Is maternal smoking during pregnancy a risk factor for Hyperkinetic disorder?—findings from a sibling design

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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 indicate behavioural difficulties as 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 from 1 January 1987 through 31 December 2001 was followed until 1 January 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 International Classification of Diseases, 10th revision, 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 [hazards ratio (HR) = 1.20, 95% confidence interval (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 what the previous studies indicate.

Keywords Smoking, pregnancy, attention deficit hyperactivity disorder, hyperkinetic disorder, sibling design
Introduction

Attention deficit hyperactivity disorder (ADHD) defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria is one of the most common childhood psychiatric disorders, with a cumulative incidence of 2–5%. In the World Health Organisation diagnostic classification system (International Classification of Diseases, 10th revision—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). Core symptoms are linked to poor school performance and other social problems.

HKD has, at least, in part genetic causes, and brain imaging studies suggest that deviant brain morphology may be present at birth, which indicates a genetic aetiology or aetiology related to prenatal environmental exposure. A number of pregnancy exposures have been suggested, with smoking as a major cause. 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 ADHD. Epidemiological studies have consistently shown that mothers who smoke during pregnancy have about twice the risk of HKD and ADHD in their offspring, and an association of this magnitude may indicate behavioural difficulties as 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 smokers. Nicotine improves attention 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 se. Ruling out this possibility in conventional observational designs is not easy and alternatives are called for. A recent study of in vitro–fertilized pregnancies examined children conceived through genetically unrelated egg donations and found no evidence of an effect of smoking. Two other recent studies found only weak associations when using a sib-ship design. 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 available. 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 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 used. We identified all singleton children born from 1 January 1987 to 31 December 2001 who were still alive on 1 January 2006, yielding a total of 894,697 singletons.

The National Institute for Health and Welfare (THL), which is the body responsible for the FMBR and FHDR, 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 the low-risk pregnancy care includes approximately 10–14 antenatal visits. The data on maternal smoking stemmed from concurrent information provided by pregnant women and systematically collected by midwives and public health nurses, during the second trimester of routine antenatal care and subsequently archived in the FMBR. During the period from 1987 to 1990, responses were categorized either as non-smokers, smokers of fewer than 10 cigarettes per day, or 10 cigarettes or more per day. During the period 1991–2001 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. For mothers of children born 1991–2001, those who reported continuing smoking as well as those only smoking during the first trimester were categorized as smokers.

Outcome definition

We studied the children’s entries in the FHDR until 1 January 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 endpoints 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 were excluded, the population included 892,796 children of whom 7226 were diagnosed with HKD. There were 24,347 (3%) with missing smoking information, leaving 868,449 available for analyses, out of which 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%) that received the HKD diagnosis during 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 in length of follow-up time, we used the Cox regression analysis, with child age as the primary time scale. To control for the increasing incidence of HKD over study time, we adjusted for each year of birth as a categorical variable (1987–2001). We further a priori decided to adjust for child sex, gestational age at birth (<30, 30–33, 34–36, 37–40, ≥41 weeks), maternal age (≤20, 21–25, 26–30, 31–35, ≥36 years) and parity (0, 1, 2, ≥3). Data on maternal occupation was available and adjusted for in the period 1991–2001 and was transformed to an indicator of socio-economic status (SES) according to a national system of classifications and standards in Finland20 (upper white collar, lower white collar, blue collar, others). The analyses were performed using Stata 9.0. Hazard ratios (HRs) are presented with 95% confidence intervals (CIs). Our analytic strategy was to analyse the entire population using regular cohort analyses and then to compare these findings with sibling-matched analyses.

Population cohort analyses

In the Cox regression model, we assumed proportional rates for the exposure and the above-mentioned potential confounders with one common baseline rate function. The proportional hazards assumption was evaluated for all variables by comparing estimated log-minus-log survivor curves over the different categories of variables investigated. Because most women contributed to the cohort with more than one child, we used robust standard errors to adjust the CIs for the presence of siblings in the population analyses (declaring each of the sibling pairs to be a cluster). All analyses were repeated by sex and adjusted for the variables described above. Additionally, in order to control for SES and because of changes in exposure registration, we separated the cohort into children born 1987–90 and 1991–2001, where SES was available for the latter group.

Sibling-matched analyses

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

Results

In the regular cohort analyses, we found that children exposed to maternal smoking in pregnancy had about twice the risk of receiving a diagnosis of HKD during up to a 19-year follow-up period (HR 2.01, 95% CI 1.90–2.12). The results of the analyses in the two periods are shown in Table 1. The analyses of children born 1987–90 indicated that HKD risk increased by level of smoking. In a similar way, the data for children born 1991–2001 suggested that children whose mothers quit smoking in early pregnancy had a slightly lower risk for HKD as compared with those children whose mothers continued smoking beyond the first trimester, but this difference was not statistically significant. Excluding children born small for gestational age or preterm did not change the results. Control for SES among children born 1991–2001 only slightly changed the estimates and the results were very similar in the two time periods.

The results comparing smokers with non-smokers in the full cohort and in the sibling-matched analyses are shown in Table 2. The adjusted analyses suggested a weak association between antenatal smoking exposure and HKD when boys and girls were analysed together and separately.

We finally analysed 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 associations were similar for women smoking in the pregnancy of the older and the younger child (HR = 1.3 and 1.2, respectively).
Discussion

During a 15-year observation period of the entire Finnish population, we found in the cohort analysis that children prenatally exposed to maternal smoking had twice the risk of being diagnosed with HKD than children of non-smokers. This finding is in line with recent studies, a number of previous conventional case–control and cohort studies that have reported a strong association between pregnancy smoking and various measures of the ADHD phenotype as well as the diagnosis of HKD.

However, in the sibling-matched analyses, when controlling for shared family confounders, the estimated association was much weaker. This finding indicates that a part of the association reported in most previous studies may be due to confounding as maternal smoking may be an indicator of a genetic trait and social factors related to HKD.

These findings are in line with the findings of three recent studies. Thapar et al. used children born after different types of in vitro fertilization techniques with egg donation as a way to distinguish between genetic
and exposure effects. They found no association between smoking and the ADHD phenotype in genetically unrelated mother–child pairs, which, however, could be due to chance by small sample size or that they had more girls among the offspring of exposed. Two recent studies used the sibling design with endpoints of relevance for ADHD. D’Onofrio et al. studied the association between pregnancy smoking and hyperactivity problems based on parents answering three screening questions and found a considerably smaller effect using the sibling design as compared with the regular cohort analyses. The same tendency was seen in a register-based Swedish study that studied the association between smoking in pregnancy in all Swedish children born 1987–2000 and prescriptions of ADHD medication in the year 2006. In their sibling analyses, they reported an estimate quite close to ours, but the crude proxy for ADHD, a 1-year registration of prescriptions, did not capture older siblings treated medically early on in life. This is quite important in the sibling design because discordant sibling pairs are misclassified as concordant and vice versa.

The present study has a number of strengths. It is based on a complete 15-year follow-up using established diagnostic criteria of clinical examinations from specialized departments within the public health service. We had almost complete follow-up data with little risk of selection bias; our data came from concurrently registered information rather than retrospective reports. Finally, our results were unlikely to be flawed by differential misclassification of HKD because children’s care is universally available, publicly financed and organized in Finland. It is unlikely that the threshold for admission to hospital clinics is related to prenatal smoking, especially when siblings are compared.

The matched-sibling design has a number of advantages in controlling for family factors. These family factors are difficult to measure and control for in conventional cohort designs. Full siblings share social environment, but only 50% of their genes, so even these analyses will tend to overestimate the tested association. One caveat of our study is that siblings were matched on the mother’s identification number and we did not have any information regarding fathers (due to strict data protection regulations in Finland). It may be that our estimates overestimate the association and that even weaker associations would have been found if we were able to identify and exclude half-siblings.

There are limitations to the sibling design that should be mentioned. The strict control for shared family factors limits the analyses to a small subset of the population. Only sibling pairs discordant for smoking as well as HKD contribute to the estimate in these analyses. In the present study, we had 40,615 sibling pairs, which were discordant for prenatal smoking exposure, but because discordance for HKD was also needed for a pair to be informative, only 880 pairs contributed with information of the smoking–HKD association. In the adjusted stratified Cox regression model, more sibling pairs discordant for some of the other factors in the model will principally add to the estimates, but the basic concept of this type of analyses can simply be illustrated by the ratio between the informative pairs supporting and discounting the hypothesis.

Table 2: HRs for HKD according to smoking during pregnancy

<table>
<thead>
<tr>
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<th>Unmatched analyses</th>
<th>Sibling-matched analyses</th>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>n (%)</td>
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<tr>
<td>All</td>
<td></td>
<td></td>
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<tr>
<td>Non-smokers</td>
<td>733 174</td>
<td>4971 (0.7)</td>
</tr>
<tr>
<td>Smokers</td>
<td>135 275</td>
<td>2052 (1.5)</td>
</tr>
<tr>
<td>Boys</td>
<td></td>
<td></td>
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<tr>
<td>Smokers</td>
<td>69 002</td>
<td>1727 (2.5)</td>
</tr>
<tr>
<td>Girls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smokers</td>
<td>359 100</td>
<td>685 (0.2)</td>
</tr>
<tr>
<td>Smokers</td>
<td>66 273</td>
<td>325 (0.5)</td>
</tr>
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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.
causal factor for HKD, one would expect more PAP than NAP, in fact twice as many to support the findings of most previous studies. Of the 880 pairs, 484 pairs were PAP and 396 NAP with a ratio (1.2) very close to the results of the crude Cox regression analyses shown in Table 2. When restricted to comparison between boy siblings, the PAP/NAP ratio was 1.3 (218/168), and restriction to girl siblings resulted in a ratio of 1.8 (45/25). Again the ratios are in line with the estimates for sibling-matched Cox regression analysis, and the small numbers explain the broad CIs.

As illustrated above, large register-based studies are needed to gain valid estimates from sibling analyses. In this type of register, the information on smoking is collected routinely, but the smoking information is quite crude. The crude smoking information limits our ability to estimate effect of timing and dose. There are, however, further potential limitations to the interpretations of our results linked to the strict selection of smoking women in the sibling analyses. As mentioned above, the sibling-matched analyses are based on a subsample of smoking women and this sample may differ from the smoking women who were not informative in the sibling analyses. We therefore compared women reporting smoking and giving birth to their first child 1987–91 according to whether they smoked in their next pregnancy. Among those who smoked in both pregnancies, 85% (95% CI 84–86%) were smoking 10 cigarettes or more in the pregnancy of the first child as compared with 71% (95% CI 70–72%) of subsequent non-smokers. This indicates that there are more heavy-smoking women among those who were unable to give up smoking in any of their pregnancies. Thus, heavy-smoking women are underrepresented in the sibling analyses and this may be part of the explanation for the attenuated estimates as compared with the regular cohort analyses.

It could further 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. Some misclassification seems likely and may be part of the explanation for the attenuation in our estimates when using sibling analyses. Women who contributed to the sibling analyses with informative siblings were characterized by having smoked in one pregnancy and by having a child with HKD. It is possible that women with HKD in the family may be more likely to under-report smoking. 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 were not able to evaluate this possibility directly, because we did not have access to detailed smoking information, but we may evaluate this potential misclassification by looking at differences in birth weight between siblings with discordant smoking exposure. The effect of antenatal smoking on birth weight is well established and 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 compared with 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, there was a reduction of 88 g (95% CI 53–123 g) in birth weight as compared with 69 g (95% CI 63–75 g) 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 serum cotinine. These findings contest the possibility that the attenuation of the association was due to more misclassification of smoking status in the informative sibling pairs.

By using an HKD diagnosis as the endpoint, we had the possibility to study the more severe phenotype. An HKD diagnosis requires hyperactivity/impulsivity as well as inattention in at least two settings and is close to the DSM-IV ADHD-combined diagnosis. Although the Finnish register contains complete information for inpatient as well as outpatient contacts in the public health system, some children are unrecognized and thus untreated or treated without contact to the hospital system. Accordingly, some cases of HKD or ADHD are undiagnosed in the hospital system, but as they are few in the general population it will have little influence on the estimation of the association in our study. Even a low sensitivity will not bias our results as long as the specificity is high, which we find likely because of the use of strict diagnostic criteria in clinical practice in Finland. Differences in referral, which in conventional studies may lead to bias, are 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 fewer 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 been reported previously. 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 interest:** None declared.
Commentary: Advent of sibling designs

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The rapidly increasing use of sibling comparisons is a welcome development in epidemiology. Although sibling designs have been used by epidemiologists since the mid-20th century, contemporary researchers are extending the range of applications, clarifying appropriate methods\textsuperscript{1} and introducing novel strategies. The proliferation of sibling studies has not been matched, however, by comparable progress towards a conceptual framework that gives coherence to the new array of approaches.

We propose that, as a starting point for a conceptual framework, a fundamental distinction be made between designs that assume a ‘stable’ vs ‘dynamic’ family context. Designs that assume a stable family context exploit the fact that siblings share stable aspects of family context as well as half their genome. In ‘sibling discordance’ studies, for example, we compare outcomes among siblings who are discordant for an exposure of interest, and we want the siblings to be as similar as possible in family context and genetic predisposition. Differences between siblings in family context are potential confounders, and, when measured (e.g. birth order), are controlled in the analyses. Influences of family members upon one another are generally disregarded. In contrast, designs that assume a dynamic family context exploit the fact that siblings and other family members influence each other in a variety of ways. In birth-order studies, for example, we compare outcomes among siblings who encounter different family contexts and may play a role in creating these contexts. Influences of family members upon one another, and the resulting changes in family context, are the topic of investigation.

We hope to show that this distinction between sibling designs based on stable vs dynamic family context is readily understood, broadly applicable to traditional as well as novel approaches, and useful as a starting point. To this end, we portray a range of recent sibling studies, and consider them within this framework. Our overarching goal is to stimulate others to further elaborate the conceptual underpinnings of sibling designs.

\textbf{Sibling designs based on stable family context}

Since the sibling discordance study is probably the most widely used sibling design, we use it to characterize designs based on stable family context. The power of this approach resides in its ability to vary one aspect of the environment while keeping so much else similar. Although sibling discordance studies can be traced to the 19th century,\textsuperscript{2} rigorous use of the design began after World War II. In the 1960s, Record et al.\textsuperscript{3,4} applied it to control familial confounding in their studies of the relation of birthweight to offspring verbal reasoning scores on school examinations. This remarkable work set an early precedent...