Original Contribution

Urinary 8-Hydroxy-2-deoxyguanosine and Cognitive Function in Puerto Rican Adults

Xiang Gao*, Chao-Qiang Lai, Tammy Scott, Jian Shen, Tianxi Cai, Jose M. Ordovas, and Katherine L. Tucker

* Correspondence to Dr. Xiang Gao, Department of Nutrition, Harvard School of Public Health, 655 Huntington Avenue, Boston, MA 02115 (e-mail: xiang.gao@channing.harvard.edu).

DNA oxidative stress has been suggested as an important pathogenic mechanism in cognitive impairment and dementia. With baseline data collected from 2004 to 2008, the authors examined whether urinary 8-hydroxy-2-deoxyguanosine (8-OHdG), a biomarker of global DNA oxidation, was associated with cognitive function in a sample of 1,003 Puerto Rican adults, aged 45–75 years, living in Boston, Massachusetts, and the surrounding area. Cognitive function was measured by using a battery of 7 tests: the Mini-Mental State Examination, word list learning, digit span, clock drawing and figure copying, Stroop, and verbal fluency tests. The primary outcome was a global cognitive score, averaging standardized scores across all cognitive tests. A higher 8-OHdG concentration was significantly associated with lower global cognitive scores, after adjustment for age, education, status of the gene for apolipoprotein E (*APOE*), and other covariates ($P_{trend} = 0.01$). The difference in the global score, comparing participants in the 2 extreme 8-OHdG quartiles, was −0.11 (95% confidence interval: −0.20, −0.02), which was equivalent to accelerating cognitive aging by about 4 years, as observed in this population. Prospective studies are needed to elucidate whether elevated urinary 8-OHdG concentrations can predict the rate of cognitive decline and incident dementia.

biological markers; DNA damage; Hispanic Americans; neurobehavioral manifestations; oxidative stress

Abbreviations: CES-D, Center for Epidemiologic Studies Depression; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; 8-OHdG, 8-hydroxy-2-deoxyguanosine.

Puerto Ricans are the largest Hispanic group in Massachusetts, comprising more than 3.1% of the state's population. We have previously shown that Puerto Rican older adults living on the US mainland suffer from excess prevalence of several major chronic conditions, including poor cognitive function, obesity, type 2 diabetes, and depression, relative to the general US population (1–4). At the same time, they are one of the poorest of the large ethnic populations in the country. As this group is both a rapidly growing and aging subset of the US population, the burden of cognitive impairment is likely to increase disproportionately among them. Thus, identification of risk factors for lower cognitive function in this population has significant public health implications. In support of this hypothesis, a recent report from the Multiethnic Study of Atherosclerosis noted that Hispanic participants

(mean age, 61 years) had higher cumulative oxidative stress, as assessed by telomere length, relative to non-Hispanic whites (mean age, 63 years), after adjustment for age, smoking, and other potential confounders (5).

Oxidative stress has been implicated as a central pathogenic mechanism in cognitive impairment because the brain is especially vulnerable to it. This is thought to be due to its high oxygen consumption, abundance of polyunsaturated fatty acid, and lack of antioxidant enzymes, relative to other tissues (6, 7). Substantial evidence from animal and in vitro studies suggests that accumulation of reactive oxygen species can trigger many of the biologic events, such as amyloid β deposition and DNA damage, that occur in the pathogenesis of cognitive impairment or dementia (8). As these biochemical and pathologic changes may begin years or decades

before the onset of disease symptoms, measuring relevant biomarkers may help in the identification of high-risk populations. More importantly, subsequent interventions with the aim of improving oxidative balance in the nervous system may help to protect against the development of dementia.

8-Hydroxy-2-deoxyguanosine (8-OHdG) is an important biomarker of DNA oxidation and has been commonly used to indicate the extent of generalized oxidative stress (8, 9). Previous clinical studies have shown that individuals with Alzheimer's dementia or mild cognitive impairment (MCI) had increased concentrations of 8-OHdG in the brain, cerebrospinal fluid, and peripheral lymphocytes, compared with controls (10–13). However, it remains unclear whether higher urinary 8-OHdG is associated with lower cognitive function in community-based populations. We, therefore, conducted a cross-sectional study to test this hypothesis in a sample of Puerto Rican adults living in Boston.

MATERIALS AND METHODS

Subjects

Subjects included Puerto Rican adults, aged 45–75 years, living in the Boston metropolitan and surrounding area in Massachusetts. This age range was selected on the basis of results from the earlier study of Hispanic elders, where there was substantial prevalence of diabetes, disability, depression, and cognitive impairment among those aged 60 years or above, with ages of onset averaging up to a decade earlier than for non-Hispanic whites (1). The baseline data were collected from 2004 to 2008. Detailed sampling and data collection methods have been described elsewhere (14, 15). In brief, we used 2000 Census data to identify census tracts with at least 25 Puerto Rican adults in the defined age range and, within these tracts, randomly selected census blocks with 10 or more Hispanic adults. Households with at least 1 Puerto Rican adult between the ages of 45 and 75 years were identified, and 1 person per household was selected randomly for participation. Most (80.4%) participants were identified in this way, with additional participants identified at major Puerto Rican events (8.9%), such as the Boston Puerto Rican Festival, and the remainder in response to media (4.6%) or personal referral (6.1%). Those who, because of serious health conditions and/or advanced dementia, were unable to answer questions were excluded. We also excluded 10 participants with a Mini-Mental State Examination (MMSE) score of less than or equal to 10 because cognitive function was too impaired to be able to complete the cognitive tests or questionnaires.

In total, 1,387 (81.8% of those eligible) participants completed the baseline interview. Interviews were conducted in the home by bilingual interviewers in either Spanish or English, as preferred by the participant. Because urinary 8-OHdG was assessed in 2006, when the baseline data collection was ongoing, only 1,003 participants had urinary 8-OHdG analyzed. These participants were slightly older (58.0 vs. 56.7 years; $P = 0.008$) but had a similar MMSE score (23.3 vs. 23.2; $P = 0.24$) and proportion of women (74.1% vs. 74.0%; $P = 0.95$) relative to those who did not have 8-OHdG data.

Standard protocol approvals, registrations, and patient consents

The Institutional Review Board of Tufts University/New England Medical Center approved the protocol. Participants gave written, informed consent before participating.

Assessment of urinary 8-OHdG DNA damage

Urinary samples were collected following the in-home interview. At the conclusion of the interview, participants were provided with urine collection containers, and the 12-hour urine collection procedure was explained, along with instructions to fast for the next day's blood draw. On the following morning, a certified phlebotomist visited the participant's home to retrieve the urine samples and to draw blood. All samples were carried back to the Human Nutrition Research Center on Aging at Tufts on the day of collection in coolers filled with dry ice.

Urinary 8-OHdG was assessed with a monoclonal antibody enzyme-linked immunosorbent assay kit from Assays Designs (Ann Arbor, Michigan). Briefly, 10 µL of urine were diluted 20-fold before analysis. Diluted urine samples were measured in duplicate with a standard provided by the vendor in a 96-well microplate format. The inter- and intraassay coefficients of variation were less than 10%. In our previous studies, we found a significant association between the urinary 8-OHdG concentration and smoking, physical activity, plasma glucose, and the presence of cardiovascular disease (16). In the current study, we calculated the total urinary 8-OHdG concentration by multiplying the measured concentration by the total volume of 12-hour urine and then normalized by the urinary creatinine concentration of the sample, to account for any difference arising from variations in urine concentrations.

Assessment of cognitive function

The participants were given a comprehensive battery of cognitive tests in their choice of either Spanish (98% of participants) or English. Seven cognitive tests were conducted: 1) the MMSE (17) to assess general cognitive function, with a range of scores from 0 to 30 (perfect); 2) 16-word list learning (18) over the course of 5 trials to assess verbal memory, from which word list learning (sum of words recalled during the 5 trials), recognition (the number of words discriminated correctly from a longer word list after a delay from 25 to 35 minutes), and percent retention (calculated by dividing the number of words recalled after delay by the number of correct responses on the fifth learning trial) were calculated; 3) digit span forward and backward (18) to assess attention and working memory; 4) the Stroop test (18) (naming the color rather than the text of words), measuring cognitive flexibility, response inhibition, and processing speed; 5) verbal fluency (18) (to name as many words as they can that start with a given letter), assessing the speed at which one can provide exemplars to a category (initial letter of a word); 6) clock drawing (19); and 7) figure copying (20) to assess visuospatial organization. Scores for the figure copying were weighted for the complexity of the figure copied: 1 point for easy figures and 4 points for the most difficult.

Table 1. Characteristics of US Puerto Rican Adult Participants According to Urinary 8-OHdG Concentration, Boston, Massachusetts, 2004–2008[a]

	Urinary 8-OHdG Concentration							
	Q1 (*n* = 251)		Q2 (*n* = 251)		Q3 (*n* = 252)		Q4 (*n* = 251)	
	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)	%	Mean (SE)
Age, years		57.2 (0.5)		58.4 (0.5)		59.2 (0.5)		57.2 (0.5)
Female	60.6		70.9		73.8		76.1**	
Body mass index, kg/m²		32.5 (0.4)		32.2 (0.4)		31.7 (0.4)		31.3 (0.4)*
Past smoker	30.9		31.2		32.5		26.8	
Current smoker	21.7		21.2		24.5		29.7*	
Physical activity score[b]		31.9 (0.3)		31.5 (0.3)		31.6 (0.3)		30.9 (0.3)*
Past drinker	31.1		28.0		34.7		37.6	
Current drinker	41.8		44.4		35.1		38.4	
Presence of diabetes	39.9		36.6		41.0		45.6	
Presence of hypertension	71.8		68.0		73.8		68.2	
Plasma homocysteine, μmol/L		8.6 (1.0)		8.6 (1.0)		8.5 (1.0)		8.8 (1.0)
Presence of *APOE*E2	15.7		12.6		18.0		9.6	
Presence of *APOE*E4	0.75		4.2		1.6		2.3	
Poverty	52.7		61.4		60.3		55.6	
CES-D score		19.5 (0.8)		20.0 (0.8)		19.7 (0.8)		21.1 (0.8)
Acculturation score		24.2 (1.4)		24.0 (1.3)		23.0 (1.3)		23.6 (1.3)

Abbreviations: *APOE*E2 and *APOE*E4, alleles producing the ε2 and ε4 types of apolipoprotein E, respectively; CES-D, Center for Epidemiologic Studies Depression [Scale]; 8-OHdG, 8-hydroxy-2-deoxyguanosine; Q, quartile; SE, standard error.

* $P < 0.05$; ** $P < 0.01$ relative to the lowest 8-OHdG quartile.

[a] Means (SE) are adjusted for age and sex.

[b] Physical activity score is based on a modified Paffenbarger questionnaire of the Harvard Alumni Activity Survey.

In the current analyses, we calculated a global cognitive function score by averaging the *z* scores for each of the 10 cognitive scores: MMSE, word list learning, recognition, percent retention, Stroop, letter fluency, digit span forward, digit span backward, clock drawing, and weighted figure copying. The global score was calculated only for participants who completed all the component tests (*n* = 880). In secondary analyses, we examined the association between urinary 8-OHdG and each individual cognitive assessment. Using principal components analysis, we further identified 3 cognitive function factors (labeled executive function, memory, and attention) (Appendix Table 1) and examined whether urinary 8-OHdG was associated with each of these factors.

Assessment of covariates

Body weight was measured with a Seca balance scale (Seca Corporation, Columbia, Maryland) with a capacity of 150 kg. Height was measured with a Harpenden pocket stadiometer (Holtain, Ltd., Crosswell, United Kindom). Body mass index was calculated as weight (kg)/height (m)². We measured blood pressure at 3 time points during the home interview. Hypertension was defined as mean systolic blood pressure of ≥140 mm Hg and/or mean diastolic blood pressure of ≥90 mm Hg. Subjects were identified as having type 2 diabetes when their fasting plasma glucose was >7.0 mmol/L, or they reported use of medications for diabetes (insulin or oral medicines) (21). Total homocys-

teine in plasma was measured by using an adaptation of the method described by Araki and Sako (22). The coefficient of variation for this assay in our laboratory is 6.0%. The *APOE* genotype was assessed by Applied Biosystems' TaqMan single nucleotide polymorphism genotyping methods (23) with a success rate of 95%.

Information on age, years of education, household income, smoking, alcohol intake, physical activity, and acculturation was collected by questionnaire. Physical activity was estimated as a physical activity score, based on a modified Paffenbarger questionnaire of the Harvard Alumni Activity Survey (24). Poverty status was computed by using the poverty guidelines released each year by the Department of Health and Human Services (http://aspe.hhs.gov/poverty/index.shtml). We administered the Center for Epidemiologic Studies Depression (CES-D) Scale to measure symptoms of depression (25).

Statistical analyses

Statistical analyses were completed with SAS, version 9.1, software (SAS Institute, Inc., Cary, North Carolina). Box-Cox transformations were performed to normalize the distribution of the 8-OHdG concentration. Subjects were divided into 4 categories based on quartile of total urinary 8-OHdG concentration. Means were compared by using the General Linear Models procedure in SAS software, with the Dunnett adjustment for multiple comparisons. Linear trends were tested for

Table 2. Cognitive Test Score by Mean (SE) According to Urinary 8-OHdG Concentration, Boston, Massachusetts, 2004–2008

	8-OHdG Concentration				P_{trend}
	Q1 (n = 223)	Q2 (n = 223)	Q3 (n = 215)	Q4 (n = 219)	
Global score[a]					
Age and sex adjusted	0.05 (0.04)	0.06 (0.04)	−0.03 (0.04)	−0.09 (0.04)*	0.004
Multivariate[b]	0.04 (0.03)	0.03 (0.04)	−0.02 (0.04)	−0.07 (0.03)*	0.01
Major cognitive function factors					
Executive function[b]	0.08 (0.06)	0.03 (0.06)	−0.05 (0.06)	−0.07 (0.06)	0.06
Memory[b]	0.08 (0.07)	0.07 (0.07)	0.03 (0.07)	−0.18 (0.07)**	0.01
Attention[b]	−0.03 (0.07)	0.02 (0.07)	−0.04 (0.07)	0.03 (0.07)	0.75

Abbreviations: APOE, gene for apolipoprotein E; 8-OHdG, 8-hydroxy-2-deoxyguanosine; Q, quartile; SE, standard error.

* $P < 0.05$; **$P < 0.01$ relative to the lowest quartile of 8-OHdG.

[a] z scores were presented to standardize comparisons.

[b] Means (SE) are adjusted for age (years); sex; body mass index (<25, 25–29.9, ≥30 kg/m^2); education ($<$5th, 5th–8th, 9th–12th grade(s), college, or graduate school); poverty (yes/no); acculturation score; physical activity score (based on a modified Paffenbarger questionnaire of the Harvard Alumni Activity Survey); smoking (never, past, current); use of alcohol (never, past, current); presence of diabetes and hypertension (each, yes/no); status of the apolipoprotein E gene (APOE); and plasma homocysteine (μmol/L). Means were compared by using the General Linear Model procedure in SAS software (SAS Institute, Inc., Cary, North Carolina) with the Dunnett adjustment for multiple comparisons.

significance by assigning to each participant the median value in each category to create a continuous variable. Analyses were adjusted for age (years); sex; body mass index (<25, 25–29.9, or ≥30 kg/m^2); education ($<$5th grade, 5th–8th grades, 9th–12th grades, college, or graduate school); physical activity score; poverty (yes/no); smoking (current, former, and never); alcohol use (current, former, and never); presence of hypertension or diabetes (yes/no for each); plasma homocysteine concentration (μmol/L); APOE status (presence of the APOE*2 allele or the APOE*4 allele, yes/no for each); and acculturation score. These covariates were selected a priori because they have previously been associated with cognitive function and/or DNA oxidative stress.

We examined the interaction between 8-OHdG and other important risk factors in relation to cognitive impairment, including age (<60 or ≥60 years); sex; current smoking status (yes/no); current alcohol use (yes/no); obesity (body mass index, <30 vs. ≥30 kg/m^2); the presence of diabetes; and the APOE*2 and APOE*4 alleles (yes/no for each). To test the significance of these interactions, we included multiplicative terms in the regression models, with adjustment for other potential confounders. We also conducted a sensitivity analysis by excluding participants who did not use Spanish during the interview.

RESULTS

Compared with those with a lower 8-OHdG concentration, participants with a higher urinary 8-OHdG concentration had a higher percentage of women and current smokers, lower physical activity, and body mass index (Table 1).

Furthermore, although not statistically significant, a higher 8-OHdG concentration tended to be associated with a higher CESD score, a higher likelihood of having diabetes and of carrying the APOE*4 allele, and a lower likelihood of carrying the APOE*2 allele. No differences were observed with other covariates.

We observed a significant inverse association between urinary 8-OHdG concentration and global cognitive function score, after adjustment for age, smoking, education, APOE status, plasma homocysteine, and other covariates ($P_{trend} = 0.01$) (Table 2). The adjusted difference in global cognitive score between the group with the highest versus the lowest 8-OHdG concentrations was −0.11 (95% confidence interval: −0.20, −0.02). This magnitude of difference corresponds to the difference observed between participants who were 4 years apart in age in this population. Higher 8-OHdG concentrations were also negatively significantly associated with memory function score ($P_{trend} = 0.01$) and marginally with executive function scores ($P_{trend} = 0.06$) (Table 2). Consistently, a higher urinary 8-OHdG concentration was significantly associated with lower scores for word list learning, recognition, Stroop, clock drawing, and weighted figure copying ($P_{trend} < 0.05$ for all) but not for the remaining cognitive tests (Table 3).

We did not find significant interactions between the urinary 8-OHdG concentration and sex, current smoking status (yes/no), current alcohol use (yes/no), obesity (body mass index, <30 vs. ≥30 kg/m^2), diabetes (yes/no), or the presence of APOE*2 or APOE*4 allele (yes/no for each) in relation to the global cognitive score ($P_{interaction} = 0.20$–0.87). However, in a subgroup analysis, the significant association between 8-OHdG and the global cognitive score

Table 3. Individual Cognitive Test Score by Mean (SE) According to Urinary 8-OHdG Concentration, Boston, Massachusetts, 2004–2008

	8-OHdG Concentration				P_{trend}
	Q1	Q2	Q3	Q4	
MMSE	23.5 (0.19)	23.5 (0.19)	23.3 (0.19)	23.1 (0.19)	0.19
Word list learning[a]	0.07 (0.06)	0.05 (0.06)	0.03 (0.06)	−0.14 (0.06)*	0.01
Recognition[a]	0.13 (0.06)	0.08 (0.06)	−0.03 (0.06)	−0.18 (0.06)**	0.0004
Percent retention[a,b]	−0.01 (0.06)	−0.004 (0.06)	0.05 (0.06)	−0.02 (0.06)	0.78
Stroop[a]	0.09 (0.06)	0.02 (0.06)	−0.04 (0.06)	−0.07 (0.06)	0.04
Letter fluency[a]	0.02 (0.06)	0.05 (0.06)	−0.07 (0.06)	−0.01 (0.06)	0.35
Digit Span, forward[a]	−0.04 (0.06)	−0.05 (0.06)	0.01 (0.06)	0.07 (0.06)	0.20
Digit Span, backward[a]	0.04 (0.06)	0.03 (0.06)	−0.001 (0.06)	−0.07 (0.06)	0.18
Clock drawing[a]	0.08 (0.06)	0.04 (0.06)	0.02 (0.06)	−0.15 (0.06)**	0.01
Figure copying[a]	0.07 (0.06)	0.08 (0.06)	−0.07 (0.06)	−0.09 (0.06)	0.03

Abbreviations: APOE, gene for apolipoprotein E; MMSE, Mini-Mental State Examination; 8-OHdG, 8-hydroxy-2-deoxyguanosine; Q, quartile; SE, standard error.

* $P < 0.05$; **$P < 0.01$ relative to the lowest quartile of 8-OHdG.

[a] z scores were presented to standardize comparisons. Means (SE) are adjusted for age (years); sex; body mass index (<25, 25–29.9, ≥30 kg/m^2); education ($<$5th, 5th–8th, 9th–12th grade(s), college, or graduate school); poverty (yes/no); acculturation score; physical activity score (based on a modified Paffenbarger questionnaire of the Harvard Alumni Activity Survey); smoking (never, past, current); use of alcohol (never, past, current); presence of diabetes and hypertension (each, yes/no); APOE status; and plasma homocysteine (μmol/L). Means were compared by using the General Linear Model procedure in SAS software (SAS Institute, Inc., Cary, North Carolina) with the Dunnett adjustment for multiple comparisons.

[b] Calculated by dividing the number of words recalled after delay by the number of correct responses on the fifth learning trial.

was seen only in participants aged ≥60 years (difference in the global cognitive score between the group with the highest vs. the lowest 8-OHdG concentrations was −0.17; $P_{trend} = 0.03$) but not in those aged <60 years (difference in the global cognitive score between the group with the highest vs. the lowest 8-OHdG concentrations was −0.06; $P_{trend} = 0.27$), although the interaction was not significant ($P_{interaction} = 0.49$). Excluding participants who did not use Spanish during the interview or those with CESD of >16 did not significantly change the inverse association between 8-OHdG and the global cognitive score (data not shown).

DISCUSSION

In this sample of Puerto Rican adults, we found that increased DNA oxidative damage, as assessed by the urinary 8-OHdG concentration, was associated with lower global cognitive function. These inverse associations were independent of several known risk factors of cognitive impairment, such as age, smoking, education level, plasma homocysteine, and APOE genotype. Our observations are consistent with those from previous clinical studies that reported increased 8-OHdG concentrations in cerebrospinal fluid or brain tissues from Alzheimer's dementia or MCI patients relative to controls (10–12). Similarly, 2 studies also found increased DNA oxidative damage at the periph-

eral cells in Alzheimer's dementia and MCI patients. In a study of 40 Alzheimer's dementia patients and 39 age- and sex-matched healthy controls, Alzheimer's dementia patients had significantly higher 8-OHdG concentrations in peripheral lymphocytes relative to the controls (13). In another study of 35 patients with Alzheimer's dementia or MCI, the mean concentrations of several DNA damage markers in leukocytes, including DNA strand breaks, endonuclease III sites, and formamidopyrimidine-DNA glycosylase sites in leukocytes, were significantly higher in Alzheimer's dementia and MCI patients ($n = 35$) than in those of healthy controls (26).

Experimental studies support a role for DNA oxidation in the pathogenesis of cognitive impairment and dementia. Attacks on DNA by reactive oxygen species result in structural damage (i.e., strand breaks), DNA-DNA and DNA-protein cross-linking, sister chromatid exchange, and translocation (8, 9). Consistently, greater numbers of DNA strand breaks have been observed in the brains of Alzheimer's dementia patients (9). Moreover, unrepaired oxidative mitochondrial DNA damage has been suggested to alter mitochondrial gene expression. This would, consequently, impair the respiratory chain and diminish respiratory function, which could, in turn, increase reactive oxygen species production (27). This vicious cycle may affect normal cellular homeostasis in the central nervous system.

Strand breaks lead to activation of poly(ADP-ribose) polymerase and, finally, could cause depletion of energy and cell death (28). On the other hand, a higher 8-OHdG concentration could also reflect diminished capacity for DNA repair, which may have a role in the progression of Alzheimer's dementia (29), as suggested by observations that DNA fragmentation and nicking were found in Alzheimer's dementia patients (30). A recent study provides further evidence, activity of oxoguanine glycosylase 1, a key enzyme in excising 8-OHdG found to be significantly lower in Alzheimer's dementia or MCI patients ($n = 15$) compared with 6 age-matched, normal controls (31).

Our observations of significant association between 8-OHdG concentration and poor memory function are consistent with those from a previous human study, which showed that DNA oxidative damage could contribute to reduced expression of selectively vulnerable genes involved in learning and memory (32). Hippocampal pyramidal and granule cells in mouse brains were particularly prone to accumulations of DNA damage products (33). Consistently, animal studies have also demonstrated that exposures to prooxidants, such as iron or d-galactose, led to impairment in learning, recognition, and spatial memory (34, 35), whereas administration of antioxidants, such as vitamin E, acetyl-L-carnitine, or (R)-α-lipoic acid, can prevent cognitive impairment due to oxidative stress and improve cognitive function (36–38).

However, most clinical studies (10–12) have used brain tissues or cerebrospinal fluid samples, which are invasive and not routinely collected in population-based studies. In this context, it is important to develop a noninvasive and easily measured biomarker for cognitive function in population-based studies. Although we found that urinary 8-OHdG was significantly associated with global cognitive function, as well as several individual cognitive scores, it is important to know whether urinary 8-OHdG reflects DNA oxidative damage status in the central nervous system. In a recent study, a strong correlation between urinary and cerebrospinal fluid 8-OHdG ($r = 0.82$; $P = 0.01$) was observed among 12 children with various forms of central nervous system disorders (i.e., status epilepticus, epilepsy, or hypoxic-ischemic encephalopathy) (39). Furthermore, a higher urinary 8-OHdG concentration has been found in patients with Parkinson's disease, relative to controls, and these concentrations increased with Parkinson's disease progression (40, 41). An animal study of Parkinson's disease reported that rats lesioned with 6-hydroxydopamine in the medial forebrain bundle displayed significantly elevated urinary 8-OHdG concentrations (42). These studies, together with our observations, suggest that urinary 8-OHdG could be a useful biomarker for brain DNA oxidative damage.

To the best of our knowledge, this is the first population study to examine the association between 8-OHdG and cognitive function. In the current study, we used a comprehensive battery of cognitive tests, which allows for analysis of specific impairments in cognition, as well as global cognitive function. We also collected extensive data on demographics, socioeconomic markers, anthropometric measures, and biochemistries and genetic markers, which allow us to control several important factors that may confound the observed associations between urinary 8-OHdG and cognitive function. However, because of the observational nature of the current study, we cannot completely exclude residual confounding caused by unmeasured/unknown factors. Our study population consisted of only Puerto Rican adults, limiting the generalizability of our findings to other ethnic populations. Finally, the cross-sectional design of the current study precludes any conclusion regarding direction of causation.

In conclusion, we found that a higher urinary 8-OHdG concentration, a marker for global DNA oxidative damage, was associated with lower cognitive performance. The difference in the global cognitive score, comparing participants in the 2 extreme 8-OHdG quartiles, was equivalent to accelerating cognitive aging by about 4 years in this population. Prospective studies are needed to elucidate whether elevated urinary 8-OHdG concentrations can predict the rate of cognitive decline and incident dementia. Future studies examining dietary determinants of 8-OHdG concentration and cognition are also of importance for the development of new prevention strategies against cognitive aging.

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APPENDIX

Appendix Table 1. Pearson's Correlation Coefficients for the Relation Between Individual Cognitive Test Score and Major Cognitive Function Factors in a Sample of Puerto Rican Adults Living in Boston, Massachusetts, 2004–2008[a]

Individual Test	Factor 1 (Executive Function)	Factor 2 (Memory)	Factor 3 (Attention)
Letter fluency	0.44		0.49
Figure copying	0.65		0.25
Digits forward			0.78
Digits backward	0.31		0.67
Clock drawing	0.63		
Stroop 1	0.70		
Stroop 2	0.81		
Stroop 3	0.75		
Word list learning sum score		0.77	
Recognition		0.75	
Short-term recall facilitated		0.87	
Long-term recall facilitated		0.88	
Mini-Mental State Examination, attention			0.49

[a] Correlation coefficients of <0.25 were omitted for simplicity.