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Behavior and Genetic: Confounding Effects on Adolescent Body Mass Index

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Abstract

Introduction: Persistently high rates of obesity have made understanding the determinants of BMI a research priority. However, the relationship between genetic disposition and behavior remains unclear. This study examines the relationship between genetic risk for body mass index (BMI) and health-related behaviors. Results show that sleep, exercise, screen time, school enrollment and disordered eating mediate heritable genetic influences.

Methods: Using a longitudinal panel, analysis tests the strength of the genetic influence on BMI controlling for demographic attributes and ancestry-specific principle components. Multilevel structural equation models evaluate the mediating/moderating influences of behavior on genetic conditioning.

Results: Sleep, exercise, and school enrollment are associated with lower BMI, while screen time, disordered eating, and age are associated with higher BMI. Polygenic risk score has the largest BMI impact. Behavior not only has a direct BMI impact, but also a mediating influence. Sleep, school enrollment, exercise and reduced screen time serve as partial mediators in the BMI-PGS relationship.

Conclusions: Mediation analysis shows that not only do these behaviors have a direct effect on BMI; they also serve as partial mediators to BMI polygenic risk scores. Sleep, school enrollment, exercise and reduced screen time serve as partial mediators, in the path from polygenic risk score to BMI by reducing the magnitude of the genetic effect on BMI. This suggests that behavioral modifications could be used to offset genetically-influenced weight increases.

Keywords: Health, Adolescence, Behavior, Genetics

Introduction

Obesity is a complex health issue resulting from a combination of causes, including behavior and genetics [1-3]. While genetic pre-disposition and changes prevalence of gene variants in the so-called "fat mass and obesity-associated" [4] can likely explain a portion of the rise in obesity in the 21st century, diet, lifestyle, or other environmental factors can interact with the genetic pathways to offset obesity-promoting gene variants [5]. Estimates on the heritability of (BMI) range from 45 to 85 percent [6-9] but weight-related behaviors including include dietary patterns, physical activity, inactivity, medication use, and other exposures have been shown to mitigate the effects of one obesity-promoting genes [10-13].

The degree to which genetics, environment, and behavior influence obesity are complicated further by research showing that behavioral patterns also influenced by genetic factors [14]. Some contest that genetic factors exert their influence on body weight by affecting those appetitive and eating behaviors that lead to excessive eating [12]. The weight and obesity determine the complex interaction of genetic variants, individual behavior and environmental circumstance [12, 15-19]. Assuming weight, weight gain and weight-related behaviors have a sizable genetic association, it is vital to determine the degree to which these facets interact to mediate/moderate BMI genetic predisposition (or resistance) to obesity [20-22].

This study investigates the independent and interactive effects of weight-related behavior, environmental characteristics, and genetic influence on BMI. First, analysis tests the strength of the genetic influence on BMI controlling for demographic characteristics. Second, ten ancestry-specific principle components are added to the model. Finally, behavior-genetic interaction terms are added to test for genetic determination of behavioral patterns.

Research suggests that the declining rates of fruit and vegetable consumption couple with an insufficient amount of physical activity has contributed heavily to the obesity phenomenon [23-25]. Regular physical activity not only assists in weight control and physical wellness, but has also been shown to reduce stress, and increases self-esteem in children and adolescents [12]. When adopted early in life, a behavioral carryover from adolescence to adulthood shows

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that active children are more likely to continue engaging in physical activity as they grow older [25].

Parents influence child and young adult BMI directly through diet and learned behaviors, including dietary habits, physical activity, and sedentary behavior [26]. However, excessive parental control over behavior and diet can result in deleterious rebound behavior when that control is relaxed [27, 28]. Parental socioeconomic status (SES) has shown to be strongly associated with BMI-low SES corresponds to higher BMI, particularly in adolescents and young adults [29-31]. However, these results vary according to gender, ethnicity, and nationality. While family and friends can encourage active/inactive habits and behaviors at home, schools provide few opportunities for physical activity, due to a greater emphasis on academic achievement in recent decades [6,8].

In addition to environmental factors, behaviors such as sleep, eating the evening meal with the family, and limiting screen-viewing time for preschool-aged children has been strongly linked to BMI and related to the prevalence of obesity [32]. 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 [32-35]. This work aims to test impact of genetic inheritance and behavior on BMI by using mediation analysis to quantify their direct and indirect effects.

Methods

Data

Analysis utilizes data from the National Longitudinal Study of Adolescent to Adult Health (Add Health)-a longitudinal study of adolescents in grades 7-12 during the 1994-95 school year followed into young adulthood with four in-home interviews. This study utilizes data from Waves I, II, and III conducted in September 1994-December 1995, April 1996-August 1997 and August 2001-April 2002, respectively. Mean values for all covariates are provided in (Table 1).

Genetic measurement

Approximately 80% of participants consented to long-term archiving of saliva samples, making them eligible for genome-wide genotyping. These samples were used to calculated

Table 1: Covariate Statistics

Add Health Wave I-III Covariates Descriptive Statistics								
			White			Black		
	Min	Max	Mean	Std Err	Var	Mean	Std Err	Var
BMI	12	91	23.967	0.125	0.016	25.414	0.237	0.056
lBMI	2.48491	4.51086	3.152	0.005	0.000	3.20735	0.00880	0.00008
Age	12	24	16.661	0.147	0.022	17.04776	0.23310	0.05434
Female	0	1	0.490	0.009	0.000	0.47033	0.01518	0.00023
# Weight Loss Behaviors	0	5	0.978	0.014	0.000	0.87359	0.02097	0.00044
Dieting	0	1	0.271	0.007	0.000	0.20869	0.01161	0.00014
Exercise hours weekly	0	1	0.671	0.009	0.000	0.62703	0.01647	0.00027
Vomiting	0	1	0.005	0.001	0.000	0.00380	0.00147	0.00000
Diet Pills	0	1	0.030	0.002	0.000	0.02749	0.00405	0.00002
Laxatives	0	1	0.002	0.001	0.000	0.00672	0.00213	0.00000
Exercise	0	20	1.388	0.023	0.001	1.35113	0.03085	0.00095
TV	0	160	13.421	0.325	0.106	19.18224	0.54074	0.29240
Sleep	0	1	0.781	0.006	0.000	0.69387	0.01201	0.00014
School	0	1	0.741	0.009	0.000	0.70006	0.01298	0.00017
Sex of Parent	0	1	0.066	0.007	0.000	0.04427	0.00999	0.00010
Age of Parent	22	80	41.152	0.184	0.034	41.31631	0.47423	0.22490
Log Household Income	0.000	6.907	3.657	0.035	0.001	2.96650	0.06334	0.00401
Parent educational level	1	9	5.701	0.083	0.007	4.97148	0.18193	0.03310
Parent ever married	0	1	0.986	0.002	0.000	0.79297	0.01970	0.00039
Polygenic Risk Score BMI	-3.665	3.819	-0.017	0.022	0.000	0.03138	0.04712	0.00222
PC1 Parent relationship to adolescent	-0.194	0.170	0.000	0.000	0.000	-0.00030	0.00091	0.00000
PC2 Bio mom in household	-0.613	0.161	0.000	0.000	0.000	0.00011	0.00064	0.00000
PC3 Ever lived with bio mom	-0.085	0.043	0.000	0.000	0.000	-0.00097	0.00156	0.00000
PC4 Most recent year lived with bio mom	-0.233	0.444	0.000	0.000	0.000	-0.00033	0.00083	0.00000
PC5 Monthly support from bio mom	-0.070	0.162	0.001	0.001	0.000	-0.00071	0.00069	0.00000
PC6 Bio dad in household	-0.371	0.480	0.000	0.000	0.000	0.00071	0.00063	0.00000
PC7 Ever lived with bio dad	-0.296	0.563	0.000	0.000	0.000	0.00095	0.00082	0.00000
PC8 Most recent year lived with bio dad	-0.234	0.218	0.000	0.000	0.000	-0.00105	0.00117	0.00000
PC9 Monthly support from bio dad	-0.372	0.462	0.000	0.000	0.000	-0.00061	0.00070	0.00000
PC10 Best friend in school	-0.516	0.246	0.000	0.000	0.000	0.00024	0.00081	0.00000
Estimates are weighted using longitudinal sample weights								
Estimates calculated with controls for sample stratification and respondent clustering.								

genotyped data for 9,974 individuals on 609,130 SNPs [36]. Using principal component analysis, Add Health genotyped samples were categorized into four genetic ancestry groups: European ancestry, African ancestry, Hispanic ancestry, and East Asian ancestry. Polygenic Scores (PGS) were calculated using summary statistics from genome-wide association studies (GWAS) to create a weighted sum of the associations between allele frequencies and the associated phenotype resulting in a free measure of the cumulative additive genetic influences on the phenotype being studied. This allows researchers to capture the broad influence of genetics in various analyses [37-39]. Add Health recommends that researchers include ancestry-specific principal components of the genome-wide data in all analyses using PGSs and consider analyzing ancestral groups separately [40, 41].

Environmental measurement

Principle component analysis (PCA) is used to identify differences in ancestry among populations and samples. PCA allows researchers to make sense of data with a large number of measurements by reducing the dimensions to the few principal components (PCs) that explain the main patterns [42]. By assessing principal components, it is possible to identify a population substructure and address population stratification-allele frequency differences between various ancestral groups-that can cause spurious associations in association studies [43]. When dealing with demographic data, Add Health suggests that principle components (PCs) be used jointly since some correspond to biological events and other environmental [42].

To understand the relationship between behavior, genetic disposition and BMI, analysis utilizes ten principle components identified by Add Health as necessary to account for population stratification and differences in genetic structure within ancestry groups. Principle components included factors judged to be confounders by previous studies and allow for valid estimation of the covariates of interest [44].

Demographic measurement

In each survey wave, respondents provide weight and height, and age. In Wave I, respondents are 12 to 18 years old and 18 to 24 in Wave III. Annual reports of height and weight are used to construct measurement-error adjusted BMI (weight in kilograms divided by height in meters squared) for individuals by a wave. Race and gender are obtained from PGS data corresponding to the respondent's ancestral group and reported gender. Gender and race are fixed effects and constant in each wave. Roughly 64 percent of the sample is white and over 22 percent black with nominal proportions American Indian/ Native American, Asian or Pacific Islander.

Behavioral measurement

In Waves I through III 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. These will be referred to as the "weight-targeted" behaviors. Behavioral question verbiage changed after Wave III, therefore analysis is limited to the first three waves. The number of behaviors respondents reported. To capture additional aspects of behavior, analysis also includes screen time (aka, 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 whether the respondent regularly has sufficient sleep, an indicator of school enrollment and the number of times in the past week they exercised, such as jogging, walking, karate, jumping rope, gymnastics or dancing or visited a fitness center.

Analysis

The model takes the form in Equation (1) where Y_{it}=log of BMI for the ith person at time t; U_1–U_{10} are the principal components used to place members of the Add Health genotyped sample into ancestry groups. T_1, t_2, t_3, t_4, and t_5 are time-independent covariates for age, screen viewing, sleep sufficiency, exercise frequently, and school enrollment. D_1 is a fixed, time-invariant control for gender. X_{it} is the count of time-dependent weight-targeted behaviors in Waves I, II and III, including exercise, dieting, vomiting, taking diet pills, and using laxatives. Finally, e_{it} is the error term of the ith person at time t.

$$(1)Y_{it} = \beta_0 + \beta_1 U_{i1} + \beta_2 Ui_2 + \beta_3 U_{i3} + \beta_4 U_{i4} + \beta_5 U_{i5} + \beta_6 U_{i6} + \beta_7 U_{i7} + \beta_8 U_{i8} + \beta_9 U_{i9} + \beta_{10} U_{i10} + \beta_{11} t_{i1} + \beta_{12} t_{i2} + \beta_{13} t_{i3} + \beta_{14} t_{i4} + \beta_{15} t_{i5} + \beta_{16} d_{i1} + \beta_{17} X_{it} + e_{it}$$

The coefficients β_1 to β_{10} measure the association between the log of BMI and the first ten ancestry-specific principal components of the ancestry- specific genome-wide data in PGSs determination. B_{i11} to β_{i15} capture the relationship between the time-variant characteristics and BMI, while β_{16} assesses the impact of gender. The coefficient β_{17} measures the average difference in BMI by each additional weight-related behavior in a given year.

Generalized estimating regression (GLR) models [45] with a robust variance simultaneously examine the cross-sectional and longitudinal relationship between the independent variables and BMI while accounting for individual repeated measures. All analyses were conducted separately women and men separately and then pooled by inverse variance–weighted fixed-effects meta-analyses. Statistical analyses were performed in SAS 9.4 using Proc Genmod. Goodness-of-fit for each equation model was assessed by examining the scatterplot of the residuals against the fitted y, with SAS 9.4 Proc Gplot.

To determine if health-related behaviors also impact the relationship between genetic risk and BMI, analysis [46] estimates and tests the indirect, mediation effect of genetic disposition and weight behaviors on BMI. Multiple-level structural equation models with cross-classified random effects can easily accommodate data which is clustered at multiple levels, like Add Health. The between-and within-level components of indirect effects are estimated separately to provide a less biased estimate of the between-level effects. Both the multi-level membership and the cross-classified

models are estimated by maximum-likelihood in SAS PROC MIXED.

Sleep, screen time, exercise, school enrollment, and count of weight targeted behaviors were tested for a mediation effect due to their association with both polygenic risk (PGR) and BMI. A significant mediation effect occurred when the product of the β coefficient of the association between PGR and the mediator and the β coefficient of the association between the mediator and the BMI was significant. This product is referred to as the "indirect effect" on BMI. Confidence intervals for the indirect effects were calculated using the parameter estimates as the means and their asymptotic variances and covariance [47]. If the direct association between the PGR and BMI remained significant when the mediator was added to the model, then the significance of the mediator indicated wither the impact represented partial or a full mediation, respectively [48-56].

Results

Results from the base regression are listed in Table II separately by ancestral groups. Unfortunately, the number of missing values and low survey response from Asian/Pacific Islanders and Native American/Alaskan native precluded robust estimation. Therefore, regression results for white and black/African American are provided. Whites represent the largest ancestral group in the sample. As expected, age is positively and significantly associated with BMI, indicating that BMI increases by one half to one percent per year. White females have higher BMI, on average than males, while black females have a lower BMI than black men. PGS is highly significant, resulting in a one percent increase in BMI for every unit increase in genetic risk. This represents the largest and most predictive relationship (Table 2).

Most of the principle components are insignificant, as seen in Table 3. Three of the ten principle components have positive BMI relationships; these include PC1- Responding Parent Relationship to Respondents, PC5-Monthly Support from Biological Mother and PC7-Has Ever Lived with Biological Mother. Those living with or having recently lived with one or both biological parents have lower BMI those who do not reside with their biological parents. Those who receive financial support from a biological mother rather than cohabitating have higher BMI. These results indicate that adolescents in a more traditional family home have lower, healthier BMI. PGR continues to be highly significant and similar in magnitude (Table 3).

Behavioral covariates are added to the model, and results are listed in (Table 4). Principle component factors, age, and gender remain consistent with previous results. Weight-related behavior assumes the expected sign getting enough sleep, exercise, and school enrollment are associated with lower BMI levels and high amounts of screen time as associated with higher levels. These results suggest that individuals with health, more active lifestyles have lower BMI levels than those with more sedentary lifestyles and less healthy habits. The count of weight-targeted behaviors is associated with a higher BMI. This suggests that vomiting, laxatives, diet pills do not result in sustained weight loss. Interestingly, while PGR continues to be positive and significant, the magnitude decreases substantially when behavioral covariates are included, the magnitude declines substantially from 1.6 to 1.4 and 1.1 to 0.7 for black and whites respectively. Interaction terms are added to the model to test the joint relationship between behavior and PGRBMI (Table 5). These terms test the relationship between behavior and genetics-the degree to which behaviors are genetically determined. However, the lack of significance of interaction terms suggests that those genetic factors influencing weight are not those that determine behavior (Table 4, 5).

Each potential mediator is tested separately using multilevel mediation, cross-classification structural equation models to determine behavior-specific behavior indirect effects. Direct effects, indirect effects, and 95 percent confidence intervals are listed in Table V. Indirect effect coefficients that lie within the given confidence intervals are significant (Table 6).
Results suggest that the impact of genetic disposition on BMI is partially transmitted through behavior. Behavior serves as a partial mediator. The magnitude of the indirect effect

Table 2: Base Regression

The Relationship between BMI, Genetic Risk and Demographic Characteristics						
	White			Black/African American		
N	10509			3449		
GEE Fit Criteria						
QIC	10542.4			3476.01		
QICu	10513			3453		
Generalized Linear Model Estimates						
	Estimate	Standard	Z	Estimate	Standard	Z
Intercept	0.9956***	0.006	165.98	1.0314***	0.0098	105.28
Age	0.0091***	0.0004	25.05	0.0084***	0.0006	13.92
Female	0.0054**	0.0024	2.26	-0.0208***	0.0047	-4.43
PGS BMI	0.0159***	0.0011	14.96	0.0092***	0.0023	4.07

Estimates are weighted using longitudinal sample weights
Estimates calculated with controls for sample stratification and respondent clustering.
***=99% significant **=95% significant *=90% significance
Dependent Variable: Log BMI_{it}

Table 3: Base Regression with Principle Components

The Relationship between BMI, Genetic Risk and Demographic Characteristics						
	White			Black/African American		
N	10509			3449		
GEE Fit Criteria						
QIC	10583.6			3539.28		
QICu	10523			3463		
Generalized Linear Model Estimates						
	Estimate	Standard	Z	Estimate	Standard	Z
Intercept	0.9959***	0.0061	163.06	1.0308***	0.01	103.26
Age	0.0091***	0.0004	24.86	0.0084***	0.0006	14.29
Female	0.0053**	0.0023	2.29	-0.0205***	0.0048	-4.23
PGS BMI	0.016***	0.0011	14.54	0.0111***	0.0027	4.12
PC1 RELATIONSHIP TO ADOLESCENT-PQ	0.1571	0.1516	1.04	0.008	0.0909	0.09
PC2 BIO MOTHER IN HOUSEHOLD-PQ	-0.149*	0.0825	-1.81	0.0487	0.0832	0.59
PC3 EVER LIVE W/BIO MOTHER-PQ	0.1035	0.0882	1.17	0.1849	0.1146	1.61
PC4 MOST RECENT YR LIVED W/BIO MOM-PQ	-0.0616	0.0948	-0.65	-0.0813	0.0935	-0.87
PC5 MONTHLY SUPPORT FROM BIO MOM-PQ	0.3396**	0.1187	2.86	0.0202	0.096	0.21
PC6 PRINCIPAL COMPONENT, 6^{TH}	-0.1735	0.1351	-1.28	0.0852	0.0993	0.86
PC7 EVER LIVE W/BIO FATHER-PQ	0.1653***	0.0601	2.75	-0.1819**	0.0916	-1.99
PC8 MOST RECENT YR LIVED W/BIO DAD-PQ	-0.171**	0.0842	-2.03	0.0269	0.1299	0.21
PC9 MONTHLY SUPPORT FROM BIO DAD-PQ	-0.0233	0.1104	-0.21	0.19*	0.0981	1.94
PC10 BEST FRIEND IN SCHOOL-PQ	0.2131	0.1554	1.37	0.0349	0.0981	0.36
Estimates are weighted using longitudinal sample weights Estimates calculated with controls for sample stratification and respondent clustering. Dependent Variable: Log BMI_{it} ***=99% significant **=95% significant *=90% significance						

Table 4: Base Regression with Principle Components and Behavioral Covariates.

The Relationship between BMI, Genetic Risk and Demographic Characteristics						
	White			Black/African American		
N	6687			2039		
GEE Fit Criteria						
QIC	6758.03			2129.1		
QICu	6706			2058		
Generalized Linear Model Estimates						
	Estimate	Standard	Z	Estimate	Standard	Z
Intercept	1.0293***	0.0126	81.58	1.0646***	0.0221	48.17
Age	0.0068***	0.0006	10.82	0.007***	0.001	6.96
Female	0.0214***	0.0029	7.34	-0.0105**	0.0048	-2.16
Count Loss Behavior	0.0242***	0.0016	15.38	0.0204***	0.0037	5.45
Exercise Frequency	-0.0056***	0.001	-5.88	0.0006	0.001	0.6
Screen time	0.0005***	0.0001	5.27	0.0003***	0.0001	2.84
Enough Sleep	0.0023	0.002	1.12	-0.0097**	0.0046	-2.11
In School	-0.0187***	0.0036	-5.12	-0.0174**	0.0074	-2.36
PGS BMI	0.0142***	0.0011	12.62	0.0073**	0.003	2.43
PC1 RELATIONSHIP TO ADOLESCENT-PQ	0.1705	0.1292	1.32	0.0098	0.1006	0.1
PC2 BIO MOTHER IN HOUSEHOLD-PQ	-0.2269**	0.0952	-2.38	0.1095	0.0957	1.14
C3 EVER LIVE W/BIO MOTHER-PQ	0.1381	0.0894	1.55	0.019	0.1254	0.15
C4 MOST RECENT YR LIVED W/BIO MOM-PQ	-0.0724	0.0845	-0.86	-0.1109	0.1043	-1.06
PC5 MONTHLY SUPPORT FROM BIO MOM-PQ	0.2405**	0.1212	1.98	0.0544	0.1095	0.5
PC6 PRINCIPAL COMPONENT, 6TH	0.0101	0.1335	0.08	0.1503	0.1041	1.44
PC7 EVER LIVE W/BIO FATHER-PQ	0.2225***	0.0524	4.24	-0.1562	0.1029	-1.52
PC8 MOST RECENT YR LIVED W/BIO DAD-PQ	-0.2037**	0.1003	-2.03	0.0533	0.1457	0.37
PC9 MONTHLY SUPPORT FROM BIO DAD-PQ	-0.0259	0.1204	-0.22	0.1738	0.1255	1.38
PC10 BEST FRIEND IN SCHOOL-PQ	0.1728	0.1285	1.34	-0.0458	0.109	-0.42
Estimates are weighted using longitudinal sample weights ***=99% significant **=95% significant *=90% significance Estimates calculated with controls for sample stratification and respondent clustering. Dependent Variable: Log BMI_{it}						

Table 5: GLR with Behavioral Covariates, Principle Components and Interaction Terms

The Relationship between BMI, Genetic Risk and Demographic Characteristics						
	White			Black/African American		
N						
GEE Fit Criteria						
QIC	6768.867			2140.539		
QICu	6711			2063		
Generalized Linear Model Estimates						
	Estimate	Standard	Z	Estimate	Standard	Z
Intercept	1.0292***	0.0126	81.66	1.0654***	0.0219	48.58
Age	0.0068***	0.0006	10.85	0.0069***	0.001	7.15
Female	0.0214***	0.0029	7.42	-0.0105**	0.0048	-2.16
Enough Sleep	0.0024	0.002	1.16	-0.0099**	0.0047	-2.12
Screen Time	0.0005***	0.0001	5.35	0.0003***	0.0001	2.91
# Weight Targeted Behaviors	0.0243***	0.0015	15.73	0.0204***	0.0037	5.48
School Enrollment	-0.0187***	0.0036	-5.13	-0.0171**	0.0073	-2.34
Exercise Frequency	-0.0055***	0.0009	-6.01	0.0006	0.001	0.6
Sleep*PGS BMI	0.0025	0.0019	1.3	-0.0035	0.0042	-0.83
TV*PGSBMI	0.0001	0.0001	0.88	-0.0001	0.0001	-0.88
# Behaviors*PGSBMI	-0.0014	0.0013	-1.07	-0.0024	0.003	-0.79
School*PGSBMI	-0.0007	0.0022	-0.3	0.0043	0.0058	0.75
Exercise*PGSBMI	-0.0006	0.0006	-1.01	-0.0007	0.0011	-0.61
PGSBMI	0.0141***	0.0032	4.39	0.011**	0.008	1.38
PC1 RELATIONSHIP TO ADOLESCENT-PQ	0.1633	0.1286	1.27	0.0103	0.0989	0.1
PC2 BIO MOTHER IN HOUSEHOLD-PQ	-0.2235**	0.0958	-2.33	0.1071	0.0958	1.12
C3 EVER LIVE W/BIO MOTHER-PQ	0.1326	0.0887	1.49	0.013	0.1238	0.1
C4 MOST RECENT YR LIVED W/BIO MOM-PQ	-0.0757	0.0862	-0.88	-0.1193	0.1032	-1.16
PC5 MONTHLY SUPPORT FROM BIO MOM-PQ	0.243**	0.1228	1.98	0.0553	0.1085	0.51
PC6 PRINCIPAL COMPONENT, 6TH	0.0075	0.1329	0.06	0.1469	0.1013	1.45
PC7 EVER LIVE W/BIO FATHER-PQ	0.2249***	0.0525	4.29	-0.1584	0.1037	-1.53
PC8 MOST RECENT YR LIVED W/BIO DAD-PQ	-0.203**	0.1007	-2.02	0.0565	0.1453	0.39
PC9 MONTHLY SUPPORT FROM BIO DAD-PQ	-0.0345	0.1186	-0.29	0.1726	0.1249	1.38
PC10 BEST FRIEND IN SCHOOL-PQ	0.1724	0.1266	1.36	-0.038	0.1086	-0.35
Estimates are weighted using longitudinal sample weights ***=99% significant **=95% significant *=90% significance Estimates calculated with controls for sample stratification and respondent clustering. Dependent Variable: Log BMI_{it}						

Table 6: Test of Indirect Mediation Effects

Mediation Effects of Behavioral Covariates										
Mediator:	**# Weight-Targetted Behavior**		**Enough Sleep**		**Screen Time**		**School Enrollment**		**Exercise Frequency**	
Effect	**Estimate**	**StdErr**	**Estimate**	**StdErr**	**Estimate**	**StdErr**	**Estimate**	**StdErr**	**Estimate**	**StdErr**
Multiple Membership model										
Intercept	0.95***	0.009879	0.7451***	0.006677	14.1299***	0.8799	0.773***	0.007558	1.4305***	0.02893
mean_PGSBMI	0.1242	0.3369	-0.1239	0.2277	8.0692	29.3986	0.2713	0.2486	0.6931	0.9608
Dependent Variable: $Mediator_t$										
Cross-Classification Structural Equation Models										
Intercept	3.0997***	0.009377	3.1455***	0.007588	3.1439***	0.007174	3.2486***	0.00695	3.1642***	0.007043
$Mediator_t$	0.08248***	0.002467	0.004175	0.00319	0.000326***	0.000099	-0.1269***	0.003215	-0.01041***	0.001016
PGSBMI	0.03869***	0.001753	0.04249***	0.001396	0.04244***	0.001398	0.04135***	0.00135	0.04252***	0.001392
	Indirect	95% CI	Indirect	95% CI	Indirect	95% CI	Indirect	95% CI	Indirect	95% CI
	0.010248	(-0.04424, 0.064735)	-0.000517	(-0.002987027, 0.001952538)	0.0026338	(-0.017086, 0.022354)	-0.034428	(-0.096312, 0.027455)	-0.007217	(-0.026969, 0.012534)
Estimates calculated with controls for sample stratification and respondent clustering. Dependent Variable: Log BMI_{it} ***=99% significant **=95% significant *=90% significance										

indicates the amount of mediation through the behavioral variable. Results show that multiple behaviors serve jointly as mediators at the same stage in a causal model, such that several indirect effects link PGR 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 between PGR and BMI. The importance of this mediation will be discussed in the next section.

Discussion

The strength of this study is that it analyzed a nationally representative population of adolescents and young adults comprising a well-phenotyped cohort. One of the limitations was that estimation relied on self-reported weight and height rather than measured values. Additionally, sample size restrictions prevented the analysis of all four ancestral cohorts and findings only reflect blacks and white. 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. 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 the risk of obesity. 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.

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. Having a better understanding of the genetic contributions to obesity-especially common obesity-and gene-environment interactions will generate a better understanding of the causal pathways that lead to obesity and potentially effective modes of intervention. The mediation analysis conducted here shows that behaviors impact BMI both directly and through their mediating effect on BMI polygenic risk scores. This type of mediation framework applies causality behaviors impact BMI through a direct and indirect effect. Results suggest that health lifestyle habits are the primary factor in BMI determination.

Conclusion

Obesity is the result of a complex interplay between inherited factors, environment, and behavior. Recent advancements made through the GWA approach have substantially contributed to our understanding of obesity and genetics; however, most of the genetic pathways identified to date have a modest effect on disease risk. The remainder is determined by lifestyle, behavior, environment, and activity level. However, relatively little is known regarding the genetic-environment interactions and the complex interplay between genes and life experiences.

The influence of genetics on BMI is clear, but the role of behavior is only realized through the mediation framework. Mediation analysis shows that not only do these behaviors have a direct effect on BMI; they also serve as partial mediators to BMI polygenic risk scores. The mediation model is a causal model-behaviors are presumed to impact BMI, not vice versa. While these healthy lifestyle attributes mediate the genetic impact and generally reduce BMI levels, disordered eating behaviors do not. This suggests that a healthy lifestyle is the primary mediator rather than intentional weight control. While weight control is often a result of a healthy lifestyle, weight does not appear to be the primary driver. This and other gene-lifestyle interaction studies suggest that lifestyle can be deterministic in development of physical conditions and diseases and that genetic susceptibility may be partially or kept under control by lifestyle modification [17].

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