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ORIGINAL CONTRIBUTION

Early development in children that are later diagnosed with disorders of attention and activity: a longitudinal study in the Danish National Birth Cohort

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Abstract Not much is known about the early development in children that are later diagnosed with disorders of attention and activity (ADHD). Using prospective information collected from mothers in the Danish National Birth Cohort (DNBC), we investigated if developmental deviations in the first years of life are associated with later ADHD. In the DNBC 76,286 mothers were interviewed about their child's development and behaviour at age 6 and 18 months. At the end of follow-up, when the children were 8–14 years of age, 2034 were registered in Danish health registers with a clinical diagnosis of ADHD. The Hazard Ratio of ADHD was estimated using Cox regression model. At 6 months of age deviations in development showed associations with the child later being diagnosed with ADHD such as duration of breastfeeding, motor functioning, and incessant crying. At 18 months, many observations clearly associated with ADHD as for example the child not being able to fetch things on request [HR 3.0 (95 % CI 2.4; 3.7)], or the child being significantly more active than average [HR 2.0 (95 % CI 1.8; 2.2)]. An association to ADHD was shown, especially at 18 months, if the mother found it difficult to handle the child [HR 2.9 (95 % CI 2.4–3.5)]. However, it goes for all observations that the positive predictive values were low. Many children with ADHD showed signs of developmental deviations during the first years of their life. In general, however, ADHD cannot be identified solely on basis of the questions in DNBC.

Keywords Attention deficit disorder · Hyperactivity · Child development · Parent interview · Longitudinal study

Introduction

The prevalence of attention deficit hyperactivity disorder (ADHD) is increasing in most countries, and it is now estimated that five to seven percent of all children and adolescents suffer from ADHD [1, 2]. Whereas previously the disorder was mostly found in children of school age, now also more preschool children are diagnosed with ADHD [3, 4]. Symptoms of ADHD have been identified in children as young as 3 years of age. In preschool children, intervention studies using parent training programmes have shown good results with regard to both child behaviour and parent skills [5]. If intervention procedures are to be started before school age the children who would benefit from training must be identified quite early. Research in ADHD among preschool children has shown that symptoms related to inattention, impulsivity, and hyperactivity are similar to those seen in school age children when the developmental stage of the child is taken into account [6]. In longitudinal studies, preschool children diagnosed with ADHD continue to show relatively stable symptoms into school age [7]. ADHD symptoms in children younger than 3 years have only been sparsely researched, but it is uncertain whether children this young show symptoms that differentiate them

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from the non-diagnosed children. Such a distinction can be difficult to make, because the clinical manifestations of the core symptoms of ADHD appear differently in different age groups, and because they also depend on the developmental level of the child [8].

Different approaches have been used to detect possible symptoms of ADHD in children before the age of three. It appears that some children that are diagnosed with ADHD later or with high scores regarding externalizing problems on rating scales have a deviant development already in the first years of life. They show temperamental problems, are more active already in infancy, and experience difficulties related to sleeping, feeding, and development of motor and language skills [9–13]. However, some studies also found that the associations between early symptoms and later ADHD diagnoses became weaker after controlling for family risk factors, e.g. harsh parenting or low education. Overall, the research results are very diverse, presumably for reasons such as small sample sizes, restriction of participants to risk groups, and short follow-up time in many of the longitudinal studies. Also, the fact that different outcome and exposure measures have been used makes it difficult to compare studies. Most studies use rating scales, and they often report the diagnostic outcome as internalizing or externalizing behaviour. Only few studies include a clinical assessment for a diagnosis of ADHD.

The purpose of this study was to investigate, if children that are later diagnosed with disorders of attention and activity, already early in life have deviations in early development reported by their mothers that can differentiate them from children with typical development. The study was based on prospective information collected from a very large population-based birth cohort and contains mothers' observations of their child's development and behaviour during the first 2 years of the child's life. Clinical diagnoses from the Danish health registers were used as outcome. We have previously performed a similar study of the early signs of autism spectrum disorders and intellectual disability based on the same type of information as used in this study [14].

Methods

The Study Cohort

The Danish National Birth Cohort (DNBC) is a longitudinal study started in 1996 [15]. At the first antenatal care visit pregnant women throughout Denmark were invited by their general practitioners to take part in the study [16]. Inclusion continued until, in 2002, 101,042 women—corresponding to approximately 50 % of the women invited—had agreed to participate [17]. The data collection included structured telephone interviews with the mothers, when their children were 6 and 18 months of age. During the project period, there has been a continuous drop-out from the DNBC cohort; 70 % of the recruited women participated in the 6-month interview and 66 % in the 18-month interview [15].

The study cohort for the present study was limited to singletons whose mothers had provided socio-economic information in the first interview in pregnancy and participated in at least one of the two interviews after birth (at 6 or 18 months). Additional requirements were that the child should be alive and living in Denmark throughout the follow-up period, and be living with the mother at the time of the interview (Fig. 1). Information about death and emigration was supplied by the Danish Civil Registration System [18, 19], and information about birth weight, gestational age, and maternal smoking during pregnancy was supplied by the Danish Medical Birth Registry [20]. Statistical significant differences between participants in the 6 or 18-month interview and those who dropped out from the cohort were studied. The children of the mothers who decided not to participate, were often firstborns, were born preterm, had lower birth weight, and the mothers had less education and smoked relatively often during pregnancy. Furthermore, at the 18-month interview, a difference in gender was observed in that mothers of boys were the most likely to leave the cohort.

Each of the interviews in the DNBC comprised more than 200 questions, and all answers to questions about early development available from the 6- and 18-month interviews were used for the present study and appear from the tables. The mothers were individually contacted for each interview, even if they had not participated in the previous one. If the interview took place more than 2 weeks later than planned, the mother was asked to give the answers that would have been at the required age. If a mother had uncertainties or did not answer a question, her answer was coded as missing, and her child was excluded from analysis concerning that specific question. The questions in the interviews were not designed with specific ADHD in mind but were of a more general character about child development (the exact wording can be found on DNBC's website [15]). Many of the questions relate to skills in various areas of functioning. A question about the mother's experience of the childcaring was repeated in both interviews at 6 and 18 months. If the mother's answer was "difficult" or "very difficult", the interviewer continued to ask why, before categorising the answers into 14 pre-defined categories. However, instead of being categorised immediately, one third of the answers were recorded in a text variable and subsequently categorised for this study according to the original criteria.

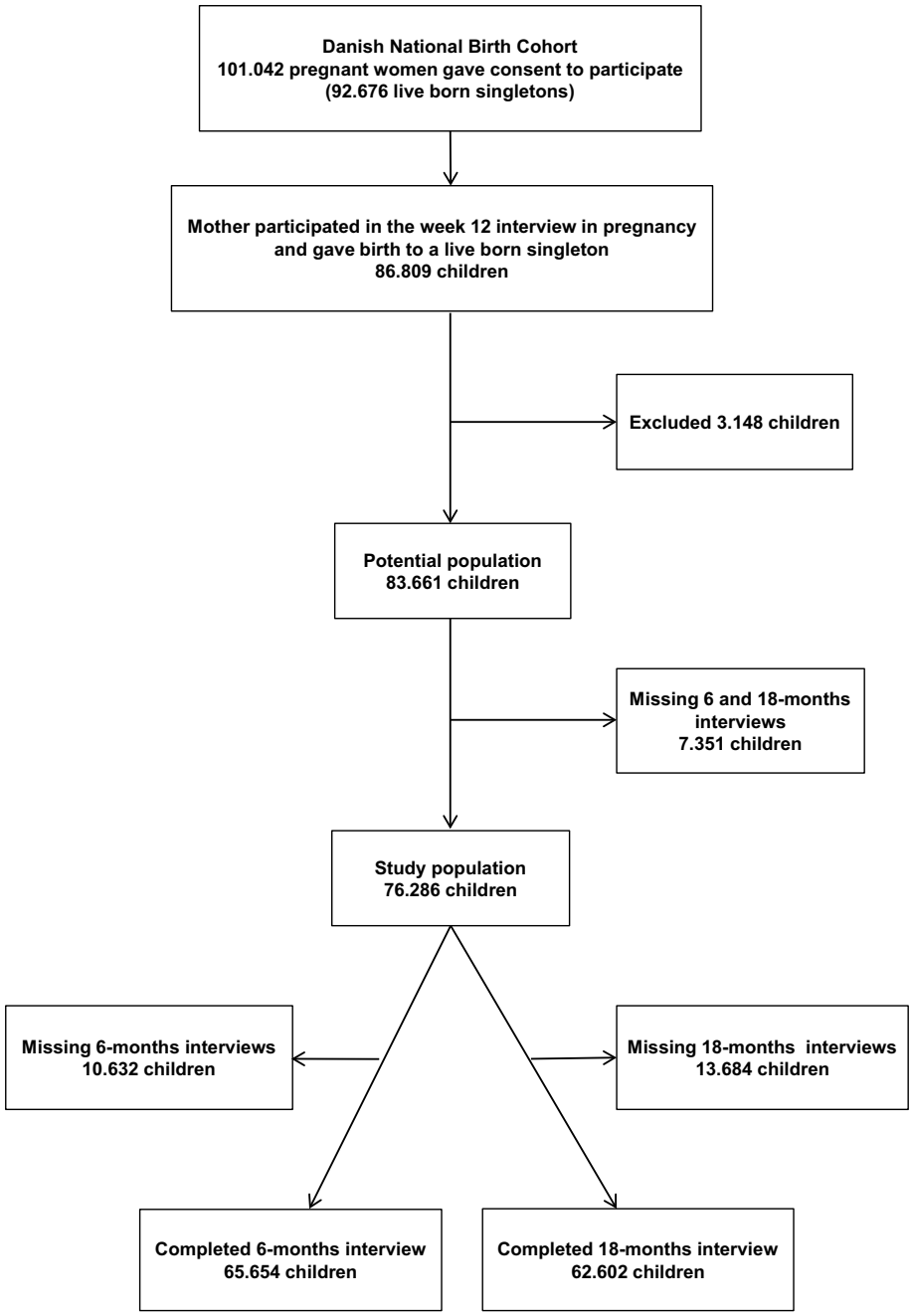

Fig. 1 Flowchart for the study population

Outcome

In the present study, the term ADHD is used to define the ICD-10 diagnoses F90.0, F90.1, and F98.8. The ICD-10 diagnostic classification has been used in Denmark since 1994 [21]. The two diagnostic systems—the International Classification of Diseases, 10th Revision (ICD-10), and the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) [22]—use two different terms, namely Hyperkinetic Disorder (HKD) and Attention Deficit Hyperactivity Disorder (ADHD). However, the lists of symptoms used by the two diagnostic systems to define HKD and ADHD are much the same; only, they differ with regard to prioritisation of the criteria necessary to define the two diagnoses [23]. HKD is defined more narrowly than ADHD, and it has been shown that all children diagnosed with HKD, based on ICD-10 criteria, would also be diagnosed with ADHD, but it does not apply the other way around [24]. Further, in the ICD-10 the diagnosis F98.8 includes children with attention deficit disorder, but without hyperactivity.

All children born in Denmark are assigned a unique personal identification number which is stored in the Civil

Registration System. It is used for registration in all public registers and allows identification across registers [19]. For the purpose of this study, an attempt was made to identify as many children in the DNBC cohort with ADHD as possible by the use of available Danish registries. In Denmark, medical and psychiatric examination and treatments at public hospitals are free of charge. Children diagnosed with ADHD in Danish public paediatric and child psychiatry departments are registered in either the Danish National Patient Register [25] or the Danish Psychiatric Central Register [26], in the following referred to as the hospital registries. Redeemed prescriptions are in Denmark registered in the National Prescription Registry [27], through which it is possible to identify children that have been medically treated for ADHD (methylphenidate or atomoxetine) in private clinics, as these are not obliged to report to the hospital registries. Thus, by linking the DNBC with the hospital registers and the National Prescription Registry it was possible to identify children diagnosed with or treated for ADHD in the cohort. Cases in which the indication for treatment was narcolepsy ($n = 12$) were removed from the cohort. According to guidelines from the Danish National Board of Health (from 2008), only child- and adolescent psychiatrists are allowed to give children medical treatment for ADHD. Children registered with a diagnose of ADHD before three years of age ($n = 24$) were excluded from the study cohort.

Statistical analyses

In the present cohort study children were followed from birth until their first ADHD diagnosis or to the end of follow-up on 8 February 2012. Because of different follow-up times for study participants, time to event analyses (Cox regression model) were chosen to analyse the association between developmental predictors and the subsequent diagnosis [28, 29], with the age of the child as the time scale. Hazard ratio (HR) was the effect measure, and for rare diseases like ADHD, it corresponds approximately to relative risk. An assumption for the Cox regression is constant hazard ratios over time for comparing variables, this was tested for each variable using log-minus-log survival plot. The ADHD group was compared to the total study cohort, and robust variance estimates were used to adjust for correlations in dependent data from siblings. To avoid unreliable results, analyses were only made for variables in which at least five children in the diagnostic group had the problem in question.

An aggregated risk marker was created for both interviews as the sum score of impairments. In the 6-month risk marker all variables from Table 2 were included, whereas for breastfeeding and crying, only one is used, namely "daily breastfeeding <6 months" and "being upset or crying >3 h per day". In the 18-month risk marker all variables from Table 3 regarding language, cognitive, and motor development were included, and for the latter two extra were added, namely sitting later than 8 months, and walking before 11 months or later than 15 months. Furthermore, the 18-month risk marker includes restless in sleep, more active than other kids, not only a happy child, not cautious and guarded, and parents suspicions about impairments in faculties. The scores were used as a categorical variable in Cox regression analysis. To get groups of reliable size for statistical test some of the scores are grouped based on both number of impairments and number of participants in each category.

The background information in Table 1 was tested for differences using the Chi squared test for categorical variables and the Wilcoxon rank sum test for continuous variables. Furthermore, the positive predictive value (PPV)—which is the probability of a later diagnosis in case the child had the symptom in question—was calculated for significant predictors, without taking varying follow-up times into account. For all analyses we use the term "significant" for findings that are statistically significant at the 5 % level, but all findings are reported with a confidence interval. No corrections were made for multiple testing. Stata Statistical Software, version 12.0, was used for the analysis.

Results

Study population

The ADHD cases included in the study consisted of 2034 children, which corresponds to 2.7 % of the study population (Table 1). The ADHD population included 1426 children identified in the hospital registers and additional 608 children from the prescription registry. No significant differences were found between children from the hospital registers and those from the National Prescription Registry with regard to gender, perinatal and prenatal information, mother's educational level, and age at the time of the interviews and follow-up. There were four times as many boys than girls in the ADHD group. Significantly more mothers in the ADHD group smoked during pregnancy, and they had a lower educational level than the mothers in the cohort. The percentage of mothers, who participated in the 6-month interview, was the same for the ADHD group as for the cohort. However, at 18 months only 78 % of the mothers in the ADHD group participated in the interview as opposed to 82 % in the cohort. The 6-month interview was performed as planned in both the ADHD group and the cohort, whereas the 18-month interview was carried out when the children were an average of 19 months old in both the ADHD group and the cohort (Table 1).

Table 1 Characteristics of the study population

	ADHD	Study cohort
Number all	2034	76,286
From hospital registries	1426	NA
From prescription registry	608	NA
Gender***		
Girls	410 (20.1 %)	37,270 (48.8 %)
Boys	1624 (79.9 %)	39,016 (51.2 %)
Mean age at diagnosis, years (min/max/SD)	8.4 (3.0/13.4/1.98)	NA
Mean age at end of follow-up, years (min/max/SD)***	11.4 (8.7/13.9/1.30)	11.3 (8.6/13.9/1.35)
First-born	976 (48.0 %)	35,677 (46.8 %)
Preterm, born before week 37***	90 (4.4 %)	2061 (2.7 %)
Mean birth weight, grams (min/max/SD)	3559 (590/5500/611)	3597 (410/6530/553)
Children with birth weight <2500 grams***	91 (4.5 %)	2061 (2.7 %)
Mother smoked in pregnancy***	536 (27.3 %)	12,579 (16.5 %)
Mother's level of education[a],***		
High	782 (40.9 %)	39,038 (53.4 %)
Middle	856 (44.8 %)	27,736 (38.0 %)
Low	275 (14.4 %)	6317 (8.6 %)
Participated in the 6-month interview	1761 (86.6 %)	65,654 (86.1 %)
Mean age at the 6-month interview, months (min/max/SD)	6.4 (5.3/15.6/0.89)	6.4 (5.0/26.3/0.80)
Participated in the 18-month interview***	1579 (77.6 %)	62,602 (82.1 %)
Mean age at the 18-month interview, months (min/max/SD)	19.2 (17.5/24.5/1.18)	19.2 (17.2/34.5/1.14)

NA not applicable, *SD* standard deviation

Statistical significant differences between ADHD and the cohort: $p \leq 0.05$ (*), $p \leq 0.01$ (**), $p \leq 0.001$ (***)

[a] Mother's level of education divided into 3 groups: high—4 years of education beyond high school or in management; middle—skilled workers or with middle range training; low—unskilled or unemployed

6-month interview

At 6 months, the most significant findings were in the areas related to early regulation (Table 2). In the first 3 months of life a small association was found between ADHD and the children who cried more than 30 min per day (HR 1.25 [95 % CI 1.12; 1.38]). In the ADHD group there seemed to be a trend towards crying for a longer time per day as well as for more days per week than with the children in the cohort. However, the PPV was only 3.2 % for a later ADHD diagnosis if a child cried more than 30 min a day. Compared to the cohort, there were significantly more mothers in the ADHD group who stopped daily breastfeeding rather early or did not breastfeed at all [HR 2.56 (95 % CI 1.83; 3.60), PPV 4.9 %] (Table 2). There was a linear correlation between the length of the breastfeeding period and the subsequent risk that the child would later be diagnosed with ADHD. Other questions in the 6-month interview show significant findings too, but for a small number of children only, as only very few failed to master the required skills (Table 2).

18-months interview

For almost all questions in the interview at 18 months, significant differences were found between the ADHD group and the cohort (Table 3). Compared to the cohort, there were more children in the ADHD group that showed language deviations, such as using few words [HR 1.57 (95 % CI 1.42; 1.75), PPV 3.0 %] or not putting words together [HR 1.38 (95 % CI 1.24; 1.54), PPV 2.8 %]. Children in the ADHD group also showed developmental deviations with regard to fine and gross motor skills. In the ADHD group 13.6 % of the children walked independently before 11 months of age [HR 1.24 (95 % CI 1.08; 1.44), PPV 3.1 %] compared to 11.2 % of the children in the cohort. However, a group of the ADHD children were late walkers; 11.3 % started walking later than 15 months of age (HR 1.66 [95 % CI 1.42; 1.94], PPV 4.1 %) as opposed to only 7.2 % in the cohort (Fig. 2); and with respect to sitting independently, 8.4 % of the children in the ADHD group sat alone after the age of 8 months [HR 1.64 (95 % CI 1.37; 1.98), PPV 4.2 %] whereas only 5.3 % in the cohort did that (Fig. 2).

Table 2 Associations between child development at 6 months of age and later diagnosis of ADHD

	ADHD		Study cohort
	Number (%)	HR (95 % CI)	Number (%)
Language, cognitive, and motor development			
Doesn't look in the direction of new sounds or voices	16 (0.9)	2.23 (1.36; 3.65)**	273 (0.4)
Cannot show that he wants to make contact by reaching out or making babbling sounds	143 (8.2)	1.11 (0.94; 1.32)	4790 (7.3)
Doesn't make noises to himself	36 (2.1)	1.52 (1.15; 2.11)*	868 (1.3)
Doesn't try to imitate voice sounds when spoken to	391 (23.0)	0.94 (0.84; 1.05)	15,341 (24.1)
Doesn't put toys in his/her mouth	12 (0.7)	1.35 (0.76; 2.38)	321 (0.5)
Doesn't throw toys onto the floor	134 (7.7)	1.19 (1.00; 1.42)*	4183 (6.4)
Doesn't try to grab things that are out of reach	51 (2.9)	1.95 (1.48; 2.58)***	999 (1.5)
Doesn't show that there are things he/she doesn't like	204 (11.7)	1.10 (0.95; 1.28)	6868 (10.5)
Doesn't like to be swung around like an airplane	66 (3.8)	1.22 (0.96; 1.57)	1989 (3.1)
Cannot hold head straight when picked up	6 (0.3)	1.90 (0.85; 4.27)	116 (0.2)
Cannot sit up straight when put on lap	253 (14.4)	1.52 (1.33; 1.74)***	6471 (9.9)
Cannot roll over from his/her back to stomach	472 (26.9)	0.96 (0.86; 1.07)	17,966 (27.5)
Cannot crawl on stomach	778 (44.3)	0.92 (0.84; 1.00)	30,482 (46.5)
Crying			
Age at periods of upset or crying for more than 30 min			
No periods	1236 (70.6)	Reference group	49,559 (75.7)
0–3 months	481 (27.5)	1.25 (1.12; 1.38)***	14,981 (22.9)
4–6 months	34 (1.9)	1.37 (0.98; 1.92)	907 (1.4)
Hours of being upset or crying during 24 h			
No periods for more than 30 min	1236 (71.1)	Reference group	49,559 (76.2)
1–3 h	292 (16.8)	1.11 (0.97; 1.26)	10,147 (15.6)
4–10 h	170 (9.8)	1.48 (1.26; 1.74)***	4469 (6.9)
11-h	41 (2.4)	1.80 (1.32; 2.46)***	872 (1.3)
Days a week of being upset or crying for more than 3 h			
None	1509 (86.7)	Reference group	59,284 (91.1)
1–3 days	23 (1.3)	1.33 (0.88; 2.01)	611 (0.9)
4–7 days	208 (11.9)	1.52 (1.32; 1.76)***	5182 (8.0)
Breast-feeding			
End of exclusively breast-feeding, child's age			
Never breast-feed	97 (7.7)	2.56 (1.83; 3.60)***	2513 (5.2)
–1 md.	234 (18.5)	3.05 (2.26; 4.12)***	5069 (10.5)
2–3 md.	266 (21.0)	2.23 (1.66; 3.00)***	7689 (15.9)
4–5 md.	619 (48.8)	1.33 (1.00; 1.77)*	29,771 (61.4)
6 md.–	52 (4.1)	Reference group	3469 (7.2)
End of daily breast-feeding, child's age			
–1 md.	287 (16.3)	2.35 (2.06; 2.69)***	5937 (9.1)
2–3 md.	289 (16.5)	1.88 (1.65; 2.15)***	7276 (11.1)
4–5 md.	248 (14.1)	1.39 (1.21; 1.60)***	8437 (12.9)
6 md.–	933 (53.0)	Reference group	43,943 (67.0)

NA not applicable, *HR* hazard ratio, *CI* confidence interval

Statistical significant differences between ADHD and the cohort: $p \leq 0.05$ (*), $p \leq 0.01$ (**), $p \leq 0.001$ (***)

Aspects of attention might be covered by some of the questions in the interview, and these questions showed statistically significant associations with ADHD being diagnosed later in the child (Table 3). For example, if the child could not fetch things when asked to, the risk of ADHD increased by three times [HR 2.95 (95 % CI 2.35; 3.70), PPV 7.0 %]. These skills were, however, also difficult for many children in the cohort. The question about the child's

Table 3 Associations between child development at 18 months of age and later diagnosis of ADHD

	ADHD		Study cohort
	Number (%)	HR (95 % CI)	Number (%)
Language, cognitive, and motor development			
Doesn't use word or word-like sounds to indicate what he wants	82 (5.2)	2.00 (1.60; 2.51)***	1681 (2.7)
Doesn't use more than ten words	1081 (68.6)	1.57 (1.42; 1.75)***	36,270 (58.0)
Doesn't make sentences of two words	962 (64.4)	1.38 (1.24; 1.54)***	34,515 (56.8)
Cannot climb stairs without support	108 (6.9)	1.72 (1.42; 2.09)***	2599 (4.2)
Cannot drink from a cup without help	51 (3.2)	2.66 (2.01; 3.53)***	795 (1.3)
Cannot take off socks or shoes, when he/she is asked to	357 (22.9)	1.38 (1.23; 1.56)***	11,125 (18.0)
Cannot fetch things or take them to others if asked to	79 (5.2)	2.95 (2.35; 3.70)***	1175 (1.9)
Cannot be occupied with the same thing for at least 15 min without adult involvement	366 (23.3)	1.39 (1.24; 1.56)***	11,222 (18.1)
Doesn't try to make marks with colour pencils or similar objects	129 (8.3)	1.67 (1.40; 2.00)***	3259 (5.2)
Doesn't automatically turn the picture right when looking in a book	842 (57.6)	1.37 (1.24; 1.52)***	29,593 (50.1)
Activity and temperament			
More or less active than kids the same age?			
Like kids his/her own age	813 (51.6)	Reference group	42,697 (68.4)
More active/hyper active/very restless	713 (45.3)	1.97 (1.78; 2.18)***	18,978 (30.4)
Less active/very passive and quiet	49 (3.1)	3.32 (2.49; 4.43)***	786 (1.3)
A cautious and guarded child?			
No	1384 (87.7)	Reference group	51,611 (82.5)
Yes	58 (3.7)	0.66 (0.51; 0.86)**	3257 (5.2)
Both yes and no	75 (4.8)	0.72 (0.57; 0.90)**	3816 (6.1)
Only among strangers	62 (3.9)	0.59 (0.46; 0.76)***	3903 (6.2)
A happy child?			
Yes	1540 (97.5)	Reference group	61,916 (98.9)
No	9 (0.6)	3.12 (1.62; 6.00)***	117 (0.2)
Both yes and no	30 (1.9)	2.09 (1.45; 3.00)***	565 (0.9)
Sleep			
Is he/she restless in his/her sleep?			
No	1114 (70.6)	Reference group	47,290 (75.6)
Yes/both yes and no	457 (28.9)	1.26 (1.13; 1.41)***	15,018 (24.0)
Does not want to fall asleep	8 (0.5)	1.40 (0.70; 2.81)	287 (0.5)
Impairments in use of faculties			
Parental suspicion of reduced hearing	253 (16.0)	1.77 (1.54; 2.02)***	6183 (9.9)
A doctor has confirmed the reduced hearing	89 (5.6)	1.74 (1.40; 2.15)***	2132 (3.4)
Parental suspicion of reduced vision[a]	35 (2.6)	2.77 (1.98; 3.87)***	526 (1.0)
A doctor has confirmed the reduced vision[a]	19 (1.4)	3.48 (2.21; 5.48)***	232 (0.4)
Parental suspicion of squinting[a]	130 (9.5)	1.58 (1.32; 1.90)***	3459 (6.2)
A doctor has confirmed the squinting[a]	58 (4.2)	1.84 (1.41; 2.39)***	1304 (2.4)

NA not applicable, *HR* hazard ratio, *CI* confidence interval

Statistical significant differences between ADHD and the cohort: $p \leq 0.05$ (*), $p \leq 0.01$ (**), $p \leq 0.001$ (***)

[a] Only in version 2 of interview at 18 months, $n = 48{,}075$

ability to occupy itself with the same thing for at least 15 min showed that 18.1 % of the children in the cohort and 23.3 % in the ADHD group were not able to concentrate for that long.

The mother perceiving her child as more active than other kids was significantly associated with the child later being diagnosed with ADHD [HR 1.97 (95 % CI 1.78; 2.18), PPV 3.7 %] (Table 3). The opposite, however, when the mother found the child to be less active, was also associated with a later ADHD diagnosis [HR 3.32 (95 % CI 2.49; 4.43), PPV 6.1 %]. The mother viewing her child as cautious was another significant

Fig. 2 Distribution in months of the age when the child started sitting and walking independently based on interview at 18 months. Information included for sitting until 12 months of age and for walking until 20 months of age

association that appeared to protect against a later ADHD diagnosis.

The interviews only include one question about sleep patterns, and if the mother perceived her child as restless in sleep, it showed a weak significant correlation with ADHD. Concerning the children's vision and hearing, there were more mothers in the ADHD group than in the cohort who had been worried, and particularly about the hearing [HR 1.77 (95 % CI 1.54; 2.02), PPV 4.2 %] (Table 3).

Mother's experience in taking care of her child

In both the 6 and 18-month interview, mothers were asked how it had been for them to take care of their child. Both interviews showed a significant linear relationship between the mother's experience of strain and the child's later risk of an ADHD diagnosis (Table 4). The strongest association was found in the 18-month interview, where approximately 11 % of the mothers with children that were later diagnosed with ADHD found it difficult or very difficult to take care of the child; in the cohort it was only 5 %. The mothers who found it difficult or very difficult were asked about the reasons for this, and mothers in the ADHD group reported for the most part that the child was either sick or handicapped [6-month: HR 2.62 (95 % CI 1.98; 3.48), 18-months HR 3.09 (95 % CI 2.38; 4.01)] or a difficult or restless child [6-month: HR 1.53 (95 % CI 1.12; 2.10), 18-month : HR 3.22 (95 % CI 2.37; 4.38)] (Table S1 online).

Aggregated risk marker

If the child failed scores—two or more in the 6-month interview, four or more in the 18-month interview—was found a significantly increased and linear association with ADHD (Table 5). As for the other variables, however, the PPV for the sum scores were low. For the score with the highest risk at 18-month, the sensitivity was 17.4 % and the specificity 93.6 %.

Discussion

This large cohort study of early child development is based on prospective information collected from mothers. Among the children with ADHD—compared to those with a typical development—we identified signs of deviant development already at a very early age. In the first year of life, these deviations were mostly related to regulation of temperament and breastfeeding, whereas the deviations found in the second year could be explained by impairments in relation to attention, impulsivity, and activity.

Table 4 The mother's experience of taking care of her child, interviews at 6 and 18 months of age

How has it been for you to take care of your child?	ADHD		Study cohort
	Number (%)	HR (95 % CI)	Number (%)
6 months			
Very easy	1053 (59.9)	Reference group	43,023 (65.6)
Fairly easy	558 (31.7)	1.19 (1.07; 1.32)***	19,353 (29.5)
Difficult	121 (6.8)	1.88 (1.56; 2.27)***	2610 (4.0)
Very difficult	28 (1.6)	1.88 (1.29; 2.73)***	609 (0.9)
18 months			
Very easy	726 (46.1)	Reference group	36,396 (58.2)
Fairly easy	672 (42.6)	1.46 (1.32; 1.62)***	23,299 (37.2)
Difficult	136 (8.6)	2.92 (2.44; 3.51)***	2364 (3.8)
Very difficult	42 (2.7)	4.33 (3.17; 5.92)***	498 (0.8)

NA not applicable, *HR* hazard ratio, *CI* confidence interval

Statistical significant differences between ADHD and the cohort: $p \leq 0.05$ (*), $p \leq 0.01$ (**), $p \leq 0.001$ (***)

Table 5 Aggregate risk marker based on the mothers' reports of deviant development

Total number of questions	ADHD			Study cohort
	N (%)	HR (95 % CI)	PPV (%)	*N* (%)
6 months[a]				
0–1 questions	694 (40.0)	Ref.	2.4	29,690 (45.7)
2–3 questions	782 (45.1)	1.16 (1.04; 1.28)**	2.7	28,751 (44.2)
4– questions	260 (15.0)	1.68 (1.45; 1.93)***	4.0	6557 (10.1)
18 months[b]				
0–3 questions	172 (10.9)	Ref.	1.3	13,473 (21.5)
4 questions	229 (14.5)	1.36 (1.12; 1.66)***	1.7	13,210 (21.1)
5 questions	326 (20.7)	1.79 (1.49; 2.16)***	2.3	14,399 (23.0)
6 questions	331 (21.0)	2.34 (1.95; 2.82)***	3.0	11,192 (17.9)
7 questions	246 (15.6)	3.19 (2.62; 3.88)***	4.0	6162 (9.8)
8– questions	275 (17.4)	5.36 (4.43; 6.49)***	6.6	4162 (6.7)

N number, *HR* hazard ratio, *CI* confidence interval, *ref.* reference group, *PPV* positive predictive value

Statistical significant differences between ADHD and the cohort: $p \leq 0.05$ (*), $p \leq 0.01$ (**), $p \leq 0.001$ (***)

[a] Including: questions from Table 2, for breastfeeding only daily breastfeeding <6 months and for being upset or crying only cry >3 h per day

[b] Including: questions from Table 3, e.g. restless in sleep, more active than other kids, not only a happy child, not cautious and guarded, for impairments in faculties only parents suspicions, plus sitting later than 8 months, and walking before 11 months or later than 15 months

The 6-month interview showed a correlation, although a modest one, between children who cried incessantly and ADHD. This is in line with a meta-analysis based on 22 longitudinal studies that also showed a statistically significant association between excessive crying and later ADHD [30]. The 18-month interview in the DNBC showed that mothers rated those children, who were later diagnosed with ADHD, to be respectively more or less active and less cautious compared to the total cohort. In both interviews there was also found a linear relationship between the difficulties of childcare experienced by the mother and the risk of a later ADHD diagnosis. Previous longitudinal studies have shown that some parents rated the children later diagnosed with ADHD to have more behavioural and temperamental problems in infancy compared to the control groups [11, 31–34]. Other studies have not been able to confirm these findings [35–38] probably due to differences in methods and populations used. Additionally, two studies have found that children diagnosed with ADHD at school age had more behavioural problems recorded at routine child healthcare check in the first years of life, which characterised them as uncooperative, difficult, and with attention and hyperactivity problems [12, 13].

In the 18-month interview, several questions that seem to relate to attention skills were associated with later ADHD. Many of these questions, however, also require a certain level of cognitive, language, and motor development. At 18 month delay in language development seems to be associated with a later diagnosis of ADHD—a finding that is in line with results from other studies [11, 12]. Only few other studies have dealt with the development of motor skills in the early years among children with ADHD and found results that cover the range from delayed [13] to good skills [12, 39]. The present study also found mixed results; most children with ADHD showed no deviations in the development of motor function. With respect to independent walking, however, a small group of children walked very early while another group was delayed. It might be that deviations in motor development are associated with children having additional comorbid conditions. Overall, our results support the conclusion drawn by Johnson et al. that assessment of motor function levels at age one year is not predictive of later ADHD diagnosis [39].

Both for the duration of exclusive breastfeeding and for the total breastfeeding period, we found associations with the child's later ADHD diagnosis. The risk decreased with the length of the breastfeeding period. However, the causal relationship between short duration of breastfeeding and ADHD is unclear and can be explained by factors that are related to both the child and the mother. The focus of the present study is on the child's development, although this can be influenced by factors related to the mother as well. Mothers in the ADHD group had a lower level of education, they smoked more during pregnancy than mothers in the cohort, and the prevalence of children born prematurely was higher in the ADHD group, all of which are well-known risk factors connected to short duration of breastfeeding [40]. This study's finding of a shorter breastfeeding

period is in line with other studies that also have found children with ADHD to be breastfed for significantly shorter periods than the control groups [9, 41–45].

Only one question about sleep was included in the DNBC interviews, and it showed an association with a higher risk of ADHD if the mother found the child to be restless in sleep. Other studies have identified sleep difficulties at an age as early as 3 months to be associating with a later ADHD diagnosis [12]. Studies have also shown that children with ADHD sleep less already from the first year of life [10, 46, 47].

As we were searching for predictors of ADHD specifically, analyses stratified for other risk factors have not been conducted. In other studies, however, an interaction between risk factors linked to the mother or the family, such as mother's age and educational level, had a great impact on the associations found between early developmental deviations and the child being diagnosed with ADHD later in life [33, 35]. These factors might also have had an impact on the results in this study, especially differences in the mother's educational level. In general, the participants in the DNBC deviated slightly from the total population by being more educated than the average population [17]. Children diagnosed with ADHD often have other comorbid disorders [48], which the analyses of the present study do not account for and it could have affected the results here reported. Another important limitation in the present study is the quality of the questions used in the DNBC interviews. They were not developed especially with ADHD in mind and the validity of the questions has not been studied. In general, we found a low PPV with regard to the identification of children that were later diagnosed with ADHD. Some of the questions regarding the child's temperament are value-loaded and open to different interpretations. The answers given by mothers of children with ADHD may have been influenced by factors like stress or psychiatric circumstances in either the family or the mother herself, as it is well-known that parents of children with ADHD are at an increased risk of having ADHD themselves [48].

The youngest children in the study cohort were 8 years old at follow-up. Some of them may not yet be diagnosed with ADHD, as no screening for ADHD has been carried out in the cohort. Other children with ADHD could be undetected as well, such as children diagnosed in the private sector, who had not been treated with medication. Furthermore, it must be presumed that, when using register data based on clinical diagnoses, more severe cases of ADHD are included while less severe cases may remain undetected. The quality of the ADHD diagnosis in the Danish Psychiatric Central Register has been validated in a study where hospital records were reviewed; 76 % of the records were classified as ADHD, and 9 % reached the subthreshold for ADHD [49]. A study based on another Danish birth cohort has shown that of all the children registered in the Danish registers with a diagnosis of ADHD, 73.5 % had been screened positive for a possible or probable diagnosis of ADHD on The Strengths and Difficulties Questionnaire at age five to seven [50]. The prevalence of ADHD in the present study population is 2.7 %, which corresponds nicely with the prevalence found in other studies based upon ICD-10 criteria; and it indicates that most children with the disorder were identified [51]. However, we expect that the limitations mentioned will have minimised only some of the differences between groups identified in the study and biased the results towards the null hypothesis.

In conclusion, this study has shown that some of the children that are later diagnosed with ADHD showed developmental deviations as early in life as six months, but especially so at 18 months. However, the study also showed, that children with a later ADHD diagnosis could not be identified by means of the general development questions in the DNBC that have been answered by the mothers. The findings of the study carry only limited implications for clinical practice when it comes to early identification of children with ADHD. They can, however, be useful for further research in the field.

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Compliance with ethical standards

Conflict of interest Per Hove Thomsen has received speaker's honoraria from Shire, Novartis, and HB-Pharma within the last 3 years. He is no member of any advisory boards, nor does he hold any stocks. The other authors have no conflicts of interests to declare.

Ethics At the enrolment in the DNBC, the mothers gave their consent to the data being used for research purposes in future, and the steering committee for the DNBC gave their permission to use the data for the present study. The study was approved by the Danish National Board of Health and registered in the Danish Data Protection Agency.

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