

High Urinary Catecholamine Excretion Predicts Mortality and Functional Decline in High-Functioning, Community-Dwelling Older Persons: MacArthur Studies of Successful Aging

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Purpose. Catecholamine release is a marker of stress, and high plasma norepinephrine levels have been associated with increased mortality. The predictive value of high urinary catecholamine excretion for functional decline and mortality in healthier older persons has not been determined.

Subjects and Methods. We used data from the MacArthur Studies of Successful Aging to determine the effects of high urinary catecholamine excretion on 3- and 7-year mortality and functional decline. In 1988, 765 high-functioning older subjects provided complete overnight urine samples for norepinephrine and epinephrine, and 199 of these provided repeat samples in 1991. Subjects who were in the top tertile of urinary norepinephrine or epinephrine excretion in 1988 were considered high excretors; those in the top tertile in both 1988 and 1991 were considered sustained high excretors. We used bivariate and multivariate analysis to examine the relations between high catecholamine excretion and mortality and Rosow-Breslau functional decline in 1991 and 1995.

Results. In multivariate analyses, subjects with high baseline urinary excretion of epinephrine, norepinephrine, or either catecholamine were at higher risk for mortality and functional decline at 3 and 7 years, although the magnitude of risk (adjusted odds-ratios ranged from 1.1 to 3.1) varied depending upon specific catecholamine and outcome measure. Subjects who had sustained high urinary norepinephrine excretion were also at increased risk for 4-year mortality or functional decline.

Conclusions. High urinary catecholamine excretion in high-functioning, community-dwelling older persons likely reflects subclinical sympathetic stimulation and is a marker of increased risk for functional decline and mortality.

ONE of the best-established physiological changes associated with normal aging is an increase in plasma norepinephrine levels (1-4). This change is the result of increased sympathetic nervous system secretion of norepinephrine (4-7) and age-related decreased clearance of norepinephrine (e.g., [3,8-9]). In contrast, both plasma levels and urinary excretion of epinephrine have been found to decrease slightly (10) (perhaps attributable to decreased physical activity or involution of the adrenal medulla) or remain unaffected with age (4). Within these overall trends, there is considerable intraindividual variability in serum and urinary catecholamine levels among healthy older persons.

Release of catecholamines in response to stress involves a complex interplay of the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis (11). Although an immediate, short-term catecholamine response to stress is considered physiologic, excessive or prolonged sympathetic activation may lead to pathologic outcomes such as the development of diabetes, aggravation of cardiovascular disease, and cognitive decline (11-14).

While plasma norepinephrine is primarily derived from the small portion of neurotransmitter that escapes reuptake

and metabolism at adrenergic synapses throughout the body (15), it reflects general levels of sympathetic activation. High plasma norepinephrine levels have been associated with reduced survival in healthy older persons (16) as well as in patients with congestive heart failure (17), previous myocardial infarction (9,18), and cirrhosis (19). Although the effects of high plasma epinephrine have been less well studied (9), high plasma epinephrine has been associated with poor survival rate in patients with previous myocardial infarction (9) but increased survival among healthy older persons (16). Plasma levels of catecholamines may be influenced by a variety of postural, diurnal, and acute stress-related factors (15), and concern about the validity and reliability of using plasma catecholamines as biomarkers has been raised (9,20).

In contrast, urinary epinephrine excretion provides an integrated assessment of adrenomedullary function over time. Thus, an increase in urine epinephrine is good evidence of adrenomedullary stimulation (15). Urinary norepinephrine excretion is more complicated and may reflect stimulation of renal sympathetic nerve endings as well as adrenomedullary stimulation and plasma levels of norepinephrine (15).

Despite the potential for urinary catecholamine excretion to be a valuable predictor of long-term sequelae of sympathetic stimulation, these potential relations have not been studied in depth. Therefore, we examined the relationship between baseline urinary catecholamine excretion in the MacArthur Studies of Successful Aging on 3- and 7-year mortality and functional decline. We also examined the effects of sustained (at baseline and 3 years) high catecholamine excretion on a subsample of subjects. Our research attempted to answer the following questions: (i) Does the level of baseline urinary catecholamine excretion predict 3- and 7-year mortality and functional decline?; (ii) If so, does the predictive ability of norepinephrine excretion differ from that of epinephrine excretion?; (iii) Do these effects persist after adjusting for smoking and other covariates?; and (iv) What is the predictive ability of sustained high urinary catecholamine excretion?

METHODS

To answer the study's research questions, we used longitudinal data from the MacArthur Studies of Successful Aging, a community-based, 7-year cohort study of high-functioning men and women aged 70–79 years at baseline in 1988. Baseline measures were obtained in 1988 and subjects were followed-up in 1991 and 1995.

The MacArthur Studies sample was derived from the National Institute on Aging's Established Populations for Epidemiologic Studies of the Elderly (EPESE), which recruited subjects from New Haven, CT; Durham, NC; and East Boston, MA in 1982. Subjects were eligible to participate in the MacArthur Study based on age (70–79 years) and high (top tertile) cognitive and physical functioning in 1988. At baseline, all subjects were functionally independent on the Katz (21) scale and had no more than one disability on the Nagi (22) or Rosow-Breslau (23) scales combined. Complete selection criteria have been published previously (24).

In 1988, 765 subjects provided complete overnight urine specimens. Urine assays were collected in 1991 from a subsample ($n = 300$) of the cohort. No difference was found between this subgroup and the group who was reinterviewed in 1991 but did not provide complete urine specimens at that time. In 1991, 3-year vital status outcomes were recorded for the entire sample ($N = 765$), and 719 (99%) of the surviving subjects had their 3-year Rosow-Breslau functional status recorded. In 1995, 7-year vital status data were available for all subjects ($N = 765$), and 562 (94.0%) of the 598 survivors had their 7-year functional status assessed.

Measures

Catecholamines.—Subjects completed an overnight urine collection from 8 PM on the evening after their home interview to 8 AM the next morning. The 12-hour collection period was used to enhance compliance, as the standard 24-hour collection period frequently yields incomplete collections. Pilot data from the MacArthur study indicated strong correlations between 12- and 24-hour collection schedules (rank-order correlations of .80 for norepinephrine and .95 for epinephrine), with the 24-hour schedule also showing higher refusal

rates and higher incidence of incomplete collection. The overnight collection protocol also minimizes the potential confounding effects of physical activity, because subjects generally spend this period of time at home (much of it in bed). Thus, overnight samples were used to minimize external factors that might influence catecholamine excretion and simulate a steady state as best as possible. A bottle within each cooler pack (to keep urine at optimal urine temperature) contained 12 ml of 6 N HCl to acidify and preserve the specimens. All samples were sent to Nichols Institute (San Juan Capistrano, CA) immediately after collection for norepinephrine and epinephrine assays. Determinations were made with high-pressure liquid chromatography (25). Interassay variation was 8% to 9% for catecholamines, regardless of age. To adjust for body size, results for norepinephrine and epinephrine are reported as micrograms (norepinephrine or epinephrine) per gram creatinine of urine excretion. Subjects were excluded from these analyses if they had abnormal creatinine clearance (<40 ml/min) or provided incomplete urine specimens at baseline. Completeness of urinary collection was determined using an algorithm (available on request from first author) based on volume (e.g., <300 ml was considered incomplete) and creatinine clearance coupled with volume if volume was >300 ml. The correlation coefficient between urinary norepinephrine and creatinine clearance was -0.04 ($p = .298$) and -0.28 between urinary epinephrine and creatinine clearance ($p < .001$).

Because there are no normative values for urinary norepinephrine and epinephrine levels, we defined high catecholamine levels as levels falling within the top tertile of norepinephrine or epinephrine of the entire sample. We first classified subjects based on their urinary norepinephrine and epinephrine excretion values in 1988 as a dichotomous variable (top tertile versus all others). These tertile cutoff points and the number of subjects in each group were: isolated high norepinephrine excretion in 1988 (>44.70 $\mu\text{g/g}$ creatinine, 224 subjects) and isolated high epinephrine excretion in 1988 (>4.26 $\mu\text{g/g}$ creatinine, 248 subjects). We then classified subjects based on their urinary norepinephrine excretion values in 1988 and 1991. Those who were in the top tertile of urinary excretion on both measures were considered to have sustained high catecholamine excretion. We similarly classified subjects based on their urinary epinephrine excretion values in 1988 and 1991. The thresholds for sustained high norepinephrine in both 1988 and 1991 were: >44.70 $\mu\text{g/g}$ creatinine in 1988, and >45.89 $\mu\text{g/g}$ creatinine in 1991. Forty subjects met this criterion. The thresholds for sustained high epinephrine in both 1988 and 1991 were: >4.26 $\mu\text{g/g}$ creatinine in 1988 and >5.72 $\mu\text{g/g}$ creatinine in 1991. Thirty-five subjects met this criterion.

We also created a variable, "high norepinephrine or epinephrine," to indicate nonspecific catecholamine stimulation (i.e., either hormone was in the top tertile of urinary excretion). We created a similar variable for sustained high values of either hormone, "sustained high norepinephrine or epinephrine." This variable included subjects who demonstrated any indicator of sympathetic stress.

Outcome Measures.—We examined 3- and 7-year mortality and 3- and 7-year functional decline as outcomes of

high urinary excretion in 1988. The 3- and 7-year time periods for outcomes provide a reasonable estimate of shorter- and longer-term consequences of high urinary catecholamine excretion. The shorter-term outcomes are least subject to the effects of competing morbidity and dilution of effect as a result of misclassification based on intercurrent changes during the follow-up period. The longer-term outcomes have the longest follow-up and, hence, the most power to detect outcomes. Examining both provides a more complete picture. For sustained high urinary excretion (1988 and 1991), we examined 4-year mortality and functional decline only. Mortality data were obtained in the MacArthur Study by following obituary listings (approximately 50% were identified through this route), follow-up contact with subjects, contact with proxies, and state death records.

To assess functional decline, we used the Rosow-Breslau scale, which evaluates the subject's ability to do heavy work around the house, walk up and down stairs, and walk half a mile (23). Change on the Rosow-Breslau scale was determined by subtracting the subject's score on this measure at both 3- and 7-year follow-up from the score at baseline in 1988. We classified change using two criteria: a 1-point decline and a 2-point decline in Rosow-Breslau function. We also created a composite outcome, "mortality or Rosow-Breslau functional decline," combining mortality and Rosow-Breslau functional decline at 3 and 7 years.

Analysis

We examined catecholamine excretion as both continuous and categorical (i.e., high excretion) variables. For all analyses assessing the categorical risk associated with 1988 norepinephrine, epinephrine, and either catecholamine excretion levels, subjects whose values were in the bottom tertile were considered to be the referent groups. A similar approach was followed for sustained increased norepinephrine and epinephrine excretion levels.

The analysis was conducted in three stages. We first determined crude odds ratios for catecholamine excretion as a continuous variable and for isolated and sustained high urinary norepinephrine and epinephrine excretion and mortality and functional decline outcomes. We then ran several correlations to examine whether previously reported rela-

tionships (26) between body mass index (BMI), age, and catecholamines were also present in our sample and should be considered in multivariate models. Finally, we ran two sets of multivariate logistic regression analyses, first adjusting for demographics only and then adjusting for both demographics and chronic health conditions. On the basis of existing literature (27–33), we identified demographic characteristics (age, gender, race, and educational level) and chronic health conditions (current smoking; overweight status [BMI >27]; and a history of myocardial infarction, stroke, cancer, or hypertension) that are predictive of higher mortality rates and functional decline. We examined these variables as possible confounders (i.e., those that were significantly associated with the outcomes of interest and changed the beta coefficient by more than 10%). This screening for confounders indicated no consistent pattern whereby any of these variables could be excluded as potential confounders. Thus, the final models adjusted for gender, age, race, educational level >12 years, smoking, overweight status, hypertension, past myocardial infarction, and diagnoses of cancer and stroke. In reporting the risks associated with high catecholamine excretions, we considered a level of $p < .05$ as statistically significant. We conducted analyses of subjects who were receiving drugs that might alter catecholamine excretion (approximately 10% of the sample) by including this term as a covariate, and the adjusted odds ratios remained essentially unchanged. All analyses were conducted using Stata 5.0 (Stata Corp., College Station, TX).

Table 1. Baseline Demographic and Chronic Illness Characteristics of Sample

Baseline Characteristic	Mean or Percentage (N = 765)
Sociodemographic	
Mean age (y)	74.2 ± 2.8
Gender (% male)	49.2%
Education (% ≤ high school)	53.1%
Race (% white)	81.7%
Chronic illnesses	
Smoking	14.0%
Overweight	39.2%
Prior myocardial infarction (% yes)	11.4%
Prior stroke (% yes)	2.5%
Cancer diagnosis	19.0%
Hypertension (% yes)	47.5%

Table 2. Relationships Between Baseline Characteristics and Urinary Catecholamine Excretion

Characteristic	Urinary Catecholamine Excretion [†] (M)	
	Norepinephrine	Epinephrine
Gender		
Female	42.69	4.48*
Male	39.92	3.52
Ethnicity		
White	41.87	4.05
Black	38.97	3.77
Education		
≤High school	42.31	4.13
>High school	40.23	3.86
Current smoker		
No	40.48*	3.93*
Yes	48.62	4.94
Overweight		
No	42.20	4.17*
Yes	39.68	3.70
Previous myocardial infarction		
No	40.81	4.04
Yes	45.69	3.71
Cancer diagnosis		
No	41.45	3.97
Yes	41.01	4.20
Hypertension		
No	40.69	4.07
Yes	42.06	3.93

* $p < .05$ between characteristic response categories.

[†]g/g creatinine.

RESULTS

Baseline demographic and chronic illness characteristics of the sample are presented in Table 1. The mean age of the sample was 74.2 (± 2.8) years, and 82% were white. Thirty-nine percent of the subjects were overweight (BMI >27), and 47.5% were hypertensive. None were dependent on Katz ADL functions, and 8.4% were dependent on 1 Rosow-Breslau task. At the 3-year follow-up, 5.5% had died and 15.7% had declined in Rosow-Breslau functional status. At the 7-year follow-up, 21.8% of the subjects had died and 41.3% had declined on the Rosow-Breslau functional status scale.

At baseline, age was not significantly correlated with norepinephrine or epinephrine ($r = .006$ and $.048$, respectively). Body mass index was also not significantly correlated with norepinephrine ($r = .021$) and was only modestly correlated with epinephrine ($r = .160, p < .0001$). Norepinephrine and epinephrine were modestly correlated with each other ($r = .193, p < .0001$). Relationships between baseline catecholamine excretion and other sociodemographic and health status variables are presented in Table 2. Urinary epinephrine excretion was significantly lower among women and among subjects with a BMI >27. Conversely, current smokers had higher levels of both urinary norepinephrine and epinephrine.

The crude odds ratios for selected demographic and chronic health factors, as well as urinary catecholamines, on mortality and functional decline at 3 and 7 years are shown in Table 3. Because of the strong effect of gender on some outcomes (e.g., male gender was associated with an odds ratio of 4.4 for 3-year mortality), the relative risks for urinary

catecholamines are reported adjusted for gender in Table 3. When considered as a continuous variable, urinary epinephrine excretion was significantly associated with 3-year mortality and 7-year functional decline. High catecholamine excretion was associated with increased risk of all outcome measures, except that high epinephrine excretion was not associated with increased 7-year mortality. The odds ratios ranged from 1.3 to 2.8, although many were not statistically significant.

Multiply adjusted (for sociodemographic and chronic disease variables) odds ratios (AOR) of high urinary catecholamine excretion predicting mortality and functional decline at 3 and 7 years are presented in Table 4. Subjects in the top tertile of 1988 urinary catecholamine excretion were at increased risk of all 3-year outcomes (AORs, 1.1–3.5), although not all reached statistical significance. The highest risks (AORs, 2.6–3.5) were for those who had high epinephrine excretion or high excretion of either catecholamine for 3-year mortality, for decline in 2 points on the Rosow-Breslau scale, and for composite measure of death or decline in 2 points on the Rosow-Breslau scale. For 7-year outcomes, the magnitude of the effect (AORs, 0.9–2.3) was less for all predictor and outcomes. The most powerful predictor of 7-year outcomes was high excretion of either catecholamine (AOR, 2.4 for mortality and 2.1 for mortality, or 2-point decline in function).

In adjusted models examining sustained high catecholamine excretion (Table 5), high excretion generally was associated with high odds of mortality (AORs, 3.2–4.2) and functional decline or mortality (AORs, 1.1–6.2), although these increased risks were not all statistically significant.

Table 3. Crude Relative Risks of Mortality and Functional Dependency at 3 and 7 Years as a Function of Selected Demographic and Health Characteristics and Baseline (1988) Catecholamine Excretion

Baseline Characteristics [†]	Mortality at 3 y (95% CI)	Rosow-Breslau 1-Point Decline at 3 y (95% CI)	Mortality at 7 y (95% CI)	Rosow-Breslau 1-Point Decline at 7 y (95% CI)
Sociodemographic				
Age (per 5 years)	1.0 (0.5, 1.8)	1.3 (0.9, 1.9)	1.2 (0.9, 1.6)	1.4 (1.2, 1.7)*
Male gender	4.4 (2.1, 9.4)*	0.6 (0.4, 0.9)*	2.2 (1.7, 3.0)*	0.8 (0.7, 1.0)
≥High school education	0.9 (0.5, 1.6)	1.0 (0.7, 1.4)	0.8 (0.6, 1.0)	0.7 (0.6, 0.9)
Race other than white	1.4 (0.7, 2.8)	0.7 (0.4, 1.1)	1.0 (0.8, 1.5)	1.0 (0.7, 1.3)
Chronic illnesses				
Smoking	2.8 (1.5, 5.3)*	1.5 (0.9, 2.3)	1.7 (1.3, 2.4)*	1.2 (0.9, 1.6)
Overweight	0.9 (0.5, 1.6)	1.3 (0.9, 1.8)	1.1 (0.8, 1.4)	1.1 (0.9, 1.4)
Prior myocardial infarction	2.2 (1.1, 4.4)*	1.6 (1.0, 2.5)*	1.9 (1.4, 2.6)*	1.2 (0.9, 1.6)
Prior stroke	1.1 (6.1, 6.5)	3.0 (1.7, 5.1)*	2.0 (1.1, 3.4)*	0.7 (0.3, 1.7)
Cancer diagnosis	1.3 (0.7, 2.6)	1.2 (0.9, 1.9)	1.4 (1.1, 1.9)*	1.0 (0.8, 1.3)
Hypertension	0.9 (0.5, 1.7)	1.2 (0.8, 1.6)	1.0 (0.8, 1.4)	1.2 (1.0, 1.5)*
Urinary catecholamines^{‡,§}				
Norepinephrine excretion (continuous)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
Epinephrine excretion (continuous)	1.2 (1.1, 1.3)*	1.0 (0.9, 1.1)	1.0 (1.0, 1.1)	1.1 (1.0, 1.2)*
High norepinephrine excretion	1.6 (0.7, 3.5)	1.5 (0.9, 2.7)*	1.8 (1.1, 2.8)*	1.5 (0.9, 2.3)
High epinephrine excretion	2.8 (1.3, 6.3)*	1.0 (0.7, 2.2)	1.2 (0.8, 1.9)	1.5 (1.0, 2.4)*
High norepinephrine or epinephrine excretion	2.6 (0.9, 7.2)	1.7 (0.8, 3.7)	2.4 (1.3, 4.4)*	1.5 (0.9, 2.7)

Note: 95% CI, 95% confidence interval.

* $p < .05$.

[†]All except age are characteristic present compared with characteristic absent.

[‡]Adjusted only for gender.

[§]Continuous, $\mu\text{g/g}$ of creatinine excretion in urine; high, top tertile; referent is bottom tertile of urinary excretion.

Table 4. Adjusted[†] Odds Ratios for 3- and 7-Year Outcomes by Baseline (1988) Catecholamine Excretion

Predictor Variable [‡]	Mortality AOR (95% CI)	Rosow-Breslau Decline AOR (95% CI)		Mortality or Rosow-Breslau Decline AOR (95% CI)	
		1 Point	2 Points	1 Point	2 Points
3-Year outcomes					
Norepinephrine excretion (continuous)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
Epinephrine excretion (continuous)	1.2 (1.1, 1.4)*	1.0 (0.9, 1.1)	1.1 (1.0, 1.3)	1.1 (1.0, 1.2)*	1.2 (1.1, 1.3)*
High norepinephrine excretion	1.6 (0.7, 3.6)	1.5 (0.8, 2.7)	1.1 (0.4, 2.9)	1.5 (0.9, 2.6)	1.4 (0.7, 2.6)
High epinephrine excretion	3.1 (1.3, 7.5)*	1.2 (0.6, 2.2)	2.6 (0.9, 7.5)	1.7 (1.0, 2.9)	3.0 (1.5, 6.0)*
High norepinephrine or epinephrine excretion	2.6 (0.9, 7.5)	1.8 (0.8, 4.4)	3.5 (0.8, 16.5)	2.1 (1.1, 4.3)*	2.9 (1.2, 7.2)*
7-Year outcomes[‡]					
Norepinephrine excretion (continuous)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
Epinephrine excretion (continuous)	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)
Baseline high norepinephrine excretion	1.6 (0.9, 2.7)	1.2 (0.7, 2.0)	1.4 (0.7, 2.6)	1.3 (0.9, 2.1)	1.5 (1.0, 2.4)
Baseline high epinephrine excretion	1.3 (0.7, 2.1)	1.6 (1.0, 2.6)	1.3 (0.7, 2.3)	1.5 (1.0, 2.1)	1.3 (0.8, 2.1)
Baseline high norepinephrine or epinephrine excretion	2.4 (1.3, 4.4)*	1.2 (0.7, 2.3)	1.4 (0.7, 3.0)	1.7 (1.0, 2.9)*	2.1 (1.2, 3.7)*

Notes: AOR, adjusted odds ratio; 95% CI, 95% confidence interval.

* $p < .05$.

[†]Adjusted for age, gender, race, education, smoking, overweight status, hypertension, past myocardial infarction, stroke, cancer diagnosis.

[‡]Continuous, $\mu\text{g/g}$ of creatinine excretion in urine; high, top tertile; referent is bottom tertile of urinary excretion.

DISCUSSION

The results of this study indicate that high urinary catecholamine excretion is predictive of mortality and functional decline among high-functioning older persons. The magnitude of such risk varied by which catecholamine was excreted and by outcome measure.

The predictive value of high urinary catecholamine excretion for 3-year mortality is consistent with previous literature linking plasma norepinephrine to increased risk of mortality in both ill patients (18,19,34–36) and community-dwelling older persons (15). Our findings in this carefully screened, high-functioning group support the hypothesis that high catecholamine excretion may represent stimulation of the sympathetic nervous system by stresses that are not obviously clinically apparent. Coupled with the diminished norepinephrine reuptake that accompanies aging (8), these disturbances may lead to chronically elevated norepinephrine levels and subsequent adverse events. This hypothesis is also supported by the results of the Studies of Left Ventricular Dysfunction study in which increased plasma norepinephrine levels in asymptomatic persons with cardiac ejection fractions $< 35\%$ were predictive of cardiovascular and all-cause mortality as well as the development of clinical events related to ischemia and congestive heart failure (36). One possible mechanism by

which high norepinephrine activation may increase the risk of mortality is by downregulation of beta-adrenergic receptors and increased free radical production (37).

Our findings did not substantiate a previous report that plasma epinephrine levels are positively related to 7-year survival among community-dwelling older persons (16). Possible explanations for this discrepancy include the use of plasma versus urinary levels and different adjustment for comorbid conditions.

We were able to examine the effect of sustained stimulation of the sympathetic nervous system in a subsample. We found that high-sustained urinary norepinephrine excretion was highly predictive of 7-year mortality or Rosow-Breslau impairment. This finding that sustained high urinary catecholamine excretion can predict functional decline in healthier older persons extends previous research findings in animals that showed that functional decline is related to the failure to efficiently turn off sympathetic and HPA axis activity after stress (11). It also is consistent with research that has found that excessive stimulation of the sympathetic response and HPA axis may lead to impaired functional performance in humans (15).

One of the main strengths of our study is that all subjects were relatively healthy and high functioning at baseline. The

Table 5. Adjusted[†] Odds Ratios for 4-Year Outcomes by Whether Sustained Urinary Catecholamine Excretion Is Present or Absent

Predictor Variable [‡]	Mortality AOR (95% CI)	Rosow-Breslau Decline AOR (95% CI)		Mortality or Rosow-Breslau Decline AOR (95% CI)	
		1 Point	2 Points	1 Point	2 Points
Sustained high norepinephrine excretion	3.2 (0.2, 48.9)	4.8 (0.9, 24.5)	3.8 (0.6, 23.6)	6.2 (1.3, 30.7)*	5.0 (0.9, 28.7)
Sustained high epinephrine excretion	4.2 (0.3, 61.8)	0.8 (0.2, 4.1)	1.5 (0.3, 8.6)	1.1 (0.2, 5.1)	1.9 (0.4, 9.2)
Sustained high norepinephrine or epinephrine excretion	4.1 (0.5, 30.2)	1.1 (0.3, 3.7)	1.8 (0.5, 6.9)	1.7 (0.5, 5.4)	2.7 (0.8, 9.1)

Notes: AOR, adjusted odds ratio; RB, Rosow-Breslau; 95% CI, 95% confidence interval.

* $p < .05$.

[†]Adjusted for age, gender, race, education, smoking, overweight status, hypertension, past myocardial infarction, stroke, and cancer diagnosis.

[‡]High, top tertile; bottom tertile of urinary excretion at baseline and in 1991.

subjects were not frail people who had high catecholamine excretion as a result of acute or chronic illness. Therefore, the high urinary catecholamine excretion in our sample was likely due to more subtle, less clinically obvious impairments. The sample was also community-based from three different communities, thereby representing a degree of geographic diversity. This contributes to the generalizability of the study as our subjects represented a diverse older US population sample. A third strength was the analytic design, which adjusted for comorbidity as well as factors (e.g., smoking) that might increase plasma norepinephrine (38,39).

Our findings, however, must be interpreted in the context of the study's limitations. Perhaps the most important of these was the sample size and the relative infrequency of some outcome measures, which limited the study's power to detect statistically significant effects. Indeed, many of the odds ratio estimates were quite large but did not achieve statistical significance. We were also limited to collection of only one specimen at baseline and do not have information about possible acute illnesses that subjects may have experienced prior to submitting the specimens. Another limitation was that our ability to assess sustained catecholamine stimulation was limited not only to two time points, 1988 and 1991, but to a smaller subsample as well. These analyses of sustained high excretion of catecholamines must, therefore, be regarded as exploratory. Finally, we were not able to determine whether urinary catecholamine excretion is part of the causal pathway toward these adverse outcomes or is merely an epiphenomenon.

In summary, we have found high urinary catecholamines to be predictors of short-term mortality and longer-term functional decline in high-functioning, community-dwelling older persons. Screening to identify patients with high urinary catecholamine excretion is unlikely to be a cost-effective strategy, but further research on these biomarkers may help elucidate possible mechanisms of functional decline and pathways to mortality in older persons. Triggers of stimulation of norepinephrine and epinephrine release among older persons who are not acutely ill need to be better identified. Previous research has distinguished between psychosocial stress increasing plasma norepinephrine levels and physiological stress increasing plasma epinephrine levels (18). In contrast, some of our findings suggest that the sequelae of increased catecholamine excretion may be similar regardless of which hormone is excessively excreted. Further research needs to focus on whether there are different outcomes of chronic adrenomedullary stimulation (as evidenced by high urinary epinephrine excretion) versus chronic local sympathetic stimulation with some adrenomedullary stimulation (as evidenced by high norepinephrine excretion). The answers to these questions may lead to the development of new interventions or the increased use of existing medications (e.g., beta blockers) that may prevent or delay the adverse outcomes of excess catecholamine production.

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REFERENCES

- Wallin BG, Sundlof G, Eriksson B, Dominiak P, Grobecker H, Lindblad LE. Plasma noradrenaline correlates to sympathetic muscle nerve activity in normotensive man. *Acta Physiol Scand*. 1981;111:69-73.
- Ziegler MG, Lake CR, Kopin IJ. Plasma noradrenaline increases with age. *Nature*. 1976;261:333-334.
- Christensen NJ. Sympathetic nervous activity and age. *Eur J Clin Invest*. 1982;12:91-92.
- Christensen NJ. Is plasma noradrenaline an index of biologic age. *Alfred Benzon Symposium*. 1986;23:266-272.
- Lakatta EG, Yin FCP. Myocardial aging: functional alterations and related cellular mechanisms. *Am J Physiol*. 1982;242:927-941.
- Sachs C, Hamberger B, Kaijser L. Cardiovascular responses and plasma catecholamines in old age. *Clin Physiol*. 1985;5:553-565.
- Hillsted J, Christensen NJ, Larsen S. Plasma clearance of noradrenaline does not change with age in normal subjects. *Clin Physiol*. 1985;5:443-446.
- Esler MD, Turner AG, Kaye DM, et al. Aging effects on human sympathetic neuronal function. *Am J Physiol*. 1995;268:R278-R285.
- Goldstein DS. Plasma catecholamines in clinical studies of cardiovascular diseases. *Acta Physiol Scand*. 1984;527(suppl):39-41.
- Kjeldsen SE, Eide I, Christensen C, Westheim A, Muller O. Renal contribution to plasma catecholamines effect of age. *Scand J Clin Lab Invest*. 1982;42:461-466.
- McEwen BS. Protective and damaging effect on mediators. *New Eng J Med*. 1998;338:171-179.
- Christensen NJ, Jensen EW. Effect of psychosocial stress and age on plasma norepinephrine levels: a review. *Psychosom Med*. 1994;56:77-83.
- McEwen BS, Stellar E: Stress and the individual. *Arch Intern Med*. 1993;153:2093-2101.
- Seeman TE, Singer BH, Rowe JW, Horwitz RI, McEwen BS: Price of adaptation-allostatic load and its health consequences. *Arch Intern Med*. 1997;157:2259-2268.
- Young JB, Landsberg L. Catecholamines and the adrenal medulla. In: Wilson JD, Foster DW, Kroenberg HM, Larsen PR, eds. *Williams Textbook of Endocrinology*. 9th ed. Philadelphia, PA: W.B. Saunders; 1998:665-728.
- Christensen NJ, Schultz-Larsen K. Resting venous plasma adrenalin in 70-year men correlated positively to survival in a population study. *J Int Med*. 1994;235:229-232.
- Semeraro C, Marchini F, Ferlenga P, et al. The role of dopaminergic agonists in congestive heart failure. *Clin and Exper Hypertension*. 1997;19(1&2):201-215.
- Boldt J, Menges T, Kuhn D, Diridis C, Hempelmann GL. Alterations in circulating vasoactive substances in the critically ill: a comparison between survivors and non-survivors. *Intensive Care Med*. 1995;21:218-225.
- Tage-Jensen U, Henriksen JH, Christensen E, Widding A, Ring-Larsen H, Christensen NJ. Plasma catecholamine level and portal venous pressure as guides to prognosis in patients with cirrhosis. *J Hepatology*. 1988;6:350-358.
- Christensen NJ, Jensen EW. Sympathoadrenal activity and psychosocial stress. *Annals New York Acad of Sciences*. 1995;640-646.
- Katz S, Downs TD, Cash HR, et al. Progress in the development of an index of ADL. *The Gerontologist*. 1970;10:2-30.
- Nagi, SZ. An epidemiology of disability among adults in the United States. *Milbank Q*. 1976;54:439-468.
- Rosow I, Breslau N. A Guttman health scale for the aged. *J Gerontol*. 1966;21:556-559.
- Berkman LF, Seeman TE, Albert M, et al. High, usual and impaired functioning in community-dwelling older men and women: findings from the MacArthur Foundation research network on successful aging. *J Clin Epidemiol*. 1993;46:1129-1140.
- Krsulovic AM. Investigations of catecholamine metabolism using high performance liquid chromatography: analytical methodology and clinical applicators. *J Chromatogr*. 1983;9:1-34.
- Ward KD, Sparrow D, Landsberg L, Young JB, Vokonas PS, Weiss ST. Influence of insulin, sympathetic nervous system activity, and obesity on blood pressure: the Normative Aging Study. *J Hypertension*. 1996;14:301-307.

27. Mor V, Murphy J, Masterson-Allen S, et al. Risk of functional decline among well elders. *J Clin Epidemiol*. 1989;42:895–904.
28. Lammi UK, Kivela SL, Nissinen A, et al. Predictors of disability in elderly Finnish men in a longitudinal study. *J Clin Epidemiol*. 1989;42:1215–1225.
29. Pinsky JL, Leaverton PE, Stokes J. Predictors of good function: the Framingham study. *J Chron Dis*. 1987;40:159S–167S.
30. Boulton C, Murphy J, Sloane P, et al. The relationship of dizziness to functional decline. *J Am Geriatr Soc*. 1991;39:858–861.
31. Guralnik JM, Kaplan GA. Predictors of healthy aging: prospective evidence from the Alameda County study. *Am J Public Health*. 1989;79:703–708.
32. Feldman JJ, Makuc DM, Kleinman JC, Cornoni-Huntley J. National trends in educational differentials in mortality. *Am J Epidemiol*. 1989;129:919–923.
33. Gronick ME, Eggers PW, Reilly TW, et al. Effect of race and income on mortality and the use of services among medicare beneficiaries. *N Eng J Med*. 1996;335:791–799.
34. Rector TS, Olivari MT, Levine B, Francis GS, Cohn JN. Predicting survival for an individual with congestive heart failure using the plasma norepinephrine concentration. *Am Heart J*. 1989;114:148–152.
35. Rouleau J, Packer M, Moye L, et al. Prognostic value of neurohumoral activation in patients with an acute myocardial infarction: effect of Captopril. *J Am Coll Cardiol*. 1994;24:583–591.
36. Benedict CR, Shelton B, Johnstone DE, et al. Prognostic significance of plasma norepinephrine in patients with asymptomatic left ventricular dysfunction. *SOLVD Investigators Circulation*. 1996;94:690–697.
37. Laycock SK, McMurray J, Kane KA, Parratt JR. Effects of chronic norepinephrine administration on cardiac function in rats. *J Cardiovascular Pharm*. 1995;26:584–589.
38. Jensen EW, Esperson K, Kanstrup IL, Christensen NJ. Plasma noradrenaline and aging: effects of smoking habits. *Eur J Clin Invest*. 1996;26:839–846.
39. Jensen EW, Eldrup E, Kelbaek H, Nielsen SL, Christensen NJ. Venous plasma noradrenaline increases with age: correlation to total blood volume and long-term smoking habits. *Clin Physiol*. 1993;13:99–109.

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