

BMJ Open Deficits in attention, motor control and perception from childhood to age 30 years: prospective case-control study of outcome predictors

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ABSTRACT

Objective Investigate predictors of adverse outcome in children with and without attention-deficit/hyperactivity disorder (ADHD) combined with developmental coordination disorder (DCD) at 6 years of age.

Design Prospective population-based cohort study.

Setting Western Sweden.

Participants From a screening-based population cohort of 589 individuals, 62 (11 female) diagnosed with ADHD+DCD at mean age 6.6 years, and a comparison group of 51 population-matched (10 female) children were followed prospectively.

Outcome measures Drawn from a clinical reassessment at age 9 years of 110 of the 113 individuals, neuropsychiatric symptoms, continuous performance test results and measures of motor function were used as predictors of outcome in linear regression models. Participants were followed in national registers up to 30–31 years of age for outcomes in adulthood. Predictors were regressed onto an adverse outcome score (range 0–7) comprising seven binary endpoints, and when applicable onto each continuous outcome separately (low educational attainment, low occupation level, psychiatric disorder, psychotropic medication prescription, sick pension, high dependence on social benefits and criminal conviction).

Results Of the 110 individuals, 3 had died. In univariable regression onto the adverse outcome score, the strongest predictors at age 9 years were symptoms of conduct disorder, oppositional defiant disorder, ADHD and motor dysfunction, with an R^2 around 25%, followed by autistic traits ($R^2=15\%$) and depressive symptoms ($R^2=8\%$). Combining these six strongest predictors in a multivariable model yielded an adjusted $R^2=38\%$. Subgroup analyses were similar, except for a strong association of autistic traits with the adverse outcome score in females ($n=20$, $R^2=50\%$).

Conclusion Several neurodevelopmental symptoms, including ADHD severity at age 9 years, accounted for a considerable amount of the variance in terms of adulthood adverse outcome. Broad neurodevelopmental profiling irrespective of diagnostic thresholds should inform research and clinical practice. The study highlights the importance of considering associated comorbidities and problems in ADHD.

Strengths and limitations of this study

- A population-based cohort, avoiding referral bias.
- Broad neurodevelopmental profiling of participants with dimensional assessment of symptoms.
- Unbiased outcomes in adulthood derived from national registers.
- Clinical variables were derived from a cross-sectional assessment, and their stability across time could not be followed.
- Statistical robustness of some findings is limited by model overfitting, probably related to modest sample size.

INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD)¹ occurs in at least 5% of children and persists into adulthood in up to two-thirds of those diagnosed in childhood.²

Although the association between persistence of ADHD and adverse outcome in adulthood has been well established, the childhood predictors for outcome are multifaceted and in need of further study. In a review of the developmental course of ADHD, the role of oppositional defiant disorder (ODD) and conduct disorder (CD) as predictors of adult outcome was highlighted.³ In a subsequent major meta-analytical study, early antisocial tendencies, male sex and low IQ were found to predict criminality.⁴ In another meta-analytical study, ADHD severity, comorbid CD and major depressive disorder predicted ADHD persistence and adverse outcomes in adulthood.⁵ The studies published have been clinic based or retrospective in nature, and thereby subject to multiple forms of bias (eg, selection, recall and attrition bias). Prospective population-based studies are needed for clarification.⁵

Multiple lines of research have converged on the shared aetiology and co-occurrence

of neurodevelopmental disorders (NDDs, including ADHD, developmental coordination disorder (DCD) and autism).^{6–9} This observation is encapsulated in concept of ESSENCE, the acronym for Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations, which emphasises the need to consider the broad panorama of neurodevelopmental/neuropsychiatric disorders in clinical practice.⁸ The conceptualisation of disorders as discrete entities has long been promulgated by influential authorities. For example, ADHD has been an exclusion criterion for a diagnosis of autism spectrum disorder (ASD) in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV), and this has probably hampered research into the extent and nature of overlap across NDDs.^{10–14} It has also suppressed the consideration of subthreshold symptoms that may have major impact regardless of whether or not a (statistically motivated) diagnostic symptom level is reached.^{7 12 15–17} Prospective population-based studies with in-depth physical and mental assessments across multiple clinical domains may therefore supplement current knowledge on prognosis and course.

Aim

The aim was to explore the strength of association between NDD problems and other clinical characteristics in childhood (age 9 years) on the one hand, and adverse outcome in adulthood (age 30–31 years) on the other, in the context of a community-based population study.

METHODS

Participants and rationale

A population-based study screening for NDD upon school entry (mean age 6.6 years) was conducted in 1992–1994 in a rural municipality of Western Sweden. Out of 589 children born 1986–1987, 570 (97%) had parents who agreed to participate in the study with their children. After a screening procedure, ‘deficits in attention, motor control and perception’ (DAMP) (corresponding to Diagnostic and Statistical Manual of Mental Disorders, third edition, revised [DSM-III-R] ADHD with coexisting DCD) was diagnosed in 28 children after clinical assessment.¹⁸ Through screening of adjacent municipalities, 34 further children with clinically diagnosed ADHD+DCD were consecutively recruited, yielding a total of 62 cases (52 male, 10 female) with coexisting ADHD and DCD (ADHD+DCD group). A population-matched comparison group (PM group) of 51 participants (39 male, 12 female) were randomly selected from screen-negative children from the same municipality (matched by sex if possible) and being assessed as ‘non-NDD’ through an identical procedure (participant flow diagram in online supplemental material 1). The diagnosis of DAMP did not exclude the possibility of coexisting conditions more commonly diagnosed today (eg, ADHD, autism, ODD). It was widely used throughout Scandinavia at the time of inception of the original study, and therefore became the

primary focus for the original and subsequent publications.^{18 19 20} Other diagnostic categories often applied, especially in severe cases, but were not required for a diagnosis of DAMP.²¹ Due to this fact, we could capitalise on the broad range of diagnostic categories assessed in childhood, in order to juxtapose their associations with outcome in adulthood.

We have previously reported that the ADHD+DCD group had poorer academic achievement than the PM group at 9 years of age as well as overall poorer outcome at age 30–31 years.^{19 22} For the purpose of the present study, we identified a range of clinical variables recorded at a detailed reassessment at 9 years of age of both the ADHD+DCD and PM groups as ‘predictors’, and a range of data on the individuals followed through to age 30–31 years in national registers as ‘outcomes’. We also used the registry-drawn comparison group from the same county and of the same age (n=310) for reference as needed to define outcomes.²²

Predictors

At 9 years of age, 3 years after study inclusion, children in the ADHD+DCD and PM groups had been reassessed with a psychiatric and neurodevelopmental examination, neuropsychological testing and speech/language evaluation, performed by a pediatrician-led multidisciplinary team. Predictor items were selected from the neuro-motor/developmental, neuropsychiatric, and neuropsychological assessment and from computerised continuous performance tests (CPTs). Analyses were performed on the collapsed sample (ADHD+DCD and PM group). This approach has the advantage of increased statistical power, and we also argued that the shared genetic aetiology of NDDs and their dimensional distribution (ie, continuous distribution in the general population where the same genetic factors account for both the extreme and normal variation of traits) across the general population justified this way of analysing the data.^{23 24}

Neuromotor items at 9 years

We constructed a composite motor score as one of the predictors. Sources for the motor items were broad assessment programmes that did not provide specific validated motor scores (apart from the operationalised criteria used for motor dysfunction in the DAMP diagnosis). To capture all aspects of motor function in the available data, we therefore constructed scores according to each informant and combined them in a global motor score. This global motor score (range 0–80) was derived from four sources: the physician’s neuromotor/developmental examination (seven items), reports from parent (six items), teacher (seven items) and child (nine items), where items were rated as 0=not present, 1=somewhat present, 2=definitely present. The physician neuromotor/developmental assessment included items from the previously published assessment programmes.^{20 25} The teacher, parent and child items were taken from among the motor items in the Aggregate Neurobehavioral Student

Health and one parental item in the Educational Review and Child Behaviour Checklist.^{26 27} Each source (physician, teacher, parent, child) was weighted equally in the global motor score through division of the subscore by number of items and multiplied by 10 (eg, physician subscore (12/7)×10). In instances of missing items in the subscore, the mean score of the other items was imputed for completeness. If there was ≥50% missing data, that subscore was excluded from analysis, and its weight in the composite motor score was subsumed by the remaining subscores (eg, if one source was missing, the composite score from the remaining subscores was multiplied by 4/3). A detailed description of the motor score items is provided in the online supplemental material 1.

Neuropsychiatric and neuropsychological items at 9 years

At the reassessment (age 9 years), psychopathology was rated by the paediatrician according to DSM-IV criteria using a DSM checklist. Autistic traits were measured both at parental interview with the Asperger Syndrome (and High-Functioning Autism) Diagnostic Interview (ASDI), and parent questionnaire-reported responses on the Autism Spectrum Screening Questionnaire (ASSQ, early version).^{28 29} The ASDI is an investigator-based interview focused on the diagnosis of Asperger syndrome, whereas the ASSQ is a questionnaire providing a dimensional measure of autistic traits regardless of diagnostic status.²⁹

Depressive symptoms were rated with the Birleson rating scale for children by reading the questions out loud to the child.³⁰

From these clinical information sources, we selected predictors, indicated in systematic reviews to moderate outcome of ADHD in adulthood.³⁻⁵

DSM-IV checklist scores for each predictor item were calculated as follows: ADHD (0–36), ODD score (0–16) (ADHD and ODD symptoms rated as 0=not present, 1=partially present, 2=definitely present), CD rated as 0=not present, 1=present, 15 items, range 0–15; autism spectrum (ie, ASDI 19 items rated 1–3, range 19–57, the motor dysfunction domain excluded because motor impairment had been an inclusion criterion for diagnosis in the ADHD+DCD group; ASSQ, 27 items rated 0–2, range 0–54); depression (Birleson, 18 items rated 0–2, range 0–36); and Full Scale IQ (FSIQ) according to the Wechsler Intelligence Scale for Children III.³¹

CPT predictors at 9 years

Predictor items were chosen from two computer-based tests of executive function: complex reaction time (mean response time) and Conners CPT (number of CPT omissions, number of CPT commissions and CPT variability of responses).³²

Outcomes

As described previously,²² outcomes were constructed with data from four national registers: the National Patient Register (NPR), the Prescribed Drug Register (NPDR), the Longitudinal Integration Database for Health

Insurance and Social Studies (LISA; 2001–2017) and the National Crime Register (NCR). Using unique personal identification numbers assigned to all citizens at birth, Statistics Sweden (the national agency holding the LISA register) linked all sources and provided de-identified individual-level data. Data were collected for the period 1993–2017 (study inclusion at age 7–30 or 31 years).

Adverse outcome scores for this cohort were previously reported on a composite outcome comprising; occurrence of (1) any psychiatric disorder in the NPR (F-diagnosis according to the International Classification of Diseases version 10), (2) psychotropic medication prescription according to NPDR (N01–N07 according to the Anatomic Therapeutic Chemical classification system, that is, anaesthetics, analgesics, antiepileptics, anti-Parkinson drugs, psycholeptics, psychoanaleptics [including stimulant medications], and other nervous system drugs), (3) sick pension according to LISA and (4) criminal sentence recorded in NCR.²² In order to balance the number of analyses and outcomes reported in this study, we reviewed previously established registry-based outcomes for ways to expand the composite score.³³ On this basis, we used the distribution of outcomes in the registry-drawn comparison group,²² (n=307) as reference, and considered education attainment <10th centile (ie, uncompleted high school), occupation level <10th centile (ie, never had a permanent contract or never worked) and average sum of social benefits received per year >90th centile as a cut-off for poor outcome. For the present study, these three outcomes were therefore collapsed together with the composite score used previously (range 0–4), into an adverse outcome score (range 0–7), with higher scores indicating poorer outcome.

Statistics

Because this study was a follow-up of a population-based study conducted in the 90s, the sample size was defined a priori. Distributions of predictors were (with appropriate indices for non-parametric or parametric data) based on their visual distribution. Correlations were analysed non-parametrically with Spearman's rank correlation coefficients. Apart from instances of partially missing data (motor score), we did no imputations for missing data, and participants were included in all analyses for which they provided data on predictor and outcome. We performed univariable linear regression with baseline variables as predictors and the adverse outcome score (0–7) as outcome. In the results, the β -coefficient describes the direction and slope of association between predictor and outcome (how an increase or decrease in, for example, ADHD symptoms renders change in the adverse outcome score), and the R^2 describes the amount of variance in outcome explained by the predictor. We considered an R^2 with 95% CIs excluding zero, to be significant. Although relevant as an overall measure, this would not elucidate what aspect of outcome the predictors most strongly explained (eg, if the R^2 of IQ as predictor of the adverse outcome score was driven by an association with

educational attainment or criminal convictions). Based on the analysis against the adverse outcome score, we therefore selected relevant predictors with a significant R^2 for univariable analysis against each component of the adverse outcome score.

All seven components of the adverse outcome score were included as binary variables, but we performed the univariable analyses against the more complex underlying data whenever possible. This was done for education level (0–7), occupation level (0–4), sum of social benefits received per year (continuous), average defined daily dose of psychotropic prescriptions received per year (continuous), total number of visits with a primary psychiatric diagnosis registered in the NPR (continuous) and total number of crimes in criminal convictions (continuous). Sick pension was handled as a binary variable.

Lastly, the strongest predictors were combined in a multivariable linear regression onto the adverse outcome score and each of the seven components. Due to multicollinearity, individual β -coefficients were unreliable and therefore not reported. This does not affect the overall R^2 of the model, which captures the joint strength of association of the strongest predictors from the clinical assessment with the adverse outcome score. As sensitivity analyses, we regressed them onto the adverse outcome score stratified by group (ADHD+DCD group and the PM group separately) and by sex. In addition to unadjusted R^2 (as for all analyses), adjusted R^2 and predicted R^2 were reported for all multivariable regressions. The predicted R^2 simulates ability of the model to accommodate new data by removing one data point at a time from the analysis. We considered small discrepancies between adjusted and predicted R^2 to indicate robustness of the model, and the contrary to indicate overfitting, low generalisability and/or high impact from outliers due to small sample size. For the multivariable models, we also reported p values adjusted for false discovery rate according to Benjamini and Hochberg.³⁴ All analyses were performed in R V.3.6.3.³⁵

RESULTS

Participants

Out of a total of 113 children (ADHD+DCD group $n=62$, PM group $n=51$), 3 individuals (2 in the ADHD+DCD group and 1 in the PM group) were excluded from analysis due to non-participation in the assessment at age 9 years. One participant in the PM group provided partial data on predictors (no symptom ratings were obtained, only the physician's assessment and computerised tests) but was kept in the study, leaving a total sample of 110 participants for analysis. A global motor score (based on 4 of 4 subscores in 84%, 3 of 4 in 12% and 2 of 4 in 4% of participants) could be computed for all participants. In 21 instances (5%) concerning 17 individuals (16%), one or more motor subscores could not be calculated ($\geq 50\%$ missing items) due to missing data from parents ($n=3$), teacher ($n=6$) or child ($n=12$). For subscores with a few

missing items, the mean value of the remaining items was imputed in 39 (1%) instances.

Predictors

Clinical characteristics are presented in [table 1](#). As expected, participants with ADHD+DCD tended to have higher symptom load regarding all clinical characteristics and motor scores than those in the PM group, as well as significantly lower full-scale IQ (FSIQ) (ADHD+DCD mean FSIQ 94, SD 17, PM group mean FSIQ 104, SD 13, mean difference 11, 95% CI 5 to 17).

Outcomes

Data on outcomes (ie, any psychiatric disorder diagnosis, psychotropic medication prescription, sick pension, criminal sentence, social benefits >90th centile, education level <10th centile and occupation skill level <10th centile) were available for all. Overall, 65 out of 110 (59%) participants experienced one or more of the seven adverse outcomes in adulthood, 42 of 60 (70%) with ADHD+DCD (mean number of outcomes 1.9 (SD 2.0)), and 23 of 50 (46%) in the PM group (mean 0.8 (SD 1.2)). Nine (15%) participants in the ADHD+DCD group and one (2%) in the PM group experienced five or more adverse outcomes ([table 1](#), [figure 1A](#)). The frequency with which each adverse outcome occurred is displayed in [figure 1B](#), ranging from 10 (9%) for sick pension to 36 (33%) for psychotropic medication prescription.

Three participants (one in the ADHD+DCD group and two in the comparison group) died at an early age (all before 19 years of age), thus having the worst outcome (death), something not included in the adverse outcome score. Although they had been unexposed in terms of one endpoint (welfare benefits) and less exposed in terms of other endpoints, we believe that this attrition bias was evened out (ie, less risk of psychiatric diagnosis, medication and criminal conviction, counterbalanced by low educational attainment and occupational status) and their poor outcome accounted for to some extent in the adverse outcome score.

Regression analyses

Results from linear regression of selected predictors onto the adverse outcome score are presented in [figure 2](#). Several clinical predictors and the global motor score had a significant R^2 , ranging from 2% for FSIQ to 28% for ODD score, whereas no CPT predictor had predictive value. The associations between adverse outcomes and global motor score, ODD and CD scores, respectively, were all comparable with that of ADHD. Selecting the strongest predictors from separate domains (ADHD, ODD, CD, depression, ASSQ and global motor score) in a combined multivariable model yielded the largest R^2 (adjusted $R^2=38\%$). Due to substantial predictor intercorrelation (ADHD, ODD, CD were moderately correlated), and modest increase of R^2 in the multivariable model compared with the strongest univariable predictor ($R^2=28\%$ for ODD, multivariable model $R^2=38\%$), it can

Table 1 Clinical characteristics at 9 years of age and adverse outcomes in adulthood

	PM group	ADHD+DCD group
n	50	60
Female, n (%)	11 (22)	9 (15)
Neuromotor items (median (IQR))		
Global motor score (range 0–80)	9.4 (4.0–15.2)	31.9 (24.0–45.7)
Physician (range 0–20)	3.0 (1.0–5.0)	9.5 (7.0–12.0)
Teacher (range 0–20)	0.0 (0.0–2.0)	5.6 (2.4–9.0)
Parent (range 0–20)	0.0 (0.0–1.0)	2.40 (1.0–4.0)
Child (range 0–20)	2.0 (1.0–4.0)	7.0 (5.0–9.0)
Dysdiadochokinesia, n (%)	19 (38)	49 (82)
Abnormal alternating jumps, n (%)	2 (4)	29 (48)
Abnormal advanced alternating jumps, n (%)	26 (52)	55 (92)
Neuropsychiatric and neuropsychological items (median (IQR))		
ADHD score (range 0–36)	3 (1–7)	12 (6–19)
ASDI score (range 19–57)	19 (19–20)	22 (20–24)
ASSQ score (range 0–54)	0 (0–1)	6 (1–17)
DAMP criteria* (range 0–5) (mean (SD))	0.8 (0.8)	4.0 (0.9)
Full scale intellectual quotient (mean (SD))	105 (13)	94 (17)
Borderline intellectual function (FSIQ <86), n (%)	3 (6)	21 (35)
Read and writing difficulties, n (%)	10 (21)	32 (55)
Neuropsychiatric predictors (median (IQR))		
Conduct disorder score (range 0–15)	0 (0–0)	0 (0–1)
Oppositional defiant disorder score (range 0–16)	0 (0–2)	2 (0–4)
Depression score (range 0–36)	7 (4–9)	8 (6–11)
Continuous performance test (CPT) predictors (median (IQR))		
Conners CPT omissions	5 (2–12)	11 (5–19)
Conners CPT commissions	20 (12–27)	22 (16–26)
Conners CPT variability	12.9 (9.2–20.3)	15.5 (11.7–28.8)
Complex reaction time	0.76 (0.71–0.87)	0.83 (0.74–0.92)
Adverse outcome composite score (range 0–7) (mean (SD))	0.84 (1.17)	1.87 (2.01)
Adverse outcomes, n (%)		
0	27 (54)	18 (30)
1–2	17 (34)	26 (43)
3–4	5 (10)	7 (12)
5–7	1 (2)	9 (15)

*The diagnosis of DAMP was defined as the combination of: (1) cross-situational impairing attention deficit, with or without impairing hyperactivity/impulsivity; and (2) impairing deficit in at least one of the following areas: gross motor, fine motor, perception (ie, the experience and interpretation of sensory information), or speech language (in the absence of intellectual disability and/or cerebral palsy/other major neurological impairment). Severe DAMP was diagnosed in cases showing the combination of (1) and all of the deficits listed under (2). ADHD+DCD group, attention-deficit/hyperactivity disorder combined with developmental coordination disorder group; ASDI, Asperger Syndrome (and High-Functioning Autism) Diagnostic Interview; ASSQ, Autism Spectrum Screening Questionnaire; DAMP, deficits in attention, motor control and perception; PM group, population-matched group.

be inferred that predictors predominately explained the same variance in the adverse outcome score.

To further elucidate differential associations between the predictors and outcomes, we regressed them separately onto each of the seven adverse outcomes. We also regressed the multivariable model onto each outcome,

with and without FSIQ. We then plotted R^2 of each predictor with 95% CIs for all outcomes as displayed in [figure 3A–G](#). The strongest predictors of the adverse outcome score (global motor score, ADHD, ODD, CD, depression and ASSQ score) recurred as strongest predictors in each outcome-specific analysis, outperforming

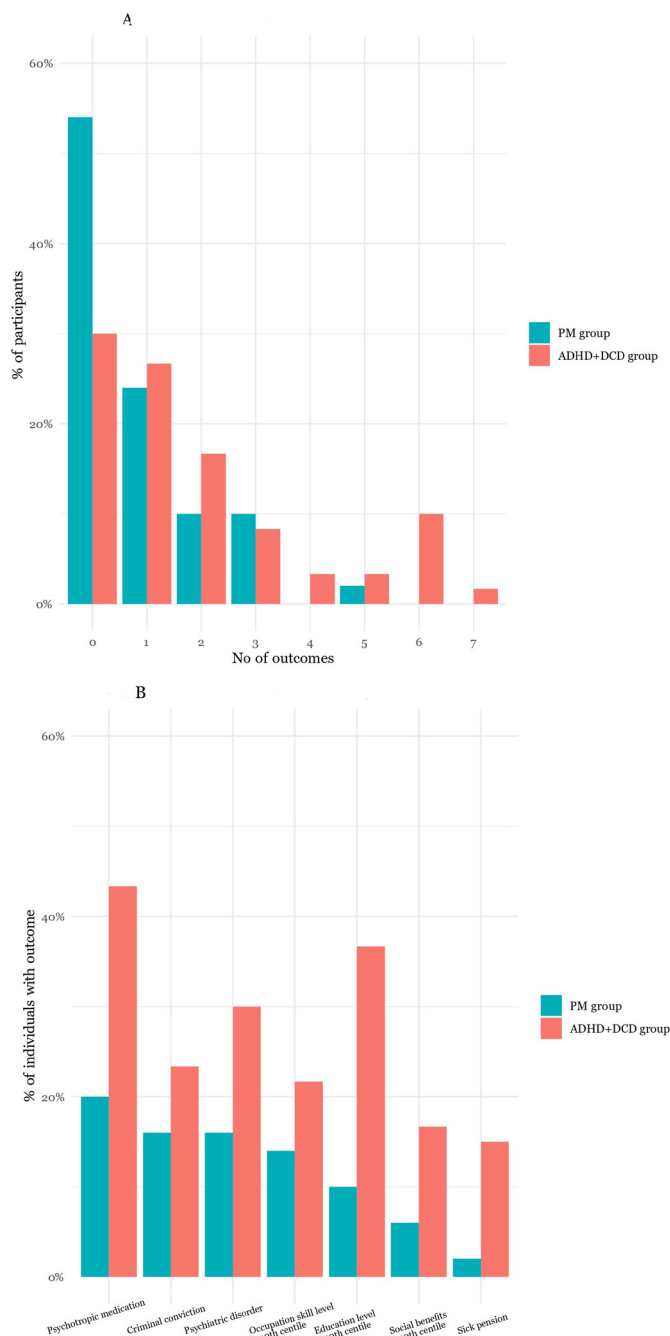


Figure 1 (A) Distributions of seven adverse outcomes across the ADHD+DCD group (n=60) and PM group (n=50). (B) Frequency with which each outcome occurred by group. ADHD+DCD group, attention-deficit/hyperactivity disorder combined with developmental coordination disorder group; PM group, population-matched group.

FSIQ as univariable predictor in almost all outcomes except educational attainment.

Predictor correlations

The correlation between diagnostic status at baseline and predictors that were significantly associated with the adverse outcome score were explored. As visualised in figure 4, the motor subscores were strongly correlated with the global motor score (Spearman's $r > 0.75$) and

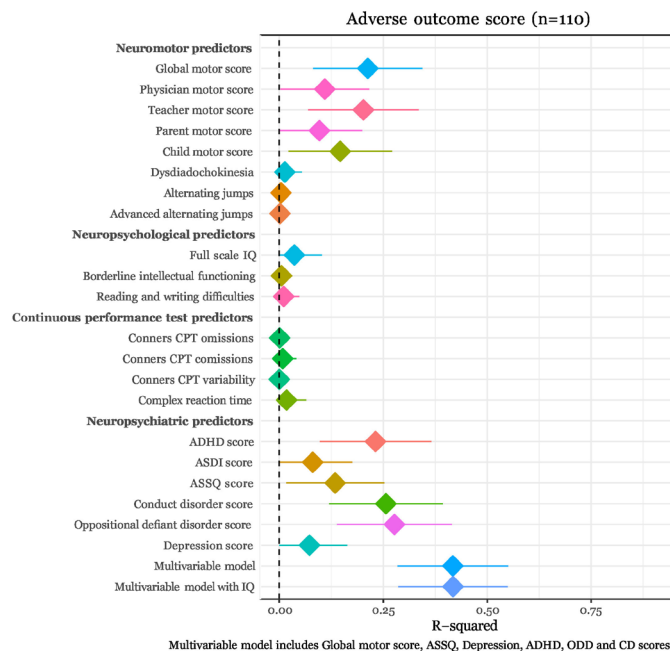


Figure 2 Unadjusted coefficients of determination (R^2) with 95% CIs of the association between childhood predictors and the adverse outcome score in adulthood. ADHD, attention-deficit/hyperactivity disorder; ASDI, Asperger Syndrome (and High-Functioning Autism) Diagnostic Interview; ASSQ, Autism Spectrum Screening Questionnaire; CD, conduct disorder; ODD, oppositional defiant disorder.

moderately correlated with each other. The weakest correlation was between child and teacher motor score ($r=0.47$) and the strongest correlation between child and parent motor score ($r=0.64$). Depressive symptoms were only weakly correlated with ODD symptoms and self-rated motor abilities (Birleson vs ODD $r=0.37$, Birleson vs child motor score $r=0.45$), whereas symptoms of ADHD, ODD and CD were moderately intercorrelated (ADHD vs ODD $r=0.62$, ADHD vs CD $r=0.56$, ODD vs CD $r=0.64$). Full-scale IQ was uncorrelated with all selected predictors except the motor predictors (FSIQ vs global motor score $r=-0.49$).

Sensitivity and subgroup analyses

Results of adjusted and predicted R^2 for each multivariable model with and without IQ are presented in online supplemental table 1. Results were most robust for associations with the adverse outcome score (adjusted $R^2=38\%$, predicted $R^2=30\%$) and social benefits (adjusted $R^2=42\%$, predicted $R^2=29\%$). There was a large difference between adjusted and predicted R^2 in associations with psychiatric medications (adjusted $R^2=37\%$, predicted $R^2=2\%$), indicating model overfitting and low generalisability. Full-scale IQ strengthened the association of the multivariable model with educational attainment (adjusted R^2 increasing from 17% to 26%), but did not strengthen the association with any other outcome.

We performed subgroup analyses of predictors onto the adverse outcome score. Associations generally were attenuated in the PM group compared with the ADHD+DCD

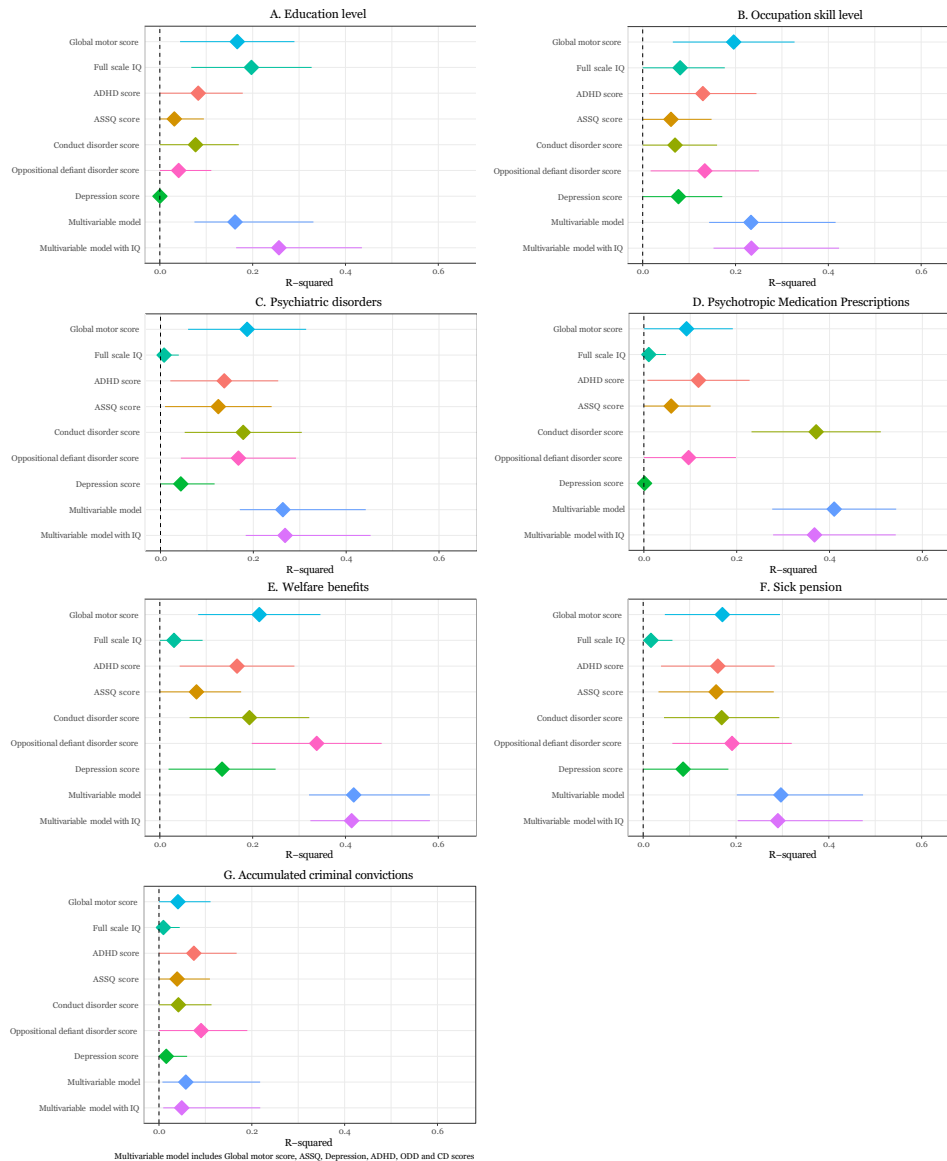


Figure 3 A-G. Unadjusted coefficients of determination (R^2) with 95% CIs of the association between the strongest childhood predictors and the seven adverse outcomes in adulthood. ADHD, attention-deficit/hyperactivity disorder; ASSQ, Autism Spectrum Screening Questionnaire; CD, conduct disorder; ODD, oppositional defiant disorder.

group (multivariable-adjusted R^2 PM group=8%, ADHD+DCD group=39%, predicted R^2 PM group=0%, ADHD+DCD group=28%, figures in online supplemental material 1). Analyses stratified by sex showed maintained R^2 in the multivariable model (adjusted R^2 males=39%, females R^2 =52%, predicted R^2 males=29%, females=0%). The strongest univariable predictors for male participants were ADHD, ODD, CD and global motor score ($R^2 > 22\%$), whereas ASSQ score was markedly associated with outcome for female participants ($R^2=55\%$), although the low predicted R^2 in the model for females is indicating overfitting.

There were seven participants in the PM group with an adverse outcome score >2 (five scoring 3, and one scoring 5) or death at an early age (age <19 years, two participants). One had missing data for symptom ratings and FSIQ. With regard to the most significant predictors and

FSIQ, five of seven exhibited high symptom load (ratings >75 th centile compared with the PM group) in any predictor (ADHD 3/7, ODD 1/7, CD 1/7, low FSIQ 1/7, global motor score 2/7), and had a mean centile rank of 48 (excluding FSIQ).

Nine participants from the ADHD+DCD group (15%) had received a diagnosis of NDD as adults in routine care (a diagnosis registered in the NPR, four ADHD, three ASD, two ADHD+ASD). They had high adverse outcome scores (two scoring 4, two scoring 5, four scoring 6, one scoring 7) and a high symptom load at age 9 years (ratings >75 th centile compared with the whole cohort in the strongest predictors: global motor score 8/9, ASSQ 7/9, ODD 8/9, CD 7/9, depression 5/9, ADHD 8/9, low FSIQ 2/9) with a mean centile rank of 78 (excluding FSIQ).

Fourteen participants from the ADHD+DCD group (23%) had received a psychiatric diagnosis in specialty

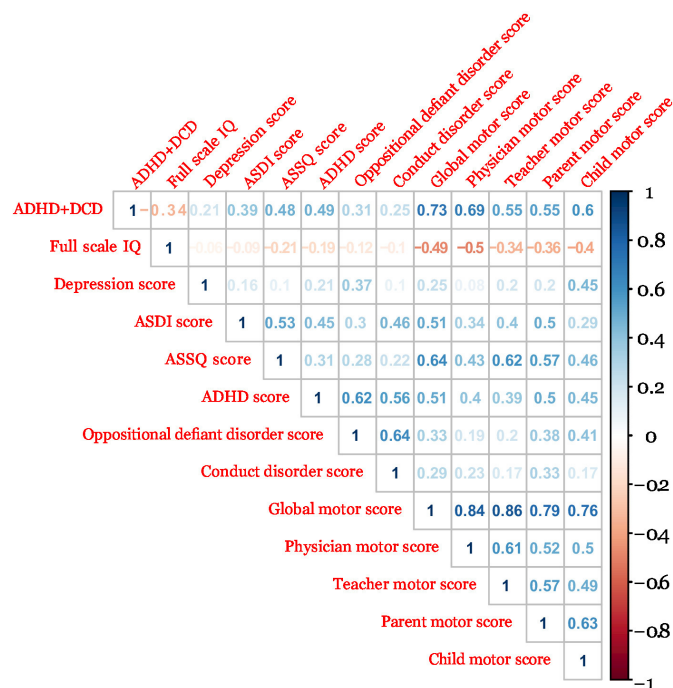


Figure 4 Spearman's r correlations between childhood predictors at age 9 years (n=110). Blue colour indicates positive correlation, red indicates negative correlation and digit opacity corresponds to the strength of the correlation. ADHD, attention-deficit/hyperactivity disorder; ASDI, Asperger Syndrome (and High-Functioning Autism) Diagnostic Interview; ASSQ, Autism Spectrum Screening Questionnaire; DCD, developmental coordination disorder.

care as adults.²² They had high adverse outcome scores (one scoring 7, four scoring 6, two scoring 5, two scoring 4, three scoring 3, two scoring 2) and a high symptom load at age 9 years (ratings >75th centile compared with the whole cohort in the strongest predictors: global motor score 11/14, ASSQ 10/14, ODD 9/14, CD 7/14, depression 7/14, ADHD 9/14, low FSIQ 5/14) with a mean centile rank of 68 (excluding FSIQ).

DISCUSSION

In this follow-up study of individuals with ADHD+DCD and a PM group, the clinical profile at age 9 years accounted for about 40% of the variance of the score that included seven adverse outcomes up to 31 years of age. Neuromotor function and subsyndromal symptoms of CD and ODD were as strongly associated with negative outcome as were ADHD symptoms, whereas rather surprisingly, FSIQ was 'non-informative', except with regard to educational attainment. Autistic traits (measured with the ASSQ) were most strongly associated with adverse outcome among female participants (although this must be interpreted cautiously due to the small sample size indicating uncertain generalisability), and externalising symptoms (ADHD, ODD, CD) and poorer global motor functioning were more prominent among males. Thus, in a community

sample enriched with ADHD and DCD, several factors were equally or more strongly associated with adverse outcome than was ADHD severity per se.

Comparisons with prior research are complicated for two important reasons. First, few previous longitudinal follow-up studies have reported in detail on 'comorbidity' in ADHD. Second, longitudinal outcome in ADHD is sometimes defined as adverse outcome (eg, unemployment) and sometimes as the degree of persistence of ADHD symptoms. In this study, participants with a community diagnosis of ADHD or ASD in adulthood (ie, 'persisters') were high in childhood symptom rating as well as in adverse outcome scores. It is in line with several other studies showing that the greater the total symptom load in childhood, the more the impairment is likely to persist into adulthood.³⁶⁻³⁸

The importance of early non-ADHD symptoms for prognosis (ODD, autistic traits, CD) is in agreement with the findings of at least two other studies using repeated assessments. Sasser *et al* reported repeated parent ratings and outcome in adolescence for a cohort of 891 participants, where elevated aggression, emotional dysregulation, and emotional distress at 9 years of age were associated with ADHD persistence and poorer outcome.³⁹ Similarly, the Avon Longitudinal Study of Parents and Children showed 'multimorbidity' (low IQ, social communication problems, impairment of pragmatic language and conduct problems at ages 7-9 years) to be associated with poorer ADHD outcome in adolescence.⁴⁰

The aforementioned studies did not include neuromotor function in the characterisation of participants. This may reflect the tendency to rely on interviews and rating scales as advised by the DSM criteria, both for research and clinical practice. In doing so, a parallel literature on clinical utility of the physical examination and neuromotor function (sometimes referred to as 'soft signs') may have been overlooked.⁴¹⁻⁴² Soft signs are a salient finding across pervasive developmental deviations and may be elicited in children with, for instance, fetal alcohol spectrum disorders, ADHD, autism and subsequent schizophrenia.⁴²⁻⁴⁸ Research data and clinical experience indicate that motor coordination problems can reflect executive dysfunction, negatively impacting academic achievement.⁴⁹ Executive dysfunction may also encompass impaired skill acquisition across a host of activities of daily life, emotion regulation and subsequent mental health problems that extend beyond discernable motor impairments.⁵⁰ This is consistent with the observation in the present study that the global motor dysfunction score had the strongest univariate association with low occupational level in adulthood. Because symptoms of ADHD, ODD and CD were highly intercorrelated in our cohort, they likely account for the 'same' variance in outcome. Neuromotor function was only weakly correlated with ODD and CD, but equally related to the adverse outcome score. Executive dysfunction is considered a hallmark for ADHD persisting into adulthood.⁵¹ Assessing neuromotor function may thereby provide

clinically meaningful prognostic information beyond that of externalising symptoms.

As a consistently strong predictor in this cohort, symptoms of ODD were reported for a majority of children with ADHD+DCD, and could be considered a marker of ADHD severity.¹⁵ A continuity of symptoms of ODD and CD in childhood and antisocial behaviour in adulthood is often emphasised.⁴ But as previously shown, ODD symptoms load on several dimensions of oppositionality (angry/irritable, argumentative and vindictiveness) that are differentially associated with outcomes (eg, vindictiveness more strongly linked to antisocial behaviour).^{52–53} Conduct disorder showed the strongest univariate association with psychotropic medication prescribed in adulthood ($R^2=37\%$), and less so with criminality. This is in line with previous reports of association between early conduct problems and not only criminality, but also high levels of internalising problems, low education and reciprocity of welfare benefits.^{54–55}

As intelligence subtests are intercorrelated and can be combined into a general index ('g factor'), a 'p factor' of psychopathology has been proposed.^{33–56} Similar to the g factor of intelligence, the p factor could have predictive validity by providing an index of severity. It accounts for the observation that clinically significant psychiatric problems start early during child development, are correlated, and predict a variety of psychiatric disorders and adverse outcomes across the lifespan.^{33–57–60} This is restating the clinically observed phenomenon that impairments co-occur and although already discernable on a population level in national registers, this association is likely stronger when subsyndromal symptoms are considered and the assessment procedure is comprehensive. Although routine care diagnoses generally have reasonable positive predictive values, some types of problems are rarely diagnostically acknowledged. For example, according to a Danish register study, the prevalence of DCD was likely underestimated by a factor of about 500 (a prevalence of 0.01% vs 5% expected).^{42–61} An 'ESSENCE factor' of neurodevelopment that takes rarely acknowledged diagnoses (eg, DCD, dyslexia) and subsyndromal symptoms into account (eg, milder tics, autistic traits, borderline intellectual function) may provide incremental value to a severity index such as the 'p factor'.

The findings from this study should be of interest both for clinicians in paediatrics/child neuropsychiatry and in adult psychiatry. First, comprehensive neurodevelopmental assessments in childhood beyond the presenting complaints (eg, temper tantrums or inattention only) call for attention of additional problems that may surface with time. Second, regardless of whether or not a diagnostic symptom level is *currently* reached, these problems should be acknowledged as possible prognostic indicators of persisting impairment. In addition, symptoms such as reading difficulties and dyslexia may be markers of a range of co-occurring NDDs, for example, ADHD and DCD, and therefore in need of being addressed to provide targeted interventions/adjustments.^{62–63}

Third, assessing syndromes with childhood onset retrospectively among adults is a challenge because the clinical picture is often muddled by symptoms that lack 'diagnostic category specificity'. In adults, symptoms of depression and anxiety, accumulated psychosocial stressors, unemployment and substance use may be consequences of undiagnosed NDDs.⁶⁴ The adult presentation may display a less typical symptom profile, for example, camouflaging autistic impairments, childhood hyperactivity—now manifested as inner restlessness—and vague secondhand information about childhood symptoms, all of which contribute to a more challenging diagnostic situation.

For the adult psychiatry setting, our findings indicate that besides prominent ADHD symptoms in childhood, participants with the most adverse outcomes as adults were those with the highest symptom load, with several co-occurring problems, in childhood. Although a neuropsychiatric diagnostic assessment in adulthood may have a primary focus of ADHD or autism, there is a need to cover the whole panorama of NDDs including neuromotor function in both adulthood and childhood. Patients with impairing symptoms of ADHD or ASD as adults are likely to have/or have had symptoms of other disorders as well. Because childhood symptoms can be difficult to ascertain retrospectively, related symptoms of NDDs can be used as supportive findings in difficult cases.⁶⁵ Symptoms of NDD in girls, reported by parents, are consistently lower than those of boys and may therefore be harder to capture adequately.^{66–69} Taking into consideration related NDD symptoms therefore may be of extra value in women evaluated as adults.

Lastly, it has been exemplified that many adults with a diagnosed psychiatric disorder also have ADHD, in many cases unrecognised and/or undertreated.⁷⁰ In line with evidence of co-occurring problems, it may therefore be prudent to look for NDDs primarily among adults with prominent impairments. Coexisting ADHD is most prevalent among patients with mood, anxiety, substance use, impulse-control disorders, and eating disorders/obesity and may both compromise compliance and be mistaken for poor treatment response.⁶⁴

Strengths and limitations

The inclusion of a population-based sample allows for tentative generalisation regarding conclusions although the sample size was small. A broad range of NDD symptoms were assessed, taking into account coexisting symptoms irrespective of diagnostic status. The objective outcome assessment through national registers allows for unbiased, validated measurements without attrition.

Predictors were derived from a cross-sectional assessment, and their stability across time is not known, as repeat measurements were not performed. This may lead to underestimation of their predictive value and may partially explain that about half of those with ADHD+DCD experienced no adverse outcome. As shown by von Wirth *et al*, persistent externalising symptoms in adolescence in

addition to 9 years of age increased the proportion of variance explained in education and occupation outcome.⁷¹ Environmental factors, family practices and life events, as well as personality traits in part operating independently of NDDs, were not measured and may contribute to outcomes.⁷²

The association of clinical characteristics with the outcome ‘psychotropic medication prescription’ may be inflated due to confounding by indication, since participants with ADHD at baseline are more likely prescribed medication for ADHD (stimulants). But as reported previously, only 6 of 61 with ADHD (10%) had been prescribed stimulants, and prescription rates were elevated in the ADHD+DCD group compared with the PM group for almost all nervous system drugs.²² We therefore think the effect from confounding by indication is marginal, and reiterate that we consider this cohort to mainly portray the natural course of the syndrome.²² Associations in the multivariable models for the cohort as a whole were generally robust for adjustment for false discovery rate and predicted R^2 . In contrast, the subgroup analyses were less reliable, and comparisons of the strength of associations between the significant predictors are due to the wide CIs not possible, and should not be given weight.

CONCLUSIONS

In this follow-up study of individuals with ADHD+DCD and a PM group, several neurodevelopmental symptoms/disorder problems other than ADHD severity at age 9 years accounted for a considerable amount of the variance in adulthood adverse outcome. Broad neurodevelopmental profiling irrespective of diagnostic thresholds should inform research and clinical practice.

Correction notice This article has been corrected since it was first published. The article title has been modified.

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Ethics approval Caregivers had signed informed consent on behalf of their children in the original study. Swedish law states that research of interest for patients with similar conditions as that being studied may not require explicit consent, if it poses minimal risks to the individual and is unattainable by other reasonable means. A waiver of consent was therefore approved from the regional ethics committee at the University of Gothenburg (Dnr 172-18) for a registry-based follow-up.

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