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Original Contribution

Maternal Smoking during Pregnancy and Children's Cognitive and Physical Development: A Causal Risk Factor?

Stephen E. Gilman[1,2], Hannah Gardener[2,3], and Stephen L. Buka[4]

[1] Department of Society, Human Development, and Health, Harvard School of Public Health, Boston, MA.
[2] Department of Epidemiology, Harvard School of Public Health, Boston, MA.
[3] Department of Neurology, Miller School of Medicine, University of Miami, Miami, FL.
[4] Department of Community Health, Brown University, Providence, RI.

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There remains considerable debate regarding the effects of maternal smoking during pregnancy on children's growth and development. Evidence that exposure to maternal smoking during pregnancy is associated with numerous adverse outcomes is contradicted by research suggesting that these associations are spurious. The authors investigated the relation between maternal smoking during pregnancy and 14 developmental outcomes of children from birth through age 7 years, using data from the Collaborative Perinatal Project (1959–1974; $n = 52{,}919$). In addition to adjusting for potential confounders measured contemporaneously with maternal smoking, the authors fitted conditional fixed-effects models among siblings that controlled for unmeasured confounders. Results from the conditional analyses indicated a birth weight difference of −85.63 g associated with smoking of ≥20 cigarettes daily during pregnancy (95% confidence interval: −131.91, −39.34) and 2.73 times' higher odds of being overweight at age 7 years (95% confidence interval: 1.30, 5.71). However, the associations between maternal smoking and 12 other outcomes studied (including Apgar score, intelligence, academic achievement, conduct problems, and asthma) were entirely eliminated after adjustment for measured and unmeasured confounders. The authors conclude that the hypothesized effects of maternal smoking during pregnancy on these outcomes either are not present or are not distinguishable from a broader range of familial factors associated with maternal smoking.

child; child development; cognition; growth; intelligence; pregnancy; smoking

Abbreviations: CI, confidence interval; CPP, Collaborative Perinatal Project; GEE, generalized estimating equations; IQ, intelligence quotient; WRAT, Wide Range Achievement Test.

In terms of public health policies and the public health imperative of tobacco control, the adverse consequences of cigarette smoking have been well-established. However, there remains considerable debate regarding the impact of maternal smoking during pregnancy on the physical and cognitive development of children. Establishing the presence of such effects could yield significant insights into the etiology of adverse child outcomes ranging from birth complications (1) to behavioral problems (2), psychological disturbances (3), asthma (4), overweight (5), and cognitive delays (6). Numerous studies documenting deficits in a wide range of developmental milestones among children whose mothers smoked during pregnancy are counterbalanced by other studies in which the effects of maternal smoking during pregnancy were eliminated after adjustment for maternal and familial factors (7–11).

While experimental studies conducted in animals (12) support the view that in-utero exposure to nicotine adversely

Correspondence to Dr. Stephen E. Gilman, Department of Society, Human Development, and Health, Harvard School of Public Health, 677 Huntington Avenue, Boston, MA 02115 (e-mail: sgilman@hsph.harvard.edu).

affects birth outcomes and subsequent development, human studies have necessarily relied on observational designs, most commonly involving comparisons of exposed and unexposed infants followed through childhood. Because maternal smoking occurs along with a broader constellation of social and behavioral factors that also influence child growth and development (13), determining the causal effects of maternal smoking has become an almost intractable problem. Potentially confounding factors include maternal socioeconomic status, marital status, personality attributes, psychiatric history, nutrition, health conditions, substance use during pregnancy, exposure to secondhand smoke during pregnancy, and an adverse home environment (10, 14–17). While some investigators have measured many of these factors, determining whether or not there is a causal effect of maternal smoking during pregnancy may require accounting for all of them.

In the current study, we used a quasi-experimental design to control for this problem of unmeasured confounding factors. We conducted an analysis of maternal smoking during pregnancy in relation to child developmental outcomes in the context of a prospective birth cohort study in which multiple offspring per family were enrolled. The power of this design comes from sibships in which there was variability in exposure to maternal smoking during pregnancy. Differences in the developmental outcomes between exposed and unexposed siblings cannot be attributed to shared aspects of the familial milieu, ranging from inherited genetic susceptibility and family history of psychopathology to environmental factors. This design can be understood as a comparison of exposed and unexposed siblings matched on family background (18), in which estimates of risk are conditioned on family-specific intercepts (for example, using conditional logistic regression). While this design cannot definitely prove a causal effect of maternal smoking during pregnancy (because of additional residual confounding due to factors not shared by siblings), the absence of significant associations from this analysis would cast serious doubt on a causal effect.

MATERIALS AND METHODS

Sample

The Collaborative Perinatal Project (CPP), a birth cohort study established in 1959, involved the systematic observation and examination of over 50,000 children through the first 7 years of life. The original aims of the CPP were to investigate prenatal and obstetric antecedents of childhood health and development (19, 20). The current study included liveborn offspring from singleton pregnancies.

Data from examinations and interviews were recorded by trained staff beginning at the time of registration for prenatal care. At the time of the first prenatal care visit, a complete reproductive, gynecologic, and medical history, a socioeconomic interview, and a family health history were obtained. Follow-up rates for survivors in the full CPP sample were 88 percent at 1 year, 75 percent at 4 years, and 79 percent at 7 years. The 4- and 7-year assessments included neurologic, psychological, and physical examinations of the child. Trained psychologists administered a 2-hour battery of cognitive, sensory, and motor tests, including ratings of child behaviors.

Measures

Maternal smoking during pregnancy. At the first prenatal care visit, women reported whether they were currently smoking and, if so, the number of cigarettes they smoked per day. These questions were repeated at each subsequent prenatal care visit until the time of delivery. From these repeated measurements, we determined the maximum number of cigarettes smoked per day at any point during pregnancy. We categorized maternal smoking in four categories to evaluate a potential dose-response relation with child outcomes: 0, 1–9, 10–19, or $\geq$20 cigarettes per day. In supplemental analyses, we defined maternal smoking both as a dichotomous variable (any vs. none) and as a continuous variable (number of cigarettes smoked per day). Klebanoff et al. (21) reported a high degree of correspondence between these maternal reports of smoking during pregnancy and serum cotinine levels.

Infant and child outcomes through age 7 years. Infant status at birth was assessed with birth weight (measured in grams) and 5-minute Apgar score as a measure of the physical condition of the newborn (22).

A primary concern among children exposed to maternal smoking during pregnancy has been deficits in cognition; therefore, we incorporated several measures of cognitive development. Cognitive performance at age 4 years was assessed with the Stanford-Binet Intelligence Scale (23). An abbreviated version of the Wechsler Intelligence Scale for Children was administered by study psychologists at age 7 years (24). The Wechsler Intelligence Scale for Children yields a total score for intelligence derived from the scaled combination of two sets of subtests, verbal and performance. These produced estimates of verbal intelligence quotient (IQ), performance IQ, and full-scale IQ. Academic performance at age 7 years was assessed using the Wide Range Achievement Test (WRAT) (25), which generates standardized scores for reading, spelling, and arithmetic. The presence of neurologic ''soft signs'' at age 7 years was assessed by physician examination as an indicator of a broad class of neurologic abnormalities that are not readily localizable to a specific brain region (26).

Behavioral observations were made by the examining psychologist during the age 7 psychological assessment. Each child was rated on 15 different behavioral items (27). We conducted factor analyses of these items and identified ''conduct problems'' as a behavioral dimension that demonstrated internal consistency and stability across different samples and paralleled current measures of child behavior problems. Six items loaded highly on this dimension, including poor cooperation, high hostility, acting out, and impulsive behavior. Cronbach's alpha, a measure of internal consistency, was 0.75 for the scale.

Body mass index (weight (kg)/height $(m)^2$) at age 7 years (recorded at age 82–86 months) was analyzed as a continuous measure. Being overweight at age 7 years was defined as being at or above the 95th percentile of body mass index for

males and females on the basis of Centers for Disease Control and Prevention growth charts (28, 29). A suspected or definite diagnosis of asthma by age 7 years was determined through medical record reviews carried out by CPP study physicians.

Correlates of maternal smoking during pregnancy. We considered a wide range of potential correlates of maternal smoking during pregnancy for inclusion as control variables in adjusted models. Family socioeconomic status was measured with an index adapted from the Bureau of the Census that was derived by averaging the percentile scores of parents' education, occupation, and income (30). Other demographic characteristics assessed upon CPP enrollment included maternal marital status (defined here as married vs. not married), maternal employment status (employed vs. not employed), presence of the husband or father of the baby in the household (yes vs. no), and household crowding (defined as severely crowded ($\geq$1.5 persons per room), crowded ($>$1 person per room), or not crowded ($<$1 person per room)).

Family history of mental illness was assessed by mother's self-report of her own or the baby's father's history of treatment for mental illness or addiction. The number of neurologic and psychiatric conditions present during pregnancy was recorded by study personnel as part of an obstetric diagnostic summary. Lastly, maternal age, number of prior pregnancies, and paternal age were investigated.

Analytic methods

Correlates of maternal smoking during pregnancy. We first fitted a model predicting maternal smoking during pregnancy. This was an ordinal logistic model fitted to the four-category maternal smoking variable, from which we derived proportional odds ratios to indicate the strength of the association between each covariate and the odds of a higher level of maternal smoking.

Effects of maternal smoking during pregnancy on child outcomes. We then fitted three sets of models to evaluate the relation between maternal smoking during pregnancy and child outcomes. The first model was fitted with the full CPP sample and included the indicator variables for maternal smoking during pregnancy (light, moderate, and heavy smoking, compared with a reference category of no smoking during pregnancy), as well as all statistically significant covariates ($p < 0.05$) from the proportional odds model predicting maternal smoking. The second model included the same covariates but was fitted among siblings. Finally, the third model was a matched, or "fixed effects" (31), analysis among siblings, which provided effect estimates that were free from bias due to potentially confounding factors to which both siblings were exposed.

Generalized estimating equations (GEE) were used to adjust variance estimates in the first two models for the nonindependence of multiple siblings per family (32). Linear and logistic regression analyses were used for continuous and dichotomous dependent variables, respectively, implemented using the PROC GENMOD procedure in SAS, version 9.1.3 (33). The matched analyses among siblings were conducted by conditioning on family-specific intercepts using PROC GLM for continuous outcomes and PROC LOGISTIC for dichotomous outcomes. Only covariates that differed between siblings could be included in the sibling fixed-effects models; in these models, we adjusted for birth order and sex.

Missing data

The sample size for the analysis of each outcome varied because of different patterns of participation in the follow-up assessments during the CPP and item-level missing data. In order to avoid fluctuation of sample sizes for models of the same outcome, we fitted the GEE models and the sibling fixed-effects model in subsamples with complete data for all covariates. In supplemental analyses, we used multiple imputation (34) to generate data sets with all siblings, for comparison with the complete-case analyses above.

RESULTS

Sample characteristics

There were 52,919 CPP livebirths resulting from singleton pregnancies with data on exposure to maternal smoking during pregnancy and with the infant's sex recorded in the CPP database. Of these offspring, 16,619 were part of 7,415 sibling sets. The demographic characteristics of mothers and offspring in each of these two groups were comparable (table 1). The distribution of maternal smoking during pregnancy across each of these samples is shown in the first rows of table 1. In the full sample, the prevalences of smoking $\geq$20, 10–19, 1–9, and 0 cigarettes per day were 22.3 percent, 12.1 percent, 17.8 percent, and 47.8 percent, respectively. This is substantially higher than current rates of smoking during pregnancy, which average approximately 10–15 percent in epidemiologic samples (13).

There were 2,064 sibling sets ($n = 4{,}827$ individuals) in which there was variability in exposure to maternal smoking during pregnancy. In other words, there were 2,064 sibling sets in which the mother smoked at different levels across her CPP pregnancies. Among these 2,064 CPP mothers, 328 were nonsmokers in their first CPP pregnancy but smokers in a subsequent pregnancy; 582 smoked in their first CPP pregnancy but did not smoke in a subsequent CPP pregnancy; and 1,154 smoked during each of their CPP pregnancies, but at different levels.

Correlates of maternal smoking during pregnancy

Results of the proportional odds model predicting maternal smoking during pregnancy are shown in table 2. Odds ratios indicate the magnitude of risk for a higher level of smoking. Demographic correlates of maternal smoking during pregnancy included family socioeconomic status, maternal and paternal age, maternal marital status, maternal employment status, household crowding, and number of prior pregnancies. Clinical correlates included maternal and paternal history of mental illness and the presence of psychiatric or neurologic problems during pregnancy. These results demonstrate the degree to which smoking during

TABLE 1. Characteristics of women and their offspring in the Collaborative Perinatal Project, 1959–1974

	Full sample* ($n = 52,919$)		Sibling sample† ($n = 16,619$)	
	Mean (SD‡) or no.	%	Mean (SD) or no.	%
Maternal smoking during pregnancy§				
0	25,315	47.8	7,730	46.5
1–9	9,398	17.8	2,814	16.9
10–19	6,403	12.1	2,069	12.5
≥20	11,803	22.3	4,006	24.1
Mean maternal age (years)	24.2 (6.0)		24.0 (5.5)	
Race/ethnicity¶				
White	24,177	45.9	8,317	50.2
Black	24,549	46.6	7,572	45.7
Other	3,978	7.6	675	4.1
Offspring sex				
Male	26,842	50.7	8,403	50.6
Female	26,077	49.3	8,216	49.4
Mean family socioeconomic status percentile#	46.9 (21.6)		47.2 (21.0)	
No. of siblings enrolled per family				
1	36,300	68.6	—**	
2	11,840	22.4	11,840	71.2
3	3,717	7.0	3,717	22.4
4	884	1.7	884	5.3
5	160	0.3	160	1.0
6	18	0.0	18	0.1

* Collaborative Perinatal Project singleton pregnancies resulting in livebirths, with complete data on maternal smoking during pregnancy and offspring sex.

† Collaborative Perinatal Project offspring with one or more siblings enrolled in the study.

‡ SD, standard deviation.

§ Maximum number of cigarettes smoked per day during pregnancy.

¶ Numbers of participants with missing data: full sample, $n = 215$; sibling sample, $n = 55$.

Numbers of participants with missing data: full sample, $n = 1,493$; sibling sample, $n = 543$.

** Not applicable.

TABLE 2. Correlates of maternal smoking during pregnancy in the Collaborative Perinatal Project, 1959–1974*

	Odds ratio	95% confidence interval
Socioeconomic status index	1.002	1.001, 1.003
Maternal age	0.978	0.973, 0.984
Paternal age	1.009	1.005, 1.014
Maternal marital status		
Married	0.82	0.72, 0.92
Not married	1	
Maternal employment status		
Employed	0.88	0.84, 0.92
Not employed	1	
Presence of father in the household		
No	0.99	0.87, 1.12
Yes	1	
Household crowding		
Severely crowded (≥1.5 persons per room)	0.69	0.66, 0.72
Crowded (≥1 person per room)	0.90	0.86, 0.95
Not crowded (<1 person per room)	1	
Paternal history of psychiatric or substance-use disorder		
Hospitalized	1.39	1.15, 1.69
Outpatient	1.21	0.93, 1.59
Addiction	3.37	1.94, 5.88
Questionable	1.34	1.09, 1.65
None	1	
Maternal history of psychiatric or substance-use disorder		
Hospitalized	1.84	1.52, 2.23
Outpatient	1.68	1.43, 1.97
Questionable	1.94	1.60, 2.35
None	1	
No. of prior pregnancies	1.07	1.06, 1.08
No. of psychiatric or neurologic problems during pregnancy	1.21	1.15, 1.27

* Results from an ordinal logistic regression model of maternal smoking during pregnancy ($n = 44,745$). Odds ratios indicate the magnitude of risk for being in a higher category of maternal smoking (0, 1–9, 10–19, or ≥20 cigarettes/day). The model included Collaborative Perinatal Project mothers of liveborn singleton offspring with complete data on the covariates shown. Variance estimates were adjusted for the presence of multiple siblings per family using generalized estimating equations.

pregnancy occurs in the context of social, environmental, and psychiatric factors that are themselves predictive of the child outcomes analyzed, and they illustrate the challenge of isolating the causal effect of smoking from the effects of other factors with which it is associated.

Analysis of maternal smoking during pregnancy in the full CPP and sibling samples

The effects of maternal smoking during pregnancy on child outcomes are shown in table 3. For each outcome, results from three models are presented: 1) GEE models in the full sample, 2) GEE models fitted among siblings, and 3) conditional models fitted among siblings. For each model, the sample size and distribution of the dependent variable (mean or percent) are shown. Metric regression coefficients are shown for continuous outcomes, and odds ratios are shown for dichotomous outcomes. Each row presents the results from a single model, and each column

TABLE 3. Generalized estimating equations and fixed-effects models of the association between maternal smoking during pregnancy and children's mental and physical development in the Collaborative Perinatal Project, 1959–1974

	No. of children	Mean (standard deviation) or no.	%	Level of maternal smoking during pregnancy (cigarettes/day)						χ^2 or F (3 df)	p value
				1–9		10–19		≥20			
				OR* or β†	95% CI*	OR or β	95% CI	OR or β	95% CI		
Birth											
Birth weight (g)											
Full sample, adjusted‡	46,559	3,185.5 (529.7)		−69.03	−82.25, −55.81	−165.48	−180.95, −150.01	−247.66	−260.98, −234.35	1,354.4	<0.001
Siblings, adjusted§	13,575	3,211.9 (530.5)		−50.25	−78.44, −22.07	−153.55	−184.53, −122.57	−255.43	−282.16, −228.70	333.4	<0.001
Siblings, fixed effects¶	13,575	3,211.9 (530.5)		−2.04	−37.69, 33.61	−62.08	−106.04, −18.13	−85.63	−131.91, −39.34	6.1	<0.001
5-minute Apgar score											
Full sample, adjusted	43,768	9.0 (1.1)		−0.04	−0.07, −0.01	−0.05	−0.09, −0.02	−0.08	−0.11, −0.05	34.9	<0.001
Siblings, adjusted	12,360	9.0 (1.1)		−0.03	−0.09, 0.03	−0.01	−0.07, 0.05	−0.04	−0.09, 0.01	3.0	0.396
Siblings, fixed effects	12,360	9.0 (1.1)		−0.04	−0.14, 0.07	0.01	−0.12, 0.14	0.00	−0.13, 0.14	0.3	0.810
Age 4 years											
Stanford-Binet IQ*											
Full sample, adjusted	34,390	97.6 (16.6)		−0.33	−0.76, 0.09	0.11	−0.40, 0.62	−0.63	−1.06, −0.19	10.9	0.012
Siblings, adjusted	9,578	98.7 (16.5)		−0.18	−1.06, 0.70	0.57	−0.46, 1.59	0.02	−0.84, 0.88	1.8	0.607
Siblings, fixed effects	9,578	98.7 (16.5)		0.48	−0.86, 1.83	1.24	−0.41, 2.89	0.63	−1.09, 2.35	0.8	0.521
Age 7 years											
Neurologic soft signs											
Full sample, adjusted	36,088	4,313	12.0	0.95	0.87, 1.05	0.92	0.82, 1.02	1.13	1.04, 1.22	15.7	0.001
Siblings, adjusted	10,933	1,385	12.7	1.05	0.89, 1.24	0.90	0.74, 1.10	1.14	0.99, 1.32	5.9	0.119
Siblings, fixed effects	10,933	1,385	12.7	0.83	0.57, 1.22	0.77	0.48, 1.22	0.86	0.53, 1.37	1.4	0.698
Wechsler verbal IQ											
Full sample, adjusted	35,566	94.6 (14.2)		−0.54	−0.91, −0.18	−0.18	−0.59, 0.24	−0.77	−1.12, −0.41	22.0	<0.001
Siblings, adjusted	10,593	94.4 (13.8)		−0.72	−1.41, −0.03	−0.19	−0.98, 0.59	−0.28	−0.96, 0.41	4.3	0.234
Siblings, fixed effects	10,593	94.4 (13.8)		−0.13	−1.24, 0.95	−0.33	−1.64, 0.99	0.20	−1.19, 1.60	0.0	0.828
Wechsler performance IQ											
Full sample, adjusted	35,567	98.9 (15.2)		−1.06	−1.46, −0.66	−1.09	−1.55, −0.63	−1.64	−2.02, −1.26	83.2	<0.001
Siblings, adjusted	10,594	98.9 (15.1)		−0.76	−1.55, 0.03	−0.85	−1.71, 0.01	−1.04	−1.76, −0.32	9.8	0.021
Siblings, fixed effects	10,594	98.9 (15.1)		−0.46	−1.76, 0.84	−0.39	−1.99, 1.20	0.38	−1.31, 2.07	0.6	0.634
Wechsler full-scale IQ											
Full sample, adjusted	35,795	96.1 (14.9)		−0.77	−1.14, −0.40	−0.66	−1.09, −0.23	−1.27	−1.64, −0.90	51.2	<0.001
Siblings, adjusted	10,712	95.9 (14.6)		−0.94	−1.67, −0.20	−0.44	−1.25, 0.36	−0.75	−1.45, −0.05	8.2	0.042
Siblings, fixed effects	10,712	95.9 (14.6)		−0.38	−1.51, 0.75	−0.34	−1.73, 1.05	0.24	−1.22, 1.71	0.5	0.716
WRAT* spelling score											
Full sample, adjusted	34,764	96.0 (12.8)		−0.27	−0.61, 0.07	−0.70	−1.09, −0.30	−0.99	−1.33, −0.65	36.5	<0.001
Siblings, adjusted	10,170	96.5 (12.7)		−0.31	−0.98, 0.36	−0.33	−1.08, 0.41	−0.77	−1.42, −0.12	5.4	0.147
Siblings, fixed effects	10,170	96.5 (12.7)		−0.12	−1.25, 1.01	−0.09	−1.47, 1.29	−0.33	−1.80, 1.14	0.1	0.970
WRAT reading score											
Full sample, adjusted	34,784	98.8 (15.6)		−0.63	−1.03, −0.23	−0.74	−1.22, −0.26	−1.41	−1.82, −1.00	47.1	<0.001
Siblings, adjusted	10,185	99.1 (15.3)		−0.79	−1.59, 0.01	−0.33	−1.26, 0.60	−1.22	−2.01, −0.43	10.6	0.014
Siblings, fixed effects	10,185	99.1 (15.3)		−0.09	−1.40, 1.22	0.56	−1.04, 2.16	−0.42	−2.12, 1.28	0.7	0.538
WRAT arithmetic score											
Full sample, adjusted	34,765	96.6 (11.0)		−0.30	−0.61, 0.02	−0.07	−0.42, 0.29	−0.25	−0.54, 0.04	5.1	0.167
Siblings, adjusted	10,173	97.0 (10.9)		0.08	−0.55, 0.72	0.20	−0.48, 0.87	0.12	−0.44, 0.68	0.4	0.945
Siblings, fixed effects	10,173	97.0 (10.9)		−0.69	−1.71, 0.33	−1.05	−2.30, 0.20	−0.59	−1.92, 0.74	1.0	0.376
Body mass index#											
Full sample, adjusted	30,043	16.0 (2.0)		0.08	0.01, 0.14	0.20	0.13, 0.27	0.19	0.13, 0.25	49.8	<0.001
Siblings, adjusted	8,060	16.0 (1.8)		0.11	−0.02, 0.23	0.22	0.08, 0.35	0.24	0.12, 0.36	19.7	<0.001
Siblings, fixed effects	8,060	16.0 (1.8)		0.11	−0.08, 0.31	0.14	−0.09, 0.38	0.17	−0.07, 0.42	0.8	0.523

Overweight##												
Full sample, adjusted	30,043	1,615	5.4	1.15	0.99, 1.33	1.35	1.15, 1.58	1.17	1.02, 1.34	15.0	0.002
Siblings, adjusted	8,058	346	4.3	1.56	1.11, 2.17	1.61	1.15, 2.26	1.35	1.00, 1.82	11.1	0.011
Siblings, fixed effects	8,058	346	4.3	2.90	1.30, 6.49	2.47	1.00, 6.10	2.55	1.01, 6.44	7.2	0.066
Conduct problems scale score											
Full sample, adjusted	35,677	0.2 (0.8)		0.02	−0.00, 0.04	0.03	0.00, 0.06	0.05	0.03, 0.07	20.4	<0.001
Siblings, adjusted	10,659	0.2 (0.8)		0.04	−0.00, 0.09	0.03	−0.02, 0.08	0.04	−0.01, 0.08	5.1	0.165
Siblings, fixed effects	10,659	0.2 (0.8)		0.05	−0.03, 0.14	0.04	−0.07, 0.14	0.04	−0.07, 0.15	0.5	0.665
Asthma											
Full sample, adjusted	36,107	1,980	5.5	1.09	0.96, 1.23	1.01	0.87, 1.18	1.19	1.05, 1.34	8.2	0.043
Siblings, adjusted	10,945	502	4.6	1.05	0.81, 1.36	0.88	0.64, 1.19	1.14	0.90, 1.45	2.9	0.405
Siblings, fixed effects	10,945	502	4.6	0.88	0.51, 1.51	1.12	0.56, 2.25	1.89	0.85, 4.19	4.5	0.214

* OR, odds ratio; CI, confidence interval; IQ, intelligence quotient; WRAT, Wide Range Achievement Test.
† Odds ratios from logistic regression models are shown for neurologic soft signs, overweight, and asthma; linear regression coefficients (β) are shown for all other dependent variables.
‡ Full Collaborative Perinatal Project sample. Generalized estimating equations models included adjustment for the presence of multiple siblings per family. *P* values from chi-squared tests of the significance of maternal smoking during pregnancy are shown in the last column. The following covariates were included in the models: sex, race/ethnicity, maternal and paternal age, household crowding, paternal and maternal history of psychiatric or substance-use disorder, maternal psychiatric or neurologic problems during pregnancy, maternal marital status, maternal employment, number of prior pregnancies, and family socioeconomic status percentile.
§ Generalized estimating equations models for the sample of Collaborative Perinatal Project offspring with one or more siblings enrolled; results were adjusted for the same covariates as listed above. *P* values from chi-squared tests of the significance of maternal smoking during pregnancy are shown in the last column.
¶ Models fitted among siblings conditioning on family fixed effects (family-specific intercepts). *P* values from *F* tests shown in the last column are from linear regression models; *p* values from chi-squared tests are from logistic regression models.
# Weight (kg)/height (m)^2.
** ≥95th percentile of body mass index for age and sex.

presents the effects of maternal smoking at increasing levels of smoking (with 0 cigarettes per day as the reference category). For example, in the full CPP sample, the mean reductions in birth weight across categories of maternal smoking during pregnancy were −69.03 g, −165.48 g, and −247.66 g, corresponding to the smoking of 1–9, 10–19, and ≥20 cigarettes per day during pregnancy, respectively. Among siblings, birth weight differences were −50.25 g, −153.55 g, and −255.43 g. These differences were substantially reduced in fixed-effects models (−2.04 g, −62.08 g, and −85.63 g).

Several patterns are notable among the results presented in table 3. First, comparing the effect sizes estimated from GEE models based on the full sample and those estimated from GEE models based on the sample of siblings, there was no consistent pattern of differences, indicating that the CPP sibling sample was not systematically different from the overall CPP cohort. Second, adjusting for correlates of maternal smoking, there were statistically significant and adverse overall effects (e.g., $p < 0.05$ on joint significance tests with 3 df) for six of the 14 outcomes in GEE models fitted among siblings. Except for birth weight and overweight at age 7 years, effect sizes were generally small (e.g., less than one quarter of a standard deviation or odds ratios less than 1.5).

Third, in the conditional models, which match siblings on family background, the effect sizes for maternal smoking were further attenuated towards the null. To follow up on prior studies showing an interaction between smoking during pregnancy and parity in models predicting birth weight (35–37), we tested the interaction between smoking during pregnancy and the number of prior pregnancies (0 vs. ≥1). As in the prior studies, the effect of maternal smoking on birth weight was somewhat stronger after the first pregnancy.

Odds ratios for childhood overweight in the conditional model were 2.90 (95 percent confidence interval (CI): 1.30, 6.49), 2.47 (95 percent CI: 1.00, 6.10), and 2.55 (95 percent CI: 1.01, 6.44) across increasing categories of maternal smoking. The similarity in these odds ratios suggests a threshold effect of any smoking during pregnancy versus none on the risk of childhood overweight; when maternal smoking was defined as the dichotomy between any exposure and no exposure, the odds ratio for overweight was 2.73 (95 percent CI: 1.30, 5.71). Consistent with Chen et al.'s analysis in the CPP cohort (5), the effect of maternal smoking on childhood overweight was not eliminated after further adjustment for birth weight (odds ratio = 2.53, 95 percent CI: 1.19, 5.39). Thus, it did not appear that the relation between smoking during pregnancy and childhood overweight was a consequence of its effect on birth weight.

Fourth, the magnitude of the effects of maternal smoking during pregnancy on other outcomes was generally trivial in the sibling models. Since these models adjusted for unmeasured confounders to which both siblings were exposed, our findings suggest that family-level factors accounted in large part for the associations between smoking during pregnancy and adverse child outcomes that were observed in the unconditional (i.e., GEE) models.

Results from conditional models among siblings using alternative definitions of maternal smoking during pregnancy

are presented in Appendix table 1. The table shows the differences in child outcomes among siblings exposed to any maternal smoking versus none, as well as the differences associated with a one-cigarette increase in maternal smoking. In these analyses, maternal smoking during pregnancy was associated with lower mean birth weight and a higher risk of being overweight at age 7 years. Finally, we refitted the conditional models among all CPP siblings ($n = 16{,}619$) by combining effect estimates from analyses of 10 complete data sets that were generated by multiple imputation (Appendix table 2). Results for birth weight were similar to those shown in table 3, although the odds ratios for overweight across the three categories of maternal smoking were smaller (1.34, 1.82, and 1.74, respectively), as was the odds ratio for any maternal smoking versus none (odds ratio = 1.46, 95 percent CI: 0.83, 2.58).

DISCUSSION

Previous studies have found adverse consequences of smoking during pregnancy across a wide range of domains, including low birth weight (38) and deficits in general intelligence (6, 10, 39), language and reading, quantitative skills (40), learning and memory (16), and academic competence (41). Smoking during pregnancy has also been related to higher levels of internalizing and externalizing symptoms, peer and social problems, hyperactivity, attention difficulties, aggression, and conduct problems (3, 14, 42–44).

Substantial evidence contradicting these studies (7–11, 43) motivated us to conduct the present investigation of the effects of smoking during pregnancy on 14 childhood outcomes in the CPP birth cohort. Prior studies of smoking during pregnancy in the CPP did not use methods to adjust for unmeasured confounding (5, 40, 45–47).

In the conditional models fitted among siblings, there was an adverse effect of smoking during pregnancy on birth weight which was robust across model specifications. There was also an association between exposure to smoking during pregnancy and childhood overweight, yet this was reduced in supplemental analyses of the full CPP sibling data set generated by multiple imputation. There was no association between smoking during pregnancy and mean body mass index at age 7 years. More work is needed to clarify the potential long-term effects of maternal smoking on patterns of childhood growth. Chen et al. (5) reviewed several potential mechanisms, which include effects of nicotine and carbon monoxide on fetal growth restriction and longer-term physiologic effects on childhood appetite and metabolism.

We did not observe effects of smoking during pregnancy on other outcomes measured in infancy (5-minute Apgar score), at age 4 years (Stanford-Binet IQ), or at age 7 years (neurologic soft signs, Wechsler IQ scores, WRAT scores, conduct problems, and asthma). Therefore, our results are consistent with those of prior studies (7–11) indicating that the commonly observed associations between smoking during pregnancy and offspring neurodevelopmental outcomes are attenuated after controlling for potentially confounding variables.

The conflicting evidence surrounding the effects of smoking during pregnancy on children's cognitive abilities and risk for neuropsychiatric and physical health problems underscores the illusiveness of causal inference in this area. Cigarette smoking is embedded within a broader constellation of social, environmental, and clinical factors that have important consequences for child development (13, 48). Correlates of smoking during pregnancy in the full CPP cohort included socioeconomic status and familial psychopathology. Measurement error in assessments of childhood cognition and neuropsychiatric impairments also reduces the ability to detect an effect if present (49). Despite the use of standardized tests of intelligence and other developmental outcomes in the CPP, the assessments of childhood health and well-being may still not have been sensitive enough to detect the type of subtle but potentially long-lasting effects of exposure to maternal smoking during pregnancy that are indicated by animal studies. With respect to asthma, we speculate that CPP diagnoses reflect only severe cases and that many cases of asthma in the CPP were not detected (50).

The sibling models used in our study had reduced power to detect effects of smoking during pregnancy because they relied on changes in smoking behavior across different pregnancies. Power to detect statistically significant differences in child outcomes across levels of exposure to maternal smoking during pregnancy was further reduced by the smaller sample size included in the sibling analyses and the adjustment for family-specific intercepts. Using this approach involves a tradeoff between bias reduction and imprecision (51). Obtaining the least biased estimates of the effects of smoking during pregnancy was the primary objective of this study given prior conflicting evidence in the literature, and the CPP cohort provides one of the largest samples of siblings available for this purpose. Therefore, our primary interpretations were based on the degree of attenuation in effect estimates between the marginal (i.e., GEE) models and the conditional (i.e., fixed-effects) models, rather than on changes in significance levels. Nonetheless, one should interpret the results of this study bearing in mind the imprecision of the regression coefficients obtained from the conditional models.

Our analyses did not incorporate information on maternal smoking after pregnancy or other sources of exposure to tobacco smoke in childhood, which may have independent influences on children's health (52). Bauman et al. (53) reviewed the possible mechanisms by which exposure to environmental tobacco smoke may directly affect the cognitive abilities of children. They speculated that environmental smoke exposure may reduce brain oxygen levels by increasing carboxyhemoglobin concentrations, which in turn decreases the capacity of blood to carry oxygen.

In sum, the detrimental effects of smoking during pregnancy on birth weight and childhood overweight provide yet additional evidence of harm associated with cigarettes. The lack of any meaningful association between smoking during pregnancy and the other child outcomes studied suggests that such effects either are not present, are not readily distinguishable from a broader range of familial factors associated with maternal smoking, or are not detectable using the assessment methods available at the time of the CPP investigation.

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REFERENCES

1. Haustein KO. Cigarette smoking, nicotine and pregnancy. Int J Clin Pharmacol Ther 1999;37:417–27.
2. Wakschlag LS, Hans SL. Maternal smoking during pregnancy and conduct problems in high-risk youth: a developmental framework. Dev Psychopathol 2002;14:351–69.
3. Thapar A, Fowler T, Rice F, et al. Maternal smoking during pregnancy and attention deficit hyperactivity disorder symptoms in offspring. Am J Psychiatry 2003;160:1985–9.
4. Jaakkola JJ, Gissler M. Maternal smoking in pregnancy, fetal development, and childhood asthma. Am J Public Health 2004; 94:136–40.
5. Chen A, Pennell ML, Klebanoff MA, et al. Maternal smoking during pregnancy in relation to child overweight: follow-up to age 8 years. Int J Epidemiol 2006;35:121–30.
6. Mortensen EL, Michaelsen KF, Sanders SA, et al. A dose-response relationship between maternal smoking during late pregnancy and adult intelligence in male offspring. Paediatr Perinat Epidemiol 2005;19:4–11.
7. Batty GD, Der G, Deary IJ. Effect of maternal smoking during pregnancy on offspring's cognitive ability: empirical evidence for complete confounding in the US National Longitudinal Survey of Youth. Pediatrics 2006;118:943–50.
8. Silberg JL, Parr T, Neale MC, et al. Maternal smoking during pregnancy and risk to boys' conduct disturbance: an examination of the causal hypothesis. Biol Psychiatry 2003;53: 130–5.
9. Breslau N, Paneth N, Lucia VC, et al. Maternal smoking during pregnancy and offspring IQ. Int J Epidemiol 2005;34: 1047–53.
10. Olds DL, Henderson CR Jr, Tatelbaum R. Intellectual impairment in children of women who smoke cigarettes during pregnancy. Pediatrics 1994;93:221–7.
11. Hill SY, Lowers L, Locke-Wellman J, et al. Maternal smoking and drinking during pregnancy and the risk for child and adolescent psychiatric disorders. J Stud Alcohol 2000;61:661–8.
12. Keith IM, Cary JR. Maternal smoking during pregnancy affects neuroendocrine cells in the neonate hamster lung. Histol Histopathol 1988;3:215–22.
13. Gilman SE, Breslau J, Subramanian SV, et al. Social factors, psychopathology, and maternal smoking during pregnancy. Am J Public Health 2008;98:448–53.
14. Fergusson DM, Horwood LJ, Lynskey MT. Maternal smoking before and after pregnancy: effects on behavioral outcomes in middle childhood. Pediatrics 1993;92:815–22.
15. Weissman MM, Warner V, Wickramaratne PJ, et al. Maternal smoking during pregnancy and psychopathology in offspring followed to adulthood. J Am Acad Child Adolesc Psychiatry 1999;38:892–9.
16. Cornelius MD, Ryan CM, Day NL, et al. Prenatal tobacco effects on neuropsychological outcomes among preadolescents. J Dev Behav Pediatr 2001;22:217–25.
17. Kodl MM, Wakschlag LS. Does a childhood history of externalizing problems predict smoking during pregnancy? Addict Behav 2004;29:273–9.
18. Karon JM, Kupper LL. In defense of matching. Am J Epidemiol 1982;116:852–66.
19. Broman SH, Nichols PL, Kennedy WA. Preschool IQ: prenatal and early developmental correlates. Hillsdale, NJ: Lawrence Erlbaum Associates, 1975.
20. Niswander KR, Gordon M. The women and their pregnancies: the Collaborative Perinatal Study of the National Institute of Neurological Diseases and Stroke. Philadelphia, PA: WB Saunders Company, 1972.
21. Klebanoff MA, Levine RJ, Clemens JD, et al. Serum cotinine concentration and self-reported smoking during pregnancy. Am J Epidemiol 1998;148:259–62.
22. Bosley AR, Newcombe RG, Dauncey ME. Maternal smoking and Apgar score. Lancet 1981;1:337–8.
23. Thorndike RL, Hagen EP, Sattler JM. The Stanford-Binet Intelligence Scale, fourth edition: guide for administering and scoring. Chicago, IL: Riverside Publishing Company, 1986.
24. Wechsler D. Wechsler intelligence scale for children; manual. New York, NY: Psychological Corporation, 1949.
25. Jastak JF, Jastak SR. Wide range achievement test: manual of instructions. Wilmington, DE: Guidance Associates, 1965.
26. Shaffer D, Schonfeld I, O'Connor PA, et al. Neurological soft signs. Their relationship to psychiatric disorder and intelligence in childhood and adolescence. Arch Gen Psychiatry 1985;42:342–51.
27. Nichols PL, Chen T-C. Minimal brain dysfunction: a prospective study. Hillsdale, NJ: Lawrence Erlbaum Associates, 1981.
28. Kuczmarski RJ, Ogden CL, Guo SS, et al. 2000 CDC growth charts for the United States: methods and development. Hyattsville, MD: National Center for Health Statistics, 2002.
29. National Center for Health Statistics. CDC growth charts: United States. Hyattsville, MD: National Center for Health Statistics, 2000. (http://www.cdc.gov/nchs/data/nhanes/growthcharts/zscore/bmiagerev.xls).
30. Myrianthopoulos NC, French KS. An application of the U.S. Bureau of the Census socioeconomic index to a large, diversified patient population. Soc Sci Med 1968;2:283–99.
31. Allison PD. Fixed effects regression methods for longitudinal data using SAS. Cary, NC: SAS Institute Inc, 2005.
32. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 1986;42:121–30.
33. SAS Institute Inc. Base SAS 9.1.3 procedures guide. Cary, NC: SAS Institute Inc, 2004.
34. Rubin DB. Multiple imputation after 18+ years. J Am Stat Assoc 1996;91:473–89.
35. Cnattingius S, Forman MR, Berendes HW, et al. Effect of age, parity, and smoking on pregnancy outcome: a population-based study. Am J Obstet Gynecol 1993;168:16–21.
36. Kolas T, Nakling J, Salvesen KA. Smoking during pregnancy increases the risk of preterm births among parous women. Acta Obstet Gynecol Scand 2000;79:644–8.
37. Misra DP, Astone N, Lynch CD. Maternal smoking and birth weight: interaction with parity and mother's own in utero exposure to smoking. Epidemiology 2005;16:288–93.
38. Ernst M, Moolchan ET, Robinson ML. Behavioral and neural consequences of prenatal exposure to nicotine. J Am Acad Child Adolesc Psychiatry 2001;40:630–41.

39. Fried PA, Watkinson B. Differential effects on facets of attention in adolescents prenatally exposed to cigarettes and marihuana. Neurotoxicol Teratol 2001;23:421–30.
40. Naeye RL, Peters EC. Mental development of children whose mothers smoked during pregnancy. Obstet Gynecol 1984;64:601–7.
41. Martin RP, Dombrowski SC, Mullis C, et al. Smoking during pregnancy: association with childhood temperament, behavior, and academic performance. J Pediatr Psychol 2006;31:490–500.
42. Brennan PA, Grekin ER, Mortensen EL, et al. Relationship of maternal smoking during pregnancy with criminal arrest and hospitalization for substance abuse in male and female adult offspring. Am J Psychiatry 2002;159:48–54.
43. O'Callaghan MJ, Williams GM, Andersen MJ, et al. Obstetric and perinatal factors as predictors of child behaviour at 5 years. J Paediatr Child Health 1997;33:497–503.
44. Faden VB, Graubard BI. Maternal substance use during pregnancy and developmental outcome at age three. J Subst Abuse 2000;12:329–40.
45. Naeye RL. Influence of maternal cigarette smoking during pregnancy on fetal and childhood growth. Obstet Gynecol 1981;57:18–21.
46. Hardy JB, Mellits ED. Does maternal smoking during pregnancy have a long-term effect on the child? Lancet 1972;2:1332–6.
47. Garn SM, Petzold AS, Ridella SA, et al. Effect of smoking during pregnancy on Apgar and Bayley scores. Lancet 1980;2:912–13.
48. Gilman SE, Abrams DB, Buka SL. Socioeconomic status over the life course and stages of cigarette use: initiation, regular use, and cessation. J Epidemiol Community Health 2003;57:802–8.
49. Breslau N. Commentary: maternal smoking during pregnancy: hazard for what? Int J Epidemiol 2007;36:832–3.
50. Nystad W, Magnus P, Gulsvik A, et al. Changing prevalence of asthma in school children: evidence for diagnostic changes in asthma in two surveys 13 yrs apart. Eur Respir J 1997;10:1046–51.
51. Kaufman JS. Commentary: why are we biased against bias? Int J Epidemiol 2008;37:624–6.
52. Eskenazi B, Castorina R. Association of prenatal maternal or postnatal child environmental tobacco smoke exposure and neurodevelopmental and behavioral problems in children. Environ Health Perspect 1999;107:991–1000.
53. Bauman KE, Flewelling RL, LaPrelle J. Parental cigarette smoking and cognitive performance of children. Health Psychol 1991;10:282–8.

APPENDIX TABLE 1. Alternative definitions of maternal smoking during pregnancy in conditional models of children's physical and mental development among siblings in the Collaborative Perinatal Project, 1959–1974*

	Definition of maternal smoking during pregnancy			
	Any maternal smoking vs. none†		Maximum no. of cigarettes smoked daily‡	
	OR§ or β¶	95% CI§	OR or β	95% CI
Birth				
Birth weight (g)	−26.55	−60.07, 6.97	−2.71	−4.33, −1.08
5-minute Apgar score	−0.02	−0.12, 0.08	0.00	−0.00, 0.01
Age 4 years				
Stanford-Binet IQ§	0.63	−0.62, 1.88	0.04	−0.02, 0.10
Age 7 years				
Neurologic soft signs	0.83	0.59, 1.17	1.00	0.98, 1.01
Wechsler verbal IQ	−0.10	−1.11, 0.91	0.02	−0.03, 0.07
Wechsler performance IQ	−0.30	−1.52, 0.92	−0.02	−0.08, 0.04
Wechsler full-scale IQ	−0.26	−1.32, 0.80	0.00	−0.05, 0.05
WRAT§ spelling score	−0.15	−1.21, 0.91	−0.01	−0.06, 0.05
WRAT reading score	−0.04	−1.26, 1.18	0.00	−0.06, 0.06
WRAT arithmetic score	−0.73	−1.69, 0.22	0.00	−0.04, 0.05
Body mass index#	0.13	−0.05, 0.31	0.00	−0.00, 0.01
Overweight**	2.73	1.30, 5.71	1.04	1.01, 1.08
Conduct problems scale score	0.05	−0.03, 0.13	−0.00	−0.00, 0.00
Asthma	0.98	0.59, 1.62	1.03	0.99, 1.06

* Sample sizes for each model were the same as those shown for the fixed-effects models in table 3.
† Dichotomous indicator of any maternal smoking during pregnancy versus no maternal smoking during pregnancy.
‡ Continuous measure of the maximum number of cigarettes smoked daily as recorded at any prenatal care visit.
§ OR, odds ratio; CI, confidence interval; IQ, intelligence quotient; WRAT, Wide Range Achievement Test.
¶ Odds ratios from logistic regression models are shown for neurologic soft signs, overweight, and asthma; linear regression coefficients (β) are shown for all other dependent variables.
# Weight (kg)/height $(m)^2$.
** ≥95th percentile of body mass index for age and sex.

APPENDIX TABLE 2. Conditional models of the association between maternal smoking during pregnancy and children's mental and physical development among all siblings ($n = 16,619$) in the Collaborative Perinatal Project, 1959–1974*

	Mean or % (standard error)	Level of maternal smoking during pregnancy (cigarettes/day)						*F* (3 df)	*p* value
		1–9		10–19		≥20			
		OR† or β‡	95% CI†	OR or β	95% CI	OR or β	95% CI		
Birth									
Birth weight (g)	3,203.0 (4.2)	−10.6	−44.8, 23.5	−78.0	−119.6, −36.4	−98.8	−143.1, −54.6	8.4	<0.001
5-minute Apgar score	9.0 (0.0)	−0.01	−0.11, 0.08	0.05	−0.07, 0.17	0.02	−0.11, 0.15	0.4	0.727
Age 4 years									
Stanford-Binet IQ†	97.3 (0.1)	0.12	−1.04, 1.30	0.31	−1.18, 1.80	0.51	−1.04, 2.06	0.1	0.938
Age 7 years									
Neurologic soft signs (%)	12.2 (0.0)	0.93	0.66, 1.30	0.90	0.60, 1.34	1.02	0.66, 1.59	0.2	0.886
Wechsler verbal IQ	93.3 (0.1)	−0.42	−1.42, 0.59	−0.58	−1.89, 0.72	0.33	−0.98, 1.64	1.1	0.371
Wechsler performance IQ	98.1 (0.1)	−0.29	−1.52, 0.94	−0.63	−2.25, 0.99	0.34	−1.28, 1.96	0.7	0.546
Wechsler full-scale IQ	95.1 (0.1)	−0.40	−1.45, 0.65	−0.64	−1.98, 0.70	0.37	−0.99, 1.72	1.1	0.343
WRAT† spelling score	95.4 (0.1)	−0.32	−1.27, 0.64	−0.56	−1.76, 0.65	−0.56	−1.83, 0.71	0.3	0.808
WRAT reading score	97.8 (0.1)	−0.38	−1.53, 0.77	−1.54	−1.58, 1.27	−0.36	−1.88, 1.17	0.2	0.909
WRAT arithmetic score	96.1 (0.1)	−0.60	−1.58, 0.29	−0.98	−2.06, 0.11	−0.12	−1.29, 1.06	1.6	0.188
Body mass index§	15.9 (0.0)	0.06	−0.12, 0.25	0.18	−0.05, 0.41	0.18	−0.07, 0.43	1.0	0.383
Overweight¶ (%)	3.9 (0.0)	1.34	0.72, 2.39	1.82	0.85, 3.87	1.74	0.83, 3.70	1.0	0.378
Conduct problems scale score	0.2 (0.0)	0.03	−0.05, 0.11	0.04	−0.05, 0.13	0.04	−0.06, 0.14	0.3	0.814
Asthma (%)	4.7 (0.0)	0.89	0.53, 1.49	0.88	0.54, 2.03	1.04	0.54, 2.03	0.2	0.896

* Multiple imputation was used to generate 10 data sets with complete data for all Collaborative Perinatal Project siblings ($n = 16,619$) using the MI and MIANALYZE procedures in SAS, version 9.1.3 (33). Variables in the imputation model included all child outcomes, statistically significant correlates of smoking during pregnancy identified in the proportional odds model (shown in table 2), birth order, and sex. Linear regression coefficients (β) and odds ratios shown in the table were generated by combining results from the 10 multiply imputed data sets.

† OR, odds ratio; CI, confidence interval; IQ, intelligence quotient; WRAT, Wide Range Achievement Test.

‡ Odds ratios from logistic regression models are shown for neurologic soft signs, overweight, and asthma; linear regression coefficients (β) are shown for all other dependent variables.

§ Weight (kg)/height $(m)^2$.

¶ ≥95th percentile of body mass index for age and sex.