

Direct and Indirect Genetic Effects on Aggression

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ABSTRACT

BACKGROUND: Family members resemble each other in their propensity for aggression. In twin studies, approximately 50% of the variance in aggression can be explained by genetic influences. However, if there are genotype-environment correlation mechanisms, such as environmental manifestations of parental and sibling genotypes, genetic influences may partly reflect environmental influences. In this study, we investigated the importance of indirect polygenic score (PGS) effects on aggression.

METHODS: We modeled the effect of PGSs based on 3 genome-wide association studies: early-life aggression, educational attainment, and attention-deficit/hyperactivity disorder (ADHD). The associations with aggression were tested in a within- and between-family design (37,796 measures from 7740 individuals, ages 3–86 years [mean = 14.20 years, SE = 12.03], from 3107 families, 55% female) and in a transmitted/nontransmitted PGS design (42,649 measures from 6653 individuals, ages 3–61 years [mean = 11.81 years, SE = 8.68], from 3024 families, 55% female). All participants are enrolled in the Netherlands Twin Register.

RESULTS: We found no evidence for contributions of indirect PGS effects on aggression in either a within- and between-family design or a transmitted/nontransmitted PGS design. Results indicate significant direct effects on aggression for the PGSs based on early-life aggression, educational attainment, and ADHD, although explained variance was low (within- and between-family: early-life aggression $R^2 = 0.3\%$, early-life ADHD $R^2 = 0.6\%$, educational attainment $R^2 = 0.7\%$; transmitted/nontransmitted PGSs: early-life aggression $R^2 = 0.2\%$, early-life ADHD $R^2 = 0.9\%$, educational attainment $R^2 = 0.5\%$).

CONCLUSIONS: PGSs included in the current study had a direct (but no indirect) effect on aggression, consistent with results of previous twin and family studies. Further research involving other PGSs for aggression and related phenotypes is needed to determine whether this conclusion generalizes to overall genetic influences on aggression.

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Aggression is behavior that aims to cause harm to others (1,2). Aggression is relatively common, but the propensity for such behavior varies between individuals. It is well established that family members resemble each other in their propensity for aggression (3–9). This resemblance is the result of family influences and is related to the psychosocial environment, socioeconomic circumstances, and genes (10,11). Because family members share both their environment and their genes, it is difficult to disentangle effects of environment and genes (12). This can only be achieved if the question is addressed using a study design that includes family members with different degrees of genetic relatedness, such as adoption or twin studies, or in a design with different degrees of environmental relatedness, such as genetically related individuals reared together versus apart.

Twin studies suggest that clustering of aggression in families is predominantly due to genetic effects because approximately 50% of the variance in aggression can be explained by genetic variance, and only a very small amount can be explained by shared environmental influences,

i.e., environmental influences that lead to phenotypical similarities between twins (7,13). However, twin and adoption studies come with assumptions, including that genetic and environmental effects are uncorrelated. There are 3 ways in which correlations between genotype and environment can be induced, through active gene-environment correlation (rGE), evocative rGE , and passive rGE . Active rGE occurs when a person seeks out an environment based on his or her genotype, evocative rGE occurs when environmental responses are evoked based on a genotype, and passive rGE can occur when the environment in which parents raise their children is partly dependent on parental genotypes (12,14,15). Because offspring inherit their genotype from their parents and are exposed to the rearing environment created by their parents, a correlation between genotype and environment can be induced. The result is that genetic effects may partly reflect environmental influences, i.e., indirect genetic effects. In a twin study, passive rGE would be captured in shared environmental influences, which are often very small (13,16). This suggests that passive rGE does not play an important role in aggression.

Direct and Indirect Genetic Effects on Aggression

However, in a review article, Labella and Masten (17) reported many family factors that may influence aggression intergenerationally, including partner violence from prenatal stages onward. This could mean that *rGE* plays a role if these effects are due to environmental influences that are driven by parental genotypes that are correlated with offspring genotype. This led us to test for *rGE* effects on aggression directly using 2 polygenic score (PGS) designs.

Polygenic Scores

In this study, we used PGSs to separate direct and indirect genetic effects on aggression. PGSs are the sum of trait-associated alleles (coded 0, 1, or 2 for the presence of a risk-increasing allele) across the genome, weighted by their effect size. Genome-wide association studies (GWASs) have identified robust associations between tens of thousands of single base pair variants (single nucleotide polymorphisms [SNPs]) and complex phenotypes (18,19). Individual SNP effects on most complex human traits tend to be small, but as the power of GWASs grows (20), so does our ability to combine the effect of multiple SNPs and construct genome-wide PGSs that are related to complex traits. As such, PGSs are dependent on well-powered, high-quality GWAS results. Because SNP heritability is often much lower than the heritability estimated in twin and family studies, we know that we are only capturing a fraction of all genetic effects in PGSs. The PGSs in the current study were based on results from GWASs of early-life aggression (EL-AGG), educational attainment (EA), and attention-deficit/hyperactivity disorder (ADHD). The PGSs of EL-AGG are based on the largest GWAS on aggression conducted to date, with an effective sample size of $N = 151,741$ ($h^2_{\text{SNP}} = 0.03$) (21). A previous study demonstrated that a PGS of EL-AGG also predicts aggression in adults (22). We also included PGSs of ADHD (23) because Ip *et al.* (21) found a high genetic correlation between ADHD and childhood aggression, $rg = 1.00$ (SE = 0.07). The effective sample size and SNP heritability, i.e., the variance in ADHD explained by SNP variance ($h^2_{\text{SNP}} = 0.22$), are much larger than in the EL-AGG GWAS, indicating more statistical power. Finally, we included a PGS of EA based on one of the most highly powered GWASs of a behavioral phenotype conducted to date ($h^2_{\text{PGS}} = 0.09$ – 0.12) (24). Aggression has been associated with academic performance (25), and a genetic correlation of $rg = -0.50$ (SE = 0.04) was estimated (21). SNP heritability is much smaller than heritability estimated in twin and family studies, indicating that we are only capturing a small part of genetic influences in PGSs.

Transmitted and Nontransmitted PGSs

The environment in which parents raise their children is partly dependent on parental genotypes. If information is available on parental and offspring genotypes, it is possible to distinguish between direct effects of genetic intergenerational transmission and indirect genetic effects through the rearing environment (16,17,26). Two PGSs are calculated: a transmitted PGS that reflects the inherited genetic variants that increase the propensity for a certain trait, and a nontransmitted PGS that reflects indirect genetic effects, i.e., effects of genetic variants that were not transmitted from parents to offspring but

which may influence the outcome in offspring through environmental influences. Nontransmitted genetic effects have previously been demonstrated for traits such as EA (16,17,26). However, results from studies on other child internalizing problems have produced mixed results for depression and found no indirect effects of PGSs on child anxiety (27–29).

Within- and Between-Family Analyses

An alternative way to separate direct and indirect genetic effects is to use a within- and between-family (WB) design. Whereas the transmitted/nontransmitted (TNT) PGS design depends on the availability of genotyped parent-offspring families, a WB design depends on the availability of genotyped siblings and dizygotic (DZ) twins. Siblings and DZ twins share on average 50% of their genotypes (30,31). Unlike unrelated individuals, siblings and DZ twins share many potential confounding factors. Confounding may occur when factors in the family environment are associated with both the predictor and the outcome trait. By modeling the effect of PGSs on aggression in a within-family design, we can test for an association between the PGSs and aggression while eliminating many potential confounding influences from the family environment (15,32). This means that if the WB effects are equal, we can conclude that we find no evidence of PGS effects reflecting family environment effects. If the within-family effects are smaller, we can conclude that PGS effects reflect confounding effects from the family environment.

The Current Study

In this study, we investigated whether direct and indirect PGS effects play a role in the familial clustering of aggression. We tested the hypotheses that 1) there is an association between the transmitted PGSs and aggression at the population level (between-family), 2) there is an association between the transmitted PGSs and aggression within families, and 3) there is an association between the nontransmitted PGSs and aggression. If a difference is observed between the within- and the between-family associations or if an association is observed between the nontransmitted PGSs and aggression, this may indicate that indirect genetic effects drive part of the between-family PGS effects.

METHODS AND MATERIALS

Participants

All participants were enrolled in the Netherlands Twin Register (NTR) by their parents at birth or contacted through city councils (33). Consent was obtained from all participants, or, for children, from their parents. All participants were twins or family members of twins and were phenotyped by parent-, teacher-, or self-report. For siblings of young twins, phenotyping mainly came from teacher reports. For adult twins and family members, phenotyping came from self-report. See Table 1 for an overview of the data collections, with phenotyping sample sizes, ages, and item-response theory (IRT) (34) aggression scores. Some participants were included in multiple data collections (Tables S1 and S3). For a complete overview of the data collection and recruitment strategies, see Ligthart *et al.* (33).

Table 1. Descriptive Statistics Phenotyping Sample: *n*, Age, and Aggression by Sex for Each Data Collection

Measure	No. Obs	No. Pers	No. Fam	Age, Years	IRTagg	Males			Females		
						<i>n</i>	Age, Years	IRTagg	<i>n</i>	Age, Years	IRTagg
TRF Age 5	1132	1132	641	5.58 (0.51)	0 (0.84)	561	5.57 (0.52)	0.17 (0.90)	571	5.60 (0.50)	-0.16 (0.74)
TRF Age 7	8891	8890	4946	6.96 (0.23)	0 (0.83)	4386	6.96 (0.23)	0.17 (0.90)	4505	6.96 (0.22)	-0.17 (0.71)
TRF Age 10	20,412	18,187	9630	9.07 (0.86)	0 (0.84)	10,155	9.06 (0.86)	0.18 (0.90)	10,252	9.09 (0.86)	-0.17 (0.72)
TRF Age 12	14,809	13,966	7812	12.00 (0.63)	0 (0.83)	7347	12.01 (0.63)	0.17 (0.90)	7455	11.99 (0.63)	-0.17 (0.71)
CBCL F Age 3	26,313	26,313	13,197	3.38 (0.50)	0 (0.94)	13,152	3.38 (0.50)	0.09 (0.95)	13,158	3.37 (0.49)	-0.09 (0.91)
DCB F Age 5	31,771	31,771	15,832	5.49 (0.66)	0 (0.87)	15,725	5.49 (0.65)	0.10 (0.89)	16,040	5.48 (0.66)	-0.10 (0.84)
CBCL F Age 7	17,883	17,883	8941	7.41 (0.49)	0 (0.90)	8950	7.42 (0.49)	0.11 (0.93)	8927	7.40 (0.49)	-0.11 (0.86)
CBCL F Age 10	16,215	15,674	7843	9.96 (0.59)	0 (0.89)	8019	9.96 (0.60)	0.10 (0.93)	8192	9.95 (0.59)	-0.10 (0.85)
CBCL F Age 12	12,341	12,299	6166	12.28 (0.48)	0 (0.88)	6047	12.28 (0.48)	0.08 (0.92)	6290	12.29 (0.48)	-0.07 (0.84)
CBCL M Age 3	38,877	38,877	19,451	3.36 (0.49)	0 (0.94)	19,376	3.36 (0.49)	0.11 (0.96)	19,493	3.36 (0.49)	-0.11 (0.91)
DCB M Age 5	35,666	35,666	17,779	5.49 (0.66)	0 (0.86)	17,687	5.49 (0.65)	0.11 (0.90)	17,973	5.49 (0.67)	-0.11 (0.82)
CBCL M Age 7	25,306	25,306	12,661	7.43 (0.50)	0 (0.91)	12,623	7.43 (0.50)	0.12 (0.94)	12,675	7.42 (0.49)	-0.12 (0.87)
CBCL M Age 10	23,357	22,586	11,309	9.95 (0.62)	0 (0.91)	11,560	9.95 (0.63)	0.11 (0.94)	11,792	9.95 (0.62)	-0.11 (0.86)
CBCL M Age 12	17,535	17,457	8735	12.29 (0.47)	0 (0.90)	8662	12.28 (0.47)	0.08 (0.93)	8868	12.30 (0.48)	-0.08 (0.85)
YSR Age 14	8672	8551	4791	14.64 (0.59)	0 (0.87)	3718	14.65 (0.60)	0.04 (0.91)	4951	14.63 (0.59)	-0.03 (0.84)
YSR Age 16	7898	7293	4319	16.70 (0.46)	0 (0.87)	3308	16.7 (0.46)	0.01 (0.91)	4587	16.7 (0.46)	-0.01 (0.83)
YSR Age 18	4384	4099	2594	18.74 (0.91)	0 (0.84)	1675	18.70 (0.90)	0.02 (0.89)	2708	18.76 (0.91)	-0.01 (0.82)
SR 1991	3327	3327	1668	17.95 (2.24)	0 (0.86)	1501	17.93 (2.25)	-0.05 (0.90)	1826	17.97 (2.24)	0.04 (0.82)
SR 1995	3344	3344	1708	19.98 (3.10)	0 (0.85)	1477	19.96 (3.09)	-0.06 (0.88)	1866	19.99 (3.11)	0.05 (0.83)
SR 1997	4715	4715	1999	26.73 (10.46)	0 (0.85)	1903	26.27 (10.52)	-0.04 (0.86)	2812	27.05 (10.41)	0.03 (0.85)
SR 2000	6702	6702	3172	30.49 (10.78)	0 (0.85)	2514	30.3 (10.45)	-0.06 (0.85)	4183	30.6 (10.98)	0.04 (0.85)
SR 2009	15,048	15,048	6805	41.49 (15.40)	0 (0.85)	5353	43.53 (15.89)	-0.11 (0.80)	9693	40.36 (15.00)	0.06 (0.88)
SR 2014	16,203	16,203	7630	40.19 (14.62)	0 (0.85)	5838	42.04 (15.09)	-0.11 (0.79)	10,362	39.15 (14.24)	0.06 (0.88)
Total	360,801	83,027	33,653	11.57 (11.50)	0 (0.89)	171,541	10.75 (10.72)	0.09 (0.92)	189,180	12.32 (12.11)	-0.08 (0.85)

Values are presented as *n* or mean (SD).

CBCL, Child Behavior Checklist; DCB, Devereux Child Behavior Rating Scale; F, father report; IRTagg, item-response theory aggression score; M, mother report; No. Fam, number of families; No. Obs, number of observations; No. Pers, number of participants; SR, self-report; TRF, Teacher Report Form; YSR, Youth Self-Report.

Table 2. Descriptive Statistics Within- and Between-Family Sample: *n*, Age, and Aggression by Sex for Each Instrument

Measure	No. Pers	No. Fam	Age, Years	IRTagg	Males			Females		
					<i>n</i>	Age, Years	IRTagg	<i>n</i>	Age, Years	IRTagg
TRF Age 5	140	70	5.79 (0.41)	-0.09 (0.79)	70	5.74 (0.44)	0.09 (0.88)	70	5.83 (0.38)	-0.27 (0.66)
TRF Age 7	1384	609	7.75 (1.10)	-0.05 (0.80)	692	7.76 (1.13)	0.12 (0.86)	692	7.74 (1.07)	-0.23 (0.68)
TRF Age 10	1492	685	9.92 (0.89)	0 (0.83)	721	9.90 (0.88)	0.16 (0.91)	771	9.94 (0.91)	-0.15 (0.72)
TRF Age 12	1091	529	12.08 (0.79)	-0.01 (0.84)	518	12.10 (0.74)	0.19 (0.92)	573	12.07 (0.83)	-0.19 (0.72)
CBCL F Age 3	1890	937	3.38 (0.49)	-0.06 (0.96)	914	3.40 (0.50)	0.00 (0.98)	976	3.36 (0.49)	-0.11 (0.94)
DCB F Age 5	2384	1183	5.59 (0.75)	0.06 (0.88)	1136	5.62 (0.77)	0.15 (0.89)	1248	5.56 (0.73)	-0.02 (0.86)
CBCL F Age 7	1937	963	7.43 (0.57)	0.02 (0.90)	924	7.43 (0.57)	0.12 (0.93)	1013	7.42 (0.57)	-0.08 (0.87)
CBCL F Age 10	1956	972	9.91 (0.68)	-0.01 (0.89)	940	9.91 (0.68)	0.05 (0.93)	1016	9.90 (0.68)	-0.06 (0.85)
CBCL F Age 12	1416	703	12.16 (0.45)	0.01 (0.89)	660	12.15 (0.44)	0.08 (0.95)	756	12.17 (0.47)	-0.05 (0.82)
CBCL M Age 3	2524	1253	3.35 (0.49)	-0.05 (0.98)	1215	3.37 (0.49)	0.04 (0.98)	1309	3.33 (0.48)	-0.14 (0.97)
DCB M Age 5	2524	1252	5.59 (0.74)	0.04 (0.87)	1211	5.63 (0.76)	0.13 (0.90)	1313	5.56 (0.72)	-0.05 (0.84)
CBCL M Age 7	2343	1165	7.43 (0.56)	0 (0.93)	1128	7.43 (0.57)	0.10 (0.97)	1215	7.42 (0.56)	-0.09 (0.89)
CBCL M Age 10	2461	1222	9.92 (0.70)	-0.02 (0.92)	1178	9.93 (0.71)	0.04 (0.96)	1283	9.91 (0.70)	-0.08 (0.87)
CBCL M Age 12	1710	850	12.18 (0.46)	0 (0.91)	797	12.16 (0.45)	0.05 (0.94)	913	12.20 (0.47)	-0.05 (0.87)
YSR Age 14	1345	585	15.32 (1.21)	-0.03 (0.83)	569	15.23 (1.12)	-0.01 (0.87)	776	15.39 (1.27)	-0.05 (0.80)
YSR Age 16	1357	583	17.26 (1.23)	-0.1 (0.82)	569	17.17 (1.18)	-0.09 (0.87)	788	17.33 (1.25)	-0.11 (0.79)
YSR Age 18	464	191	18.28 (1.48)	0.17 (0.84)	201	18.28 (1.51)	0.25 (0.87)	263	18.29 (1.46)	0.10 (0.81)
YSR Pilot	228	99	16.49 (1.19)	0.31 (0.85)	102	16.43 (1.27)	0.43 (0.97)	126	16.53 (1.11)	0.21 (0.72)
SR 1991	583	291	17.74 (2.28)	0.02 (0.90)	252	17.62 (2.27)	-0.04 (0.95)	331	17.83 (2.28)	0.06 (0.86)
SR 1995	680	339	20.04 (3.17)	0 (0.84)	280	20.08 (3.17)	-0.04 (0.86)	400	20.02 (3.18)	0.03 (0.83)
SR 1997	1788	649	28.19 (11.69)	-0.03 (0.86)	722	27.80 (11.94)	-0.07 (0.85)	1066	28.45 (11.52)	0.00 (0.86)
SR 2000	1921	729	32.48 (11.85)	-0.04 (0.84)	693	32.12 (12.51)	-0.10 (0.84)	1228	32.69 (11.46)	-0.01 (0.84)
SR 2009	2193	900	36.61 (13.76)	0.04 (0.86)	755	36.65 (14.33)	-0.09 (0.81)	1438	36.59 (13.46)	0.10 (0.88)
SR 2014	1985	843	34.30 (12.13)	0.02 (0.86)	676	32.97 (11.92)	-0.08 (0.79)	1309	34.99 (12.19)	0.07 (0.88)
Total	7740	3107	14.20 (12.03)	0 (0.88)	16,923	12.98 (11.02)	0.05 (0.92)	20,873	15.20 (12.70)	-0.05 (0.86)

Values are presented as *n* or mean (SD). The measure reflects the data collection for twins. Siblings of twins are included in the same data collection, so that the family structure in the data is preserved. Because some data collections are age dependent, some siblings were phenotyped as part of other, correct age-appropriate instrument samples. The total number of measures was 37,796 from 7740 individuals.

CBCL, Child Behavior Checklist; DCB, Devereux Child Behavior Rating Scale; F, father report; IRTagg, item-response theory aggression score; M, mother report; No. Fam, number of families; No. Pers, number of participants; SR, self-report; TRF, Teacher Report Form; YSR, Youth Self-Report.

For the WB sample PGS prediction, all genotyped participants with at least 1 DZ twin or sibling were included in the analyses (37,796 measures from 7740 individuals, 3–86 years old [mean = 14.20, SE = 12.03], from 3107 families, 55% female). See Table 2 for an overview of the samples per rater and data collection. For the TNT sample PGS prediction, genotyped participants with 2 genotyped parents were included in the analyses (42,649 measures from 6653 individuals, 3–61 years old [mean = 11.81, SE = 8.68], from 3024 families, 55% female). See Table 3 for an overview of the samples per rater and data collection.

Phenotyping

Phenotyping was done in several ways: 1) by parental ratings starting at age 3 years, 2) by teacher report starting at age 5 years, and 3) by self-report starting at age 12 years. Teachers completed the aggression syndrome scale from the Achenbach System of Empirically Based Assessment (ASEBA) Teacher Report Form (TRF) for ages 6–18 (20 items) (35). Parents completed the aggression syndrome scale from the Child Behavior Checklist (CBCL) for ages 1.5–5 years (19 items) (36) or the CBCL for ages 6–18 years (18 items) (35),

and/or the Devereux Child Behavior Rating Scale (DCB, 7 items) (37,38). Self-reports were obtained with the ASEBA Youth Self-Report (YSR, 17 items) (35), the ASEBA Young Adult Self Report (YASR, 17 items) (39), and the ASEBA Adult Self Report (ASR, 15 items) (40). All items on the TRF, CBCL, YSR, YASR, and ASR were scored on a 3-level scale: 0 = not true (as far as you know), 1 = somewhat/sometimes true, 2 = very true/often true. Items on the DCB were scored on a 5-level scale: 1 = never, 5 = frequently. CBCL and TRF data were collected as a function of child age, and YSR and ASR were collected in specific time frames.

IRT aggression scores were calculated regardless of genotyping status with the generalized partial credit model in R with the mirt package (41). The generalized partial credit model is a form of IRT that was specifically developed to analyze polytomous data (41). IRT appropriately weights the relative contributions of the individual aggression items, resulting in a scale that has a more favorable distribution than a sum score and can handle missing item data. Aggression scores were calculated for all NTR data collections separately (e.g., for all 7-year-olds independent of the year the data were obtained or for all adolescent and adult participants in the survey collected in 1993). Data collections were restructured for the IRT scoring so

Table 3. Descriptive Statistics Transmitted/Nontransmitted Sample: *n*, Age, and Aggression by Sex for Each Data Collection

Measure	No. Pers	No. Obs	No. Fam	Age, Years	IRTagg	Males			Females		
						<i>n</i>	Age, Years	IRTagg	<i>n</i>	Age, Years	IRTagg
TRF Age 5	122	122	66	5.64 (0.48)	0 (0.82)	57	5.56 (0.50)	0 (0.84)	65	5.71 (0.46)	0 (0.82)
TRF Age 7	1687	1687	849	7.68 (1.04)	-0.07 (0.78)	847	7.67 (1.04)	0.08 (0.85)	840	7.70 (1.04)	-0.22 (0.67)
TRF Age 10	1886	1886	996	9.84 (0.87)	-0.05 (0.81)	879	9.82 (0.88)	0.14 (0.89)	1007	9.86 (0.86)	-0.21 (0.69)
TRF Age 12	1398	1398	776	12.15 (0.67)	0 (0.83)	669	12.16 (0.67)	0.23 (0.90)	729	12.15 (0.67)	-0.20 (0.69)
CBCL F Age 3	2556	2556	1324	3.46 (0.52)	-0.09 (0.92)	1232	3.48 (0.54)	-0.06 (0.92)	1324	3.45 (0.51)	-0.12 (0.92)
DCB F Age 5	3238	3238	1665	5.61 (0.74)	-0.06 (0.87)	1516	5.66 (0.75)	0.03 (0.89)	1722	5.58 (0.72)	-0.14 (0.85)
CBCL F Age 7	2343	2343	1219	7.46 (0.60)	0 (0.91)	1110	7.48 (0.61)	0.10 (0.93)	1233	7.44 (0.60)	-0.09 (0.88)
CBCL F Age 10	2499	2499	1297	9.87 (0.72)	-0.04 (0.89)	1168	9.88 (0.73)	0.03 (0.93)	1331	9.85 (0.72)	-0.10 (0.85)
CBCL F Age 12	1519	1519	791	12.17 (0.46)	0.02 (0.89)	659	12.18 (0.45)	0.08 (0.94)	860	12.16 (0.47)	-0.03 (0.84)
CBCL M Age 3	3347	3347	1734	3.40 (0.51)	-0.09 (0.97)	1588	3.42 (0.53)	-0.01 (0.97)	1759	3.38 (0.50)	-0.16 (0.97)
DCB M Age 5	3353	3353	1726	5.62 (0.74)	-0.04 (0.87)	1583	5.66 (0.75)	0.07 (0.89)	1770	5.58 (0.72)	-0.14 (0.84)
CBCL M Age 7	2788	2788	1446	7.46 (0.60)	-0.05 (0.92)	1332	7.48 (0.60)	0.03 (0.94)	1456	7.45 (0.60)	-0.12 (0.89)
CBCL M Age 10	3007	3007	1556	9.87 (0.74)	-0.07 (0.91)	1423	9.88 (0.73)	-0.01 (0.94)	1584	9.87 (0.75)	-0.13 (0.88)
CBCL M Age 12	1770	1770	921	12.19 (0.47)	0 (0.91)	792	12.19 (0.46)	0.05 (0.95)	978	12.19 (0.48)	-0.04 (0.87)
YSR Age 14	1117	1117	556	15.21 (1.07)	0.03 (0.84)	446	15.15 (0.92)	0.04 (0.85)	671	15.25 (1.16)	0.02 (0.83)
YSR Age 16	1186	1186	595	17.32 (1.09)	-0.04 (0.83)	491	17.24 (1.05)	-0.03 (0.91)	695	17.37 (1.11)	-0.05 (0.77)
YSR Age 18	415	415	185	18.31 (1.36)	0.11 (0.82)	194	18.31 (1.36)	0.19 (0.87)	221	18.30 (1.35)	0.04 (0.77)
YSR Pilot	147	147	67	16.52 (1.22)	0.25 (0.84)	68	16.51 (1.40)	0.29 (0.97)	79	16.53 (1.06)	0.21 (0.71)
SR 1991	755	755	416	17.65 (2.23)	0.01 (0.86)	303	17.68 (2.21)	-0.01 (0.93)	452	17.63 (2.24)	0.02 (0.82)
SR 1995	972	972	544	19.95 (3.06)	-0.01 (0.84)	384	19.95 (3.07)	-0.06 (0.86)	588	19.95 (3.05)	0.03 (0.83)
SR 1997	1269	1269	572	22.73 (4.86)	0.01 (0.86)	533	22.52 (4.63)	-0.03 (0.86)	736	22.89 (5.02)	0.03 (0.86)
SR 2000	1329	1329	666	25.78 (5.25)	-0.01 (0.84)	504	25.48 (4.74)	-0.04 (0.81)	825	25.96 (5.53)	0.01 (0.86)
SR 2009	1967	1967	1132	29.96 (8.65)	0.08 (0.88)	635	29.24 (7.91)	-0.05 (0.81)	1332	30.30 (8.97)	0.15 (0.90)
SR 2014	1977	1977	1165	31.40 (9.10)	0.04 (0.85)	661	30.45 (8.66)	-0.08 (0.76)	1316	31.88 (9.28)	0.10 (0.89)
Total	6652	42,647	3024	11.81 (8.68)	-0.03 (0.88)	19,074	10.95 (7.75)	0.03 (0.91)	23,573	12.50 (9.31)	-0.08 (0.86)

Values are presented as *n* or mean (SD). The measure reflects the data collection for twins. Siblings of twins are included in the same data collection, so that the family structure in the data is preserved. Because some data collections are age dependent, some siblings were phenotyped as part of other, correct age-appropriate instrument samples.

CBCL, Child Behavior Checklist; DCB, Devereux Child Behavior Rating Scale; F, father report; IRTagg, item-response theory aggression score; M, mother report; No. Fam, number of families; No. Obs, number of observations; No. Pers, number of participants; SR, self-report, TRF, Teacher Report Form; YSR, Youth Self-Report.

Direct and Indirect Genetic Effects on Aggression

that all siblings and twins were scored relative to participants of similar age. By fitting a separate model for each data collection, aggression scores for each participant are relative to those of all other participants in that data collection, thereby filtering out potential data collection effects. Because the IRT score for each individual is relative to all other participants in the same data collection, the mean score for each data collection is 0. All participants with a maximum of 20% missing items on the different aggression scales were included in the generalized partial credit models. See [Figures S1](#) and [S2](#) for a histogram of the IRT aggression scores in the WB and TNT samples.

Genotype Data

Participants were genotyped on multiple Affymetrix and Illumina platforms. Samples were removed when call rate was <0.90 , PLINK heterozygosity F was <-0.10 or >0.10 , and when X chromosome genotypes were inconsistent with reported gender. Genotype data were filtered using the following criteria: only ACGT SNPs on the autosomes, no SNPs with duplicate positions, no SNPs with 3 or more alleles, minor allele frequency >0.01 , Hardy-Weinberg equilibrium $p > 10^{-5}$, and genotype call rate >0.99 . Genotype data were aligned with the 1000 Genomes reference panel and filtered for SNPs with allele frequency differences from the Northern and Western European ancestry population larger than 0.20, palindromic SNPs, and DNA strand issues. DNA identity by descent state was estimated based on $\sim 10,800$ SNPs that all platforms have in common for all individual pairs in PLINK (42) and King (43). Samples were removed if identity by descent did not match expected family relations. The Northern and Western European ancestry population outliers were removed from the data with Smartpca software based on per platform 1000 Genomes principal component projection. Per platform, data were phased by Eagle and imputed to 1000 Genomes with Minimac (44). The final merged genotype data used for calculating PGSs included 7,411,699 SNPs.

Polygenic Score Construction

We obtained GWAS summary statistics from the Ip *et al.* (21) early-life aggression genome-wide association meta-analysis, the Demontis *et al.* (23) ADHD genome-wide association meta-analysis, and the Lee *et al.* (24) EA genome-wide association meta-analysis after leaving out all participants from the NTR. The GWAS effect sizes were used to calculate PGSs using SBayesR version 2.03 (45). With SBayesR, estimates for the GWAS SNP effects are rescaled based on Bayesian multiple regression. SBayesR assumes that the standardized SNP effects are drawn from 4 normal distributions with a mean of 0 and different variances (default = 0, 0.01, 0.1, and 1.0). The correlations between the PGSs were $r_{EL-AGG \times ADHD} = 0.15$, $r_{EL-AGG \times EA} = -0.11$, and $r_{ADHD \times EA} = -0.22$. In the WB analyses, the between-family element is the average of all family members' PGSs (\overline{PGS}_j), and the within-family element is the deviation of individual family members from that average ($PGS_{ij} - \overline{PGS}_j$). For the TNT subsamples, 2 PGSs were computed for each individual: the transmitted PGS (PGS_T) and the nontransmitted PGS (PGS_{NT}). In total, there were 6652 individuals from 3024 families with 2 genotyped parents for whom PGS_T and PGS_{NT} could be calculated.

Based on the parental genotype information, the set of 4 parental alleles at each locus was assigned a transmitted (either from father or mother) or nontransmitted (also from either father or mother) status. This was done with the PLINK-tuicc option, which is based on a transmission-disequilibrium test. For each offspring with genotyped parents, the PGS_T and PGS_{NT} were then calculated in SBayesR. Note that the PGS_T and PGS_{NT} do not differ for monozygotic twins because they share the same genotype.

Analyses: Within/Between Family PGS Prediction

First we modeled the WB effects between the PGSs and aggression for each included data collection ($n = 24$) (Table 2) in a mixed-effects model with the package lme4 (46) in R. The model included 2 fixed effects to separate the total PGS effect on aggression into WB effects (26) as follows:

$$AGG_{ij} = \alpha_{0j} + \beta_W * (PGS_{ij} - \overline{PGS}_j) + \beta_B * \overline{PGS}_j + \beta_{3-v} * x_{3-v} + \varepsilon_{ij} \quad (1)$$

AGG denotes the aggression IRT score, i are the individual twins or siblings that are clustered within family j , so that PGS_{ij} is the polygenic score of individual i in family j , and \overline{PGS}_j is the mean PGS value in family j . $PGS_{ij} - \overline{PGS}_j$ indicates the individual deviation of family member i from the family average. The notation α_{0j} represents the overall intercept and deviation from that intercept in family j , and ε_{ij} denotes the independent random error (residual) for individual i in family j . The between-family fixed effect β_B represents the expected change in aggression given a 1 standard deviation (SD) change in the family PGS average, and the within-family effect β_W represents the expected change given a 1 SD change in the difference between the individual PGS and the family average PGS. By including both β_W and β_B in one model, the individual estimates are adjusted for, and independent of, the effect of the other estimate. β_{3-v} represent the expected change in the aggression outcome given a 1 SD change in the included covariates x_{3-v} (age, sex, dummy variables for genotyping arrays, and 10 ancestry-based principal components). The random intercept accounts for any additional dependence between measures in twins or siblings that is unaccounted for by the mean family PGS.

The results from the 24 data collections (Table 3) were meta-analyzed with a fixed-effects model in Metafor (47) in R. Because individuals may be phenotyped on multiple occasions and by multiple raters, the results from the 24 data collections are not independent. We quantified the dependence between subsamples by calculating the elements in the variance-covariance matrix of the sampling errors (V) as follows:

$$V_{kl} = se_k \left(\frac{N_{kl} r_p}{\sqrt{N_k N_l}} \right) se_l \quad (2)$$

where V_{kl} is the element in the variance-covariance matrix V of the sampling errors for subsamples k and l , se_k is the standard error for the estimate in subsample k , se_l is the standard error of the regression estimate in subsample l , N_{kl} is the overlap between subsamples k and l , and N_k and N_l are the sample

sizes for subsamples k and l . The meta-analysis model is then given by $y \sim N(\theta, V)$, where y is a vector with the observed subsample outcomes, θ is the (average) true outcome, and V is the variance-covariance matrix of the sampling errors (see Tables S1 and S2 for the sample overlap and cross-sample correlation matrices). Post hoc tests of between-rater contrasts were performed by meta-analyzing the results with rater as moderator. Contrasts were tested for equality with the package multcomp (48) in R. For post hoc tests for WB contrasts, we ran a meta-analysis on the combined WB results and included a dummy moderator variable, i.e., 0 = within-family, and 1 = between-family. The V -matrices in this case were given by expanding the V_{between} matrix from a 24×24 matrix to a 48×48 matrix and adding all elements from the V_{within} matrix to the extended diagonal of the V_{between} matrix, setting all between-within covariances to 0:

$$\begin{pmatrix} V_{\text{between}} & 0 \\ 0 & V_{\text{within}} \end{pmatrix}$$

As such, we assumed that estimates for the WB PGS effects were uncorrelated, which was also supported by the implied correlations in the empirical model (all $r_s < .01$). Explained variance was calculated in a separate mixed-effects model for the full combined WB sample, combining information from all raters and taking the dependency between observations into account by including a random intercept for family.

Analyses: Transmitted/Nontransmitted Alleles

We modeled the effects of the transmitted (PGS_T) and the nontransmitted PGSs (PGS_{NT}) with aggression for each of the 24 data collections in a mixed-effects model with the package lme4 (48) in R. The mixed-effects regression model can be written as follows:

$$AGG_{ij} = \alpha_{0j} + \beta_T \times PGS_T + \beta_{NT} \times PGS_{NT} + \beta_{3-v} \times x_{3-v} + \epsilon_{ij} \quad (3)$$

In this notation, AGG_{ij} is the aggression outcome of individual i in family j , the intercept α_{0j} is a combination of the overall intercept and the family-level deviation of that intercept, and β_T and β_{NT} represent the expected change in the aggression outcome Y given a 1 SD change in the PGS_T and PGS_{NT}, respectively. β_{3-v} represent the expected change in the aggression outcome given a 1 SD change in the included covariates x_{3-v} (age, sex, dummy variables for genotyping arrays, and 10 ancestry-based principal components). The random intercept accounts for any dependence between measures in twins or siblings.

The results from the analyses in the 24 data collections were meta-analyzed in a fixed-effects model in Metafor (47) in R. The meta-analytic method is identical to the WB PGS meta-analysis described previously, with dependence between subsamples accounted for by including the variance-covariance matrix of the sampling errors in the model. See Tables S3 and S4 for the sample overlap and cross-sample correlation matrices. The same post hoc tests of between-rater and WB contrasts were performed for the TNT results. Explained variance was calculated in a separate mixed-effects

model for the full combined TNT sample, combining information from all raters and taking into account the dependency between observations by including a random intercept for family.

RESULTS

Full Genotyped Sample PGS Prediction

All 3 PGSs were significantly associated with aggression in the complete combined genotyped sample ($\beta_{\text{EL-AGG}} = 0.07, p < .000$; $\beta_{\text{ADHD}} = 0.08, p < .000$; $\beta_{\text{EA}} = 0.04, p < .000$). The amount of explained variance in aggression was low for all 3 PGSs ($R^2_{\text{EL-AGG}} = 0.2\%$, $R^2_{\text{ADHD}} = 0.6\%$, $R^2_{\text{EA}} = 0.5\%$).

WB PGS Prediction

After running WB PGS analyses for each of the 24 data collections, we meta-analyzed the results, both per rater and for all measures combined (Figure 1, Table 4, and Figures S3–S8). Results indicated significant associations between aggression and the PGSs for EL-AGG, EA, and ADHD in both the between-family and the within-family analyses. The point estimates for the within-family effects were smaller than for the between-family effects. However, these differences were not significant, indicating that there was no significant confounding of between-family PGS effects by correlated family factors. Rater-specific meta-analyses indicated significant between-rater differences in the effects of the PGSs, most notably between parent-report on the one hand and teacher- and self-report on the other. However, the direction of the effects was consistently the same, and differences between raters were small (Table 4). For the analyses based on the ADHD PGSs, there were no significant rater differences in the between-family results, but there were significant rater differences in the within-family results. The rater differences were all small and could reflect sample size/power differences (Tables 2 and 4).

Transmitted and Nontransmitted PGS Prediction

Results from the TNT PGS analyses for each of the 24 data collections were meta-analyzed both per rater and for all measures combined (Figure 2; Table 5; Figures S9–S14). Results based on the meta-analyses indicated significant associations between aggression and the transmitted EL-AGG, EA, and ADHD PGSs. The nontransmitted EL-AGG, EA, and ADHD

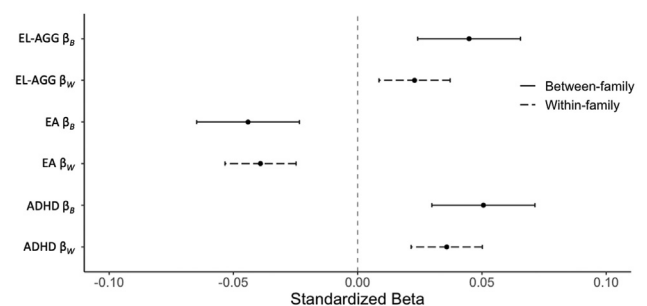


Figure 1. Within- and between-family polygenic score effects, with bars depicting 95% CIs. ADHD, attention-deficit/hyperactivity disorder; B, between-family model; EA, educational attainment; EL-AGG, early-life aggression; W, within-family model.

Direct and Indirect Genetic Effects on Aggression

Table 4. Within- and Between-Family PGS Meta-analysis Results

PGS Model	Between			Within		
	β_B	CI min	CI max	β_W	CI min	CI max
EL-AGG						
EL-AGG	0.04 ^a	0.02	0.07	0.02 ^b	0.01	0.04
Rater Contrasts						
SR-PR	-0.02	-0.06	-0.02	-0.01	-0.04	0.02
TR-PR	-0.01	-0.06	0.03	-0.01	-0.04	0.02
TR-SR	0.01	-0.04	0.06	0.00	-0.04	0.03
Within-between contrast	-0.02	-0.05	0.00	-	-	-
Educational Attainment						
Educational Attainment	-0.04 ^a	-0.06	-0.02	-0.04 ^a	-0.05	-0.02
Rater Contrasts						
SR-PR	0.07 ^a	0.03	0.11	0.04 ^b	0.01	0.06
TR-PR	0.00	-0.04	0.05	0.02	-0.01	0.05
TR-SR	-0.07 ^b	-0.12	-0.02	-0.02	-0.06	0.01
Within-between contrast	0.01	-0.02	0.03	-	-	-
ADHD						
ADHD	-0.04 ^a	-0.06	-0.02	0.04 ^a	0.02	0.05
Rater Contrasts						
SR-PR	-0.01	-0.05	0.03	-0.03 ^c	-0.06	-0.01
TR-PR	0.02	-0.02	0.07	0.00	-0.03	0.03
TR-SR	0.03	-0.01	0.08	0.04 ^c	0.00	0.07
Within-between contrast	-0.01	-0.04	0.01	-	-	-

R^2 for EL-AGG = 0.003, for EA = 0.006, and for ADHD = 0.007. R^2 refers to explained variance calculated for the complete combined sample.

ADHD, attention-deficit/hyperactivity disorder; B, between; β , standardized regression coefficient; CI max, confidence interval upper bound; CI min, confidence interval lower bound; EA, educational attainment; EL-AGG, early-life aggression; PGS, polygenic score; PR, parent report; SR, self-report; TR, teacher report; W, within.

^a $p < .001$.

^b $p < .01$.

^c $p < .05$.

PGSs were not significantly associated with the aggression outcome. This indicates that there was no significant contribution of indirect genetic effects from parental rearing environment to offspring aggression. Rater-specific meta-analyses indicated significant between-rater differences in the effects of the transmitted PGSs, most notably between parent report on the one hand and teacher and self-report on the other. As in the WB results, the direction of the rater-specific effects was consistently the same, and differences between raters were small (Tables 3 and 5).

DISCUSSION

In this study, we investigated whether indirect PGS effects play a role in familial clustering of aggression. Results indicate significant positive direct effects between aggression and the PGSs for EL-AGG and ADHD and a significant negative effect between aggression and the EA PGS. Within-family PGS effect

estimates were smaller than between-family estimates. These differences were not significant, indicating that there was no significant contribution of indirect PGS effects on aggression. We found no significant contribution of the nontransmitted PGSs (PGS_{NT}) on aggression, again indicating no significant contribution of indirect PGS effects on aggression. Our results are consistent with evidence obtained from twin and adoption studies that suggests that (direct) genetic effects are the most important driver of familial clustering of aggression. Further research involving other PGSs for aggression and related phenotypes is needed to determine whether this conclusion generalizes to overall genetic influences on aggression.

The observed absence of indirect PGS effects may be surprising because cross-sectional studies that have investigated familial influences on aggression have found forms of aggression, e.g., intimate partner violence from prenatal stages onward, to be associated with aggression in offspring. This means that offspring possibly inherit a high-risk genotype and a correlated high-risk environment (17). Thus, PGS effects could reflect correlated environmental influences. The lack of indirect PGS effects combined with a lack of shared environmental influences in twin and adoption studies (7,13) suggest that findings from cross-sectional studies, such as those reported by Labella and Masten (17), reflect genetic confounding. Indirect PGS effects should, after all, be captured in the shared environmental influences estimated in twin studies. Such indirect PGS effects have been found for behavioral traits such as EA (16,17,26) and child depression (28), but not in other studies of child internalizing problems (29) or EA (49). It is important to note here that we analyzed a wide range of ages. Surveys that included young children were completed by parents and teachers as opposed to self-reports completed by adolescents and adults. This makes any differences between these surveys hard to interpret and/or ascribe to age differences. Shared environmental influences tend to decrease with age (13), indicating that indirect effects are more likely to play a role at younger ages.

Our models do not account for possible effects of active or evocative rGE. This means that the PGSs can still reflect environmental influences that were evoked or selected based on their genotypes. Elam *et al.* (50,51) did find that offspring genotypes can evoke negative family environments, which

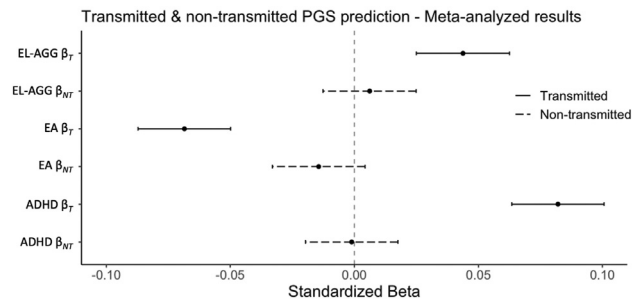


Figure 2. Transmitted and nontransmitted PGS effects, with bars depicting 95% confidence intervals. ADHD, attention-deficit/hyperactivity disorder; EA, educational attainment; EL-AGG, early-life aggression; NT, nontransmitted PGS model; PGS, polygenic score; T, transmitted PGS model.

Table 5. Transmitted and Nontransmitted PGS Meta-analysis Results

PGS Model	Transmitted			Nontransmitted		
	β_T	CI min	CI max	β_{NT}	CI min	CI max
EL-AGG						
EL-AGG	0.04 ^a	0.02	0.06	0.01	-0.01	0.03
Rater Contrasts						
SR-PR	-0.03	-0.06	0.01	-0.02	-0.06	0.02
TR-PR	-0.01	-0.05	0.02	0.01	-0.03	0.05
TR-SR	0.01	-0.03	0.06	0.03	-0.01	0.08
PGS _T -PGS _{NT} contrast	0.04 ^b	0.01	0.07	-	-	-
Educational Attainment						
Educational Attainment	-0.07 ^a	-0.09	-0.05	-0.01	-0.03	0.01
Rater Contrasts						
SR-PR	0.06 ^a	0.03	0.10	0.00	-0.03	0.04
TR-PR	0.02	-0.02	0.05	0.00	-0.03	0.04
TR-SR	-0.05 ^c	-0.09	0.00	0.00	-0.04	0.05
PGS _T -PGS _{NT} PGS contrast	-0.06 ^a	-0.08	-0.03	-	-	-
ADHD						
ADHD	0.08 ^a	0.06	0.10	0.00	-0.02	0.02
Rater Contrasts						
SR-PR	-0.02	-0.06	0.01	0.01	-0.02	0.05
TR-PR	0.02	-0.01	0.06	0.01	-0.02	0.05
TR-SR	0.05 ^c	0.00	0.09	0.00	-0.04	0.05
PGS _T -PGS _{NT} contrast	0.09 ^a	0.06	0.11	-	-	-

R^2 for EL-AGG = 0.002, for EA = 0.009, and for ADHD = 0.006. R^2 refers to explained variance calculated for the complete combined sample.

ADHD, attention-deficit/hyperactivity disorder; β , standardized regression coefficient; CI max, confidence interval upper bound; CI min, confidence interval lower bound; EA, educational attainment; EL-AGG, early-life aggression; NT, nontransmitted; PGS, polygenic score; PR, parent report; SR, self-report; T, transmitted; TR, teacher report.

^a $p < .001$.

^b $p < .01$.

^c $p < .05$.

subsequently increases risk for later psychopathology, aggression, family cohesion, and substance use. As in the current study, the effect sizes in these studies were small.

The observed direct PGS effects on aggression were expected based on previous studies (7,13). Direct PGS effects indicate genetic transmission of aggression from parent to offspring and a partially shared genetic basis among EL-AGG, EA, ADHD, and aggression. This may reflect a causal association between these phenotypes and/or a genetic effect on another trait that influences all 3 traits. The direct EL-AGG PGS effects have already been shown to influence aggression in adults (20). The direct effects of the EA and ADHD PGSs were expected based on the genetic correlations with EL-AGG, as demonstrated in previous work by Ip *et al.* ($rg = -0.50$, $SE = 0.04$, $rg = 1.00$, $SE = 0.07$) (22).

We found significant but small inter-rater differences. All effects were in the same direction across raters. Rater differences in assessing aggression have been well documented

(52,53). In the GWAS of EL-AGG, genetic correlations between rater-specific assessment of aggression ranged from $rg = 0.46$ between self and teacher assessment to $rg = 0.81$ between mother and teacher assessment (22). Inter-rater differences may be caused by rater bias, i.e., scoring individuals differently because they see them in different contexts or because they compare them to their siblings or even themselves (53). However, there were also clear sample size differences between raters, which could have caused inter-rater differences. Respondents' age also differs across raters, with teacher and parent ratings covering only children.

Our study depends on the statistical power of discovery GWASs. The explained variance in aggression for each PGS was very low in both the WB results ($R^2_{EL-AGG} = 0.3\%$, $R^2_{ADHD} = 0.6\%$, $R^2_{EA} = 0.7\%$) and the TNT PGS results ($R^2_{EL-AGG} = 0.2\%$, $R^2_{ADHD} = 0.9\%$, $R^2_{EA} = 0.5\%$). When looking at the WB results, there is a possibility that we failed to detect significant WB differences due to a lack of power. The within-family effect estimates are slightly smaller than the between-family effect estimates, especially for the lowest-powered PGS, EL-AGG. The PGS_{NT} effect estimates were all very close to 0. This leads us to conclude that PGS influences on aggression are likely mainly direct and that the contribution of indirect PGS effects seems to be small compared with other behavioral traits, such as EA, where significant effects of nontransmitted PGSs have often been detected (16,26), although not always (51). Our results are based on PGSs that cover only a small part of the ~50% heritability estimated in twin and family studies (7,13). Whether our results are representative of all genetic influences depends on whether rarer variants and variants with smaller effect sizes (i.e., those not covered by our PGSs) behave in a manner that is similar to the variant effects included in our PGS. To make more reliable estimates of the indirect genetic effects, we need higher-powered GWASs of aggression that result in stronger PGSs. This will mean less uncertainty in the point estimates of the regression estimates and more generalizability to genetic influences estimated in twin and family studies.

Our sample consists of twins and their family members. There are no families with singletons in the data. There may be some selection bias in the NTR, resulting in less aggressive families signing up. We have no way to test this, but we did observe a large range of aggression scores, indicating that we are not completely missing out on aggressive families. There were no clear differences between the phenotyping sample and the genotyping sample, indicating that there was no selection bias in the genotyping of participants.

In sum, we found no significant contributions of indirect PGS effects on aggression across different designs. Results indicated small, significant direct PGS effects on aggression for 3 PGSs: early-life aggression, EA, and ADHD. This study did not find evidence in contrast to findings from twin and family studies that the main drivers of familial clustering and intergenerational transmission of aggression are direct genetic influences.

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Direct and Indirect Genetic Effects on Aggression

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ARTICLE INFORMATION

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