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Disparities in insulin resistance between black and white adults in the United States: The role of lifespan stress exposure☆

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ABSTRACT

Background: Disparities in insulin resistance between Black and White adults in the United States are well documented, yet relatively little is known about the psychosocial or biological antecedents of these inequities. The current study examined childhood adversity and contemporaneous psychosocial stressors in adulthood as possible mediators of the racial disparity in insulin resistance. Inflammatory and hypothalamic-pituitary adrenal (HPA) axis mechanisms implicated in associations between lifespan stress exposure and insulin resistance were also considered.

Methods: Data were derived from the biomarker component of the Midlife in the United States Study (N = 1170, 20% Black, 56% female, Mean age = 54.7 years, SD = 11.6). A homeostatic model assessment of insulin resistance (HOMA-IR) was calculated from fasting glucose and insulin concentrations. Twelve risk factors relating to household dysfunction, socioeconomic disadvantage, and maltreatment were sum scored to index childhood adversity. Measures of adult stress included socioeconomic adversity, major stressful events, everyday discrimination, and lifetime discrimination.

Results: Levels of insulin resistance were higher among Black than White adults. Childhood adversity was positively associated with HOMA-IR, and attenuated 18% of the race difference. Measures of adult stress mediated 33% of the association between childhood adversity and HOMA-IR, and accounted for an additional 47% of the race difference. Higher inflammation and lower nocturnal cortisol both played an important role in mediating the association between stress exposure and HOMA-IR.

Conclusions: Findings are consistent with prior research showing that childhood adversity and adult stress are salient predictors of glucose metabolism, and extend this work by showing that lifespan stress exposures attenuate a significant portion of the Black-White disparity in HOMA-IR. Results also suggest stress effects on insulin resistance through inflammatory and HPA-axis pathways.

1. Introduction

Racial disparities in type 2 diabetes (T2D) are substantial in the United States, with an approximately two-fold higher prevalence among Black/African-American (AA) relative to White/European-American (EA) adults (Chatterjee et al., 2014). Furthermore, T2D is a leading contributor to enduring race differences in mortality (Wong et al., 2002). Understanding the determinants of disparities in glucose regulation is thus a crucial component of broader efforts to address health disparities (CDC, 2017).

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Lifespan stressors may be key in understanding racial disparities in glucoregulation. These include aspects of childhood adversity as well as adult stress exposures. Both have been linked to diabetes and glucose regulation in several studies (Maniam et al., 2014). In one large population study, childhood socioeconomic disadvantage was associated with subsequent risk for T2D and impaired fasting glucose concentrations more than 30 years later (Puolakka et al., 2016). Other population studies of midlife adults have also documented associations between childhood adversity or maltreatment and subsequent glucose regulation or T2D incidence (Thomas et al., 2008). With respect to adult psychosocial stress, one large study of Hispanic adults in the United States reported significant associations between chronic stress, fasting glucose, and glucose tolerance (McCurley et al., 2015), while a population study of Scandinavian adults found that stressful life events predicted glucose regulation and metabolic syndrome (Pyykkönen et al., 2010). Race differences in stress exposure across the life span, stemming from social and historical oppression, are also well documented (Fuller-Rowell et al., 2016; Sternthal et al., 2011). Together, these findings suggest that both childhood adversity and adult psychosocial exposures may be important mediators of race differences in glucoregulation. However, despite the clear significance of understanding social determinants of disparities in T2D, the role of life span stress exposures as mediators of race differences in glucoregulation remains largely unexamined (Fuller-Rowell et al., 2018).

Insulin resistance—defined as the inability of insulin to stimulate glucose disposal—is an important indicator of health risk across the glucoregulation spectrum, irrespective of whether glucose levels are in the T2D range. In particular, insulin resistance is central to the pathogenesis of T2D, as well as a salient risk factor for subsequent cardiovascular disease and other comorbidities (Reaven et al., 2004). Reliable indexes of insulin resistance can be calculated from fasting glucose and insulin concentrations (Bonora et al., 2000) and may be important mediators of psychosocial stress effects on cardiometabolic disease (Rosmond, 2003).

Mechanisms for contemporaneous stress effects on insulin resistance are likely to operate through various physiologic conduits including the hypothalamic-pituitary adrenal (HPA) axis and inflammatory pathways (Rosmond, 2003). Stress effects on regulation of diet, eating behaviors, sleep patterns, and physical activity are also likely to play an important role (Aschbacher et al., 2014; Stults-Kolehmainen and Sinha, 2014). In addition to these pathways, childhood and adolescent stress exposure may further influence insulin resistance through epigenetic mechanisms and by setting glucocorticoid responses to stress early in the life span (Maniam et al., 2014; Miller et al., 2011). According to theories of the stress process (Pearlin, 1989), childhood adversity may also proliferate into adult psychosocial stressors, which in turn are hypothesized to influence insulin resistance through the mechanisms described above. Childhood adversity and adult stress may also have cumulative or additive effects such that each operates as an independent predictor of adult health (Montez and Hayward, 2014).

Although socioeconomic factors have been shown to account for a portion of the race difference in T2D (Gaskin et al., 2013; LaVeist et al., 2009), few studies have considered the degree to which childhood adversity or adults stress exposures mediate race differences in glucoregulation. A deeper understanding of the biological mechanisms linking lifespan stress exposures to dysregulated glucose metabolism (Maniam et al., 2014; McCurley et al., 2015; Puolakka et al., 2016) is also needed. With these objectives in mind, the overarching hypotheses of the present inquiry were that childhood adversity and adult psychosocial stress would each partially mediate race differences in insulin resistance, and that some of the effects of childhood adversity on insulin resistance would be accounted for by adult psychosocial stress. We also hypothesized that psychosocial stress effects on insulin resistance would be mediated through inflammatory and HPA-axis pathways.

2. Methods

Analyses draw on data from the Midlife in the United States (MIDUS) Study (Brim et al., 2004; Love et al., 2010). MIDUS is a national study of health and aging that began in 1995 with a sample of 7000 non-institutionalized adults from the 48 contiguous states (Brim et al., 2004). The second wave (MIDUS 2) began in 2004, with 75% of surviving MIDUS 1 respondents participating. An oversample of AAs from Milwaukee, WI (N = 592) was added at MIDUS 2 to increase representation of AAs and facilitate analysis of racial disparities in health. Forty three percent of MIDUS 2 subjects also participated in a biological data collection protocol (N = 1255; 2004–2009). This subsample was not significantly different from MIDUS 2 participants on age, sex, race, marital status, or income, but were slightly more educated than the larger MIDUS 2 sample (Love et al., 2010). The protocol involved an overnight clinic stay and included a fasting blood draw in the morning of the second day (see Love et al., 2010 for a detailed protocol description). Due to our focus on Black-White disparities, 148 individuals not categorized as AA or EA were excluded from analyses. The final analytic sample of 228 AAs and 942 EAs (N_{total} = 1170), included a wide age range (35–85 years; M = 57.4; SD = 11.6) and was 57% female. Descriptive statistics for each racial/ethnic group are presented in Table 1. All data collection and analysis was approved by an institutional review board, and all participants provided written informed consent.

2.1. Measures

2.1.1. Insulin resistance

Fasting glucose and insulin concentrations were determined using established techniques (Gruenewald et al., 2012). Full descriptions of assay procedures are publicly available as part of MIDUS 2 biomarker protocol documentation (midus.wisc.edu). In brief, glucose was determined using an enzymatic colorimetric method, and had inter- and intra-assay CV of 1%. Insulin was measured using immunochemiluminescent technology with inter-assay CV of 2.4–4.6% and intra-assay CV of 2.5–4%. The homeostatic model assessment of insulin resistance (HOMA-IR) was computed from fasting glucose (G0, mg/dL) and insulin (I0, μIU/mL) concentrations with the following formula: HOMA-IR = (G0 × I0)/405 (Matthews et al., 1985). HOMA-IR is a commonly used measure of insulin resistance that has been prospectively associated with cardiovascular disease (Jeppesen et al., 2007). To correct for a non-symmetric distribution, the log of HOMA-IR was used in all analyses.

2.1.2. Childhood adversity

To index childhood adversity, twelve factors relating to household stress, family socioeconomic disadvantage, and childhood maltreatment were assessed. Specific indicators, shown in supplemental Table 2, were similar to items commonly included on childhood adversity measures (Felitti et al., 1998; Slopen et al., 2010). A detailed description of this measure alongside syntax for scoring is provided in supplemental online content.

2.1.3. Adult stress exposures

Three domains of adult stress were examined:

2.1.3.1. Major stressful events. An inventory of nineteen stressful events and their age of occurrence was completed by participants (Turner and Wheaton, 1995). A sum score indicating the number of events experienced prior to age 19 was calculated (detailed description of events and scoring available in supplemental online content). Experiences referred to major family, economic, or miscellaneous stressors.

2.1.3.2. Discrimination. Lifetime discrimination was assessed using an

Table 1
Descriptive Statistics for Study Variables, Shown for African Americans (n = 228) and European Americans (n = 942).

	African American *Mean ± SD* (%)	European American *Mean ± SD* (%)	Race difference *P value*
Age (years)	53.6 ± 10.3	58.4 ± 11.7	< .001
Sex (male)	(32.9)	(46.0)	< .001
Cohabitation status (partnered)	(44.4)	(76.2)	< .001
Childhood adversity (#)	4.0 ± 2.9	2.4 ± 2.3	< .001
Major stressful events (#)	3.2 ± 2.2	1.9 ± 1.7	< .001
Major discrimination events (#)	2.9 ± 2.7	.88 ± 1.4	< .001
Everyday discrimination (range: 9–36)	14.8 ± 6.4	12.5 ± 4.1	< .001
Socioeconomic adversity (range: 0–7)	4.1 ± 2.4	1.4 ± 1.6	< .001
Fasting insulin (uIU/mL)	16.5 ± 15.4	12.7 ± 12.5	< .001
Fasting glucose (mg/dL)	111.1 ± 42.3	99.9 ± 23.4	< .001
HOMA-IR (Ln [insulin*glucose/405])	1.5 ± .64	1.3 ± .55	< .001
Diabetes Medication	(19.3)	(8.3)	< .001
C-reactive protein (ug/dL)	1.34 ± .80	1.0 ± .68	< .001
Interleukin-6 (pg/mL)	1.5 ± .54	1.2 ± .51	< .001
E-selectin (ng/mL)	52.1 ± 28.9	41.3 ± 20.6	< .001
Overnight urinary cortisol (Ln [ug/dL])	2.2 ± .68	2.6 ± .72	< .001
Daytime salivary cortisol (nmol/L)	8.0 ± 5.4	11.2 ± 5.9	< .001
Body mass index (kg/m^2)	32.8 ± 8.6	29.0 ± 5.9	< .001
Waist circumference (cm)	101.4 ± 18.1	96.5 ± 15.7	< .001
Prudent diet (range: 0-7)	3.9 ± 1.4	4.3 ± 1.4	< .001
Physical activity (Ln [METs/Week])	4.1 ± 1.8	5.1 ± 1.9	< .001
Sleep problems (range: 0-21)	7.8 ± 4.2	5.8 ± 3.4	< .001
Cigarette smoker	(30.7)	(11.2)	< .001
Heavy drinker	(16.2)	(7.6)	.001

Table 2
Descriptive Statistics for Childhood Adversity and Adult Stress Measures, Shown by Race.

	African American (n = 228) *Mean ± SD* (%)	European American (n = 942) *Mean ± SD* (%)	Race Difference *P-value*
Childhood Adversity	3.4 ± 2.7	2.0 ± 2.1	< .001
Emotional abuse	(27.9)	(22.4)	.081
Physical abuse	(34.2)	(20.1)	< .001
Sexual abuse	(26.5)	(22.2)	.178
Emotional neglect	(28.4)	(23.0)	.088
Physical neglect	(31.6)	(19.6)	< .001
Family received public assistance	(27.3)	(4.8)	< .001
Parental education	(41.8)	(19.7)	< .001
Moved 3+ times	(32.0)	(27.5)	.183
Did not live with biological parents	(48.7)	(19.0)	< .001
Low status parental occupation	(58.6)	(22.5)	< .001
Parental death	(23.2)	(9.3)	< .001
Sibling death	(6.6)	(3.3)	.819
Adult Stress			
Major stressful events	3.2 ± 2.2	1.9 ± 1.7	< .001
Major discrimination events	2.9 ± 2.7	.88 ± 1.4	< .001
Everyday discrimination	14.8 ± 6.4	12.5 ± 4.1	< .001
Socioeconomic adversity	4.1 ± 2.4	1.4 ± 1.6	< .001

inventory of 11 major events (e.g., not hired for a job, hassled by police), with a possible score of 0–11 (α = .88) (Kessler et al., 1999; Williams et al., 2008, 1997). Everyday discrimination (Williams et al., 1997) was assessed from nine forms of discrimination (e.g., treated with less courtesy than other people). Items were on a four point scale (1 = never, 4 = often) and had high internal consistency (α = .91).

2.1.3.3. Socioeconomic adversity. Socioeconomic adversity was assessed as the sum of eight dichotomous socioeconomic risk factors (α = .73). Aggregate indexes of socioeconomic status or disadvantage are frequently used and are optimal when attempting to capture overall disadvantage within a single variable (Chapman et al., 2010). A detailed description of this measure is provided in supplemental online content.

2.1.4. Inflammatory mediators

Biomarkers of inflammatory physiology were assessed from serum or plasma samples. Detailed description of assay procedures and statistics for C-reactive protein, interleukin-6, and E-selectin are available in the protocol documentation and have been described elsewhere (Coe et al., 2011; Gruenewald et al., 2012).

2.1.5. HPA-axis mediators

Two measures of cortisol output were collected to index overnight and daytime hypothalamic-pituitary-adrenal (HPA) axis activity. A 12-hour overnight urinary sample was collected during the lab visit from which cortisol concentration (ug) adjusting for creatinine levels (g) was determined via high-pressure liquid chromatography. On the second day of the lab visit, four saliva samples were collected before and during a protocol consisting of cognitive tasks. Cortisol concentrations across the four samples were highly correlated (*r* coefficients ranged from .47 to .93) and thus were averaged as a crude index of daytime cortisol output (α = .88). This approach is similar to indexes of total cortisol output used in prior research (Pruessner et al., 2003).

2.1.6. Adiposity

Nursing staff collected anthropometric measurements as part of the biomarker protocol. Body mass index (BMI) was calculated using the standard formula: weight (kg)/height (m)^2. Waist circumference was measured at the point between the ribs and iliac crest (Gruenewald et al., 2012).

2.1.7. Health behavior controls

Cigarette smoking (0 = nonsmoker, 1 = current smoker), alcohol consumption (0 = nonsmoker, 1 = current smoker), physical activity, sleep quality, and diet were assessed via self-report measures. Descriptions of these measures are provided in supplemental online content.

2.1.8. Medication use

Participants were instructed to bring all prescription and over-the-

counter medications to their study visit. All medications and reasons for use were documented. A dichotomous variable was used to indicate whether medications were being taken for diabetes.

2.1.9. Sociodemographic controls

Sociodemographic variables included sex (coded as 0 = female, 1 = male), age (in years), race (0 = White/European American, 1 = Black/African American), and cohabitation status (1 = married or living with partner, 0 = not married or living with partner).

2.2. Analysis plan

Analyses were conducted in Mplus v. 7.11. A two-pronged analytic approach was used. First, a series of linear regression models was estimated (Table 2) to examine predictors of HOMA-IR adjusting for covariates. Diabetes medication use was not directly controlled in analyses due to conceptual and empirical overlap with insulin resistance. However, sensitivity analyses considering the influence of medication use on the reported results are examined.

Next, path analyses were conducted to probe indirect effects and test mediation hypotheses. Indirect effects were estimated using the product of coefficients method with bias-corrected bootstrapped confidence intervals. Additional information relating to path model analyses is provided in supplemental online materials. Full information maximum likelihood estimation was used to deal with missing data on individual variables. This allowed for the sample size to be consistent across all estimated models. Daytime salivary cortisol had the most missing data (33.4%) followed by major stressful events (28.0%), major experiences of discrimination (6.2%), and sleep problems (6.3%). All other variables had < 1% missing data.

3. Results

Descriptive statistics for study variables are shown separately for Black and White participants in Table 1. Independent sample *t*-tests and chi-square tests were used to estimate the significance of group differences. Differences between racial groups were present across nearly all study variables such that Black adults had greater socioeconomic disadvantage, more childhood and adulthood stress exposure, and more behavioral and biological risk factors. Race differences in exposure to each component of the childhood adversity index are shown in Table 2. Black adults were more likely to be exposed to seven of the twelve childhood adversity components relative to Whites.

Of the twelve childhood adversity indicators, seven were significantly correlated with HOMA-IR, as was the childhood adversity composite. The remaining five indicators, although non-significant, had associations with HOMA-IR in the expected direction. In addition, all four of the adult stress measures were correlated with HOMA-IR. A correlation matrix showing associations between stress measures, health behaviors, and biological indicators is included in supplemental materials (Table S1).

3.1. Mediators of Race differences in HOMA-IR

A series of models examining predictors of HOMA-IR are shown in Table 3. HOMA-IR and continuous predictor variables were standardized to have a mean of 0 and SD of 1. Thus, associations with HOMA-IR can be interpreted as standardized coefficients for continuous predictors and as mean standardized differences for binary predictor variables. Supplemental analyses were also conducted to estimate the magnitude and statistical significance of indirect effects (e.g., of race on insulin resistance through childhood adversity and adult stress measures). These models included additional paths from exogenous predictor variables to relevant mediator variables, and were estimated such that direct effects on insulin resistance were identical to the parameter estimates reported in corresponding regression models (shown in Table 3). The percent attenuation of regression coefficients reported in the text, which can be calculated from the parameter estimates in Table 3, is therefore identical to the magnitude of the corresponding total indirect effect divided by the total effect. Where relevant to our hypotheses, total indirect effects are reported alongside regression results. More detailed meditation pathways for stress effects on insulin resistance are then examined in the path analyses below.

Findings from Model 1 indicated a significant race difference in HOMA-IR, equivalent to .43 *SD* units higher levels among Black adults relative to White adults ($p < .001$). In Model 2, childhood adversity was a significant predictor of insulin resistance ($p < .001$), and attenuated race differences in HOMA-IR by 18% (indirect effect: β = .076, SE = .022, $p = .001$). In supplemental analyses relating to Model 2, a significant indirect effect of race on HOMA-IR through childhood adversity was evident (β = .030, SE = .009, $p = .001$).

Adult stressors were added in Model 3. In total, adjusting for adult stressors reduced the race difference in HOMA-IR by an additional 47% (total indirect effect: β = .258, SE = .064, $p < .001$). Childhood adversity and adult stressors together attenuated approximately two thirds (65%) of the original race difference (β = .314, SE = .065, $p < .001$). When adjusting for adult stress measures, the association between childhood adversity and HOMA-IR was attenuated by 33% (total indirect effect: β = .048 SE = .013, $p < .001$) but remained a significant independent predictor ($p = .007$). Major experiences of discrimination ($p = .024$) and socioeconomic adversity ($p = .028$) were significantly associated with insulin resistance, whereas estimates for the other adults stress measures did not reach statistical significance (after adjusting for the other adult stress measures).

In supplemental analyses relating to Model 3, each measure of adult stress was also considered separately as a predictor of HOMA-IR (Table S2) and indirect effects of race on HOMA-IR through each adult stress measure were estimated. Indirect effects of race on HOMA-IR were statistically significant for three of the four adult stress measures: major stressful life events (β = .017, SE = .008, $p = .030$), major discrimination events (β = .048, SE = .015, $p = .002$), and economic adversity (β = .038, SE = .016, $p = .014$). Standard errors were similar across models and variance inflation factor values were less than 1.15, suggesting that multicollinearity was not a problem in models that included all adult stress measures.

Model 4 findings indicated that inclusion of adiposity and health behavior measures as controls reduced the association between childhood adversity and HOMA-IR by 41% (from .090 to .053; total indirect effect: β = .022, SE = .019, $p = .245$) and substantially attenuated significant associations between adult stress variables and HOMA-IR. Specifically, effects of economic adversity (β = .020 SE = .034, $p = .554$) and major experiences of discrimination (β = .059 SE = .034, $p = .083$) were attenuated by 76% (total indirect effect: β = .053 SE = .022, $p = .016$) and 36% (total indirect effect: β = .023, SE = .0214, $p = .288$) respectively, and dropped below statistical significance. Healthy dietary behaviors ($p = .002$), physical activity ($p = .001$), and waist circumference ($p < .001$) were associated with HOMA-IR in expected directions, whereas cigarette smoking, heavy alcohol use, and body mass index were not significant predictors (net of waist circumference and other health behaviors).

Model 5 results indicated that when measures of inflammation and HPA-axis activity were added, stress effects on HOMA-IR were substantially attenuated. As compared to Model 3, effects of economic adversity (β = .036, SE = .036, $p = .316$) and major experiences of discrimination (β = .063, SE = .037, $p = .086$) were attenuated by 58% (total indirect effect: β = .076, SE = .015, $p < .001$) and 32% (total indirect effect: β = .049, SE = .014, $p < .001$), respectively, and dropped below statistical significance. The association between childhood adversity and HOMA-IR was attenuated by 19% (total indirect effect: β = .020, SE = .012, $p = .086$) and remained significant ($p = .018$). CRP ($p < .001$), E-selectin ($p < .001$), and overnight urinary cortisol ($p < .001$) were significantly associated with HOMA-IR,

Table 3
Results of Regression Models Examining Predictors of Insulin Resistance (HOMA-IR).

	Model 1 B (SE)	Model 2 B (SE)	Model 3 B (SE)	Model 4 B (SE)	Model 5 B (SE)	Model 6 B (SE)
Intercept (Ln[HOMA-IR])	**−.219*** (.064)**	**−.221** (.064)**	**-.220*** (.062)**	−.036 (.056)	**−.169** (.059)**	−.001 (.057)
Race (Black = 1, White = 0)	**.433*** (.086)**	**.357*** (.086)**	.153 (.101)	.035 (.090)	−.025 (.097)	-.033 (.091)
Childhood Adversity		**.135*** (.032)**	**.090** (.033)**	**.053* (.027)**	**.073* (.031)**	**.053* (.026)**
Major Stressful Life Events			.050 (.037)	.020 (.031)	.025 (.034)	.023 (.030)
Major Discrimination Events			**.092* (.041)**	.059+ (.034)	.063+ (.037)	.053 (.033)
Everyday Discrimination			.046 (.036)	.001 (.031)	.027 (.034)	−.003 (.031)
Socioeconomic Adversity			**.085* (.039)**	.020 (.034)	.036 (.036)	.016 (.034)
Prudent Diet				**−.078** (.025)**	–	**−.072** (.025)**
Physical Activity				**−.086** (.025)**	–	**−.067** (.025)**
Sleep Problems				**.045* (.028)**	–	.020 (.028)
Current Smoker				−.068 (.083)	–	−.105 (.081)
Heavy Drinker				−.105 (.080)	–	−.119 (.079)
Body Mass Index				.077 (.071)	–	.038 (.067)
Waist Circumference				**.445*** (.075)**	–	**.427*** (.072)**
Ln (CRP)					**.215*** (.034)**	.057+ (.031)
Ln (IL-6)					.040 (.034)	−.021 (.028)
E-selectin					**.197*** (.033)**	**.149*** (.030)**
Ln (Overnight Urinary Cortisol)					**−.141*** (.027)**	**−.080** (.023)**
Daytime Salivary Cortisol					−.023 (.027)	−.019 (.024)
R^2	.034**	.051***	.073***	.340***	.199***	.367***

Note. Unstandardized coefficients are shown with standard errors in parentheses. HOMA-IR and continuous predictor variables were z-scored to have a mean of 0 and *SD* of 1. All models also include controls for sex, age, and cohabitation status. Estimates significant at $p < .05$ are shown in bold.
+ $p < .10$.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

whereas daytime cortisol ($p = .402$) and IL-6 ($p = .239$) were not significant predictors.

A final model was fit in which all variables were added (Model 6). Results indicated that the association between childhood adversity and HOMA-IR was attenuated by 41% relative to Model 3 estimates (total indirect effect: β = .024, SE = .020, $p = .233$) but remained significant ($p = .045$). Effects of economic adversity (β = .016, SE = .034, $p = .641$) and major experiences of discrimination (β = .053, SE = .033, $p = .105$) were attenuated by 81% (total indirect effect: β = .069, SE = .023, $p = .003$) and 42% (total indirect effect: β = .037, SE = .023, $p = .110$) and were non-significant.

Sensitivity analyses excluding those taking medication for diabetes showed the same pattern of findings. Specifically, among these generally healthier participants, Black adults continued to be at a disadvantage relative to Whites in terms of higher HOMA-IR (.38 SD units, $p < .001$). The inclusion of stress variables in Models 2 and 3 explained 20 and 76% of the Black-White difference in HOMA-IR, and further adjustment in Models 4–6 attenuated childhood adversity and adult stress effects on HOMA-IR. Full model results for sensitivity analyses relating to medication use are presented in Table S3 of the supplemental material.

3.2. Path analysis results

A complete path model was estimated to further elucidate mediation pathways implied by regression results. The advantage of path models was that multiple endogenous variables could be modeled simultaneously, which facilitated estimation of indirect effects (i.e., statistical tests of mediation). Path coefficients for the final path model are shown in Fig. 1 and a full description of path model results and justification for the final fitted model is reported in supplemental online content. Of the potential biological mechanisms examined, inflammatory markers were consistent in mediating the link between stress variables and HOMA-IR. Overnight urinary cortisol was a significant mediator of the path between childhood adversity and HOMA-IR such that more exposure to childhood adversity was associated with blunted overnight cortisol levels, which in turn were associated with higher levels of insulin resistance

To examine stress effects on HOMA-IR and biomarkers net of health behaviors and adiposity, a second path model was fit. Results of this model were consistent with findings from regression models shown in Table 3 that adjust for health behaviors and adiposity and are reported in Supplemental materials (Fig. S1).

4. Discussion

The burden of T2D in the United States is substantial. Prevalence has more than doubled since 1990, and T2D is now a contributing factor in at least 10 percent of all deaths annually (CDC, 2017). However, this burden is not evenly distributed within the population. Racial disparities are notable, with significantly higher prevalence among Black, Hispanic, and Native American adults relative to Whites and Asians (CDC, 2017). Social determinants of these disparities are not well understood, and biological mechanisms for stress effects on glucoregulation remain unclear (Fuller-Rowell et al., 2018). By examining psychosocial predictors of Black-White differences in insulin resistance, alongside inflammatory and HPA-axis mediators, this investigation begins to address these knowledge gaps.

The results document that childhood adversity and contemporaneous adult stress mediate a substantial portion of the Black-White disparity. Regarding adult stress measures, major stressful events, socioeconomic adversity, major experiences of discrimination, and everyday discrimination, all attenuated a portion of the disparity in HOMA-IR when examined in separate models. In concurrent models, socioeconomic adversity and major experiences of discrimination remained independent mediators. These findings build on prior research showing an association between psychosocial stress and glucose metabolism (Puolakka et al., 2016; Thomas et al., 2008), and add to research showing race differences in glucoregulation (Gaskin et al., 2013; LaVeist et al., 2009). Importantly, the findings extend this work by demonstrating that race differences are mediated by modifiable psychosocial exposures. The finding that discrimination and socioeconomic adversity were the strongest mediators of racial disparities is consistent with research linking socioeconomic adversity to glucoregulation

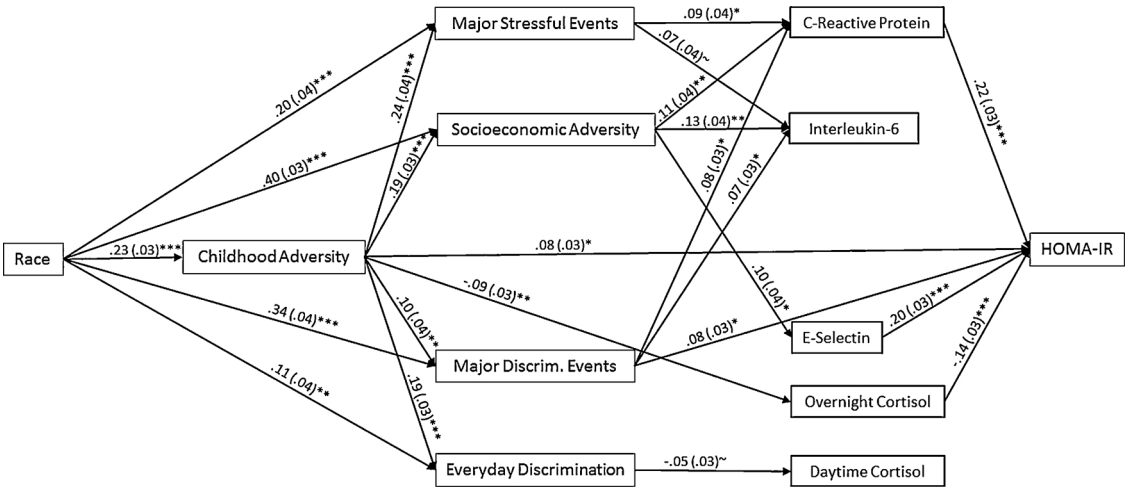

Fig. 1. Path model results showing psychosocial and biological mechanisms for race differences in insulin resistance (HOMA-IR).
Note. Standardized coefficients are shown with standard errors in parentheses. Age, sex, and cohabitation status are controlled. Estimates shown on underside of paths are additionally adjusted for health behaviors and adiposity. Covariances, residual variances, and direct paths from race to biomarkers were estimated, but are not shown for parsimony. $\sim p < .10$. $^{*}p < .05$. $^{**}p < .01$. $^{***}p < .001$.

(Stringhini et al., 2013), and showing that racial discrimination is a consequential factor in black-white health disparities (Chambers et al., 2004; Ryan et al., 2008). The current study extends this work by documenting an association between perceived racial discrimination and insulin resistance, and is the first to show that experiences of discrimination partially mediate Black-White disparities in glucose metabolism.

In showing that the association between childhood adversity and insulin resistance was partially explained by adult stress measures, the results also support the notion that childhood adversity can proliferate across the life span, and that early life exposures may be associated with several domains of subsequent adults stress (Ong et al., 2009; Pearlin, 1989; Pearlin et al., 2005). These findings are also in line with conceptualizations of cumulative inequality—e.g., that childhood adversity is associated with subsequent stressful life events that in turn are linked with physiologic dysregulation (Hatch, 2005). That childhood adversity remained a significant independent predictor after adjusting for contemporaneous exposures suggests the unique significance of childhood experiences, and is congruent with calls for special attention to addressing disadvantage early in the life span (Shonkoff, 2016) in addition to tackling adult stressors disproportionately experienced by racial/ethnic minority groups (Slopen et al., 2012; Sternthal et al., 2011).

Another key focus of this study was to examine biological mechanisms for psychosocial stress effects on insulin resistance with a focus on inflammatory and HPA-axis pathways. With respect to inflammatory pathways, major stressful events, economic adversity, and major experiences of discrimination were all associated with one or more inflammatory markers, which in turn were linked with insulin resistance. Indirect effects of all three adult stress measures on HOMA-IR through inflammation were also significant, thus providing strong support for an inflammatory pathway from stress exposure to insulin resistance. These results add to prior research (animal and human models) linking glucose metabolism to inflammation and psychosocial stress (Maniam et al., 2014; McCurley et al., 2015; Puolakka et al., 2016). The results also link literatures on racial disparities in inflammatory physiology (Fuller-Rowell et al., 2015; Slopen et al., 2010) and glucoregulation (Gaskin et al., 2013; LaVeist et al., 2009).

Regarding HPA-axis mediators, results indicated support for a "hypocortisolism" pathway linking childhood adversity to insulin resistance. Specifically, childhood adversity was associated with lower overnight urinary cortisol concentrations, which in turn were associated with higher levels of insulin resistance. These findings build on a large and complex literature examining stress and the HPA-axis. Elevated basal cortisol levels have been frequently observed in maltreated children (Carrion et al., 2002; Cicchetti and Rogosch, 2001). However, low or blunted cortisol output has more frequently been observed when the effects of childhood adversity have been considered on more distal, adult glucocorticoid measures (Danese and McEwen, 2012; Ellis and Del Giudice, 2019; Miller et al., 2007). Results of the current study bolster this perspective. Furthermore, that blunted cortisol output functions as a mediator of the association between childhood adversity and insulin resistance is a novel contribution of this research, and serves to bring together two growing areas of study: the link between the HPA-axis and glucoregulation, and the association between childhood adversity and cortisol.

With respect to the finding that lower cortisol concentrations were associated with higher insulin resistance, it is noteworthy that this result adds complexity to the current scientific consensus. In particular, an established finding is that high levels of glucocorticoids (such as in Cushings Syndrome), induce insulin resistance (Andrews and Walker, 1999; Purnell et al., 2009). In contrast, the results of the current study show that in a population sample of adults, it was low or blunted overnight cortisol concentrations that were associated with higher insulin resistance. Rather than being seen as directly contradictory, these differing results might more accurately be seen to reflect differences in the sample, timing/age of cortisol exposure, or the range of cortisol concentrations under consideration (e.g., in clinical vs. non-clinical sample) (Miller et al., 2007). With very few population studies examining biological mechanisms for stress effects on insulin resistance through HPA-axis pathways, additional research on this topic is needed.

Several limitations and related future directions should be noted. Although depth and breadth of psychosocial assessments is a significant strength of this study, one limitation of the reported analyses was that stress assessments were self-report and retrospective. Examination of objective measures of stress exposure is therefore an important consideration, which could help to provide further insight into the reported findings. As reported herein, alternative model specifications and prior research provided support for the direction of associations specified in the reported models. However, the cross-sectional nature of the data limits our ability to make strong claims about the directionality of associations and precludes the possibility of completely ruling out third variable explanations. Longitudinal models or alternative methodological approaches (e.g., natural or quasi experiments; Bor et al., 2018) will be especially important in developing robust evidence. Specifically, an important future focus will be to replicate and strengthen the reported stress mediation results relating to explanations for black-white

disparities in insulin resistance. Attention to when in the life span disparities in insulin resistance emerge, and the relative importance of specific social determinants at different life stages will be key considerations.

With little prior work examining psychosocial factors as mediators of Black-White differences in glucoregulation, the current study adds importantly to research on racial health disparities. However, a clear limitation was that Native American and Hispanic populations—among whom glucoregulation outcomes are similar to African Americans—were not considered. Studies focusing on the social determinants of glucoregulation in these populations are clearly needed and should be a priority in future research.

With respect to consideration of social determinants, the current study is the most comprehensive examination of Black-White disparities in insulin resistance to date. Overall, the findings suggest that childhood adversity and adult stress exposures are consequential predictors of group differences in insulin resistance, and that stress effects on insulin resistance operate through both inflammatory and HPA-axis pathways. Moving forward, additional research will be needed to pinpoint stress exposures at particular points in the life span that are most consequential determinants of disparities in glucoregulation. Consideration of programmatic or policy interventions to address group disparities more broadly, through reduction of psychosocial stress exposures will also be essential.

Conflicts statement

The authors of this manuscript declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.psyneuen.2019.04.020.

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