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Association of Genetic Risk Variants With Attention-Deficit/Hyperactivity Disorder Trajectories in the General Population

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IMPORTANCE Attention-deficit/hyperactivity disorder (ADHD) is a heritable neurodevelopmental disorder that shows clinical and genetic overlap with other childhood neurodevelopmental disorders. Levels of ADHD symptoms typically decline across childhood and adolescence, although they remain elevated for some individuals. The determinants of symptom persistence and decline are not yet fully understood.

OBJECTIVES To test the hypothesis that genetic risk variant load for ADHD (indexed by polygenic risk scores [PRS]), but not for other psychiatric disorders, is associated with population-based ADHD symptom trajectories across childhood and adolescence, and to examine whether higher genetic liability for ADHD is correlated with total number of additional neurodevelopmental disorders (multimorbidity) in childhood.

DESIGN, SETTING, AND PARTICIPANTS The Avon Longitudinal Study of Parents and Children, an ongoing prospective population-based cohort study, has been collecting data on 14 701 children, including 9757 with data on symptoms of ADHD at multiple time points, since September 6, 1990. The primary exposure variables, PRS, were generated using results of a genome-wide association study from the Psychiatric Genomics Consortium. Childhood multimorbidity scores (ages 7-9 years) were measured by total impairments in 4 domains known to share genetic liability with ADHD: IQ, social communication, pragmatic language, and conduct. Data analysis was conducted from March 1 to September 8, 2016.

MAIN OUTCOMES AND MEASURES Attention-deficit/hyperactivity disorder symptom trajectories from ages 4 to 17 years (7 time points).

RESULTS Among 9757 children with data on symptoms of ADHD at multiple time points (age range, 4-17 years; 4968 boys and 4789 girls), 4 ADHD symptom trajectories were identified: low (82.6%), intermediate (7.7%), childhood-limited (5.8%), and persistent (3.9%). Mean (SE) PRS for ADHD were higher in children in the persistent trajectory (0.254 [0.069]) compared with each of the other 3 trajectories (low, −0.018 [0.014], $\chi^2_1 = 14.67$, $P < .001$, odds ratio, 1.31; intermediate, 0.054 [0.055], $\chi^2_1 = 4.70$, $P = .03$, odds ratio, 1.22; and childhood-limited, 0.017 [0.060], $\chi^2_1 = 6.50$, $P = .01$, odds ratio, 1.27). Findings were specific to PRS for ADHD; PRS for other psychiatric conditions did not differ across trajectories. The proportion of children with multimorbidity was also highest in those in the persistent trajectory (42.5%; 95% CI, 33.9%-51.1%; $P < .001$) and was associated with persistence of ADHD symptoms independent of PRS.

CONCLUSIONS AND RELEVANCE Persistence of ADHD symptoms across childhood and adolescence in the general population is associated with higher PRS for ADHD. Childhood multimorbidity was also associated with persistence of ADHD symptoms and may help to identify children with ADHD whose symptoms are most likely to continue into adolescence.

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Supplemental content

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Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with an onset in childhood.[1-3] Although it is considered to manifest most commonly in children, approximately 15% of people with a childhood diagnosis continue to meet clinical criteria for ADHD in adulthood, with up to 65% showing symptoms of ADHD that do not meet the criteria for diagnosis.[4] Furthermore, recent work suggests that for some individuals, ADHD first emerges in adulthood,[5-7] emphasizing the need to investigate the natural history of ADHD in general population samples. Although ADHD is relevant across the lifespan, most children show a decline in symptom levels across childhood and adolescence, which also occurs in other childhood-onset neurodevelopmental disorders, such as autism spectrum disorder, communication disorders, and specific learning disorders.[1] The determinants of the persistence of a neurodevelopmental disorder are not fully understood, although for ADHD, severity of initial symptoms, comorbidities, cortical maturation, and family history of ADHD, among other factors, have been considered as contributors.[8-15]

Attention-deficit/hyperactivity disorder has a heritability estimate of 71% to 90%.[16] Twin studies suggest that persistence of ADHD symptoms is also heritable, but it has only recently become possible to directly assess genetic contributions.[8,17-19] Genomic studies of ADHD have revealed a genetic architecture of multiple common risk alleles as well as rare mutations.[16] Although individual common risk alleles typically have small effect sizes for multifactorial disorders, such as ADHD, composite measures—polygenic risk scores (PRS)—representing an individual's estimated total burden of common risk alleles (where risk alleles are defined by their association statistics and effect sizes in a discovery genome-wide association study) are useful biological indicators of disease risk.[19] Polygenic risk scores for ADHD are higher in patients with disorder than in controls[20] and are associated with ADHD symptom levels in the general population.[21,22] Attention-deficit/hyperactivity disorder also shares genetic liability with other neurodevelopmental traits and conduct problems,[1,20,23] suggesting that those with higher genetic loading for ADHD are likely to manifest elevated levels of problems in these domains.

We examine the associations between psychiatric PRS and population-based developmental trajectories of ADHD symptoms from early childhood to adolescence. We hypothesized that PRS for ADHD, but not for other psychiatric disorders (eg, schizophrenia, bipolar disorder, and depression) would be associated with persistence of ADHD symptoms from ages 4 to 17 years. We also postulated that a trajectory of persistent ADHD symptoms would be associated with a higher burden of childhood neurodevelopmental impairments and conduct problems, as this multimorbidity would index underlying ADHD genetic liability.

Key Points

Question Are symptom trajectories of attention-deficit/hyperactivity disorder (ADHD) across childhood and adolescence associated with an individual's genetic risk variant load for ADHD, as indexed by polygenic risk scores, and childhood multimorbidity, measured as the number of neurodevelopmental disorders or conduct problems?

Findings This cohort study found that polygenic risk scores for ADHD and multimorbidity were significantly higher in individuals with persistent ADHD. Polygenic risk scores for ADHD were also significantly associated with multimorbidity.

Meaning The course of ADHD symptoms across childhood and adolescence in the general population is associated with polygenic risk scores for ADHD; childhood multimorbidity may help clinicians identify children most likely to show ADHD persistence.

Methods

Sample

The Avon Longitudinal Study of Parents and Children (ALSPAC) is a well-established ongoing prospective longitudinal birth cohort study that has been collecting data since September 6, 1990. The enrolled core sample consisted of 14 541 mothers living in Avon, England, who had expected delivery dates between April 1, 1991, and December 31, 1992. Of these pregnancies, 13 988 children were alive at 1 year. When the oldest children were approximately 7 years, the initial sample was increased by recruiting eligible families who did not originally join the study, resulting in an additional 713 children being enrolled. The resulting total sample size of children who were alive at 1 year was 14 701. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. All participants provided written informed consent. Full details of the study, measures, and sample can be found elsewhere[24,25] (see http://www.bristol.ac.uk/alspac/researchers/access/). For families with multiple births, we included the oldest sibling. Individuals were included in our analyses when primary data on ADHD symptoms were available for at least 2 time points (n = 9757). The numbers of individuals with data available at different time points are in eFigure 1 in the Supplement.

Symptoms of ADHD

The primary outcome was ADHD symptoms assessed repeatedly across time using the parent-rated 5-item Strengths and Difficulties Questionnaire (SDQ)[26] subscale designed to measure hyperactive and inattentive symptoms (score range, 0-10). In line with recommendations and to maintain consistency with previous work in ALSPAC,[26,27] abnormal scores were defined as those 7 or higher, while 6 was considered a borderline score. The SDQ showed high sensitivity and specificity for detecting a *DSM-IV* diagnosis of ADHD assessed using a diagnostic interview at age 7 years (eAppendix in the Supplement). Data were available from parent reports at ages 47, 81, 97, 115, 140, 157, and 198 months (approximately aged 4-17 years).

Polygenic Risk Scores

Polygenic risk scores were generated as the standardized mean number of disorder risk alleles in approximate linkage equilibrium (R^2<0.25), weighted by genome-wide association study

allele effect size, derived from dosage data of imputed autosomal single-nucleotide polymorphisms using standard procedures.[28] Risk alleles were defined as those associated with case status in the Psychiatric Genomics Consortium analyses of several phenotypes at a threshold of $P < .50$ for ADHD, bipolar disorder, and depression and $P < .05$ for schizophrenia. These thresholds maximally capture phenotypic variance.[29-34] Genome-wide association study case and control sample sizes were as follows: ADHD, 5621 cases and 13 589 controls; schizophrenia, 35 476 cases and 46 839 controls; bipolar disorder, 7481 cases and 9250 controls; and depression, 9240 cases and 9519 controls). Genotyping and full PRS details are in the eAppendix in the Supplement. Power was estimated using the Dudbridge calculator with approximations for some of the required parameters.[35]

Other Characteristics

We investigated whether co-occurring neurodevelopmental traits and conduct problems in childhood (aged 7-9 years) are associated with ADHD genetic liability (defined by PRS). Problems (defined categorically using established cut-points to enable computation of multimorbidity) included the following: low IQ (defined as a score of <80 on the Wechsler Intelligence Scale for Children[36]); social communication problems (defined as a score of ≥9 on the parent-rated Social and Communication Disorders Checklist[37]); impairment of pragmatic language (defined as a score of ≤132 on the parent-rated Children's Communication Checklist subscale[38]); and conduct problems, measured at age 81 months (defined as a score ≥4 on the parent-rated SDQ subscale[26]). Multimorbidity was defined as the sum of the number of impairments in domains i-iv (range, 0-4).

Statistical Analysis

Data analysis was conducted from March 1 to September 8, 2016. Latent class growth analysis was conducted in Mplus (Muthén and Muthén)[39] to identify ADHD developmental trajectories across all 7 time points using binary data on ADHD symptoms, in line with previous work in ALSPAC.[27] Latent class growth analysis aims to group individuals into categories (classes) based on different patterns of change (growth curves) across multiple time points, with within-class covariance matrices fixed to zero (ie, individuals within the same class are specified to have the same growth curve).[40] Starting with a single k-class solution, k+1 solutions are fitted until the optimum solution is reached. Models were run using a robust maximum likelihood parameter estimator and full information maximum likelihood estimation.[39] The optimal number of categories was determined using adjusted Bayesian information criterion to assess model fit and entropy to assess classification accuracy. Differences in PRS and multimorbidity were assessed by a Wald test of equality of means using posterior probability-based multiple imputations (odds ratios [ORs] were generated using multinomial logistic regressions),[41] which takes profile measurement error into account (PRS and multimorbidity were not used to generate the trajectories). Finally, we investigated the independent associations of PRS for ADHD and multimorbidity with class membership using a bias-free 3-step approach (R3STEP)[42] that performs better than conventional 3-step methods.[43]

Results

Symptom Trajectories of ADHD

Latent class growth analysis indicated that the 4-class solution of ADHD trajectories had the best model fit (adjusted Bayesian information criterion, 25574.45; Vuong-Lo-Mendell-Rubin likelihood ratio test, $P < .001$ vs a 3-class solution) and classification accuracy (entropy, 0.82), consistent with previous work in ALPSAC.[27] As shown in **Figure 1**, this solution included the 4 classes: low (82.6%), intermediate (7.7%), childhood-limited (5.8%), and persistent (3.9%). The solution did not include an adolescent-onset group. The proportion of boys differed across the trajectories, with the largest proportion in the persistent (72.9%), smallest in the low (48%), and intermediate levels in the child-limited (62.3%) and intermediate (63%) trajectories (overall $\chi^2_3 = 45.22$; $P < .001$).

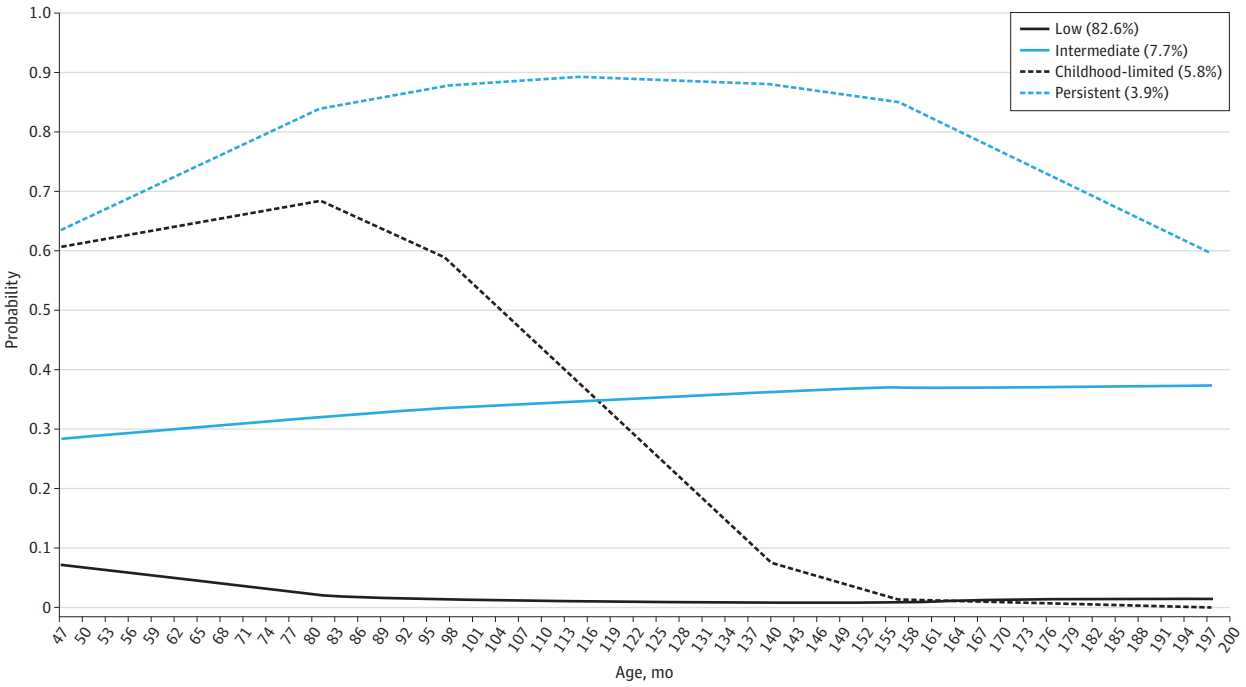
Genetic Variables: Psychiatric PRS

Polygenic risk scores for ADHD differed across the 4 trajectories; mean (SE) scores were highest in the persistent trajectory (0.254 [0.069]), lowest for the low symptom group (-0.018 [0.014]), and intermediate for the childhood-limited (0.017 [0.060]) and intermediate (0.054 [0.055]) trajectories (**Table 1**). Differences were observed for the persistent trajectory when compared separately with the childhood-limited (OR, 1.27; $\chi^2 = 6.50$; $P = .01$), intermediate (OR, 1.22; $\chi^2 = 4.70$; $P = .03$), and low (OR, 1.31; $\chi^2 = 14.67$; $P < .001$) trajectories. The association with trajectory was specific to the PRS for ADHD: PRS for schizophrenia, bipolar disorder, and depression were not associated with ADHD symptom trajectories (Table 1).

Childhood Multimorbidity

The proportion of individuals with neurodevelopmental traits and conduct problems across the 4 trajectories are shown in **Table 2**. Low IQ, social communication problems, impairment of pragmatic language, and conduct problems at ages 7 to 9 years differed by trajectory, with the highest levels in the persistent trajectory compared with all other trajectories. The childhood-limited and intermediate trajectories also showed elevated levels compared with the low trajectory. Low IQ was seen in 5.4% (95% CI, 4.8%-6%) of those in the low trajectory, 11.4% (95% CI, 8.1%-14.7%) of those in the intermediate trajectory, 11.7% (95% CI, 7.8%-15.6%) of those in the childhood-limited trajectory, and 21.4% (95% CI, 15.5%-27.3%) of those in the persistent trajectory. Social communication problems were seen in 3.4% (95% CI, 3%-3.8%) of those in the low trajectory, 19.9% (95% CI, 16%-23.8%) of those in the intermediate trajectory, 22.9% (95% CI, 18.2%-27.6%) of those in the childhood-limited trajectory, and 53.1% (95% CI, 46.6%-59.6%) of those in the persistent trajectory. Impairment of pragmatic language was seen in 1.2% (95% CI, 1%-1.4%) of those in the low trajectory, 7.7% (95% CI, 5%-10.4%) of those in the intermediate trajectory, 10.3% (95% CI, 7%-13.6%) of those in the childhood-limited trajectory, and 27.8% (95% CI, 22.1%-

Figure 1. Probability of Being in the High-Scoring Range for Attention-Deficit/Hyperactivity Disorder Symptoms by Latent Class



Trajectories of attention-deficit/hyperactivity disorder symptoms identified by latent class growth analysis.

Table 1. Associations Between Psychiatric Polygenic Risk Scores and All ADHD Latent Trajectory Classes

	Trajectory, Polygenic Risk Score, Mean (SE)				Overall Test	
Disorder	Low	Intermediate	Childhood-Limited	Persistent	χ^2_3	*P* Value
ADHD	−0.018 (0.014)	0.054 (0.055)	0.017 (0.060)	0.254 (0.069)	7.83	.05[a]
Schizophrenia	−0.008 (0.014)	0.026 (0.054)	0.037 (0.059)	0.064 (0.072)	0.44	.93
Bipolar disorder	−0.003 (0.014)	−0.022 (0.055)	0.059 (0.066)	0.018 (0.070)	1.15	.77
Depression	−0.011 (0.014)	0.022 (0.055)	0.067 (0.060)	0.092 (0.071)	1.10	.78

Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

[a] Higher polygenic risk scores for ADHD in the persistent compared with low (χ^2_1 = 14.67; *P* < .001), intermediate (χ^2_1 = 4.70; *P* = .03), and childhood-limited trajectories (χ^2_1 = 6.50; *P* = .01).

33.5%) of those in the persistent trajectory. Conduct problems were seen in 6.7% (95% CI, 6.1%-7.3%) of those in the low trajectory, 21.1% (95% CI, 17%-25.2%) of those in the intermediate trajectory, 27.5% (95% CI, 22.6%-32.4%) of those in the childhood-limited trajectory, and 42% (95% CI, 35.7%-48.3%) of those in the persistent trajectory.

The proportions of children with multimorbidities across the 4 trajectories are shown in Table 2. Multimorbidity varied by latent trajectory, with a higher burden of childhood neurodevelopmental impairments or conduct problems in those in the persistent trajectory compared with all other trajectories and elevated levels in the childhood-limited and intermediate trajectories compared with the low trajectory (>1 neurodevelopmental or conduct domain affected: low trajectory, 1.7% [95% CI, 1.3%-2.1%]; intermediate trajectory, 13.1% [95% CI, 8.6%-17.6%]; childhood-limited trajectory, 16.1% [95% CI, 10.8%-21.4%]; and persistent trajectory, 42.5% [95% CI, 33.9%-51.1%]; χ^2_3 = 38.93; *P* < .001; >2 neurodevelopmental or conduct domains affected: low trajectory, 0.2% [95% CI, 0%-0.4%]; intermediate trajectory, 2.8% [95% CI, 0.6%-5%]; childhood-limited trajectory, 3.4% [95% CI, 0.7%-6.1%]; and persistent trajectory, 17.8% [95% CI, 11.3%-24.3%]; χ^2_3 = 17.31, *P* = .001).

Independent Contributions of PRS for ADHD and Childhood Multimorbidity to Persistence of ADHD

Multimorbidity at ages 7 to 9 years was associated with PRS for ADHD (OR, 1.16; *P* < .001) but not with PRS for schizophrenia (OR, 1.02; *P* = .61), bipolar disorder (OR, 1.09; *P* = .06), or depression (OR, 1.06; *P* = .18).

When entered simultaneously (n = 3870), both multimorbidity and PRS for ADHD were independently associated with the persistent trajectory compared with the low trajectory (OR per additional neurodevelopmental or conduct domain, 9.21; multimorbidity β [SE], 2.22 [0.15]; *P* < .001; OR per SD increase in PRS for ADHD, 1.42; PRS β [SE], 0.35 [0.13]; *P* = .01).

Table 2. Associations Between Co-occurring Childhood Characteristics at Ages 7 to 9 Years and ADHD Trajectory Class

Characteristic	Trajectory, % (95% CI)				Overall Test	
	Low	Intermediate	Childhood-Limited	Persistent	χ^2_3	*P* Value[a]
Low IQ	5.4 (4.8-6)	11.4 (8.1-14.7)	11.7 (7.8-15.6)	21.4 (15.5-27.3)	12.76	.005
Social communication problems	3.4 (3-3.8)	19.9 (16-23.8)	22.9 (18.2-27.6)	53.1 (46.6-59.6)	103.50	<.001
Impairment of pragmatic language	1.2 (1-1.4)	7.7 (5-10.4)	10.3 (7-13.6)	27.8 (22.1-33.5)	36.51	<.001
Conduct problems	6.7 (6.1-7.3)	21.1 (17-25.2)	27.5 (22.6-32.4)	42 (35.7-48.3)	56.62	<.001
Multimorbidity						
>1 Additional problem	1.7 (1.3-2.1)	13.1 (8.6-17.6)	16.1 (10.8-21.4)	42.5 (33.9-51.1)	38.93	<.001
>2 Additional problems	0.2 (0-0.4)	2.8 (0.6-5)	3.4 (0.7-6.1)	17.8 (11.3-24.3)	17.31	.001

Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

[a] Greater proportion in the persistent compared with low, intermediate, and childhood-limited trajectories (low IQ vs low trajectory, $\chi^2_1 = 28.12$; $P < .001$; low IQ vs intermediate trajectory, $\chi^2_1 = 7.87$; $P = .005$; low IQ vs childhood-limited trajectory, $\chi^2_1 = 6.73$; $P = .009$; social communication problems vs low trajectory, $\chi^2_1 = 225.86$; $P < .001$; social communication problems vs intermediate trajectory, $\chi^2_1 = 72.43$; $P < .001$; social communication problems vs childhood-limited trajectory, $\chi^2_1 = 51.80$; $P < .001$; pragmatic language impairment vs low trajectory, $\chi^2_1 = 82.75$; $P < .001$; pragmatic language impairment vs intermediate trajectory, $\chi^2_1 = 35.09$; $P < .001$; pragmatic language impairment vs childhood-limited trajectory, $\chi^2_1 = 25.57$; $P < .001$; conduct problems vs low trajectory, $\chi^2_1 = 120.25$; $P < .001$; conduct problems vs intermediate trajectory, $\chi^2_1 = 27.79$; $P < .001$; conduct problems vs childhood-limited trajectory, $\chi^2_1 = 11.98$; $P = .001$; more than 1 additional problem vs low trajectory, $\chi^2_1 = 85.84$; $P < .001$; more than 1 additional problem vs intermediate trajectory, $\chi^2_1 = 32.62$; $P < .001$; more than 1 additional problem vs childhood-limited trajectory, $\chi^2_1 = 25.05$; $P < .001$; more than 2 additional problems vs low trajectory, $\chi^2_1 = 28.09$; $P < .001$; more than 2 additional problems vs intermediate trajectory, $\chi^2_1 = 17.31$; $P < .001$; more than 2 additional problems vs childhood-limited trajectory, $\chi^2_1 = 15.28$; $P < .001$) and in the intermediate and childhood-limited compared with low trajectory (low IQ: intermediate vs low trajectory, $\chi^2_1 = 12.42$; $P < .001$; low IQ: childhood-limited vs low trajectory, $\chi^2_1 = 9.23$; $P = .002$; social communication problems: intermediate vs low trajectory, $\chi^2_1 = 68.15$; $P < .001$; social communication problems: childhood-limited vs low trajectory, $\chi^2_1 = 66.01$; $P < .001$; pragmatic language impairments: intermediate vs low trajectory, $\chi^2_1 = 21.76$; $P < .001$; pragmatic language impairments: childhood-limited vs low trajectory, $\chi^2_1 = 28.73$; $P < .001$; conduct problems: intermediate vs low trajectory, $\chi^2_1 = 42.41$; $P < .001$; conduct problems: childhood-limited vs low trajectory, $\chi^2_1 = 66.66$; $P < .001$; more than 1 additional problem: intermediate vs low trajectory, $\chi^2_1 = 23.95$; $P < .001$; more than 1 additional problem: childhood-limited vs low trajectory, $\chi^2_1 = 27.55$; $P < .001$; more than 2 additional problems: intermediate vs low trajectory, $\chi^2_1 = 5.25$; $P = .02$; more than 2 additional problems: childhood-limited vs low trajectory, $\chi^2_1 = 5.33$; $P = .02$).

Table 3. Associations Between Psychiatric Polygenic Risk Scores and ADHD Symptoms at Ages 7 and 17 Years

Disorder	Trajectory, Polygenic Risk Score, Mean (SE)				Overall Test	
	Low	Childhood-Limited	Persistent	Adolescent-Onset	$F_{3,3644}$	*P* Value
ADHD	−0.035 (0.018)	0.043 (0.061)	0.252 (0.101)	0.101 (0.104)	3.01	.03[a]
Schizophrenia	−0.035 (0.018)	−0.014 (0.058)	0.098 (0.107)	0.050 (0.118)	0.66	.58
Bipolar disorder	−0.001 (0.018)	0.081 (0.061)	0.117 (0.120)	−0.133 (0.107)	1.43	.23
Depression	−0.017 (0.018)	0.089 (0.057)	0.036 (0.130)	−0.196 (0.108)	2.01	.11

Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

[a] Higher ADHD polygenic risk scores in the persistent compared with low subgroup (B [SE], 0.29 [0.11]; $P = .01$) (see Figure 2).

There was also evidence that multimorbidity was independently associated with persistence of ADHD relative to the childhood-limited trajectory (OR per additional neurodevelopmental or conduct domain, 1.46; β [SE], 0.38 [0.14]; $P = .01$), whereas evidence for the PRS for ADHD was weak (OR per SD increase in PRS for ADHD, 1.30; β [SE], 0.26 [0.18]; $P = .14$).

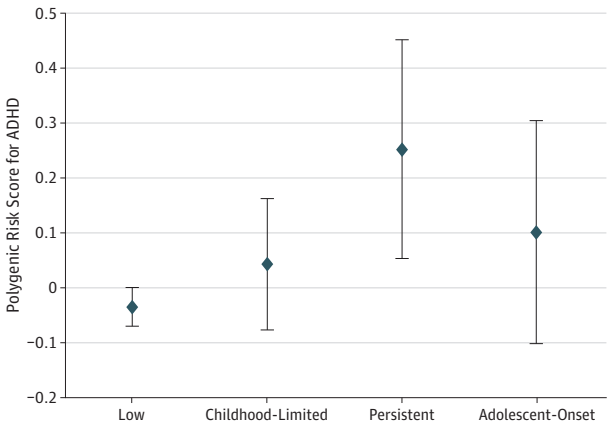
Grouping Individuals Using ADHD Cut-Points at 2 Time Points

Given recent findings on adolescent-onset ADHD,[5-7] in a post-hoc investigation, we categorized individuals as showing ADHD symptom persistence if they scored above the SDQ ADHD subscale cut-point at 2 time points: ages 7 and 17 years (n = 4824; individuals with data on ADHD symptoms at both time points).

Most individuals did not meet the threshold for high levels of ADHD symptoms at either age and were categorized in the low trajectory (4193 [86.9%]). Ten percent of individuals (n = 476) met the cut-point at age 7 years; most no longer met the cut-point at age 17 years and were categorized in the childhood-limited trajectory (370 [7.7%]), with those meeting the cut-point at both ages categorized in the persistent trajectory (106 [2.2%]). One hundred fifty-five children (3.2%) did not meet the threshold for high levels of ADHD symptoms at age 7 years, but did at age 17 years (33 [0.7%] had borderline levels of ADHD traits at age 7 years).[26] We categorized an adolescent-onset subgroup as those who met the cut-point at age 17 years but did not have borderline or abnormal symptoms at age 7 years (122 [2.5%]).

As shown in **Table 3**, mean (SE) PRS for ADHD differed across the 4 ADHD subgroups (low, −0.035 [0.018]; childhood-limited, 0.043 [0.061]; persistent, 0.252 [0.102]; and adolescent-onset, 0.101 [0.104]; $P = .03$) but PRS for schizophrenia, bipolar disorder, and depression were not associated with ADHD symptom subgroups. Specifically, there was evidence of higher PRS for ADHD in the persistent compared with the low subgroup (OR per SD increase in PRS for ADHD, 1.33; B [SE], 0.29 [0.11]; $P = .01$) (**Figure 2**). Follow-up analyses categorizing individuals using symptoms at ages 4 and 17 years, symp-

Figure 2. Mean Polygenic Risk Score for Attention-Deficit/Hyperactivity Disorder (ADHD) by Subgroup



Subgroups based on 2 time points (ages 7 and 17 years). Error bars indicate 95% CI.

toms at ages 12 and 17 years, and inattentive and hyperactive or impulsive traits separately revealed the same pattern of results (eAppendix and eFigure 2 in the Supplement).

Discussion

Our study aimed to test the hypothesis that ADHD common risk allele burden as indexed by PRS contributes to population-based ADHD developmental trajectories from early childhood to adolescence. Defining susceptibility alleles for a range of psychiatric disorders from large patient case-control discovery samples,[29-34] we found that in a population cohort, higher PRS for ADHD were associated with persistence of ADHD symptoms but that PRS for other disorders were not. The persistent trajectory also had the highest burden of multimorbidity for neurodevelopmental traits and conduct problems in childhood.

Although ADHD typically has an onset—and is thought to be most common—in childhood, approximately 15% of children with a childhood diagnosis show persistence across childhood and adolescence and still meet diagnostic criteria for ADHD in adulthood[4] while only approximately 35% achieve full remission.[2,4] In line with this finding and previous work in the ALSPAC population cohort,[27] we identified 2 trajectory groups of children with a high probability of having ADHD symptoms in childhood that were initially elevated (total of 9.7%). Of these children, approximately 40% were estimated to be in the persistent trajectory, with a high probability of elevated ADHD traits at age 17 years. The other 60% were estimated to be in a childhood-limited trajectory, with a low probability of high levels of ADHD symptoms after approximately age 10 years.

We found that ADHD genetic risk scores were higher specifically in the trajectory with persistent symptoms compared with individuals with consistently low symptoms and childhood-limited symptoms. Twin studies that indirectly infer genetic contributions have suggested that most of the persistence in ADHD symptoms is explained by additive genetic variance and is heritable.[8,17-19] Those with persistent ADHD symptoms also have a higher familial load, with almost a 4-fold higher risk of ADHD in their families than among individuals with childhood ADHD.[18,44] Some twin studies suggest that different genetic risk factors are associated with persistence of ADHD symptoms compared with baseline levels of symptoms.[45] Our work suggests that common genetic variants associated with ADHD diagnosis contribute to the persistence of ADHD symptoms in the general population, as well as initial childhood levels, found in previous work.[21,23] The finding that PRS for ADHD were higher in those with persistent vs childhood-limited symptoms is novel and potentially clinically important given that these trajectories would be indistinguishable on the basis of their ADHD symptoms in early childhood, although this finding would need to be replicated in a clinical sample.

As well as being associated with genetic risk of ADHD, we also found the persistent ADHD trajectory class to be strongly associated with multimorbidity: low IQ, social communication problems, impairment of pragmatic language, and conduct problems in childhood. Individual childhood comorbidities have been implicated as possible predictors of the persistence of ADHD[14] but a global burden of multimorbidity has not previously been assessed, to our knowledge. Although multimorbidity was highest among children in the persistent trajectory, it was also elevated among those in the childhood-limited trajectory. Attention-deficit/hyperactivity disorder shares genetic liability with childhood neurodevelopmental traits and conduct problems in the general population[20,21,23] and our study shows PRS for ADHD to be associated with multimorbidity in these domains. Thus, it is plausible that multimorbidity might be an observable early phenotype marker of this loading and be associated with ADHD developmental trajectories. When controlling for multimorbidity, PRS for ADHD were no longer associated with persistence compared with childhood-limited symptoms, suggesting that the overall childhood burden of neurodevelopmental morbidity may be a phenotypic correlate, and perhaps for now a better index, of a higher genetic loading. Further work will be needed to assess the predictive value of multimorbidity. Although this is a population-based sample, the findings highlight the likely developmental, biological, and clinical importance of multimorbidity, an issue that until now has been considered a health care problem in old age.[46,47] In clinical settings, a hierarchical approach is typically used to simplify and reduce the number of diagnoses. Assessing and describing multimorbidity are therefore not easily achieved with current approaches, yet might be very important for clinical reasons and scientific research.

Recent work has suggested that some forms of ADHD first emerge in adulthood.[5-7] Although our analyses did not identify an adolescent-onset trajectory, using an alternative method for defining the course of ADHD, we identified a subgroup of approximately 2.5% of individuals who had elevated levels of ADHD symptoms at age 17 but not age 7 years. Although our study focused on an earlier age, in line with the observation made by Moffitt and colleagues,[5] this adolescent-onset sub-

group did not show elevated genetic risk scores for ADHD. Although it is possible this finding is owing to low PRS power, we did find an association for the persistent subgroup, despite the subgroup being smaller. This study is now the fourth population study that suggests that a substantial proportion of adolescents and young adults with ADHD have onset at later ages and that finds a very low rate of persistence of ADHD symptoms; moreover, our study finds this pattern when using the same informant (parent) at both time points.

Our findings should be considered in light of some limitations. The Avon Longitudinal Study of Parents and Children is a longitudinal birth cohort study with nonrandom attrition, and more complete data are likely to have been available for individuals with lower levels of psychopathology as well as PRS.[48] However, we used full information maximum likelihood estimation, which fits the model to the nonmissing values for each observation, allowing the use of all individuals, including those with missing data.[49] Results using an alternative method examining 2 time points (ages 7 and 17 years) in individuals with complete data revealed the same pattern of higher PRS for ADHD in children with persistent ADHD traits. In addition, we used a questionnaire to investigate trajectories of ADHD symptoms, which may not generalize to ADHD diagnosis although the SDQ cut-point is well validated against diagnosis. Furthermore, owing to current discovery sample sizes, psychiatric PRS currently explain only a small proportion of the heritability and of phenotypic variance and are therefore underpowered (approximately 0.60 for the analysis using 2 time points).[35] However, our intention was not to explain substantial proportions of phenotype variance but to use PRS as a molecular index of common genetic loading. Finally, ADHD data in ALSPAC were only available up to age 17 years. Future work is needed on environmental factors that may also contribute to the developmental course of ADHD.

Conclusions

We found genetic risk of ADHD to be associated with the developmental course of ADHD traits from early childhood to adolescence in the general population: specifically, ADHD genetic loading was highest in children with persistent symptoms. Genome-wide association studies may benefit from deeper phenotyping of cases to characterize the developmental course of psychiatric disorders. Persistence of ADHD was also associated with greater multimorbidity of childhood neurodevelopmental impairments and conduct problems, which may be a phenotypic correlate of genetic loading and help to identify children with ADHD who are most likely to show persistence of symptoms into adolescence.

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