Disentangling genetic overlap between Attention-Deficit/Hyperactivity Disorder, literacy and language


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Abstract

Background: Interpreting polygenic overlap between ADHD and both literacy- and language-related impairments is challenging as genetic confounding might bias associations. Here, we investigate evidence for links between polygenic ADHD risk and multiple literacy- and language-related abilities (LRAs), beyond genetic effects shared with educational attainment (EA).

Methods: Thirteen LRAs were studied in UK children (N ≤ 5,919). Genome-wide summary statistics on clinical ADHD and years-of-schooling were obtained from large consortia (N ≤ 326,041). ADHD-LRA genetic overlap was assessed with ADHD-polygenic scores (ADHD-PGS, P-threshold ≤ 0.1). Using multivariable regressions (MVR), polygenic links were dissected into trait-specific associations and pleiotropic influences shared with EA.

Results: ADHD-PGS were inversely associated with all LRAs, explaining ≤ 1.6% phenotypic variation. These links are, however, potentially confounded as both ADHD (rg(SE) = -0.53(SE=0.03)) and LRAs (rg(SE)min=0.56(0.09)) are genetically correlated with EA. Using MVR, ADHD-specific genetic influences on reading, spelling, phonemic awareness and verbal intelligence were detected, whereas associations with listening comprehension and non-word repetition were fully attributable to pleiotropic effects involving EA. Using conservative ADHD-instruments (P-threshold<5x10^-8), pooled reading performance showed the strongest trait-specific association, corresponding to a 0.35 decrease in Z-scores per log odds in ADHD-liability (P=9.2x10^-5), with little evidence for confounding. Using subthreshold ADHD-instruments (P-threshold<0.0015), trait-specific associations had lower magnitude, but higher predictive accuracy (e.g. pooled reading: β=-0.03(SE=0.01), P=1.4x10^-6), while EA-related pleiotropic influences of equal strength and, once standardized, at least equal magnitude were present throughout.

Conclusion: Genetic confounding distorts genetic overlap with polygenic ADHD risk and conceals an association profile that primarily involves reading-related impairments, but few language-related problems, with implications for intervention targets.