# Self-reported cataract surgery and 10-year all-cause and cause-specific mortality: findings from the National Health and Nutrition Examination Survey

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bjophthalmol-2021-319678).

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Received 18 May 2021
Accepted 14 September 2021

## ABSTRACT

**Purpose** To investigate the association of self-reported cataract surgery with all-cause and cause-specific mortality using a large-scale population-based sample.

**Methods** Data from the 1999–2008 cycles of the National Health and Nutrition Examination Survey were used. A self-reported history of cataract surgery was considered a surrogate for the presence of clinically significant cataract surgery. Mortality data were ascertained from National Death Index records. Hazard ratios (HRs) and 95% confidence intervals (CIs) for survival were estimated using Cox proportional hazards regression models.

**Results** A total of 14 918 participants were included in the analysis. During a median follow-up of 10.8 (Interquartile range, IQR, 8.25–13.7) years, 3966 (19.1%) participants died. Participants with self-reported cataract surgery were more likely to die from all causes and specific causes (vascular disease, cancer, accident, Alzheimer's disease, respiratory disease, renal disease and others) compared with those without (all Ps <0.05). The association between self-reported cataract surgery and all-cause mortality remained significant after multiple adjustments (HR=1.13; 95% CI 1.01 to 1.26). For cause-specific mortality, multivariable Cox models showed that self-reported cataract surgery predicted a 36% higher risk of vascular-related mortality (HR=1.36; 95% CI 1.01 to 1.82). The association with other specific causes of mortality did not reach statistical significance after multiple adjustments.

**Conclusions** This study found significant associations of self-reported cataract surgery with all-cause and vascular mortalities. Our findings provide potential insights into the pathogenic pathways underlying cataract.



**To cite:** Chen Y, Wang W, Liao H, *et al*. *Br J Ophthalmol* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/bjophthalmol-2021-319678

## INTRODUCTION

Cataract is a major cause of visual impairment (VI) and blindness globally.[1] In 2010, 33.4% of blindness and 18.4% of moderate to severe VI worldwide were caused by cataract.[2] As the only effective treatment for cataract and the most performed ophthalmic procedure, cataract surgery confers a large health economic return-on-investment to society at 4500%.[3] Despite the efficacy of surgery, approximately 20 million people globally remain blind due to cataract—the majority of whom in developing countries.[4 5]

Although many previous studies have investigated the associations between cataract or cataract surgery and all-cause mortality, results have been conflicting.[6–21] Of note, only a few studies to date have explored the associations between cataract and cause-specific mortality.[9–11 13 22–27] Furthermore, these previous studies were mainly focused on cancer-related[11 13 22 26] and vascular[7 10 22–24 27] mortality. However, little is known about the association of cataract with other causes of deaths, such as Alzheimer's disease and renal disease-related deaths. A comprehensive understanding of the associations of cataract with specific causes of deaths may provide insights into the pathological processes underlying cataract.

We, therefore, aimed to investigate the association between self-reported cataract surgery and all-cause as well as cause-specific mortality using a large-scale population-based sample.

## METHODS

### Sample and population

The National Health and Nutrition Examination Survey (NHANES) is carried out by the National Center for Health Statistics (NCHS), which is part of the Center for Disease Control and Prevention. Multistage, stratified and probability sampling methods have been employed by the NHANES with the aim of providing nationally representative statistics on the non-institutionalised civilian population in the USA. All participants complete household interviews and extensive physical examinations, which have been described in details elsewhere.[28] In this survey analysis, we analysed data from the 1999–2008 cycles of the NHANES. All NHANES protocols were reviewed and approved by the NCHS research ethics review committee. All participants provided written informed consent.

### Cataract identification

From household interviews, details of cataract surgery status were collected through the following questions: 'Have you ever had cataract surgery?'. If participants gave a positive initial answer, they were subsequently asked: 'Which eye(s)?'. The possible answers included left eye, right eye, both eyes or I don't know. Self-reported cataract surgery in the left or right eye was defined as unilateral cataract surgery. Self-reported cataract surgery in

both eyes was defined as bilateral cataract surgery. Participants who answered 'I don't know' were excluded from the analysis of mortality by unilateral or bilateral cataract surgical status. Because of an increasing rate and lower visual threshold of cataract surgery in the USA,[29] self-reported cataract surgery may be a surrogate for the presence of clinically significant cataract. Consistent with a previous study,[30] participants who reported cataract surgery in at least one eye were considered cataract cases.

### Mortality data

Mortality data were confirmed from the National Death Index (NDI). Linking mortality was achieved by matching a series of personal identifiers, including name, gender, date of birth, social security number, from the NHANES to the underlying cause of death in the NDI database. All participants were followed up to 31 December 2015. Participants who were not matched with the NDI were assumed to be alive as of that date. The underlying cause of death was determined using codes from the International Classification of Disease (ICD) tenth version (ICD-10). In this survey analysis, we identified deaths from all causes, vascular disease (I00-I09, I11, I13, I20-I51, I60-I69), cancer (C00-C97), accident (V01-X59, Y85-Y86), Alzheimer's disease (G30), respiratory disease (J40-J47, J09-J18), renal disease (N00-N07, N17-N19, N25-N27) and other conditions. Participant survival was measured using the duration between interview and date of death, or 31 December 2015; whichever came first.

### Confounding variables

Sociodemographic characteristics including age, gender, ethnicity/race, educational attainment, income level, smoking status and alcohol consumption were obtained from the household interviews. The presence of diabetes mellitus, hypertension and hypercholesterolemia was determined by physician diagnosis, claims of pertinent medications or evidence from physical examinations (glycosylated haemoglobin levels ≥6.5% for diabetes mellitus, systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg for hypertension, total cholesterol ≥240 mg/dL). Body mass index (BMI) was calculated by dividing body weight (kg) by the square of height ($m^2$). The C reactive protein (CRP) >1 mg/dL was used to define elevated CRP. We obtained self-reported health status from the household interviews. Baseline chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate of less than 60 mL/min/1.73 $m^2$. A history of cardiovascular disease (CVD) was defined as having a self-reported history of congestive heart failure, coronary heart disease, angina, heart attack or stroke. Presenting VI was defined as presenting visual acuity worse than 20/40.

### Statistical analysis

Based on the NHANES Analytic and Reporting Guidelines, all statistical analyses were accounted for the NHANES' complex and stratified survey design. We used log-rank tests to compare survival distributions between the cataract surgery group and non-surgery group. Hazard ratios (HRs) and 95% confidence intervals (CIs) for survival were estimated through Cox proportional hazards regression models. We adjusted all primary models for age (continuous), sex and ethnicity (white, black, Mexican-American and others). We further adjusted in the full models for educational attainment (degree <high school, or ≥high school), marital status (unmarried and other or married/with a partner), income level (poverty income ratio <1.00 or ≥1.00), smoking status (never/former smoker or current smoker), alcohol consumption (lifetime abstainer/former drinker or current drinker), diabetes mellitus, hypertension, hypercholesterolaemia, BMI, CRP level, presenting VI and self-rated health status (poor/fair or good/excellent). For the analysis of vascular mortality, we additionally adjusted for history of CVD in the full model. For the analysis of renal disease-related mortality, we additionally adjusted for baseline CKD in the full model. In the analysis of the association between cataract surgery and all-cause mortality, we also investigated whether there was any interaction by age, gender or diabetes status. The proportional hazards assumption was tested by Schoenfeld residuals, and none of the models in the present analyses violated this assumption. The multicollinearity among variables was checked by the variance inflation factor (VIF), and the average VIF was 1.21. Analyses were performed with the use of Stata V.14.0 (StataCorp LLC, College Station, Texas). All tests were two sided, and $p<0.05$ was used as the level of significance.

## RESULTS

### Study population

The sample population included 15 942 adults aged 40 years or older. Of these, 1024 participants had missing information for cataract surgery status and/or mortality status. Thus, 14 918 participants were included in this analysis. Characteristics of participants included in the analysis differed from those with missing data for some characteristics, such as age, sex, ethnicity, educational attainment, marital status, income level, smoking status, alcohol consumption, comorbidities and general health status (online supplemental table 1).

The weighted distributions of study population characteristics of the total sample (n=14 918) and the two groups are shown in table 1. In brief, the mean±SE age of the participants was 56.8±0.21 years old. Women represented 52.7% of the sample. The weighted prevalence of self-reported cataract surgery was 9.61% (n=2009). Participants who reported a history of cataract surgery were younger, men, of non-white ethnicity, more educated, married and less likely to have diabetes mellitus, hypertension, history of heart disease, CKD, presenting VI, hypercholesterolaemia, elevated CRP levels and poorer self-rated health status. They were also more likely to have higher BMI and consume higher amounts of alcohol. Online supplemental table 2 presents the baseline characteristics of participants by cataract surgical status.

### All-cause mortality

During a median follow-up of 10.8 years (IQR: 8.25–13.7), 3966 (19.1%) participants died. Participants with cataract surgery had significantly higher all-cause mortality compared with those without (53.0% vs 15.5%, log-rank test $p<0.001$, table 2). The unadjusted Cox proportional hazards regression model showed that cataract surgery was significantly associated with an increased risk of all-cause mortality (HR 4.70; 95% CI 4.29 to 5.16; $p<0.001$, table 3). This association remained statistically significant after adjusting for age, gender and ethnicity (HR 1.27; 95% CI 1.16 to 1.38; $p<0.001$, table 3). Further adjustments for educational attainment, income level, marital status, smoking status, alcohol consumption, diabetes mellitus, hypertension, hypercholesterolaemia, BMI, CRP level and self-rated health status indicated poorer survival among participants with self-reported cataract surgery at baseline (HR 1.13; 95% CI 1.01 to 1.26, table 3). We did not find any interaction by age, gender

**Table 1** Baseline characteristics of participants by cataract surgical status

| Characteristics | Total (n=14 918) | Cataract surgery group (n=12 909) | Non-surgery group (n=2009) | P value* |
|---|---|---|---|---|
| Age (SE), years | 56.8±0.21 | 55.0±0.19 | 73.9±0.30 | **<0.001** |
| Gender | | | | |
| Male | 7440 (47.3) | 6529 (48.2) | 911 (38.0) | **<0.001** |
| Female | 7478 (52.7) | 6380 (51.8) | 1098 (62.0) | |
| Race | | | | |
| Non-Hispanic white | 7975 (76.8) | 6600 (76.0) | 1375 (84.5) | **<0.001** |
| Non-Hispanic black | 2921 (9.79) | 2670 (10.1) | 251 (6.51) | |
| Mexican American | 2764 (4.98) | 2526 (5.24) | 238 (2.57) | |
| Other | 1258 (8.42) | 1113 (8.63) | 145 (6.41) | |
| Education level† | | | | |
| Less than high school | 4976 (20.4) | 4149 (19.1) | 827 (32.3) | **<0.001** |
| High school and over | 9941 (79.6) | 8760 (80.9) | 1181 (67.7) | |
| Marital status† | | | | |
| Unmarried and other | 5358 (31.4) | 4413 (29.9) | 945 (45.5) | **<0.001** |
| Married/with a partner | 9273 (68.6) | 8249 (70.1) | 1024 (54.5) | |
| Income level† | | | | |
| Below poverty (<1) | 2207 (10.3) | 1903 (10.2) | 304 (11.6) | 0.076 |
| At or above poverty (≥1) | 11 471 (89.7) | 9951 (89.8) | 1520 (88.4) | |
| Smoking status† | | | | |
| Never | 7044 (47.6) | 6123 (47.8) | 921 (45.5) | 0.165 |
| Former/current | 7857 (52.4) | 6772 (52.2) | 1085 (54.5) | |
| Alcohol consumption† | | | | |
| Lifetime abstainer/former drinker | 3776 (22.8) | 3071 (21.2) | 705 (37.2) | **<0.001** |
| Current drinker | 10 475 (77.2) | 9251 (78.8) | 1224 (62.8) | |
| Diabetes mellitus† | | | | |
| No | 11 634 (86.1) | 10 237 (87.3) | 1397 (74.3) | **<0.001** |
| Yes | 2799 (13.9) | 2247 (12.7) | 552 (25.7) | |
| Hypertension† | | | | |
| No | 6935 (55.7) | 6384 (58.4) | 551 (29.5) | **<0.001** |
| Yes | 7425 (44.3) | 6054 (41.6) | 1371 (70.5) | |
| Hypercholesterolaemia† | | | | |
| No | 8955 (63.4) | 7890 (64.5) | 1065 (53.8) | **<0.001** |
| Yes | 5340 (36.6) | 4480 (35.5) | 860 (46.2) | |
| BMI (SE), kg/m$^2$ | 28.8±0.09 | 28.8±0.10 | 28.1±0.16 | **<0.001** |
| C reactive protein level† | | | | |
| Low (<1) | 12 538 (89.2) | 10 872 (89.4) | 1666 (87.5) | **0.019** |
| High (≥1) | 1661 (10.8) | 1423 (10.6) | 238 (12.5) | |
| Self-rated health† | | | | |
| Poor/fair | 3134 (19.3) | 2593 (18.2) | 541 (29.9) | **<0.001** |
| Good/excellent | 8528 (80.7) | 7463 (81.8) | 1065 (70.1) | |
| Chronic kidney disease† | | | | |
| No | 12 161 (89.8) | 10 963 (92.5) | 1198 (64.1) | **<0.001** |
| Yes | 1941 (10.2) | 1248 (7.53) | 693 (35.9) | |
| History of heart disease | | | | |
| No | 12 418 (86.7) | 11 058 (88.7) | 1360 (68.4) | **<0.001** |
| Yes | 2500 (13.3) | 1851 (11.3) | 649 (31.6) | |
| Presenting visual impairment† | | | | |
| No | 13 248 (93.1) | 11 641 (93.9) | 1607 (85.5) | **<0.001** |
| Yes | 1474 (6.95) | 1116 (6.15) | 358 (14.5) | |

Boldface indicates statistical significance.
All proportions are weighted estimates of the US population characteristics, taking into account the complex sampling design of the National Health and Nutrition Examination Survey.
*All p values were calculated using t-test for continuous variables and the design-adjusted Rao-Scott Pearson $\chi^2$ test for categorical variables.
†Characteristics with missing values.
BMI, body mass index.

**Table 2** Mortality rates in participants by cataract surgical status

| Cause of mortality | Mortality rate (%) Cataract surgery group (n=2009) | Nonsurgery group (n=12 909) | P value* |
|---|---|---|---|
| All-cause mortality | 1165 (53.0) | 2801 (15.5) | **<0.001** |
| Vascular | 277 (12.5) | 607 (3.05) | **<0.001** |
| Cancer | 194 (8.387) | 677 (4.135) | **<0.001** |
| Accident | 19 (0.78) | 63 (0.41) | **0.003** |
| Alzheimer's disease | 42 (2.16) | 74 (0.47) | **<0.001** |
| Respiratory disease | 92 (4.46) | 178 (1.08) | **<0.001** |
| Renal disease | 31 (1.26) | 55 (0.25) | **<0.001** |
| Others | 509 (23.4) | 1135 (6.08) | **<0.001** |

All-cause and cause-specific mortality were assessed through 31 December 2015. All mortality rates are weighted estimates of the US population characteristics, taking into account the complex sampling design of the National Health and Nutrition Examination Survey.
*Log-rank test.

or diabetes status in the association between cataract surgery and all-cause mortality.

### Cause-specific mortality

Among the 3966 participants who died of all causes, 884, 871, 82, 116, 270, 86 and 1657 were attributable to vascular, cancer, accident, Alzheimer's disease, respiratory disease, renal disease and other causes, respectively. Cataract surgical status was associated with significantly higher mortality rates for each specific cause (table 2). The fully adjusted Cox models for each specific cause mortality showed that cataract surgery status predicted a 36% higher risk of vascular mortality (HR 1.36; 95% CI 1.01 to 1.82, table 3) after multiple adjustments.

### Sensitivity analysis

We performed a sensitivity analysis of the association between cataract surgery and all-cause mortality at 5-year follow-up. Time to death was counted from baseline to the date of death or 31 December 2011, whichever the earliest. No significant association was found between cataract surgery and 5-year all-cause mortality.

**Table 3** Hazards of total and cause-specific mortality in participants by cataract surgical status

| Cause | Unadjusted HR (95% CI) | AHR (95% CI)* | AHR (95% CI)† |
|---|---|---|---|
| All-cause mortality | **4.70 (4.29 to 5.16)** | **1.27 (1.16 to 1.38)** | **1.13 (1.01 to 1.26)** |
| Vascular | **5.50 (4.62 to 6.55)** | **1.40 (1.15 to 1.70)** | **1.36 (1.01 to 1.82)** |
| Cancer | **2.68 (2.16 to 3.33)** | 1.01 (0.82 to 1.25) | 0.85 (0.66 to 1.09) |
| Accident | **2.57 (1.39 to 4.74)** | 1.33 (0.70 to 2.51) | 1.47 (0.58 to 3.71) |
| Alzheimer's disease | **2.57 (1.39 to 4.74)** | 0.83 (0.56 to 1.23) | 0.82 (0.40 to 1.68) |
| Respiratory disease | **6.91 (4.65 to 10.3)** | 1.27 (0.92 to 1.76) | 1.02 (0.63 to 1.66) |
| Renal disease | **7.34 (4.79 to 11.3)** | **2.12 (1.39 to 3.22)** | 1.70 (0.90 to 3.20) |
| Others | **5.43 (4.72 to 6.26)** | **1.33 (1.13 to 1.56)** | 1.15 (0.94 to 1.41) |

Boldface indicates statistical significance.
All-cause and cause-specific mortality were assessed through 31 December 2015.
*Adjusted for age, gender and ethnicity.
†Further adjusted for education level, marital status, income level, smoking status, alcohol consumption, diabetes mellitus, hypertension, hypercholesterolaemia, body mass index, C reactive protein level, self-rated health status and visual impairment. For renal disease-related mortality, baseline chronic kidney disease was adjusted for. For vascular disease-related mortality, history of cardiovascular disease was adjusted for.
AHR, adjusted HR; HR, Hazard Ratio.

We also compared the associations of different cataract surgical status with all-cause and cause-specific mortalities (online supplemental table 3). Compared with participants who had no cataract surgery, those who had bilateral cataract surgery, had a 20% higher risk of all-cause mortality (HR=1.20; 95% CI 1.08 to 1.34), a 48% higher risk of vascular mortality (HR=1.48; 95% CI 1.09 to 2.00) and a 120% higher risk of renal disease-related mortality (HR=2.20; 95% CI 1.02 to 4.73). Participants who had unilateral cataract surgery had similar all-cause and cause-specific mortalities compared with those who did not have any cataract surgery.

## DISCUSSION

The present study showed that participants with self-reported cataract surgery had a significantly higher risk of all-cause mortality compared with those without any history of cataract surgery. In addition, following multiple adjustments, we found that self-reported cataract surgery was associated with increased cause-specific mortality due to vascular disease. No significant association was observed specifically between self-reported cataract surgery and cancer, respiratory disease, renal disease, Alzheimer's disease, accidents or other cause-related mortality.

Consistent with the majority of previous large-scale population-based prospective studies,[6–8 10 11 13 16–19] we demonstrated a positive association between cataract and all-cause mortality. Furthermore, we also identified a significant association between self-reported cataract surgery and vascular mortality. Of note, the relationship between cause-specific mortality and cataract is poorly understood. Previous studies have mainly focused on vascular and cancer-related mortality.[7 9–11 13 20 22–27] Our finding of a significant association between cataract and vascular mortality is supported by previous studies.[7 10 22–24 27] Notably, Hu *et al*[27] analysed the data of 60 657 women aged 45–63 from the Nurses' Health Study cohort and showed that after 10 years of follow-up, participants who had cataract extraction had significantly increased mortality from CVDs. The 11-year follow-up data from the Blue Mountains Eye Study also showed that any cataract was significantly associated with vascular mortality independent of confounders.[10] There have been a few hypotheses postulated to explain the association between cataract and vascular mortality. Oxidative stress has been implicated in the pathogenesis of both cataract and atherosclerosis.[31–33] Previous studies of human lens epithelial cells found that the senescence of lens cells, triggered by oxidative stress-induced DNA damage and telomere shortening, contributed to cataract formation.[34] Oxidative stress affects vascular reactivity and oxidised low-density lipoproteins promote atherogenesis.[35] Therefore, the presence of cataract may be an indicator of high levels of cumulative oxidative damage resulting from physiological and pathological ageing. An alternative hypothesis is that crystallins, which are the major components of the lens, are also involved in regulating apoptosis, cell survival and responses to stressors such as inflammation and ischaemia, not only at an ocular level but also at a systemic level. It was previously reported that the absence of crystallins normally found in the brain, heart and skeletal muscles is associated with ageing phenotypes.[36 37] Additionally, mutations in αB-crystallins could cause cardiac disorders.[38 39] Therefore, the degeneration of crystallins in cataract may represent a more widespread systemic disorder involving other organ systems and may have contributed to the higher vascular mortality.[36 40 41] Another possible explanation for the association between cataract and higher vascular mortalities is depression. Patients with cataract have been shown to be more likely to develop depression compared with those without cataract, even after they had undergone cataract surgery.[42–44] Meanwhile, some studies have found that patients with depression were at higher risks of developing CVD and depression in patients who already had CVD conferred higher CVD mortalities.[45–50]

To the best of our knowledge, no previous study has reported a significant association between bilateral cataract and renal disease-related mortality. In the present study, we found that participants with a history of bilateral cataract surgery had a more than two-fold increase in renal disease-related mortality risk compared with those who had no cataract surgery. A plausible mechanism linking cataract and renal disease-related mortality is increased oxidative stress, which is implicated in both cataractogenesis and CKD.[51–53]

For cancer-related mortality, no significant association with self-reported cataract surgery was found in the current analysis. Consistent with our result, a few studies did not identify any association between cataract and cancer-related mortality.[7 23–25 27] However, some previous studies have found that mixed[11 13 26] or any nuclear cataract[9 11] was significantly associated with cancer-related mortality. Interestingly, Cugati *et al* found that cancer-related deaths were less frequent in participants with cataract.[10] The association between cataract and Alzheimer's disease-related mortality has been poorly investigated. Despite the potential link between cataract and Alzheimer's disease as shown in human studies,[54 55] the current study did not find any significant association between self-reported cataract surgery and Alzheimer's disease-related mortality.

The strengths of this study include the large sample size and high power to detect significant associations, relatively long duration of follow-up, multiple adjustments for a range of relevant confounders and the detailed causes of deaths. A few weaknesses should be considered. Self-reported cataract surgery was used as a surrogate for clinically significant cataract, leading to potential recall bias and the possibility of missing some cataract cases. It was not possible to determine the types of cataract, which may be useful in future studies to investigate the associations between specific types of cataract and specific causes of deaths. Additionally, there was a lack of assessment of time from surgery to mortality. Despite adjusting for a wide range of relevant confounders, the possibility of residual confounding cannot be excluded.

## CONCLUSIONS

The current study found a positive association between self-reported cataract surgery and all-cause mortality. In addition, we found that self-reported cataract surgery increases the risks of vascular mortality by 36% after multiple adjustments. More studies are needed to confirm these associations and to further investigate the mechanisms behind these associations.

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**Funding** The present work was supported by the Fundamental Research Funds of the State Key Laboratory of Ophthalmology, Project of Investigation on Health Status of Employees in Financial Industry in Guangzhou, China (Z012014075), Science and Technology Program of Guangzhou, China (202002020049). ZZ receives the support from the National Natural Science Foundation of China (82101173) and the Research Foundation of Medical Science and Technology of Guangdong Province (B2021237). MH receives support from the University of Melbourne at Research Accelerator Programme and the CERA Foundation.

**Disclaimer** The Centre for Eye Research Australia receives Operational Infrastructure Support from the Victorian State Government. The sponsor or funding organisation had no role in the design or conduct of this research.

**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request.



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