Associations between Childhood Refraction and Parental Smoking

Richard A. Stone,[1,2] *Lorri B. Wilson,*[1,2] *Gui-shuang Ying,*[1] *Chengcheng Liu,*[1] *Jonathan S. Criss,*[2] *Joshua Orlow,*[2] *Jon M. Lindstrom,*[3] *and Graham E. Quinn*[1,2]

Purpose. Motivated by pharmacologic findings linking nicotinic acetylcholine receptors to eye development in chicks, the authors studied whether the refractions of children who were passively exposed to cigarette smoke by their parents differed from those of nonexposed children.

Methods. A cross-sectional study was conducted among 323 patients (mean ± SD age, 8.7 ± 4.4 years; range, 1–20) in a tertiary care pediatric ophthalmology clinic. Half (162/323) of the subjects had strabismus. The accompanying parent completed a detailed questionnaire on parental smoking history and on putative risk factors for myopia. The results were compared to the subjects' cycloplegic refractions.

Results. If one or both parents ever smoked, their children had a lower myopia prevalence (12.4% vs. 25.4%; $P = 0.004$) and more hyperopic mean refractions (1.83 ± 0.24 vs. 0.96 ± 0.27 diopters; $P = 0.02$) than those whose parents never smoked. Smoking by either parent during the mother's pregnancy had a similar effect on the child's refraction. The associations largely persisted, both in multivariate models that included adjustments for the child's age, child's body mass index, child's nearwork activity, parental myopia, and parental education and also in analysis by subgroups stratified by strabismus status.

Conclusions. Despite the complex constituents of cigarette smoke, neuropharmacology perspectives may prove useful in the development of new hypotheses to understand the mechanisms governing refractive development, not only in experimental animals but also in children. The associations of less prevalent myopia and a more hyperopic mean refraction with both prenatal and childhood exposures to tobacco smoke suggest that nongenetic, environmental exposures may have long-term influences on refraction and that further study of the role of nicotinic acetylcholine receptors in refractive development is warranted. (*Invest Ophthalmol Vis Sci.* 2006;47: 4277–4287) DOI:10.1167/iovs.05-1625

Despite long-held and extensively studied hypotheses about environmental and genetic factors' influencing refractive development, the etiologies of ametropias are poorly understood. Laboratory research has now shown that visual input governs the refractive development of chicks and mammals, that the retina plays a dominant role in controlling refractive development, and that identifiable receptor systems seem involved in the regulatory process.[1,2]

Acetylcholine receptors are among the most extensively studied receptor systems that influence refractive development.[1] Most research has addressed muscarinic acetylcholine receptors, which are metabotropic receptors acting through G-proteins.[3,4] For instance, the muscarinic antagonist atropine has antimyopia properties in children[3] and in experimental myopia of chicks and mammals.[5–7]

The other broad class of acetylcholine receptors is a large and diverse family of rapidly acting cation channels, termed nicotinic acetylcholine receptors because they are activated by the endogenous agonist acetylcholine, the plant alkaloid nicotine and other specific agonists.[8] In chicks, drugs that block nicotinic acetylcholine receptors affect experimental myopia.[9] Seeking evidence that nicotinic acetylcholine receptors might be pertinent to human refractive development, two of us (RAS and JML) previously stimulated an epidemiologic investigation of the relation of parental smoking with myopia in children of Singapore,[10] a country with a particularly high myopia prevalence[11] That investigation found an association of maternal smoking, but not paternal smoking, with lower myopia prevalence among children; but interpreting these results is confounded by the low smoking prevalence among women (3% compared to 27% of men).[10] A study of Japanese schoolchildren did not identify an association of parental smoking history with visual acuity below 0.7, probably a surrogate marker for myopia in most children (odds ratio [OR] = 0.73, 95% CI: 0.44–1.22 for maternal smoking; OR = 1.16, 95% CI: 0.72–1.86 for paternal smoking).[12] Compared with Singapore, smoking prevalence rates are higher in Japan, 57.5% of men and 14.2% of women overall, and recently have been approaching 25% of young women.[13]

We re-examined the relation of passive exposure to tobacco smoke with refraction by conducting a risk-factor analysis in the outpatient Pediatric Ophthalmology Clinic at the Children's Hospital of Philadelphia, a U.S. community with racial, refractive, and smoking characteristics different from these Asian populations. The racial composition of the patients at this clinic is chiefly white and African-American. As patients in a tertiary pediatric ophthalmology clinic, the study population also has greater representation of children with significant hyperopia and strabismus than Singapore or Japanese school-age children. Finally, the tristate area of Pennsylvania, New Jersey, and Delaware surrounding Philadelphia has a more balanced gender proportion of adult smokers, as some 22% to 28% of men and 21% to 23% of women were reported to smoke in a 2001 survey.[14]

From the Departments of [1]Ophthalmology, Scheie Eye Institute, and [3]Neuroscience, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania; and the [2]Division of Pediatric Ophthalmology, The Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, Pennsylvania.

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Corresponding author: Richard A. Stone, D-603 Richards Building, University of Pennsylvania School of Medicine, Philadelphia, PA 19104-6075; stone@mail.med.upenn.edu.

METHODS

Subjects

The 342 subjects, outpatients in the Pediatric Ophthalmology Clinic of the Children's Hospital of Philadelphia, all had complete eye examinations within the prior 6 months, including cycloplegic refractions, as part of ongoing care. Cycloplegia was induced in each eye by topical 1% cyclopentolate and either 1% tropicamide or 2.5% phenylephrine, and refraction was measured by streak retinoscopy 30 to 40 minutes later. Personnel performing refractions were unaware of the subjects' questionnaire responses. Exclusion criteria included diagnoses of glaucoma, uveitis, cataracts, or retinal disorders or a history of intraocular surgery. The purpose of the questionnaire (i.e., determining risk factors for refractive errors in children) was verbally explained to the accompanying parent(s), and they assented by completing the questionnaire if they wanted to participate. Each subject's birth date, gender, race, and ophthalmic diagnoses were obtained from the clinical record. The procedure and the protocol were approved by the Institutional Review Board at the Children's Hospital of Philadelphia and conformed to the Declaration of Helsinki.

Questionnaire

Parents provided their child's height, weight, birth weight, history of prematurity, and age at which glasses were first worn. They estimated the number of hours per week that their child studied, read for pleasure, played video or computer games, worked on the computer, and watched television. Parents also indicated whether the child slept in darkness, with a small night light, or with a room light, both before age 2 years and at present.[15] Parental information included educational background and whether the father or mother wore glasses or contact lenses for distance, near, or both, indirect methods of assessing parental refractive status.[16] Smoking-exposure questions included whether the mother or father was a current or former smoker (defined as at least one cigarette per day for 1 year or longer). If either parent had a positive smoking history, further information was obtained including the form of tobacco product used (e.g., cigarettes, cigars), parental age, the age smokers began smoking, when former smokers stopped, whether either parent smoked during the mother's pregnancy, the number of packs of cigarettes smoked daily, and whether the parent smoked in the home.

Data Analysis

Refraction is reported as the mean spherical equivalent (sphere plus ½ cylinder) of the two eyes due to the high correlation of spherical equivalent in paired eyes (Pearson correlation coefficient = 0.90). Myopia was defined as a spherical equivalent refraction of ≤ -0.5 diopters (D) for the mean of both eyes, and hyperopia was defined as a spherical equivalent refraction $\geq +2.0$ D for the mean of both eyes. Body mass index (BMI) was calculated as (weight in kg)/(height in m)^2. Total nearwork was estimated as a weighted parameter accounting for task proximity and amount of accommodation, as follows: weighted nearwork = 3 × (studying + reading) + 2 × (video/computer games + computer work) + television.[17] From the questionnaire responses, parents were classified as current or former smokers or nonsmokers. Former smokers were analyzed without regard to when they stopped. A parent who smoked at any time after the child's birth was classified as having smoked during the child's life. "Pack-years" of smoking was defined as (packs of cigarettes smoked per day) × (years of smoking).

A parent's smoking status for a particular parameter was classified as "unknown" when the pertinent question was unanswered. In most instances, the unknowns corresponded to partial responses to specific questions on the smoking behavior of the mother and/or father. For seven children, the questionnaires contained no responses to the questions on the smoking behavior of either parent; because responses to the smoking questions were not exclusion criteria in the study design, these subjects were retained. Unknowns in parental smoking status are listed in the tables. Descriptive statistics such as means and proportions are reported for unknowns as a group, but unknowns were not included in the calculation of probabilities relating the subjects' refractive status to tobacco smoke exposure.

The proportion of subjects with myopia or strabismus was compared for groups based on parental smoking status by using the Fisher exact test. The odds ratio (OR) and its 95% confidence interval (CI) for subject myopia or strabismus versus parental smoking status were calculated from logistic regression without (univariate) and with (multivariate) adjustment for possible confounders identified from either the literature or the present study. Spherical equivalent refractions were compared by analysis of variance (ANOVA). Trends were assessed with the Cochran-Armitage test for the proportions of myopia and strabismus and with the linear trend test from ANOVA for refractions. Unless otherwise noted, data are shown as mean ± SEM, and $P \leq 0.05$ was considered to be statistically significant. All data analyses were performed with commercially available software (SAS ver. 9.1; SAS Institute, Inc., Cary, NC).

RESULTS

Among the 342 subjects whose parents completed the questionnaire, there were 18 sets of siblings: 2 children from each of 17 families and 3 children from one family. One sibling from each of these families was selected randomly for inclusion in the data analysis. Of the 323 subjects thus included, the mean (± SD) age was 8.7 ± 4.4 (median 8.0; range 1–20) years: 35 (10.8%) subjects were <4 years old; 120 (37.2%) subjects, from 4 to <8 years old; 85 (26.3%) subjects, from 8 to <12 years old; and 83 (25.7%) subjects, at least 12 years old. Males accounted for 165 (51.1%) subjects. 173 subjects (53.6%) were white; 82 (25.4%), African-American; 24 (7.4%), other; and 44 (13.6%), unknown due to absent information. A history of premature birth (<36 weeks gestational age) was recorded for 48 (14.9%) subjects.

Reflecting the population of a tertiary care pediatric ophthalmology clinic, half of the subjects (162/323, or 50.2%) had strabismus. The mean age of subjects with strabismus (8.3 ± 0.4 years) did not differ from that of subjects without strabismus (9.1 ± 0.4 years; $P = 0.11$). Of those 162 subjects with strabismus, 98 (60.5%) had accommodative esotropia, 42 (25.9%) had exotropia, and 22 (13.6%) had other types of strabismus including infantile esotropia, hypertropia, Duane syndrome, a congenital III nerve palsy and a congenital elevator palsy. Compared with those without strabismus, subjects with strabismus had a more hyperopic mean refraction (2.58 ± 0.23 vs. 0.19 ± 0.23 D; $P < 0.0001$), a lower prevalence of myopia (20 [12.4%] subjects vs. 43 [26.7%] subjects; $P = 0.001$), and a higher prevalence of hyperopia (101 [62.4%] subjects vs. 25 [15.5%] subjects; $P < 0.0001$). As expected, the high prevalence of hyperopia (90.8%) and lack of myopia among subjects with accommodative esotropia accounted for the hyperopic refractive shift in subjects with strabismus. Specifically, the mean refraction of subjects with accommodative esotropia (4.28 ± 0.25 D) differed significantly ($P < 0.0001$, for each comparison) from subjects without strabismus (0.19 ± 0.21 D), with exotropia (−0.20 ± 0.39 D), or with other deviations (0.29 ± 0.54 D). However, the latter three cohorts did not differ among themselves ($P > 0.8$).

Sixty-three (19.5%) subjects had myopic refractions, and myopic subjects were older ($P < 0.0001$) as a cohort than the study population overall. Whereas more weighted nearwork activity, a slightly higher BMI, and sleeping with less nighttime lighting at the time of the questionnaire appeared to be associated with myopia, each of these parameters was related to age; and the statistical significance of each association disappeared when adjusted for age (data not shown). Subjects born

TABLE 1. Smoking Exposure from Either Parent Versus Child's Refractive Status

Parental Smoking Status	*N*	Myopia in Child		Refraction of child (Spherical Equivalent)	
		n (%)	*P**	Mean ± SEM	*P*†
Smoking by either parent					
Ever smoke					
Yes	169	21 (12.4)	0.004	1.83 ± 0.24	0.02
No	134	34 (25.4)		0.96 ± 0.27	
Unknown	20	8 (40.0)		0.51 ± 0.83	
Smoking					
Current	101	10 (9.9)	0.008	2.01 ± 0.31	0.03
Former	68	11 (16.2)		1.56 ± 0.37	
Never	134	34 (25.4)		0.96 ± 0.27	
Unknown	20	8 (40.0)		0.51 ± 0.83	
Smoking during child's life					
Yes	133	15 (11.3)	0.007	1.84 ± 0.27	0.051
No	167	40 (24.0)		1.13 ± 0.24	
Unknown	23	8 (34.8)		0.63 ± 0.73	
Smoke in the home					
Yes	56	8 (14.3)	0.01	1.67 ± 0.41	0.04
No (but smoker)	109	12 (11.0)		1.97 ± 0.30	
No (nonsmoker)	134	34 (25.4)		0.96 ± 0.27	
Unknown	24	9 (37.5)		0.45 ± 0.70	
Prenatal exposure					
Smoking during pregnancy: either parent					
Yes	81	7 (8.6)	0.003	2.19 ± 0.34	0.006
No	197	47 (23.9)		1.07 ± 0.22	
Unknown	45	9 (20.0)		1.31 ± 0.49	
Parental smoking during pregnancy					
Both parents smoke	19	2 (10.5)	0.04	2.95 ± 0.71	0.03
Only father smokes	41	3 (7.3)		1.89 ± 0.48	
Only mother smokes	21	2 (9.5)		2.10 ± 0.68	
None	197	47 (23.9)		1.07 ± 0.22	
Unknown	45	9 (20.0)		1.31 ± 0.49	

$n = 323$. Child myopia, defined as mean spherical equivalent of paired eyes ≤ -0.5 D. Smoking exposure from either parent: yes, at least one parent smokes; no, neither parent smokes; unknown, one nonsmoking parent and unknown smoking status of other parent, or smoking status of both parents unknown. Unknowns are shown but excluded from the statistical analyses. *N,* number of parents; *n,* number of child subjects.

* Fisher exact test, excluding unknowns.

† ANOVA, excluding unknowns.

prematurely did not differ from those born at term with regard to mean refraction, the proportion with myopia or hyperopia, or the proportion with strabismus (data not shown). Nighttime lighting conditions before 2 years, gender, and race were not significantly associated with prevalent myopia (data not shown).

There were no statistically significant differences in age, gender, racial distribution, history of prematurity, weighted nearwork, or nighttime lighting conditions among children ($n = 169$) from families with at least one parent who ever smoked compared with those ($n = 134$) from families with nonsmoking parents (data not shown). Reduced birth weight was more likely to be associated with smoking during pregnancy by the mother ($P = 0.04$) but not the father ($P = 0.12$) individually, but with interacting effects from each parent ($P = 0.007$, linear trend test): both parents smoked, 2622 ± 200 g; mother only smoked, 3016 ± 186 g; father only smoked, 3130 ± 132 g; neither parent smoked, 3180 ± 59 g.

Refraction and Passive Smoke Exposure during Childhood

Smoking by at least one parent during the child's lifetime was reported by 133 (44.3%) of the subjects included in the data analysis (Table 1). By many criteria (Tables 1–5), parental smoking was associated with lower myopia prevalence and more hyperopic mean refractions in their children compared with the children of nonsmokers, regardless of whether the parents reported smoking in the home or only outside the home (Table 1). In contrast to myopia prevalence, the children's age at myopia onset based on the age at initial glasses prescription was not influenced by parental smoking status or parental myopia (data not shown).

When analyzed by the smoking status of each parent considered individually (Tables 2A, 2B), associations of the children's refractive status with parental smoking were generally weaker than those found for passive smoke exposure from either parent (Table 1). An estimate of the annual postnatal passive exposure to cigarette smoke, the parameter (pack-year smoking during the child's life)/(child's age) suggested possible monotonic dose responses for the associations of less myopia and more hyperopia with passive smoke exposure (Table 2B).

Regarding parental characteristics previously associated with children's refractions, a myopic refractive error in the child was not associated with paternal or maternal myopia (Table 2C) or with the number of myopic parents (data not shown) in this population. Statistically significant associations of parental educational level with childhood myopia prevalence or mean refraction were weak or absent, and these variations were not monotonically related to an ordering of educational attainment for either parent (Table 2C). A smaller proportion of mothers and fathers who ever smoked or smoked during the pregnancy was associated with higher educational attainment based on the ordering of educational

TABLE 2. Parental Characteristics as Risk Factors for Myopia in Their Child

	Mother					Father				
		Myopia in Child		Refraction of Child (Spherical Equivalent)			Myopia in Child		Refraction of Child (Spherical Equivalent)	
Parental Characteristic	***N***	***n* (%)**	***P****	**Mean ± SEM**	***P*†**	***N***	***n* (%)**	***P****	**Mean ± SEM**	***P*†**
A. Parental smoking status										
Ever Smoke										
Yes	113	15 (13.3)	0.052	1.79 ± 0.29	0.09	117	15 (12.8)	0.02	1.81 ± 0.29	0.06
No	197	45 (22.8)		1.16 ± 0.22		171	41 (24.0)		1.10 ± 0.24	
Unknown	13	3 (23.1)		1.28 ± 1.06		35	7 (20.0)		1.38 ± 0.50	
Smoking										
Current	62	6 (9.7)	0.07	2.48 ± 0.39	0.008	73	8 (11.0)	0.053	1.87 ± 0.37	0.17
Former	51	9 (17.7)		0.96 ± 0.43		44	7 (15.9)		1.70 ± 0.48	
Never	197	45 (22.8)		1.16 ± 0.22		171	41 (24.0)		1.10 ± 0.24	
Unknown	13	3 (23.1)		1.28 ± 1.06		35	7 (20.0)		1.38 ± 0.50	
Pack-years§										
Nonsmoker	197	45 (22.8)	0.11	1.16 ± 0.22	0.19	171	41 (24.0)	0.008	1.10 ± 0.24	0.03
Smoker, <median	45	5 (11.1)		1.40 ± 0.46		44	2 (4.6)		2.48 ± 0.47	
Smoker, ≥median	46	6 (13.0)		2.09 ± 0.46		45	8 (17.8)		1.33 ± 0.47	
Unknown	35	7 (20.0)		1.72 ± 0.60		63	12 (19.1)		1.44 ± 0.39	
B. Child's smoke exposure										
Smoking during child's life										
Yes	89	12 (13.5)	0.11	1.81 ± 0.33	0.13	96	11 (11.5)	0.02	1.82 ± 0.32	0.10
No	221	48 (21.7)		1.22 ± 0.21		192	45 (23.4)		1.17 ± 0.23	
Unknown	13	3 (23.1)		1.28 ± 1.06		35	7 (20.0)		1.38 ± 0.50	
Smoking in the home										
Yes	37	5 (13.5)	0.14	1.84 ± 0.52	0.32	35	4 (11.4)	0.06	2.08 ± 0.53	0.13
No, but smoker	69	9 (13.0)		1.65 ± 0.38		77	10 (13.0)		1.75 ± 0.36	
No and nonsmoker	197	45 (22.8)		1.16 ± 0.22		171	41 (24.0)		1.10 ± 0.24	
Unknown	20	4 (20.0)		1.85 ± 0.70		40	8 (20.0)		1.29 ± 0.50	
(Pack-year smoking during child's life)/(child's age)										
0	221	48 (21.7)	0.09	1.22 ± 0.21	0.06	192	45 (23.4)	0.03	1.17 ± 0.23	0.10
0.01–0.5	48	7 (14.6)	0.04‡	1.34 ± 0.45	0.02‡	49	6 (12.2)	0.04‡	1.93 ± 0.45	0.08‡
≥0.51	31	2 (6.5)		2.66 ± 0.56		38	3 (7.9)		2.17 ± 0.51	
Unknown	23	6 (26.1)		1.35 ± 0.68		44	9 (20.5)		1.04 ± 0.46	
C. Parental characteristics										
Parental Myopia										
Yes	101	23 (22.8)	0.36	1.05 ± 0.32	0.17	77	19 (24.7)	0.18	0.92 ± 0.36	0.07
No	211	38 (18.0)		1.57 ± 0.22		227	39 (17.2)		1.66 ± 0.21	
Unknown	11	2 (18.2)		1.03 ± 0.74		19	5 (26.3)		−0.04 ± 0.71	
Parental education										
Grade school	18	3 (16.7)	0.73	1.63 ± 0.74	0.06	53	14 (25.9)	0.048	0.83 ± 0.43	0.08
High school	109	19 (17.4)	0.22‡	1.67 ± 0.30	0.14‡	99	13 (13.1)	0.69‡	2.01 ± 0.31	0.68‡
Vocational/technical school	26	4 (15.4)		2.55 ± 0.61		26	2 (7.7)		2.05 ± 0.61	
College	112	22 (19.6)		1.23 ± 0.30		85	23 (27.1)		1.05 ± 0.34	
Graduate school	58	15 (25.9)		0.55 ± 0.41		60	11 (18.3)		1.05 ± 0.40	
D. Prenatal smoke exposure										
Smoking during pregnancy										
Yes	40	4 (10.0)	0.13	2.51 ± 0.49	0.01	60	5 (8.3)	0.01	2.22 ± 0.41	0.02
No	267	56 (21.0)		1.20 ± 0.19		217	50 (23.0)		1.18 ± 0.21	
Unknown	16	3 (18.8)		1.71 ± 0.93		46	8 (17.4)		1.28 ± 0.46	
Smoking during pregnancy										
Yes	40	4 (10.0)	0.12	2.51 ± 0.49	0.04	60	5 (8.3)	0.03	2.22 ± 0.41	0.06
No, but smoker	70	11 (15.7)		1.31 ± 0.37		46	9 (19.6)		1.46 ± 0.46	
No and nonsmoker	197	45 (22.8)		1.16 ± 0.22		171	41 (24.0)		1.10 ± 0.24	
Unknown	16	3 (18.8)		1.71 ± 0.93		46	8 (17.4)		1.28 ± 0.46	
Pack-year smoking during pregnancy										
0	267	56 (21.0)	0.10	1.20 ± 0.19	0.01	217	50 (23.0)	0.02	1.18 ± 0.21	0.03
0.5	18	1 (5.6)	0.03‡	2.32 ± 0.73	0.009‡	29	2 (6.9)	0.01‡	2.74 ± 0.59	0.22‡
≥1	19	1 (5.3)		3.13 ± 0.71		29	2 (6.9)		1.94 ± 0.59	
Unknown	19	5 (26.3)		1.39 ± 0.81		48	9 (18.8)		1.18 ± 0.43	

$n = 323$. Child myopia was defined as mean spherical equivalent of paired eyes ≤ -0.5. Mother's or father's smoking status indicated, without regard to smoking status of spouse. N, number of parents; *n,* number of child subjects. Unknowns are shown but excluded from the statistical analyses.

* Fisher exact test, unless otherwise specified; unknowns excluded.

† ANOVA, unless otherwise specified; unknowns excluded.

‡ Test for linear trend, excluding unknowns.

§ Median number of pack-years: 8.5 pack-years for mother, 13 pack-years for father.

TABLE 3. Association of Smoking by Either Parent with Myopia in Their Child without (Univariate) and with (Multivariate) Adjustment of Possible Confounders*

	Univariate		Multivariate*	
Parental Smoking	**OR† (95% CI)**	***P***	**OR† (95% CI)**	***P***
Smoking		0.007‡		0.01‡
Never-	1	—	1	—
Former smoker	0.57 (0.26–1.18)	0.14	0.52 (0.19–1.34)	0.19
Current smoker	0.32 (0.14–0.67)	0.004	0.22 (0.07–0.64)	0.008
Smoking during child's life				
No	1	—	1	—
Yes	0.40 (0.21–0.77)	0.006	0.22 (0.08–0.59)	0.003
Smoking in the home		0.01‡		0.02‡
No, for nonsmokers	1	—	1	—
No, for smokers	0.36 (0.17–0.73)	0.006	0.42 (0.17–1.02)	0.06
Yes	0.49 (0.20–1.09)	0.10	0.23 (0.06–0.79)	0.03
Smoking during pregnancy				
No	1	—	1	—
Yes	0.30 (0.13–0.70)	0.005	0.15 (0.04–0.53)	0.003

* Possible confounders included in the analyses are child's age, body mass index, weighted nearwork, parental myopia status, and education of either parent.

† OR, odds ratio of having myopic child in this group vs. the reference (never-smoked) group.

‡ Test of overall difference among the 3 smoking status groups.

levels in Table 2C ($P < 0.0001$ for each comparison, Cochran-Armitage trend test; data not shown).

Both univariate and multivariate analyses confirmed reduced risk of myopia in children with at least one parent who smoked (Table 3). Adding nighttime light exposure before age 2 years to the multivariate analysis did not alter these associations (data not shown). Analysis by the smoking behavior of individual parents yielded weaker but still statistically significant associations in most comparisons for current smoking and smoking during the child's lifetime (Table 4).

From classifying the children into five refraction categories (Table 5, Fig. 1), parental smoking seemed to shift the overall distribution toward more children in the hyperopic refraction categories and fewer in the myopic refraction categories without meaningfully altering the proportion of emmetropic children.

Refraction and Prenatal Smoke Exposure

Smoking by either parent during the pregnancy was associated with lower myopia prevalence and a more hyperopic mean

TABLE 4. Association of Smoking by Each Parent with Myopia in Their Child without (Univariate) and with (Multivariate) Adjustment of Possible Confounders*

	Mother				Father			
	Univariate		Multivariate*		Univariate		Multivariate*	
Parental Smoking	**OR† (95% CI)**	***P***	**OR† (95% CI)**	***P***	**OR† (95% CI)**	***P***	**OR† (95% CI)**	***P***
Smoking		0.08‡		0.03‡		0.06‡		0.13‡
Never	1	—	1	—	1	—	1	—
Former smoker	0.72 (0.33–1.60)	0.42	0.37 (0.11–1.16)	0.09	0.60 (0.25–1.45)	0.26	0.80 (0.24–2.65)	0.71
Current smoker	0.36 (0.15–0.90)	0.03	0.19 (0.05–0.79)	0.02	0.39 (0.17–0.88)	0.02	0.28 (0.08–0.96)	0.04
Smoking during child's life								
No	1	—	1	—	1	—	1	—
Yes	0.56 (0.28–1.12)	0.10	0.31 (0.11–0.92)	0.04	0.42 (0.21–0.86)	0.02	0.30 (0.10–0.85)	0.02
Pack-years§		0.11‡		0.049‡		0.03‡		0.26‡
Nonsmoker	1	—	1	—	1	—	1	—
Smoker, <median	0.42 (0.16–1.13)	0.09	0.29 (0.06–1.39)	0.12	0.15 (0.04–0.65)	0.01	0.17 (0.02–1.46)	0.11
Smoker, ≥median	0.51 (0.20–1.27)	0.15	0.29 (0.09–0.94)	0.04	0.69 (0.30–1.59)	0.38	0.79 (0.27–2.30)	0.66
Smoking in the home		0.14‡		0.02‡		0.06‡		0.24‡
No, for nonsmokers	1	—	1	—	1	—	1	—
No, for smokers	0.51 (0.23–1.10)	0.09	0.50 (0.17–1.51)	0.22	0.47 (0.22–1.003)	0.051	0.59 (0.21–1.64)	0.31
Yes	0.53 (0.19–1.43)	0.21	0.12 (0.03–0.57)	0.007	0.41 (0.14–1.23)	0.11	0.29 (0.06–1.45)	0.13
Smoking during pregnancy								
No	1	—	1	—	1	—	1	—
Yes	0.42 (0.14–1.23)	0.11	0.13 (0.02–0.72)	0.02	0.30 (0.12–0.80)	0.02	0.14 (0.03–0.73)	0.02

* Possible confounders included in the analyses are child's age, body mass index, weighted nearwork, myopia status of either parent, and either mother's education for the mother's model or father's education for the father's model.

† OR, odds ratio of having myopic child in this group vs. the reference (never-smoked) group.

‡ Test of overall difference among three groups of smoking status.

§ Median number of pack-years: 8.5 for mother, 13 for father.

TABLE 5. The Distribution of Mean Spherical Equivalent Refractions versus Parental Smoking Status

	N	High hyperopia *n* (%)	Hyperopia *n* (%)	Emmetropia *n* (%)	Myopia *n* (%)	High Myopia *n* (%)
Current parental smoking						
Yes	101	18 (17.8)	28 (27.7)	45 (44.6)	7 (6.9)	3 (3.0)
No	202	23 (11.4)	51 (25.3)	83 (41.1)	37 (18.3)	8 (4.0)
P	0.06*					
Parental smoking during child's life						
Yes	133	22 (16.5)	39 (29.3)	57 (42.9)	10 (7.5)	5 (3.8)
No	167	19 (11.4)	39 (23.4)	69 (41.3)	34 (20.4)	6 (3.6)
P	0.02*					
Parental smoking during pregnancy						
Yes	81	16 (19.8)	22 (27.2)	36 (44.4)	6 (7.4)	1 (1.2)
No	197	21 (10.7)	50 (25.4)	79 (40.1)	38 (19.3)	9 (4.6)
P	0.03*					

High hyperopia: refraction $\geq$5 D; hyperopia: 2 D $\leq$refraction $<$ 5 D; emmetropia: -0.5 D $<$ refraction $<$ 2 D; myopia: -5 D $<$ refraction ≤ -0.5 D; high myopia: refraction ≤ -5 D. Parental pairs and their children were excluded if it was indeterminate whether the child was exposed to tobacco smoke from at least one parent (i.e., one parent a nonsmoker and the other unknown, or smoking status of both parents unknown).

* Exact *P*-value for the test of the overall proportion difference in high hyperopia, hyperopia, emmetropia, myopia, and high myopia.

refraction (Table 1). For the smoking behavior of individual parents, similar relations held that reached statistical significance for mean refraction and maternal smoking and for both myopia prevalence and mean refraction for paternal smoking (Table 2D). When smoking was quantified by pack-years during the pregnancy, there was a monotonic dose–response toward more hyperopia for maternal smoking, with a more complex but still statistically significant relation for paternal smoking (Table 2D). Although the number of myopic children is too few to comment meaningfully on whether a dose–response is present for myopia prevalence, the pack-year index confirms reduced myopia prevalence with smoking during pregnancy. Univariate and multivariate analysis for smoking by either parent during the pregnancy confirmed a reduced risk for myopia in their children (Table 3). In assessing each parent individually, smoking during pregnancy was associated with lower myopia prevalence in the multivariate model for maternal smoking and in both models for paternal smoking (Table 4).

Based on the same refraction categories (Table 5, Fig. 1), prenatal exposure to cigarette smoke from either parent was associated with a shift in the overall distribution toward hyper-

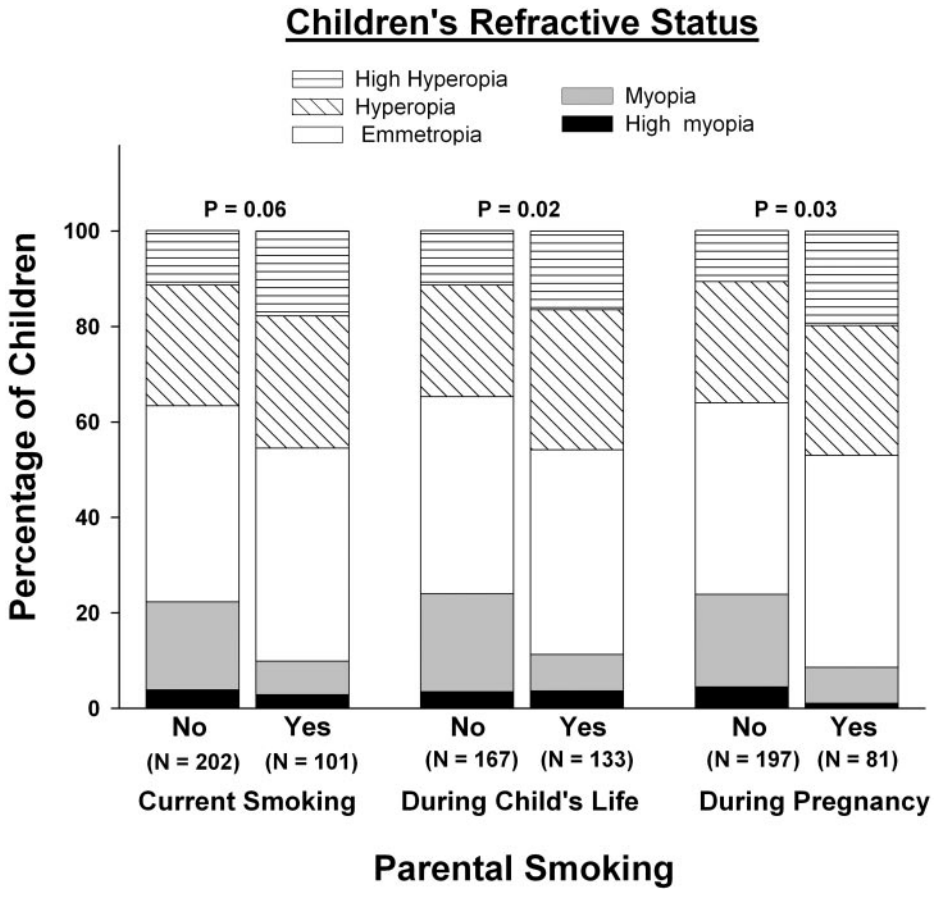

FIGURE 1. Children's refractive status versus parental smoking status. Based on the data in Table 5, with the smoking behavior of either parent, the percentage of children in each of five refractive categories is shown for parents who reported either smoking or not smoking currently, during the child's life and during the pregnancy. The refractive categories are defined in Table 5.

TABLE 6. Associations of Parental Smoking during Pregnancy with Strabismus

Parental Smoking Status during Pregnancy	*N*	Children with Strabismus, *n* (%)			
		Any Type (*n* = 162)	Accommodative Esotropia (*n* = 98)	Exotropia (*n* = 42)	Other Types (*n* = 22)
Parental smoking					
Both	19	13 (68.4)	7 (36.8)	3 (15.8)	3 (15.8)
Mother only	21	18 (85.7)	9 (42.9)	7 (33.3)	2 (9.5)
Father only	41	15 (36.6)	10 (24.4)	1 (2.4)	4 (9.8)
None	197	93 (47.2)	61 (31.0)	20 (10.2)	12 (6.1)
Unknown	45	23 (51.1)	11 (24.4)	11 (24.4)	1 (2.2)
*P**		0.0005	0.46	0.004	0.26
Unadjusted OR (95% CI)					
Both vs. none		2.42 (0.89–6.63)	1.30 (0.49–3.47)	1.66 (0.45–6.19)	2.89 (0.74–11.31)
Mother only vs. none		6.71 (1.91–23.49)	1.67 (0.67–4.18)	4.43 (1.60–12.25)	1.62 (0.34–7.80)
Father only vs. none		0.65 (0.32–1.29)	0.72 (0.33–1.56)	0.22 (0.03–1.70)	1.67 (0.51–5.45)
Adjusted OR (95% CI)†					
Both vs. none		3.17 (0.66–15.22)	3.13 (0.69–14.15)	0.78 (0.12–4.86)	4.50 (0.30–67.02)
Mother only vs. none		10.97 (2.19–54.90)	2.57 (0.76–8.66)	3.19 (0.86–11.84)	2.00 (0.26–15.14)
Father only vs. none		0.53 (0.22–1.28)	0.81 (0.29–2.25)	0.20 (0.02–1.69)	0.89 (0.14–5.64)
Mother smoked					
Yes	40	31 (77.5)	16 (40.0)	10 (25.0)	5 (12.5)
No	267	122 (45.7)	77 (28.8)	28 (10.5)	17 (6.4)
Unknown	16	9 (56.3)	5 (31.3)	4 (25.0)	0
*P**		0.0002	0.20	0.02	0.18
Unadjusted OR (95% CI)		4.09 (1.88–8.93)	1.65 (0.83–3.27)	2.85 (1.26–6.43)	2.10 (0.73–6.05)
Adjusted OR (95% CI)†		6.55 (2.24–19.14)	2.75 (1.06–7.09)	2.10 (0.75–5.88)	2.89 (0.59–14.22)
Father smoked					
Yes	60	28 (46.7)	17 (28.3)	4 (6.7)	7 (11.7)
No	217	111 (51.2)	72 (33.2)	26 (12.0)	13 (6.0)
Unknown	46	23 (50.0)	9 (19.6)	12 (26.1)	2 (4.4)
*P**		0.56	0.53	0.35	0.16
Unadjusted OR (95% CI)		0.84 (0.47–1.48)	0.80 (0.43–1.49)	0.53 (0.18–1.57)	2.07 (0.79–5.45)
Adjusted OR (95% CI)†		0.67 (0.32–1.42)	1.02 (0.44–2.35)	0.37 (0.10–1.41)	1.37 (0.32–5.87)

Unknowns in parental smoking status are shown but excluded from the statistical analyses. Other types of strabismus include infantile esotropia, hypertropia, Duane syndrome, a congenital III nerve palsy, and a congenital elevator palsy. OR, odds ratio, with nonsmoking as reference.

* Fisher exact test.

† Adjusted by age, gender, birth weight, history of prematurity, BMI, education (mother's education for the mother's model, father's education for the father's model, or both parents' education for the parental model) and weighted nearwork.

opia, increasing the proportion of hyperopic children, reducing the proportion of myopic children, and having little influence on the proportion of emmetropic children.

Strabismus and Prenatal Smoking Exposure

When assessed either by overall parental smoking or by individual parents, smoking by the mother but not the father during pregnancy associated with childhood strabismus based on both unadjusted and adjusted odds ratios (Table 6). The type of strabismus associated with parental smoking was uncertain in these data, however, because the unadjusted ORs suggested an association of maternal smoking with exotropia, but the multivariate adjustments of the mothers' smoking behavior instead suggested an association with accommodative esotropia (Table 6).

Because the mean refraction of subjects with accommodative esotropia was shifted toward hyperopia, we also compared passive smoke exposure from either parent with their child's refractive status by analyzing subgroups stratified by strabismus (Table 7). For the subjects without strabismus the association of passive smoke exposure with reduced myopia prevalence remained strong (Table 7), despite the reduced sample size in the stratification (161 subjects in the nonstrabismus subgroup vs. 323 subjects overall). The association of passive smoke exposure with more hyperopic mean refractions persisted in the nonstrabismus subgroup for the current-former-never and for both prenatal exposure parameters but not for the ever-smoked or during-the-child's-life parameters (Table 7). For the stratification excluding subjects with accommodative esotropia, passive smoke exposure was associated significantly with both reduced myopia prevalence and hyperopic refractive shifts in all parameters except mean refraction with the ever-smoked parameter (Table 7). Thus, the same relations between passive smoke exposure and refractive status largely persisted in the subgroup analyses (Table 7) as in the population as a whole (Tables 1–5).

DISCUSSION

Childhood Smoke Exposure

By many criteria, smoking by either parent is associated with lower myopia prevalence and more hyperopic mean refractions in their children. Childhood smoke exposure would be passive, due to "second-hand" smoke. Passive exposure to cigarette smoke shifted the subjects' mean refractions toward hyperopia (Table 5, Fig. 1). Thus, the overall hyperopic refractive shift seems to account for the reduced myopia prevalence, rather than an effect of passive smoke exposure on myopia prevalence per se.

TABLE 7. Smoking Exposure from Either Parent Versus Child's Refractive Status, Stratified for Strabismus

	All Subjects without Strabismus (n = 161)					All Subjects Except Those with Accommodative Esotropia (n = 225)				
		Myopia in Child		Refraction of Child (Spherical Equivalent)			Myopia of Child		Refraction of Child (Spherical Equivalent)	
Parental Smoking Status	***N***	***n* (%)**	***P****	**Mean ± SEM**	***P*†**	***N***	***n* (%)**	***P****	**Mean ± SEM**	***P*†**
Smoking by either parent										
Ever smoked										
Yes	74	13 (17.6)	0.04	0.39 ± 0.30	0.52	112	21 (18.8)	0.01	0.49 ± 0.26	0.08
No	77	25 (32.5)		0.12 ± 0.29		97	34 (35.1)		−0.18 ± 0.27	
Unknown	10	5 (50.0)		−0.72 ± 0.42		16	8 (50.0)		−0.53 ± 0.82	
Smoking										
Current	45	4 (8.9)	0.008	1.00 ± 0.38	0.03	72	10 (13.9)	0.007	0.96 ± 0.32	0.01
Former	29	9 (31.0)		−0.56 ± 0.47		40	11 (27.5)		−0.37 ± 0.42	
Never	77	25 (32.5)		0.12 ± 0.29		97	34 (35.1)		−0.18 ± 0.27	
Unknown	10	5 (50.0)		−0.72 ± 0.42		16	8 (50.0)		−0.53 ± 0.82	
Smoked during child's life										
Yes	59	7 (11.9)	0.002	0.65 ± 0.33	0.12	92	15 (16.3)	0.004	0.63 ± 0.28	0.03
No	90	31 (34.4)		−0.02 ± 0.27		115	40 (34.8)		−0.19 ± 0.25	
Unknown	12	5 (41.7)		−0.52 ± 0.38		18	8 (44.4)		−0.42 ± 0.73	
Prenatal exposure										
Smoking during pregnancy: either parent										
Yes	35	3 (8.6)	0.004	1.04 ± 0.44	0.02	55	7 (12.7)	0.002	1.12 ± 0.37	0.002
No	104	35 (33.7)		−0.13 ± 0.25		136	47 (34.6)		−0.27 ± 0.23	
Unknown	22	5 (22.7)		0.34 ± 0.34		34	9 (26.5)		0.12 ± 0.47	
Parent smoking during pregnancy										
Both parents smoked	6	0	0.04	2.77 ± 1.05	0.04	12	2 (16.7)	0.02	1.88 ± 0.79	0.01
Only father smoked	26	3 (11.5)		0.74 ± 0.50		31	3 (9.7)		1.04 ± 0.49	
Only mother smoked	3	0		0.17 ± 1.49		12	2 (16.7)		0.58 ± 0.79	
None	104	35 (33.7)		−0.13 ± 0.25		136	47 (34.6)		−0.27 ± 0.23	
Unknown	22	5 (22.7)		0.34 ± 0.34		34	9 (26.5)		0.12 ± 0.47	

Child myopia, defined as mean spherical equivalent of paired eyes ≤−0.5 D. Smoking exposure from either parent: yes, at least one parent smokes; no, neither parent smokes; unknown, one nonsmoking parent and unknown smoking status of other parent, or smoking status of both parents unknown. Unknowns are shown but excluded from the statistical analyses. *N,* number of parents; *n,* number of child subjects.

* Fisher exact test, excluding unknowns.

† ANOVA test, excluding unknowns.

The parameter (pack-year smoking during child's life)/(child's age) provides a rough estimate of the annual exposure to cigarette smoke. For both maternal and paternal smoking, this parameter suggests a dose–response relation, with more postnatal parental smoking being associated with less myopia and more hyperopic mean refractions in their children. For myopia prevalence in particular, such quantitative estimates are limited by potential confounding from the small number of myopic offspring of smoking parents in this study. The protective effect on myopia seemed comparable with parents who smoked in the home and with smoking parents who reported not smoking in the home (Table 2B) but perhaps exposed their children to passive smoke only under more limited circumstances, such as in the automobile. The apparent protective effect of potentially low exposures complicates the issue of whether a true dose–response exists. The threshold for an effect of tobacco smoke on refractive development may be quite low, with a dose–response. Alternatively, other risk factors unknown to us may associate with parental cigarette smoking and refractive development. However, the associations in our study persisted after adjustment for the commonly studied risk factors of age, BMI, nearwork, parental myopia, and parental education. In our survey, increased prevalence of parental smoking was associated with lower educational attainment (see the Results section), as noted in other studies.[18] Although we do not have other data pertinent to the putative risk factor of socioeconomic status, parental educational attainment seems to be a reasonable surrogate.[18]

The current investigation found a much stronger relation between exposure to parental smoking and refractive development in their children than that seen in prior Asian studies.[10,12] Why the results in the present U.S population differ from these available Asian data is speculative. In addition to the demographic differences between the studies described in the introduction, including the differences in smoking rates, analytic differences may contribute. We used passive smoke exposure from either parent (Tables 1, 3, 5) as our primary analytical parameter because it seemingly best reflects any exposure of children to tobacco smoke irrespective of source. The statistical strength of the associations lessened in analyses based on smoke exposure from individual parents (Tables 2, 4), probably because of confounding of the exposure from individual parents by dissimilar exposures from the two parents in families in which only one spouse smoked. Each Asian study assessed smoke exposure by individual parents only, not by either parent, possibly contributing to reduced strength of the associations in those reports. Analysis by either parent of the Singapore study group did not reveal an association (Seang-Mei Saw, personal communication, 2006). The small proportion of Singapore women who smoke implies that analysis by either parent in this population would not be likely to differ much from the analysis by paternal exposure alone. The analysis by

maternal exposure may have underestimated the strength of the association because of the substantial number of control subjects exposed to smoke by their fathers, if our findings apply to this Singapore population. The Japanese study reported smoke exposure by individual parents only, not by either parent.[12] Myopia prevalence also is higher in Asian than Western societies, and yet-to-be-defined environmental and/or genetic causes for myopia in Asian populations may differ from Western societies and partly conceal an association with passive exposure to tobacco smoke.

Prenatal Smoke Exposure

Exposure in utero from either maternal or paternal smoking was also associated in our report with lower myopia prevalence and a hyperopic refractive shift. Prenatal maternal smoking directly exposes the fetus through the placenta[19]; but for nonsmoking mothers, the prenatal paternal exposure would be indirect via passive smoke exposure of the mother and then direct transfer across the placenta. Because so few parents stopped smoking near their child's birth (one father, six mothers smoking during pregnancy but stopping within a year of their children's births), we cannot meaningfully compare prenatal versus postnatal exposures from our data.

Prenatal and early life experiences are inadequately addressed in the research on refraction. However, the behavioral and neural effects of gestational exposure to tobacco smoke have been widely studied in other areas.[19] Nicotine easily penetrates the placental barrier, and the brain of the fetus seems particularly susceptible to effects from nicotine. In the brains of experimental animals, for instance, exposure to nicotine only in utero alters overall development, expression of neural nicotinic acetylcholine receptors, and nicotine-stimulated dopamine release into adolescence.[20,21] The notion that early and perhaps transient environmental exposures, including prenatal exposures, might have a prolonged effect on refractive development is a reasonable hypothesis to explore by analogy with the literature on tobacco smoke exposure and brain development. Breastfeeding during infancy associates with reduced myopia prevalence later in childhood and similarly suggests that early life exposures might influence later refractive development.[22]

Although much work is needed to relate such observations to refractive development, the refractive associations of prenatal paternal as well as maternal smoking suggest that the signaling system responsible for refractive development may be quite sensitive to nicotine or some other component of tobacco smoke. The myopia prevalence and refraction of children with smoking parents not smoking during pregnancy appear to differ from those whose parents smoked during pregnancy (Table 2D), suggesting that the associations may relate to actual exposures rather than to common genes' being responsible for both a propensity to parental smoking and hyperopic refractions in their children.

Strabismus and Parental Smoking

We found an association of childhood strabismus with maternal but not paternal smoking during pregnancy, though specific strabismus types were not strongly linked with maternal smoking in these data. The effects on refraction and strabismus may reflect independent responses to smoke exposure since the refractive effects were associated with passive smoke exposure from both parents, but strabismus was associated only with maternal smoking. A prior case–control study also identified an association of strabismus with prenatal maternal smoking, in that case with esotropia, but refraction data were not included in this report.[23]

Hyperopia is generally believed to be a cause rather than a consequence of accommodative esotropia.[24] Accordingly, the mean refractions of our subjects with accommodative esotropia were more hyperopic than those of subjects without strabismus or those of subjects in the other strabismus categories. Although a few associations did not reach statistical significance, most associations of passive smoke exposure with reduced myopia prevalence and hyperopic refractive shift persisted in subgroup analyses that excluded either all subjects with strabismus or those with accommodative esotropia (Table 7), despite the reduced sample sizes (and hence power) of the subgroups. Thus, strabismus does not seem to be a major confounder of the smoking–refraction associations in our study.

Possible Biochemical Mechanisms for Smoking–Refraction Interactions

Because cigarette smoke is chemically complex and the current investigation is a cross-sectional survey, firm conclusions about the biological basis for the smoking and refraction associations are not possible. Nonetheless, the neuroscience and psychiatry literature on the addictive and other brain effects of smoking provides some parallels with the available experimental pharmacology of myopia.

Nicotine is the constituent of tobacco smoke responsible for many of its effects. The pharmacology of nicotinic acetylcholine receptors is quite complicated.[25,26] Depending on the subunit composition, dose, temporal exposure patterns, genetics, specific neural pathways, and other parameters, nicotine can elicit a wide range of complex and sometimes conflicting biological responses that persist well after the exposure.[27,28] Frequently, nicotine exposure induces a paradoxical upregulation of nicotinic receptors but also a rapid receptor desensitization, sometimes causing agonists to behave as time-averaged antagonists in many biological systems.[29,30]

The literature on refractive development pertinent to smoking, including the present study, is scant but reflects many of the issues in the well-developed brain literature, assuming that nicotine is the pertinent component of cigarette smoke. In chicks, nicotinic antagonists inhibit experimental myopia, but potentially with multiphasic dose responses.[9] Any protective action in human myopia of nicotine clearly requires more investigation, but the reduced myopia prevalence with tobacco smoke exposure could reflect the dose of exposure or the upregulation and desensitization of ocular receptors by nicotine as occurs in brain. At least, the present findings justify further study of nicotinic acetylcholine receptor pharmacology for possible etiologic or therapeutic leads for human myopia.

Both dopamine and γ-aminobutyric acid (GABA) localize to specific retinal neurons, and evidence implicates each of these retinal transmitter systems as being involved in refractive development.[1,31–34] In brain, nicotine stimulates dopamine release, and nonnicotine constituents of cigarette smoke inhibit the activity of monoamine oxidase, an enzyme that can degrade dopamine.[26,27,35,36] Cigarette smoking is well-established to protect against Parkinson disease, an observation consistent with the interaction of cigarette smoke and the brain dopamine neurons known to be affected in this disease.[36] Nicotine also interacts with brain neurons containing GABA.[27,35,36] Any effects of nicotine or other constituents of tobacco smoke on the signaling or metabolism of dopamine or GABA in the retina also may provide a mechanism to explain the epidemiologic associations found in our study.

Ambient Nighttime Light Exposure

Also stimulated by neuropharmacology results in laboratory investigations of refractive development,[37–40] we have found

that increased nighttime ambient light exposure before age 2 years associated with lower myopia prevalence later in childhood and suggested that nighttime lighting may be a risk factor for myopia.[15] Some subsequent reports have tended to support an association of refraction or ocular components with qualities of ambient lighting,[41–47] but others have not,[48–51] including the present survey.

Although the present study and our prior study were conducted in the same clinic, there are two intriguing differences that may be pertinent to the different lighting associations. First, the subjects' parents reported less use of artificial nighttime lighting in the current survey. The proportion of subjects reported to have slept before age 2 years with a room light or a nightlight or in darkness in the present study (4.0%, 54.5%, and 41.5%, respectively) differed from our prior report (15.7%, 48.4%, and 35.9%, respectively; χ^2 test, $P < 0.001$).[15] Why parents now report more children sleeping under lower lighting conditions is unknown. To the extent that parents were aware of our previous findings from the considerable media coverage, the different questionnaire responses may reflect reporting bias because of an unwillingness to acknowledge behavior with perceived adverse consequences or may indicate an actual change in behavior thought to be perhaps of lower risk.

Second, the refraction distributions were different, with the current survey containing more hyperopes and fewer myopes than our prior report.[15] For identically defined refractive categories of high hyperopia, hyperopia, emmetropia, myopia, and high myopia, the corresponding proportions of subjects were as follows: present study: 13.6%, 25.4%, 41.5%, 15.5%, and 4.0%; present study, excluding children with a history of prematurity: 14.6%, 25.8%, 40.4%, 14.9%, and 4.4%; prior study: 1.5%, 17.5%, 52.4%, 25.7%, and 2.9% ($P < 0.0001$, comparing either current distribution with the prior study).

Conceivably, sampling variability, demographic differences, or behavioral changes may account for the dissimilar associations of nighttime lighting and refraction in our present and prior studies. Because available cross-sectional surveys have provided contradictory results, other research techniques are needed to examine the possible role of the light–dark cycle in human refractive development.

General Conclusions

This investigation was motivated by pharmacologic findings in chicks that identified a potential role for neural nicotinic acetylcholine receptors in refractive development.[9] Among many constituents, tobacco smoke contains the agonist nicotine that activates these receptors. We identified an association of less myopia prevalence and a mean hyperopic shift in refraction with passive exposure to tobacco smoke from either parent during childhood. A similar relation of children's refractions with either maternal or paternal smoking during the mother's pregnancy also was observed. The complex pharmacology of nicotinic acetylcholine receptors, the diverse constituents of tobacco smoke, the potential involvement of other receptors, the potential bias in questionnaire responses, and the characteristics of the patients in the tertiary care ophthalmology clinic surveyed each qualify the results of the present study. Certainly, the many health risks of tobacco smoke and the addictive properties of nicotine prohibit recommending that children be exposed either to tobacco smoke or to nicotine alone as by patches or gum. For this reason and because of the limitations of cross-sectional studies using questionnaire techniques, the chief value of the present report may be in generating hypotheses for further research, of which we propose three: (1) neuropharmacology perspectives may prove useful for understanding the mechanisms of refractive development in children; (2) prenatal nongenetic exposures may have long-term influences on refraction; and (3) further study seems warranted of the role of nicotinic acetylcholine receptors in refractive development.

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