

ADHD symptoms and their neurodevelopmental correlates in children born very preterm

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Abstract

This study investigated the association between attention-deficit/hyperactivity disorder (ADHD) symptomatology in preschool-aged children who were born very preterm (<32 weeks) and cognitive outcomes, clinical risk and socio-demographic characteristics. 119 very preterm children who participated in the Evaluation of Preterm Imaging Study at term-equivalent age were assessed at a mean age of 4.5 years. Parents completed the ADHD Rating Scale IV, a norm-referenced checklist that evaluates ADHD symptomatology according to diagnostic criteria, and the Behavior Rating Inventory of Executive Function-Preschool version. Children completed the Wechsler Preschool and Primary Scales of Intelligence and the Forward Digit Span task. Longitudinal data including perinatal clinical, qualitative MRI classification, socio-demographic variables and neurodevelopmental disabilities were investigated in relation to ADHD symptomatology. All results were corrected for multiple comparisons using false discovery rate. Results showed that although the proportion of very preterm children with clinically significant ADHD did not differ from normative data after excluding those with neurodevelopmental disabilities, 32.7% met criteria for subthreshold ADHD inattentive type and 33.6% for combined type, which was higher than the expected 20% in normative samples. Higher ADHD symptom scores (all) were associated with greater executive dysfunction (inhibitory self-control, flexibility, and emergent metacognition, corrected $p < 0.001$ for all tests). Higher inattentive ADHD symptom scores were associated with lower IQ ($p = -0.241$, $p = 0.036$) and higher perinatal clinical risk (more days on mechanical ventilation ($p = 0.206$, $p = 0.025$) and more days on parenteral nutrition ($p = 0.223$, $p = 0.015$)). Higher hyperactive ADHD symptom scores instead were associated with lower socio-economic status ($p = 0.278$, $p = 0.002$). These results highlight the importance of monitoring and supporting the development of very preterm children throughout the school years, as subthreshold ADHD symptoms represent risk factors for psychosocial problems and for receiving a future clinical diagnosis of ADHD.

46 **List of Abbreviations and Acronyms:**

47 ADHD (Attention-deficit/hyperactivity disorder)

48 MRI (magnetic resonance imaging)

49 NDD (Neurodevelopmental disability)

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61 Introduction

62 Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition which affects 5-7%
63 of children, depending on the source of information used to reach a diagnosis (1, 2). Children who were
64 born very preterm (< 32 weeks of gestation) have a 2- to 3-fold increased risk of being diagnosed with
65 ADHD compared to their term born peers (4-fold risk in those born at < 26 weeks) (3-7).

66 According to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-
67 V), ADHD is characterized by two main symptom presentations, inattention and hyperactivity-
68 impulsivity (8). Although symptoms often co-occur, their expression can be unbalanced, leading to a
69 clinical subdivision of the disorder into inattentive, hyperactive-impulsive and combined types. In general
70 population samples the most common form of ADHD presentation is the combined type, but among very
71 preterm born children the inattentive subtype has higher prevalence (9, 10). There is further evidence that
72 very preterm children display higher levels of subclinical inattentive symptomatology compared to
73 controls, which falls below diagnostic thresholds (11, 12).

74 ADHD symptoms in very preterm children exhibit specific cognitive correlates that are not
75 observed in term-born children with ADHD (3), and research has suggested that behavioural symptoms of
76 inattention in very preterm children could be completely accounted for by slow responses and
77 impairments in visuo-spatial working memory (13). Preterm children with ADHD do not show the typical
78 pattern of higher prevalence in males compared to females (14, 15), and they tend not to have co-
79 occurring conduct disorder (15, 16). Socio-demographic and environmental risks show a weaker
80 association with ADHD in very preterm compared to term-born children, while, and perhaps not
81 surprisingly, perinatal medical and neurological factors significantly contribute to their vulnerability to
82 develop the disorder (17). These converging strands of evidence have led to the hypothesis of a possible
83 ‘purer’ biological aetiology of ADHD following very preterm birth (3), supporting the idea of multiple
84 pathways to ADHD (18).

85 The majority of studies to date in very preterm samples have focused on school age, when ADHD
86 is typically diagnosed. However, the importance of detecting early risk factors associated with ADHD is
87 well recognised (19). Attention problems identified during the pre-school years may mark the beginning
88 of escalating academic problems, school drop-out and psychopathology later in life (20); indeed attention
89 could be regarded as a building block for the development of many other cognitive functions and as a
90 prerequisite for learning (21).

91 Here we investigate ADHD symptoms, their cognitive and clinical correlates in preschool-aged
92 children who were born very preterm. We hypothesised that higher ADHD symptoms in very preterm
93 children would be associated with lower executive functions and intelligence, even in the absence of a
94 clinical diagnosis. We further hypothesised that inattentive ADHD symptoms would be associated with
95 perinatal clinical adversity rather than environmental risk.

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97 **Methods**

98 **Sample**

99 Study participants were 119 very preterm born children who were recruited at birth in 2010-2013 as part
100 of the Evaluation of Preterm Imaging Study (e-Prime Eudra: CT 2009-011602-42) from hospitals within
101 the North and Southwest London Perinatal Network (22). Infants were eligible if born before 33 weeks
102 gestational age and their mother was aged over 16 years and not a hospital inpatient; they were excluded
103 if they had major congenital malformation, prior Magnetic Resonance Imaging (MRI), metallic implants,
104 parents unable to speak English, or were subject to child protection proceedings. The original sample
105 recruited studied 511 of 1831 eligible infants and accurately reflected the population of preterm infants.
106 Full data on the trial are available (22). The current study was a convenience sample created by families
107 who accepted invitations to undergo further examination and testing at pre-school age (see Table 1 for a
108 description of children's perinatal, socio-demographic and cognitive characteristics). Current study

109 participants did not differ from those in the larger cohort in terms of gestational age ($F = 3.42$, $p > 0.05$)
 110 and birth weight z score ($F = 0.013$, $p > 0.05$). Written informed consent was obtained from children's
 111 carer(s) following procedures approved by the National Research Ethics Committee (14/LO/0677), in
 112 accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).
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Gestational age in weeks, median (range)	30.00 (25.00 – 32.00)
Birth weight in grams, median (range)	1305 (600 – 2600)
Males, No (%)	54 (45.4)
Days on mechanical ventilation, median (range)	0 (0 – 21)
Days on parenteral nutrition, median (range)	5 (0 – 54)
Intrauterine growth restriction, N (%)	17 (14.3)
Index of multiple deprivation quintile, N (%)	
1 (Least Deprived)	23 (19.3)
2	24 (20.2)
3	28 (23.5)
4	24 (20.2)
5 (Most Deprived)	20 (16.8)
Corrected age at assessment in months, mean (range)	53.78 (50.06 – 59.19)
Mother's age leaving full time education, at birth, N (%)*	
18 years or younger	33 (27.7)
19 years or older	82 (68.9)
Unknown	4 (3.4)
Qualitative MR rating*	
No perinatal brain lesions N (%)	35 (29.4)
Minor perinatal brain lesions N (%)	64 (53.8)
Major perinatal brain lesions N (%)	17 (14.3)
Full scale intelligence quotient, mean (range)	106 (50 -147)

114 Table 1. Study participants' perinatal, socio-demographic and cognitive characteristics.

115 **Three MRI datasets were corrupted and could not be evaluated

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117 **Perinatal clinical and socio-demographic variables**

118 Perinatal clinical and socio-demographic data were collected with permission from the
119 Standardized Electronic Neonatal Database and included gestational age at birth, sex, days of mechanical
120 ventilation, days of parenteral nutrition, intrauterine growth restriction (diagnosed by the obstetric team at
121 the hospital where antenatal care was provided), mother's age when leaving full time education and Index
122 of Multiple Deprivation (IMD) score, determined by parents' postcode at the time of infant's birth
123 (<http://imd-by-postcode.opendatacommunities.org>), which provide a proxy for socio-economic status.

124 Infants received MRI at term-equivalent age on a Philips 3 Tesla (Philips Medical Systems, Best,
125 The Netherlands) system sited on the neonatal intensive care unit using an eight-channel phased array
126 head coil. T2-weighted images were acquired (TR 8,670 ms; TE 160 ms; flip angle 90°; slice thickness 2
127 mm; in plane resolution 0.86×0.86 mm). An experienced neonatal radiologist qualitatively rated the
128 MRI scan of each infant and assigned an overall global score that described the clinical severity of brain
129 abnormalities. Scores ranged from 2-0; 2 = major lesion, defined as cystic periventricular leukomalacia,
130 >10 punctate white matter lesions, grade 3 or 4 germinal matrix haemorrhage; 1 = minor lesion, defined
131 as all any other lesions; 0 = no lesion.

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133 **Behavioural outcomes**

134 The ADHD Rating Scale-IV (ADHD-RS-IV) (23) was used to measure behaviours associated with
135 different ADHD presentations according to DSM-V diagnostic criteria (8). This 18-item norm-referenced
136 questionnaire provides scores from two separate subscales (Inattention and Hyperactivity/Impulsivity)
137 and a combined score. These scales have been shown to have strong psychometric properties in preschool
138 children (23). Raw scores were transformed into z scores using age- and sex-matched normative means
139 and standard deviations. Scores were defined as clinically significant when equal or greater than the 90th

percentile of the sex-matched normative score distribution. The 80th percentile was also used to include sub-threshold symptoms.

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143 **Neuropsychological outcomes**

144 General intellectual development was assessed with the Wechsler Preschool and Primary Scales of
145 Intelligence battery (WPPSI-IV) (24). Age corrected for prematurity was used to calculate scaled scores
146 (25, 26). Phonological short term memory was assessed using the digit span forward test, using an
147 adapted version of the Wechsler Intelligence Scale for Children IV digit span task (27). Inhibitory Self-
148 Control Index (Inhibition and Emotional Control scores), Flexibility Index (Shifting and Emotional
149 Control scores) and Emergent Metacognition Index (Working Memory and Planning/organisation scores)
150 were obtained from the Behavior Rating Inventory of Executive Function-Preschool version (BRIEF-P)
151 (28). Scores are reported as T-scores, with higher scores indicating greater executive dysfunction.

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153 **Neurodevelopmental Disabilities**

154 Motor impairment was determined on the basis of scores below 2 standard deviations on the Gross Motor
155 Scale of the Bayley Scales of Infant Development-III (29) obtained at 18-22 months of age. Neuromotor
156 development was further evaluated at current assessment by a trained researcher and reviewed by an
157 experienced paediatrician. The assessment consisted of a brief neurological examination to confirm the
158 presence or absence of cerebral palsy. Sensory deprivation, speech problems and psychiatric diagnoses
159 (or suspected clinical significance together with the child waiting for a specialist's opinion) were not
160 directly assessed and were based on parental reports. Psychiatric diagnoses included autism spectrum
161 disorder (ASD) and global developmental delay (GDD). In case of reported problems, the child's General
162 Practitioner was contacted, and medical notes were accessed after obtaining caregivers' consent.

Children with at least one of the following were regarded as having a neurodevelopmental disability (NDD): neuromotor impairment (assessed at 18-22 months and confirmed by subsequent diagnosis of cerebral palsy), diagnosis of ASD and/or GDD, sensory or/and speech problems.

Data analysis

SPSS version 22.0 (SPSS Inc, Chicago, IL) and Matlab (MathWorks Inc, Natick, MA, U.S.A) were used for analyses. Binomial tests were used to compare the proportion of very preterm children with clinically significant (and subclinical) levels of behavioural problems against age-matched UK population norms. Analyses were run before and after exclusion of children with NDD.

To assess the prevalence of inattention and hyperactivity/impulsivity, a data-driven clustering procedure was also used on the ADHD-RS-IV scores to fractionate the sample into groups, defined by the imbalance between their inattentive and hyperactive/impulsive symptoms, similar to (30). An Expectation-Maximisation (EM) algorithm fitting a Gaussian mixture model was used to identify relatively homogeneous groups of cases. Coordinates for centroids were initialized by running k-means clustering, for which centroid coordinates were initialised at random.

The associations between ADHD symptoms, IQ and neurocognitive skills (phonological short-term memory, inhibitory self-control, flexibility and emergent metacognition) were investigated using non-parametric Spearman's rank-order correlation. Analyses were run after exclusion of children with NDD and p values were always corrected for multiple comparisons using a false discovery rate (FDR) approach controlling alpha error to 5% (31). Spearman's correlations were used to investigate the relationship between ADHD symptoms and perinatal clinical variables and socio-economic status. Sex differences in ADHD scores were investigated using the Mann-Whitney U test. After testing for the presence of significant outliers (calculated using an interquartile range), variance homogeneity among groups (Levene's test of Equality of Error Variances), and approximately normal distribution in the different

groups, Kruskal-Wallis tests were used to test the association between severity of neonatal brain abnormalities and ADHD symptoms.

Comorbidities between NDD and behavioural problems were defined by having NDD plus ADHD symptoms above the 90th centile of the sex-matched normative score distribution.

Results

ADHD Symptomatology

The proportion of very preterm children with clinically significant inattentive (20.2%), hyperactive/impulsive (16.0%) and combined symptoms (16.8%) was higher than the expected 10% in normative samples of predominantly term-born individuals (after FDR correction; see Table 2). However, after exclusion of children with NDD, who represented 10.1% of the sample, the proportion of very preterm children with clinically significant ADHD symptoms did not differ from the population norm. In fact, comorbidity between NDD and clinically significant ADHD symptoms was high: 66.7% of children with NDD had inattention symptoms above the 90th centile cut-off, 25.0% had hyperactivity/impulsivity and 58.3% had combined symptoms. When using the 80rd percentile cut-off and excluding children with NDD, 32.7% of very preterm children had inattentive symptoms and 33.6% had combined symptoms, which was higher than the expected 20% in normative samples.

Table 2. Rates of clinical (>90th centile cut-off) and subthreshold (>80th centile cut-off) ADHD symptoms in very preterm children before and after exclusion of those with NDD.

	Norms	Very Preterm			Very preterm no NDD		Adj <i>p</i>
	%	N	%		N	%	
ADHD-RS-IV I >90th	10	24	20.2	.003	16	15.0	.100
ADHD-RS-IV H/I >90th	10	19	16.0	.021	16	15.0	.100
ADHD-RS-IV C >90th	10	20	16.8	.028	13	12.1	.271

ADHD-RS-IV I >80 th	20	44	37.0	.000	35	32.7	.002
ADHD-RS-IV H/I >80 th	20	34	28.6	.016	27	25.2	.109
ADHD-RS-IV C >80 th	20	44	37.0	.000	36	33.6	.000

I = Inattention; H/I = Hyperactivity/Impulsivity; C = Combined; p= probability of binomial tests uncorrected; Adj p = probability values of binomial tests after FDR correction.

K-means clustering identified four ADHD groups: 13 children with predominantly inattentive symptoms (10.9%), 12 with high levels of both inattentive and hyperactive/impulsive symptoms (10.1%), 44 with medium levels of both symptoms (37%), 50 with low levels of both symptoms (42%) and no child with mainly hyperactive/impulsive symptoms.

Figure 1. Visual representation of inattentive and hyperactive symptoms in all study participants after exclusion of children with NDD.

Sex differences in ADHD symptomatology

Mann-Whitney tests showed no sex differences in inattentive ($U = 1.429$; $p = 0.082$), hyperactive/impulsive ($U = 1.656$; $p = 0.598$) and combined ADHD symptom scores ($U = 1.536$; $p = 0.243$), even after exclusion of children with NDD.

Associations between ADHD symptomatology and cognitive variables

After excluding children with NDD, higher inattentive ADHD symptom scores were associated with lower full-scale IQ ($\rho = -0.245$, $p = 0.011$) but not with hyperactive and combined ADHD symptom scores ($\rho = -0.135$, $p = 0.168$ and $\rho = -0.190$, $p = 0.050$, respectively). Higher ADHD symptom scores

(all) were associated with poorer inhibitory self-control, flexibility and emergent metacognition scores, as shown in Table 3.

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Table 3. Associations between ADHD-RS-IV symptom subtype scores and cognitive outcomes after exclusion of children with NDD (n=107).

	Digit Span		Inhibitory Self-Control		Flexibility		Emergent Metacognition	
	ρ	p	ρ	p	ρ	p	P	p
Inattentive	-0.064	0.516	0.542	<0.001*	0.481	<0.001*	0.735	<0.001*
Hyperactive	-0.140	0.150	0.554	<0.001*	0.459	<0.001*	0.582	<0.001*
Combined	-0.101	0.299	0.586	<0.001*	0.505	<0.001*	0.718	<0.001*

Spearman correlation; ρ =Rho; p = probability values; * significant after FDR correction.

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Associations between ADHD symptomatology, perinatal clinical risk and socio-demographic variables

Higher inattentive ADHD symptom scores were associated with more days on mechanical ventilation ($\rho(119) = 0.196, p = 0.032$) and more days on parenteral nutrition ($\rho(119) = 0.222, p = 0.015$). All results survived FDR correction. There was no evidence of differences in ADHD symptom scores according to severity of perinatal brain lesions (inattentive, $H = 3.038, p = 0.219$; hyperactive, $H = 1.646, p = 0.439$; combined, $H = 1.858, p = 0.395$).

Hyperactive/impulsive and combined ADHD symptom scores were correlated with higher IMD scores which reflect lower socio-economic status ($\rho(119) = 0.259, p = 0.004$ and $\rho(119) = 0.198, p = 0.031$, respectively). Children belonging to the 5th IMD quintile, reflecting the most deprived socio-economic group, had a z score of 0.438, while those children belonging to the 1st IMD quintile, reflecting the least deprived socio-economic group, had a z score of -0.433. After FDR correction, these

associations remained unaltered. Similar findings persisted when children with NDD were excluded from each analysis.

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251 Discussion

252 Although the proportion of very preterm children with clinically significant ADHD did not differ
253 from normative data after excluding those with neurodevelopmental disabilities, 32.7% met criteria
254 for subthreshold ADHD inattentive type and 33.6% for combined type, which was higher than the
255 expected 20% in normative samples. These results highlight the importance of monitoring and supporting
256 the development of very preterm children throughout the school years, as subthreshold ADHD symptoms
257 have been associated with an increasing risk of psychosocial problems and of receiving a future diagnosis
258 of the clinical disorder (32-34).

259 In addition to the high subthreshold ADHD inattentive symptom prevalence, our results showed
260 that inattention was a core deficit in this sample of very preterm children. K-means clustering identified a
261 group of very preterm children with predominantly inattentive or combined symptoms, but did not
262 identify a subgroup of children with predominantly hyperactive/impulsive ADHD symptoms. This is in
263 contrast with what described by Sanefuji and colleagues (2016) who similarly used k-means clustering in
264 a sample of 165 children diagnosed with ADHD and were able to parse children based on the three
265 typical ADHD clinical presentations (30).

266 Psychiatric risk in extremely preterm children has been found to be higher in those with coexisting
267 neurodevelopmental disabilities (35), although neurodevelopmental disabilities have been also associated
268 with psychopathology irrespective of very preterm birth (36). In this study, up to two thirds of children
269 with clinically significant ADHD-inattentive symptoms had comorbid neurodevelopmental disabilities, as
270 did one quarter of those with clinically significant ADHD-hyperactive/impulsive symptoms. In atypically
271 developing children a complex relationship exists between cognitive outcome, biological and

environmental factors (37), and here we attempted to elucidate the association between ADHD symptomatology, cognitive and environmental outcomes, cerebral injury and perinatal clinical risk.

Inattentive ADHD symptoms were associated with lower IQ, which has been studied as a longitudinal predictor of educational outcomes (20). There is a strong phenotypic association between ADHD and lower IQ which has been attributed to shared genes (38) and previous research suggested that this association may be particularly strong for inattentiveness (39). It is therefore possible that preterm birth may share common genetic influences with IQ and academic achievement (40).

Previous findings in older preterm children suggested that a core executive difficulty underlined their inattentive problems (13, 41, 42), while the current study reported an association between higher ADHD symptoms (all types) and executive scores. These included inhibitory self-control, flexibility and emergent metacognition, which refers to the process of active control over one's own cognition, encompassing processes involved in self-appraisal and self-management (43) and have been studied as core features of ADHD (44, 45). The lack of ADHD symptom specificity in relation to executive functions observed here could be explained by methodological issues associated with modelling executive function early in development (46). More studies are therefore required to further investigate these associations.

The current finding of a positive correlation between inattentive ADHD symptoms and perinatal medical complications suggests that preterm-born pre-schoolers display a phenotypic profile that differs from that observed in the general population, with aetiological underpinnings in the clinical risk associated with preterm birth. This was assessed using markers of general infant health: number of days of parenteral nutrition (reflecting gut failure) and number of days spent on invasive ventilation via an endotracheal tube (reflecting respiratory failure). In a larger sample of infants the current study participants were drawn from, these two risk factors were independently associated with lower fractional anisotropy values throughout the white matter at term equivalent age, reflecting alterations in brain development (47). These results suggest that although in this study ADHD symptomatology did not differ

297 according to qualitatively-rated severity of perinatal brain lesions (unlike previous findings in 11 years
298 old children who were born extremely preterm (5)), future studies should include measures of brain
299 structure and function to further characterise the association between clinical risk and brain development
300 in order to better understand possible causative pathways leading to inattention in preterm children.

301 The idea that perinatal events can be implicated in the aetiology of psychiatric disorders has long
302 since been proposed (48) and several studies have supported this hypothesis by showing that preterm birth
303 may act as independent predictor of later psychopathology (49). The causal pathway to later psychiatric
304 disorder could be interpreted in the context of the neurodevelopmental sequelae of preterm birth (50),
305 although little is known about the neurobiological mechanisms leading to different ADHD subtypes. In
306 children with ADHD a double dissociation has been shown between resting state functional connectivity
307 in specific networks associated with inattentiveness and hyperactivity-impulsivity, indicating that
308 different brain alterations may characterise ADHD subtypes (30).

309 The early identification of a preterm profile characterised by inattentive ADHD symptomatology
310 associated with lower IQ and perinatal clinical risk suggests the need for early screening and educational
311 interventions aimed at improving specific attention problems in very preterm children, many of whom
312 exhibit academic difficulties at school age and are three times more likely to have special educational
313 needs than their term-born peers (51). Attention is a crucial requirement in school settings as it allows the
314 child to engage with classroom education activities. A strong relation between attention problems and
315 academic achievement has been shown in previous studies (even after accounting for IQ) (20) and
316 attention is considered one of the major areas of competence, which contribute to determine a successful
317 transition to school (“school readiness”) (52). The use of easy and quick screening questionnaires, such as
318 the ADHD-RS-IV, could help to identify potential targets for the prevention of the escalation of academic
319 problems that have been associated with inattentiveness (53). This is especially important, given that
320 attention problems tend to be more persistent in time and more difficult to be detected in the school
321 setting compared to hyperactive/impulsive behaviours (10, 20). Moreover, preschool-age inattention is

associated with other areas of difficulty, including communication and socio-emotional skills (52). Therefore, the allocation of additional support for very preterm children before school entry could enable them to enter school on a more equal footing with their peers.

Environmental variables including socio-economic status have been studied as risk factors for ADHD (54), although the majority of published studies have not differentiated between ADHD symptoms subtypes. Our results showed that children from socially disadvantaged families had increased hyperactive/impulsive but not inattentive ADHD symptoms. These findings are in line with others, showing selective associations between hyperactivity/impulsivity and environmental variables, i.e. an unsupportive home environment (55). The relationship between socioeconomic disadvantage and ADHD is likely to be intricate and may be mediated by other factors that are associated with lower socioeconomic status, such as lower parental education and a less stimulating home environment (56).

Limitation of this study include the lack of a locally matched control group. This could have influenced the results, possibly underestimating the level of problems experienced by very preterm children (57). Strengths of this study include the use of a wide battery of tests and of a questionnaire aimed at exploring ADHD subtypes, the use of a strict statistical procedure to correct for multiple testing, the inclusion of children with NDD in the analysis, the use of data driven together with theory driven approaches, the use of longitudinal information together with cross-sectional data.

In summary, this study shows that already during preschool age very preterm children are at increased risk of sub-threshold ADHD symptoms, especially the inattentive type. Inattentive ADHD symptoms were associated with intellectual functioning at time of assessment, and with perinatal clinical risk, supporting the hypothesis of a possible neurobiological origin of ADHD. In light of these findings, further investigation of early inattentive symptoms may support the development of effective interventions and provide new models for understanding the neurofunctional trajectories leading to ADHD in children born very preterm.

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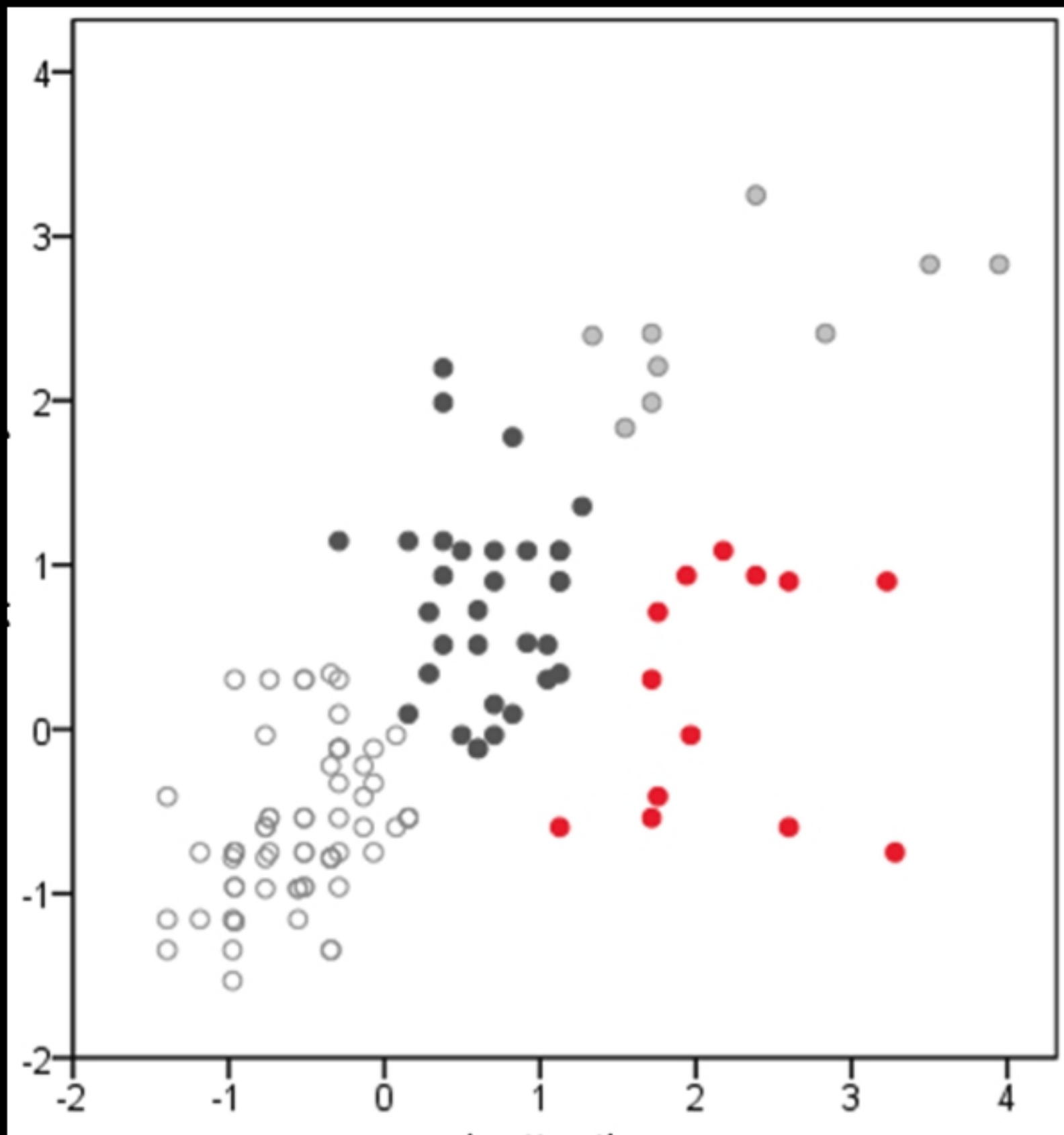
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