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# Smoking during pregnancy and risk of Autism Spectrum Disorder in a Finnish National Birth Cohort

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## Abstract

**Background—**Results of previous population-based studies examining associations between smoking during pregnancy and autism spectrum disorders (ASD) are contradictory. Furthermore, there is a lack of population-based studies examining the relationship between smoking during pregnancy and the main diagnostic subtypes of ASD.

**Methods—**We conducted a population-based nested case-control study based on the Finnish Prenatal Study of Autism (FIPS-A) among live-born infants delivered in Finland between 1987-05. Data on maternal smoking during pregnancy was available from the Finnish Medical Birth Register (FMBR) since October 1990. Data on ASD in the offspring was obtained from the Finnish Hospital Discharge Register (FHDR).

**Results—**Among the three subtypes of ASD, maternal smoking during the whole pregnancy was associated with an increased risk of pervasive developmental disorder (PDD) (odds ratio 1.2, 95% confidence interval 1.0, 1.5). The increase in odds persisted after controlling for maternal age, mother's socioeconomic and psychiatric status, and infant's weight for gestational age. However, smoking exposure limited to the first trimester was not associated with PDD or any of the other ASD subtypes.

**Conclusions—**Maternal smoking is related to a modest increase in risk of PDD, while no associations were observed for childhood autism and Asperger's syndrome.

### Keywords

Maternal smoking; Autism Spectrum Disorders; childhood autism; Asperger's syndrome; pervasive developmental disorders; fetal; risk factors; epidemiology

Smoking during pregnancy has been associated with numerous adverse cardiovascular, respiratory,[1,2] endocrine, and metabolic outcomes in the offspring.[3]Maternal smoking is also a risk factor for several neurodevelopmental disorders, including attention-deficit/ hyperactivity disorder[4], conduct disorder[5] and antisocial behaviour.[6,7]

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There are six population-based studies that have examined the association between maternal smoking during pregnancy and autism spectrum disorders (ASD) (Table 1). The results are contradictory. A Swedish study by Hultman et al.[8] found a mild association between smoking during pregnancy and the risk of childhood autism whereas the two Danish studies[9,10] did not report similar associations. In all three studies the outcome was defined as childhood autism. The two studies in which the outcome was defined as "any ASD"[11,12] also yielded contradictory findings. Finally, in a study including 72 cases with childhood autism, Asperger's and Tourette's syndrome, there was a positive association with smoking.[13]

Table 1 reveals significant heterogeneity among study designs, which complicates the comparison of results between different studies. First, the previous epidemiological studies are limited by the size of the study groups, from as low as 72 to as high as 698 autism cases. Smaller sample sizes diminish statistical power to test the associations between smoking and ASD outcome. Second, data on smoking were collected either retrospectively, which increases the risk of maternal recall bias, or was ascertained at the beginning of the pregnancy, rather than throughout pregnancy. Therefore previous studies on smoking are limited to first trimester exposure. Third, the case definition for autistic disorders was relatively broad, including the whole ASD group or different subtypes of diagnoses. Thus, it is unclear whether the associations between maternal smoking and ASD differ by diagnostic subtype.

According to the International Classification of Diseases, 10th Revision (ICD-10), childhood autism, Asperger's syndrome and other pervasive developmental disorders/ pervasive developmental disorder, unspecified (PDD) belong to the broader category of pervasive developmental disorders.[14] This group is characterized by qualitative abnormalities in reciprocal social interactions and patterns of communication, and a restrictive, stereotyped, repetitive repertoire of interests and activities. Childhood autism, the most severe disorder of the three subtypes, is diagnosed based on impaired development in all three of these domains, with onset by the age of three years. About 75% of these cases have significant cognitive problems or are affected by mental retardation.[15,16] Asperger's syndrome differs from childhood autism based on the absence of a delay in language development and cognitive functioning. PDD is somewhat less well defined; a child with PDD is likely to have developmental delays in several basic domains of functioning including learning, communication, and socialization skills. A diagnosis of PDD may be used when a child does not meet criteria for childhood autism or Asperger's syndrome.

This study addresses several limitations of the previous studies by employing a large, national, population-based sample. The first aim is to investigate the association between smoking during pregnancy and ASD subtypes (childhood autism, Asperger's syndrome, PDD). The second aim is to explore whether the associations are different if smoking is limited to, or continued after, the first trimester.

## METHODS

### Study design

This nested case-control study is based on the Finnish Prenatal Study of Autism and Autism Spectrum Disorders (FIPS-A) for which a full description of the study design and sources of data is available[14]. The FIPS-A aims to identify risk factors for autism spectrum disorders in all live births in Finland from 1990 to 2005 and who were followed up for ASD until 2007. Data on smoking during first trimester and later pregnancy was available from October 1990. This study was authorised by the Ministry of Social Affairs and Health in Finland (STM/2593/2008) with the approval from the ethics committee of the Hospital District of

Southwest Finland and the National Institute for Health and Welfare, and approved by the New York State Psychiatric Institute Institutional Review Board.

## Nationwide registers

The FIPS-A relies upon linkages between national registers, including the Finnish Hospital Discharge Register (FHDR) and the Finnish Medical Birth Register (FMBR), using a personal identity code provided for each Finnish citizen born in or outside Finland. The code remains unchanged throughout the person's lifetime and is unique for each person.

The FHDR was used for the identification of ASD cases. This registry covers all specialized treatment in inpatient settings since January 1967 and outpatient settings since January 1998. The registry includes the primary diagnosis at discharge, together with three possible subsidiary diagnoses. In a diagnostic validation study, we demonstrated that 96% of registry-based childhood autism diagnoses fulfill diagnostic criteria of the Autism Diagnostic Interview-Revised (ADI-R).[17]

The FMBR was established in January 1987 in order to provide information for research, maternity, obstetrics, and newborn care, and includes standardized data on pregnancy, the prenatal period, and the neonatal period up to age 7 days on all births in Finland (less than 0.1% of the births are missing).

## Autism Case identification

All ASD cases diagnosed during the follow-up period were identified from the FHDR by ICD criteria. In Finland, access to special health care services is available for all citizens and is free of charge. The case definition in the present study included diagnoses of Childhood Autism (F84.0), Asperger's Syndrome (F84.5), and Other Pervasive Developmental Disorder (F84.8)/Pervasive Developmental Disorder Unspecified (F84.9) (PDD) and other rare diagnoses belonging to the ASD category, such as Rett's syndrome, disintegrative disorder, atypical autism etc. In this study, we combined F84.8 and F84.9 and refer to it as PDD. The most recent register diagnosis was used for classification. The children born between October 1990 and December 2005 included 4,148 ASD cases and 16,582 controls. However, in 71 cases the social security number could not be linked with the registries. There were 397 individuals who were missing data about smoking among the controls, and 128 among the cases, resulting in 4019 ASD cases and 16,123 controls. Among these cases, 94% of all ASD cases belonged to one of the following three subtypes: childhood autism (960 subjects), Asperger's syndrome (1,328), and PDD (1,484). Rare diagnostic categories were not examined separately due to small sample sizes.

Controls were defined as offspring from the FMBR who were without ASD or severe/profound mental retardation according to the FHDR. Each case was matched to four controls on date of birth, gender, and residency in Finland at the time of birth. One to four matching was based on power calculations reported in our previous paper describing the design and methods of FIPS-A study.[14] If the birth place was a very small community and a control could not be found, the first option was to match by birth hospital and the second by a regional hospital district.

## Exposure to maternal smoking

Information about smoking during pregnancy was obtained from the FMBR. These data were collected by maternity clinic nurses during routine obstetric visits, and documented in health records, which are subsequently forwarded to the hospital in which the delivery takes place. These data are transferred to a standardized form in use by the FMBR by hospital staff. From October 1990 onwards, the information about the smoking has four categories:

"no smoking" (reference group), "quit smoking during the first trimester", "smoking throughout the whole pregnancy" and "information not available".

### Covariates

Four potential confounding factors were included in the analyses: maternal age at birth, maternal socioeconomic status (SES), and infant's weight for gestational age (WGA), all derived from the FMBR, and maternal psychiatric diagnosis, issued from the FHDR. These confounding factors were included in the analyses because of their strong association both with ASD in the offspring and smoking during pregnancy both in literature and in the present sample as shown in Table 2.[13,18,19]

Maternal age at birth was classified as: ≤ 19 years old, 20-34 (reference), 35-39, and ≥ 40 years old. Maternal psychiatric diagnosis before childbirth was classified as a dichotomous variable (present, absent), and included at least one of the following hospital diagnoses: in ICD 9: 291-316 (nonorganic psychoses, neurotic and personality disorders and other non-psychotic mental disorders), excluding 293-294, in ICD 10: F10-F99 (psychoactive substance use, schizophrenic disorders, mood disorders, neurotic and somatoform disorders, disorders of adult personality and behavior, disorders of psychological development, disorders with onset usually occurring in childhood and adolescence, unspecified mental disorder), excluding F70-F79 (these excluded diagnoses in both classifications refer mainly to organic disorders). Maternal SES was determined via a computer program (using SAS and SQL software) used to transform the occupation name (or the highest education level) into a socioeconomic grouping. Both codings were based on national standards by Statistics Finland. If only the highest education level was given instead of an occupation name, education was converted into a socioeconomic group according to the national classification on education. The categories included: upper white collar, blue collar worker, lower white collar worker and others (e.g.: students, retired, unemployed). More detailed information about SES classification in this registry has been reported previously.[20] Finally, infant WGA was estimated according to Finnish birthweight standards and was categorized into three groups: small for gestational age (SGA, <−2SD), appropriate for gestational age (AGA, −2SD to +2SD), and large for gestational age (LGA, >+2SD).

### Statistical Analyses

Conditional logistic regression was used to examine the association between the ASD outcome and maternal smoking.[21] Unadjusted odds ratios (OR) and 95% confidence intervals (CI) were first calculated for the whole ASD group, then separately for each ASD subtype. Afterwards, the ORs were adjusted separately for each covariate: maternal age at birth, maternal psychiatric diagnosis, maternal SES and infant WGA. The final model included all of these covariates. In all analyses, a two-sided p-value of <0.05 was considered statistically significant. The population attributable risk (PAR) was calculated according to this cohort. The sensitivity analysis was accomplished by simulation of missing data in maternal smoking. The simulation and the final model were applied separately for each ASD subtype with statistically significant ORs. Statistical analyses were performed with SAS statistical software (Version 9.2; SAS Institute Inc., Cary, NC).

## RESULTS

Table 3 depicts the results for the outcome defined as the entire ASD group (including all ICD-10 F84 cases). Among ASD cases 1.9% of mothers smoked only during the first trimester and 16.0% continued during the whole pregnancy, while the respective figures for the control group were 1.7% and 14.3%. Maternal smoking limited to the first trimester was not associated with ASD status. In crude analyses, maternal smoking during all pregnancy

was weakly associated with offspring's ASD status (OR= 1.1 [95% CI: 1.0–1.3]), although adjustments for confounding factors attenuated the association to the null.

The associations between maternal smoking and the three ASD subtypes (childhood autism, Asperger's syndrome, PDD) are shown in Table 4. Smoking during the whole pregnancy was associated with offspring PDD in individual adjustment for maternal age, psychiatric history, SES and WGA. Furthermore, the association remained significant in the final model including all these covariates. Among PDD cases, 19.0% of mothers continued smoking after the first trimester, while the respective frequency for the control group was 14.2%. The population attributable risk of smoking during pregnancy and having PDD offspring was 2.3%.

As illustrated in Table 4, there is no association between smoking and childhood autism or Asperger's syndrome.

## COMMENT

This is the first population-based study to examine the relationship between smoking during pregnancy and the three main diagnostic subtypes of ASD, namely childhood autism, Asperger's syndrome, and PDD. The main finding is that women who continued smoking during the whole pregnancy had a 20% increased odds of having a child later diagnosed with PDD, after controlling with the effect of maternal age, socioeconomic status, psychiatric history, and infant's WGA. However, smoking restricted to the first trimester was not associated with PDD. While previous studies yielded contradictory results regarding ASD no previous population-based study has reported that smoking is specifically associated with PDD. Smoking during pregnancy was not independently associated with childhood autism or Asperger's syndrome. Our results are consistent with the reports by Maimburg[9] and Larsson[10] showing no association between smoking and childhood autism.

There are several hypotheses which may explain the association between prenatal exposure to smoking and PDD. First, in animal studies, nicotine has been established to be a neuroteratogen, which compromises the development of critical neural pathways in the developing brain.[22,23] Nicotine mimics the neurotransmitter acetylcholine that normally acts as a differentiation signal during nervous system development via its actions on nicotinic acetylcholine receptors. A second explanation is that cigarette smoking acts to increase risk of PDD by causing infarcts and calcifications in the placenta and uteroplacental vasoconstriction. This can result in intrauterine growth restriction, which, in turn, is correlated with a host of neuropsychological developmental delays.[24] Third, women with a predisposition to mental health and behavioral problems have a higher tendency to smoke during their pregnancy.[25] Continuation of smoking after being aware of pregnancy may particularly be associated with psychosocial problems. The transmission of genetic risk may partly explain the association between prenatal smoking exposure and offspring's increased risk for neurodevelopmental disorders.[25] Surely these mechanisms have been suggested in relation to neurological defects in general but they may try to explain a part of the association between smoking and PDD, and further studies should be conducted to confirm it.

Previous studies have identified maternal smoking during pregnancy as a risk factor for ADHD.[26,27] Some other studies have shown that 40 to 50% of PDD children meet symptom criteria for at least one DSM-IV subtype of ADHD.[28] Indeed, Barkley[29] and Jensen et al.[30] reported that it was common for the children with PDD to be initially given, at an early age, a diagnose of ADHD. There is a lack of studies comparing the rates of psychiatric comorbidity between different ASD subtypes. Because ASD is an exclusive diagnose we did

not have any registry-based information about the proportion of ASD cases who would possibly fulfill criteria of ADHD. Moreover, the present study cannot address the following question, could the association between smoking and PDD be caused by an underlying association between smoking and ADHD, and the misclassification that "PDD" is actually ADHD for a proportion of the children. Alternatively, there might be some genetic/epigenetic overlap between ADHD and PDD.[31] Note that childhood autism and Asperger's syndrome are also reported to have higher rates of ADHD compared with the general population, but in this study they were not associated with maternal smoking during pregnancy. Future research on the interactions between genetic and environmental factors[32] of ASD and its subtypes is warranted to understand the specific association between maternal smoking and PDD.

There are several limitations to be considered when interpreting the study findings. First, smoking data were acquired by self-report of mothers and the amounts of tobacco smoked during the pregnancy are not known. We do not have information neither about post-natal tobacco exposure. However, the FIPS-A will include assays of archived sera for cotinine, a nicotine metabolite, from each pregnancy. In the future, the amount of cotinine in sera will provide an objective measure of smoking, at least during the last week before the blood collection, and may allow us to establish a possible dose-response relationship between smoking during pregnancy and PDD. For an even better quantification of smoking, future studies should consider measurements of metabolites in meconium or in mothers' hair.

Second, information about maternal mental health was restricted to data on psychiatric treatment in specialized services. The independent association between maternal smoking and PDD was present when mothers continued smoking during the whole pregnancy, i.e. even after they knew that they are pregnant. To continue smoking during pregnancy might be a sign of a strong addiction to nicotine, or a personality characteristic, that in turn might be a risk factor for psychiatric problems in the offspring. In addition to that, no information about alcohol or other substance use was available in the birth register. The co-morbidity of other addictive behaviors in pregnant women who smoke during pregnancy has been documented by the National Institute on Drug Abuse.[33] Hence, our finding of the association between PDD and maternal smoking should be interpreted cautiously.

Third, information about ASD was based on nationwide registries. We do not know the proportion of ASD cases that also fulfill criteria of ADHD, an important question given comorbidity between these two disorders. Fourth, register data on average number of cigarettes smoked per day was not available.

Finally, the present study does not provide definite answer why smoking during pregnancy is associated specifically with PDD but not with childhood autism or Asperger syndrome. However, the findings may shed light on the etiology of PDD. Further studies on maternal smoking and its association with other environmental as well as genetic factors are needed.

## CONCLUSIONS

The finding showing an association between maternal smoking and PDD adds to mounting evidence that smoking during pregnancy may be associated with childhood neurodevelopmental disabilities. Maternal smoking continued during the whole pregnancy was specifically associated with PDD, but not with childhood autism or Asperger's syndrome. Strategies for the prevention of smoking during pregnancy need to be reinforced, since the rate of smoking mothers is still alarmingly high, in the range of 12-36% according to studies from the Nordic countries, the UK, and the USA.[34-36]

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## Table 1

A Review of Previously Published Population-based Studies of Smoking During Pregnancy and ASD in the Offspring.

| Author/ year/ country | Design | Measurement of exposure | Outcome | Covariates | Subjects | Association? |
|---|---|---|---|---|---|---|
| Ronald et al (11) 2010 England & Wales | population-based twins born 1994-1996 | retrospective, self-report : "How much did you smoke during pregnancy?" | ASD (DSM-IV-TR,CAST, DAWBA) | SES & child general cognitive ability | cases (n=154), remaining cohort (n=6771 × 2 twins) | YES correlation r = .03–.10 p<.01 |
| Larsson et al (13) 2009 Sweden | population-based cohort study born 1994-1999, | retrospective, self-report : smoking? No/ Yes but stopped/ Yes | parental questionnaire (Autism, asperger or Tourette's syndrome) | type of flooring in the bedrooms of the home | cases (n=72) remaining cohort (n= 4779) | YES OR = 2,09 (1,08- 4,03) |
| Bilder et al (12)2009 Utah, USA | population-based case- control study born 1994 | | ASD (DSM-IV-TR) | Not reported | cases (n=132) controls * (n=13200) | NO OR = 0,506 (0,222-1,152) |
| Maimburg et al (9) 2006 Denmark | population-based case-control study born 1990-1999 | self-report to midwives at the first antenatal visit generally at 12 weeks : smoking? Yes/No | infantile autism (ICD 8 or 10) | maternal & paternal age, mothers citizenship, BW & GA, Apgar score, birth defect & irregular fetal position | cases (n= 473) controls * (n= 4730) | NO adjusted OR = 0.9 (0.7–1.4) |
| Larsson et al (10)2005 Denmark | population-based nested case-control study born 1973-1999 | self-report at 1st antenatal visit : smoking? Yes/No | infantile or atypical autism (ICD-8 or 10) | perinatal risk factors, parental psychiatric history, and SES | cases (n=698) Controls * (n= 17450) | NO RR = 1,06 (0,80-1,39) |
| Hultman et al (8) 2002 Sweden | population-based nested case-control study born 1974-1993 | self-report to midwives at registration for antenatal care : daily/nondaily smoking | infantile autism (ICD-9) | maternal demographic factors, delivery and infant factors(BW, weight for gestational age) | cases (n= 408) controls * (n= 2040) | YES adjusted OR = 1,4 (1,1-1,8) |

ASD = autism spectrum disorder; DSM = Diagnostic and Statistical Manual of Mental Disorders ; ICD = International Classification of Diseases ; CAST = childhood Asperger syndrome test ; DAWBA = diagnostic and wellbeing assessment ; OR = odds ratio ; RR = relative risk ; BW = birthweight ; GA = gestational age

* controls were matched for gender, year of birth +/− place of birth

## Table 2

Covariates in relation to Smoking During Pregnancy in controls and in relation to risk of Autism Spectrum Disorders (ASD).

| | Relationship between covariates and Smoking during pregnancy | | | | Relationship between covariates and ASD |
|---|---|---|---|---|---|
| | No smoking, n (%) | Only 1st trimester, n (%) | All pregnancy, n (%) | p | p |
| Maternal age | | | | <.0001 | <.0001 |
| 19 years or under | 173 (1.3) | 24 (8.9) | 101 (4.4) | | |
| 20–34 years | 10950 (80.6) | 214 (79.0) | 1852 (79.8) | | |
| 35–39 years | 2009 (14.8) | 28 (10.3) | 296 (12.8) | | |
| 40 years or over | 460 (3.4) | 5 (1.9) | 73 (3.1) | | |
| Maternal mental diagnosis | | | | <.0001 | <.0001 |
| No | 13341 (98.4) | 258 (95.2) | 2193 (94.6) | | |
| Yes | 215 (1.6) | 13 (4.8) | 125 (5.4) | | |
| Maternal SES | | | | <.0001 | 0.004 |
| Upper white collar workers | 2300 (18.4) | 18 (7.4) | 111 (5.2) | | |
| Lower white collar workers | 5864 (46.8) | 104 (42.5) | 802 (37.9) | | |
| Blue collar workers | 2217 (17.7) | 78 (31.8) | 761 (36.0) | | |
| Others | 2141 (17.1) | 45 (18.4) | 443 (20.9) | | |
| Weight for gestational age | | | | <.0001 | 0.0009 |
| SGA | 204 (1.5) | 11 (4.1) | 88 (3.8) | | |
| AGA | 12910 (95.2) | 250 (92.3) | 2180 (94.1) | | |
| LGA | 452 (3.3) | 10 (3.7) | 48 (2.1) | | |

*)SGA=small for gestational age, AGA=appropriate for gestational age, LGA=large for gestational age

## Table 3

Association Between Smoking During Pregnancy and Autism Spectrum Disorders (ASD). Results of Logistic Regression Analyses

| | Distribution | | Unadjusted | Multivariable analysis |
|---|---|---|---|---|
| | Cases, n (%) | Controls, n (%) | OR (CI 95%) | |
| No smoking (reference) | 3,300 (82.1) | 13,592 (84.0) | 1.0 | 1.0 |
| Only 1st trimester | 75 (1.9) | 271 (1.7) | 1.1 [0.9 , 1.5] | 1.0 [0.7 , 1.3] |
| All pregnancy | 645 (16.0) | 2,322 (14.3) | 1.1 [1.0 , 1.3] | 1.0 [0.9 , 1.2] |

OR = odds ratio; CI = confidence interval

Multivariable analysis included all covariates: maternal age, maternal mental diagnosis, socioeconomic status and weight for gestational age.

## Table 4

Association Between Smoking During Pregnancy and ASD Subtypes : Childhood Autism, Aspergers's Syndrome, and Pervasive Developmental Disorder (PDD). Results of Logistic Regression Analyses

| | Distribution | | Unadjusted | Multivariable analysis |
|---|---|---|---|---|
| | Cases, n (%) | Controls, n (%) | OR (CI 95%) | OR (CI 95%) |
| Childhood Autism | | | | |
| No smoking (reference) | 790 (82.3) | 3,220 (83.0) | 1.0 | 1.0 |
| Only 1st trimester | 19 (2.0) | 74 (1.9) | 1.0 [0.6 , 1.7] | 0.9 [0.5 , 1.6] |
| All pregnancy | 151 (15.7) | 584 (15.1) | 1.0 [0.9 , 1.3] | 0.9 [0.8 , 1.2] |
| Asperger's syndrome | | | | |
| No smoking (reference) | 1,140 (85.8) | 4,497 (84.2) | | |
| Only 1st trimester | 26 (2.0) | 89 (1.7) | 1.1 [0.7 , 1.8] | 1.2 [0.7 – 1.9] |
| All pregnancy | 163 (12.2) | 751 (14.1) | 0.9 [0.7 , 1.0] | 0.9 [0.7 , 1.1] |
| PDD | | | | |
| No smoking (reference) | 1,176 (79.3) | 5,043 (84.4) | 1.0 | 1.0 |
| Only 1st trimester | 26 (1.7) | 83 (1.4) | 1.3 [0.8 – 2.1] | 0.9 [0.5 , 1.6] |
| All pregnancy | 282 (19.0) | 851 (14.2) | 1.4 [1.2,1.6] | 1.2 [1.04 , 1.5] |

OR = odds ratio; CI = confidence interval