Exposure to Secondhand Smoke in Children is Associated with a Thinner Retinal Nerve Fiber Layer: The Hong Kong Children Eye Study

JIAN LI, NAN YUAN, WAI KIT CHU, CAROL Y. CHEUNG, SHUMIN TANG, FEN FEN LI, LI JIA CHEN, KA WAI KAM, ALVIN L. YOUNG, PATRICK IP, CLEMENT C. THAM, CHI PUI PANG, AND JASON C. YAM

• PURPOSE: We sought to assess the effects of exposure to secondhand smoke (SHS) on peripapillary retinal nerve fiber layer (p-RNFL) thickness in children.
• DESIGN: Cross-sectional study.
• METHODS: Children 6-8 years of age were consecutively recruited from the population-based Hong Kong Children Eye Study. All participants received comprehensive ophthalmic examinations and p-RNFL thickness was measured by spectral-domain optical coherence tomography. SHS data were derived from a validated questionnaire. Associations between p-RNFL thickness and SHS exposure status, number of smokers in the family, and quantity of smoking in the family were determined by multivariate linear regression after adjusting for potential confounders.
• RESULTS: Among the Hong Kong Children Eye Study cohort (n = 3,103), approximately one-third of children were exposed to SHS (35.4%, n = 1,097). Compared to those without exposure to SHS, children exposed to SHS had similar age ($P = .83$), gender ($P = .17$), body mass index ($P = .44$), birth weight ($P = .23$), and axial length ($P = .34$), but had lower family income ($P < .001$) and lower parental education level ($P < .001$). After adjusting for all the above factors, exposure to SHS was associated with a thinner global p-RNFL by 4.4 μm ($P < .001$). Reduced p-RNFL was also associated with increased numbers of smokers in the family ($\beta = -3.40$, $P < .001$) and increased quantity of SHS ($\beta = -0.22$, $P < .001$).
• CONCLUSIONS: Exposure to SHS in children was associated with a thinner p-RNFL. A thinner p-RNFL may increase the risk of irreversible visual impairment in the future. Our results provide evidence to recommend that children avoid exposure to SHS. (Am J Ophthalmol 2021;223:91–99. © 2020 Elsevier Inc. All rights reserved.)

TOBACCO SMOKING CAN LEAD TO ADVERSE EFFECTS on multiple organs, including the central nervous system and the visual system.[1,2] Specifically, smoking is associated with various ocular diseases, including glaucoma,[3] age-related macular degeneration (AMD),[4] pterygium,[5] cataracts,[6] and Graves ophthalmopathy.[7] The pathophysiologic effects of smoking are likely induced by ischemic or oxidative mechanisms related to toxic compounds in tobacco smoke.[8] Exposure to secondhand smoke (SHS) is just as dangerous as smoking, because SHS contains thousands of chemicals that can harm both adults and children. SHS is linked to cardiovascular and respiratory diseases[9–11] and even sudden infant death syndrome.[12] Unfortunately, children are commonly exposed to SHS in many regions of the world and the magnitude of this hazard has been poorly addressed. Worldwide, 40% of children and >30% of adults are exposed to SHS, contributing to about 1% of all deaths.[13] Moreover, 61% of disability-adjusted life-years were found in children exposed to SHS.[13] This is a wakeup call for the public to be aware of the serious consequences of SHS, particularly as 16%-31% of mothers were found to have smoked during their pregnancy in western countries.[14,15]

Active and passive smoking in mothers during pregnancy is associated with lower birth weight[16] and shorter telomere length in their offspring.[17] Children exposed to SHS also have an increased risk of disrupted brain development,[18] leading to behavioral abnormalities, including conduct disorders, oppositional defiant behavior, attention deficit hyperactivity disorder, and lower intelligence quotient.[19] A study of 1,406 children 11-12 years of age revealed that in utero exposure of children to maternal smoking was associated with a thinner retinal nerve fiber layer (RNFL).[20] Of note, our previous study found an

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From the Department of Ophthalmology and Visual Sciences (J.L., N.Y., W.K.C., C.Y.C., S.T., F.F.L., L.J.C., K.W.K., A.L.Y., C.C.T., C.P.P., J.C.Y.), The Chinese University of Hong Kong, Hong Kong SAR, China; Department of Ophthalmology (J.L.), Affiliated Hangzhou First People's Hospital, Zhejiang University School of Medicine, Hangzhou, China; Department of Ophthalmology (S.T.), The First Affiliated Hospital of Fujian Medical University, Fuzhou, China; Department of Ophthalmology and Visual Sciences (L.J.C., K.W.K., A.L.Y., C.C.T., J.C.Y.), Prince of Wales Hospital, Hong Kong; Department of Paediatrics and Adolescent Medicine (P.I.), LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China; Hong Kong Eye Hospital (C.C.T., J.C.Y.), Hong Kong SAR, China; and the Department of Ophthalmology (J.C.Y.), Hong Kong Children's Hospital SAR, China.
[1] Drs Li and Yuan served jointly as first authors.
Inquiries to Jason C. Yam, Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong Eye Hospital, 147K Argyle St, Kowloon, Hong Kong, China; e-mail: yamcheuksing@cuhk.edu.hk

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association between children's exposure to SHS and choroidal thinning, which is one of the first signs suggesting potential ocular damage in children caused by SHS.[21]

In this study, we aimed to examine the effects of SHS on peripapillary RNFL (p-RNFL) thickness in school-age children from the population-based Hong Kong Children Eye Study (HKCES). We hypothesized that early exposure to SHS is associated with a thinner p-RNFL in childhood. As the RNFL is part of the central nervous system, its thinning may have potentially harmful implications on long-term neurodevelopment, and progressive thinning of the p-RNFL from childhood to adulthood may lead to optic neuropathy and glaucoma later in life.

METHODS

• **STUDY POPULATION:** Primary school children from grades 1-3 (approximately 6-8 years of age) were recruited from the ongoing HKCES, which has been described previously.[21–23] In brief, the HKCES was designed to determine the occurrence and development of childhood eye diseases, including refractive errors, strabismus, amblyopia, and allergic eye diseases, and to identify the environmental and genetic determinants of these ocular disorders. Sample selection was based on a stratified and clustered randomized sampling frame. In Hong Kong, all primary schools (n = 571) registered in the Education Bureau were stratified into 7 clusters according to population density.

All study subjects underwent a full ophthalmic examination, physical examination, and a standardized interview. Children who had congenital malformations, previous eye trauma, a history of ocular surgery, and ocular disorders (except refractive error) or who were incapable of cooperating during optical coherence tomography or axial length and other examinations were excluded from this study. Children's parents were interviewed using on a standardized questionnaire.[24,25] The study procedure was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee Board of the Chinese University of Hong Kong. Informed written consent was obtained from all children and their legal guardians before the study began. Subjects were consecutively recruited from March 2015 to June 2017 at the Chinese University of Hong Kong Eye Centre.[22] Only the right eye was included in the analysis in this study.

• **OPHTHALMIC AND PHYSICAL EXAMINATIONS:** A logarithm of minimal angle of resolution chart (Nidek, Gamagori, Japan) was used to measure visual acuity with or without spectacles. For each subject, complete ocular examinations, including anterior segment, posterior segment, and ocular motility examinations, were conducted by trained ophthalmologists (J.C.Y., L.J.C., K.W.K.). Refraction was measured before and after cycloplegia using an autorefractor (ARK-510A; Nidek). Spherical equivalent refraction was calculated as the algebraic sum of the value of the sphere and half the cylinder. Cycloplegia was performed by 2 cycles of 1% cyclopentolate (Alcon Laboratories, Bornem, Belgium) and 1% tropicamide (Santen Pharmaceutical, Osaka, Japan) which were applied 10 minutes apart. Ocular axial length (AL) was evaluated by an interferometric device (IOL Master; Carl Zeiss Meditec, AG, Jena, Germany). Height and body weight were measured using a professional integrated set of equipment (Seca, Hamburg, Germany). Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared.

• **P-RNFL IMAGING:** Spectral-domain optical coherence tomography (OCT; Spectralis, Heidelberg Engineering, Heidelberg, Germany) was used for imaging the p-RNFL at a central wavelength of 870 nm. The scan circle with a diameter of approximately 3.45 mm (1536 A-scans) was manually positioned at the center of the optic disc while the eye tracking system was activated. Fifteen B-scans were captured at the same location and were averaged automatically with an image quality score (ranging 0-40 dB) for the averaged scan by the built-in software (Heidelberg Eye Explorer, version 1.6.1.0; Heidelberg Engineering) to increase the image signal-to-noise ratio. The minimum image quality requirement was 15 dB as recommended by the manufacturer. Images were checked for errors of RNFL boundary detection and thickness measurement. Global RNFL thickness as well as sectoral p-RNFL thickness in 6 sectors (nasal, temporal, superonasal, inferonasal, inferotemporal, and superotemporal regions) were analyzed (Figure).

• **SMOKING STATUS AND QUESTIONNAIRE:** Parents or legal guardians were asked to complete questionnaires with the assistance of trained staff in person or over the phone.[21,24,25] Smoking status of parents and other family members were obtained through the following questions: 1) Is the mother smoking at home after the child was born? How long does she smoke and how many cigarettes a day at home? 2) Is the father smoking at home after the child was born? How long does he smoke and how many cigarettes a day at home? 3) Do other members of the family smoke at home after the child was born? How long does he or she smoke and how many cigarettes a day at home? Parent's smoking outside home was not counted as children's SHS exposure. Information of all family members living with the children, including grandparents, brothers, sisters, and other relatives living together, were provided by the parents or legal guardians after verifying with the specific family members. All questionnaires were completed with assistance by trained staff. Support from translators were provided if required. Missing and uncertain information were further confirmed by an additional phone call after onsite interview. Eventually, respondents who could

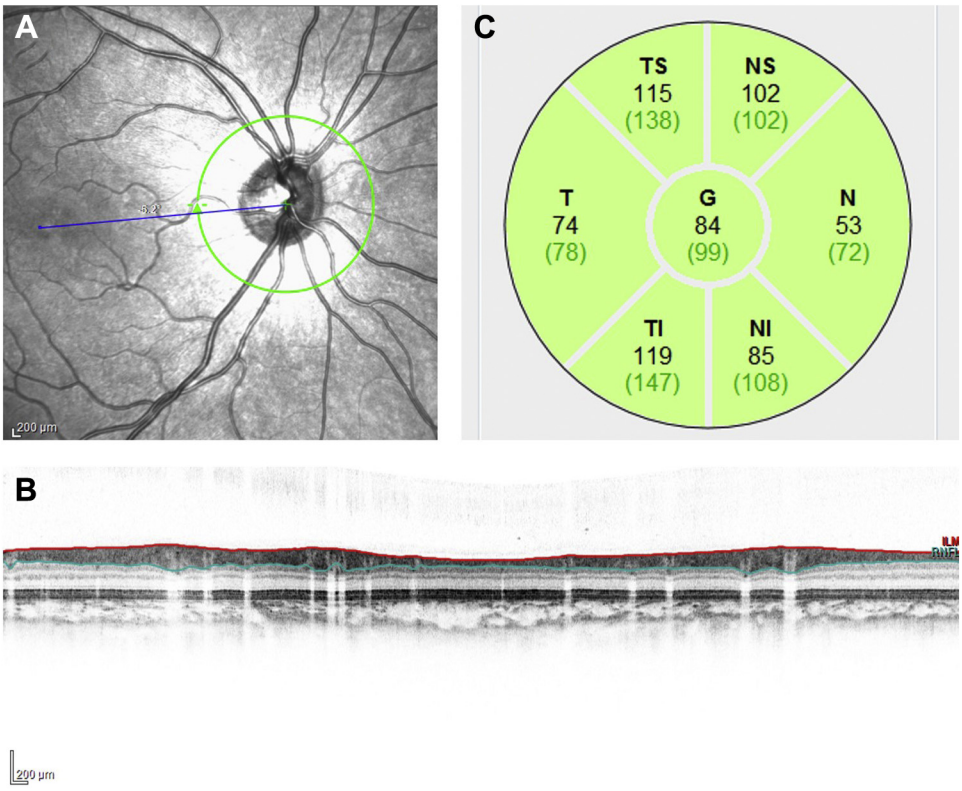

FIGURE. Measurement of peripapillary retinal nerve fiber layer (p-RNFL) thickness using spectral-domain optical coherence tomography. A. Visualization of the p-RNFL measurement on a fundus image. B. Segmentation of the p-RNFL. C. Presentation of the p-RNFL thickness using the built-in software. G = overall global; N = nasal; NI = nasal inferior; NS = nasal superior; T = temporal; TI = temporal inferior. TS = temporal superior.

not finish the questionnaire were excluded. After verification of the questionnaires by trained staff, information provided by the father, mother, or caregiver were treated equally in the analyses. Children will be allocated into SHS group if ≥1 family member(s) smoked at home after the child was born. The number of cigarettes smoked per day was also documented. The total number of cigarettes smoked at home per day by all family members living with the children were combined into the quantity of SHS. The gradient effects of smoking were investigated by using 10 cigarettes as a cutoff, followed from previous publications.[26–28] Information about daily living including living environment, children's lifestyle, children's time spent on outdoor activities and near-work activities were also obtained. Parents' medical conditions including mother's obstetric history, child's birth history, past and current medical history, and a thorough family history of eye disorders were also recorded. Mother smoking habits during her pregnancy were also recorded. Questions were validated in a random subsample of the cohort by repeating the questionnaire at weeks to test for the reproducibility. The test–retest reliability between the 2 repeated surveys was 0.92 (95% confidence interval 0.91-0.92) from a sample of 53 parents.[22]

Associations of children's p-RNFL thickness and their exposure to SHS were assessed by 3 strategies: 1) comparison of p-RNFL thickness between SHS exposure group vs nonexposure group, 2) correlation of p-RNFL thickness and number of smokers in the family, and 3) correlation of p-RNFL thickness with quantity of cigarettes smoked. The quantity was measured as the total number of cigarettes smoked by all family members per day.

• **STATISTICAL ANALYSIS:** Statistical analyses were performed using SPSS software (v 22; SPSS Inc, Chicago, Illinois, USA). Mean and standard deviation (SD) were calculated for continuous parameters. Skewed distributions were presented with medians and interquartile ranges. The independent *t* test was used to compare variables between nonexposure and exposure groups. Fisher exact or χ^2 tests were used to analyze the differences for categorical data between groups. Associations between p-RNFL thickness and potential confounders were assessed using linear regression and bivariate (Pearson) correlation test. Analysis of covariance was used to estimate sectoral and global p-RNFL thicknesses in association with SHS exposure. For each p-RNFL thickness parameter, 2 multivariable models were constructed. In model 1, the selection of variables

TABLE 1. Demographic Characteristics of the Study Subjects

Characteristics	No Smoking Exposure, n = 2,006	Smoking Exposure, n = 1,097	*P* Value[a]
Age, y, mean (SD)	7.6 (1.03)	7.6 (1.0)	.83
Body mass index, kg/m^2, mean (SD)	25.3 (6.5)	25.7 (6.5)	.44
Birth weight, kg, mean (SD)	3.2 (0.52)	3.2 (0.49)	.23
Axial length, mm, mean (SD)	23.0 (0.87)	23.1 (0.90)	.34
Spherical equivalent, diopters, mean (SD)	−0.49 (1.21)	−0.62 (1.24)	.41
Gender, n (%)			.17
Male	1011 (50.4)	581 (53.0)	
Female	995 (49.6)	516 (47.0)	
Outdoor activity time, hours, n (%)[b]			.31
≤2	1865 (93.0)	1009 (92.0)	
>2	141 (7.0)	88 (8.0)	
Reading distance, cm, n (%)			.08
≤20	1218 (60.7)	701 (63.9)	
>20	788 (39.3)	396 (36.1)	
Family income per month, HK$, n (%)			<.001
≤20,000[c]	591 (29.4)	525 (47.9)	
>20,000[c]	1415 (70.6)	572 (52.1)	
Parents' education level, n (%)			
Father			<.001
High school	1122 (56.0)	916 (83.5)	
Bachelor's degree or higher	884 (44.0)	181 (16.5)	
Mother			<.001
High school	1282 (63.9)	977 (89.1)	
Bachelor's degree or higher	724 (36.1)	120 (10.9)	
Pregnant smoking			
Yes	8 (0.4)	68 (6.2)	<.001
No	1998 (99.6)	1029 (93.8)	

HK$ = Hong Kong dollar; SD = standard deviation.

[a]Statistical significance was tested using independent *t* test; χ^2 or Fisher exact tests were used to test the group difference for categorical data.

[b]Outdoor activity = outdoor exercise and outdoor leisure activities.

[c]USD $2576.40.

(AL, age, gender, birth weight, and BMI) was based on a univariate analysis of all potential factors of p-RNFL thickness in this study (Supplemental Table 1). These factors have been reported to be associated with p-RNFL thickness.[20,29,30] In model 2, sociodemographic parameters (including outdoor activity time, reading distance, family income, father's education level, and mother's education level) and all the parameters from model 1 were included for a comprehensive analysis. In the sensitivity analysis, those with in utero exposure to maternal smoking were excluded to repeat the analysis.

P values for trends were analyzed by treating number of smokers (0 smokers, 1 smoker, or ≥2 smokers) as a continuous ordinal variable; and by treating the quantity of smoking per day (none, ≤10 cigarettes per day, or >10 cigarettes per day) as a continuous ordinal variable. RNFL thickness with quintiles of cigarettes were further evaluated. The analyses were adjusted by including all the variables in a general linear model, and estimates were presented with 95% confidence intervals. $P < .05$ was considered statistically significant.

RESULTS

• **CHARACTERISTICS OF THE STUDY POPULATION:** A total of 3,416 Chinese children underwent ophthalmic investigations, but 286 children were excluded because of poor-quality OCT images. Twenty-seven children were further excluded because of incomplete ophthalmic examinations, leaving 3,103 children in the final analysis. The demographic data are presented in Supplemental Table 2. There were 133 families with ≥1 child joined the HKCES, and only 1 of them from each family was randomly recruited. Among the study subjects, 1,097 (35.4%) had exposure

TABLE 2. Association Between Exposure to Smoking and p-RNFL Thickness in Each Sector

p-RNFL Thickness in Different Sectors, μm, Mean (95% CI)	No Smoking Exposure, n = 2,006	Smoking Exposure, n = 1,097	Mean Difference (95% CI)	*P* Value	Adjusted R^2
Model 1[a]					
Global	110.3 (110.0-110.7)	105.9 (105.4-106.3)	−4.4 (−3.9 to −5.0)	<.001	0.3
Nasal	71.9 (71.4-72.5)	70.4 (69.6-71.1)	−1.6 (−2.7 to −0.7)	.001	0.17
Temporal	84.6 (84.1-85.2)	82.6 (81.9-83.3)	−2.0 (−3.0 to −1.1)	<.001	0.19
Nasal superior	125.6 (124.8-126.5)	122.2 (121.1-123.4)	−3.4 (−4.9 to −2.0)	<.001	0.18
Nasal inferior	123.0 (121.8-124.1)	120.3 (118.7-121.9)	−2.7 (−4.6 to −0.7)	.008	0.22
Temporal inferior	159.3 (158.4-160.1)	155.6 (154.5-156.7)	−3.6 (−5.0 to −2.2)	<.001	0.14
Temporal superior	158.7 (156.8-160.5)	155.4 (152.8-157.9)	−3.3 (−6.4 to −0.2)	.038	0.05
Model 2[b]					
Global	110.4 (109.9-110.8)	105.9 (105.4-106.3)	−4.4 (−3.9–5.0)	<.001	0.3
Nasal	72.1 (71.5-72.6)	70.1 (69.3-70.9)	−1.9 (−2.9 to −0.9)	.001	0.17
Temporal	84.6 (84.1-85.2)	82.8 (82.0-83.6)	−1.8 (−2.8 to −0.9)	<.001	0.21
Nasal superior	125.5 (124.6-126.4)	122.4 (121.2-123.6)	−3.1 (−4.6 to −1.5)	<.001	0.19
Nasal inferior	123.0 (121.8-124.1)	120.2 (118.6-121.8)	−2.8 (−4.8 to −0.7)	.008	0.23
Temporal inferior	159.3 (158.5-160.2)	155.6 (154.5-156.7)	−3.7 (−5.2 to −2.3)	<.001	0.13
Temporal superior	158.6 (156.8-160.5)	155.5 (152.9-158.1)	−3.2 (−6.5 to −0.1)	.059	0

CI = confidence interval; p-RNFL = peripapillary retinal nerve fiber layer.

[a]Adjusted for age, gender, body mass index, axial length, and birth weight. Mean value: adjusted mean value.

[b]Adjusted for age, gender, body mass index, axial length, birth weight, outdoor activity time, reading distance, family income, father's education level, and mother's education level. Mean value: adjusted mean value.

to SHS and 2,006 (64.6%) had no exposure, with mean (SD) ages of 7.60 (1.03) and 7.60 (1.00) years, respectively. There were no significant differences for age, gender, birth weight, BMI, AL, spherical equivalent, outdoor activity, or reading distance between the exposure and nonexposure groups ($P > .05$, Table 1). However, family income, parental education level, and pregnant smoking were significantly different between the exposure and nonexposure groups ($P < .001$, Table 1). Among the possible determinants of p-RNFL, AL was shown to be a significant factor (Supplemental Table 1). Notably, every 1-mm increase in AL was associated with 1.56 μm of thinning of the global p-RNFL thickness ($P < .001$, Supplemental Table 3).

• **P-RNFL THICKNESS IN CHILDREN EXPOSED OR NOT EXPOSED TO SMOKING:** Children's p-RNFL thickness was 1.6-4.4 μm thinner in the exposure group (n = 1,097) compared with the nonexposure group (n = 2,006) across all sectors after adjusting for age, gender, BMI, AL, birth weight, outdoor activity time, reading distance, family income, father's education level, and mother's education level (Table 2). Comparisons of p-RNFL between the 2 groups of children without adjustment were also statistically significant (Supplemental Table 4). p-RNFL values in each group are shown in Supplemental Figure 1. In the sensitivity analysis, we excluded 76 of the 3,103 children (2.45%) with in utero exposure to maternal smoking and the associations between children exposed to SHS and those not exposed to SHS largely remained the same (Supplemental Tables 5-7).

• **ASSOCIATION OF CHILDREN'S P-RNFL THICKNESS WITH THE EXTENT OF EXPOSURE TO SMOKE:** The study subjects were further classified according to the number of smokers in the family: no smokers (n = 2,006), 1 smoker (n = 958), and ≥2 smokers (n = 139). Children's p-RNFL thickness was negatively correlated to the number of smokers in their family. Children with more smokers in the family had thinner p-RNFL in most sectors (*P*-trend < .05), except the superotemporal region (*P*-trend = .086, Table 3). For each additional smoker, children's p-RNFL was thinner by 3.40 μm globally, 1.19 μm in the nasal, 1.68 μm in the temporal, 3.11 μm in the nasal superior, 2.18 μm in the nasal inferior, 2.68 μm in the temporal inferior, and 2.94 μm in the temporal superior regions (Supplemental Table 8).

Study subjects were also categorized by the quantity of smoking at home in the family per day: 0 cigarettes per day (n = 2,006), ≤10 cigarettes per day (n = 745), and >10 cigarettes per day (n = 352). RNFL thickness with quintiles of cigarettes was evaluated (Supplemental Table 9). The p-RNFL thickness in children was negatively associated with the quantity of smoking in the family in most sectors (*P*-trend < .05), except the temporal superior region (*P*-trend = .073, Table 4). Overall, the children's p-RNFL was thinner with more smokers in the family; exposure to 10 cigarettes per day was associated with thinning of the p-RNFL by 2.2 μm globally, 1.1 μm in the temporal, 1.9 μm in the nasal superior, 1.5 μm in the nasal inferior, and 2.1 μm in the temporal inferior regions (Supplemental Table 10).

TABLE 3. Association Between Number of Smokers and p-RNFL Thickness in Each Sector

p-RNFL Thickness in Different Sectors, μm, Mean (95% CI)	Nonsmoker, n = 2,006	1 Smoker, n = 958	≥ 2 Smokers, n = 139	*P* Value for Trend	Adjusted R^2
Model 1[a]					
Global	110.3 (110.0-110.7)	105.6 (104.8-106.3)	105.1 (103.7-406.6)	<.001	0.3
Nasal	71.9 (71.4-72.5)	70.3 (69.5-71.1)	70.9 (68.7-73.0)	.004	0.16
Temporal	84.6 (84.1-85.2)	82.7 (81.9-83.5)	82.3 (80.2-84.3)	<.001	0.19
Nasal superior	125.6 (124.8-126.5)	122.8 (121.5-124.0)	118.5 (115.2-121.8)	<.001	0.19
Nasal inferior	123.0 (121.8-124.1)	120.4 (118.7-122.1)	119.6 (115.2-124.0)	.027	0.22
Temporal inferior	159.3 (158.4-160.1)	155.5 (154.3-156.7)	156.8 (153.7-159.9)	<.001	0.14
Temporal superior	158.7 (156.8-160.5)	155.7 (153.0-158.4)	152.8 (145.7-159.8)	.086	0.05
Model 2[b]					
Global	110.3 (110.0-110.7)	105.9 (105.4-106.4)	105.5 (104.2-406.8)	<.001	0.3
Nasal	72.1 (71.5-72.6)	70.1 (69.2-70.9)	70.6 (68.5-72.8)	.001	0.16
Temporal	84.6 (84.1-85.2)	82.8 (82.0-83.6)	82.6 (80.5-84.1)	.001	0.21
Nasal superior	125.5 (124.6-126.2)	123.0 (121.7-124.3)	118.4 (115.1-121.7)	<.001	0.19
Nasal inferior	123.0 (121.8-124.1)	120.4 (118.6-122.1)	119.1 (114.7-123.5)	.027	0.23
Temporal inferior	159.3 (158.5-160.2)	155.4 (154.2-156.6)	157.0 (153.8-160.1)	<.001	0.13
Temporal superior	158.7 (156.8-160.5)	155.8 (153.0-158.6)	153.0 (145.9-160.2)	.129	0

CI = confidence interval; p-RNFL = peripapillary retinal nerve fiber layer.

[a]Adjusted for age, gender, body mass index, axial length, and birth weight. Mean value: adjusted mean value.

[b]Adjusted for age, gender, body mass index, axial length, birth weight, outdoor activity time, reading distance, family income, father's education level, and mother's education level. Mean value: adjusted mean value.

TABLE 4. Association Between Quantity of Smoking in the Family and p-RNFL Thickness in Each Sector

p-RNFL Thickness in Different Sectors, μm, Mean (95% CI)	No. of Cigarettes Smoked by All Smokers in the Family Per Day			*P* Value for Trend	Adjusted R^2
	0, n = 2,006	≤10, n = 745	>10, n = 352		
Model 1[a]					
Global	110.3 (110.0-110.7)	105.9 (105.3-106.4)	105.8 (105.1-106.7)	<.001	0.3
Nasal	71.9 (71.4-72.5)	70.0 (69.1-70.9)	70.9 (69.6-72.3)	<.001	0.17
Temporal	84.6 (84.1-85.2)	82.6 (81.7-83.5)	82.6 (81.4-83.9)	<.001	0.21
Nasal superior	125.6 (124.8-126.5)	122.3 (120.9-123.7)	122.1 (120.0-124.1)	<.001	0.19
Nasal inferior	123.0 (121.8-124.1)	120.7 (118.9-122.6)	119.3 (116.6-122.0)	.02	0.25
Temporal inferior	159.3 (158.4-160.1)	155.9 (154.6-157.3)	155.0 (153.1-157.0)	<.001	0.13
Temporal superior	158.7 (156.8-160.5)	156.2 (153.2-159.2)	153.6 (149.2-158.1)	.073	0.03
Model 2[b]					
Global	109.9 (109.3-110.5)	105.5 (104.7-106.3)	105.5 (104.5-106.5)	<.001	0.3
Nasal	84.6 (84.1-85.2)	82.7 (81.8-83.6)	82.9 (81.6-84.2)	.001	0.21
Temporal	123.0 (121.8-124.1)	120.6 (118.7-122.6)	119.2 (116.4-122.0)	.02	0.23
Nasal superior	159.3 (158.5-160.2)	155.9 (154.5-157.3)	154.9 (152.9-156.9)	<.001	0.13
Nasal inferior	158.7 (156.8-160.6)	156.2 (153.1-159.3)	153.8 (149.2-158.3)	.112	0
Temporal inferior	110.0 (109.7-110.3)	107.2 (106.6-107.8)	107.3 (106.4-108.1)	<.001	0.25
Temporal superior	72.1 (71.5-72.6)	70.0 (68.9-70.8)	70.7 (69.4-72.1)	<.001	0.17

CI = confidence interval; p-RNFL = peripapillary retinal nerve fiber layer.

[a]Adjusted for age, gender, body mass index, axial length, and birth weight. Mean value: adjusted mean value.

[b]Adjusted for age, gender, body mass index, axial length, birth weight, outdoor activity time, reading distance, family income, father's education level, and mother's education level. Mean value: adjusted mean value.

DISCUSSION

TO THE BEST OF OUR KNOWLEDGE, THIS STUDY IS THE ONE of the first to report that early exposure to SHS is associated with thinner p-RNFL in children. The findings show that children 6-8 years of age who were exposed to SHS had a thinner p-RNFL after adjusting for age, gender, BMI, AL, birth weight, outdoor activity time, reading distance,

family income, and parents' education level. Our study provides further evidence to support the recommendation that the public should avoid smoking around children.

Our findings are in line with previous studies on direct smoking in adults associated with changes in their RNFL and maternal smoking during pregnancy associated with changes in children's RNFL. In a case-control study of 44 chronic heavy adult smokers compared with 44 healthy age-matched nonsmokers, the mean p-RNFL thickness was reduced by 5.36 μm in smokers.[31] Another study of 80 active chronic smokers and 80 healthy passive smokers found that the latter also had reduced RNFL thickness by 6.71 to 9.18 μm.[32] In a meta-analysis of 13 observational studies, direct smoking was not significantly associated with retinal or choroidal thickness in adults but was associated with a thinner p-RNFL.[33] Furthermore, maternal smoking during pregnancy was found to be harmful to child development. Pueyo and associates[34] noted a reduction in p-RNFL thickness by 8.7 μm in 15 children with in utero exposure to maternal smoking compared with 55 children without exposure. This was further supported by a study investigating 1,323 children by Ashina and associates,[20] who found the p-RNFL was thinner by 5.7 μm in 227 children whose mothers had smoked during pregnancy. After excluding those with in utero exposure to maternal smoking, our sensitivity analysis showed the results remained largely similar. Furthermore, birth weight and AL have been reported to be associated with p-RNFL thickness.[35,36] Our study showed that AL but not birth weight was a potential determinant of p-RNFL thickness. Nevertheless, we adjusted for both factors in our analysis and found that the association of p-RNFL thinning with SHS exposure was independent of birth weight and AL. Because exposure to SHS is strongly associated with sociodemographic status,[37] we also adjusted for these parameters in our analysis; nevertheless, the association of thinner p-RNFL and SHS exposure remained. This study is first to reveal an association between children's postnatal exposure to SHS and a thinning effect on peripapillary retinal nerve fibers that was noticeable from the ages of 6-8 years. Attenuation of the RNFL is a possible early sign of loss of optic nerve tissue. Chronic exposure of SHS in children may lead to a progressive loss of RNFL, which may be related to optic neuropathy and visual field defects. However, longitudinal cohorts are required to ascertain these long-term implications. Various studies have consistently shown that smoking is one of the major risk factors for glaucoma.[38–40] Law and associates[3] evaluated 3,864 noninstitutionalized subjects in the U.S. National Health and Nutrition Examination Survey and found that people with a heavy smoking history were 1.7-fold ($P = .02$) more likely to suffer from glaucoma. A Spanish cohort of 16,797 participants with a median follow-up of 8.5 years[41] showed that current smokers had a 1.88-fold ($P = .002$) higher risk of developing glaucoma compared with nonsmokers. In our study, we observed thinning of all 6 subregions of p-RNFL. The harmful smoking effects on ocular tissues including RNFL may be related to disrupted ocular circulation,[17,31] free radical generation, increased oxidative stress, and reduced antioxidants.[32,33] However, the superotemporal peripapillary region showed insignificant changes. The underlying mechanism as to why this sector was privileged needs further investigation.

Despite a generally accepted concept that children should avoid exposure to SHS, there are still thousands of children inevitably exposed to SHS in their daily lives. Our findings presented potential ophthalmologic evidence to support this claim, which has previously been less developed. However, it should be noted that the clinical implications of the statistically significant but clinically small difference of p-RNFL thickness with large SDs are uncertain. Long-term follow-up is needed.

The RNFL is the only part of central nervous system that can be directly visualized and is a putative biomarker of axonal damage.[42,43] There was a direct correlation between axonal loss observed in the RNFL with either brain atrophy measured by magnetic resonance imaging[44] or cognitive dysfunction.[45] In the present study, the thinning effect of SHS on the p-RNFL of children was 1.6-4.4 μm, which was comparable with previous studies in adults.[31,32] Although the long-term implications of RNFL thinning require further longitudinal study, the present findings suggest that toxicity caused by SHS can potentially affect central nervous system development. This is in line with reported cognitive deficits in children exposed to SHS.[46] There has also been evidence showing intergenerational influences of SHS on the development of attention deficits and hyperactive behavior in children.[47,48] It is not known whether the p-RNFL thinning will slow down, stop, or even recover after the SHS exposure is halted, and further investigations into this are warranted.

The present study had several strengths including 1) a relatively large population-based cohort; 2) study families were from Hong Kong, where the household exposure to SHS is more important as smoking in public had been banned for 13 years; 3) the use of high-resolution optical coherence tomography; and 4) comprehensive evaluations of ocular parameters and systemic status. However, this study had some limitations. First, the reliability of self-reported smoking history by the family members may introduce potential recall bias. To provide objective and robust evidence, urinary cotinine measurements are recommended, although spot or even serial cotinine measurement cannot reflect smoking history over the years.[24] Second, the cross-sectional study revealed an association effect, but not a causative relationship, which will require a future longitudinal study. Lastly, the adjusted R^2 in our models were weak, suggesting that other residual confounding factors could have biased or modified the associations observed in our samples.

In summary, childhood exposure to SHS in children 6-8 years of age was associated with reduced p-RNFL thickness

by 1.6-4.4 μm. Our findings provide evidence to support public education for the banning of smoking in households with children and the promotion of children's ocular health and development.

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