Early-Life Trajectories in Socioeconomic Disadvantage and Adult Blood Pressure: The Moderating Role of *DRD4*

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Abstract

Although hypertension has a complex disease etiology that emerges from both environmental and genetic factors, the interplay of contextual disadvantage and genetic risk to produce cardiovascular outcomes is rarely examined. Using the nationally representative Add Health Study, this study builds on prior sociological and genetic research to investigate whether the effect of early-life trajectories of family and neighborhood socioeconomic disadvantage on adult blood pressure and hypertension is moderated by variants in the *DRD4* gene. Preliminary results identify a significant main effect of adolescent family and neighborhood disadvantage on adult blood pressure. Further, individuals who are homozygous for the *DRD4* long variant (7R-11R) have significantly greater risk for developing hypertension as adults compared to those that are homozygous for the short variant. On-going analyses will examine whether trajectories of socioeconomic disadvantage across the transition to adulthood interact with *DRD4* to predict risk for adverse cardiovascular outcomes.

Extended Abstract

Introduction

Extensive research has identified the detrimental effects of early-life socioeconomic disadvantage on cardiovascular health (Galorbardes et al. 2006; Kivimaki et al. 2005; Poulton et al. 2002; Wamala et al. 2001). Contexts of socioeconomic disadvantage during childhood and adolescence are thought to affect future health through exposure to stressful social circumstances during a sensitive period of individual development, thus influencing behavioral, psychological, and physiological pathways across the transition to adulthood. While this conceptualization of longitudinal relationships between socioeconomic disadvantage and cardiovascular health is widely embraced, few studies operationalize disadvantage as a longitudinal and multilevel construct with cardiovascular effects that depend on the timing, duration, and domain of disadvantage. Further, although hypertension is understood as a complex disorder that emerges through both genetic and environmental influences, no studies consider how contextual measures of disadvantage interact with genetic risk to produce cardiovascular outcomes across the life course. Genes related to dopaminergic functioning may provide crucial insight into the link between contextual disadvantage and cardiovascular health given the role of dopamine in physiological responses to stress across neurological and peripheral body systems (Imumorin et al. 2005; Kuchel 2003). The dopamine receptor D4 (*DRD4*) gene is of particular interest because it is thought to be involved in autonomic nervous system activity, and the long variant of *DRD4* has been found to adversely affect blood pressure regulation (Bek et al. 2006; Sen et al. 2005; Emilien et al. 1999).

Based on prior evidence of the contextual and genetic contributors to cardiovascular outcomes, this study examines the interaction between socioeconomic disadvantage at multiple

levels over time and a common genetic polymorphism within *DRD4* that is implicated in blood pressure regulation. We hypothesize that patterns of long-term exposure to socioeconomic disadvantage will differentially affect cardiovascular outcomes depending on variants in *DRD4*. Specifically, we expect that socioeconomic disadvantage at younger ages and of longer duration will result in increased blood pressure and greater hypertension risk overall, though risk will be substantially higher for individuals with the *DRD4* long variant. This is the first examination of the interplay between life course trajectories of disadvantage measured at multiple levels and genetic contributors to cardiovascular function, an orientation that reflects the complex etiology of adult hypertension.

Data

The data come from 10,135 participants in the National Longitudinal Study of Adolescent Health (Add Health). Respondents were age 12-18 in Wave I (1994-95) and followed up at ages 18-26 (Wave III; 2001-02) and 24-32 (Wave IV; 2008-09). Cardiovascular measures were collected at Wave IV and include systolic blood pressure, diastolic blood pressure, and a three-category indicator of hypertension based on clinical cut points for hypertension diagnosis ("Normal" systolic <120 mmHg and diastolic <80 mmHg; "Pre-hypertension" systolic 120-139 mmHg and diastolic 80-89 mmHg; "Hypertension" systolic 140+ mmHg and diastolic 90+ mmHg).

Census data were used to create neighborhood disadvantage indices in adolescence (Wave I), young adulthood (Wave III), and adulthood (Wave IV) based on five disadvantage indicators that were available at all waves and capture tract-level prevalence of poverty, low educational attainment, utilization of welfare, female-headed households, and unemployment. Each disadvantage scale ranges from 0-5 with higher numbers indicating higher disadvantage. A

family disadvantage index was created for Wave I based on five parellel indicators: low family income, low parent educational attainment, parent welfare receipt, single parent household, and parent unemployment. Consistent with the neighborhood disadvantage indices, the family disadvantage index ranges from 0-5. Family disadvantage indices will be constructed for Waves III and IV using measures that appropriately reflect disadvantage within each subsequent developmental stage of early adulthood. Cumulative indices of family and neighborhood disadvantage across all three waves will be constructed to capture overall exposure to disadvantage within these domains, and trajectories of increasing, decreasing, or stable disadvantage will be identified to capture the timing of exposure to socioeconomic disadvantage.

Saliva samples were collected in Wave IV, and genomic DNA was isolated from buccal cells and assayed for the *DRD4* gene. *DRD4* has a 48 bp VNTR in the third exon that ranges from 2 to 11 repeats, with 4R and 7R being the most common. Respondents were grouped based on genotype, with 2R-6R variants coded as "short" (S) and 7R-11R variants were coded as "long" (L); alternative coding strategies will be examined. *DRD4* genotypes consist of S/S, S/L, or L/L.

Methods

We used OLS regression models to examine the baseline associations between family and neighborhood disadvantages at Wave I and continuous measures of blood pressure at Wave IV (systolic and diastolic). Ordinal logistic regression models were used to identify associations between disadvantage indicators and risk of hypertension. We also identified baseline associations between *DRD4* and these three cardiovascular measures using the appropriate linear and ordinal models. All models adjusted for age, sex and race/ethnicity, and were run on the full

sample and stratified by race/ethnicity. Sampling weights were applied to provide nationally-representative estimates by adjusting for unequal probability sampling and attrition across study waves, and variance estimates were corrected for the clustered sampling design.

Additional models will interact *DRD4* genotypes with cumulative indices and trajectories of disadvantage to examine the moderating effect of *DRD4* on the longitudinal relationship between disadvantage indicators and cardiovascular outcomes. Models will also adjust for age, sex, race/ethnicity, body mass index, cigarette smoking, and use of anti-hypertensive medication. Sibling fixed effect models will also be examined to rule out potential unmeasured, time-invariant sources of bias.

Results

Tables 2 and 3 show that both family and neighborhood disadvantage in adolescence significantly increased blood pressure and risk of hypertension in adulthood among the full sample: higher family disadvantage was associated with an increase in both systolic and diastolic blood pressure, while experiencing higher neighborhood disadvantage increased diastolic blood pressure and the odds of hypertension. Stratification by race reveals that this association appears to be driven by the White sample. Table 4 identifies a significant positive association between the L/L *DRD4* genotype and elevated blood pressure (systolic, diastolic, and hypertension) relative to the S/S genotype among the full sample and the Black sample. Collectively, these results highlight several main effects of disadvantage and *DRD4* that are consistent across cardiovascular outcomes. Further analysis will incorporate additional waves of contextual data to capture the dynamic interaction between disadvantage and genetic risk to produce cardiovascular outcomes.

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Table 1. Descriptive Statistics: Disadvantage, DRD4, and Blood Pressure, Mean (SD) or % (N=10,135)

	Full Sample	**White** (N=5,850)	**Black** (N=1,915)	**Hispanic** (N=1,471)
Blood Pressure				
Systolic	125.19 (13.52)	125.07 (12.08)	126.39 (17.22)	124.54 (15.32)
Diastolic	79.47 (10.00)	79.38 (8.99)	80.06 (12.55)	78.93 (11.32)
Hypertension				
Binary (1=hypertension)	26.13	25.60	29.66	24.82
Categorical				
Normal	32.11	32.40	29.71	33.32
Pre-hypertension	48.08	48.27	48.53	47.90
Hypertension	19.81	19.32	21.76	18.78
DRD4				
S/S	62.26	62.85	58.05	56.87
S/L	32.85	32.73	34.05	37.52
L/L	4.89	4.42	7.90	5.61
Family Disadvantage Index (Wave I)				
0	43.39	50.04	21.90	25.89
1	28.42	29.48	22.94	29.14
2	14.16	11.24	22.24	22.57
3	9.26	6.75	19.73	13.73
4	3.85	2.09	9.12	8.00
5	0.93	0.39	4.07	0.67
Neighborhood Disadvantage Index (Wave I)				
0	63.43	75.01	21.28	43.96
1	8.83	8.05	11.45	10.31
2	4.53	2.64	7.19	10.89
3	5.62	4.45	10.59	7.40
4	9.75	7.04	18.92	16.08
5	7.84	2.81	30.57	11.37

Table 2. Associations between Family Disadvantage Index and Blood Pressure, Coefficients (SE) or Odds Ratios (95% CI) (N=10,135)

	Full Sample	**White** (N=5,850)	**Black** (N=1,915)	**Hispanic** (N=1,471)
Systolic Blood Pressure	0.334**	0.614***	0.0283	-0.392
	(0.165)	(0.220)	(0.282)	(0.438)
Diastolic Blood Pressure	0.250**	0.510***	-0.0999	-0.334
	(0.116)	(0.151)	(0.214)	(0.251)
Hypertension	1.035	1.090***	0.988	0.888*
	(0.987 - 1.086)	(1.025 - 1.159)	(0.901 - 1.084)	(0.783 - 1.006)

*** p<0.01, ** p<0.05, * p<0.1

Note: Associations between family disadvantage and systolic and diastolic blood pressure were analyzed using OLS regression. Family disadvantage and hypertension was assessed using ordinal logistic regression.

All models adjust for age, sex, and race/ethnicity.

Table 3. Associations between Neighborhood Disadvantage and Blood Pressure, Coefficients (SE) or Odds Ratios (95% CI) (N=10,135)

	Full Sample	**White** (N=5,850)	**Black** (N=1,915)	**Hispanic** (N=1,471)
Systolic Blood Pressure	0.267	0.656***	-0.348	-0.359
	(0.171)	(0.191)	(0.229)	(0.376)
Diastolic Blood Pressure	0.223**	0.436***	-0.139	-0.227
	(0.103)	(0.120)	(0.183)	(0.231)
Hypertension	1.054**	1.114***	0.977	0.946
	(1.007 - 1.103)	(1.057 - 1.174)	(0.918 - 1.040)	(0.850 - 1.053)

*** p<0.01, ** p<0.05, * p<0.1

Note: Associations between neighborhood disadvantage and systolic and diastolic blood pressure were analyzed using OLS regression. Neighborhood disadvantage and hypertension was assessed using ordinal logistic regression.

All models adjust for age, sex, and race/ethnicity.

Table 4. Associations between DRD4 and Blood Pressure, Coefficients (SE) or Odds Ratios (95% CI) (N=10,135)

	Full Sample	**White** (N=5,850)	**Black** (N=1,915)	**Hispanic** (N=1,471)
Systolic Blood Pressure				
S/L	0.290	-0.0572	-0.895	1.534
	(0.364)	(0.436)	(1.066)	(0.998)
L/L	2.259***	1.844*	4.018**	1.778
	(0.755)	(1.022)	(1.865)	(2.140)
Diastolic Blood Presure				
S/L	0.250	-0.0308	-0.582	1.437
	(0.276)	(0.317)	(0.682)	(0.901)
L/L	1.372**	0.754	3.369**	1.430
	(0.673)	(0.894)	(1.368)	(1.926)
Hypertension				
S/L	1.102*	1.077	0.876	1.411**
	(0.992 - 1.224)	(0.945 - 1.226)	(0.656 - 1.168)	(1.052 - 1.893)
L/L	1.310**	1.153	1.806***	1.687
	(1.054 - 1.628)	(0.872 - 1.524)	(1.165 - 2.802)	(0.740 - 3.842)

*** p<0.01, ** p<0.05, * p<0.1

Note: Associations between *DRD4* and systolic and diastolic blood pressure were analyzed using OLS regression. *DRD4* and hypertension was assessed using ordinal logistic regression.

All models adjust for age, sex, and race/ethnicity.

Reference category is S/S