discussed below, specific analyses were undertaken to evaluate potential bias in the analysis sample due to these exclusions. The results indicate few significant differences.

The change in cortisol excretion was calculated by subtracting each subject's 1988 urinary free cortisol excretion (micrograms per g creatinine) from their 1991 value; positive scores reflect increases in cortisol excretion while negative scores reflect decreases.

### *Cognitive performance*

Measures of cognition included in this study were designed to assess those aspects of higher cortical function that are required to perform complex cognitive activities, namely language, abstraction, spatial ability, and memory. Five tasks were included in the analyses: 1) incidental recall of pictures of common objects from the Boston Naming Test after a 10-min delay (range, 0–18) (41), 2) delayed recall of a story (range, 0–6 story elements recalled), 3) delayed spatial recognition (range, 0–17) (42), 4) abstraction (range, 0–16) (43), and 5) spatial ability (copying; range, 0–20) (44). Scores on each of the tasks reflect the number of correct responses. A measure of language, based on confrontation naming of 18 items from the Boston Naming Tests (41), was not included in these analyses due to reduced variance and a strong ceiling effect in this sample of older subjects. In light of previous research suggesting a specific association between cortisol and explicit memory performance (29), a summary measure of memory was created by summing scores across 3 memory tasks: incidental recall of pictures, delayed recall of the story, and delayed spatial recognition.

### *Covariates*

The possible confounding effects of socio-demographic, health status, health behavior, and psychosocial factors on the relationship between cortisol and memory performance were also considered. Socio-demographic characteristics included as covariates in these analyses included age, gender, ethnicity, income, and education. Ethnicity was coded Black *vs.* other, education as the highest grade completed, and annual household income was classified as less than $10,000 *vs.* $10,000 or more.

### *Health status*

The baseline prevalence of seven chronic conditions (myocardial infarction, stroke, cancer, diabetes, high blood pressure, and broken hip or other bones) was determined from self-reports of doctor-diagnosed conditions. Systolic and diastolic pressures were calculated as the average of the second and third of three seated blood pressure readings (45). Waist/hip ratio was calculated as a measure of relative fat distribution (46). Peak expiratory flow rate was measured using a mini-Wright meter (47).

### *Health behaviors*

Physical activity was assessed in terms of current leisure- and work-related activities (48, 49). Pack-years of cigarette smoking were calcu-

lated based on self-reported history of cigarette smoking. Monthly alcohol consumption was assessed in terms of frequency and quantity of beer, wine, and hard liquor consumption (50).

### *Psycho-social factors*

Summary measures of social network ties (*e.g.* marital status and ties with children, close friends, and relatives) and frequency of emotional and instrumental support from network ties were included (51) along with summary measures of self-efficacy beliefs (52), personal mastery beliefs (53), and depressive symptomatology (54).

### *Statistical analyses*

Measures of urinary free cortisol and cognitive performance were continuous and relatively normally distributed variables. Therefore, cross-sectional and longitudinal analyses used correlational and multiple linear regression techniques. Analyses of changes in cortisol and changes in cognitive performance were conducted using normalized change scores to adjust for individuals' initial baseline value. A normal score transformation (55) was used. For cortisol and each of the cognitive scores, individual differences in score between the first and second interviews were ranked within each level of initial score. These ranks were transformed to the normal score that an observation would have at the corresponding percentile in a normal distribution with a mean of 0 and a variance of 1. SAS version 6.04 was used for all analyses (56). All analyses were stratified by gender because previous analyses of the MacArthur data had revealed a number of significant gender differences in correlates and predictors of both physical and cognitive performance (57, 58) as well as between urinary free cortisol and social support (51).

As indicated, data on patterns of change in urinary free cortisol were available for a subset of the cohort (n = 194). Comparisons of this subgroup with those excluded from the longitudinal analyses due to missing data on 1988 and 1991 cortisol excretion and/or cognitive performance indicated that the subgroup for whom complete data were available did not differ in their 1988 cortisol excretion. Those included in the analyses did score higher on the incidental recall task and verbal and total memory, although the absolute differences were relatively small (see *Appendix 1*). There were no significant differences in any of the other cognitive tasks, nor were there differences with respect to age, gender, socio-economic status, health status, psychological symptomatology, or physical activity (data not shown).

## Results

Table 1 provides descriptive statistics for baseline values for cortisol excretion and cognitive performance. The mean cortisol excretion in 1988 was 19.6 $\mu$g/g creatinine for the men and 22.8 for the women, although in both cases the interquartile ranges indicate considerable variation with groups. The measures of cognitive performance reveal considerable variation among both men and women (see Table 1), as previously described (1, 32, 58).

### *Cross-sectional data on cortisol and cognition*

Cross-sectional correlations between initial (1988) urinary free cortisol and cognitive performance revealed a significant negative association among the women; those exhibiting greater cortisol excretion also exhibited poorer performance on the delayed recall of the story (r = −0.20; $P = 0.04$). There were no associations for the men. Multivariate regression analyses, adjusting for socio-demographic characteristics, health status, health behaviors, and psychosocial factors previously found to be associated with either cortisol levels and/or cognitive performance did not alter these findings.

### *Changes in urinary free cortisol excretion (1988–1991)*

The mean change in cortisol from 1988 to 1991 was −3.98 $\mu$g/g creatinine among the men and −1.12 $\mu$g/g creatinine among the women. However, the distribution of 2-yr change scores for cortisol excretion reveal patterns of both increase and decrease. Approximately 41% of the men and 34% of the women exhibited a decrease of 5 $\mu$g cortisol/g creatinine or more, whereas 20.4% of the men and 26% of the women exhibited increases of this magnitude ($\chi^2 = 1.19$ for gender difference; $P = 0.6$). Moreover, 19.8% of the women exhibited increases of 10 $\mu$g cortisol/g creatinine or more compared with 14.8% of the men ($\chi^2 = 5.22$; $P = 0.07$).

Changes in cortisol were examined first as predictors of cognitive performance at follow-up. Consistent with the study by Lupien *et al.* (29), no adjustments were made for baseline cognitive performance. Among the women, results parallel those reported by Lupien *et al.* (29), showing a significant negative association between increases in cortisol excretion and explicit verbal memory (*i.e.* delayed story recall) at follow-up (r = −.23; $P = 0.01$). A marginal, negative association with overall memory performance was also found (r = −0.16; $P = 0.10$). There were no significant associations among the men.

These associations with 1991 cognitive performance, however, do not tell us whether the increases in cortisol were associated with poorer 1991 performance due to actual declines in cognitive performance, as would be predicted from the animal literature. Bivariate analyses of actual changes in cognitive performance in relation to changes in cortisol excretion revealed a significant negative association between increasing cortisol and decline in delayed verbal recall (recall of the story), although, again, this effect was significant only

**TABLE 1.** Baseline data: descriptive statistics

| Variables: 1988 scores | Men | | | | Women | | | | Gender difference in means ($P$ value) |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | Median | Interquartile range | Full range | Mean | Median | Interquartile range | Range | |
| Cortisol ($\mu$g/g creatinine) | 19.6 | 9.3 | 12.7–25.7 | 0.7–68.6 | 22.8 | 13.3 | 17.6–27.8 | 6.9–70 | 0.13 |
| Delayed recall of story | 4.5 | 4 | 4–5 | 3–6 | 4.3 | 4 | 4–5 | 3–6 | 0.32 |
| Incidental recall of naming | 5.6 | 4 | 6–7 | 2–11 | 6.0 | 5 | 6–7 | 0–15 | 0.16 |
| Spatial recognition | 9.7 | 8 | 10–11 | 3–17 | 9.1 | 5 | 10–12 | 2–17 | 0.26 |
| Spatial ability (copying) | 15.3 | 13 | 16–18 | 8–19 | 15.2 | 13 | 15.5–18 | 1–20 | 0.72 |
| Abstraction | 7.0 | 2 | 7–12 | 0–16 | 6.7 | 2 | 6–12 | 0–16 | 0.67 |
| Verbal memory | 10.0 | 9 | 10–11 | 5–15 | 10.4 | 9 | 10–12 | 3–19 | 0.31 |
| Total memory | 19.7 | 17 | 19–23 | 10–30 | 19.5 | 15 | 20–23 | 7–31 | 0.76 |
| Total cognition | 54.5 | 48 | 56–63 | 29–72 | 53.9 | 47 | 54.5–61 | 30–75 | 0.70 |

among the women (r = −0.19; $P = 0.04$). Increases in cortisol excretion were also marginally (and negatively) related to declines in overall memory performance for the women (r = −0.17; $P = 0.07$). There were no significant associations among the men. Hierarchical regression analyses, controlling for the possible effects of socio-demographic, health status, health behavior, and psychosocial factors, did not alter these findings. For both delayed recall and total memory, adjustments for these other factors resulted in stronger associations between increases in cortisol excretion and declines in memory performance (see Table 2).

To further test the robustness of the associations between increases in cortisol and declines in delayed recall, we examined the distribution of change scores for men and women classified into one of three groups on the basis of their pattern of change in cortisol: cortisol excretion increased 10 μg/g creatinine or more, decreased 10 μg/g creatinine or more, or did not change (*i.e.* 1991 score within 10 μg/g creatinine of their 1988 score). Figure 1 presents these distributions, showing the mean values for each group (*dashed line*), the median (+), and the interquartile ranges (*box*). There are several noteworthy features to these data. First, for the women, the distributions of change scores for story recall are shifted toward relatively larger declines in story recall as one moves from left to right, *i.e.* from the group exhibiting declines in cortisol excretion to the group exhibiting increases of 10 μg/g creatinine or more. This is true with respect to the mean, median, and interquartile ranges; each of these descriptive statistics indicates more negative changes in story recall for those experiencing increases in cortisol. This same pattern is not clearly seen among the men.

A second noteworthy feature of these data is the suggestion that those exhibiting declines in cortisol excretion tend to show greater improvement in story recall. To test this apparent association, we classified subjects to indicate those whose story recall improved between 1988 and 1991 and those whose recall declined. As shown in Table 3, there was a significant and striking pattern of association between the pattern of change in cortisol and the pattern of change in story recall among the women; 70% of those who experienced an increase in cortisol exhibited a decline in story recall, whereas 76% of those who experienced a decline in cortisol exhibited an improvement in story recall. Again, no significant pattern of association was seen among the men.

## Discussion

### *Relationship between cortisol excretion and memory performance*

The findings reported above provide support for the hypothesis that increasing levels of HPA axis activity, as measured by urinary free cortisol excretion, are associated with declines in memory performance, although this was true only in females. Cross-sectionally, women with higher baseline cortisol levels exhibited poorer delayed recall at baseline. Longitudinally, a pattern of increasing cortisol excretion was associated with declines in memory performance among the women. This finding confirms and extends the findings reported by Lupien *et al.* (29), where increases in cortisol activity were associated with poorer memory performance at follow-up. Moreover, our finding that women who experienced declines in cortisol excretion were more likely to exhibit improvements in memory performance suggests potentially important plasticity in the relationship between cortisol and memory impairment. As discussed below, this finding is consistent with evidence for similar reversibility of memory impairments in patients with Cushing's disease and those receiving steroid therapy when cortisol levels are lowered (59, 60) as well as evidence of plasticity in hippocampal neuronal responses to glucocorticoid exposure (61–63).

The fact that observed associations were significant only among the women was unexpected. The hypothesized relationship between cortisol exposure and hippocampal function has, to date, been framed without consideration of gender-specific variations. One recent exception, however, is a study of age and gender effects on 24-h cortisol activity by van Cauter *et al.* (64) in which greater age-related changes among women were reported, including a higher evening nadir and a shorter quiescent period, resulting in an overall increase in 24-h cortisol excretion. Based on our own data, we offer several possible explanations for the observed gender difference. First, consistent with the report by van Cauter *et al.* (64), examination of changes in cortisol excretion indicate that more women than men showed increases in cortisol over time (19.8% *vs.* 14.8% with increases of 10 μg cortisol/g creatinine or greater; $P = 0.07$). These gender differences cannot be attributed to differences in body mass or differential change in the latter, as our measure of cortisol excretion is expressed as micrograms per g creatinine, a measure that

**TABLE 2.** Longitudinal regression analyses predicting changes in cognitive performance from changes in urinary free cortisol levels

| | b coefficient for change in cortisol | | | |
|---|---|---|---|---|
| | Change in delayed verbal recall (recall of story) | | Total memory | |
| | Men | Women | Men | Women |
| Model 1: cortisol only | −0.064 | −0.24[a] | −0.057 | −0.183[b] |
| Model 2: model 1 + demographics | −0.06 | −0.291[c] | −0.02 | −0.26[a] |
| Model 3: model 2 + health behaviors and psychosocial | −0.066 | −0.413[d] | 0.001 | −0.349[c] |

Change in cognitive performance modeled as normalized cognitive change score = normalized change in cortisol + covariates. Covariates: age, education, income, race, chronic conditions, systolic and diastolic blood pressures, peak flow rate, physical performance, waist/hip ratio, pack-years smoking, ethyl alcohol consumption, moderate and strenuous leisure activities, emotional and instrumental support, network demands/conflict, marital status, other social ties, self-efficacy, personal mastery, and depressive symptomatology.

[a] $0.01 < P < 0.05$.
[b] $0.05 < P < 0.10$.
[c] $0.001 < P < 0.01$.
[d] $P < 0.001$.

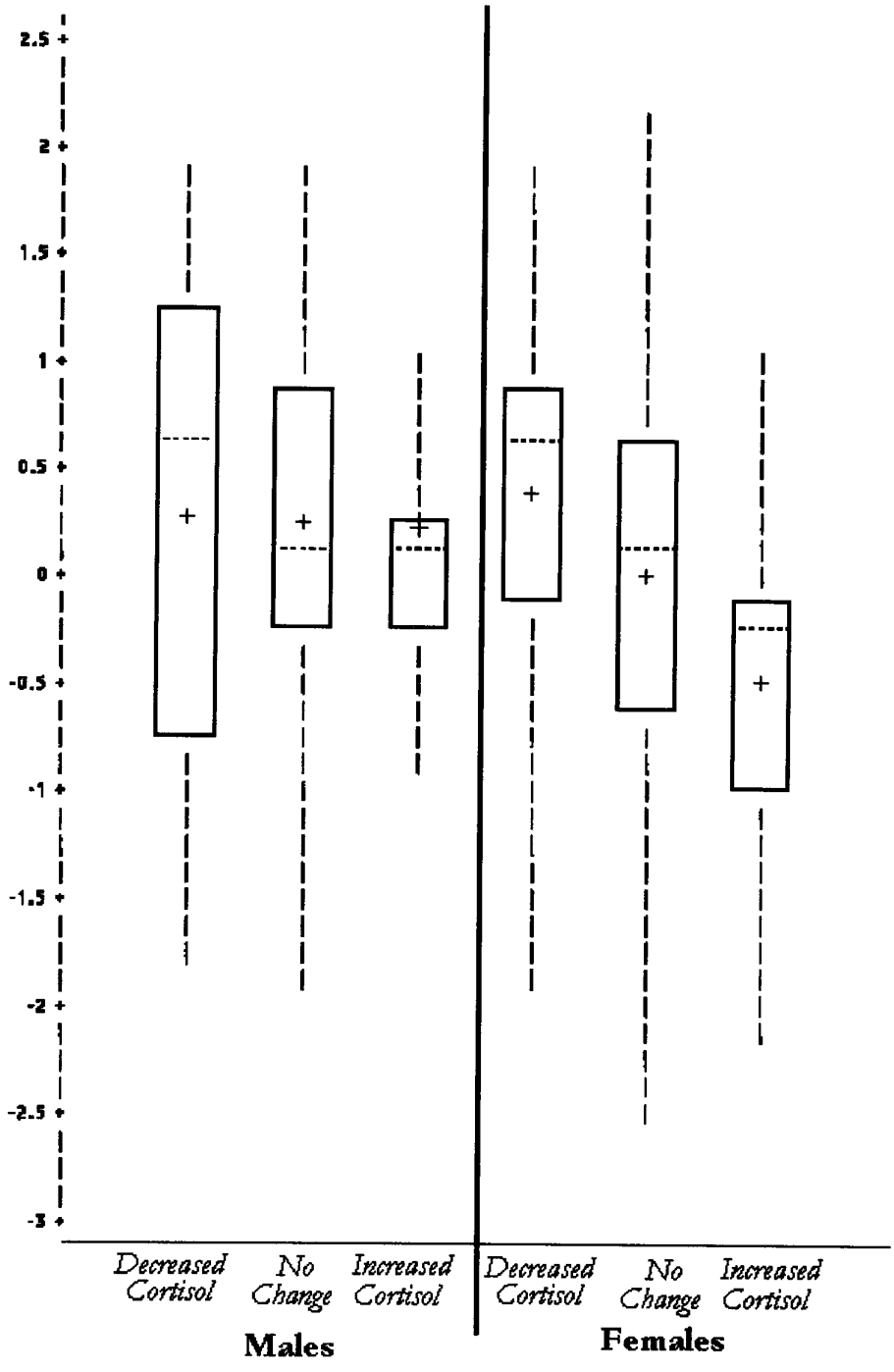


FIG. 1. Distributions of normalized change in story recall for men and women categorized by their degree of change in cortisol (1988–1991): 1) cortisol decreased 10+ μg/g creatinine, 2) cortisol did not change (*i.e.* change <10 μg/g creatinine), and 3) cortisol increased 10+ μg/g creatinine. Distributions show group-specific mean change (*dashed line*), median change (+), and interquartile range for change scores (*box*).

adjusts for gender differences in body mass and its possible effects on cortisol excretion. Our multivariate analyses also adjust directly for relative weight along with adjustments for other covariates.

A second possible contributor to the observed gender differences in associations between cortisol and memory is the fact that the men in our cohort along with their relatively smaller increases in cortisol, perhaps not coincidentally, also exhibited somewhat smaller declines in memory performance than those seen in the women. The pattern of gender differences, with smaller changes among the men, may have weakened our ability to detect associations between cortisol and memory performance among the men. Our 8-yr follow-up, which is currently underway, will offer the opportunity to reexamine these associations. With the longer follow-up, it is expected that there will be a considerably greater range in the patterns of change in cortisol excretion and memory performance in both women and men.

Several additional considerations are germane to the evaluation of our findings. First, use of an overnight urine sample, rather than a full 24-h sample, provides a more basal estimate of cortisol activity. It does not reflect individual

**TABLE 3.** Gender-specific associations between pattern of change in cortisol and pattern of change in delayed recall of story

| | Women | | Men | |
|---|---|---|---|---|
| | Recall improved | Recall declined | Recall improved | Recall declined |
| Cortisol decreased | 12 (70.6%) | 2 (29.4%) | 16 (61.5%) | 10 (38.5%) |
| No change in cortisol | 39 (57.4%) | 29 (42.6%) | 29 (59.2%) | 20 (40.8%) |
| Cortisol increased | 5 (23.8%) | 16 (76.2%) | 8 (61.5%) | 5 (38.5%) |
| | | $\chi^2 = 9.8$, df = 2, $P = 0.007$ | | $\chi^2 = 0.05$; df = 2, $P = 0.97$ |

df, degrees of freedom.

differences in daytime excretion, when greater variations in levels of physical activity as well as exposure to various stimuli may lead to increased variation in actual cortisol excretion. By not including the daytime hours, our overnight sampling of cortisol excretion will tend to minimize individual differences due to these other factors; this reduction in individual variation would be expected to reduce (not enhance) our ability to detect significant associations with memory performance. Thus, the observed associations are likely, if anything, to underestimate the association between cortisol and memory. A second consideration is the question of possible regression to the mean effects. There are several reasons to believe that they do not account for our findings. First, the vast majority of those exhibiting a change from baseline to follow-up did not initially have very high or low cortisol values as would be expected in cases of regression to the mean. Second, the findings regarding the longitudinal data (where regression to the mean effects would be possible) parallel the findings from the cross-sectional 1988 data, where such effects would not pertain. Third, and perhaps most telling, the presence of consistent gender differences in both the cross-sectional and longitudinal data make regression to the mean an unlikely candidate, as it would not be a gender-specific phenomenon. Of additional note is the specificity of the observed associations with memory performance, particularly explicit/verbal memory performance, showing the only consistently significant associations with cortisol excretion across the range of cognitive abilities assessed in this study. As noted above, this finding is consistent not only with previous research, but also with proposed models linking cortisol activity specifically to hippocampal function (with its central role in learning and memory). Thus, regression to the mean seems an unlikely explanation for our findings.

### *Possible mechanisms underlying changes in memory performance*

The observed patterns of association indicate that the strongest effects of cortisol excretion were on explicit/verbal memory (*i.e.* delayed recall of a story). This pattern of association is consistent with the report by Lupien *et al.* (29), and both sets of findings are consistent with the general hypothesis that increasing levels of cortisol may be associated with increased risk of neuronal atrophy and damage to the hippocampus. There are two types of glucocorticoid effects on the hippocampus that affect memory: rapid actions of the steroid during stress and gradual effects that cause atrophy to the structure of hippocampal neurons. Acute glucocorticoid effects on human explicit memory have been reported (65; see Ref. 5 for review); they are characterized by rapid and reversible impairments in memory. More prolonged effects include changes in hippocampal structure that have themselves been associated with impairment of explicit memory (5, 66). The extent to which more prolonged increases in cortisol actually result in irreversible hippocampal neuronal atrophy and/or damage, and permanent alterations in memory performance, in humans is not known.

Data from rodent studies suggest that damage to hippocampal neurons becomes progressively less reversible the more prolonged and extreme the elevation in glucocorticoids (61). Existing evidence from human studies does show a relationship between greater cortisol exposure and smaller hippocampal volume. Cross-sectional studies in normal volunteers, for example, have shown links between higher cortisol levels and smaller hippocampal volume and have linked smaller hippocampal volume to poorer delayed memory performance (67–70). More recently, Lupien *et al.* have extended their earlier findings relating increases in cortisol to poorer memory and have now shown that those who experienced increases in cortisol over 4 yr also have smaller hippocampal volumes (71). The apparent hippocampal atrophy and accompanying memory impairments evident in these studies, however, may not be irreversible and, in fact, may reflect a form of reversible plasticity of the brain (62). Gould *et al.* (63) have recently shown that in tree shrews (a species considered phylogenetically between insectivores and primates) not only does neurogenesis occur in adults, but it is impaired by social stress [where cortisol levels are elevated (72)] and is enhanced by blockage of N-methyl-D-aspartate (NMDA) receptors (63). The possibility of such plasticity in human populations is suggested by evidence indicating the reversibility of memory impairments in patients on steroid treatment (60) and those with Cushing's disease (59) after reductions in cortisol levels. These data suggest that the increasing levels of cortisol related to hippocampal atrophy and dysfunction may be a reversible phenomenon.

Our own data, indicating that declines in cortisol levels were associated with improvements in memory, are also consistent with longitudinal data from Lupien *et al.* (29), indicating that subjects whose average 24-h cortisol declined over a 4-yr period exhibited better results on explicit memory tasks at the end of this follow-up. These findings suggest that exposure to elevated cortisol levels may not be irreversibly linked to memory impairments. They do not, however, pro-

vide information on the duration of the higher cortisol exposures, leaving open the question of whether continued exposure to higher cortisol levels at some point results in irreversible damage, as has been shown in animal models (61). Insofar as the mechanisms are similar between animal models and humans, interventions using agents that inhibit excitatory amino acid release, reduce glucocorticoid actions, or enhance inhibitory input may be worth trying as a means of reversing or, more importantly, preventing hippocampal atrophy.

The data presented here provide support for the hypothesis that exposure to increasing cortisol is associated with declines in memory performance in older women. Although the present analyses examine only a subset of the full MacArthur cohort, the fact that these subjects come from a community-based cohort offers greater generalizability than previous studies using volunteer and clinical samples. The findings provide further evidence of the detrimental effects on memory performance of increases in cortisol levels as well as intriguing evidence for beneficial effects on memory performance of decreases in cortisol levels.

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## APPENDIX 1
**Comparing analysis group with excluded subjects**

| Variables | Subjects missing cortisol and/or cognitive data (n = 993) | Analysis sample with 88 + 91 cortisol and cognitive data (n = 194) | *P* value for difference between groups |
|---|---|---|---|
| Urinary cortisol ($\mu$g/g creatinine) | 21.7 | 21.5 | 0.84 |
| Cognitive performance | | | |
| Story Recall | 4.3 | 4.4 | 0.28 |
| Incidental Recall | 5.4 | 5.8 | 0.02 |
| | 9.2 | 9.4 | 0.44 |
| Verbal memory | 9.7 | 10.2 | 0.02 |
| Total memory | 18.9 | 19.6 | 0.05 |
| Abstraction | 6.6 | 6.9 | 0.38 |
| Spatial ability | 14.8 | 15.2 | 0.06 |