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Further evidence for the role of pregnancy induced hypertension and other early life influences in the development of ADHD: Results from the IDEFICS study

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Abstract: The aim of this study is to investigate whether in addition to established early risk factors other, less studied pre-, peri-, and postnatal influences, like gestational hypertension or neonatal respiratory disorders and infections, may increase a child's risk of developing attention-deficit/hyperactivity disorders (ADHD). In the IDEFICS study more than 18.000 children, aged 2 to 11.9 years, underwent extensive medical examinations supplemented by parental questionnaires on pregnancy and early childhood. The present analyses are restricted to children whose parents also completed a supplementary medical questionnaire (n=15,577), including the question whether or not the child was ever diagnosed with ADHD. Multilevel multivariable logistic regression was used to assess the association between early life influences and the risk of ADHD. Our study confirms the well-known association between maternal smoking during pregnancy and a child's risk of ADHD. In addition, our study showed that children born to mothers younger than 20 years old were 3-4 times more likely to develop ADHD as compared to children born to mothers aged 25 years and older. Moreover, we found that children whose mothers suffered from pregnancy induced hypertension had an approximately twofold risk of ADHD (OR 1.95; 95% CI 1.09-3.48). This also holds true for infections during the first four weeks after birth (OR 2.06; 95% CI 1.05-4.04). In addition, although not statistically significant, we observed a noticable elevated risk estimate for neonatal respiratory disorders (OR 1.76; 95% CI 0.91-3.41). Hence, we recommend that these less often studied pre-, peri, and postnatal influences should get more attention when considering early indicators or predictors for ADHD in children. However, special study designs such as genetically sensitive designs may be needed to derive causal conclusions.

Keywords: Attention-deficit/hyperactivity disorders, European children cohort, gestational hypertension, maternal age, neonatal respiratory disorders, smoking

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition with several behavioral symptoms, including inattention, restlessness, impulsive behavior, and impaired concentration, which can lead to severe academic and social problems for the affected individual, as well as an increased social and economic burden for their families and the society as a whole [1, 2]. ADHD occurs in about three to five percent of the population worldwide [3] with a slightly higher prevalence in children and adolescents (5.3%) as compared to adults (4.4%) [4]. A single, specific cause of ADHD has not been found yet. However, heritability seems to be considered as the strongest factor in the development of ADHD and it has been estimated that genetic factors are responsible for approximately three-quarters of the variability in ADHD [5].

Several studies found that living conditions of children, e.g. permanent stress, inconsistent education, a poor living environment, or broken family relationships are associated with ADHD and/or aggravate the behavioral problems [6]. But it seems questionable whether they are independent primary underlying causes of the disease - rather they might be the result of the child's disorder [7]. Several environmental factors also may increase the risk of developing ADHD. Some studies reported an association between childhood exposure to certain food additives or lead contamination with an increased risk and symptoms of ADHD, others suggested that cigarette and alcohol exposure during pregnancy may also play a role in the etiology of ADHD [8-17] whereas it is increasingly discussed whether such associations are the direct effect of tobacco or alcohol exposure in utero or the result of insufficient control for genetic and shared family environmental factors [18-20]. Finally, several other causes such as preterm birth and/or low birthweight and also obstetric complications are suspected to increase the risk of ADHD [21-24]. Here as well, it is difficult to judge which of these (correlated) causes the main trigger is for ADHD – not at least since each of them "might reflect underlying foetal problems" [25]. The current study focusses on a specific set of pre-, perinatal and early life postnatal (e.g. neonatal) risk factors to pursue two objectives. First, we will examine the influence of established pre-, peri- and postnatal exposures, like smoking and/or alcohol

intake during pregnancy or low birthweight and/or premature delivery on the risk for ADHD. Second, we want to add further evidence regarding variables that have been examined in only few studies until now (primarily due to a lack of data) but are suspected to increase a child's risk of ADHD. In particular our data enable us to investigate the potential influence of complications during pregnancy, e.g. gestational hypertension [24, 26], as well as the impact of health problems during the first four weeks after birth [27, 28].

Methods

Ethics Statement

We certify that all applicable and governmental regulations concerning the ethical use of human volunteers were followed during this research (Helsinki Declaration). Ethical approval was obtained from the relevant local or national ethics committees by each of the eight study centers. Children and their parents were informed about all aspects of the study and parents gave their written informed consent prior inclusion in the study. Children and their parents could consent to single components of the study while abstaining from others.

Study Population

The European IDEFICS study (Identification and prevention of dietary- and lifestyle-induced health effects in children and infants) is a prospective multi-center cohort study that took place in eight European countries (Belgium, Cyprus, Estonia, Germany, Hungary, Italy, Spain and Sweden) between 2006 and 2012. The main focus of the study was to assess the health status of European children with special focus on overweight, obesity, and comorbid disorders. A more detailed description of the overall study design may be found in Ahrens et al. [29].

The initial study sample for this investigation includes in total 18,783 children, of whom 16,228 children, aged 2 to 9.9 years, were recruited during the baseline survey (T0) between September 2007 and May 2008, and additional 2,555 children, aged 2 to 11.9 years, were newly recruited during

the first follow-up survey (T1) two years later. All children completed the same survey protocol. The examination program included standard anthropometric measurements, the assessment of clinical parameters such as blood pressure, and the collection of urine, saliva, and blood. Additionally, a self-administered questionnaire was filled by the parents to gather information, among others, on pregnancy, early childhood, and on sociodemographics (IDEFICS parental questionnaire). A second questionnaire on health-related and medical information was completed in course of the physical examination of the child (IDEFICS medical questionnaire). For filling this questionnaire, the help of medical personnel was offered directly at the survey sites. The present cross-sectional analyses are restricted to children whose parents also completed at least one medical questionnaire (n=15,577), either at T0 (80%) or T1 (69%).

Outcome

Children were considered as affected by ADHD if their parents (or caregivers) responded to the question "Has the child ever been diagnosed with any of the following diseases?" in the IDEFICS medical questionnaire by ticking the answer "Attention-deficit/hyperactivity disorder (ADHD)" in at least one of the two surveys.

Exposures

Information on pre-, peri- and postnatal factors was collected from the parental questionnaire, which was subdivided into several sections dealing with various aspects of the child's development, lifestyle, and social environment. To assess pregnancy and early childhood we asked for prenatal exposures like mother's age at child's birth, her obstetric history regarding to following diagnoses during pregnancy: gestational hypertension (which is usually defined as having a blood pressure higher than 140/90 measured on two separate occasions, more than 6 hours apart), proteinuria, sugar in urine (glycosuria), and gestational diabetes, her consumption of alcoholic beverages during pregnancy (never, rarely (at maximum once a month), several occasions a week, daily), as well as her smoking behavior during pregnancy (never, rarely, almost daily). Further we asked for peri- and

postnatal factors like weight and height of the child at birth, potential health problems (respiratory adjustment disorders or infections) which might have occurred during the first four weeks after birth, the duration of breastfeeding (exclusive and in combination with other types of feeding), and, in case of preterm birth, the number of weeks the child was born before the estimated date of birth. Since some study centers could also provide additional child information from maternity cards or children's routine check-ups, we were able to use this externally recorded information in cases where birthweight (n=223) and gestational age (n=196) were missing.

Statistical Analysis

The associations between pre-, peri-, and postnatal influences and ADHD were examined in two steps: In a first step, we used a 'partially-adjusted' multilevel logistic regression model for each separate independent variable to estimate sex- and age-adjusted odds ratios (OR) and 95% confidence intervals (95% CI) using the dichotomous outcome *parent-reported diagnosis of ADHD* as dependent variable and country as second-level random effect. Moreover, since several studies have shown that ADHD is more prevalent among socioeconomically disadvantaged groups [16, 21, 30], in this model we also accounted for socioeconomic status (SES) considering the highest ISCED-level of education (International Standard Classification of Education, UNESCO 2012) attained by father or mother as a proxy for SES in our analyses [31]. The educational level was classified as low, if the highest ISCED-level was between 0 and 2 (early childhood education, primary education, lower secondary education), as medium for ISCED-levels between 3 and 5 (upper secondary education, post-secondary non-tertiary education, short-cycle tertiary education), and as high for ISCED-levels 6 to 8 (Bachelor's degree or equivalent, master's degree or equivalent, and doctoral degree or equivalent).

For some exposure variables (e.g. complications during pregnancy and birth) it was mandatory that the questionnaire was completed by the biological mother. If this was not the case, the given information was treated as if it were missing. We introduced a separate category for missing values

without reporting risk estimates for this category. We prefer this approach since case-wise deletion (complete-case analysis) would have implied that all data for a child who has one or more missing values had to be removed, resulting in a reduced sample size, a loss of power, and therefore also a loss of precision of the estimates.

In a second step, we constructed a fully adjusted model, simultaneously comprising *all* predictors and confounders in a final multivariable model. All models were estimated using the procedure GLIMMIX procedure in SAS 9.3 (SAS Institute, Cary, NC, USA). Please note that all tests were conducted at a significance level of α=0.05 without adjusting for multiple testing. This means that statistically significant results have to be interpreted with caution. We therefore report the respective p-values as additional exploratory measures.

Results

A total of 15,577 children from eight European countries were included in the analyses (age range: 2-11.9 years, mean age: 6.2 years, SD: 1.9 years). Based on questionnaire information 192 (64 of them firstly reported at T0, and 128 reported at T1) out of 15.577 children (1.2%) were classified as affected by ADHD. While the ratio between the number of boys and girls without ADHD is nearly 1:1, we found that boys were three times more likely (OR 2.95; 95% CI 2.11-4.11, p<0.0001) to be diagnosed than girls (Table 1). The odds ratio for the continuous variable age (in years) was 1.32 (95% CI 1.21-1.45, p<0.0001).

Table 1

As might be expected from previous studies, the prevalence increased by age group (data not shown): 2-≤4 years (girls: 0.4%; boys: 0.5%), 4-≤6 years (girls: 0.4%; boys: 1.2%), 6-≤8 years (girls: 0.8%; boys: 2.3%), 8-≤11.9 years: (girls: 0.7%, boys: 3.3%) and parents of children without ADHD tended to be higher educated.

With regard to prenatal influences (Table 2), our study did not show an association between maternal alcohol consumption during pregnancy and the child's risk of being diagnosed with ADHD. However, the risk of ADHD was 1.8 times higher in children whose mothers smoked almost daily as compared to children whose mothers did not smoke during pregnancy.

Table 2

In addition to this well-established prenatal risk factor, we also observed that children whose mothers suffered from pregnancy induced hypertension had an approximately twofold risk of ADHD; whereas other pregnancy complications (proteinuria, sugar in urine, gestational diabetes, C-section) seem to play no role according to our data.

Regarding perinatal and postnatal influences we found a very strong association between maternal age and the risk of being diagnosed with ADHD: Children born to mothers younger than 20 years old were 3-4 times more likely to develop ADHD as compared to children born to mothers aged 25 years and older (Table 3). Beyond this, it is also worth mentioning that we detected significantly elevated risk estimates for children with neonatal respiratory disorders and infections during the first four weeks after birth.

Table 3

In addition, our data suggest that preemies (children born three and more weeks preterm) are more susceptible to developing ADHD.

To adequately account for all factors suggesting an elevated risk for ADHD, we carried out a simultaneous logistic regression including all predictors and confounders (covered by the present study) in one final multivariable model, i.e., alcohol consumption and smoking during pregnancy, young maternal age at birth, gestational hypertension, proteinuria, glycosuria, gestational diabetes, C-section, preterm birth, birthweight, breastfeeding, and neonatal respiratory disorders or infections during the first four weeks after birth, as well as sex, age, country, and SES.

Table 4

As can be seen from Table 4, the risk estimates for maternal smoking during pregnancy, gestational hypertension and young maternal age (<20 years) only slightly decreased and remained statistically significant, whereas the risk estimates for preterm birth, low birthweight, neonatal respiratory problems and infections (though still significant) declined by up to 25% after full adjustment.

Discussion

Analyzing data from 15,577 children (2-11.9 years) from eight European countries, we estimated a prevalence of 1.2% for being diagnosed with ADHD. In comparison, the worldwide prevalence estimates for ADHD vary between 3% and 7% [32]. The overall prevalence in our study is somewhat below these estimates, but this can at least partly be explained by our very young study sample (45% of the children were 6 years or younger) and the fact that parental-reported information may underestimate the prevalence. Our data are consistent, however, with the well-known three-to-fourfold male-to-female ratio in population-based studies [32-34], which is often explained by the fact that boys with ADHD have more externalizing symptoms, while girls with ADHD have fewer such impulsive/hyperactive and more inattentive symptoms (depression, anxiety, low self-esteem). Since the inattentive type of ADHD is harder to diagnose this might contribute to a gender bias and underdiagnoses of ADHD in girls [35].

Our study is also in line with several other epidemiological studies, suggesting that maternal smoking during pregnancy might raise children's risk of developing ADHD [36-38]. Nevertheless, the final assessment of the risk potential of smoking during pregnancy is still a matter of debate. The designs of the studies vary greatly, the instruments and questionnaires differ among the surveys, age ranges of children involved show a large variability, and, not at least, there are differences in confounding factors considered in the analysis. In addition, it must be assumed that mothers who smoke during pregnancy are more likely to also have other unhealthy behaviors (e.g. poorer nutrition) that may

also have adverse effects on the fetus [39], but which have not been considered or controlled for in previous studies.

However, in their recently published study [18], Palmer et al. were able to carefully consider a total of ten familial risk factors for maternal smoking during pregnancy by means of propensity score analysis. In fact, they found that controlling for familial confounding significantly attenuated the observed univariate effect of prenatal smoking on offspring externalizing problems, but some sub-types of behavior (e.g. inattention, self-reported symptoms of DSM-IV conduct disorder) were still significantly increased, even when accounting for the effects of confounders by using a propensity score approach. Their findings thus suggest a direct association between maternal smoking during pregnancy and offspring externalizing problems.

However, it is also important to note that there are also studies questioning that smoking may have a direct effect [40]. Likewise, Thapar et al. expressed their skepticism regarding a causal relationship between maternal smoking and ADHD. By using in-vitro fertilization (IVF) techniques, the study was able to address genetic confounding and separate genetically-related and -unrelated mother-child pairs. The authors found found a significantly larger association between maternal smoking during pregnancy and ADHD symptoms in the related pairs as compared to the unrelated pairs, leading the authors to the conclusion that results from traditional observational studies could be misleading and might represent an inherited confound [41].

Our results are consistent with some recently published studies, which reported that mothers of children with ADHD were significantly more likely to be younger [42, 43]. There may be several explanations for such an association: On the one hand, young mothers may be more impulsive or more stressed, which is perhaps transferred to their children. On the other hand, Chang et al. noted that teenage childbearing predicts offspring ADHD - but all offspring (particular also later-born siblings) born to mothers who began childbearing early were at increased risk of ADHD [44] . From our point of view, it seems most likely that children of young mothers (parents) may also be exposed

to a larger number of social and economic disadvantages (risk factors) [45, 46] which are also independently associated with poor outcomes for offspring, including anti-social behavior and ADHD [25, 30, 47, 48]. This association may get even stronger by shared genetic factors that trigger both teenage childbirth and the offspring behavior[48].

With respect to mothers' obstetric history, we found that children, whose mothers were diagnosed with gestational hypertension, were twice as likely as their peers to develop ADHD. There are only very few other studies that reported such a relationship, which might be due to the fact that most studies lack necessary data to investigate this association. According to our knowledge, Mann and Dermott [24] were among the first to provide an indication that gestational hypertension could be a risk factor. Likewise, a recently published record-linkage case-control study indicates such an association [43]. Already in 2010, Pasker-de Jong et al [26] suggested that *medication* used in the treatment of mild-to-moderate hypertension (labetalol and methyldopa) may influence the functional development in children of primary school age. These results, however, should be interpreted with caution since a pregnancy induced hypertension can lead to serious complications (cardiovascular diseases, stroke, diabetes) if left untreated. In our study, we did not collect information about whether maternal gestational hypertension was treated with drugs, so we were not able to analyze the effect of antihypertensive medication. However, since it generally appears to be difficult to distinguish the effects due to medication from those due to hypertension by means of retrospective or cross-sectional studies and since the mechanisms behind this association are still not fully understood, perhaps more well-designed (ethically justifiable) prospective studies are needed to evaluate the effects of different therapies and treatments whilst simultaneously considering the severity of gestational hypertension.

Our data also suggest that preemies tend to be more susceptible to develop ADHD. However, since preterm birth might reflect underlying fetal problems, it is still not clear whether preterm birth may be considered to have a causal effect on ADHD [25]. Therefore, and since gestational hypertension is also known as a risk factor for preterm birth [49, 50], it might be reasonable to hypothesize, that

gestational hypertension is a trigger for ADHD *and* preterm birth, which would imply that at least part of the ADHD risk often attributed to preterm birth may be explained by its correlation with gestational hypertension. To check this assumption, we analyzed the association between maternal gestational hypertension and the most obvious influence factors for ADHD identified in our study.

Figure 1

Figure 1 shows differences in prevalence between mothers with/without gestational hypertension and indicates a strong and significant difference ($p<0.0001$) regarding preterm birth (3 weeks or more prior to the calculated date of birth). No differences were found for smoking behavior and mother's age at birth, whereas children with a mother's diagnosis of gestational hypertension suffered slightly more often from neonatal respiratory disorders ($p=0.004$) and infections ($p=0.04$) during the first four weeks after birth. To adequately account for all these influences and associations, we used a fully adjusted model, simultaneously comprising all predictors and confounders in a final multivariable logistic regression model.

Here it became evident that the statistically significant odds ratios (derived from the partially adjusted model) for preterm birth, neonatal respiratory problems, and infections partly declined considerably, suggesting that at least parts of the risks attributed to these factors may be explained by relationships to other, often unrecognized influences. However, due to sparse data (few events) we are not able to disentangle direct and indirect effects of exposures (mediation effects).

Nonetheless, in the results derived from the simultaneously adjusted regression still show an elevated but not statistically significant risk estimate for neonatal respiratory disorders (OR 1.76; 95% CI 0.91-3.41) and a statistically significant approximately twofold increase in risk for infections during the first four weeks after birth. To the best of our knowledge there are only few studies that reported and confirmed such associations. For instance, Pringsheim et al. [27] found that children with Tourette syndrome *and* ADHD had a greater odds of newborn breathing problems as compared to children with Tourette syndrome *without* ADHD and Rand et al. [28] showed that children with

confirmed infection had an increased risk for ADHD. Not at least, Silva et al. [51] demonstrated in their large population-based record-linkage study that early respiratory disorders and all infection-related hospitalizations were significantly more common among children who were subsequently diagnosed with and treated for ADHD. Until today, not much is known about the underlying mechanism behind these associations. A simplified explanation may be based on the existing knowledge about the relationship between anomalous white-matter development and ADHD, demonstrated in a diffusion tensor imaging study in children with ADHD [52]. Together with the results derived by Inder et al. [53], who identified in an unselected population of premature infants (n=100) that the major perinatal risk factors for white-matter abnormality are related to perinatal infection, this could be the bridge which might explain the elevated risk for infections during the first four weeks after birth and ADHD in our study.

Finally, our results are consistent with findings from Chau et al., who analyzed the microstructural and metabolic brain development in a prospective cohort of 117 premature newborns [54]. Chau et al. found that newborns who were exposed to postnatal infection were more likely to need respiratory support and were also neurologically more impaired. This underlines the relevance of postnatal infections as risk factor for altered brain development, but also underlines the preventable nature of these neurological impairments.

A major strength of the current study is the large sample size of the IDEFICS cohort with participants from eight different European countries. All field measurements of the IDEFICS study were highly standardized, following detailed standard operating procedures. Despite the large sample size, we did not present sex-specific analyses, since only 48 girls suffered from ADHD. However, we see more pronounced effects for girls, which are -due to the small sample size- less reliable, i.e. confidence intervals are rather large. Moreover, since we had no information regarding parental mental health, we were not able to consider the effect of family history of ADHD in our analyses. The outcome variables as well as the influencing factors in our investigation are based on parents' or caregivers' reported questionnaire information. Therefore, on the one hand, it was not possible to distinguish

different subtypes of ADHD and, on the other hand, this might increase the risk of confounding by recall bias and social desirability bias. This is mainly true for variables like drinking behavior and cigarette consumption, because social desirability is likely to affect parental answers and to attenuate risk estimates. However, the majority of comparable studies had to rely on self-reported information regarding smoking during pregnancy [39]. Nevertheless, since several studies showed a high reliability and stability of reporting about events during pregnancy [55, 56] especially with regard to smoking [57, 58] there might be only minor concern about the validity of our study results.

In conclusion, our results confirm several earlier studies suggesting that smoking during pregnancy and a maternal age below 20 years increase a child's risk of developing ADHD. In addition, our findings yield further evidence supporting some recently identified, less studied risk factors for attention-deficit/hyperactivity disorder in children, namely pregnancy induced hypertension as well as neonatal respiratory disorders and infections during the first four weeks after birth. Hence, we recommend that these early exposures should get more attention when considering indicators or predictors for ADHD in children.

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Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Table 1 Sociodemographic characteristics

Demographic characteristics	ADHD diagnosis[a]				All	
	Non-ADHD		ADHD			
	n	%	n	%	n	%
Sex						
Male	7740	50.3	144	75.0	7884	50.6
Female	7645	49.7	48	25.0	7693	49.4
Age at diagnosis						
<=4	2787	18.1	13	6.8	2800	18.0
4-<=6	4118	26.8	34	17.7	4152	26.7
6-<=8	5904	38.4	93	48.4	5997	38.5
8+	2576	16.7	52	27.1	2628	16.9
Country						
Estonia	2058	13.4	22	11.5	2080	13.4
Sweden	1787	11.6	9	4.7	1796	11.5
Germany	2147	14.0	42	21.9	2189	14.1
Belgium	912	5.9	15	7.8	927	6.0
Hungary	3051	19.8	35	18.2	3086	19.8
Italy	2430	15.8	8	4.2	2438	15.7
Spain	1474	9.6	33	17.2	1507	9.7
Cyprus	1526	9.9	28	14.6	1554	10.0
Weight status[b]						
Thin/Normal	12272	79.8	152	79.2	12424	79.8
Overweight	1978	12.9	28	14.6	2006	12.9
Obese	1135	7.4	12	6.3	1147	7.4
Highest level of education of spouse or partner (ISCED-Level)[c]						
Low SES	1068	6.9	15	7.8	1083	7.0
Medium SES	6919	45.0	104	54.2	7023	45.1
High SES	7028	45.7	66	34.4	7094	45.5
Missing	370	2.4	7	3.6	377	2.4
All	**15385**	**100.0**	**192**	**100.0**	**15577**	**100.0**

[a] Parent-reported ADHD diagnosis by a physician or medical health professional

[b] According to Cole and Lobstein (2012)

[c] International Standard Classification of Education (UNESCO, 2012)

Table 2 Adjusted odds ratios and 95% confidence intervals for the association between ADHD and prenatal influences

	ADHD classification[a]					
	Non-ADHD		ADHD			
	N	%	N	%	OR[b] (95% CI)	p-value
Mothers consumption of alcoholic beverages during pregnancy						
Never	9900	98.8	117	1.2	1.00 (Reference)	
<=1x/month	2730	98.8	32	1.2	1.06 (0.71-1.60)	0.763
Several occasions a month (week)	324	99.1	3	0.9	0.79 (0.24-2.54)	0.686
Missing or not the child's biol. mother	2431	98.4	40	1.6	-	-
Mothers consumption of cigarettes or other sorts of tobacco during pregnancy						
Never	11078	99.0	111	1.0	1.00 (Reference)	
Rarely (at maximum once a month)	526	98.3	9	1.7	1.43 (0.71-2.85)	0.316
Several occasions a week / daily	1333	97.7	32	2.3	1.80 (1.18-2.74)	0.006
Missing or not the child's biol. mother	2448	98.4	40	1.6	-	-
Mother has been diagnosed during pregnancy with gestational hypertension						
No	12473	98.9	140	1.1	1.00 (Reference)	
Yes	727	98.0	15	2.0	2.03 (1.18-3.51)	0.011
Not the child's biol. mother	2185	98.3	37	1.7	-	-
Mother has been diagnosed during pregnancy with proteinuria						
No	12920	98.8	151	1.2	1.00 (Reference)	
Yes	280	98.6	4	1.4	1.33 (0.48-3.66)	0.584
Not the child's biol. mother	2185	98.3	37	1.7	-	-
Mother has been diagnosed during pregnancy with glycosuria						
No	12968	98.8	151	1.2	1.00 (Reference)	
Yes	232	98.3	4	1.7	1.40 (0.51-3.87)	0.512
Not the child's biol. mother	2185	98.3	37	1.7	-	-
Mother has been diagnosed during pregnancy with gestational diabetes						
No	12773	98.9	147	1.1	1.00 (Reference)	
Yes	427	98.2	8	1.8	1.42 (0.69-2.95)	0.344
Not the child's biol. mother	2185	98.3	37	1.7	-	-
C-section						
No	9923	98.8	119	1.2	1.00 (Reference)	
Yes	3277	98.9	36	1.1	1.04 (0.71-1.52)	0.859
Not the child's biol. mother	2185	98.3	37	1.7	-	-
All children	**15385**	**98.8**	**192**	**1.2**		

[a] Parent-reported ADHD diagnosis by a physician or medical health professional

[b] Adjusted for sociodemographics (sex, age, and SES), and country as random effect

Table 3 Adjusted odds ratios and 95% confidence intervals for the association between ADHD and peri- and postnatal influences

	ADHD classification[a]					
	Non-ADHD		ADHD			
	N	%	N	%	OR[b] (95% CI)	p-value
Maternal age at childbirth						
25 years and older	10580	98.9	121	1.1	1.00 (Reference)	
20-24 years	1921	98.8	24	1.2	0.93 (0.59-1.46)	0.737
15-19 years	303	95.3	15	4.7	3.54 (1.98-6.31)	<0.0001
Missing	2581	98.8	32	1.2	-	-
Weeks before calculated date of birth						
In time	10609	98.9	117	1.1	1.00 (Reference)	
1-2 weeks before	2452	98.6	36	1.4	1.19 (0.81-1.75)	0.374
3-4 weeks before	1136	98.4	19	1.6	1.45 (0.88-2.37)	0.145
5+ weeks before	559	97.9	12	2.1	1.79 (0.98-3.28)	0.060
Missing	629	98.7	8	1.3	-	-
Birthweight						
<2500 gr	939	98.4	15	1.6	1.37 (0.80-2.38)	0.255
2500-<3000 gr	2374	98.6	33	1.4	1.23 (0.83-1.82)	0.307
3000-<4000 gr	9843	98.8	116	1.2	1.00 (Reference)	
4000+ gr	1642	98.9	18	1.1	0.87 (0.52-1.44)	0.590
Missing	587	98.3	10	1.7	-	-
Duration of breastfeeding						
Not breastfed	1943	98.3	34	1.7	1.00 (Reference)	
>0-<=6 months breastfed	6401	98.8	79	1.2	0.87 (0.57-1.31)	0.496
>6 months breastfed	4444	99.1	39	0.9	0.64 (0.39-1.05)	0.075
Missing or not the child’s biol. mother	2597	98.5	40	1.5	-	-
Neonatal respiratory disorders						
No	12787	98.9	143	1.1	1.00 (Reference)	
Yes	413	97.2	12	2.8	2.42 (1.32-4.43)	0.004
Not the child's biol. mother	2185	98.3	37	1.7	-	-
Infection during the first 4 weeks after birth						
No	12832	98.9	144	1.1	1.00 (Reference)	
Yes	368	97.1	11	2.9	2.62 (1.39-4.95)	0.003
Not the child's biol. mother	2185	98.3	37	1.7	-	-
Highest level of education of spouse or partner (ISCED-Level)[c]						
Low SES	1068	98.6	15	1.4	1.72 (0.95-3.09)	0.072
Medium SES	6919	98.5	104	1.5	1.69 (1.23- 2.33)	0.001
High SES	7028	99.1	66	0.9	1.00 (Reference)	
Missing	370	98.1	7	1.9	-	-
All children	**15385**	**98.8**	**192**	**1.2**		

[a] Parent-reported ADHD diagnosis by a physician or medical health professional

[b] Adjusted for sociodemographics (sex, age, and SES), and country as random effect

[c] Not additionally adjusted for SES

Table 4 Univariable (partially adjusted) and simultaneously adjusted (for all other covariates and confounder) odds ratios and 95% confidence intervals for pre-, peri- and postnatal risk factors for ADHD

	Model 1[a]: Univariable (partially adjusted) model		**Model 2[b]: Simultaneously adjusted model**		
	Odds Ratio	95% CI	Odds Ratio	95% CI	p-value
Prenatal influences					
Alcohol during pregnancy[c]	0.79	(0.24-2.54)	0.76	(0.23-2.48)	0.652
Smoking during pregnancy[d]	1.80	(1.18-2.74)	1.74	(1.13-2.67)	0.015
Gestational hypertension	2.03	(1.18-3.51)	1.95	(1.09-3.48)	0.025
Proteinuria	1.33	(0.48-3.66)	0.86	(0.29-2.52)	0.781
Glycosuria	1.40	(0.51-3.87)	1.05	(0.35-3.14)	0.933
Gestational diabetes	1.43	(0.69-2.95)	1.28	(0.59-2.80)	0.536
C-section	1.04	(0.71-1.52)	0.88	(0.59-1.32)	0.541
Peri- and postnatal influences					
Maternal age <=19 years	3.54	(1.98-6.31)	3.31	(1.83-5.97)	<0.0001
Preterm birth (5+ weeks before)	1.79	(0.98-3.28)	1.47	(0.65-3.29)	0.353
Low birthweight (<2500 gr)	1.37	(0.80-2.38)	0.87	(0.42-1.78)	0.694
Breastfeeding (>6 months)	0.64	(0.39-1.05)	0.75	(0.46-1.25)	0.270
Respiratory problems	2.42	(1.32-4.43)	1.76	(0.91-3.41)	0.092
Infections	2.62	(1.39-4.95)	2.06	(1.05-4.04)	0.035
Sociodemographics					
Sex (boys vs. girls)			2.95	(2.11-4.11)	<0.0001
Age (years)			1.32	(1.21-1.45)	<0.0001
Low SES			1.39	(0.75-2.56)	0.298
Medium SES			1.48	(1.06-2.06)	0.021

[a] Model 1: Adjusted for sociodemographics (sex, age, and SES), and country as random effect

[b] Model 2: Adjusted like Model 1 and further adjustment for all other covariates in this table

[c] Mother consumed alcoholic beverages (several occasions month/week) during pregnancy

[d] Mother smoked (almost daily) during pregnancy