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Behavior and Genetics: Confounding Effects on Adolescent BMI

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Abstract

Introduction: Despite persistently high rates of obesity among American children and adults, the complex interplay between behavior, genetics and weight outcomes is not well understood. This study explores the roll that genetic inheritance and behavior play in weight determination.

Methods: Analysis utilizes polygenic risk score-a genome-wide score based on variation in multiple genetic loci and their associated weights-to quantify inherited susceptibility to obesity. First, linear mixed models compared the impact of behavior, situational controls and demographic characteristics on change in BMI from baseline. Second, multilevel structural equation models tested for mediating effects of behavior on genetic BMI predisposition. Mediation algorithms quantified the indirect effect of sleep, exercise, smoking frequency, alcohol consumption, screen time and school enrollment on BMI.

Results: Results showed a direct effect between BMI and polygenic risk, sleep, school enrollment, disordered eating, alcohol consumption and smoking frequency. Mediation models indicate that, in addition to the direct effect, these behaviors also asserted an indirect effect on BMI through their correlation with polygenic risk. Therefore, behavioral factors mediated the influence of genetic predisposition on BMI. Effects showed slight differences for African, European and Hispanic ancestral cohorts.

Discussion: Despite genetic tendency towards a given weight, analysis shows that behavior can moderate or moderate BMI impacts. The present study indicated that the degree of behavioral offset varies by ancestral group, but that sleep, disordered eating, screen time, smoking and educational attainment played a significant role in weight determination. Findings suggested that obesity prevention and weight loss programs should focus on adoption of healthy behaviors in addition weight and BMI.

Keywords: Health; Adolescence; Latent Class; Urban; Behavior

Introduction

Body weight is determined by multiple factors including genetic background, eating habits, metabolic rate and general activity level [1-4]. The influence of heritability on body weight is estimated to be between 47% to 90% and most recent genome-wide association study meta-analyses identified 97 variants robustly associated with adult body mass index (BMI) [5]. While genome-wide association studies have been successful in identifying several genes associated with body weight and obesity, these genes may work by modulating the way individuals respond to environmental variation, develop eating habits and perform activities-interactions that may not be readily captured by association studies [5-11].

Despite the large genetic component of BMI, studies suggest that dietary patterns, physical activity, inactivity, medication use, lifestyle or other environmental factors can interact with the genetic pathways to offset weight determining gene variants [12,13]. The possibility that genetic predisposition is mediated or modified by behavior has been explored, but the extent to which behavior can offset the effects of weight-promoting genes has not been determined [14-20]. Therefore, this study investigates the independent and interactive effects of weight-related behavior, environmental characteristics, and genetic influence on BMI to determine which behaviors, to what extend and for which ancestral groups health related behavior can mitigate hereditary BMI tendencies. First, analysis tests the strength of the genetic influence on BMI using polygenic risk scores (PRGs). Second, behavioral characteristics are added to evaluate direct and indirect effects of lifestyle on BMI. Multilevel structural equation models evaluate the mediating and moderating influences of sleep, exercise, school enrollment, screen time, and disordered eating. Finally, mediation/moderation algorithms quantify degree to which behaviors and genetics interact offset BMI genetic predisposition [21-25].

The degree to which genetics, environment, and behavior influence BMI is complicated by research showing that behavior can also be influenced by genetics [26,27]. It is possible that genetic factors exert their influence on body weight by affecting appetitive and eating behaviors; therefore, weight is determined by the interaction of genetics, behavior and environmental circumstance [28-33].

Several smaller studies have explored the relative contribution of behavioral, environmental and genetic influence on BMI [34,35] but the nature of the interaction remains unclear due to inadequate variation in the genetic locus of interest [36,37]. While males and females present different genetic profiles, some studies show similar genetic etiology among adolescent males and females, while others found higher heritability in female BMI with results broadly consistent across racial and ethnic groups [26,38]. More recent analyses incorporated variants from genome-wide meta-analyses of BMI [39] like the measure used in this analysis-which can be easily extended using weighted polygenic risk scores based on a genome-wide genotypes [40].

During adolescence and young adulthood, research suggests consumption of fruit and vegetable, regular physical activity and physical wellness are important to maintaining a healthy weight [41-43]. When adopted early in life, healthy behavior, lifestyle and regular physical activity have been shown to carryover from adolescence to adulthood [44].

In addition to individual behavior, environmental and household influences play a role in BMI determination. Socioeconomic status (SES) has shown to be strongly associated with BMI-low SES corresponds to higher BMI, particularly in adolescents and young adults. However, these results vary according to gender, ethnicity, and nationality [44-50]. Oftentimes, lifestyle and behavioral patterns such as dietary habits, physical activity, and sedentary behavior are adopted from those observed in the local environment [51]. However, excessive control over behavior and diet can result in deleterious rebound behavior when that control is relaxed [19,52].

Furthermore, behaviors such as sleep, eating the evening meal with the family, and limiting screen-viewing time have been strongly linked to BMI [53]. Sleeping less than 8 hours per day, watching television for 3 hours per day and having more than 5 hours per day of screen time was associated with higher body fat and greater risk of overweight [54-57].

Despite the complex weight determination process, this study examines behavioral mitigation of polygenic BMI disposition. Not only are sleep, exercise, school enrollment, disordered eating, screen time, smoking frequency and disorder eating directly related to BMI, but they also serve as partial mediators to BMI polygenic risk scores. This study proceeds with a discussion of the data and statistical methods in Section II followed the estimation results in Section III. Finally, principle findings, policy implications and need for further study are outlined in Section IV.

Methods

Data

Analysis utilizes data from the National Longitudinal Study of Adolescent to Adult Health (Add Health)-a longitudinal study of adolescents who are in grades 7-12 during the 1994-95 school year then surveyed periodically thereafter with five in-home interviews. Add Health combines longitudinal survey data on respondents' social, economic, and physical characteristics well-being with contextual data on the family, neighborhood, school and biological data, providing a unique opportunity to study how behavior and genetics interact as adolescents enter young adulthood. This study utilizes data from Waves I through V which contain consistent survey elements allowing longitudinal assessment of similar environmental, behavioral, and demographic characteristics. Mean values for all covariates are provided in Table 1.

Descriptive statistics for the participants include in the study												
Observations	**21065**				**6080**				**1157**			
	European Ancestry				**African Ancestry**				**Hispanic Ancestry**			
Variable	**Min**	**Max**	**Mean**	**Std Err Mean**	**Min**	**Max**	**Mean**	**Std Err Mean**	**Min**	**Max**	**Mean**	**Std Err Mean**
BMI	13	55	25.804	0.121	13	55	27.840	0.220	13	55	26.763	0.300
Baseline	13	54	22.252	0.113	14	51	23.660	0.197	13	42	23.094	0.279
PGSBMI*	-3.332	3.819	-0.009	0.019	-3.256	2.888	-0.017	0.048	-2.791	2.932	-0.045	0.075
Age	12	44	24.732	0.130	12	44	24.941	0.197	12	43	25.168	0.260
Female	0	1	0.440	0.009	0	1	0.358	0.014	0	1	0.462	0.016
Exercise (avg. weekly frequency)	0	3	1.168	0.009	0	3	1.132	0.012	0	3	1.146	0.013
Enough Sleep (0=No, 1=Yes)	0	1	0.673	0.005	0	1	0.629	0.007	0	1	0.666	0.011

Variable	Min	Max	Mean	Std Err Mean	Min	Max	Mean	Std Err Mean	Min	Max	Mean	Std Err Mean
TV (weekly hours)	0	100	12.878	0.215	0	100	17.195	0.385	0	100	13.937	0.433
Smoking (avg. days smoked each month)	0	30	11.083	0.323	0	30	6.670	0.433	0	30	6.648	0.719
Drinking (days drink alcohol in last 12 months)	0	6	3.398	0.029	0	6	3.037	0.036	0	6	3.238	0.039
Disordered Eating (count of behaviors)	0	5	0.989	0.011	0	3	0.902	0.020	0	4	0.991	0.028
Enrolled in School (0=No, 1=Yes)	0	1	0.493	0.006	0	1	0.508	0.009	0	1	0.490	0.007
PC1 Parent relationship to adolescent**	-0.779	0.170	0.000	0.000	-0.132	0.107	0.000	0.001	-0.628	0.085	0.000	0.001
PC2 Ever lived with bio mom**	-0.613	0.161	0.000	0.000	-0.097	0.097	0.000	0.001	-0.034	0.246	-0.001	0.001
PC3 Ever lived with bio mom**	-0.085	0.017	0.000	0.001	-0.051	0.078	0.001	0.002	-0.063	0.056	-0.001	0.005
PC4 Most recent year lived with bio mom**	-0.450	0.444	0.000	0.000	-0.088	0.082	0.000	0.001	-0.123	0.124	0.001	0.002
PC5 Monthly support from bio mom**	-0.070	0.186	0.000	0.000	-0.067	0.095	0.001	0.001	-0.116	0.055	0.000	0.003

*=PGSBMI represents a general measure of the influence of additive genetics on a specific phenotype. The calculation of PGSs relies on summary statistics from genome-wide association studies (GWASs) to create a weighted sum of the associations between allele frequencies at individual SNPs and the associated phenotype

**= PC represents ancestry-specific principal components of the genome-wide data. These are used to control within the ancestral population. Ancestry-specific principal components are estimated from a sample restricted to individuals in the respective genetic ancestry groups. The process estimates the principal components for all unrelated individuals in the ancestry specific sample, and then projects those principal components onto the small number of related individuals within each ancestry group

Table 1: Covariate Statistics

Genetic Measurement

Identifying the biological pathways and genes associated with BMI has the potential to facilitate understanding of the physiological components [58]. As with other complex health outcomes that are common in the population, BMI appears to be a multifactorial, polygenic trait, influenced by multiple environmental factors and multiple genetic loci whose individual effects are small. Since individual effects are quite small, one way to identify causal variants is to consider the cumulative associations of multiple single nucleotide polymorphisms (SNPs) simultaneously [59]. A Polygenic Risks Score (PGS) is generated by running a genome-wide association study (GWAS) on a discovery sample, selecting SNPs on the basis of their association with the phenotype, and creating a sum of their phenotype-associated alleles (often weighted by the SNP-specific coefficients from the GWAS), that can be evaluated in a separate replication sample.

A PGS can be thought of as a measure of 'genetic burden' associated with a phenotype [59]. PGS represent a weighted sum of the associations between allele frequencies and the phenotype resulting in a free measure of the cumulative genetic influences on the phenotype being studied. This allows researchers to capture the broad influence of genetics in various analyses [60].

Add Health genotyped samples were categorized into four genetic ancestry groups: European ancestry, African ancestry, Hispanic ancestry, and East Asian ancestry. Since results comparing PGSs for individuals of different ancestry groups may be less predictive, ancestral groups are analyzed separately [61,62]. Due to sample size restrictions, this analysis is limited to European, African and Hispanic ancestry groups. To further account for environmental and other unobserved individual differences, principle components are included in the regression model. These controls are discussed in the next section 'Environmental Measurement'. Add Health recommends adding these principle components; however, the structural equation framework would not allow for the inclusion of all PCs due to problems of multicollinearity. Therefore, this study calculated a weighted linear combination of the PCs where each item's weight is its factor loading representing its contribution. This index measure accounts for the within group variation and stratification of genetic structure using a single, weight component.

Environmental Measurement: To understand the relationship between behavior, genetic disposition and BMI, it is important to address population stratification and account for differences in genetic structure within ancestry groups as they can relate to allele frequency [63]. When dealing with model of genetic and demographic data, [64] research suggests that population's substructure be captured using elements of personal and family background, childhood circumstances and parental characteristics. Five such controls that were found to be confounders by previous studies are included in this analysis: relationship to household parent, biological mother living in household, ever lived with the biological mother, most recent year lived with the biological mother and receiving monthly support from the biological mother [65]. Therefore, these measures, referred to as PCs, are included in the analysis via a weighted index.

Demographic Measurement: Self-reported height and weight is used to construct measurement-error adjusted BMI (weight in kilograms divided by height in meters squared) for individuals by a wave. Waves I-V are collected when respondents are age 12 to 18, 13 to 19, 18 to 24, 24 to 30 and 32 to 44 respectively. Race and gender are obtained from genetic data corresponding to the respondent's ancestral cohort. The sample is 63 percent European ancestry, 22 percent African ancestry, 11 percent Hispanic ancestry and 4 percent East Asian ancestry.

Behavioral Measurement: Behavioral controls include sleep, exercise, smoking frequency, alcohol consumption, school enrollment, screen time and disordered eating. Respondents were asked whether they dieted, exercised, induced vomiting, took diet pills or used laxatives as a means of losing weight or preventing weight gain in the last seven days. Respondents indicated which if any, behaviors they intended to target weight. The total number of behaviors respondents reported in a week was used to measure frequency of disordered eating. Analysis also includes the number of hours each week spent watching television or videos, playing computer or video games or using a computer for surfing the Web, exchanging email, or participating in a chat room, an indicator of total screen time. Sleep sufficiency is a binary indicator of having had enough sleep. Smoking frequency captures the number of days out of the last 30 that respondents smoked cigarettes. Likewise, the number of days during the past 12 months during which the respondent drank alcohol indicates regularity of alcohol consumption. Exercise includes the number of times in the past week they exercised, including activities, such as jogging, walking, karate, jumping rope, gymnastics or dancing or visited a fitness center. School enrollment provides a binary indicator that the respondent was enrolled at least part-time in an educational program over the least 12 months.

Analysis

Approximately 12,200, or 80% of Add Health participants, consented to long-term archival of genetic information and were consequently eligible for genome-wide genotyping. Those participants who provided saliva samples, remained in the survey until the third wave, provided requisite behavioral information and had a valid BMI values were included in the sample. Descriptive statistics for the sample are listed in Table 1. The analysis was conducted in two stages. In the first stage, analysis explored those factors that impact BMI change during the panel. General linear mixed (GLM) models compared the impact of behavior, situational controls and demographic characteristics on change in BMI from baseline. Models included gender as a fixed factor and an unstructured covariance matrix that allowed for unequal variances and covariances (correlations) between repeated measures. To account for BMI genetic predisposition, polygenic risk score for BMI (PGSBMI) was included as a random factor in the model. The model takes the form in Equation (1) where Y_{it}= logarithm of BMI for the ith person at time t; U_1-U_5 are the situational controls. T_1, t_2, t_3, t_4, t_5 t_6, t_7 and t_8 are time-independent covariates for age, screen viewing, sleep sufficiency, exercise frequency, smoking frequency, alcohol consumption, disordered eating and school enrollment. D_1 is a fixed, time-invariant control for gender, X_{it} is a vector of demographic characteristics and $PGSBMI_i$ is risk score.

$$(1) Y_{it}=\beta_0+\beta_1 U_{i1}+\beta U_{i2}+\beta_3 U_{i3}+\beta_4 U_{i4}+\beta_5 U_{i5}+\beta_6 t_{i1}+\beta_7 t_{i2}+\beta_8 t_{i3}+\beta_9 t_{i4}+\beta_{10} t_{i5}+\beta_{11} t_{i6}+\beta_{12} t_{i7}+\beta_{13} t_{i8}+\beta_{14} PGSBMI_i+\beta_{15} d_{i1}+\beta_{16} X_{it}+e_{it}$$

The coefficients β_1 to β_5 measure the association between the log of BMI and the five situational controls included to account for unobserved variation within ancestral cohorts. β_6 to β_{13} capture the relationship between the time-variant characteristics-age, screen time, disordered eating, smoking frequency, alcohol consumption, hours of exercise, school enrollment and sleep-and BMI, while β_{14} assesses the impact of polygenic risk, a time-invariant covariant relationship. The coefficient β_{15} measures the average difference in BMI by gender each year. Lastly, β_{16} captures the effect of demographic characteristics. The error term, e_{it}, accounts for respondent and time specific random variation not otherwise controlled.

The logarithm of BMI is used as a dependent variable, rather than using the simple BMI, which could amplify the heterogeneity of the effects in the distribution. While one BMI point represents only a small proportion of the body mass of a person with obesity, one BMI point accounts for a substantial proportion of the body mass of a person with low weight. In estimating relative or proportional changes, using logarithms re-scales the effects, thus avoiding such amplification. The model is run twice, once without the behavioral specifications and once with the behaviors, for each ancestral group. While all ancestral group models are similar, the probability values, rather than the magnitudes of the coefficients, highlight differences between cohorts. Regressions were performed in SAS 9.4 using Proc Genmod. Goodness-of-fit for each equation model was assessed using the scatterplot of the residuals against the fitted y, with SAS 9.4 Proc Gplot.

In the second stage, structural equation modelling (SEM) assessed possible mediating effects of behavior. Mediation analysis enables the decomposition of total causal effects into an indirect effect and direct effect. Mediation refers to the transmission of the effect of an independent variable on a dependent variable through one or more other variables-referred to as mediators. Mediation analysis allows the total effect of PGS on BMI to be decomposed into an indirect and direct effect. The direct effect measures the extent to which the BMI changes when the PGS increases by one unit and the mediator variables (behaviors) remain unaltered. In Figure 1, the direct is represented by *c* or *c'* when the mediators are included. The indirect effect measures the change in BMI when PGS is fixed and the mediator variables change. In Figure 1, the indirect effect is represented by *ab*. The total effect is equal to the sum of the direct and indirect effects (*c'* + *ab*).

Analyses uses structural equation modeling (SEM). SEM can capture complex, dynamic relationships by incorporating the path model presented in Figure 1 through a system of linked regression-style equations [66-68]. This application of SEM allows the indirect effect of multiple mediators to be separated and their relative mediation effects compared [68]. The model is estimated using the R package lavaan, which is available from the Comprehensive R Archive Network (CRAN) at https://cran.r-project.org/web/packages/lavaan/index.html [69].

Regression analysis specifies mediation pathways for smoking, drinking, exercising, disordered eating, screen watching and sleeping. Polygenic risk was included as an exogenous predictor BMI. The 'lavaan' package allowed for missing data to be imputed using the full information maximum likelihood method within SEM. To facilitate interpretation, smoking and screen time were scaled to a variance of 1. Pathway estimation uses the bootstraps method to measure uncertainty in estimating the mediation effects. A vector of weights is used to account for longitudinal sampling variation and response patterns.

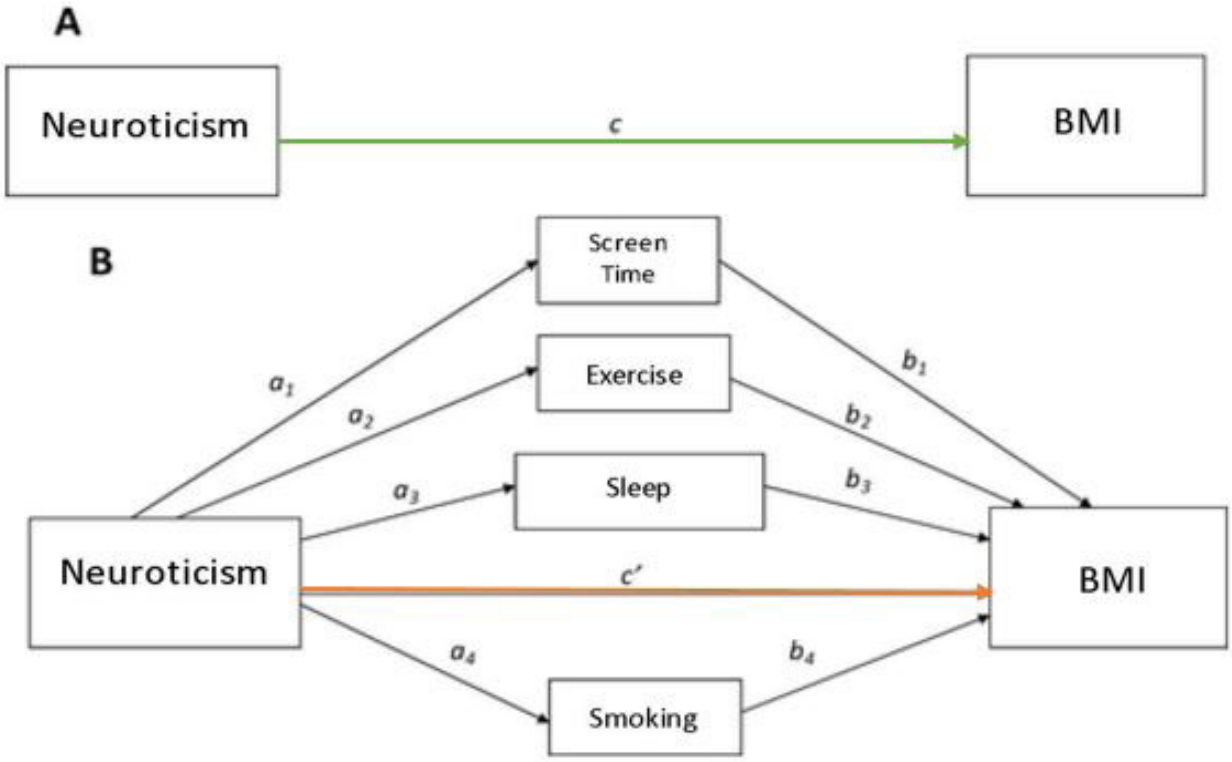

Figure 1: Behaviors have both (**A**) indirect effects; (**B**) direct effects transmitted through PGS on BMI

Results

Stage 1

Results from first stage GLM models are listed by ancestral groups. Unfortunately, the number of missing values and low survey response from the East Asian ancestral group left a relatively small sample size which precluded robust estimation. The GLM model is estimated twice, without behavioral controls (Table 2) and with behavioral controls (Table 3). Recall that the dependent variable is log of BMI. Given that the logarithmic transformation is also applied to baseline BMI, the coefficient represents the percent change in BMI. BMI increase by roughly 25 percent over the panel for all ancestry groups. The age coefficient shows a five to six percent increase in BMI each year. Females of European ancestry have higher relative BMI than males suggesting larger BMI growth among females in this cohort, rather than larger BMI level. Other ancestral groups show similar gender differences in BMI growth.

Behavioral covariates generally have the expected impact on BMI. Sleep, exercise and school enrollment have a negative impact of BMI since healthy physical and mental habits reduce body weight. Screen time, an indicator of a sedentary lifestyle, is positively related to BMI. Disordered eating is associated with higher BMI--an indication that individuals with higher BMI are more likely to adopt extreme behaviors as an effort to lower body weight. While smoking and drinking frequency are not significant, they have a small negative relationship with BMI suggesting that these behaviors could be used as substitutes for food or to curb appetite.

To appropriately interpret the effect of polygenic risk, results from GLM estimation with and without behavioral indicators (Tables 2 and 3) should be compared. In the models without behavioral controls, genetic influence is highly significant and increases BMI by three to five percent. Since situational and demographic characteristics are controlled, this positive coefficient indicates a strong innate tendency towards higher BMI. However, when behavioral controls are added to the model, both the impact and significance decreases (0.55-0.34 for European Ancestry; 0.41-0.33 for Hispanic Ancestry; 0.4-0.23 for African Ancestry). While the decline in magnitude and significance suggests that the genetic effect could be offset by behavior, this model does not provide sufficient evidence to draw this conclusion.

The Relationship between BMI, Genetic Risk, and Demographic Characteristics						
European Ancestry						
	Base			Full		
N	18415			2273		
GEE Fit Criteria						
QIC QIC_u	18510.903 18425			2319.046 2290		
Analysis of GEE Parameter Estimates						
	Estimate	Standard	Z	Estimate	Standard	Z
Intercept	0.3026***	0.012	25.27	0.2534***	0.0235	10.77
Exercise	--	--	--	-0.0035***	0.0009	-3.75
Sleep	--	--	--	0.005**	0.0023	2.17
TV	--	--	--	0.0002	0.0001	1.65
Smoking	--	--	--	0.00014	0.0001	0.67
Drinking	--	--	--	-0.003***	0.0008	-3.64
Disordered Eating	--	--	--	0.0086***	0.0013	6.43
School	--	--	--	-0.004	0.0035	-1.13
PGS	0.0055***	0.0007	7.78	0.0034***	0.001	3.31
BMI0	0.255***	0.0038	67.93	0.2652***	0.006	44.53
Female	-0.0017**	0.0014	-1.23	0.0041**	0.0019	2.1
Age	0.0034***	0.0001	56.23	0.0043***	0.0005	8.45
Situational 1	-0.1385	0.0909	-1.52	-0.2911**	0.15	-1.94
Situational 2	0.0594	0.1003	0.59	0.1391	0.195	0.71
Situational 3	0.0102	0.057	0.18	0.0032	0.0676	0.05
Situational 4	0.0169	0.0518	0.33	-0.0477	0.0539	-0.89
Situational 5	0.1015	0.0607	1.67	0.1335*	0.0766	1.74
African American Ancestry						
	Base			Full		
N	5106			259		
GEE Fit Criteria						
QIC QIC_u	5182.71 305.2571			305.2571 276		
Analysis of GEE Parameter Estimates						
	Estimate	Standard	Z	Estimate	Standard	Z
Intercept	0.3641	0.0206	17.66	0.2719**	0.0718	3.79
Exercise	--	--	--	-0.0008*	0.0021	-0.36
Sleep	--	--	--	-0.0093**	0.0046	-2
TV	--	--	--	0	0.0001	-0.17
Smoking	--	--	--	0.0003*	0.0002	1.63
Drinking	--	--	--	-0.001*	0.0017	-0.63
Disordered Eating	--	--	--	0.0118**	0.0035	3.38
School	--	--	--	-0.0016	0.0099	-0.16
PGS	0.0023	0.0015	1.56	0.0044*	0.0027	1.65
BMI0	0.2385***	0.0063	37.68	0.2705***	0.0146	18.58
Female	-0.0188***	0.0028	-6.73	0.0027*	0.0059	0.46
Age	0.0035***	0.0002	23.18	0.0021	0.0021	1.19
Situational 1	-0.1074	0.0704	-1.53	-0.323	0.1789	-1.81
Situational 2	0.3641	0.0637	0.78	0.015	0.0992	0.15
Situational 3	0.031	0.0812	0.38	-0.0485	0.1466	-0.33
Situational 4	0.0081	0.0704	0.12	0.0843	0.1406	0.6

	Estimate	Standard	Z	Estimate	Standard	Z
Situational 5	0.0008	0.0712	0.01	-0.267**	0.0762	-3.51
Hispanic Ancestry						
	Base			**Full**		
N	18415			262		
GEE Fit Criteria						
QIC	18510.903			301.1568		
QIC_u	18425			279		
Analysis of GEE Parameter Estimates						
	Estimate	**Standard**	**Z**	**Estimate**	**Standard**	**Z**
Intercept	0.3128***	0.0268	11.69	0.2007***	0.0482	4.16
Exercise	--	--	--	-0.0022	0.0022	-1.03
Sleep	--	--	--	0.0009	0.0034	0.25
TV	--	--	--	0.0001	0.0001	0.58
Smoking	--	--	--	-0.0001	0.0002	-0.48
Drinking	--	--	--	-0.0028	0.0018	-1.55
Disordered Eating	--	--	--	0.0049	0.0037	1.31
School	--	--	--	-0.0051	0.0099	-0.52
PGS	0.004*	0.0022	1.81	-0.0033	0.003	-1.08
BMI0	0.2522***	0.0082	30.69	0.274***	0.0144	18.97
Female	-0.0017	0.0035	-0.48	-0.003	0.0053	-0.57
Age	0.0033***	0.0001	28.33	0.0064***	0.0011	5.75
Situational 1	0.2116	0.1679	1.26	0.0352	0.1881	0.19
Situational 2	-0.075*	0.0461	-1.62	-0.0478	0.1594	-0.3
Situational 3	0.0237	0.1012	0.23	-0.0731	0,.0812	-0.9
Situational 4	0.0066*	0.0656	0.1	-0.0934	0.1184	-0.79
Situational 5	0.0583	0.0829	0.7	-0.0169	0.0737	-0.23

Table 2: Base Regression

Mediation Model: Relationship Between BMI, Genetic Risk, and Demographic Characteristics					
European Ancestry					
lhs	**rhs**	**label**	**est**	**se**	**Z**
lBMI	Exercise	b1	-0.0099***	0.0018	-5.4893
lBMI	Sleep	b2	0.0114**	0.0050	2.3012
lBMI	TV	b3	0.0044*	0.0023	1.8641
lBMI	Smoking	b4	0.0037**	0.0018	2.0287
lBMI	Drinking	b5	-0.0077***	0.0017	-4.5693
lBMI	Disordered Eating	b6	0.0246***	0.0034	7.1440
lBMI	School	b7	-0.0292***	0.0070	-4.1681
lBMI	PGSBMI	c	0.0109***	0.0026	4.2370
lBMI	lBaseline		0.8715***	0.0146	59.4908
lBMI	Female		0.0111**	0.0046	2.4002
lBMI	Age		0.0125***	0.0008	15.0852
lBMI	PC_Sum		0.0239	0.0777	0.3069
Exercise	PGSBMI	a1	-0.0115	0.0198	-0.5814
Sleep	PGSBMI	a2	0.0272**	0.0101	2.6923
TV	PGSBMI	a3	-0.0194	0.0202	-0.9591
Smoking	PGSBMI	a4	0.0527	0.0201	2.6170
Drinking	PGSBMI	a5	-0.0418	0.0270	-1.5481
Disordered Eating	PGSBMI	a6	0.0249	0.0160	1.5534
School	PGSBMI	a7	-0.0053	0.0067	-0.7876

lhs	rhs	label	est	se	Z
ExerciseIDE	a1*b1	ExerciseIDE	0.0001	0.0002	0.5861
SleepIDE	a2*b2	SleepIDE	0.0003*	0.0002	1.7801
TVIDE	a3*b3	TVIDE	-0.0000***	0.0001	-0.8124
SmokeIDE	a4*b4	SmokingIDE	0.0002*	0.0001	1.6869
DrinkIDE	a5*b5	DrinkingIDE	0.0003	0.0002	1.3825
Count_loseIDE	a6*b6	Disordered_EatingIDE	0.0006	0.0004	1.4556
SchoolIDE	a7*b7	SchoolIDE	0.0002	0.0002	0.7736
sumIDE	(a1*b1)+(a2*b2)+(a3*b3)+(a4*b4)+(a5*b5)+(a6*b6)+(a7*b7)	sumIDE	0.0016**	0.0006	2.5144
Total	c+(a1*b1)+(a2*b2)+(a3*b3)+(a4*b4)+(a5*b5)+(a6*b6)+(a7*b7)	total	0.0125***	0.0025	5.0169

Significance: ***=1%, **=5%, *=10%

Table 3(A): European Ancestry

Mediation Model: Relationship Between BMI, Genetic Risk, and Demographic Characteristics					
African Ancestry					
lhs	**rhs**	**label**	**est**	**se**	**z**
lBMI	Exercise	b1	-0.0008	0.0057	-0.1458
lBMI	Sleep	b2	-0.0102	0.0137	-0.7471
lBMI	TV	b3	0.0006	0.0052	0.1235
lBMI	Smoking	b4	0.0016	0.0072	0.2241
lBMI	Drinking	b5	-0.0029	0.0043	-0.6632
lBMI	Disordered Eating	b6	0.0304***	0.0082	3.6889
lBMI	School	b7	-0.0736**	0.0258	-2.8534
lBMI	PGSBMI	c	0.0053	0.0068	0.7857
lBMI	lBaseline		0.9107***	0.0405	22.5044
lBMI	Female		-0.0061	0.0134	-0.4553
lBMI	Age		0.0089**	0.0037	2.4199
lBMI	PC_Sum		-0.1748	0.1160	-1.5075
Exercise	PGSBMI	a1	-0.0469**	0.0696	-0.6729
Sleep	PGSBMI	a2	-0.0506**	0.0286	-1.7680
TV	PGSBMI	a3	-0.1124	0.1058	-1.0622
Smoking	PGSBMI	a4	-0.0167	0.0577	-0.2896
Drinking	PGSBMI	a5	-0.1251	0.1220	-1.0255
Disordered Eating	PGSBMI	a6	-0.0228	0.0530	-0.4310
School	PGSBMI	a7	-0.0227	0.0218	-1.0443
ExerciseIDE	a1*b1	ExerciseIDE	0.0000	0.0003	0.1420
SleepIDE	a2*b2	SleepIDE	0.0005	0.0007	0.7258
TVIDE	a3*b3	TVIDE	-0.0001	0.0006	-0.1230
SmokeIDE	a4*b4	SmokingIDE	0.0000	0.0001	-0.1799
DrinkIDE	a5*b5	DrinkingIDE	0.0004	0.0006	0.5981
Count_loseIDE	a6*b6	Disordered_ EatingIDE	-0.0007	0.0017	-0.4131
SchoolIDE	a7*b7	SchoolIDE	0.0017	0.0018	0.9144
sumIDE	(a1*b1)+(a2*b2)+(a3*b3)+(a4*b4)+(a5*b5)+(a6*b6)+(a7*b7)	sumIDE	0.0018	0.0029	0.6159
Total	c+(a1*b1)+(a2*b2)+(a3*b3)+(a4*b4)+(a5*b5)+(a6*b6)+(a7*b7)	total	0.0071	0.0075	0.9523

Significance: ***=1%, **=5%, *=10%

Table 3 (B): African Ancestry

Stage 2

To assess whether behaviors can offset genetic disposition, structural equation mediation models are run for each ancestral group (Table 4). The mediation analysis revealed that the path PGS, BMI and behavioral mediators. While analysis tested the use of polygenic risk as the mediator, the model showed higher explanatory power when behaviors were used to mediate genetic disposition (Table 4). Since no one behavior was likely to fully mediate genetic influence, all seven behavioral factors were included

in a partial mediation model. The model therefore tested which behaviors, if any, offset PGS and to what extent. Models are run separately for European, African and Hispanic ancestral groups. Models provide magnitude and significance for the direct effect of each behavior on BMI, indirect effect of each behavior on BMI, indirect effect of each behavior on PGS and the cumulative direct, indirect and total effects. Estimates of direct behavior effects remain consistent with those found in the GLM model.

Mediation Model: Relationship Between BMI, Genetic Risk, and Demographic Characteristics					
European Ancestry					
lhs	**rhs**	**label**	**est**	**se**	**z**
lBMI	Exercise	b1	-0.0028	0.004660207	-0.5941227
lBMI	Sleep	b2	0.0090	0.0083479	1.08971848
lBMI	TV	b3	0.0010**	0.004694199	2.05872279
lBMI	Smoking	b4	0.0067	0.008504501	0.78795138
lBMI	Drinking	b5	-0.0071**	0.003601913	-1.9790835
lBMI	Disordered Eating	b6	0.0192**	0.007328107	2.63318699
lBMI	School	b7	-0.0207	0.01707633	-1.2126
lBMI	PGSBMI	c	-0.0087	0.007316321	-1.1901517
lBMI	lBaseline		0.8978***	0.030544002	29.3927302
lBMI	Female		0.0025	0.01102408	0.23108489
lBMI	Age		0.0182***	0.002358813	7.69880804
lBMI	PC_Sum		-0.0456	0.152984034	-0.2980459
Exercise	PGSBMI	a1	0.0436	0.064041786	0.68004027
Sleep	PGSBMI	a2	-0.0261	0.029849985	-0.8757767
TV	PGSBMI	a3	0.0190	0.055244051	0.34405834
Smoking	PGSBMI	a4	-0.0447	0.069735073	-0.6413974
Drinking	PGSBMI	a5	0.0046	0.090392127	0.05110427
Disordered Eating	PGSBMI	a6	0.0767**	0.037307265	2.05717099
School	PGSBMI	a7	-0.0400**	0.014992917	-2.6714404
ExerciseIDE	a1*b1	ExerciseIDE	-0.0001	0.000287276	-0.419739
SleepIDE	a2*b2	SleepIDE	-0.0002	0.000276354	-0.8605249
TVIDE	a3*b3	TVIDE	0.0002	0.000535335	0.34312411
SmokeIDE	a4*b4	SmokingIDE	-0.0003	0.000449187	-0.6672675
DrinkIDE	a5*b5	DrinkingIDE	-0.0000	0.000644096	-0.0511251
Count_loseIDE	a6*b6	Disordered_EatingIDE	0.0015	0.00096417	1.53597371
SchoolIDE	a7*b7	SchoolIDE	0.0008	0.000819888	1.01155457
sumIDE	(a1*b1)+(a2*b2)+(a3*b3)+(a4*b4)+(a5*b5)+(a6*b6)+(a7*b7)	sumIDE	0.0018	0.001709691	1.05454087
total	c+(a1*b1)+(a2*b2)+(a3*b3)+(a4*b4)+(a5*b5)+(a6*b6)+(a7*b7)	total	-0.0069	0.007939727	-0.8696259

Significance: ***=1%, **=5%, *=10%

Table 4: Hispanic Ancestry

Sleeping, school enrollment and disordered eating appear to be correlated with PGS for all ancestral groups and alcohol consumption has a significant effect for Hispanics and European ancestral groups only. Therefore, these characteristics have a direct and indirect effect on BMI. Exercise, screen time and smoking do not show strong associations with PGS or BMI. The sum of the direct and indirect effects combined with the level of the genetic association score result in the overall weight effect. For sleep and school enrollment, adoption of these behavior lessens the PGS association. For disordered eating and alcohol consumption, their associations enhance the role that PGS plays in BMI determination.

These significant associations between disordered eating, alcohol consumption, sleep and school enrollment can be explained by the recent evidence from other genetic association studies. Evidence suggests that eating disorders, such as anorexia nervosa, are 50 to 60 percent heritable. These studies show a connection between anorexia and a locus overlapping six genes on chromosome 12 [70]. Likewise, heavy alcohol consumption, alcohol use disorder (AUD) or both were found to be linked to 18 genetic variants [71]. A study in the United Kingdom identified 78 loci for self-reported habitual sleep duration these same loci were also associate with accelerometer-derived sleep duration, daytime inactivity, sleep efficiency and number of sleep bouts in secondary analysis [72]. Similar associations have also been found for genetic loci of education and school attendance [73]. In general, research

involving genetic associations shows shared links with anthropometric, cognitive, metabolic, and psychiatric traits. Therefore, the causal links between individual traits and the genetic basis for inter-individual variations is a complex process involving multiple biological pathways.

Discussion

Results suggest that the impact of genetic disposition on BMI is partially transmitted through behavior. Behavior-school enrollment disordered eating, sleep and alcohol consumption-serves as a partial mediator. The mediation corresponds to an indirect effect of PGS on BMI that passes through each of the behavioral covariates. The magnitude of the indirect effect indicates the amount of mediation that passes through the behavioral variables. Results show that multiple behaviors serve jointly as mediators at the same stage in a causal model, such that several indirect effects linking polygenic risk score to BMI. While it is virtually impossible to disentangle the relationship between genetic traits and behaviors, results show that the behaviors included in the model serve as partial mediators. The importance of this mediation is discussed in the next section.

The strength of this study is that it analyzed a nationally representative population of adolescents and young adults comprising a well-phenotyped cohort. Furthermore, it utilized longitudinal data on lifestyle behavior using a systematic approach to address potential lifestyle mediators in the relationship between genetic variants and BMI. The first stage of analysis showed that these associations transcend age, ancestral cohort and gender. The second stage illustrated the nature of these associations and which behaviors mediate polygenic risk score providing insight into the weight determination process.

One of the limitations was that estimation relied on self-reported weight and height rather than body mass index based on measured values. Additionally, sample size restrictions prevented the analysis of all four ancestral cohorts. The paper did not rely on any formal theoretical framework to select lifestyle and behavioral covariates but rather selected those most robust response items from Add Health questionnaire items and those found to be significant in previous analyses.

The major limitation of this and other genetic-lifestyle studies is their inability to identify the individual and combined effects of the genetic and lifestyle risk factors i.e., answer the question of how genetic predisposition and behavior combine to determine body weight. Moreover, observational studies are susceptible to multiple sources of bias (e.g., selection or recall bias) because environmental exposure and the outcome of interest are assessed simultaneously. Critics of genome association studies argue that the single-nucleotide polymorphisms (SNPs) identified in GWAS explain only a small fraction of the heritability of complex traits [74] and may represent spurious associations [75], that do not necessarily pinpoint causal variants [76] thus yielding too many loci rendering them uninformative [77].

Conclusion

Body weight is the result of a complex interplay of inherited factors, environment, and behavior. Using data from GWASs, research can explore the relationship between body weight, genetics and behavior; however, disentangling the relationship between heredity, behavior and weight is difficult because genetics also plays a role in eating and other weight-related behavior. Despite the importance of genetics, lifestyle, behavior, environment, and activity level can interact to dampen or amplify polygenic BMI risk. To date, little is known about which behaviors and to what extent they can offset/accelerate genetic BMI disposition. This study attempts to explain which behaviors can offset genetic influence, the degree to which behavior can serve to dampen genetic influences, and whether targeted weight loss behaviors can be effective. Results generate a better understanding of the causal pathways that lead to BMI level and potentially effective modes of intervention.

This study examines the impact of sleep, exercise, school enrollment, screen time, smoking frequency, alcohol consumption and disorder eating on BMI. These behavioral influences are only realized through the mediation framework. Mediation analysis shows that sleep, disordered eating and school enrollment are significant for all ancestral groups and alcohol is significant for non-blacks. Not only do these behaviors have a direct effect on BMI; they also serve as partial mediators to BMI polygenic risk scores in the path from PGS to BMI altering the magnitude of the genetic effect on BMI.

It is important to note that the mediation model is a causal model and behaviors are presumed to impact BMI, not vice versa. While these healthy lifestyle attributes mediate the genetic impact and generally reduce BMI levels, unhealthy attributes can amplify the genetic impact and increase BMI. This suggests that lifestyle, either healthy or unhealthy, is the primary mediator. However, recent research suggests that education, disordered eating, alcohol consumption and sleep are at least, in part, hereditary. Therefore, it is possible that similar SNPs could be related to BMI, behavior and lifestyle choices.

Despite the complexities of analyses including genomic association, this study provides evidence that lifestyle impacts BMI through a variety of channels. While genetic BMI susceptibility may be managed by healthy lifestyle modifications, it can also be exacerbated by unhealthy choices [78-81]. Nevertheless, a healthy lifestyle and lifestyle modifications appear to be the most efficient tools for weight management, obesity prevention and overall health. Since genetics and lifestyle both influence individual weight, interventions should likely be personalized according to genotype in order to be more effective.

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