Early Life Neurodevelopmental Indicators of ADHD and Autism at Age 10: A Prospective Cohort Study

Camilla Grube
Copenhagen Prospective Studies on Asthma in Childhood
María Hernández-Lorca
Copenhagen Prospective Studies on Asthma in Childhood
Rebecca K Vinding
Copenhagen Prospective Studies on Asthma in Childhood
Julie Rosenberg
Copenhagen Prospective Studies on Asthma in Childhood
Kristina Aagaard
Copenhagen Prospective Studies on Asthma in Childhood
Michael Widdowson
Copenhagen Prospective Studies on Asthma in Childhood
Tingting Wang
Copenhagen Prospective Studies on Asthma in Childhood
Nilo Vahman
Copenhagen Prospective Studies on Asthma in Childhood
Hanne Lunn Nissen
Copenhagen Prospective Studies on Asthma in Childhood
Jens Richardt Møllegaard Jepsen
Mental Health Services
Bjørn H Ebdrup
Mental Health Services
Klaus Bønnelykke
Copenhagen Prospective Studies on Asthma in Childhood
Bo Chawes
chawes@copsac.com

Copenhagen Prospective Studies on Asthma in Childhood

Research Article

Keywords: ADHD, ASD, Neurodevelopment, Neurodevelopmental disorders, Risk Indicators

Posted Date: March 28th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-9105614/v1

Additional Declarations: No competing interests reported.

Abstract

Purpose

Attention-Deficit/Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) are the two most prevalent neurodevelopmental disorders, characterized by early-onset impairments across multiple developmental domains, including language, motor coordination, cognition and behavioral regulation. Despite the early signs, diagnoses are often delayed, limiting opportunities for timely interventions. Evidence suggest that deviations in these domains may be predictive of later ADHD and ASD. However, findings have been inconsistent, and further clarification is needed to improve early identification.

Methods

This prospective study followed 590 children from the COPSAC2010 birth cohort to examine associations between neurodevelopmental measurements from birth to age 3 years and later clinical diagnoses and traits manifestations of ADHD and ASD at age 10. Early life neurodevelopment data included motor milestones, language production measured at age 12 and 24 months, cognitive functioning and behavioral/emotional observations at 36 months, as well as a general development questionnaire at 3 years. Associations were analyzed using logistic and linear regression analyses adjusted for demographic and perinatal covariates.

Results

We found that lower word production, shorter sentence, lower cognitive functioning and more behavioral/emotional problems in early life were significantly associated with increased risk of ADHD and elevated ADHD and ASD traits at age 10.

Conclusion

Deficits in language, cognitive functioning and more behavioral and emotional problems in early life could serve as risk indicators for later neurodevelopmental disorders. Recognizing these risk indicators could inform timely detection and improve developmental outcomes.

What is Known – What is New

- ADHD and ASD are highly heritable neurodevelopmental disorders that may be preceded by early differences in language, cognition, and motor development. Evidence on early developmental markers, particularly motor milestones, remains inconsistent and few prospective cohorts combine developmental, clinical, and genetic data.

- In this population-based birth cohort, poorer early language, cognition, and behavioural regulation were associated with later ADHD diagnosis and with increased ADHD and autistic traits at age 10.

INTRODUCTION

Attention-Deficit/Hyperactivity Disorder (ADHD) and Autism Spectrum Disorder (ASD) represent the two most prevalent neurodevelopmental disorders worldwide affecting around 7% and 1% of children, respectively[1]. They are characterized by impairments in developmental domains such as language, motor skills, communication and social interaction, behavioral flexibility, regulation of attention, activity and impulses[2,3].

The Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-V) classifies ADHD into three presentations: Inattentive, Hyperactive-Impulsive, and Combined[4]. ADHD is associated with long-term adverse outcomes including academic underachievement, addiction, psychiatric comorbidities and increased suicide risk[5]. Symptoms typically begin before age seven, but diagnosis often occurs at 10–11 years old, creating a diagnostic gap[6]. Early recognition and intervention may improve long-term outcomes[7] and quality of life[8].

ASD is characterized by impaired social communication, repetitive behaviors and hyperresponsiveness to sensory stimuli[9]. Symptom severity varies widely[10]. Although ASD can be diagnosed before age three, many children remain undiagnosed until school age or adolescence, and some reach adulthood without diagnosis[11]. Early interventions can improve functioning[12]. As with ADHD, diagnosis relies on a detailed developmental history and observations using standardized diagnostic tools[13].

ADHD and ASD show strong genetic components, with heritability estimates of about 70% and to 90%, respectively[3,14]. Genome-wide association studies (GWAS) identify risk variants that can be summarized into polygenic risk scores (PRS)[15], reflecting an individual’s inherited susceptibility[14].

Existing studies show mixed findings on early neurodevelopment. Children later diagnosed with ADHD may walk early (before 11 months) or late (after 15 months)[16], though systematic reviews report no consistent associations between early motor development and ADHD[17]. Lower cognition functioning between 15 months and four years have been linked to later ADHD diagnosis at age 9-11[18]. Higher ADHD PRS has been associated with enhanced motor development at 18 months[19] and language difficulties at ages 5 and 8 years[3]. For ASD, delays in motor skills, language and cognition at age 12–60 month, have been reported, and that motor delays becoming more pronounced with age[20]. Motor and

communication (both verbal and non-verbal) skills may be interrelated, as motor skills shape children's interaction with outher[21], and early motor skill impairments may precede autism symptoms[21]. Higher ASD PRS has been linked to language difficulties at 18 months and motor difficulties at 36 months[3]. These inconsistencies, especially regarding motor skills, highlight the need to clarify early life manifestations of ADHD and ASD.

$COPSAC_{2010}$ cohort[22] is a population-based, prospective cohort consisting of 700 mother-child pairs followed from pregnancy throughout childhood, with detailed neurodevelopmental data (milestones, language, cognition), and deep clinical neuropsychiatric assessment at age 10 (the COPSYCH study)[23]. Data also includes genome-wide data for PRS analyses. Few cohorts combine detailed developmental, clinical, and genetic data in the same children together with psychiatric diagnoses later in life. Using this dataset, we aimed to investigate associations between early neurodevelopmental measures from birth to age three and both categorical and dimensional ADHD and ASD outcomes at age 10. We hypothesized that i) deviations in early neurodevelopment are associated with increased risk of ADHD or ASD; ii) deviations are associated with more and ADHD or ASD traits; iii) higher ADHD or ASD PRSs is associated with early neurodevelopment deviations; and iv) higher ADHD or ASD PRS is associated with both and diagnosis and more traits.

METHODS

Participants

The children participating in this study are part of the $COPSAC_{2010}$ cohort, an ongoing population-based mother-child cohort (n = 700). The families have been followed for scheduled visits at the COPSAC clinical research unit, with early childhood asthma as the primary outcome and neurodevelopment as secondary outcome, including an extensive neurocognitive and psychopathological evaluation at age 10 as part of the COPSYCH study[23].

Neurodevelopment measures in first years of life (0–3 years)

We assessed early neurodevelopment from birth to age three by motor milestones, language development, cognitive performance, and general development. At age ten, categorical diagnoses of ADHD and autism were established through K-SADS-PL clinical interviews and assigned according to ICD-10. Dimensional traits were captured using validated parent-report scales (ADHD-RS and SRS-2). Polygenic risk scores for ADHD and autism were generated using large GWAS meta-analyses. Full descriptions of all instruments, demographic and perinatal factors are provided in Supplementary.

Statistics

Data analysis was conducted in R (R Foundation for Statistical Computing, Vienna, Austria). Developmental milestones were reduced using principal component analysis (PCA). ADHD/autism and non-ADHD/autism groups were compared using Student's t-test for normally distributed continuous variables, Mann–Whitney U test for skewed continuous variables, and chi-square tests for categorical variables. Associations between early neurodevelopmental measures and ADHD/ASD traits were estimated with adjusted linear regression, and with ADHD/autism diagnosis (yes/no) at age 10 using adjusted logistic regression. Neurodevelopmental measures significantly associated with ADHD diagnosis were grouped into quartiles to assess linearity. Associations between ADHD/ASD PRS and diagnosis (yes/no) and traits were estimated with adjusted logistic and linear models. Covariates included sex, household income, maternal education, paternal education, gestational age, and maternal age at birth. As a second step, adjusted sensitivity analyses were performed: i) logistic regression between early neurodevelopment and ADHD diagnosis stratified by ADHD presentation, and ii) linear regression between early neurodevelopment and ADHD-RS subscales. Multiple comparisons were corrected using a 0.05 false discovery rate (FDR).

RESULTS

Out of 700 children, 604 (86%) participated in the COPSYCH study at age 10 with complete psychopathological data from 593 (85%) children. Three children were excluded from the analyses due to developmental coordination disorder, delayed psychomotor development and hydrocephalus, resulting in a final sample of 590 children. Of these, we diagnosed 65 children (11%, 49 boys) with ADHD and 16 (3%, 10 boys) with autism.

Baseline characteristics regarding demography and perinatal factors among children with and without ADHD and with and without autism are presented in Table 1. Pair-wise comparisons showed that the proportion of boys was significantly higher in the ADHD group and that mothers had a lower level of education in the ADHD compared to the no ADHD group. Mothers in the ADHD group were more likely to have smoked during pregnancy and had generally lower household income compared to the no ADHD group, although not statistically significant. There were no significant differences between the autism and no autism groups.

Table 1
Baseline characteristics regarding demographic and perinatal factors of the ADHD, no ADHD, autism and no autism groups. The children in no ADHD or no autism group are healthy or have other psychiatric diagnosis except from ADHD or autism, respectively
Abbreviations: ADHD: Attention Deficit /Hyperactivity Disorder, N (%): Number (Percentage), SD: Standard Deviation, IQR: Interquartile Range

DEMOGRAPHIC	ADHD	NO ADHD	P-VALUE	AUTISM	NO AUTISM	P-VALUE
N (%)	65 (11)	528 (89)		16 (2.69)	574 (97.3)	
Sex (male, N (%))	49 (75.4)	256 (48.5)	**< 0.001**	10 (62.5)	294 (51.2)	0.524
Maternal age at birth (mean (SD))	32.2 (4.7)	31.4 (4.3)	0.745	33.1 (5.1)	32.3 (4.3)	0.490
Paternal age at birth (mean (AD))	34.9 (5.7)	34.6 (5.2)	0.747	35.4 (6.3)	34.6 (5.2)	0.524
Household income 3 month before birth N (%)			0.093			0.926
high > 250,000 DKK	5 (7.7)	86 (16.3)		2 (12.5)	89 (15.5)	
medium > 150,000-250,000 DKK	33 (50.8)	274 (52.3)		9 (56.2)	298 (52.0)	
low 150,000 DKK	27 (41.5)	164 (31.3)		5 (31.2)	186 (32.5)	
Maternal level of education N (%)			**0.006**			0.296
university	9 (13.8)	160 (30.3)		2 (12.5)	166 (28.9)	
tradesman certificate	46 (70.8)	328 (62.1)		13 (81.2)	359 (62.5)	
elementary	10 (15.4)	40 (7.6)		1 (6.2)	49 (8.5)	
Paternal level of education N (%)			0.719			0.218
university	15 (23.1)	148 (29.0)		1 (6.7)	162 (28.9)	
tradesman certificate	44 (67.7)	310 (60.8)		11 (73.3)	343 (61.3)	
elementary	6 (9.2)	52 (10.2)		3 (20.0)	55 (9.8)	

DEMOGRAPHIC	ADHD	NO ADHD	P-VALUE	AUTISM	NO AUTISM	P-VALUE
Parents seperated (at any time up to age 10) N (%)	16 (24.6)	93 (17.8)	0.371	4 (25.0)	105 (18.5)	0.785
PREGNANCY AND BIRTH						
Gestational age (median [IQR])	40 [39.1, 41.1]	40.1 [39.1, 41]	0.745	40.3 [39.3, 41.2]	40.1 [39.1, 41]	0.576
Delivery N (%)			0.750			0.320
acute sectio	8 (12.3)	62 (11.8)		1 (6.2)	69 (12.0)	
planned sectio	4 (6.2)	47 (9.0)		0 (0.0)	51 (8.9)	
vaginal birth	53 (81.5)	416 (79.2)		15 (93.8)	454 (79.1)	
Gestational diabetes N (%)	2 (3.1)	12 (2.5)	1.000	1 (6.2)	14 (2.4)	0.883
Preeclampsia N (%)	2 (3.1)	25 (4.7)	0.770	0 (0.0)	27 (4.7)	0.777
Smoking during pregnancy N (%)	5 (7.7)	14 (2.7)	0.071	0 (0.0)	19 (3.3)	0.983

Primary analyses

Associations between early neurodevelopment and ADHD diagnosis at age 10 are shown in **eTable 1** and Fig. 1. Earlier achievement of early milestones PC (adjusted OR, [95%CI], p; 0.73 [0.57;0.93] 0.013), fewer total gestures (0.93 [0.87;0.93] 0.015), lower word production at 2 years (per SD) (0.69 [0.48;0.95] 0.028), shorter sentence length (0.71 [0.56;0.88] 0.003), lower cognitive functioning as measured by Bayley Scales (0.96 [0.93;0.99] 0.025), and more behavioral and emotional problems, measured by TOF (1.05 [1.00;1.09] 0.034) were associated with increased ADHD risk. After FDR correction, only sentence length remained significant. Moreover, lower ASQ social/personal scores (unadjusted OR [95%CI] p; 0.91 [0.86;0.96] < 0.001) and problem solving (0.97 [0.93;1.00] 0.049) were associated with increased risk of ADHD at age 10 in unadjusted models.

Sensitivity analysis stratified by ADHD presentations, combined ($N = 36$) and inattentive ($N = 29$), Fig. 2, showed significant associations between shorter sentence (adjusted OR [95%CI] 0.59 [0.40;0.84] 0.006), lower cognitive functioning 0.95 [0.89;1.00] 0.049) and

the ADHD inattention presentation, though not significant after FDR correction. Unadjusted analyses also linked lower word production at 2 years (per SD) (OR [95%CI] p; 0.56 [0.32;0.92] 0.032), shorter sentence length (0.55 [0.38;0.77] 0.001), lower cognitive functioning (0.93 [0.88;0.98] 0.012), lower ASQ problem solving (0.94 [0.89;0.98] 0.008), and lower ASQ social/personal scores (0.9 [0.83;0.98] 0.01) to the inattentive presentation. For the combined presentation, earlier achievement of early milestones PC (OR [95%CI] p; 0.75 [0.55;0.99] 0.049), lower word production at 2 years (per SD) (0.66 [0.43;0.98] 0.046), and lower ASQ social/personal scores (0.93 [0.87;1.00] 0.041) were significant in unadjusted models. No neurodevelopmental measures remained significant for the combined presentation after adjustment.

Results from the analysis investigating associations between neurodevelopment in first years of life and ADHD traits at age 10 are visualized in Fig. 3 and listed in **eTable 2**. Shorter sentence at age 2 years (adjusted β [95% CI]; -0.63 [-1.12; -0.15], 0.011), more behavioral and emotional problems (0.16 [0.04; 0.28], 0.01), and lower ASQ social/personal scores (-0.22 [− 0.39; −0.06], 0.009) were associated with more severe ADHD traits at age 10. However, these findings were not significant after FDR correction. We also found significant associations between lower word production at 2 years (per SD) (-1.13 [-1.91;-0.34] 0.005), and worse score in ASQ fine motor (-0.11 [-0.20;-0.02] 0.015) and ASQ problem solving (-0.15 [-0.26;-0.05] 0.006) and more severe ADHD traits at age 10, but these findings were not significant after covariate adjustments.

Sensitivity analyses of inattentive and hyperactive/impulsive ADHD traits showed that earlier achievement of late milestones PC was associated with higher burden of hyperactive/impulsive traits at age 10 (adjusted β -0.18 [-0.37;0.00] 0.049), Fig. 4, a pattern not observed without stratifying ADHD presentations. After FDR correction, shorter sentence length (-0.49 [-0.79;-0.19], P_{FDR} 0.015), lower cognitive functioning (-0.07 [-0.11;-0.02] P_{FDR} 0.02), and lower ASQ social/personal scores (-0.19 [-0.29;-0.09], P_{FDR} 0.005) were negatively associated with inattentive traits, and more behavioral and emotional problems were positively associated (0.12 [0.04;0.19] P_{FDR} 0.02).

No statistically significant associations were observed between neurodevelopmental measures and autism diagnosis, although borderline associations with total gestures at 1 year (adjusted OR [95%CI] p; 0.89 [0.78;0.99] 0.056) and word production at 2 years (per SD) (0.05 [0.23; 0.96] 0.053), **eTable 3**.

For autistic traits, lower word production at 2 years (adjusted β [95%CI] p; -2.83 [-4.45;-1.21] < 0.001), shorter sentence length (-1.99 [-3.01;-0.98] < 0.001), more behavioral problems (0.38 [0.13;0.62] 0.003), lower cognitive functioning (-0.2 [-0.34;-0.05] 0.008), and lower ASQ social/personal scores (-0.44 [-0.79;-0.10] 0.012) were significantly associated with more severe autistic traits at age 10, **eTable 4**. Word

production and sentence length at 2 years remained significant after FDR correction. In unadjusted analysis, poorer ASQ communication scores (-0.37 [-0.71;-0.04] 0.028) were also associated with more autistic traits.

Secondary analyses

Thereafter, we estimated associations between ADHD/ASD PRS and early neurodevelopmental measures, diagnoses, and traits to test genetic contributions.

Earlier achievement of the late milestone PC was associated with higher ADHD PRS (unadjusted β [95% CI]; − 0.20 [–0.38; − 0.03], 0.024), with a similar trend after adjustment (–0.17 [–0.35; 0.01], 0.061). Higher ADHD PRS was significantly associated with ADHD diagnosis (adjusted OR 1.76 [1.31;2.38] < 0.001), the ADHD combined presentation (2.1 [1.43;3.17] < 0.001), and more ADHD traits at 10 years (adjusted β 1.69 [0.95;2.42] 0.001), but not the inattentive presentation, **eTable 5**.

Lower word production at 1 year (adjusted β − 0.12 [–0.24; 0.00], 0.043) and fewer total gestures (–0.86 [–1.59; − 0.13], 0.022) were associated with higher ASD PRS, though these findings did not remain after FDR correction. Higher ASD PRS (1.90 [0.45; 3.34], 0.01) was associated with more autistic traits, and showed a trend toward association with autism diagnosis (1.58 [0.93; 2.76], 0.097), **eTable 6**.

Sub-analysis dividing early neurodevelopmental measures into quartiles, **eFigure 1**, showed that only the highest quartiles was associated with lower ADHD risk. For sentence length, the two highest quartiles predicted lower risk. Total gestures were associated with ADHD in all quartiles. Children achieving milestones later had lower ADHD risk. The highest quartile of cognitive functioning showed significantly lower risk, while more behavioral and emotional problems trended toward higher risk. Spearman correlations between cognitive functioning and language measures were weak: word production at 1 year ($\rho = 0.15$), at 2 years ($\rho = 0.41$), and sentence length ($\rho = 0.35$).

Eight children in the cohort had both ADHD and autism diagnoses. We repeated the ADHD analysis excluding the children with autism in a sensitivity analysis, which did not change the findings. Due to low numbers, we could not make an analysis on solely autism, therefore, we excluded the ADHD children in the analysis of autistic traits, and the results remained consistent.

DISCUSSION

In this prospective mother-child cohort study, impairments in language development, early milestones, cognitive functioning, and behavior from birth to age 3 were associated with later neurodevelopmental outcomes. These included a higher risk of ADHD diagnosis, as

well as more pronounced ADHD- and autistic traits at age 10. We did not observe significant associations with autism diagnosis, likely due to limited statistical power resulting. This aligns with existing evidence suggesting early neurodevelopmental vulnerabilities may precede psychopathology, though the precise nature of these connections remains complex[39].

Less gesture use at 1 year and lower word production and shorter sentence at 2 years were associated with higher ADHD risk. These results align with existing literature indicating early language difficulties as potential risk factor for ADHD traits[40]. Earlier acquisition of the late milestone component was associated with more hyperactive/impulsive traits, agreeing with a prior longitudinal study describing that children who later develop ADHD tend to start walking either at an earlier or later age than average[16]. However, systematic reviews have generally failed to establish consistent associations between atypical early motor development and ADHD[17]. While motor milestone deviations are present in some individuals with ADHD, a consistent directionality of such associations remain unclear, suggesting a substantial heterogeneity in developmental trajectories in ADHD. Notably, the inattentive presentation of ADHD appears to be the primary contributor to the significant association with word production, longest sentence, and cognitive functioning. While both the inattentive and combined ADHD presentation have deficits in attention, it has been suggested that the nature of the inattention symptoms differs between the two presentations[41]. Prior research indicates that deficits in working memory and processing speed are more likely to be associated with the inattention presentation compared to the combined presentation of ADHD[42]. Our findings reinforce the distinction between ADHD presentations and could explain why we mostly see deviations in cognition and language in the inattentive presentation.

We also observed trends between ADHD PRS and more behavioral and emotional problems, and earlier achievement of the late milestone component, consistent with prior findings of earlier walking in children with higher ADHD PRS[19].

Few studies have linked early cognitive development, assessed by the Bayley Scales, to later ADHD. One such study found lower Bayley scores at 15 and 24 months to be associated with greater ADHD severity, thus evaluated by The Disruptive Behavior Disorders Rating Scale[18]. Cognitive impairments in ADHD are frequently observed within the domain of executive functions[43]. The relationship between language and cognition has long been of interest in developmental research, though findings remain inconsistent and the nature of this association is not yet fully understood[44]. While some studies suggest that cognition and language mutually influence each other[45], others have not found association between the two domains[46]. In our study, we observed a positive correlation between language measurements and cognitive functioning, suggesting they reflect

overlapping developmental measures. The subgroup analysis, using quartile-based comparisons, showed that children with the highest word production and cognitive scores had significantly reduced odds of an ADHD diagnosis, and those achieving milestones earlier had lower risk. Gesture use did not differentiate ADHD risk, indicating that word production, sentence length and cognitive functioning may be effective for ruling out the risk of ADHD.

Lower word production and shorter sentence at 2 years, lower cognitive functioning and more behavioral and emotional problems at age 2.5 years were associated with more autistic traits. Lower communication scores, as measured by the ASQ, were also associated with more autistic traits, consistent with evidence that communication delays are characteristic of ASD[10,47]. Another study evaluated whether ASQ could detect ASD and found that scores below the 'monitor' cutoff in the communication domain identified 95% of the children with ASD. The study emphasized that the 'monitor' cutoff on the communication domain only, is both sensitive and specific to ASD[48]. Together, these results emphasize the utility of the ASQ communication domain as a targeted screening tool for early ASD detection, in line with the findings in our study. Further, we found an association between ASD PRS and lower word production and less total gestures. Other studies have found that language difficulties were associated with ASD PRS[3] and that ASD PRS was associated with delays in cognition, language and motor skills[49].

A key strength of this study is the prospective design with children followed from birth with exhaustive clinical data collection and detailed psychopathological assessments at age 10. It is an unselected cohort with more than 86% follow-up rate, and the prospective and clinical design mitigates limitations such as recall and subjective biases. Our data on language acquisition are reported by parents, which has been demonstrated to be a reliable source to report the status of their child's language, even when their children have developmental disorders such as ASD[50]. Further, we have objective markers regarding cognition and behavior at age 2.5 years. The expected associations we found between PRS and diagnoses and traits validate our psychopathology data. We found more children with ADHD than expected in the population, which could underpin the assumption of ADHD being under-diagnosed[7] or reflect that population-based register estimates are based on referred neurodevelopmental disorder cases. Limitations of our study include limited statistical power, especially related to children with autism, and interpreting our results should therefore be done with precaution, also taking into consideration that some estimates and OR are close to zero and one, respectively. However, we had the opportunity to substantiate the findings with our trait scores, where we found comparable significant results. Finally, few results remained significant after FDR correction, which we consider a minor issue as many of the early neurodevelopmental assessments are correlated.

In conclusion, specific neurodevelopmental measures, including reduced cognitive functioning, delayed language development, and behavioral/emotional deviations were associated with increased risk of ADHD and higher ADHD and autistic traits at age 10. While these findings are not immediately applicable to clinical practice, they offer valuable theoretical insights into the early developmental trajectories of children with ADHD and autism and could potentially play a role in early detection of these traits. Future prospective research employing larger sample sizes is necessary to validate these findings and ultimately improve clinicians' ability to predict ADHD and autism and improve developmental outcomes.

Abbreviations

ADHD
Attention-Deficit/Hyperactivity Disorder
ASD
Autism Spectrum Disorder
NDD
Neurodevelopmental Disorder
DSM-V
Diagnostic and Statistical Manual of Mental Disorders V
COPSAC2010
COpenhagen Prospective Studies on Asthma in Childhood 2010
COPSYCH
COpenhagen Prospective Study on Neuro-PSYCHiatric Development
ADHD-RS
Attention Deficit/Hyperactivity Disorder Rating Scale
SRS-2
Social Responsiveness Scale-2
TOF
Test Observation Form
PRS
Polygenic Risk Score
GWAS
Genome-wide Association Studies
PCA
Principal Component Analysis
FDR
False Discovery Rate

Declarations

Authors Contributions:

Dr Camilla Grube, Dr Rebecca Kofod Vinding, Dr María Hernández-Lorca and Prof Bo Chawes conceptualized and designed the study and gave valuable input to the analysis. Dr María Hernández-Lorca helped with analysis, statistical support and figure design.

Dr Julie B. Rosenberg, Dr Kristina Aagaard, MSc Michael Widdowson, MSc Tingting Wang, Dr Nilo Vahman, RN Hanne Lunn Nissen, Dr Jens Richardt Møllegaard Jepsen, Dr Klaus Bønnelykke, Dr Bjørn H. Ebdrup, Prof Bo Chawes contributed substantially to the acquisition, analyses, and interpretation of the data and provided important intellectual input to the manuscript.

All authors critically reviewed and revised the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agreed to be accountable for all

aspects of the work. No honorarium, grant, or other form of payment was given to any of the

authors to produce this manuscript.

Ethics:

The study was conducted in accordance with the guiding principles of the Declaration of Helsinki and was approved by the Local Ethics Committee (H-B-2008-093), and the Danish Data Protection Agency (2015-41-3696). Both parents gave written informed consent before enrolment.

Source of Funding:

All funding received by COPSAC is listed on www.copsac.com. The

Lundbeck Foundation (Grant no R16-A1694); The Lundbeck grant for COPSYCH is (Grant

no. R269-2017-5); The Danish Ministry of Health (Grant no 903516); Danish Council for

Strategic Research (Grant no 0603-00280B) and The Capital Region Research Foundation

have provided core support to the COPSAC research center.

NOTE: The above-mentioned are the major funds supporting all of COPSAC.

Funder/Sponsor: Beside the funding mentioned above the project was done with no other

specific support.

Acknowledgement

Acknowledgements: We express our deepest gratitude to the children and families of the COPSAC2010 cohort study for all their support and commitment. We acknowledge and appreciate the unique efforts of the COPSAC research team. We also like to acknowledge the huge work of late professor Hans Bisgaard, who was the founder of COPSAC and was head of the clinical research center for more than 25 years.

References

1. Fast K, Wentz E, Roswall J, Strandberg M, Bergman S, Dahlgren J (2024) Prevalence of attention-deficit/hyperactivity disorder and autism in 12-year-old children: A population-based cohort. Dev Med Child Neurol 66(4):493–500. 10.1111/dmcn.15757
2. Thapar A, Cooper M, Rutter M (2017) Neurodevelopmental disorders. Lancet Psychiatry 4(4):339–346. 10.1016/S2215-0366(16)30376-5
3. Askeland RB, Hannigan LJ, Ask H et al (2022) Early manifestations of genetic risk for neurodevelopmental disorders. J Child Psychol Psychiatry 63(7):810–819. 10.1111/jcpp.13528
4. Epstein JN, Loren REA (2013) Changes in the Definition of ADHD in DSM-5: Subtle but Important. Neuropsychiatry 3(5):455–458. 10.2217/npy.13.59
5. Green A, Baroud E, DiSalvo M, Faraone SV, Biederman J (2022) Examining the impact of ADHD polygenic risk scores on ADHD and associated outcomes: A systematic review and meta-analysis. J Psychiatr Res 155:49–67. 10.1016/j.jpsychires.2022.07.032
6. Oerbeck B, Overgaard KR, Pripp AH, Reichborn-Kjennerud T, Aase H, Zeiner P (2020) Early Predictors of ADHD: Evidence from a Prospective Birth Cohort. J Atten Disord 24(12):1685–1692. 10.1177/1087054717696765
7. Sayal K, Prasad V, Daley D, Ford T, Coghill D (2018) ADHD in children and young people: prevalence, care pathways, and service provision. Lancet Psychiatry 5(2):175–186. 10.1016/S2215-0366(17)30167-0
8. Bellato A, Perrott NJ, Marzulli L, Parlatini V, Coghill D, Cortese S (2025) Systematic Review and Meta-Analysis: Effects of Pharmacological Treatment for Attention-Deficit/Hyperactivity Disorder on Quality of Life. J Am Acad Child Adolesc Psychiatry 64(3):346–361. 10.1016/j.jaac.2024.05.023
9. Hadders-Algra M (2022) Emerging signs of autism spectrum disorder in infancy: Putative neural substrate. Dev Med Child Neurol 64(11):1344–1350. 10.1111/dmcn.15333

10. Hirota T, King BH (2023) Autism Spectrum Disorder: A Review. JAMA 329(2):157–168. 10.1001/jama.2022.23661
11. Mandy W, Midouhas E, Hosozawa M, Cable N, Sacker A, Flouri E (2022) Mental health and social difficulties of late-diagnosed autistic children, across childhood and adolescence. J Child Psychol Psychiatry 63(11):1405–1414. 10.1111/jcpp.13587
12. Sandbank M, Pustejovsky JE, Bottema-Beutel K et al (2024) Determining Associations Between Intervention Amount and Outcomes for Young Autistic Children. JAMA Pediatr 178(8):763–773. 10.1001/jamapediatrics.2024.1832
13. Cainelli E, Bisiacchi P (2022) Neurodevelopmental Disorders: Past, Present, and Future. Children 10(1):31. 10.3390/children10010031
14. Faraone SV, Larsson H (2019) Genetics of attention deficit hyperactivity disorder. Mol Psychiatry 24(4):562–575. 10.1038/s41380-018-0070-0
15. de Wit MM, Morgan MJ, Libedinsky I et al A Systematic Review and Meta-Analysis: Research Using the Autism Polygenic Score. *medRxiv*. Preprint posted online March 9, 2024:2024.03.08.24303918. 10.1101/2024.03.08.24303918
16. Lemcke S, Parner ET, Bjerrum M, Thomsen PH, Lauritsen MB (2016) Early development in children that are later diagnosed with disorders of attention and activity: a longitudinal study in the Danish National Birth Cohort. Eur Child Adolesc Psychiatry 25(10):1055–1066. 10.1007/s00787-016-0825-6
17. Havmoeller SR, Thomsen PH, Lemcke S (2019) The early motor development in children diagnosed with ADHD: a systematic review. Atten Deficit Hyperact Disord 11(3):233–240. 10.1007/s12402-018-0280-y
18. Arnett AB, MacDonald B, Pennington BF (2013) Cognitive and Behavioral Indicators of ADHD Symptoms Prior to School Age. J Child Psychol Psychiatry 54(12). 10.1111/jcpp.12104
19. Hannigan LJ, Askeland RB, Ask H et al Developmental milestones in early childhood and genetic liability to neurodevelopmental disorders. Psychol Med. 53(5):1750–1758. 10.1017/S0033291721003330
20. Mohd Nordin A, Ismail J, Kamal Nor N (2021) Motor Development in Children With Autism Spectrum Disorder. Front Pediatr 9:598276. 10.3389/fped.2021.598276
21. Posar A, Visconti P (2022) Early Motor Signs in Autism Spectrum Disorder. Children 9(2):294. 10.3390/children9020294
22. Bisgaard H, Vissing NH, Carson CG et al (2013) Deep phenotyping of the unselected COPSAC2010 birth cohort study. Clin Exp Allergy J Br Soc Allergy Clin Immunol 43(12):1384–1394. 10.1111/cea.12213
23. Mohammadzadeh P, Rosenberg JB, Vinding R et al (2022) Effects of prenatal nutrient supplementation and early life exposures on neurodevelopment at age 10: a

randomised controlled trial - the COPSYCH study protocol. BMJ Open 12(2):e047706. 10.1136/bmjopen-2020-047706

24. Frankenburg W, Dodds J (1990) The Denver Developmental Assessment (Denver II). University of Colorado Medical School
25. Wijnhoven TM, de Onis M, Onyango AW et al (2004) Assessment of gross motor development in the WHO Multicentre Growth Reference Study. Food Nutr Bull 25(1 Suppl):S37–45
26. Bjarnadóttir E, Stokholm J, Chawes B et al (2019) Determinants of neurodevelopment in early childhood – results from the Copenhagen prospective studies on asthma in childhood (COPSAC2010) mother–child cohort. Acta Paediatr 108(9):1632–1641. 10.1111/apa.14753
27. Bleses D, Vach W, Slott M et al (2008) The Danish Communicative Developmental Inventories: validity and main developmental trends. J Child Lang 35(3):651–669. 10.1017/S0305000907008574
28. Bayley N (2006) Bayley Scales of Infant and Toddler Development (Third Edition),Administration Manual. Harcourt Assessment.
29. McConaughy S, Achenbach T (2004) Manual for the Test Observation Form for Ages 2–18. Center for Children, Youth & Families
30. Singh A, Yeh CJ, Boone Blanchard S (2017) Ages and Stages Questionnaire: a global screening scale. Bol Med Hosp Infant Mex 74(1):5–12. 10.1016/j.bmhimx.2016.07.008
31. Kaufman J, Birmaher B, Brent D et al (1997) Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 36(7):980–988. 10.1097/00004583-199707000-00021
32. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Diagnostic Criteria for Research. World Health Organization (1993) Accessed May 11, 2023. https://apps.who.int/iris/handle/10665/37108
33. Makransky G, Bilenberg N (2014) Psychometric properties of the parent and teacher ADHD Rating Scale (ADHD-RS): measurement invariance across gender, age, and informant. Assessment 21(6):694–705. 10.1177/1073191114535242
34. Bruni TP (2014) Test Review: Social Responsiveness Scale–Second Edition (SRS-2). J Psychoeduc Assess 32(4):365–369. 10.1177/0734282913517525
35. Demontis D, Walters GB, Athanasiadis G et al (2023) Genome-wide analyses of ADHD identify 27 risk loci, refine the genetic architecture and implicate several cognitive domains. Nat Genet 55(2):198–208. 10.1038/s41588-022-01285-8
36. Grove J, Ripke S, Als TD et al (2019) Identification of common genetic risk variants for autism spectrum disorder. Nat Genet 51(3):431–444. 10.1038/s41588-019-0344-8

37. Ge T, Chen CY, Ni Y, Feng YCA, Smoller JW (2019) Polygenic prediction via Bayesian regression and continuous shrinkage priors. Nat Commun 10(1):1776. 10.1038/s41467-019-09718-5
38. Purcell S, Neale B, Todd-Brown K et al (2007) PLINK: A Tool Set for Whole-Genome Association and Population-Based Linkage Analyses. Am J Hum Genet 81(3):559–575. 10.1086/519795
39. Miller M, Arnett AB, Shephard E et al (2023) Delineating early developmental pathways to ADHD: Setting an international research agenda. JCPP Adv 3(2):e12144. 10.1002/jcv2.12144
40. Peyre H, Galera C, van der Waerden J et al (2016) Relationship between early language skills and the development of inattention/hyperactivity symptoms during the preschool period: Results of the EDEN mother-child cohort. BMC Psychiatry 16(1):380. 10.1186/s12888-016-1091-3
41. de la Peña IC, Pan MC, Thai CG, Alisso T (2020) Attention-Deficit/Hyperactivity Disorder Predominantly Inattentive Subtype/Presentation: Research Progress and Translational Studies. Brain Sci 10(5):292. 10.3390/brainsci10050292
42. Simone AN, Bédard ACV, Marks DJ, Halperin JM (2016) Good Holders, Bad Shufflers: An Examination of Working Memory Processes and Modalities in Children with and without Attention-Deficit/Hyperactivity Disorder. J Int Neuropsychol Soc 22(1):1–11. 10.1017/S1355617715001010
43. Coghill DR, Seth S, Matthews K (2014) A comprehensive assessment of memory, delay aversion, timing, inhibition, decision making and variability in attention deficit hyperactivity disorder: advancing beyond the three-pathway models. Psychol Med 44(9):1989–2001. 10.1017/S0033291713002547
44. Perszyk DR, Waxman SR (2018) Linking Language and Cognition in Infancy. *Annu Rev Psychol*. ;69(Volume 69, 2018):231–250. 10.1146/annurev-psych-122216-011701
45. Cahyaningsih T, Gunarsih I, Abdurrauf NLR, Rahmadhani YSN, Islamiyah N, Saodi S (2024) The Influence Of Cognition On Children's Language Development: The Relationship Between Comprehension, Memory and Language. *Social Science Research Network*. Preprint posted online November 26. 10.2139/ssrn.5035251
46. Webster RI, Erdos C, Evans K et al (2006) The Clinical Spectrum of Developmental Language Impairment in School-Aged Children: Language, Cognitive, and Motor Findings. Pediatrics 118(5):e1541–e1549. 10.1542/peds.2005-2761
47. Iverson JM, Northrup JB, Leezenbaum NB, Parlade MV, Koterba EA, West KL (2018) Early Gesture and Vocabulary Development in Infant Siblings of Children with Autism Spectrum Disorder. J Autism Dev Disord 48(1):55–71. 10.1007/s10803-017-3297-8
48. Hardy S, Haisley L, Manning C, Fein D (2015) Can Screening With the Ages and Stages Questionnaire Detect Autism? J Dev Behav Pediatr JDBP 36(7):536–543.

10.1097/DBP.0000000000000201

49. Takahashi N, Harada T, Nishimura T et al (2020) Association of Genetic Risks With Autism Spectrum Disorder and Early Neurodevelopmental Delays Among Children Without Intellectual Disability. JAMA Netw Open 3(2):e1921644. 10.1001/jamanetworkopen.2019.21644
50. Miller LE, Perkins KA, Dai YG, Fein DA (2017) Comparison of Parent Report and Direct Assessment of Child Skills in Toddlers. Res Autism Spectr Disord 41–42:57–65. 10.1016/j.rasd.2017.08.002

Tables

Table 1 is available in the Supplementary Files section.

Figures

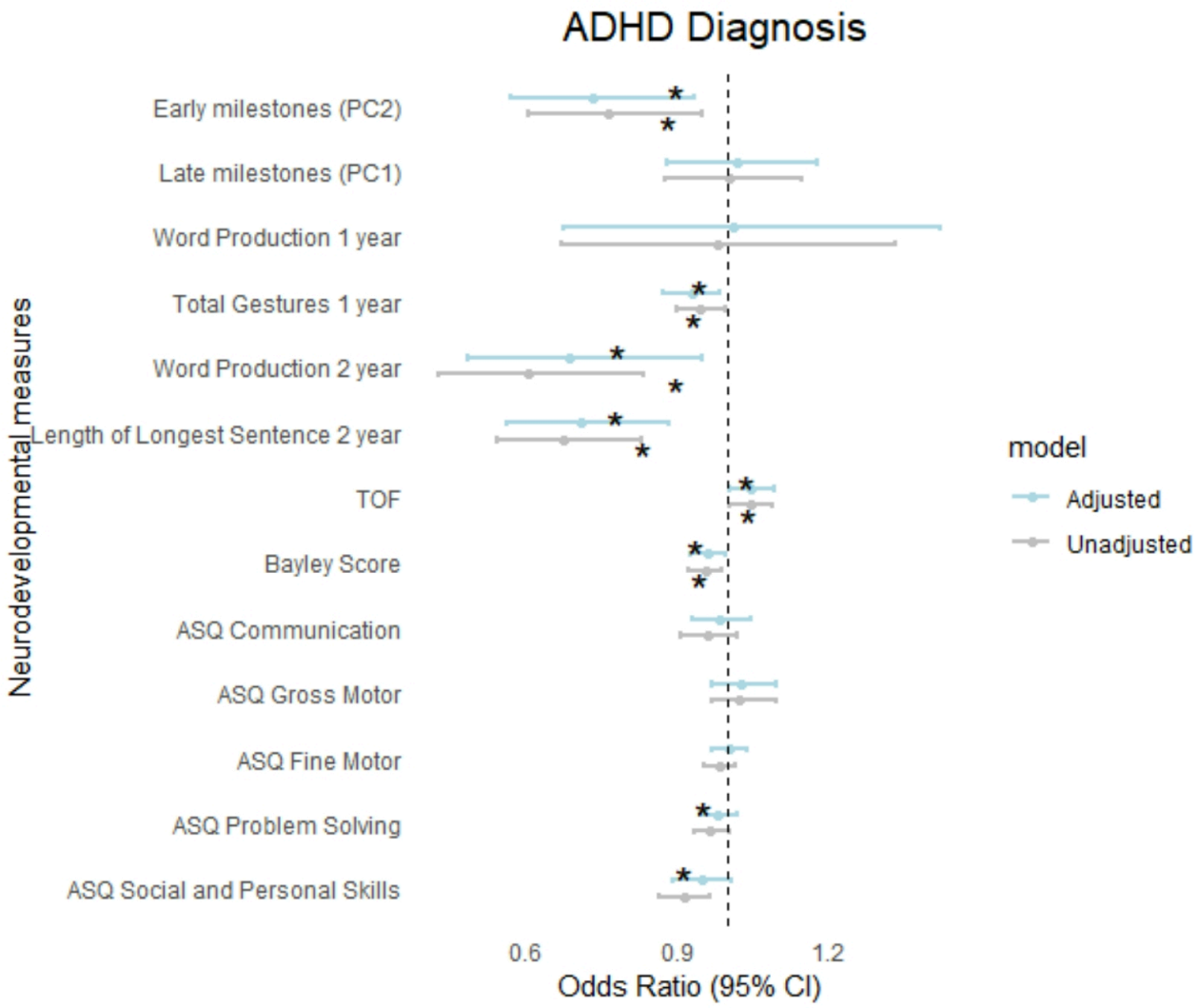

Figure 1

Forest plot illustrating results from logistic regression analyses between early life neurodevelopmental measures and ADHD diagnosis at age 10. **Abbreviations**: PC: Principal Component, ASQ: Ages and Stages Questionnaire, TOF: Test Observation Form (Behavioral and emotional problems), Bayley Score (Cognitive functioning). *: $p<0.05$.

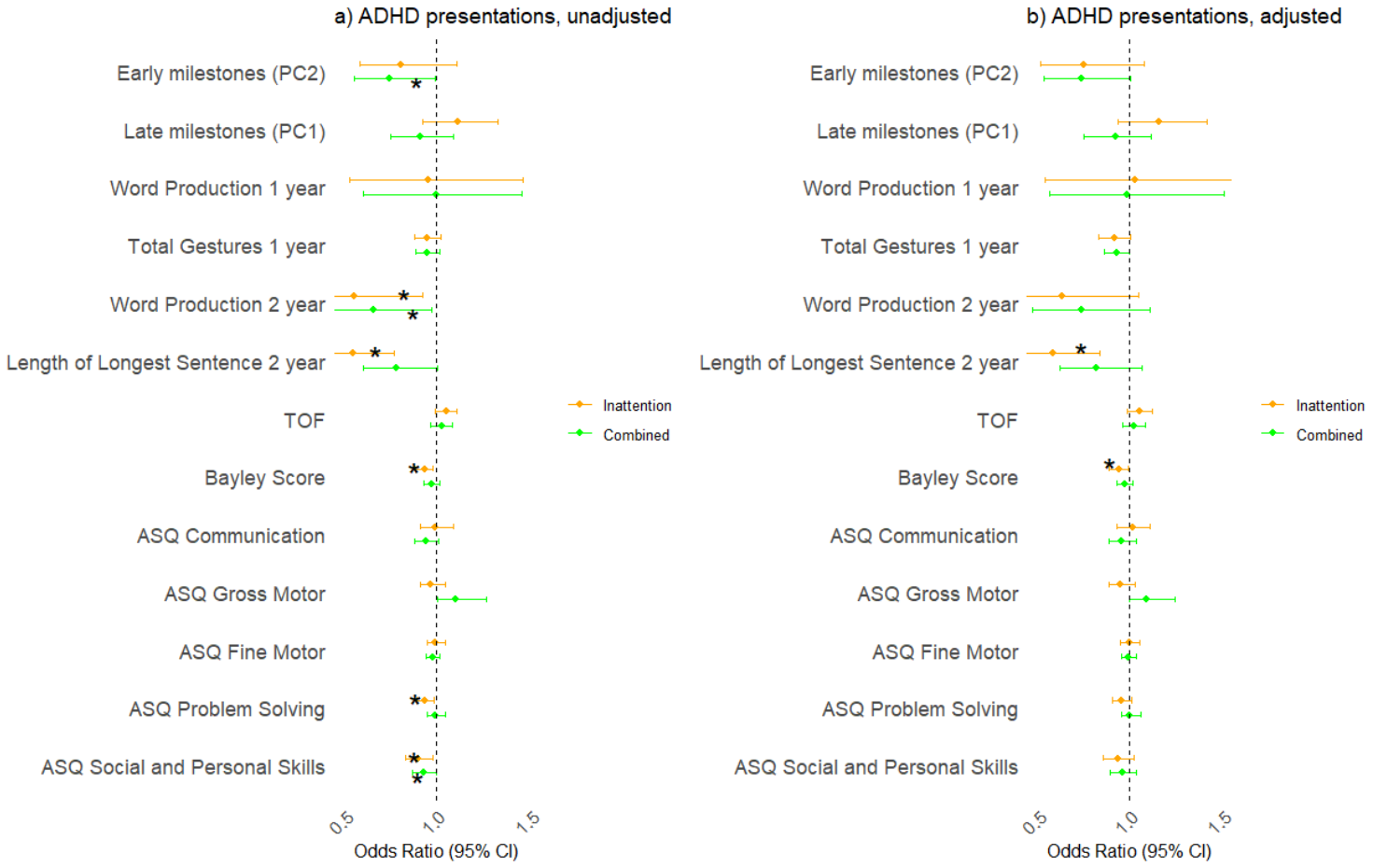

Figure 2

Forest plot illustrating results from a) unadjusted and b) adjusted logistic regression stratifying between early life neurodevelopmental measured and ADHD diagnosis, stratified by ADHD presentations: combined presentation (green line) and inattentive presentation (orange line). **Abbreviations**: PC: Principal Component, ASQ: Ages and Stages Questionnaire, TOF: Test Observation Form (Behavioral and emotional problems), Bayley Score (Cognitive functioning). *: $p<0.05$

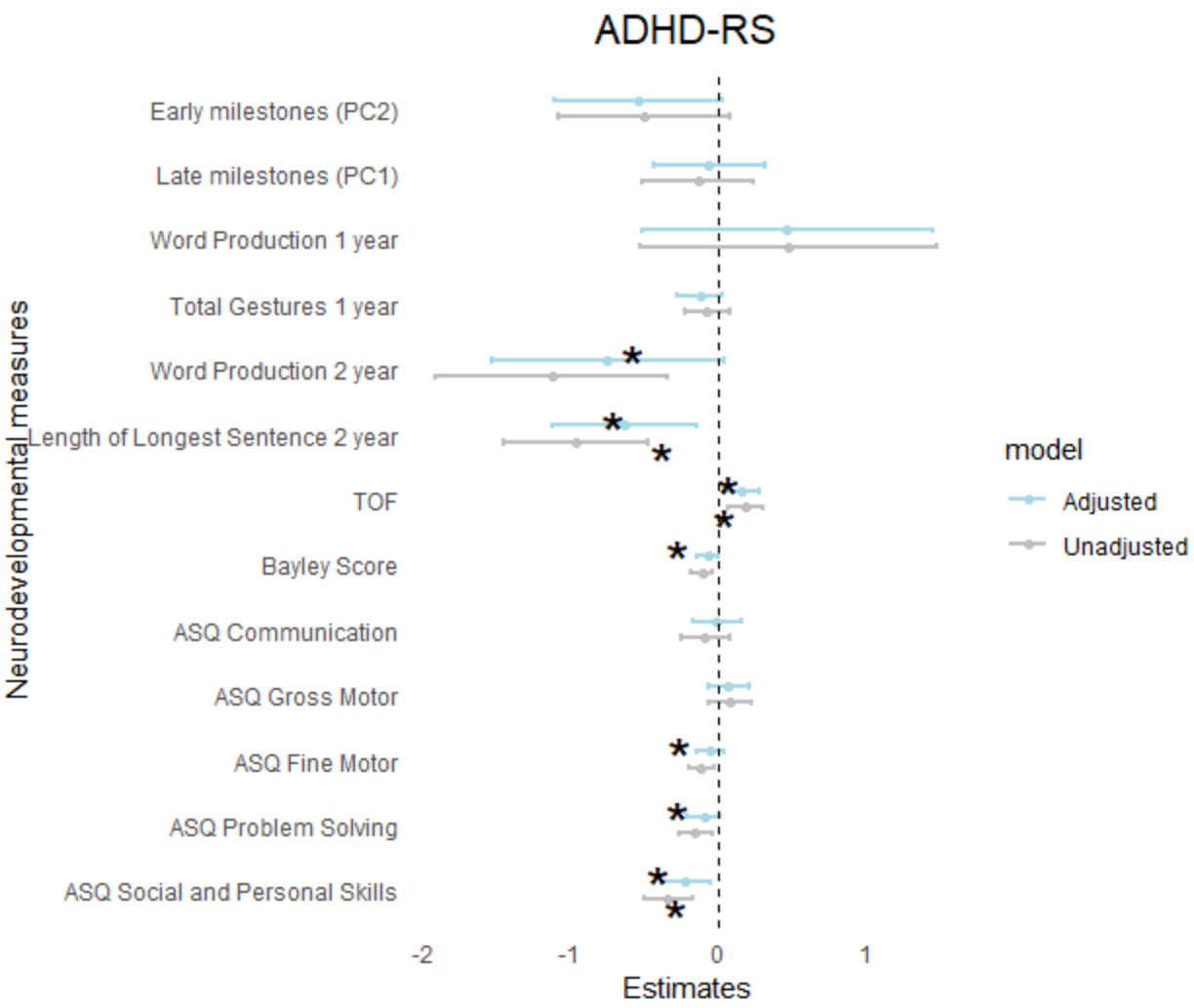

Figure 3

Forest plot illustrating associations between early life neurodevelopmental measures and ADHD traits (ADHD-RS) at age 10. **Abbreviations**: PC: Principal Component, ASQ: Ages and Stages Questionnaire, TOF: Test Observation Form (Behavioral and emotional problems), Bayley Score (Cognitive functioning). *: $p<0.05$

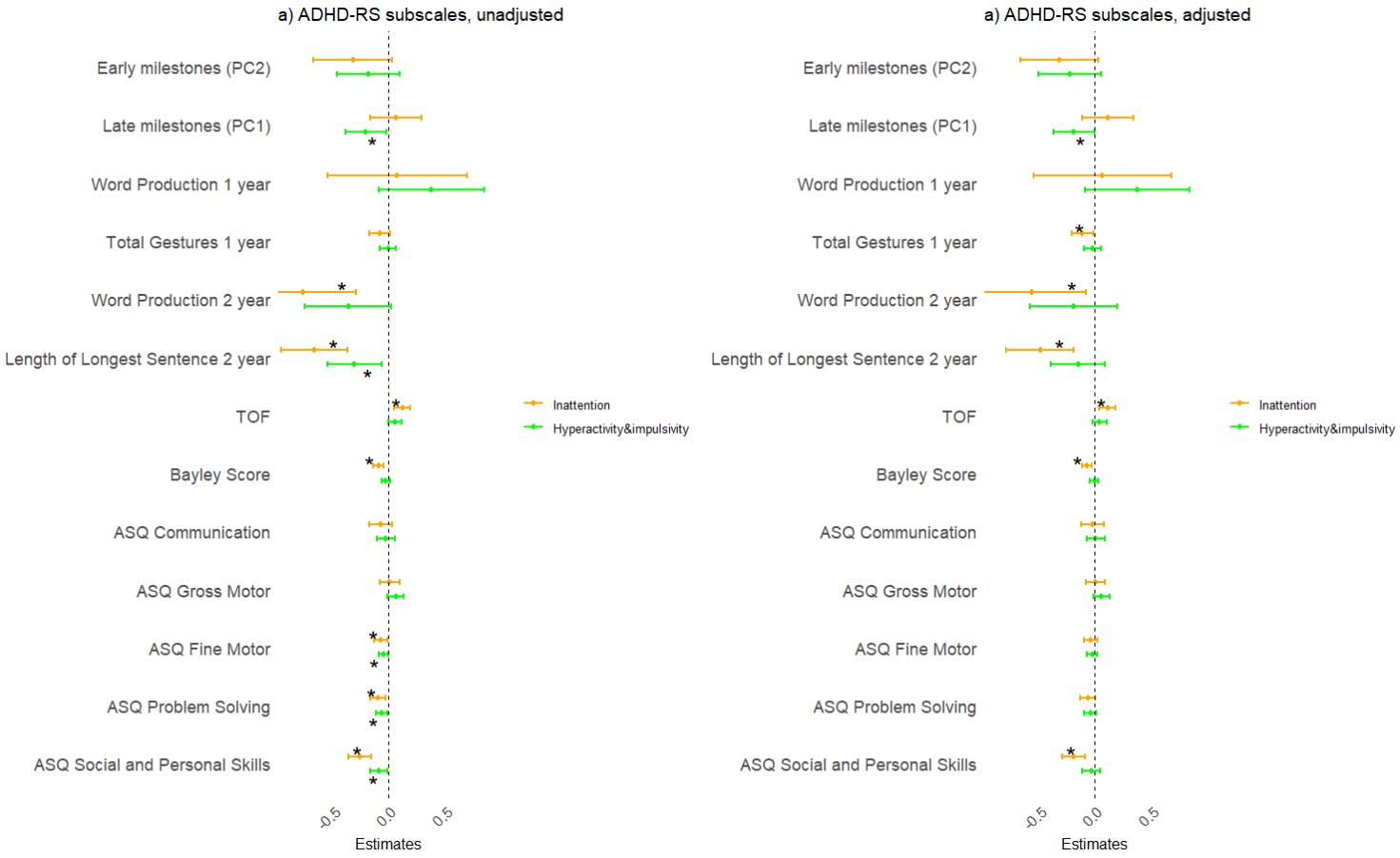

Figure 4

Results from a) unadjusted and b) adjusted regression analysis between early life neurodevelopment measures and inattentive and hyperactive traits as measured with the ADHD-RS subscales: inattention subscale (orange) and Hyperactivity/impulsivity (green). **Abbreviations:** PC: Principal Component, ASQ: Ages and Stages Questionnaire, TOF: Test Observation Form (Behavioral and emotional problems), Bayley Score (Cognitive functioning). *: $p<0.05$

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementary.docx
- Table1.docx