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Maternal smoking during pregnancy and risks of suicidal acts in young offspring

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Abstract

Obstetric and neonatal complications have been associated with completed and attempted suicide (suicidal acts) in young offspring. Maternal smoking is one of the most important risk factors for obstetric complications, but the association between prenatal smoking exposure and offspring risk of suicidal acts is unknown.

We performed a population-based study of 1 449,333 single births born in Sweden between 1983 and 1996, derived from linked registry data. Maternal smoking and risks of suicidal acts in offspring were estimated using hazard ratios, derived from proportional-hazard models, controlling for potential confounding of parental socio-demographic factors and psychiatric care in first degree relatives. To control for unmeasured familial confounding, a matched case-control analysis of suicidal acts was performed within sibling pairs discordant for prenatal smoking exposure.

In the cohort analysis, the adjusted hazard ratio for completed suicide among offspring to women smoking 1-9 cigarettes and at least 10 cigarettes per day were 1.67, 95% confidence interval (CI), 1.29- 2.16, and 1.54, 95% CI, 1.12- 2.10. For suicidal acts, corresponding hazard ratios were 1.28, 95% CI 1.21- 1.35 and 1.48, 95% CI 1.39- 1.57, respectively.

However, in sibling pairs discordant for suicidal acts and prenatal smoking exposure, we found no evidence that prenatal smoking exposure increased the risk of suicidal acts. We conclude that the association between prenatal smoking exposure and offspring risk of suicidal acts is probably confounded by unmeasured familial factors.

Word count: 230

Key words pregnancy, prenatal, psychiatry, smoking, suicide.

Introduction

Each year, there are around 1 million completed suicides in the world. According to the WHO statistics, suicide is now one of the three leading causes of deaths among adolescents and young adults [1]. Psychiatric disorders are commonly present in suicide victims or suicide attempters [2], including adolescent and young victims [3]. Both suicides and psychiatric disorders have strong hereditary components [4, 5], but there are evidence for a familial clustering of suicidal acts even after psychiatric disorders have been taken into account [6].

Obstetric and neonatal complications may have a long-term influence on offspring mental health, including risks of schizophrenia [7], depression [8], and suicidal acts [9-12]. Maternal smoking has been recognized as one of the most important risk factors for adverse pregnancy outcomes, including placental complications, fetal growth restriction, preterm birth and associated conditions [13]. Women with mental disorders are more often smokers than women without such disorders [14]. Thus, compared with offspring of women without mental disorders, offspring of women with mental disorders are more likely to be prenatally exposed to smoking [15]. We are unaware of any study investigating if prenatal smoking influences offspring risks of suicidal acts. Prenatal smoking exposure may have a long-term influence on offspring serotonin metabolism. Chronic nicotine exposure reduces serotonin metabolism in animals [16], smokers have reduced serotonin levels in the cerebrospinal fluid [17], and reduced serotonin levels is associated with increased risks of suicidal acts [18]. Using a large population-based data set, we studied the association between maternal smoking during pregnancy and risk of completed suicide and suicidal acts in young offspring after taking family history of psychiatric diseases into account. To account for residual family

confounding, we also studied risks of suicidal acts in sibling pairs discordant for suicidal acts and prenatal smoking exposure.

Subjects and Method

Data sources

This cohort study is based on linkage of population-based registers from the Swedish National Board of Health and Welfare and Statistics Sweden. Individual record linkage across these registers was possible through the individually unique national registration number, assigned to each Swedish resident.

The Medical Birth Register includes information on 98 to 99% of all deliveries in Sweden.[19] Starting with the first antenatal visit (generally at 8 to 12 gestational weeks), information is prospectively collected on standardized antenatal, obstetric and neonatal records. Copies of these records are forwarded to the Medical Birth Register after delivery. Self-reported information on maternal smoking at the first visit to antenatal care has been collected since 1983, using checkboxes for non-daily smoking, 1 to 9 cigarettes per day and at least 10 cigarettes per day, respectively.

The Multigeneration Register contains information on children born in Sweden since 1932 and their parents [20]. This registry was used to identify fathers, full and half siblings. The Hospital Discharge Register provides a nation-wide coverage on hospital discharges and diagnoses for psychiatric care determined by the treating physician since 1973 [21]. The

Cause of Death Register contains the date and cause of death on all Swedish residents. The completeness has been estimated to exceed 99% [22]. Diseases and causes of death in the Medical Birth-, Hospital Discharge- and Cause of Death Registers are classified according to the International Classification of Diseases (ICD). The Education Register provides information on highest attained educational level for all Swedish residents [23]. The National Population Register includes dates of death and migration. The study was approved by the research ethics committee at Karolinska Institutet (Stockholm, Sweden).

Outcomes

All individuals surviving until their tenth birth day were followed up with respect to completed determined or undetermined suicide or attempted suicide (ICD-9 codes E950-E959 and E980-E989; ICD-10 codes X60-X84 and Y10-Y34), as recorded in the Cause of Death Register and the Hospital Discharge Register, respectively.

Exposures

From the Birth Register, we retrieved information on maternal smoking and living or not living with the father-to-be at registration to antenatal care (yes/no), mother's age at delivery, parity, mother's country of birth, pregnancy complications (hypertensive diseases [ICD-8 code 637 and ICD-9 code 642] and placental abruption [ICD-8 codes 632.1 and 651.4 and ICD-9 code 641C]), mode of delivery, sex of infant, gestational age, birth weight, birth length and head circumference. Gestational age was based on the last menstrual period, since early ultrasound investigations to date pregnancies were not in regular use. If information about the last menstrual period was lacking, we used information about early second trimester

ultrasound, when available. Birth weight- birth length-, and head circumference- for gestational age were standardized according to the Swedish birth weight-, birth length-, and head circumference standards [24], and expressed in standard deviation scores (SDS). Information about paternal age at delivery was retrieved from the Multigeneration Register and information about mother's education was retrieved from the Education Register in 1995.

Information about inpatient psychiatric care for the study population and their first degree relatives (parents, full and half siblings) was derived from the Hospital Discharge Register. For both study subjects and first degree relatives, such information was dichotomized into having received inpatient care for a mental disorder or not (ICD-8 or ICD-9 codes 290-315 and ICD-10 codes F00-F99). For first degree relatives, we also collected information from the Hospital Discharge and Cause of Death Registers of attempted and completed suicide (ICD-8 and ICD-9 codes E950-959 and E980-989; ICD-10 codes X60-X84 and Y10-Y34). We only included information about psychiatric care and suicidal acts of relatives up to the time of suicidal act of the study subjects.

Statistical Analyses

The study base included 1 449,333 singletons born from 1983 through 1996, who survived until their tenth birth day. Risk time (person-years) was accrued from the time of the 10th birth day until completed suicide or time for first suicidal act (also including attempted suicide), or censored at the date of first emigration from Sweden, death from another cause, or December 31, 2007.

We used Cox proportional hazard regression models to evaluate associations of maternal smoking with respect to suicidal acts by estimating hazard ratios with 95% confidence intervals (CI). All applied models were stratified by birth year cohort and sex, implying adjustment for sex, attained age and calendar year of follow-up. For completed suicide, we calculated hazard ratios for the following variables: maternal smoking, maternal and paternal age at delivery, parity, living with the father-to-be or not, mother's country of birth, mother's education, complications during pregnancy (hypertensive diseases and placental abruption), mode of delivery, gestational age, birth weight for gestational age (Table 1), and for inpatient psychiatric care and suicidal acts among relatives as time-dependent co-variables (Table 2).

In multivariate models of the effects of maternal smoking and risks of completed suicide or suicidal acts, we further adjusted for parental characteristics, including maternal and paternal age at delivery, parity, living with infant's father or not at delivery, mother's education and mother's country of birth. In separate analyses, we also adjusted for first occurrence of either inpatient care for psychiatric disorders or suicidal acts in first degree relatives (i.e., mothers, father or siblings).

We also wanted to investigate two possible pathways for an association between maternal smoking and risks of completed suicide and suicidal acts. First, to investigate whether a possible association was mediated by pregnancy or birth characteristics, we adjusted for hypertensive diseases, placental abruption, mode of delivery, gestational age, and birth weight for gestational age. Second, to investigate whether a possible association was mediated by offspring psychiatric disease, we censored subjects at the time for their first admission to psychiatric care. In both these analyses, we also adjusted for parental characteristics and for

previous in-patient care for psychiatric diseases or suicidal acts in first degree relatives. All adjustment variables were categorized as presented in Tables 1 and 2.

Finally, in order to control for familial confounding, we performed a sib-pair analysis on maternal smoking and risk of suicidal acts. A Cox' regression model stratified on maternal identity numbers was used to estimate the effect of maternal smoking during pregnancy on the risk of suicidal act among the first and second sibling. In order to estimate the effect of smoking, this analysis only utilizes the sibling pairs that are discordant for maternal smoking during pregnancy and where at least one of the sibs has an event. The time scale used is attained age starting at the age of 10. This implies that only pairs where the unaffected sib is under observation at the age of the other sibling's suicidal act are informative. Potential confounders in this analysis were sibling order, calendar time at follow-up, and sex. When estimating the effects of these potential confounding factors, pairs concordant for maternal smoking are also informative. Thus, in the adjusted model, we included all sibling pairs discordant for suicidal acts, and adjusted for sibling order, sex and birth year cohort as categorical variables. Effect modification of sex and attained age, categorized by below 18 years and from 18 years of age, were tested by likelihood ratio tests. The estimated effects are presented as hazard ratios with 95% confidence intervals. All analyses were performed by SAS[®] version 9.2.

Results

In the cohort of 1 449,333 singletons born from 1983 through 1996, who survived until their tenth birth day, 374 committed suicide during the time of follow-up, of whom 322 were assessed as determined and 52 as undetermined suicides.

Compared with offspring to non-smokers, both offspring to moderate and heavy smokers were at increased risk of completed suicide (Table 1). Other parental factors associated with an increased risk of suicide in offspring were teenage parenthood, if the mother was not living with the father-to-be in early pregnancy, and if the mother was born in another Nordic country (i.e., Denmark, Finland, Iceland or Norway). Offspring to mothers with medium-high (13 to 14 years) education and to mothers giving birth at 30 to 34 years were at reduced risk of suicide. Compared with females, males had an increased risk of suicide, but other birth or pregnancy characteristics did not influence risk. There were no associations between birth length- or head circumference for gestational age and risk of suicide (data not shown).

Table 2 shows risks of completed suicide with respect to in-patient psychiatric care and suicidal acts in first degree relatives. If a first degree relative previously had been hospitalized for a psychiatric disorder or performed a suicidal act (attempted or completed suicide), the risk of completed suicide among study subjects was generally substantially increased.

Compared with offspring to non-smoking mothers, the risk of completed suicide was increased by around 80% among offspring to smokers after adjusting for parental characteristics (Table 3a). When we also adjusted for previous psychiatric history and suicidal acts among first degree relatives, these risk estimates were reduced. We used identical analyses to analyze maternal smoking during pregnancy and offspring risk of suicidal acts (i.e., completed or attempted suicide), including 350 offspring with completed suicide and 8,060 offspring with attempted suicide and information on maternal smoking (Table 3b).

There was a dose-response relationship between amount smoked and risks of suicidal acts, but

these risks were reduced when we also adjusted for previous psychiatric history and suicidal acts among first degree relatives.

Next, we wanted to investigate possible mediating factors for the association between maternal smoking and offspring risk of completed suicide or suicidal acts. First, we investigated whether the smoking-related risks were mediated by smoking-related pregnancy and birth complications. However, after adjusting for such complications, there was no attenuation in the smoking-related risks of completed suicide (adjusted hazard ratios for 1-9 cigarettes and ≥ 10 cigarettes per day were 1.67 [95% CI: 1.28, 2.17] and 1.53 [95% CI: 1.12, 2.10], respectively) or suicidal acts (adjusted hazard ratios for 1-9 cigarettes and ≥ 10 cigarettes per day were 1.29 [95% CI: 1.22, 1.36] and 1.50 [95% CI: 1.41, 1.59], respectively). Second, to investigate whether the association was mediated by psychiatric diseases in study subjects, we censored subjects admitted to psychiatric care at the date of their first admission. Of individuals with no previous admission for psychiatric care, there were in all 280 individuals with completed suicide and 7,291 individuals with suicidal acts, respectively. After censoring subjects admitted to psychiatric care, we found that the smoking-related risks remained increased: for completed suicide, the adjusted hazard ratios for 1-9 cigarettes and ≥ 10 cigarettes per day were 1.81 (95% CI: 1.34, 2.43) and 1.38 (95% CI: 1.09, 2.03), respectively, and for suicidal acts, corresponding adjusted hazard ratios were 1.28 (95% CI: 1.20, 1.36) and 1.50 (95% CI: 1.40, 1.59), respectively.

Finally, in order to control for familial confounding, we analyzed the influence of maternal smoking on suicidal acts in sibling pairs. In 334,505 sibling pairs, there were 396 sibling pairs who were discordant for suicidal acts (12 completed suicides and 384 suicide attempts) and

for maternal smoking (Table 4). Of cases, 37.1% were non-exposed to maternal smoking during pregnancy, while corresponding rate among sibling controls was 38.1%. Cases and sibling controls also had similar rates of prenatal exposure to moderate (30.1% in cases and 28.5% in controls) and heavy smoking (8.1% in cases and 8.6% in controls). In the sibling case-control analyses, prenatal smoking exposure was not associated with increased risks of suicidal acts (Table 4). There was no interaction between maternal smoking and offspring sex or attained age with respect to risks of suicidal acts ($P=0.25$ and $P=0.30$, respectively). Thus, in the sibling analysis, there was no association between maternal smoking and risk of suicidal acts in neither boys nor girls, and no association between maternal smoking and suicidal acts below 18 years or from 18 years and onwards (data not shown).

Discussion

In this nation-wide study, we initially found that maternal smoking during pregnancy was associated with increased risks of completed suicide and suicidal acts in young offspring. These risks were reduced when we adjusted for effects of family history of psychiatric disorders and suicidal acts requiring inpatient care. However, using data on hospital admissions for such diagnoses does not allow us to capture the effect of family history of psychiatric illness or psychopathology not requiring inpatient care. In analysis within sibling pairs, we found no association between prenatal smoking exposure and risk of suicidal acts in offspring. This suggests that the association between prenatal smoking exposure and risk of suicidal acts obtained in the cohort analysis is explained by unmeasured familial factors.

Analyses restricted to sibling pairs discordant for suicidal acts, provide control for familial (genetic and environmental) factors shared by the siblings. Full siblings share on average 50%

of their genes, but the segregation of alleles to different eggs is a random process. Thus, sibling analysis should account for genetic confounding. A hereditary component has been suggested for suicidal acts [3] and smoking [25], and the search for candidate genes has recently started for both suicidal [26-28] and smoking [25] behaviors. Sibling analysis also control for important environmental factors shared by the siblings. Both smoking and suicidal acts are associated with family dysfunction, other life-style habits, psychological problems and psychiatric diseases not requiring in-patient care [3, 14, 29, 30]. Similar to the present findings, prenatal smoking exposure has recently been associated with increased risks of both attention deficit hyperactivity disorder (ADHD) and low intellectual performance in cohort analyses, but not in analysis within sibling pairs, suggesting underlying familial confounding [31, 32].

One serious concern that cannot be addressed in the sibling analysis, is the validity of self-reported information about smoking exposure in early pregnancy. The validity of self-reported smoking is generally high, but is lower among women stating that they recently changed smoking habits [33]. We only had information on smoking in early pregnancy, and during the 1980's in Sweden, around 10% of these smokers stopped smoking later during pregnancy [34]. Women who stated that they only smoked in one pregnancy may be more likely to temporarily stop smoking in the other pregnancy (and thus be recorded as non-smokers), and later during pregnancy resume smoking [34]. Moreover, we cannot rule out differential misclassification of smoking exposure between mothers from dysfunctional and non-dysfunctional families. We also lack information on other specific exposures that may be related to maternal smoking during pregnancy. For example, we had no information on alcohol use or infections.

We also investigated two possible biological pathways by which prenatal smoking exposure may influence offspring risk of suicidal acts. First, smoking is causally associated with reduced fetal growth [35], and low birth weight has previously been associated with suicidal acts [9, 10]. However, we found no evidence that birth weight for gestational age (a measure of fetal growth) was associated with risk of suicide, or that the association between prenatal smoking exposure and risk of suicidal acts was attenuated after taking birth weight for gestational age into account. Second, maternal smoking has in some studies been associated with offspring risks of psychiatric disorders [36], which in turn is associated with high risks of suicidal acts among young men and women [3]. We found no support for the hypothesis that a possible association between prenatal smoking exposure and offspring risk of suicide is mediated by smoking-related effects of developing psychiatric diseases requiring inpatient care.

Strengths of the present investigation include the population-based design, prospectively collected information about smoking habits in early pregnancy, and that we were able to take family history of psychiatric diseases into account. Importantly, the analyses of prenatal smoking exposure within siblings provide control for confounding by unmeasured familial factors shared by the siblings.

Maternal smoking during pregnancy is in many countries recognized as the most important preventable risk factor for an unsuccessful pregnancy outcome. Much less is known about possible long-term effects of prenatal smoking exposure [13, 36]. Our results support the importance of familial factors for the association between prenatal smoking exposure and

offspring risk of suicidal acts. Our discrepant results, when using cohort and sibling pair analyses, also emphasize the importance of study design when investigating long-term effects of prenatal smoking exposure, such as offspring mental health.

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References

1. Suicide Prevention (SUPRE). World Health Organization.
http://www.who.int/mental_health/prevention/suicide/suicideprevent/en. Accessed by June 24, 2010.
2. Nock MK, Borges G, Bromet EJ, Alonso J, Angermeyer M, Beautrais A, Bruffaerts R, Chiu WT, de Girolamo G, Gluzman S, de Graaf R, Gureje O, et al. Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. *Br J Psychiatry* 2008;192:98-105.
3. Bridge JA, Goldstein TR, Brent DA. Adolescent suicide and suicidal behavior. *J Child Psychol Psychiatry* 2006;47:372-94.
4. Baldessarini RJ, Hennen J. Genetics of suicide: an overview. *Harv Rev Psychiatry* 2004;12:1-13.
5. Kendler KS. Twin studies of psychiatric illness: an update. *Arch Gen Psychiatry* 2001;58:1005-14.
6. Mann JJ. Neurobiology of suicidal behaviour. *Nat Rev Neurosci* 2003;4:819-28.
7. Hultman CM, Sparén P, Takei N, Murrar RM, Cnattingius S. Prenatal and perinatal risk factors for schizophrenia, affective psychosis, and reactive psychosis of early onset: case-control study. *BMJ* 1999;318:421-6.
8. Gale CR, Martyn CN. Birth weight and later risk of depression in a national birth cohort. *Br J Psychiatry* 2004;184:28-33.
9. Mittendorfer-Rutz E, Rasmussen F, Wasserman D. Restricted fetal growth and adverse maternal psychosocial and socioeconomic conditions as risk factors for suicidal behaviour of offspring: a cohort study. *Lancet* 2004;364:1135-40.
10. Riordan DV, Selvaraj S, Stark C, Gilbert JS. Perinatal circumstances and risk of offspring suicide. Birth cohort study. *Br J Psychiatry* 2006;189:502-7.

11. Salk L, Lipsitt LP, Sturner WQ, Reilly BM, Levat RH. Relationship of maternal and perinatal conditions to eventual adolescent suicide. *Lancet* 1985;1:624-7.
12. Jacobson B, Bygdeman M. Obstetric care and proneness of offspring to suicide as adults: case-control study. *BMJ* 1998;317:1346-9.
13. Cnattingius S. The epidemiology of smoking during pregnancy: smoking prevalence, maternal characteristics, and pregnancy outcomes. *Nicotine Tob Res* 2004;6 Suppl 2:S125-40.
14. Diaz FJ, James D, Botts S, Maw L, Susce MT, de Leon J. Tobacco smoking behaviors in bipolar disorder: a comparison of the general population, schizophrenia, and major depression. *Bipolar disorders* 2009;11:154-65.
15. Nilsson E, Lichtenstein P, Cnattingius S, Murray RM, Hultman CM. Women with schizophrenia: pregnancy outcome and infant death among their offspring. *Schizophr Res* 2002;58:221-9.
16. Olausson P, Engel JA, Soderpalm B. Involvement of serotonin in nicotine dependence: processes relevant to positive and negative regulation of drug intake. *Pharmacol Biochem Behav* 2002;71:757-71.
17. Malone KM, Waternaux C, Haas GL, Cooper TB, Li S, Mann JJ. Cigarette smoking, suicidal behavior, and serotonin function in major psychiatric disorders. *Am J Psychiatry* 2003;160:773-9.
18. Hughes JR. Smoking and suicide: a brief overview. *Drug Alcohol Depend* 2008;98:169-78.
19. National Board of Health and Welfare. The Swedish Medical Birth Register: a summary of content and quality. <http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/10655/2003-112-3-20031123.pdf>. Accessed by June 24, 2010.

20. Statistics Sweden, Background facts. Multigeneration Register 2005 - A description of content and quality. Population and Welfare Statistics 2006:5.
http://www.scb.se/statistik/publikationer/BE9999_2005A01_BR_BE96ST0605.pdf. Accessed by June 24, 2010.
21. Centre for Epidemiology, Inpatient diseases in Sweden 1987-2008. The National Board of Health and Welfare, Sweden.
<http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/17782/2009-10-114.pdf>. Accessed by June 24, 2010.
22. The National Board of Health and Welfare, Causes of Death 2007. Centre for Epidemiology, The National Board of Health and Welfare, Sweden.
http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/8309/2009-125-18_200912518_rev.pdf. Accessed by June 24, 2010. .
23. Statistics Sweden, Educational attainment of the population 2006. ISSN: 1654-3483.
http://www.scb.se/statistik/UF/UF0506/2007A02/UF0506_2007A02_SM_UF37SM0701.pdf. Accessed by June 24, 2010.
24. Niklasson A, Ericson A, Fryer JG, Karlberg J, Lawrence C, Karlberg P. An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977-1981). *Acta Paediatr Scand* 1991;80:756-62.
25. Schnoll RA, Johnson TA, Lerman C. Genetics and smoking behavior. *Curr Psychiatry Rep* 2007;9:349-57.
26. Hawton K, van Heeringen K. Suicide. *Lancet* 2009;373:1372-81.
27. Currier D, Mann JJ. Stress, genes and the biology of suicidal behavior. *Psychiatr Clin North Am* 2008;31:247-69.

28. Rujescu D, Thalmeier A, Moller HJ, Bronisch T, Giegling I. Molecular genetic findings in suicidal behavior: what is beyond the serotonergic system? *Arch Suicide Res* 2007;11:17-40.
29. U.S. Department of Health and Human Services. Surgeon General 2001. Factors influencing tobacco use among women Women and smoking. A report from the Surgeon General.ed. Rockville, MD.: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office of Smoking and Health, 2001:453-546.
30. Gilman SE, Breslau J, Subramanian SV, Hitsman B, Koenen KC. Social factors, psychopathology, and maternal smoking during pregnancy. *Am J Public Health* 2008;98:448-53.
31. Lindblad F, Hjern A. ADHD after fetal exposure to maternal smoking. *Nicotine Tob Res* 2010;12:408-15.
32. Lundberg F, Cnattingius S, D'Onofrio B, Altman D, Lambe M, Hultman C, Iliadou A. Maternal smoking during pregnancy and intellectual performance in young adult Swedish male offspring. *Paediatr Perinat Epidemiol* 2010;24:79-87.
33. George L, Granath F, Johansson AL, Cnattingius S. Self-reported nicotine exposure and plasma levels of cotinine in early and late pregnancy. *Acta Obstet Gynecol Scand* 2006;85:1331-7.
34. Cnattingius S, Lindmark G, Meirik O. Who continues to smoke while pregnant? *J Epidemiol Community Health* 1992;46:218-21.
35. Kramer MS. Intrauterine growth and gestational duration determinants. *Pediatrics* 1987;80:502-11.
36. Huizink AC, Mulder EJ. Maternal smoking, drinking or cannabis use during pregnancy and neurobehavioral and cognitive functioning in human offspring. *Neuroscience and biobehavioral reviews* 2006;30:24-41.

Table 1. Numbers and Hazard Ratios (HR) of Completed Suicide as a function of Parental, Pregnancy and Birth Characteristics.

Characteristic	Cohort		Completed suicide		
	Number	(%)	Number	HR ^a	(95% CI)
Parental characteristics					
Maternal smoking ^b					
None ^c	1 027,718	70.9	196	1.00	
1-9 cigarettes per day	207,419	14.3	92	1.85	(1.45-2.37)
≥10 cigarettes per day	126,717	8.7	62	1.97	(1.48-2.62)
Missing information	87,479	6.0	24		
Maternal age (years)					
<19	40,628	2.8	29	2.47	(1.65-3.69)
20-24	321,903	22.2	102	1.19	(0.92-1.54)
25-29 ^c	540,483	37.3	133	1.00	
30-34	374,163	25.8	65	0.73	(0.54-0.98)
≥35	172,156	11.9	45	1.11	(0.79-1.56)
Paternal age (years)					
<19	6,190	0.4	6	4.02	(1.77-9.17)

20-24	135,512	9.3	47	1.44 (1.02-2.04)
25-29 ^c	430,356	29.7	99	1.00
30-34	460,930	31.8	116	1.10 (0.84-1.43)
35-39	262,475	18.1	64	1.07 (0.78-1.47)
≥40	142,269	9.8	34	1.19 (0.80-1.75)
Missing information	11,601	0.8	8	

(cont.)

(Table 1, cont.)

Parity				
Primiparous ^c	603,835	41.7	140	1.00
Multiparous	845,498	58.3	234	1.18 (0.95-1.45)
Living with infant's father ^b				
Yes ^c	1 281,886	88.4	323	1.00
No	73,998	5.1	29	1.54 (1.05-2.25)
Missing information	93,449	6.4	22	
Mother's education (years)				
≤9	238,880	16.5	83	1.15 (0.89-1.49)
10-12 ^c	755,829	52.2	195	1.00

13-14	224,950	15.5	37	0.61 (0.43-0.87)
≥15	167,181	11.5	50	0.99 (0.72-1.34)
Missing information	62,493	4.3	9	
Mother's country of birth				
Sweden ^c	1 250,784	86.3	322	1.00
Other Nordic ^d	63,296	4.4	32	1.65 (1.14-2.37)
Outside Nordic countries	125,049	8.6	19	0.82 (0.52-1.31)
Missing information	10,204	0.7	1	
Pregnancy and birth characteristics				
Hypertensive disease				
No ^c	1 397,180	96.4	360	1.00
Yes	52,153	3.6	14	1.07 (0.63-1.82)

(cont.)

(Table 1, cont.)

Placental abruption

No ^c	1 442,590	99.5	371	1.00
Yes	6,743	0.5	3	1.60 (0.51-4.98)

Mode of delivery

Vaginal, non-instrumental ^c	1 205,622	83.2	306	1.00	
Vaginal, instrumental	88,487	6.1	22	0.92	(0.60-1.42)
Cesarean delivery	155,224	10.7	46	1.13	(0.83-1.54)
Sex of infant					
male	744,205	51.3	232	1.54	(1.25-1.90)
female ^c	705,128	48.7	142	1.00	
Gestational age (weeks)					
<-36	74,276	5.1	23	1.16	(0.76-1.77)
≥37 ^c	1 372,280	94.7	349	1.00	
Missing information	2,777	0.2	2		
Birth weight for gestational age (standard deviation scores)					
<-2	43,931	3.0	13	1.13	(0.65-1.98)
-2 to ≤-1	189,908	13.1	54	1.08	(0.81-1.45)
>-1 to <+1 ^c	974,710	67.3	246	1.00	
≥+1 to ≤+2	189,729	13.1	52	1.14	(0.85-1.54)
>+2	42,827	3.0	5	0.51	(0.21-1.23)
Missing information	8,228	0.6	4		

(cont.)

(Table 1, cont.)

^aHazard ratios (HR) are adjusted for sex, age and calendar period.

^bInformation was retrieved at time of registration to antenatal care.

^cReference category

^dOther Nordic countries include Denmark, Finland, Iceland and Norway.

Table 2. Numbers and Hazard Ratios (HR) of Completed Suicide as a function of Previous Psychiatric Inpatient Care and Suicidal Acts in First Degree Relatives.

Characteristic	Cohort		Completed suicide		
	N	(%)	N	HR ^a	(95% CI)
Psychiatric care in first degree relatives					
No admission ^b	1 204,819	83.1	245	1.00	
Admission of one relative					
Mother	68,144	4.7	30	2.30	(1.59-3.35)
Father	71,040	4.9	42	2.84	(2.05-3.94)
Sibling	65,270	4.5	28	1.96	(1.32-2.89)
Admission of at least two relatives	40,060	2.8	29	3.31	(2.25-4.87)
Suicidal acts in first degree relatives					
No suicidal act ^b	1 353,843	93.4	305	1.00	
Suicidal act of one relative					
Mother	34,279	2.4	25	3.37	(2.24-5.07)
Father	27,196	1.9	11	1.72	(0.94-3.14)
Sibling	26,077	1.8	21	3.29	(2.11-5.12)
Suicidal act of at least two relatives	7,938	0.5	12	6.91	(3.97-12.05)

^aHazard Ratios (HR) are adjusted for sex, age and calendar period.

^bReference category

Table 3a. Maternal Smoking during pregnancy and Offspring Risk of Completed Suicide.

	Hazard Ratio ^a (95 % CI)	
	Model 1	Model 2 ^b
Maternal smoking (cigarettes per day)		
0 ^c	1.00	1.00
1-9	1.81 (1.40-2.35)	1.67 (1.29-2.16)
≥10	1.78 (1.31-2.42)	1.54 (1.12-2.10)

^aBoth models are adjusted for sex, age, calendar period, maternal and paternal age at delivery, parity, living with infant's father, mother's education and mother's country of birth.

^bAlso adjusted for first event of either previous inpatient care for psychiatric diseases or suicidal acts in first degree relatives

^cReference category

Table 3b. Maternal Smoking during pregnancy and Offspring Risk of Suicidal Acts.

	N	Hazard ratio ^a (95 % CI)	
		Model 1	Model 2 ^b
Maternal smoking (cigarettes per day)			
0 ^c	4,898	1.00	1.00
1-9	1,925	1.42 (1.37-1.50)	1.28 (1.21-1.35)
≥10	1,587	1.76 (1.66-1.87)	1.48 (1.39-1.57)
Missing	845		

Suicidal acts include completed and attempted suicide. N denotes number of individuals with suicidal acts.

^aBoth models are adjusted for sex, age, calendar period, maternal and paternal age at delivery, parity, living with infant's father, mother's education and mother's country of birth.

^bAlso adjusted for first event of either previous inpatient care for psychiatric diseases or suicidal acts in first degree relatives

^cReference category

Table 4. Associations between maternal smoking during pregnancy and suicidal acts in offspring discordant for suicidal a

Cases		Sibling controls								Hazard Crude ^a
		Total		Maternal smoking						
		Non-smoking		1-9 cig./day		≥10 cig./day				
N	(%)	N	(%)	N	(%)	N	(%)	N	(%)	
Maternal smoking										
Non-smoking ^c		147	(37.1)	-	-	113	(28.5)	34	(8.6)	1.00
1-9 cig./day		161	(40.7)	119	(30.1)	-	-	42	(10.6)	1.05 (0.81-1.36)
≥10 cig./day		88	(22.2)	32	(8.1)	56	(14.1)	-	-	0.94 (0.58-1.53)
Total				151	(38.1)	169	(42.7)	76	(19.2)	

^aAnalysis includes siblings discordant for suicidal acts and maternal smoking exposure.

^bAnalysis includes siblings discordant for suicidal acts. Hazard ratios are adjusted for offspring sex, sibling order and birth

^cReference category