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The association of interacting neighborhood gene-environment risk with cortisol and blood pressure in African-American adults

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Abstract

Background—African-American adults are disproportionately affected by stress-related chronic conditions like high blood pressure (BP), and both environmental stress and genetic risk may play a role in its development.

Purpose—This study tested whether the dual risk of low neighborhood socioeconomic status (SES) and glucocorticoid genetic sensitivity interacted to predict waking cortisol and BP.

Methods—Cross-sectional waking cortisol and BP were collected from 208 African-American adults who were participating in a follow-up visit as part of the Positive Action for Today's Health trial. Three single nucleotide polymorphisms were genotyped, salivary cortisol samples were collected, and neighborhood SES was calculated using 2010 Census data.

Results—The sample was mostly female (65%), with weight classified as overweight or obese ($M_{BMI}=32.74$, $SD=8.88$), and a mean age of 55.64 ($SD=15.21$). The gene-by-neighborhood SES interaction predicted cortisol ($B=0.235$, $p=.001$, $r^2=.036$), but not BP. For adults with high genetic

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Conflicts of Interest The authors have no conflicts of interest to report.

Adherence to Ethical Standards

The research was conducted in accordance with ethical standards outlined by the University of South Carolina's Institutional Review Board. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

risk, waking cortisol was lower with lower SES but higher with higher SES ($B=0.87$). Lower neighborhood SES was also related to higher systolic BP ($B=-0.794$, $p=.028$).

Conclusions—Findings demonstrated an interaction whereby African-American adults with high genetic sensitivity had high levels of waking cortisol with higher neighborhood SES, and low levels with lower neighborhood SES. This moderation effect is consistent with a differential susceptibility gene-environment pattern, rather than a dual-risk pattern. These findings contribute to a growing body of evidence that demonstrates the importance of investigating complex gene-environment relations in order to better understand stress-related health disparities.

Keywords

Neighborhood; socioeconomic status; genetic; cortisol; blood pressure; African American

Introduction

African-American adults and other socioeconomically disadvantaged groups in the U.S. experience greater rates of high blood pressure (BP) as part of a long-standing disparity in cardiovascular health (1–3). Approximately 40% of African-American adults suffer high BP in contrast to 28% of Caucasians (4–6), and chronic exposure to environmental or neighborhood-related stressors may account in part for this disparity (7–9). Further, genetic differences in physiologic stress-responding may moderate socioeconomic and cardiovascular relations (5, 10, 11). Because the estimated heritability of high BP ranges from 30% up to 70% (12, 13), the simultaneous estimation of genetic risk can provide a more complete picture of the complex determinants of high BP. Gene-environment interaction frameworks therefore offer unique insight into how socioeconomic disadvantage confers and perpetuates stress-related health disparities (9, 14, 15).

Socioeconomic disadvantage and its impact on health is typically investigated as a function of individual socioeconomic status (SES), through the use of individual income, occupation, and/or education indices (16, 17). However, the impact of *contextual SES*, or the use of neighborhood-level income, occupation, and/or education indices, is less frequently considered, despite evidence of its relevance above and beyond individual factors (9). Specifically, lower contextual SES, sometimes termed *ecological SES* but referred to herein as *neighborhood SES* (9), has been linked to poorer cardiovascular outcomes (18–22) and health behaviors (17). Anderson (7, 23) and Matthews (9) broadly theorize that these multi-level links (e.g. micro-level genetic risk and macro-level neighborhood risk) are especially relevant in vulnerable minority populations. They note also that advances in genomics may shed light on the pervasiveness of health disparities and high BP in African-Americans (24).

Integrated biomedical models define pathways by which the stress-related secretion of glucocorticoid steroid hormones (e.g. cortisol), through the hypothalamic-pituitary-adrenal axis, impacts BP, and may be moderated by genetic risk factors (25–27). Indeed, the role of excess cortisol in the development of high BP and cardiovascular dysfunction is well-established through experimental and clinical trials (28). Though mechanisms are complex and not fully understood, it is thought that genetic single nucleotide polymorphisms (SNPs) in the glucocorticoid receptor gene region intensify the adverse impact of cortisol on

cardiovascular health, increasing the likelihood of chronically elevated BP under adverse environmental or neighborhood conditions. Based on this dual- or additive-risk framework within which gene-environment effects may be additive (29, 30), the present study investigated whether glucocorticoid receptor SNPs moderated the association of neighborhood SES with cortisol and BP (Figure 1).

While gene-environment interactions linking neighborhood SES to cortisol and BP have not been previously investigated, there is evidence for direct links between these risk factors and glucocorticoid and cardiovascular functioning (12, 31). For example, lower neighborhood SES has been linked to preclinical atherosclerosis in African-American and Caucasian men with untreated hypertension, above and beyond the influence of individual SES (32). These findings are further supported by links between lower neighborhood SES and BP reactivity (19), cardiovascular mortality (33), systolic and diastolic BP in multiethnic adult samples (34), with waking cortisol in children (8) and adults (35), and with plasma cortisol (8). However, other studies have shown no relation of neighborhood SES and high BP or basal cortisol (21, 22).

Cortisol is related to socioeconomic disadvantage also, however these associations are more complex, have infrequently been assessed relative to neighborhood-level risk, and have not been assessed relative to genetic risk in African-American adults. For example, lower individual SES has been linked to cortisol generally (36) and to a reduction in waking cortisol values of 1.45 ng/mL in lower SES African-American adults (37). Regarding neighborhood SES, a study of the Whitehall II cohort found that lower neighborhood SES was related to blunted cortisol reactivity (38), and another study linked it to quicker recovery rates in African-American children (39), with hypothalamic-pituitary-adrenal dysregulation cited as a possible explanation for these effects.

The present study targeted *Bcl1* (rs41423247), *FHBP5* (rs1360780), and *9β* (rs6198) glucocorticoid receptor polymorphisms, which have been linked to stress-related health outcomes, including basal and reactive cortisol levels, high BP, obesity, type II diabetes, perceived stress, and stressful life events (31, 40–42). The *Bcl1* minor allele is actually protective, and has been consistently associated with more positive outcomes for hypertension status (43) and cortisol reactivity (44, 45). *FHBP5* has been associated with increased stress reactivity and the development of chronic stress conditions such as depression and post-traumatic stress disorder (46, 47). Importantly, this SNP has been studied primarily as it relates to mental manifestations of stress (e.g. post-traumatic stress disorder). Though its potential effects on physical biomarkers (e.g. cortisol, high BP) are largely unknown, two studies have linked its risk allele to increased cortisol reactivity (48) and to a higher prevalence of physical health problems in adults (49). The minor allele of *9β* is also protective, with its common allele associated with increased adrenocorticotropin hormone secretion (a precursor to cortisol) in response to psychosocial stress (45), high BP and a dose-dependent relation with systolic BP (50), glucocorticoid receptor dysfunction (51), and cardiovascular development in infants (52). Overall, studies testing associations of these glucocorticoid receptor SNPs with cortisol and cardiovascular outcomes have produced mixed findings.

The purpose of the present study was to build on previous research by testing the gene-environment impact of neighborhood SES and glucocorticoid genetic risk on cortisol and BP. This study hypothesized that lower neighborhood SES would be related to lower/blunted waking cortisol, and to higher systolic and diastolic BP. The study also hypothesized that genetic risk would moderate this relation, such that the effect of neighborhood SES on cortisol and BP would be stronger with increasing genetic risk, consistent with a dual-risk interaction pattern.

Methods

Participants and Procedures

Baseline data from a subset of African-American male and female adults who provided genetic samples during the Positive Action for Today's Health (PATH) trial were used (53, 54). PATH was a 24-month community-based intervention to increase physical activity in three at-risk (high crime, low income) communities. Participants were initially recruited through volunteer advertisements and word of mouth (54%), and by contacting random list of households (46%). Consenting individuals were enrolled in the trial if they: 1) were African-American (three of four grandparents of African heritage), 2) 18 years of age, 3) were not moving within two years, 4) were not limited from participating in moderate intensity exercise, 5) resided in specified census areas within the three identified communities, and 6) had controlled BP (<180 / <110) and blood sugar levels (<300 non-fasting, <250 fasting).

During the final PATH assessment participants were given the option to provide a buccal swab sample, and 75% agreed, resulting in a final genetic sample of $N=236$ for this study. Survey, anthropometric, blood pressure, and buccal swab data were collected by trained staff at community-based health assessments, and participants were instructed on the collection of at-home waking saliva samples. Participants were compensated monetarily for their time as part of the larger study. Approval from the Independent Review Board of the University of South Carolina was obtained, and informed consent procedures were completed prior to enrollment.

Demographics and Anthropometrics

Anthropometric, demographic, and individual SES data were included as control variables. Body mass index (BMI) during the final PATH assessment (24-month time point) was calculated using objective weight and height data, which were collected twice and averaged. Information regarding age, sex, education level and annual income was collected via self-report questionnaire. These variables are risk factors for high BP, as identified by the American Heart Association (1). Education and income were assessed with 7-point interval scales and individual SES was calculated as their mean. Participants were asked to report whether they had been prescribed medications, and whether they were taking their medications regularly and as directed by their physician (i.e. whether they were compliant). Based on their responses, participants were categorized as unmedicated, medicated and compliant, or medicated and noncompliant. To control for the three PATH communities/cities, participants were coded as residing in community 1, 2, or 3.

Environmental Risk (Neighborhood SES)

Neighborhood SES was calculated using 2010 census data, and participants' addresses were geocoded using latitude and longitude coordinates on a map (ArcGIS®, Esri). Geocoded addresses were then linked to census block groups, which are the smallest geographic entities for which the U.S. Census bureau collects and quantifies data for all census variables (55). Blocks groups are determined using visible, geographic features such as roads, streams, railroad tracks, or city blocks, or by nonvisible boundaries such as property lines, and county limits. Census variables that comprised neighborhood SES were based on an established index (21), and included: 1) median household income, 2) median value owner-occupied housing, 3) proportion of households receiving interest, dividend, or net rental income, 4) proportion of adults with a high school diploma, 5) proportion of adults with a college education, and 6) proportion of people employed in executive, managerial, or professional occupations. These census variables comprise a factor of neighborhood SES (factor loadings = 0.60) with high internal consistency at the block level ($\alpha=0.92$)(56). In this sample, internal consistency was adequate with $\alpha=.80$.

Genetic Risk (Glucocorticoid SNPs)

Buccal swabs were delivered without subject identification to the biochemistry laboratory for genotyping. DNA were isolated using QIAGEN kits (QIAGEN, Valencia, CA) and stored at -80°C until analysis. Genotypes for *Bcl1* (rs41423247), FKBP5 (rs1360780), and 9 β (rs6198) variants were obtained with the use of a TaqMan allelic discrimination assay that employs the 5' nuclease activity of Taq polymerase to detect a fluorescent reporter (VIC and FAM) signal-generated during polymerase chain reactions. Two methods of quality control for genotyping were used: negative controls, and genotyping of replicate samples (at least 5% of total). Replicate samples were checked and if there was no match, the genotyping was repeated.

Genetic risk was quantified as a single variable by indexing the presence of alleles that have previously been linked to increased glucocorticoid stress-responding for each of the three targeted SNPs. Individuals received an index score of 0, 1, or 2 for each SNP, corresponding to the genotypes homozygous for the low-risk allele, heterozygous, and homozygous for the high-risk allele, respectively. A mean of these three SNP indices was calculated for each participant. This method of indexing of genetic risk across SNPs linked either mechanistically or empirically to common outcomes has been used in similar gene-environment studies (57). Descriptive information for each of these SNPs, including the risk allele, nucleotide variant, and common and minor alleles based on the 1000 Genomes Project (58), is included in Table 1.

Stress-related Outcomes (Waking Cortisol, BP)

Cortisol—For collection of the waking samples, participants were given verbal and written instructions to collect the sample immediately upon waking the following morning, without rising or rinsing their mouths, and to return the sample to the study staff that same afternoon, during their scheduled appointment. Salivette collection devices were used and saliva sampling provides a valid measure of basal cortisol activity (59). Studies of adherence indicate that individuals asked to collect waking samples typically do so 6 minutes after

waking, with samples reliably collected 1–15 minutes after waking and providing stable values of cortisol concentrations (60). Samples were centrifuged, aliquotted, and stored and cortisol concentrations were measured using a radioimmunoassay procedure per manufacturer's directions (R&D Systems, Minneapolis, MN, USA). Average interassay and intraassay variation was less than 5–6%. Assays and/or samples not meeting these criteria were included in additional radioimmunoassays. Assays had high specificity and low cross-reactivity (<1%), and cortisol concentration was determined in ng/ml of saliva collected (for reference, 1 ng/ml=2.759 nmol/L), based on a sigmoidal four-parameter curve at a fit of $r = .9632$. The waking cortisol distribution was positively skewed and this issue was addressed by removing cortisol concentrations that were physiologically implausible (e.g. 125.20 ng/mL), truncating values that were greater than 3 standard deviations above the mean to the highest value detectable via the assay (>14.15 ng/mL), and transforming positively skewed data using a natural log function, an approach frequently applied (61, 62).

Blood Pressure—Dinamap BP equipment (model 8100; Critikon Inc., Tampa, FL) was used with a standard research protocol (63). During BP assessments, participants were seated in a relaxed position with their legs uncrossed. Based on upper-arm diameter the appropriately sized cuff was placed on the left arm and participants rested for 5 minutes before 3 BP assessments were taken. One minute passed between assessments, and results from the first assessment were discarded from analyses (64). Thus, mean systolic and diastolic BP values were quantified using the second and third assessments.

Data Analyses

Primary analyses were conducted using the MPlus statistical software package (Muthén & Muthén, Los Angeles, LA), with model assumptions and case diagnostics completed with the SAS software packages (SAS Institute, Cary, NC). The primary aim was assessed through multiple linear regression to estimate direct effects and interaction effects among the variables of interest. Cortisol and BP were regressed on control variables (β_1 – β_6), neighborhood SES (β_7), genetic risk (β_8), and on the gene-environment interaction representing the effect of neighborhood SES on cortisol and BP at varying levels of genetic risk (β_9):

$$\begin{aligned} \text{Cortisol, BP} = & \beta_0 + \beta_1 \text{Age} + \beta_2 \text{Sex} + \beta_3 \text{Community} \\ & + \beta_4 \text{BP Medication} \\ & + \beta_5 \text{BMI} + \beta_6 \text{Individual SES} \\ & + \beta_7 \text{Neighborhood SES} \\ & + \beta_8 \text{Genetic Risk} + \beta_9 \text{Genetic Risk} * \text{Neighborhood SES} + \varepsilon \end{aligned}$$

Final control variables were included because they were significantly correlated with or predictive of outcomes in preliminary models, and also because they have been mechanistically and/or empirically linked to outcomes in previous research. To account for clustering within neighborhoods block groups, parameter estimates and standard errors were adjusted using a sandwich estimator and the MPlus COMPLEX command.

Full information maximum likelihood estimation was implemented to address missing data for the outcome variables (65). It was assumed that data were Missing at Random (66) and variables that were theoretical correlates of missingness for waking cortisol (perceived stress, afternoon cortisol) were also included as auxiliary variables in the statistical models. This approach improves maximum likelihood estimations and reduces potential bias in parameter estimates, to ensure validity of the missing-at-random assumption (66). Cases were listwise deleted to address missing genetic or neighborhood SES data for predictor variables, which occurred for 28 cases of the total subsample for which genetic data were collected with ($N=236$).

Results

Participant Characteristics

The final sample consisted of 208 adults, and was predominantly overweight (BMI, $M=32.74$, $SD=8.88$) and 65% female ($n=136$). Descriptive data for the sample are presented for each of the model variables in Table 2. The sample generally fell within the lower half of the 10-point range of neighborhood SES values that were represented ($min=-5.18$, $max=5.14$). Average genetic risk indicated overall higher risk across the three SNPs, two of which had common alleles associated with increased risk (*Bcl1*, 9β ; Table 1). Mean systolic BP fell within the prehypertension range ($M=127.93$, $SD=20.13$), and diastolic BP within the normal range ($M=77.21$, $SD=10.88$); values for each were normally distributed across the sample. Mean cortisol was 4.16 ($SD=3.33$), and after log transformation to obtain a normal distribution, was 1.10 ($SD=1.05$).

Association of Neighborhood SES and Genetic Effects with Cortisol and BP

Bivariate correlations indicated that age ($r=-.123$), systolic BP ($r=-.105$), and the gene-environment interaction ($r=.175$) were related to waking cortisol. Systolic BP was also correlated with diastolic BP ($r=.702$) and age ($r=.128$). Results of the multiple regression are presented in Tables 3. The model accounted for 7.4% of the variance in log-transformed waking cortisol, and 4.7% and 9.6% of the variance and systolic and diastolic BP, respectively. Regarding the primary aim of this study, the interaction of neighborhood SES with genetic risk was significant ($B=-.235$, $p=.001$) and accounted for 3.6% of the variance in waking cortisol. Simple slopes were calculated at one standard deviation above and below the mean of genetic risk to compare individuals with low versus high genetic risk (Figure 2). The slope pattern indicated that individuals with high genetic risk had lower/blunted waking cortisol when neighborhood SES was low, but had higher waking cortisol when neighborhood SES was high ($B=.87$); individuals with low genetic risk did not show a relation of neighborhood SES to waking cortisol ($B=.06$). Neighborhood SES ($B=-.794$, $p=.028$) and age ($B=-.180$, $p=.024$) predicted systolic BP, such that lower SES and age were related to higher systolic BP. Results also indicated that age ($B=-.120$, $p=.002$), sex ($B=-3.265$, $p=.023$) and community ($B=3.038$, $p<.001$) variables predicted diastolic BP. Individual SES was not predictive of cortisol or BP. Neither genetic risk nor the gene-environment interaction predicted BP.

Discussion

This investigation links neighborhood SES with waking cortisol and systolic BP in at-risk African-American adults. It also demonstrates a significant gene-environment interaction, such that the relation of neighborhood SES with waking cortisol is dependent in part on the genetic sensitivity of an individual's glucocorticoid receptor functioning. Further, the interaction finding provides evidence for a differential susceptibility pattern of effects, rather than for the more common dual-risk or additive-risk model. Thus, findings supported hypotheses that interacting genetic and environmental risks would relate to waking cortisol, but did not support the hypothesized dual-risk pattern. Though the gene-environment interaction was not related to systolic or diastolic BP, lower neighborhood SES was directly related to higher systolic BP. This study is the first, to our knowledge, to investigate a gene-environment model that focuses on neighborhood SES and stress-related outcomes, and to demonstrate a differential susceptibility interaction pattern, in at-risk African-American adults.

Research has increasingly focused on both gene-environment models and glucocorticoid functioning across a host of stress-related outcomes, presumably to demonstrate links between contextual and biological processes. Still, the gene-environment impact of contextual factors such as neighborhood SES remains largely unknown (67), and the collective effects of *Bcl1*, FKBP5, and 9β glucocorticoid SNPs have not been previously targeted in such a model. Nonetheless, previous investigations have demonstrated that independently, these SNPs may moderate the impact of stressors and other contextual factors on stress-related outcomes. FKBP5 has been shown to moderate the impact of childhood trauma on adult symptoms of post-traumatic stress disorder (68), and has been linked to reduced adrenocorticotrophic hormone suppression in adults with both the FKBP5 risk allele and co-occurring depression (69). Findings from animal studies also support the role of FKBP5 as a moderator of hypothalamic-pituitary-adrenal functioning (70). The *Bcl1* risk allele has been shown to moderate the relation of prenatal maternal psychological symptoms on child emotional and behavioral problems (71). Previous research therefore provides some foundation for significant glucocorticoid gene-environment effects, as was found in the present study, however it is worth noting that the "environment" in these "gene-environment" investigations has been quantified previously as life events (childhood trauma) or clinical stressors (depression, maternal psychological symptoms), and has not been quantified using indices of the neighborhood-environmental context.

A handful of studies that have investigated gene-environment effects using census-derived indices of the neighborhood-environmental context, but that did not focus on glucocorticoid SNPs, reported findings that are relevant to the present study. Wickrama and colleagues showed that community adversity, quantified using socioeconomic census data, interacted with dopamine- and serotonin-related genetic factors to predict variable BMI trajectories in a multiethnic sample of youth. Consistent with the present study, a differential susceptibility pattern characterized this interaction (57), and it is worth noting that this pattern was stronger in African-American versus Caucasian adolescents. In contrast, Barnes and colleagues found a significant dual-risk interaction pattern when examining whether a monoamine oxidase SNP index moderated the impact of census-derived neighborhood

disadvantage on risk for violent behavior (72). It is worth noting however that only a small proportion (18%) of their sample was African-American.

While the differential susceptibility pattern found for high versus low genetic risk is less commonly observed or hypothesized than the dual-risk pattern, this pattern has previously been seen in studies that investigated cortisol functioning, independent of interacting neighborhood and genetic effects. Specifically, infants with high neonatal cortisol reactivity have been shown to display better emotional regulation when maternal reactivity is low, but poorer regulation when maternal reactivity is high (73); thus, neonatal cortisol reactivity conferred a differential susceptibility effect, comparable to that of genetic risk in the present study. Similarly, there is evidence that social fearfulness in children interacts with caregiver cortisol levels to influence well-being, such that more fearful children reported higher well-being with lower caregiver cortisol, and lower well-being with higher caregiver cortisol, in contrast to less fearful children (74). Though limited in scope, these studies, combined with the current findings, highlight the relevance of neighborhood and contextual factors for stress-related outcomes, as well as the likelihood that these relations vary as a function of genetic susceptibility. Future research might consider both differential susceptibility and dual-risk gene-environment patterns, as well as the possibility that they might vary across the types of risks measured, the populations targeted, and the developmental time periods being studied.

The genetic characteristics of the sample targeted in this study should be considered independent of environmental effects. Sample frequencies were higher for *Bcl1* and 9β risk alleles than global frequencies, and were lower for the FHBP5 risk allele. The potential for reduced genetic variation due to stratification of the gene pool could be investigated in studies with larger samples and more comprehensive genotyping. Historically, lower SES communities have been geographically restricted and this also could account for differences in African-American allele frequencies relative to global frequencies. Indeed, previous research suggests that this is the case, and further that controlling for socioeconomic factors is necessary when assessing genetic relations with chronic-disease outcomes in African Americans (75).

Within the overall differential susceptibility gene-environment pattern, higher neighborhood SES was related to higher waking cortisol in adults with greater genetic risk, and the direction of this relation was somewhat unexpected. In general, it is assumed that greater exposure to chronic stressors (e.g. residence in a low-SES neighborhood) is linked with higher cortisol values, however findings in the literature have been mixed, and the diurnal pattern of cortisol secretion complicates this link. Consistent with the findings of this study, Bennet and colleagues found that African-American adults with lower SES had waking cortisol values approximately 4 nmol/L (1.45 ng/mL) lower than higher SES adults, though in Caucasian adults this relation showed an opposite, inverse direction (37). Living in a lower SES neighborhood has been linked to lower basal cortisol levels in a largely African-American sample of adolescents (76), and similar results have been found linking neighborhood disorder to lower waking cortisol levels in African-American children (8). However again, the opposite was true for European-American children (8). Finally, citing the hypothalamic-pituitary-adrenal dysregulation as an explanation for findings in this same,

traditionally unexpected direction, a study of the Whitehall II cohort linked greater neighborhood socioeconomic deprivation to decreased cortisol reactivity (38).

A healthy diurnal cortisol rhythm is characterized by an immediate, sharp cortisol elevation upon waking, a sharp drop within a few hours of waking, and a gradual decline through the afternoon and evening; relatively low waking cortisol can therefore signify dysfunction in the circadian pattern, and has been linked to a failure for levels to decline over the afternoon and evening (77). Illustrating this phenomenon within the context of neighborhood factors, higher neighborhood social cohesion and safety were linked to higher waking cortisol and a steeper waking-to-bed slope in the Multi-ethnic Study of Atherosclerosis (35). Thus, findings in this study that higher neighborhood SES was linked to higher waking cortisol are actually not inconsistent with previous research, especially research conducted in African-American samples, nor with the dysfunction that might be expected due to chronic exposure to neighborhood stressors. Further, it is possible that the cortisol response to chronic stress, which is complicated by the potential for circadian dysregulation, varies across demographic groups, the type or nature of the chronic stressor, and genetic risk of differential responding (78).

Limitations related to the present study's cross-sectional design, relatively small sample size, and single assessment of cortisol and BP must be considered. The design prohibits any inferences regarding gene-environment mechanisms, and single time-point measures of BP and cortisol may be confounded by issues of reactivity and lability. Indeed, no effects were found linking genetic susceptibility to BP, and it is possible that true relations that may exist were masked by unmeasured error related to BP medications, the study's small sample size, and/or by unmeasured mediators that might link SNPs to the more distal outcome of BP (31, 40, 41). Though this study collected only one waking cortisol sample, it is the first to account for such an outcome within a contextual gene-environment design, in an at-risk sample of African-American adults. However, neuroendocrine regulation of stress hormones in response to the environment is complex, and any chronic dysregulation or habituation of the hypothalamic-pituitary-adrenal system could confound the relations that are observed (79, 80). Other cortisol measures, such as the cortisol awakening response, might be investigated in the future, though their possible limitations relative to waking cortisol, such as being influenced by situational factors (wake time, sleep duration, and season/number of daylight hours), should be carefully considered (62, 81). More research is needed to generalize these findings beyond the current sample of African-American adults that participated in the PATH trial. Future research may aim to compare across more diverse SES and ethnic groups.

This work has implications for conceptualizations of stress-related health outcomes, and potentially for public health efforts to ameliorate SES-related disparities in cardiovascular health. These findings are the first to link FKBP5 to outcomes that do not fall under traditional classifications of mental health, and they provide an example of a single genetic susceptibility SNP relating to different health outcomes, potentially via the same pathway. In the future, such examples of multifinality in genetic-environment relations should receive more cross-disciplinary attention, and may further challenge societal divisions of "physical" and "mental" health. Neighborhood SES was linked to waking cortisol and BP, consistent

with previous research, and public health efforts such as the *Healthy People 2020* should continue to investigate neighborhood-level prevention and intervention efforts for reducing SES-related disparities (82, 83). In summary, this study found that stress-related neighborhood risk and genetic susceptibility operated in tandem to influence waking cortisol. The observed pattern of effects builds on a small body of work that suggests a more hopeful message, with genetic “susceptibility” rather than “risk” relating not only to poorer outcomes, but to better outcomes as well.

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Figure 1.
Conceptual risk model of gene-environment risk predicting cortisol, and blood pressure.

Figure 2.

Neighborhood socioeconomic effects on waking cortisol by genetic risk.

Note. Simple slopes for the association of neighborhood socioeconomic status with waking cortisol are graphed at one standard deviation above and below the mean of genetic risk.

Table 1

Genetic Characteristics of Glucocorticoid Receptor SNPs.

SNP	Gene	CA→MA	RA ^b	gMAF ^a	sMAF ^a
Bcl1 ^c , rs41423247	NR3C1	G→C	G	0.255	.305
FHBP5, rs1360780	NR3C1	C→T	T	0.327	.193
9p ^c , rs6198	NR3C1	A→G	A	0.084	.053

Note: CA, common allele; gMAF, global minor allele frequency; MA, minor allele; sMAF, sample minor allele frequency; RA, risk allele; SNP, single nucleotide polymorphism.

^aGlobal Minor Allele Frequency obtained via National Center for Biotechnology Information (NCBI) dbSNP database; represents MAF for each rs based on the default global population of 1000Genome phase 1 genotype sample, released May 2011.

^bDenotes risk allele linked previously to adverse outcomes.

^cMinor alleles for these SNPs are protective, see Introduction.

Table 2

Descriptive Data (N=208).

	<i>M</i>	<i>SD</i>	<i>Min</i>	<i>Max</i>
Age	55.64	15.21	21.00	89.00
Female	65%	–	–	–
BMI	32.74	8.88	17.65	59.26
Genetic Risk	1.49	0.38	0.00	2.00
ISES ^a	3.240	1.024	1	7
NSES	−1.92	2.25	−5.18	5.14
Systolic BP (mmHg)	127.93	20.13	74.50	201.50
Diastolic BP (mmHg)	77.21	10.88	50.50	118.50
WCort (ng/mL)	4.16	3.33	0.13	12.08
Log WCort (ng/mL)	1.10	1.05	−2.05	2.49

Note. BMI, body mass index; BP, blood pressure; ISES, individual socioeconomic status; Log, log-transformed; mmHg, millimeters of mercury; NSES, neighborhood socioeconomic status; WCort, waking cortisol.

^aAn ISES score of 3 equated to the annual income category of \$25,000 to \$30,000, and to the education category of having completed grades 9–11 (some high school).

Table 3
Gene-by-Neighborhood Effects on Waking Cortisol and Blood Pressure (N=208).

	B	β	SE	Est/SE	p-value
<i>Log Waking Cortisol (ng/mL)</i>					
Intercept	1.358	1.290	0.427	3.180	0.001 *
Age	-0.010	-0.143	0.006	-1.778	0.075
Sex	-0.059	-0.027	0.354	-0.167	0.867
Community	0.040	0.030	0.103	0.387	0.699
Medication	0.048	0.045	0.089	0.538	0.591
BMI	0.013	0.111	0.010	1.269	0.204
Individual SES	-0.066	-0.064	0.100	-0.656	0.512
Neighborhood SES ^a	-0.046	-0.099	0.049	-0.942	0.346
Genetic Risk ^a	0.103	0.037	0.180	0.572	0.567
GRxNSES	0.235	0.184	0.072	3.240	0.001 *
<i>Systolic BP (mmHg)</i>					
Intercept	110.247	5.477	12.709	8.674	0.000 *
Age	0.180	0.136	0.080	2.262	0.024 *
Sex	0.549	0.013	2.534	0.217	0.828
Community	2.860	0.114	1.552	1.842	0.065
Medication	-0.332	-0.016	1.450	-0.229	0.819
BMI	0.156	0.069	0.209	0.748	0.455
Individual SES	-0.927	-0.047	1.805	-0.514	0.607
Neighborhood SES ^a	-0.794	-0.089	0.360	-2.202	0.028 *
Genetic Risk ^a	-2.653	-0.050	2.135	-1.242	0.214
GRxNSES	-1.627	-0.067	1.082	-1.504	0.133
<i>Diastolic BP (mmHg)</i>					
Intercept	79.310	7.287	5.149	15.403	0.000 *

	B	β	SE	Est/SE	p-value
Age	-0.120	-0.168	0.038	-3.158	0.002 *
Sex	-3.265	-0.143	1.433	-2.278	0.023 *
Community	3.038	0.223	0.608	4.996	0.000 *
Medication	-0.270	-0.025	0.702	-0.385	0.700
BMI	0.049	0.040	0.098	0.501	0.616
Individual SES	-0.120	-0.011	0.899	-0.133	0.894
Neighborhood SES ^a	-0.299	-0.062	0.185	-1.616	0.106
Genetic Risk ^a	0.598	0.021	1.784	0.335	0.737
GRxNSES	-0.520	-0.039	0.637	-0.816	0.415

Note: BMI, body mass index; BP, blood pressure; GRxNSES, genetic risk-by-neighborhood socioeconomic status; Medication, blood pressure medication status; mmHg, millimeters of mercury; SES, socioeconomic status.

* $p < .05$, two-tailed test.

^aVariables were mean-centered.