ORIGINAL ARTICLE

Prenatal Smoking Exposure and the Risk of Psychiatric Morbidity Into Young Adulthood

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Context: Prenatal smoking exposure modulates brain development, which may deviate mental development of the offspring.

Objective: To study the effects of prenatal smoking exposure on psychiatric morbidity and mortality among Finnish young adults by means of population-based longitudinal register data.

Design: Information on maternal smoking as reported by the mothers (0, <10, or >10 cigarettes a day) and other background factors (maternal age and parity and child's sex, gestational age, birth weight, and 5-minute Apgar score) was derived from the Finnish Medical Birth Register. Information on children's psychiatric diagnoses related to outpatient visits (1998-2007), children's inpatient care (1987-2007), and mothers' psychiatric inpatient care (1969-1989) was derived from the Finnish Hospital Discharge Register. Information on deaths and their causes for the children (1987-2007) was received from the Cause-of-Death Register.

Setting: Population-based study of all singletons born in Finland from 1987 to 1989 with information on prenatal smoking exposure.

Patients: The source population included all singleton births in Finland from January 1, 1987, through December 31, 1989 (n=175 869), excluding children with major congenital anomalies (3.1%) and children who died during the first week of life (0.3%).

Main Outcome Measures: Psychiatric morbidity and mortality.

Results: The prevalence of maternal smoking was 15.3%. The risk of psychiatric morbidity was significantly higher in the exposed children than in the unexposed children. Among the offspring of mothers who smoked fewer than 10 cigarettes a day, 21.0% had any psychiatric diagnoses (adjusted odds ratio [OR], 1.53 [95% confidence interval (CI), 1.47-1.60]) compared with 24.7% among those of mothers who smoked more than 10 cigarettes a day (1.85 [1.74-1.96]) and 13.7% in the unexposed children (the reference group). The risk was significantly increased for most of the psychiatric diagnoses. The strongest effects were in psychiatric disorders due to psychoactive substance use and in behavioral and emotional disorders. The risk of mortality was significantly higher in children exposed to more than 10 cigarettes a day (OR, 1.69 [95% CI, 1.31-2.19]) compared with unexposed children.

Conclusion: Prenatal smoking exposure is associated with an increased risk of psychiatric morbidity, whereas prenatal exposure to more than 10 cigarettes a day increases the risk of mortality in childhood, adolescence, and young adulthood.

Arch Gen Psychiatry. 2010;67(8):841-849

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SMOKING DURING PREGNANCY has many harmful effects on the growing fetus, including impairment of fetal growth.[1-3] In recent years, smoking exposure has also been described to have harmful effects on the developing brain.[4] Animal studies have shown that prenatal nicotine exposure modulates the development of axons and synapses of the neural cell.[5] In rats, nicotine has modifying and damaging effects on brain development.[6-8] The same effects have also been shown in first-trimester human fetal brain cell cultures.[9] Thus, prenatal smoking exposure may have long-lasting consequences and a robust influence on individual developmental trajectories. The mechanisms of these effects are not yet well known among humans.

It is possible that the neural effects of prenatal smoking exposure lead to developmental and behavioral problems. Prenatal smoking exposure has been associated with the risk of internalizing and externalizing psychiatric symptoms in children,[10-12] and these symptoms seem to persist into adolescence.[13] Prenatal smoking exposure may increase the risk of subsequent behavioral problems, including conduct disorders, antisocial behavior, delinquency, and alcohol and other substance

abuse.[10,14,15] Attention-deficit/hyperactivity disorder has also been associated with prenatal smoking exposure,[14-18] although background factors explain part of this association.[19,20] Maternal smoking during pregnancy may also confer an increased risk of death from injuries and accidents in early adult life for male offspring.[21]

Previous epidemiological studies were limited by the size of the study groups because the largest study includes no more than 22 545 children (followed up to 3 years of age).[22] In addition, several well-known social correlates of smoking during pregnancy include race, parental education, economic level, and age.[23-25] The same factors are associated with psychiatric problems of the offspring.[24] In addition, the outcome variables have been limited to only a few diagnoses (ie, major depression and conduct disorders) and do not include all psychiatric morbidity.[10] Because the prevalence of psychiatric disorders starts to increase significantly in adolescence, research on the associations requires a long follow-up. Only a few studies have succeeded in following up children to early adulthood.

Our objective was to investigate the effects of prenatal smoking exposure on psychiatric morbidity among Finnish young adults born from January 1, 1987, through December 31, 1989, by means of population-based longitudinal register data. Our hypothesis was that maternal smoking during pregnancy interferes with the development of the fetal brain and therefore increases the risk of psychiatric morbidity in late adolescence and young adulthood. We also hypothesized that mortality attributable to psychiatric morbidity is increased and correlates with prenatal smoking exposure.

METHODS

DATA SOURCES

All live births and stillbirths of fetuses with a gestational age of 22 weeks or more or with a birth weight of 500 g or more are included in the Medical Birth Register. The register data are collected from all delivery hospitals and, in the case of home births, from the assisting health care personnel and sent to the register keeper, currently the National Institute for Health and Welfare (THL). The register includes information on the mother's and the child's identification numbers; maternal background, health care, and interventions during pregnancy and delivery; and the newborn's outcome until 7 days of age. After data linkage to the Central Population Register and the Cause-of-Death Register, the Medical Birth Register is considered to be a complete record of all births and newborns in Finland. Two data quality studies showed that most of the register content corresponds well or satisfactorily with hospital record data.[26,27]

The Hospital Discharge Register collects information on all episodes of inpatient care (including all hospitalizations requiring an overnight stay) in public and private hospitals (since 1969) and outpatient visits in public hospitals (since 1998). The register contains information on the patient's background, hospitalization period, and procedures and the main diagnosis plus up to 2 other diagnoses by *International Classification of Diseases* (*ICD*) code (*Eighth Revision* [*ICD-8*] in 1969-1986, *Ninth Revision* [*ICD-9*] in 1987-1995, and *Tenth Revision* [*ICD-10*] since 1996). All hospitals send their data electronically to the THL. A 1986 data quality study reported that 99% of hospitalizations relating to mental disorders were registered under the correct *ICD* chapter and that 98% of the main diagnoses had been correctly reported at the 3-digit *ICD* code level.[28]

The Finnish Cause-of-Death Register contains data from the death certificates written by the physician who took care of the patient or who performed the autopsy. All death certificates are checked by a physician in the provincial government and by medical experts at Statistics Finland, which is the register keeper. This register includes comprehensive information on all deaths of Finnish citizens and permanent residents who died in Finland and at least basic information on deaths of Finnish citizens that occurred abroad.

PARTICIPANTS AND BACKGROUND INFORMATION

The study population consisted of all children born in the period from 1987 through 1989 in Finland (n=186 246) registered in the Medical Birth Register. Children who had died during the first week of life (597 children [0.3%]) and multiple births (3960 [2.1%]) were excluded. Furthermore, we excluded children with major congenital anomalies (5820 [3.1%]) from the study. However, cryptorchism (n=954), luxation of the hip (n=943), and subluxation of the hip (n=845) as the only diagnoses were not considered major anomalies and, therefore, infants with these diagnoses were included in the study. After exclusions, the final study population consisted of 175 869 children born in the study years (94.4%). The data protection legislation in Finland prohibits the collection of data on racial or ethnic origin, political opinions, and religious or philosophical beliefs. However, the information on main language can be registered. According to official statistics, less than 0.5% of children born from 1987 through 1989 had a native language other than Finnish or Swedish, the 2 official languages in Finland.[29]

Information on maternal smoking was requested from the mothers by a midwife during antenatal care (0, <10, or >10 cigarettes a day), and other background factors (the child's sex, gestational age, birth weight, and 5-minute Apgar score and maternal age and parity) were derived from the Finnish Medical Birth Register (**Table 1**).

INFORMATION ON PSYCHIATRIC MORBIDITY

Information on psychiatric morbidity was obtained from the Finnish Hospital Discharge Register and included all inpatient episodes in public and private hospitals from 1987 through 2007 and all outpatient visits to public hospitals from 1998 through 2007. Therefore, our data include all inpatient episodes from birth until 18 to 20 years of age and all outpatient visits of the children beginning from 9 to 11 years of age. For this study we included all episodes and visits with a psychiatric diagnosis (*ICD-9* codes 290-319 in 1987-1995 and *ICD-10* codes F00-F99 in 1996-2007), whether occurring as a primary or other diagnosis. We studied the following diagnoses separately by *ICD-10* F diagnosis:

1. F10 through F19 psychiatric disorders due to psychoactive substance use (including *ICD-9* codes 291, 292, 303, 305, and 304), subgroup F10 psychiatric disorders due to use of alcohol (*ICD-9* codes 291, 303, and 3050A), and subgroup F11 through F19 psychiatric disorders due to use of other drugs (*ICD-9* codes 292, 304, and 305, excluding 3050A);
2. F20 through F29, F31.2, F31.20, F32.3, and F33.3 psychosis (*ICD-9* codes 295, 296.xE, 297, and 298) and the subgroup of schizophrenias with F20 through F21 diagnoses (*ICD-9* code 295);
3. F30 through F39 mood disorders (*ICD-9* codes 296 and 3004A);
4. F40 through F59 behavioral syndromes, neurotic disorders, and stress-related disorders (*ICD-9* codes 300 [exclud-

ing 3004A], 3071A, and 3075B) and subgroup F50.0 anorexia nervosa (*ICD-9* code 3071A);

5. F60 through F69 disorders of adult personality and behavior (*ICD-9* code 301);

6. F70 through F79 mental retardation (*ICD-9* code 317);

7. F80 through F89 disorders of psychological development (*ICD-9* codes 299 and 315); and

8. F90 through F99 behavioral and emotional disorders occurring in childhood and adolescence (*ICD-9* codes 3072A-D, 313, and 314), subgroup F90 hyperkinetic disorders (*ICD-9* code 314), and subgroup F91 through F92 disorders of conduct and emotions (*ICD-9* codes 3072A-D and 313).

Information on the mother's psychiatric morbidity leading to inpatient care before the birth of the child was obtained from the Hospital Discharge Register for the period from 1969 through 1989.

Data were complemented with information on all deaths and their causes for children from 1987 through 2007 from the Cause-of-Death Register (Statistics Finland). We analyzed suicides and self-inflicted deaths separately (*ICD-10* codes X60–X84).

All register data were combined by using the mother's and child's unique personal identification number. The combined data included complete follow-up information until December 31, 2007, or the death of the child. Our data did not include information on children migrating out of Finland. Permission was sought and granted by the register-keeping organizations (THL and Statistics Finland) to use their confidential health register data in this study, as required by national data-protection legislation. The ethical evaluation was made by the statistics authorities (THL and Statistics Finland). The data linkages were performed by the statistical authorities, and only unidentifiable data were delivered for the researchers working outside the THL.

STATISTICAL ANALYSES

The confounding factors were considered to be the child's sex, gestational age, birth weight, and 5-minute Apgar score and maternal age, parity, and psychiatric morbidity before the birth of the child. Logistic regression analysis was used to compare the prevalence of any psychiatric diagnosis, inpatient and outpatient care, the type of psychiatric diagnosis, and mortality between the children exposed and unexposed to prenatal smoking. The survival probability was analyzed by calculating the probability of surviving without a psychiatric diagnosis in the study groups with 18-year Kaplan-Meier survival analyses. The data analysis was performed using commercially available software (SAS, version 9.1; SAS Institute Inc, Cary, North Carolina).

RESULTS

Information on maternal smoking by the background factors is shown in Table 1. Of the total study population for whom smoking data were available, 26 075 of the mothers (15.3%) smoked during pregnancy. Of these, 8866 (34.0%) smoked more than 10 cigarettes a day. There were 5487 children (3.2%) with unknown maternal smoking data. The last column of Table 1 shows children's subsequent F diagnoses by background factors.

INPATIENT AND OUTPATIENT PSYCHIATRIC CARE

The prevalence of any psychiatric diagnosis resulting in hospital care (inpatient or outpatient care) was 15.0% (n=25 590) after excluding children with unknown maternal smoking data. The prevalence was 13.7% in the children unexposed to smoking, 21.0% in the children exposed to fewer than 10 cigarettes a day, and 24.7% in the children exposed to more than 10 cigarettes a day. The association with prenatal smoking exposure was statistically significant after adjusting for background factors (**Table 2**). The prevalence of psychiatric morbidity by age and maternal smoking data is shown using the Kaplan-Meier method (**Figure 1**). There was a significant group difference beginning at 6 years of age.

Table 1. Information on Maternal Smoking and Child's Subsequent F Diagnoses by Background Factors of Children Born From 1987 Through 1989 From the Finnish Medical Birth Register

Characteristic	No. of Births	Maternal Smoking, %[a]	Psychiatric F Diagnoses in Child, %
All children	175 869	15.3	15.1
Maternal age, y			
<20	5320	37.8	24.9
20-34	147 374	15.0	14.7
≥35	23 113	11.9	14.9
Unknown	62	8.6	0
Parity			
0	69 457	16.9	15.4
1	61 008	14.3	14.5
2 or 3	37 478	14.9	15.4
≥4	5535	9.8	14.4
Unknown	2391	23.7	16.3
Mother's previous psychiatric diagnosis			
No	171 932	14.9	14.7
Yes	3937	35.1	29.5
Sex			
Male	89 862	15.3	13.6
Female	86 007	15.3	16.6
Gestational age, wk			
22-27	223	22.6	31.8
28-31	642	19.8	24.3
32-36	6406	19.2	17.3
≥37	166 094	15.1	14.9
Unknown	2504	23.2	16.4
Birth weight, g			
<1500	666	22.1	29.3
1500-2499	3757	26.8	20.1
2500-3999	133 322	16.5	15.2
≥4000	36 024	9.5	13.5
Unknown	2100	10.5	16.5
Weight adjusted for gestational age			
SGA	3115	31.4	22.2
AGA	163 858	15.3	14.9
LGA	6392	8.3	14.9
Unknown	2504	23.2	16.4
5-min Apgar score[b]			
0-3	238	17.9	15.1
4-6	1147	16.4	18.9
7-10	171 708	15.3	15.0
Unknown	2640	20.7	17.1

Abbreviations: AGA, average for gestational age; F diagnoses, psychiatric diagnoses listed in section F of the *International Classification of Diseases, Tenth Revision*; LGA, large for gestational age; SGA, small for gestational age.

[a] Excludes those with unknown smoking data (n=5487).

[b] If the 5-minute Apgar score was missing, the 1-minute Apgar score was used in case the score was 8, 9, or 10. Information was missing for 136 children.

Table 2. Children With Psychiatric Diagnosis by Maternal Smoking and Sex

	Maternal Smoking Data			
	No Smoking	<10 Cigarettes/d	>10 Cigarettes/d	Total
No. of children[a]				
Male	73 684	8801	4538	**87 023**
Female	70 615	8413	4331	**83 359**
Total	**144 299**	**17 214**	**8869**	**170 382**
Any psychiatric diagnosis				
Sex, No. (%)				
Male	9099 (12.3)	1681 (19.1)	1031 (22.7)	**11 811** (13.6)
Female	10 685 (15.1)	1934 (23.0)	1160 (26.8)	**13 779** (16.5)
Total	**19 784** (13.7)	**3615** (21.0)	**2191** (24.7)	**25 590** (15.0)
Total crude OR (95% CI)	1 [Reference]	1.44 (1.39-1.50)	1.64 (1.57-1.72)	
Total adjusted OR (95% CI)[b]	1 [Reference]	1.53 (1.47-1.60)	1.85 (1.74-1.96)	
Inpatient care psychiatric diagnosis				
Sex, No. (%)				
Male	3431 (4.7)	700 (8.0)	442 (9.7)	**4573** (5.3)
Female	3246 (4.6)	640 (7.6)	358 (8.3)	**4244** (5.1)
Total	**6677** (4.6)	**1340** (7.8)	**800** (9.0)	**8817** (5.2)
Total crude OR (95% CI)	1 [Reference]	1.63 (1.54-1.74)	1.87 (1.73-2.02)	
Total adjusted OR (95% CI)[b]	1 [Reference]	1.65 (1.55-1.75)	1.91 (1.76-2.07)	
Outpatient care psychiatric diagnosis				
Sex, No. (%)				
Male	8025 (10.9)	1483 (16.9)	909 (20.0)	**10 417** (12.0)
Female	10 052 (14.2)	1813 (21.5)	1093 (25.2)	**12 958** (15.5)
Total	**18 077** (12.5)	**3296** (19.1)	**2002** (22.6)	**23 375** (13.7)
Total crude OR (95% CI)	1 [Reference]	1.44 (1.39-1.50)	1.65 (1.57-1.74)	
Total adjusted OR (95% CI)[b]	1 [Reference]	1.55 (1.48-1.61)	1.87 (1.77-1.97)	

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Excludes those with unknown maternal smoking data (5487 children: 2839 males and 2648 females).
[b] Adjusted by the child's sex, gestational age, birth weight, and 5-minute Apgar score and maternal age, parity, and psychiatric diagnosis before the child's birth.

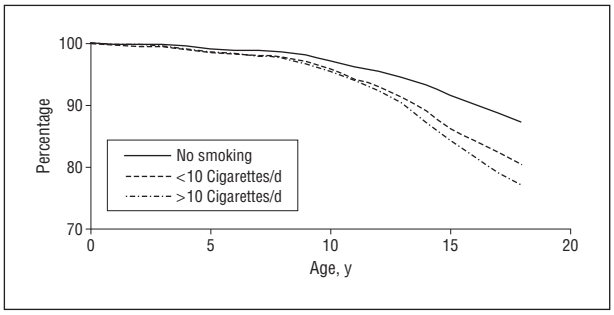

Figure 1. Psychiatric morbidity-free survival by age and maternal smoking.

The prevalence of psychiatric inpatient and outpatient care is shown by maternal smoking data and sex with crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) in Table 2. Prevalence of inpatient and outpatient care significantly increased with increased smoking.

The study population had a total of 510 685 psychiatric treatment episodes, of which 24 579 (4.8%) were for inpatient care and 95.2% for outpatient visits. The mean number of all inpatient and outpatient treatment episodes per child was 19.3 (16.1 for male vs 22.0 for female children) for those with at least 1 psychiatric care episode. The mean number of inpatient treatment episodes per child was 2.7 (2.7 for male and 2.6 for female children) and of outpatient treatment episodes was 20.1 (17.0 for male and 22.6 for female children). The number of treatment episodes per child was not affected by prenatal smoking exposure in those with psychiatric care.

EFFECT OF MATERNAL PSYCHIATRIC MORBIDITY

The children whose mothers had any psychiatric diagnoses before the birth of the child had a probability of 0.72 (Kaplan-Meier 95% CI, 0.71-0.74) of remaining without a psychiatric diagnosis until 18 years of age, whereas the children whose mothers had no psychiatric diagnoses had a probability of 0.86 (0.86-0.87). The difference became statistically significant at 5 years of age.

The effect of prenatal smoking exposure was further examined in children born to mothers with previous psychiatric morbidity (**Figure 2**). Smoking exposure had a significant effect on the probability of remaining without a psychiatric diagnosis until 18 years of age ranging from 0.76 (95% CI, 0.74-0.78) for unexposed children to 0.64 (0.60-0.69) for those exposed to fewer than 10 cigarettes a day and 0.67 (0.62-0.71) for those exposed to more than 10 cigarettes a day. The effect of smoking was also significant in children born to mothers without psychiatric morbidity probabilities and ranged from 0.87 (95% CI, 0.87-0.88) to 0.81 (0.81-0.82) and 0.78 (0.77-0.79), respectively.

EFFECT OF SEX

The effect of prenatal smoking exposure was examined in male and female children separately (**Figure 3**). Smoking exposure had a significant effect on the probability of

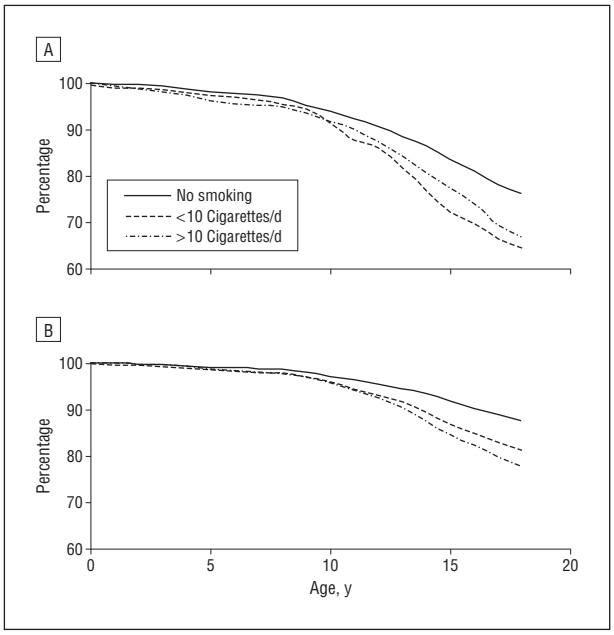

Figure 2. Psychiatric morbidity-free survival by age and maternal smoking in children born to mothers with (A) and without (B) previous psychiatric morbidity.

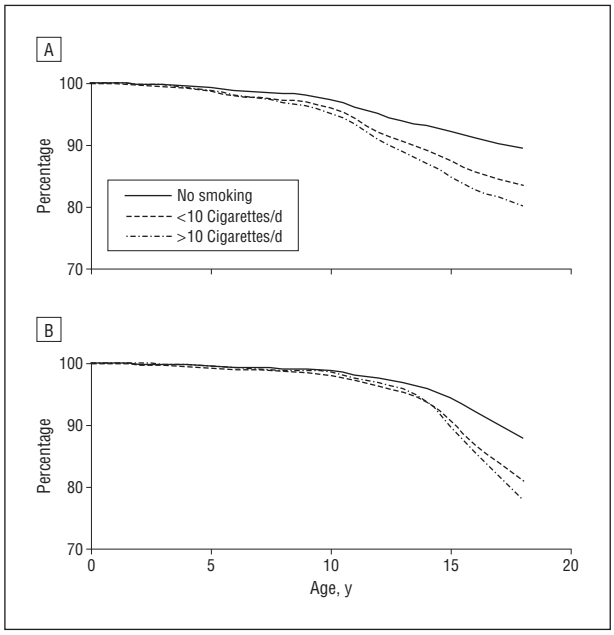

Figure 3. Psychiatric morbidity-free survival by age and maternal smoking in male (A) and female (B) children.

remaining without a psychiatric diagnosis until 18 years of age ranging from 0.88 (95% CI, 0.88-0.89) in unexposed male children to 0.82 (0.81-0.83) in those exposed to fewer than 10 cigarettes a day and 0.79 (0.77-0.80) in those exposed to more than 10 cigarettes a day. The effect of smoking was also significant in female children, with probabilities ranging from 0.86 (95% CI, 0.86-0.86) to 0.79 (0.78-0.80) and 0.75 (0.74-0.77), respectively.

There was a significant group difference beginning at 7 years of age in male children and at 12 years of age in female children.

TYPE OF PSYCHIATRIC DIAGNOSIS

The psychiatric diagnoses according to *ICD-10* by maternal smoking are shown with adjusted ORs and 95% CIs in **Table 3**. Prenatal smoking exposure increased the risk of all diagnoses except for schizophrenia subgroup and anorexia diagnoses. A dose relationship was seen in the risk of mood disorders and behavioral and emotional disorders occurring in childhood and adolescence and for disorders of conduct and emotions. The risk of mental retardation was significantly increased only in male children (OR, 1.44 [95% CI, 1.07-1.94] for those exposed to <10 cigarettes a day and 1.67 [1.15-2.44] for those exposed to >10 cigarettes a day). The risk of disorders of psychological development (*ICD-10* codes F80-F89) was not increased in female children exposed to more than 10 cigarettes a day, although the risk was increased in those exposed to fewer than 10 cigarettes a day. Smoking exposure was shown to be protective against anorexia nervosa (*ICD-10* code F50.0) in female children exposed to fewer than 10 cigarettes a day (57 children; OR, 0.70 [95% CI, 0.54-0.92]). The adjusted ORs for other diagnoses did not differ between male and female children.

MORTALITY

Mortality according to prenatal smoking exposure is shown in **Table 4**. The total number of deaths in the study population was 870 (5.1 per 1000), of which 64 (7.4%) were suicides when we excluded children with unknown maternal smoking data. After adjusting for confounding factors, prenatal exposure of more than 10 cigarettes a day significantly increased total mortality (OR, 1.69 [95% CI, 1.31-2.19]) compared with unexposed children. The risk of suicide did not differ between the unexposed children (51 children [0.4 per 1000]) and children exposed to fewer than 10 cigarettes a day (9 children [0.5 per 1000]; OR, 1.42 [95% CI, 0.68-2.95]) and more than 10 cigarettes a day (4 children [0.5 per 1000]; 0.91 [0.28-2.96]) after adjusting for confounding factors.

COMMENT

To our knowledge, there are no large-scale epidemiological studies of this kind that have investigated the effect of prenatal smoking exposure on psychiatric morbidity into early adulthood. Moreover, previous studies have not controlled for maternal psychiatric morbidity. Our study showed that children exposed to maternal smoking had a higher risk of psychiatric morbidity even after adjusting for confounding factors, including maternal psychiatric hospital care. This association seemed to be robust because it could be found in a large group of diagnoses and the dose relationship was also strong.

Previous studies have investigated only a few psychiatric diagnoses at the same time. Fergusson et al[10] studied the relationship between maternal smoking during pregnancy and the risk of major depression, anxiety, conduct disorders, and substance abuse or dependence. After adjusting for the confounders, the risk was increased only

Table 3. Psychiatric Morbidity by Diagnoses Among All Children Born From 1987 Through 1989 According to *ICD-10* Classifications

ICD-10 Diagnosis	Maternal Smoking Data				Total (% Male Sex)
	No Smoking	<10 Cigarettes/d	>10 Cigarettes/d	Unknown	
F10-F19 due to psychoactive substance use					
No. of children	1417	406	232	80	**2135** (52.6)
Rate per 1000	9.8	23.6	26.2	14.6	12.1
Adjusted OR (95% CI)[a]	1 [Reference]	2.40 (2.15-2.68)	2.66 (2.32-3.05)	1.50 (1.20-1.88)	
F10 due to use of alcohol					
No. of children	1239	344	195	67	**1845** (51.3)
Rate per 1000	8.6	20.0	22.0	12.2	10.5
Adjusted OR (95% CI)[a]	1 [Reference]	2.33 (2.07-2.62)	2.56 (2.20-2.97)	1.44 (1.13-1.84)	
F11-F19 due to use of other drugs					
No. of children	389	130	76	26	**621** (54.0)
Rate per 1000	2.7	7.6	8.6	4.7	3.5
Adjusted OR (95% CI)[a]	1 [Reference]	2.80 (2.30-3.41)	3.18 (2.49-4.06)	1.78 (1.20-2.64)	
F20-F29, F31.2, F31.20, F32.3, and F33.3 psychosis					
No. of children	2375	453	284	106	**3218** (35.5)
Rate per 1000	16.5	26.3	32.0	19.3	18.3
Adjusted OR (95% CI)[a]	1 [Reference]	1.60 (1.45-1.76)	1.94 (1.72-2.19)	1.19 (0.98-1.44)	
F20-F21 subgroup of schizophrenias					
No. of children	207	29	16	10	**262** (50.7)
Rate per 1000	1.4	1.7	1.8	1.8	1.5
Adjusted OR (95% CI)[a]	1 [Reference]	1.17 (0.80-1.73)	1.26 (0.76-2.09)	1.29 (0.68-2.42)	
F30-F39 mood disorders					
No. of children	4881	960	580	214	**6635** (30.4)
Rate per 1000	33.8	55.8	65.4	39.0	37.7
Adjusted OR (95% CI)[a]	1 [Reference]	1.65 (1.54-1.76)	1.93 (1.78-2.10)	1.17 (1.02-1.33)	
F40-F59 behavioral syndromes, neurotic and stress-related disorders					
No. of children	5458	873	498	228	**7057** (30.1)
Rate per 1000	37.8	50.7	56.2	41.6	40.1
Adjusted OR (95% CI)[a]	1 [Reference]	1.34 (1.25-1.44)	1.48 (1.36-1.62)	1.11 (0.98-1.27)	
F50.0 subgroup of anorexia nervosa					
No. of children	723	61	38	21	**843** (5.7)
Rate per 1000	5.0	3.5	4.3	3.8	4.8
Adjusted OR (95% CI)[a]	1 [Reference]	0.71 (0.54-0.92)	0.85 (0.62-1.18)	0.83 (0.54-1.28)	
F60-F69 disorders of adult personality and behavior					
No. of children	410	88	54	19	**571** (32.7)
Rate per 1000	2.8	5.1	6.1	3.5	3.2
Adjusted OR (95% CI)[a]	1 [Reference]	1.80 (1.43-2.26)	2.14 (1.16-2.84)	1.23 (0.78-1.95)	
F70-F79 mental retardation					
No. of children	509	82	50	20	**661** (57.0)
Rate per 1000	3.5	4.8	5.6	3.6	3.8
Adjusted OR (95% CI)[a]	1 [Reference]	1.35 (1.07-1.70)	1.60 (1.20-2.13)	1.05 (0.67-1.63)	
F80-F89 disorders of psychological development					
No. of children	3788	611	329	190	**4918** (70.6)
Rate per 1000	26.3	35.5	37.1	34.6	28.0
Adjusted OR (95% CI)[a]	1 [Reference]	1.35 (1.24-1.47)	1.41 (1.26-1.58)	1.33 (1.16-1.54)	
F90-F99 behavioral and emotional disorders occurring in childhood and adolescence					
No. of children	4605	998	636	234	**6473** (56.7)
Rate per 1000	31.9	58.0	71.7	42.6	36.8
Adjusted OR (95% CI)[a]	1 [Reference]	1.82 (1.70-1.94)	2.25 (2.07-2.43)	1.35 (1.19-1.54)	
F90 subgroup of hyperkinetic disorders					
No. of children	729	184	122	38	**1073** (83.3)
Rate per 1000	5.1	10.7	13.8	6.9	6.1
Adjusted OR (95% CI)[a]	1 [Reference]	2.11 (1.80-2.48)	2.72 (2.25-3.29)	1.39 (1.00-1.92)	
F91-F92 subgroup of disorders of conduct and emotions					
No. of children	2025	566	395	111	**3097** (59.8)
Rate per 1000	14.0	32.9	44.5	20.2	17.6
Adjusted OR (95% CI)[a]	1 [Reference]	2.34 (2.14-2.57)	3.17 (2.85-3.53)	1.46 (1.21-1.76)	

Abbreviations: CI, confidence interval; *ICD-10*, *International Classification of Diseases, Tenth Revision*; OR, odds ratio.
[a] Adjusted by the child's sex, gestational age, birth weight, and 5-minute Apgar score and maternal age, parity, and psychiatric diagnosis before the child's birth.

Table 4. Mortality Among Children Exposed and Unexposed to Maternal Smoking[a]

	No Smoking		<10 Cigarettes		>10 Cigarettes		Total	
	No. of Children	Rate per 1000	No. of Children	Rate per 1000	No. of Children	Rate per 1000	No. of Children	Rate per 1000
All deaths								
Male children	414	5.6	69	7.8	56	12.3	**539**	6.2
Female children	266	3.8	40	4.8	25	5.8	**331**	4.0
Total	**680**	4.7	**109**	6.3	**81**	9.1	**870**	5.1

	No Smoking	<10 Cigarettes	>10 Cigarettes
Crude OR (95% CI)			
Male children	1 [Reference]	1.39 (1.08-1.80)	2.18 (1.65-2.89)
Female children	1 [Reference]	1.26 (0.90-1.76)	1.53 (1.01-2.31)
Total	1 [Reference]	1.34 (1.08-1.80)	1.93 (1.53-2.43)
Adjusted total OR (95% CI)[b]	1 [Reference]	1.17 (0.93-1.45)	1.69 (1.31-2.19)

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Excludes those with unknown maternal smoking data (n=5487).
[b] Adjusted by the child's sex, gestational age, birth weight, and 5-minute Apgar score and maternal age, parity, and psychiatric diagnosis before the child's birth.

for conduct disorders. A retrospective study investigated the risks of major depression, anxiety, conduct disorder, attention-deficit/hyperactivity disorder, and substance abuse in children exposed to 10 or more cigarettes a day. It found an increased risk of conduct disorders in boys younger than 13 years and of drug abuse in girls aged 13 to 17 years.[30] In children exposed to prenatal smoking, the risk of hyperkinetic disorders was 1.9-fold that of unexposed children,[19] and the risk of psychiatric morbidity due to substance abuse was 2.5-fold.[31] The magnitude of the effect of smoking in our study seems to be similar when compared with earlier studies. We found that the risk of psychoses was significantly higher in exposed than in unexposed children. Earlier literature shows controversial findings about psychoses and psychotic symptoms.[32,33] Our finding is of interest because the incidence of psychosis starts to increase in young adulthood. The lack of a statistically significant difference in the risk of schizophrenia between the groups in our study might be due to a fairly low number of cases in young adulthood. Although our results support those of the earlier studies, we showed increased risks of an even broader range of psychiatric disorders in the exposed children. This might be explained by a broad effect of smoking exposure on the development of the fetal brain.[34]

There were differences in the risks of diagnoses at different ages between the male and female children. The earlier occurrence of psychiatric morbidity in male children is explained by their higher incidence of hyperkinetic disorders, which usually occur in early childhood. Female children have more behavioral syndromes and both neurotic and stress-related disorders with later manifestation. The risk of psychiatric morbidity was almost identical in unexposed children of mothers with psychiatric diagnoses and in children of heavy-smoking mothers without psychiatric diagnoses.

Common causes of death in this age group are related to injuries and accidents, which may be more prevalent in individuals with psychiatric problems. A Swedish study has indicated that deaths in early adult life that were mostly related to injuries and accidents were increased only in men exposed to maternal smoking,[21] but we showed that the mortality risk was also increased in women exposed to more than 10 cigarettes a day. There were no differences in the prevalence of suicide between the groups, which might be due to the low number of suicides in our study.

The strengths of our study included a large national study population that covered all singleton births without major congenital anomalies in Finland from 1987 through 1989, for a total of 94.4% of all children born in Finland. Because we had complete data on mothers' psychiatric hospital care before delivery, we were able to control the child's outcome for severe maternal mental illness. Such adjustment has not been performed previously in similar large epidemiological studies. We had a complete follow-up until December 31, 2007, or the death of the child. Unfortunately, the information on children migrating out of Finland was missing. An important strength of our study was a long follow-up of 18 to 20 years. A long follow-up was important because most of the differences between the unexposed and exposed children emerged in adolescence and later.

Information was reliably gathered, and most of the data in the Medical Birth Register corresponded well or satisfactorily with hospital record data.[26,27] A previous data quality study reported that 98% of the main diagnoses had been correctly reported at the 3-digit *ICD* code level.[25] A wide range of background factors were adjusted for in the analyses, such as 5-minute Apgar scores, the child's birth weight, maternal age, and the mother's psychiatric morbidity before the child's birth. Information on alcohol and illicit drug use during pregnancy was not available. However, we did not adjust for residence or area because the regional health differences in children's health are very small in Finland.[35]

The limitations of our study included self-report of maternal smoking during pregnancy, which is known to underestimate the true extent of smoking.[36,37] The Medical Birth Register data on smoking during pregnancy was

in excellent agreement with the data from 1 Finnish survey.[25] We lack information on mothers who quit smoking during pregnancy. This information has been collected since 1990, when only 10% of mothers quit smoking during the first trimester. There were no differences in the quitters' socioeconomic status (SES) from 1991 through 1993 in Finland.[23]

Another limitation is that diagnoses were set in a variety of hospitals. Therefore, there remains a concern about the accuracy of the diagnoses. However, there is no reason to assume a systematic bias between the groups. In addition, we analyzed the data according to main diagnostic categories, which is reliable because it likely lowers categorization bias with the exception of schizophrenia.[38] It is possible that we underestimated the true prevalence of psychiatric diagnoses because those seeking help from private health care and those not seeking help at all are not included in our data. However, only a limited number of children use private sector services exclusively in Finland because of the comprehensiveness of public services and low availability of private psychiatric services for children in most regions of the country.[39] The limitations concerning outcome measures include a lack of information on common psychiatric diagnoses that have not required psychiatric specialist services. Such common mental disorders include some mild to moderate depressive disorders, anxiety disorders, some of the somatoform disorders, and mild forms of personality disorder.

In addition, we could adjust for severe maternal mental illnesses (inpatient psychiatric care) only because the diagnoses in outpatient care were not available for the mothers. To continue smoking during pregnancy might be a sign of a strong addiction to nicotine or a personality characteristic. Such characteristics might be genetic risk factors for psychiatric problems or may indicate poor parenting skills leading to psychiatric problems. However, the genetic effect is higher in problems that require inpatient hospital care (eg, psychoses and difficult mood disorders). Although we could not control for all maternal genetic factors or any paternal genetic factors, our results suggest an independent effect of smoking exposure.

Socioeconomic background factors, including the parents' educational level and the exposure to household tobacco smoke during the first years of life, which we could not adjust for, can also affect the risk of psychiatric problems, such as conduct disorders.[40-42] Our data did not contain information on SES. Socioeconomic status affects the prevalence of smoking during pregnancy, which complicates modeling.[23] Even if the data existed, an additional problem is the difficulty of categorizing the SES of young mothers because they might not have reached their ultimate level of economic status or education yet. The effect of SES differs according to the problem; for example, in schizophrenia, SES might be a consequence rather than a reason.[43] Because of strict confidentiality legislation, the Finnish Medical Birth Register cannot collect information on fathers. Therefore, we could not obtain any information on their psychiatric morbidity and smoking habits and therefore could not adjust these important variables. Information on alcohol and illicit drug use during pregnancy was not available, although it might affect the association.[44]

Although group differences were clear, there are individual differences in the sensitivity to prenatal exposures. Information about education, such as school grades of the mothers and children and the mothers' educational levels, was not available for this study. It would be interesting to add information on school grades and education to these data. In addition, it would be interesting to study the gene-environment interactions between smoking exposure and different genomic alleles on brain development and psychiatric morbidity in the future. It would also be important to study the effects of prenatal smoking exposure on milder psychiatric morbidities treated in primary health care.

In conclusion, prenatal smoking exposure is associated with an increased risk of psychiatric morbidity in childhood, adolescence, and young adulthood. Prenatal exposure to more than 10 cigarettes a day is associated with increased mortality. It might be possible to reduce psychiatric morbidity by reducing smoking exposure during pregnancy.

Submitted for Publication: August 6, 2009; final revision received November 19, 2009; accepted December 28, 2009.
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Author Contributions: Dr Ekblad had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Financial Disclosure: None reported.
Funding/Support: This study was supported by the Turku University Hospital Research Foundation, the Finnish Foundation for Alcohol Studies, and the South-West Finnish Fund of Neonatal Research.
Role of the Sponsors: The funding sources had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.
Previous Presentation: Preliminary results of this study were presented at the Annual Meeting of the Pediatric Academic Societies; May 2, 2009; Baltimore, Maryland.

REFERENCES

1. Jaddoe VW, Verburg B, de Ridder M, Hofman A, Mackenbach JP, Moll HA, Steegers EA, Witteman JC. Maternal smoking and fetal growth characteristics in different periods of pregnancy: the Generation R Study. *Am J Epidemiol*. 2007;165(10):1207-1215.
2. Kanellopoulos TA, Varvarigou A, Karatza A, Beratis N. Course of growth during the first 6 years in children exposed in utero to tobacco smoke. *Eur J Pediatr*. 2007;166(7):685-692.
3. Karatza AA, Varvarigou A, Beratis NG. Growth up to 2 years in relationship to maternal smoking during pregnancy. *Clin Pediatr (Phila)*. 2003;42(6):533-541.
4. Roza SJ, Verburg BO, Jaddoe VW, Hofman A, Mackenbach JP, Steegers EA, Witteman JC, Verhulst FC, Tiemeier H. Effects of maternal smoking in pregnancy on prenatal brain development: the Generation R Study. *Eur J Neurosci*. 2007;25(3):611-617.
5. Huang LZ, Abbott LC, Winzer-Serhan UH. Effects of chronic neonatal nicotine exposure on nicotinic acetylcholine receptor binding, cell death and morphology in hippocampus and cerebellum. *Neuroscience*. 2007;146(4):1854-1868.

6. Button TM, Maughan B, McGuffin P. The relationship of maternal smoking to psychological problems in the offspring. *Early Hum Dev*. 2007;83(11):727-732.
7. Navarro HA, Seidler FJ, Eylers JP, Baker FE, Dobbins SS, Lappi SE, Slotkin TA. Effects of prenatal nicotine exposure on development of central and peripheral cholinergic neurotransmitter systems: evidence for cholinergic trophic influences in developing brain. *J Pharmacol Exp Ther*. 1989;251(3):894-900.
8. Shea AK, Steiner M. Cigarette smoking during pregnancy. *Nicotine Tob Res*. 2008; 10(2):267-278.
9. Hellström-Lindahl E, Seiger A, Kjaeldgaard A, Nordberg A. Nicotine-induced alterations in the expression of nicotinic receptors in primary cultures from human prenatal brain. *Neuroscience*. 2001;105(3):527-534.
10. Fergusson DM, Woodward L, Horwood J. Maternal smoking during pregnancy and psychiatric adjustment in late adolescence. *Arch Gen Psychiatry*. 1998; 55(8):721-727.
11. Indredavik MS, Brubakk A, Romundstad P, Vik T. Prenatal smoking exposure and psychiatric symptoms in adolescence. *Acta Paediatr*. 2007;96(3):377-382.
12. Williams GM, O'Callaghan M, Najman JM, Bor W, Andersen MJ, Richards D, U C. Maternal cigarette smoking and child psychiatric morbidity: a longitudinal study. *Pediatrics*. 1998;102(1):e11. http://pediatrics.aappublications.org/cgi/content/full/102/1/e11. Accessed June 6, 2009.
13. Ashford J, van Lier PA, Timmermans M, Cuijpers P, Koot HM. Prenatal smoking and internalizing and externalizing problems in children studied from childhood to late adolescence. *J Am Acad Child Adolesc Psychiatry*. 2008;47(7):779-787.
14. Button TM, Thapar A, McGuffin P. Relationship between antisocial behaviour, attention-deficit hyperactivity disorder and maternal prenatal smoking. *Br J Psychiatry*. 2005;187:155-160.
15. Markussen Linnet K, Obel C, Bonde E, Hove Thomsen P, Secher NJ, Wisborg K, Brink Henriksen T. Cigarette smoking during pregnancy and hyperactive-distractible preschoolers: a follow-up study. *Acta Paediatr*. 2006;95(6):694-700.
16. Obel C, Linnet KM, Henriksen TB, Rodriguez A, Järvelin MR, Kotimaa A, Moilanen I, Ebeling H, Bilenberg N, Taanila A, Ye G, Olsen J. Smoking during pregnancy and hyperactivity-inattention in the offspring: comparing results from three Nordic cohorts. *Int J Epidemiol*. 2009;38(3):698-705.
17. Orlebeke JF, Knol DL, Verhulst FC. Increase in child behavior problems resulting from maternal smoking during pregnancy. *Arch Environ Health*. 1997;52(4): 317-321.
18. Thapar A, Fowler T, Rice F, Scourfield J, van den Bree M, Thomas H, Harold G, Hay D. Maternal smoking during pregnancy and attention deficit hyperactivity disorder symptoms in offspring. *Am J Psychiatry*. 2003;160(11):1985-1989.
19. Linnet KM, Wisborg K, Obel C, Secher NJ, Thomsen PH, Agerbo E, Henriksen TB. Smoking during pregnancy and the risk for hyperkinetic disorder in offspring. *Pediatrics*. 2005;116(2):462-467.
20. Maughan B, Taylor A, Caspi A, Moffitt TE. Prenatal smoking and early childhood conduct problems: testing genetic and environmental explanations of the association. *Arch Gen Psychiatry*. 2004;61(8):836-843.
21. Nilsson PM, Hofvendahl S, Hofvendahl E, Brandt L, Ekbom A. Smoking in pregnancy in relation to gender and adult mortality risk in offspring: the Helsingborg Birth Cohort Study. *Scand J Public Health*. 2006;34(6):660-664.
22. Stene-Larsen K, Borge AI, Vollrath ME. Maternal smoking in pregnancy and externalizing behavior in 18-month-old children: results from a population-based prospective study. *J Am Acad Child Adolesc Psychiatry*. 2009;48(3):283-289.
23. Gissler M, Rahkonen O, Arntzen A, Cnattingius S, Andersen AM, Hemminki E. Trends in socioeconomic differences in Finnish perinatal health 1991-2006. *J Epidemiol Community Health*. 2009;63(6):420-425.
24. Roza SJ, Verhulst FC, Jaddoe VW, Steegers EA, Mackenbach JP, Hofman A, Tiemeier H. Maternal smoking during pregnancy and child behaviour problems: the Generation R Study. *Int J Epidemiol*. 2009;38(3):680-689.
25. Jaakkola N, Jaakkola MS, Gissler M, Jaakkola J. Smoking during pregnancy in Finland: determinants and trends, 1987-1989. *Am J Public Health*. 2001;91 (2):284-286.
26. Teperi J. A multi-method approach to the assessment of data quality in the Finnish Medical Birth Registry. *J Epidemiol Community Health*. 1993;47(3):242-247.
27. Gissler M, Teperi J, Hemminki E, Meriläinen J. Data quality after restructuring a national medical registry. *Scand J Soc Med*. 1995;23(1):75-80.
28. Keskimäki I, Aro S. Accuracy of data on diagnoses, procedures and accidents in the Finnish Hospital Discharge Register. *Int J Health Sci*. 1991;2(1):15-21.
29. Statistics Finland. Population statistics 2009. http://www.stat.fi/tup/suoluk/suoluk_vaesto_en.html. Accessed November 16, 2009.
30. Weissman MM, Warner V, Wickramaratne PJ, Kandel DB. Maternal smoking during pregnancy and psychopathology in offspring followed to adulthood. *J Am Acad Child Adolesc Psychiatry*. 1999;38(7):892-899.
31. Brennan PA, Grekin ER, Mortensen EL, Mednick SA. Relationship of maternal smoking during pregnancy with criminal arrest and hospitalization for substance abuse in male and female adult offspring. *Am J Psychiatry*. 2002;159 (1):48-54.
32. Dombrowski SC, Martin RP, Huttunen MO. Gestational exposure to cigarette smoke imperils the long-term physical and mental health of offspring. *Birth Defects Res A Clin Mol Teratol*. 2005;73(3):170-176.
33. Zammit S, Thomas K, Thompson A, Horwood J, Menezes P, Gunnell D, Hollis C, Wolke D, Lewis G, Harrison G. Maternal tobacco, cannabis and alcohol use during pregnancy and risk of adolescent psychotic symptoms in offspring. *Br J Psychiatry*. 2009;195(4):294-300.
34. Ekblad M, Korkeila J, Parkkola R, Lapinleimu H, Haataja L, Lehtonen L; PIPARI Study Group. Maternal smoking during pregnancy and regional brain volumes in preterm infants. *J Pediatr*. 2010;156(2):185-190.e1. doi:10.1016/j.jpeds.2009.07.061.
35. Gissler M, Keskimäki I, Teperi J, Järvelin M, Hemminki E. Regional equity in childhood health—register-based follow-up of the Finnish 1987 birth cohort. *Health Place*. 2000;6(4):329-336.
36. Ford RP, Tappin DM, Schluter PJ, Wild CJ. Smoking during pregnancy: how reliable are maternal self-reports in New Zealand? *J Epidemiol Community Health*. 1997;51(3):246-251.
37. Walsh RA, Redman S, Adamson L. The accuracy of self-report of smoking status in pregnant woman. *Addict Behav*. 1996;21(5):675-679.
38. Isohanni M, Mäkikyrö T, Moring J, Räsänen P, Hakko H, Partanen U, Koiranen M, Jones P. A comparison of clinical and research *DSM-III-R* diagnoses of schizophrenia in a Finnish national birth cohort: clinical and research diagnoses of schizophrenia. *Soc Psychiatry Psychiatr Epidemiol*. 1997;32(5):303-308.
39. Statistical yearbook of the Social Insurance Institution 2007. http://www.kela.fi/it/kelasto/kelasto.nsf/NET/121208122509TL/$File/Vk_07.pdf?OpenElement. Accessed November 17, 2009.
40. Hölling H, Kurth BM, Rothenberger A, Becker A, Schlack R. Assessing psychopathological problems of children and adolescents from 3 to 17 years in a nationwide representative sample: results of the German health interview and examination survey for children and adolescents (KiGGS). *Eur Child Adolesc Psychiatry*. 2008;17(1)(suppl 1):34-41.
41. Monuteaux MC, Blacker D, Biederman J, Fitzmaurice G, Buka SL. Maternal smoking during pregnancy and offspring overt and covert conduct problems: a longitudinal study. *J Child Psychol Psychiatry*. 2006;47(9):883-890.
42. Kollins SH, Garrett ME, McClernon FJ, Lachiewicz AM, Morrissey-Kane E, FitzGerald D, Collins AL, Anastopoulos AD, Ashley-Koch AE. Effects of postnatal parental smoking on parent and teacher ratings of ADHD and oppositional symptoms. *J Nerv Ment Dis*. 2009;197(6):442-449.
43. Dohrenwend BP, Levav I, Shrout PE, Schwartz S, Naveh G, Link BG, Skodol AE, Stueve A. Socioeconomic status and psychiatric disorders: the causation-selection issue. *Science*. 1992;255(5047):946-952.
44. Marmorstein NR, Iacono WG, McGue M. Alcohol and illicit drug dependence among parents: associations with offspring externalizing disorders. *Psychol Med*. 2009; 39(1):149-155.