Higher Cognitive Function in Elderly Individuals with Previous Cataract Surgery: Cross-Sectional Association Independent of Visual Acuity in the HEIJO-KYO Cohort

Abbreviated title: Cataract Surgery and Cognition and Vision

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Abstract

Cataract surgery improves visual acuity and drastically increases the capacity for light reception to the retina. Although previous studies suggested that both light exposure and visual acuity were associated with cognitive function, the relationships between cataract surgery, visual acuity, and cognitive function have not been evaluated in large populations. In this cross-sectional study, we measured cognitive function using the Mini-Mental State Examination and best-corrected visual acuity in pseudophakic (previous cataract surgery) and phakic (no previous cataract surgery) elderly individuals. Of 945 participants (mean age: 71.7 years), 166 (17.6%) had pseudophakia and 317 (33.5%) had impaired cognitive function (score ≤26). The pseudophakic group showed significantly better visual acuity than the phakic group (P=0.003) and lower age-adjusted odds ratio for cognitive impairment (odds ratio, 0.66; P=0.038). Consistently, in multivariate logistic regression models, after adjusting for confounding factors, including visual acuity and socioeconomic status, odds ratios for cognitive impairment were significantly lower in the pseudophakic group than in the phakic group (odds ratio, 0.64; 95% confidence interval, 0.43–0.96; P = 0.031). This association remained significant in sensitivity analysis, excluding participants with low cognitive score ≤23 (n=36). In conclusion, in a general elderly population, prevalence of cognitive impairment was significantly lower in pseudophakic individuals independently of visual acuity. The association was also independent of several major causes of cognitive impairment such as aging, gender, obesity, socioeconomic status, hypertension, diabetes, sleep disturbances, depressive symptoms, and physical inactivity.
Introduction

A growing interest has been in the pre-dementic state such as mild cognitive impairment because of its higher prevalence than dementia and more frequent conversion to dementia than that from normal cognitive status. Functional impairment, decreased quality of life, and early mortality occurs in elderly individuals with this cognitive status. Therefore, most investigators consider preventing/postponing cognitive decline before reaching this status. However, progressive factors for cognitive decline are not fully understood.

Visual impairment is associated with cognitive decline. In the elderly, cataract, age-related cloudiness of the crystalline lens, is frequent and represents the worldwide leading cause of visual impairment. Cataract surgery, replacement of the clouded crystalline lens with intraocular lens (IOL), is a common procedure and visual acuity is significantly better in pseudophakic (previous cataract surgery) than phakic (no previous cataract surgery) individuals. Previous interventional studies using a pretest-posttest design reported significant increases in cognitive score after treating visual impairment by cataract surgery, although some studies have shown no significant associations between cataract surgery and cognitive performance, including one randomized control trial on the subject.

Recent advances in chronobiological knowledge have linked light reception to cognitive function. Light is crucial for synchronizing the internal biological rhythm to the environmental rhythm. Previous studies suggested that daytime bright light intervention prevents cognitive decline and improves mood and sleep quality in the elderly. Age-related cloudiness of crystalline lens causes decreased light reception to the retina, even before cataract diagnosis. In general, the capacity for light reception in the 70s corresponds to one-fifth of that in teens. Particularly, lens aging is associated with the loss of shorter
wavelengths, below 500 nm, for which intrinsically photosensitive retinal ganglion cells, primary light receptors in the retina are most sensitive.\textsuperscript{20}

Cataract surgery improves visual acuity and drastically increases the capacity for light reception to the retina. Therefore, cataract surgery may improve cognitive function independently of visual acuity. However, the relationships between cataract surgery, visual acuity, and cognitive function have not been evaluated in large populations. In this cross-sectional study including 945 community-dwelling elderly participants, we measured cognitive function using the Mini-Mental State Examination (MMSE) and best-corrected visual acuity in pseudophakic and phakic elderly individuals.
Methods

Participants

Between September and April in 2010 to 2014, 1127 community-dwelling elderly subjects (≥60 years) were voluntarily enrolled in the Housing Environments and Health Investigation among Japanese Older People in Nara, Kansai Region: a prospective community-based cohort (HEIJO-KYO) study. Of these, ocular status, visual acuity, and cognitive function were evaluated in 945 participants. All participants provided written informed consent; the study protocol was approved by the medical ethics committee of Nara Medical University.

Measurement of cognitive function

Cognitive function was assessed by trained clinical psychologists using the MMSE. Higher MMSE scores indicate better cognitive function (range: 0–30). In this study, cognitive impairment was defined as MMSE scores ≤ 26. According to a previous study, higher cut-off value provide better balance of sensitivity and specificity than the traditional value of 23 in an educated population (0.69 and 0.91 vs. 0.45 and 1.00, respectively, for cognitive impairment and 0.79 and 0.90 vs. 0.58 and 0.98, respectively, for Alzheimer’s disease).

Ascertainment of cataract surgery and measurement of visual acuity

A standardized questionnaire was used to ascertain whether participants were pseudophakic or phakic for at least one eye. Accuracy of self-reported pseudophakia was assessed by ophthalmologist’s direct observation of the IOL using slit lamp examination in the initial 194 participants. Agreement for pseudophakia between the two data sets was sufficiently high (Kappa coefficient = 0.95).
The best-corrected visual acuity was measured by trained orthoptists, using Landolt ring chart. Better value of log-transformed minimal angle resolution (LogMAR) was used for analysis.

**Other measurements**

Educational level, household income, and information on medicines were evaluated using a self-administered questionnaire. Hypertension was defined based on self-reported previous diagnosis and current antihypertensive therapy. Diabetes mellitus was defined based on self-reported previous diagnosis, current antidiabetic therapy, and fasting plasma glucose and glycated hemoglobin levels. Subjective sleep quality and depressive symptoms were evaluated using self-administered questionnaires from the Pittsburgh Sleep Quality Index (PSQI) and the short version of the Geriatric Depression Scale (GDS-15), respectively. Subjective insomnia was defined based on PSQI score $\geq 6$. Depressed mood was defined based on GDS-15 score $\geq 6$. Physical activity counts were measured at 1-min intervals during waking hours using an actigraph (Actiwatch 2; Respironics Inc., PA, USA) worn on the non-dominant wrist. Average physical activity collected on two consecutive days was used for analysis.

**Statistical Analysis**

Means and proportions between normal and impaired cognitive function groups were compared using the unpaired $t$-test and Chi-square test, respectively. Logistic regression models included cognitive status as a dependent variable and ocular status, age (per year), gender, body mass index (BMI), educational level ($\geq 13$ years), household income ($\geq 4$ million Japanese yen per year), hypertension, diabetes, subjective sleep quality (PSQI score $\geq 6$), depressive symptoms (GDS score $\geq 6$), daytime physical activity (per 100 counts/min), and
visual acuity (per logMAR) as independent variables, which are reported to be associated with cognitive function. In multivariate statistical models, model 1 was adjusted for age, education, and visual acuity; model 2 for independent variables associated with cognitive status in Table 1 ($P < 0.25$); and model 3 for all independent variables in Table 1. No serious multicollinearity was observed (all variance inflation factors $< 10$) in any of those. For missing data, values of the mean or proportion were substituted. Statistical analysis was performed using the SPSS version 19.0 for Windows (IBM SPSS Inc., IL, USA). A two-sided $P$ value $< 0.05$ was considered statistically significant.
Results

Mean age of participants was 71.7 ± 7.1 years, and 442 (46.8%) were male. Of 945 participants, 166 (17.6%) had pseudophakia. The impaired cognitive function group (n = 317) showed significantly higher age, lower educational level and household income, more hypertension, and worse visual acuity than the preserved cognitive function group (n = 628, Table 1). Significantly better visual acuity was detected in the pseudophakic group than in the phakic group (age-adjusted logMAR: −0.001 vs. 0.069, P = 0.003).

The pseudophakic group showed significantly lower odds ratio (OR) for cognitive impairment in a logistic regression model after adjusting for age [OR, 0.66; 95% confidence interval (CI), 0.45–0.98; P = 0.038; Table 2]. Consistently, in multivariate logistic regression models after adjusting for confounding factors, including visual acuity, ORs for cognitive impairment were significantly lower in the pseudophakic group than the phakic group (model 1: OR, 0.66; 95% CI, 0.44–0.98; P = 0.039; model 2: OR, 0.64; 95% CI, 0.43–0.95; P = 0.026; model 3: OR, 0.64; 95% CI, 0.43–0.96; P = 0.031).

In sensitivity analysis excluding participants with low MMSE score ≤23 (n = 36), the association between pseudophakia and cognitive impairment remained significant in the multivariate models (model 1: OR, 0.59; 95% CI, 0.39–0.91; P = 0.016; model 2: OR, 0.57; 95% CI, 0.37–0.87; P = 0.009; model 3: OR, 0.58; 95% CI, 0.38–0.89; P = 0.013).
Discussion

We found clear evidence in a large population that pseudophakia was significantly associated with lower prevalence of cognitive impairment in multivariate statistical models adjusting for visual acuity and several major causes of cognitive impairment such as aging, gender, obesity, socioeconomic status, hypertension, diabetes, sleep disturbances, depressive symptoms, and physical inactivity.

These results were consistent with those in previous observational and interventional studies, and we added evidence that the association between pseudophakia and cognitive function was independent of visual acuity in a large general population. In an English epidemiological study, MMSE score in pseudophakic elderly individuals (n = 302) was significantly higher than that in phakic elderly individuals (n = 443). Another English study using a pretest-posttest design reported significant increases in mean MMSE score between baseline and 6 months after cataract surgery on the first-eye (n = 46) and second-eye (n = 39). A Japanese study using the same design indicated that cataract surgery significantly improved the mean MMSE score at 2 months after cataract surgery (n = 102). Another Japanese study, using pretest-posttest control group design, indicated that cataract surgery significantly improved the mean score of the Revised Hasegawa Dementia Scale compared with that in the control group (n = 40). These results showed beneficial effects of cataract surgery on cognitive function accompanied by improved visual acuity; however, statistical analysis adjusting for improved visual acuity by cataract surgery was not considered.

Our findings suggest a potential mechanism underlying the association between pseudophakia and better cognitive function other than improving visual acuity.
Chronobiological researches indicate that light is a primary environmental cue for regulating the biological clock and that misalignment in circadian rhythmicity may predispose to cognitive impairment.\textsuperscript{25,26} Daytime bright light prevents cognitive decline in elderly individuals as shown in a long-term randomized controlled trial.\textsuperscript{17} Major causes of cognitive decline, including depression and sleep disturbances, were also improved by daytime light exposure in previous interventional studies.\textsuperscript{18,19}

These effects of daytime light may be based on increased melatonin secretion. Melatonin is involved in sleep quality and circadian biological rhythmicity, and acts as a potent antioxidant by free radical scavenging and may have a protective effect against oxidative brain injury.\textsuperscript{28,29} Indeed, physiological melatonin levels are significantly reduced in patients with Alzheimer's disease or major depressive disorder.\textsuperscript{29,30} In previous experimental studies, daytime light intervention increases total amount of melatonin secretion in the young and elderly people.\textsuperscript{19,32,33} Consistently, in our previous study, daytime light exposure was positively associated with melatonin secretion.\textsuperscript{21} In addition, although daytime ambient light intensity was similar in pseudophakic and phakic elderly people, levels of endogenous melatonin did not significantly differ between the two groups.\textsuperscript{23} An interventional study is required to better understand the effects of cataract surgery on melatonin secretion.

Our findings may be underestimated when considering the effect of cataract surgery on cognitive function. In our study, prevalence of cognitive impairment was 36% (95% CI, 4%-57%) lower in pseudophakic elderly individuals than in phakic individuals. However, most of our phakic participants may not have advanced cataract; therefore, the magnitude of influence of cataract surgery on cognitive function may be greater when compared between pseudophakic individuals and individuals with advanced cataract. In addition, the IOLs implanted in the pseudophakic group may include yellow lenses, although we have no information related to the IOLs. This may also cause an underestimation of our findings.
because yellow IOLs filter short wavelengths, mostly sensitive to alignment of circadian biological rhythms.\textsuperscript{20}

There are some limitations in our study. First, the cross-sectional design precluded assessment of causality. Although previous pretest-posttest studies support the beneficial effects of cataract surgery on cognitive function,\textsuperscript{12-14} it is possible that people with good cognition are more likely to receive cataract surgery. Future randomized controlled trials are required to confirm the causality. Second, the lack of participants with clinically diagnosed cognitive impairment may have led to the misclassification of cognitive status. However, the moderately high agreement in previous validation studies suggests infrequent misclassification. Third, ocular status was ascertained using a self-reported questionnaire rather than objective measurement, possibly leading to some misclassification of pseudophakia. However, the validation analysis suggested sufficiently high agreement between self-reported questionnaire and objective measurement of pseudophakia. In addition, the results of sensitivity analysis excluding individuals with low cognition were consistent with those in whole samples, and the association between pseudophakia and cognitive function became mildly stronger, possibly suggesting a more accurate ocular status detected in this group. Finally, we have no information related to the period between cataract diagnosis and cataract surgery. Indeed, long cataract period may cause irreversible cognitive impairment; however, this would cause an underestimation of our findings. Non-significant associations between pseudophakia and cognitive function observed in a previous telephone survey might be caused by the differences in this period or data collection method from our study.\textsuperscript{34}

In conclusion, in a large general elderly population, prevalence of cognitive impairment was significantly lower in pseudophakic individuals independently of visual acuity. This association was also independent of several major causes of cognitive impairment such as
aging, gender, obesity, socioeconomic status, hypertension, diabetes, sleep disturbances, depressive symptoms, and physical inactivity.

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Author Disclosure Statement

All authors report no conflicts of interest.
References


Table 1. Basic and Clinical Characteristics for 945 Participants by Cognitive Status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Preserved (MMSE ≥27)</th>
<th>Impaired (MMSE ≤26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>628</td>
<td>317</td>
<td></td>
</tr>
<tr>
<td>Examination score, median (range)</td>
<td>29 [27, 30]</td>
<td>25 [13, 26]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Basic parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), years</td>
<td>70.7 (7.0)</td>
<td>73.7 (6.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gender (male), number (%)</td>
<td>303 (48.2)</td>
<td>139 (43.8)</td>
<td>0.20</td>
</tr>
<tr>
<td>Body mass index, mean (SD), kg/m²</td>
<td>23.1 (3.0)</td>
<td>23.2 (3.2)</td>
<td>0.50</td>
</tr>
<tr>
<td>Education (≥13 years), number (%)</td>
<td>206 (32.8)</td>
<td>60 (18.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Household income (≥4 million JPY/year), number (%)</td>
<td>276 (46.6)</td>
<td>97 (35.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Clinical parameters</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, number (%)</td>
<td>259 (41.2)</td>
<td>159 (50.2)</td>
<td>0.009</td>
</tr>
<tr>
<td>Diabetes, number (%)</td>
<td>72 (11.5)</td>
<td>38 (12.1)</td>
<td>0.82</td>
</tr>
<tr>
<td>Subjective sleep quality (PSQI ≥6), number (%)</td>
<td>208 (33.1)</td>
<td>119 (37.5)</td>
<td>0.17</td>
</tr>
<tr>
<td>Depressive symptoms (GDS ≥6), number (%)</td>
<td>90 (14.4)</td>
<td>55 (17.5)</td>
<td>0.22</td>
</tr>
<tr>
<td>Daytime physical activity, mean (SD), count/min</td>
<td>300.8 (103.0)</td>
<td>297.0 (104.7)</td>
<td>0.60</td>
</tr>
<tr>
<td>Visual acuity, mean (SD), LogMAR</td>
<td>0.043 (0.234)</td>
<td>0.088 (0.256)</td>
<td>0.012</td>
</tr>
</tbody>
</table>

SD, standard deviation; JPY, Japanese Yen; MMSE, Mini-Mental State Examination; PSQI, Pittsburg Sleep Questionnaire Index; GDS, Geriatric Depression Scale
## Table 2. Logistic Regression Analysis for the Association between Ocular Status and Cognitive Impairment

<table>
<thead>
<tr>
<th>Ocular status</th>
<th>Age-adjusted</th>
<th>Multivariate OR for cognitive impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Model 1</td>
</tr>
<tr>
<td>Phakia (no previous cataract surgery)</td>
<td>1.00 (ref)</td>
<td>1.00 (ref)</td>
</tr>
<tr>
<td>Pseudophakia (previous cataract surgery)</td>
<td>0.66 (0.45, 0.98)</td>
<td>0.66 (0.44, 0.98)</td>
</tr>
<tr>
<td>P value</td>
<td>0.038</td>
<td>0.039</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval.
Model 1: Adjusted for age, education, and visual acuity.
Model 2: Adjusted for variables associated with impaired cognitive function in Table 1 (P <0.25).
Model 3: Adjusted for all variables shown in Table 1.