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Is maternal smoking during pregnancy a risk factor for Hyperkinetic disorder? - Findings from a sibling design.

Carsten Obel^{1,2}, Jørn Olsen^{2,3}, Tine Brink Henriksen³, Alina Rodriguez^{5, 6,7} Marjo-Riitta Järvelin^{5 8} Irma Moilanen⁹, Erik Parner¹⁰, Karen Markussen Linnet⁴, Anja Taanila^{8, 10}, Hanna Ebeling⁹, Einar Heiervang¹² and Mika Gissler^{13,14} .

- ¹ Dept. of General Practice, School of Public Health, Aarhus University, Denmark
- ² Dept. of Epidemiology, School of Public Health, Aarhus University, Denmark
- ³ UCLA School of Public Health, Department of Epidemiology, Los Angeles, USA,
- ⁴ Dept. of Obstetrics and Pediatrics, Aarhus University Hospital, Skejby, Denmark,
- ⁵ Dept. of Epidemiology and Biostatistics, Imperial, London, UK
- ⁶ Dept. of Psychology, Uppsala University, Sweden
- ⁷ MRC Social Genetic Developmental Psychiatry, King's College, London UK
- ⁸ Unit of General Practice, Oulun University Hospital, Oulu, Finland
- ⁹ Clinic of Child Psychiatry, University and University Hospital of Oulu, Finland
- ¹⁰ Institute of Health Sciences, University of Oulu, Finland
- ¹¹ Dept. of Biostatistics, School of Public Health, Aarhus University, Denmark
- ¹² Dept. of Adolescent Mental Health, Forde Hospital, Forde, Norway
- ¹³ THL, National Institute for Health and Welfare, Helsinki, Finland
- ¹⁴ Nordic School of Public Health, Gothenburg, Sweden

Corresponding author:

Carsten Obel
Department of General Medicine, School of Public Health
Aarhus University
Bartholins alle 2
DK- 8000 Aarhus C
Phone: +4589426072
Fax:
Email: co@alm.au.dk

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Abstract

Background Studies have consistently shown that pregnancy smoking is associated with twice the risk of hyperactivity/inattention problems in the offspring. An association of this magnitude may make behavioural difficulties one of the most important health effects related to smoking during pregnancy. However, social and genetic confounders may fully or partially account for these findings.

Methods A cohort including all singletons born in Finland January 1, 1987 through December 31, 2001 was followed until January 1, 2006 based on linkage of national registers. Data were available for 97% (N=868 449) of the population. We followed singleton children of smoking and non-smoking mothers until they had an ICD-10 diagnosis of Hyperkinetic disorder (HKD) or to the end of the observation period. We used sibling-matched Cox regression analyses to control for social and genetic confounding.

Results We found a much smaller association between exposure to maternal smoking during pregnancy and risk of HKD in children using the sibling-matched analysis (HR=1.20, 95% CI 0.97-1.49) than was observed in the entire cohort (HR 2.01, 95% CI: 1.90-2.12).

Conclusions Our findings suggest that the strong association found in previous studies may be due to time stable familial factors, such as environmental and genetic factors. If smoking is a causal factor, the effect is small and less important than previous studies indicate.

Keywords: smoking, pregnancy, Attention Deficit Hyperactivity Disorder, Hyperkinetic Disorder, sibling design

Background

Attention Deficit Hyperactivity Disorder (ADHD) defined by the DSM-IV criteria is one of the most common childhood psychiatric disorders¹, with a cumulative incidence of 2-5%². In the WHO diagnostic classification system (ICD-10) used in Europe, only children with the most severe ADHD combined type (both inattention and hyperactivity/impulsivity symptoms) receive a diagnosis of Hyperkinetic Disorder (HKD)³. Core symptoms are linked to poor school performance and other social problems⁴.

HKD has at least in part genetic causes⁵ and brain imaging studies suggest that deviant brain morphology may be present at birth, which indicates a genetic etiology or aetiology related to prenatal environmental exposure⁶. A number of pregnancy exposures have been suggested with smoking as a strong candidate^{7,8}. An association between prenatal exposure of the brain to nicotine and attention problems in the offspring seems biologically plausible. A number of animal studies, including studies on monkeys, with endpoints that mimic the disorder, suggest that prenatal exposure to nicotine may influence fetal brain development in a way that is compatible with ADHD⁹. Epidemiological studies have consistently shown that mothers who smoke during pregnancy have about twice the risk of HKD¹⁰ and ADHD¹¹ in their offspring and an association of this magnitude may make behavioural difficulties one of the most important health effect related to smoking during pregnancy.

However, both smoking and HKD correlate with social conditions and women with attention problems may be likely to be smokers¹². Nicotine improves attention¹³ and smoking may simply be an indicator of a genetic disposition to HKD. It has therefore been suggested that the association between prenatal smoking and offspring ADHD could be due to genetic and social confounding rather than the smoking exposure per se¹⁴. Ruling out this possibility in conventional observational designs is not easy and alternatives are called for. A recent study of in vitro fertilised pregnancies examined children conceived through genetically unrelated egg-donations and found no evidence of an effect of smoking¹⁵. Two other recent studies found only weak associations when using a sib-ship design^{16,17}. Both studies raise doubt about the causality of the association, but all were based on proxy measures of the disorder and had serious limitations.

The sibling design may provide one of the most efficient approaches to control for family factors when large epidemiological cohorts and sufficient discordant siblings are available¹⁸. In this study we followed the entire population of children born in Finland during a 15-year period and estimated the association between prenatal smoking and the ICD-10 diagnosis of HKD in sibling pairs discordant for prenatal exposure to smoking and HKD.

Materials and methods

Setting

Finland has a mandatory registration of all births in the Finnish Medical Birth Register (FMBR). By using the unique personal identification number covering all residents in Finland, we linked all births from 1987 to 2001 with data from the Finnish Hospital Discharge Register (FHDR) including all inpatient (established in 1967) and all outpatient visits (established in 1998). Registration is mandatory for all inpatient care in public and

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5 private hospitals as well as for all outpatient visits in public hospitals. All diagnoses were
6 reported using ICD-9 up to 1996 where ICD-10 was used¹⁹. We identified all singleton
7 children born from January 1, 1987 to December 31, 2001 who were still alive on January
8 1st, 2006 yielding a total of 894,697 singletons.
9

10 The National Institute for Health and Welfare (THL), which is the body responsible for the
11 Finnish Medical Birth Register and Finnish Hospital Discharge Register, gave permission
12 to link and use encrypted health register data for this study. The data protection
13 ombudsman was informed about the study, as requested by the national data protection
14 regulation.
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18 **Exposure information**

19 Antenatal care in Finland is tax-paid and offered to all pregnant women and the care in low
20 risk pregnancy includes approximately 10-14 antenatal visits. The data on maternal
21 smoking stemmed from concurrent information provided by pregnant women and
22 systematically collected by midwives and public health nurses, during the second trimester
23 of routine antenatal care and subsequently archived in the FMBR. During the period from
24 1987 to 1990, responses were categorised either as non-smokers, smokers of less than
25 10 cigarettes per day, or 10 cigarettes or more per day. During the period 1991 to 2001 the
26 average number of cigarettes per day was not collected, but replaced with information on
27 whether or not women stopped smoking during first trimester. In the sibling-matched
28 analyses we defined pregnancy smoking as smoker and non-smoker, and for mothers of
29 children born 1991-2001 only those who reported continuing smoking as well as those only
30 smoking during the first trimester were categorised as smokers.
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35 **Outcome definition**

36 We studied the children's entries in the FHDR until January 1st, 2006 using ICD-10
37 diagnoses to identify children with HKD including hyperkinetic disorder (F90.0),
38 hyperkinetic conduct disorder (F90.1) or other hyperkinetic disorder (F90.8 and F90.9) as
39 endpoints in the analyses. We excluded 1901 children with pervasive developmental
40 disorders, including autism, F84 (N=1095), mental retardation, F70-79, (N=262) and 325
41 with both these diagnoses. Further 219 children who had the ICD-9 (but not the ICD-10)
42 diagnosis of 314 were excluded from the analyses, because the definition was not fully
43 comparable with ICD-10.
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47 **Cohort definition**

48 After the above were excluded, the population included 892,796 children of whom 7,226
49 were diagnosed with HKD. There were 24,347 (3%) with missing smoking information,
50 leaving 868,449 available for analyses, where 7023 children (0.8%) had HKD. Among the
51 443,076 boys, there were 6013 (1.4 %) and among the 425,353 girls there were 1010
52 (0.2%) that received the HKD diagnosis during the observation period. The 513,198
53 participating women contributed with an average of 1.7 children to the entire cohort.
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56 **Statistical analyses**

57 To control for differences in length of follow up time we used the Cox regression analysis,
58 with child age as the primary time scale. To control for the increasing incidence of HKD
59 over study time, we adjusted for each year of birth as a categorical variable (1987-2001).
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4 We further a priori decided to adjust for child sex, gestational age at birth (less than 30, 30-
5 33, 34-36,37-40,41 or more), maternal age (20 or less, 21-25, 26-30,31-35, 36 or more)
6 and parity (0,1,2,3 or more). Data on maternal occupation was available and adjusted for
7 in the period 1991 to 2001 and was transformed to an indicator of socioeconomic status
8 (SES) according to a national system of classifications and standards in Finland ²⁰ (upper
9 white collar, lower white collar, blue collar, others). The analyses were performed using
10 STATA 9.0. Hazard Ratios (HR) and are presented with 95% confidence intervals (CI).
11 Our analytic strategy was to analyze the entire population using regular cohort analyses
12 and then to compare these findings with sibling-matched analyses.
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16 *Population cohort analyses*

17 In the Cox regression model, we assumed proportional rates for the exposure and the
18 above-mentioned potential confounders with one common baseline rate function. The
19 proportional hazards assumption was evaluated for all variables by comparing estimated
20 log-minus-log survivor curves over the different categories of variables investigated.
21 Because most women contributed to the cohort with more than one child, we used robust
22 standard errors to adjust the confidence intervals for the presence of siblings in the
23 population analyses (declaring each of the sibling pairs to be a cluster). All analyses were
24 repeated by sex and adjusted for the variables described above. Additionally, in order to
25 control for SES and because of changes in exposure registration, we separated the cohort
26 into children born 1987-1990 and 1991-2001, where SES was available for the latter
27 group.
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31 *Sibling-matched analyses*

32 We performed sibling-matched analyses to control for shared genetic and social
33 confounding. We used stratified Cox regression with a separate stratum for each family
34 identified by the mothers encrypted identification number. In the stratified Cox regression
35 model, each family has its own baseline rate function reflecting the family's shared genetic
36 and social factors. The exposure comparisons, smoking versus non-smoking, are thus
37 made within the family. We controlled for the same factors as in the cohort analyses,
38 except for SES, which is part of the shared social factors and therefore already controlled
39 for in the sibling-matched analysis. The stratified Cox regression model is an extension of
40 the paired binomial model, taking into account the differences in follow-up time. Thus only
41 sibling pairs discordant for smoking as well HKD were 'informative', i.e. contributed
42 information to the estimates. Indeed, to be informative, the sibling without HKD should
43 have at least as long a follow-up time as the sibling with HKD.
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48 **Results**

49 In the regular cohort analyses we found that children exposed to maternal smoking in
50 pregnancy had about twice the risk of receiving a diagnosis of HKD during up to 19 years
51 follow-up period (HR 2.01, 95% CI: 1.90-2.12). The results of the analyses in the two
52 periods are shown in table 1. The analyses of children born 1987-1990 indicated that HKD
53 risk increased by level of smoking. In a similar way, the data for children born 1991-2001
54 suggested that those who quit smoking in early pregnancy had a slightly lower risk for
55 HKD as compared with those who continued smoking beyond the first trimester, but this
56 difference was not statistically significant. Excluding children born small for gestational age
57 or preterm did not change the results. Control for SES among children born 1991-2001
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4 only slightly changed the estimates and the results were very similar in the two time
5 periods.
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8 *(TABLE 1 about here)*
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10 The results comparing smokers with non-smokers in the full cohort and in the sibling-
11 matched analyses are shown in Table 2. The adjusted analyses suggested a weak
12 association between antenatal smoking exposure and HKD when boys and girls were
13 analysed together and separately.
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16 We finally analysed possible birth order effects by stratifying the analyses by whether the
17 smoking exposure was in the pregnancy of the older or the younger sibling and then
18 whether the HKD diagnosis was given to the older or the younger sibling. The associations
19 were similar for women smoking in the pregnancy of the older and the younger child
20 (HR=1.3 and 1.2 respectively)
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23 *(TABLE 2 about here)*
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26 **Discussion**

27 During a 15 year observation period of the entire Finnish population, we found in the
28 cohort analysis that children prenatally exposed to maternal smoking had twice the risk of
29 being diagnosed with HKD than children of non-smokers. This finding is in line with recent
30 studies,^{21;22} a number of previous conventional case control and cohort studies that have
31 reported a strong association between pregnancy smoking and various measures of the
32 ADHD phenotype,¹¹ as well as the diagnosis of HKD¹⁰.
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35 However, in the sibling-matched analyses, when controlling for shared family confounders,
36 the estimated association was much weaker. This finding indicates that a part of the
37 association reported in most previous studies may be partly due to confounding as
38 maternal smoking may be indicator of a genetic trait and social factors related to HKD.
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41 These findings are in line with the findings of three recent studies. Thapar et al. used
42 children born after different types of in vitro fertilisation with egg-donation as a way to
43 distinguish between genetic and exposure effects¹⁵. They found no association between
44 smoking and the ADHD phenotype in genetically unrelated mother-child pairs, which
45 however could be due to chance by small sample size or that they had more girls among
46 the offspring of exposed²³. Two recent studies used the sibling design with endpoints of
47 relevance for ADHD. D'Onofrio et al. studied the association between pregnancy smoking
48 and hyperactivity problems based on parents answering three screening questions and
49 found a considerably smaller effect using the sibling design as compared to the regular
50 cohort analyses¹⁶. The same tendency was seen in a register-based Swedish study that
51 studied the association between smoking in pregnancy in all Swedish children born 1987-
52 2000 and prescriptions of ADHD medication in the year 2006¹⁷. In their sibling analyses,
53 they reported an estimate quite close to ours, but the crude proxy for ADHD, a one-year
54 registration of prescriptions, did not capture older siblings treated medically early on in life.
55 This is quite important in the sibling design because discordant sibling pairs are
56 misclassified as concordant and vice versa.
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4 The present study has a number of strengths. It is based on a complete 15 year follow-up
5 using established diagnostic criteria of clinical examinations from specialised departments
6 within the public health service. We had almost complete follow-up data with little risk of
7 selection bias, our data came from concurrently registered information rather than
8 retrospective reports. Finally our results were unlikely to be flawed by differential
9 misclassification of HKD because children's care is universally available, publicly financed
10 and organised in Finland. It is unlikely that the threshold for admission to hospital clinics is
11 related to the prenatal smoking, especially when siblings are compared.
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15 The matched-sibling design has a number of advantages in controlling for family factors.
16 These family factors are difficult to measure and control for in conventional cohort designs.
17 Full siblings share social environment, but only 50% of their genes, so even these
18 analyses will tend to overestimate the tested association. One caveat of our study is that
19 siblings were matched on the mother's identification number and we did not have any
20 information regarding fathers (due to strict data protection regulations in Finland). It may
21 be that our estimates overestimate the association and that even weaker associations
22 would have been found if we were able to identify and exclude half-siblings.
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26 There are limitations to the sibling design that should be mentioned. The strict control for
27 shared family factors limits the analyses to a small subset of the population. Only sibling
28 pairs discordant for smoking as well as HKD contribute to the estimate in these analyses.
29 In the present study, we had 40,615 sibling pairs, that were discordant for prenatal
30 smoking exposure, but because discordance for HKD was also needed for a pair to be
31 informative, only 880 pairs contributed with information of the smoking-HKD association. In
32 the adjusted stratified Cox regression model, more sibling pairs discordant for some of the
33 other factors in the model will primarily add to the estimates, but the basic concept of this
34 type of analyses can simply be illustrated by the ratio between the informative pairs
35 supporting and discounting the hypothesis.
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39 Positive association pairs (PAP) are sibling pairs that support a positive association
40 between smoking and HKD i.e. where the mother smoked during the pregnancy of the
41 child with HKD and did not smoke in the pregnancy with the child without HKD. Negative
42 association pairs (NAP) on the other hand were pairs where the mother did not smoke in
43 the pregnancy of the child with HKD and smoked in the pregnancy of the child without
44 HKD. To support the idea that prenatal smoking is a causal factor for HKD, one would
45 expect more PAP than NAP, in fact twice as many to support the findings of most previous
46 studies. Of the 880 pairs, 484 pairs were PAP and 396 NAP with a ratio (1.2) very close to
47 the results of the crude Cox regression analyses shown in Table 2. When restricted to
48 comparison between boy siblings, the PAP/NAP ratio was 1.3 (218/168) and restriction to
49 girl siblings resulted in a ratio of 1.8 (45/25). Again the ratios are in line with the estimates
50 for sibling-matched Cox regression analysis and the small numbers explain the broad
51 confidence intervals.
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55 As illustrated above, large register-based studies are needed to gain valid estimates from
56 sibling analyses. In this type of register, the information on smoking is collected routinely,
57 but the smoking information is quite crude. The crude smoking information limits our ability
58 to estimate effect of timing and dose. There are, however, further potential limitations to
59 the interpretations of our results linked to the strict selection of smoking women in the
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5 sibling analyses. As mentioned above, the sibling-matched analyses are based on a
6 subsample of smoking women and this sample may differ from the smoking women who
7 were not informative in the sibling analyses. We therefore compared women reporting
8 smoking and giving birth to their first child 1987-1991 according to whether they smoked in
9 their next pregnancy. Among those who smoked in both pregnancies, 85% (95% CI: 84-
10 86%) were smoking 10 cigarettes or more in the pregnancy of the first child as compared
11 with 71% (95% CI: 70-72%) of subsequent non-smokers. This indicates that there are more
12 heavy smoking women among those who were unable to give up smoking in any of their
13 pregnancies. Thus heavy smoking women are underrepresented in the sibling analysis
14 and this may be part of the explanation for the attenuated estimates as compared with the
15 regular cohort analyses.
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19 It could further be argued that because information on smoking was based on personal
20 contact between midwives/public health nurses and the pregnant women, the difference in
21 unmatched and matched results could be due to misclassification of smoking status. Some
22 misclassification seems likely and may be part of the explanation for the attenuation in our
23 estimates when using sibling analyses. Women who contributed to the sibling analyses
24 with informative siblings were characterised by having smoked in one pregnancy and by
25 having a child with HKD. It is possible that women with HKD in the family may be more
26 likely to under-report smoking. If this bias is non-differential, which is expected, it would
27 bias toward null-values and could partly explain the attenuation of the association. We
28 were not able to evaluate this possibility directly, because we did not have access to
29 detailed smoking information, but we may evaluate this potential misclassification by
30 looking at differences in birth weight between siblings with discordant smoking exposure.
31 The effect of antenatal smoking on birth weight is well established and if women
32 contributing to our informative pairs more often under-reported true smoking in the
33 subsequent pregnancy, we would expect a smaller difference in birth weight between
34 these sibling pairs compared with all sibling pairs discordant for smoking exposure. This
35 was however not the case. We found no difference in the effect of smoking on birth weight.
36 In the informative pairs adjusted for parity, gestational age at birth and gender, there was a
37 reduction of 88 grams (95% CI: 53-123 grams) in birth weight as compared with 69 grams
38 (95% CI: 63-75 grams) in all the sibling pairs discordant for smoking. These differences in
39 birth weight are in line with results from a recent report, where smoking information was
40 validated against serum cotinine²⁴. These findings contest the possibility that the
41 attenuation of the association was due to more misclassification of smoking status in the
42 informative sibling pairs.
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49 By using a HKD diagnosis as the endpoint, we had the possibility to study the more severe
50 phenotype. A HKD diagnosis requires hyperactivity/impulsivity as well as inattention in at
51 least two settings and is close to the DSM-IV ADHD-combined diagnosis. Although the
52 Finnish register contains complete information for in- as well as outpatient contacts in the
53 public health system, some children are unrecognized and thus untreated or treated
54 without contact to the hospital system. Accordingly, some cases of HKD or ADHD are
55 undiagnosed in the hospital system, but as they are few in the general population it will
56 have little influence on the estimation of the association in our study. Even a low sensitivity
57 will not bias our results as long as the specificity is high, which we find likely due to the use
58 of strict diagnostic criteria in clinical practice in Finland. Differences in referral, which in
59 conventional studies may lead to bias, are less likely to do so in a sibling design because
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this bias is likely to be linked to the families. However, it is also possible that a diagnosis given to a child will make it more likely that an undiagnosed sibling with the disorder will be diagnosed. In the sibling design this would generate less discordant pairs, but if linked to smoking attenuate the estimate.

In conclusion, previous reports may have overestimated the association between pregnancy smoking and HKD because they have not been able to control for shared family factors. We cannot completely discount the possibility that smoking is a causal factor, but then the size of the effect is probably smaller than what previously has been reported. Our findings are based on women, who were able to change smoking status between pregnancies and these results most probably cannot be extrapolated to women who smoked in all their pregnancies. From a public health perspective, however, it is of interest to estimate whether women, who manage to quit smoking during a pregnancy actually reduce their risk of having a child with behaviour problems. This study indicates that this may be the situation for very few.

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Conflicts of interests: None declared

KEY Messages:

- *In a matched sib-ship design we found a weaker association between smoking during pregnancy and a diagnosis of Hyperkinetic Disorder in the offspring than has been found in previous studies*
- *The strong association found in previous studies may be due to confounding by social and genetic factors*
- *Despite some limitations, the sib-ship design may provide an efficient design to control for confounding by family factors in studies of the effect of prenatal exposures.*

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		N	n	%	HR _{crude}	HR _{adjusted}	(95% CI)
1987-1990							
All	Non-smokers	200,886	957	0,5	Ref.	Ref.	
	Smokers	36,811	372	1.0	2.13	1.92	(1.69; 2.18)
	1-9/day	18,136	141	0.8	1.59	1.77	(1.47; 2.12)
	10 or more/day	18,675	231	1.2	2.68	2.03	(1.74; 2.37)
Boys	Non-smokers	102,578	844	0,8	Ref.	Ref.	
	Smokers	18,872	323	1.7	2.09	1.88	(1.64; 2.15)
	1-9/day	9,261	122	1.3	1.57	1.75	(1.43; 2.13)
	10 or more/day	9,611	201	2.1	2.62	1.97	(1.67; 2.33)
Girls	Non-smokers	98,308	113	0,1	Ref.	Ref.	
	Smokers	17,939	49	0.3	2.39	2.23	(1.56; 3.18)
	1-9/day	8,875	19	0.2	1.75	1.93	(1.15; 3.23)
	10 or more/day	9,064	30	0.3	3.10	2.46	(1.59; 3.81)
1991-2001							
All	Non-smokers	532,288	4,014	0,8	Ref.	Ref.	
	Smokers	98,464	1,680	1.7	2.23	1.92	(1.80; 2.04)
	only first trimester	10,336	126	1.2	1.64	1.34	(1.11; 1.62)
	after first trimester	88,128	1,554	1.8	2.29	1.98	(1.86; 2.12)
Boys	Non-smokers	271,496	3,442	1,3	Ref.	Ref.	
	Smokers	50,130	1,404	2.8	2.18	1.88	(1.75; 2.01)
	only first trimester	5,257	105	2.0	1.61	1.34	(1.09; 1.64)
	after first trimester	44,873	1,299	2.9	2.24	1.94	(1.81; 2.08)
Girls	Non-smokers	260,792	572	0,2	Ref.	Ref.	
	Smokers	48,334	276	0.6	2.56	2.13	(1.82; 2.49)
	only first trimester	5,079	21	0.4	1.89	1.35	(0.82; 2.22)
	after first trimester	43,255	255	0.6	2.64	2.21	(1.88; 2.60)

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Table 1 Hazard ratio for Hyperkinetic Disorder (HKD) according to prenatal exposure for smoking. Children born in Finland 1987-2001 (N=868,449). All Cox regressions adjusted for robust standard error. All adjusted analyses are controlled for gender, year of birth, maternal age, gestational age at birth and parity. Adjusted analyses in children born 1991-2001 included adjustment for socioeconomic factors.

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		Unmatched analyses					Sibling matched analyses			
		N	n	%	HR _{crude}	HR _{adjusted}	95% CI	HR _{crude}	HR _{adjusted}	95% CI
All	Non-smokers	733,174	4,971	0,7	Ref.	Ref.		Ref.	Ref.	
	Smokers	135,275	2,052	1.5	2.22	2.01	(1.90; 2.12)	1.21	1.20	(0.97; 1.49)
Boys	Non-smokers	374,074	4,286	1,1	Ref.	Ref.		Ref.	Ref.	
	Smokers	69,002	1,727	2.5	2.17	1.96	(1.85; 2.08)	1.19	1.21	(0.93; 1.59)
Girls	Non-smokers	359,100	685	0,2	Ref.	Ref.		Ref.	Ref.	
	Smokers	66,273	325	0.5	2.55	2.28	(1.99; 2.63)	1.85	1.51	(0.71; 3.19)

Table 2 Hazard ratio for Hyperkinetic Disorder (HKD) according to smoking during pregnancy. Children born in Finland 1987-2001 Cox regression analyses unmatched adjusted for robust standard error adjusting for sibling relations. Matched analyses on maternal encrypted identification number. All adjusted analyses are controlled for gender, year of birth, maternal age, gestational age at birth and parity.

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Is maternal smoking during pregnancy a risk factor for Hyperkinetic disorder? - Findings from a sibling design.

Carsten Obel^{1,2}, Jørn Olsen^{2,3}, Tine Brink Henriksen³, Alina Rodriguez^{5, 6,7} Marjo-Riitta Järvelin^{5 8} Irma Moilanen⁹, Erik Parner¹⁰, Karen Markussen Linnet⁴, Anja Taanila^{8, 10}, Hanna Ebeling⁹, Einar Heiervang¹² and Mika Gissler^{13,14} .

- ¹ Dep. of General Practice, Institute of Public Health, Aarhus University, Denmark
- ² Dep. of Epidemiology, Institute of Public Health, Aarhus University, Denmark
- ³ UCLA School of Public Health, Department of Epidemiology, Los Angeles, USA,
- ⁴ Dep. of Obstetrics and Pediatrics, Aarhus University Hospital, Skejby, Denmark,
- ⁵ Dep. of Epidemiology and Biostatistics, Imperial, London, UK
- ⁶ Dep. of Psychology, Uppsala University, Sweden
- ⁷ MRC Social Genetic Developmental Psychiatry, King's College, London UK
- ⁸ Unit of General Practice, Oulun University Hospital, Oulu, Finland
- ⁹ Clinic of Child Psychiatry, University and University Hospital of Oulu, Finland
- ¹⁰ Institute of Health Sciences, University of Oulu, Finland
- ¹¹ Dep. of Biostatistics, Institute of Public Health, Aarhus University, Denmark
- ¹² Dep. of Adolescent Mental Health, Forde Hospital, Forde, Norway
- ¹³ THL, National Institute for Health and Welfare, Helsinki, Finland
- ¹⁴ Nordic School of Public Health, Gothenburg, Sweden

Corresponding author:

Carsten Obel
Department of general medicine, Institute of Public Health
Aarhus University
Bartolins alle 2
DK- 8000 Aarhus C
Phone: +4589426072
Fax:
Email: co@alm.au.dk

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Abstract

Background Studies have consistently shown that pregnancy smoking is associated with twice the risk of hyperactivity/inattention problems in the offspring. An association of this magnitude may make behavioral difficulties one of the most important health effect related to smoking during pregnancy. However, social and genetic confounders may fully or partially account for these findings.

Methods A cohort including all singletons born in Finland January 1, 1987 through December 31, 2001 was followed until January 1, 2006 based on linkage of national registers. Data were available for 97% (N=868 449) of the population. We followed singleton children of smoking and non-smoking mothers until they had an ICD-10 diagnosis of Hyperkinetic disorder (HKD) or to the end of the observation period. We used sibling matched Cox regressions analyses to control for social and genetic confounding.

Results We found a much smaller association between exposure to maternal smoking during pregnancy and risk for HKD in children using the sibling matched analysis (HR=1.20, 95% CI 0.97-1.49) than seen in the entire cohort (HR 2.01, 95% CI: 1.90-2.12).

Conclusions Our findings suggest that the strong association found in previous studies may be due to time stable familial factors, such as environmental and genetic factors. If smoking is a causal factor, the effect is small and less important than previous studies indicate.

Keywords: smoking, pregnancy, Attention Deficit Hyperactivity Disorder, Hyperkinetic Disorder, sibling design

Background

Attention Deficit Hyperactivity Disorder (ADHD) defined by the DSM-IV criteria is one of the most common childhood psychiatric disorders¹, with a cumulative incidence of 2-5%². In the WHO diagnostic system (ICD-10) used in Europe only children with the most severe ADHD combined type (both inattention and hyperactivity/impulsivity symptoms) receive a diagnosis of Hyperkinetic Disorder (HKD)³. Core symptoms are linked to poor school performance and other social problems⁴.

HKD has at least in part genetic causes⁵ and brain imaging studies suggest that deviant brain morphology may be present at birth which indicate a genetic etiology or etiology related to prenatal environmental exposure⁶. A number of pregnancy exposures have been suggested with smoking as a strong candidate^{7;8}. An association between prenatal exposure of the brain to nicotine and attention problems in the offspring seems biologically plausible. A number of animal studies, including studies on monkeys, with endpoints that mimic the disorder, suggest that prenatal exposure to nicotine may influence fetal brain development in a way that is compatible with ADHD⁹. Epidemiological studies have consistently shown that mothers who smoke during pregnancy have about twice the risk of HKD¹⁰ and ADHD¹¹ in their offspring and an association of this magnitude may make behavioral difficulties one of the most important health effect related to smoking during pregnancy.

However, both smoking and HKD correlate with social conditions and women with attention problems may be likely to be smokers¹². Nicotine improves attention¹³ and smoking may simply be an indicator of a genetic disposition to HKD. It has there for been suggested that the association between prenatal smoking and offspring ADHD could be due to genetic and social confounding rather than the smoking exposure per se¹⁴. To rule out this possibility out in conventional observational designs is not easy and call for alternative designs. A recent study of in vitro fertilized pregnancies examined children conceived by egg-donation who are genetically unrelated to their mothers and found no evidence of an effect of smoking¹⁵. Two other recent studies found only weak associations when using a sib-ship design^{16 17}. These studies together raise doubt about causality of the association. However, all were based on proxy measures of the disorder and had serious limitations.

The sibling design may provide one of the most efficient approaches to control for family factors within when large epidemiological cohorts are available when sufficient discordant siblings are available¹⁸. In this study we followed the entire population of children born in Finland during a 15-year period and estimated the association between prenatal smoking and the ICD-10 diagnosis of HKD in sibling pairs discordant for prenatal exposure to smoking and HKD.

Materials and methods

Setting

Finland has a mandatory registration of all births in the Finnish Medical Birth Register (FMBR). By using the unique personal identification number covering all residents in Finland, we linked all births from 1987 to 2001 with data from the Finnish Hospital

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Discharge Register (FHDR) including all inpatient (established in 1967) and all outpatient visits (established in 1998). Registration is mandatory for all inpatient care in public and private hospitals as well as for all outpatient visits in public hospitals. All diagnoses were reported using ICD-9 up to 1996 where ICD-10 was used¹⁹. We identified all singleton children born from January 1, 1987 to December 31, 2001 who were still alive on January 1st, 2006 yielding a total of 894,697 singletons.

The National Institute for Health and Welfare (THL), responsible for the Finnish Medical Birth Register and Finnish Hospital Discharge Register, gave permission to link and use encrypted health register data for this study. The data protection ombudsman was informed about the study, as requested by the national data protection regulation.

Exposure information

Antenatal care in Finland is tax-paid and offered to all pregnant women and care in low risk pregnancy includes approximately 10-14 visits. Data on maternal smoking came from concurrent information provided by pregnant women and systematically collected by midwives and public health nurses during the second trimester as part of routine antenatal care and archived in the FMBR. During the period from 1987 to 1990 responses were categorised as either non-smokers, smokers of less than 10 cigarettes per day, or 10 cigarettes or more per day. During the period 1991 to 2001 the average number of cigarettes per day was not collected, but replaced with information on whether or not women stopped smoking during first trimester. In the sibling matched analyses we defined pregnancy smoking as smoker and non-smoker and in mothers of children born 1991-2001 only those reported continued smoking as well as those only smoking during the first trimester were categorised as smokers.

Outcome definition

We studied children's entries in the FHDR until January 1st, 2006 using ICD-10 diagnoses to identify children with HKD including hyperkinetic disorder (F90.0), hyperkinetic conduct disorder (F90.1) or other hyperkinetic disorder (F90.8 and F90.9) as endpoint in the analyses. We excluded 1901 children with pervasive developmental disorders, including autism, F84 (N=1095), mental retardation, F70-79, (N=262) and 325 with both these diagnoses. Further 219 children who had the ICD-9 (but not the ICD-10) diagnosis of 314 were excluded from the analyses, because the definition was not fully comparable with ICD-10.

Cohort definition

After the above exclusions the population included 892,796 children of whom 7,226 were diagnosed with HKD. There were 24,347 (3%) with missing smoking information, leaving 868,449 available for analyses, where 7023 children (0.8%) had HKD. Among the 443,076 boys there were 6013 (1.4 %) and among the 425,353 girls there were 1010 (0.2%) who received the HKD diagnosis over the observation period. The 513,198 participating women contributed with an average of 1.7 children to the entire cohort.

Statistical analyses

To control for differences length of follow up time we used Cox regression analysis, with child age as the primary time scale. To control for the increasing incidence of HKD over

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5 study time we adjusted for each year of birth as a categorical variable(1987-2001). We
6 further a priori decided to adjust for child sex, gestational age at birth (less than 30, 30-33,
7 34-36,37-40,41 or more), maternal age (20 or less, 21-25, 26-30,31-35, 36 or more) and
8 parity (0,1,2,3 or more). Data on maternal occupation was available and adjusted for in the
9 period 1991 to 2001 and was transformed to an indicator of socioeconomic status (SES)
10 according to a national system of classifications and standards in Finland ²⁰ (upper white
11 collar, lower white collar, blue collar, others). The analyses were performed using STATA
12 9.0. Hazard Ratios (HR) are presented with 95% confidence intervals (CI). Our analytic
13 strategy was to analyze the entire population using regular cohort analyses and then to
14 compare these findings with sibling-matched analyses.
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17 *Population cohort analyses*

18 In the Cox regression model we assumed proportional rates for the exposure and the
19 above mentioned potential confounders with one common baseline rate function. The
20 proportional hazards assumption was evaluated for all variables by comparing estimated
21 log-minus-log survivor curves over the different categories of variables investigated.
22 Because most women contributed to the cohort with more than one child we used robust
23 standard errors to adjust the confidence intervals for the presence of siblings in the
24 population analyses (declaring each of the sibling pairs to be a cluster). All analyses were
25 repeated by sex and adjusted for the variables described above. Additionally in order to
26 control for SES and because of change in exposure registration we separated the cohort
27 into children born 1987-1990 and 1991-2001, where SES was available for the latter
28 group.
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33 *Sibling matched analyses*

34 We performed sibling-matched analyses to control for shared genetic and social
35 confounding. We used stratified Cox regression with a separate stratum for each family
36 identified by the mothers encrypted identification number. In the stratified Cox regression
37 model each family have its own baseline rate function reflecting the family's shared genetic
38 and social factors. The exposure comparisons, smoking versus non-smoking, are thus
39 made within the family. We controlled for the same factors as in the cohort analyses,
40 except for SES which is part of the shared social factors and therefore already controlled
41 for in the sibling matched analysis. The stratified Cox regression model is an extension of
42 the paired binomial model, taking differences in follow-up time into account. Thus only
43 sibling pairs discordant for smoking as well HKD were 'informative', i.e. contributed
44 information to the estimates. Indeed, the sibling without HKD should have at least as long
45 follow-up time as the sibling with HKD to be informative.
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49 **Results**

50 In the regular cohort analyses we found that children exposed to maternal smoking in
51 pregnancy had about twice the risk of having a diagnosis of HKD during the up to 19 years
52 of follow-up period (HR 2.01, 95% CI: 1.90-2.12). The results of the analyses in the two
53 periods are shown in table 1. The analyses of children born 1987-1990 indicated the HKD
54 risk increased by level of smoking. In a similar way the data for children born 1991-2001
55 suggested that those who quit smoking in early pregnancy had a slightly lower risk for
56 HKD as compared with those who continued smoking beyond the first trimester, but this
57 difference was not statistically significant. Excluding children born small for gestational age
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4 or preterm did not change the results. Control for SES among children born 1991-2001 did
5 only change the estimates slightly and the results were very similar in the two time periods.
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8 *(TABLE 1 about here)*
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10 The results comparing smokers with non-smokers in the full cohort and in the sibling-
11 matched analyses are shown in Table 2. The adjusted analyses suggested a weak
12 association between antenatal smoking exposure and HKD when boys and girls were
13 analysed together and separately.
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15 We finally analyzed possible birth order effects by stratifying the analyses by whether the
16 smoking exposure was in the pregnancy of the older or the younger sibling and then
17 whether the HKD diagnosis was given to the older or the younger sibling. The associations
18 were similar for women smoking in the pregnancy of the older and the younger child
19 (HR=1.3 and 1.2 respectively)
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22 *(TABLE 2 about here)*
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26 Discussion

27 In this cohort of the entire Finish population during a 15 year observation period we found
28 in the cohort analysis that children prenatally exposed to maternal smoking had twice the
29 risk of being diagnosed with HKD than children of non-smokers. This finding is in line with
30 recent studies^{21;22} a number of previous conventional case control and cohort studies that
31 have reported a strong association between pregnancy smoking and various measures of
32 the ADHD phenotype¹¹ as well as the diagnosis of HKD¹⁰.
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35 However, in the sibling-matched analyses, when controlling for shared family confounders,
36 the estimated association was much weaker. This finding indicates that a part of the
37 association reported in most previous studies may be partly due to confounding as
38 maternal smoking may be indicator of a genetic trait and social factors related to HKD.
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41 These findings are in line with the findings of three recent studies. Thapar et al. used
42 children born after different types of in vitro fertilization with egg-donation as a way to
43 distinguish between genetic and exposure effects¹⁵. They found no association between
44 smoking and the ADHD phenotype in genetically unrelated mother-child pairs which
45 however could be due to chance by small sample size or that they had more girls among
46 the offspring of exposed²³. Two recent studies used the sibling design with endpoints of
47 relevance for ADHD. D'Onofrio et al. studied the association between pregnancy smoking
48 and hyperactivity problems based on parents answering three screening questions and
49 found a considerable smaller effect using the sibling design as compared to the regular
50 cohort analyses¹⁶. The same tendency was seen in a register based Swedish study, that
51 studied the association between smoking in pregnancy in all Swedish children born 1987-
52 2000 and prescription of ADHD medication in the year 2006¹⁷. In their sibling analyses
53 they reported an estimate quite close to ours, but the crude proxy for ADHD, a one-year
54 registration of prescription, does not capture older sibling treated medically early in life.
55 This is quite important in the sibling design because discordant sibling pairs are
56 misclassified as concordant and vice versa.
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5 The present study has a number of the strengths in being based on a complete 15 years
6 follow-up using established diagnostic criteria based on clinical examination within in
7 specialised departments within the public health service. We had practically complete
8 follow-up data with little risk of selection bias, our data came from concurrently registered
9 information rather than retrospective reports, and further our results were unlikely to be
10 flawed by differential misclassification of HKD because children's care is universally
11 available, publicly financed and organised in Finland. It is unlikely that the threshold for
12 admission to hospital clinics is related to the prenatal smoking especially when siblings are
13 compared.
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16 The matched sibling design has a number of advantages in controlling for family factors.
17 These family factors are difficult to measure and thus control for in conventional cohort
18 designs. Full siblings share social environment but only half of their genes so even these
19 analyses will tend to overestimate the tested association. One caveat of our study is that
20 siblings were matched on mothers identification number and we did not have any
21 information regarding fathers (due to strict data protection regulations in Finland). It may
22 be the case that our estimates may overestimate the association and that even weaker
23 associations had been found if we were able to identify and exclude half-siblings.
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27 There are limitations to the sibling design that should be mentioned. The strict control for
28 shared family factors limits the analyses to a small subset of the population. Only sibling
29 pairs discordant for smoking as well as HKD contribute to the estimate in these analyses.
30 In the present study we had 40,615 sibling pairs, that were discordant for prenatal smoking
31 exposure, but because discordance for HKD was also needed for a pair to be informative
32 only 880 pairs contributed with information of the smoking-HKD association. In the
33 adjusted stratified Cox regression model more sibling pairs discordant for some of the
34 other factors in the model will principally add to the estimates, but the basic concept of this
35 type of analyses can simply be illustrated by the ratio between the informative pairs
36 supporting and discounting the hypothesis.
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40 Positive association pairs (PAP) are sibling pairs that support a positive association
41 between smoking and HKD i.e. where the mother smoked during the pregnancy of the
42 child with HKD and did not smoke in the pregnancy with the child without HKD.
43 Negative association pairs (NAP) on the other hand were pairs where the mother did not
44 smoke in the pregnancy of the child with HKD and smoked in the pregnancy of the child
45 without HKD. To support the idea that prenatal smoking is a causal factor for HKD, one
46 would expect more PAP than NAP, in fact twice as many to support the findings of most
47 previous studies. Of the 880 pairs 484 pairs were PAP and 396 NAP with a ratio (1.2) very
48 close to the results of the crude Cox regression analyses shown in Table 2. When
49 restricted to comparison between boy siblings the PAP/NAP ratio was 1.3 (218/168) and
50 restriction to in girl siblings this was 1.8 (45/25). Again the ratios are in line with the
51 estimates for sibling matched Cox regression analysis and the small numbers explain the
52 broad confidence intervals.
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56 As illustrated above large register based studies are needed to gain valid estimates from
57 sibling analyses. In this type of registers the information on smoking is collected routinely,
58 but the smoking information is quite crude. The crude smoking information limits our ability
59 to estimate effect of timing and dose. There are, however, further potential limitations to
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4 the interpretations of our results linked to the strict selection of smoking women in the
5 sibling analyses. As mentioned above the sibling matched analyses are based on a
6 subsample of smoking women and this sample may differ from the smoking women who
7 were not informative in the sibling analyses. We therefore compared women reporting
8 smoking and giving birth to their first child 1987-1991 according to whether they smoked in
9 their next pregnancy. Among those, who smoked in both pregnancies 85% (95% CI: 84-
10 86%) were smoking 10 cigarettes or more in the pregnancy of the first child as compared
11 with 71% (95% CI: 70-72%) of subsequent non-smokers This indicates that there are more
12 heavy smoking women among those who are not able to give up smoking in any of their
13 pregnancies. Thus heavy smoking women are underrepresented in the sibling analysis
14 and this may be part of the explanation for the attenuated estimates as compared with the
15 regular cohort analyses.
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20 It could further be argued that because information on smoking was based on personal
21 contact between midwives/public health nurses and the pregnant women, the difference in
22 unmatched and matched results could be due to misclassification of smoking status. Some
23 misclassification seems likely and may be part of the explanation for the attenuation in our
24 estimates when using sibling analyses. Women who contributed to the sibling analyses
25 with informative siblings were characterised by having smoked in one pregnancy and by
26 having a child with HKD. It is possible that women with HKD in the family may be more
27 likely to under-report smoking If this bias is non-differential, which is expected, it would
28 bias toward null-values and could partly explain the attenuation of the association. We
29 were not able to evaluate this possibility directly because we did not have access to
30 detailed smoking information, but we may evaluate this potential misclassification by
31 looking at differences in birth weight between siblings with discordant smoking exposure.
32 The effect of antenatal smoking on birth weight is well established and if women
33 contributing to our informative pairs more often under-reported true smoking in the
34 subsequent pregnancy we would expect a smaller difference in birth weight between these
35 sibling pairs compared with all sibling pairs discordant for smoking exposure. This was
36 however not the case. We found no difference in the effect of smoking on birth weight. In
37 the informative pairs adjusted for parity, gestational age at birth and gender there was a
38 reduction of 88 grams (95% CI: 53-123 grams) in birth weight as compared with 69 grams
39 (95% CI: 63-75 grams) in all the sibling pairs discordant for smoking. These differences in
40 birth weight are in line with results from a recent report, where smoking information was
41 validated against serum cotinine²⁴. These findings speak against the possibility that the
42 attenuation of the association was due to more misclassification of smoking status in the
43 informative sibling pairs.
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49 By using a HKD diagnosis as the endpoint we had the possibility to study the more severe
50 phenotype. A HKD diagnosis requires hyperactivity/impulsivity as well as inattention in at
51 least two settings and is close to the DSM-IV ADHD-combined diagnosis. Although the
52 Finnish register contains complete information for in- as well as outpatient contacts in the
53 public health system, some children are unrecognized and thus untreated or treated
54 without contact to the hospital system. Thus some cases of HKD or ADHD are
55 undiagnosed in the hospital system but as they are few in the general population it will
56 have little influence on estimation of the association we study. Even a low sensitivity will
57 not bias our results as long as the specificity is high, which we find likely due to the use of
58 strict diagnostic criteria in clinical practice in Finland. Differences in referral that in
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conventional studies may lead to bias, is less likely to do so in a sibling design because this bias is likely to be linked to the families. However, it is also possible that a diagnosis given to a child will make it more likely that an undiagnosed sibling with the disorder will be diagnosed. In the sibling design this would generate less discordant pairs but if linked to smoking attenuate the estimate.

In conclusion, previous reports may have overestimated the association between pregnancy smoking and HKD because they have not been able to control for shared family factors. We cannot completely discount the possibility that smoking is a causal factor, but then the size of the effect is probably smaller than what has previously been reported. Our findings are based on women, who were able to change smoking status between pregnancies and we probably cannot be extrapolated to women, who smoked in all their pregnancies. From a public health perspective, however, it is of interest to estimate if women, who manage to drop smoking in a pregnancy actually reduce their risk of getting a child with behavior problems. This study indicates that this may only be the situation for few.

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Conflicts of interests: None declared

KEY Messages:

- *In a matched sib-ship design we found a weaker association between smoking during pregnancy and a diagnosis of Hyperkinetic Disorder in the offspring than has been found in previous studies*
- *The strong association found in previous studies may be due to confounding by social and genetic factors*
- *Despite some limitations, the sib-ship design may provide an efficient design to control for confounding by family factors in studies of the effect of prenatal exposures.*

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Is maternal smoking during pregnancy a risk factor for Hyperkinetic disorder? - Findings from a sibling design.

Carsten Obel¹, Jørn Olsen², Tine Brink Henriksen³, Alina Rodriguez^{4,5,6}, Marjo-Riitta Järvelin^{4,7}, Irma Moilanen^{4,8}, Erik Parner⁹, Karen Markussen Linnet³, Anja Taanila⁷, Hanna Ebeling⁸, Einar Heiervang¹⁰ and Mika Gissler^{11, 12}.

¹Dep. Of General Practice, Institute of Public Health, Aarhus University, Denmark

²UCLA School of Public Health, Department of Epidemiology, Los Angeles, USA,

³Dep. of Obstetrics and Pediatrics, Aarhus University Hospital, Skejby, Denmark,

⁴Dep. of Epidemiology and Public Health, Imperial College Faculty of Medicine, London, UK

⁵Dep. of Psychology, Uppsala University, Sweden

⁶MRC Social Genetic Developmental Psychiatry, King's College, London UK

⁷Dep. of Public Health Science and General Practice, University of Oulu, Finland

⁸Clinic of Child Psychiatry, University and University Hospital of Oulu, Finland

⁹Dep. of Biostatistics, Institute of Public Health, Aarhus University, Denmark

¹⁰Dep. of Child and Adolescent Psychiatry, Haukeland University Hospital, Bergen, Norway

¹¹National Institute for Health and Welfare (THL), Helsinki, Finland

¹²Nordic School of Public Health, Gothenburg, Sweden

Corresponding author:

Carsten Obel

Department of general medicine, Institute of Public Health

Aarhus University

Bartolins alle 2

DK- 8000 Aarhus C

Phone +4589426072

Email: co@alm.au.dk

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Abstract

Background Studies have consistently shown that pregnancy smoking is associated with twice the risk of hyperactivity/inattention problems in the offspring. An association of this magnitude may make behavioral difficulties the most important health effect related to smoking during pregnancy. However, social and genetic confounders may fully or partially account for these findings.

Methods A cohort including all singletons born in Finland January 1, 1987 through December 31, 2001 was followed until January 1, 2006. We identified mothers with at least one child with HKD and a sibling discordant for prenatal smoking exposure. Data were available for 97% (N=868 449) and 880 sibling pairs were informative for the matched sibling analyses (one of the sibs exposed and one of the sibs had HKD). We used matched Cox regressions to estimate the association between prenatal exposure to smoking and HKD within these sibling pairs.

Results We found a weak non-significant association between exposure to maternal smoking during pregnancy and risk for HKD in children using the sibling matched analysis (HR=1.20, 95% CI 0.97-1.49). In contrast, the general population estimate, without matching siblings, was in line with previous studies and substantially higher (HR 2.01, 95% CI: 1.90-2.12).

Conclusions Analysis using a matched sibling design resulted in a weaker and insignificant association between exposure to smoking during pregnancy and HKD than has been found in previous studies. We cannot completely discount the possibility that smoking is a causal factor, but then effect is probably small.

Keywords: smoking, pregnancy, Attention Deficit Hyperactivity Disorder, sibling design

BACKGROUND

Attention Deficit Hyperactivity Disorder (ADHD) defined by the DSM-IV criteria is one of the most common childhood psychiatric disorders¹, with a cumulative incidence of 2-5% in Europe². In the WHO diagnostic system (ICD-10) only children with the ADHD combined type (both inattention and hyperactivity/impulsivity symptoms) receive Hyperkinetic Disorder (HKD) diagnosis³, and is the focus of this study. Core symptoms are linked to poor school performance and other social problems⁴.

HKD has at least in part genetic causes⁵ and brain imaging studies suggest that deviant brain morphology may be present already at birth⁶. Prenatal exposures have therefore been considered to be causally related to the disorder^{7, 8}. The association is biologically plausible and a number of animal studies, including studies on monkeys, suggest that prenatal exposure to nicotine may affect fetal brain development that mimics the disorder⁹. A recent meta-analysis estimated a two-fold increased risk for the disorder in children of women who smoked during pregnancy¹⁰. An association of this magnitude may make behavioral difficulties the most important health effect related to smoking during pregnancy.

However, both smoking and HKD correlate with social conditions and mothers with attention problems may frequently be smokers¹¹ because nicotine improves attention¹². It is therefore possible that smoking is an indicator of a genetic disposition to HKD and that the published associations reflect genetic and/or social confounding as indicated in a recent study¹³. They used an interesting design using children born after egg-donation as a way to distinguish between genetic and exposure effects¹³. Such alternative designs are needed, but their sample size was so small that the reported negative findings may be due to the limited information.

We estimated the association between prenatal smoking and HKD in the entire population of Finland born during a 15-year period using a discordant-sibling design, where siblings were discordant for both exposure to prenatal tobacco and HKD.

METHODS

Participants and outcome definition

Finland has a mandatory registration of all births into the Finnish Medical Birth Register (FMBR). The FMBR includes information on all pregnancies and births within the country. We identified all singleton children born from January 1, 1987 to December 31, 2001 who were still alive on January 1st, 2006 yielding a total of 894,697 singletons. Data on maternal occupation was available for the period 1991 to 2001 and was transformed to an indicator of socioeconomic status (SES) according to a national system of classifications and standards in Finland¹⁴.

By using the unique personal identification number covering all residents in Finland, we were able to link the birth cohort with data from the Finnish Hospital Discharge Register (FHDR) including all inpatient (established in 1987) and all outpatient visits (established in 1998). Registration is mandatory for all inpatient care in public and private hospitals as well as for all outpatient visits in public hospitals. All diagnoses were reported using ICD-9 and since 1996 according to the ICD-10.

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4 We studied children's entries in the FHDR until January 1st, 2006 using ICD-10 diagnoses
5 to identify children with HKD including hyperkinetic disorder (F90.0), hyperkinetic conduct
6 disorder (F90.1) or other hyperkinetic disorder (F90.8 and F90.9) as endpoint in the
7 analyses. We excluded 1901 children with pervasive developmental disorders, including
8 autism, F84 (N=1095), mental retardation, F70-79, (N=262) and 325 with both these
9 diagnoses. Further 219 children who had the ICD-9 (but not the ICD-10) diagnosis of HKD
10 were excluded from the analyses. In the remaining group of 892,796 children in the birth
11 cohort, 7226 were diagnosed with HKD. There were 24,347 (3%) with missing smoking
12 information, leaving 868,449 available for analyses, where 7023 (0.8%) children had HKD.
13 The 513,198 participating women contributed with an average of 1.7 children to the entire
14 cohort.
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18 For the sibling study we identified two groups of informative pairs, positive association
19 pairs (PAP) and the negative association pairs (NAP). PAP were sibling pairs that support
20 a positive association between smoking and HKD i.e. where the mother smoked during the
21 pregnancy of the child with HKD and did not smoke in the pregnancy with the child with
22 without HKD. Negative association pairs (NAP) were pairs where the mother did not
23 smoke in the pregnancy of the child with HKD and smoked in the pregnancy of the child
24 without HKD. If prenatal smoking is a causal factor for HKD one would expect more PAP
25 than NAP. A total of 40,615 sibling pairs were discordant for prenatal smoking exposure,
26 but because discordance for HKD was also needed for a pair to be informative only 880
27 pairs was left for the analyses, 484 pairs indicating a positive association and 396
28 indicating a negative association (table 2).
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33 **Exposure information**

34 Antenatal care in Finland is tax-paid and offered to all pregnant women and care in low
35 risk pregnancy includes approximately 10-14 visits. Data on maternal smoking came from
36 concurrent information provided by pregnant women and systematically collected by
37 midwives and public health nurses during the second trimester as part of routine antenatal
38 care and archived in the FMBR . During the period from 1987 to 1990 responses were
39 categorised as either non-smokers, smokers of less than 10 cigarettes per day, or 10
40 cigarettes or more per day. During the period 1991 to 2001 the average number of
41 cigarettes per day was not collected, but rather replaced with information on whether or
42 not women stopped smoking during first trimester.
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46 In the sibling matched analyses we defined pregnancy smoking as smoker and non-
47 smoker and in mothers of children born 1991-2001 those who reported continued smoking
48 or smoking only during the first trimester were categorised as smokers.
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50 **Statistical analyses**

51 To control for differences in follow up time and the increasing incidence of HKD over study
52 time we used Cox regression analysis. We adjusted for year of birth (1987-2001) to control
53 for age of the child at first diagnosis. We a priori decided to adjust for child sex, maternal
54 age (20 or less, 21-25, 26-30,31-35, 36 or more), gestational age at birth (less than 30, 30-
55 33, 34-36,37-40,41 or more) and parity (0,1,2,3 or more). The analyses were performed
56 using STATA 9.0. Statistical significance was defined by a p-value below 5%. Hazard
57 Ratios (HR) are presented with 95% confidence intervals (CI).
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In the population analyses we used robust standard errors to adjust the confidence intervals for the presence of siblings (stcox, vce). All analyses were repeated for each sex. SES was included in all analyses of children born between 1991 and 2001.

To control for common genetic and social confounding we performed sibling matched analyses. We used Cox regression (stcox, strata) matching siblings by the mothers encrypted identification number and controlled for the same factors as in the population analyses. The sibling-matched analyses were performed on all siblings but only sibling pairs discordant for smoking as well HKD were informative and contributed to the estimates.

Ethics

The National Institute for Health and Welfare (THL), responsible for the Finnish Medical Birth Register and Finnish Hospital Discharge Register, gave permission to link and use encrypted health register data for this study. The data protection ombudsman was informed about the study, as requested by the national data protection regulation.

RESULTS

Children exposed to maternal smoking in pregnancy had about twice the risk of having a diagnosis of HKD during the up to 19 years of follow up period. The analyses of children born 1987-1990 indicated the HKD risk increased by level of smoking (Table 1). In a similar way the data for children born 1991-2001 suggested that those who quit smoking in early pregnancy had a slightly lower risk for HKD as compared with those who continued smoking beyond the first trimester, but this difference was not statistically significant (Table 1). The analyses stratified for sex of the child suggested that the association was slightly stronger among girls than boys, but this difference did not reach statistical significance. Excluding children born small for gestational age or preterm did not change the results.

(TABLE 1 about here)

The results comparing smokers with non-smokers in the population and sibling-matched analyses are shown together in Table 2. There were slightly more Positive (PAP) than negative (NAP) and the PAP/NAP ratios were as expected in line with the unadjusted sibling matched analyses (Table 2). The adjusted analyses suggested a weak non-significant association between antenatal smoking exposure and HKD when both sexes were analysed together and separately. There was no overlap between the confidence intervals of the sibling-matched versus the population analyses when both sexes were analysed together and separately.

We analyzed possible birth order effects by stratifying the analyses by whether the smoking exposure was in the pregnancy of the older or the younger sibling and then whether the HKD diagnosis was given to the older or the younger sibling. The estimates were similar for women smoking in the pregnancy of the older and the younger (HR=1.3 and 1.2 respectively) as well as in pairs where the older sibling had HKD (HR 1.2) and where the younger was the child with HKD (HR=1.3)

(TABLE 2 about here)

DISCUSSION

Children prenatally exposed to maternal smoking had twice the risk of being diagnosed with HKD than children of non-smokers. However, in the sibling-matched analyses, the association was much lower. This finding suggests that a part of the association reported in the literature may be due to confounding by family factors that correlate with parental smoking.

The results of the population analyses are in line with a number of previous reports¹⁰ including our own¹⁵ which have addressed genetic confounding indirectly. Because parents with HKD may be more likely to smoke¹⁶ made us and others question whether the smoking association is causal or spurious.¹³

Maternal smoking may be an indicator of a genetic trait related to HKD and this heritable factor rather than smoking exposure per se may contribute to HKD in children. Our findings based on the sibling-matched analyses support this idea and is in line with a recent study by Thapar et al. who found significant association between smoking in pregnancy and offspring's ADHD behaviours as rated by mothers. This study was of particular interest because they used a design based on egg-donation pregnancies where mothers and children were genetically related and unrelated¹³. This quite innovative study leaves, however, questions still unanswered because it was based on a very small and selected sample and included twins. The present study has the strength of being based on a full population sample and thus a relatively large set of informative sibling pairs with the potential to partly control for heritable and social factors.

The present study has the strength of using the HKD diagnosis as endpoint in a large, complete population. In contrast to most previous follow up studies, we had practically complete data (97%), data based on concurrently registered information rather than based on retrospective reports, and further our results are unlikely to be flawed by selection bias¹⁷ because care is tax-financed and universally available in Finland.

It can be argued that because information on smoking was based on personal contact between midwives/ public health nurses and the pregnant women, the difference in unmatched and matched results could be due to misclassification of smoking status. Women who contributed to the sibling analyses with informative siblings were characterised by having smoked in one pregnancy and by having a child with HKD. It is possible that smoking in subsequent pregnancies is under-reported. If this bias is non-differential, which is expected, it would bias toward null-values and could partly explain the attenuation of the association. We examined this possibility by looking at differences in birth weight between siblings with discordant smoking exposure. If women contributing to our informative pairs more often under-reported true smoking in the subsequent pregnancy, we would expect a smaller difference in birth weight between these sibling pairs than between all sibling pairs discordant for smoking exposure. This was however not the case. We found no difference in the effect of smoking on birth weight. In the informative pairs adjusted for parity, gestational age at birth and gender a reduction of 88 grams (95% CI 53-123 grams) in birthweight as compared with 69 grams (95% 63-75 grams) in all the sibling pairs discordant for smoking. These differences in birth weight are in line with results from a recent report, where smoking information was validated against

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4 serum cotinine.¹⁸ Therefore, our results are not likely to be due to misclassification of
5 smoking status.
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8 By using a HKD diagnosis as the endpoint we had the possibility to study the more severe
9 and most common form of the DSM-IV ADHD-combined diagnosis. Others have
10 compared the DSM-IV ADHD diagnosis with HKD³ and the HKD diagnosis primarily
11 identifies children with the most severe of the ADHD combined phenotype. We have also
12 failed to identify all children with HKD. Although the Finnish register contains complete
13 information for in- and outpatient contacts in the public health system, some children may
14 be unrecognized and thus untreated or treated without contact to the hospital system.
15 Thus some cases of HKD or ADHD will be misclassified because they are undiagnosed in
16 the hospital system but as they are few in the general population it will have little influence
17 on the association we study. Even a low sensitivity will not bias our results as long as the
18 specificity is high, which we find likely due to the use of strict diagnostic criteria in clinical
19 practice in Finland.
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23 In conclusion, previous reports are likely to have overestimated the association between
24 pregnancy smoking and HKD in the offspring and using the sibling design. We cannot
25 completely discount the possibility that smoking is a causal factor, but this study indicates
26 that the effect size is smaller than previously expected.
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31 and Therese Koops Grønberg for helping with the analyses.
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		N	n	%	HR _{crude}	HR _{adjusted}	(95% CI)
1987-1990							
All	Non-smokers	200886	957	0,5	Ref.	Ref.	
	Smokers	36811	372	1.0	2.13	1.92	(1.69; 2.18)
	1-9/day	18136	141	0.8	1.59	1.77	(1.47; 2.12)
	10+/day	18675	231	1.2	2.68	2.03	(1.74; 2.37)
Boys	Non-smokers	102578	844	0,8	Ref.	Ref.	
	Smokers	18872	323	1.7	2.09	1.88	(1.64; 2.15)
	1-9/day	9261	122	1.3	1.57	1.75	(1.43; 2.13)
	10+/day	9611	201	2.1	2.62	1.97	(1.67; 2.33)
Girls	Non-smokers	98308	113	0,1	Ref.	Ref.	
	Smokers	17939	49	0.3	2.39	2.23	(1.56; 3.18)
	1-9/day	8875	19	0.2	1.75	1.93	(1.15; 3.23)
	10+/day	9064	30	0.3	3.10	2.46	(1.59; 3.81)
1991-2001							
All	Non-smokers	532288	4014	0,8	Ref.	Ref.	
	Smokers	98464	1680	1.7	2.23	1.92	(1.80; 2.04)
	only first trimester	10336	126	1.2	1.64	1.34	(1.11; 1.62)
	after first trimester	88128	1554	1.8	2.29	1.98	(1.86; 2.12)
Boys	Non-smokers	271496	3442	1,3	Ref.	Ref.	
	Smokers	50130	1404	2.8	2.18	1.88	(1.75; 2.01)
	only first trimester	5257	105	2.0	1.61	1.34	(1.09; 1.64)
	after first trimester	44873	1299	2.9	2.24	1.94	(1.81; 2.08)
Girls	Non-smokers	260792	572	0,2	Ref.	Ref.	
	Smokers	48334	276	0.6	2.56	2.13	(1.82; 2.49)
	only first trimester	5079	21	0.4	1.89	1.35	(0.82; 2.22)
	after first trimester	43255	255	0.6	2.64	2.21	(1.88; 2.60)

Table 1 Hazard ratio for Hyperkinetic Disorder (HKD) according to prenatal exposure for smoking. Children born in Finland 1987-2001 (N=868 449). All Cox regressions adjusted for robust standard error.

For Review Only

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		Unmatched analyses					PAP/NAP	Sibling matched analyses			
		N	n	%	HR _{crude}	HR _{adjusted}	95% CI	Ratio	HR _{crude}	HR _{adjusted}	95% CI
All	Non-smokers	733174	4971	0,7	Ref.	Ref.		484/396	Ref.	Ref.	
	Smokers	135275	2052	1.5	2.22	2.01	(1.90; 2.12)		1.21	1.20	(0.97; 1.49)
Boys	Non-smokers	374074	4286	1,1	Ref.	Ref.		218/168	Ref.	Ref.	
	Smokers	69002	1727	2.5	2.17	1.96	(1.85; 2.08)		1.19	1.21	(0.93; 1.59)
Girls	Non-smokers	359100	685	0,2	Ref.	Ref.		45/25	Ref.	Ref.	
	Smokers	66273	325	0.5	2.55	2.28	(1.99; 2.63)		1.85	1.51	(0.71; 3.19)

Table 2 Hazard ratio for Hyperkinetic Disorder (HKD) according to smoking during pregnancy. Children born in Finland 1987-2001 Cox regression analyses unmatched adjusted for robust standard error. Ratio of Positive (PAP) and negative (NAP) association pairs and sibling matched analyses on maternal encrypted identification number.