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Smoking during pregnancy and hyperactivity-inattention in the offspring—comparing results from three Nordic cohorts

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Background Prenatal exposure to smoking has been associated with Attention Deficit Hyperactivity Disorder (ADHD) in a number of epidemiological studies. However, mothers with the ADHD phenotype may 'treat' their problem by smoking and therefore be more likely to smoke even in a society where smoking is not acceptable. This will cause genetic confounding if ADHD has a heritable component, especially in populations with low prevalence rates of smoking since this reason for smoking is expected to be proportionally more frequent in a population with few 'normal' smokers. We compared the association in cohorts with different smoking frequencies.

Methods A total of 20 936 women with singleton pregnancies were identified within three population-based pregnancy cohorts in Northern Finland (1985–1986) and in Denmark (1984–1987 and 1989–1991). We collected self-reported data on their pre-pregnancy and pregnancy smoking habits and followed the children to school age where teachers and parents rated hyperactivity and inattention symptoms.

Results Children, whose mothers smoked during pregnancy, had an increased prevalence of a high hyperactivity-inattention score compared with children of nonsmokers in each of the cohorts after adjustment for confounders but we found no statistical significant difference between the associations across the cohorts.

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Conclusion The estimated association was not strongest in the population with the fewest smokers which does not support the hypothesis that the association is entirely due to genetic confounding.

Keywords smoking, confounding, prenatal, child behaviour, ADHD

Background

Brain imaging studies suggest that some differences in brain morphology associated with Attention Deficit Hyperactivity Disorder (ADHD) are already present at birth.[1] If early environmental factors influence the risk of ADHD, exposure to smoking *in utero* is a good candidate.[2] Nicotinic acetylcholine receptors are present early in the fetal brain and exposure to nicotine has been shown to up-regulate these receptors[3] to stimulate release of dopamine[4] which may play a causal role in ADHD pathology.[5] Furthermore, animal studies have shown a specific effect of prenatal nicotine exposure on attention span in the offspring[6] and human data support to some extend such a long-lasting effect on cognitive function.[7,8]

In line with a number of observational studies,[9,10] we have previously found that smoking during pregnancy is associated with the diagnosis of hyperkinetic disorder (HKD)[11] as well as with sub-clinical symptoms of inattention and hyperactivity.[12–14] However, these observational studies are vulnerable to genetic confounding. Mothers with inattention problems may more often be smokers[15] because nicotine has a positive effect on attention.[16] Therefore, it is difficult to disentangle whether this association is due to exposure to cigarette smoke during prenatal brain development or due to a genetic predisposition that could link both maternal smoking habits and ADHD.

A randomized trial could deal with confounding by genetic factors, but such a trial is not an option. We therefore study if the strength of the association differs in relation to smoking habits in pregnant women. In populations where smoking is socially acceptable many women smoke during pregnancy and only few of these would smoke to self-medicate inattention symptoms. In populations where the prevalence of smoking during pregnancy is low, and smoking is a norm breaking behaviour, a larger proportion of smokers may have an underlying ADHD psychopathology. Consequently, if the strength of the empirical association is similar in populations with different smoking prevalence, that would speak against strong uncontrolled genetic confounding. If the strength of the association is greater in populations with only few smokers, then genetic confounding is more likely.

In the present study we compare the magnitude of the association between prenatal smoking exposure and offspring hyperactivity-inattention symptoms in two Danish population cohorts, both characterized by high prevalence of pregnancy smokers, vs a Finish population cohort where smoking during pregnancy is much less accepted and less frequent.

Methods

Participants

From the three cohorts displayed in Table 1, we included a total of 20 936 women and their singleton children.

The Northern Finland Birth Cohort (NFBC)

The Northern Finland Birth Cohort (NFBC) invited all pregnant women living in the provinces of Oulu and Lapland with expected deliveries from July 1985 to June 1986. About 99% of these women provided background information using structured self-administered questionnaires handed out at the first prenatal visit (around 12 weeks of gestation) and returned to antenatal care personnel by the 24th gestational week. Perinatal data including birthweight and gestational age at birth were coded from hospital records at the time of delivery. At follow-up when children were 7–8 years old parents filled in questionnaire on health and social circumstances, and teachers rated child behaviour. The questions referred to behaviour during the past half year. Teachers completed questionnaires for nearly 85% of the children.

The Danish 'Aarhus Birth Cohort' (ABC)

The Aarhus Birth Cohort (ABC) started recruitment in 1989 and invited all Danish-speaking women before their first antenatal visit in late first or early second trimester at the Department of Obstetrics, Aarhus University Hospital. In the present report we used data from pregnant women who gave birth between January 1990 and March 1992. About 98% of all women completed a self-administered questionnaire prior to 16 gestational weeks. At follow up during spring 2001, the mothers received a questionnaire on child health and social conditions and 74% of the eligible parents responded. Of these 85% gave consent to contact the child's primary teacher. The participating parents as well as the children's primary teachers were contacted 1 year later when the children were 10–12 years old and asked to complete identical questions on child behaviour referring to the past half year. The questionnaires

Table 1 Characteristics of the cohorts

	Northern Finnish Birth Cohort NFBC	Aarhus Birth Cohort ABC	Healthy Habits for Two cohort HHT
Place	Oulu, Finland	Århus, Denmark	Ålborg/Odense, Denmark
Year of birth	1985–86	1990–92	1984–87
Base population	9135	8036	11140
Exposure information			
Prenatal information	Week 24	Week 16	Week 34
Pre-pregnancy smokers	27%	40%	45%
Pregnancy smokers	16%	29%	36%
Endpoint information			
Informants	Teacher	Teachers/Parents	Parents
Participants	7763(85%)	4208(52%)/4968(62%)	7773(70%)
Evaluation, age	8 years	10, 11 or 12 years	7–15 years
Instrument	Rutters scale	SDQ	SDQ[a]
~10%, cut off	4+	4+/3+	4+

[a]An unofficial modified version covering the whole basic school period.

were completed by 85% of the contacted teachers and 84% of the participating parents.

In the ABC we also collected data on all children who fulfilled the DSM-IV and the ICD-10 HKD. The cases were identified by the national hospital register[17] and verified by one of the authors (K.M.L.).

The Danish 'Healthy Habits for Two' Birth Cohort (HHT)

The Healthy Habits for Two Study (HHT) approached all pregnant women in Odense and Aalborg, Denmark from April 1984 to April 1986 at the time they attended the last scheduled routine antenatal care visit usually at about 35 completed gestational weeks. More than 80% of all pregnant women in the region completed a self-administered questionnaire on socio-demographic characteristics and lifestyle factors. In 2002, when their children were 16–18 years, the mothers were asked to report child behaviour during school-age i.e. from 7 to 15 years of age. The response rate was 70%.

Smoking data

Pregnant women reported their current and pre-pregnancy smoking habit in each of the cohorts. In the HHT cohort smoking before and during pregnancy was reported as non-smoking or smoking 1–4, 5–9, 10–14, 15–19 and 20+ cigarettes per day. In the two other cohorts the women were asked to write the number of cigarettes they smoked daily. In order to make the analyses comparable we used the categories from the HHT cohort. Few reported heavy smokers (especially in the Finnish cohort), therefore we categorized smokers into either those who smoked 1–9 or 10+ cigarettes per day. *Non-smokers* were defined as women, who neither smoked prior to pregnancy nor during pregnancy. *Quitters* were defined as women who smoked before pregnancy but stopped smoking before or very early in pregnancy. *Continued smokers* were defined as those who reported smoking before and during pregnancy.

Finnish mothers were much less likely to report smoking before as well as during pregnancy than Danish women (Table 1). Nearly 41% of Finnish smokers stopped smoking in early pregnancy, compared with only 27% and 20% in the ABC and HHT studies, respectively. In the HHT cohort there was more than twice as many women who smoked during pregnancy and three times as many women who were heavy smokers during pregnancy compared with women in the NFBC. There were slightly fewer smokers in the ABC compared to the HHT. The difference in smoking habits in ABC and HHT reflects the declining time trend in smoking habits seen among pregnant women in Denmark.[18]

Child behaviour

We assessed three common core symptoms of hyperactivity-inattention in all cohorts. Teachers in the NFBC completed the Rutter B2 questionnaire on child behaviour referring to the past 6 months.[19] The wording of the three items was (by item number) as follows: (1) 'Very restless. Has difficulty staying seated for long' (3) 'Squirmy, fidgety child' (16) 'Cannot settle to anything for more than a few moments'.

In the ABC the Strength and Difficulties Questionnaire[20] (SDQ) was administered to parents and teachers. The SDQ has for the last 10 years been widely used especially in the Nordic countries.[21] The SDQ is based on the Rutter questionnaire[22] and the three Rutter B2 items are similar to three of the

five-item hyperactivity-inattention subscale of the SDQ. The items by (item number are): (2) 'Is restless, overactive, cannot stay still for long' (10) 'Is constantly fidgety and squirming', and (15) 'Is easily distracted, concentration wanders'. For the present analyses the three items common to both scales were used.

The HHT used a modified version of the SDQ in which mothers were asked to provide a report of children's average behaviour during school-age i.e. covering ages 7–15 years. This was done to avoid influence of short-term fluctuations in behaviour.

The symptoms were in all studies scored: *0* (not true), *1* (somewhat true), *2* (certainly true) and the sum of the three item scores ('hyperactivity-inattention score') ranged from 0 to 6 as the hyperactivity score of the Rutter Behaviour rating scale.[19] Due to differences between the three studies we defined a high score as the 10% highest scored children in each of the cohorts. This was 5 or above the HHT and NFBC cohorts and for teachers report in the ABC cohort. For parents' report in the ABC the cut off closest to 10% was 4 or above.

Statistical analysis

The hyperactivity-inattention score had a highly skewed distribution. We therefore used an *a priori* defined high score as primary outcome and logistic regression analyses to adjust for possible confounding factors. That smoking is causally related to low birth weight and since low birth weight is associated with ADHD the perinatal factors are more likely to be interemediate in the causal chain than being confounders. We therefore controlled for these factors by restriction analyses. We used children of non-smokers i.e. women who neither smoked before nor during pregnancy as the reference group. Statistical significance was defined at a $P < 0.05$.

Potential confounding factors

We *a priori* decided to evaluate the potential confounding factors; child gender, alcohol intake during pregnancy, mothers' and fathers' education and family structure (coded as shown in Table 2). Socioeconomic status (SES) was registered in different ways in the cohorts. SES in the HHT and ABC was categorized in the same way as academics/entrepreneurs, intermediate positions such as teacher or nurse, skilled worker, worker and no vocational education. In the NFBC the social groups were categorized differently as entrepreneurs/academics, skilled workers, workers, farmers and no vocational education. Thus, it was not possible to define the SES variables in a similar way across all cohorts, so we repeated the analyses using the specific cohort measures of SES.

Childhood diagnosis

In the ABC we had data on the ICD-10 diagnoses of HKD for participants as well as for non participants.

Results

The distribution of maternal smoking during pregnancy and a high hyperactivity-inattention score by potential confounding and perinatal factors is shown in Table 2. The associations were rather similar in the three cohorts. Parental education and family structure were associated with exposure as well as the endpoint suggesting potential confounding by social conditions. Boys had 2–3 times as often as girls a high hyperactivity-inattention score but gender was not associated with prenatal smoking exposure. Smoking was associated with low birth weight as well as preterm delivery, but these measures were not associated with a high hyperactivity-inattention score.

The unadjusted associations between maternal smoking and a high hyperactivity-inattention score in the offspring evaluated by parents and teachers respectively are shown in Tables 3 and 4. Women who continued smoking during pregnancy were more likely than non-smokers to have children with higher hyperactivity-inattention scores, especially in the Danish cohorts. Quitters also had children who were slightly more likely to have a high score in comparison with children of non-smoking mothers.

The unadjusted associations attenuated slightly after adjustment for confounders, but in all three cohorts a statistically significant difference between nonsmokers and continued smokers remained after adjustment. There was no statistically significant difference between the associations in the three cohorts. In the ABC and in the HHT (but not in the Finnish cohort) there was a tendency to a dose–response association between number of cigarettes smoked during pregnancy and the risk of a high hyperactivity-inattention score in the offspring. In all cohorts there was a statistically significant difference between nonsmokers and smokers in pregnancy after controlling for confounders, but there was no significant difference between children of quitters and continued smokers.

When boys and girls were analysed separately we found the same relative differences but the absolute differences were generally larger among boys. We finally performed the analyses restricted to children born at term and with a birth weight of 2500 g or more. These analyses revealed the same associations between smoking and hyperactivity-inattention.

To evaluate if attrition explained our results, we studied the association between smoking during pregnancy and the HKD diagnosis in the ABC, where we had the largest attrition (Table 5). When adjusting for gender we found a significant higher risk among those smoking ten cigarettes or more for HKD in the offspring (OR = 2.0, 95% CI 1.1–3.5) among those who had missing data (from the parents

Table 2 Maternal smoking during pregnancy and a high inattention score according to potential confounders and birth characteristics

	Oulu, Finland			Århus, Denmark				Ålborg/Odense, Denmark		
	N	% Smokers	Teachers% high score	*N*	% Smokers	Teachers% high score	Parents% high score	*N*	% Smokers	Parents% high score
Gender of child										
Female	3891	16	3	2709	30	4	8	3736	37	6
Male	4060	16	11	2769	29	18	15	3958	35	14
Family structure at FU										
Yes	6253	13	6	4307	26	9	10	5605	32	8
No	1027	33	12	1138	43	17	18	2056	48	15
Missing	0			0				32	50	6
Mothers basic education										
<11 years	2104	21	8	2316	39	13	15	4768	42	12
11years+	4942	13	7	3122	22	8	9	2908	26	6
Missing	715	22	9	40	35	12	22	19	42	11
Fathers basic education										
<11 years	2712	19	8	2802	36	13	15	4993	40	12
11years+	4203	13	6	2485	20	8	7	2442	27	5
Missing	848	24	10	191	51	16	19	260	51	15
Alcohol during (drinks/week)										
<1	6681	14	7	2914	28	11	12	2572	37	11
1 +	1001	35	8	1936	36	9	10	5123	35	9
Birthweight										
Missing	0			118	27	9	20	0		
<2500 g	258	22	7	183	42	15	12	192	59	10
2500 g +	7693	16	7	5295	29	10	12	7503	36	10
Gestational age at birth										
<37 weeks	357	19	8	196	38	10	14	192	45	12
37 weeks+	7594	16	7	5282	29	11	12	7503	36	10

or teachers). In contrast, this association was not significant among those whom we had complete data (OR = 1.3, 95% CI 0.3–6.0). Table 5 further shows that families in which the child had an ADHD diagnosis were less likely to participate in the follow up.

Discussion

Women who smoked during pregnancy had a higher risk of getting child with a high hyperactivity-inattention score than women who did not smoke during pregnancy and the magnitude of the associations was similar across cohorts with very different smoking habits. A stronger association in the low smoking population (Finnish data) than in Danish data would corroborate the hypothesis of genetic confounding but that was not the case. Furthermore, we found a tendency towards a dose–response-like association in the two Danish cohorts.

If prenatal smoking exposure is a causal factor for ADHD, we would expect to see the highest risk among heavy smokers. We found this pattern only in the Danish cohorts perhaps related to misclassification of smoking in the Finnish cohort. We rely on self reported smoking and the reliability of the reporting may vary between countries and perhaps be lowest in Finland. In Finland, some self-reported quitters have been found to have levels of cotinine (nicotine metabolite) indicative of active smoking.[23]

Our results may further be biased by selection. Our cohorts had high recruitment rates but attrition at the follow-up varied between 30% and 50%. Attrition is a more serious threat to internal validity than low recruitment rates because the mothers at the time of responding to the follow up were aware of both their smoking habits and the child behaviour. On the other

Table 3 Teachers high hyperactivity-inattention score according to maternal smoking before and during pregnancy

	Oulu, Finland						Århus, Denmark					
	N	*n*	%	OR (unadj.)	OR (adj[a] w. 95% CI)	OR (adj[b] w. 95% CI)	N	n	%	OR (unadj.)	OR (adj w. 95% CI)	OR (adj[b] w. 95% CI)
No smoking at all (reference)	5649	347	6	1.0	1.0		2499	221	9	1.0	1.0	
Quitters, cigarettes before pregnancy												
1–9	633	62	10	1.7	1.6 (1.2; 2.2)	1.4 (1.0; 2.0)	217	19	9	1.0	1.0 (0.6; 1.6)	0.9 (0.6; 1.6)
10+	221	14	6	1.0	0.9 (0.5; 1.7)	0.9 (0.5; 1.7)	244	24	10	1.1	1.0 (0.7; 1.6)	1.0 (0.6; 1.6)
Smoker, number of cigarettes during pregnancy												
1–9	750	86	11	2.0	1.5 (1.1; 2.1)	1.5 (1.1; 2.1)	618	77	12	1.5	1.3 (1.0; 1.7)	1.3 (0.9; 1.7)
10+	273	27	10	1.7	1.5 (1.0; 2.5)	1.3 (0.8; 2.2)	630	101	16	2.0	1.7 (1.3; 2.2)	1.5 (1.2; 2.0)
Total	7526	536	7				4208	442	11			

[a]control for gender of child, alcohol during pregnancy, parental school education and family structure of parents.
[b]+ control for SES.

Table 4 Parents high hyperactivity-inattention score according to maternal smoking before and during pregnancy

	Åborg/Odense, Denmark						Århus, Denmark					
	N	*n*	%	OR (unadj.)	OR (adj[a] w. 95% CI)	OR (adj[b] w. 95% CI)	N	n	%	OR (unadj.)	OR (adj w. 95% CI)	OR (adj[b] w. 95% CI)
No smoking at all (reference)	4178	321	8	1.0	1.0	2993	301	10	1.0	1.0		
Quitters, cigarettes before pregnancy												
1–9	437	40	9.2	1.2	1.2 (0.9;1.8)	1.2 (0.9; 1.7)	265	33	12	1.3	1.3 (0.9; 1.9)	1.3 (0.8; 1.9)
10+	303	33	11	1.5	1.4 (0.9; 2.0)	1.3 (0.9; 1.9)	282	32	11	1.1	1.0 (0.7; 1.5)	1.0 (0.7; 1.5)
Smoker, number of cigarettes during pregnancy												
1–9	1390	161	12	1.6	1.3 (1.1; 1.7)	1.3 (1.0; 1.6)	725	85	12	1.2	1.0 (0.8; 1.3)	1.0 (0.8; 1.3)
10+	1387	200	14	2.0	1.7 (1.4; 2.0)	1.6 (1.3; 1.9)	703	127	18	2.0	1.5 (1.2; 1.9)	1.4 (1.1; 1.8)
Total	7695	755	10				4968	578	12			

[a]control for gender of child, alcohol during pregnancy, parental school education and cohabitance of parents.
[b]+ Control for SES.

Table 5 The association between smoking and Hyperkinetic disorder (HKD) in the Aarhus Birth Cohort stratified for attrition

Smoking	Full information			Missing parents or teachers info		
	N	*n*	HKD%	*N*	*n*	HKD%
0	2650	8	0.3	2763	24	0.9
1–9	539	1	0.2	663	5	0.8
10+	523	2	0.4	865	15	1.7

hand, the follow-up studies were not presented as a study on smoking and behavioural problems, but rather as a general study on the frequency of behavioural problems in childhood. The largest attrition was found in the ABC cohort and if selection bias is a problem it may have been most serious in this cohort. Our findings using the HKD diagnosis as endpoint speaks against this possibility. The association between smoking and HKD was weaker among non-participants, instead it suggests that selection may have caused bias toward the null.

We did not use clinical diagnoses as endpoints, but rather parent and teacher reports of specific behavioural symptoms. Only a fraction of the children with deviant behaviour will fulfill the diagnostic criteria of ADHD and there is no reason to believe that the clinical entity should represent an etiological entity of higher relevance than the behavioural pattern. We believe it is more important to focus on the trait rather than a clinical diagnosis. Behavioural problems follow a continuous rather than a discrete pattern[24] and behavioural symptoms were associated

with impairment in ABC and NFBC.[25] Furthermore, a number of factors influence whether or not children come to clinical attention and referral bias may become a problem.[26–28]

We *a priori* decided to use a cut off at 10% as done in previous studies.[29] Study-specific classifications were needed because of the differences in design between the three cohorts and the prevalence of the study specific summary scores are probably not directly comparable.[30] However, they express the same phenotypic behaviour which justifies our comparison of the results from the three cohorts.

We observed a slightly higher frequency of behavioural symptoms in offspring of mothers who stopped smoking before getting pregnant compared with those who did not smoke at all. This could be due to uncontrolled residual social confounding. However, it is likely that some of these women actually smoked to some extent during pregnancy, at least early in pregnancy before the pregnancy was recognized.

Our findings provide no support to the idea that the association between prenatal exposures to tobacco smoke and behavioural problems in childhood is entirely due to genetic confounding. The next step may be designs to study the relative contribution of prenatal smoking and genetic factors and how these factors interact. Recent studies suggest that the DAT1 and DRD4 interact with prenatal smoking in relation to ADHD. Some studies indicate that the DAT1 and DRD4 gene may play a role.[31,32]

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Conflict of interest: None declared.

KEY MESSAGES

- Smoking during pregnancy may be an indicator of genetic disposition of ADHD and unknown genetic factors are difficult to control for in observational studies.
- If this type of confounding explains the association, the association is expected to be strongest in the cohort with lowest exposure prevalence, but this is not what we found.
- Using cohorts with different exposure prevalence may be a valuable approach to minnimizing confounding related to genetic factors with impact on the behaviour being studied.

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