American Journal of Epidemiology

Vol. 149, No. 5
Printed in U.S.A.

Maternal Smoking and Down Syndrome: The Confounding Effect of Maternal Age

Chi-Ling Chen,[1,2] Tim J. Gilbert,[3] and Janet R. Daling[1,2]

Inconsistent results have been reported from studies evaluating the association of maternal smoking with birth of a Down syndrome child. Control of known risk factors, particularly maternal age, has also varied across studies. By using a population-based case-control design (775 Down syndrome cases and 7,750 normal controls) and Washington State birth record data for 1984–1994, the authors examined this hypothesized association and found a crude odds ratio of 0.80 (95% confidence interval 0.65–0.98). Controlling for broad categories of maternal age (<35 years, ≥35 years), as described in prior studies, resulted in a negative association (odds ratio = 0.87, 95% confidence interval 0.71–1.07). However, controlling for exact year of maternal age in conjunction with race and parity resulted in no association (odds ratio = 1.00, 95% confidence interval 0.82–1.24). In this study, the prevalence of Down syndrome births increased with increasing maternal age, whereas among controls the reported prevalence of smoking during pregnancy decreased with increasing maternal age. There is a substantial potential for residual confounding by maternal age in studies of maternal smoking and Down syndrome. After adequately controlling for maternal age in this study, the authors found no clear relation between maternal smoking and the risk of Down syndrome. *Am J Epidemiol* 1999;149:442–6.

Down syndrome; smoking; trisomy

The association between maternal smoking and the risk of giving birth to a child with Down syndrome has been the focus of several studies. The published results have been inconsistent and have included reports of strong negative associations (1), a negative association among older women only (2), overall positive associations (3), positive associations in certain ethnic groups (4), or no association (5–10). Among those reporting a negative association, it has been suggested that smoking among older women may inhibit the production, fertilization, or survival of gametes with trisomy 21 or reduce the survival of such conceptuses during intrauterine life, which would contribute to a decreased prevalence of liveborn babies with Down syndrome (2). On the other hand, smoking is known to affect the female reproductive system and is associated with reduced fertility and an earlier age of menopause (11), which in turn may be associated with the precocious aging of oocytes and may predispose to an increased risk for trisomy 21 (12).

Possible reasons for the inconsistent results of previous studies of maternal smoking and the risk of Down syndrome are differences in study design, small sample sizes, and differences in how controls were selected; variations in the definition and ascertainment of maternal smoking; and control of potential confounding variables, particularly maternal age. Controlling for maternal age seems of critical importance, since it is such a strong risk factor for Down syndrome. Although there is no consensus regarding a biologic mechanism by which advanced maternal age increases the risk of having a Down syndrome child (13), hypotheses have been suggested for the possible interaction of maternal age and maternal smoking to explain differences in risk for different age groups (14). In this study, we used a population-based case-control design to examine the relation between maternal smoking and the risk of having a child with Down syndrome.

MATERIALS AND METHODS

We conducted a case-control study of children born with Down syndrome by using Washington State birth record data for 1984–1994. A case was defined as a woman whose child was born with Down syndrome,

Received for publication October 7, 1997, and accepted for publication September 2, 1998.

Abbreviations: BERD, Birth Events Record Database; CI, confidence interval; OR, odds ratio.

[1] Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA.
[2] Department of Epidemiology, University of Washington, Seattle, WA.
[3] School of Medicine, Native American Center of Excellence, University of Washington, Seattle, WA.

which was indicated as such in the record of singleton births. To identify as many Down syndrome cases as possible, we also searched for *International Classification of Diseases,* Ninth Revision diagnosis code 7580 for Down syndrome in the Birth Events Record Database (BERD), which was created in Washington State in 1987 and is updated continually. This comprehensive database links Washington State hospital inpatient discharge records for mothers and newborns with birth certificate and infant death records, and it is designed to provide a single source of detailed hospital charge, prenatal care, and birth outcome information. Overall, 775 Down syndrome cases were identified, 306 (40 percent) from birth records only, 227 (29 percent) from BERD only, and 242 (31 percent) from both birth records and BERD. Controls were selected randomly, matched only by birth year for women whose children were born without any congenital malformations (n = 7,750). A high case-control ratio (1:10) was used to ensure that enough older controls (aged ≥35 years) would be available for comparison. Information on whether women smoke during pregnancy is ascertained routinely via a "yes" or "no" check box on the birth record and was available for the entire study period.

We analyzed the data in a number of ways chosen to duplicate methods used in other studies, including controlling for confounding. Potential confounding factors such as maternal age (<35 years, ≥35 years), paternal age (<35 years, ≥35 years), marital status (married/unmarried), parity (0, 1, 2, ≥3), trimester during which prenatal care began (none, first, second, or third), alcohol consumption (yes/no), prior fetal loss (yes/no), and race (white/nonwhite) were included individually in the unconditional logistic regression model. Except for maternal age (<35 years, ≥35 years), race, and parity, the other variables did not appreciably affect risk estimates of the association between maternal smoking and Down syndrome and were not included. An analysis was performed by using broad categories of maternal age (<35 years, ≥35 years), five categories of race, and parity (0, 1, 2, ≥3) as confounding factors. Finally, we controlled for the effect of maternal age by using the exact year and the same race and parity categories. Adjusted odds ratios and corresponding 95 percent confidence intervals were used to estimate the odds ratios. The effect of maternal smoking on the risk of having a Down syndrome child, after adjustment for confounders, was estimated by using unconditional logistic regression.

RESULTS

The prevalence of Down syndrome for the entire study period was 0.95 per 1,000 livebirths. The sharp increase in Down syndrome with increasing maternal age is shown in figure 1. Selected characteristics of cases and controls, including maternal age, race, and smoking status, are shown in table 1. Overall, cases tended to smoke less than controls, particularly in the age group ≥35 years (7.0 percent of cases, 14.2 percent of controls). Among controls, the relation between smoking during pregnancy and maternal age is shown in figure 2. The proportion of controls who smoked during pregnancy decreased substantially with increasing maternal age.

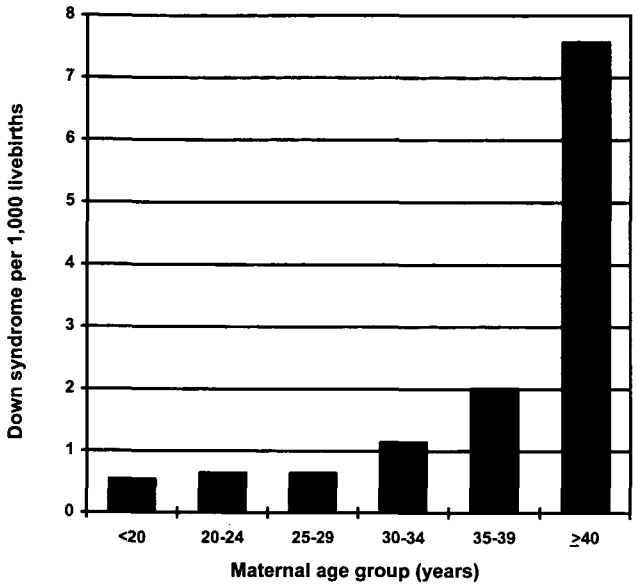

FIGURE 1. Prevalence of Down syndrome births (n = 775) in Washington State, 1984–1994. The crude rate was 0.95 per 1,000 livebirths.

Results of the logistic regression analyses are presented in table 2. The crude odds ratio of maternal smoking and Down syndrome was 0.80 (95 percent confidence interval (CI) 0.65–0.98); when we included maternal age (<35 years, ≥35 years) alone in the model, the odds ratio was 0.87 (95 percent CI 0.71–1.07). Controlling for marital status, paternal age, when prenatal care began, and number of prenatal visits did not affect the risk estimates in the initial analysis. A second analysis, in which we controlled for maternal age in the same broad categories and for parity and race, resulted in a similar odds ratio (odds ratio (OR) = 0.89, 95 percent CI 0.73–1.10). However, controlling for single-year maternal age, race, and parity produced a risk estimate of unity (OR = 1.00, 95 percent CI 0.82–1.24). Since the relation between maternal age and Down syndrome is not linear (figure 1), we put the age-squared term into the model and found no difference in the resulting odds ratio.

TABLE 1. Selected characteristics of Down syndrome cases and birth-year-matched controls, Washington State, 1984–1994

	Cases (n = 775)		Controls (n = 7,750)	
	No.	%	No.	%
Age (years)				
<20	50	6.5	801	10.3
20–24	143	18.5	2,092	27.0
25–29	163	21.0	2,431	31.4
30–34	205	26.5	1,664	21.5
≥35	214	27.6	762	9.8
Race				
White	629	81.2	6,322	81.6
Hispanic	68	8.8	450	5.8
Black	22	2.8	289	3.7
American Indian	14	1.8	171	2.2
Other	31	4.0	395	5.1
Unknown	11	1.4	123	1.6
Marital status				
Married	614	79.2	6,016	77.6
Unmarried	161	20.8	1,717	22.2
Unknown			17	0.2
Smoking during pregnancy				
Age <35 years				
Yes	112	20.0	1,411	20.2
No	421	75.0	5,214	74.6
Unknown	28	5.0	363	5.2
Age ≥35 years				
Yes	15	7.0	108	14.2
No	186	86.9	611	80.2
Unknown	13	6.1	43	5.6
Parity				
Age <35 years				
0	214	38.1	2,933	42.0
1	186	33.2	2,261	32.4
2	88	15.7	1,053	15.1
≥3	67	11.9	573	8.2
Unknown	6	1.1	168	2.4
Age ≥35 years				
0	22	10.3	160	21.0
1	45	21.0	236	31.0
2	48	22.4	165	21.7
≥3	95	44.4	181	23.8
Unknown	4	1.9	20	2.6
Amniocentesis				
Yes	50	6.5	380	4.9
No	674	87.0	6,983	90.1
Unknown	51	6.6	387	5.0
Trimester prenatal care began				
None	4	0.5	52	0.7
First	607	78.3	6,024	77.7
Second	129	16.7	1,378	17.8
Third	35	4.5	296	3.8
Number of prenatal visits				
0	4	0.5	67	0.9
1–6	70	9.0	599	7.7
7–12	458	59.1	4,276	55.2
≥13	197	25.4	2,429	31.3
Unknown	46	6.0	379	4.9
Prior fetal loss				
<20 weeks				
Yes	187	24.1	1,496	19.3
No	579	74.7	6,059	78.2
Unknown	9	1.2	195	2.5
≥20 weeks				
Yes	30	3.9	216	2.8
No	733	94.6	7,342	94.7
Unknown	12	1.5	192	2.5

Table continues

DISCUSSION

Limitations to the present study should be considered when interpreting the results. First, by relying on a "yes" or "no" answer regarding whether women smoked during pregnancy, we clearly missed potentially important information, such as when before and during pregnancy smoking occurred. Also, it is likely that women may have underreported their smoking status during pregnancy. However, we have no reason to believe that this underreporting occurred more often among mothers who subsequently had a Down syndrome child as compared with normal controls. Second, we were unable to fully address the effect of recognized and unrecognized spontaneous abortions on risk estimates in studies of livebirths.

Controlling for the confounding effect of maternal age was critical in our study, because an apparent negative association with smoking was present until we controlled for this variable. In our data, the prevalence of Down syndrome births increased with maternal age, particularly after age 35 years, but the prevalence of maternal smoking decreased with increasing age.

In previous studies, the selection of cutoff points used to control for maternal age has varied. Two early studies produced contrasting results: Kelsey et al. (3) reported an increased risk of having a Down syndrome child associated with smoking 21 or more cigarettes a day, whereas Shiono et al. (1) found a strong negative association (OR = 0.2, 95 percent CI 0.1–0.9). The precise method used to control for maternal age was not indicated in either study, and the number of Down syndrome cases was small in both. Stratification to control for maternal age occurred in four previous studies. Two used <35 years and ≥35 years to define strata (4, 5), whereas the third used three strata to control for maternal age (6). The maternal age cutoff points were not specified in the fourth study (7).

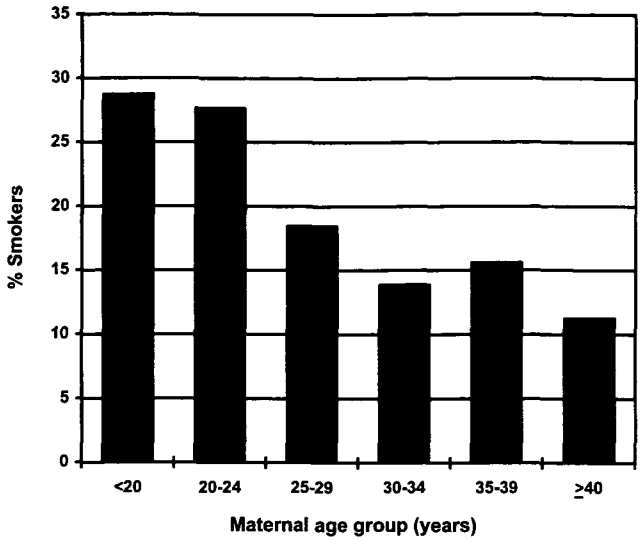

FIGURE 2. Reported prevalence of smoking during pregnancy among controls (n = 7,750) in Washington State, 1984–1994.

TABLE 2. Adjusted odds ratios for maternal smoking during pregnancy and the risk of Down syndrome, Washington State, 1984–1994

	Odds ratio	95% confidence interval
Crude odds ratio	0.80	0.65–0.98
First regression analysis*	0.87	0.71–1.07
Second regression analysis†	0.89	0.73–1.10
Third regression analysis‡	1.00	0.82–1.24

* Adjusted for maternal age (<35 years, ≥35 years).
† Adjusted for maternal age (<35 years, ≥35 years), parity (0, 1, 2, ≥3), and race (five categories).
‡ Adjusted for exact year of maternal age, parity (0, 1, 2, ≥3), and race (five categories).

Among the remaining studies, three used a matched design to control for the effect of maternal age (2, 8, 9). Hook and Cross (2) reported a negative association that was stronger in older women (aged ≥30 years) than in women younger than age 30 years after closely matching maternal age for cases and normal controls. Cuckle et al. (8) individually matched cases to controls according to maternal age at birth to within 3.5 years and reported a risk estimate of unity. More recently, Kline et al. (9) found a reduced risk of Down syndrome at amniocentesis associated with maternal smoking (OR = 0.8, 95 percent CI 0.4–1.4) after matching cases to chromosomally normal controls by exact year of maternal age. Kallen, who conducted a study with the largest number of cases to date (10), reported no association between maternal smoking and Down syndrome (OR = 0.98, 95 percent CI 0.86–1.11) after stratification of maternal age in 1-year intervals.

By using both birth records and the BERD database, we were able to identify a more complete series of livebirth Down syndrome cases in Washington State and therefore minimize the possibility of bias caused by underreporting when only birth certificate data are used. However, it is likely that substantial underreporting still existed because of prenatal diagnosis and termination of Down syndrome fetuses. We do not believe that this affected the main goal of our study, which was to demonstrate the need for careful control of confounding by age in any analysis of Down syndrome and smoking or any other exposure that decreases with age. Selection of an appropriate control group has been the subject of some debate in case-control studies of congenital malformations (15, 16). In our study, using a population-based design to select controls helped to ensure that controls were representative of the population from which the cases arose and to avoid biases associated with hospital-based control groups. Also, the number of Down syndrome cases available for study was substantially larger than in many prior studies, which increased the power to detect significant associations.

In summary, there is a substantial potential for residual confounding by maternal age in studies of maternal smoking and Down syndrome. In some prior studies, there could well have been downward bias in the risk estimates. However, among studies that have adequately taken maternal age into account, no clear relation exists between smoking and Down syndrome.

ACKNOWLEDGMENTS

The authors are indebted to Dr. Noel S. Weiss for his helpful comments on the manuscript.

REFERENCES

1. Shiono PH, Klebanoff MA, Berendes HW. Congenital malformations and maternal smoking during pregnancy. Teratology 1986;34:65–71.
2. Hook EB, Cross PK. Cigarette smoking and Down syndrome. Am J Hum Genet 1985;37:1216–24.
3. Kelsey JL, Dwyer T, Holford TR, et al. Maternal smoking and congenital malformations: an epidemiological study. J Epidemiol Community Health 1978;32:102–7.
4. Hook EB, Cross PK. Maternal cigarette smoking, Down syndrome in live births, and infant race. Am J Hum Genet 1988; 42:482–9.
5. Christianson RE, Torfs CP. Maternal smoking and Down syndrome. Am J Hum Genet 1988;43:545–6.
6. Van Den Eeden SK, Karagas MR, Daling JR, et al. A case-control study of maternal smoking and congenital malformations. Paediatr Perinatal Epidemiol 1990;4:147–55.
7. Palomaki GE, Knight GJ, Haddow JE, et al. Cigarette smoking

and levels of maternal serum alpha-fetoprotein, unconjugated estriol, and hCG: impact on Down syndrome screening. Obstet Gynecol 1993;81:675–8.
8. Cuckle HS, Alberman NJ, Royston WP, et al. Maternal smoking habits and Down's syndrome. Prenat Diagn 1990;10: 561–7.
9. Kline J, Levin B, Stein Z, et al. Cigarette smoking and trisomy 21 at amniocentesis. Genet Epidemiol 1993;10:35–42.
10. Kallen K. Down's syndrome and maternal smoking in early pregnancy. Genet Epidemiol 1997;14:77–84.
11. Midgette AS, Baron JA. Cigarette smoking and the risk of natural menopause. Epidemiology 1990;1:474–80.
12. Janerich DT, Bracken MB. Epidemiology of trisomy 21: a review and theoretical analysis. J Chron Dis 1986;39:1079–93.
13. Gaulden ME. Maternal age effect: the enigma of Down syndrome and other trisomic conditions. Mutat Res 1992;296: 69–88.
14. Seidman DS, Ever-Hadani P, Gale RG. Effect of maternal smoking and age on congenital anomalies. Obstet Gynecol 1990;76:1046–50.
15. Swan SH, Shaw GM, Schulman J. Reporting and selection bias in case-control studies of congenital malformations. Epidemiology 1992;3:356–63.
16. Hook EB. Normal or affected controls in case-control studies of congenital malformations and other birth defects: reporting bias issues. Epidemiology 1993;4:182–4.