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A polygenic score for body mass index is associated with depressive symptoms via early life stress: Evidence for gene-environment correlation

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ABSTRACT

Increasing childhood obesity rates are associated with not only adverse physical, but also mental health outcomes, including depression. These negative outcomes may be caused and/or exacerbated by the bullying and shaming overweight individuals experience. As body mass index (BMI) can be highly heritable, we hypothesized that a genetic risk for higher BMI, will predict higher early life stress (ELS), which in turn will predict higher depressive symptoms in adulthood. Such a process will reflect an evocative gene-environment correlation (rGE) wherein an individual's genetically influenced phenotype evokes a reaction from the environment that subsequently shapes the individual's health. We modeled genetic risk using a polygenic score of BMI derived from a recent large GWAS meta-analysis. Self-reports were used for the assessment of ELS and depressive symptoms in adulthood. The discovery sample consisted of 524 non-Hispanic Caucasian university students from the Duke Neurogenetics Study (DNS; 278 women, mean age 19.78 ± 1.23 years) and the independent replication sample consisted of 5930 white British individuals from the UK biobank (UKB; 3128 women, mean age 62.66 ± 7.38 years). A significant mediation effect was found in the DNS (indirect effect = 0.207, bootstrapped SE = .10, bootstrapped 95% CI: 0.014 to 0.421), and then replicated in the UKB (indirect effect = 0.04, bootstrapped SE = .01, bootstrapped 95% CI: 0.018 to 0.066). Higher BMI polygenic scores predicted higher ELS, which in turn predicted higher depressive symptoms. Our findings suggest that evocative rGE may contribute to weight-related mental health problems and stress the need for interventions that aim to reduce weight bias, specifically during childhood.

Overweight individuals suffer from stigmatization, bias, and bullying, from multiple sources including peers, health care providers, educators, and, most surprisingly perhaps, family members (Puhl and Latner, 2007). In a study of adolescents enrolled in weight loss camps, 37% reported being teased or bullied by a parent (Puhl et al., 2013). Another study on 2449 women recruited from a weight loss support group organization, found that 44% experienced stigma from their mothers more than once, while 34% experienced it from their fathers (Puhl and Brownell, 2006). Emotional and physical abuse are forms of early life stress (ELS), which has been associated with various negative physical and mental health outcomes (Goodwin and Stein, 2004; Mersky et al., 2013).

Gene environment correlations (rGE; Avinun and Knafo-Noam, 2014; Plomin et al., 1977) can represent passive, evocative, and active processes that create associations between individuals' genes and the environment. Evocative rGE, which refers to instances in which a genetically influenced phenotype of an individual evokes a certain reaction from the environment, may be relevant to weight-related teasing and bullying, such that individuals with a genetic propensity toward a higher body mass index (BMI), will be more likely to experience teasing, especially in the current Western cultural climate, which is characterized by negative and prejudicial attitudes towards overweight and obese individuals (Pearl, 2018).

A recent meta-analysis of genome-wide association studies (GWAS; Yengo et al., 2018), consisting of 681,275 participants on average, explained 5% of the variance in BMI with GWAS significant single nucleotide polymorphisms (SNPs). In the current study, we hypothesized that a polygenic score based on the results from this meta-analysis, will predict early life stress (ELS), consistent with an evocative rGE, which in turn will predict depressive symptoms in adulthood. We tested our hypothesis in two independent samples: a discovery sample of 524 non-Hispanic Caucasian university students from the Duke Neurogenetics Study and a replication sample of 5930 adult white British volunteers from the UK Biobank (UKB). As the GWAS meta-

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analysis included data from the UKB, which may bias our results, in the UKB analyses we also used BMI polygenic scores that were based on a GWAS that did not include the UKB as a discovery sample (Locke et al., 2015).

1. Materials and methods

1.1. Participants

Our discovery sample consisted of 524 self-reported non-Hispanic Caucasian participants (278 women, mean age 19.78 ± 1.23 years) from the Duke Neurogenetics Study (DNS) who were not related and for whom there was complete data on genotypes, ELS, depressive symptoms, and all covariates. Participants were recruited through posted flyers on the Duke University campus and through a Duke University listserv. All procedures were approved by the Institutional Review Board of the Duke University Medical Center, and participants provided informed consent before study initiation. All participants were free of the following study exclusions: 1) medical diagnoses of cancer, stroke, diabetes requiring insulin treatment, chronic kidney or liver disease, or lifetime history of psychotic symptoms; 2) use of psychotropic, glucocorticoid, or hypolipidemic medication; and 3) conditions affecting cerebral blood flow and metabolism (e.g., hypertension). Importantly, neither current nor lifetime mental disorder diagnosis were an exclusion criterion, as the DNS sought to establish broad variability in multiple behavioral phenotypes related to psychopathology.

The replication sample consisted of 5930 white British individuals (3128 women, mean age 62.66 ± 7.38 years), who participated in the UKB's imaging wave, completed an online mental health questionnaire (Davis et al., 2018), and had complete genotype, ELS, depressive symptoms and covariate data. The UKB (www.ukbiobank.ac.uk; Sudlow et al., 2015) includes over 500,000 participants, between the ages of 40 and 69 years, who were recruited within the UK between 2006 and 2010. The UKB study has been approved by the National Health Service Research Ethics Service (reference: 11/NW/0382), and our analyses were conducted under UKB application 28174.

1.2. Race/ethnicity

Because self-reported race and ethnicity are not always an accurate reflection of genetic ancestry, an analysis of identity by state of whole-genome SNPs in the DNS was performed in PLINK (Purcell et al., 2007). Before running the multidimensional scaling components analysis, SNPs were pruned for high LD ($r^2 > 0.1$) and the following were removed: C/G and A/T SNPs, SNPs with a missing rate > 0.05 or a minor allele frequency < 0.01, SNPs that did not pass the Hardy-Weinberg equilibrium test (p < 1e-6), sex chromosomes, and regions with long range LD (the MHC and 23 additional regions; Price et al., 2008). Further, one from each pair of individuals with proportion identity by descent > 0.1875 was removed. The first two multidimensional scaling components computed for the non-Hispanic Caucasian subgroup, as determined by both self-reports and the multidimensional scaling components of the entire mixed race/ethnicity DNS sample, were used as covariates in analyses of data from the DNS. The decision to use only the first two components was based on an examination of a scree plot of the variance explained by each component. Additional details can be found at: http://haririlab.com/methods/genetics.html. For analyses of data from the UKB, only those who were 'white British' based on both self-identification and a principal components analysis of genetic ancestry were included. Additionally, the first 10 multidimensional scaling components received from the UKB's data repository (unique data identifiers: 22009-0.1-22009-0.10) were included as covariates as previously done (e.g., Whalley et al., 2016). Further details on the computation of the multidimensional scaling components can be found elsewhere: http://www.ukbiobank.ac.uk/wp-content/uploads/2014/04/UKBiobank_genotyping_QC_documentation-web.pdf.

1.3. Body mass index (BMI)

In both DNS and UKB samples, BMI was calculated at the time of imaging based on the height and weight of the participants. In the DNS, this calculation was based on imperial system values (pounds/inches2*703), while in the UKB the metric system was used (kg/m2). In the DNS 1.3% of the sample was obese (BMI > =30), compared to 18.7% in the UKB.

1.4. Depressive symptoms

In the DNS, the 20-item Center for Epidemiologic Studies Depression Scale (CES-D) was used to assess depressive symptoms in the past week (Radloff, 1977). All items were summed to create a total depressive symptoms score. In the UKB, the Patient Health Questionnaire 9-question version (PHQ-9) was used to assess depressive symptoms in the past 2 weeks (Kroenke et al., 2001). All items were summed to create a total depressive symptoms score.

1.5. Early life stress

In the DNS, ELS was estimated using the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003). The CTQ has 28-items and it assesses the frequency of emotional, physical, and sexual abuse as well as emotional and physical neglect. The scores on the 5 subscales (each ranging from 5 to 25) were summed to create a total score of ELS. In the UKB, the Childhood Trauma Screener – 5 item (CTS-5) was used to assess adverse events during childhood (Glaesmer et al., 2013). CTS-5 is a short version of the CTQ consisting of 5 items: "Felt hated by family member as a child", "Physically abused by family as a child", "Felt loved as a child" (reverse coded), "Sexually molested as a child", and "Someone to take to doctor when needed as a child" (reverse coded). The 5 items, each ranging from 0 to 4, were summed to create a total score of ELS.

1.6. Genotyping

In the DNS, DNA was isolated from saliva using Oragene DNA self-collection kits (DNA Genotek) customized for 23andMe (www.23andme.com). DNA extraction and genotyping were performed through 23andMe by the National Genetics Institute (NGI), a CLIA-certified clinical laboratory and subsidiary of Laboratory Corporation of America. One of two different Illumina arrays with custom content was used to provide genome-wide SNP data, the HumanOmniExpress (N = 329) or HumanOmniExpress-24 (N = 195; Do et al., 2011; Eriksson et al., 2010; Tung et al., 2011). In the UKB, samples were genotyped using either the UK BiLEVE (N = 569) or the UKB axiom (N = 5361) array. Details regarding the UKB's quality control can be found elsewhere (Bycroft et al., 2017).

1.7. Quality control and polygenic scoring

For genetic data from both the DNS and UK Biobank, PLINK v1.90 (Purcell et al., 2007) was used to apply quality control cutoffs and exclude SNPs or individuals based on the following criteria: missing genotype rate per individual > .10, missing rate per SNP > .10, minor allele frequency < 0.01, and Hardy-Weinberg equilibrium p < 1e-6. Additionally, in the UKB, quality control variables that were provided with the dataset were used to exclude participants based on a sex mismatch (genetic sex different from reported sex), a genetic relationship to another participant, outliers for heterozygosity or missingness (unique Data Identifier 22010–0.0), and UKBiLEVE genotype quality control for samples (unique Data Identifiers 22050-0.0-22052-0.0).

Polygenic scores were calculated using PLINK's (Purcell et al., 2007) "–score" command based on published SNP-level summary statistics from a recent BMI GWAS meta-analysis (Yengo et al., 2018). SNPs from

the GWAS of BMI meta-analysis were matched with SNPs from the DNS and the UKB. For each SNP the number of the alleles (0, 1, or 2) associated with BMI was multiplied by the effect estimated in the GWAS. The polygenic score for each individual was an average of weighted BMI-associated alleles. All SNPs matched with SNPs from the DNS and UKB were used regardless of effect size and significance in the original GWAS, as previously recommended and shown to be effective (Dudbridge, 2013; Ware et al., 2017). A total of about 386,679 SNPs from the DNS and 215,200 SNPs from the UKB were included in the polygenic scores. For validation of the indirect effect in the UKB, BMI polygenic scores were also calculated based on an older GWAS that did not include the UKB as a discovery sample (Locke et al., 2015).

1.8. Statistical analysis

Linear regression analyses in SPSS v25 were conducted to test for an association between the BMI polygenic score and BMI in adulthood. The PROCESS SPSS macro, version 3.1 (Hayes, 2017), was used to conduct the mediation analyses. Participants' sex (coded as 0 = males, 1 = females), age, and genomic components (two for the DNS and 10 for the UK biobank) were entered as covariates in all analyses. In the mediation analyses, bias-corrected bootstrapping (set to 5000) was used to allow for non-symmetric 95% confidence intervals (CIs). Specifically, indirect effects are likely to have a non-normal distribution, and consequently the use of non-symmetric CIs for the determination of significance is recommended (MacKinnon et al., 2004). However, bias-corrected bootstrapping also has its faults (Hayes and Scharkow, 2013) and, consequently, as supportive evidence for the indirect effect, we also present the test of joint significance, which examines whether the *a path* (BMI polygenic score to ELS) and the *b path* (ELS to depressive symptoms, while controlling for the BMI polygenic score) are significant. The BMI polygenic scores were standardized (i.e., M = 0, SD = 1) in SPSS to make interpretability easier. The mediation was first analyzed in the DNS, and then a replication was tested in the UKB. As a validation of the indirect effect in the UKB, it was also tested with an older BMI polygenic score that was not based on a GWAS that included the UKB (Locke et al., 2015).

2. Results

Descriptive statistics are presented in Table 1.

2.1. Confirming an association between BMI polygenic scores and measured BMI

As a preliminary analysis we confirmed that higher BMI polygenic scores were significantly associated with higher measured BMI in both the DNS (N = 522, b = 0.837, SE = 0.117, $p < .001$; $R^2 = 0.085$) and the UKB (N = 5 925, b = 1.41, SE = 0.054, $p < .001$; $R^2 = 0.10$). As the UKB was included in the recent BMI GWAS the latter association is inflated. Consequently, we also present the association from a polygenic score that is based on a smaller sample GWAS (Locke et al., 2015) that did not include the UKB. This association was significant (N = 5 925, b = 0.823, SE = 0.056, $p < .001$; $R^2 = 0.03$). The R^2 values are based on the difference between a model with the polygenic score and a model without it. The models included sex, age, and genomic components as covariates. The sample sizes for these analyses were slightly different from the mediation analyses below because measured BMI was missing for a few participants.

Table 1
Descriptive statistics of study variables.

	DNS				UK Biobank			
	Min	Max	Mean	SD	Min	Max	Mean	SD
Age	18	22	19.78	1.24	45	78	62.66	7.38
BMI	16.30	39.15	22.29	2.83	14.94	58.04	26.60	4.419
Early life stress	25	74	31.29	7.16	0	20	1.68	2.32
Depressive symptoms	0	43	8.99	7.18	0	27	2.45	3.39

2.2. BMI polygenic scores and ELS (a path) in the DNS

The BMI polygenic scores were significantly associated with ELS (b = 0.65, SE = 0.31, p = .038), so that higher scores predicted higher ELS. Of the covariates, only age was significantly and negatively associated with ELS (b = −0.73, SE = 0.25, $p < .01$).

2.3. ELS and depressive symptoms (b path) in the DNS

With the BMI polygenic scores in the model, ELS significantly and positively predicted depressive symptoms (b = 0.32, SE = 0.04, $p < .001$).

2.4. BMI polygenic scores and depressive symptoms in the DNS

The BMI polygenic scores did not significantly predict depressive symptoms (b = −0.34, SE = 0.31, *ns*). Notably, however, the significance of a direct path from X (BMI polygenic scores) to Y (depressive symptoms) or the 'total effect' (the *c path*), is not a prerequisite for the testing of a mediation/indirect effect (Hayes, 2009; MacKinnon et al., 2000; Rucker et al., 2011), which was the main interest of the current study.

2.5. Mediation model in the DNS

The indirect path (*a*b*), BMI polygenic scores – > ELS – > depressive symptoms, was significant as indicated by the bias corrected bootstrapped 95% CI not including zero (Fig. 1a; indirect effect = 0.207, bootstrapped SE = .10, bootstrapped 95% CI: 0.014 to 0.421). This mediation remained significant when 10 genomic components, instead of two, were included as covariates (indirect effect = 0.20, bootstrapped SE = .10, bootstrapped 95% CI: 0.008 to 0.41), and when 2 participants who self reported as non-Hispanic Caucasians, but had genomic components that suggested otherwise, were excluded (indirect effect = 0.20, bootstrapped SE = .10, bootstrapped 95% CI: 0.009 to 0.42).

2.6. Mediation model in the UBK

The *a path*, from the BMI polygenic scores to ELS, and the *b path*, from ELS to depressive symptoms while controlling for BMI polygenic scores, were significant (*a path*: b = 0.10, SE = 0.03, $p < .01$; *b path*: b = 0.40, SE = 0.018, $p < .001$). The indirect path also replicated (Fig. 1b; indirect effect = 0.04, bootstrapped SE = .01, bootstrapped 95% CI: 0.018 to 0.066), supporting a mediation in which BMI polygenic scores are associated with depressive symptoms indirectly through ELS. Similar results were obtained with the BMI polygenic scores that were based on a GWAS that did not include the UKB as a discovery sample (*a path*: b = 0.066, SE = 0.03, $p < .01$; *b path*: b = 0.40, SE = 0.018, $p < .001$; indirect effect = 0.026, bootstrapped SE = .01, bootstrapped 95% CI: 0.004 to 0.05).

3. Discussion

Here, in two independent samples, we provide novel evidence supporting evocative rGE as a possible mechanism in weight-related depression. We demonstrate a significant mediation in which higher GWAS-derived BMI polygenic scores are associated with higher levels of depressive symptoms in adulthood through elevated levels of ELS. These results suggest that in the current Western cultural climate,

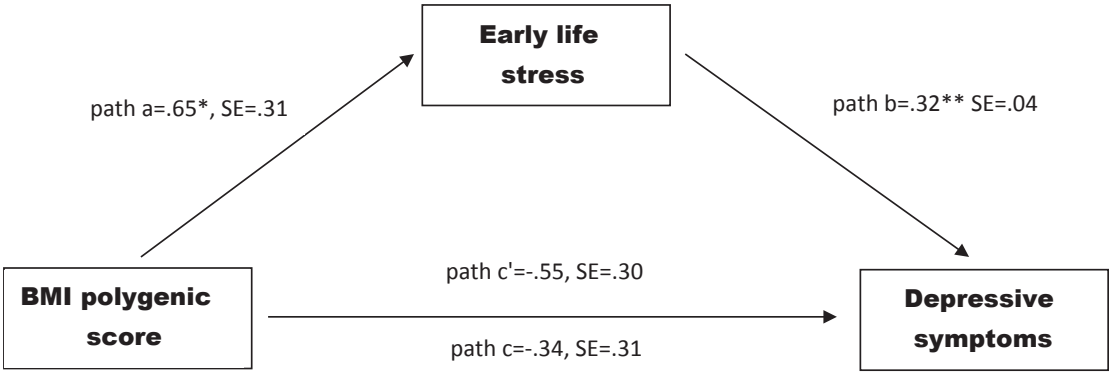

Fig. 1. Mediation model linking genetic risk for higher BMI to higher depressive symptoms, via elevated levels of early life stress.
Note. *p < .05, **p < .001. c-the total effect of the BMI polygenic scores on depressive symptoms; c'-the effect of BMI polygenic scores on depressive symptoms, while controlling for early life stress.

having a genetic makeup that increases the risk of a high BMI, may lead to a phenotype that evokes increased stress, which increases the experience of depressive symptoms in adulthood.

Various studies have reported links between being overweight and experiencing stigmatization, teasing, and bullying from peers, educators, co-workers, health care providers, and family members (Puhl and Latner, 2007). This negativity can lead to adverse mental health outcomes, including depression (Greenleaf et al., 2017), but is not limited to mental health. Obesity, childhood trauma, and depression have all been linked to physical illness including cardiovascular disease, type 2 diabetes, and autoimmune disorders (Carney and Freedland, 2017; Goodwin and Stein, 2004; Kahn et al., 2006; Van Gaal et al., 2006; Versini et al., 2014).

While several strategies have been proposed to battle the growing prevalence of childhood obesity, including nutrition standards for school meals; improved early care and education; and increased access to adolescent bariatric surgery (Gortmaker et al., 2015), our findings further encourage weight stigma reduction efforts, specifically among family members and parents. In addition to the myriad of mental and physical health disorders that are associated with ELS and childhood trauma, one of the most prevalent coping responses to weight stigma is eating (Puhl and Brownell, 2006). Consequently, ELS may lead to additional weight gain and is itself a risk factor for obesity (Danese and Tan, 2014). Thus, interventions that aim to reduce weight stigma may have a broad positive effect on health.

Although our study has several strengths, including the use of two independent samples with markedly different characteristics (e.g., young university students versus older community volunteers) and a GWAS-derived polygenic score, it is not without limitations. First, retrospective reports were used for the estimation of ELS and childhood trauma. Ideally, prospective data should be used to model ELS in the absence of reporting bias. Second, we did not have measures of childhood BMI in either sample. Although previous research does support a link between childhood BMI, teasing, and depression, and genetic influences on BMI have been shown to be relatively stable throughout development (Haberstick et al., 2010; Silventoinen and Kaprio, 2009), genetically informed longitudinal studies across development are needed to further validate our findings. Third, our measure of ELS was mostly restricted to familial stress, future studies should investigate stress from additional sources, such as peers. Fourth, the non-Hispanic Caucasian DNS sample is relatively homogeneous in terms of social background, which may have led to an underestimation of the effect in this sample. Lastly, our findings are limited to populations of European descent and to the Western culture. Additional research in diverse populations is needed to determine the extent to which the observed evocative rGE mechanism shapes weight-related mental health. Further replication is also needed to evaluate the potential of the BMI polygenic score as a risk biomarker of depression associated with ELS.

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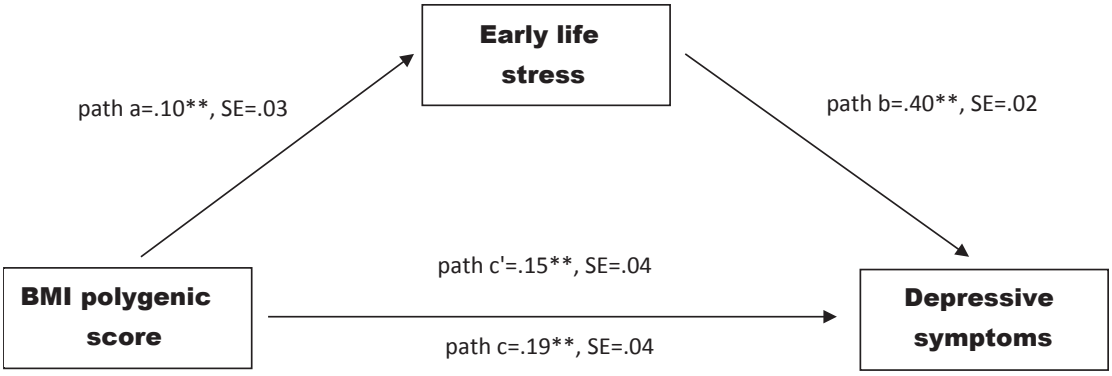

Fig. 1. (*continued*)

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