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ORIGINAL RESEARCH

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Do adverse childhood experiences and genetic obesity risk interact in relation to body mass index in young adulthood? Findings from the National Longitudinal Study of Adolescent to Adult Health

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Summary

Background: Few studies have focused on the role of adverse childhood experiences (ACEs) in relation to genetic susceptibility to obesity.

Objective: We aimed to examine the interaction between the presence of ACEs (i.e., physical, psychological and sexual abuse) before the age of 18 and BMI polygenic score.

Methods: Data came from the National Longitudinal Study of Adolescent to Adult Health (Add Health) Wave IV (2007/2008) where saliva samples were collected for DNA genotyping and information on BMI and ACEs were obtained from 5854 European American (EA), 2073 African American (AA) and 1448 Hispanic American (HA) participants aged 24 to 32 years old. Polygenic scores were calculated as the sum of the number of risk alleles of BMI-related SNPs which were weighted by effect size. A race/ethnicity-stratified mixed-effects linear regression model was used to test for differential association between BMI polygenic score and BMI by the presence of ACEs.

Results: We did not find any evidence of significant interaction between ACEs and polygenic score in relation to BMI among EA ($p = 0.289$), AA ($p = 0.618$) or HA ($p = 0.870$). In main effects models, polygenic score was positively associated with BMI in all race/ethnic groups, yet the presence of ACEs was associated with increased BMI only among EA.

Abbreviations: AA, African American; ACE, adverse childhood experience; BMI, body mass index; EA, non-Hispanic European American; HA, Hispanic American; SNP, single-nucleotide polymorphism.

Conclusion: We did not find any evidence that ACEs exacerbate genetic predisposition to increased BMI in early adulthood.

KEYWORDS
childhood adversity, gene–environment interaction, genetic predisposition to disease, obesity, single nucleotide polymorphism

1 | INTRODUCTION

Along with genome-wide association studies (GWAS) identifying hundreds of loci associated with body mass index (BMI) or obesity,[1–7] a growing body of research has started to focus on gene–environment interaction in relation to increased BMI or obesity. Some studies have investigated factors which may exacerbate or attenuate the genetic predisposition to obesity, such as physical activity,[8–10] screen time,[11] smoking,[8,12] dietary energy,[8] alcohol consumption[8] and neighbourhood socio-economic status.[13]

Despite potential for exacerbating genetic susceptibility to obesity, little research has focused on the role of adverse childhood experiences (ACEs), such as physical, psychological, and sexual abuse, which have been shown to have adverse health effects that stretch across the life course.[14] Reviews by Hemmingsson et al.[15] and Danese et al.[16] concluded that ACEs were associated with obesity, but few studies have investigated whether ACEs have differential association with BMI by genetic risk. This is an important gap in our understanding of the contribution of modifiable risk factors, which may inform effective efforts to mitigate disease burden associated with obesity.

To address this issue, we calculated a BMI polygenic score from single-nucleotide polymorphism (SNPs) known to be associated with BMI[6,7,17,18]; and investigated the estimated interaction effect of ACEs on the association between genetic BMI risk score and BMI in young adulthood using the National Longitudinal Study of Adolescent to Adult Health (Add Health).

2 | METHODS

2.1 | Participants

Add Health is a nationally-representative longitudinal study of U.S. youth launched in 1994/95, when 20 745 participants of diverse ethnicity were drawn from a probability sample of 132 US middle and high schools.[19,20] The cohort was followed in 1996 (Wave II), 2001/02 (Wave III), 2007/08 (Wave IV) and 2016 (Wave V).

We used information obtained in Wave IV in which 15 701 people were interviewed when they were aged 24–34 (mean age = 28.5 years) (Figure 1). We excluded individuals who did not

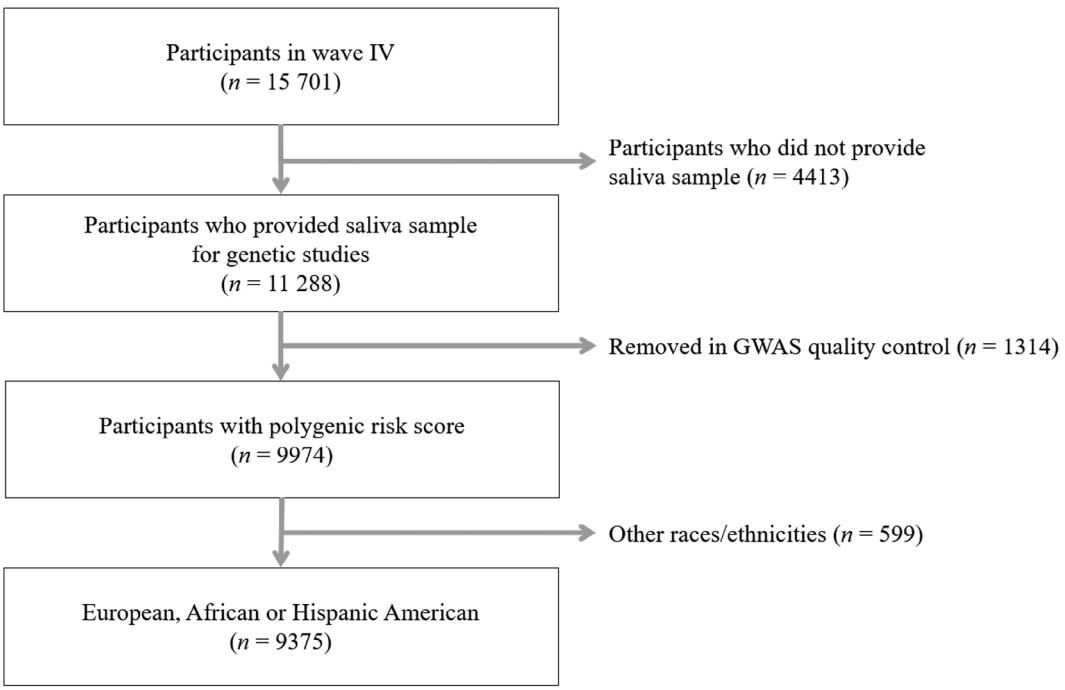

FIGURE 1 Study participant flow chart

TABLE 1 Descriptive characteristics of the study participants in the analytic sample from Wave IV of Add Health (2007/2008), stratified by race/ethnicity.

	European American ($n = 5854$)		African American ($n = 2073$)		Hispanic American ($n = 1448$)	
Age, mean [SD]	28.4	[1.8]	28.4	[1.8]	28.8	[1.7]
Sex (%Female)	3096	(52.9)	1149	(55.4)	708	(48.9)
Household income, *n* (%)						
1st (lowest)	1279	(21.8)	1023	(49.4)	737	(50.9)
2nd	2038	(34.8)	597	(28.8)	452	(31.2)
3rd (highest)	2513	(42.9)	432	(20.8)	241	(16.6)
Missing	24	(0.4)	21	(1.0)	18	(1.2)
High education sample (AA)	–	–	459	(22.1)	–	–
Ethnicity (HA)						
Mexico	–	–	–	–	745	(51.5)
Puerto Rico	–	–	–	–	238	(16.4)
Cuba	–	–	–	–	235	(16.2)
Central/South American	–	–	–	–	135	(9.3)
Other Hispanic	–	–	–	–	95	(6.6)
Foreign-born status (HA)	–	–	–	–	309	(21.3)
Current smoking, *n* (%)						
No	3587	(61.3)	1468	(70.8)	1095	(75.6)
Yes	2261	(38.6)	585	(28.2)	351	(24.2)
Missing	6	(0.1)	20	(1.0)	2	(0.1)
Alcohol consumption, *n* (%)						
Do not drink	1305	(22.3)	799	(38.5)	446	(30.8)
Less than once a week	2558	(43.7)	771	(37.2)	608	(42.0)
Once a week or more	1974	(33.7)	479	(23.1)	389	(26.9)
Missing	17	(0.3)	24	(1.2)	5	(0.4)
Physical abuse (any), *n* (%)						
No	3947	(67.4)	1338	(64.5)	904	(62.4)
Yes	1893	(32.3)	724	(34.9)	537	(37.1)
Missing	14	(0.2)	11	(0.5)	7	(0.5)
Psychological abuse (any), *n* (%)						
No	3007	(51.4)	1044	(50.4)	754	(52.1)
Yes	2786	(47.6)	992	(47.9)	674	(46.6)
Missing	61	(1.0)	37	(1.8)	20	(1.4)
Sexual abuse (any), *n* (%)						
No	5408	(92.4)	1847	(89.1)	1294	(89.4)
Yes	428	(7.3)	216	(10.4)	144	(9.9)
Missing	18	(0.3)	10	(0.5)	10	(0.7)
The number of ACE types, *n* (%)						
0	2436	(41.6)	802	(38.7)	566	(39.1)
1	1856	(31.7)	655	(31.6)	454	(31.4)
2+	1488	(25.4)	574	(27.7)	405	(28.0)
Missing	74	(1.3)	42	(2.0)	23	(1.6)
BMI, mean [SD]	28.5	[7.0]	30.5	[8.3]	29.9	[7.4]

Note: The proportions of those with missing information were: 0.3% ($n = 28$) for smoking status, 0.5% ($n = 46$) for alcohol consumption, 0.7% ($n = 63$) for household income, 0.3% ($n = 32$) for physical abuse, 1.3% ($n = 118$) for psychological abuse, 0.4% ($n = 38$) for sexual abuse, 1.2% ($n = 113$) for body mass index and 0.6% ($n = 55$) for study regions.

Abbreviations: AA, African American; ACE, adverse childhood experience; BMI, body mass index; EA, European American; HA, Hispanic American; SD, standard deviation.

provide consent for banking and use of saliva samples in genetic studies ($n = 4413$) and individuals whose sample did not meet quality assurance measures for genotype (described below; $n = 1314$). As we confined our analysis to self-reported European American (EA), African American (AA) and Hispanic American (HA) participants, we further excluded participants of other races/ethnicities ($n = 599$). The information on race/ethnicity was constructed using two questions querying self-report identification of: (1) Hispanic or Spanish/Latino origin; and (2) white, African American or black, Asian American or Pacific Islander, American Indian or Alaskan Native or other races. Consequently, we had an analytic sample of 9375 participants (EA: $n = 5854$; AA: $n = 2073$; HA: $n = 1448$).

The protocol of this study was approved by the University of North Carolina School of Public Health Institutional Review Board. Subjects gave written informed consent for participation.

2.2 | Body mass index

BMI at Wave IV was calculated based on measured height and weight (kg/m^2). Body height and weight were measured to the nearest 0.5 cm and to the nearest 0.1 kg, respectively, by nonmedicalfield interviewers. It was log-transformed to reduce skewness for subsequent analyses.

2.3 | Adverse childhood experiences

We used information on ACEs (i.e., physical, psychological and sexual abuse) before the age of 18 which was collected at Waves III and IV. Questions on physical abuse include "By the time you started 6th grade, how often had your parents or other adult care-givers slapped, hit, or kicked you?" (Wave III) and "Before your 18th birthday, how often did a parent or adult caregiver hit you with a fist, kick you, or throw you down on the floor, into a wall, or downstairs?" (Wave IV). Psychological abuse was assessed using questions such as: "Before your 18th birthday, how often did a parent or other adult caregiver say things that really hurt your feelings or made you feel like you were not wanted or loved?" (Wave IV). Information on sexual abuse was assessed using questions such as: "How often had one of your parents or other adult care-givers touched you in a sexual way, forced you to touch him or her in a sexual way, or forced you to have sexual relations?" (Wave III) and "How often did a parent or other adult caregiver touch you in a sexual way, force you to touch him or her in a sexual way, or force you to have sexual relations?" (Wave IV). Response options to these questions include: *one time*; *two times*; *three to five times*; *six to ten times*, *more than ten times*; and *this has never happened*.

The presence of ACEs was defined as those who reported any episodes of ACEs (i.e., those who reported other than "this has never happened" to any of the questions). In addition, to see if a dose–response relationship exists, we additionally operationalized ACEs by the number of types of ACEs they experienced (0; 1; and 2+).

2.4 | Calculating polygenic score

Participant DNA was isolated from Oragene saliva samples. A total of 11 288 unique Add Health samples were genotyped on either the Illumina Human Omni1-Quad BeadChip or the Illumina Human Omni-2.5 Quad BeadChip. Individual level quality control included heterogeneity, concordance with prior genotyping, sex-concordance, call

TABLE 2 Results of a race/ethnicity-stratified mixed-effects linear regression model investigating the association between adverse childhood experience (ACEs), BMI polygenic score, and log-transformed BMI.

	Model 1		Model 2	
	Coefficient	95% CI	Coefficient	95% CI
European American ($n = 5854$)				
ACEs (ref. none)	0.021	(0.010, 0.033)	1.614	(−1.202, 4.430)
Genetic risk score (per 1-SD)	0.051	(0.045, 0.058)	0.626	(−0.664, 1.917)
ACEs × Genetic risk score			0.007	(−0.006, 0.019)[1]
African American ($n = 2073$)				
ACEs (ref. none)	−0.004	(−0.023, 0.016)	−0.894	(−5.156, 3.377)
Genetic risk score (per 1-SD)	0.017	(0.008, 0.026)	−0.200	(−2.412, 2.012)
ACEs × Genetic risk score			−0.007	(−0.034, 0.020)[2]
Hispanic American ($n = 1448$)				
ACEs (ref. none)	0.000	(−0.028, 0.029)	1.219	(−4.283, 6.720)
Genetic risk score (per 1-SD)	0.042	(0.032, 0.052)	−2.661	(−5.576, 0.254)
ACEs × Genetic risk score			0.002	(−0.023, 0.027)[3]

Note: Models were adjusted for age, sex, household income at Wave I (i.e., a proxy of economic status during childhood), current smoking status and study regions. We additionally adjusted for oversampling of highly educated African Americans, country of origin and foreign-born status for Hispanic Americans. In Model 2, all covariates were entered as main effects and as the interactions with ACEs and with BMI polygenic score. 1: $p = 0.289$; 2: $p = 0.618$; 3: $p = 0.870$.

Abbreviations: AA, African American; ACE, adverse childhood experience; CI, confidence interval; EA, European American; HA, Hispanic American; SD, standard deviation.

rate < 90%, and displaying excessive relatedness to other samples (final $N = 9974$). Marker level QC, included removing palindromic (A/T and G/C) markers, call rate < 90%, MAF < 0.5%, Hardy–Weinberg equilibrium within any ancestry $<10^{-6}$. A total of 609 130 markers shared across the two genotyping panels were used to impute out to markers in the 1000 Genomes Project.[21] We removed A/T and G/C SNPs from the genotyped data before imputing to the 1000 genomes data.

Polygenic score was calculated based on BMI-related SNPs selected from Yengo et al.[7] After excluding SNPs with low imputation quality (Rsq < 0.4) and SNPs not available in our data, we included 918 SNPs in the calculation of the polygenic score (Table S1). We weighted the number of risk alleles, defined as the BMI increasing allele, with corresponding effect sizes in relation to BMI (based on rank-based inverse normal transformation), which we then summed to generate a polygenic score. The resulting score was standardized to a mean of 0 and a standard deviation (SD) of 1 by each race/ethnicity.

2.5 | Statistical analysis

Of the 9375 participants with genetic information: 0.3% ($n = 28$) were missing data on smoking status, 0.5% ($n = 46$) alcohol consumption, 0.7% ($n = 63$) household income, 0.3% ($n = 32$) physical abuse, 1.3% ($n = 118$) psychological abuse, 0.4% ($n = 38$) sexual abuse, 1.2% ($n = 113$) body mass index and 0.6% ($n = 55$) study region. To account for these missing variables, we used multiple imputation to generate 20 data sets.[22] More specifically, we performed multiple imputations using the chained equation method with 200 iterations.[23] We included the following variables in the imputation model, that is, age, sex, race/ethnicity, study region, household income, current smoking, alcohol consumption, physical abuse, psychological abuse, sexual abuse and BMI. Linear, logistic and multinomial logistic regression models were used when appropriate for each variable depending on whether it was continuous, binary or categorical. Imputation estimates were combined using Rubin's rules.[24] As shown in Table S2, we did

TABLE 3 Results of a race/ethnicity-stratified mixed-effects linear regression model investigating the association between adverse childhood experience (ACEs), BMI polygenic score, and log-transformed BMI.

	Model 1		Model 2	
	Coefficient	95% CI	Coefficient	95% CI
European American ($n = 5854$)				
Number of ACE types (ref. none)				
1	0.012	(−0.002, 0.025)	1.291	(−1.961, 4.543)
2+	0.034	(0.021, 0.047)	2.032	(−1.296, 5.359)
Genetic risk score (per 1-SD)	0.051	(0.045, 0.057)	0.614	(−0.684, 1.911)
Number of ACEs × Genetic risk score				
1			0.008	(−0.006, 0.022)[1]
2+			0.004	(−0.011, 0.018)[2]
African American ($n = 2073$)				
Number of ACE types (ref. none)				
1	−0.009	(−0.031, 0.013)	−0.937	(−6.079, 4.204)
2+	0.003	(−0.024, 0.029)	−0.645	(−5.453, 4.163)
Genetic risk score (per 1-SD)	0.017	(0.008, 0.026)	−0.308	(−2.560, 1.944)
Number of ACEs × Genetic risk score				
1			−0.008	(−0.039, 0.024)[3]
2+			−0.005	(−0.034, 0.024)[4]
Hispanic American ($n = 1448$)				
Number of ACE types (ref. none)				
1	−0.005	(−0.039, 0.028)	3.229	(−3.376, 9.834)
2+	0.007	(−0.024, 0.038)	−1.207	(−7.132, 4.718)
Genetic risk score (per 1-SD)	0.042	(0.032, 0.052)	−2.628	(−5.609, 0.239)
Number of ACEs × Genetic risk score				
1			−0.001	(−0.030, 0.027)[5]
2+			0.002	(−0.032, 0.036)[6]

Note: Models were adjusted for age, sex, household income at Wave I (i.e., a proxy of economic status during childhood), current smoking status and study regions. We additionally adjusted for oversampling of highly educated African Americans, and country of origin and foreign-born status for Hispanic Americans. In Model 2, all covariates were entered as main effects and as the interactions with ACEs and with BMI polygenic score. 1: $p = 0.240$; 2: $p = 0.601$; 3: $p = 0.628$; 4: $p = 0.742$; 5: $p = 0.926$; 6: $p = 0.901$.

Abbreviations: AA, African American; ACE, adverse childhood experience; CI, confidence interval; EA, European American; HA, Hispanic American; SD, standard deviation.

not observe material differences in basic characteristics based on the complete dataset and those based on the imputed datasets.

A race/ethnicity-specific mixed model was used to investigate the association between ACEs, the polygenic score, and log-transformed BMI while accounting for multiple individuals in each school, which was the original unit of sampling in Add Health. Our analytic framework is illustrated in Figure S1. In Model 1, we adjusted for covariates including age (in years), sex (male and female), household income at Wave I (standardized by dividing the income by square root of the number of household members, which we then categorized into tertiles as a proxy of economic status during childhood), current smoking status (yes/no) and study regions (i.e., four study regions of Add Health). We additionally adjusted for additional oversampling of highly educated AAs in Add Health, as well as country of origin (i.e., Mexico, Cuba, Central/South America/ Puerto Rico/Other Hispanic) and foreign-born status (i.e., US born/Non-US born) for HA. In Model 2, we included the interaction term between ACEs and the risk score; all covariates were entered as both main effects and as the interaction with ACEs and with BMI polygenic score.[25]

To identify any potential dose–response relationship between ACEs and log-transformed BMI, we used the same set of analyses while using the number of ACEs they experienced (0; 1; and 2+) as the exposure. Statistical analyses were conducted using Stata version 16.0 (Stata Corp, College Station, TX).

3 | RESULTS

The mean age of participants in the Wave IV analytic sample was 28.5 years old and approximately half of the participants were female (53.0%). EA tended be from higher income families compared to AA and HA (Table 1). Current smoking ranged from 38.6% of EA, 28.2% of AA and 24.2% of HA. Over half of participants had exposure to any ACEs, with variation across race/ethnicity (57.1% EA, 59.3% AA and 59.4% HA). Mean BMI was highest among AA (30.5 kg/m^2), followed by HA (29.9 kg/m^2) and EA (28.5 kg/m^2).

Table 2 shows the results of mixed-effects linear regression model investigating the association between log-transformed BMI, ACEs and the BMI polygenic score, stratified by race/ethnicity. In Model 1, the presence of ACEs was associated with higher BMI in EA (coef. = 0.021, 95% CI = 0.010, 0.033), but not AA (coef. = −0.004, 95% CI = −0.023, 0.016) or HA (coef. = 0.000, 95% CI = −0.028, 0.029). The polygenic score was associated with higher BMI in all race/ethnic groups. When interaction terms were incorporated into the models (Model 2), we found no evidence of statistically significant interaction between the presence of ACEs and polygenic score in relation to increased BMI (EA: $p = 0.289$; AA: $p = 0.618$; HA: $p = 0.870$).

In models examining the association of one or two or more ACEs relative to no ACEs (Table 3), we found similar findings to those reported in models with the binary exposure. More specifically, while the polygenic score was linked with higher BMI in all race/ethnic groups (Model 1), the number of ACEs was associated with higher BMI among EA (one ACE: coef. = 0.012, 95% CI = −0.002, 0.025; two or more ACEs: coef. = 0.034, 95% CI = 0.021, 0.047) and not in AA or HA. We found no evidence of statistically significant interaction between ACEs and polygenic score in any race/ethnic group (Model 2).

4 | DISCUSSION

Using data collected from a racially/ethnically diverse Add Health cohort, we found no evidence of statistically significant interaction between the presence of adverse childhood experience before the age of 18 and polygenic score in relation to higher BMI. In the main effects models, the association between the presence of ACEs and BMI was statistically significant in European Americans, but not in African Americans or Hispanic Americans while the polygenic score was significantly associated with higher BMI in all race/ethnic groups.

Our analysis with 918 BMI-related SNPs identified in Yengo et al.[7] did not support our hypothesis that ACEs and polygenic BMI risk score interacted in relation to BMI. One possible interpretation is that while some SNPs can exhibit interactive effects on the association between the presence of ACEs and increased BMI, such effects can be weakened by the presence of other BMI-related SNPs with no, weak or opposite estimated direction. It is likely that the composite score with higher number of SNPs may explain the variation in BMI better as exemplified in our study but our study results suggest that this is not the case for the interaction effect with ACEs.

Our finding that the presence of ACEs was positively associated with BMI among EA young adults is in line with previous reviews by Hemmingsson et al.[15] and Danese et al.,[16] both of which concluded that ACEs were associated with elevated risk of developing obesity by 34%–36%. It has been suggested that ACEs may induce structural and functional changes in the brain that result in dysregulated executive function.[26,27] In particular, the function and structure of the lateral and ventromedial fronto-limbic brain areas and networks of behavioural and affect controls have been suggested to be most influenced by childhood maltreatment.[27]

On the other hand, our null-findings in relation to the association between ACEs and BMI among AA or HA were not in line with the above mentioned systematic reviews as well as several previous studies conducted among AA or HA.[28,29] For example, Boynton-Jarrett et al.[28]analysed data from the Black Women's Health Study (mean age = 49 years old; $n = 33\,298$), and found that compared to participants who did not experience abuse, participants who were exposed to the highest severity of ACEs (i.e., child/teenager physical and sexual abuse) were at 1.29 times (95% CI = 1.20–1.38) higher risk of obesity (BMI ≥ 30 kg/m^2) in mid-life. Similarly, Rohde et al.[29] reported higher risks of developing obesity associated with child sexual abuse (OR = 1.66; 95% CI = 0.99–2.79) and child physical abuse (OR = 2.44; 95% CI = 1.34–4.45) in AA, HA, and American Indians (mean age = 52 years old; $n = 759$). These study populations were older than Add Health participants, so it is possible that there are cohort differences and/or age-related differences in these associations. There is a need for larger studies to understand the differences in risk by race/ethnicity in the association between ACEs and BMI/obesity.

It should be also mentioned that as a consequence of the historical bias of studying European ancestry individuals,[30] minority populations, who are in fact at higher risk of obesity than EA, have not been extensively studied in obesity genetic research.[18] We also need to understand whether the same social environmental factors (e.g., early-life stressful life events) may be differently perceived and biologically manifested by race/ethnicity. It should be also reminded that AA and HA might have experienced other stressful experiences that were not included in the present study more frequently than EA (e.g., discrimination[31] and poverty[32]). More studies are needed to elucidate ethnicity/race-specific mechanisms in relation to increased BMI.

There are several limitations to our study. First, people may not report properly their ACEs given the nature of these questions as previously pointed out by Hardt and Rutter.[33] One supporting evidence for this supposition is that some participants provided contradictory responses to ACEs between Wave III and Wave IV (e.g., affirmative answer to an episode in Wave III but negative answer to the same question in Wave IV). That said, there could be some participants who did not provide information on their traumatic experiences in any wave, which might lead to underestimations of ACEs. Second, the Add Health survey did not include a validated tool for assessing ACEs, although it did include data on experience of physical, psychological and sexual abuse. Third, in the calculation of BMI polygenic score, we assumed the same direction of estimated SNP by ACEs interaction effects, which might be the reason of non-significant association between ACEs and polygenic risk score in our study. Fourth, it is possible that individual susceptibility to the same ACE may differ across individuals. Fifth, it is possible that unobserved factors may influence both the presence of ACEs and other factors that predispose an individual to obesity, though we controlled for parental income. Sixth, given the predominance of genetic data based on EA in the literature, the polygenic risk score likely captures susceptibility better in EA relative to AA or HA. Future research should broaden studies to include more data on non-white race/ethnic groups and should also include more comprehensive information on related SNPs to better capture genetic predisposition to obesity/increased BMI.

In conclusion, in this study of young adults, we found no evidence supporting the idea that ACEs exacerbate genetic predisposition to increased BMI in early adulthood.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Yosuke Inoue, **Mariaelisa Graff**, **Annie Green Howard**, **Heather M. Highland**, **Kristin L. Young**, **Kathleen Mullan Harris**, **Kari E. North**, **Penny Gordon-Larsen** contributed to study design; **Yosuke Inoue**, **Mariaelisa Graff**, **Yun Li**, **Heather M. Highland** contributed to data analysis; and **Yosuke Inoue**, **Mariaelisa Graff**, **Annie Green Howard**, **Heather M. Highland** contributed to writing of the manuscript. All other authors provided critical evaluation of the manuscript. **Yosuke Inoue** and **Penny Gordon-Larsen** had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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SUPPORTING INFORMATION

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