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Discrimination Exposure and Polygenic Risk for Obesity in Adulthood: Testing Gene-Environment Correlations and Interactions

Adolfo G. Cuevas[a] Frank D. Mann[b] Robert F. Krueger[c]

[a]Department of Social and Behavioral Sciences Department, School of Global Public Health, New York University, New York, NY, USA; [b]Department of Family, Population, and Preventative Medicine, Program in Public Health, Stony Brook University, New York, NY, USA; [c]Department of Psychology, University of Minnesota, Minneapolis, MN, USA

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Polygenic scores · Discrimination · Obesity

Abstract

Introduction: Exposure to discrimination has emerged as a risk factor for obesity. It remains unclear, however, whether the genotype of the individual can modulate the sensitivity or response to discrimination exposure (gene × environment interaction) or increase the likelihood of experiencing discrimination (gene-environment correlation). ***Methods:*** This was an observational study of 4,102 white/European Americans in the Health and Retirement Study with self-reported, biological assessments, and genotyped data from 2006 to 2014. Discrimination was operationalized using the average of nine Everyday Discrimination Scale items. Polygenic risk scores (PRSs) for body mass index (BMI) and waist circumference (WC) were calculated using the weighted sum of risk alleles based on studies conducted by the Genetic Investigation of Anthropometric Traits (GIANT) consortium. ***Results:*** We found that greater PRS-BMI was significantly associated with more reports of discrimination ($\beta = 0.04 \pm 0.02$; $p = 0.037$). Further analysis showed that measured BMI partially mediated the association between PRS-BMI and discrimination. There was no evidence that the association between discrimination and BMI, or the association between discrimination and WC, differed by PRS-BMI or PRS-WC, respectively. ***Conclusion:*** Our findings suggest that individuals with genetic liability for obesity may experience greater discrimination in their lifetime, consistent with a gene-environment correlation hypothesis. There was no evidence of a gene-environment interaction. More genome-wide association studies in diverse populations are needed to improve generalizability of study findings. In the meantime, prevention and clinical intervention efforts that seek to reduce exposure to all forms of discrimination may help reduce obesity at the population level.

Introduction

Obesity is a rapidly growing public health issue in the USA [1]. About 42% of the US adult population currently have obesity, which is more than a 3-fold increase over the 12% in 1991 [2, 3]. It is projected that by 2030 about half of the population will suffer from obesity and bear its consequences [4]. Compared to people with healthy weight, people with obesity are at greater risk of several illnesses and diseases, including psychiatric disorders,

karger@karger.com
www.karger.com/lfg

Correspondence to:
Adolfo G. Cuevas, Adolfo.cuevas@nyu.edu

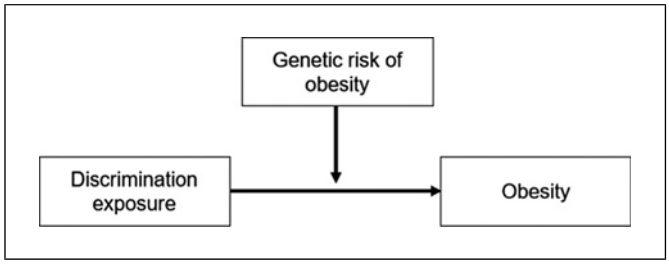

Fig. 1. Conceptual framework of the potential moderating effect of genetic risk on the relationship between discrimination and obesity.

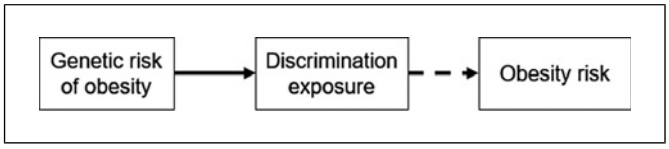

Fig. 2. Conceptual framework of the potential relationship between genetic risk of obesity and discrimination exposure that, in turn, can lead to greater risk of obesity.

diabetes, hypertension, coronary heart disease, and stroke [5–10]. The etiology and rise of obesity are multifactorial, reflecting a complex interaction of genetic and socio-environmental factors [11–13].

Over the last 3 decades, a large body of research has shown that exposure to discrimination has deleterious effects on physical and mental health [14–17]. Growing attention has been given to the link between discrimination exposure and obesity [18–20]. Discrimination exposure can operate like other stressors in that it could induce negative emotional states (e.g., anger, hostility) that in turn lead to obesity-related behaviors (e.g., binge eating and physical inactivity) and dysregulation of multiple physiological systems [16, 21–28]. Epidemiological studies have found that greater exposure to discrimination is associated with increased waist circumference (WC), higher body mass index (BMI), and higher risk of having severe obesity [18–20, 29–31]. Nevertheless, exposure to discrimination may not unequivocally determine the risk of obesity as genetic influence may also play a role in the relationship.

Individual differences in obesity may be partially explained by an interplay between genetic vulnerability and discrimination exposure. The diathesis-stress model proposes that genetic vulnerability and environmental exposure interact (GxE) to increase the risk of disease [32–37]. Thus, it is plausible that individuals genetically predisposed to obesity are susceptible to the obesogenic effects of discriminatory experiences (see Fig. 1). It is also plausible that an individual's genetically influenced phenotype can evoke certain reactions from the environment [38–44]. Commonly referred to as evocative gene-environment correlation (rGE), individuals with greater genetic propensity for obesity may be exposed to multiple forms of discrimination in their social environment (e.g., racism, weight stigma, sexism) [45] that, in turn, increase the risk of obesity (see Fig. 2).

The purpose of the present study was to examine GxE interactions and evocative rGE with a particular focus on discrimination exposure and genetic risk for obesity. Assessing a GxE interaction model can help determine the extent to which genetic risk enhances the impact of discrimination exposure on obesity-related phenotypes, whereas evidence for evocative rGE can indicate a potential relationship between genetic liability and discrimination exposure. Both paths can provide insight into the etiology of obesity and identify individuals who may be at high risk for obesity and, thus, help develop comprehensive prevention efforts and clinical interventions.

Methods

Sample

The current study analyzed data from the Health and Retirement Study (HRS). Details on the recruitment of participants and study procedures can be found elsewhere [46, 47]. The sample for the current study consisted of white/European American participants with self-reported and genotyped data from 2006 to 2014 (n = 7,976), with the analytic sample (n = 4,102) excluding participants with missing data on focal study variables, specifically polygenic risk scores (PRSs), BMI, WC, and daily discrimination. The average age of participants was 68.21 years (SD = 13.32). Approximately, 60% of the sample was female (40% male), 13% of participants did not graduate from high school, 4% obtained a general education diploma, 30% obtained a high school diploma, 20% attended some college, 6% an associate's or technical degree, 16% a bachelor's degree, 8% a master's degree, and 2% a J.D., M.D., or PH.D.

Measures

Self-reported demographic factors included chronological age (in years), gender (female and male), the highest level of completed education, and birth cohort (born before 1924 or after 1943).

Measures of Obesity

Obesity was measured using two common indicators, BMI and WC. BMI was measured as weight in kilograms divided by height into m^2. WC was measured at the navel using a tape measure for participants who were able to stand and raise their arms.

Polygenic Risk Scores

PRSs for BMI and WC were constructed by the HRS staff using summary statistics from a large-scale genome-wide association study (GWAS), specifically the Genetic Investigation of Anthropometric Traits (GIANT) consortium [48, 49]. Polygenic scores are a weighted linear summation of the single-nucleotide polymorphisms (SNPs) associated with a phenotype in a GWAS (k), weighted by the effect sizes of those polymorphisms (β_i) ($PRS_k = \sum_i \beta_i SNP_{ik}$, whereby i is the ith SNP of all SNPs associated with phenotype k). An a priori p value threshold of 1.0 was used to calculate PRSs to include the effects of all measured and imputed SNPs that passed quality control checks.

DNA collection and genotype calling for HRS are described in the study documentation [50]. In brief, the Illumina Human Omni 2.5 BeadChips (Human Omni 2.5-4v1, Human Omni 2.5-8v1) measured polymorphisms across ~2.4 million SNPs. Those with chromosomal abnormalities and first-degree relatives were removed from the sample, and SNPs out of Hardy-Weinberg equilibrium ($p < 0.0001$), with ambiguous strand orientation, or >5% missing calls were excluded prior to imputation. The 1000 Genomes Project cosmopolitan reference panel phase 3 version 5 was used to impute genotypes, resulting in ~21 million imputed SNPs from the 1,905,968 SNPs that were genotyped and passed quality control metrics.

Daily Discrimination

Participants reported how often they had experienced nine discriminatory events, including "(1) You are treated with less courtesy or respect than other people; (2) You receive poorer service than other people at restaurants or stores; (3) People act as if they think you are not smart; (4) People act as if they are afraid of you; (5) You are threatened or harassed; (6) You receive poorer service or treatment than other people from doctors or hospitals." All items were rated using a 6-point ordinal scale (1 = Almost every day, 2 = At least once a week, 3 = A few times a month, 4 = A few times a year, 5 = Less than once a year, 6 = Never) and reversed coded before creating an average score, such that higher scores reflect more discrimination.

Data Analytic Procedures

Descriptive Statistics

Data were imported into R Studio version 1.2.5003, processed, and then exported from R using the "MplusAutomation" package version 0.7.1 [51]. First, using R Studio, descriptive statistics were calculated, and gender differences were examined using Welch's t tests and Mann-Whitney U tests (see online suppl. Table S1; for all online suppl. material, see www.karger.com/doi/10.1159/000529527). In addition, zero-order Pearson product-moment and Spearman rank-order correlations were calculated (see online suppl. Table S2).

Next, using Mplus version 8.4, a series of multiple linear regressions were estimated using maximum likelihood with robust standard errors. These multiple regressions were used to (1) test the prediction of BMI and WC by PRSs for BMI and WC, respectively, (2) adjusting for the effects of PRSs and genetic principal components, test the prediction of BMI and WC by daily discrimination, (3) test the prediction of daily discrimination by PRSs for BMI and WC, and (4) test for gene-by-environment interactions, whereby the prediction of BMI and WC by daily discrimination is magnified by polygenic risk for BMI and WC. All multiple regressions included the linear effects of age, gender, level of education, birth cohort, and the first ten genetic principal components, such that coefficients predicting BMI and WC are adjusted for the influence of the other predictors in the model.

Gene-by-environment interactions were tested by adding additional predictors to multiple regressions, specifically product terms between PRS and daily discrimination (PRS × DD), between PRS, demographic factors, and genetic principal components (PRS × Age, PRS × Gender, PRS × EDU, PRS × Cohort, PRS × PC1, PRS × PC2 . . .), between daily discrimination, demographic factors, and genetic principal components (DD × Age, DD × Gender, DD × EDU, DD × Cohort, DD × PC1, DD × PC2 . . .), and between demographic factors and genetic principal components (Age × PC1, Gender × PC1, EDU × PC1, Cohort × PC1, Age × PC2, Gender × PC2, EDU × PC2, Cohort × PC2 . . .). These product terms help ensure that potential gene-by-environment interactions are not biased by the potential moderating effects of demographic factors. Age was mean-centered, education and daily discrimination were standardized (M = 0, SD = 1), and gender (male = 0, female = 1) and birth cohort (born after 1924 = 0, born before 1924 = 1) were dummy-coded prior to computing product terms.

Results

Descriptive statistics are reported in the supplement, including means, medians, standard deviations, minimum values, maximum values, skew, and kurtosis. The results of multiple regressions are reported in Tables 1, 2, including unstandardized regression coefficients (b), standard errors, p values (p), standardized regression coefficients (β), and the percent of variance explained (R^2). Several results are noteworthy. First, PRSs for BMI were significantly associated with higher BMI (b = 1.42, CI 95% = 1.25–1.60, β = 0.25). Similarly, PRSs for WC were significantly associated with higher WC (b = 1.29, CI 95% = 1.10–1.47, β = 0.23).

Second, the association between daily discrimination and BMI was statistically significant, even after adjusting for demographic factors and potential genetic confounds using PRS and genetic principal components (b = 0.43, CI 95% = 0.16–0.69, β = 0.07). The association between daily discrimination and WC was also statistically significant for respondents even after adjusting for demographic factors and potential genetic confounds using PRS and genetic principal components (b = 0.55, CI 95% = 0.28–0.77, β = 0.10). These results indicate that the association between discrimination and measures of obesity cannot be explained by potential genetic confounds, at least those captured by PRSs, as well as the first ten genetic principal components.

Third, PRSs for high BMI were significantly associated with higher reports of daily discrimination (b = 0.04, CI 95% = 0.002–0.071, β = 0.05). PRSs for high WC were also

Table 1. Results of multiple linear regressions testing the prediction of body mass index (BMI) and waist circumference by demographic factors, polygenic risk scores, and individual differences in daily discrimination

n = 4,102	BMI (R^2 = 0.13)				Waist circumference (R^2 = 0.15)			
	b	SE	*p* value	β	*b*	SE	*p* value	β
Intercept	34.64	0.75	<0.001		45.16	0.75	<0.001	
PC1	−0.01	0.09	0.823	−0.00	−0.18	0.08	0.026	−0.03
PC2	0.04	0.09	0.609	0.01	0.16	0.08	0.045	0.03
PC3	0.23	0.09	0.008	0.04	0.05	0.08	0.578	0.01
PC4	0.04	0.08	0.600	0.01	−0.01	0.08	0.886	−0.00
PC5	0.24	0.09	0.005	0.04	−0.46	0.09	<0.001	−0.08
PC6	0.07	0.08	0.430	0.01	0.02	0.08	0.799	0.00
PC7	−0.01	0.08	0.954	−0.00	−0.06	0.08	0.482	−0.01
PC8	−0.15	0.08	0.074	−0.03	−0.06	0.08	0.509	−0.01
PC9	0.03	0.08	0.697	0.01	0.07	0.08	0.429	0.01
PC10	0.07	0.08	0.415	0.01	−0.14	0.08	0.093	−0.02
Age	−0.07	0.01	<0.001	−0.17	−0.00	0.01	0.962	−0.00
Female	−0.44	0.17	0.009	−0.08	−3.49	0.16	<0.001	−0.61
Level of education	−0.27	0.05	<0.001	−0.09	−0.32	0.05	<0.001	−0.10
Birth cohort	−1.30	0.26	<0.001	−0.22	−0.98	0.27	<0.001	−0.17
Daily discrimination	0.43	0.14	0.002	0.05	0.55	0.13	<0.001	0.07
Polygenic risk score (BMI or WC)	1.42	0.09	<0.001	0.25	1.29	0.09	<0.001	0.23

n, sample size; *b*, unstandardized regression coefficient; SE, robust standard error; *p,* probability of the observed association if the null hypothesis is true; β, standardized regression coefficient; R^2, percent of variance explained; PC1–PC10, first ten genetic principal components.

significantly associated with higher reports of daily discrimination, but this effect was no longer statistically significant after adjusting for PRSs for BMI (b = 0.01, CI 95% = −0.034–0.041; see Table 2). These results are consistent with rGE, such that individuals with higher genetic risk scores for BMI and WC tended to report more discrimination. Gene-by-environment interactions between daily discrimination and polygenic scores predicting BMI and WC were not statistically significant ($p > 0.05$), indicating that the associations between discrimination and measures of obesity remained relatively unchanged across levels of genetic liability for obesity (online suppl. Table S3).

Sensitivity Analysis

Finally, a sensitivity analysis was conducted to test (1) whether the PRS for high BMI was significantly associated with higher reports of daily discrimination, after adjusting for measured BMI, and (2) whether measured BMI statistically mediated the association between the PRS for high BMI and higher reports of daily discrimination. This was achieved using the path analysis model depicted in Figure 3. Notably, measured BMI partially mediated the association between the PRS for high BMI and daily discrimination, as the 95% bootstrapped confidence intervals for the indirect effect did not include zero. Moreover, the association between the PRS for high BMI and daily discrimination was greater than zero, even after adjusting for the effect of measured BMI on daily discrimination.

Discussion

The present study used a large sample of genotyped adults from HRS to test two models that can help elucidate the association between discrimination and obesity: (1) evocative rGE and (2) GxE interaction. There was evidence supporting a rGE, such that PRSs for high BMI were significantly associated with higher reports of daily discrimination. Higher reports of daily discrimination were also associated with higher BMI and WC, even after adjusting for demographic factors and potential genetic confounds using PRSs and genetic principal components. There was no evidence to suggest a GxE interaction. In other words, the strength of the associations between discrimination and obesity measures (i.e., BMI and WC) did not differ as a function of genetic liability.

Discrimination exposure is a potent social determinant that contributes to a wide range of illnesses [52, 53].

Table 2. Results of multiple linear regression testing the prediction of daily discrimination by demographic factors and polygenic risk scores for body mass index (BMI) and waist circumference (WC)

n = 4,102	Daily discrimination (R^2 = 0.09)			
	b	SE	*p* value	β
Intercept	3.01	0.09	<0.001	
PC1	0.01	0.01	0.224	0.02
PC2	0.00	0.01	0.961	0.00
PC3	0.01	0.01	0.181	0.02
PC4	−0.01	0.01	0.553	−0.01
PC5	0.00	0.01	0.922	0.00
PC6	−0.01	0.01	0.556	−0.01
PC7	−0.01	0.01	0.223	−0.02
PC8	0.00	0.01	0.730	0.01
PC9	0.00	0.01	0.991	0.00
PC10	−0.01	0.01	0.212	−0.02
Age	−0.02	0.00	<0.001	−0.31
Female	−0.15	0.02	<0.001	−0.22
Level of education	−0.02	0.01	0.006	−0.05
Birth cohort	0.14	0.03	<0.001	0.20
Polygenic risk score for BMI	0.04	0.02	0.037	0.05
Polygenic risk score for WC	0.01	0.02	0.842	0.01

n, sample size; *b,* unstandardized regression coefficient; *SE,* robust standard error; *p,* probability of the observed association if the null hypothesis is true; β, standardized regression coefficient; R^2, percent of variance explained; PC1–PC10, first ten genetic principal components.

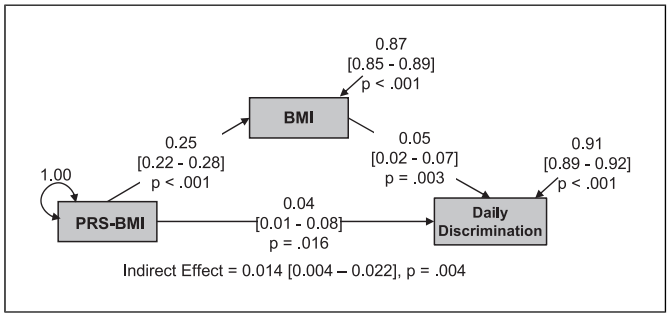

Fig. 3. Results of sensitivity analysis testing whether measured BMI accounts for the link between polygenic liability for BMI and daily discrimination.

Growing research suggests that discrimination is associated with increased risk of obesity [19, 30, 54]. Genetic vulnerability may play a role in the relationship between discrimination and obesity. We find that greater genetic risk for BMI is associated with greater discrimination exposure, and sensitivity analyses revealed this association is only partially explained by measured BMI, supporting an evocative rGE hypothesis. It may be that people with greater genetic risk have higher weight status, which increases the risk of being exposed to discrimination due to their weight. It may also be that expression of certain obesity-related genes influences emotional arousal and vigilance that, in turn, increase the propensity of perceiving environmental stimuli as threatening or discriminatory experiences. Future research should consider potential parallel mediators that were not included in the present study to better understand the pathways by which genetic risk for obesity is associated with discrimination exposure.

Using a diathesis-stress framework, we expected that the association between genetic risk and BMI and WC would be stronger for individuals exposed to greater discrimination. However, we did not find evidence of a gene-by-environment interaction. Nevertheless, discrimination exists across multiple levels and settings, and often coexists in individuals' lives [55–58]. Focusing on a single dimension of discrimination is likely to underestimate or mischaracterize the impact of discrimination on health. Such approach can reveal how discrimination affects individual outcomes and potentially interact with genetic risk.

Important limitations need to be considered in the present study. First, the cross-sectional design of our study limits our ability to identify a causal relationship between discrimination and obesity. Previous longitudinal studies have found that discrimination is associated with a greater increase in BMI and WC over an 8-year period [19, 31]. Nevertheless, more epidemiological research is needed to establish causality and increase generalizability. This is particularly important within the context of rGE. It is unclear what may explain the link between polygenic risk and discrimination exposure. Future research should use prospective data to disentangle the interrelationship between genetic risk, discrimination, and obesity. The SNPs used in calculating the polygenic scores in this study derive largely from a GWAS meta-analysis. However, future GWAS meta-analyses may identify additional obesity-related SNPs that would strengthen the predictive validity of the polygenic scores. 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 [48, 59–61]. Using European-derived GWAS can lead to biased estimates that can further exacerbate existing disparities and discrimination, which is why we strictly used a cohort of white-identifying respondents. The inferences based on

study findings are limited to white adults living in the USA. While the health effects of discrimination are similar across racial/ethnic groups [53], racial/ethnic minorities, particularly black Americans, experience more discrimination than whites, placing them at an increased risk for obesity [62]. Genetic analyses of more diverse populations are direly needed to improve genetic-based risk predictions and, ultimately, better characterize our GxE and rGE findings for racial/ethnic minorities.

Conclusions

We found evidence of a rGE as greater genetic propensity for obesity was associated with greater exposure to discrimination. This suggests that individuals with higher genetic risk may be more likely to be exposed to unfair treatment in their social environment. There was no evidence of a gene-environment interaction. Further research is also needed to illuminate the pathways by which discrimination exposure and genetic liability can increase the risk of obesity. Multi-racial/ethnic GWAS is needed to improve the predictive performances of genetic scores and clarify gene-environment findings for racial/ethnic minorities. Such findings can lead to optimal societal interventions to reduce the prevalence of discrimination and obesity.

Statement of Ethics

Tufts University Institutional Review Board (IRB) approved the study protocol (STUDY00001031). This study was performed in line with the principles of the Declaration of Helsinki. Ethical approval and consent were not required as this study was based on publicly available data.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Author Contributions

Adolfo G. Cuevas developed the idea for the study and selected the variables for analyses. Frank D. Mann conducted the analyses and drafted the methods and results. A.G.C. drafted the introduction and discussion. Robert F. Krueger assisted with the interpretation of results and the drafting of the manuscript. All authors provided critical revisions and approved a final version of the manuscript.

Data Availability Statement

Data are publicly available and can be found in https://hrs.isr.umich.edu/data-products. Further inquiries can be directed to the corresponding author.

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