

Peer Review File

Article information: <http://dx.doi.org/10.21037/atm-21-742>

Reviewer A:

Comment 1: What do you mean by 10 year follow-up, when you are analyzing data already gathered by the 45 and Up Study?

Reply 1: Thank you for your comments. The baseline recruitment of the 45 and Up Study was conducted between January 2006 and December 2009. Participants completed a mailed questionnaire and provided written consent for follow-up and linkage of their information to routine health databases which were available from 2004 to 2016. Therefore, the participants in this cohort achieved up to 10 years of follow-up. Similar expressions are used in other published articles.¹⁻³ Moreover, the data of the present study were analyzed in August, 2020. We have added these missing details in the revised version.

References:

1. Wu C, et al. Associations between physical activity and cataract treated surgically in patients with diabetes: findings from the 45 and Up Study. *Br J Ophthalmol.* 2019;103(8):1099-1105.
2. Yan X, et al. Effect of physical activity on reducing the risk of diabetic retinopathy progression: 10-year prospective findings from the 45 and Up Study. *PLoS One.* 2021;16(1):e0239214.
3. Wu C, et al. Impact of Diet on the Incidence of Cataract Surgery among Diabetic Patients: Findings from the 45 and Up Study. *Curr Eye Res.* 2019;44(4):385-392.

Changes in the text: (*In “Methods”, Page 7, paragraph 1-2, Participants*)

- *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.*
- *We selected participants aged 45 to 55 years at baseline to be followed up until*

December 31, 2016.

Comment 2: How were they diagnosed to have cataract, and what gradation of cataract ? It will be beneficial for the study to address this question though it might have been explained previously somewhere else. The endpoint of study was 'cataract surgery,' but how to determine that there was/was not cataract present at the time of enrollment of 45 and Up Study?

Reply 2: Thank you for your valuable suggestion. The types and stages of cataract could not be analyzed due to the unavailability of the data and the design of 45 and up study. In the present study, the date of cataract surgery was used as an endpoint, which could enable us to capture cataracts sufficiently visually impairing to require surgical intervention, given that this was of the greatest clinical and socioeconomic significance. Similar methods were also utilized in previous studies.¹⁻³ We admitted that the endpoint could lead to the omission of some EOC patients who had not undergone surgery, thus we have added further explanation in the revised version. Hoping this addresses your concern.

References:

1. Wu C, et al. Associations between physical activity and cataract treated surgically in patients with diabetes: findings from the 45 and Up Study. *Br J Ophthalmol.* 2019;103(8):1099-1105.
2. Yan X, et al. Effect of physical activity on reducing the risk of diabetic retinopathy progression: 10-year prospective findings from the 45 and Up Study. *PLoS One.* 2021;16(1):e0239214.
3. Wu C, et al. Impact of Diet on the Incidence of Cataract Surgery among Diabetic Patients: Findings from the 45 and Up Study. *Curr Eye Res.* 2019;44(4):385-392.

Changes in the text: (In “Discussion”, Page 15, paragraph 3)

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.

Comment 3: It is commonly understood that educated and more affluent population in general is less prone to smoke and have healthier lifestyle and physical activities which is in a way contrary to your findings and data analysis.

Reply 3: Thank you very much for pointing out this critical issue. We rechecked the database from the 45 and up study carefully, and found that the problem lies in the order of the labels in Table 1, which should be never, former and current according to the smoking status of participants. We sincerely apologize for this mistake.

For all baseline participants, 59.9% had never smoked, 30.5% were former smokers, and 9.6% were current smokers. The smoking rate was similar to the National Drug Strategy Household Survey in Australia.¹ Moreover, population with lower education and income levels showed higher smoking rates in revised version, which was consistent with previous studies.²

Reference:

1. Australian institute of health and welfare.

<https://www.aihw.gov.au/reports/australias-health/tobacco-smoking>. accessed by March 27, 2021.

2. Kim JH, et al. Association of Education and Smoking Status on Risk of Diabetes Mellitus: A Population-Based Nationwide Cross-Sectional Study. *Int J Environ Res Public Health*. 2017;14(6):655.

Changes in the text:

For all baseline participants, 59.9% had never smoked, 30.5% were former smokers, and 9.6% were current smokers. (In “Results”, Page 8, paragraph 4)

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

Characteristics	Total	Smoking status			P-value
		Never	Former	Current	
<i>Gender</i>					<0.001
<i>Male</i>	29447(41.5%)	16985(40.0%)	9435(43.7%)	3027(44.5%)	
<i>Female</i>	41439(58.5%)	25494(60.0%)	12167(56.3%)	3778(55.5%)	
<i>Country of birth (%)</i>					<0.001
<i>Australia</i>	54723(77.2%)	32425(76.3%)	16897(78.2%)	5401(79.4%)	
<i>Others</i>	15883(22.4%)	9891(23.3%)	4623(21.4%)	1369(20.1%)	
<i>Missing</i>	280(0.4%)	163(0.4%)	82(0.4%)	35(0.5%)	
<i>Household income (%)</i>					<0.001
≤\$20000 AUD	4455(6.3%)	2237(5.3%)	1201(5.6%)	1017(14.9%)	
\$20000-39999 AUD	8156(11.5%)	4450(10.5%)	2463(11.4%)	1243(18.3%)	
\$40000-69999 AUD	15521(21.9%)	8875(20.9%)	5028(23.3%)	1618(23.8%)	
≥\$70000 AUD	32031(45.2%)	20331(47.9%)	9914(45.9%)	1786(26.2%)	
<i>Missing</i>	10723(15.1%)	6586(15.5%)	2996(13.9%)	1141(16.8%)	
<i>Education level (%)</i>					<0.001
<10 years	3988(5.6%)	1711(4.0%)	1383(6.4%)	894(13.1%)	
High school	42656(60.2%)	23949(56.4%)	13960(64.6%)	4747(69.8%)	
University or higher	23758(33.5%)	16526(38.9%)	6129(28.4%)	1103(16.2%)	
<i>Missing</i>	484(0.7%)	293(0.7%)	130(0.6%)	61(0.9%)	
<i>BMI (kg/m²)</i>					<0.001
Underweight and normal	707(1.0%)	429(1.0%)	140(0.6%)	138(2.0%)	
Overweight	27993(39.5%)	17558(41.3%)	7567(35.0%)	2868(42.1%)	
Obese	26965(38.0%)	15990(37.6%)	8602(39.8%)	2373(34.9%)	
<i>Missing</i>	15221(21.5%)	8502(20.0%)	5293(24.5%)	1426(21.0%)	

<i>Alcohol intake (%)</i>					<0.001
0 units/week	707(1.0%)	429(1.0%)	140(0.6%)	138(2.0%)	
1-2 units/week	27993(39.5%)	17558(41.3%)	7567(35.0%)	2868(42.1%)	
2-14 units/week	26965(38.0%)	15990(37.6%)	8602(39.8%)	2373(34.9%)	
15+ units/week	15221(21.5%)	8502(20.0%)	5293(24.5%)	1426(21.0%)	
<i>Physical activity (%)</i>					<0.001
0-4 sessions/week	12477(17.6%)	7508(17.7%)	3514(16.3%)	1455(21.4%)	
5-9 sessions/week	20516(28.9%)	12596(29.7%)	6085(28.2%)	1835(27.0%)	
10-14 sessions/week	16602(23.4%)	10124(23.8%)	5124(23.7%)	1354(19.9%)	
≥15 sessions/week	19908(28.1%)	11449(27.0%)	6516(30.2%)	1943(28.6%)	
Missing	1383(2.0%)	802(1.9%)	363(1.7%)	218(3.2%)	
<i>Diet health scores</i>					<0.001
Quintile 1	12245(17.3%)	5631(13.3%)	4203(19.5%)	2411(35.4%)	
Quintile 2	14798(20.9%)	8645(20.4%)	4578(21.2%)	1575(23.1%)	
Quintile 3	18304(25.8%)	11606(27.3%)	5440(25.2%)	1258(18.5%)	
Quintile 4	14922(21.1%)	9948(23.4%)	4328(20.0%)	646(9.5%)	
Quintile 5	7215(10.2%)	4814(11.3%)	2156(10.0%)	245(3.6%)	
Missing	3402(4.8%)	1835(4.3%)	897(4.2%)	670(9.8%)	
<i>CVD history (%)</i>					<0.001
No	68688(96.9%)	41339(97.3%)	20785(96.2%)	6564(96.5%)	
Yes	2198(3.1%)	1140(2.7%)	817(3.8%)	241(3.5%)	
<i>Stroke history (%)</i>					<0.001
No	70443(99.4%)	42241(99.4%)	21463(99.4%)	6739(99.0%)	
Yes	443(0.6%)	238(0.6%)	139(0.6%)	66(1.0%)	
<i>Diabetes mellitus (%)</i>					<0.001
No	68264(96.3%)	41028(96.6%)	20735(96.0%)	6501(95.5%)	

<i>Yes</i>	<i>2622(3.7%)</i>	<i>1451(3.4%)</i>	<i>867(4.0%)</i>	<i>304(4.5%)</i>	
<i>Hypertension (%)</i>					<i>0.565</i>
<i>No</i>	<i>56500(79.7%)</i>	<i>34028(80.1%)</i>	<i>16919(78.3%)</i>	<i>5553(81.6%)</i>	
<i>Yes</i>	<i>14386(20.3%)</i>	<i>8451(19.9%)</i>	<i>4683(21.7%)</i>	<i>1252(18.4%)</i>	

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

Comment 4: Major missing subset of patients with EOC is what we commonly call ‘Familial EOC’, with strong family history of cataract formation at a younger age. Also, it is common understanding that cataract formation starts at a much younger age (10 years earlier) in Indian sub-continent and African population than Caucasian.

Reply 4: Thank you for your suggestion, and we totally agree with you that family history and ethnicity may play an important role in patients with EOC. Unfortunately, there was no valid information about family history in the 45 and up study. Moreover, only the Indians could be distinguished from the participants, and we observed no significant differences in the EOC risk between former or current smokers with non-smokers after adjusted for ethnicity both in total and in Indians.

Changes in the text: (In “Supplemental Table”)

Supplemental Table *The relationship between smoking habits and early onset cataract surgery risk, adjusted for ethnicity and outdoor time.*

	<i>Event</i>	<i>N</i>	<i>No. of person years</i>	<i>Model 1</i>		<i>Model 2</i>		
				<i>HR</i>	<i>95% CI</i>	<i>HR</i>	<i>95% CI</i>	
Overall								
	<i>Never</i>	1035	42479	374371.7	1.0 (Ref)	1.00-1.00	1.0 (Ref)	1.00-1.00
	<i>Former</i>	550	21602	190366.57	1.07	0.96-1.19	1.07	0.96-1.19
	<i>Current</i>	128	6805	60303.02	0.81	0.67-0.98	0.95	0.78-1.15
In Indians								
	<i>Never</i>	39	1275	11184.09	1.0 (Ref)	1.00-1.00	1.0 (Ref)	1.00-1.00
	<i>Former</i>	2	120	1045.68	0.94	0.20-4.43	0.51	0.11-2.34
	<i>Current</i>	1	53	470.06	0.92	0.11-7.61	0.88	0.11-7.17

HR=Hazard ratio; *CI*=Confidence interval.

Model 1 was adjusted for age, gender, and ethnicity only.

Model 2 was adjusted for age, gender, ethnicity, income, education level, body mass index, history of hypertension, cardiovascular disease, diabetes, insulin use, alcohol drinking, physical activity, outdoor time, and dietary factors.

Comment 5: It is hard, if not impossible, to determine what type of cataract was prevalent in these patients of EOC; PSC, Cortical or Nuclear Sclerotic? .

Reply 5: Thank you for pointing out this critical issue. The types and stages of cataract could not be analyzed due to the unavailability of the data and the design of 45 and up study. Previous study reported that the most common type of cataract predominantly observed was PSC in 182 (53.5%) eyes followed by nuclear cataract in 71 (20.9%), mixed cataract in 57 (16.8%), and posterior polar cataract in 30 (8.8%).¹ Further studies on risk factors of different types of EOC were needed. We have added further explanation in the revised version. Hoping this addresses your concern.

Reference:

1. Praveen MR, et al. A study to explore the risk factors for the early onset of cataract in India. Eye (Lond). 2010 Apr;24(4):686-94.

Changes in the text: (In “Discussion”, Page 15, paragraph 3)

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.

Comment 6: Sunlight exposure and exposure to thermal heat etc. are known contributors to formation of EOC, while full time use of spectacles block UV light and prevent cataract formation. Is there a way to rule such factors in/out in this group of patients?

Reply 6: Thanks for your valuable suggestion. We totally agree with you that UV light was associated with cataract formation. Although we could not directly obtain the time of daylight exposure, we investigated the association between smoking and EOC risk after adjusted the outdoor time based on the baseline questionnaire. 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?”. The multivariate regression adjusted for the outdoor time, and the subgroup analysis observed the same results.

Changes in the text:

*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 weekend?”. (In “Methods”, Page 9, paragraph 2, **Covariates**)*

*Univariate and multivariate regression models were also tested after adjusting the ethnicity and outdoor time (Supplemental Table). (In “Methods”, Page 11, paragraph 1, **Statistical Analysis**)*

*A gender-specific analysis and analysis adjusted for ethnicity and outdoor time (Supplemental Table) showed similar results. (In “Results”, Page 12, paragraph 3, **Statistical Analysis**)*

(In “Supplemental Table”)

Supplemental Table The relationship between smoking habits and early onset cataract surgery risk, adjusted for ethnicity and outdoor time.

	Event	N	No. of person years	Model 1		Model 2		
				HR	95% CI	HR	95% CI	
Overall								
	Never	1035	42479	374371.7	1.0 (Ref)	1.00-1.00	1.0 (Ref)	1.00-1.00
	Former	550	21602	190366.57	1.07	0.96-1.19	1.07	0.96-1.19
	Current	128	6805	60303.02	0.81	0.67-0.98	0.95	0.78-1.15
Outdoor time less than mean value (2.8 hours/day) during the workday								
	Never	749	30223	266366.85	1.0 (Ref)	1.00-1.00	1.0 (Ref)	1.00-1.00
	Former	383	14499	127720.59	1.11	0.98-1.26	1.12	0.98-1.27
	Current	70	3711	32914.18	0.78	0.60-1.00	0.92	0.71-1.19
Outdoor time more than mean value (2.8 hours/day) during the workday								
	Never	286	12256	108004.8	1.0 (Ref)	1.00-1.00	1.0 (Ref)	1.00-1.00
	Former	167	7103	62645.97	0.97	0.79-1.18	0.97	0.79-1.18
	Current	58	3094	27388.84	0.85	0.64-1.14	0.96	0.71-1.29
Outdoor time less than mean value (5.1 hours/day) on weekends								
	Never	730	29106	257092.19	1.0 (Ref)	1.00-1.00	1.0 (Ref)	1.00-1.00
	Former	346	13702	121031.53				
	Current	65	3884	34515				
Outdoor time more than mean value (5.1 hours/day) on weekends								
	Never	305	13373	117279.46	1.0 (Ref)	1.00-1.00	1.0 (Ref)	1.00-1.00
	Former	204	7900	69335.04	1.04	0.91-1.18	1.06	0.93-1.21
	Current	63	2921	25788.02	0.68	0.53-0.89	0.83	0.63-1.08

HR=Hazard ratio; CI=Confidence interval.

Model 1 was adjusted for age, gender, and ethnicity only.

Model 2 was adjusted for age, gender, ethnicity, income, education level, body mass index, history of hypertension, cardiovascular disease, diabetes, insulin use, alcohol drinking, physical activity, outdoor time, and dietary factors.

Reviewer B:

Comment 1: Although sampling size of your cohort is not small, sampling method is not probability. So, you need to compare your cohort with population in order to prove your cohort is similar to the population. Of course, the information of population is limited. Instead, you could use results of the representative sampling study or administrative data about sociodemographic variables of New South Wales

Reply 1: Thank you for your valuable suggestion. According to official documents,¹ individuals aged 45 and over and resident in New South Wales are randomly sampled from the Medicare Australia enrolment database. This is the database through which national healthcare is administered and includes all citizens and permanent residents of Australia, as well as some temporary residents and refugees. Eligible individuals are mailed an invitation to take part, an information leaflet, the study questionnaire and consent form and a reply paid envelope. People may also volunteer to join the study by calling the study helpline and requesting an invitation pack. The 45 and Up Study included 10% of the general population in the target age range and participants displayed a good spread of responses across most variables. We have added further explanation in the revised version. Hoping this addresses your concern.

Reference:

1. 45 and Up Study Collaborators, et al. Cohort profile: the 45 and up study. *Int J Epidemiol*, 2008,37(5), 941-7.

Changes in the text: (In “Methods”, Page 6, paragraph 2, **Participants**).

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 enrolment 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.

Comment 2: Your study frame is based on the cohort study. But the incidence is very low. How about using CASE-COHORT STUDY that is a hybrid of cohort study and case-control study?

Reply 2: Thank you for your suggestion. In the present study, we investigated the relationship between smoking habits and early onset cataract surgery risk, which was based on the prospective cohort design. Although the incidence of EOC is very low, our sample size is large enough to detect statistical differences powerfully. What's more, the case-cohort study might increase potential for information bias because subcohort may have been established after the time which identified the case and non-cases, and the incidence of EOC could not be identified. Hoping this addresses your concern.

Changes in the text: *None.*