International Journal of Obesity www.nature.com/ijo

ARTICLE

Check for updates

Epidemiology and Population Health

The weight of childhood adversity: evidence that childhood adversity moderates the impact of genetic risk on waist circumference in adulthood

Adolfo G. Cuevas[1]✉, Frank D. Mann[2] and Robert F. Krueger[3]

OBJECTIVE: The present study tested the interactive effects of childhood adversity and polygenic risk scores for waist circumference (PRS-WC) on waist circumference (WC). Consistent with a diathesis-stress model, we hypothesize that the relationship between PRS-WC and WC will be magnified by increasing levels of childhood adversity.
METHODS: Observational study of 7976 adults (6347 European Americans and 1629 African Americans) in the Health and Retirement Study with genotyped data. PRS-WC were calculated by the HRS administrative core using the weighted sum of risk alleles based on a genome-wide association study conducted by the Genetic Investigation of Anthropometric Traits (GIANT) consortium. Childhood adversity was operationalized using a sum score of three traumatic events that occurred before the age of 18 years.
RESULTS: There was a statistically significant interaction between PRS-WC and childhood adversity for European Americans, whereby the magnitude of PRS-WC predicting WC increased as the number of adverse events increased.
CONCLUSIONS: This study supports the idea of the interactive effects of genetic risks and childhood adversity on obesity. More epidemiological studies, particularly with understudied populations, are needed to better understand the roles that genetics and childhood adversity play on the development and progression of obesity.

International Journal of Obesity; https://doi.org/10.1038/s41366-022-01191-3

THE WEIGHT OF CHILDHOOD ADVERSITY: THE ROLE OF GENETIC RISK IN WAIST CIRCUMFERENCE IN ADULTHOOD

Obesity increases the risk of many of the leading causes of morbidity—including cardiovascular disease, type 2 diabetes, and certain cancer types—and mortality in the US [1–3]. Currently, 4 out of 10 adults have obesity, with disproportionately high prevalence among middle-aged and older adults [4]. The public health and economic costs associated with obesity will continue to rise as studies project that 1 out of 2 adults will have obesity by 2030 [5–9].

Obesity is a multifactorial disorder that is caused by complex interactions between multiple genetic and environmental factors [3, 10–12]. Childhood adversity is an environmental factor that has been implicated as a risk factor for the development of obesity in adulthood. For example, a meta-analysis of 41 studies (190,285 participants) revealed that childhood adversity was associated with elevated risk of developing obesity over the life course [13]. Childhood adversity increases the risk of obesity-related behaviors and undermines the body's physiologic and biological response to environmental demands, leading to multisystem physiological dysregulation that, in turn, increases the risk of obesity [13–15]. Adversity in early life, particularly infancy and early childhood, is more pernicious than in later stages as humans are most vulnerable and reliant on external security and support [16]. However, not every individual exposed to the same adversity will have equal risk of developing obesity [17–19]. A diathesis-stress hypothesis suggest that those with higher genetic risks are more susceptible to the obesogenic effects of stressors like childhood adversity [18, 20]. Nevertheless, the interplay between childhood adversity, genetic risk, and obesity remains unclear.

Genome-wide association studies have quantified the association between millions of single nucleotide polymorphisms (SNPs) and waist circumference in large sample cohorts [21–23]. While no one individual SNP accounts for a large proportion of variation, the aggregate of SNPs associated with WC is predictive of WC [21, 23–25]. Polygenic scores combine the effects of multiple SNPs into a single weighted score, such that variants that are robustly associated with the phenotype (i.e., above a chosen threshold of statistical significance) are included in the polygenic score (PRS) [26]. Thus, PRSs serve as a valuable tool for disease prediction and discovering interactions with environmental risk factors, providing

[1]Department of Social and Behavioral Sciences, School of Global Public Health, New York University, New York, NY, USA. [2]Program in Public Health, Department of Family, Population, and Preventive Medicine, Stony Brook University, Stony Brook, NY, USA. [3]Department of Psychology, University of Minnesota, Minneapolis, MN, USA.
✉email: Adolfo.cuevas@nyu.edu

Received: 15 November 2021 Revised: 26 June 2022 Accepted: 7 July 2022
Published online: 05 August 2022

a broad-band marker of molecular genetic risk for a "target" phenotype [27].

As BMI is perhaps the most commonly used measure of adiposity to identify adults at increased risk of overweight- and obesity-related morbidity and mortality [28–30], GWAS have predominantly used this common phenotype to understand the molecular etiology of obesity with the goal of improving diagnostic precision [31]. However, BMI alone is unable to comprehensively capture information about total body fat or fat distribution patterns. Moreover, regional distribution of body fat can differ across individuals with different BMI [32]. The measurement of waist circumference (WC), thus, serves as an enhanced tool for studying obesity as it estimates visceral fat around the abdomen and serves as a reliable predictor of obesity-related morbidity and mortality above and beyond BMI [33–37].

With the growing number of WC-associated SNPs that have been identified in genome-wide association studies [38], there is an opportunity to better understand the potential interaction of polygenic risk scores for waist circumference (PRS-WC) and childhood adversity in predicting WC in adulthood. The present study focuses on understanding the combined and interactive effects of childhood adversity and PRS-WC using data from the Health and Retirement Study (HRS). A better understanding of these potential gene-environment interactions has the potential to serve as a valuable resource for precision medicine and preventive measures that seek to reduce the obesogenic burden of childhood adversity.

METHOD

Sample

The present study analyzed data from the HRS. Information regarding participant recruitment, study design, and data collection can be found elsewhere [39, 40]. HRS implemented a cross-sequential design using stratified random sampling, with a focus on over-sampling African Americans. The present study utilized data from participants with self-reported and genotyped data from 2006 to 2014 ($n = 7976$).

Measures

Measures of waist circumference. HRS interviewers measured participants' WC in centimeters using a tape measure that was placed around the participant's waist, right above the iliac crest.

Polygenic risk scores. HRS staff calculated PRSs for WC using summary statistics from studies conducted by the Genetic Investigation of Anthropometric Traits (GIANT) consortium [23, 41]. As reported in the HRS study documentation, ~2.4 million SNPs were measured using the Illumina HumanOmni2.5 BeadChips. Data from participants with missing call rates >2%, SNPs with call rates <0.0001, chromosomal anomalies, and first-degree relatives were discarded from the sample. Imputation was performed using IMPUTE2 to the 1000 Genomes Project cosmopolitan reference panel phase 3 version 5, with phasing performed using SHAPEIT2. In total, ~21 million SNPs were imputed from the original 1,905,968 SNPs that were genotyped and passed screening criteria. More information can be found online via the HRS documentation, including quality control and imputations reports [38].

The HRS administrative core investigated the influence of different factors when calculating polygenic risk scores, including whether to use imputed SNPs, the criteria for selecting SNPs, and whether and how to account for linkage disequilibrium (clumping vs. pruning). Tests of predictive validity across different analytic routines indicated that neither clumping, pruning, nor p value thresholding increased the percent of phenotypic variance explained (ΔR^2) by the polygenic scores. Consequently, polygenic scores were made publicly available that include all SNPs (p value = 1) that overlap between the GWAS meta-analysis and the HRS genetic data. The GWAS meta-analysis from which SNP weights were obtained to calculate the polygenic score for waist circumference included 142,762 participants from 57 studies using 2,507,022 SNPs. For European Americans in the HRS, the polygenic score for waist circumference included 778,121 SNPs that overlapped between the genotype data and the GWAS meta-analysis; For African Americans, the polygenic score contained 776,945 overlapping SNPs.

HRS released PRSs for both the European ancestry and African ancestry groups, separately. The first five Ancestry-specific principal components were used as covariates in multiple regressions to account for population structure. All the PRSs were standardized to a normal curve (mean = 0, standard deviation = 1) within ancestry. The SNP weights that were developed from the European GWAS were applied to the African ancestry PRS. Consequently, the PRS of Black participants do not have the same predictive capacity as that of participants with predominately European ancestry. Therefore, all analyses were stratified by race.

Childhood adversity. Childhood adversity was measured using three items that asked whether traumatic events occurred before the age of 18 years. The events included having trouble with the police ($n = 347$ [7%] for European Americans, $n = 120$ [10%] for African Americans), parental alcohol or drug use that caused family problems ($n = 921$ [16%] for European Americans, $n = 251$ [19%] for African Americans), and physical abuse by any parent ($n = 414$ [7%] for European Americans, $n = 96$ [7%] for African Americans). Participants provided "Yes" = 1 or "No" = 0 responses to each event, with sum composites ranging from 0 to 3 indicating the number of adverse events that occurred before the age of 18 years (see Table 1).

Covariates. Chronological age (in years), birth cohort (born before 1924), and biological sex as determined by genotype were included as covariates. Self-reported education was also included as a covariate because childhood adversity and genetic risk for obesity are associated with midlife educational attainment [42–44].

Data analytic procedures

Data was imported into R Studio version 1.2.5003; The following packages were used to conduct inferential analyses and plot results: "mice", "lmtest", "sandwich", "interactions", and "ggplot2". Data analytic procedures consisted in several steps, and all analyses were conducted separately for White/European Americans and Black/African Americans, as recommended in the HRS study documentation for a polygenic risk score analysis. First, descriptive statistics were calculated, parametric and non-parametric zero-order correlations were estimated, and sex differences were examined.

Next, one main effects model and one interaction model were estimated. Specifically, multiple linear regressions were estimated with robust standard errors to test the main effects of study variables on waist circumference and whether the polygenic score for WC was moderated by childhood adversity, controlling for demographic factors (age, sex, level of education, and birth cohort) and the first five genetic principal components. In these models, product terms between PRS and demographic factors (PRS × Age, PRS × Gender, PRS × Cohort_{1914}, PRS × Education_2, PRS × Education_3 … PRS × Education_8), between childhood adversity and demographic factors (Adversity × Age, Adversity × Gender, Adversity × Cohort_{1914}, Adversity × Education_2, Adversity × Education_3 … Adversity × Education_8), and between the first five genetic principal components and PRS, childhood adversity, and demographic factors (PC_{1-5} × PRS, PC_{1-5} × Adversity, PC_{1-5} × Age, PC_{1-5} × Gender, PC1–5 × Cohort_{1924}, PC1–5 × Education_2, PC1–5 × Education_3 … PC1–5 × Education_8) were included as predictors of WC. All main and interaction effects were estimated simultaneously, such that regression coefficients predicting WC were adjusted for the presence of the other interaction terms in the model. Age was mean-centered, and sex (Male = 0, Female = 1), birth cohort (born after 1924 = 0, born before 1924 = 1), and levels of education were dummy coded (Not completed = 0, Completed = 1, with "did not graduate from high school" serving as the reference group) prior to computing interaction terms.

Listwise deletion was initially used for missing data, but Little's test indicated that the data were not MCAR ($\chi^2 = 82.70$, df = 32, $p < 0.001$). Consequently, using the "mice" package in R, we conducted multiple imputation as a sensitivity analysis under an assumption of MAR. Specifically, we created 50 imputations for missing data by chained equations using fully conditional specification. We then fit the main effects and gene-by-environment interaction models on each imputed dataset and pooled the estimates from each model by Rubin's rules [45]. Results are reported in the supplement (Tables S1, S2) and noted in the results when findings were discrepant with listwise deletion.

RESULTS

Approximately 59% of the sample was female (41% male), and approximately 81% non-Hispanic White/European American (19% of the sample was non-Hispanic Black/African American). The average age of participants was approximately 64 years. Approximately 12% of participants did not graduate from high school, 4% obtained a general education diploma (GED), 29% a high school diploma, 21% attended some college, 7% obtained an associate's or technical degree, 17% a bachelor's degree, 8% a master's degree, and <2% a J.D., M.D., or Ph.D. For multiple regressions, the two highest categories of educational attainment (Master's and J.D., M.D., or Ph.D.) were combined for Black/African Americans to ensure adequate coverage for inferential analyses because only two participants reported having obtained a J.D., M.D., or Ph.D. Descriptive statistics and zero-order correlations stratified by race/ethnicity are reported in Table 1, and sex differences are reported in Table 2.

For White/European Americans, age was negatively correlated with educational attainment ($r = -0.20$ [−0.23, −0.18], $\tau = -0.13$, $p < 0.001$) and childhood adversity ($r = -0.23$ [−0.25, −0.21], $\tau = -0.18$, $p < 0.001$). There was also a small, negative correlation between educational attainment and average waist circumference ($r = -0.08$ [−0.10, −0.05], $\tau = -0.06$, $p < 0.001$), and between educational attainment and the polygenic score for waist circumference ($r = -0.08$ [−0.11, −0.05], $\tau = -0.05$, $p < 0.001$). Finally, average waist circumference was positively correlated with the polygenic risk score for larger waist circumference ($r = 0.21$ [0.18, 0.23], $\tau = 0.14$, $p < 0.001$). A similar pattern of zero-order correlations emerged for Black/African Americans albeit smaller in magnitude; Age was negatively correlated with educational attainment ($r = -0.16$ [−0.21, −0.11], $\tau = -0.08$, $p < 0.001$) and childhood adversity ($r = -0.13$ [−0.18, −0.07], $\tau = -0.06$, $p = 0.003$), and average waist circumference was positively correlated with the polygenic risk score for larger waist circumference ($r = 0.13$ [0.07, 0.18], $\tau = 0.08$, $p < 0.001$). However, correlations between educational attainment and average waist circumference, and between educational attainment and the polygenic score for waist circumference were not statistically significant ($p > 0.05$; see Table 1). For European Americans, there were sex differences for all variables, except for PRS-WC. For African Americans, there were no sex differences, except for childhood adversity (see Table 2).

Unstandardized coefficients, 95% confidence intervals, and p-values from multiple regressions are reported in Tables 3, 4. Coefficients of determination (R^2) indicate the percent of variation in waist circumference explained collectively by all predictors in the model. First, the polygenic risk score for waist circumference predicted larger waist circumference for European Americans, such that a standard deviation increase in polygenic liability was associated with a 1.47 cm increase in WC (*95% CI* = 1.31, 1.64, $R^2 = 0.043$). There was also a statistically significant interaction between PRS-WC and childhood adversity for European Americans, such that the magnitude of polygenic effects on waist circumference increased as the number of adverse events increased. Put differently, adults with the highest predicted waist circumference were those with high polygenic risk scores for WC who also reported the occurrence of all three adverse events. A scatter plot of WC (y-axis) and PRS-WC (x-axis) with slopes of the PRS-WC predicting WC at different levels of childhood diversity is depicted in Fig. 1 (left panel), along with 95% confidence intervals for slopes (right panel). This gene-by-environment interaction was statistically significant, irrespective of whether listwise deletion ($b = 0.32$, $SE = 0.14$, $p = 0.028$) or multiple imputation ($b = 0.32$, $SE = 0.14$, $p = 0.026$) was used for missing data.

In contrast to the gene-by-adversity interaction observed for White/European adults, the effects of adversity and PRS were not significantly moderated by each other or by sociodemographic factors ($p > 0.05$) for Black/African Americans (see Table 4), with the exception of the age-by-adversity interaction and cohort-by-

Table 1. Descriptive statistics, parametric, and non-parametric correlations stratified by race/ethnicity.

	Descriptive statistics						Parametric and non-parametric correlations				
	n	*M*	Med	SD	Min.	Max.	Age	EDU	WC	PRS	ADV
European Americans											
Age	6347	65.02	60.00	13.34	32.00	101.00	1.00	−0.13	−0.03	−0.03	−0.18
Education (EDU)	6347	4.12	4.00	1.80	1.00	8.00	−0.20	1.00	−0.06	−0.05	−0.03
Waist circumference (WC)	6007	39.44	39.00	6.20	20.50	73.50	−0.08	−0.08	1.00	0.14	0.03
Polygenic risk score (PRS)	6347	−0.01	0.04	1.01	−4.23	3.53	−0.05	−0.08	0.21	1.00	0.04
Childhood adversity (ADV)	6198	0.32	0.00	0.61	0.00	3.00	−0.23	−0.05	0.05	0.05	1.00
Childhood adversity (ADV)	None: 4380 (75%)			1 event: 1149 (20%)			2 events: 292 (5%)			3 events: 53(1%)	
African Americans											
Age	1629	60.11	57.00	10.29	27.00	100.00	1.00	−0.10	−0.03	−0.01	−0.07
Education (EDU)	1629	3.34	3.00	1.75	1.00	8.00	−0.18	1.00	0.01	−0.03	−0.02
Waist circumference (WC)	1500	40.89	40.00	6.60	25.00	74.00	−0.08	0.02	1.00	0.08	0.03
Polygenic risk score (PRS)	1629	0.01	−0.01	0.98	−3.52	3.91	−0.02	−0.04	0.12	1.00	0.00
Childhood adversity (ADV)	1487	0.31	0.00	0.60	0.00	3.00	−0.13	−0.02	0.03	−0.01	1.00
Childhood adversity (ADV)	None: 1029 (75%)			1 event: 269 (20%)			2 events: 69 (5%)			3 events: 12 (1%)	

Pearson's correlations are reported below the diagonal and Kendall's tau are reported above the diagonal.
n sample size, *M* mean, *Med* median, *SD* standard deviation, *Min.* minimum value, *Max.* maximum value.

Table 2. Sex differences stratified by race/ethnicity.

	Female	Male	*d*	Lower 95%	Upper 95%
European Americans					
Age	65.54	64.31	−0.09	−0.14	−0.04
Education (EDU)	3.98	4.30	0.18	0.13	0.23
Waist circumference (WC)	37.89	41.56	0.62	0.56	0.67
Polygenic risk score (PRS)	0.00	−0.03	−0.03	−0.08	0.02
Childhood adversity (ADV)	0.29	0.36	0.12	0.07	0.17
African Americans					
Age	60.15	60.04	−0.01	−0.11	0.09
Education (EDU)	3.40	3.25	−0.09	−0.19	0.01
Waist circumference (WC)	41.00	40.71	−0.04	−0.15	0.06
Polygenic risk score (PRS)	0.01	0.00	−0.02	−0.12	0.08
Childhood adversity (ADV)	0.25	0.40	0.25	0.14	0.36

Means reported for female and male participants.
d standardized mean difference, *Lower and Upper 95%* 95% confidence interval for Cohen's d.

adversity interaction. However, the age-by-adversity interaction ($b = 0.09$, $SE = 0.05$, $p = 0.078$) and cohort-by-adversity interaction ($b = -4.42$, $SE = 2.89$, $p = 0.126$) were not statistically significant when multiple imputation was used for missing data. Also, fewer main effects emerged in the Black/African American sample. The PRS-WC predicted larger waist circumference, such that a standard deviation increase in polygenic liability was associated with a 0.88 cm (95% CI = 0.52, 1.24, $R^2 = 0.016$) increase in WC, but all other main effects were not statistically significant ($p > 0.05$).

DISCUSSION

Our study examined the interaction effect of childhood adversity and PRS-WC in a large multiracial sample of middle-aged and older adults. There was evidence of an interaction between PRS-WC and childhood adversity on WC for White/European American participants. In other words, the association between polygenic risk and WC was greater for those who reported having experienced more adverse events in childhood, a fan-shaped interaction effect that is broadly consistent with a diathesis-stress model. However, we did not observe an interaction between the PRS-WC and childhood adversity for African American participants.

Childhood adversity is an insidious health determinant that contributes to early mortality and a wide range of chronic conditions [46]. There is overwhelming evidence that early life trauma increases the risk of obesity [13, 46, 47]. Nevertheless, the diathesis-stress hypothesis suggests that people with greater genetic liability are more susceptible to the adverse effects of stress. We found that childhood adversity had a "fan-shaped" interaction with polygenic liability; thus, consistent with a putative moderation effect within a diathesis-stress framework [48]. We did not fully test for the differential susceptibility hypothesis, often viewed as an alternative to the diathesis-stress hypothesis. The differential susceptibility hypothesis suggests that individuals most sensitive to adversity, are also most likely to benefit from supportive environments [49]. For example, Dalle Mole[20] finds that mother-child relationship and individual traits (e.g., personality traits) are important modifiers that interact with gene variants to either exacerbate or improve BMI. Similarly, protective factors (e.g., positive neighborhood context, maternal nurturance) have been shown to buffer the effects of early life adversity on health outcomes [50–52]. The present study measured the presence of childhood adversity but did not account for protective factors or positive social environments (e.g., parenting style, social support, neighborhood resources) that can mitigate the deleterious effects of childhood adversity, and, therefore, provide support for differential susceptibility. Future research should examine a wider range of adverse and favorable psychosocial factors that likely play a role in linking polygenic and environmental risk to obesity.

We did not find an interaction effect between PRS-WC and childhood adversity for African Americans. This is not surprising as the calculations of the polygenic scores depend on the estimated effects of SNPs obtained from GWAS, which have been based almost exclusively on populations of European descent [23, 25, 53, 54]. Therefore, the predictive validity of polygenic scores will generally be weaker for Black respondents, as we observed here. Because Black children are exposed to more adversities than White children, there is an urgent need to expand GWAS efforts in non-European populations to improve our understanding of the interrelationship between childhood adversity, genetics, and racial obesity disparities [55, 56].

The lack of a significant main effect of childhood adversity in present study for both European and African Americans was unexpected. Recall and selection biases of early life adversity may play a role in these findings [57]. Although results of the present study are consistent with deleterious genetic effects being magnified in an adverse environment, results are inconsistent with an environmental effect (i.e., childhood adversity) increasing in magnitude across individual differences in genetic liability, as the slope of childhood adversity predicting waist circumference was not significantly greater than zero across the observed range of polygenic lability in waist circumference captured by polygenic scores. This might be due to the limited number of adverse childhood experiences recorded in the study. Future research should consider a wider range of early life adverse events to improve the characterization between childhood adversity and obesity. Moreover, future research should replicate and extend the study findings using different age groups, with particular focus on youth for which the effects of early childhood adversity on body composition may be more salient.

Table 3. Results of multiple linear regressions for European Americans.

	Main effects only				Including interaction effects			
	b	Lower 95%	Upper 95%	*p*	*b*	Lower 95%	Upper 95%	*p*
(Intercept)	42.57	42.02	43.12	<0.001	42.53	41.93	43.14	<0.001
Age (mean-centered)	−0.02	−0.04	−0.01	0.005	−0.02	−0.04	−0.01	0.018
Gender (Female = 1, Male = 0)	−3.83	−4.12	−3.53	<0.001	−3.90	−4.23	−3.56	<0.001
Education GED	−0.69	−1.65	0.26	0.154	−0.90	−2.02	0.23	0.117
HS graduate	−0.19	−0.76	0.38	0.514	−0.14	−0.78	0.51	0.678
Some college	−0.94	−1.54	−0.34	0.002	−0.77	−1.45	−0.10	0.025
Associates/Technical	−0.46	−1.23	0.32	0.251	−0.63	−1.50	0.24	0.158
Bachelor's	−1.57	−2.19	−0.96	<0.001	−1.49	−2.17	−0.80	<0.001
Master's	−2.19	−2.89	−1.50	<0.001	−1.92	−2.7	−1.13	<0.001
JD/MD/Ph.D.	−2.09	−3.13	−1.06	<0.001	−2.59	−3.72	−1.45	<0.001
Birth Cohort (before 1924)	−0.81	−1.32	−0.30	0.002	−1.04	−1.59	−0.48	<0.001
Genetic PC1	−20.05	−35.98	−4.12	0.014	−19.16	−79.43	41.12	0.533
Genetic PC2	27.74	13.02	42.46	<0.001	−3.93	−61.96	54.11	0.894
Genetic PC3	6.66	−9.61	22.92	0.422	−5.60	−60.10	48.90	0.840
Genetic PC4	7.46	−7.40	22.31	0.325	1.59	−60.84	64.01	0.960
Genetic PC5	−53.69	−71.56	−35.83	<0.001	−30.93	−97.68	35.82	0.364
PRS—waist circumference	1.47	1.31	1.64	<0.001	1.48	0.87	2.08	<0.001
Adversity	0.01	−0.25	0.28	0.922	−0.31	−1.20	0.59	0.503
Age × PRS−WC					−0.02	−0.03	−0.00	0.043
Age × adversity					−0.01	−0.04	0.02	0.464
Gender × PRS-WC					0.30	−0.03	0.62	0.077
Gender × adversity					0.38	−0.14	0.90	0.157
GED × PRS-WC					−0.63	−1.62	0.36	0.214
HS graduate × PRS-WC					−0.21	−0.84	0.42	0.515
Some college × PRS-WC					−0.49	−1.15	0.16	0.141
Associate's × PRS-WC					−0.33	−1.20	0.55	0.464
Bachelor's × PRS-WC					−0.09	−0.77	0.59	0.797
Master's × PRS-WC					−0.36	−1.11	0.39	0.351
JD/MD/Ph.D. × PRS-WC					−0.05	−1.08	0.99	0.932
GED × adversity					0.44	−0.81	1.69	0.487
HS graduate × adversity					0.11	−0.84	1.05	0.826
Some college × adversity					−0.29	−1.28	0.71	0.571
Associate's × adversity					0.63	−0.60	1.87	0.314
Bachelor's × adversity					0.17	−0.88	1.22	0.754
Master's × adversity					−0.71	−1.89	0.47	0.240
JD/MD/Ph.D. × adversity					2.49	0.25	4.74	0.029
Birth cohort × PRS-WC					−0.19	−0.77	0.39	0.529
Birth cohort × adversity					0.94	−0.67	2.55	0.253
PRS-WC × adversity					0.32	0.03	0.61	0.028
Model R^2		0.154				0.169		

Interaction terms between study variables and the first five genetic principal components were included in the interaction model but omitted to ease presentation. Listwise deletion was used for missing data. Results using multiple imputation for missing data are reported in the Supplementary Information.
b unstandardized regression coefficient, *SE* robust standard error, *Lower and Upper 95%* 95% Wald confidence intervals, *p* probability of the observed association if the null hypothesis is true.

Table 4. Results of multiple linear regressions for Black/African Americans.

	Main effects only				Including interaction effects			
	b	Lower 95%	Upper 95%	*p*	*b*	Lower 95%	Upper 95%	*p*
Intercept	40.53	39.64	41.42	<0.001	40.78	39.79	41.77	<0.001
Age (mean-centered)	−0.03	−0.07	0.02	0.218	−0.03	−0.08	0.02	0.264
Gender (Female = 1, Male = 0)	0.41	−0.30	1.11	0.258	0.24	−0.58	1.06	0.567
Education GED	1.06	−0.47	2.58	0.175	1.08	−0.87	3.03	0.279
HS Graduate	−0.08	−1.08	0.93	0.877	−0.32	−1.49	0.86	0.597
Some college	0.22	−0.84	1.28	0.687	0.22	−1.00	1.44	0.722
Associate's	0.39	−1.14	1.92	0.619	0.53	−1.13	2.20	0.531
Bachelor's	−0.13	−1.37	1.12	0.841	−0.38	−1.85	1.09	0.611
Master's or JD/MD/Ph.D.	0.71	−1.25	2.66	0.477	1.21	−0.82	3.25	0.243
Birth Cohort (before 1924)	−1.65	−3.36	0.06	0.059	−1.31	−3.13	0.50	0.157
Genetic PC1	−18.33	−37.24	0.59	0.058	24.93	−24.43	74.28	0.322
Genetic PC2	−0.77	−20.45	18.91	0.939	11.13	−42.97	65.23	0.687
Genetic PC3	4.75	−14.28	23.79	0.624	−14.98	−66.70	36.75	0.570
Genetic PC4	2.11	−16.92	21.14	0.828	−4.91	−54.89	45.06	0.847
Genetic PC5	−4.21	−23.68	15.26	0.672	−55.19	−112.82	2.44	0.060
PRS—waist circumference	0.88	0.52	1.24	<0.001	0.76	−0.20	1.71	0.121
Adversity	0.20	−0.39	0.80	0.504	0.04	−1.35	1.43	0.960
Age × PRS-WC					−0.04	−0.09	0.01	0.110
Age × adversity					0.09	0.00	0.19	0.048
Gender × PRS-WC					−0.08	−0.86	0.70	0.837
Gender × adversity					0.29	−0.96	1.54	0.648
GED × PRS-WC					0.38	−1.06	1.82	0.607
HS graduate × PRS-WC					0.10	−0.94	1.15	0.848
Some college × PRS-WC					0.00	−1.07	1.08	0.996
Associate's × PRS-WC					0.82	−0.64	2.28	0.273
Bachelor's × PRS-WC					0.17	−1.19	1.53	0.803
Master's × PRS-WC					1.19	−1.08	3.45	0.305
GED × adversity					−0.08	−2.10	1.94	0.941
HS graduate × adversity					0.95	−0.82	2.71	0.291
Some college × adversity					0.06	−1.71	1.82	0.949
Associate's × adversity					−0.64	−4.21	2.93	0.726
Bachelor's × adversity					1.07	−1.25	3.40	0.366
Master's or higher × adversity					−0.36	−3.95	3.23	0.844
Birth cohort × PRS-WC					1.57	−0.49	3.64	0.135
Birth cohort × adversity					−5.02	−9.67	−0.37	0.034
PRS-WC × adversity					−0.26	−0.91	0.40	0.437
Model R^2	0.032					0.074		

Interaction terms between study variables and the first five genetic principal components were included in the interaction model but omitted to ease presentation. Listwise deletion was used for missing data. Results using multiple imputation for missing data are reported in the Supplementary Information. *b* unstandardized regression coefficient, *Lower and Upper 95%* 95% Wald confidence intervals, *p* probability of the observed association if the null hypothesis is true.

Limitations

The present study is not without limitations. First, the SNPs used in calculating the PRS derive largely from a relatively recent GWAS meta-analysis. Nevertheless, future GWAS meta-analyses may identify additional obesity-related SNPs that would strengthen the predictive validity of PRS and potentially affect our gene-environment findings. Future research with more recent and larger GWAS meta-analyses should replicate our findings. Most GWAS are based on European samples, which translates into PRS performing better in White samples than in Black samples, as was observed in the present study [58]. Without considering the performance of PRS, the findings may suggest that Black participants exhibit greater resilience in the face of early adversity. Few studies have examined the interaction between race and childhood adversity on obesity risk [13, 17, 59, 60]. Therefore, it remains unclear whether White Americans are more vulnerable to the effects of childhood adversity compared to Black Americans. Further research is needed to examine the interactive effects of

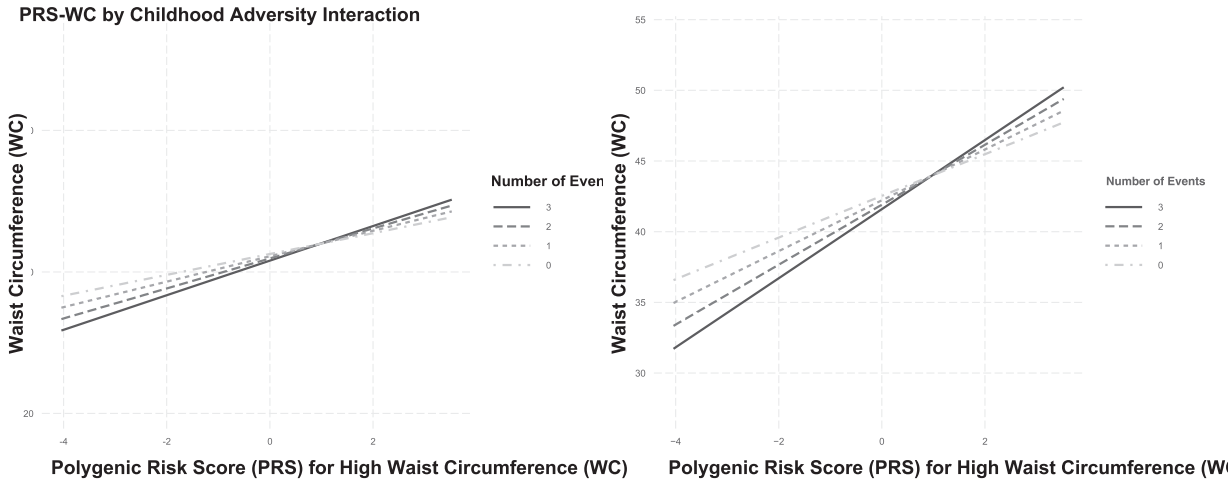

Fig. 1 Polygenic risk score by childhood adversity interaction effect predicting average waist circumference for White/European adults. On the left, average waist circumference (y-axis) is plotted as a function of polygenic risk scores for waist circumference (x-axis) across different levels of childhood adversity, specifically the number of adverse events that occurred before turning 18 years old. On the right panel, the same interaction effect is plotted with 95% confidence intervals for the slopes of the polygenic risk score predicting waist circumference at different levels of childhood adversity.

race and childhood adversity on obesity risk and the extent resilience plays in moderating these effects. Nevertheless, to prevent the potential mischaracterization of findings for Blacks, future research will depend on advances in genome-wide analyses that captures African admixture. However, it is worth noting that individuals of predominately European and African ancestry likely share risk alleles for obesity, as the PRS for obesity-related phenotypes in the current study were significantly predictive of respective outcomes for Black participants, despite being derived from GWASs that were based on samples of almost exclusively European participants. Lastly, our findings may be influenced by methodological and sampling procedures that are specific to HRS, as well as recall and survival bias [57]. Future research should replicate our study with other population-based cohorts.

CONCLUSION

To our knowledge, this is the first study to examine the interactive effects of childhood adversity and polygenic risk for waist circumference in a multiracial sample of middle-aged and older adults. Among European Americans, the association between genetic risk and waist circumference was greater for those who reported greater childhood adversity. More genetic analyses in diverse populations are needed to increase the generalizability of findings. Nevertheless, results suggest that reducing exposure to childhood adversity has the potential to lower the obesogenic effects of underlying genetic liability.

DATA AVAILABILITY

Data and analysis scripts are available on the Open Science Framework (OSF; https://osf.io/rnjxz).

REFERENCES

1. Vucenik I, Stains JP. Obesity and cancer risk: evidence, mechanisms, and recommendations. Ann NY Acad Sci. 2012;1271:37–43.
2. Xu H, Cupples LA, Stokes A, Liu C-T. Association of obesity with mortality over 24 years of weight history: findings from the Framingham Heart Study. JAMA Netw Open. 2018;1:e184587.
3. Hruby A, Hu FB. The epidemiology of obesity: a big picture. PharmacoEconomics. 2015;33:673–89.
4. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of Obesity and Severe Obesity Among Adults: United States, 2017-2018. NCHS Data Brief. 2020;360:1–8.
5. Ward ZJ, Bleich SN, Cradock AL, Barrett JL, Giles CM, Flax C, et al. Projected U.S. state-level prevalence of adult obesity and severe obesity. N Engl J Med. 2019;381:2440–50.
6. Wang Y, Beydoun MA, Liang L, Caballero B, Kumanyika SK. Will all Americans become overweight or obese? estimating the progression and cost of the US obesity epidemic. Obesity. 2008;16:2323–30.
7. Wang YC, Pamplin J, Long MW, Ward ZJ, Gortmaker SL, Andreyeva T. Severe obesity in adults cost state medicaid programs nearly $8 billion in 2013. Health Affairs. 2015;34:1923–31.
8. Spieker EA, Pyzocha N. Economic impact of obesity. Prim Care. 2016;43:83–95.
9. Hammond RA, Levine R. The economic impact of obesity in the United States. Diabetes Metab Syndr Obes. 2010;3:285.
10. Meldrum DR, Morris MA, Gambone JC. Obesity pandemic: causes, consequences, and solutions—but do we have the will? Fertil Steril. 2017;107:833–9.
11. Hruby A, Manson JE, Qi L, Malik VS, Rimm EB, Sun Q, et al. Determinants and consequences of obesity. Am J Public Health. 2016;106:1656–62.
12. Huang T, Hu FB. Gene-environment interactions and obesity: recent developments and future directions. BMC medical. Genomics. 2015;8:S2.
13. Danese A, Tan M. Childhood maltreatment and obesity: systematic review and meta-analysis. Mol Psychiatry. 2014;19:544–54.
14. Shonkoff JP, Garner AS, Siegel BS, Dobbins MI, Earls MF, The Committee on Psychosocial Aspects of Child and Family Health C on EC, et al. The lifelong effects of early childhood adversity and toxic stress. Pediatrics.2012;129:e232–46.
15. Harada M, Guerrero A, Iyer S, Slusser W, Szilagyi M, Koolwijk I. The relationship between adverse childhood experiences and weight-related health behaviors in a national sample of children. Acad Pediatr. 2021. https://www.sciencedirect.com/science/article/pii/S187628592100276X.
16. Hemmingsson E. Early childhood obesity risk factors: socioeconomic adversity, family dysfunction, offspring distress, and junk food self-medication. Curr Obes Rep. 2018;7:204–9.
17. Hemmingsson E, Johansson K, Reynisdottir S. Effects of childhood abuse on adult obesity: a systematic review and meta-analysis. Obes Rev. 2014;15:882–93.
18. Sun Y, Fang J, Wan Y, Hu J, Xu Y, Tao F. Polygenic differential susceptibility to cumulative stress exposure and childhood obesity. Int J Obes. 2018;42:1177–84.
19. Scott KA, Melhorn SJ, Sakai RR. Effects of chronic social stress on obesity. Curr Obes Rep. 2012;1:16–25.
20. Dalle Molle R, Fatemi H, Dagher A, Levitan RD, Silveira PP, Dubé L. Gene and environment interaction: is the differential susceptibility hypothesis relevant for obesity? Neurosci Biobehav Rev. 2017;73:326–39.
21. Speliotes EK, Willer CJ, Berndt SI, Monda KL, Thorleifsson G, Jackson AU, et al. Association analyses of 249,796 individuals reveal 18 new loci associated with body mass index. Nat Genet. 2010;42:937–48.
22. Meyre D, Delplanque J, Chèvre J-C, Lecoeur C, Lobbens S, Gallina S, et al. Genome-wide association study for early-onset and morbid adult obesity identifies three new risk loci in European populations. Nat Genet. 2009;41:157–9.
23. Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature. 2015;518:197–206.

24. Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science. 2007;316:889–94.
25. Fall T, Ingelsson E. Genome-wide association studies of obesity and metabolic syndrome. Mol Cell Endocrinol. 2014;382:740–57.
26. Dudbridge F. Polygenic epidemiology. Genet Epidemiol. 2016;40:268–72.
27. Figueroa JF, Frakt AB, Jha AK. Addressing social determinants of health: time for a polysocial risk score. JAMA. 2020;323:1553–4.
28. Stein CJ, Colditz GA. The epidemic of obesity. J Clin Endocrinol Metab. 2004;89:2522–5.
29. Rothman KJ. BMI-related errors in the measurement of obesity. Int J Obes. 2008;32:ijo200887.
30. US Preventive Services Task Force. Screening for obesity in adults: recommendations and rationale. Ann Int Med. 2003;139:930.
31. Lambert SA, Abraham G, Inouye M. Towards clinical utility of polygenic risk scores. Hum Mol Genet. 2019;28:R133–42.
32. Després J-P. Body fat distribution and risk of cardiovascular disease: an update. Circulation. 2012;126:1301–13.
33. Klein S, Allison DB, Heymsfield SB, Kelley DE, Leibel RL, Nonas C, et al. Waist circumference and cardiometabolic risk: a consensus statement from shaping America's Health: association for weight management and obesity prevention; NAASO, the obesity society; the American Society for Nutrition; and the American Diabetes Association. Diabetes Care. 2007;30:1647–52.
34. Wang Y, Rimm EB, Stampfer MJ, Willett WC, Hu FB. Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. Am J Clin Nutr. 2005;81:555–63.
35. Feller S, Boeing H, Pischon T. Body mass index, waist circumference, and the risk of type 2 diabetes mellitus. Deutsch Ärztebl Int. 2010;107:470–6.
36. Canoy D. Distribution of body fat and risk of coronary heart disease in men and women. Curr Opin Cardiol. 2008;23:591–8.
37. Jacobs EJ, Newton CC, Wang Y, Patel AV, McCullough ML, Campbell PT, et al. Waist circumference and all-cause mortality in a large US cohort. Arch Intern Med. 2010;170:1293–301.
38. Ware E, Schmitz L, Gard A, Faul J HRS polygenic scores—release 2: 2006–2012 genetic data. Ann Arbor, University of Michigan: Survey Research Center; 2018.
39. Fisher GG, Ryan LH. Overview of the health and retirement study and introduction to the special issue. Work Aging Retire. 2018;4:1–9.
40. Sonnega A, Faul JD, Ofstedal MB, Langa KM, Phillips JW, Weir DR. Cohort profile: the health and retirement study (HRS). Int J Epidemiol. 2014;43:576–85.
41. Shungin D, Winkler TW, Croteau-Chonka DC, Ferreira T, Locke AE, Mägi R, et al. New genetic loci link adipose and insulin biology to body fat distribution. Nature. 2015;518:187–96.
42. Forsman H, Jackisch J. Cumulative childhood adversity and long-term educational outcomes in individuals with out-of-homecare experience: do multiples matter for a population defined by adversity? Br J Soc Work. 2021:1–20.
43. Montez JK, Hayward MD. Cumulative childhood adversity, educational attainment, and active life expectancy among US adults. Demography. 2014;51:413–35.
44. Patel PC, Rietveld CA. Effect of genetic propensity for obesity on income and wealth through educational attainment. Obesity. 2019;27:1423–7.
45. Rubin DB. Multiple imputation for Nonresponse in Surveys. New York: John Wiley & Sons;1987.
46. Grummitt LR, Kreski NT, Kim SG, Platt J, Keyes KM, McLaughlin KA. Association of childhood adversity with morbidity and mortality in US adults: a systematic review. JAMA Pediatr. 2021. https://doi.org/10.1001/jamapediatrics.2021.2320.
47. Hughes K, Bellis MA, Hardcastle KA, Sethi D, Butchart A, Mikton C, et al. The effect of multiple adverse childhood experiences on health: a systematic review and meta-analysis. Lancet Public Health. 2017;2:e356–66.
48. Widaman KF, Helm JL, Castro-Schilo L, Pluess M, Stallings MC, Belsky J. Distinguishing ordinal and disordinal interactions. Psychol Methods. 2012;17:615.
49. Belsky J. The differential susceptibility hypothesis: sensitivity to the environment for better and for worse. JAMA Pediatr. 2016;170:321–2.
50. Traub F, Boynton-Jarrett R. Modifiable resilience factors to childhood adversity for clinical pediatric practice. Pediatrics. 2017;139. https://pediatrics.aappublications.org/content/139/5/e20162569.
51. Miller GE, Lachman ME, Chen E, Gruenewald TL, Karlamangla AS, Seeman TE. Pathways to resilience: Maternal nurturance as a buffer against the effects of childhood poverty on metabolic syndrome at midlife. Psychol Sci. 2011;22:1591–9.
52. Slopen N, Non A, Williams DR, Roberts AL, Albert MA. Childhood adversity, adult neighborhood context, and cumulative biological risk for chronic diseases in adulthood. Psychosom Med. 2014;76:481–9.
53. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat Genet. 2018;50:668.
54. Hägg S, Ganna A, Van Der Laan SW, Esko T, Pers TH, Locke AE, et al. Gene-based meta-analysis of genome-wide association studies implicates new loci involved in obesity. Hum Mol Genet. 2015;24:6849–60.
55. Stryjecki C, Alyass A, Meyre D. Ethnic and population differences in the genetic predisposition to human obesity. Obes Rev. 2018;19:62–80.
56. Peprah E, Xu H, Tekola-Ayele F, Royal CD. Genome-wide association studies in Africans and African Americans: expanding the framework of the genomics of human traits and disease. Public Health Genom. 2015;18:40–51.
57. Bürgin D, Boonmann C, Schmid M, Tripp P, O'Donovan A. Fact or artefact? Childhood adversity and adulthood trauma in the U.S. population-based Health and Retirement Study. Eur J Psychotraumatol. 2020.;11. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7034429/.
58. Duncan L, Shen H, Gelaye B, Meijsen J, Ressler K, Feldman M, et al. Analysis of polygenic risk score usage and performance in diverse human populations. Nat Commun. 2019;10:1–9.
59. Wiss DA, Brewerton TD. Adverse childhood experiences and adult obesity: a systematic review of plausible mechanisms and meta-analysis of cross-sectional studies. Physiol Behav. 2020;223:112964.
60. Midei A, Matthews K. Interpersonal violence in childhood as a risk factor for obesity: a systematic review of the literature and proposed pathways. Obes Rev. 2011;12:e159–72.

AUTHOR CONTRIBUTIONS

FDM and AGC developed the idea for the study and selected the variables for analyses. FDM conducted the analyses and drafted the methods and results. AGC drafted the introduction and discussion. RFK assisted with the interpretation of results and the drafting of the paper All authors provided critical revisions and approved a final version of the paper.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41366-022-01191-3.

Correspondence and requests for materials should be addressed to Adolfo G. Cuevas.