Original Article

Findings from the 45 and Up Study: smoking is not associated with the risk of early-onset cataract

Jiaqing Zhang[1], Xiaotong Han[1], Wei Wang[1], Jason Ha[2], Zhenzhen Liu[1], Xianwen Shang[2], Lei Zhang[2,3,4,5], Xuhua Tan[1], Mingguang He[1,6], Lixia Luo[1]

[1]State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou, China; [2]Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, Melbourne, Australia; [3]Artificial Intelligence and Modelling in Epidemiology Program, Melbourne Sexual Health Centre, Alfred Health, Melbourne, Australia; [4]Central Clinical School, Faculty of Medicine, Monash University, Melbourne, Australia; [5]Department of Epidemiology and Biostatistics, College of Public Health, Zhengzhou University, Zhengzhou, China; [6]Ophthalmology, Department of Surgery, University of Melbourne, Melbourne, Australia

Contributions: (I) Conception and design: L Luo; (II) Administrative support: M He; (III) Provision of study materials or patients: L Luo; (IV) Collection and assembly of data: W Wang, J Ha, L Zhang, X Tan; (V) Data analysis and interpretation: J Zhang, X Han, Z Liu, X Shang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Prof. Lixia Luo. State Key Laboratory of Ophthalmology, Zhongshan Ophthalmic Center, Sun Yat-sen University, Guangzhou 510623, China. Email: luolixia@mail.sysu.edu.cn.

Background: To determine if tobacco smoking is a risk factor for early-onset cataracts.

Methods: This was a prospective population-based cohort study. A total of 70,886 participants aged 45–55 years in the 45 and Up Study were included in our analysis. Early-onset cataracts (EOC) were defined as cataract surgeries performed before 65 years old, based on participant data linked to the Medicare Benefits Schedule (MBS). Smoking habits were assessed at baseline, based on a self-administered questionnaire. A Cox proportional hazards model was used to evaluate the association between tobacco smoking and the risk of early-onset cataracts over the follow-up period.

Results: At baseline recruitment, 59.9% of study participants never smoked, 30.5% were former smokers, and 9.6% were current smokers. A total of 1,713 participants underwent cataract surgery over a mean follow-up of 625,042 person-years, with an incidence of 2.74 cases per 1,000 person-years. For current smokers, patients with EOC had longer smoking durations (P=0.019). For former smokers, patients with EOC had higher smoking intensities (P=0.001), were older at smoking commencement (P=0.011), and longer times since quitting (P=0.04). The risk of EOC was not found to be significantly different between current smokers or former smokers, compared to those who had never smoked. Both stratification and sensitivity analyses by gender, surgery year, alcohol intake, physical activity, and income yielded similar results.

Conclusions: Smoking has neither a beneficial nor harmful effect on the long-term incidence of EOC.

Keywords: Smoking; aging; cohort; Australia; early-onset cataracts

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Introduction

Cataract is the leading cause of visual impairment and blindness worldwide (1). While the prevalence of cataract in its most common age-related form continues to rise in patients older than 65 (1), there is another subset of patients who develop early onset cataracts (EOC), a form of cataract that develops prior to the age of 65. This subset of cataract has drawn significant attention in recent years, as it impacts the working-age population, and is reported to be associated with an increased risk of other serious systemic diseases, including cancer (2) and cardiovascular diseases (3). Despite

numerous studies having investigated the risk factors for cataracts in general, few studies have been undertaken to explore risk factors for EOC specifically.

Previous study has suggested that there may be a discrepancy in the pathogenesis of age-related cataracts and EOC (2). Therefore, it is crucial to identify risk factors for EOC so as to improve outcomes in patients with EOC, who are often in their most productive years of life, and are subject to significant decreases in their quality of life, and financial hardship secondary to visual impairment. Moreover, many of these risk factors may be potentially modifiable, and thus suitable targets for the future prevention of visual impairment and blindness.

Smoking is the second leading risk factor for early death and disability worldwide and has been widely implicated in its pathogenesis for a myriad of diseases, including lung cancer, cardiovascular disease, and age-related macular degeneration (3-5). Positive associations between smoking and the risk of cataract have also been demonstrated. A meta-analysis revealed that smoking was associated with a higher risk of age-related cataracts, especially nuclear cataracts (4). Other studies have observed a dose-response effect between smoking and cataracts (5,6), and conversely, smoking cessation has been shown to reduce the risk for cataracts, particularly after prolonged quitting periods (7,8). The prevalence of smoking generally peaks between the ages of 25 to 35. However, these studies are primarily concerned with the effects of smoking on cataract in general, and to our knowledge, no existing studies have specifically studied the relationship between smoking and EOC. Thus, the purpose of this study was to investigate the effects of smoking on the risk of EOC based on the largest prospective 10-year population-based cohort study of its kind in Australia. We presented the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-21-742).

Methods

Participants

The Sax Institute's 45 and Up Study is a population-based prospective cohort study. Participants aged 45 years and over in New South Wales (NSW), Australia were randomly recruited from Services Australia (formerly the Australian Government Department of Human Services) Medicare enrollment database. Baseline recruitment was conducted between January 2006 and December 2009. A total of 267,153 participants were recruited at baseline for the study, representing an estimated 10% of the NSW population in this age group. Eligible participants completed a mailed questionnaire and provided written consent for follow-up and linkage of their information to other routine health databases. These databases included the Medicare Benefits Schedule (MBS) database that collates records for diagnostic tests and procedures, and the Pharmaceutical Benefits Scheme (PBS) database that collects information about community-based dispensing of prescription medications. Linkage of the 45 and Up cohort data to the MBS and PBS data is facilitated by the Sax Institute using a unique identifier provided by Services Australia, which were available from 2004 to 2016. The method used to link records in the MBS and PBS is deterministic matching. The details of the study's methodology have been introduced elsewhere (9).

We selected participants aged 45 to 55 years at baseline to be followed up until December 31, 2016. The following participants were excluded: those aged ≥56 years; participants with a history of cataract surgeries based on their responses to the baseline questionnaires or the MBS database; participants who did not have available data for follow-up purposes; participants with physical function scores lower than 25. During the follow-up period, the following participants were further excluded: participants who underwent juvenile cataract extractions or other ophthalmic surgeries, including ocular traumatic surgeries, cornea or scleral surgeries, and glaucoma or vitreoretinal procedures. After these exclusions, 70,886 participants were included for the present analysis. The conduct of the 45 and Up Study was approved by the University of New South Wales Human Research Ethics Committee (HREC). The study was approved by the Royal Victorian Eye and Ear Hospital Human Research Ethics Committee (17/1330HS/20). All procedures of the present study were conducted in compliance with the Declaration of Helsinki (as revised in 2013).

Exposures

We obtained smoking status from participants based on their self-reported responses from the baseline questionnaires, including the age when participants started smoking, the average number of cigarettes smoked each day, and their quitting age if they were no longer smoking. Participants were classified into three groups, including current smoker, never smoked, or former smoker. The

group the participants belonged to was based on responses to the questions, "Have you ever been a regular smoker?" and "Are you a regular smoker now?" The starting age was defined from the question, "How old were you when you started smoking regularly?" The quitting age was based on the question, "How old were you when you stopped smoking regularly?"

The smoking duration was calculated as the difference between the starting age and either current age (current smokers) or quitting age (former smokers). The time since quitting was defined as the difference between the age at which smoking cessation started and the participant's current age. The smoking intensity was defined as the average number of cigarettes and pipes/cigars smoked each day based on answers to the question, "About how much do you/did you smoke on average each day?" The cumulative number of pack-years of tobacco exposure was obtained by dividing the smoking intensity by 20 and multiplying by the duration. The above indicators were all categorized into quartiles or quintile for categorical analyses.

Covariates

Covariates included gender, income, education level, body mass index (BMI), alcohol intake, physical activity (PA), diet health scores (DHS), history of diabetes (yes/no), and history of hypertension (yes/no). Participants' income was categorized into four groups: <$20,000, $20,000–39,999, $40,000–69,999, and more than $70,000, all measured in AUD. Educational attainment was determined by the highest qualification participants had completed, for which options included no school certificate or other qualifications amounting to less than 10 years of school, high school or trade, or a university degree or higher. BMI was calculated from self-reported weights from the question, "About how much do you weigh?" and heights were based on answers to the question, "How tall are you without shoes?" The calculated BMI had previously been validated in a sub-sample of the 45 and Up Study (10). BMI was categorized into three groups, according to the World Health Organization's criteria: underweight and normal (15 to <24.9 kg/m^2), overweight (25.0 to <29.9 kg/m^2), and obese (≥30.0 to 50 kg/m^2).

Alcohol intake was defined as the number of alcohol drinks per week based on the question, "About how many alcoholic drinks do you have each week?" Results were further classified into four groups: 0, 1–2, 2–14, and 15+ units/week. We calculated the metabolic equivalent intensity level number of sessions of PA per week and classified them into four groups: 0–4, 5–9, 10–14, and ≥15 sessions/week. The DHS, as a measure of dietary variety, was calculated by determining the sum of discrete food groups as based on the recommendations in the Australian Dietary Guidelines (11), with a score of 1 for each of the pre-defined food groups and a maximum of 7. The DHS was classified into five quintiles for analysis. Outdoor time was defined as the hours of a day the participants spend outdoors on a workday or weekend, based on the questions, "About how many hours a day would you usually spend outdoors on a weekday?" and "About how many hours a day would you usually spend outdoors on a weekday?".

Outcomes

EOC was defined as the incidence of cataract surgery during the follow-up period, occurring before the age of 65. Cataract surgery data were obtained by linking unique participant identifiers to the MBS database, using the Current Procedural Terminology codes for cataract surgeries of 42698 and 42702. The follow-up period was defined as the time elapsed from the date of the baseline, to the date of cataract surgery or December 31, 2016, whichever came first.

Statistical analysis

The person-years incidence rate of cataract surgery, and thus cataract, was calculated during the follow-up period. The baseline characteristics of the participants were descriptively analyzed according to smoking status (never, former, or current smokers), and the differences were examined using a χ^2-test. *T*-test and χ^2-test were used to compare the smoking habits between participants who did and did not undergo cataract surgery during the follow-up period. Cox proportional hazards models were used to assess the effects of smoking on the risk of early-onset cataract surgery. Hazard ratios (HRs) with 95% confidence intervals (CI) were estimated for current and former smokers in total, or by gender separately. Those who never smoked were used as the reference category. Univariate and multivariate regression models were tested: only age and gender were adjusted in Model 1, while there was further adjustment for income, education level, BMI, history of hypertension, cardiovascular disease, diabetes, insulin use, alcohol drinking, PA, and dietary factors in Model 2. Univariate and multivariate regression models were also tested after adjusting the

ethnicity and outdoor time (Table S1).

Missing values for covariates were included for analysis as separate categories. We also examined whether the association between smoking habits and cataract surgeries was modified by gender, surgery year, alcohol intake, PA, and income. Sensitivity analyses were also performed by restricting the analysis population to only participants aged 45–50 years at the baseline. All analyses were performed using the SAS statistical package (SAS version 9.4; SAS Institute, Cary, NC, USA). The significance of variables was tested using the likelihood ratio test and a two-tailed P value of <0.05 was used as the level of statistical significance for all comparisons.

Results

In this cohort of 70,886 participants aged 45–55 years, a total of 1,713 participants underwent cataract surgeries during an average follow-up period of 625,042 person-years, with an incidence rate of 2.74 cases per 1,000 person-years. For all baseline participants, 59.9% had never smoked, 30.5% were former smokers, and 9.6% were current smokers. *Table 1* shows the characteristics of participants stratified by smoking status at the baseline. There were significant differences in the distribution of baseline characteristics among different smoking statuses (all P<0.001), except for the prevalence of hypertension (P=0.565).

The percentage of all three smoking statuses was higher in women. Compared with those who had never smoked, current and former smokers tended to have lower incomes, and educational attainment. Participants with any smoking history were also more likely to engage in less healthy dietary habits, and be more likely to have histories of strokes or diabetes.

Table 2 presents the smoking habits between participants who did and did not undergo cataract surgeries during the follow-up period. Among current smokers, participants who underwent cataract surgeries had longer smoking durations

Table 1 Characteristics of study participants, grouped by smoking status at baseline

Characteristics	Total	Smoking status			P value
		Never	Former	Current	
Gender (%)					<0.001
Male	29,447 (41.5)	16,985 (40.0)	9,435 (43.7)	3,027 (44.5)	
Female	41,439 (58.5)	25,494 (60.0)	12,167 (56.3)	3,778 (55.5)	
Country of birth (%)					<0.001
Australia	54,723 (77.2)	32,425 (76.3)	16,897 (78.2)	5,401 (79.4)	
Others	15,883 (22.4)	9,891 (23.3)	4,623 (21.4)	1,369 (20.1)	
Missing	280 (0.4)	163 (0.4)	82 (0.4)	35 (0.5)	
Household income (%)					<0.001
≤$20,000 AUD	4,455 (6.3)	2,237 (5.3)	1,201 (5.6)	1,017 (14.9)	
$20,000–39,999 AUD	8,156 (11.5)	4,450 (10.5)	2,463 (11.4)	1,243 (18.3)	
$40,000–69,999 AUD	15,521 (21.9)	8,875 (20.9)	5,028 (23.3)	1,618 (23.8)	
≥$70,000 AUD	32,031 (45.2)	20,331 (47.9)	9,914 (45.9)	1,786 (26.2)	
Missing	10,723 (15.1)	6,586 (15.5)	2,996 (13.9)	1,141 (16.8)	
Education level (%)					<0.001
<10 years	3,988 (5.6)	1,711 (4.0)	1,383 (6.4)	894 (13.1)	
High school	42,656 (60.2)	23,949 (56.4)	13,960 (64.6)	4,747 (69.8)	
University or higher	23,758 (33.5)	16,526 (38.9)	6,129 (28.4)	1,103 (16.2)	
Missing	484 (0.7)	293 (0.7)	130 (0.6)	61 (0.9)	

Table 1 *(continued)*

Table 1 *(continued)*

Characteristics	Total	Smoking status			P value
		Never	Former	Current	
BMI (kg/m^2) (%)					<0.001
Underweight and normal	707 (1.0)	429 (1.0)	140 (0.6)	138 (2.0)	
Overweight	27,993 (39.5)	17,558 (41.3)	7,567 (35.0)	2,868 (42.1)	
Obese	26,965 (38.0)	15,990 (37.6)	8,602 (39.8)	2,373 (34.9)	
Missing	15,221 (21.5)	8,502 (20.0)	5,293 (24.5)	1,426 (21.0)	
Alcohol intake (%)					<0.001
0 units/week	707 (1.0)	429 (1.0)	140 (0.6)	138 (2.0)	
1–2 units/week	27,993 (39.5)	17,558 (41.3)	7,567 (35.0)	2,868 (42.1)	
2–14 units/week	26,965 (38.0)	15,990 (37.6)	8,602 (39.8)	2,373 (34.9)	
15+ units/week	15,221 (21.5)	8,502 (20.0)	5,293 (24.5)	1,426 (21.0)	
Physical activity (%)					<0.001
0–4 sessions/week	12,477 (17.6)	7,508 (17.7)	3,514 (16.3)	1,455 (21.4)	
5–9 sessions/week	20,516 (28.9)	12,596 (29.7)	6,085 (28.2)	1,835 (27.0)	
10–14 sessions/week	16,602 (23.4)	10,124 (23.8)	5,124 (23.7)	1,354 (19.9)	
≥15 sessions/week	19,908 (28.1)	11,449 (27.0)	6,516 (30.2)	1,943 (28.6)	
Missing	1,383 (2.0)	802 (1.9)	363 (1.7)	218 (3.2)	
Diet health scores (%)					<0.001
Quintile 1	12,245 (17.3)	5,631 (13.3)	4,203 (19.5)	2,411 (35.4)	
Quintile 2	14,798 (20.9)	8,645 (20.4)	4,578 (21.2)	1,575 (23.1)	
Quintile 3	18,304 (25.8)	11,606 (27.3)	5,440 (25.2)	1,258 (18.5)	
Quintile 4	14,922 (21.1)	9,948 (23.4)	4,328 (20.0)	646 (9.5)	
Quintile 5	7,215 (10.2)	4,814 (11.3)	2,156 (10.0)	245 (3.6)	
Missing	3,402 (4.8)	1,835 (4.3)	897 (4.2)	670 (9.8)	
CVD history (%)					<0.001
No	68,688 (96.9)	41,339 (97.3)	20,785 (96.2)	6,564 (96.5)	
Yes	2,198 (3.1)	1,140 (2.7)	817 (3.8)	241 (3.5)	
Stroke history (%)					<0.001
No	70,443 (99.4)	42,241 (99.4)	21,463 (99.4)	6,739 (99.0)	
Yes	443 (0.6)	238 (0.6)	139 (0.6)	66 (1.0)	
Diabetes mellitus (%)					<0.001
No	68,264 (96.3)	41,028 (96.6)	20,735 (96.0)	6,501 (95.5)	
Yes	2,622 (3.7)	1,451 (3.4)	867 (4.0)	304 (4.5)	
Hypertension (%)					0.565
No	56,500 (79.7)	34,028 (80.1)	16,919 (78.3)	5,553 (81.6)	
Yes	14,386 (20.3)	8,451 (19.9)	4,683 (21.7)	1,252 (18.4)	

y, years; AUD, Australian dollars; CVD, cardiovascular disease; BMI, body mass index.

Table 2 Smoking habits of participants who did and did not undergo cataract surgery during the follow-up period

Smoking habits	Variable	Cataract surgery		P value
		Yes	No	
Current smoker				
Smoking duration (years)	Mean ± SD	34.0±5.6	32.8±5.6	0.019
Cumulative dose (packs-year)	<10	14 (10.9%)	815 (12.2%)	0.445
	10–19	27 (21.1%)	1,330 (19.9%)	
	20–29	21 (16.4%)	1,342 (20.1%)	
	≥30	65 (50.8%)	3,062 (45.9%)	
	Missing	1 (0.8%)	128 (1.9%)	
Smoking intensity (cig/day)	Mean ± SD	17.4±9.6	17.1±8.9	0.663
	<10	22 (17.2%)	1,050 (15.7%)	0.881
	10–15	45 (35.2%)	2,394 (35.9%)	
	16–20	30 (23.4%)	1,682 (25.2%)	
	≥21	31 (24.2%)	1,551 (23.2%)	
Age at starting smoking (years)	Mean ± SD	17.8±4.8	17.7±5.0	0.767
	<13	4 (3.1%)	356 (5.3%)	0.454
	13–17	69 (53.9%)	3,600 (53.9%)	
	18–25	45 (35.2%)	2,243 (33.6%)	
	≥25	10 (7.8%)	478 (7.2%)	
Former smoker				
Smoking duration (years)	Mean ± SD	16.6±9.5	16.6±9.6	0.896
Cumulative dose (packs-year)	<10	243 (44.2%)	9,942 (47.2%)	0.086
	10-19	136 (24.7%)	5,238 (24.9%)	
	20-29	70 (12.7%)	2,808 (13.3%)	
	≥30	94 (17.1%)	2,931 (13.9%)	
	Missing	7 (1.3%)	133 (0.6%)	
Smoking intensity (cig/day)	Mean ± SD	18.2±11.8	16.7±10.6	0.001
	<10	95 (17.3%)	4,178 (19.8%)	0.005
	10–15	178 (32.4%)	7,328 (34.8%)	
	16–20	146 (26.5%)	5,521 (26.2%)	
	≥21	131 (23.8%)	4,025 (19.1%)	
Age at starting smoking (years)	Mean ± SD	17.8±4.5	17.4±3.6	0.011
	<13	21 (3.8%)	633 (3.0%)	0.025
	13–17	266 (48.4%)	11,465 (54.5%)	
	18–25	236 (42.9%)	8,129 (38.6%)	
	≥25	27 (4.9%)	825 (3.9%)	

Table 2 *(continued)*

Table 2 *(continued)*

Smoking habits	Variable	Cataract surgery		P value
		Yes	No	
Age at quitting smoking (years)	Mean ± SD	34.5±9.3	34.0±9.4	0.262
	<25	10 (1.8%)	428 (2.0%)	0.404
	25–34	243 (44.2%)	9,518 (45.2%)	
	35–44	113 (20.5%)	4,231 (20.1%)	
	45–54	135 (24.5%)	5,522 (26.2%)	
	≥55	49 (8.9%)	1,353 (6.4%)	
Time since quitting (years)	<5	79 (14.4%)	3,284 (15.6%)	0.040
	5–14	116 (21.1%)	5,182 (24.6%)	
	15–24	211 (38.4%)	7,613 (36.2%)	
	≥25	144 (26.2%)	4,973 (23.6%)	

SD, standard deviation.

Table 3 The relationship between smoking habits and early onset cataract surgery risk in the sample population

	Event	N	No. of person years	Model 1		Model 2	
				HR	95% CI	HR	95% CI
Overall							
Never	1,035	42,479	374,372	1.0 (Ref)	1.00–1.00	1.0 (Ref)	1.00–1.00
Former	550	21,602	190,367	1.06	0.95–1.17	1.07	0.96–1.20
Current	128	6,805	60,303	0.77	0.64–0.93	0.96	0.79–1.16
Male							
Never	373	16,985	149,817	1.0 (Ref)	1.00–1.00	1.0 (Ref)	1.00–1.00
Former	234	9,435	83,409.3	1.06	0.90–1.25	1.07	0.90–1.27
Current	49	3,027	26,892	0.7	0.52–0.95	0.81	0.59–1.11
Female							
Never	662	25,494	224,555	1.0 (Ref)	1.00–1.00	1.0 (Ref)	1.00–1.00
Former	316	12,167	106,957	1.05	0.92–1.21	1.07	0.93–1.23
Current	79	3,778	33,411	0.82	0.65–1.03	1.07	0.84–1.36

Model 1 was adjusted for age and gender only. Model 2 was adjusted for age, gender, income, education level, body mass index, history of hypertension, cardiovascular disease, diabetes, insulin use, alcohol drinking, physical activity and dietary factors. HR, hazard ratio; CI, confidence interval.

than those who did not (P=0.019). However, no significant differences were identified while comparing smoking doses, intensities, or age of smoking commencement. Among former smokers, participants who underwent cataract surgeries were found to have higher smoking intensities (P=0.001), older ages when starting smoking (P=0.011), and longer times since quitting (P=0.040). Smoking durations and the ages at quitting were not significantly different between the two groups.

The relationship between smoking habits and EOC risk

Table 4 Multivariable cox regression analyses in subgroups stratified by baseline characteristics

	Former *vs.* never	Current *vs.* never	P for trend
Sex			
Male	1.07 (0.90–1.27)	0.76 (0.54–1.06)	0.136
Female	1.08 (0.94–1.24)	1.06 (0.83–1.36)	0.548
Surgery year			
2005–2008	0.94 (0.54–1.64)	0.54 (0.16–1.78)	0.596
2009–2013	0.95 (0.80–1.12)	0.77 (0.58–1.03)	0.215
2013–2016	0.97 (0.82–1.14)	1.04 (0.77–1.41)	0.878
Alcohol intake			
0 units/week	0.98 (0.77–1.25)	0.98 (0.68–1.42)	0.989
1–2 units/week	1.00 (0.80–1.26)	0.87 (0.55–1.36)	0.821
2–14 units/week	0.94 (0.69–1.28)	0.96 (0.52–1.76)	0.928
15+ units/week	1.13 (0.90–1.42)	0.93 (0.58–1.50)	0.491
Physical activity (%)			
0–4 sessions/week	1.06 (0.81–1.38)	0.91 (0.60–1.38)	0.790
5–9 sessions/week	1.14 (0.93–1.40)	0.93 (0.64–1.37)	0.361
10–14 sessions/week	1.00 (0.80–1.25)	1.01 (0.67–1.52)	0.999
≥15 sessions/week	1.09 (0.89–1.34)	0.83 (0.55–1.24)	0.373
Household income (%)			
<$20,000 AUD	0.93 (0.55–1.57)	1.02 (0.54–1.94)	0.953
$20,000–39,999 AUD	0.87 (0.59–1.26)	0.97 (0.58–1.60)	0.758
$40,000–69,999 AUD	1.29 (1.02–1.64)	1.04 (0.69–1.56)	0.102
≥$70,000 AUD	1.04 (0.90–1.22)	0.93 (0.67–1.30)	0.753

AUD, Australian dollars. Adjusted for age, gender, income, education level, body mass index, history of hypertension, cardiovascular disease, diabetes, insulin use, alcohol drinking, physical activity and dietary factors.

is shown in *Table 3*. In the fully adjusted regression analysis, neither current smokers (RR, 0.96; 95% CI, 0.79–1.16) nor former smokers (RR, 1.07; 95% CI, 0.96–1.20) showed significantly different risks of EOC compared to non-smokers. A gender-specific analysis and analysis adjusted for ethnicity and outdoor time (Table S1) showed similar results. As shown in *Table 4*, the effect of smoking on EOC risk was not impacted by gender, surgery year, alcohol intake, PA, and income. One exception was that former smokers with household incomes between $40,000–69,999 AUD/year showed significantly higher risks of EOC than those who never smoked (RR, 1.29; 95% CI, 1.02–1.64). A sensitivity analysis, which included only participants aged 45–50 years at the baseline, also showed no significant differences in the EOC risk between former or current smokers with non-smokers (see *Table 5*).

Discussion

In this large prospective population-based cohort study, we reported the incidence of EOC and identified no significant associations between smoking and the risk of EOC over a 10-year follow-up period.

There is a paucity of literature exploring EOC, and epidemiological studies determining the incidence of EOC are scarce. We reported an incidence rate of 2.74 cases per 1,000 person-years in our study's sample, which is much lower than the incidence of senile cataracts (7). Given that the vast majority of cataracts are predominantly age-related, with an increasing prevalence with age, a lower incidence of EOC is largely to be expected. However, data on the prevalence and incidence of EOC are still lacking and should be further investigated in other populations.

Several previous studies have been performed to explore the risk factors for EOC. Some known risk factors include sunlight exposure, trauma, steroid use, and diabetes mellitus (12-15). Despite the widely reported associations between smoking and cataracts, it is unclear from the existing literature if this is true for EOC as well.

Pre-existing studies have conflicting findings regarding the association of smoking and EOC. Mishra *et al.* retrospectively analyzed data from 287 cataract patients aged 20 to 49 years. They reported that there was no difference in the use of tobacco between patients with idiopathic EOC and those with cataracts were associated with organic disease, which suggests that smoking may not be a risk factor of idiopathic EOC (16). Lesiewska-Junk *et al.* compared the incidence of some cataract risk factors between 106 patients from Poland with a mean age of 60, and 103 patients from Norway with a mean age of 76. While frequent smoking was found in the Polish group (P<0.01) which may be suggestive of a positive relationship between smoking and EOC (17), it is difficult to interpret given the lack of any sensitivity analyses restricted to patients less than 65 years of age. Nam *et al.* reported presenile nuclear cataracts were related to the current smoking status (Odds ratio 2.80, 95% CI, 1.10–7.12, P=0.0310] and no significant association was observed between former smokers and EOC (18).

Table 5 Sensitivity analysis by restricting to participants aged 45–50 at baseline only

	Event	N	No. of person years	Model 1		Model 2	
				HR	95% CI	HR	95% CI
Overall							
Never	244	17,468	153,907	1.0 (Ref)	1.00–1.00	1.0 (Ref)	1.00–1.00
Former	125	8,863	78,114.3	1	0.81–1.24	1.02	0.81–1.28
Current	40	3,195	28,359.8	0.82	0.59–1.15	1.04	0.72–1.48
Male							
Never	99	7015	61,810.7	1.0 (Ref)	1.00–1.00	1.0 (Ref)	1.00–1.00
Former	44	3487	30,784.4	0.89	0.62–1.26	0.82	0.56–1.20
Current	11	1332	11,848.5	0.53	0.29–1.00	0.5	0.26–1.00
Female							
Never	145	10,453	92,096	1.0 (Ref)	1.00–1.00	1.0 (Ref)	1.00–1.00
Former	81	5,376	47,329.9	1.09	0.83–1.43	1.14	0.86–1.52
Current	29	1,863	16,511.3	1.02	0.69–1.52	1.46	0.95–2.23

Model 1 was adjusted for age and gender only. Model 2 was adjusted for age, gender, income, education level, body mass index, history of hypertension, cardiovascular disease, diabetes, insulin use, alcohol drinking, physical activity and dietary factors. HR, hazards ratio; CI, confidence interval.

All of the studies mentioned above were limited by small numbers and cross-sectional designs, which cannot establish causality. Furthermore, it is difficult to draw comparisons between these earlier papers and our present analysis due to differences in definitions of EOC and measured outcomes. That said, our study is, to the best of our knowledge, the only prospective population-based study to have specifically investigated the association between smoking and EOC risk.

Previous studies have suggested multiple potential mechanisms underlying the positive associations between tobacco smoking and cataracts in the general population (6). The prevailing theory of accumulated oxidative damage may play a crucial role by which smoking promotes cataractogenesis. Smokers have been observed to have a lower level of zinc in their blood and lens, and an accumulation of cadmium in their lens. This may affect the activity of superoxide dismutase and decrease the level of glutathione and glutathione peroxidase, leading to oxidative damage of the lens (19-21). However, smoking was not found to be related to the risk of EOC in our study. This was supported by other studies which suggested different pathological mechanisms existed for senile cataracts and EOC, as well as another study which also found no significant association between smoking and cataracts among diabetic participants (22).

In addition to oxidative stress factors, other possible mechanisms may play important roles in the development of EOC. Other proposed factors include inflammation, metabolic syndrome, and genetics. For example, subjects with diabetes, steroid use, high myopia, and ultraviolet light exposure have been reported to have a higher risk of EOC (13). We speculate that the pathogenesis of EOC is a more complicated multifactorial process, and that the role of smoking may have been masked by other risk factors not measured in this study's population. Moreover, the biochemical changes associated with smoking that mediate cataractogenesis are likely to be accumulative in nature, and thus are more likely to be seen in age-related cataract rather than EOC, which may be better explained by other organic risk factors as outlined above. More studies are therefore needed to explore the role of smoking in EOC development and progress in multiethnic populations.

The strengths of this study included a population-based design, a large sample size, a long follow-up period, and the availability of multiple smoking statuses and covariates. Our study also has some potential limitations. Firstly, we could not analyze for the types and stages of cataracts due to the unavailability of data. Further studies on risk factors of different types of EOC were needed. In addition, the use of cataract surgery as an endpoint could lead to the omission of some EOC patients who had not

undergone surgery. However, our current definition for EOC enables us to capture cataracts sufficiently visually impairing to require surgical intervention, given that this was of the greatest clinical and socioeconomic significance. Secondly, the participants' surgical histories before 2004 are unknown. However, the exclusion of participants aged 56 years and over, who were the age group most likely to have had cataract surgery performed before 2004 was aimed at reducing the bias associated with this limitation. Thirdly, the MBS database only included cataract surgeries performed in private settings which accounted for the majority (72%) of Australian surgeries during the study's period (23). Finally, since smoking was categorized into never/former/current smokers at the baseline only, a retrospective recall bias existed and subsequent changes in smoking habits could not be incorporated. Furthermore, all self-reported responses on smoking habits should be interpreted with caution as individuals may have invariably underrepresented their true smoking history.

In conclusion, we found no significant association between smoking and the risk of EOC in this large population-based study with a follow-up period of over 10 years. This does not minimize the need for smoking minimization and cessation for its other health benefits. Further research is needed to better understand the associations between smoking and EOC.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All the procedures in this study were arranged strictly with the approval of the Royal Victorian Eye and Ear Hospital Human Research Ethics Committee (17/1330HS/20). Written informed consents have been obtained from all participants.

References

1. Liu YC, Wilkins M, Kim T, et al. Cataracts. Lancet 2017;390:600-12.
2. Chiang CC, Lin CL, Peng CL, et al. Increased risk of cancer in patients with early-onset cataracts: a nationwide population-based study. Cancer Sci 2014;105:431-6.
3. Pourafkari L, Mahdavi Fard A, et al. Is cataract surgery more common in patients with higher cardiovascular risk? Int J Cardiol 2016;214:316.
4. Ye J, He J, Wang C, et al. Smoking and risk of age-related cataract: a meta-analysis. Invest Ophthalmol Vis Sci 2012;53:3885-95.
5. McCarty CA, Nanjan MB, Taylor HR. Attributable risk estimates for cataract to prioritize medical and public health action. Invest Ophthalmol Vis Sci 2000;41:3720-5.
6. Foster PJ, Wong TY, Machin D, et al. Risk factors for nuclear, cortical and posterior subcapsular cataracts in the Chinese population of Singapore: the Tanjong Pagar Survey. Br J Ophthalmol 2003;87:1112-20.
7. Weintraub JM, Willett WC, Rosner B, et al. Smoking cessation and risk of cataract extraction among US women and men. Am J Epidemiol 2002;155:72-9.
8. Lindblad BE, Hakansson N, Wolk A. Smoking cessation and the risk of cataract: a prospective cohort study of cataract extraction among men. JAMA Ophthalmol 2014;132:253-7.
9. 45 and Up Study Collaborators, Banks E, Redman S, et al. Cohort profile: the 45 and up study. Int J Epidemiol 2008;37:941-7.
10. Ng SP, Korda R, Clements M, et al. Validity of self-reported height and weight and derived body mass index in middle-aged and elderly individuals in Australia. Aust N Z J Public Health 2011;35:557-63.
11. Hendrie GA, Baird D, Golley RK, et al. The CSIRO Healthy Diet Score: An Online Survey to Estimate Compliance with the Australian Dietary Guidelines. Nutrients 2017;9:47.
12. Schwab IR, Armstrong MA, Friedman GD, et al. Cataract extraction. Risk factors in a health maintenance organization population under 60 years of age. Arch Ophthalmol 1988;106:1062-5.
13. Praveen MR, Shah GD, Vasavada AR, et al. A study to explore the risk factors for the early onset of cataract in India. Eye (Lond) 2010;24:686-94.
14. Jyothi R, Sathyan S. Etiopathogenesis of presenile cataracts in Central Kerala: A cross-sectional observational study. Kerala J Ophthalmol 2017;29:179-83.
15. Patel D, Ahuja N. Analysis of presenile cataract risk factors and type of cataracts. Int J Sci Res 2018;6.
16. Mishra AV, Ramsey MS, Orr AC. Causes of presenile cataracts extracted at the Halifax Infirmary Hospital, 1976-85. Can J Ophthalmol 1989;24:117-9.
17. Lesiewska-Junk H. Senile and presenile cataract. Survey of patients undergoing cataract surgery. Acta Ophthalmol (Copenh) 1994;72:602-5.
18. Nam SW, Lim DH, Cho KY, et al. Risk factors of presenile nuclear cataract in health screening study. BMC Ophthalmol 2018;18:263.
19. Konerirajapuram S, Ranganathan P, Ramakrishnan S. Effect of cigarette smoking on cataract: Antioxidant enzymes and constituent minerals in the lens and blood of humans. Indian J Pharmacol 2002;34:428-31.
20. Issa A, Haider I, Adelah T. Blood and lens glutathione and catalase activity in patients with age-related cataract. J Kerbala University 2013;11:104-8.
21. Cekic O. Effect of cigarette smoking on copper, lead, and cadmium accumulation in human lens. Br J Ophthalmol 1998;82:186-8.
22. Han X, Wu C, Yan X, et al. Are smoking intensity and cessation related to cataract surgical risk in diabetic patients? Findings from the 45 and Up Study. Eye (Lond) 2020;34:383-91.
23. Australian commission on safety and quality in health care. Cataract surgery. Surgical Interventions 2016:305-14. Available online: https://www.safetyandquality.gov.au/

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