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RISK OF FEBRILE SEIZURES IN CHILDHOOD IN RELATION TO PRENATAL MATERNAL CIGARETTE SMOKING AND ALCOHOL INTAKE

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The case-control study of febrile seizures in childhood described here, comprising 472 case-control pairs in western Washington, was designed to investigate the importance of prenatal exposures as risk factors for febrile seizures and to determine the degree to which two clinical subtypes of febrile seizures (simple and complex) have different risk factors. Maternal cigarette smoking and alcohol intake during pregnancy were associated with the risk of a febrile seizure in the child. Prenatal maternal cigarette smoking was associated with a twofold increase in the risk of a simple febrile seizure (95% confidence interval 1.2–3.4), and a strong dose-response relation was found. This association could not be explained by maternal demographic variables, maternal alcohol intake, child's birth weight, or childhood medical history variables. Prenatal maternal alcohol intake was associated with a twofold increase in the risk of a complex febrile seizure (95% confidence interval 1.3–3.8), and a strong dose-response relation was present. This association could not be explained by maternal age, race, education, or cigarette smoking. These results suggest that curtailment of smoking and alcohol consumption during pregnancy, a measure already widely prescribed during pregnancy, may also be an effective means of preventing childhood febrile seizures.

alcohol drinking; convulsions, febrile; smoking

Editor's note: *For a discussion of this paper and for the authors' response, see pages 474 and 477, respectively.*

A febrile seizure has been defined as "an event (cerebral seizure) in infancy or childhood, usually occurring between 3 months and 5 years of age, associated with fever but without evidence of intracranial infection or defined cause" (1, p. 377). Febrile seizures are considered a special syndrome in the recently revised scheme for classification of the epilepsies and related syndromes (2), to be distinguished from epilepsy, in which seizures occur in the

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Abbreviations: CI, confidence interval; OR, odds ratio.

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absence of fever. Febrile seizures are the most common type of seizures in childhood, affecting 2–4 percent of children under 5 years of age (3–5). For the majority of affected children, a febrile seizure is a benign event, although certainly frightening for those who witness it. Approximately 30 percent of children with febrile seizures experience one or more recurrences during subsequent bouts of fever (6, 7). For a few children, febrile seizures are associated with an increased risk of developing epilepsy in later life, although this elevation in risk is not uniform and depends on several factors including the clinical features of the febrile seizure, the family history of afebrile seizures, and the presence of preexisting neurologic deficits (6, 8).

Despite the frequency of febrile seizures, relatively little is known about whether there are factors that predispose certain children to convulse with fever. The age-specific incidence rates show a consistent pattern across studies. The age period of highest risk is 6 months to 3 years, with a peak in incidence in the second year of life (3–5). Some studies report an increase in the risk of febrile seizures in males, with relative risk estimates ranging from 1.2 to 1.7 (4, 7). Other studies have reported little difference in the risk by sex (3, 4, 9), and one study found an excess risk in black males only (8). Generally, information available on the effects of race (6, 7) and socioeconomic status (5) suggests relatively little variation in risk according to these factors.

For the purpose of making treatment decisions and in quantifying the risk of subsequent epilepsy in children who have experienced a febrile seizure, the event is often characterized as complex or simple. Most recent studies define complex febrile seizures as seizures which are prolonged (>15 minutes) or lateralized or which recur within 24 hours (5, 6, 9). Simple febrile seizures are defined as single, brief, generalized seizures. Although it is well known that complex and simple febrile seizures pose different long-term risks to the child, there are few studies which examine whether the two types are etiologically distinct.

The case-control study of febrile seizures in childhood described here, comprising 472 case-control pairs, was designed to examine a variety of prenatal, perinatal, and postnatal events as possible risk factors for febrile seizures and to assess the degree to which risk factors for the two clinical subtypes of febrile seizures (simple and complex) are different. The analyses reported here focus on maternal smoking and alcohol consumption during pregnancy.

MATERIALS AND METHODS

Identification of study subjects

The present case-control study of febrile seizures was an outgrowth of a randomized trial of treatment of certain types of febrile seizures. The randomized trial sought to identify all children in the greater Seattle, Washington, area between 8 and 34 months of age who had experienced a febrile seizure. The surveillance system was based on the regular review of emergency room logs in 20 western Washington hospitals and referrals from area pediatricians. All children thus identified with febrile seizures were eligible to participate in the case-control study.

Children with febrile seizures who had experienced previous afebrile seizures or in whom another acute central nervous system disease (for example, encephalitis or meningitis) was present at the time of the index seizure were excluded from further study. Children were also ineligible if the mother did not speak English, the child was adopted or in foster care, or the child was not a resident of western Washington (for example, children of vacationing families).

Both complex and simple febrile seizure subtypes were considered. As in previous studies, a febrile seizure was defined as complex if it lasted more than 15 minutes, had lateralized onset, or was followed by another febrile seizure within 24 hours. Simple febrile seizures lacked all of these

characteristics. The simple febrile seizure group comprised children experiencing their first febrile seizure as well as children with a history of previous febrile seizures. In the analyses of these data, the distinction of interest was between the complex and simple febrile seizure groups, and although children may have had repeat febrile seizures before or after identification by the study, they were categorized into subtype on the basis of the characteristics of the first screened seizure event; thus, each child appears only once in the case group. Complex and repeat febrile seizure cases were enrolled between January 1, 1983, and January 31, 1985. First simple febrile seizure cases were enrolled between January 1, 1984, and October 31, 1985, with the exception of 16 who were enrolled in the first year of the study (January 1–December 31, 1983). The different enrollment periods for the two subtypes reflect changes in the level of study funding and an attempt to obtain similar numbers of cases of each subtype.

A matched control was chosen for each case from among infants born at the same hospital and within the same week as the case child. The first choice for a control was the child born closest in time to the case; if the first choice was unavailable, subsequent choices were made, in order, based on proximity to the case child's time of birth. Contact was attempted using the parent's name and address on the birth certificate. If a telephone number was not obtained through directory assistance and telephone book searches, a standard procedure was followed which called for several mailed contacts before the next control was chosen. This protocol was followed until a control was enrolled for each case born in Washington State.

Controls were ineligible for study participation if the child had had a febrile or afebrile seizure, had died sometime between birth and the time of our contact with the parents, had been given up for adoption, had a non-English-speaking mother, or was a twin or triplet to the matched case.

Data collection

Data about each case and control were obtained from four sources: the initial and follow-up telephone interviews, the hospital medical record of labor and delivery, and the birth certificate. Regardless of how a subject was identified for enrollment in the study, the initial interview was conducted by telephone. For cases who were enrolled in both the randomized trial and the case-control study (24 percent of cases), the telephone interview was restricted to gathering information not already supplied by the parent during participation in the randomized trial. The telephone interview contained questions regarding pregnancy history, use of contraceptive methods, illnesses, medications, cigarette smoking and alcohol use during pregnancy, labor and delivery events, health and immunization history of the child, details of the last febrile illness (and, for cases, details of the seizure), race, occupation and educational level of the parents, and family history of neurologic diseases and febrile convulsions. For all subjects, a follow-up telephone call took place approximately 2 weeks after the initial interview. Its purpose was twofold: First, the interviewer asked additional questions about the family history of febrile seizures; second, a random selection of about one tenth of the questions asked in the first interview was repeated as a reliability check. In addition, the hospital medical record of labor and delivery was abstracted at the hospital of birth, but these data are not considered here because they contained no relevant information for the analyses presented (maternal smoking information was not added to Washington State birth certificates until 1984).

Data analysis

Since cases had been individually matched to controls, initial analyses used the ratio of discordant pairs for each characteristic as an estimate of the relative risk (10). The case groups were treated separately; that is, for each exposure, the rela-

tive risk of a simple febrile seizure was calculated separately from the relative risk of a complex febrile seizure. Multivariate techniques were used in the later stages of analysis to adjust for variables that were not matching factors. These analyses accounted for the matched design through use of the conditional logistic regression model (10, 11) and allowed for statistical adjustment of demographic factors which were seen to differ between cases and controls. This model also provided a convenient tool with which to assess the degree of interaction or effect modification between the various exposures and matching factors.

We also sought to evaluate differences in the constellation of risk factors for a complex versus a simple febrile seizure. In the conditional logistic regression model, an interaction term between the exposure of interest and a dummy variable to represent seizure subtype was added to the model. Controls were assigned the value of their matched case on the seizure subtype dummy variable. The test of whether the coefficient for the interaction term was statistically significantly different from zero provided a test of whether the effect of exposure differed by seizure subtype.

RESULTS

Composition of the study sample

Over both case subgroups and the entire enrollment period, 69 percent (528 of 770) of the eligible cases identified were enrolled in the study. The reasons for not enrolling the remaining 242 cases were as follows: 45 percent because the study was unable to contact them, 33 percent because of parental refusal, 4 percent because of physician refusal, and 18 percent for a variety of other reasons (almost half of these were cases who were overlooked in error).

Over the study period (January 1, 1983–October 31, 1985), the number of subjects with a febrile seizure who were deemed ineligible, comprising mainly children who were not 8–34 months of age when identified, was 147. A number of other possibly eligible children ($n = 94$) were identified, but information on the event which came to the attention of the surveillance system was incomplete and the child's parents could not be contacted to obtain further details.

Of the 528 enrolled cases, 53 had been born outside of Washington State and therefore could not be matched to controls. For three cases, a matched control was not identified before the end of the data collection period. The 472 matched cases and the 56 unmatched cases were compared with regard to several variables. Among the unmatched cases, the fathers were slightly better educated (mean years of education, 14.9 (standard deviation, 2.8) vs. 14.0 (standard deviation, 2.4) and were more often employed (94.3 vs. 88.7 percent), while mothers were less often employed (28.6 vs. 51.2 percent). Aside from these differences, the matched and unmatched cases were similar with respect to the other variables considered, including racial distribution, prenatal maternal cigarette smoking and alcohol-drinking behaviors, seizure characteristics, and family history of epilepsy.

A total of 472 case-control pairs were available for the main study analyses. For 51.3 percent of the cases in the study (242 of 472), the first control identified through the birth certificate file was enrolled. For the majority of remaining cases, the second, third, or fourth control identified was enrolled (19.5, 11.7, and 8.3 percent of the cases, respectively). Out of 1,055 attempted contacts to identify controls, 33 were ineligible, 279 were not successfully contacted because no forwarding address was available, 37 parents verbally refused to participate, 234 did not respond to study letters, and 472 were enrolled in the study.

Cases and their matched controls were first compared with regard to demographic factors (table 1). For simplicity, the presentation of the distribution of cases and controls by race ignored the pair matching, but the comparisons of maternal and paternal age and years of education were based on paired t tests which accounted for the

TABLE 1

*Demographic characteristics of cases and controls in a study of febrile seizures in childhood, western Washington, 1983–1985**

Characteristic	Febrile seizure subtype					
	Complex		Simple		Total	
	Cases (n = 163)	Controls (n = 163)	Cases (n = 309)	Controls (n = 309)	Cases (n = 472)	Controls (n = 472)
Maternal education (years)	13.0 ± 2.0†	14.0 ± 2.0	13.6 ± 2.1	14.2 ± 2.5	13.4 ± 2.1	14.1 ± 2.3
Paternal education (years)	14.0 ± 2.6	14.6 ± 2.5	14.0 ± 2.4	14.6 ± 2.7	14.0 ± 2.4	14.6 ± 2.6
Maternal age (years)	26.0 ± 5.0	28.0 ± 4.5	26.1 ± 5.0	28.2 ± 4.6	26.0 ± 5.0	28.1 ± 4.6
Maternal race (%)						
White	88.9	90.8	85.1	94.8	86.4	93.4
Nonwhite	11.1	9.2	14.9	5.2	13.6	6.6

* n may vary by 1 or 2 for different characteristics because of missing data.
† Mean ± standard deviation.

matched study design. The case parents were less educated than the parents of controls, and the case mothers were about 2 years younger than the control mothers for both the complex and simple febrile seizure subgroups. Complex febrile seizure cases and their matched controls had similar distributions by maternal race. In the simple febrile seizure group, cases and controls had quite different distributions by maternal race; about 85 percent of case mothers were white compared with 95 percent of control mothers. Because of these important and statistically significant case-control differences in maternal race, age, and education, all subsequent multivariate analyses adjusted for these factors. The conditional logistic regression model used in the multivariate analyses allows one, in essence, to match on covariates which were not included as matching variables in the study design.

Mother's use of alcohol and cigarettes during pregnancy

Information on maternal alcohol drinking and cigarette smoking during the pregnancy involving the case or control child was collected during the interview with the mother of each study subject. For 87 study participants, the questions on alcohol and smoking were administered a second time approximately 2 weeks after the first interview to assess the test-retest reliability of responses using the weighted kappa statistic (12). The same interviewer performed both interviews, and the women who were asked a second time about smoking and alcohol use in pregnancy were chosen at random from the entire study population. The percentage of agreement between the two responses was consistently between 94 and 99 percent. The weighted kappas ranged from 0.60 to 0.97 for the subject's responses on smoking and alcohol intake in each trimester of pregnancy.

The frequency of maternal alcohol intake in pregnancy is presented separately for complex and simple febrile seizure cases and controls (table 2), ignoring the matched design of the study for ease of presentation. Frequencies are presented for drinking at any time during pregnancy (yes/no) and also for first-trimester alcohol use. All alcoholic beverage types were combined, and the original six categories from the questionnaire (no drinks per week, <1/week, 1–2/week, ≥3/week, 1–2/day, and ≥3/day) were combined in three groups: less than one drink per week, 1–6 drinks per week, and seven or more drinks per week. The last category was the highest level of drinking which could be examined because of the paucity of women drinking at higher levels.

TABLE 2

*Frequency of prenatal maternal alcohol use and cigarette smoking in a study of febrile seizures in childhood, western Washington, 1983–1985**

Characteristic	Febrile seizure subtype					
	Complex		Simple		Total	
	Cases (n = 163)	Controls (n = 163)	Cases (n = 309)	Controls (n = 309)	Cases (n = 472)	Controls (n = 472)
Maternal alcohol use (%)						
Any time during pregnancy						
Nondrinker	45.1	59.5	59.5	64.4	54.6	62.7
Drinker	54.9	40.5	40.5	35.6	45.4	37.3
During the first trimester						
Nondrinker	50.9	61.1	63.6	69.6	59.3	66.7
Drinker						
Total	49.1	38.9	36.4	30.4	40.7	33.3
By frequency						
<1 drink/week	21.7	22.8	16.6	11.3	18.3	15.3
1–6 drinks/week	23.0	14.8	15.9	16.8	18.3	16.1
≥7 drinks/week	4.3	1.2	3.9	2.3	4.1	1.9
Maternal cigarette smoking (%)						
Nonsmoker	62.1	77.3	66.9	79.3	65.2	78.6
Quit smoking during pregnancy	8.7	6.1	8.1	5.8	8.3	5.9
Smoked throughout pregnancy						
Total	29.2	16.5	25.0	14.9	26.4	15.4
By amount smoked						
1–10 cigarettes/day	11.2	4.3	9.7	6.5	10.2	5.7
11–20 cigarettes/day	12.4	10.4	11.7	6.5	11.9	7.8
≥21 cigarettes/day	5.6	1.8	3.6	1.9	4.3	1.9

* n may vary by 1 or 2 for different characteristics because of missing data.

The mothers of simple febrile seizure cases and controls had fairly similar frequency distributions for alcohol drinking in the first trimester (table 2). The mothers of complex febrile seizure cases and controls, however, had more dissimilar patterns of alcohol intake in the first trimester. In this subgroup, first-trimester alcohol drinkers comprised 49 and 39 percent of the mothers of the cases and controls, respectively. Approximately the same proportions of case and control mothers reported consuming less than one drink per week, but more mothers of cases reported having 1–6 drinks per week and seven or more drinks per week compared with the mothers of controls.

Although the results are not shown in detail, the association between maternal alcohol intake at any time during pregnancy (coded as yes/no) and the risk of a febrile seizure was assessed through calculation of the odds ratio, adjusting for mother's race, age, and educational level. Children exposed to prenatal alcohol had an approximately twofold increase in the risk of a complex febrile seizure compared with the children of nondrinkers (odds ratio (OR) = 2.2, 95 percent confidence interval (CI) 1.3–3.8), but prenatal alcohol exposure had little relation to the risk of a simple febrile seizure (OR = 1.2, 95 percent CI 0.8–1.8). A statistical test was performed to determine whether the effect of prenatal alcohol on the risk of a febrile seizure varied by seizure subtype. The likelihood ratio statistic (1 df) for the coefficient of the interaction term between disease subgroup and prenatal alcohol exposure was 3.54 (p = 0.06), and although this did not quite reach the 0.05 level of statistical significance, the effect of alcohol was examined separately for complex and simple febrile seizure subgroups.

TABLE 3

Risk of a complex febrile seizure in childhood, by maternal alcohol intake during each trimester of pregnancy, western Washington, 1983–1985

	Odds ratio adjusted for maternal age, education, and race		
	First trimester	Second trimester	Third trimester
Nondrinker	1.0	1.0	1.0
Alcohol drinker			
Total	1.8 (1.1–3.0)*	1.5 (0.9–2.7)	1.4 (0.8–2.6)
By frequency			
<1 drink/week	1.3 (0.6–2.5)	0.9 (0.4–1.8)	1.1 (0.5–2.2)
1–6 drinks/week	1.9 (0.9–3.8)	2.6 (1.2–5.7)	2.5 (1.0–6.1)
≥7 drinks/week	7.5 (1.3–42.0)	2.9 (0.4–22.2)	1.1 (0.2–9.0)

* Numbers in parentheses, 95 percent confidence interval.

The relation between maternal alcohol intake in each trimester and the risk of a complex febrile seizure in the child was examined (table 3). The strength of the effect, as measured by the odds ratio estimate, was greatest in the first trimester, with an odds ratio of 1.8 (95 percent CI 1.1–3.0). The dose-response relation was also assessed in each trimester. The trend tests were statistically significant for both the first and second trimesters ($p = 0.005$ and $p = 0.018$, respectively) but not for the third trimester, and the pattern of the odds ratios was most striking in the first trimester. All further analyses on the relation between maternal alcohol intake in pregnancy and the risk of a complex febrile seizure focused on first-trimester exposure to alcohol.

The adjustment for demographic factors, while changing the point estimates of the odds ratios somewhat, did not have much effect on the statistical significance of the dose-response relation, and both the crude and adjusted odds ratios for first-trimester maternal alcohol intake showed a statistically significant trend (table 4). Little elevation in risk was seen for children whose mothers drank alcohol less than once per week. There was about a twofold and a 7.5-fold increase in the risk of a complex febrile seizure among children of mothers drinking 1–6 drinks per week and seven or more drinks per week, respectively, when compared with the risk among children of nondrinking mothers.

Smoking and alcohol intake are related behaviors, and it is possible that the effect of one of these exposures may be explained at least partially by the other. To address this, the odds ratios for a complex febrile seizure according to level of first-trimester maternal alcohol intake were further adjusted for maternal smoking in pregnancy (coded as nonsmoker and smoker at one of three levels). The odds ratios for a complex febrile seizure by maternal alcohol intake were not materially changed from the earlier values (table 4), and the test for trend remained statistically significant.

The complex and simple febrile seizure subgroups were examined for differences in the effect of smoking during pregnancy. The association between smoking at any time during pregnancy (coded as yes/no) and the risk of a febrile seizure was assessed through calculation of the odds ratio, adjusting for mother's race, age, and educational level. Children of mothers who smoked during pregnancy had a 1.5-fold increase in the risk of a complex febrile seizure compared with the children of nonsmokers (95 percent CI 0.9–2.6). There was a somewhat greater increase in the risk of a simple febrile seizure for children of mothers who smoked compared with children of nonsmokers (OR = 1.9, 95 percent CI 1.3–2.9). The likelihood ratio statistic (1 df) for the regression coefficient of the smoking × case subgroup interaction term was not statistically significant ($p = 0.84$), and the subsequent analyses on smoking

TABLE 4

Risk of a complex febrile seizure in childhood, by maternal alcohol intake during the first trimester of pregnancy, western Washington, 1983–1985

	Crude		Adjusted for mother's age, education, and race		Adjusted for mother's age, education, race, and cigarette smoking	
	Odds ratio	p_{trend}	Odds ratio	p_{trend}	Odds ratio	p_{trend}
Nondrinker	1.0		1.0		1.0	
Alcohol drinker						
Total	1.6 (1.0–2.4)*		1.8 (1.1–3.0)		1.6 (0.95–2.8)	
By frequency						
<1 drink/week	1.1 (0.6–2.0)		1.3 (0.6–2.5)		1.2 (0.6–2.5)	
1–6 drinks/week	2.0 (1.1–3.7)		1.9 (0.9–3.8)		1.8 (0.9–3.7)	
≥7 drinks/week	3.5 (0.7–17.1)	0.007	7.5 (1.3–42.0)	<0.005	7.5 (1.1–50.7)	0.02

* Numbers in parentheses, 95 percent confidence interval.

considered all febrile seizure cases together. Twenty-six percent of the mothers of cases smoked throughout pregnancy, compared with 15 percent of the mothers of controls (table 2).

The risk of a febrile seizure across levels of cigarette smoking was considered, and the dose-response relation was assessed in two ways (table 5). First, the effect of duration of smoking was examined, comparing women who quit smoking during the first or second trimester and women who smoked throughout pregnancy with nonsmokers. Second, the intensity of smoking was addressed, comparing women who smoked throughout pregnancy at three levels (1–10, 11–20, and ≥21 cigarettes/day) with nonsmokers, omitting women who quit smoking during pregnancy. These two measures of dose were not independent; women who quit smoking during pregnancy comprised mostly women who had been smoking 1–10 cigarettes per day, whereas women who smoked throughout pregnancy had a different distribution. For each analysis, these two dose-response relations were assessed and a test for trend was computed using the likelihood ratio statistic from the conditional logistic regression model.

The crude and adjusted results for maternal cigarette smoking were similar, and in both instances the trend tests for duration and intensity of smoking exposure were statistically significant. Children of women who quit smoking during pregnancy were similar to the children of nonsmokers in their risk of a febrile seizure. Children of women who kept smoking throughout pregnancy had a twofold increase in the risk of a febrile seizure compared with the children of nonsmokers. There was an increasing risk with increasing amount smoked, and children of the heaviest smokers had a 2.6-fold increase in the risk of a febrile seizure (95 percent CI 1.0–6.6) compared with the children of nonsmokers.

The relation between maternal smoking and the risk of a febrile seizure in the child was examined, adjusting for maternal alcohol intake in the first trimester (coded as nondrinker and alcohol drinker at one of three levels) (table 6). The estimates of the odds ratios for smoking were calculated separately for the simple febrile seizure and complex febrile seizure subgroups because the effect of alcohol differed across the case subgroups. In the simple febrile seizure group, controlling for first-trimester maternal alcohol intake had little effect on the odds ratios for smoking. However, in the complex febrile seizure group, controlling for alcohol intake in the first trimester had a striking effect on the relation between smoking and the risk of a febrile seizure. The odds ratios were reduced and approached the null value, and the tests for trend for both duration and intensity of exposure were no longer statistically significant.

In an attempt to understand the mecha-

TABLE 5

Risk of a febrile seizure in childhood, by maternal cigarette smoking during pregnancy, western Washington, 1983–1985

	Crude odds ratio	p_{trend}	Odds ratio adjusted for maternal age, education, and race	p_{trend}
Nonsmoker	1.0		1.0	
Quit smoking during pregnancy	1.6 (1.0–2.7)*		1.2 (0.7–2.1)	
Smoked throughout pregnancy				
Total	2.1 (1.5–2.9)	<0.001	2.0 (1.3–2.8)	<0.001
By amount smoked				
1–10 cigarettes/day	2.1 (1.2–3.5)		1.6 (0.9–2.9)	
11–20 cigarettes/day	2.0 (1.2–3.2)		2.0 (1.2–3.4)	
≥21 cigarettes/day	2.7 (1.2–6.1)	<0.001	2.6 (1.0–6.6)	<0.001

* Numbers in parentheses, 95 percent confidence interval.

TABLE 6

Risk of a febrile seizure in childhood, by maternal cigarette smoking during pregnancy, adjusted for maternal alcohol intake during the first trimester, western Washington, 1983–1985

	Odds ratio adjusted for maternal first-trimester alcohol intake, age, education, and race			
	Complex febrile seizure	p_{trend}	Simple febrile seizure	p_{trend}
Nonsmoker	1.0		1.0	
Quit smoking during pregnancy	1.0 (0.4–2.7)*		1.2 (0.6–2.5)	
Smoked throughout pregnancy				
Total	1.2 (0.6–2.3)	0.63	2.0 (1.2–3.4)	<0.005
By amount smoked				
1–10 cigarettes/day	1.3 (0.4–4.2)		1.5 (0.7–3.2)	
11–20 cigarettes/day	1.1 (0.5–2.7)		2.6 (1.3–5.3)	
≥21 cigarettes/day	0.9 (0.2–4.9)	0.81	2.4 (0.7–8.2)	<0.005

* Numbers in parentheses, 95 percent confidence interval.

nism through which maternal prenatal smoking might increase the risk of a simple febrile seizure, we considered the possibility that the children of mothers who smoked were sick more often and were at increased risk of a simple febrile seizure through their exposure to more fevers. This question seemed especially important to consider vis-à-vis the smoking-in-pregnancy finding, because the incidence of upper respiratory illness is reportedly increased among the children of smokers (13). When the analyses for smoking were adjusted for a history of medical problems with the ears, nose, or lungs, as reported by the mother, the effect of smoking was virtually unchanged. Similarly, adjustment for the number of febrile illnesses the child had had in the past year (maternal report) had little effect on the odds ratio estimates for the effect of smoking. Adjusting for birth weight, which is known to be decreased among the children of smokers (14), also had little effect on the odds ratio estimates.

DISCUSSION

Maternal alcohol drinking in the first trimester of pregnancy was associated with an increase in the risk of a complex febrile seizure, and a strong dose response was observed, but there was little association between alcohol and the risk of a simple febrile seizure. Maternal cigarette smoking in pregnancy was associated with a twofold increase in the risk of a simple febrile seizure, and a strong dose response was found. Although initial results showed an associ-

ation between maternal prenatal smoking and the risk of a complex febrile seizure in the child, after adjustment for prenatal maternal alcohol intake there was little or no relation. Before we commence further discussion of the study results, some strengths and possible weaknesses of the study deserve attention.

The present study identified children with febrile seizures primarily through emergency room logs, not through hospital inpatient records or specialty clinics where patients are likely to be referred for care. Previous studies which used cases ascertained through hospitals or specialty-care clinics have been shown to suffer from selection bias, leading to an overestimation of the severity of sequelae (15). Just as this type of referral bias is known to affect studies on the prognosis of febrile seizures, it may also affect studies on the etiology of febrile seizures. Although a lesser degree of this kind of selection bias may operate in the case group considered here, the bias is probably not as large as in past studies because of the broader method of case identification. Cases most likely to be missed in the current study include children who were managed entirely by their pediatricians (without use of hospital emergency room services) and children whose parents sought no medical advice after a febrile seizure occurrence. The cases identified may also have come disproportionately from families who use the hospital emergency room for primary care. To the extent that the hospital of birth reflects these case selection factors, the fact that controls were matched to cases on hospital of birth should help to circumvent any bias in the results.

Additionally, not all cases known to have occurred participated in the study. Since no demographic information was available for the nonparticipating cases, it was impossible to delineate any bias which might have resulted from the selection of certain cases for the study. Although the extent of selection bias is unknown, it is probably less of a factor in this study than in previous case-control studies of febrile seizures, since approximately 70 percent of cases participated.

The 27 percent of controls for whom we could obtain no telephone number or forwarding address undoubtedly included many families who had moved either out of the Seattle area or out of state; this figure roughly corresponds to the 21 percent which might have been expected based on US Census estimates of population stability (16). Such migration would make these families ineligible rather than nonparticipants, because had the child experienced a febrile seizure, he or she would not have been identified through the surveillance system. Thus, the filtering mechanism which applied to controls was roughly similar to that which applied to cases in that both cases and controls had to have been born in Washington State and had to be resident in the study area at the time of data collection to be included in the study.

For the control group, availability of data from the birth certificates provided an opportunity to examine factors associated with recruitment into the study. Within the group of controls who were our first choice (born closest to case), mothers who participated were an average of 3 years older, more often white, and less often of lower socioeconomic status than mothers who did not participate. Of particular concern is whether this selective participation might bias the findings presented here—for instance, if smoking and alcohol use among participating control mothers were not representative. Among all study mothers, smoking was more common among younger, less educated women. Alcohol intake was less common among nonwhite mothers but had little relation to age or education. All multivariate analyses were controlled for maternal age, race, and education in an attempt to remedy any bias which might have resulted from selective participation in the control group. Additionally, the finding of a significant dose response argues that these findings are not merely the result of an unrepresentative group of controls.

In the control group, approximately 22 percent of women smoked during pregnancy. This figure agrees closely with expectation based on all Washington State births; in 1984, the first year smoking information was added to the birth certificate, 22.9 percent of mothers reported smoking during their pregnancies (S. Schwartz, University of Washington, personal communication, 1989). In the present study, there was an approximately twofold increase in the risk of a febrile seizure associated with smoking. Among the complex febrile seizure group, this effect was explained entirely by maternal alcohol use in the first trimester. For the simple febrile seizure group, in contrast, each attempt to elucidate the mechanism through which smoking might increase the risk of a febrile seizure was unsuccessful. Although no previous studies have specifically considered maternal smoking and febrile seizure risk, in two studies which considered maternal prenatal smoking and the risk of epilepsy in the child (5, 17), no association was demonstrated.

The relation between maternal smoking and the risk of a simple febrile seizure appears to merit further study, both to confirm the association and (if verified) to determine the underlying mechanism. Investigation of an entity such as febrile seizures is difficult because the event under study occurs in association with a febrile illness. Hence, there is a possibility that differences which are assessed between cases and controls may be related to the risk of fever and not necessarily related to the risk of seizing with fever. Exploration of several hypothesized mechanisms in these data suggested that the effect of maternal prenatal smoking on the risk of a simple febrile seizure was independent of the frequency of feverish illness or the type of illness that these children may have experienced. In another prospective study, an increased risk of febrile seizures was noted among children with a history of ear infection, frequent sore throats, or pneumonia (18), although neither prenatal nor postnatal maternal smoking was considered and there was no information on whether a history of any of these illnesses preceded the occurrence of a febrile seizure.

Data from several cohort studies of parturient women have reported that 2.8 percent of women had seven or more alcoholic drinks per week during pregnancy (19, 20); this figure corresponds closely to the frequency of alcohol drinking at this level observed in the current study. The frequency of drinking among the mothers of controls differed for the two subgroups: 41 percent of the mothers of complex febrile seizure controls drank at some time during pregnancy compared with 36 percent of the mothers of simple febrile seizure controls. This difference is not likely to be explained by demographic differences in these groups, since the two control groups appeared quite similar in their distributions by maternal age, education, and race. In any case, the association between drinking and the risk of a complex febrile seizure would be strengthened if the simple febrile seizure control group were somehow a better representation of the behavior of mothers of controls.

In considering maternal alcohol intake as a potential risk factor for complex febrile seizures in the child, other factors that may differ between mothers who drink alcohol and mothers who abstain must be considered. If there are maternal characteristics which lead to maternal alcohol use and these factors are also related to the risk of a febrile seizure in the child, then the study findings would be biased. All multivariate analyses were adjusted for maternal age, educational level, and race, and the adjusted odds ratios showed a strong trend of increasing risk of a complex febrile seizure with increasing level of maternal alcohol intake. In an attempt to adjust for differences in maternal care practices (e.g., fever control), we examined the effect of maternal alcohol intake adjusted for the number of fevers the child had had in the past year (as reported by the mother); there was little change in the estimated odds ratios. The

mechanism through which alcohol may be related to the risk of a complex febrile seizure is unknown.

The results of this study provide yet another reason for clinicians to instruct their pregnant patients to avoid the use of both tobacco and alcohol during pregnancy. Further research is required to confirm the effects of maternal prenatal alcohol intake and smoking on the risk of a febrile seizure in the child. Additionally, research efforts directed toward elucidating the underlying pathophysiologic mechanisms of these relations would be useful. The present study makes clear the importance of gathering data that allow febrile seizures to be studied by subtype, because the results suggest that the subtypes may be etiologically distinct.

References

1. Proceedings: Consensus Development Conference on Febrile Seizures, National Institutes of Health, May 19–21, 1980. Epilepsia 1981;22:377–81.
2. Dreifuss FE, Martinez-Lage M, Roger J, et al. Proposal for classification of epilepsies and epileptic syndromes. Epilepsia 1985;26:268–78.
3. Vandenberg BJ, Yerushalmy J. Studies on convulsive disorders in young children. I. Incidence of febrile and nonfebrile convulsions by age and other factors. Pediatr Res 1969;3:298–304.
4. Hauser WA, Kurland LT. The epidemiology of epilepsy in Rochester, Minnesota, 1935 through 1967. Epilepsia 1975;16:1–66.
5. Ross EM, Peckham CS, West PB, et al. Epilepsy in childhood: findings from the National Child Development Study. Br Med J 1980;1:207–10.
6. Nelson KB, Ellenberg JH. Predictors of epilepsy in children who have experienced febrile seizures. N Engl J Med 1976;295:1029–33.
7. Vandenberg BJ. Studies on convulsive disorders in young children. III. Recurrence of febrile convulsions. Epilepsia 1974;15:177–90.
8. Nelson KB, Ellenberg JH. Prognosis in children with febrile seizures. J Pediatr 1978;61:720–7.
9. Verity CM, Butler NR, Golding J. Febrile convulsions in a national cohort followed up from birth. I. Prevalence and recurrence in the first five years of life. Br Med J 1985;290:1307–10.
10. Breslow NE, Day NE, eds. Statistical methods in cancer research. Vol 1. The analysis of case-control studies. Lyon, France: International Agency for Research on Cancer, 1980. (IARC Scientific Publication no. 32).
11. Breslow NE, Day NE, Halvorsen KT, et al. Estimation of multiple relative risk functions in matched case-control studies. Am J Epidemiol 1978;108:299–307.
12. Fleiss JL. Statistical methods for rates and proportions. New York: John Wiley & Sons, Inc., 1981:224.
13. Rantakallio P. A follow-up study up to the age of 14 of children whose mothers smoked during pregnancy. Acta Pediatr Scand 1983;72:747–53.
14. Rush D, Cassano P. Relationship of cigarette smoking and social class to birth weight and perinatal mortality among all births in Britain, 5–11 April 1970. J Epidemiol Community Health 1983;37:249–55.
15. Ellenberg J, Nelson KB. Sample selection and the natural history of disease: studies of febrile seizures. JAMA 1980;243:1337–40.
16. US Bureau of the Census. Statistical Abstract of the United States: 1987. 107th ed. Washington, DC: Bureau of the Census, 1987.
17. Nelson KB, Ellenberg JH. Antecedents of seizure disorders in early childhood. Am J Dis Child 1986;140:1053–61.
18. Verity CM, Butler NR, Golding J. Febrile convulsions in a national cohort followed up from birth. II. Medical history and intellectual ability at 5 years of age. Br Med J 1985;290:1311–15.
19. Marbury MC, Linn S, Monson R, et al. The association of alcohol consumption with outcome of pregnancy. Am J Public Health 1983;73:1165–8.
20. Mills JL, Graubard BI, Harley EE, et al. Maternal alcohol consumption and birth weight: How much drinking during pregnancy is safe? JAMA 1984;252:1875–9.