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ORIGINAL CONTRIBUTION

Polygenic risk for aggressive behavior from late childhood through early adulthood

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Abstract

Twin studies suggest a substantial role for genes in explaining individual differences in aggressive behavior across development. It is unclear, however, how directly measured genetic risk is associated with aggressive behavior at different moments across adolescence and how genes might distinguish developmental trajectories of aggressive behavior. Here, a polygenic risk score derived from the EAGLE-Consortium genome-wide association study of aggressive behavior in children was tested as predictor of latent growth classes derived from those measures in an adolescent population ($n = 2229$, of which $n = 1246$ with genetic information) and a high-risk sample ($n = 543$, of which $n = 335$ with genetic information). In the population sample, the polygenic risk score explained variation in parent-reported aggressive behavior at all ages and distinguished between stable low aggressive behavior and moderate and high-decreasing trajectories based on parent–report. In contrast, the polygenic risk score was not associated with self- and teacher-reported aggressive behavior, and no associations were found in the high-risk sample. This pattern of results suggests that methodological choices made in genome-wide association studies impact the predictive strength of polygenic risk scores, not just with respect to power but likely also in terms of generalizability and specificity.

Keywords Polygenic risk score · Aggressive behavior · Latent class growth model

Aggressive behavior is a common symptom of childhood psychopathology and linked to lower academic performance and social functioning [1], crime involvement [2], substance use [3], and lower earnings [4]. Negative outcomes are particularly common among those who display persistent high levels of aggressive behavior across childhood and adolescence [5, 6]. The etiology of aggressive behavior has been studied extensively in longitudinal and genetically informed designs, alluding to a substantial role for genes to explain individual differences in aggressive behavior across development [7, 8]. Genetic influence is implicated in the stability of aggressive behavior over time [9–11] and is stronger for early-onset persistent antisocial behavior [12] than trajectories with later onset or desisting patterns. Thus far, this field has largely relied on twin samples to estimate the amount of variance in aggressive behavior that is explained by genetic versus environmental factors. This work has been crucial to estimate the heritability of child and adolescent aggressive behavior but studies are needed that explore individual genetic liability. Here, we utilized a polygenic risk score (PRS) to test whether general genetic risk for aggressive behavior predicts developmental variation in the adolescent course, modeled as latent trajectories of aggressive behavior that reflect distinct patterns of onset, persistence, and desistance from childhood to adulthood.

PRSs reflect a person's genetic predisposition for a given phenotype and aggregate information on genetic risk of

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individual genetic variants estimated from genome-wide association studies (GWAS). Derived from the EAGLE-consortium genome-wide association study of children's aggressive behavior [13], associations were reported between a PRS for aggressive behavior (PRS_{AGG}) and behavioral inhibition and negative affectivity in early childhood [14], aggressive behavior in early adolescence [15], and lifetime incarceration risk in males [16]. Shaw and colleagues [17] examined the role of PRS_{AGG} in distinguishing emerging patterns of conduct problems across childhood in a high-risk intervention sample but failed to find an association. Genetic risk might play out at a later stage during development [18] and it is also possible that Shaw et al.'s [17] sample was underpowered ($n = 515$, note that $F = 2.34$, $p = 0.064$ in the ANOVA that tested genetic risk across trajectories). Moreover, variance in aggressive behavior might be differently distributed in population samples than the high-risk sample employed, such that high-risk samples might have a truncated phenotypic variance which could limit the potential for associations with the PRS. To further understand how methodological factors might impact results and learn more about the genetic architecture of development of aggressive behavior, we examined associations between PRS_{AGG} and developmental trajectories from late childhood through early adulthood in a population and a high-risk sample, using the same aggressive behavior measure as in the GWAS from which the PRS_{AGG} was derived. Based on results from twin research, we expected that the PRS_{AGG} would distinguish trajectories, specifically early-onset persistent aggressive behavior from less or only temporarily aggressive trajectories. We conducted analyses not only for parent-reported aggressive behavior to stay close to the GWAS phenotype but also for self- and teacher-reports to explore whether associations between PRS and aggressive behavior extend across different reporters. We controlled for socioeconomic status of the family and child sex as both have been linked to aggressive behavior in prior work [19–21].

Methods

Participants and procedure

The present study includes data from the first six waves of the TRacking Adolescents' Individual Lives Survey (TRAILS), which is a prospective cohort study of Dutch adolescents, with bi- or triennial follow-up assessments. TRAILS consists of a population and high-risk sample: the TRAILS population sample was collected in five municipalities in the north of the Netherlands, including urban and rural areas. Initially, 135 primary schools were approached of which 122 agreed to participate. In brief, 2935 children were invited to participate of whom 2229 (51% female) did so at T1. Data collection at the first assessment wave (T1) took place in 2001 and 2002 (mean age 11.1 years), the second wave (T2) in 2003 and 2004 (mean age 13.6 years), the third wave (T3) in 2006 and 2007 (mean age 16.3 years), the fourth wave (T4) in 2008 to 2010 (mean age 19.1 years), the fifth wave (T5) was conducted in 2012 and 2013 (average age 22.3 years), and the sixth wave took place in 2016 when participants were on average 25.7 years old. Data availability for aggressive behavior measures at every wave is depicted in Table 1, these numbers refer to n's suitable for the analyses conducted in this study, i.e., with parents born in the Netherlands and one sibling per family. Ethics approval for the study was obtained from the Dutch national ethics committee CCMO and both parents and children provided informed consent. Details about the study and attrition have been published in several reports [22–24].

The TRAILS population sample was complemented by a sample selected based on contact with child and adolescent mental health services before age 11. This "high-risk sample" was set up in 2004, with the inclusion of 543 children (response rate 43%). Boys were over-represented (66%), in line with boy/girl ratios for the most common childhood psychopathologies. Comparable to the population sample, follow-up data collection waves occurred at intervals of 2–3 years but lags behind by approximately one assessment wave, which means that T6 is not included in the analyses reported here.

Analyses involving PRS_{AGG} were conducted on the sample of participants for whom genetic data were available and whose parents were both born in the Netherlands as indicated by parents at T1. There were a small number of sibling pairs in the sample, which could bias analyses involving genetic information. Therefore, from each sibling pair, the member with genetic data present was retained, where both siblings missed these data or were genetic data were present for both, one sibling per pair was randomly removed from the analyses sample. Following these adjustment, analyses are based on $n = 1246$ and $n = 335$ from population and high-risk sample, respectively. Participants in the population sample without genetic data were more often male ($\chi^2 = 4.08$, $p = 0.04$), from lower-SES families ($t = -8.62$, $p < 0.001$), and were rated more aggressive by parents ($t = 2.30$, $p = 0.02$) and teachers ($t = 3.27$, $p = 0.001$) at T1, by teachers at T2 ($t = 3.11$, $p = 0.002$), and they rated their own aggressive behavior higher at T6 ($t = 2.29$, $p = 0.02$) than participants for whom genetic data were available. Participants in the high-risk sample without genetic data were more often male ($\chi^2 = 4.98$, $p = 0.03$) from lower-SES families ($t = -2.37$, $p = 0.02$), rated as more aggressive by teachers at T1 ($t = 2.00$, $p = 0.05$) and parents at T5 ($t = 2.17$, $p = 0.03$), and also rated their own aggressive behavior as higher at T5 ($t = 2.01$, $p = 0.05$) than participants for whom genetic data were available. Note that these comparisons are based on

Table 1 Descriptive statistics of aggression assessments across waves and reporters and pairwise correlations with PRS_{AGG} for population and high-risk sample

		n	Population		*n*	High-risk	
			M (SD)	*r* PRS_{AGG} (*p*)		*M (SD)*	*r* PRS_{AGG} (*p*)
	PRS	1246			335		
Reporter	Wave						
Parent	T1	1787	0.34 (0.29)	0.22 (<0.001)	514	0.69 (0.40)	0.09 (0.10)
	T2	1676	0.23 (0.25)	0.14 (<0.001)	436	0.54 (0.39)	0.04 (0.49)
	T3	1343	0.21 (0.25)	0.13 (<0.001)	403	0.45 (0.39)	0.08 (0.14)
	T5	1424	0.16 (0.23)	0.15 (<0.001)	360	0.33 (0.31)	0.05 (0.38)
Self	T1	1865	0.31 (0.25)	0.04 (0.17)	517	0.40 (0.29)	0.05 (0.37)
	T2	1797	0.31 (0.23)	0.02 (0.57)	418	0.39 (0.27)	0.05 (0.36)
	T3	1454	0.31 (0.23)	0.04 (0.15)	405	0.38 (0.26)	0.06 (0.38)
	T4	1494	0.23 (0.25)	0.09 (0.003)	346	0.32 (0.29)	0.03 (0.68)
	T5	1325	0.21 (0.24)	0.03 (0.33)	297	0.28 (0.28)	−0.09 (0.19)
	T6	1177	0.24 (0.25)	0.06 (0.08)	n/a		
Teacher	T1	1628	0.30 (0.48)	0.07 (0.02)	472	0.45 (0.57)	0.04 (0.43)
	T2	1343	0.30 (0.52)	0.02 (0.54)	378	0.48 (0.63)	0.10 (0.10)
	T3	832	0.27 (0.47)	0.10 (0.01)	330	0.42 (0.59)	0.03 (0.66)

Pairwise correlations were computed for available data with exception of participants whose parents were not born in the Netherlands; sample size might thus differ across correlation coefficients. Correlations were computed without accounting for covariates. Correlations between parent- and self-reported aggression ranged from $r = .18$ to $r = .42$ (population sample) and $r = .14$ to $r = .38$ (high-risk sample). Correlations between parent- and teacher-reported aggression ranged from $r = .14$ to $r = .32$ (population sample) and $r = .12$ to $r = .43$ (high-risk sample). Correlations between self- and teacher-reported aggression ranged from $r = .00$ to $r = .26$ (population sample) and $r = .01$ to $r = .35$ (high-risk sample)

data availability for the respective measure. Exact sample sizes per analysis step are provided in the relevant section.

Measures

Polygenic risk score (PRS_{AGG}) Subsamples of both the population and high-risk sample were genotyped at T3 of the study. DNA was extracted from blood samples or, in a small proportion of samples, buccal swabs (Cytobrush; $n = 360$) using a manual salting out procedure as described by Miller, Dykes, and Polesky (1988). Genotyping was performed on the Golden Gate Illumina BeadStation 500 and the Infinium™ HumanCytoSNP-12 v2.1 BeadChip platforms (Illumina Inc., San Diego, CA), according to the manufacturers' protocols. These datasets were merged and checked for genotype concordance. One SNP showed > 5% mismatches and was excluded from the Golden Gate dataset after checking the minor allele frequency with HapMap. In addition, DNA samples that had > 5% missing data, were too heterogeneous, were duplicated or related, or were from non-European descend (as determined by principal component analysis of our samples combined with all 1000G samples) were removed. Genotypes were next imputed using the Haplotype Reference Consortium's global reference panel on the Michigan Imputation server [25, 26]. The PRS_{AGG} was generated as the weighted sum of alleles using LDPred [27] where weights were the effect sizes taken from the child aggressive behavior in the EAGLE GWAS [13] (with the TRAILS sample removed) multiplied by linkage disequilibrium scores as calculated by LDPred from the combined data set of the TRAILS population and high-risk samples. We used the most liberal threshold (*fraction of causal variants* = 1.00), thus included all available SNP. This approach is in keeping with the suggestion that for complex traits such as aggressive behavior full PRS models (i.e., that include all SNP) should capture the genetic architecture most optimally [28]. We z-transformed the PRS_{AGG} prior to analyses to harmonize scaling with other measures and to support model convergence.

Parent-reported (PR) aggressive behavior was assessed using the subscale on Aggressive behavior from the Child behavior Checklist (CBCL, T1-T3) and Adult behavior Checklist (ABCL, T5) [29]. The CBCL Aggressive behavior subscale consists of 18 items including "threatens others", "is mean to others", and "fights a lot", which are rated on a 3-point scale from 0 = does not apply to 2 = definitely applies. The subscale showed good reliability at T1 ($\alpha = 0.86/0.91$ for population and high-risk sample, respectively), T2, ($\alpha = 0.88/0.91$), and T3 ($\alpha = 0.83/0.93$). The ABCL Aggressive behavior subscale consists of 16 items that largely resemble those in the CBCL and also showed good reliability ($\alpha = 0.88/0.88$).

Self-report (SR) aggressive behavior was assessed using the Youth Self Report (YSR, T1-T3) and Adult Self-Report (ASR, T4-T6) [29]. The YSR Aggressive behavior subscale consists of 17 items including "I fight a lot" and "I am mean to others", which are rated on a 3-point scale from 0 = does not apply to 2 = definitely applies. The subscale showed good reliability at T1 ($\alpha = 0.82/0.84$ for population and high-risk sample, respectively), T2 ($\alpha = 0.80/0.82$), T3 ($\alpha = 0.81/0.81$). The ASR consists of 15 items that largely resemble those in the YSR and showed good reliability at T4 ($\alpha = 0.85/0.85$), T5 ($\alpha = 0.84/0.84$), and T6 ($\alpha = 0.84$; note that T6 data are not yet available for the high-risk sample).

Teacher-report (TR) aggressive behavior was assessed at T1, T2, and T3 using the Teacher's Checklist of Psychopathology, a shortened version of the Teacher's Report Form [30] which was developed for TRAILS to diminish the burden for teachers in comparison to completing the full report [31]. The TCP assesses nine problem domains including aggressive behavior, for which example behaviors that resemble those in the CBCL/ABCL and YSR/ASR are listed. Teachers rated each child's behavior on a scale from 0 = does not apply at all to 4 = definitely applies; these scores were recoded such that 1 = 0.5 and 3 = 1.5 to ensure the same range as for parent- and self-reports.

Covariates

Next to child *Sex* and *Age at T1*, we controlled for family socioeconomic status (SES). *Family SES* was constructed from mothers' and fathers' educational and occupational levels and family income as measured at T1. Educational level of parents was coded in five categories based on the International Standard Classification of Occupations [32]. Disposable family income was measured on a scale ranging from less than €680 (1) to more than €3857 (9). Family SES was consequently operationalized as the average of the standardized five items ($\alpha = 0.84$); this indicator is commonly used in TRAILS analyses [33]. Finally, ten principal components were added to regression models to account for population stratification.

Analytic strategy

We first examined pairwise correlations between PRS_{AGG} and parent-, self-, and teacher-reported aggressive behavior across all waves. Second, we fit latent class growth models[1] of aggressive behavior based on parent-reports. All available data points were considered, we thus included all participants for whom data from at least on assessment was available. We estimated intercepts, linear slopes, and quadratic effects and increased the number of classes subsequently, comparing Bayesian Information Criterion (BIC, lower values indicate better fit), entropy (higher values indicate better classification), and class size (classes with fewer than 5% of participants are undesirable) across models with varying number of classes. We continued to increase the number of classes until the Lo–Mendell–Rubin adjusted likelihood ratio test (LMR-LRT) returned a non-significant difference. Third, we used multinomial logistic regression to calculate the relative risk of classification into one class over a comparison class as a function of PRS_{AGG}. Relative risk ratios (*RRR*) are interpreted like odd's ratio such that a $RRR = 1$ indicates that PRS_{AGG} is not associated with trajectory class, $RRR < 1$ indicates that higher PRS_{AGG} is associated with lower likelihood for a certain trajectory class compared to the reference group, and $RRR > 1$ indicates that higher PRS_{AGG} is associated with higher likelihood for a trajectory class compared to the reference group. Regression models were weighted for classification uncertainty. Fourth, we fit latent class growth models based on self- and teacher-reports of aggressive behavior, following the same model fit comparison strategies as for parent-reported aggressive behavior, and computed multinomial logistic regressions as described. We estimated trajectories on the combined population and high-risk sample and also included participants for whom PRS_{AGG} was not available to increase the sample size for this analytic step and cover the full range of aggression symptoms but conducted subsequent analyses separately for population and high-risk samples.

Results

Means and standard deviations for all measures of aggressive behavior are presented in Table 1, as are correlations between measures of aggressive behavior and PRS_{AGG}. Participants in the high-risk sample scored higher on all aggression measures than participants in the population sample (*t*'s ranging from 4.16 to 22.13, all $p < 0.001$). In the population sample, the PRS_{AGG} was associated with parent-reported aggressive behavior at all waves, T4 self-reported aggressive behavior and T1 and T3 teacher-reported aggressive

[1] We computed growth mixture models (GMM, which allow for within-class variance) and latent class growth models (LCGM, which restrict within-group variance of intercept and slope to zero) with the aim to compare model fit between both types. However, GMM did not converge in all cases, owing to non-positive covariance matrices. For this reason, we moved forward with the more restrictive yet easier to model latent class growth models. We also computed more parsimonious models with intercept and slope but without quadratic effect, however, quadratic means and variances were statistically significant in most models, thus for consistency we moved forward with quadratic models.

Table 2 Model fit of latent class growth models with varying number of classes based on self-, parent-, and teacher-reported aggression and models based on multiple reporters

	BIC	LMR-LRT p	Entropy	Class sizes (%)
Parent-reported				
2 classes	628.24	< 0.001	0.90	19, 81
3 classes	**− 539.82**	**< 0.001**	**0.86**	**8, 25, 67**
4 classes	− 891.95	0.06	0.84	6, 7, 19, 67
Self-reported				
2 classes	− 1291.66	< 0.001	0.78	23, 77
3 classes	− 1795.42	< 0.001	0.76	5, 27, 68
4 classes	**− 2214.97**	**0.007**	**0.75**	**5, 12, 18, 65**
5 classes	− 2492.65	< 0.001	0.75	4, 4, 16, 19, 57
6 classes	− 2628.86	< 0.001	0.72	4, 4, 9, 12, 15, 57
7 classes	− 2736.43	< 0.001	0.70	3, 4, 5, 7, 12, 15, 55
8 classes	− 2769.76	0.24	0.71	2, 2, 3, 5, 7, 12, 15, 53
Teacher-reported				
2 classes	7067.18	< 0.001	0.87	18, 82
3 classes	6391.66	< 0.001	0.82	13, 19, 67
4 classes	**5886.44**	**< 0.001**	**0.87**	**7, 9, 10, 73**
5 classes	5401.66	0.50	0.86	0, 4, 12, 16, 67

Self-report models are based on $n = 2769$, parent-report models are based on $n = 2705$, and teacher-report models are based on $n = 2706$. Class sizes are based on final class counts based on most likely class membership

behavior. The PRS_{AGG} was not associated with aggressive behavior in the high-risk sample, regardless of informant.

PRS as predictor of parent-reported aggressive behavior trajectories

Parent-reported aggressive behavior trajectories are based on assessments from T1–T3 and T5, $n = 2705$. The upper part of Table 2 contains model fit for models with two to four trajectory classes. Although BIC continued to decrease for the 4-class compared to 3-class model, the LMR-LRT suggested that the additional class did not significantly improve model fit ($p = 0.06$). To account for this ambiguity, we moved forward with the 3-class model but also conducted supplementary analyses based on a 4-class model. Figure 1a depicts original parent-reported aggression scores based on most likely class membership and indicates that the largest group showed low levels of aggression (67%, "Low-Stable"), approximately one in four participants followed a moderate trajectory of aggressive behavior with a decreasing trend (25%, "Moderate-Decreasing") and a small group showed initially high but decreasing levels of aggressive behavior (8%, "High-Decreasing").

Table 3 depicts results from multinomial logistic regressions. In the population sample, PRS_{AGG} differentiated the Low-Stable trajectory class from Moderate-Decreasing and High-Decreasing classes such that higher genetic risk was associated with an increased likelihood of aggressive behavior in late childhood and early adolescence. PRS_{AGG} also differentiated the High-Decreasing and Moderate-Decreasing trajectory, with relative risk ratios of similar magnitude as those involving the Low-Stable group though note that this effect would not be significant anymore if Bonferroni-correction for multiple testing would be applied. In the high-risk sample, PRS_{AGG} did not distinguish between trajectories.

PRS as predictor of self-reported aggressive behavior trajectories

The middle part of Table 2 contains fit indices for models based on self-reported aggressive behavior (T1-T6, $n = 2769$). The BIC continued to decrease and the LMR-LRT continued to indicate significant improvements in model fit upon adding classes, up to seven classes. Entropy decreased as classes were added. We thus based our decision on meaningful group size, earlier determined to be at least 5% of the total sample and moved forward with the 4-class model. Figure 1b depicts original self-reported scores based on most likely class membership and indicates that most individuals followed a stable low trajectory of aggressive behavior (65%, "Low-Stable"). Two smaller groups were detected, showing initially low but increasing aggressive behavior (18%, "Moderate-Increasing"), as well as initially high but decreasing aggressive behavior (12%, "High-Decreasing"). Finally, a small group showing increasing aggressive behavior on a high level was found (5%, "High-Increasing"). PRS_{AGG} did

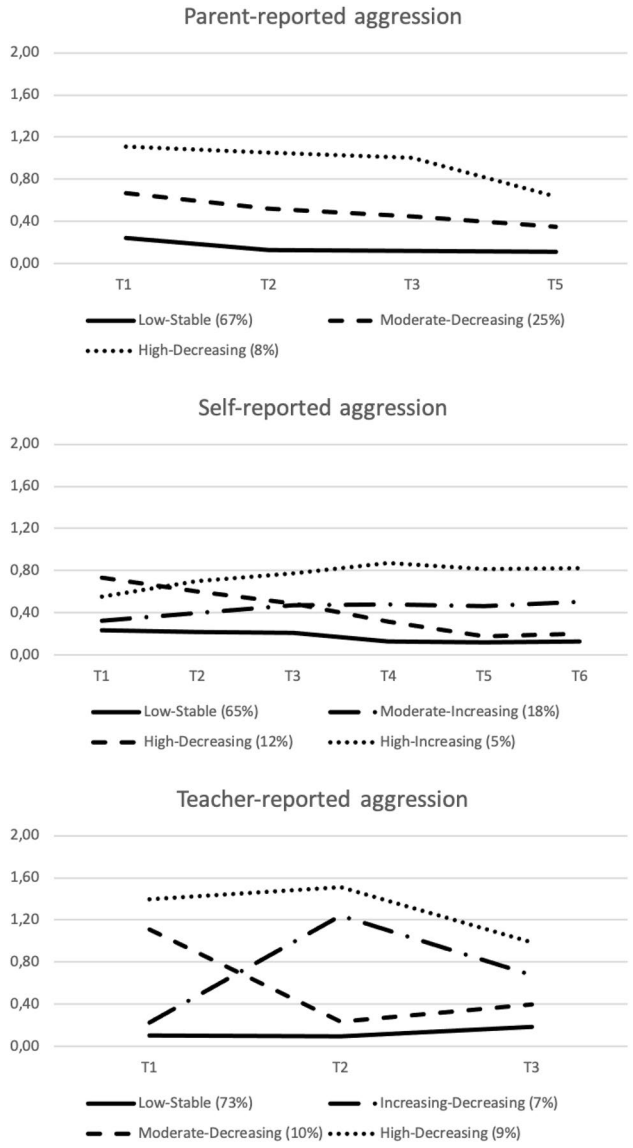

Fig. 1 **a–c** Trajectories of aggressive behavior based on parent-, self-, and teacher-report

not predict trajectory class membership, for neither sample (Supplementary Tables 1a and 1b).

PRS as predictor of teacher-reported aggressive behavior trajectories

The lower part of Table 2 contains model fit for models based on teacher-reported aggressive behavior T1–T3 ($n = 2706$). Although BIC continued to decrease for the 5-class compared to 4-class model, the LMR-LRT suggested that the additional class did not significantly improve model fit and convergence issues suggested model non-identification as well, probably due to the small number of available assessment waves for teachers. We thus selected the 4-class model for subsequent analyses. Figure 1c depicts original teacher-reported scores based on most likely class membership and indicates that the largest group showed low aggressive behavior (73%, "Low-Stable"), one in ten individuals started out with elevated levels of aggressive behavior but decreased substantially (10%, "Moderate-Decreasing"), 9% showed high levels of aggressive behavior with some decrease toward age 16 (9%, "High-Decreasing"), and a small group followed an initially increasing and then decreasing trajectory (7%, "Increasing–Decreasing"). The PRS_{AGG} predicted trajectory class membership for the comparison between the Increasing–Decreasing and Moderate-Decreasing trajectories in in the population sample but no other associations were found, also not for the high-risk sample (Supplementary Tables 2a and 2b).

A number of supplementary analyses were carried out to examine patterns of results under different conditions, and these can be found in the Supplementary Analyses.

Discussion

Quantitative genetic analyses have repeatedly suggested that child and adolescent aggressive behavior is genetically influenced and that genes also play an important role in explaining stability and changes over time [9–11]. Recent work has explored the role of polygenic risk scores for individual variation in phenotypes related to aggressive behavior and developmental variation in aggressive behavior, with inconclusive findings [15, 17]. Here, we built on longitudinal data and information from different informants from a population as well as from a high-risk sample to clarify the role of PRS_{AGG} for the development of aggressive behavior. We expected that the PRS_{AGG} would distinguish developmental trajectories, specifically early-onset persistent aggressive behavior from less or child-limited aggressive developmental groups [9–12].

In models based on parent-reports and population sample data, PRS_{AGG} distinguished between developmental trajectories such that higher genetic risk for aggressive behavior was linked to greater risk for following an elevated trajectory, both in the 3- and in the 4-class model. The 3-class model essentially depicts different levels of aggressive behavior rather than qualitatively distinct patterns and both the moderate-decreasing and high-decreasing trajectory were more common among adolescents with higher genetic risk. A "dose–response" relationship could be observed in the 4-class model where PRS_{AGG} also distinguished the moderate (i.e., increasing and decreasing) from Low and High-Decreasing aggression trajectories; this association just failed to reach statistical significance at $p < 0.05$ in the 3-class model. We were particularly interested in whether genetic risk would distinguish a trajectory of

Table 3 Prediction of parent-reported aggression trajectory class membership

	Low-Stable vs. High-Decreasing			Moderate-Decreasing vs. High-Decreasing			Low-Stable vs. Moderate-Decreasing		
	RRR	*P*	95% CI	RRR	*p*	95% CI	RRR	*p*	95% CI
Population sample									
Sex	1.52	0.24	0.76/3.06	1.39	0.38	0.67/2.86	1.10	0.52	0.82/1.47
Age	0.71	0.25	0.40/1.27	0.75	0.35	0.40/1.37	0.95	0.71	0.73/1.23
SES	0.30	< 0.001	0.19/0.46	0.44	< 0.001	0.28/0.69	0.68	< 0.001	0.56/0.82
PRS	1.97	< 0.001	1.35/2.86	1.53	0.03	1.03/2.25	1.29	0.002	1.10/1.51
High-risk sample									
Sex	1.84	0.09	0.92/3.68	1.32	0.44	0.65/2.68	1.39	0.26	0.78/2.49
Age	0.81	0.51	0.43/1.52	0.77	0.41	0.41/1.44	1.05	0.87	0.60/1.82
SES	0.44	0.001	0.27/0.71	0.82	0.39	0.53/1.28	0.54	0.002	0.36/0.80
PRS	1.06	0.75	0.76/1.47	0.82	0.20	0.61/1.11	1.29	0.09	0.96/1.72

The first-named class served as reference category. *RRR* Relative Risk Ratios. Analyses were based on $n = 1229$ population and $n = 334$ high-risk sample participants. Ten principal components were included in all analyses

aggressive behavior with persistently high symptoms from late childhood through young adulthood, as these children are at greatest risk for future maladjustment: overall, higher genetic predisposition indeed appears to be linked to higher risk for such a developmental course compared to stable low or more moderate levels of aggressive behavior.

We did not find associations with PRS_{AGG} when self- and teacher-reports of aggressive behavior were used. It is possible that parents' perceptions better captured within-person stability and trait-aspects of aggression that might be more strongly associated with genetic factors. Parents might take past behavior into account whereas teachers' assessments were completed by a different person each year. It is also possible that self- and teacher-reports are more environmentally influenced as they likely are more "relative", that is, derived from comparison to other adolescents than reports by parents. In line, a meta-analysis of genetic and environmental influence on antisocial behavior showed that heritability was lower when self-reports compared to reports by others[2] were used [8]. Overlap between reporters was modest but in line with other studies [21], which further suggests that perceptions of aggressive behavior are not universal across reporters but differ according to a number of factors, including context.

Associations between the PRS_{AGG} and trajectories were also not found for the high-risk sample. Although this finding replicates earlier absence of association in another high-risk sample [17], it seems counterintuitive and might suggest that this PRS_{AGG}—derived from population samples [13]—might not capture individual variation in a more extreme or non-normative range very well or that variation in the phenotype is insufficient or truncated in high-risk samples. Density plots of raw scores (Supplementary Fig. 2) suggest differences in the distribution at least for parent-reported aggressive behavior with greater skew toward very low values in the population cohort and a more balanced distribution across possible scores in the high-risk cohort. Another explanation might be that the PRS distinguishes between very low and elevated levels of aggressive behavior and that such very low levels are not present in the high-risk cohort. Of note, whereas low levels of aggressive behavior were most normative in the population cohort (75% of adolescents fell into this class), only 36% of adolescents in the high-risk cohort showed stable low levels of aggressive behavior. On a related point, it might be that the EAGLE GWAS benefited from a wider range of aggressive behaviors and included children at all levels of the phenotypic distribution in their aggregated sample composed of nine population-based cohorts. This might have increased their power to detect small incremental changes in genetic risk as aggression scores increased. The available power to detect these small incremental genetic effects may not have be sufficient across the phenotypic distribution in our high-risk sample. Differences between parent-reported aggressive behavior in the population cohort and all other assessments are already visible when inspecting plots of explained variance at increasing p-thresholds for SNP inclusion (Supplementary Fig. 3)—whereas the amount of explained variance in parent-reported aggressive behavior (population cohort) increases as the p-threshold of inclusion is lowered and additional SNP are included in the PRS construction, prediction remains non-significant and low for all other assessments, even at the most liberal threshold.

[2] The meta-analysis did not differentiate between parent- and teacher-report in moderation analyses but the vast majority of studies using "other" report were based on parent-reports.

Taken together, the findings in this paper raise some questions with regard to available GWAS-derived polygenic risk scores. That is, the PRS as used here has been derived from a GWAS in which only parent-reports were used and which was based on population samples. When these characteristics were met in our analyses, significant associations were found, regardless of how the trajectory model was specified. As such, PRS_{AGG} predicted the phenotype on which the GWAS was based—parent-reported aggressive behavior in a population sample—but hardly otherwise. A PRS that reflects genetic risk for a phenotype more broadly, across informants and contexts, could be more useful. Would it thus be advisable to conduct GWAS on a greater diversity of assessments? Already now, GWAS often pool quite different samples to increase statistical power. The GWAS from which the PRS_{AGG} was derived, for instance, included children from age 8 to 15, i.e., quite distinct developmental periods, with potentially different genetic and environmental factors underlying aggressive behavior. It is likely that the predictive capacity of the PRS might be negatively affected if GWAS include samples that are highly diverse in terms of measurement of the phenotype, in that the PRS loses specificity if pooling is based on the smallest common denominator. That said, recent work illustrates that pooling data across different genetically related traits increases sample sizes and power for GWAS dramatically [34] and, by consequence, might improve the predictive power of a PRS. Such a more general score indexes genetic liability to a broader phenotype such as externalizing behavior. Following similar reasoning, it is possible that a PRS for aggressive behavior based on assessments from multiple reporters—which thus covers more dimensions of the phenotype—could have explained variance in self- and teacher-reports. Like with reducing specificity through widening the phenotype, a trade-off may be that the inclusion of additional informants increases the nonspecific nature of the PRS [35].

Despite the several strengths of this study including being based on a large sample and longitudinal multi-reporter data that span adolescence and early adulthood, some limitations need to be noted. First, parent- and teacher-reports were not available for all time points which might have impacted the modeling of latent growth classes. That said, it is not common to collect teacher information beyond age 17 and parent-report information was included even for the 22 years' assessment, which is also not common. Second, latent class growth modeling where variance within classes is constrained is sometimes considered to be more biased than growth mixture modeling where within-class variance is modeled [36]. However, the latter is computationally much more demanding and caused convergence issues in the present study. Third, genetic data were not available for the full sample, which reduced the sample size for analyses involving PRS_{AGG}. Fourth, understanding the genetic risk associated with most extreme aggression would have required identifying those participants who are rated as stably aggressive by parents, teachers, and themselves. Convergence could not be achieved for such a computationally intensive second-order model in exploratory analyses, likely because of modest interrater correlations that indicate that different reports should not actually be combined. Fifth, the GWAS on which PRS_{AGG} was based is relatively small ($N < 20{,}000$). This might have impacted results as the predictive value of a PRS depends on the GWAS sample size as impressively demonstrated for the PRS for educational attainment [37], which has also been linked to aggressive behavior across childhood [38] and persistent elevations in symptoms of conduct problems [39].

To conclude, associations between PRS_{AGG} and parent-reported aggressive behavior underline the value of polygenic risk scores for better understanding the genetic architecture of a behavior in non-twin, population samples. However, caution is warranted with respect to the integration of polygenic risk scores in research on child development and psychopathology as divergent findings suggest that effect sizes might depend quite substantially on the equivalence of the GWAS and study phenotype.

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Code availability Syntax files for latent class growth models and subsequent multinomial logistic regressions are deposited on the Open Science Framework.

Declarations

Conflict of interest None.

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