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Gene-Environment Interplay in the Development of Overweight

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A B S T R A C T

Purpose: Overweight in youth is influenced by genes and environment. Gene-environment interaction (G×E) has been demonstrated in twin studies and recent developments in genetics allow for studying G×E using individual genetic predispositions for overweight. We examine genetic influence on trajectories of overweight during adolescence and early adulthood and determine whether genetic predisposition is attenuated by higher socioeconomic status and having physically active parents.
Methods: Latent class growth models of overweight were fitted using data from the TRacking Adolescents' Individual Lives Survey (n = 2720). A polygenic score for body mass index (BMI) was derived using summary statistics from a genome-wide association study of adult BMI (N = ~700,000) and tested as predictor of developmental pathways of overweight. Multinomial logistic regression models were used to examine effects of interactions of genetic predisposition with socioeconomic status and parental physical activity (n = 1675).
Results: A three-class model of developmental pathways of overweight fitted the data best ("non-overweight", "adolescent-onset overweight", and "persistent overweight"). The polygenic score for BMI and socioeconomic status distinguished the persistent overweight and adolescent-onset overweight trajectories from the non-overweight trajectory. Only genetic predisposition differentiated the adolescent-onset from the persistent overweight trajectory. There was no evidence for G×E.
Discussion: Higher genetic predisposition increased the risk of developing overweight during adolescence and young adulthood and was associated with an earlier age at onset. We did not find that genetic predisposition was offset by higher socioeconomic status or having physically active parents. Instead, lower socioeconomic status and higher genetic predisposition acted as additive risk factors for developing overweight.

IMPLICATIONS AND CONTRIBUTIONS

Studies that examine gene-environment interactions (G×E) in non-twin samples using individual genetic predispositions for overweight are rare. Using a polygenic score approach, this study demonstrates that the development of overweight in adolescence is influenced by genes but does not find evidence for G×E.

Overweight in young people is increasingly prevalent and forms a major public health threat [1] given its negative consequences for physical and psychological health [2,3]. The origins

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of individual differences in overweight are complex and include genetic and environmental influences and their interplay. Twin studies suggest that genetic factors explain between 41% and 85% of individual differences in body mass index (BMI) during childhood and adolescence, with genetic influence typically increasing from mid-childhood to early adulthood [4]. Next to this substantial genetic component, environmental characteristics, such as the availability of unhealthy foods and limited opportunities for physical activity, contribute to overweight in youth [5]. The environment can attenuate or exacerbate genetic predispositions, indicating G×E.

Although G×E studies in twins suggest that genetic predisposition for overweight can be modified by environmental conditions [6], G×E studies using individual genetic predispositions for overweight are rare. Such analyses are now possible due to progress in the identification of genetic variants associated with BMI in genome-wide association studies [7]. In these studies, BMI is regressed on millions of genetic variants, and summary statistics of the association between each genetic variant and BMI are derived. With these summary statistics, polygenic scores can be created for any individual for whom genetic data have been collected. Polygenic scores reflect an individual's genetic predisposition for a phenotype, such as BMI or overweight [8]. A key benefit of using polygenic scores is that they can be applied in any study in which genotype data is available, without the need for and limitations of specific populations such as twins. Twin studies are useful in estimating the contributions of genetics and environment to traits, but they do not provide information about the specific genes involved [9]. In contrast, molecular genetic approaches, including polygenic scores, focus on associations between individual differences in DNA structure and variation in traits. Polygenic scores thus provide an easily applicable and powerful tool for investigating developmental questions traditionally addressed by twin designs.

Here, we use polygenic scores to examine the gene-environment interplay associated with the development of overweight in terms of both continuity and change during adolescence and young adulthood, modeled as latent trajectories of overweight status. Group-based trajectory modeling approaches such as latent class growth analysis and growth mixture models have been used extensively to identify distinct trajectories of weight status across the life course, but thus far, only few studies have focused on this specific period in development and explored associations with gene-environment interplay [10]. We examine socioeconomic status and parental physical activity as environmental factors, because the home environment is important for overweight development. Twin studies suggest that higher socioeconomic status is associated with a decreased risk of overweight in genetically predisposed individuals [11,12]. Studies using polygenic scores have corroborated these findings in adult samples [13,14], but studies on children and adolescents are lacking [15]. Further, parental physical activity may reduce the risk of overweight in offspring through parental modeling and support [16,17], but it is unknown if having physically active parents attenuates genetic influence. Importantly, although we conceptualize socioeconomic status and parental physical activity as environmental exposures, these are also under genetic influence [18]. Any association between these exposures and adolescent overweight may therefore also represent gene-environment correlation, such that, for example, less active parents may pass on genes associated with being less active, which may lead to higher rates of overweight in their children.

Insight into genetic and environmental factors associated with the development of overweight is needed to inform on the potential usefulness and timing of targeted prevention strategies and eventually reduce future health care costs associated with obesity. By testing socioeconomic status and parental physical activity as potential moderators of genetic predisposition for overweight, we contribute to the identification of distal and proximal environmental factors that may buffer against genetic risk.

In line with previous studies [10], we expected to identify three or four groups with distinct overweight trajectories, including a non-overweight group, a group with persistent overweight, and a group that would develop overweight during adolescence. We further hypothesized 1) that genetically predisposed adolescents would be at higher risk for persistent overweight than adolescents with a lower genetic predisposition and 2) that the effects of genetic predisposition on overweight patterns would be attenuated by higher socioeconomic status and parental physical activity. We controlled for pubertal status and medication use for emotional and behavioral problems as both are linked to BMI [19–21].

Methods

We preregistered this study before conducting the analyses. The preregistration and all analysis scripts can be found on the Open Science Framework (https://osf.io/upexd/).

Participants

We used data from the TRacking Adolescents' Individual Lives Survey (TRAILS), an ongoing longitudinal study of Dutch adolescents, with follow-up assessments since 2001 [22]. Ethics approval was obtained from the Dutch Central Committee on Research Involving Human Subjects (CCMO) before the start, and written consent was acquired from all participants and their parents. The TRAILS population cohort was recruited through community registers and primary schools. A total of 2935 children were approached for enrollment, of which 2229 (50.8% girls) agreed to participate. Participation was more likely when children were female, from higher socioeconomic status background, and with better school performance [23]. From T4, parental consent was no longer needed for participation and a web-based survey method was used to recruit and assess participants.

The population cohort was complemented by a high-risk cohort to include more vulnerable children and thus have more variation in mental health problems and their risk factors. The high-risk cohort was set up in 2004 and consisted of 543 children selected on the basis of having been in contact with child and adolescent mental health services before age eleven. Boys were overrepresented (66%) in line with sex ratios for the most common childhood psychopathologies. Retention rates ranged between 73% and 96% for the population cohort and between 73% and 85% for the high-risk cohort. Details about TRAILS and attrition are published elsewhere [23,24].

The present study used data from the first six assessments. The mean age (*SD*) of participants in our sample (N = 2734) at T1 was 11.1 (0.54), 13.5 (0.61) at T2, 16.2 (0.72) at T3, 19.1 (0.63) at T4,

22.2 (0.68) at T5, and 25.7 (0.65) at T6. Genetic data were collected from n = 1694 individuals with European ancestry at T3 (n = 1353 and n = 341 from population and high-risk cohorts).

Measures

Overweight

Participants' weight and height were measured by trained research assistants at T1-T5 using a calibrated scale (Seca 770, Hamburg, Germany) and a stadiometer (Seca 214, Hamburg, Germany). At T6, weight and height were self-reported. BMI was calculated by dividing weight by height squared (kg/m^2), and the resulting scores were dichotomized, such that *0 = non-overweight* and *1 = overweight or obese*. We used age and sex-specific cutoffs for overweight, corresponding to the International Obesity Task Force classification system [25].

Polygenic score for BMI

Information on DNA extraction and participant exclusion can be found in the supplemental information (Appendix A). The BMI polygenic score was based on summary statistics reported by the Genetic Investigation of Anthropometric Traits (GIANT) Consortium that identified 941 genetic variants associated with adult BMI in a sample of ~700,000 Europeans [7]. TRAILS data were removed from the summary statistics using MetaSubtract (version 1.60) [26]. We derived the polygenic score for BMI using LDpred2-auto, which automatically estimates the single nucleotide polymorphism-heritability (h^2) and the proportion of causal variants (p) from the data and therefore does not require a validation dataset [27]. Only HapMap3+ variants were included in the polygenic score (n = 920,337), which have passed rigorous quality control and provide a good coverage of the whole genome [27]. We used the LD reference panel based on European individuals of the UK Biobank provided by the developers of LDpred2. The polygenic score for BMI explained up to 13.7% of variance in BMI in TRAILS (Figure A1).

Socioeconomic status

Parental socioeconomic status was assessed at baseline using five indicators, including both parents' educational and occupational levels and family income. Educational level was assessed in five categories ranging from elementary to university education. Occupational level was based on the International Standard Classification for Occupation [28]. Family net income was measured on a scale ranging from 1 (*<€680* per *month*) to 9 (*>€3857* per *month*). Socioeconomic status has been measured as the mean of the standardized five items. The scale has a high internal consistency (Cronbach's $\alpha = 0.84$).

Parental physical activity

At T1, one parent reported on the duration and frequency of their own and their partner's habitual physical activity (e.g., walking, cycling, sports activities) by selecting from four categories representing the number of hours per week engaged in physical activity. Responses for both parents were averaged. If information for one parent was missing, the score was based on one parent's physical activity level. We created a categorical variable such that *1 = <1 hour/week, 2 = 1-2 hours/week, 3 = 3-4 hours/week,* and *4 = >4 hours/week.*

Covariates

We controlled for sex, age at baseline, pubertal development, and medication use for emotional and behavioral problems. Pubertal development was assessed at T3 using the pubertal development scale [29], consisting of five items for each sex. Participants rated their physical development on a 4-point scale, with higher scores indicating more mature development. The overall score was determined by calculating the average score for all items, and the resulting variable was standardized. Cronbach's α ranged from 0.52 (girls) to 0.73 (boys) in the population cohort and from 0.40 (girls) to 0.73 (boys) in the high-risk cohort. Parents were asked at T3 if their child had used medication for emotional and behavioral problems in the past two years (*0 = no*, *1 = yes*). Finally, 20 principal components of the genetic data were included to control for population stratification.

Analytic strategy

We first specified a single-class latent growth model without within-class variation, using Mplus v8.6 [30]. To model the unequal time spacing between measurement waves, we specified the metric of time by calculating the average time in years since T1 in our full sample (N = 2734). This resulted in the following time coding: 0.0 for T1, 2.35 for T2, 5.10 for T3, 7.98 for T4, 11.12 for T5, and 14.62 for T6. We estimated an intercept-only model, a model with linear change and a model in which we added a quadratic polynomial. Models were fit using maximum likelihood estimation, and full information maximum likelihood was used to handle missing data on the indicator variables. Thus, analyses included all participants for whom at least one data point was available (n = 2720). After fitting the single-class model, we incrementally added classes to identify meaningful subgroups with distinct trajectories of overweight. We evaluated model fit using Bayesian information criterion (BIC; lower values indicate better fit), entropy (values close to one indicate better classification), Lo-Mendell-Rubin-adjusted likelihood ratio test (LMR-LRT) and bootstrap likelihood ratio test (BLRT) that compare the k and the k-1 class model, average classification probability (values close to one indicate better classification), and smallest class size (minimum of 5% of sample per class). We also evaluated well-fitting models based on theoretical expectations and interpretability.

In the main analyses, we conducted three sets of multinomial logistic regression analyses and included predictors of class membership as auxiliary variables using the three-step approach with adjustment for classification errors [31]. To test for main genetic effect, the polygenic score for BMI was entered as a predictor of class membership (Model 1). In the next step, socioeconomic status (Model 2a) and parental physical activity (Model 3a) were added as predictors of class membership, in addition to the polygenic score. For the G×E analyses, we added an interaction term with the polygenic score for BMI to test whether socioeconomic status (Model 2b) and parental physical activity (Model 3b) in interaction with genetic predisposition differentiated trajectories of overweight. Sex, age, pubertal development, medication use, and 20 principal components were added as covariates in each model. If the main effect of socioeconomic status was significant, we added socioeconomic

Table 1
Descriptive statistics of all variables before imputation for the full sample (N = 2734) and for participants with genetic data (n = 1676)

	Full sample (N = 2734)			Participants with genetic data (n = 1676)		
Variable	*M* ± *SD* or percentages	n total	%-missing	*M* ± *SD* or percentages	n total	%-missing
Overweight at T1[a]	16.7% overweight	2649	3.1%	14.8% overweight	1632	2.6%
Overweight at T2[b]	13.2% overweight	2417	11.6%	12.6% overweight	1616	3.6%
Overweight at T3[c]	15.6% overweight	1935	29.2%	14.9% overweight	1556	7.2%
Overweight at T4[d]	22.6% overweight	1887	31.0%	22.4% overweight	1416	15.5%
Overweight at T5[d]	30.2% overweight	1727	36.8%	30.4% overweight	1314	21.6%
Overweight at T6[d]	33.7% overweight	1548	43.4%	33.8% overweight	1168	30.3%
Parental physical activity	9.7% < 1 hour/week 33.3% 2–3 hours/week 34.6% 3–4 hours/week 22.4% > 4 hours/week	2536	7.2%	8.0% < 1 hour/week 33.5% 2–3 hours/week 36.4% 3–4 hours/week 22.1% > 4 hours/week	1605	4.2%
Covariates						
Sex	52.6% male	2734	0%	51.8%	1676	0%
Age in years at baseline	11.11 ± 0.54	2734	0%	11.09 ± 0.54	1676	0%
Medication use for emotional and behavioral problems in past two years	7.9% used medication	1881	31.2%	10.00% used medication	1458	13.0%

Values are presented as percentages or means (*M*) ± standard deviations (*SD*). The polygenic score for BMI (n = 1676), socioeconomic status (n = 2690), and pubertal development (n = 2031) were standardized and are therefore not included in this table.
[a] BMI cutoff for overweight in boys was 20.55 kg/m^2; cutoff for girls was 20.74 kg/m^2.
[b] BMI cutoff for overweight in boys was 21.91 kg/m^2; cutoff for girls was 22.58 kg/m^2.
[c] BMI cutoff for overweight in boys was 23.90 kg/m^2; cutoff for girls was 24.37 kg/m^2.
[d] BMI cutoff for overweight was 25 kg/m^2.

status as a covariate in models focusing on parental physical activity and vice versa. Moreover, in each set of G×E analyses (Models 2b and 3b), we entered secondary interaction terms (i.e., covariate-by-moderator and covariate-by-polygenic score) to control for potential confounding [32]. We standardized the polygenic score to aid interpretation of the estimated coefficients. Continuous predictors were mean-centered prior to the G×E analyses to reduce problems with multicollinearity. Only participants with genetic data were included in the analyses (n = 1676) and we used multiple imputation to deal with missing values on environmental variables and covariates. Twenty datasets with fifty iterations were generated using SPSS's (version 28.0.0.0) Fully Conditional Specification Method (Predictive Mean Matching). Analyses were performed in the imputed datasets in Mplus and pooled estimates are reported.

In sensitivity analyses, we repeated the G×E analyses using different operationalizations of the environmental variables (Tables A10-13). We included socioeconomic status as a categorical variable consisting of three categories: the lowest 25%, middle 50%, and highest 25%. We computed a parental physical activity score based on the most active parent rather than the average of both parents. Additionally, we estimated models 1) without secondary interaction terms, 2) only with covariates, and 3) with environmental variables as primary predictors of class membership (Tables A14-19).

Results

Table 1 shows descriptive statistics for the full sample (N = 2734) and for participants with genetic data (n = 1676). We found that participants who were excluded due to missing genotype data were more often overweight (χ^2 (1) = 10.90, $p < .001$) and older (t (2732) = −3.16, $p = .002$) at baseline, from lower socioeconomic backgrounds (t (2688) = 11.19, $p < .001$), and had parents with a lower physical activity level (χ^2 (3) = 17.44, $p < .001$) than participants for whom genetic data was available.

Developmental trajectories of overweight status

We first fitted latent class growth models of overweight. The quadratic term was statistically significant in the single-class model, and the quadratic model resulted in a lower BIC value than the linear model. We therefore moved forward with a quadratic model and found a three-class model to be the best-fitting solution based on fit indices (BIC = 8700.4, entropy = 0.79) and theoretical considerations. The three-class model provided a significantly better fit than the two-class model (LMR-LRT = 531.8, $p < .001$; BLRT = 548.6, $p < .001$). Quadratic means were statistically significant in two of the three trajectories. When comparing the three-class to the four-class model, LMR-LRT and BLRT suggested that a four-class solution resulted in significant improvement in model fit, but the additional class was not theoretically meaningful as it merely subdivided one class into two similar, smaller classes. Thus, we performed the main analyses using the three-class solution (see Tables A2-4 for full details). Based on posterior probabilities, 66.6% (n = 1811) followed a trajectory of no overweight, 17.4% (n = 474) showed an increase in overweight at the onset of adolescence, and 16.0% (n = 435) was characterized by persistent overweight, with average posterior probabilities of 0.92, 0.95, and 0.89, respectively (Figure 1).

Polygenic score for BMI, socioeconomic status, and parental physical activity as predictors of overweight trajectories

The odds of being in the persistent overweight trajectory rather than the non-overweight trajectory were 3.02 (95% CI: [2.47, 3.69]) times higher for individuals with higher genetic risk (Table 2, Model 1). Likewise, higher genetic risk increased the odds of classification into the adolescent-onset overweight trajectory compared to the non-overweight trajectory (OR = 2.00,

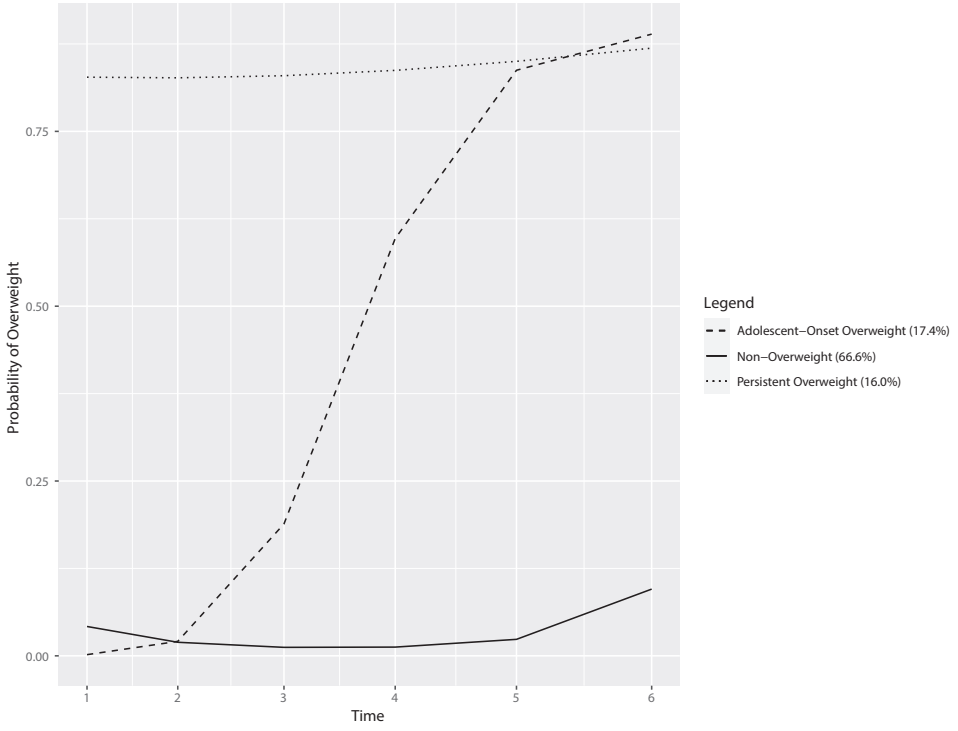

Figure 1. Trajectories of overweight status from the best-fitting three-class model (n = 2720). Reported class sizes are based on posterior probabilities.

95% CI [1.64, 2.44]). Relative to the adolescent-onset overweight trajectory, higher genetic risk also increased the likelihood of being in the persistent overweight trajectory (OR = 1.51, 95% CI [1.22, 1.87]).

Socioeconomic status distinguished individuals following persistent overweight (OR = 0.57, 95% CI: [0.45, 0.71] and adolescent-onset overweight (OR: 0.74, 95% CI: [0.57, 0.95] trajectories from individuals in the non-overweight trajectory after adjustment for the polygenic score for BMI (Model 2a). In contrast to genetic predisposition, socioeconomic status did not differentiate the adolescent-onset from the persistent overweight trajectory. Parental physical activity was not associated with class membership (Model 3a). Genetic influence on class membership did not decrease substantially in magnitude after adding the environmental exposures.

Gene-environment interactions

We did not find support for moderation by socioeconomic status and parental physical activity (Models 2b and 3b). We also estimated G×E models without secondary interaction terms, but these models did not provide evidence for G×E either (Tables A14-15). Results of the sensitivity analyses using different operationalizations of the environmental variables were consistent with those from the main analyses (Tables A10-13).

Discussion

We used a polygenic score for BMI to examine its association with developmental pathways of overweight. We further examined interactions between the polygenic score and environmental conditions under which individual behavior is formed, namely socioeconomic status and parental physical activity. Consistent with previous studies [10], we identified three trajectories: no overweight, adolescent-onset overweight, and persistent overweight. As those with persistent overweight likely develop health problems later in life [2,3], research should focus on risk factors that explain this particular developmental pattern. We found that both overweight trajectories were associated with genetic predisposition, but the effect was stronger for the persistent overweight than the adolescent-onset overweight trajectory. This finding supports earlier findings that children at higher genetic risk for overweight gain weight earlier than children at lower genetic risk [33].

Also in line with recent work [34,35], lower socioeconomic status increased the risk of developing overweight over and above the influence of genetic predisposition. Socioeconomic disadvantage could be a structural barrier to opportunity and may increase the likelihood of living in a household and neighborhood with poorer access to healthy food and physical activity resources. Importantly, environmental exposure and genetic make-up were associated. In the presence of gene-environment correlation, any parent-offspring association that was not adjusted for parental and offspring genes may be attributable to shared genetic factors [36]. That said, previous work suggests that shared genetic factors and direct environmental causation contribute equally to the association between parental socioeconomic status and offspring overweight [37], so our results may in part reflect a causal link. Of note, socioeconomic status did not differentiate the adolescent onset and persistent overweight trajectory. This might indicate that lower socioeconomic background is associated with an elevated risk of developing overweight but not with time of onset. Finally, we did not observe that genetic predisposition was attenuated by socioeconomic background, although G×E has been reported previously [11–15]. Earlier interactions were primarily found in

Table 2
Main genetic effect of the polygenic score for BMI (Model 1), main effect of socioeconomic status (Model 2a), polygenic score for BMI × socioeconomic status (Model 2b), main effect of parental physical activity (Model 3a), and polygenic score for BMI × parental physical activity (Model 3b) in the prediction of class membership

		Non-overweight versus adolescent-onset overweight		Non-overweight versus persistent overweight		Adolescent-onset overweight versus persistent overweight	
Model		OR (*SE*)	95% CI	OR (*SE*)	95% CI	OR (*SE*)	95% CI
1. Main effect	Sex[a]	0.76 (0.14)	[0.52, 1.09]	0.72 (0.13)	[0.50, 1.02]	0.95 (0.21)	[0.62, 1.46]
Polygenic score for BMI	Age	0.70 (0.12)*	[0.50, 0.98]	1.44 (0.23)*	[1.06, 1.97]	2.06 (0.41)*	[1.39, 3.06]
	Pubertal development	1.26 (0.12)*	[1.04, 1.52]	1.22 (0.12)*	[1.00, 1.48]	0.97 (0.12)	[0.77, 1.23]
	Medication use[b]	2.35 (0.64)*	[1.38, 4.00]	0.79 (0.30)	[0.38, 1.67]	0.34 (0.13)*	[0.16, 0.73]
	Polygenic score for BMI	2.00 (0.20)*	[1.64, 2.44]	3.02 (0.31)*	[2.47, 3.69]	1.51 (0.17)*	[1.22, 1.87]
2a. Main effect	Sex[a]	0.76 (0.14)	[0.53, 1.10]	0.73 (0.13)	[0.51, 1.04]	0.95 (0.21)	[0.62, 1.46]
Socioeconomic status	Age	0.71 (0.12)	[0.51, 1.00]	1.46 (0.24)*	[1.06, 2.01]	2.05 (0.41)*	[1.38, 3.05]
	Pubertal development	1.28 (0.13)*	[1.05, 1.55]	1.27 (0.13)*	[1.05, 1.54]	0.99 (0.12)	[0.79, 1.26]
	Medication use[b]	2.36 (0.66)*	[1.37, 4.08]	0.79 (0.31)	[0.37, 1.70]	0.34 (0.13)*	[0.15, 0.73]
	Polygenic score for BMI	1.93 (0.20)*	[1.58, 2.35]	2.80 (0.29)*	[2.29, 3.44]	1.46 (0.16)*	[1.17, 1.81]
	Socioeconomic status	0.74 (0.10)*	[0.57, 0.95]	0.57 (0.06)*	[0.45, 0.71]	0.77 (0.11)	[0.58, 1.01]
2b. Polygenic score for	Sex[a]	0.80 (0.16)	[0.54, 1.18]	0.69 (0.15)	[0.46, 1.06]	0.87 (0.24)	[0.51, 1.48]
BMI × Socioeconomic	Age	0.73 (0.13)	[0.51, 1.03]	1.40 (0.27)	[0.96, 2.06]	1.93 (0.47)*	[1.21, 3.10]
status	Pubertal development	1.30 (0.15)*	[1.04, 1.62]	1.40 (0.16)*	[1.12, 1.76]	1.08 (0.16)	[0.81, 1.44]
	Medication use[b]	2.15 (0.66)*	[1.18, 3.91]	1.00 (0.39)	[0.46, 2.16]	0.46 (0.21)	[0.19, 1.14]
	Polygenic score for BMI	1.92 (0.31)*	[1.40, 2.64]	2.75 (0.39)*	[2.08, 3.64]	1.43 (0.23)*	[1.05, 1.96]
	Socioeconomic status	0.64 (0.12)*	[0.45, 0.91]	0.56 (0.10)*	[0.40, 0.78]	0.87 (0.18)	[0.58, 1.31]
	PGS_{BMI} × Socioeconomic status	1.10 (0.17)	[0.82, 1.48]	1.05 (0.16)	[0.79, 1.41]	0.96 (0.15)	[0.71, 1.30]
3a. Main effect	Sex[a]	0.75 (0.14)	[0.52, 1.08]	0.71 (0.13)	[0.49, 1.02]	0.95 (0.21)	[0.62, 1.47]
Parental physical	Age	0.70 (0.12)*	[0.50, 0.98]	1.46 (0.24)*	[1.06, 2.02]	2.09 (0.42)*	[1.41, 3.11]
activity	Pubertal development	1.27 (0.13)*	[1.05, 1.55]	1.27 (0.13)*	[1.04, 1.54]	1.00 (0.12)	[0.79, 1.26]
	Medication use[b]	2.37 (0.67)*	[1.37, 4.12]	0.80 (0.31)	[0.37, 1.71]	0.34 (0.13)*	[0.16, 0.73]
	Socioeconomic status	0.72 (0.09)*	[0.56, 0.93]	0.57 (0.07)*	[0.45, 0.71]	0.79 (0.11)	[0.59, 1.05]
	Polygenic score for BMI	1.93 (0.20)*	[1.58, 2.36]	2.80 (0.29)*	[2.28, 3.44]	1.45 (0.17)*	[1.16, 1.82]
	Parental physical activity[c]						
	1–2 hours/week	1.11 (0.47)	[0.48, 2.52]	1.38 (0.58)	[0.61, 3.13]	1.25 (0.59)	[0.49, 3.17]
	3–4 hours/week	1.80 (0.72)	[0.82, 3.96]	1.42 (0.58)	[0.64, 3.14]	0.79 (0.36)	[0.32, 1.94]
	>4 hours/week	1.26 (0.55)	[0.54, 2.96]	1.06 (0.47)	[0.44, 2.54]	0.84 (0.43)	[0.31, 2.28]
3b. Polygenic score for	Sex[a]	3.07 (2.86)	[0.49, 19.08]	3.43 (2.76)	[0.71, 16.59]	1.12 (1.05)	[0.18, 7.04]
BMI × Parental	Age	0.21 (0.21)	[0.03, 1.52]	1.94 (1.50)	[0.43, 8.81]	9.17 (8.63)*	[1.45, 58.01]
physical activity	Pubertal development	1.48 (0.46)	[0.80, 2.73]	1.49 (0.52)	[0.75, 2.97]	1.01 (0.44)	[0.43, 2.36]
	Medication use[b]	0.19 (0.25)	[0.01, 2.55]	1.63 (1.83)	[0.18, 14.82]	8.76 (11.87)	[0.62, 124.58]
	Socioeconomic status	0.86 (0.38)	[0.36, 2.03]	0.76 (0.35)	[0.31, 1.88]	0.89 (0.47)	[0.32, 2.51]
	Polygenic score for BMI	1.95 (0.77)	[0.90, 4.22]	2.73 (1.30)*	[1.08, 6.92]	1.40 (0.69)	[0.54, 3.68]
	Parental physical activity[c]						
	1–2 hours/week	2.1 (1.52)	[0.51, 8.64]	3.09 (2.18)	[0.78, 12.30]	1.47 (1.38)	[0.24, 9.19]
	3–4 hours/week	3.11 (2.18)	[0.79, 12.31]	2.82 (1.93)	[0.74, 10.78]	0.91 (0.84)	[0.15, 5.62]
	>4 hours/week	3.06 (2.21)	[0.74, 12.62]	2.42 (1.76)	[0.59, 10.04]	0.79 (0.76)	[0.12, 5.15]
	Polygenic score for BMI × Parental physical activity						
	PGS_{BMI}× 1–2 hours/week	0.93 (0.43)	[0.37, 2.32]	1.07 (0.54)	[0.40, 2.86]	1.14 (0.61)	[0.40, 3.23]
	PGS_{BMI}× 3–4 hours/week	1.03 (0.46)	[0.44, 2.46]	1.05 (0.54)	[0.38, 2.88]	1.01 (0.52)	[0.37, 2.78]
	PGS_{BMI} × >4 hours/week	1.22 (0.62)	[0.45, 3.31]	1.22 (0.68)	[0.41, 3.64]	1.00 (0.56)	[0.33, 2.98]

The first-named class served as the reference category. Analyses were based on n = 1675 participants (note that sample sizes differed for each comparison). Parameters for the 20 principal components (Models 1–3) and secondary interaction terms (Models 2b and 3b) are given in Tables A5-9.
OR = odds ratio, *SE* = standard error, CI = confidence interval, PGS_{BMI} = polygenic score for BMI.
[a] 1 = male, 0 = female.
[b] Reference category for medication use for emotional and behavioral problems was "did not use medication".
[c] Reference category for parental physical activity was "<1 hour/week".
* indicates $p < .05$.

studies on adults, and that used participants' educational level as a proxy for the socioeconomic environment rather than a measure of parental socioeconomic status.

We also did not find a link between parental physical activity and overweight trajectories nor an interaction with genetic predisposition, although parental activity has been linked to offspring overweight in prior research [16,17]. Parents may be more influential in childhood, whereas in adolescence, young people gain more freedom to select and create environments in accordance with their genetic predispositions. That is, genetic differences between adolescents may affect, for example, the extent to which they spend their free time on sports [38]. Indeed, the effects of genetic predispositions on weight become stronger as people age [4]. Future studies should elucidate the role of parental physical activity as a modifier of genetic predisposition for overweight in childhood to draw informed conclusions about the role of developmental stage.

Despite the usefulness of polygenic scores to disentangle factors associated with trajectories of overweight, the mechanisms through which genetic predisposition is translated into overweight remain unclear. Polygenic scores also currently lack the precision to have clinical utility. As the combination of

environmental and genetic factors places some individuals in disadvantaged positions, understanding how genetic factors operate within young people's environments to influence the development of overweight remains an important avenue for further research.

The longitudinal data and objective measurement of overweight were important strengths of this study, but some limitations need to be acknowledged. First, we considered a limited number of environmental exposures and recognize that other factors, such as the built neighborhood environment, may also play a role. In addition, future research should consider the impact of weight teasing, emotional support, and household sleeping patterns on weight status. Second, we modeled parental activity as the time spent engaging in sports activities but did not consider the frequency with which offspring observed these behaviors. Third, it was not possible to include parental physical activity as a continuous variable due to its categorical measurement in TRAILS. This is a limitation of secondary data analysis. Fourth, we used a polygenic score based on adult BMI which does not capture changes in the genetic architecture of BMI across development [39] nor does it capture all genetic variants that may be specifically associated with overweight status, which was our choice of outcome variable. The explanatory power of the polygenic score likely improves when age-specific polygenic scores are used or when summary statistics obtained from genome-wide association studies for overweight are used to derive the polygenic score, which are currently unavailable. Fifth, we could not account for passive gene-environment correlation, i.e., the possibility that adolescents' genetic predisposition and family environment were correlated because both were inherited from their parents. To tease apart gene-environment correlation effects, we would need parental polygenic scores to test for overlap in parent-offspring genotypes [36]. Finally, our findings cannot be generalized to non-Western contexts, because polygenic scores cannot be compared across populations with different genetic ancestries [8].

Conclusion

Our findings demonstrate that adolescents with a higher genetic predisposition for overweight and from lower socioeconomic status were at an increased risk of following a developmental course characterized by persistent or adolescent onset overweight. Only genetic predisposition was associated with an earlier age at onset. We did not find that genetic predisposition was attenuated in adolescents from higher socioeconomic status or in adolescents with physically active parents. Instead, these findings suggest that genetic predisposition for higher BMI and lower socioeconomic status act as additive risk factors for the development of overweight. Our study underlines the value of a polygenic score approach to differentiate groups of individuals following distinct trajectories of overweight and for studying the joint contributions of genes and environments to traits. The mechanisms through which genetic predisposition for overweight translates into these trajectories and the environments that effectively modify genetic risk, remain areas for future research.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jadohealth.2023.04.028.

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