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Cataract Surgery and Falls, Fractures, and Mortality in the United States Population

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Cataract Surgery and Falls, Fractures, and Mortality in the United States Population

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Epidemiology

by

Victoria Li-Ting Tseng

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ABSTRACT OF THE DISSERTATION

Cataract Surgery and Falls, Fractures, and Mortality

in the United States Population

by

Victoria Li-Ting Tseng

Doctor of Philosophy in Epidemiology

University of California, Los Angeles, 2016

Professor Anne L. Coleman, Chair

Cataract surgery is the mainstay of treatment for visually significant cataract. Aside from vision improvement, one secondary benefit of cataract surgery that has been reported is the reduction of fracture risk. This dissertation examines associations between cataract surgery and factors related to fracture risk, including the association between cataract surgery and falls and the association between cataract surgery and long-term mortality.

The first study of this dissertation uses data from the Women's Health Initiative (WHI) to examine the association between cataract surgery and short and long-term fall frequency in WHI participants with cataract. In the WHI study population, cataract surgery was potentially associated with increased risk of falling at least twice within one year of surgery (odds ratio [OR]=1.06, 95% confidence interval [CI]=0.97, 1.17) and throughout the entire study period (OR=1.10, 95% CI=1.01, 1.19 in repeated measures analysis). In stratified analyses, there were

potentially decreased risks of two or more falls within one year after cataract surgery in participants who were older (OR=0.78; 95% CI=0.53, 1.16 for 80-84 years old) or with the highest systemic disease burden (OR=0.80; 95% CI=0.61, 1.05 for Charlson Comorbidity Index [CCI] ≥5), but potentially increased risks in participants who were younger (OR=1.11; 95% CI=0.94, 1.30 for 65-70 years old) or with moderate systemic disease burden (OR=1.17; 95% CI=1.01, 1.35 for CCI 3-4).

The second study examined the association between cataract surgery and long term mortality in the United States (US) Medicare population. In Medicare patients with cataract, patients with cataract surgery had lower adjusted hazards of mortality compared to patients without cataract surgery (hazards ratio [HR]=0.73, 95% CI=0.72, 0.74). The strongest protective associations between cataract surgery and mortality were observed in patients most likely to receive cataract surgery based on high propensity score decile (HR=0.52, 95% CI=0.50, 0.54), patients 80-84 years old (HR=0.63, 95% CI=0.62, 0.65), females (HR=0.69, 95% CI=0.68, 0.70), patients with a moderate systemic disease burden (HR=0.71, 95% CI=0.69, 0.72 for CCI 3-4), and patients with severe cataract (HR=0.68, 95% CI=0.66, 0.70).

The third study examined the association between cataract surgery and long term mortality in WHI participants with cataract, and included additional covariates such as smoking, alcohol use, and body mass index that were not available in the Medicare database. In WHI participants with cataract, there was a protective adjusted association between cataract surgery and mortality (HR=0.60, 95% CI=0.58, 0.63). The strongest protective associations were observed in participants in the highest propensity score decile (HR=0.51, 95% CI=0.40, 0.66), ≥85 years old

(HR=0.50, 95% CI=0.36, 0.69), and with a CCI score of 0 or ≥5 (95% CI=0.51, 0.63 for CCI of 0 and 0.51, 0.62 for CCI ≥5).

In conclusion, in patients with cataracts, cataract surgery may be associated with increased risk of falls overall over up to 12 years of follow-up, but decreased risk of falls in older and sicker patients. These findings may partially explain the previously reported protective association between cataract surgery and fracture risk, but there is the need for further study on the association between cataract surgery and fracture risk factors. Additionally, we have found that cataract surgery is associated with improved long term survival in two US populations, and we hypothesize that this may be due to improvement of overall functioning and quality of life after cataract surgery. Further studies of the mechanisms of the protective association between cataract surgery and mortality would be worthwhile in populations within the US and elsewhere.

The dissertation of Victoria Li-Ting Tseng is approved.

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Table of Contents

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Age-related macular degeneration (AMD)
Autoregressive 1 (AR1)
Body mass index (BMI)
Centers for Medicare and Medicaid Services (CMS)
Charlson Comorbidity Index (CCI)
Clinical Trial arm (CT)
Confidence interval (CI)
Current Procedural Terminology (CPT)
Diabetes mellitus (DM)
Hazards ratio (HR)
International Classification of Diseases, Clinical Modification, 9th revision (ICD-9-CM)
Metabolic equivalent hours (METs)
National Death Index (NDI)
National Drug Codes (NDCs)
Observational Study arm (OS)
Odds ratio (OR)
Social Security Administration (SSA)
United States (US)
Women's Health Initiative (WHI)

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Chapter 1: Introduction and Background

1.1 Background

1.1.1 Overview of Cataract

Cataract is a clouding of the lens of the eye that can decrease vision and lead to blindness if left untreated. Cataracts are the leading cause of low vision among adults 40 years and older in the United States (US), and it is estimated that 30.1 million Americans will have cataract by the year 2020.[1,2] The pathogenesis of cataract is multifactorial and not well understood but may be related to oxidative stress of crystalline lens material, which may cause chemical and structural alterations that lead to the loss of lens transparency.[3]

Cataract extraction with implantation of an artificial intraocular lens is the mainstay of treatment for all types of cataract. Cataract surgery is elective and serves to reverse the vision impairment caused by cataract.[4] Cataract surgery is a widely performed procedure and is the leading diagnosis at ambulatory surgical centers in the US, with 3.0 million cataract-related visits to US surgical centers in 2006.[5]

1.1.2 Cataract Surgery and Fracture Risk

In addition to vision improvement, cataract surgery has several potential secondary benefits such as the improvement of overall functioning and quality of life. One secondary outcome that has been studied is the occurrence of fractures following cataract surgery. A study[6] published in 2012 in the *Journal of the American Medical Association* found that in patients with cataract in the national US Medicare population, patients who received cataract surgery had 16% decreased risk of fractures compared to patients who did not receive cataract surgery, after adjusting for demographics, systemic comorbidities, and ocular comorbidities. This association was also found to be modified by the effects of age, systemic disease burden, and cataract severity.

While this study established a protective association between cataract surgery and fracture risk, the factors related to this protective association and its subsequent effects are not well understood. First of all, it is unknown how cataract surgery influences the nature of falls that lead up to fractures. It is possible that improved vision following cataract surgery reduces the frequency of falls, or also that improved vision changes the characteristics of a fall so that it is less severe and does not result in a fracture. Secondly, it is unknown how the reduced risk of fractures after cataract surgery affects the subsequent association between cataract surgery and mortality. Mortality in individuals with cataract may be related to vision impairment, systemic oxidative damage, and overall functioning and quality of life, and it is unclear how cataract surgery may modify these factors.

1.2 Gaps in the Literature

Vision impairment is objectively defined as visual acuity less than 20/40 and can occur as a result of many types of eye disease, with cataracts being one of the leading causes.[1,2] Several studies have found an association between vision impairment and increased risk of mortality, and falls and fractures have been proposed as a mediating mechanism in the association between vision impairment and mortality.[7-17] The mechanism of association between falls and fractures is not straightforward[18-21], and studies have demonstrated that both fall frequency[22,23] and fall severity[24] are fall-related characteristics that contribute to the risk of fracture after a fall. Existing studies of cataract surgery and falls[25-29] have differed in the fall characteristic that was examined as an outcome, making their conflicting findings difficult to compare. Additionally, the only study of the subject in the US was conducted within a cohort of 214 patients in Alabama[28], suggesting the need for additional studies of cataract surgery and specific fall outcomes related to fractures in larger generalizable US cohorts.

It is well established in the literature that cataracts are associated with increased mortality risk. While this association may be explained in part by the vision impairment from cataracts, it has also been suggested that cataracts may serve as a proxy for oxidative damage within the body.[7,8,12,30-42] It is thus not clear how cataract surgery influences mortality risk, and existing studies have not been able to establish a consistent association between cataract surgery and mortality. These studies have mainly been conducted outside the US, and almost all of these studies have comparison groups that include patients without cataract, which creates a problem of confounding because associations between cataract surgery and mortality could be explained by the presence of cataract rather than by the occurrence of cataract surgery.[7,8,35,39-47] Only two studies[48,49] have attempted to examine the association between cataract surgery and mortality in a cohort of patients who all have cataract. Both studies were conducted in cohorts within Western Sydney, Australia, and reported that patients with vision improvement after cataract surgery experienced increased survival compared to patients with vision impairment. A major limitation of both studies is their limited generalizability due to the study of small cohorts in Western Sydney, and additional studies are needed of cataract surgery and mortality in larger populations outside of Australia.

1.3 Overall Objective

The purpose of this dissertation is to examine factors surrounding the protective association between cataract surgery and fracture risk in the US population. We will examine the association between cataract surgery and fall frequency as a means of studying potential factors that lead up to the protective association between cataract surgery and fractures. Additionally, we will examine the association between cataract surgery and mortality as a means of studying the potential outcomes that result from the protective association between cataract surgery and fractures. These studies will be conducted in two large US cohorts, the national US Medicare population and the Women's Health Initiative (WHI) cohort.

The first study will examine cataract surgery and falls in the WHI cohort. The study of the prevention of osteoporotic fractures was an original aim of the WHI study, and the WHI thus has a rich database of information related to falls, fractures, and their respective risk factors. The WHI is additionally linked to Medicare for diagnoses and procedures that are not examined in the WHI, such as cataract surgery. These factors make the WHI cohort an ideal population to examine the association between cataract surgery and falls.

The second study will examine cataract surgery and mortality in the national US Medicare population. The Medicare database encompasses the majority of the US population 65 years and older, so findings from this database are generalizable to the aging US population. The Medicare database is based on International Classification of Diseases, Clinical Modification, 9th revision (ICD-9-CM)[50] diagnosis codes and Current Procedural Terminology (CPT)[51] procedure codes. These codes cover a wide variety of diagnoses and procedures from common medical practice, which will allow for the inclusion of several covariates of interest. However, there are other important covariates that are not routinely coded such as smoking and alcohol use, leaving the possibility of residual confounding. Diagnosis and procedure codes are also subject to coding errors, which could lead to misclassification and information bias.

To address these concerns, the third study will examine cataract surgery and mortality in the WHI cohort. The WHI contains additional information on covariates not available in Medicare, such as smoking, alcohol use, income, and education level. Additionally, WHI data are collected by detailed interviews, questionnaires, and physical examinations and also linked to Medicare codes, which can address some of the problems with misclassification that are present in the purely code-based Medicare database.

Chapter 2: Cataract Surgery and Falls in the Women's Health Initiative

2.1 Abstract

Purpose: To determine the association between cataract surgery and short and long term falls for participants of the WHI with a diagnosis of cataract.

Methods: Participants of the WHI with cataract were identified by linking WHI files with diagnosis and procedure codes from the Medicare database. Those with cataract surgery were followed from the date of surgery, while those without surgery were followed from the date of cataract diagnosis. Baseline characteristics that were examined included demographics, socioeconomic status, WHI study group, Charlson Comorbidity Index (CCI) score, medication use, physical activity, body mass index, cataract severity, and ocular comorbidities. The occurrence of one or more falls and two or more falls at regular study follow-up time points was examined within one year and at any time following cataract surgery or diagnosis. Logistic regression was used to analyze the association between cataract surgery and falls within one year of surgery or diagnosis. Propensity score analysis and a case-crossover comparison examining falls within one year after surgery were performed to account for potential residual confounding. Stratified analyses by age, CCI score, and cataract severity were performed to assess for potential effect modification. A repeated measures model was used to analyze the association between cataract surgery and falls at any time after cataract surgery or diagnosis.

Results: During the WHI Main Study period from 1993-2005, there were 37,380 women with a diagnosis of cataract in Medicare, of whom 16,812 (45.0%) received cataract surgery. There were 3,961 (27.0%) women who fell at least once within one year after cataract surgery or diagnosis and 1,564 (10.7%) women who fell at least twice within one year after surgery or diagnosis. When comparing women with and without cataract surgery, the adjusted odds ratios

(ORs) and 95% confidence intervals (CIs) were 1.01 (0.95, 1.08) and 1.06 (0.97, 1.17) for falling at least once or at least twice within one year after surgery, respectively. There were no associations between cataract surgery and falls within one year of surgery in the propensity score analysis or case-crossover comparison. There was potential effect modification by age, CCI score, and cataract severity for falling two or more times within one year of cataract surgery or diagnosis. In repeated measures analyses, cataract surgery was associated with increased odds of falling at least twice throughout the entire duration of the study (OR=1.10, 95% CI=1.01, 1.19).

Conclusions: For WHI participants with cataract, cataract surgery is potentially associated with falling at least twice in the short and long term. Further studies are needed to investigate the mechanisms of association between cataract surgery, falls, and fractures in the US population.

2.2 Introduction

Falls and fractures are a leading cause of morbidity and mortality in the elderly population.[52,53] Vision impairment is a known risk factor for falls and fractures[15,18,54-57], and cataract is a leading cause of vision impairment in elderly patients.[1,2] In a previous study of the national US Medicare population, patients with cataract who received surgery experienced a 16% reduction in fracture risk compared to patients with cataract who did not receive surgery.[6] While the study suggested that a protective association exists between cataract surgery and fracture risk, the nature of the association between cataract surgery and falls is less clear. Studies of cataract surgery and falls[25-29] have reported conflicting findings and have mainly been conducted in small isolated populations outside the US, with no studies conducted in any national US cohorts. Additionally, studies have suggested that there are specific fall-related characteristics such as fall frequency and fall severity that increase subsequent fracture risk, but most existing studies of cataract surgery and falls have not examined these fall-related characteristics.[22-24] Finally, existing studies have focused on short-term falls following cataract surgery and have not assessed long term fall risk or accounted for the correlation of falls over time.

The purpose of the present study is to examine the association between cataract surgery and falls in the WHI population, which represents a large national cohort of US women. Specifically, this study will examine associations between cataract surgery and different frequencies of falling, and will additionally examine the occurrence of falls over a long duration of follow-up after cataract surgery or diagnosis.

2.3 Methods

2.3.1 Overview of the Women's Health Initiative

The WHI began in 1993 as a national health study designed to evaluate interventions for heart disease, breast and colorectal cancer, and osteoporotic fractures in postmenopausal women. Study recruitment was completed between 1993 and 1998 at 40 clinical centers in 24 states in the US. Eligible women were 50-79 years old and postmenopausal at the time of recruitment. Those who agreed to participate could either choose to be part of the Clinical Trial (CT) or Observational Study (OS) arms. The CT arm consisted of randomized trials evaluating hormone therapy, dietary modification, and calcium/vitamin D interventions, and eligible women in the CT cohort could be part of one, two, or all three trials. There were 68,132 women in the CT arm and 93,676 in the OS arm for a total of 161,808 participants enrolled in the WHI at baseline.[58]

Data collected at baseline for all participants included a questionnaire of demographics, medical history, reproductive history, family history, personal habits, diet, and thoughts and feelings, physical measurements of height, weight, and waist to hip ratio, and blood collection. Participants in the CT arm were followed up every six months, while participants of the OS arm were followed up annually.[59] Data collection for the main WHI study ended in 2005. Additional observational data were collected in two WHI extension studies from 2005-2010 and 2010-2015, but fall-related outcomes were not collected in the first of these extension studies.

2.3.2 Study population

For WHI participants who are also enrolled in Medicare, data from the WHI study has been linked on an individual level to all ICD-9-CM[50] diagnosis codes and CPT[51] procedure codes in the national Medicare database. The study population consisted of all participants of the WHI who were 65 years or older with an ICD-9-CM diagnosis code for cataract in the linked

Medicare database during the period of the WHI Main Study from 1993-2005 (Appendix 1). Because fall-related outcomes were not analyzed in the first WHI Extension Study, this study only used data from the WHI Main Study; WHI participants diagnosed with cataract after the completion of the WHI Main Study were not included, and fall-related outcomes examined in the second WHI Extension Study were not included. The study was approved by the Institutional Review Board at the University of California, Los Angeles.

2.3.3 Exposure

The exposure of interest was cataract surgery. The cataract surgery (exposed) group consisted of all patients with an ICD-9-CM diagnosis code for cataract and a CPT code for cataract surgery in Medicare (Appendix 1). The cataract diagnosis (unexposed) group consisted of all patients with an ICD-9-CM code for cataract without a CPT code for cataract surgery in Medicare. Patients in the cataract surgery group were followed starting from the date of the first service bill for cataract surgery. Patients in the cataract diagnosis group were followed from the date when the cataract diagnosis code first appeared.

Participants with an ICD-9-CM code for aphakia or pseudophakia without a CPT code for cataract surgery were the aphakic/pseudophakic group. Participants in the aphakic/pseudophakic group were analyzed by (1) excluding them from the study population completely, and (2) including them in the cataract surgery group and starting their follow-up from the first date when the aphakia or pseudophakia diagnosis appeared.

2.3.4 Outcome

The outcome of interest was the occurrence of falls after cataract surgery or diagnosis. The WHI follow-up form contained the question “Since your last medical update, how many times did you fall and land on the floor or ground?” Answer choices included none, one time, two times, and three or more times. Participants in the CT arm were asked this question every six months, while participants in the OS arm were asked this question every year. To examine fall frequency, two separate dichotomous outcomes were created of (1) reporting one or more falls versus not on a follow-up form within one year after cataract surgery or diagnosis, and (2) reporting two or more falls versus not on a follow-up form within one year after cataract surgery or diagnosis. To examine the occurrence of falls over the duration of the study period, participants were considered to have fallen at each follow-up time point if they reported falling at least once or at least twice on the follow-up form.

2.3.5 Covariates

Demographics that were collected included age, race, US region of residence, education level, annual income, and WHI study arm. All demographics were based on self-reported data at the time of WHI study enrollment. Age was analyzed as a continuous variable and also categorized into five-year age groups. Race, region of residence, and study arm were analyzed as categorical variables.

Both systemic and ocular comorbidities were included as covariates (Appendix 2). The CCI score[60,61] was used as a covariate to represent overall systemic health. The CCI is a weighted index of systemic disease burden based on the presence or absence of 17 systemic comorbidities, which include myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, cirrhosis, hepatic failure, immunosuppression, diabetes mellitus (DM) with or without complications, hemi/paraplegia, chronic renal disease, malignant neoplasms, multiple myeloma/leukemia, lymphomas, metastatic solid tumor, and AIDS. The CCI score variable was categorized into scores of 0, 1-2, 3-4, and ≥5. Ocular comorbidities included age-related macular degeneration (AMD), glaucoma, and DM with ophthalmic manifestations. For diseases where data was collected in both the WHI and Medicare, a participant was counted as having the disease if they either had the WHI indicator variable for the disease or the ICD-9-CM code for the disease within Medicare. For diseases where data was only collected in Medicare and not in the WHI, participants were counted as having the disease if they have the ICD-9-CM code for the disease within Medicare (Appendices 2 and 3).

As objective visual acuity data are not available within the WHI or Medicare, the presence of severe cataract subtypes was examined as a proxy for poor visual acuity. Patients with ICD-9-CM codes for subcapsular cataracts, total/mature cataract, hypermature cataract, and combined cataracts were considered to have severe cataract (Appendix 1).

Additional covariates that were collected included alcohol intake, physical activity, body mass index (BMI), and use of medications that increase fall risk, as these were considered potential confounders for the association between cataract surgery and falls. Self-reported alcohol intake was collected at study enrollment in the WHI and was categorized into non-drinker, past drinker, <1 drink per month, <1 drink per week, 1 to <7 drinks per week, and 7+ drinks per week. Physical activity was reported in the WHI as metabolic equivalent hours (METs) per week based on participant reports of different types of physical activity, and categorized into 0, >0 to <5, and ≥5 METs per week. This categorization was based on a previous categorization of METs in a validated model in the WHI used to assess fracture risk.[62] Medication data was collected at the WHI study baseline. Participants were asked to bring in all their medications to the first screening visit and these medications were recorded by study staff. Medications within the WHI database are categorized by Medication National Drug Codes

(NDCs). Participants who had NDCs for hypoglycemic agents, antiepileptic agents, and opioid analgesics were classified as using medications that increase fall risk.

2.3.6 Statistical analyses

Descriptive statistics were performed for all exposure, outcome, and covariate variables. Logistic regression modeling was used to conduct multivariable analyses for the association between (1) cataract surgery and one or more falls within one year and (2) cataract surgery and two or more falls within one year. Analyses were performed with an age-adjusted model and a fully adjusted model, which included all demographics, CCI score, ocular comorbidities, and additional fall-related risk factors as covariates in the model. As frequent falling is a potentially rare outcome, adjusted risk ratios were also calculated using a generalized linear model with a log link and negative binomial distribution, adjusting for the same covariates as the logistic regression models. To account for potential confounding by indication, propensity scores were constructed by regressing cataract surgery status on all covariates, and logistic regression analyses were conducted within propensity score strata for the same two outcomes. To additionally address potential confounding, a case-crossover comparison was conducted within the cataract surgery group by comparing the percentage of participants who reported one or more falls and two or more falls one year prior to cataract surgery versus one year following cataract surgery. These comparisons were conducted using McNemar's test for matched pairs. To assess for potential effect modification, stratified analyses were performed in age, CCI, and cataract severity subgroups for the association between cataract surgery and falling one or more times within one year of cataract surgery or diagnosis, and between cataract surgery and falling two or more times within one year of cataract surgery or diagnosis. To examine the association between cataract surgery and falls over the entire duration of the study period while accounting for the potential correlation of falls over time, a repeated measures model was created with cataract surgery status as the time-independent fixed effect and falling one or more times at each follow-up time point as the time-dependent outcome. All covariates mentioned above were included in the model, and the model assumed an autoregressive (AR1) correlation structure. All statistical analyses were conducted using SAS 9.4 (Cary, NC).

2.4 Results

2.4.1 Baseline characteristics

Baseline characteristics are described in Table 2.1. There were 37,380 women included in the study population who were followed for a mean of 1,562.4 ± 905.6 days. Of these women, 16,812 (45.0%) were in the cataract surgery group, 16,640 (44.5%) were in the cataract diagnosis group, and 3,928 (10.5%) were in the aphakic/pseudophakic group. The largest group of participants in the cataract surgery and aphakic/pseudophakic groups were 70-74 years old (n=6,108; 36.3% and n=1,321; 33.6%, respectively) and lived in the southern US (n=5,125; 30.5% and n=1,168; 29.7%, respectively), while the largest group of participants in the cataract diagnosis group were 65-69 years old (n=9,051; 54.4%) and lived in the northeastern US (n=4,748; 28.5%). In all three groups, the largest group of participants were white, completed more than high school, had an income less than $50,000 per year, and were enrolled in the OS arm of the WHI.

The largest group of participants in the cataract surgery group had a CCI score of 1-2 (n=6,741; 40.1%), while the largest group of participants in the cataract diagnosis and aphakic/pseudophakic groups had a CCI score of 0 (n=6,898; 41.5% and n=1,582; 40.2%, respectively). The CCI comorbidity with the highest prevalence in the cataract surgery group was chronic pulmonary disease (n=4,868; 29.0%), while the comorbidity in the cataract diagnosis and aphakic/pseudophakic groups with the highest prevalence was solid malignant neoplasm (n=3,727; 22.4% and n=1,028; 26.2%, respectively). In all three groups, the largest group of participants completed 5-12 METs per week and had a BMI less than 25. The ocular comorbidity with the highest prevalence in all three groups was glaucoma.

2.4.2 Risk of falls

Table 2.2 summarizes data on the risk of falls. In the cataract surgery group, approximately 27% of participants reported falling at least once in the year prior to cataract surgery and in the year immediately following cataract surgery, and approximately 10% of participants reported falling at least twice in the year prior to cataract surgery and in the year immediately following cataract surgery. These proportions applied both when the aphakic/pseudophakic group was excluded from the study population and included in the cataract surgery group.

In the cataract diagnosis group, approximately 23% of participants reported falling at least once in the year prior to cataract diagnosis and in the year immediately after cataract diagnosis. Approximately 8% of participants reported falling at least twice in the year prior to cataract surgery and in the year immediately after cataract surgery.

2.4.3 Associations between cataract surgery and falls within one year

Table 2.3 summarizes the association between cataract surgery and falls in participants of the WHI Main Study. In the age-adjusted model, participants in the cataract surgery group had 8% increased odds of falling at least once and 16% increased odds of falling at least twice within one year after surgery compared to participants in the cataract diagnosis group when the aphakic/pseudophakic group was excluded from the study population. The estimated effect sizes were similar when the aphakic/pseudophakic group was included in the cataract surgery group.

In the fully adjusted logistic regression model, cataract surgery did not appear to be associated with falling at least once within one year of surgery (OR=1.01, 95% CI=0.95, 1.08), but was potentially associated with increased odds of falling at least twice within one year of surgery (OR=1.06, 95% CI=0.97, 1.17) when the aphakic/pseudophakic group was excluded. When the aphakic/pseudophakic group was included in the cataract surgery group, cataract surgery was associated with increased odds of falling at least once (OR=1.08, 95% CI=1.02, 1.14) and falling at least twice (OR=1.08, 95% CI=1.00, 1.18) within one year of surgery when compared to the cataract diagnosis group.

In the fully adjusted generalized linear model, cataract surgery was associated with increased risk of falling at least once within one year of surgery (risk ratio [RR]=1.05; 95% CI=1.01, 1.11) and of falling at least twice within one year of surgery (RR=1.08; 95% CI=0.99, 1.17) when the aphakic/pseudophakic group was excluded. When the aphakic/pseudophakic group was included, cataract surgery was not associated with falling at least once within one year of surgery (RR=1.01; 95% CI=0.96, 1.07), but was potentially associated with increased risk of falling at least twice within one year of surgery (RR=1.06; 95% CI=0.97, 1.15).

2.4.4 Propensity score analyses

Table 2.4 summarizes results of propensity score analyses of the association between cataract surgery and falls in the WHI Main Study. There were no statistically significant associations between cataract surgery and falling at least once or at least twice within one year of surgery in any propensity score deciles, both when the aphakic/pseudophakic group was excluded from the study population and included in the cataract surgery group.

2.4.5 Case crossover comparison

Within the cataract surgery group, there appeared to be a similar proportion of participants who fell at least once in the year prior to surgery and in the year after surgery (Table 2.2). There was no statistically significant difference in the proportion of participants who fell at least once within one year preoperatively and postoperatively when the proportions were compared using McNemar's test for matched pairs (Table 2.5). There also appeared to be a similar proportion of participants who fell at least twice in the year prior to surgery and in the year after surgery, and there were also no statistically significant differences in these proportions (Tables 2.2 and 2.5).

2.4.6 Assessment of potential effect modifiers

Table 2.6 summarizes the results of effect modifier analysis. When examining the occurrence of one or more falls within one year of cataract surgery or diagnosis, there did not appear to be effect modification by age or CCI score. There was possible effect modification by cataract severity both when the aphakic/pseudophakic group was excluded and included (p for interaction=0.11 and 0.02, respectively). When the aphakic/pseudophakic group was excluded, in participants with severe cataract, there was a potential protective association between cataract surgery and falling one or more times within one year (OR=0.91; 95% CI=0.78, 1.06) while in participants without severe cataract, there was no association between cataract surgery and falling one or more times (OR=1.03; 95% CI=0.96, 1.10). Similar results were observed when the aphakic/pseudophakic group was included.

When examining the occurrence of two or more falls within one year of cataract surgery or diagnosis, there appeared to be potential effect modification by age, CCI score, and cataract severity. When the aphakic/pseudophakic group was excluded, there were potential protective associations between cataract surgery and falling two or more times in participants 80-84 years old (OR=0.78; 95% CI=0.53, 1.16) and with CCI score ≥5 (OR=0.80; 95% CI=0.61, 1.05). Cataract surgery was potentially associated with increased risk of falling two or more times in participants 65-69 years old (OR=1.11; 95% CI=0.94, 1.30), 70-74 years old (OR=1.15; 95% CI=0.99, 1.35), with CCI 1-2 (OR=1.17; 95% CI=1.01, 1.35), with CCI 3-4 (OR=1.12; 95% CI=0.91, 1.38), and with non-severe forms of cataract (OR=1.08; 95% CI=0.97, 1.19). Similar results were observed when the aphakic/pseudophakic group was excluded.

2.4.7 Associations between cataract surgery and falls over time

Table 2.7 summarizes the results of the repeated measures models examining the association between cataract surgery and falls over time in the WHI Main Study. In the age-adjusted models, participants in the cataract surgery group had 10-20% increased odds of falling one or more times and two or more times at any time after cataract surgery during the study period compared to participants in the cataract diagnosis group. These positive associations were maintained but attenuated in the fully adjusted models, with participants in the cataract surgery group having 2-10% increased odds of falling one or two or more times at any time compared to participants in the cataract diagnosis group. These associations were similar both when the aphakic/pseudophakic group was excluded from the study population and included in the cataract surgery group.

2.5 Discussion

This study found that in participants of the WHI with cataract, cataract surgery was potentially associated with increased risk of falling at high frequencies both in the short and long term postoperatively. Specifically, our results suggest that participants with cataract surgery were at increased risk of falling two or more times within one year after surgery and throughout the duration of study follow-up compared to participants with cataract without surgery. However, in stratified analyses, cataract surgery was potentially associated with decreased risk of falling two or more times in participants who were older and with the greatest systemic disease burden, while cataract surgery was potentially associated with increased risk of falling two or more times in participants who were younger, with moderate systemic disease burden, and with non-severe forms of cataract. This combination of findings suggests that cataract surgery may be protective against falling within one year of surgery in some but not all subsets of the elderly population. Additionally, the protective association between cataract surgery and falls in the older and sicker population may contribute to the previously reported protective association between cataract surgery and fractures in the US population.[6]

Cataract surgery was not consistently associated with increased fall risk in propensity score analyses, and a case-crossover comparison of participants with cataract surgery suggested that there was no difference in the risk of falls before and after cataract surgery. Given the findings of the propensity score analyses and case-crossover comparison, it is possible that the increased risk of falls in the cataract surgery group is explained at least in part by residual confounding. There was a higher proportion of participants in the cataract surgery group with high CCI scores, and it is possible that an increased systemic disease burden contributed to increased fall risk in this group, but that this disease burden was not fully accounted for by the CCI score. Additionally, we used the presence of severe cataract as a proxy for visual impairment as visual acuity data were not available within the WHI database. Given the well-established association between visual impairment and increased fall risk[7,27,54-57], it is possible that there is residual confounding from vision impairment due to conditions other than severe cataract that we were unable to account for in this study.

Only one previous study[28] in the literature has examined the association between cataract surgery and falls in the US. This study examined a cohort of 214 patients from ten ophthalmology practices and two optometry clinics in Birmingham, Alabama. The study reported that in patients with cataract, there was no association between cataract surgery and falls, mobility, or having balance difficulties within one year of cataract surgery or the baseline visit. The varying combination of findings from the present study and the previous literature suggests the need for further studies of potential explanations for the protective association between cataract surgery and fractures, including outcomes such as fall severity, frailty, and specific aspects of systemic disease related to fracture risk such as bone density and nutritional status.

The limitations of this study are mainly related to its observational nature. Since the study population is created based on people who voluntarily participate in the WHI, it is possible that participants in the study are differentially lost with regard to cataract surgery and fall status which would lead to selection bias in this cohort. Another potential source of selection bias is the inclusion of the aphakic/pseudophakic group, as this group appeared to be healthier at baseline compared to the cataract surgery group. However, study results overall remained consistent whether the aphakic/pseudophakic group was included or excluded. Another potential limitation is the possibility of misclassification of study variables, but this was minimized with the linkage of WHI and Medicare data. Additionally, since both WHI and Medicare data are recorded prior to participants developing the falls outcome, it is unlikely that the exposure and covariates would be differentially misclassified with regard to the outcome. Additionally, the cataract surgery group was followed starting from the date of cataract surgery, which was the time where it was decided to perform a clinical intervention for a visually significant cataract. However, the cataract diagnosis group was followed from the date the cataract diagnosis first appeared in Medicare, and this time may not have consistently represented the same clinical stage of disease for all participants with a diagnosis of cataract who did not undergo surgery. Therefore, findings in the cataract diagnosis group may have been biased if participants had varying stages of cataract due to follow-up starting from different stages of disease. Finally, there is a possibility of residual confounding which was previously discussed.

The main strength of this study is the ability to assess the association between cataract surgery and falls in a large cohort of US women. In other large generalizable US databases such as Medicare, falls are not routinely coded and therefore cannot be used as a reliable outcome measure. Additionally, because one of the original aims of the WHI study was to assess potential interventions for the prevention of osteoporotic fractures, we were able to include several covariates related to fall risk such as alcohol use and physical activity that are not routinely available in large administrative databases. Finally, the long duration of follow-up in the WHI allowed the examination of fall occurrence over an extended period of time.

In summary, this study found that in WHI participants with cataract, cataract surgery was potentially associated with overall increased risk of falling at higher frequencies, but that cataract surgery was potentially protective against falling in older and sicker patients. Additional studies are needed to further examine the mechanisms of association between cataract surgery, falls, and fractures in the US population.

2.6 Tables

Table 2.1. Baseline Characteristics of Patients with Cataract in the Women's Health Initiative (WHI) Main Study from 1993-2005 (n=37,380)

	Number (%) of Participants with Characteristic		
	Cataract Surgery Group; n=16,812	**Cataract Diagnosis Group; n=16,640**	**Aphakia/Pseudophakia Group; n=3,928**
Age Group (Years)			
65-69	4,050 (24.1)	9,051 (54.4)	1,083 (27.6)
70-74	6,108 (36.3)	5,070 (30.5)	1,321 (33.6)
75-79	5,137 (30.6)	2,169 (13.0)	1,202 (30.6)
80-84	1,449 (8.6)	332 (2.0)	303 (7.7)
≥85	68 (0.4)	18 (0.1)	19 (0.5)
WHI Study Arm			
Clinical Trial	7,223 (43.0)	7,494 (45.0)	1,541 (39.2)
Observational Study	9,589 (57.0)	9,146 (55.0)	2,387 (60.8)
Race			
White	15,106 (90.1)	14,385 (86.6)	3,570 (90.9)
Black/African American	876 (40.3)	1,299 (7.8)	171 (4.4)
Asian/Pacific Islander	308 (1.8)	379 (2.3)	73 (1.9)
Hispanic/Latino	302 (1.8)	335 (2.0)	55 (1.4)
American Indian/Alaskan Native	48 (0.3)	51 (0.3)	12 (0.3)
Other	135 (0.8)	155 (0.9)	37 (0.9)
Unknown	37(0.0)	36 (0.0)	10 (0.3)
Region of United States Residence			
Northeast	3,707 (22.0)	4,748 (28.5)	686 (17.5)
West	3,564 (21.2)	4,147 (19.2)	993 (25.3)
Midwest	4,416 (26.3)	4,551 (27.4)	1,081 (27.5)
South	5,125 (30.5)	3,194 (24.9)	1,168 (29.7)
Education Level			
High School or Less[a]	6,046 (36.1)	5,696 (34.4)	1,398 (35.6)
More than High School[b]	10,690 (63.9)	10,860 (65.6)	2,505 (63.8)
Unknown	76 (0.0)	84 (0.0)	25 (0.6)
Annual Income			
<$50,000	11,128 (70.9)	10,331 (66.8)	2,724 (69.3)
≥$50,000	4,558 (29.1)	5,147 (33.3)	951 (24.2)
Unknown	1,126 (0.1)	1,162 (0.1)	253 (6.4)
Charlson Comorbidity Index (CCI) Score			
0	4,393 (26.1)	6,898 (41.5)	1,582 (40.2)
1-2	6,741 (40.1)	6,598 (39.7)	1,500 (38.2)
3-4	3,635 (21.6)	2,255 (13.6)	582 (14.8)
≥5	2,043 (12.2)	889 (5.3)	264 (6.7)
Systemic Comorbidities in the CCI			
Myocardial Infarction	1,980 (11.8)	1,346 (8.1)	428 (10.9)
Congestive Heart Failure	2,026 (12.1)	1,026 (6.2)	316 (8.0)
Peripheral Vascular Disease	2,891 (17.2)	1,466 (8.8)	419 (10.7)
Cerebrovascular Disease	3,235 (19.2)	1,591 (9.6)	429 (10.9)
Dementia	238 (1.4)	138 (0.8)	47 (1.2)
Chronic Pulmonary Disease[c]	4,868 (29.0)	2,804 (16.9)	686 (17.5)
Chronic Renal Disease	393 (2.3)	148 (0.9)	55 (1.4)
Connective Tissue Disease	1,699 (10.1)	884 (5.3)	219 (5.6)
Peptic Ulcer Disease	1,893 (11.3)	1,354 (8.1)	454 (11.6)
Diabetes Mellitus (DM) Without Complications	2,976 (17.7)	1,915 (11.5)	357 (9.1)
DM With Complications	61 (0.4)	55 (0.3)	10 (0.3)
Hemiplegia	252 (1.5)	131 (0.8)	32 (0.8)
Leukemia/Multiple Myeloma	128 (0.8)	98 (0.6)	14 (0.4)

Lymphoma	183 (1.1)	129 (0.8)	25 (0.6)
Solid Malignant Neoplasm	4,540 (27.0)	3,727 (22.4)	1,028 (26.2)
Metastatic Solid Malignant Neoplasm	387 (2.3)	293 (1.8)	34 (0.8)
Mild Liver Disease	865 (5.2)	532 (3.2)	110 (2.8)
Moderate/Severe Liver Disease	19 (0.0)	10 (0.0)	3 (0.1)
Acquired Immune Deficiency Syndrome	11 (0.0)	3 (0.0)	2 (0.1)
Alcohol Intake			
Non-Drinker	2,101 (12.6)	1,947 (11.8)	500 (12.7)
Past Drinker	3,229 (19.4)	3,028 (18.3)	782 (19.9)
<1 Drink Per Month	1,881 (11.3)	1,929 (11.7)	419 (10.7)
<1 Drink Per Week	3,310 (19.9)	3,381 (20.5)	789 (20.1)
1 to <7 Drinks Per Week	4,015 (24.1)	4,300 (26.0)	915 (23.3)
7+ Drinks Per Week	2,142 (12.8)	1,942 (11.8)	482 (12.3)
Unknown	134 (0.0)	113 (0.0)	41 (1.0)
Medications Increasing Fall Risk			
Hypoglycemics	1,027 (6.1)	895 (5.4)	251 (6.4)
Narcotics	723 (4.3)	541 (3.3)	199 (5.1)
Sedatives	2,252 (13.4)	1907 (11.5)	577 (14.7)
Metabolic Equivalent Tasks (METs) Per Week			
0	2,367 (14.9)	2,312 (14.7)	624 (15.9)
1-4	3,316 (20.9)	3,271 (20.8)	852 (21.7)
5-12	10,187 (64.2)	10,156 (64.5)	2,297 (58.5)
Unknown	942 (0.1)	901 (0.1)	155 (3.9)
Body Mass Index			
<25	6,081 (36.2)	5952 (35.8)	1,478 (37.6)
25-29	5,051 (30.0)	4916 (29.5)	1,183 (30.1)
>29	5,680 (33.4)	5772 (34.7)	1,267 (32.3)
Ocular Comorbidities			
Age-Related Macular Degeneration	3,356 (20.0)	1,706 (10.3)	448 (11.4)
DM with Ophthalmic Manifestations	680 (4.0)	376 (2.3)	82 (2.1)
Glaucoma	4,080 (24.3)	2,405 (14.5)	522 (13.3)
Severe Cataract[d]	7,398 (44.0)	1,286 (7.7)	107 (2.7)

[a]Includes no school, 1-4 years of grade school, 5-8 years of grade school, some high school, high school diploma or GED

[b]Includes vocational/training school, some college/associate degree, college graduate/baccalaureate degree, some post-graduate or professional, master's degree, doctoral degree

[c]Includes chronic bronchitis, emphysema, asthma, bronchiectasis, alveolitis, chronic airway obstruction, pneumoconioses, and asbestosis

[d]Includes anterior and posterior subcapsular cataracts, total/mature cataract, hypermature cataract, combined forms of cataract

Table 2.2. Risk of Falls in Patients with Cataract Surgery versus Cataract Diagnosis in the Women's Health Initiative (WHI) Main Study from 1993-2005 (n=37,380)

Excluding Aphakic/Pseudophakic Group in Exposed Group		
	Cataract Surgery Group; n=16,812	**Cataract Diagnosis Group; n=16,640**
Number (%) of Participants with One or More Falls within One Year Before Cataract Surgery or Diagnosis	3,961 (27.0)[a]	3,954 (23.8)[a]
Number (%) of Participants with One or More Falls within One Year After Cataract Surgery or Diagnosis	4,525 (26.9)	2,943 (22.8)
Number (%) of Participants with Two or More Falls within One Year Before Cataract Surgery or Diagnosis	1,564 (10.7)[a]	1,439 (8.7)[a]
Number (%) of Participants with Two or More Falls within One Year After Cataract Surgery or Diagnosis	1,793 (10.7)	1,054 (8.2)
Including Aphakic/Pseudophakic Group in Exposed Group		
	Cataract Surgery Group; n=20,740	**Cataract Diagnosis Group; n=16,640**
Number (%) of Participants with One or More Falls within One Year Before Cataract Surgery or Diagnosis	4,662 (27.2)[b]	2,943 (22.8)[b]
Number (%) of Participants with One or More Falls within One Year After Cataract Surgery or Diagnosis	5,717 (27.6)	3,954 (23.8)
Number (%) of Participants with Two or More Falls within One Year Before Cataract Surgery or Diagnosis	1,849 (10.8)[b]	1,054 (8.2)[b]
Number (%) of Participants with Two or More Falls within One Year After Cataract Surgery or Diagnosis	2,232 (10.8)	1,439 (8.7)

[a]n=14,668 in cataract surgery group and n=12,935 in cataract diagnosis group

[b]n=17,153 in cataract surgery group and n=12,935 in cataract diagnosis group

Table 2.3. Risk of Falls in Patients with Cataract Surgery versus Cataract Diagnosis in the Women's Health Initiative (WHI) Main Study from 1993-2005 (n=37,380)

Excluding Aphakic/Pseudophakic Group from Exposed Group		
Model Type	**Odds Ratio (95% Confidence Interval); One or More Falls Following Cataract Surgery or Diagnosis[a]**	**Odds Ratio (95% Confidence Interval); Two or More Falls Following Cataract Surgery or Diagnosis[a]**
Age-Adjusted	1.08 (1.03, 1.14)	1.16 (1.08, 1.26)
Fully Adjusted[b]	1.01 (0.95, 1.08)	1.06 (0.97, 1.17)
Fully Adjusted Risk Ratio[b,c]	1.05 (1.01, 1.11)	1.08 (0.99, 1.17)
Including Aphakic/Pseudophakic Group in Exposed Group		
Model Type	**Odds Ratio (95% Confidence Interval); One or More Falls Following Cataract Surgery or Diagnosis[a]**	**Odds Ratio (95% Confidence Interval); Two or More Falls Following Cataract Surgery or Diagnosis[a]**
Age-Adjusted	1.12 (1.06, 1.18)	1.17 (1.09, 1.26)
Fully Adjusted[b]	1.08 (1.02, 1.14)	1.08 (1.00, 1.18)
Fully Adjusted Risk Ratio[b,c]	1.01 (0.96, 1.07)	1.06 (0.97, 1.15)

[a]Cataract diagnosis group was used as a reference

[b]Adjusted for age, WHI study arm, race, sex, region of residence, education level, income, Charlson Comorbidity Index (CCI) score, alcohol intake, medications increasing fall risk, physical activity, body mass index, cataract severity, age-related macular degeneration, glaucoma, and diabetic retinopathy

[c]Risk ratio calculated using a generalized linear model with log link and negative binomial distribution

Table 2.4. Risk of Falls by Propensity Score Subgroup in Patients with Cataract Surgery versus Cataract Diagnosis in the Women's Health Initiative (WHI) Main Study from 1993-2005 (n=37,380)

Propensity Score Decile Subgroup a	Excluding Aphakic/Pseudophakic Group from Exposed Group		Including Aphakic/Pseudophakic Group in Exposed Group	
	OR (95% CI) of One or More Falls Following Cataract Surgery or Diagnosis[b]	OR (95% CI) of Two or More Falls Following Cataract Surgery or Diagnosis[b]	OR (95% CI) of One or More Falls Following Cataract Surgery or Diagnosis[b]	OR (95% CI) of Two or More Falls Following Cataract Surgery or Diagnosis[b]
1	0.87 (0.65, 1.16)	1.17 (0.77, 1.79)	0.92 (0.73, 1.15)	1.14 (0.82, 1.60)
2	1.09 (0.87, 1.37)	1.28 (0.91, 1.80)	1.22 (1.01, 1.48)	1.38 (1.04, 1.83)
3	1.09 (0.89, 1.32)	1.13 (0.85, 1.50)	1.17 (0.99, 1.39)	1.13 (0.88, 1.45)
4	1.10 (0.92, 1.32)	1.23 (0.93, 1.61)	1.13 (0.96, 1.33)	1.19 (0.93, 1.52)
5	1.06 (0.90, 1.25)	1.18 (0.93, 1.50)	1.16 (0.99, 1.35)	1.17 (0.94, 1.47)
6	1.03 (0.87, 1.21)	1.07 (0.84, 1.36)	1.08 (0.92, 1.27)	1.07 (0.84, 1.35)
7	0.90 (0.76, 1.06)	0.86 (0.67, 1.10)	1.00 (0.85, 1.18)	0.94 (0.74, 1.19)
8	1.01 (0.84, 1.22)	1.06 (0.81, 1.39)	0.97 (0.81, 1.16)	1.11 (0.86, 1.45)
9	0.88 (0.70, 1.10)	0.87 (0.64, 1.19)	0.97 (0.79, 1.20)	0.80 (0.61, 1.05)
10	0.89 (0.63, 1.25)	0.71 (0.46, 1.10)	0.86 (0.63, 1.16)	0.79 (0.53, 1.19)

OR = odds ratio; CI = confidence interval

[a]Propensity score of cataract surgery was calculated based on following factors: age, WHI study arm, race, sex, region of residence, education level, income, Charlson Comorbidity Index (CCI) score, alcohol intake, medications increasing fall risk, physical activity, body mass index, cataract severity, age-related macular degeneration, glaucoma, and diabetic retinopathy

[b]Cataract diagnosis group was used as a reference

Table 2.5. Case Crossover Comparison of Fall Risk in Patients Before and After Cataract Surgery in the Women's Health Initiative (WHI) Main Study from 1993-2005 (n=20,740)

	P-Value for McNemar's Test of Matched Pairs	
Period of Comparison for Fall Risk	**Excluding Aphakic/Pseudophakic Group from Exposed Group**	**Including Aphakic/Pseudophakic Group in Exposed Group**
One Year Before Cataract Surgery versus One Year After Cataract Surgery	0.29	0.74
Two Years Before Cataract Surgery versus Two Years After Cataract Surgery	0.34	0.59

Table 2.6. Odds of Falls in Participants with Cataract Surgery versus Cataract Diagnosis by Age, Charlson Comorbidity Index (CCI) Score, and Cataract Severity in the Women's Health Initiative (WHI) Main Study from 1993-2005 (n=37,380)

	Excluding Aphakic/Pseudophakic Group from Study Population	Including Aphakic/Pseudophakic Group in the Cataract Surgery Group
Age	**Adjusted Odds Ratio (95% Confidence Interval) of ≥1 Falls After Cataract Surgery versus Diagnosis[a]**	**Adjusted Odds Ratio (95% Confidence Interval) of ≥1 Falls After Cataract Surgery versus Diagnosis[a]**
65-69	1.00 (0.90, 1.11)	1.07 (0.97, 1.18)
70-74	1.08 (0.97, 1.20)	1.11 (1.01, 1.22)
75-79	0.94 (0.82, 1.27)	1.02 (0.90, 1.16)
80-84	0.92 (0.68, 1.24)	1.02 (0.77, 1.36)
≥85	1.22 (0.22, 12.16)	1.37 (0.22, 8.60)
P for interaction	0.23	0.32
CCI Score	**Adjusted Odds Ratio (95% Confidence Interval) of ≥1 Falls After Cataract Surgery versus Diagnosis[b]**	**Adjusted Odds Ratio (95% Confidence Interval) of ≥1 Falls After Cataract Surgery versus Diagnosis[b]**
0	0.99 (0.88, 1.12)	1.06 (0.96, 1.17)
1-2	1.03 (0.94, 1.14)	1.11 (1.02, 1.22)
3-4	1.02 (0.88, 1.18)	1.02 (0.92, 1.21)
≥5	1.02 (0.82, 1.25)	1.03 (0.85, 1.26)
P for interaction	0.35	0.70
Cataract Severity	**Adjusted Odds Ratio (95% Confidence Interval) of ≥1 Falls After Cataract Surgery versus Diagnosis[c]**	**Adjusted Odds Ratio (95% Confidence Interval) of ≥1 Falls After Cataract Surgery versus Diagnosis[c]**
Severe	0.91 (0.78, 1.06)	0.91 (0.78, 1.06)
Not Severe	1.03 (0.96, 1.10)	1.10 (1.03, 1.17)
P for interaction	0.11	0.02
Age	**Adjusted Odds Ratio (95% Confidence Interval) of ≥2 Falls After Cataract Surgery versus Diagnosis[a]**	**Adjusted Odds Ratio (95% Confidence Interval) of ≥2 Falls After Cataract Surgery versus Diagnosis[a]**
65-69	1.11 (0.94, 1.30)	1.12 (0.98, 1.29)
70-74	1.15 (0.99, 1.35)	1.16 (1.00, 1.34)
75-79	0.95 (0.79, 1.16)	0.98 (0.82, 1.18)
80-84	0.78 (0.53, 1.16)	0.86 (0.59, 1.25)
≥85	--[d]	--[d]
P for interaction	0.14	0.32
CCI Score	**Adjusted Odds Ratio (95% Confidence Interval) of ≥2 Falls After Cataract Surgery versus Diagnosis[b]**	**Adjusted Odds Ratio (95% Confidence Interval) of ≥2 Falls After Cataract Surgery versus Diagnosis[b]**
0	1.01 (0.84, 1.21)	1.00 (0.86, 1.18)
1-2	1.17 (1.01, 1.35)	1.21 (1.06, 1.38)
3-4	1.12 (0.91, 1.38)	1.14 (0.94, 1.38)
≥5	0.80 (0.61, 1.05)	0.81 (0.63, 1.05)
P for interaction	0.55	0.55
Cataract Severity	**Adjusted Odds Ratio (95% Confidence Interval) of ≥2 Falls After Cataract Surgery versus Diagnosis[c]**	**Adjusted Odds Ratio (95% Confidence Interval) of ≥2 Falls After Cataract Surgery versus Diagnosis[c]**
Severe	0.94 (0.74, 1.18)	0.93 (0.74, 1.17)
Not Severe	1.08 (0.97, 1.19)	1.10 (1.00, 1.21)
P for interaction	0.22	0.13

[a]Adjusted for age as a continuous variable, race, region of residence, education level, annual income, CCI score, cataract severity, age-related macular degeneration, glaucoma, diabetic retinopathy, alcohol intake, medication use, metabolic equivalent tasks per week, and body mass index

[b]Adjusted for age, race, region of residence, education level, annual income, cataract severity, age-related macular degeneration, glaucoma, diabetic retinopathy, alcohol intake, medication use, metabolic equivalent tasks per week, and body mass index

[c]Adjusted for age, race, region of residence, education level, annual income, CCI score, age-related macular degeneration, glaucoma, diabetic retinopathy, alcohol intake, medication use, metabolic equivalent tasks per week, and body mass index

[d]Model unable to converge due to small cell sizes

Table 2.7. Repeated Measures Model of Fall Risk in Patients with Cataract Surgery versus Cataract Diagnosis in the Women's Health Initiative (WHI) from 1993-2013 (n=37,380)

Excluding Aphakic/Pseudophakic Group from Exposed Group		
Model Coefficient	**Age-Adjusted Model**	**Fully Adjusted Model[b]**
≥1 Falls		
Cataract Surgery	0.0938 (0.0492, 0.1385)	0.0203 (-0.0309, 0.0716)
Cataract Surgery*Time	-0.0003 (-0.0006, 0.0001)	0.0002 (-0.0002, 0.0006)
OR (95% CI)[a]	1.09 (1.05, 1.15)	1.02 (0.97, 1.07)
≥2 Falls		
Cataract Surgery	0.1902 (0.1186, 0.2619)	0.0962 (0.0150, 0.1774)
Cataract Surgery*Time	-0.0007 (-0.0012, 0.0001)	0.0000 (-0.0006, 0.0006)
OR (95% CI)[a]	1.21 (1.12, 1.30)	1.10 (1.01, 1.19)
Including Aphakic/Pseudophakic Group in Exposed Group		
Model Coefficient	**Age-Adjusted Model**	**Fully Adjusted Model[b]**
≥1 Falls		
Cataract Surgery	0.1168 (0.0748, 0.1588)	0.0540 (0.0068, 0.1011)
Cataract Surgery*Time	-0.0003 (-0.0007, 0.0000)	0.0000 (-0.0003, 0.0004)
OR (95% CI)[a]	1.12 (1.08, 1.17)	1.06 (1.01, 1.12)
≥2 Falls		
Cataract Surgery	0.1886 (0.1210, 0.2563)	0.0913 (0.0162, 0.1663)
Cataract Surgery*Time	-0.0006 (-0.0011, 0.0001)	-0.0001 (-0.0007, 0.0005)
OR (95% CI)[a]	1.21 (1.13, 1.29)	1.10 (1.02, 1.18)

OR=odds ratio, CI=confidence interval

[a]Cataract diagnosis group was used as a reference

[b]Adjusted for age, WHI study arm, race, sex, region of residence, education level, income, Charlson Comorbidity Index (CCI) score, alcohol intake, medications increasing fall risk, physical activity, body mass index, cataract severity, age-related macular degeneration, glaucoma, and diabetic retinopathy

Chapter 3: Cataract Surgery and Mortality in the United States Medicare Population

3.1 Abstract

Purpose: To determine the association between cataract surgery and all-cause mortality in US Medicare patients with cataract.

Methods: The study population included a 5% random sample of US Medicare beneficiaries with cataract from the 2002-2012 Denominator and Physician/Supplier Part B files. The exposure of interest was cataract surgery and the outcome of interest was all-cause mortality at any time during the study period. Baseline characteristics that were examined included demographics, systemic comorbidities in the CCI, and ocular comorbidities. Cox proportional hazards regression modeling was used to assess the association between cataract surgery and mortality, adjusting for all baseline covariates. Additional subgroup analyses were performed in propensity score deciles and within strata of age, sex, systemic disease burden, and cataract severity.

Results: There were 1,501,420 patients with cataract in the 5% Medicare sample, of whom 544,984 (36.3%) received cataract surgery. The incidence of mortality was 2.78 deaths per 100 person-years in patients who received cataract surgery and 2.98 deaths per 100 person-years in patients who did not receive cataract surgery ($p<0.0001$). In the overall study population, patients with cataract surgery had lower adjusted hazards of mortality compared to patients without cataract surgery (hazards ratio [HR]=0.73, 95% CI=0.72, 0.74). The strongest protective associations between cataract surgery and mortality were observed in patients most likely to receive cataract surgery based on high propensity score decile (HR=0.52, 95% CI=0.50, 0.54), patients 80-84 years old (HR=0.63, 95% CI=0.62, 0.65), females (HR=0.69, 95% CI=0.68, 0.70), patients with a moderate systemic disease burden based on CCI Score (HR=0.71, 95% CI=0.69, 0.72), and patients with severe cataract (HR=0.68, 95% CI=0.66, 0.70).

Conclusions: In a national cohort of US Medicare beneficiaries with cataract, cataract surgery was associated with decreased long term all-cause mortality in the overall study population and in multiple subgroups. Further studies are needed of the benefits of cataract surgery beyond vision improvement.

3.2 Introduction

Cataracts are a leading cause of visual impairment among adults in the United States (US).[1,2] Visual impairment secondary to cataracts has been shown to be associated with increased mortality, likely secondary to a combination of poor systemic health, lower functional status, and decreased quality of life.[8,12,35] Cataract surgery is the mainstay of treatment for visually significant cataract and serves to reverse the vision impairment associated with cataract. While the vision-improving benefits of cataract surgery are well understood, it is unknown whether vision improvement from cataract surgery can subsequently improve long term survival.

Previous studies have examined the association between cataract surgery and mortality with conflicting findings. Only two existing studies[48,49] have examined the association between cataract surgery and mortality in a cohort of patients entirely with cataract, and both of these studies found that cataract surgery was associated with decreased mortality. However, both of these studies were conducted in cohorts within Western Sydney, Australia, and it is unknown whether their findings are generalizable to the US population. The remainder of studies examining the association between cataract surgery and mortality[7,12,35,39-47] have all included patients without cataract in the comparison group, which could lead to confounded findings as any associations detected between cataract surgery and mortality could be explained by the presence of cataract rather than by the intervention of cataract surgery.

Given the conflicting findings in previous studies of cataract surgery and mortality, further studies are warranted, especially in the US population. To this end, the purpose of the present study is to examine the association between cataract surgery and all-cause mortality in patients with cataract in the national US Medicare population between 2002 and 2012.

3.3 Methods

3.3.1 Study population

Data were extracted from a 5% random sample of Medicare beneficiaries from the 2002-2012 Denominator and Physician/Supplier Part B files from the Centers for Medicare and Medicaid Services (CMS). Patients with an ICD-9-CM[50] code for cataract during this time period were included in the study population (Appendix 1). Patients with the following characteristics were excluded: age less than 65 years, residence outside the 50 states of the US or the District of Columbia, lack of Medicare Part B coverage, and coverage from a health maintenance organization outside of CMS. The study was approved by the Institutional Review Board at the University of California, Los Angeles.

3.3.2 Exposure

The cataract surgery group was the exposed group and consisted of all patients with an ICD-9-CM diagnosis code for cataract and a CPT[51] code for cataract surgery (Appendix 1). The cataract diagnosis group was the unexposed group and consisted of all patients with an ICD-9-CM diagnosis code for cataract without a CPT code for cataract surgery. Patients in the cataract surgery group were followed starting from the fiscal quarter with the first service bill for cataract surgery. Patients in the cataract diagnosis group were followed starting from the fiscal quarter when the ICD-9-CM code for cataract first appeared.

Patients with an ICD-9-CM code for aphakia or pseudophakia without a CPT code for cataract surgery were included in the aphakic/pseudophakic group (Appendix 1). The aphakic/pseudophakic group was analyzed two ways, by (1) excluding them from the study population entirely and (2) including them in the exposed group. When included, patients in the aphakic/pseudophakic group were followed from the fiscal quarter when the ICD-9-CM code for aphakia or pseudophakia first appeared.

3.3.3 Outcome

The outcome of interest was all-cause mortality at any time from patient inclusion in the study until the end of the study period on December 31, 2012. Mortality status was ascertained from an indicator variable in the CMS Denominator File. Deaths of Medicare beneficiaries were automatically reported to CMS by the US Social Security Administration (SSA).[63] Data regarding the cause of death was not available in the Physician/Supplier Part B files.

For the cataract surgery group, the time-to-event variable was generated by calculating the number of fiscal quarters between the quarter of cataract surgery and the quarter of mortality from any cause. For the cataract diagnosis group, the time-to-event variable was generated by calculating the number of fiscal quarters between the quarter of cataract diagnosis and the quarter of mortality from any cause. For both groups, patients who were still alive at the end of the study period were administratively censored after the last fiscal quarter of 2012. Patients who were lost to follow-up without a confirmed death before the end of the study period were censored during the last quarter in which they had administrative data available within CMS.

To account for potential lead-time bias from starting follow-up in the cataract surgery group at a potentially later stage of disease compared to the cataract diagnosis group, an alternative time-to-event variable was created for the cataract surgery group taking the time between cataract diagnosis and cataract surgery into account. This variable was created by determining the median number of quarters between cataract diagnosis and cataract surgery for patients in the cataract surgery group, and adding this duration of time to the original time-to-event variable for all patients in the cataract surgery group.

3.3.4 Covariates

Demographics that were collected included age, sex, self-reported race/ethnicity, and US region of residence. Age was analyzed as a continuous variable and also categorized into five-year age groups that truncated at age 98, because all patients 98 years and older are coded as age 98 in the Medicare database. Sex, race/ethnicity, and region of residence were analyzed as categorical variables.

Both systemic and ocular comorbidities were included as covariates in the study. The CCI score[60,61], which was described in Chapter 2, was used as a covariate to represent overall systemic health. The CCI score variable was categorized into scores of 0, 1-2, 3-4, and ≥5. Ocular comorbidities that were examined included AMD, glaucoma, and DM with ophthalmic manifestations. Determination of the presence of systemic and ocular comorbidities was based on the presence of ICD-9-CM codes for these conditions (Appendix 2).

As visual acuity data are not available within Medicare, one additional baseline characteristic that was examined was the presence of severe cataract subtypes as a proxy for these factors. Patients with ICD-9-CM codes for anterior and posterior subcapsular cataracts, total/mature cataract, hypermature cataract, and combined forms of cataract were considered as having severe forms of cataract (Appendix 1). These subtypes were grouped into one indicator variable representing the presence or absence of severe cataract.

3.3.5 Statistical analysis

Continuous variables were analyzed using descriptive statistics and histograms. Categorical variables were analyzed using frequency distributions and contingency tables. Cox proportional hazards regression was used to analyze the association between cataract surgery and time to death from any cause, using both the original and alternative time-to-event variables for the cataract surgery group as described earlier. Data were analyzed with an age and sex-adjusted model, and a fully adjusted model including all demographics, each individual disease included in the CCI, ocular comorbidities, and cataract severity as covariates. Kaplan-Meier curves and log-negative-log plots were used to check the proportional hazards assumption. In case of potential violation of the proportional hazards assumption, the association between cataract surgery and mortality was further assessed using an accelerated failure time model with log-normal distribution, adjusting for all baseline covariates. To address potential confounding by indication, propensity scores were created by regressing cataract surgery status on all covariates, and comparisons were made in propensity score decile subgroups with cataract surgery status as the exposure and time to death as the outcome. To assess for potential effect measure modification, stratified analyses were conducted within age, sex, CCI score, and severe cataract subgroups. All statistical analyses were conducted using SAS version 9.3 (Cary, North Carolina).

3.4 Results

3.4.1 Baseline characteristics

Baseline demographics and comorbidities are described in Table 3.1. There were 1,501,420 patients with cataract in the 2002-2012 Medicare population included in the study followed for a mean of 13.0±12.0 quarters. Of these patients, there were 544,984 (36.3%) patients in the cataract surgery group, 715,405 (47.6%) patients in the cataract diagnosis group, and 241,031 (16.1%) patients in the aphakic/pseudophakic group.

The largest group of patients in the cataract surgery group were 75 to 79 years old (n=142,009; 26.1%), while the largest group of patients in the cataract diagnosis group were 65 to 69 years old (n=346,245; 48.4%) and the largest group of patients in the aphakic/pseudophakic group were ≥85 years old (n=53,026; 22.0%). In all three groups, the largest group of patients were female, white, and lived in the Eastern US. The largest group of patients had a CCI score of one to two in the cataract surgery and aphakic/pseudophakic groups (n=223,294; 41.0% and n=98,136; 40.7%, respectively), while the largest group of patients in the cataract diagnosis group had a CCI score of zero (n=281,531; 39.4%). In the cataract surgery and aphakic/pseudophakic groups, the CCI comorbidity with the highest prevalence was chronic pulmonary disease (n=119,169; 21.9% and n=54,632; 22.7%, respectively), while the comorbidity with the highest prevalence in the cataract diagnosis group was uncomplicated diabetes (n=134,324; 18.8%). The ocular comorbidity with the highest prevalence in all three groups was AMD. There were 222,663 patients (40.9%) in the cataract surgery group, 68,008 patients (9.5%) in the cataract diagnosis group, and 6,295 patients (2.6%) in the aphakic/pseudophakic group with severe cataract.

3.4.2 Mortality incidence

Data on mortality incidence are summarized in Table 3.2. In the cataract surgery group, the incidence of mortality at any time during the study period was 2.78 deaths per 100 person-years when time between cataract diagnosis and cataract surgery was excluded, and 1.72 deaths per 100 person-years when time between cataract diagnosis and cataract surgery was included. The incidence of mortality was 2.98 deaths per 100 person-years in the cataract diagnosis group and 3.76 deaths per 100 person-years in the aphakic/pseudophakic group.

3.4.3 Association between cataract surgery and mortality

Data examining the associations between cataract surgery and mortality are outlined in Table 3.3. When the aphakic/pseudophakic group was excluded from the study population and when time between cataract diagnosis and cataract surgery was excluded, cataract surgery was associated with decreased hazards of mortality in the age and sex-adjusted model (HR=0.69;

95% CI=0.68, 0.70). This protective association maintained after adjusting for demographics, systemic comorbidities, and ocular comorbidities (HR=0.72; 95% CI=0.71, 0.73). These associations were in the same direction but much stronger when time between cataract diagnosis and cataract surgery was included (adjusted HR=0.37; 95% CI=0.36, 0.37). When the aphakic/pseudophakic group was included in the exposed group, cataract surgery was associated with decreased hazards of mortality in the age and sex-adjusted model (HR=0.71; 95% CI=0.70, 0.72) and in the fully adjusted model (HR=0.73; 95% CI=0.72, 0.74). In the accelerated failure time model, cataract surgery was associated with improvement of expected survival time by a factor of 1.35 (95% CI 1.33, 1.36) when the aphakic/pseudophakic group was excluded, and by a factor of 1.32 (95% CI 1.31, 1.33) when the aphakic/pseudophakic group was included.

3.4.4 Propensity score analyses

Results from propensity score analyses are outlined in Table 3.4. For patients who were in the first three propensity score deciles and therefore least likely to receive cataract surgery, patients who received cataract surgery had increased hazards of all-cause mortality compared to patients who did not receive cataract surgery. In the fourth through the tenth propensity score deciles, there was a consistently protective association between cataract surgery and mortality that increased by decile, with patients in the ninth and tenth deciles and therefore most likely to receive cataract surgery experiencing the strongest protective association between cataract surgery and mortality. These trends were observed both when the aphakic/pseudophakic group was excluded from the study and included in the exposed group. When the aphakic/pseudophakic group was excluded, patients in the highest propensity score decile who received cataract surgery had 48% lower hazards of all-cause mortality compared to patients who did not receive cataract surgery (HR=0.52; 95% CI=0.50, 0.54). When the aphakic/pseudophakic group was included in the exposed group, patients in the highest propensity score decile who received cataract surgery had 42% lower hazards of all-cause mortality compared to patients who did not receive cataract surgery (HR=0.58; 95% CI=0.57, 0.60).

3.4.5 Examination of proportional hazards assumptions

In the overall study population, there appeared to be potential violation of the proportional hazards assumption based on the appearance of the Kaplan-Meier plot and log-negative-log plot both when the aphakic/pseudophakic group was excluded and included in the exposed group (Figures 3.1-3.2). However, after stratifying by propensity score deciles, there no longer appeared to be violation of the proportional hazards assumption in any propensity score strata based on the appearance of Kaplan-Meier plots, both when the aphakic/pseudophakic group was excluded and included in the exposed group (Figures 3.3-3.4).

3.4.6 Assessment of potential effect modifiers

Stratified analyses are summarized in Table 3.5. There were significant interactions for the age*cataract surgery, sex*cataract surgery, CCI score*cataract surgery, and cataract severity*cataract surgery interaction terms in separate fully adjusted models, both when the aphakic/pseduophakic group was excluded and when they were included in the exposed group ($p<0.0001$ for all interaction terms).

When stratifying by age, there was no association between cataract surgery and mortality in patients 65-69 years old, but a protective association in between cataract surgery and mortality in all age strata with patients 70 years and older. These trends were observed both when the aphakic/pseudophakic group was excluded and when they were included in the exposed group. Patients 80-84 years old experienced the strongest protective association between cataract surgery and mortality. When the aphakic/pseudophakic group was excluded, patients 80-84 years old who received cataract surgery experienced 39% lower hazards of mortality compared to patients who did not receive cataract surgery (HR=0.61; 95% CI=0.59, 0.63). When the aphakic/pseudophakic group was included in the exposed group, patients 80-84 years old who received cataract surgery experienced 37% lower hazards of mortality compared to patients who did not receive cataract surgery (HR=0.63; 95% CI=0.62, 0.65).

When stratifying by sex, there was a protective association between cataract surgery and mortality in both males and females, though females demonstrated a stronger association than males. When the aphakic/pseudophakic group was excluded, females who received cataract surgery had 32% lower hazards of mortality compared to females who did not receive cataract surgery (HR=0.68; 95%=0.67, 0.69). When the aphakic/pseudophakic group was included in the exposed group, females who received cataract surgery had 31% lower hazards of mortality compared to females who did not receive surgery (HR=0.69; 95% CI=0.68, 0.70).

When stratifying by CCI score, there was a protective association between cataract surgery and mortality in all CCI score strata. When the aphakic/pseudophakic group was excluded, patients with a CCI score of 3-4 demonstrated the strongest protective association (HR=0.69; 95% CI=0.67, 0.71). When the aphakic/pseudophakic group was included in the exposed group, patients with a CCI score of 1-2 and 3-4 demonstrated the strongest protective associations (HR=0.71; 95% CI=0.69, 0.72 for both strata).

When stratifying by cataract severity, there was a protective association between cataract surgery and mortality both in patients with severe cataracts and in patients without severe cataracts, though the protective association was stronger in patients with severe cataracts. Both when the aphakic/pseudophakic group was excluded and when they were included in the exposed group, patients with severe cataract who received cataract surgery had 32% lower hazards of mortality compared to patients with severe cataract who did not receive surgery (HR=0.68; 95% CI=0.66, 0.70 for both situations).

3.5 Discussion

This study found that in US Medicare patients with cataract, those who received cataract surgery had decreased hazards of all-cause mortality compared to those who did not receive cataract surgery. This protective association increased after adjusting for demographics, systemic comorbidities, and ocular comorbidities, and patients who received surgery had close to 30% reduced adjusted hazards of mortality compared to those who did not receive surgery in the overall national US Medicare population. The protective association between cataract surgery and mortality also increased by propensity score decile, where patients who were in the highest propensity score decile and therefore most likely to receive surgery experienced the greatest reduction in mortality hazards with cataract surgery.

The protective association between cataract surgery and mortality appeared to be modified by the effects of age, sex, systemic disease burden as measured by the CCI, and cataract severity. Based on the findings from this study, patients with cataract who were 80-84 years old, female, had a moderate burden of systemic disease as measured by the CCI, or had severe cataracts appeared to experience the greatest reductions in mortality hazards from receiving cataract surgery. Patients outside of these subgroups who received cataract surgery still had decreased hazards of mortality compared to patients who did not receive surgery, though the protective association was not as strong.

Two existing studies[48,49] have examined mortality after cataract surgery in a cohort of patients entirely with cataract. Both studies were conducted by Fong and colleagues and examined populations from Western Sydney, Australia. Fong's studies compared mortality in (1) patients who were visually impaired with cataract versus patients with no visual impairment after cataract surgery, and (2) patients who were visually impaired after cataract surgery versus patients with no visual impairment after cataract surgery. Both studies found that correction of vision impairment with cataract surgery was associated with decreased mortality, suggesting that the protective association between cataract surgery and mortality is observed in multiple populations.

Based on our findings, we hypothesize that in patients with cataract, cataract surgery is protective against long term mortality through an improvement in overall functioning from mechanisms such as decreased falls and accidents, increased ability to properly take medications and receive routine medical care, improved mental health, and an increased ability to remain active in social and physical activities secondary to the ability to see better following cataract surgery. Previous studies have demonstrated that vision impairment from cataract and other ocular diseases is associated with increased fall and fracture incidence[6,15,18,55,56,64], and one prospective study also found that patients with cataract who received cataract surgery had 53% reduced risk of motor vehicle accidents within four to six years following surgery compared to patients with an unremoved cataract.[65] These findings all suggest that the protective association between cataract surgery and mortality could be mediated by a mechanism related to fracture and accident reduction. Other studies have demonstrated improvements in quality of life and reduction in depression symptoms following cataract surgery, supporting the hypothesis that cataract surgery is protective against mortality through mechanisms associated with overall functioning and mental health.[66,67] This study did not examine specific mechanisms explaining the protective association between cataract surgery and mortality, and it would be of interest to investigate potential explanatory mechanisms in future research.

The main strength of this study is its large sample size and generalizability to the US population 65 years and older. As of 2011, 39,631,062 of the estimated 41,394,201 (95.7%) US adults 65 years and older were enrolled in Medicare.[68,69] Of all Medicare enrollees, approximately 70% are enrolled in the traditional Medicare fee-for-service program which was used to select the 5% random sample for this study.[70] This suggests that findings from the present study are generalizable to a large proportion of the US population ≥65 years old.

One of the main limitations of this study is the possibility of misclassification of coding data. However, given that diagnosis and procedure codes are coded at the time of the patient encounter, we anticipate that any misclassification bias related to exposure and covariate information would be nondifferential and toward the null. There is also the possibility of misclassification of the mortality outcome. Existing validation studies of the SSA death files[71-73] have found that deaths recorded in the SSA database have sensitivities ranging from 80-100. Additionally, the cataract surgery group was followed starting from the date of cataract surgery, which was the time where it was decided to perform a clinical intervention for a visually significant cataract. However, the cataract diagnosis group was followed from the date the cataract diagnosis first appeared in Medicare which may not have consistently represented the same clinical stage of disease for all participants in this group, and this may have biased the estimation of survival time in the cataract diagnosis group. There is also the possibility of uncontrolled or residual confounding in our study, especially from the lack of availability of certain relevant covariates such as physical activity, smoking, and BMI, and further studies including these covariates would be beneficial.

This study found that cataract surgery was associated with reduced long term mortality in national US Medicare patients with cataract, especially in patients 80-84 years old, female, or with a moderate systemic disease burden. While cataract surgery is known to improve vision, the findings in this study suggest that there may be secondary benefits of cataract surgery beyond vision improvement, proposing the need for further studies to examine the association between cataract surgery and overall functioning and systemic health.

3.6 Tables and Figures

Table 3.1. Baseline Characteristics of Patients with Cataract in the 5% Medicare Sample from 2002 to 2012 (n=1,501,420)

	Number (%) of Patients with Characteristic		
	Cataract Surgery Group; n=544,984	**Cataract Diagnosis Group; n=715,405**	**Aphakia/Pseudophakia Group; n=241,031**
Age (years)			
65-69	112,911 (20.7)	346,245 (48.4)	49,326 (20.5)
70-74	140,365 (25.8)	156,792 (21.9)	37,340 (15.5)
75-79	142,009 (26.1)	100,619 (14.1)	50,129 (20.8)
80-84	98,350 (18.1)	62,966 (8.8)	51,210 (21.3)
≥85	51,349 (9.4)	48,783 (6.8)	53,026 (22.0)
Gender			
Male	210,322 (38.6)	306,720 (42.9)	81,053 (33.6)
Female	334,662 (61.4)	408,685 (57.1)	159,978 (66.4)
Race			
White	484,040 (88.8)	618,241 (86.4)	215,791(89.5)
Black	33,546 (6.2)	58,306 (8.2)	13,891 (5.8)
Asian	9,592 (1.8)	13,017 (1.8)	3,767 (1.6)
Hispanic	9,163 (1.7)	11,471 (1.6)	4,157 (1.7)
Native American	1,998 (0.4)	2,526 (0.4)	826 (0.3)
Other	5,937 (1.1)	9,994 (1.4)	2,029 (0.8)
Unknown	708 (0.1)	1,850 (0.3)	570 (0.2)
Region of United States Residence			
East	214,574 (39.4)	306,650 (42.9)	88,981 (36.9)
West	90,152 (16.5)	119,615 (16.7)	38,494 (16.0)
Midwest	139,844 (25.7)	175,007 (24.5)	67,307 (27.9)
South	100,414 (18.4)	114,133 (16.0)	46,249 (19.2)
Charlson Comorbidity Index (CCI) Score			
0	178,716 (32.8)	281,531 (39.4)	75,212 (31.2)
1-2	223,294 (41.0)	272,135 (38.0)	98,136 (40.7)
3-4	93,949 (17.2)	102,571 (14.3)	43,617 (18.1)
≥5	49,025 (9.0)	59,168 (8.3)	24,066 (10.0)
Systemic Comorbidities in the CCI			
Myocardial Infarction	22,008 (4.0)	24,099 (3.4)	10,245 (4.3)
Congestive Heart Failure	75,005 (13.8)	83,381 (11.7)	43,260 (18.0)
Peripheral Vascular Disease	84,952 (15.6)	95,693 (13.4)	44,019 (18.3)
Cerebrovascular Disease	86,184 (15.8)	98,788 (13.8)	43,264 (18.0)
Dementia	14,793 (2.7)	31,673 (4.4)	13,973 (5.8)
Chronic Pulmonary Disease	119,169 (21.9)	127,469 (17.8)	54,632 (22.7)
Chronic Renal Disease	40,299 (7.4)	39,173 (5.5)	15,825 (6.6)
Connective Tissue Disease	24,426 (4.5)	26,167 (3.7)	11,236 (4.7)
Peptic Ulcer Disease	9,482 (1.7)	11,828 (1.7)	5,322 (2.2)
Diabetes Mellitus (DM) Without Complications	108,013 (19.8)	134,324 (18.8)	44,089 (18.3)
DM With Complications	49,364 (9.1)	51,735 (7.2)	21,522 (8.9)
Hemiplegia	4,434 (0.8)	8,484 (1.2)	3,039 (1.3)
Leukemia/Multiple Myeloma	4,695 (0.9)	5,606 (0.8)	1,837 (0.8)
Lymphoma	5,129 (0.9)	6,213 (0.9)	2,006 (0.8)
Solid Malignant Neoplasm	64,415 (11.8)	76,624 (10.7)	26,891 (11.2)
Metastatic Solid Malignant Neoplasm	7,884 (1.5)	13,388 (1.9)	3,570 (1.5)
Mild Liver Disease	16,376 (3.0)	22,959 (3.2)	6,508 (2.7)
Moderate/Severe Liver Disease	1,306 (0.2)	1,872 (0.3)	572 (0.2)
Acquired Immune Deficiency Syndrome	285 (0.1)	547 (0.1)	115 (0.1)
Ocular Comorbidities			
Age-Related Macular Degeneration	120,787 (22.2)	89,266 (12.5)	59,862 (24.8)
DM with Ophthalmic Manifestations	35,705 (6.6)	36,069 (5.0)	16,213 (6.7)
Glaucoma	125,224 (9.9)	119,840 (9.5)	52,749 (21.9)
Severe Cataract	222,663 (40.9)	68,008 (9.5)	6,295 (2.6)

Table 3.2. Incidence of Mortality in Patients with Cataract Surgery versus Cataract Diagnosis in the 5% Medicare Sample from 2002-2012 (n=1,501,420)

	Cataract Surgery Group; n=544,984 or 786,015[a]	Cataract Diagnosis Group; n=715,405	P-Value for Log-Rank Test
Mortality Incidence over Entire Duration of Study Excluding the Aphakic/Pseudophakic Group from the Study Population	43,276 deaths / 1,557,818 person-years (2.78 / 100 person-years)[b] or 43,276 deaths / 2,511,545 person-years (1.72 / 100 person-years)[c]	68,941 deaths / 2,312,697 person-years (2.98 / 100 person-years)	<0.0001
Mortality Incidence over Entire Duration of Study Including the Aphakic/Pseudophakic Group in Cataract Surgery Group	80,800 deaths / 2,555,856 person-years (3.16 / 100 person-years)[d]	68,941 deaths / 2,312,697 person-years (2.98 / 100 person-years)	<0.0001

[a]n=544,984 when patients with a diagnosis code for aphakia/pseudophakia without a procedure code for cataract surgery are excluded, n=786,015 when these patients are included

[b]Excluding median number of days between cataract diagnosis and cataract surgery

[c]Including median number of days between cataract diagnosis and cataract surgery

[d]Separate analyses including median time between cataract diagnosis and cataract surgery was not performed when aphakic/pseudophakic group was included in the cataract surgery group because surgery date for aphakic/pseudophakic group is unknown

Table 3.3. Hazards of Mortality in Patients with Cataract Surgery versus Cataract Diagnosis in the 5% Medicare Sample from 2002 to 2012 (n=1,501,420)

	Excluding Median Days between Cataract Diagnosis and Cataract Surgery	
Model Type	**Hazards Ratio (95% Confidence Interval) Excluding Aphakic/Pseudophakic Group from the Study Population[a]**	**Hazards Ratio (95% Confidence Interval) Including Aphakic/Pseudophakic Group in the Cataract Surgery Group[a]**
Age and Sex-Adjusted	0.69 (0.68, 0.70)	0.71 (0.70, 0.72)
Fully Adjusted[b]	0.72 (0.71, 0.73)	0.73 (0.72, 0.74)
Accelerated Failure Time Model[c]	1.35 (1.33, 1.36)	1.32 (1.31, 1.33)
	Including Median Days between Cataract Diagnosis and Cataract Surgery	
Model Type	**Hazards Ratio (95% Confidence Interval) Excluding Aphakic/Pseudophakic Group from the Study Population[a]**	**Hazards Ratio (95% Confidence Interval) Including Aphakic/Pseudophakic Group in the Cataract Surgery Group[d]**
Age and Sex-Adjusted	0.39 (0.38, 0.39)	--
Fully Adjusted[b]	0.37 (0.36, 0.37)	--
Accelerated Failure Time Model[c]	2.30 (2.28, 2.32)	--

[a]Cataract diagnosis group was used as a reference

[b]Adjusted for age, race, sex, region of residence, Charlson Comorbidity Index (CCI) score, all individual conditions included in the CCI, cataract severity, age-related macular degeneration, glaucoma, and diabetic retinopathy

[c]Effect estimate in accelerated failure time model represents ratio of mean survival in cataract surgery vs. cataract diagnosis groups with log normal distribution

[d]Separate analyses including median time between cataract diagnosis and cataract surgery was not performed when aphakic/pseudophakic group was included in the cataract surgery group because surgery date for aphakic/pseudophakic group is unknown

Table 3.4. Hazards of Mortality in Patients with Cataract Surgery versus Cataract Diagnosis in the 5% Medicare Sample from 2002 to 2012 by Propensity Score Decile (n=1,501,420)

Propensity Score Decile Subgroup[a]	Mortality Incidence Excluding the Aphakic/Pseudophakic Group from the Study Population			Mortality Incidence Including the Aphakic/Pseudophakic Group in the Cataract Surgery Group		
	Cataract Surgery Group (Deaths Per 100 Person-Years)	Cataract Diagnosis Group (Deaths Per 100 Person-Years)	HR (95% CI) of Mortality Following Cataract Surgery[b]	Cataract Surgery Group (Deaths Per 100 Person-Years)	Cataract Diagnosis Group (Deaths Per 100 Person-Years)	HR (95% CI) of Mortality Following Cataract Surgery[b]
1	1,618 / 63,203 (2.6)	7,350 / 354,883 (2.1)	1.22 (1.16, 1.30)	2,001 / 108,618 (1.8)	5,901 / 366,677 (1.6)	1.15 (1.09, 1.21)
2	1,389 / 88,168 (1.6)	4,591 / 355,997 (1.3)	1.23 (1.16, 1.31)	2,084 / 143,618 (1.5)	4,494 / 357,912 (1.3)	1.17 (1.11, 1.23)
3	1,946 / 112,131 (1.7)	5,328 / 326,401 (1.6)	1.08 (1.03, 1.14)	2,989 / 179,217 (1.7)	5,185 / 326,842 (1.6)	1.06 (1.01, 1.11)
4	2,547 / 144,804 (1.8)	5,870 / 291,819 (2.0)	0.89 (0.85, 0.93)	4,034 / 221,801 (1.8)	5,886 / 290,575 (2.0)	0.91 (0.87, 0.94)
5	3,511 / 176,822 (2.0)	6,445 / 254,280 (2.5)	0.81 (0.77, 0.84)	5,535 / 267,085 (2.1)	6,481 / 252,403 (2.6)	0.82 (0.79, 0.85)
6	4,422 / 197,199 (2.2)	6,998 / 213,417 (3.3)	0.70 (0.67, 0.73)	7,322 / 303,063 (2.4)	7,059 / 210,915 (3.3)	0.73 (0.71, 0.76)
7	5,279 / 213,203 (2.5)	7,249 / 176,530 (4.1)	0.62 (0.60, 0.64)	9,080 / 333,982 (2.7)	7,623 / 173,950 (4.4)	0.63 (0.61, 0.65)
8	6,472 / 216,076 (3.0)	7,716 / 142,075 (5.4)	0.57 (0.55, 0.59)	11,797 / 350,576 (3.4)	8,033 / 139,530 (5.8)	0.59 (0.58, 0.61)
9	7,558 / 199,113 (3.8)	8,141 / 112,939 (7.2)	0.54 (0.53, 0.56)	14,887 / 342,698 (4.3)	8,508 / 111,355 (7.6)	0.57 (0.56, 0.59)
10	8,534 / 147,100 (5.8)	9,253 / 82,359 (11.2)	0.52 (0.50, 0.54)	21,071 / 305,198 (6.9)	9,771 / 82,540 (11.8)	0.58 (0.57, 0.60)

HR = hazards ratio; CI = confidence interval

[a]Propensity score of cataract surgery was calculated based on following factors: age, race, gender, region of US residence, Charlson Comorbidity Index score, osteoporosis, hyperthyroidism, hyperparathyroidism, age-related macular degeneration, diabetes mellitus with ophthalmic manifestations, glaucoma, presence of physically limiting conditions, and severe cataract

[b]Cataract diagnosis group was used as a reference

Table 3.5. Hazards of Mortality in Patients with Cataract Surgery versus Cataract Diagnosis by Age, Gender, Charlson Comorbidity Index (CCI) Score, and Cataract Severity in the 5% Medicare Sample from 2002 to 2012(n=1,501,420)

	Excluding Aphakic/Pseudophakic Group from Study Population	**Including Aphakic/Pseudophakic Group in the Cataract Surgery Group**
Age	**Adjusted Hazards Ratio (95% Confidence Interval) of Mortality After Cataract Surgery versus Diagnosis[a,b]**	**Adjusted Hazards Ratio (95% Confidence Interval) of Mortality After Cataract Sugery versus Diagnosis[a,b]**
65-69	0.98 (0.95, 1.00)	0.99 (0.95, 1.03)
70-74	0.79 (0.77, 0.81)	0.79 (0.77, 0.82)
75-79	0.67 (0.66, 0.69)	0.67 (0.65, 0.69)
80-84	0.63 (0.62, 0.65)	0.61 (0.59, 0.63)
≥85	0.69 (0.67, 0.70)	0.66 (0.64, 0.68)
P for interaction	<0.0001	<0.0001
Sex	**Adjusted Hazards Ratio (95% Confidence Interval) of Mortality After Cataract Surgery versus Diagnosis[a,c]**	**Adjusted Hazards Ratio (95% Confidence Interval) of Mortality After Cataract Surgery versus Diagnosis[a,c]**
Male	0.78 (0.77, 0.79)	0.77 (0.76, 0.79)
Female	0.69 (0.68, 0.70)	0.68 (0.67, 0.69)
P for interaction	<0.0001	<0.0001
CCI Score	**Adjusted Hazards Ratio (95% Confidence Interval) of Mortality After Cataract Surgery versus Diagnosis[a,d]**	**Adjusted Hazards Ratio (95% Confidence Interval) of Mortality After Cataract Surgery versus Diagnosis[a,d]**
0	0.73 (0.71, 0.75)	0.71 (0.69, 0.74)
1-2	0.71 (0.69, 0.72)	0.70 (0.69, 0.72)
3-4	0.71 (0.69, 0.72)	0.69 (0.67, 0.71)
≥5	0.75 (0.73, 0.76)	0.74 (0.72, 0.76)
P for interaction	<0.0001	<0.0001
Cataract Severity	**Adjusted Hazards Ratio (95% Confidence Interval) of Mortality After Cataract Surgery versus Diagnosis[a,e]**	**Adjusted Hazards Ratio (95% Confidence Interval) of Mortality After Cataract Surgery versus Diagnosis[a,e]**
Severe	0.68 (0.66, 0.70)	0.68 (0.66, 0.70)
Not Severe	0.73 (0.73, 0.74)	0.73 (0.72, 0.74)
P for interaction	<0.0001	<0.0001

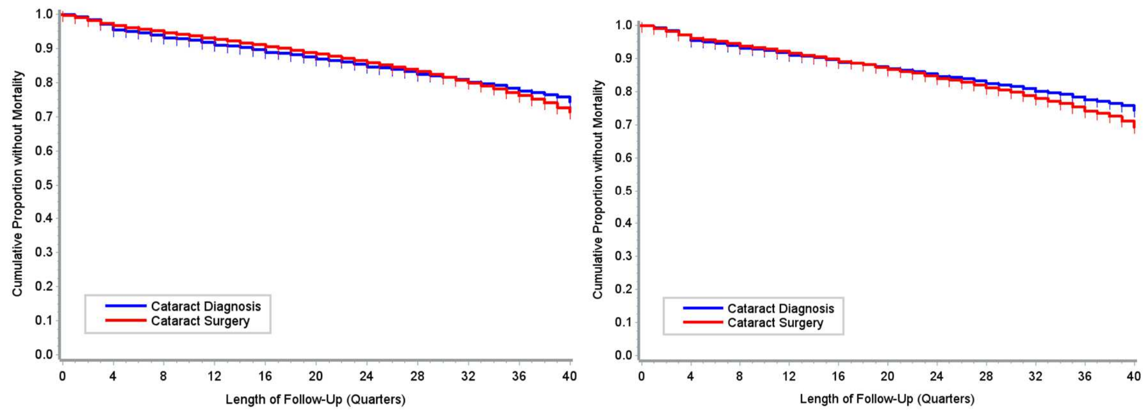
[a]Cataract diagnosis group was used as a reference.

[b]Adjusted for age as a continuous variable, race, gender, region of residence, CCI score, all individual conditions included in the CCI, cataract severity, age-related macular degeneration, glaucoma, and diabetic retinopathy

[c]Adjusted for age, race, region of residence, CCI score, all individual conditions included in the CCI, cataract severity, age-related macular degeneration, glaucoma, and diabetic retinopathy

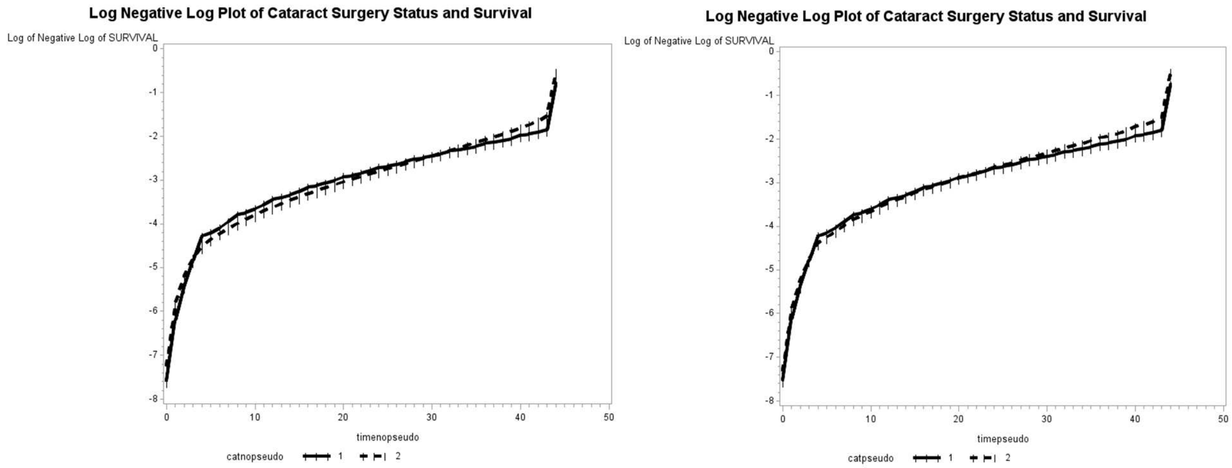
[d]Adjusted for age, gender, race, region of residence, all individual conditions included in the CCI, cataract severity, age-related macular degeneration, glaucoma, and diabetic retinopathy

[e]Adjusted for age, gender, race, region of residence, CCI score, all individual conditions included in the CCI, age-related macular degeneration, glaucoma, and diabetic retinopathy



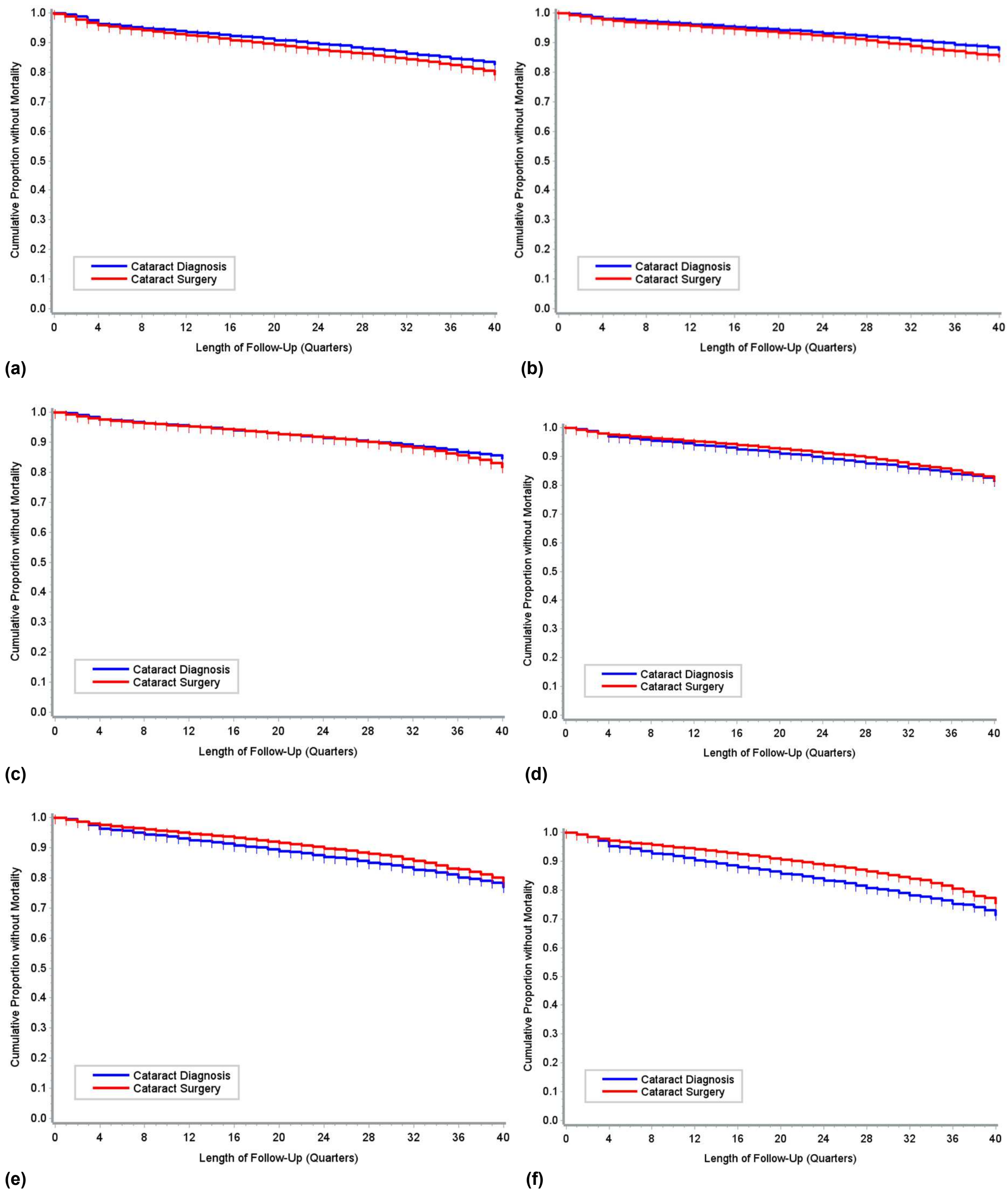
(a) **(b)**

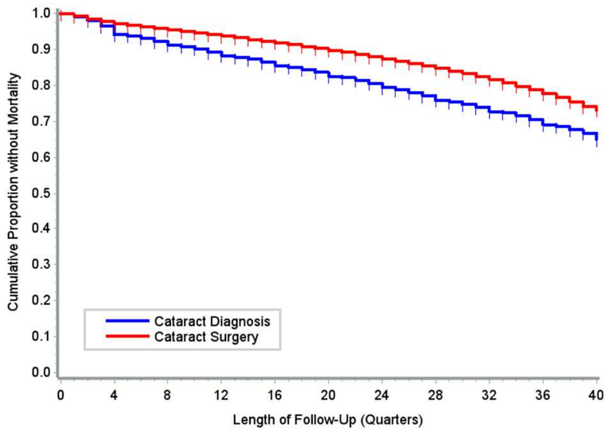
Figure 3.1. Kaplan-Meier Plots for Mortality over Entire Duration of Study by Cataract Surgery Group when Aphakia/Pseudophakia Group is (a) Excluded and (b) Included in Cataract Surgery Group in the 5% Medicare Sample from 2002-2012 (n=1,501,420)



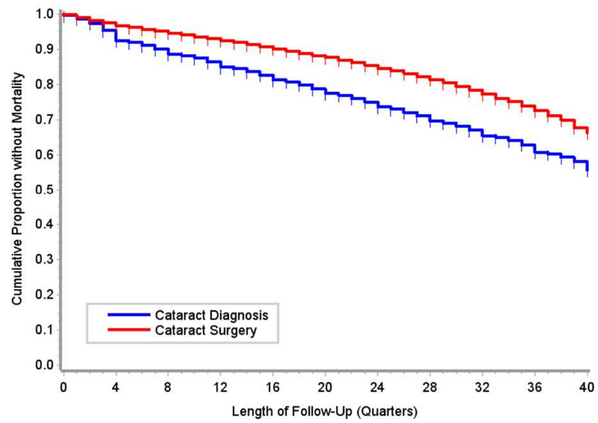
(a) **(b)**

Figure 3.2. Log Negative Log Plot of Mortality over Entire Duration of Study by Cataract Surgery Group when Aphakia/Pseudophakia Group is (a) Excluded and (b) Included in Cataract Surgery Group in the 5% Medicare Sample from 2002-2012 (n=1,501,420)

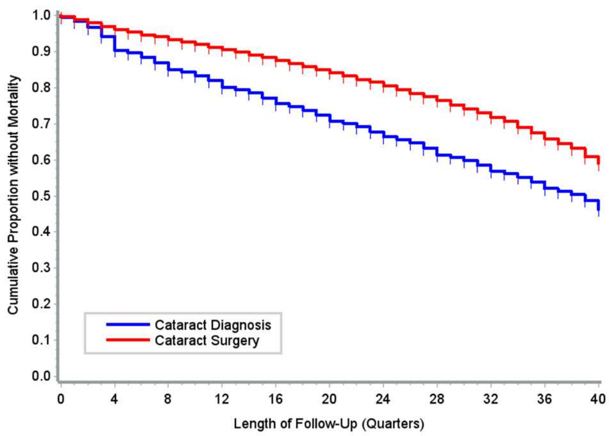

Cumulative Proportion without Mortality
Length of Follow-Up (Quarters)
Cataract Diagnosis
Cataract Surgery
(a)
(b)
(c)
(d)
(e)
(f)



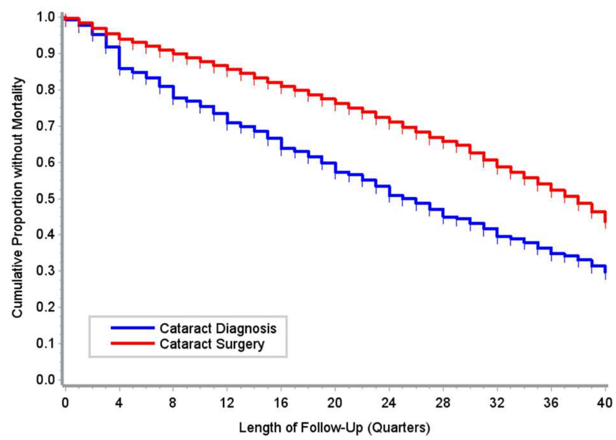
(g)



(h)

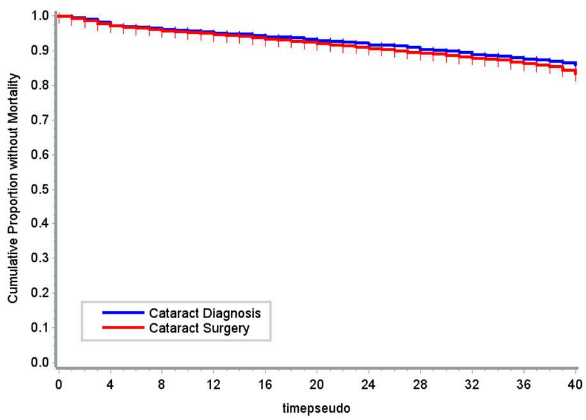


(i)

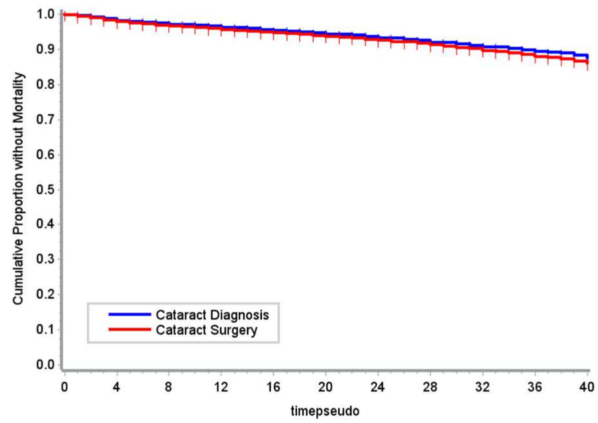


(j)

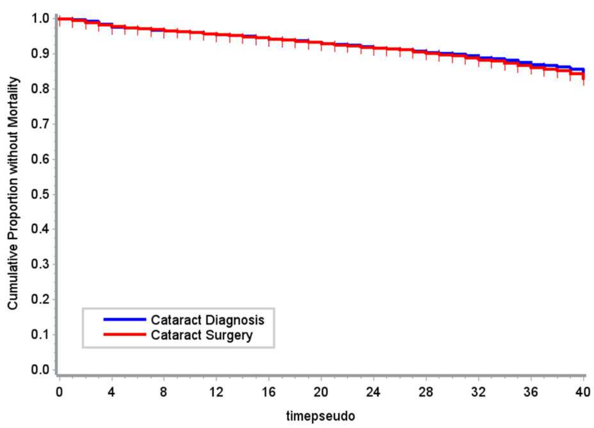
Figure 3.3. Kaplan Meier Curves for Mortality over Entire Duration of Study by Cataract Surgery Group by Propensity Score Decile Excluding Aphakic/Pseudophakic Group in the 5% Medicare Sample from 2002-2012 (n=1,501,420); (a) 1st decile, (b) 2nd decile, (c) 3rd decile, (d) 4th decile, (e) 5th decile, (f) 6th decile, (g) 7th decile, (h) 8th decile, (i) 9th decile, (j) 10th decile


Cumulative Proportion without Mortality
1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.0
Cataract Diagnosis
Cataract Surgery
0 4 8 12 16 20 24 28 32 36 40
timepseudo

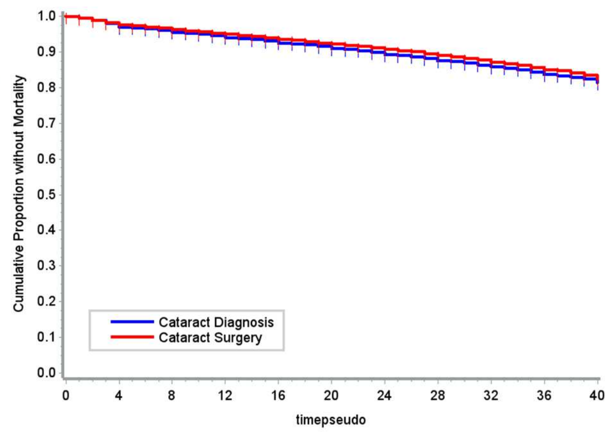
(a)


Cumulative Proportion without Mortality
1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.0
Cataract Diagnosis
Cataract Surgery
0 4 8 12 16 20 24 28 32 36 40
timepseudo

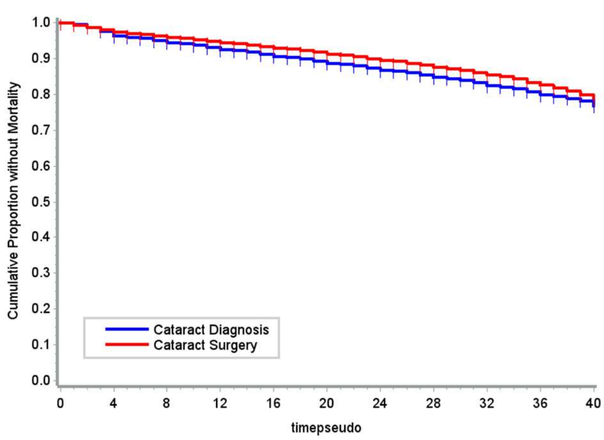
(b)


Cumulative Proportion without Mortality
1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.0
Cataract Diagnosis
Cataract Surgery
0 4 8 12 16 20 24 28 32 36 40
timepseudo

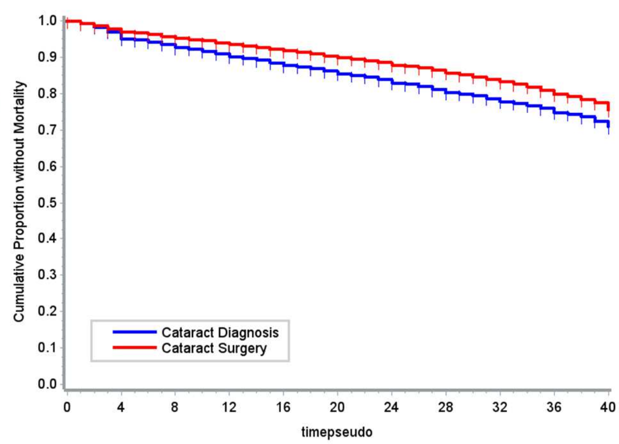
(c)


Cumulative Proportion without Mortality
1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.0
Cataract Diagnosis
Cataract Surgery
0 4 8 12 16 20 24 28 32 36 40
timepseudo

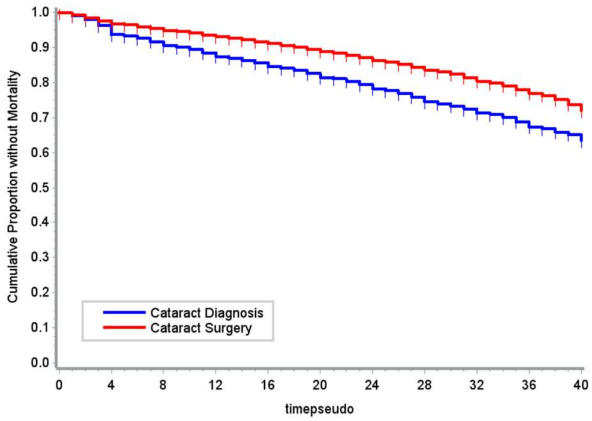
(d)


Cumulative Proportion without Mortality
1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.0
Cataract Diagnosis
Cataract Surgery
0 4 8 12 16 20 24 28 32 36 40
timepseudo

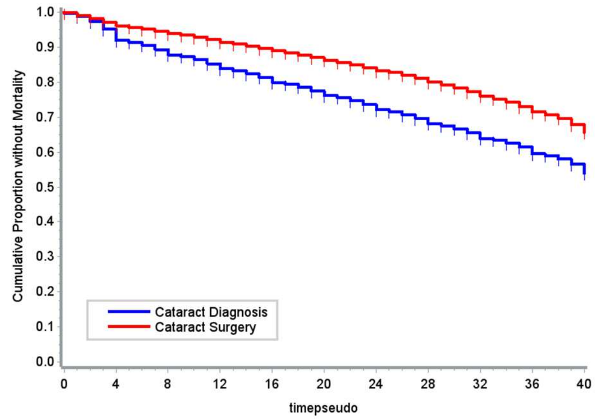
(e)


Cumulative Proportion without Mortality
1.0 0.9 0.8 0.7 0.6 0.5 0.4 0.3 0.2 0.1 0.0
Cataract Diagnosis
Cataract Surgery
0 4 8 12 16 20 24 28 32 36 40
timepseudo

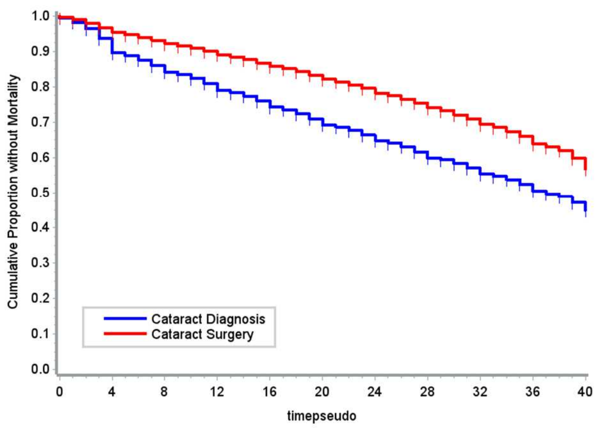
(f)



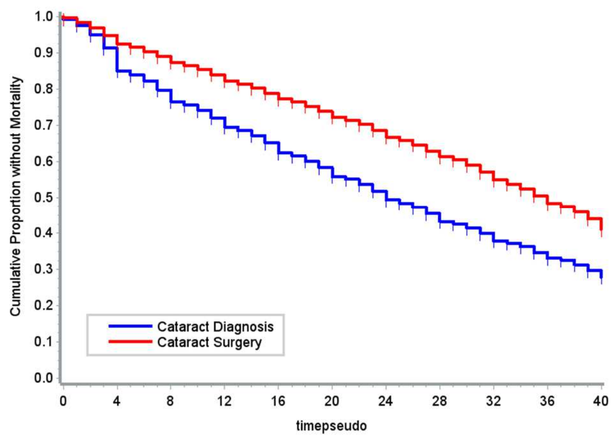
(g)



(h)



(i)



(j)

Figure 3.4. Kaplan Meier Curves for Mortality over Entire Duration of Study by Cataract Surgery Group by Propensity Score Decile Including Aphakic/Pseudophakic Group in the 5% Medicare Sample from 2002-2012 (n=1,501,420); (a) 1st decile, (b) 2nd decile, (c) 3rd decile, (d) 4th decile, (e) 5th decile, (f) 6th decile, (g) 7th decile, (h) 8th decile, (i) 9th decile, (j) 10th decile

Chapter 4: Cataract Surgery and Mortality in the Women's Health Initiative

4.1 Abstract

Purpose: To examine the association between cataract surgery and all-cause mortality in participants of the WHI with cataract.

Methods: The study population was created by linking WHI data to the administrative Medicare database and identifying WHI participants 65 years and older with a diagnosis of cataract in the linked Medicare database. The exposed group consisted of women with cataract surgery in Medicare. The outcome of interest was all-cause mortality during the WHI study follow-up period. Baseline covariates included demographics, systemic comorbidities in the CCI, ocular comorbidities, smoking, alcohol use, BMI, and physical activity. The associations between cataract surgery and each type of mortality were examined using Cox proportional hazards regression modeling, adjusting for all baseline covariates. Additional subgroup analyses were performed in propensity score deciles and within strata of age, systemic disease burden as determined by CCI score, and cataract severity.

Results: There were 80,406 women with cataract in the WHI, including 41,635 with cataract surgery and 32,309 without. The incidence of mortality was 2.56 deaths per 100 person-years in the cataract surgery group and 2.56 deaths per 100 person-years in the cataract diagnosis group. In the overall study population, there was a protective adjusted association between cataract surgery and all-cause mortality (HR=0.60, 95% CI=0.58, 0.63). The strongest protective associations were observed in WHI participants most likely to receive cataract surgery based on high propensity score decile (HR=0.51, 95% CI=0.40, 0.66), ≥85 years old (HR=0.50, 95% CI=0.36, 0.69), and with a CCI score of 0 or ≥5 (95% CI=0.51, 0.63 for CCI of 0 and 0.51, 0.62 for CCI ≥5).

Conclusions: In participants of the WHI with cataract, there is a protective association between cataract surgery and all-cause mortality. Further study of the mechanisms of the association between cataract surgery and mortality would be informative for increased understanding of the benefits of cataract surgery beyond vision improvement.

4.2 Introduction

Cataract surgery is the mainstay of treatment for visually significant cataract, and its primary purpose is to reverse the vision impairment associated with cataract.[4] Previous studies have demonstrated that in patients with cataract, a potential secondary benefit of cataract surgery is the improvement of long term survival.[48,49,74] While these studies have all demonstrated a protective association between cataract surgery and mortality in patients with cataract, only one study[74] was conducted in the US and the other two[48,49] were conducted in cohorts in Western Sydney, Australia. The only study in the US was conducted in the administrative Medicare database which lacks information on important covariates such as smoking, alcohol intake, BMI, and physical activity.

The purpose of the present study is to examine the association between cataract surgery and mortality in the WHI cohort.[58] The WHI database contains extensive information on demographics, comorbidities, and lifestyle factors not available in other large administrative databases in a national cohort of US women with extended follow-up over a period of more than 20 years. Additionally, the WHI encompasses an entirely female cohort and there have been no studies of the association between cataract surgery and mortality in women, who may have unique risk factors for mortality such as increased risk of falls, fractures, and certain types of cancer.[75-77] Finally, WHI data are linked to administrative codes within Medicare, allowing for decreased misclassification of important covariates and analysis of an expanded repertoire of variables. All these features of the WHI database suggest that it will allow detailed examination of factors related to cataract surgery and mortality that were not addressed in previous studies of this subject.

4.3 Methods

4.3.1 Study population

An overview of the WHI study design has been described in Chapter 3 of this dissertation. The study population consisted of all WHI participants from either the CT or OS arms who were 65 years or older and had an ICD-9-CM diagnosis code[50] for cataract in the linked Medicare database at any time from the beginning of the WHI Main Study in 1993 until the December 31, 2013 which was the last date follow-up data were available from the second WHI Extension Study (Appendix 1). Participants less than 65 years old at the time of cataract diagnosis in Medicare were excluded due to selective indications for Medicare enrollment before age 65. The study was approved by the Institutional Review Board at the University of California, Los Angeles.

4.3.2 Exposure

The exposure of interest was cataract surgery. The cataract surgery (exposed) group consisted of all participants with an ICD-9-CM diagnosis code for cataract and a CPT code[51] for cataract surgery (Appendix 1). The cataract diagnosis (unexposed) group consisted of all participants with an ICD-9-CM diagnosis code for cataract without a CPT code for cataract surgery. Patients in the cataract surgery group were followed starting from the date when the CPT code for cataract surgery first appeared. Patients in the cataract diagnosis group were followed starting from the date when the ICD-9-CM code for cataract first appeared.

Patients with an ICD-9-CM code for aphakia or pseudophakia without a CPT code for cataract surgery were included in the aphakic/pseudophakic group (Appendix 1). The aphakic/pseudophakic group was analyzed two ways, by (1) excluding them from the study population entirely and (2) including them in the exposed group. When included, patients in the aphakic/pseudophakic group were followed from the first date when the ICD-9-CM code for pseudophakia or aphakia first appeared.

4.3.3 Outcome

The outcome of interest was all-cause mortality at any time from patient inclusion in the study until the end of the study period on December 31, 2013. Mortality status was ascertained from an indicator variable in the WHI, which was recorded based on report of death on a WHI follow-up form (95.2% of deaths), or from the National Death Index (NDI) for patients whose families did not report to the WHI (6.8% of deaths).

For the cataract surgery group, time to death was calculated as the number of days between cataract surgery and death. For the cataract diagnosis group, time to death was calculated as the number of days between cataract diagnosis and death. For both groups, participants who were still alive on December 31, 2013 were administratively censored, and those who were lost to follow-up without a confirmed death before the end of the study period were censored during the last day in which they had WHI data available.

An alternative time to death variable was created for the participants in the cataract surgery group to account for potential lead-time bias from potentially starting follow-up at a later disease state. This variable was created by determining the median number of days between cataract diagnosis and cataract surgery for participants in the cataract surgery group, and adding this duration of time to the original time-to-event variable for these participants.

4.3.4 Covariates

Demographics that were collected included age, race, US region of residence, education level, annual income, and WHI study arm. Age was analyzed as a continuous variable and also categorized into five-year age subgroups. All other demographic variables were analyzed as categorical variables.

Systemic comorbidities in the CCI[60,61] were included as covariates (Appendix 2). The CCI score was described in Chapter 2 and was categorized into scores of 0, 1-2, 3-4, or ≥5. Ocular comorbidities collected included AMD, glaucoma, and DM with ophthalmic manifestations. A participant was counted as having a systemic or ocular comorbidity if she had the disease based on the WHI indicator variable for the disease, an ICD-9-CM code for the disease in Medicare, or both (Appendix 3).

As objective visual acuity data are not available within the WHI or Medicare, the presence of severe cataract was examined as a proxy for poor vision. Patients with ICD-9-CM codes for subcapsular cataracts, total/mature cataract, hypermature cataract, and combined cataracts were considered to have severe subtypes of cataract (Appendix 1).

Additional covariates that were collected include smoking status, alcohol intake, BMI, and physical activity. Smoking status was self-reported at study baseline and categorized as never smoker, past smoker, current smoker, or unknown. Alcohol intake was self-reported at study baseline and categorized as non-drinker, past-drinker, <1 drink per week, <1 drink per month, 1 to <7 drinks per week, 7+ drinks per week, or unknown. Body mass index was determined based on height and weight measurements from study baseline and categorized into <25, 25-29, or >29. Physical activity was based on METs per week which were calculated from self-reported physical activity habits and categorized into 0, 1-4, 5-12 METs per week, or unknown.

4.3.5 Statistical Analysis

Univariate analyses were conducted using descriptive statistics and histograms for continuous variables, and frequency distributions and contingency tables for categorical variables. Cox proportional hazards regression was used to conduct multivariable analyses of the association between cataract surgery and time to death from any cause. Data were analyzed using an age-adjusted model and a fully adjusted model that included all demographics, systemic comorbidities included in the CCI, ocular comorbidities, cataract severity, smoking status, alcohol intake, and physical activity as covariates. The proportional hazards assumption was checked using Kaplan-Meier curves and log-negative-log plots. In case of potential violation of the proportional hazards assumption, the association between cataract surgery and mortality was also assessed using the accelerated failure time model with a log-normal distribution, adjusting for all baseline covariates. To account for potential confounding by indication, propensity scores were constructed by regressing cataract surgery status on all covariates, and Cox regression analyses were conducted within strata of propensity score deciles. To assess for potential effect measure modification, stratified analyses were conducted within age, CCI score, and cataract severity strata.

4.4 Results

4.4.1 Baseline characteristics

Baseline characteristics are summarized in Table 4.1. The study population included 80,406 women followed for a mean of 2,541.5 ± 1,599.4 days. Of these women, 41,635 (51.8%) were in the cataract surgery group, 32,309 (40.2%) were in the cataract diagnosis group, and 6,362 (7.9%) were in the aphakic/pseudophakic group. The majority of participants in the cataract surgery group and aphakic/pseudophakic group were 70-74 years old (n=13,427; 32.2% and n=1,814; 28.5%, respectively) while the majority of participants in the cataract diagnosis group were 65-69 years old (n=17,948; 55.6%). In all three groups, the majority of participants were enrolled in the OS arm of the WHI, white, lived in the southern US, attended more than high school, and had an annual income over $50,000 per year. In the cataract surgery and cataract diagnosis groups, the majority of participants had a CCI score of one to two (n=15,122; 36.2% and n=12,728; 39.4%, respectively), while the majority of participants in the aphakic/pseudophakic group had a CCI score of zero (n=2,635; 41.4%). The most common systemic comorbidity in all three groups was solid malignant neoplasm, and the most common ocular comorbidity in all three groups was glaucoma. In all three groups, the largest group of participants were never smokers, had one to less than seven alcoholic beverages per week, had a BMI of less than 25, and performed five to twelve METs per week.

4.4.2 Mortality incidence

Data on the incidence of all-cause mortality are summarized in Table 4.2. The incidence of mortality in the cataract surgery group was 2.56 deaths per 100 person-years when average time between cataract diagnosis and cataract surgery was excluded, and 1.62 deaths per 100 person-years when the average time was included. When the aphakic/pseudophakic group was included in the exposed group, the incidence of all-cause mortality was 2.76 deaths per 100 person-years. In the cataract diagnosis group, the incidence of all-cause mortality was 2.56 deaths per 100 person-years.

4.4.3 Association between cataract surgery and mortality

Associations between cataract surgery and all-cause mortality are summarized in Table 4.3. When the median number of days between cataract diagnosis and cataract surgery was excluded for participants in the cataract surgery group, there was a protective association between cataract surgery and all-cause mortality, both when the aphakic/pseudophakic group was excluded (age-adjusted HR=0.69, 95% CI=0.67, 0.72; fully adjusted HR=0.60, 95% CI=0.58, 0.63) and when they were included (age-adjusted HR=0.74, 95% CI=0.72, 0.77; fully adjusted HR=0.68, 95% CI=0.65, 0.71).

When the median number of days between cataract diagnosis and cataract surgery was included, both the age-adjusted and fully adjusted models demonstrated a protective association between cataract surgery and mortality, though the adjusted association was stronger (unadjusted HR=0.34, 95% CI=0.33, 0.36; adjusted HR=0.28, 95% CI=0.26, 0.29).

In the accelerated failure time model, cataract surgery was associated with improvement in expected survival time by a factor of 1.55 (95% CI 1.49, 1.61) when the aphakic/pseudophakic group was excluded, and by a factor of 1.37 (95% CI 1.33, 1.42) when the aphakic/pseudophakic group was included.

4.4.4 Propensity score analysis

Propensity score analyses are summarized in Table 4.4. Both when the aphakic/pseudophakic group was excluded and included, there was a progressively stronger protective association between cataract surgery and mortality with increasing propensity score decile. In the highest propensity score decile, cataract surgery was associated with 49% decreased hazards of mortality in the cataract surgery group compared to the cataract diagnosis group when the aphakic/pseudophakic group was excluded (HR=0.51, 95% CI=0.40, 0.66) and 44% decreased hazards of mortality when the aphakic/pseudophakic group was included (HR=0.56, 95% CI=0.44, 0.70).

4.4.5 Examination of proportional hazards assumptions

There appeared to be potential violation of the proportional hazards assumption in the overall study population based on the appearances of the Kaplan-Meier curve and log-negative log plot (Figures 4.1-4.2). When stratifying by propensity score deciles, there no longer appeared to be violation of the proportional hazards assumption in any strata based on the appearances of Kaplan-Meier plots, both when the aphakic/pseudophakic group was excluded and included in the exposed group (Figures 4.3-4.4).

4.4.6 Assessment of potential effect modifiers

Results from the assessment of potential effect modifiers including p-values for interaction terms are summarized in Table 4.5. When the aphakic/pseudophakic group was excluded, participants ≥85 years old demonstrated the strongest protective association between cataract surgery and mortality (HR=0.50, 95% CI=0.36, 0.69). When the aphakic/pseudophakic group was included, there were similar strengths of protective associations between cataract surgery and mortality across all age groups, except in participants 65-69 years old who demonstrated the least protective association (HR=0.79, 95% CI=0.73, 0.86).

When stratifying by CCI score and excluding the aphakic/pseudophakic group, there were similar strengths of association between cataract surgery and mortality in all CCI strata, with possibly stronger associations in participants with a CCI score of zero or five or greater (CCI 0: HR=0.56, 95% CI=0.51, 0.63; CCI ≥5: HR=0.56, 95% CI=0.51, 0.62). When the aphakic/pseudophakic group was included, the strongest protective association was observed in participants with a CCI score of five or greater (HR=0.56, 95% CI=0.51, 0.62).

When stratifying by cataract severity, participants with non-severe forms of cataract and severe forms of cataract had similar protective associations between cataract surgery and mortality when the aphakic/pseudophakic group was excluded (severe: HR=HR=0.61, 95% CI=0.55, 0.86; not severe: HR=0.59, 95% CI=0.56, 0.62). When the aphakic/pseudophakic group was included, participants with severe forms of cataract had a potentially stronger protective association (HR=0.62, 95% CI=0.55, 0.69).

4.5 Discussion

In participants of the WHI with cataract, there was a protective association between cataract surgery and all-cause mortality after adjusting for demographics, systemic and ocular comorbidities, and selected lifestyle factors. This protective association was strongest in women most likely to receive cataract surgery as indicated by high propensity score decile. When excluding participants with aphakia or pseudophakia prior to the study period, there was potential effect modification by age, where the oldest women experienced the greatest protective benefit from cataract surgery. When including participants with aphakia or pseudophakia, there was potential effect modification by systemic disease burden, where women with the highest burden of systemic disease experienced the greatest protective benefit from cataract surgery.

The overall findings in the present study parallel our previous findings in the US Medicare population, which demonstrated protective adjusted associations between cataract surgery and mortality both in the overall study population and in women within Medicare.[74] In the present study, we were able to adjust additionally for smoking, alcohol use, BMI, and physical activity, which are all covariates that are not available in the Medicare database. The findings in the present study did not change from those in Medicare after adding these covariates, suggesting that potential residual confounding from these factors was minimal in the Medicare population. To further address the possibility of uncontrolled confounding and confounding by indication, we conducted a propensity score analysis, which confirmed the protective association between cataract surgery and mortality that was observed in the fully adjusted model in the overall population.

Unlike the Medicare study, the present study found that the aphakic/pseudophakic group had differing baseline characteristics from the cataract surgery group. Specifically, compared to the cataract surgery group, the aphakic/pseuophakic group in the WHI population had a much higher proportion of participants with a CCI score of zero, and much lower proportions of participants with each ocular comorbidity. These findings suggest the possibility of selection bias with inclusion of the aphakic/pseudophakic group, due to a healthier subgroup of participants who chose to enroll in WHI. However, crude mortality incidence in the exposed group was higher when the aphakic/pseudophakic group was included compared to when they were excluded. These findings suggest that the lower prevalence of systemic and ocular comorbidities in the aphakic/pseudophakic group may also be due to misclassification. While study findings did not change noticeably with the inclusion of the aphakic/pseudophakic group beyond minor changes in effect modifier analyses, the potential miscoding of comorbidities in the aphakic/pseudophakic group suggest that study findings excluding this group of participants are potentially more valid within the WHI.

The main strengths of this study are the addition of smoking, alcohol use, BMI, and physical activity as covariates in the analyses of the association between cataract surgery and mortality. The similarity of results between the two studies after accounting for these factors increases the validity of findings from both the Medicare study and the present study. Additionally, this study focused on a large cohort of US women enrolled in a long term study, and our findings demonstrated that the protective association between cataract surgery and mortality was similar between women in this cohort and of the general US Medicare population despite potential differences in demographics, socioeconomic status, and systemic health between the two populations.

This study is mainly limited by its observational nature. Participation in the WHI is voluntary and generalizability of findings from this cohort may be limited by differential participant dropout, though the findings in this study were similar to those of the Medicare study. Another potential source of bias is misclassification of the mortality outcome, though mortality in the WHI is mainly ascertained from family report on participant follow-up forms or from the NDI, which has been reported to correctly identify a higher proportion of deaths compared to the SSA.[74] Additionally, the cataract surgery group was followed starting from the date of cataract surgery, which was the time where it was decided to perform a clinical intervention for a visually significant cataract. However, the cataract diagnosis group was followed from the date the cataract diagnosis first appeared in Medicare, and this time may not have consistently represented the same clinical stage of disease for all participants in this group, which may have led to biased estimation of survival time in this group. Finally, while this study was able to include more covariates than the Medicare study, there is still a possibility of unmeasured confounding, and we addressed this by conducting a propensity score analysis which yielded similar results to the original analysis.

In summary, this study found a protective association between cataract surgery and all-cause mortality in participants of the WHI with cataract, which is consistent with our previously reported findings in the Medicare database. Further studies of the mechanisms of the association between cataract surgery and mortality would be informative to understand the benefits of cataract surgery beyond vision improvement.

4.6 Tables and Figures

Table 4.1. Baseline Characteristics of Patients with Cataract in the Women's Health Initiative (WHI) from 1993-2013 (n=80,406)

	Number (%) of Patients with Characteristic		
	Cataract Surgery Group; n=41,735	**Cataract Diagnosis Group; n=32,309**	**Aphakia/Pseudophakia Group; n=6,362**
Age (years)			
65-69	8,016 (19.2)	17,948 (55.6)	1,739 (27.3)
70-74	13,427 (32.2)	9,241 (28.6)	1,814 (28.5)
75-79	12,884 (30.9)	3,963 (12.3)	1,738 (27.3)
80-84	6,057 (14.5)	927 (2.9)	753 (11.8)
≥85	1,351 (3.2)	230 (0.7)	318 (5.0)
WHI Study Arm			
Clinical Trial	17,719 (42.5)	14,138 (43.8)	2,482 (39.0)
Observational Study	24,016 (57.5)	18,171 (56.2)	3,880 (59.7)
Race			
White	36,992 (88.9)	27,438 (85.1)	5,636 (88.6)
Black/African American	2,495 (6.0)	2,798 (8.7)	368 (5.8)
Asian/Pacific Islander	798 (1.9)	712 (2.2)	117 (1.8)
Hispanic/Latino	855 (2.1)	868 (2.7)	134 (2.1)
American Indian/Alaskan Native	122 (0.3)	110 (0.3)	26 (0.4)
Other	368 (0.9)	306 (1.0)	70 (1.1)
Unknown	105 (0.2)	77 (0.2)	11 (0.2)
Region of United States Residence			
Northeast	9,610 (23.0)	8,585 (26.6)	1,128 (17.7)
West	8,807 (21.1)	6,621 (20.5)	1,702 (26.8)
Midwest	10,682 (25.6)	8,509 (26.3)	1,650 (25.9)
South	12,636 (30.3)	8,594 (26.6)	1,882 (29.6)
Education Level			
High School or Less[a]	9,504 (22.8)	6,767 (20.9)	1,482 (23.3)
More than High School[b]	32,041 (76.8)	25,379 (78.6)	4,842 (76.1)
Unknown	190 (0.5)	163 (0.5)	38 (0.6)
Annual Income			
<$50,000	24,867 (59.6)	17,296 (53.5)	4,134 (65.0)
≥$50,000	15,241 (36.5)	13,820 (42.8)	1,979 (31.1)
Unknown	1,627 (3.9)	1,193 (3.7)	249 (3.9)
Charlson Comorbidity Index (CCI) Score			
0	7,797 (18.7)	11,925 (36.9)	2,635 (41.4)
1-2	15,122 (36.2)	12,728 (39.4)	2,385 (37.5)
3-4	10,241 (24.5)	5,032 (15.6)	927 (14.6)
≥5	8,575 (20.6)	2,624 (8.1)	415 (6.5)
Systemic Comorbidities in the CCI			
Myocardial Infarction	4,777 (11.5)	2,228 (6.9)	622 (9.8)
Congestive Heart Failure	6,734 (16.1)	2,367 (7.3)	490 (7.7)
Peripheral Vascular Disease	10,499 (25.2)	3,782 (11.7)	677 (10.6)
Cerebrovascular Disease	11,946 (28.6)	4,225 (13.1)	699 (11.0)
Dementia	1,222 (2.9)	515 (1.6)	94 (1.5)
Chronic Pulmonary Disease[c]	15,238 (36.5)	6,511 (20.2)	1,053 (16.6)
Chronic Renal Disease	2,300 (5.5)	773 (2.4)	100 (1.6)
Connective Tissue Disease	5,668 (13.6)	2,072 (6.4)	314 (4.9)
Peptic Ulcer Disease	5,008 (12.0)	2,595 (8.0)	662 (10.4)
Diabetes Mellitus (DM) Without Complications	10,610 (25.4)	5,069 (15.7)	629 (9.9)
DM With Complications	200 (0.5)	118 (0.4)	17 (0.3)
Hemiplegia	916 (2.2)	317 (1.0)	55 (0.9)
Leukemia/Multiple Myeloma	517 (1.2)	252 (0.8)	27 (0.4)
Lymphoma	714 (1.7)	329 (1.0)	46 (0.7)

Solid Malignant Neoplasm	12,472 (29.9)	7,616 (23.6)	1,646 (25.9)
Metastatic Solid Malignant Neoplasm	1,422 (3.4)	672 (2.1)	55 (0.9)
Mild Liver Disease	4,142 (9.9)	1,732 (5.4)	175 (2.8)
Moderate/Severe Liver Disease	81 (0.2)	23 (0.1)	3 (0.0)
Acquired Immune Deficiency Syndrome	53 (0.1)	16 (0.1)	2 (0.0)
Ocular Comorbidities			
Age-Related Macular Degeneration	10,993 (26.3)	3,702 (11.5)	739 (11.6)
DM with Ophthalmic Manifestations	2,207 (5.3)	893 (2.8)	145 (2.3)
Glaucoma	13,173 (31.6)	5,639 (17.5)	862 (13.5)
Severe Cataract[d]	18,611 (44.6)	2,470 (7.6)	202 (3.2)
Smoking Status			
Never smoker	21,206 (51.5)	16,534 (51.8)	3,233 (50.8)
Past smoker	17,676 (42.9)	13,487 (42.2)	2,681 (42.1)
Current smoker	2,312 (5.6)	1,910 (6.0)	331 (5.2)
Unknown	541 (1.3)	378 (1.2)	117 (1.8)
Alcohol Intake			
Non-Drinker	4,747 (11.5)	3,395 (10.6)	784 (12.3)
Past Drinker	7,533 (18.2)	5,485 (17.1)	1,275 (20.0)
<1 Drink Per Month	4,807 (11.6)	3,884 (12.1)	719 (11.3)
<1 Drink Per Week	8,419 (20.3)	6,712 (20.9)	1,257 (19.8)
1 to <7 Drinks Per Week	10,709 (25.8)	8,703 (27.1)	1,482 (23.3)
7+ Drinks Per Week	5,225 (12.6)	3,905 (12.2)	784 (12.3)
Unknown	295 (0.7)	225 (0.7)	61 (1.0)
Body Mass Index			
<25	15,104 (36.2)	11,856 (36.7)	2,376 (37.3)
25-29	12,537 (30.0)	9,364 (29.0)	1,894 (29.8)
>29	14,094 (33.8)	11,089 (34.3)	2,092 (32.9)
Metabolic Equivalent Tasks (METs) Per Week			
0	5,867 (14.8)	4,587 (14.9)	1,010 (15.9)
1-4	8,091 (20.4)	6,326 (20.6)	1,344 (21.1)
5-12	25,726 (64.8)	19,811 (64.5)	3,740 (58.8)
Unknown	2,051 (4.9)	1,585 (4.9)	268 (4.2)

[a]Includes no school, 1-4 years of grade school, 5-8 years of grade school, some high school, high school diploma or GED

[b]Includes vocational/training school, some college/associate degree, college graduate/baccalaureate degree, some post-graduate or professional, master's degree, doctoral degree

[c]Includes chronic bronchitis, emphysema, asthma, bronchiectasis, alveolitis, chronic airway obstruction, pneumoconioses, and asbestosis

[d]Includes anterior and posterior subcapsular cataracts, total/mature cataract, hypermature cataract,combined forms of cataract.

Table 4.2. Incidence of All-Cause Mortality in Patients with Cataract Surgery versus Cataract Diagnosis in the Women's Health Initiative (WHI) from 1993-2013 (n=80,406)

	Cataract Surgery Group; n=41,735 or 48,097[a]	Cataract Diagnosis Group; n=32,309	P-Value for Log-Rank Test
Mortality Incidence over Entire Duration of Study Excluding the Aphakic/Pseudophakic Group from the Study Population	6,878 deaths / 268,636 person-years (2.56 / 100 person-years)[b] or 6,878 deaths / 424,828 person-years (1.62 / 100 person-years)[c]	6,123 deaths / 239,609 person-years (2.56 / 100 person-years)	0.002
Mortality Incidence over Entire Duration of Study Including the Aphakic/Pseudophakic Group in Cataract Surgery Group	8,847 deaths / 320,247 person-years (2.76 / 100 person-years)[d]	6,123 deaths / 239,609 person-years (2.56 / 100 person-years)	<0.0001

[a]n=41,735 when patients with a diagnosis code for aphakia/pseudophakia without a procedure code for cataract surgery are excluded, n=48,097 when these patients are included

[b]Excluding median number of days between cataract diagnosis and cataract surgery

[c]Including median number of days between cataract diagnosis and cataract surgery

[d]Separate analyses including median time between cataract diagnosis and cataract surgery was not performed when aphakic/pseudophakic group was included in the cataract surgery group because surgery date for aphakic/pseudophakic group is unknown

Table 4.3. Hazards of All-Cause Mortality in Patients with Cataract Surgery versus Cataract Diagnosis in the Women's Health Initiative (WHI) from 1993-2013 (n=80,406)

	Excluding Median Number of Days between Cataract Diagnosis and Cataract Surgery	
Model Type	**Hazards Ratio (95% Confidence Interval) Excluding Aphakic/Pseudophakic Group from the Study Population[a]**	**Hazards Ratio (95% Confidence Interval) Including Aphakic/Pseudophakic Group in the Cataract Surgery Group[a]**
Age-Adjusted	0.69 (0.67, 0.72)	0.74 (0.72, 0.77)
Fully Adjusted[b]	0.60 (0.58, 0.63)	0.68 (0.65, 0.71)
Accelerated Failure Time Model[c]	1.55 (1.49, 1.61)	1.37 (1.33, 1.42)
	Including Median Number of Days between Cataract Diagnosis and Cataract Surgery	
Model Type	**Hazards Ratio (95% Confidence Interval) Excluding Aphakic/Pseudophakic Group from the Study Population[a]**	**Hazards Ratio (95% Confidence Interval) Including Aphakic/Pseudophakic Group in the Cataract Surgery Group[c]**
Age-Adjusted	0.34 (0.33, 0.36)	--
Fully Adjusted[b]	0.28 (0.26, 0.29)	--

[a]Cataract diagnosis group was used as a reference

[b]Adjusted for age, race, region of residence, all individual conditions included in the CCI, smoking status, alcohol intake, metabolic equivalent tasks per week, cataract severity, age-related macular degeneration, glaucoma, and diabetic retinopathy

[c]Effect estimate in accelerated failure time model represents ratio of mean survival in cataract surgery vs. cataract diagnosis groups with log normal distribution

[d]Separate analyses including median time between cataract diagnosis and cataract surgery was not performed when aphakic/pseudophakic group was included in the cataract surgery group because surgery date for aphakic/pseudophakic group is unknown

Table 4.4. Hazards of All-Cause Mortality by Propensity Score Decile in Patients with Cataract Surgery versus Cataract Diagnosis in the Women's Health Initiative (WHI) from 1993-2013 (n=80,406)

Propensity Score Decile[a]	Hazards Ratio (95% Confidence Interval) of Mortality Following Cataract Surgery Excluding Aphakic/Pseudophakic Group from the Study Population[b]	Hazards Ratio (95% Confidence Interval) of Mortality Following Cataract Surgery Including Aphakic/Pseudophakic Group in the Cataract Surgery Group[b]
1	0.98 (0.77, 1.24)	1.20 (1.00, 1.43)
2	0.79 (0.66, 0.95)	0.85 (0.73, 1.00)
3	0.65 (0.55, 0.75)	0.79 (0.70, 0.90)
4	0.62 (0.55, 0.70)	0.71 (0.63, 0.79)
5	0.64 (0.57, 0.71)	0.74 (0.67, 0.82)
6	0.57 (0.51, 0.63)	0.68 (0.61, 0.75)
7	0.53 (0.47, 0.59)	0.58 (0.52, 0.64)
8	0.55 (0.48, 0.63)	0.59 (0.52, 0.67)
9	0.54 (0.46, 0.65)	0.50 (0.43, 0.59)
10	0.51 (0.40, 0.66)	0.56 (0.44, 0.70)

[a]Propensity score of cataract surgery was calculated based on following factors: age, race, region of US residence, , all individual conditions included in the CCI, smoking status, alcohol intake, metabolic equivalent tasks per week, cataract severity, age-related macular degeneration, glaucoma, and diabetic retinopathy

[b]Cataract diagnosis group was used as a reference

Table 4.5. Hazards of All-Cause Mortality in Patients with Cataract Surgery versus Cataract Diagnosis by Age, Gender, Charlson Comorbidity Index (CCI) Score, and Cataract Severity in the Women's Health Initiative (WHI) from 1993-2013 (n=80,406)

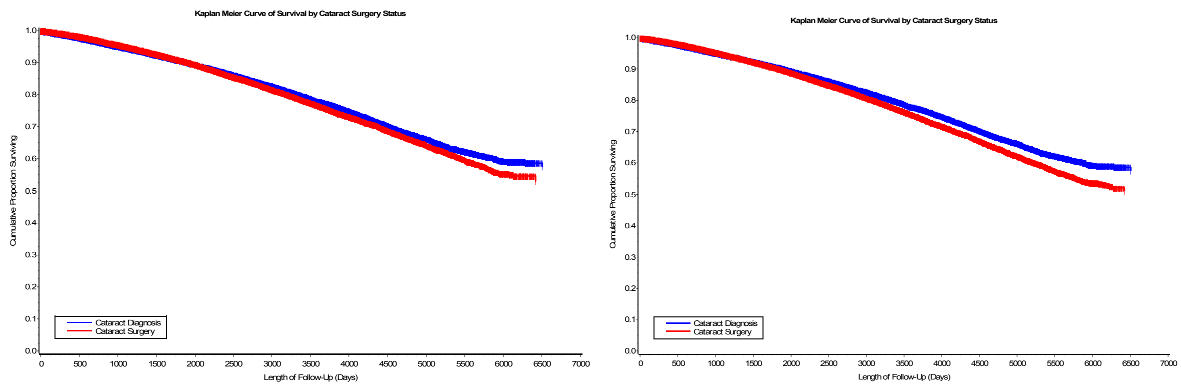
	Excluding Aphakic/Pseudophakic Group from Study Population	**Including Aphakic/Pseudophakic Group in the Cataract Surgery Group**
Age	**Adjusted Hazards Ratio (95% Confidence Interval) of Mortality After Cataract Surgery[a,b]**	**Adjusted Hazards Ratio (95% Confidence Interval) of Mortality After Cataract Sugery[a,b]**
65-69	0.72 (0.65, 0.79)	0.79 (0.73, 0.86)
70-74	0.59 (0.54, 0.63)	0.67 (0.62, 0.71)
75-79	0.54 (0.50, 0.59)	0.61 (0.57, 0.66)
80-84	0.53 (0.46, 0.62)	0.61 (0.53, 0.70)
≥85	0.50 (0.36, 0.69)	0.67 (0.50, 0.91)
P for interaction	<0.0001	<0.0001
CCI Score	**Adjusted Hazards Ratio (95% Confidence Interval) of Mortality After Cataract Surgery[a,c]**	**Adjusted Hazards Ratio (95% Confidence Interval) of Mortality After Cataract Surgery[a,c]**
0	0.56 (0.51, 0.63)	0.74 (0.68, 0.81)
1-2	0.62 (0.58, 0.67)	0.71 (0.67, 0.76)
3-4	0.59 (0.54, 0.65)	0.65 (0.60, 0.71)
≥5	0.56 (0.51, 0.62)	0.56 (0.51, 0.62)
P for interaction	0.05	<0.0001
Cataract Severity	**Adjusted Hazards Ratio (95% Confidence Interval) of Mortality After Cataract Surgery[a,d]**	**Adjusted Hazards Ratio (95% Confidence Interval) of Mortality After Cataract Surgery[a,d]**
Severe	0.61 (0.55, 0.68)	0.62 (0.55, 0.69)
Not Severe	0.59 (0.56, 0.62)	0.69 (0.66, 0.72)
P for interaction	0.34	0.004

[a]Cataract diagnosis group was used as a reference.

[b]Adjusted for age as a continuous variable, race, region of residence, all individual conditions included in the CCI, smoking status, alcohol intake, body mass index, metabolic equivalent tasks per week, cataract severity, age-related macular degeneration, glaucoma, and diabetic retinopathy

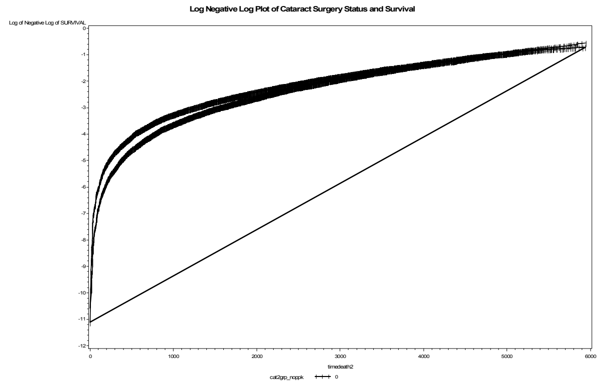
[c]Adjusted for age, race, region of residence, all individual conditions included in the CCI, smoking status, alcohol intake, body mass index, metabolic equivalent tasks per week, cataract severity, age-related macular degeneration, glaucoma, and diabetic retinopathy

[d]Adjusted for age, race, region of residence, all individual conditions included in the CCI, smoking status, alcohol intake, body mass index, metabolic equivalent tasks per week, age-related macular degeneration, glaucoma, and diabetic retinopathy

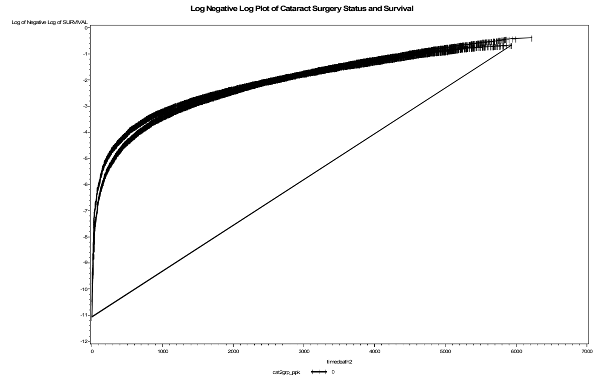


(a) **(b)**

Figure 4.1. Kaplan-Meier Plots for Mortality over Entire Duration of Study by Cataract Surgery Group when Aphakia/Pseudophakia Group is (a) Excluded and (b) Included in Cataract Surgery Group in the Women's Health Initiative (WHI) from 1993-2013 (n=80,406)

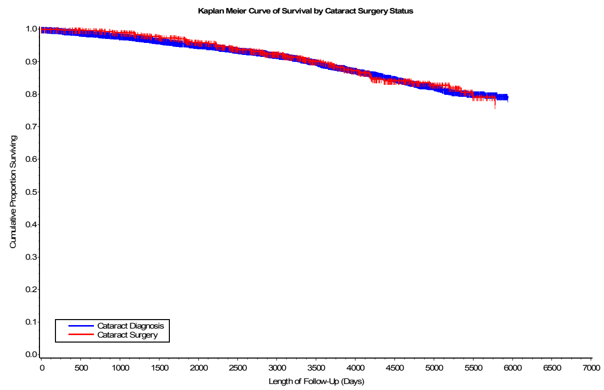


(a)

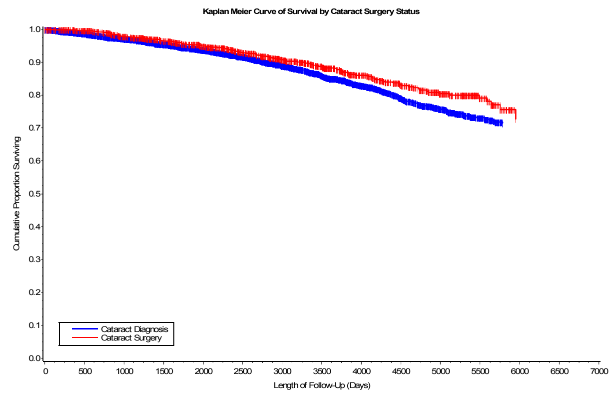


(b)

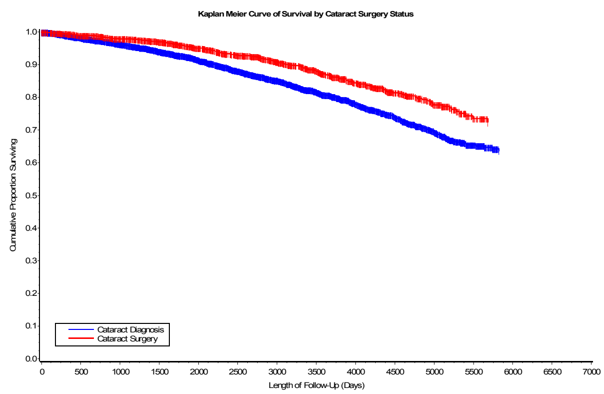
Figure 4.2. Log Negative Log Plot of Mortality over Entire Duration of Study by Cataract Surgery Group when Aphakia/Pseudophakia Group is (a) Excluded and (b) Included in Cataract Surgery Group in the Women's Health Initiative (WHI) from 1993-2013 (n=80,406)


Kaplan Meier Curve of Survival by Cataract Surgery Status
Cumulative Proportion Surviving
Length of Follow-Up (Days)
Cataract Diagnosis
Cataract Surgery

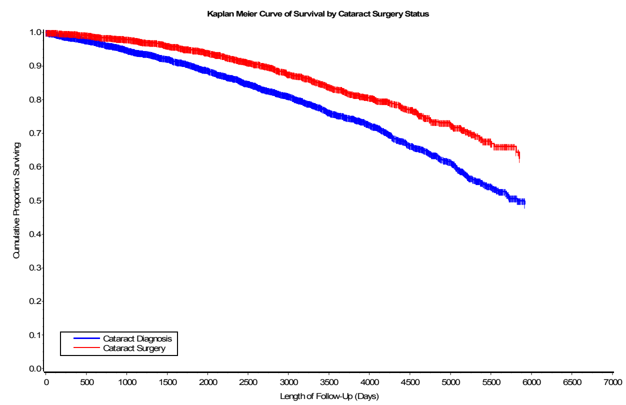
(a)


Kaplan Meier Curve of Survival by Cataract Surgery Status
Cumulative Proportion Surviving
Length of Follow-Up (Days)
Cataract Diagnosis
Cataract Surgery

(b)


Kaplan Meier Curve of Survival by Cataract Surgery Status
Cumulative Proportion Surviving
Length of Follow-Up (Days)
Cataract Diagnosis
Cataract Surgery

(c)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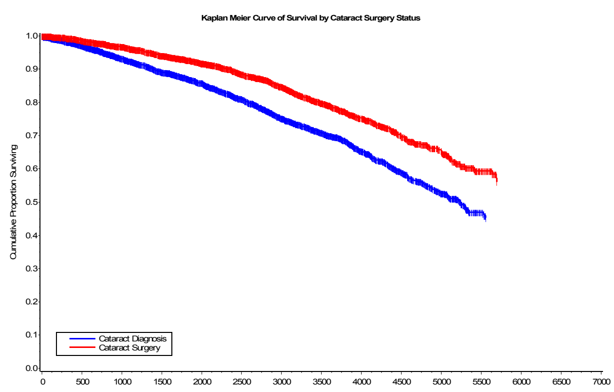
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Cumulative Proportion Surviving
Length of Follow-Up (Days)
Cataract Diagnosis
Cataract Surgery

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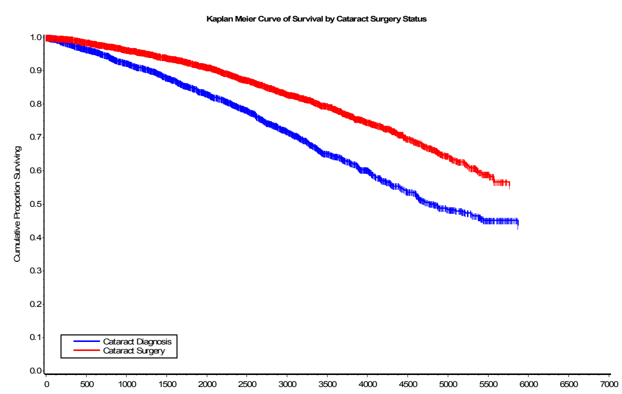
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Cumulative Proportion Surviving
Length of Follow-Up (Days)
Cataract Diagnosis
Cataract Surgery

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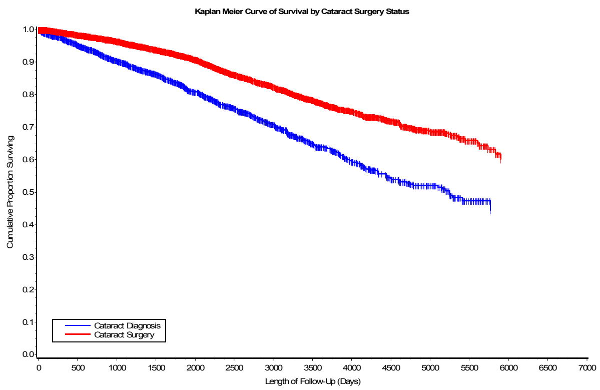

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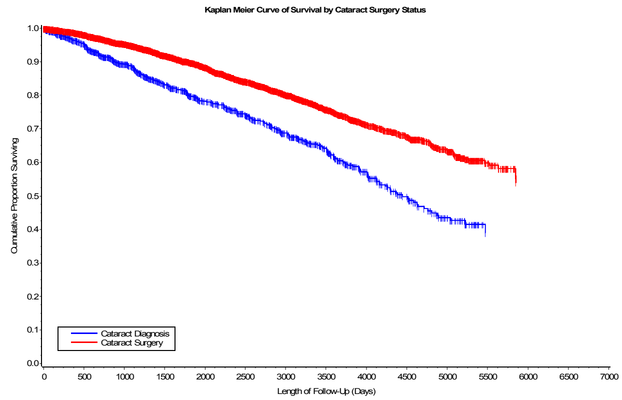

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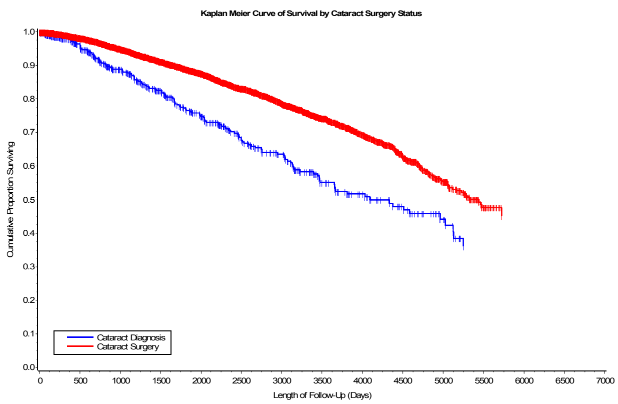

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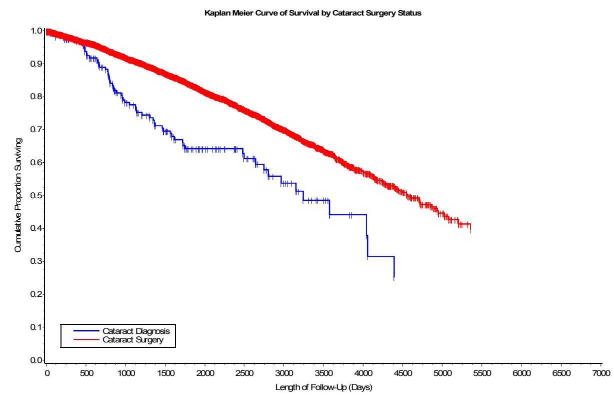
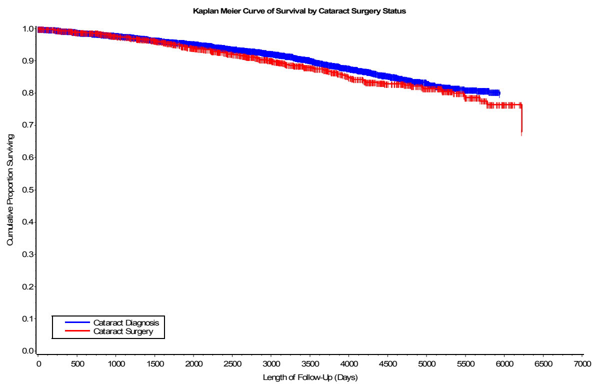
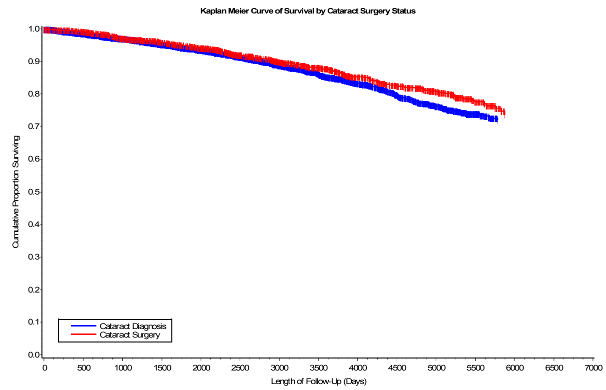


(j)

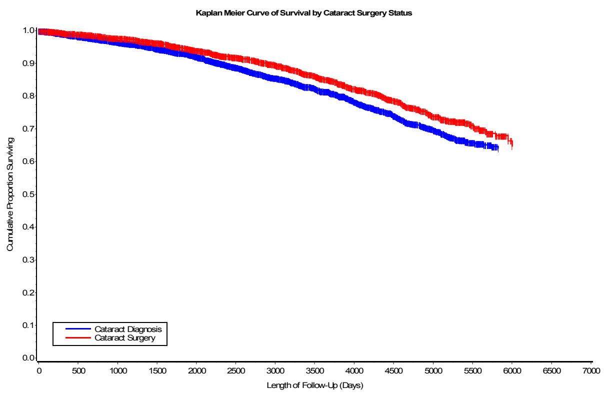
Figure 4.3. Kaplan Meier Curves for Mortality over Entire Duration of Study by Cataract Surgery Group by Propensity Score Decile Excluding Aphakic/Pseudophakic Group in the Women's Health Initiative (WHI) from 1993-2013 (n=80,406); (a) 1st decile, (b) 2nd decile, (c) 3rd decile, (d) 4th decile, (e) 5th decile, (f) 6th decile, (g) 7th decile, (h) 8th decile, (i) 9th decile, (j) 10th decile


Kaplan Meier Curve of Survival by Cataract Surgery Status
Cumulative Proportion Surviving
Length of Follow-Up (Days)
Cataract Diagnosis
Cataract Surgery

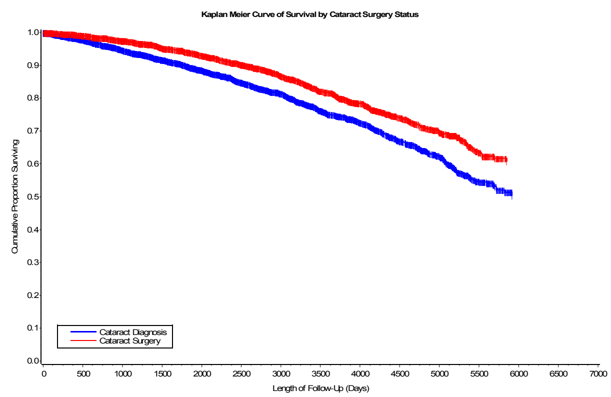
(a)


Kaplan Meier Curve of Survival by Cataract Surgery Status
Cumulative Proportion Surviving
Length of Follow-Up (Days)
Cataract Diagnosis
Cataract Surgery

(b)


Kaplan Meier Curve of Survival by Cataract Surgery Status
Cumulative Proportion Surviving
Length of Follow-Up (Days)
Cataract Diagnosis
Cataract Surgery

(c)


Kaplan Meier Curve of Survival by Cataract Surgery Status
Cumulative Proportion Surviving
Length of Follow-Up (Days)
Cataract Diagnosis
Cataract Surgery

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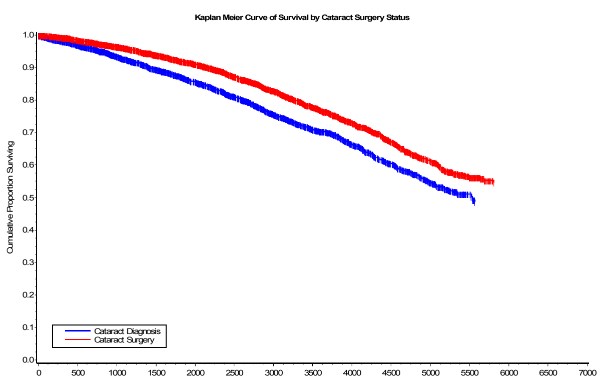
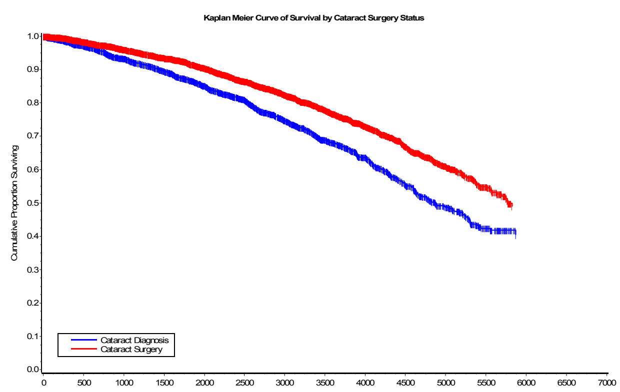
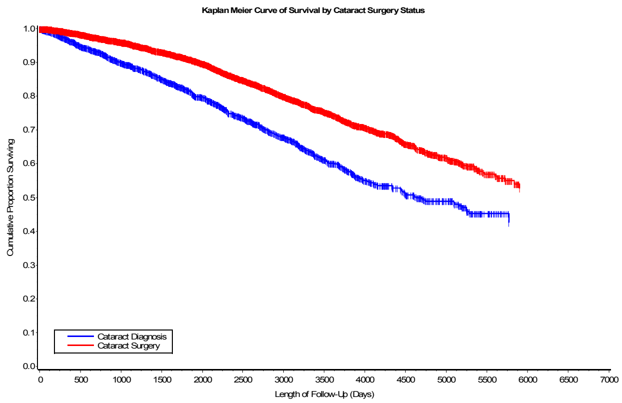

Kaplan Meier Curve of Survival by Cataract Surgery Status
Cumulative Proportion Surviving
Length of Follow-Up (Days)
Cataract Diagnosis
Cataract Surgery

(e)


Kaplan Meier Curve of Survival by Cataract Surgery Status
Cumulative Proportion Surviving
Length of Follow-Up (Days)
Cataract Diagnosis
Cataract Surgery

(f)



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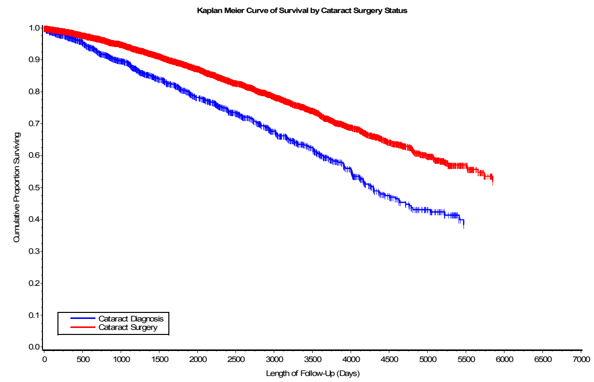

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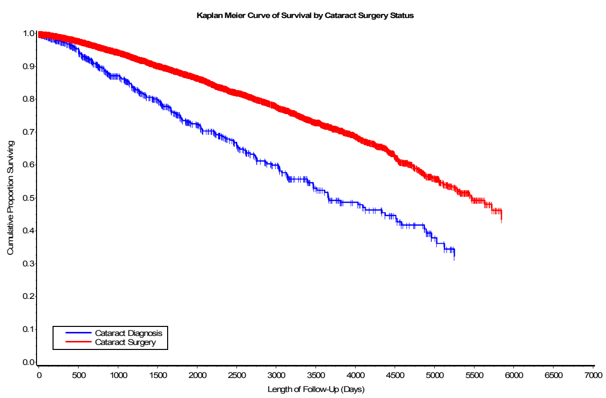

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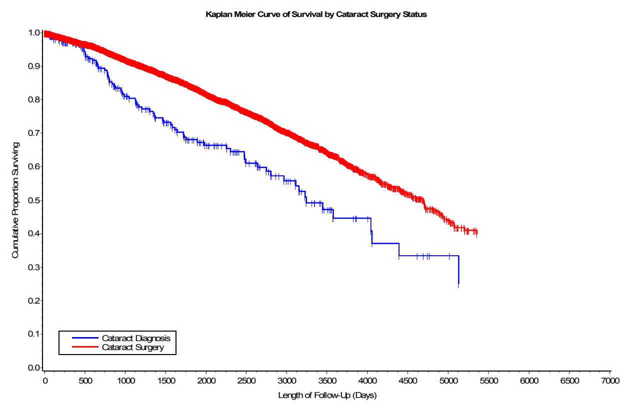

(j)

Figure 4.4. Kaplan Meier Curves for Mortality over Entire Duration of Study by Cataract Surgery Group by Propensity Score Decile Including Aphakic/Pseudophakic Group in the Women's Health Initiative (WHI) from 1993-2013 (n=80,406); (a) 1st decile, (b) 2nd decile, (c) 3rd decile, (d) 4th decile, (e) 5th decile, (f) 6th decile, (g) 7th decile, (h) 8th decile, (i) 9th decile, (j) 10th decile

Chapter 5: Public Health Importance

Cataract surgery is a widely performed procedure in the US, with cataract being one of the leading diagnoses at US ambulatory surgical centers.[5] While it is well understood that cataract surgery improves visual acuity, the secondary benefits of cataract surgery beyond vision improvement have not been well studied. With the rapidly aging US population, the incidence and prevalence of cataract will likely increase and it will be important to increase understanding of its management and related outcomes.

The research in this dissertation has contributed by providing information on the associations between cataract surgery, and falls, fractures, and subsequent long term mortality in a diverse population of patients who have cataract. The first study demonstrates that cataract surgery is potentially associated increased risk of falling at high frequencies overall, but potentially protective against falls in patients who are older, sicker, or with severe forms of cataract. These findings suggest that additional investigations are needed to understand how cataract surgery influences specific fall characteristics and other risk factors for fractures. The other two studies in this dissertation demonstrate that cataract surgery is associated with improved long term survival in multiple subsets of the US population after accounting for a broad array of demographic, systemic, and ocular comorbidities and characteristics.

Our findings support previous reports that cataract surgery may have benefits beyond vision improvement, and suggest that the management of reversible vision impairment is a worthy consideration for the improvement of overall systemic health, functioning, and quality of life. We hope that these findings will contribute to future cross-disciplinary studies of common visual conditions and their management, and to the overall improvement of ocular and systemic health.

Chapter 6: Appendices

Appendix 1. International Classification of Diseases-9th Revision-Clinical Modification (ICD-9-CM) and Current Procedural Terminology (CPT) Codes Included in Definition of Cataract and Related Procedures

Condition	Eligible ICD-9 Diagnosis Code
Cataract	366.x
Pseudophakia	V43.1
Severe cataract	366.13,14,17,18,19
Procedure	**Eligible CPT Code**
Simple cataract surgery	66984
Complex cataract surgery	66982
Secondary cataract removal	66830
Removal of lens material	66840, 66850, 66852, 66920, 66930, 66940
Intracapsular cataract surgery	66983
Procedure	**Eligible ICD-9 Procedure Code**
Insertion of intraocular lens	13.71
Phacoemulsification and aspiration of cataract	13.41
Mechanical phacofragmentation and other aspiration of cataract	13.43
Other cataract extraction	13.69
Intracapsular cataract surgery	13.19

Appendix 2. International Classification of Diseases-9th Revision-Clinical Modification (ICD-9-CM) Codes Included in the Definition of Comorbidities

Comorbidity	Eligible ICD-9 Codes
Myocardial Infarction	410-412.x
Congestive Heart Failure	398.91, 402.x, 404.x, 428.x
Peripheral Vascular Disease	440.24, 443.81, 443.89, 443.9, 785.4
Cerebrovascular Disease	430-438.x,
Dementia	290.x, 291.2, 292.82, 294.1, 294.8
Chronic Pulmonary Disease	490-496.x, 500-505.x, 506.4, 508.1
Rheumatologic Disease	710.x, 714.x, 720.x, 725.x
Peptic Ulcer Disease	531-534.x
Cirrhosis	571.x
Hepatic Failure	070.x, 456.x, 570.x, 572.x
Immunosuppression	279.9
Diabetes Mellitus	250.0-3x, 250.8-9x
Diabetes Mellitus w/ Complications	250.4-7x
Hemi/Paraplegia	342-344.x
Chronic Renal Disease	403-404.x, 582-583.x, 585-586.x, 588.x, 593.9
Malignant Neoplasms	140-172.x, 174-176.x 179-195.x
Multiple Myeloma/Leukemia	203, 204, 205, 206,207,207208
Lymphomas	200-202.x
Metastatic Solid Tumor	196-198.x, 199.0-1x
AIDS	042-043.x
Glaucoma	365.x
Diabetes Mellitus with Ophthalmic Manifestations	250.5x, 362.0x
Age-Related Macular Degeneration	362.50-52

Appendix 3. Systemic and Ocular Comorbidities Collected within the Women's Health Initiative (WHI) and Medicare Databases

Comorbidity	Available in WHI	Available in Medicare
Myocardial Infarction	X	X
Congestive Heart Failure	X	X
Peripheral Vascular Disease	X	X
Cerebrovascular Disease	X	X
Dementia		X
Chronic Pulmonary Disease	X	X
Rheumatologic Disease	X	X
Peptic Ulcer Disease	X	X
Cirrhosis		X
Hepatic Failure		X
Immunosuppression	X	X
Diabetes Mellitus		X
Diabetes Mellitus w/ Complications		X
Hemi/Paraplegia		X
Chronic Renal Disease		X
Malignant Neoplasms	X	X
Multiple Myeloma/Leukemia	X	X
Lymphomas	X	X
Metastatic Solid Tumor		X
AIDS		X
Glaucoma		X
Diabetes Mellitus with Ophthalmic Manifestations		X
Age-Related Macular Degeneration		X

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