VNIVERSITAT
DE VALÈNCIA

Intraocular Scattering Changes with Age

PROGRAMA DE DOCTORADO EN OPTOMETRÍA Y CIENCIAS DE LA VISIÓN

Doctorando:
Sonia Gholami

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Thomas J. T. P. van den Berg
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Jan C. van Meurs

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Burjassot, Junio 2017

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Intraocular Scattering Changes with Age

Thesis presented by Sonia Gholami

To apply for the Degree of DOCTOR OF PHILOSOPHY

in

OPTOMETRY AND VISION SCIENCES

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This project has received funding from the European Union’s FP7 research and innovation program under the Marie Curie Initial Training Network AGEYE (FP7- PEOPLE-ITN-2013), grant agreement No 608049.

DECLARATION

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other University or other institution of Learning.

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Prof. Thomas JTP van den Berg, from The Netherlands Institute for Neuroscience, **Dr. Nicolaas J Reus**, from Amphia Hospital, **Prof. Jan van Meurs**, from Rotterdam Ophthalmic Institute, and **Dr. Alejandro Cerviño Expósito**, from University of Valencia, CERTIFY that the present report entitled “Intraocular scattering changes with age”, summarizes the research work carried out, under their supervision, by **Ms. Sonia Gholami** and constitutes her thesis to apply for the degree of **Doctor of Philosophy in Optometry and Vision Sciences**.

And to make it be on record, and complying with current legislation, they sign the present certificate in Valencia, on the first day of June of the year two thousand and seventeen.

Prof. Thomas J. T. P. van den Berg

Dr. Nicolaas J. Reus

Prof. Jan van Meurs

Dr. Alejandro Cerviño Expósito

I dedicate this thesis to my parents,

Mahnaz and Esfandiar,

for their unconditional love and support.

تقدیم به مادرم و پدرم،

مهناز و اسفندیار

`

“There are no incurable diseases – only the lack of will.

There are no worthless herbs – only the lack of knowledge.”

— Avicenna, 980-1037

Acknowledgements

I would like to express my gratitude to those who helped me to bring this work to an end.

First and foremost, I deeply thank my parents, for their love and support throughout my life. I can never thank you enough for giving me the freedom and strength to choose my path and chase my dreams. My sister, my biggest fan, you believed in me even when I didn’t believe in myself. My little brother, my nephew, my siblings-in-law, I thank you all wholeheartedly.

I would like to express my special gratitude to my daily supervisors, Dr. Thomas van den Berg and Dr. Nicolaas Reus, for their guidance, constructive criticism, and support. I am grateful to Prof. Dr. Robert Montés-Micó, and my supervisor Dr. Alejandro Cerviño, who made it possible for me to graduate from University of Valencia and helped me at every step of it. I also thank Prof. Dr. Jan van Meurs my supervisor and the scientific director at Rotterdam Ophthalmic Institute.

I am grateful to anyone whom I worked with over the past three years, who either contributed to this work in some way or offered me moral support.

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Resumen

Durante la conducción nocturna es posible experimentar deslumbramiento producido por las luces delanteras de los coches que vienen en sentido contrario. Esto también puede ocurrir cuando el sol se encuentra bajo. La falta de homogeneidad en los medios pueden producir dispersión de la luz, resultando en un velo de luz que se proyecta sobre la imagen retiniana. La Commission Internationale de l'Éclairage (CIE) define esta luz dispersada sobre la retina (en adelante se empleará su denominación en inglés, straylight) como deslumbramiento discapacitante. Este straylight se manifiesta, sin embargo, como algo más que únicamente un deslumbramiento. La pérdida de color y contraste, visión con neblina, y dificultad en el reconocimiento facial a contraluz son algunas de las quejas referidas por sujetos con niveles elevados de straylight. Incluso en ojos jóvenes sanos, una pequeña parte de la luz que entra en el ojo es dispersada. La dependencia con la edad del straylight en la población sana ha sido ampliamente estudiada. Hoy se sabe que el envejecimiento y varias condiciones patológicas, tales como catarata, pueden elevar el straylight. Aunque el straylight no aumenta antes de los 40 años de edad, algunas condiciones patológicas, tales como catarata congénita, pueden incrementarlas, algunas veces a niveles extremos. La dependencia del straylight con la catarata ha sido estudiado en varios tipos de catarata. Mientras que el straylight varia entre cataratas de diferentes morfologías, en algunos casos un nivel de straylight marcadamente elevado puede estar acompañada de una buena agudeza visual.

Se cree que la catarata, la opacificación progresiva del cristalino, ocurre cuando las proteínas que forman el cristalino resultan dañadas o desorganizadas. A medida que la catarata progresa, puede causar una pérdida gradual de la visión y, eventualmente, llevar a ceguera total. La catarata es la causa más frecuente de pérdida de visión en el mundo. A pesar del cada vez mayor número de cirugías de catarata en el mundo y el avance en las técnicas de medida e instrumentación quirúrgica, el proceso de toma de decisiones que indica la cirugía de catarata sigue siendo el tradicional, esto es, los

oftalmólogos únicamente tienen en cuenta medidas subjetivas (por ej. quejas visuales del paciente, agudeza visual, y transparencia de los medios oculares evaluados con lámpara de hendidura). La información es contrastada entonces con las demandas visuales del paciente. Sin embargo, una evaluación más objetiva del impacto de la catarata en la función visual, y el impacto de la cirugía en la función visual, podría ser interesante. Por esa razón, parecen lógicos la identificación y empleo de variables cuantificables, y su equilibrado frente a las medidas subjetivas. En esta tesis doctoral se han evaluado varias funciones ópticas a ser consideradas como medidas objetivas del efecto visual de la catarata. El principal interés de este trabajo fue, sin embargo, estudiar el cambio en la cantidad de luz dispersada en el ojo envejecido, con un enfoque en los ojos con catarata. Potencialmente, en el futuro tales medidas objetivas podrías ser utilizadas en el desarrollo de un algoritmo que podría convertirse en un sustituto apto para el proceso actual de toma de decisiones sobre la catarata.

Conocer el efecto funcional de la catarata en la función visual es esencial. Las imperfecciones ópticas determinan la calidad de la imagen retiniana. En la práctica, ésta puede ser evaluada mediante la determinación de la cantidad de luz (proveniente de una fuente puntual) que es esparcida sobre la retina. Esta es la denominada función de esparcimiento de punto, o point spread function (PSF), la cual es aceptada como la función que proporciona una descripción completa de la calidad óptica del sistema. En ausencia de imperfecciones de cualquier tipo (es decir, en un ojo perfecto), la respuesta de un sistema óptico es idéntica a la luz incidente . Sin embargo, en el ojo humano con imperfecciones en los medios ópticos, la luz se esparce y genera un punto brillante en el centro, perdiendo intensidad de forma gradual pero continua hacia la periferia. Dos aspectos de la PSF que pertenecen a dos dominios funcionales diferentes deben ser combinados: una porción central y un faldón exterior. Este faldón exterior (mayor a 1º), es el denominado dominio de ángulo amplio, y es producido por el straylight. El straylight puede ser cuantificado utilizando un straylightmeter disponible comercialmente (C-Quant, Oculus Optikgeräte GmbH, Wetzlar, Germany). La porción central de la PSF, denominado dominio de ángulo estrecho (hasta 0.3°), está afectado

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por las aberraciones ópticas. En la práctica clínica, es este dominio de ángulo estrecho el que es evaluado mediante las pruebas de agudeza visual, sensibilidad al contraste, y con los sistemas de aberrometría que determinan las aberraciones de alto y bajo orden. Las aberraciones ópticas del ojo limitan la calidad de la imagen retiniana y restringen la visión espacial reduciendo la agudeza visual y el contraste. Mediante la evaluación de las aberraciones del frente de onda puede obtenerse información importante. La aberrometría ocular ha venido siendo realizada durante las últimas décadas. Los métodos primarios se basaban en medidas subjetivas. Sin embargo, con la aparición de los aberrómetros automatizados, se ha vuelto posible para los oftalmólogos medir las aberraciones de alto orden de forma tan sencilla como la medida de las de bajo orden con un refractómetro. Los aberrómetros comerciales utilizan diversos principios de medida para determinar las aberraciones del ojo, como Shack-Hartmann, trazado de rayos, o Tscherning, y proporcionan mapas aberrométricos con gran cantidad de detalle. La cantidad de detalle contenida en esos mapas pueden hacer de su interpretación una tarea dura y confusa. Para facilitar la comprensión de los mapas aberrométricos, éstos pueden ser descritos mediante polinomios de Zernike. Algunas métricas tales como la ratio de Strehl y la raíz cuadrática media (RMS) del error de frente de onda han sido utilizados ampliamente en oftalmología. Algunos estudios, sin embargo, han mostrado que estas métricas no son predictores adecuados de la solvencia visual. Hay múltiples maneras de formular métricas de calidad de imagen en el ojo humano. Una publicación demostró la correlación de 31 métricas de calidad de imagen con la agudeza visual de alto contraste. Las correlaciones fueron estimadas para una pupila de 6-mm donde la RMS del error se mantenía constante. Este estudio concluyó que la mejor métrica en términos de alta correlación con la agudeza visual, como medida de solvencia visual, fue una métrica de calidad de imagen basada en la ratio de Strehl denominada ratio de Strehl visual (VSR). Esta métrica es la ratio de la intensidad actual de la PSF del ojo en presencia de aberraciones en el punto imagen Gaussiana y la intensidad máxima de un punto limitado por la difracción en ausencia de cualquier aberración. Lo que distingue esta métrica de la métrica de ratio de Strehl, es la inclusión de componentes neurales

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del sistema visual. Previamente se ha mostrado que 0.25 µm de aberración sobre una pupila de 6-mm podrían cambiar la agudeza visual en dos líneas logMAR, mientras que el error RMS total permanece inalterado. También se ha mostrado que la combinación de modos de Zernike pueden ser más importantes que la magnitud de cada uno de manera individual. El tipo y proporciones relativas de cada modo en la combinación determinan la cantidad de ganancia/pérdida en solvencia visual, permaneciendo el error RMS y el tamaño pupilar constante. Se ha referido que la mejor métrica VSR responde al 81% de la varianza en agudeza LogMAR de alto contraste en ojos normales (sin catarata), y se ha mostrado por parte de los autores originales que es un predictor preciso de la agudeza visual. Otros estudios también han confirmado que hay una fuerte correlación entre las métricas VSR y a agudeza visual.

Como se ha mencionado antes, los objetivos de esta tesis fueron (1) estudiar el straylight in vivo en ojos envejecidos con un enfoque hacia los ojos cataratosos; (2) estudiar la idoneidad de ciertas funciones ópticas y la morfología de la catarata como discriminadores fiables para poder desarrollar un algoritmo de ayuda en la toma de decisión quirúrgica en el futuro.

En el **Capítulo 2**, el objetivo era intentar averiguar cuales son las condiciones pupilares durante la medida del straylight, y qué efecto potencial podría tener en el valor de straylight obtenido. En otras palabras, se investigó si el tamaño pupilar y el straylight medido bajo condiciones de iluminación tenue son las mismas que el tamaño pupilar y valor de straylight obtenidos bajo condiciones de oscuridad. Con este objetivo se diseñó un estudio que englobaba dos partes: (1) La medida del diámetro pupilar bajo varios niveles de iluminación ambiental; (2) La medida del straylight ocular bajo varios niveles de iluminación ambiental. Un grupo de 21 sujetos, 6 de ellos entre con edades comprendidas entre los 26 y los 29, y 15 de ellos entre los 50 y los 68 años de edad, del personal del Rotterdam Ophthalmic Institute, todos ellos con respuestas pupilares normales, se ofrecieron voluntarios para participar en este estudio. Tres de los sujetos más jóvenes no eran caucásicos, mientras que los 18 restantes sí lo eran. La primera parte de las medidas fueron realizadas en 20 de ellos; uno de los sujetos del grupo más joven se retiró del estudio. Primero se determinó el tamaño pupilar bajo tres niveles de iluminación ambiental: 4, 40, y 400 lux, medidos sobre la superficie de la mesa. Para eliminar el efecto del hippus, se permitió un tiempo de adaptación de 15 segundos. Las medidas fueron tomadas del nivel de iluminación más bajo al más elevado. A continuación, el straylight fue determinado utilizando el C-Quant straylightmeter. El C-Quant funciona basándose en el método de comparación de compensación, que compara la amplitud de un parpadeo contra-fase de luz requerido para compensar el parpadeo de luz inducido por la fuente de straylight. Simultáneamente, el cambio de tamaño pupilar del ojo contralateral fue registrado con una cámara montada sobre la cubierta del straylightmeter. Los resultados mostraron que el tamaño de la pupila disminuyó con la iluminación ambiental y con la edad (ambos $p < 0.05$). La dependencia del tamaño pupilar con la edad disminuye a medida que se incrementa la iluminación de la habitación (0.018 mm/año a 4 lux, 0.014 mm/año a 40 lux, y 0.008 mm/año a 400 lux). Sin embargo, durante la medida del straylight, los tamaños pupilares difícilmente difirieron entre los 4 y los 40 lux. Los tamaños pupilares respectivos se correspondían en promedio con la adaptación a 399 y 451 lux. No se encontraron diferencias estadísticamente significativas entre el straylight obtenido bajo ambas iluminancias, con un R2 promedio de 0.85, $p < 0.05$. Aunque el tamaño pupilar se ve afectado por más factores, tales como el tamaño del campo y el número de ojos adaptados, deducimos de los resultados que con niveles bajos de iluminación, el tamaño de la pupila varía más con la edad. Es más, el diámetro pupilar promedio mostró muy poco cambio de las condiciones de iluminación baja a intermedia. Tampoco se encontró una dependencia entre el tamaño de la pupila y los valores de la luz de la calle usando dos condiciones de luz. Los datos mostraron que la desviación estándar de la diferencia de straylight entre los ojos derecho e izquierdo aumentó con la edad, aunque ligeramente. Sin embargo, el valor medio de estas diferencias y las desviaciones estándar fueron pequeñas en ambos niveles de iluminancia. En conjunto, se llega a la conclusión de que la iluminancia de la sala de examen durante la evaluación del

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straylight no afecta al resultado en ojos normales. Bajo condiciones mesópicas y escotópicas, la luminancia del campo de prueba es mucho más alta que la de la habitación, que determina el tamaño de la pupila. Independientemente del nivel de iluminación, el straylight determinado en un laboratorio es válido para pupilas fotópicas a un nivel de adaptación correspondiente a una iluminación de sala de aproximadamente 400 lux.

En el **capítulo 3**, se prueba la utilidad de la VSR ocular derivada de aberraciones de frente de onda, calculado en el dominio de frecuencia utilizando la función de transferencia de modulación (VSMTF), para cuantificar la severidad de la catarata relacionada con la edad en términos de agudeza visual. En consecuencia, se establecen los siguientes objetivos: (1) estudiar la correlación entre el VSMTF y la agudeza visual en ojos con catarata y sin corrección y comparar el resultado con el de ojos normales; (2) Avanzar con la estimación de la correlación entre VSMTF y la agudeza visual en ojos con catarata después de corregir sus aberraciones de bajo orden. En este estudio exploratorio observacional, se incluyeron 18 ojos sanos de 9 sujetos y 15 ojos de 15 pacientes con catarata nuclear, cortical o subcapsular posterior. La edad media en el grupo sano fue de 36,5 ± 12,6 años (rango de 25 a 56) y 68,9 ± 9,1 años (de 54 a 82) en el grupo con catarata. Se calculó el VSMTF basado en aberraciones de bajo orden (desenfoque Z_2^0, astigmatismo Z_2^{-2} y Z_2^2) y varias aberraciones de alto orden (coma Z_3^{-1} y Z_3^1, trefoil Z_3^{-3} y Z_3^3, esférica primaria Z_4^0, astigmatismo secundario Z_4^{-2} y Z_4^2, y quadrafoil Z_4^{-4} y Z_4^4). El aberrómetro utilizado en este estudio analiza el total de WFAs hasta el décimo orden. La métrica de plano de imagen VSMTF es una función matemática que toma coeficientes de expansión de Zernike normalizados como entrada y entrega un valor único entre cero y uno como salida. El VSMTF se calculó utilizando un código Matlab desarrollados para este fin (escritos por el Prof. Dr. Larry Thibos de la Universidad de Indiana). Esta métrica se deriva de los mapas de frente de onda como se describe por los espectros de Zernike. Todos los coeficientes de Zernike fueron reescalados para una pupila de 3 mm. Se calculó el coeficiente medio de Zernike de

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cada modo y se comparó con el del grupo no catarata. La agudeza visual se midió en todos los sujetos usando el optotipo ETDRS estándar. Los resultados mostraron que en estos dos grupos, la agudeza visual disminuyó linealmente en función de la VSMTF ocular. La pendiente de la línea de regresión fue de -0,50 en el grupo sano y -0,36 en el grupo con catarata, pero la diferencia en la regresión entre los dos grupos no fue significativa. La correlación entre logVSR ocular y logMAR fue significativa en ambos grupos (r = -0,90 en el grupo sano y r = -0,81 en el grupo con catarata, p <0,05 en ambos grupos). La relación que se encontró se corresponde con la referida por los autores originales. En este capítulo se ha confirmado que la métrica VSMTF tiene una fuerte correlación con la agudeza visual en los ojos sin catarata sin corregir. También se encontró una alta correlación entre las dos medidas en ojos de catarata no corregidos. La alta correlación sugiere que esta métrica puede actuar como un sustituto para la prueba de la agudeza visual en ojos con funcionamiento normal de retina y cerebro, independientemente de su estado de catarata. También los resultados del grupo de cataratas después de la corrección se correspondió con los datos anteriores. La conclusión fue que el VSMTF es una métrica adecuada para predecir la agudeza visual tanto en ojos sanos como en cataratas. Como se mencionó anteriormente, la agudeza visual es un criterio importante en el proceso de toma de decisiones quirúrgicas de la catarata. Sin embargo, varios estudios han demostrado que en un número significativo de casos de cataratas, la agudeza visual no es una medida adecuada para juzgar la función visual. Estudios posteriores han apoyado esta noción. Por otra parte, ha habido informes de ningún cambio o incluso un aumento en straylight después de la cirugía de catarata cuando la decisión se tomó exclusivamente en base a la agudeza visual. La razón de esto es que la agudeza visual sólo evalúa el impacto de la difusión de luz de ángulo estrecho debido a errores de refracción, y por lo tanto sólo puede medir una parte limitada de la visión de un paciente. Se observó que se necesitaban pruebas visuales adicionales que pudieran reflejar la pérdida de la función visual, pero al mismo tiempo no deberían estar relacionadas con la agudeza visual. El método de comparación de compensación para cuantificar el straylight ha sido reconocido como una técnica estándar para evaluar la validez de las pruebas de deslumbramiento discapacitante. Una revisión de la literatura estableció una curva de normalización para los ojos pseudofáquicos. Además, se construyó una curva de referencia que permite estimar la cantidad esperada de straylight tras la cirugía de catarata mediante el cálculo de la mejoría de straylight en función de la edad y del straylight preoperatorio. Aunque esta referencia es una buena medida para el manejo de la catarata en un ojo promedio, puede pasar por alto la influencia del tipo, ubicación e intensidad de la catarata en el resultado porque el tipo de catarata no se especificó en la curva de normalización. Para establecer referencias clasificadas morfológicamente, se necesita una norma fáquica estratificada al tipo de catarata. Por lo tanto, se investigó el straylight en ojos con cataratas de diferentes morfologías, en función de la edad y la agudeza visual.

En el **Capítulo 4**, se realizó una revisión bibliográfica para identificar publicaciones relevantes sobre straylight, edad y agudeza visual en tres tipos comunes de catarata. Además, se recalculó la importancia de la relación entre el straylight y la agudeza visual, teniendo en cuenta la morfología de la catarata. Los estudios publicados incluidos en esta revisión bibliográfica evidenciaron individualmente que tal correlación varía de un tipo de catarata a otro. El tamaño de la población y la severidad de la catarata difería entre todos estos estudios. Sin embargo, se considera que el número final relativamente grande de observaciones y sus diversos grados de intensidad de la catarata como punto fuerte de este estudio para mejorar la generalización de los resultados. Este capítulo incluye dos partes: la primera parte abarca una revisión bibliográfica exhaustiva para estudiar el efecto de diferentes morfologías de la catarata, es decir, cataratas nucleares, cataratas corticales y cataratas subcapsulares posteriores (PSC), en el straylight y determinar modelos de valores straylight en función de la edad para diferentes tipos de catarata; en segundo lugar, se calcularon las correlaciones entre straylight y agudeza visual, la cantidad de progresión del straylight y la agudeza visual de los de un grupo normal, y las relaciones entre la edad y la agudeza visual en cada grupo de cataratas. Se realizó un examen bibliográfico que incluyó todos los estudios disponibles que refirieron valores de straylight, en ojos con catarata con especificación

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de su morfología. El idioma de los artículos, edad, sexo y raza de los participantes no influyeron en este proceso. Todos los documentos proporcionaron información sobre el straylight intraocular, edad y agudeza visual de los participantes con especificación del tipo de catarata. Todos los trabajos habían excluido pacientes con antecedentes de cirugía ocular o enfermedades, como retinopatía diabética, glaucoma y degeneración macular relacionada con la edad. Se consideraron fiables para el análisis los datos de *straylight* con una desviación estándar esperada de 0,12 unidades o menos. Se utilizaron datos de cinco artículos para desarrollar las curvas normativas de log(s)-edad para los tres tipos de catarata. Las correlaciones entre las dos variables fueron calculadas y comparadas entre sí. Se calculó el valor normal esperado normal de *straylight* para cada tipo de catarata, todos los tipos de catarata combinados y el grupo control mediante el uso de una ecuación normativa log(s)-edad. El valor medio del valor de *straylight* fue de 1,22 log (s) ± 0,20 (SD) en catarata nuclear (592 ojos), 1,26 log (s) ± 0,23 en la cortical (776 ojos) y 1,48 log (s) ± 0,34 en la catarata PSC (75 ojos). La pendiente de la relación entre edad y *straylight* fue de 0,009 (R^2 = 0,20) en la catarata nuclear, 0,012 (R^2 = 0,22) en la cortical y 0,014 (R^2 = 0,11) en la PSC. La pendiente de la relación entre *straylight* y agudeza visual fue de 0,62 (R^2 = 0,25) en la catarata nuclear, 0,33 (R^2 = 0,13) en la cortical y 1,03 (R^2 = 0,34) en la PSC. Otros hallazgos fueron las ratios entre s*traylight* y edad, y entre straylight y agudeza visual. La mediana del parámetro de *straylight*/edad tuvo el valor más bajo en el grupo de catarata nuclear y el valor más alto en el grupo PSC, aunque con una distribución más sesgada comparando los otros dos grupos de cataratas. La mediana de log (s) / logMAR mostró valores similarmente inferiores en los grupos nuclear y cortical en comparación con el grupo PSC. En ambos casos, los valores medianos tanto de los grupos nuclear como cortical fueron estadísticamente significativamente inferiores a los del grupo PSC. De acuerdo con la literatura, se encontró que la edad promedio de la población PSC que se desarrolla o se somete a cirugía para PSC es más joven que para otros tipos de cataratas. En cada grupo de catarata, la diferencia en los valores medios de *straylight* de estudios individuales y la función de dependencia respectiva fue significativa. Esto se explicó por los diferentes

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niveles de severidad de la catarata y la diferencia significativa en el número de ojos del estudio más grande y el resto. Sin embargo, esta diferencia no se observó entre las pendientes de cada estudio y las respectivas funciones de dependencia. Independientemente de la gravedad de las cataratas, este estudio apoyó la hipótesis de que el *straylight* es el más alto en PSC. Se consideró que las fluctuaciones en la densidad y el índice de refracción discontinuo eran responsables de dicha amplificación. Nuestros resultados también confirmaron que en las primeras etapas de la catarata, para los pacientes con PSC, la agudeza visual por sí sola no es una evaluación adecuada del rendimiento visual y el manejo de la catarata. La correlación entre log (s) y agudeza visual logMAR varió de nada a un valor moderado en los estudios individuales y dentro de los tipos de catarata, pero nunca fue fuerte. En general, ningún tipo de catarata mostró correlación fuerte log(s)-logMAR. En la práctica clínica, esto significa que no se puede predecir el *straylight* en base a la agudeza visual para ningún tipo de catarata. Por lo tanto, este capítulo corroboró que el *straylight* en ojos con catarata varía bastante independientemente de la edad y la agudeza visual mejor corregida. Se especuló que la independencia de estos dos aspectos era causada por diferentes procesos ópticos en el cristalino de escalas espaciales muy diferentes. En conclusión, tener en cuenta la morfología de la catarata proporcionará una mejor visión de la disfunción visual del ojo con catarata. En la PSC, en particular, los valores notablemente elevados de *straylight* no se corresponden necesariamente con una pérdida de agudeza visual. La catarata es un defecto óptico multifactorial, que afecta a las PSF del ojo de diferentes maneras. Un cristalino cataratoso puede tener varios dispersores de luz ultraestructurales que provocan varias cantidades de dispersión de luz hacia atrás y hacia adelante. Sin embargo, la parte central de la PSF está asociada con aberraciones ópticas y está formada por parte de la luz entrante que no es perturbada por los dispersores en los medios oculares. Sólo un pequeño porcentaje de la luz entrante se ve afectada por las irregularidades que dispersan la luz en los medios, y proyecta un velo de luz no deseada sobre la imagen de la retina. Se ha establecido que la intensidad de *straylight* disminuye considerablemente con el ángulo (θ), con una dependencia aproximadamente cuadrática. El parámetro *straylight* definido como θ^2 x PSF, cambia ligeramente de 2,5° a 25,4° con un comportamiento parabólico con un mínimo en proximidad a 7 ° en ojos sanos así como en ojos con catarata. En un tipo de catarata congénita, es decir, catarata congénita pulverulenta, se ha observado que la visión puede ser fuertemente alterada sin demasiada pérdida de agudeza. Se encontró accidentalmente un caso dramático en el que un profesional de alto nivel fue amenazado con perder su trabajo debido a un *straylight* elevado, mientras que su agudeza visual era normal. Se decide entonces estudiar los efectos sobre el *straylight* de esta afección. El interés primordial en el **Capítulo 5** fue estudiar el grado en que el *straylight* está elevado en ojos con cataratas congénitas pulverulentas. El objetivo secundario era comprobar si la dependencia angular del *straylight* se corresponde con lo que es típico para las cataratas como se mencionó anteriormente. Se incluyeron tres casos. En 6 ojos de 3 casos jóvenes con catarata congénita pulverulenta se observó unos valores de *straylight* notablemente elevados, mientras que se conservaba la agudeza visual. Un caso (caso 1) se estudió con más detalle, es decir, la morfología de la catarata, *straylight* multi-ángulo, agudeza visual y aberraciones de frente de onda (VSMTF). Los resultados se compararon con los de estudios realizados previamente en grupos sin catarata y con catarata asociada a edad. La dependencia angular del *straylight* de este caso se comparó con la de 33 de ojos azules caucásicos sin catarata y 65 pacientes con catarata cortical, nuclear y subcapsular posterior de dos estudios anteriores. En el caso 1, la catarata era del tipo central congénito pulverulento, bilateral, estático y perfectamente simétrico en ambos ojos. Se puede describir mejor como una catarata floriforme granular con 3 estructuras lamelares en forma de pétalo inscritas en dos opacidades punteadas circulares concéntricas en el núcleo. Su agudeza visual con su mejor corrección fue de -0,24 logMAR (ojo derecho) y -0,30 logMAR (ojo izquierdo), a pesar de un *straylight* 5 veces más elevado (ojo derecho: 1,62 log (s), ojo izquierdo: 1,59 log (s)). Las aberraciones del frente de onda estaban dentro de los límites normales.

La dependencia angular del *straylight* fue diferente en este caso de la de los ojos normales o de las formas usuales de catarata asociada a la edad. Esta peculiaridad ha sido interpretada como el resultado de dispersión por partículas mucho más grandes (aproximadamente 20-30 μm de diámetro) que aquellas de cristalinos normales y con catarata. A saber, para cristalinos de ojos humanos jóvenes y envejecidos se ha encontrado que las partículas con un radio medio de aproximadamente 0,7 μm dominan el *straylight*. La dispersión a grandes ángulos (30°-180°) está dominada por partículas mucho más pequeñas que la longitud de onda de la luz incidente. Por el contrario, cuando el tamaño de partícula es mucho mayor que la longitud de onda de la luz incidente, como en el caso 1, la difracción causa patrones de dispersión con una distribución más fuerte en dirección hacia adelante y ángulos más pequeños. Esto explica la diferencia en la dependencia angular según se informa en este capítulo. Se explican las muy buenas agudezas visuales de los tres casos, a pesar de la elevada dispersión de la luz, por diferentes contribuciones a la PSF de las aberraciones ópticas (evaluadas por medio de la agudeza visual) y el *straylight*, así como las diferentes procedencias. Desde el punto de vista óptico, esta falta de relación explica por qué el proceso de dispersión de la luz (que da lugar al *straylight*) tiene poco impacto en la región central de la PSF, que está asociada con la agudeza visual, independientemente del nivel de *straylight*.

Como conclusión general de esta tesis doctoral, cabe señalar que el *straylight* y la agudeza visual parecen ser bastante autónomas. Sin embargo, en promedio, existe cierta correlación. La tasa de esta dependencia parecía ser una función de la morfología de la catarata. Estos hallazgos están de acuerdo con la literatura y aseguran que *straylight* es potencialmente una medida importante para la calidad de la visión y el indicador para la cirugía de catarata, junto con la agudeza visual y la morfología de la catarata. Otro hallazgo importante de esta tesis es la competencia de VSMTF en la predicción de la agudeza visual objetivamente en los ojos con catarata. Los resultados muestran que la combinación de las funciones óptico-visuales mencionadas y la morfología del cristalino podrían ser ingredientes fiables para desarrollar un algoritmo para predecir el momento óptimo para realizar la cirugía. Se han realizado muchos estudios sobre la importancia de considerar el *straylight* en esta ecuación. Esta tesis confirma esta

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propuesta. Sin embargo, se necesita más investigación para validar la fiabilidad de la VSMTF para predecir la agudeza visual en la población con catarata teniendo en cuenta la morfología de la lente. Además, la peculiar dependencia angular del *straylight* en ojos con catarata congénita pulverulenta merece un amplio estudio en más sujetos con más diversos tipos de defectos de dispersión óptica.

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Abstract

Driving at night, you may experience being blinded by the headlights of an oncoming car. This may also happen when looking at a low sun. Inhomogeneities in the ocular media can cause light scattering, resulting in a veil of light, called straylight, projected onto the retinal image. The Commission Internationale de l'Éclairage (CIE) defines straylight as disability glare. Straylight, however, manifests itself with more than glare alone. Contrast and color loss, hazy vision, and difficulty with face recognition against the light are some complaints people with increased straylight may experience. Even in young healthy eyes, a small part of the light entering the eye is scattered. The age-dependence of straylight in a healthy normal population has been extensively studied. It is now known that ageing and various ocular pathological conditions, such as cataract, can elevate straylight. Although straylight does not increase before the age of 40, some pathological conditions, such as congenital (early onset) cataracts, can increase it, sometimes to an extreme degree. Cataract-dependence of straylight has been studied in various cataract types; a significant difference in straylight has been shown to exist between cataract types. While straylight varies among different cataract morphologies, in some cases, strongly elevated straylight can be accompanied by good visual acuity.

The main goals of this thesis were (1) to study *in vivo* straylight of ageing eyes with a focus on cataractous eyes; (2) to study the eligibility of certain optical functions and cataract morphology to be considered as reliable discriminators for establishing a surgical decision algorithm in the future.

As general conclusions of this doctoral thesis, it should be noted that straylight and visual acuity seem to be quite autonomous. However, on average, some correlation exists. The rate of this dependency appeared to be a function of cataract morphology. These findings are in accordance with the literature and ensure that straylight is potentially an important measure for quality of vision and indicator for cataract surgery, along with visual acuity and cataract morphology. Another important finding of this thesis is the competence of visual Strehl ratio (VSMTF), an image quality metric derived from wavefront aberrations, in predicting visual acuity objectively in cataract eyes. The results show that the combination of mentioned optical-visual functions and lens morphology could be dependable ingredients for an algorithm to predict the optimal timing for performing surgery. Many studies have been conducted on the importance of considering straylight in such equation. This thesis confirms this notion. However, further investigation is needed to validate the liability of the VSMTF to predict the visual acuity in cataract population with taking the lens morphology into account. Moreover, the peculiar angular-dependence of straylight in pulverulent congenital cataract eyes deserves an extensive study in more subjects with more diverse types of optical scattering defects.

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Chapter 1

Introduction

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1. Introduction

The eye is the most delicate, sensitive, and perhaps the most amazing organ in the human body. Our eyes are responsible for 80% of all the information our brain receives from the surroundings [1][2], and perhaps that is why eyes are said to be our windows to the world and that is why we rely on our eyesight more than any other senses. Their small size (about 25 mm) and intricacy (more than two million operational parts), make them complex structures. With their eyes, humans can distinguish and perceive shapes, colors, tone, distance, dimensions by processing the light they receive from the objects. They can do these tasks over a spectrum of light wavelengths from 390 to 700 nm, and for intensities (brightness) from starlight to brightest sunlight.

1.1. Anatomy of the eye and image formation

The cornea is a transparent tissue and the front layer of the eye. It is highly curved and refracts the entering light before being partially blocked by the iris. The iris is a disk-shaped structure with a circular opening in the center known as pupil. The iris controls the size of the pupil and thus the amount of light reaching the retina. The diameter of the pupil varies from about 1 to 8 mm in response to changes in illumination. To increase the amount of energy reaching the retina, in low light, the dilator muscles pull the iris radially to enlarge the pupil. By contrast, these muscles contract in normal and intense light and decrease the pupil dimeter. Next lies the crystalline lens, posterior to the iris and anterior to the vitreous body. The circular ciliary muscles enable accommodation by changing the curvatures of the lens. Approximately two-thirds of the refractive power of the eye comes from the cornea. This amount of refraction is the equivalent of nearly 40 diopters [3]. This is because of the highly curved corneal surface and the high refractive index differential on its outer surface with air. Other intraocular refractive index differences have much weaker effects on the optical power and ocular aberrations. The main part of the eye has an approximate spherical shape mainly existing of a clear gel called vitreous which fills the eyeball. Before it reaches the retina, the light passes through this medium. The refractive power of the eye, is primarily the result of refraction at the air-cornea interface and bending by the crystalline lens, which aim to produce images with sharp focus on the retina.

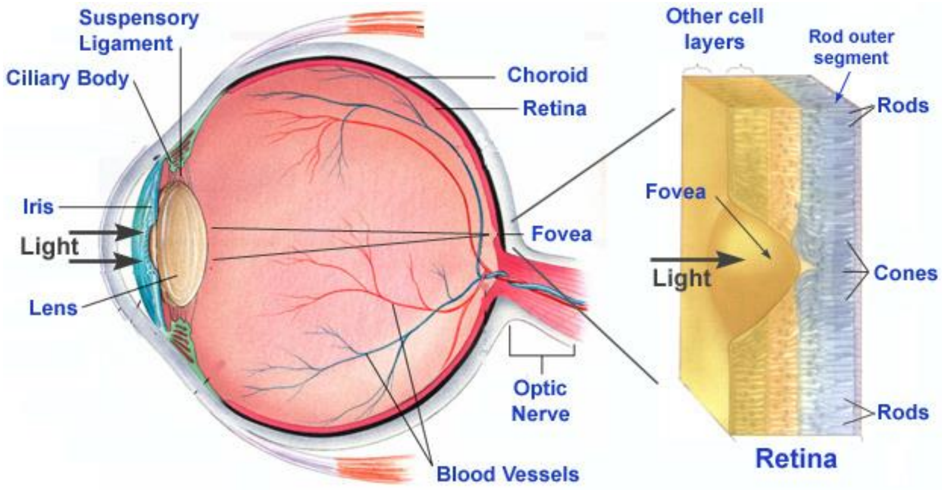

Figure 1.1. An illustration of the cross-section of the human eye

The retina, which is in fact a brain tissue, is a thin light-sensitive multilayer membrane, containing two types of photoreceptor cells – rods and cones – that respond to the visible light by transforming it to neural signals. These impulses are sent to other retinal cells and finally to the brain through the optic nerve. The visual perception is achieved by decoding and processing these signals in the brain.

1.2. Optical quality

The optical quality of the human eye, like any other optical system, can be determined by the point spread function (PSF) that is the response of the optical system to a single point of light [4]. The PSF is a sensitive way to describe changes; a change in the PSF can lead to great disturbances. In a perfect optical system, the PSF would look identical to the light source, *i.e.* a point of light. However, in the human eye with imperfections in the optical media, the light is spread out and generates a bright spot in the center, losing intensity gradually but continuously towards the periphery. Two aspects of the PSF that belong to different functional domains should be discriminated: a central portion and an outer skirt [5] (Figure 1.2).

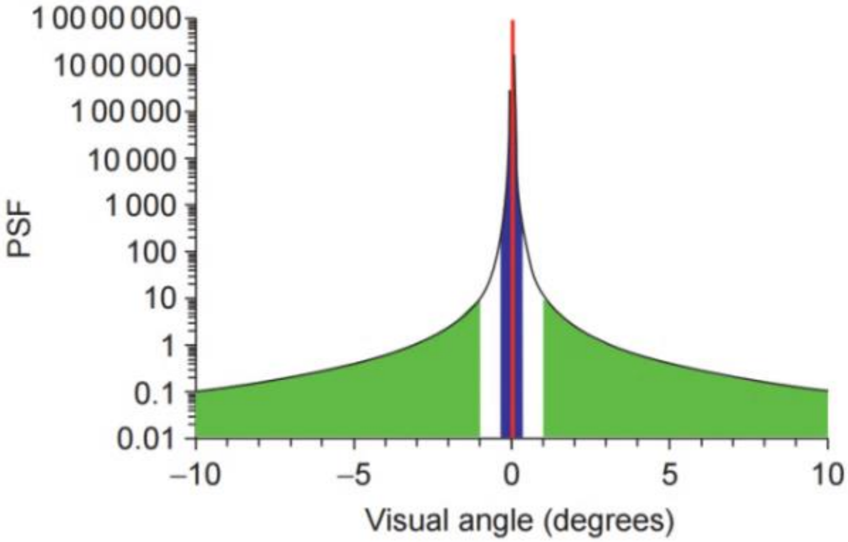

Figure 1.2. Point spread function (PSF) of a human eye (CIE 1999). The central peak is linked to the image of the object in the field of view on the retina. This is traditionally measured by visual acuity tests (red) and contrast sensitivity (blue). Wavefront aberrations shape this part of the PSF. Straylight (green) rooted from inhomogeneities in the ocular media shapes the rest of the PSF. *Image source: van den Berg et al., 2010.*

The central portion of the PSF (up to 0.3°) is affected by optical aberrations. In clinical practice, it is this small-angle domain that is assessed by visual acuity tests, contrast sensitivity, and with wavefront aberrometry. Optical aberrations of the eye limit the quality of the retinal image and constrain spatial vision by decreasing visual acuity and contrast. By assessing ocular wavefront aberrations, important information can be obtained. The outer skirt of the PSF (beyond 1°), on the other hand, is caused by light scatter, and known as straylight. Straylight does not contribute to visual acuity and higher order aberrations. Studies [6][7] showed that there is in fact, very weak correlation between straylight and visual acuity. They explained this event by pointing out that the process of light scatter which results in straylight, has little impact on the central region of the PSF, which is associated with visual acuity, regardless of the level of straylight.

1.3. Aberrations of the human eye

According to geometrical optics, a perfect eye would focus a bundle of parallel light rays (described with wavefronts in modern physics) coming from one point on the object into one point on the retina. Every component of the eye, surface boundaries and imperfections can change the direction of the wavefront leading to aberrations. In other words, aberration is a deviation of a ray from a predicted path by paraxial optics [8]. A number of aberrations in the human eye degrade the image quality. The aberrations are divided into lower order (LOA) and higher order (HOA). These aberrations are from the class of *monochromatic aberrations*. The difference in refractive power between various wavelengths also changes the focal length of the eye. This is known as *chromatic aberration*, which produces more than 2 diopters difference in refractive power between the two ends of the visible light spectrum. Spectacles and contact lenses can counterbalance LOAs, *e.g.* spheres and cylinders; but only for a single wavelength. To correct the chromatic aberration, an optical system composed of several lenses with different V-numbers (Abbe numbers) [9] would be needed.

The HOAs of the human eye were measured objectively in 1994 for first time using a Hartmann-Shack wavefront-sensor. Today, aberrometry is used for various reasons; from diagnosing irregularities for performing refractive surgeries, to designing contact and intraocular lenses. The HOA is numerically described by various metrics, *e.g.* Zernike terms, root-mean-squared (RMS) wavefront errors, PSF, and Strehl ratio.

1.3.1. Visual Strehl ratio, an image quality metric

Several studies [10][11] showed, however, that the aforesaid metrics are not appropriate predictors of visual performance. There are several ways to formulate image quality metrics using monochromatic aberrations. One study [12] investigated the correlation of 31 single-value image quality metrics with high-contrast visual acuity. The correlations were estimated for a 6-mm pupil where the RMS error was kept constant. This study concluded that the best metric in terms of high correlation with visual acuity, as a measure of visual performance, was a visual Strehl-based image quality metric called the visual Strehl ratio (VSR). This metric is the ratio of the PSF in the presence of aberrations at the Gaussian image point to the maximum intensity of a diffraction-limited spot. The difference between the VSR and Strehl ratio is that the VSR weights the PSF with a neural weighting function before computing the Strehl ratio. The same study showed that 0.25 μm of aberration over a 6-mm pupil, can shift visual acuity by nearly two lines on a logMAR chart, whereas the total RMS error remained unchanged. It has also been shown that the combination of Zernike modes can be more important than the magnitude of each individual mode. The type and the relative proportions of each mode in the combination determine the amount of gain/loss in visual performance, with the RMS error and pupil size remaining constant. The VSR was found to be the best metric accounting for 81% of the variance in high-contrast logMAR acuity.

1.4. Straylight

When light enters the eye, it is refracted by the transparent substances of the eye (*i.e.* the cornea, and the crystalline lens) and forms an image on the retina. A small fraction of this light, however, is scattered. The Commission Internationale de l'Éclairage (CIE) defines straylight as disability glare. Straylight, however, manifests itself with more than glare alone. Contrast and color loss, hazy vision, and difficulty with face recognition against the light are some complaints people with increased straylight may experience [13]. Even in young healthy eyes, a small part (approximately 10%) of the light entering the eye is scattered. Two-thirds of light scattering in the eye is produced by the cornea and the crystalline lens, the remaining is caused by translucency of the ocular wall and reflectance from the fundus [14][15]. The age-dependence of straylight in a healthy normal population has been extensively studied. As the lens grows older, it takes a more dominant role as a source for straylight. This notion holds even in the clearest lenses [16]. It is now known that ageing and various ocular pathological conditions, such as cataract, can elevate straylight. Although straylight does not increase before the age of 40, some pathological conditions, such as congenital (early onset) cataracts, can increase it, sometimes to an extreme degree. It has been established that straylight intensity decreases greatly with angle (θ), with an approximately quadratic dependence [17]. The straylight parameter defined as $\theta^2 \, x \, PSF$, changes slightly from 2.5° to 25.4° with a parabolic behavior with a minimum in proximity to 7° in healthy as well as cataract eyes. Intraocular straylight can be quantified by C-Quant (Oculus Optikgerate GmbH, Wetzlar, Germany). The C-Quant measures the retinal straylight based on the compensation comparison method [18][19].

1.4.1. Straylight in cataract eyes

There are numerous studies on the association of cataract with a significant straylight elevation [5][14][15][20−23]. The primary reason of image deterioration in cataract eyes can be the increased amount of light scattered compared to their non-cataract peers, because of little to abundant inhomogeneities in the crystalline lens.

Some of these studies [20−22] found a dependence of the amount of forward light scatter on cataract morphology. While straylight varies among different cataract morphologies, in some cases, strongly elevated straylight can be accompanied by good visual acuity [6]. According to the literature, posterior subcapsular cataracts in particular have higher rates of straylight impairment and therefore will benefit most from cataract surgery [20][22][24]. Fluctuations in density and discontinuous refractive index can be responsible for such amplification [25][26]. It has also been noted that the average age of patients with this type of cataract is significantly younger than those with other type of cataract.

1.5. Thesis outline

Continuous deterioration of visual performance caused by increased straylight in cataract eyes [20−23], may need to be resolved by a cataract operation. Because of the increased demand, cataract operation has become one of the most frequently performed procedures worldwide. For this reason, visual tests and visual complaints of patient, as primary indicators for cataract operation have received attention in recent years. Rightfully, the question arises whether relying purely on subjective measures is a reliable approach towards cataract operation decision-making. Studies showed that in a considerable number of cataract cases, visual acuity is not an apt determinant for cataract operation [27][28]. One study reported straylight increase above the normal level, postoperatively, in 10% of the eyes [16]. This might be due to the fact that the objective measures, *e.g.* optical functions, do not contribute to the traditional decision-making process. A literature review, found that straylight improvement postoperatively, is a function of preoperative straylight [29]. Therefore, the research project, described in this thesis, aimed: (1) to study *in vivo* straylight of cataract eyes; (2) to investigate the competence of certain optical functions, including straylight, and cataract morphology as reliable predictors for establishing a surgical decision algorithm with an objective approach in the future.

Chapter 2 addresses the pupillary response during straylight evaluation using the C-Quant in older eyes. Several [16][30][31] studies have confirmed increase in straylight with age, not only in cataract eyes but also in normal eyes. The question that has been answered in this chapter is at what pupil size, and corresponding adaptation level, straylight measurement is performed, in case of natural pupils.

To pursue the second goal of this thesis, **Chapter 3** evaluates the usability of the VSR to quantify by optical means the effect of age-related cataract on visual acuity. This metric was well-correlated with visual acuity. This suggests that optical measurements can be used as more reliable means in clinical decision-making. The main contribution of this chapter is introducing this metric as a potential parameter for developing a cataract surgical decision-making algorithm.

Chapter 4 presents a literature review on straylight in cataract eyes with three common morphologies. The age- and visual acuity-dependence of straylight were studied in this chapter. We noticed that different morphologies showed different dependency. Therefore we concluded that, stratification of cataract by morphology, can provide more accurate insight in assessing visual function in cataract eyes.

Chapter 5 addresses increased straylight in three young cases with pulverulent congenital cataract, in the presence of good visual acuity. Straylight and visual acuity govern two separate angular domains of the PSF. This results in the autonomy of the two entities [6][7]. The unusual angular-dependency of straylight in both eyes studied in one case, was the subject of the further investigation in this chapter. The presence of particles larger than the wavelength of light in the lens, was explained as the source of stronger forward light scatter in smaller angles (*Mie scattering*).

Chapter 6 presents the general conclusions and future work.

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Chapter 2

The significance of changes in pupil size during straylight measurement and with varying environmental illuminance

2.1. Introduction

The amount of vision loss caused by disturbances in the eye's optical media can be assessed by visual acuity testing. However, these disturbances can also cause forward light scattering [1−3]. This scatter generates a veil of undesired light on the retinal image, leading to decreased image contrast and color, increased glare and hazy vision. Such increased glare becomes alarming often when the individual stops driving at night. The loss of contrast, on the other hand, may lead to difficulties such as against-the-light face recognition. The amount of straylight is expressed by a single-valued number, called straylight parameter. This parameter is the ratio between the undesired light scattered by disturbances in the optical media which generates the veil on the retina, and the desired non-scattered light, which forms the retinal image.

An issue that has been previously studied [4], is the effect of pupil size on straylight. It might be thought that straylight is more bothersome at night, because the larger pupil size allows more light to enter the eye causing more glare. Therefore, it might be thought that the amount of straylight changes under low environmental light intensity. However, one should consider the fact that as the amount of scattered light increases by the enlarged pupil, the amount of constructive light entering the eye also increases. In other words, the ratio between the destructive and constructive light remains constant. The study by Franssen et al. concluded that the amount of straylight measured in a small group of dominantly young subjects with normal eyes (four subjects younger than 37 years and one 59 years old), only weakly depends on pupil diameter. Therefore, straylight values obtained in healthy young eyes under photopic conditions are valid for mesopic and scotopic conditions as well.

The crystalline lens changes with age. The lens grows over time and its color changes from clear to milky to yellow and then brown in eyes over 65 years of age. An old lens, even the clearest one, is a substantial source of straylight [5]. Ocular straylight was first studied in a group of elderly normal eyes and it was reported that it increased with age [6]. Later, several studies [7−9] have confirmed that straylight increases with age;

dominantly due to changes in the lens, even in normal eyes. A question then arises as to whether changes in the crystalline lens in older eyes that cause an increase in straylight, changes the straylight independency of the pupil size. As shown in several studies [10][11], pupil size decreases with age and with environmental illumination. It is thought that the effect of partial eye wall translucency may be more important in small pupil sizes [4]. This trait of eye wall makes it another source of straylight.

In the present study, we wanted to find out what the pupillary conditions are during straylight measurement, and what potential effect this might have on the measured straylight value. In other words, we investigated whether pupil size and straylight measured under dim room light conditions is the same as pupil size and straylight measured under dark room light conditions.

2.2. Methods

This study encompasses two parts: (1) The measurement of pupil diameter under various room illuminances; (2) The measurement of ocular straylight under various room illuminances. A group of 21 subjects, 6 of them between 26 and 29, and 15 of them between 50 to 68 years of age, all with normal pupillary responses were recruited from the staff of *Rotterdam Ophthalmic Institute.* Three of the younger subjects were non-Caucasian; the remaining 18 subjects were Caucasian. First part of the measurements were performed on all 21 subjects, however, the second part of the measurements were performed on 20 of them; one subject from the younger group dropped out. Exclusion criteria were pupillary anomalies (such as anisocoria, Argyll Robertson pupil, fixed pupil, and Hutchinson's pupil), pre-existing factors that can cause pupillary constriction, *e.g.* medications including narcotics and topical beta-blockers, a high refractive error (more than ±3 diopters) or astigmatism, cataract and any eye infection or injury at the time of measurement. Informed consent was obtained after an explanation of the experimental protocol. This study was conducted in accordance with the principles of the Declaration of Helsinki (October, 2013), the guideline for Good Clinical Practice

(CPMP/ICH/135/95) and the Medical Research Involving Human Subjects Act (WMO; 2006).

Images of the pupil diameter were taken using a Trust SpotLight webcam (with a 640 x 480 hardware resolution for obtaining a sharp image and powerful integrated infra-red LED lights with dim function for enhanced image quality in low-light environment) connected to a computer to register the images. All the measurements were performed on the subjects' non-dilated eyes without glasses or contact lenses.

2.2.1 Part 1 - Pupil change with changes in illuminance level

Pupil diameter was measured at three levels of room illuminance, 4, 40, and 400 lux, measured at the table surface. To eliminate the effect of hippus, a fifteen-second adaption time to each level of illumination was given. Measurements were carried out from the lowest to the highest level of illumination. Results of pupil size measurements are plotted against age for three levels of illumination in Figure 2.1.

2.2.2 Part 2 - Straylight change with changes in illuminance level

Ocular straylight was assessed using a commercially available straylight-meter (C-Quant, OCULUS, Germany) [12]. The C-Quant straylight-meter works based on the compensation comparison method, which compares the amplitude of a counter-phase flickering light required to compensate the induced flickering light produced by the straylight source. The device was connected to a computer set. To record the changes in pupil size, the Trust webcam was mounted against the tubus of the straylight meter and connected to a computer set. All the straylight measurements were performed on subjects' one eye while the other eye was under pupil size measurement. Both eyes had natural dilation, with no glasses or contact lenses. However, proper refractive trial glasses were added to the straylight-meter when needed according the practical guide of the manual. Each measurement provides an expected standard deviation (ESD) and a quality factor (Q). Our instrument considered the measurement optimal when ESD < 0.08 and Q > 1. The measurement was repeated if the device considered it sub-optimal. Before repeating a measurement, the range setting was adjusted according the practical guide of the manual. It must be noted that these criteria are rather strict [13].

We used the data from the first part of the study to estimate the adaptation level during straylight assessment. The pupil sizes of all subjects were regressed against the respective room illuminances. The pupil sizes during straylight measurement were used to estimate from the resultant linear relationship the adaptation level during C-Quant measurement.

2.2.3. Statistical analysis

All the calculations in this work are performed by using Microsoft Excel 2010 (Microsoft corp.). To investigate the strength of association of change in pupil size with the level of environmental illumination, we performed a Student's *t*-test. Having three levels of illumination, we have taken into account the Bonferroni correction. Average pupil size is plotted against three levels of illuminations. The effect of age on pupil size is shown in Figure 2.1. We can also see that this dependency decreases with increasing environmental illumination. Simple linear regression was used to describe the correlations. The correlation coefficient is calculated using the nonparametric method, the Spearman's r.

In the second part of the study, to investigate the strength of association of change in illumination with straylight value, we performed a paired *t*-test. The pupil size changes during the straylight measurement, as the intensity of the straylight source varies with each step. In the first half of the measurement (initial phase), a course assessment of the straylight value is achieved. In the second half of the measurement (final phase) the straylight value is assessed with precision using 13 presentations. For the effective pupil value, we chose to consider only the last 13 steps in the analysis. The fluctuation in pupil diameter in the last 13 steps is illustrated in Figure 2.3. The average pupil size during the straylight measurement under 4 lux-illumination condition is plotted against that under 40 lux-illumination condition in Figure 2.2. The results are presented with the 95% confidence interval (95% CI) and the corresponding P-value. A P-value of less than 5% was considered statistically significant.

2.3. Results

Part 1. The average pupil diameter of both eyes of both groups for three levels of illumination are given in Table 2.1. Except for one subject, the pupil diameter was roughly the same under different levels of illumination in both eyes of each subject. It was no surprise that the effect of environmental illumination on pupil size appeared to be highly significant in all eyes ($p < 0.05$). The dependency of pupil size on age is depicted under three levels of environmental illumination (Figure 2.1). The dependency of pupil size on age seems to be stronger under lower light intensities and decreases as illuminance increases. At the lowest illuminance level of 4 lux, the average gradient is 0.018 mm per year and it lowers to 0.014 mm per year at the 40 lux and to 0.008 mm per year at the 400 lux room illuminance.

Illuminance [lux]	*Count*	*Average pupil diameter [mm]*		*SD [mm]*	
		OD	*OS*	*OD*	*OS*
4	21	6.4	6.4	1.0	1.0
40	21	5.8	5.7	1.1	0.9
400	15	4.4	4.3	0.8	0.8

Table 2.1. Number of subjects, average pupil sizes and standard deviations

Part 2. The average pupil size during straylight measurement is calculated. The average values obtained under 40 lux illuminance are compared with those under 4 lux illuminance in Figure 2.2. There are high correlations between the two sets of measurements for both eyes (*OD*: $R^2 = 0.77$, and *OS*: $R^2 = 0.71$). Straylight values of right and left eyes under 40 lux illuminance are plotted against those under 4 lux illuminance in the smaller plot in Figure 2.2.

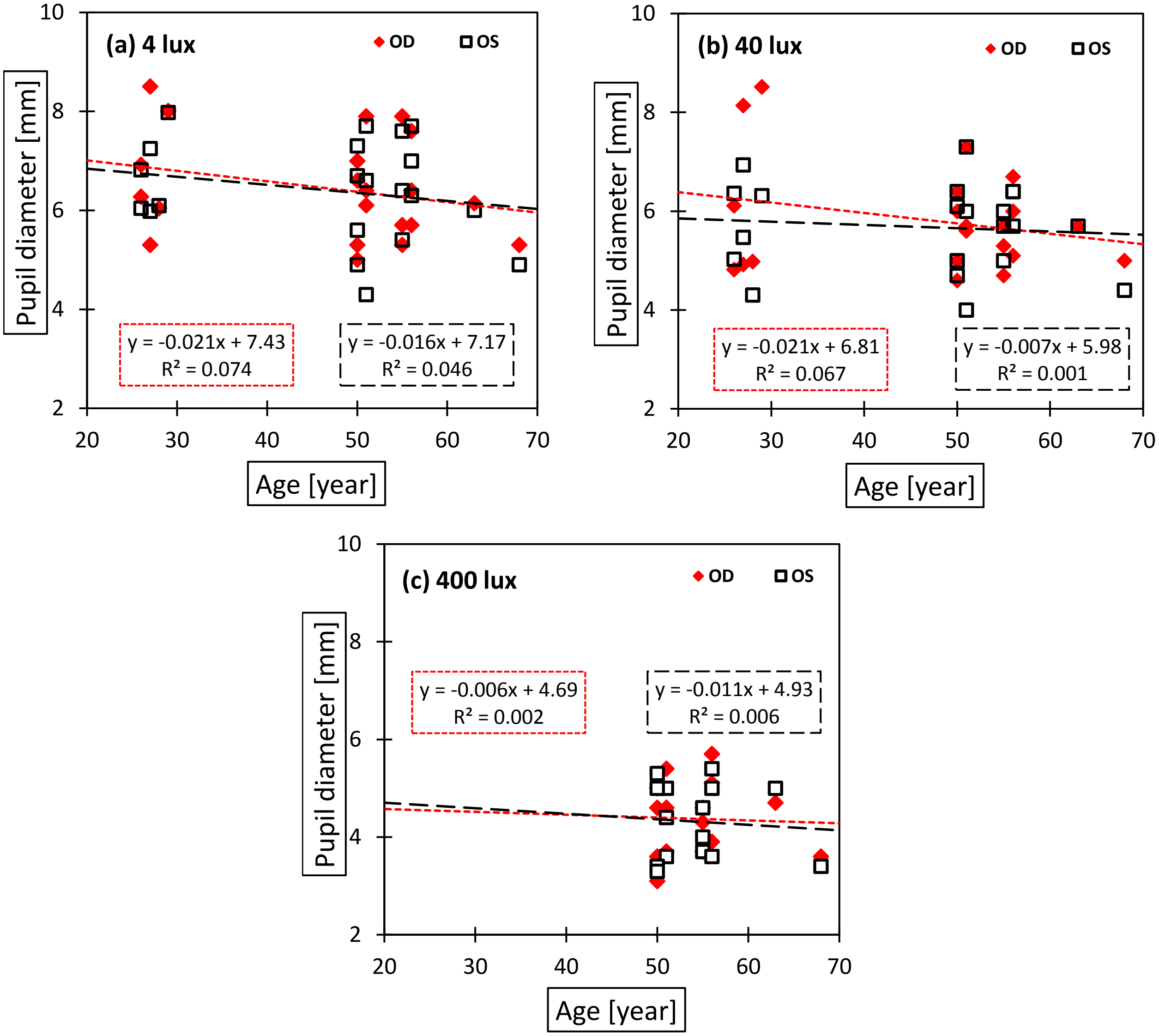

Figure 2.1. Dependency of pupil diameter on age under three levels of illumination. Data are fitted by linear regression. The slope of the regression line decreases as illumination increases (from *a* to *c*). Red diamonds show the right eyes and the empty squares show the left eyes. Red dotted lines and black dashed lines show linear regression lines for right and left eyes respectively.

No statistically significant difference was found between scattered light under two light conditions, whereas high correlations were found between them in both eyes (*OD*: R^2 = 0.82 and *OS*: R^2 = 0.84).

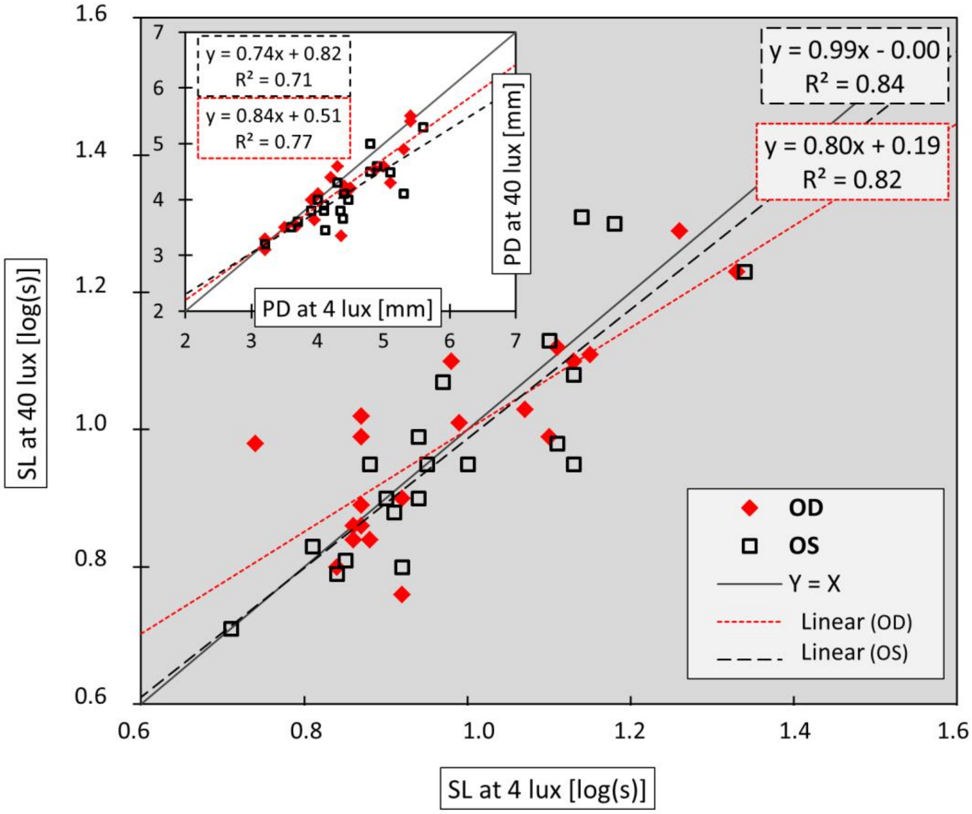

Figure 2.2. Mean pupil diameters (PD) of 20 subjects at 40 lux room illuminance (photopic condition) show high correlation with average pupil diameters at 4 lux room illuminance (mesopic condition). Ocular straylight measured under 40 lux background illuminance (photopic condition) shows high correlation with straylight under 4 lux background illuminance (mesopic condition). Red diamonds show the right eyes and the empty squares show the left eyes.

No correlation was found between pupil size and corresponding straylight in both eyes under the two levels of illumination. With $\alpha = 0.05$, df =18, and $r_{\text{critical}} = 0.514$ ($R^2 = 0.00$ for *OD*, and $R^2 = 0.07$ for *OS* at both illuminance levels). For the straylight difference between right and left eyes, we found means and standard deviations of 0.011 ± 0.084 log units under 4 lux illuminance and -0.006 ± 0.093 log units under 40 lux illuminance.

Figure 2.3 shows the average pupil diameters of all 20 subjects collected in the last thirteen steps of straylight measurement at 4 and 40 lux environmental illuminance. Figure 2.4 presents the estimated equivalent adaptation level of the straylight meter, using the linear relationship between pupil diameter and room illuminance, over the course of the final phase (second half of the steps).

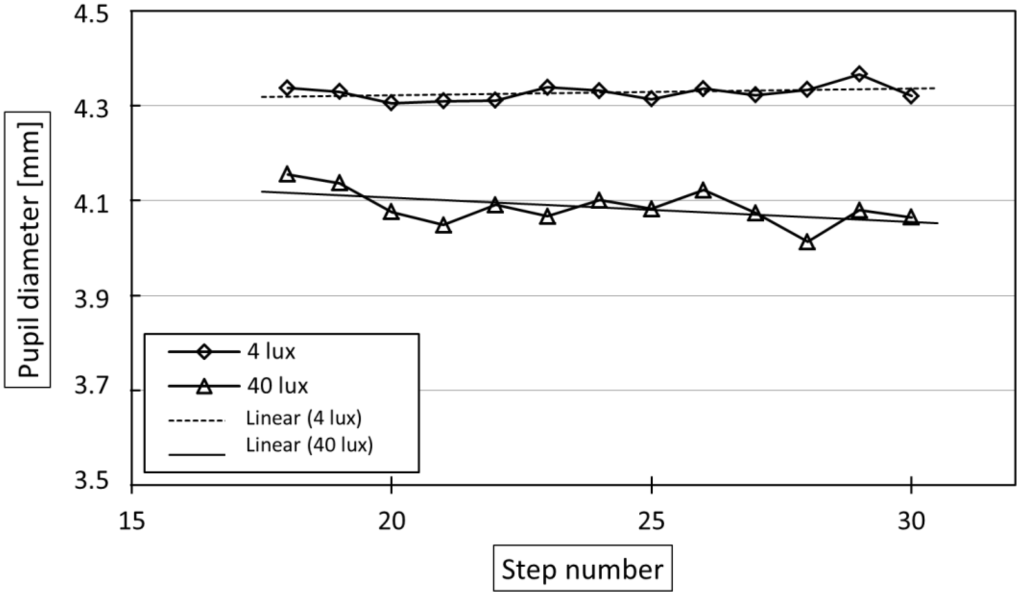

Figure 2.3. Average pupil diameter of all 20 subjects with normal eyes, obtained in the last 13 steps of straylight measurement at 4 lux (diamonds) and at 40 lux (triangles) room illuminances. The not-tested eye was exposed to mesopic and photopic room conditions.

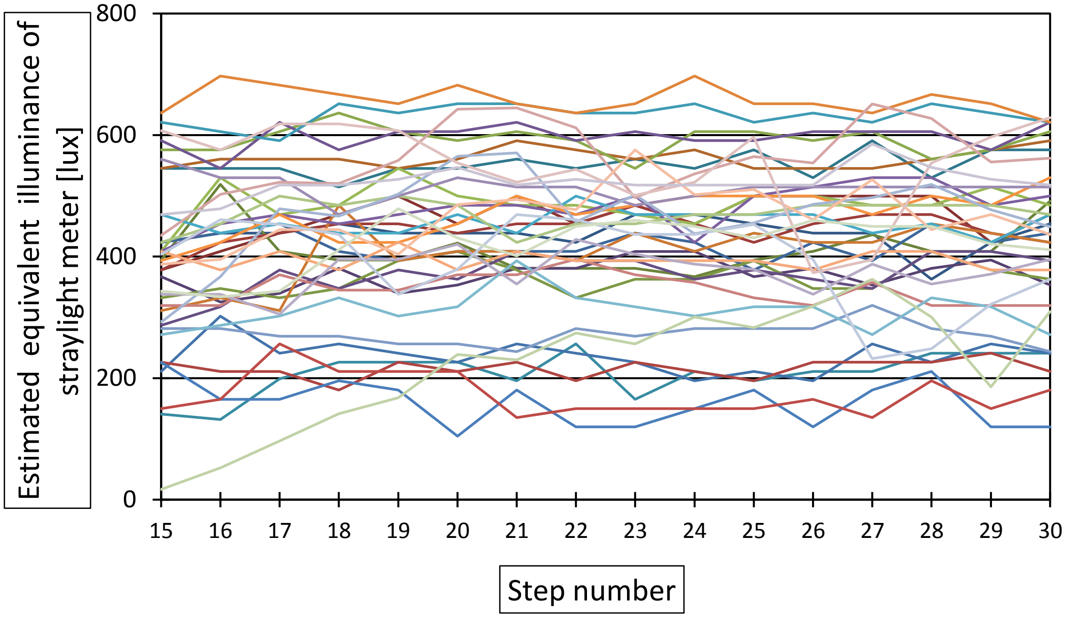

Figure 2.4. Estimated adaptation of C-Quant straylight meter during final phase of measurement for both eyes of 20 subjects. The eyes show an average value of 425 lux.

2.4. Discussion

The results in part 1, are in consistency with well-established knowledge. Pupil size, in a steady state, is a function of the corneal flux density [14] and age [7][10]. However, pupil size is influenced by more factors, such as field size and the number of eyes adapted [11]. The size of the pupil decreases linearly with age at all uniform illumination levels as suggested by Winn et al.[10] Our data also confirm what has been suggested by Winn et al. [10], that under low levels of illumination, pupil size varies more with age. Left and right pupil sizes vary from low to intermediate illuminance in a highly similar manner which is expected according to consensual (indirect) pupillary response.

In the second part of the study, we studied the dependence of ocular straylight on environmental illumination. The average pupil diameter showed very little change from low to intermediate illumination conditions (Figure 2.3). Franssen et al. [4] showed that straylight in normal eyes depends weakly on pupil size ranging from 2 to 7 mm diameter.

We did not find a dependency between pupil size and straylight values using two light conditions. This can be understood as the recorded pupil values were largely in the middle range of the values reported by Franssen et al., and were moreover very close together. In the same study it was discussed that straylight is rather independent from environmental light intensity; pupil reflex experiments show that the headlights of an upcoming car at night-time, simulate a day-time condition which contracts the pupils to natural day-time sizes. Therefore, one can conclude that illuminance level and subsequently the pupil size are not crucial factors affecting the amount of induced ocular straylight. The data showed that the standard deviation of straylight difference between right and left eyes increased with age, albeit slightly. However, the average value of these differences and the standard deviations were small under either illuminance level. Both results are in agreement with findings by Montenegro et al. [15]. They presumed asymmetrical lens ageing of contralateral eyes as possible cause of the difference. During this psychometric determination of ocular straylight, almost independent from environment, the size of the pupil is determined by the straylight meter. The compensation comparison method used in the C-Quant has a photopic character, therefore, the eye is exposed to the stimulus that is quite brighter than the illuminance of the examination room. In addition, routinely, while measuring the study eye, the fellow eye is occluded. Our data also enabled estimating the adaptation of the C-Quant (Figure 2.4).

For the 40 lux room illuminance condition, pupil size corresponded with 451 ± 122 lux room condition. For the 4 lux room condition the respective values are 399 ± 128. The eyes with estimated lower equivalent lux values were among those with relatively larger natural pupils at 400 lux room illuminance, and the eyes with estimated higher equivalent lux values were among the eyes with relatively smaller natural pupils at 400 lux room illuminance. With a large number of eyes estimating an average of 425 equivalent lux values, one can infer that the straylight meter sets the eye to a condition encountered with normal daytime room lighting.

2.5. Conclusion

We conclude that the illuminance of the examination room does not affect ocular straylight in normal eyes. In fact, the C-Quant test determines largely the size of the pupil. Thus, regardless of the lighting level, the straylight value obtained, is valid for normal photopic pupils.

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Chapter 3

Visual Strehl ratio metric derived from wave aberrations to predict visual performance in cataract eyes

3.1. Introduction

Despite an increasing number of cataract operations worldwide and advancement of measurement techniques and surgical instrumentation, the decision-making process for the indication for cataract surgery has kept its traditional frame. Ophthalmologists take subjective measures into account, *i.e.* the visual complaints that patients have, their visual acuity, and the aspect of their lenses at the slit-lamp. They weigh all this information against the visual demands of the patients. However, a more objective assessment of the cataract's effect on visual function, and the effect surgery might have, may be interesting. To this end, we need to identify and use quantifiable variables and balance these objective measures against the subjective measures. In the present work, we have evaluated a known single-value metric to be considered as an objective measure for part of the visual effect of cataract. Potentially, in the future such objective measures could be used for creating an algorithm that might support the cataract indication in a more objective way.

Understanding the functional effect of cataract on visual functions is essential. Optical imperfections determine the quality of the retinal image. In practice, this can be assessed by determining to what extent light from a point source is spread across the retina. This is called the point spread function (PSF). The PSF is accepted as full description of optical quality [1][2]. In the absence of any imperfections (*i.e.* an ideal eye), the response is identical to the incident light. However in the human (real) eye with imperfections in the optical media, the light is spread out and generates a bright spot in the center while losing intensity gradually but continuously towards the periphery. Two aspects of the PSF that belong to different functional domains should be combined: a central portion and an outer skirt [3]. The outer skirt (outside of 1°), is called the wide-angle domain, and is caused by ocular straylight. It is quantifiable with a straylight-meter called C-quant (Oculus Optikgeräte GmbH, Wetzlar, Germany) [3][4]. The central portion, called the small-angle domain (up to 0.3°), on the other hand is affected by optical aberrations. In clinical practice, it is this small-angle domain that is assessed by visual acuity tests and contrast sensitivity [3].

Optical aberrations in the eye limit the quality of the retinal image and constrain spatial vision by decreasing visual acuity and contrast. By assessing ocular wavefront aberrations, important information can be obtained. The ocular aberrometry has been practiced over the past few decades. Primary methods were based on subjective evaluations [5]. However, with the advent of automated aberrometers it has become possible for ophthalmologists to measure higher order aberrations as easy as they measure lower order aberrations with a refractometer. Commercial aberrometers utilize either the Shack-Hartmann wave-front sensing technique [6][7] or an objective [8] or subjective [9] ray-tracing technique. Either way, these aberrometers provide informative aberrometric maps with profuse details. The amount of details contained in such maps can make the interpretation a hard and confusing task. To facilitate the understanding of aberrometric maps, they are described by Zernike polynomials [10]. Zernike polynomials are complex descriptions and have complicated relationships with visual functions [11]. Some summarizing metrics such as Strehl ratio and root mean squared (RMS) wavefront error have been used somewhat widely in ophthalmology. Several studies [11][12], however, showed that these metrics are not proper predictors of visual performance. One study [13] has summarized multiple ways to formulate image quality metrics of the human eye and introduced a variety of optical metrics defined in terms of wavefront quality and image quality. Another publication [14] demonstrated the correlation of 31 single-value image quality metrics with high-contrast visual acuity. The correlations were estimated for a 6-mm pupil where the RMS error was kept constant. This study concluded that the best metric in terms of high correlation with visual acuity (as a measure of visual performance) was a visual Strehl-based image quality metric called the Visual Strehl Ratio (VSR). This metric is the ratio of the actual intensity of the eye's PSF in the presence of aberrations at the Gaussian image point to the maximum intensity of a diffraction-limited spot in the absence of any aberrations. What distinguishes this metric from the Strehl ratio metric, is that the VSR takes into account the neural components of the visual system.

Marsack et al. [14] showed that 0.25 μm of aberration over a 6-mm pupil, could shift visual acuity by two lines on a logMAR chart, whereas the total RMS error remained unchanged. It was also shown that specifics of combinations of Zernike modes can be important, more important than the magnitude of each individual mode. The type and the relative proportions of each mode in the combination determine the amount of gain/loss in visual performance, with the RMS error and pupil size remaining constant [15]. The best VSR metric was reported to account for 81% of the variance in high-contrast logMAR acuity in normal (non-cataract) eyes, and was shown by the original authors to be an accurate predictor of visual acuity. Other studies [16−19] also confirmed that there is a strong correlation between VSR metrics and visual acuity.

In this work, we aimed to evaluate the VSR metric that is computed in the frequency domain using the modulation transfer function (VSMTF) [13] to quantify the impact of cataract on visual acuity. Accordingly, we set out the following objectives: we studied the correlation between the VSMTF and visual acuity in cataract eyes with uncorrected vision and compared the result with that of normal eyes. We then furthered with estimating the correlation between VSMTF and VA in cataract eyes after correcting their lower-order aberrations.

3.2. Methods

This exploratory observational case-control study comprised 18 normal eyes of 9 healthy volunteers, and 15 cataract eyes of 15 patients. Healthy volunteers were recruited from employees of the Rotterdam Ophthalmic Institute and the Rotterdam Eye Hospital. Cataract patients were recruited from the cataract clinic of the Rotterdam Eye Hospital. Exclusion criteria were retinal disorders (*e.g.* macular degeneration), history of eye surgery, trauma, ocular surface and intraocular diseases, and corneal disorders (*e.g.* injuries and infections). Informed consent was obtained prior to enrollment and after an explanation of the experimental protocol. The mean age in the healthy group was 36.5 ± 12.6 years (ranging from 25 to 56) and 68.9 ± 9.1 years (ranging from 54 to 82) in the cataract group. This study was conducted in accordance with the principles of the Declaration of Helsinki (October, 2013), the guideline for Good Clinical Practice (CPMP/ICH/135/95) and the Medical Research Involving Human Subjects Act (WMO; 2006), and obtained approval from the institutional review board.

All eyes underwent two consecutive measurements: ocular wavefront aberrometry and measurement of visual acuity. The ocular wavefront analyzer, OWA (SCHWIND, eye-tech-resolutions, Germany) was used to analyze the total wavefront aberrations. All data were analyzed according to the Optical Society of America standards [20]. Visual acuity of each patient was assessed with standard Early Treatment Diabetic Retinopathy Study (ETDRS) charts and protocol [21]. In case of corrected visual acuity, the lower order aberrations were assumed zero.

3.2.1. Ocular wavefront analyzer (OWA)

The OWA (diode power ≤ 250 μW, λ = 850 nm and CW light source) measures ocular wavefront aberrations of the eye by means of a high-resolution Shack-Hartmann sensor. Patients were asked to take a position centered on a chin rest with their forehead against a headrest. The body of the device was placed in front of the eye under examination. To allow natural pupil dilation, the ambient light was dimmed (mesopic). Patients were asked to keep their gaze into the examination field and focus on the center of the fixation target (spider web). This was to align the optical axis of the eye and link it to the optical axis of the analyzer. The fixation target appears blurred to the patient by using “fogging” mode to bring the eye to an induced accommodation-free state. However, the image of the fixation target on the examiner’s monitor needs to be aligned. For this purpose, the joystick is moved front/back and rotated to focus the iris image. The acquisition time is about one second. All measurements were carried out under the same room illumination. Each eye was examined three times and eventually the best analysis was considered. The reported pupil diameters were between 4.09 and 6.00 mm.

3.2.2. Computations and statistical analysis

In this study, we considered lower-order aberrations (defocus Z_2^0, astigmatism Z_2^{-2} and Z_2^2) and several higher-order aberrations (coma Z_3^{-1} and Z_3^1, trefoil Z_3^{-3} and Z_3^3, primary spherical Z_4^0, secondary astigmatism Z_4^{-2} and Z_4^2, and quadrafoil Z_4^{-4} and Z_4^4).

The aberrometer used in this study analyzes the total WFAs up to the tenth order. The image plane metric is a mathematical function which takes normalized Zernike expansion coefficients as input and delivers a single value between zero and one as output. The VSMTF was computed using a purpose-written Matlab program (Mathworks, Inc.). This metric is derived from the wavefront maps which are described by Zernike spectra. All the Zernike coefficients were rescaled over a 3-mm pupil. The average Zernike coefficient of each mode is calculated and compared with that of the non-cataract group in Figure 3.1. The values of the VSMTF do not contain any experimental variance, therefore they are the independent variables in the analysis. Thus, we regressed logMAR acuity against the logVSMTF for both non-cataract and cataract groups. The Pearson's correlation coefficient was calculated. We employed Fisher's Z-transformation test to examine the significance of difference between regression lines. Significance was assessed at the levels of $P < 0.05$. We compared the results of the two groups with each other and with that of an early study on this subject on normal (non-cataract) eyes [17]. We extracted data from this study by means of GSYS2.4 software. It must be noted that because of a large number of overlapping data points, there was some degree of difference between the extracted data points and the original ones. To avoid any inconsistency, we used the original regression line and correlation coefficient from the study (Figure 3.2b).

To eliminate the dominant effect of the lower order aberrations, we removed them from the analysis and kept our focus on the higher order aberrations in cataract eyes. By the same token we measured the (best-spectacle) corrected visual acuity in cataract eyes. The logMAR-logVSMTF graph is depicted for corrected cataract eyes as well.

3.3. Results

Figure 3.1a displays the mean value of each Zernike coefficient (up to the 4^{th} order) for both groups. It can be seen that lower order aberrations, *i.e.* defocus and vertical astigmatism, are by far the most dominant modes. The only higher-order aberration whose difference in means between the two groups shows significance is vertical coma ($P < 0.05$). However, the difference in variances between the two groups is significant for every aberration ($P < 0.05$) (Figure 3.1b). The mean values (± SD) for each Zernike coefficient are depicted in Table 3.1.

Figure 3.2 shows that in both groups (uncorrected eyes), logMAR visual acuity decreased linearly as a function of ocular logVSMTF. In the non-cataract group, the mean logMAR visual acuity was 0.24 ± 0.40 and the mean ocular logVSMTF was -1.09 ± 0.72. In the cataract group the mean logMAR visual acuity value was 0.59 ± 0.27 and the mean ocular logVSMTF was -1.54 ± 0.60. The regression line for the non-cataract group was $\text{logMAR} = -0.31 - 0.50 \times \text{logVSMTF}$, and for the cataract group $\text{logMAR} = 0.03 - 0.36 \times$

logVSMTF. The correlation between ocular logVSMTF and VA (logMAR) was significant in both groups (r = -0.90, $P < 0.05$ for the non-cataract and r = -0.81, $P < 0.05$ for the cataract group, respectively). The results are shown in Table 3.2.

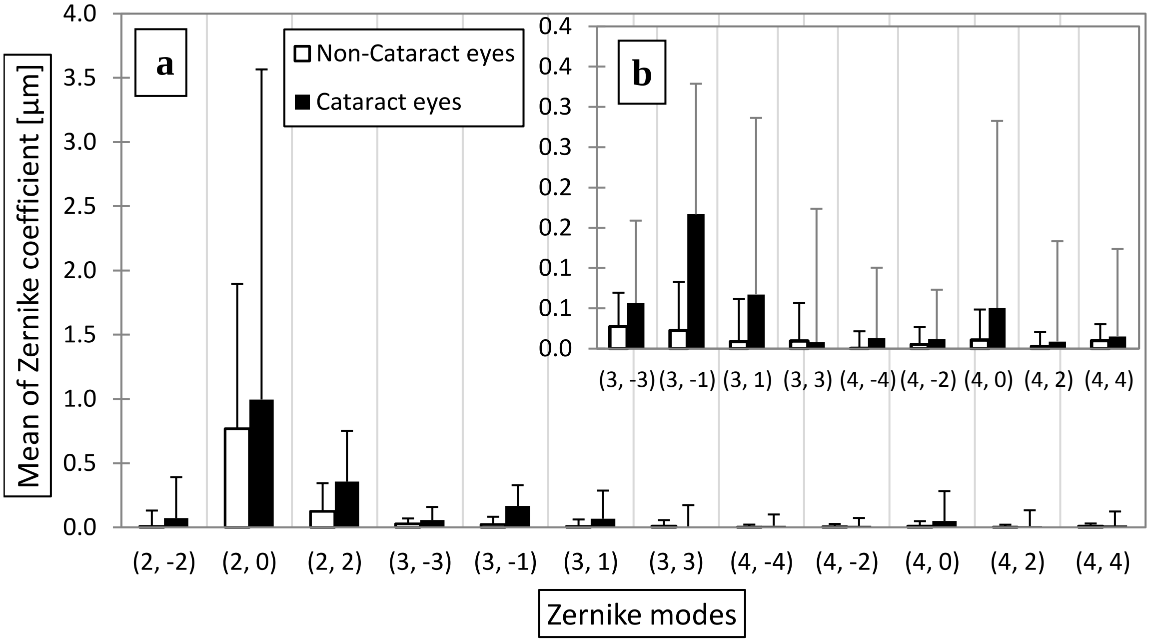


Figure 3.1. (a) Absolute average normalized Zernike coefficients for 2nd-, 3rd- and 4th-order aberrations over a 3-mm pupil for healthy (non-cataract) (n = 18) and cataract (n = 15) eyes. In terms of absolute value, the most predominant Zernike modes, in order, were defocus Z_2^0 and vertical astigmatism Z_2^2. (b) The differences in variances between the two groups was significant for all the shown modes.

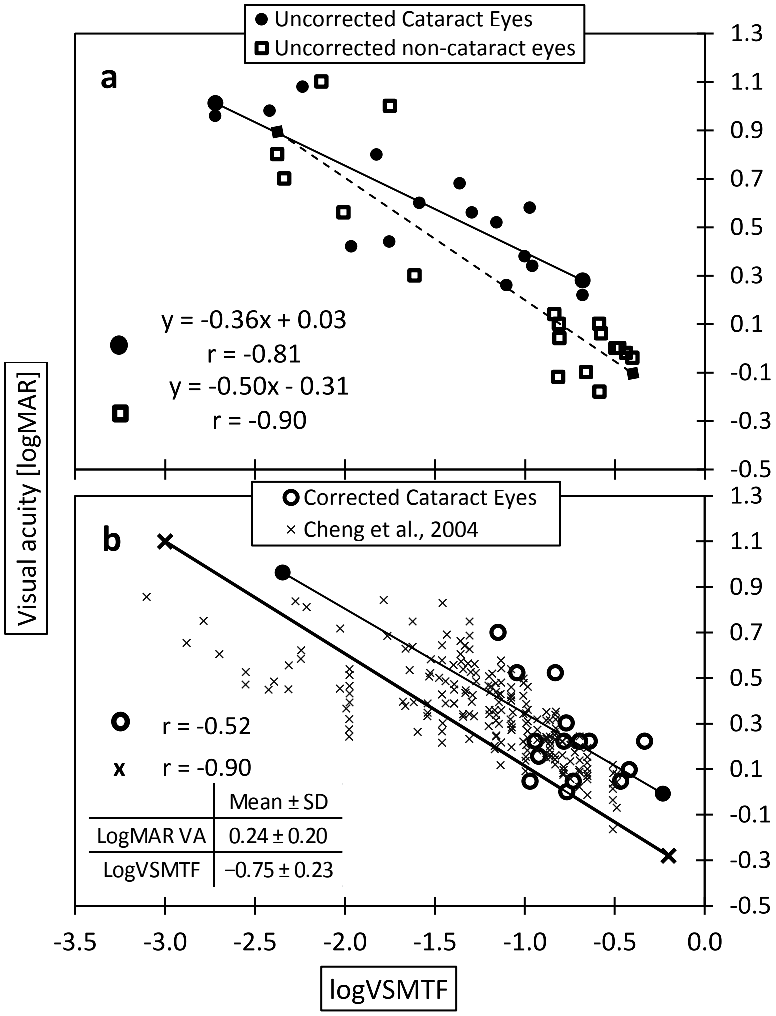
		Healthy eyes		Cataract eyes	
n	m	mean	SD	mean	SD
		Mm			
2	-2	0.01	0.12	0.07	0.32
2	0	0.77	1.13	1.00	2.57
2	2	-0.13	0.22	0.36	0.40
3	-3	-0.03	0.04	0.06	0.10
3	-1	0.02	0.06	0.17	0.16
3	1	-0.01	0.05	0.07	0.22
3	3	0.01	0.05	0.01	0.17
4	-4	0.00	0.02	0.01	0.09
4	-2	-0.01	0.02	-0.01	0.06
4	0	0.01	0.04	0.05	0.23
4	2	0.00	0.02	0.01	0.12
4	4	0.01	0.02	-0.02	0.11

Table 3.1. Average normalized Zernike coefficients for 2nd-, 3rd- and 4th-order aberrations over a 3-mm pupil for non-cataract (n = 18) and cataract (n = 15) eyes

Parameters		Healthy eyes	Cataract eyes
Mean ± SD	LogMAR VA	0.24 ± 0.40	0.59 ± 0.27
	LogVSMTF	−1.09 ± 0.72	−1.54 ± 0.60
LogMAR-LogVSMTF correlation	Slope of regression line	−0.50	−0.36
	r - coefficient	−0.90	−0.81
	P - value	< 0.05	< 0.05

Table 3.2. Mean (±standard deviation) logMAR and logVSMTF of 18 healthy (non-cataract) and 15 cataract eyes; also shown are the slopes of the regression lines and the correlation coefficients of both groups.

The results show that the VSMTF metric is very good at predicting how a change in wavefront aberration affects the logMAR visual acuity in uncorrected non-cataract and cataract eyes. The logVSMTF–logMAR graphs of non-cataract and cataract eyes displays rather similar relationships (Figure 3.2a); no significant difference was observed between regression lines ($P_{slopes} = 0.287$, $P_{r\text{-}coefficients} = 0.373$). This might be caused by the dominance of lower-order aberrations in both groups. It is thought, however, that the problem with cataract is that it causes higher-order aberrations (in addition to straylight).



	Mean ± SD
LogMAR VA	0.24 ± 0.20
LogVSMTF	−0.75 ± 0.23

Figure 3.2. (a) Correlation between logVSMTF and logMAR visual acuity measures are shown for (a) 15 uncorrected cataract eyes (circles) and 18 uncorrected healthy (non-cataract) eyes (squares), and (b) the corrected cataract eyes (circles) and Cheng et al., 2004, a study on healthy (non-cataract) eyes (x's).

The increased higher order aberrations cannot be corrected and cause acuity to deteriorate. To find out whether that is a valid conjecture and to eliminate the dominant effect of lower-order aberrations, we removed these lower-order aberrations from the analysis of cataract eyes. For the same reason, we assessed the (lower-order) corrected logMAR visual acuities in this group (Figure 3.2b). In corrected cataract eyes, the mean logMAR visual acuity value was 0.24 ± 0.20 log units and the mean ocular logVSMTF was -0.75 ± 0.23 log units. Despite lower mean values, compared to the uncorrected non-cataract and cataract eyes, logMAR acuity and logVSMTF still display a moderate correlation (r = -0.52). Moreover, the difference between the regression lines of the cataract group before and after correction, was not statistically significant ($P_{slopes} = 0.334$; $P_{r\text{-coefficients}} = 0.177$).

Subject	logMAR VA		logVSMTF	
	UC	BC	UC	BC
1	0.98	0.10	−2.42	−0.42
2	1.08	0.22	−2.24	−0.64
3	0.60	0.22	−1.59	−0.78
4	0.52	0.05	−1.16	−0.47
5	0.44	0.00	−1.75	−0.76
6	0.22	0.22	−0.68	−0.69
7	0.68	0.52	−1.36	−1.04
8	0.26	0.22	−1.10	−0.94
9	0.38	0.30	−1.00	−0.77
10	0.42	0.22	−1.97	−0.33
11	0.58	0.52	−0.98	−0.83
12	0.34	0.15	−0.96	−0.92
13	0.56	0.05	−1.30	−0.97
14	0.96	0.05	−2.72	−0.73
15	0.80	0.07	−1.83	−1.15

Table 3.3. LogMAR visual acuity (VA) and logVSMTF of 15 cataract eyes, associated with uncorrected (UC) and best corrected (BC) visual acuities

3.4. Discussion

Despite the increasing number of cataract surgeries per year around the world and advancements in surgical technique, the clinical decision making process for cataract surgery has not changed much. Today ophthalmologists make their decisions based on the traditional guidelines, and consider mainly subjective measures such as visual acuity. Thus, there is a need to develop a more objective decision-making method based on objective measures. In recent years, there has been remarkable progress in developing objective measures of visual performance. Several studies [16−19] concluded that the VSR metric is the best predictor of visual performance. Our study complements this conclusion by focusing on evaluating a certain VSR (VSMTF) metric as means to quantify the effect of cataract on visual acuity. This metric measures some aspects of optical quality of the eye and takes into account the neural aspect of the visual system.

In this contribution, we confirm that the aforesaid metric has a strong correlation with logMAR visual acuity in uncorrected non-cataract eyes. We also found a high correlation between the two measures in uncorrected cataract eyes. The high correlation suggests that this metric may act as a surrogate for testing visual acuity in eyes with normal-functioning retina and cerebrum, regardless of their cataract status. The mean Zernike coefficients of higher-order aberrations are not big in non-cataract and cataract eyes. However, the variations in higher order aberrations are large in the cataract group, and significantly different between the groups, especially for spherical aberration. Although we did not classify cataracts into morphological categories, the results seem consistent with previous studies that have reported coma and spherical aberrations as being the predominant higher-order aberrations in eyes with nuclear [22][23] and cortical [22] cataracts. Several studies [24][25] showed that a decrease in visual performance is linked to a reduction in retinal image quality, in particular due to an increase in the spherical aberration of the crystalline lens, whereas corneal aberrations either remain unchanged or increase only to a small degree [26].

Comparing the uncorrected and corrected cataract eyes, Figure 3.2 shows a shift of logMAR VA and logVSMTF to smaller values. Table 3.3 gives the numerical comparison. We also found moderate correlation between the two parameters. This might be due to the fact that the inter-subject variation in the higher-order aberrations was not large enough in our population. However, the data points of the corrected cataract eyes aggregate around those of uncorrected cataract eyes, suggesting coherence of the VSR model. Nevertheless, one would like to expand the study, and to include an analysis with different types of cataract and severity, and take the inter-subject variation in each higher-order aberration into account.

In this work, we investigated the relation between visual acuity and ocular (total) VSMTF. Therefore, we do not know the strength of the relation between visual acuity and intraocular (lenticular) VSMTF, which distinctly stresses the role of crystalline lens on formation of aberrometric map. This can be the subject of future studies.

3.5. Conclusion

We looked at the possibility of using an image quality metric called visual Strehl ratio measured in the frequency domain (VSMTF), which is derived from wavefront aberrations as a means to quantify particularly the severity of age-related cataract in terms of visual acuity. We conclude that visual acuity can be predicted from the optical quality of the eye by means of this metric in cataract eyes.

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Chapter 4

Changes in intraocular straylight and visual acuity with age in cataracts of different morphologies

4.1. Introduction

The eye is an optical system with imperfections. Entering this optical system, light is refracted by the ocular media (*e.g.* cornea and crystalline lens) to form an image on the retina. However, part of this light is scattered by optical imperfections. Depending on the direction of scattering (forward or backward), it can have different influences on vision. The forward light scattering causes (intraocular) straylight or disability glare [1]. It produces undesired veiling of the retinal image which leads to reduced vision, glare, and other visual impairments. In young healthy eyes, almost 10% of the inbound light is scattered [2]. However, in eyes older than 50 years of age, this number increases considerably [3]. A phakic norm curve has been established that can be used as reference for clinical practice [3]. Some pathological conditions, in particular cataract, increase the amount of intraocular straylight above normal. In clinical practice, a patient's visual complaints, ophthalmic examination with a slit-lamp and measurement of visual acuity are the predominant scales for managing cataract. It should be noted that a slit-lamp examination provides only backscatter-based assessments. As the correlation between forward and backward light scattering has been shown to be small, methods that measure the amount of backscatter, such as slit-lamp examination, cannot reliably quantify straylight and glare [4–7]. Various studies have shown that straylight is a vision impairment that is not directly related to visual acuity and is only weakly correlated to it [3][8]. A computerized purpose-built device called C-Quant (Oculus Optikgeräte GmbH), measures the amount of ocular straylight and renders a parameter in the logarithmic unit (log(s)) with good reliability and repeatability [9–11].

As mentioned earlier, visual acuity is an important criterion in the cataract surgical decision-making process. However, various studies [12][13] have shown that in a significant number of cataract cases, visual acuity is not an adequate measure to judge visual performance. Subsequent studies have supported this notion [14][15]. Moreover, there have been reports of no change or even an increase in straylight after cataract surgery when the decision was made solely based on visual acuity [16]. The reason for this is that visual acuity only evaluates the impact of narrow-angle light spreading due to refractive errors and therefore can only measure a limited part of a patient's vision [13][17]. Elliot et al. [7] expressed that additional visual tests were needed that could mirror visual loss but at the same time should be unrelated to visual acuity. They acknowledged the direct compensation method to quantify straylight as a standard technique to evaluate the validity of disability glare tests.

Recently, a literature review [18] established a norm curve for pseudophakic eyes and also a reference curve to estimate the amount of straylight to be expected after cataract surgery by introducing *straylight improvement* as a function of age and preoperative straylight. Although this reference is a good measure for cataract management in an average eye, it may overlook the influence of the type, location and intensity of the cataract on the outcome because the type of cataract was not specified in the norm curve. To establish morphologically categorized references, we need a phakic norm stratified to the type of cataract. In the present study, we performed a literature review to identify relevant papers on straylight, age, and visual acuity in three common types of cataract. In addition, we recalculated the significance of the relation between straylight and visual acuity with taking cataract morphology into account. The published studies included in this literature review evidenced individually that such correlation varies from one type of cataract to another. The population sizes and severities of the cataracts were different across these studies. We consider the relatively large final number of observations and their diverse degrees of cataract intensity as the strength of this study to improve the generalizability of the results.

4.2. Materials and Methods

This study includes two parts. The first part encompasses a comprehensive literature review to study the effect of different cataract morphologies on straylight and to determine models for straylight values as a function of age for different types of cataract. Second, we calculated the correlations between straylight and visual acuity, the amount of progression of straylight and visual acuity from those of a normal group, and the ratios of straylight to age and visual acuity in each cataract group.

A literature examination was carried out including all available studies that reported straylight values, measured with a C-Quant instrument (Oculus Optikgeräte GmbH), in cataract eyes with specification of its morphology. The language of the articles, and age, gender, and race of the participants had no influence in this process. All papers provided information on intraocular straylight, age and visual acuity of participants with the specification of the type of cataract. All papers had excluded patients with history of ocular surgery or diseases, diabetic retinopathy, glaucoma, and age-related macular degeneration. We considered data with expected standard deviation (ESD) of 0.12 log units or less reliable for analysis.

PubMed, Medline, and Google Scholar were the scientific databases we screened using the following keywords: *straylight, C-Quant, age, visual acuity, cataract, cataract morphology, cataract classification, LOCS III, nuclear cataract, cortical cataract and posterior-subcapsular cataract (PSC)*. In case of overlapping data in the studies, the one with the larger population was included for the review. Five papers met the eligibility criteria: de Waard et al., Nischler et al., Bal et al., Congdon et al., and Filgueira et al. [6][19–22]. Because of lack of the desired data in four cases, we contacted the corresponding authors. In one case there was no response, therefore GSYS2.4 (a graph digitizing system developed by Nuclear Reaction Data Center, University of Hokkaido, Japan) was used to extract data from the published graphs. Table 4.1 shows which data were reported by the five included studies. It has to be noted that the various studies classified the types of cataract differently based on LOCS (Table 4.2).

Data from all five articles were used to develop the log(s)-age normative curves for the three types of cataract. The correlations between the two variables were calculated and compared with each other. We calculated the normally expected mean straylight value for each cataract type, all types of cataract combined and the control group by using the log(s)-age normative equation obtained by van den Berg et al. [23], which reads

$$\log(\text{straylight parameter}) = \log(s) = 0.9 + \log(1 + (\text{age}/65)^4).$$

The results were compared with the measured straylight values. The residuals are displayed by using histograms. To study the possible differentiative impact of morphology on the progressive process of cataract, we used the largest control group—which belonged to

Nischler et al.—with the best straylight and visual acuity values. We then compared the straylight and visual acuity of each cataract group in each study by connecting the mean values to those of the control group using arrows to show the magnitude and direction of progression. The slopes and lengths of the arrows were compared with each other. The correlations between log(s) and logMAR visual acuity values were calculated and compared with each other. We also calculated the ratio of straylight to age and visual acuity for each type of cataract; the results are illustrated using box-and-whisker plots. The log(s)-logMAR normative curves for each type of cataract are also derived using data from all five articles.

Cataract	*Study (Year)*	*Age*	*SL*	*VA*
Nuclear	Filgueira (2016)	🟢	🟢	🟢
	Congdon (2012)	🟢	🟢	🟢
	Bal (2011)	🟢	🟢	🟢
	Nischler (2010)	🟢	🟢	🟢
	de Waard (1992)	🔴	🟢	🟢
Cortical	Filgueira (2016)	🔴	🔴	🔴
	Congdon (2012)	🔴	🔴	🔴
	Bal (2011)	🟢	🟢	🟢
	Nischler (2010)	🟢	🟢	🟢
	de Waard (1992)	🔴	🟢	🟢
Posterior subcapsular	Filgueira (2016)	🟢	🟢	🟢
	Congdon (2012)	🔴	🔴	🔴
	Bal (2011)	🟢	🟢	🟢
	Nischler (2010)	🟢	🟢	🟢
	de Waard (1992)	🔴	🟢	🟢

Table 4.1. Red circles show deficient data and green circles show available data in each individual study

Study	*Cataract definition*
Filgueira et al. (2016)	Early age-related cataracts: Nuclear (NO=1 and 2), Posterior-subcapsular (P=1 and 2)
Congdon et al. (2012)	Nuclear (NO≥3)
Bal et al. (2011)	Nuclear (NO>2, NC>2, C≤2, P≤1), cortical (NO≤2, NC≤2, C>2, P≤1), Posterior-subcapsular (C≤2, P>1)
Nischler et al. (2010)	Nuclear (2≤NO≤4, 2≤NC≤4, C<2, P≤1.5), cortical (NO<2, NC<2, 2≤C≤4, P≤1.5), posterior-subcapsular (NO<2, NC<2, C<2, 1.5≤P≤4)
de Waard et al. (1992)	Advanced age-related cataracts (morphologically not categorized)

Table 4.2. Range of intensity defined for each type of cataract in the studies

Linear regression analysis was performed with Excel software (2010, Microsoft Corporation) and SPSS Statistics 21 (IBM Corporation) on the straylight values − log(s) − to describe it as a function of age and logMAR visual acuity. Unpaired *t*-tests were used to calculate the significance of differences in means (±95% CI) between each study and the normative curve of each cataract type. The significance level was set at *P*-value less than 0.05.

4.3. Results

4.3.1. Comprehensive review

As explained in Materials and Methods, five reports fulfilled the eligibility criteria. Table 4.3 shows a summary of outcomes of each study. Table 4.4 shows the outcomes for each type of cataract, all types of cataract combined, and the control group. Figure 4.1 illustrates age, visual acuity and straylight distributions in each cataract group.

The evaluations concerning log(s)-logMAR related analyses were based on 776 total observations, with mean visual acuity of 0.02 ± 0.18 log units (range -0.30 to 0.70 log units) and mean straylight of 1.23 ± 0.22 log units (range 0.61 to 2.09 log units). The total number of cataract eyes was 725 for evaluations concerning log(s)-age related analyses with a mean age of 63 ± 9 years (range 44 to 85 years of age). Figures 4.2 and 4.3 show the log(s)-age, and log(s)-logMAR linear regressions for studies comprising the required data.

Cataract	First Author (Year)	Eyes (n)	Mean ± SD			log s - Age		log s - logMAR	
			Age (Y)	VA (logMAR)	SL (log s)	Dependency	R^2	Dependency	R^2
NC	Filgueira (2016)	14	69 ± 18	0.10 ± 0.08	1.33 ± 0.21	log(s) = 0.008 x age + 0.75	0.02	log(s) = 0.14 x logMAR - 0.08	0.14
	Congdon (2012)	24	65 ± 10	0.22 ± 0.14	1.36 ± 0.33	log(s) = 0.019 x age + 0.12	0.36	log(s) = 0.82 x logMAR + 1.17	0.13
	Bal (2011)	23	67 ± 9	0.28 ± 0.18	1.50 ± 0.24	log(s) = 0.001 x age + 1.54	0.00	log(s) = 0.51 x logMAR + 1.36	0.14
	Nischler (2010)	512	63 ± 9	−0.05 ± 0.12	1.19 ± 0.17	log(s) = 0.008 x age + 0.65	0.21	log(s) = 0.44 x logMAR + 1.21	0.10
	de Waard (1992)	18	NA	0.39 ± 0.14	1.54 ± 0.16	NA	NA	log(s) = 0.01 x logMAR + 1.42	0.08
CC	Filgueira (2016)	NA	NA	NA	NA	NA	NA	NA	NA
	Congdon (2012)	NA	NA	NA	NA	NA	NA	NA	NA
	Bal (2011)	15	67 ± 7	0.25 ± 0.20	1.48 ± 0.29	log(s) = 0.020 x age + 0.13	0.26	log(s) = −0.28 x logMAR + 1.55	0.04
	Nischler (2010)	78	62 ± 8	−0.06 ± 0.09	1.20 ± 0.17	log(s) = 0.008 x age + 0.69	0.17	log(s) = 0.13 x logMAR + 1.21	0.00
	de Waard (1992)	16	NA	0.24 ± 0.13	1.34 ± 0.29	NA	NA	log(s) = 1.22 x logMAR + 1.04	0.29
PSC	Filgueira (2016)	20	56 ± 5	0.03 ± 0.05	1.17 ± 0.27	log(s) = 0.013 x age + 0.42	0.06	log(s) = 0.04 x logMAR - 0.02	0.11
	Congdon (2012)	NA	NA	NA	NA	NA	NA	NA	NA
	Bal (2011)	20	64 ± 9	0.30 ± 0.22	1.79 ± 0.20	log(s) = 0.001 x age + 1.77	0.00	log(s) = 0.13 x logMAR + 1.76	0.02
	Nischler (2010)	18	61 ± 8	0.02 ± 0.11	1.30 ± 0.27	log(s) = 0.000 x age + 1.19	0.00	log(s) = 1.02 x logMAR + 1.28	0.17
	de Waard (1992)	17	NA	0.26 ± 0.18	1.67 ± 0.21	NA	NA	log(s) = 0.33 x logMAR + 1.58	0.08

Table 4.3. Overview of the analysis on the data derived from raw data or published plots of each individual study (NC: nuclear cataract, CC: cortical cataract, and PSC: posterior-subcapsular cataract)

Group	Number of eyes		Mean ± SD			log s - Age		log s - logMAR	
	SL-Age	SL-VA	Age (Year)	VA (logMAR)	SL (log s)	Dependency	R^2	Dependency	R^2
Nuclear	573	592	63 ± 9	−0.01 ± 0.16	1.22 ± 0.20	log(s) = 0.009 x age + 0.60	0.20	log(s) = 0.62 x logMAR + 1.22	0.25
Cortical	93	109	62 ± 8	0.03 ± 0.18	1.26 ± 0.23	log(s) = 0.012 x age + 0.50	0.22	log(s) = 0.33 x logMAR + 1.24	0.13
Posterior	58	75	60 ± 8	0.15 ± 0.20	1.48 ± 0.34	log(s) = 0.015 x age + 0.53	0.11	log(s) = 1.03 x logMAR + 1.32	0.34
All cataract	724	776	63 ± 9	0.02 ± 0.18	1.23 ± 0.22	log(s) = 0.009 x age + 0.64	0.14	log(s) = 0.68 x logMAR + 1.24	0.26
Control	1761	1761	57 ± 8	−0.07 ± 0.11	1.12 ± 0.16	log(s) = 0.008 x age + 0.68	0.17	log(s) = 0.25 x logMAR + 1.14	0.03

Table 4.4: Overview of the analysis on collected data from individual studies for each cataract group

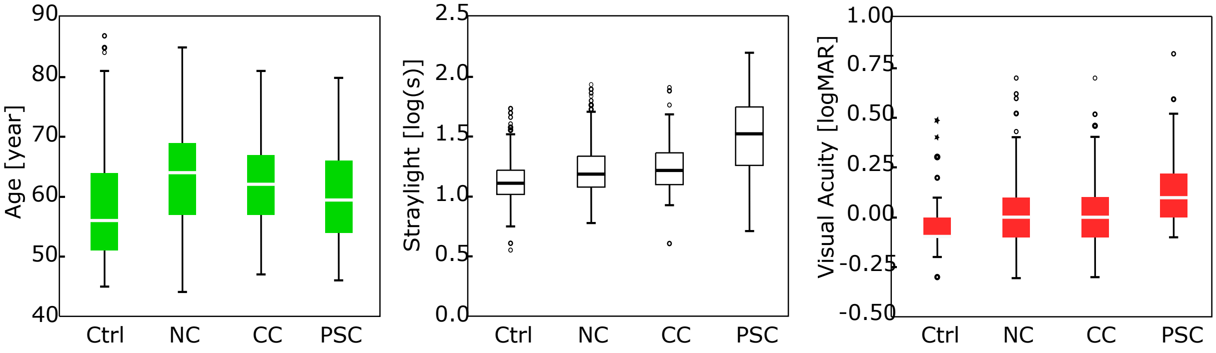

Figure 4.1. Age, intraocular straylight and best-corrected visual acuity plotted for cataract and control groups. Straylight and visual acuity differed significantly from PSC to the other cataracts and control group. (NC: nuclear cataract, CC: cortical cataract, and PSC: posterior-subcapsular cataract)

4.3.2. Effect of cataract morphology on straylight

Straylight varied as a function of cataract morphology (Table 4.3); it was significantly higher in the three cataract groups (1.22 ± 0.20 log units in nuclear cataract, 1.26 ± 0.23 log units in cortical cataract, and 1.48 ± 0.34 log units in PSC) compared to the control group (1.12 ± 0.16 log units, $P < 0.05$). In addition, in all cataracts combined, straylight significantly was increased (1.26 ± 0.12 log units) relative to the control group ($P < 0.05$).

4.3.3. Correlation with age

Straylight showed the highest correlation with age in Congdon et al.'s nuclear group ($R^2 = 0.36$, $P < 0.05$) and it showed no to a very weak correlation in several other groups (Table 4.3). Figure 4.1 shows phakic normative curves for each type of cataract; the data were derived from 574 eyes of nuclear, 93 of cortical and 58 eyes of PSC. Overall, cortical cataract showed the highest correlation between log(s) and age ($R^2 = 0.22$, $P < 0.05$), and the overall PSC showed the lowest correlation between the two variables ($R^2 = 0.11$, $P < 0.05$) (Table 4.4). Figure 4.2 shows reference curves for cataracts and control group. The overall relationships read

Straylight value = 0.009 × age + 0.60 (Nuclear group; $R^2 = 0.20$, $P < 0.05$)

Straylight value = 0.012 × age + 0.50 (Cortical group; $R^2 = 0.22$, $P < 0.05$)

Straylight value = 0.014 × age + 0.53 (PSC group; $R^2 = 0.11$, $P < 0.05$),

whereas that of the control group reads

Straylight value = 0.007 × age + 0.68 (Control group; $R^2 = 0.17$, $P < 0.05$).

Mean straylight values are displayed in Tables 4.2 and 4.3. The figures show differences in different studies.

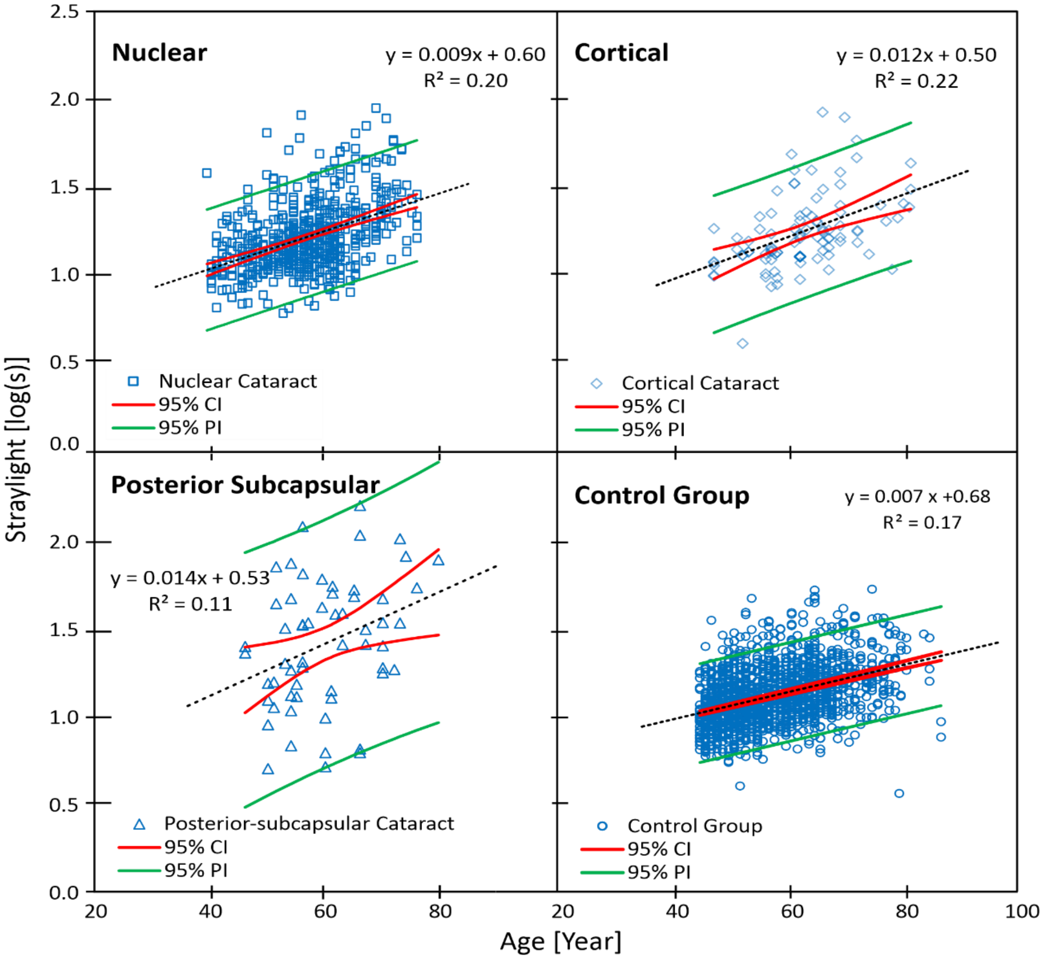

Figure 4.2. Linear models of log(s)-age dependency for nuclear cataract derived from four studies, cortical cataract derived from two studies, posterior-subcapsular cataract derived from three studies and control group are plotted. Black dotted lines are the regression lines.

The mean age of each group is depicted in Figure 4.3. Using the log(s)-age norm curve equation obtained by van den Berg et al. (2013), we calculated the expected mean straylight for each cataract type of each study, overall cataract types, all cataract types combined, and control groups. The results were compared with the measured straylight values. The residuals are displayed in Figure 4.4. We must remind the reader that not every study provided information on age (Table 4.1). Among three cataract groups, the mean straylight of PSC group showed the highest difference from the expected mean straylight of an age-matched phakic group; by contrast, nuclear group showed the smallest difference. The same figure shows negligible difference between measured and expected straylight in control group.

4.3.4. Correlation with visual acuity

Straylight showed the highest correlation with logMAR visual acuity in de Waard et al.'s cortical group ($R^2 = 0.29$, $P < 0.05$) and the lowest correlation in Nischler et al.'s cortical group ($R^2 = 0.00$, $P = 0.99$). Overall, PSC showed the highest correlation between straylight and logMAR visual acuity ($R^2 = 0.34$, $P < 0.05$) and cortical cataract showed the lowest correlation, however significant, between the two variables ($R^2 = 0.13$, $P < 0.05$). The relations and correlation coefficients between log(s) and logMAR visual acuity are reported in Tables 4.3 and 4.4.

Figure 4.5 shows log(s)-logMAR reference curves for cataracts and control group. The overall relationships read

$$\text{straylight value} = 0.62\times\text{visual acuity} + 1.22 \quad (\text{Nuclear group; } R^2 = 0.25,\ P < 0.05)$$

$$\text{straylight value} = 0.33\times\text{visual acuity} + 1.24 \quad (\text{Cortical group; } R^2 = 0.13,\ P < 0.05)$$

$$\text{straylight value} = 1.03\times\text{visual acuity} + 1.34 \quad (\text{PSC group; } R^2 = 0.34,\ P < 0.05),$$

whereas the norm of the control group reads:

$$\text{straylight value} = 0.25\times\text{visual acuity} + 1.1 \quad (\text{Control group; } R^2 = 0.03,\ P < 0.05).$$

From the above relationship, one can see that straylight varies as a function of morphology. Patients with PSC for a similar logMAR visual acuity have a higher straylight than the other cataracts and control group.

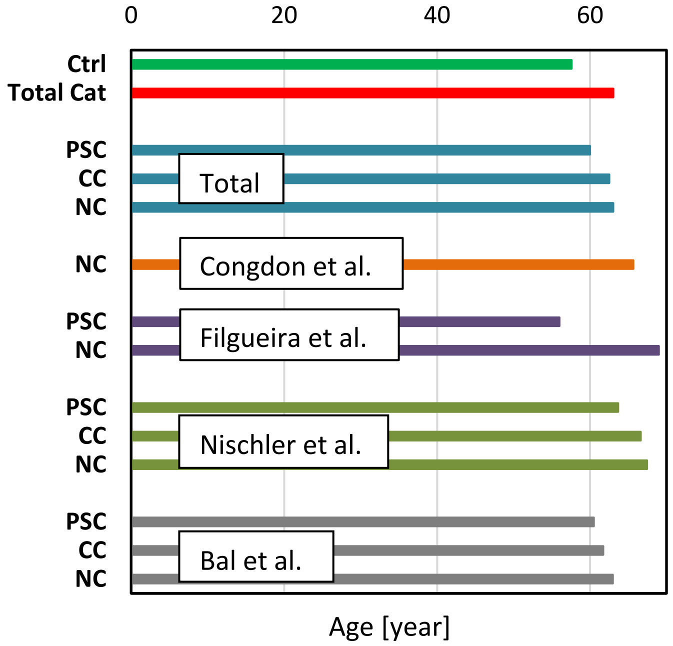

Figure 4.3. Mean age of each type of cataract in each published study. In average, patients with PSC cataract are the youngest. (Ctrl: control group, NC: nuclear cataract, Total Cat: all cataract groups combined, CC: cortical cataract, and PSC: posterior-subcapsular cataract)

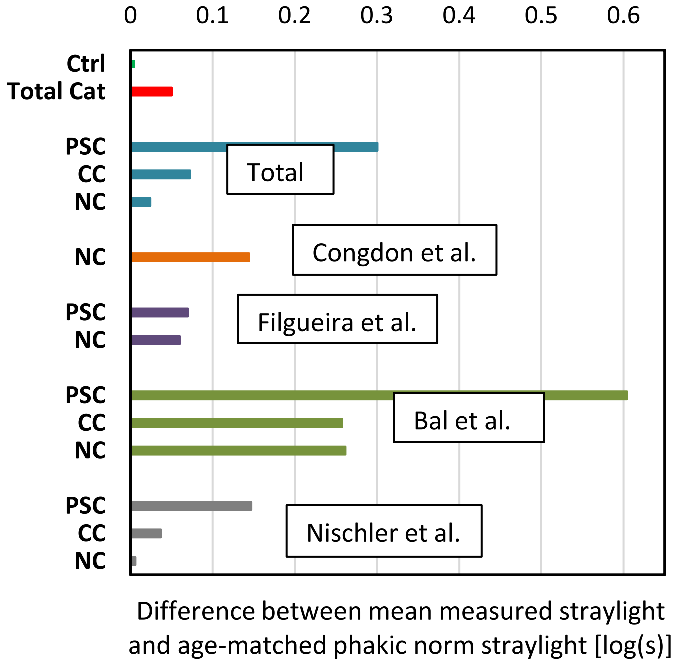

Figure 4.4. Differences between the mean straylight value in patients with different types of cataract for the various studies and the age-matched straylight value derived from the phakic norm curve by van den Berg et al. (2013) are plotted. In all data, straylight in patients with PSC cataract showed the highest deviation from that of a non-cataract (phakic) group. (Ctrl: control group, Total Cat: all cataract groups combined, NC: nuclear cataract, CC: cortical cataract, and PSC: posterior-subcapsular cataract)

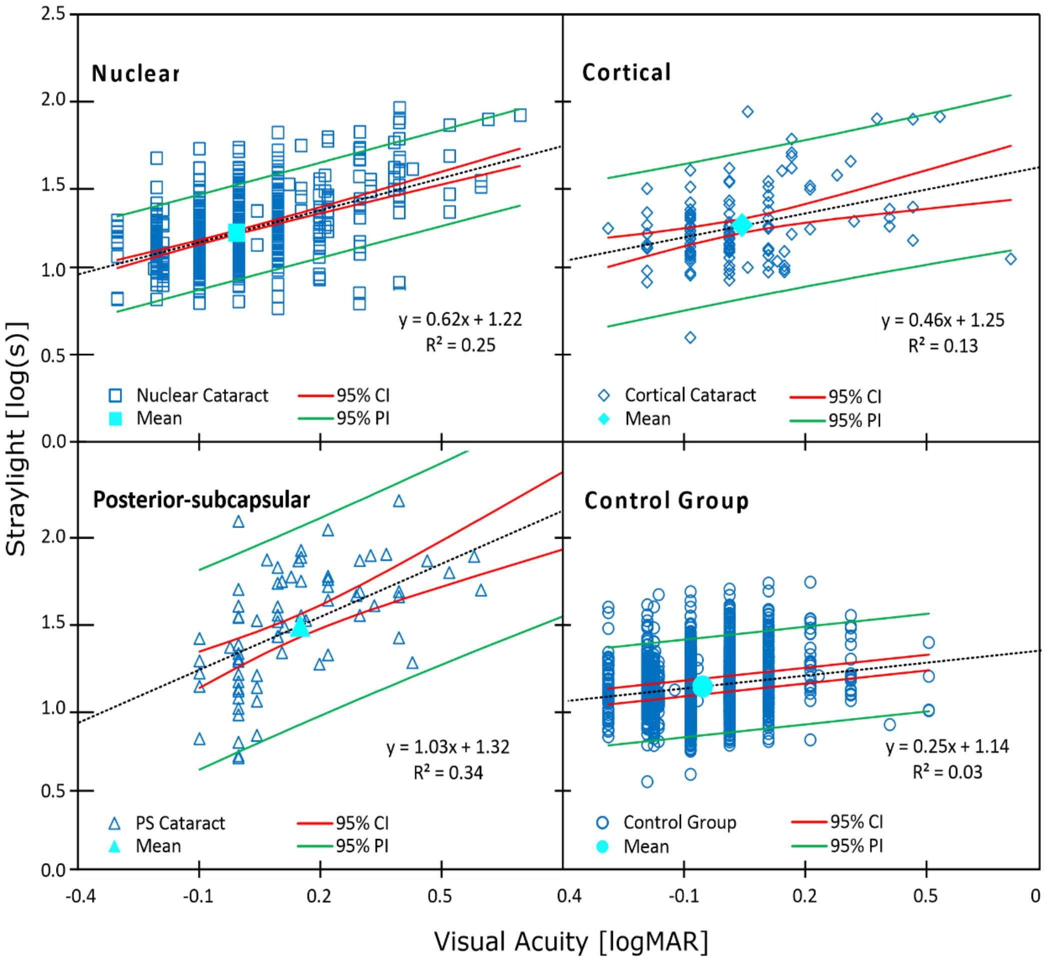

Figure 4.5. Linear models of log(s)-logMAR visual acuity dependency for nuclear cataract derived from five studies, cortical cataract derived from three studies, PSC cataract derived from four studies and control group are plotted. Black dotted lines are the regression lines.

4.3.5. Cataract: Progression from healthy eyes

We estimated the amount of progression of mean straylight and mean visual acuity from those of the control group in each individual study and cataract groups. The progression lines are demonstrated in Figure 4.6. Data showed that PSC in Bal et al. had the highest progression from non-cataract status in terms of both straylight (ΔSL = 0.68 log units) and visual acuity (ΔVA = 0.37 log units). However, with respect to the progression of individual variables, the mean visual acuity increased the most in de Waard et al.'s nuclear group (ΔVA = 0.46 log units), whereas its mean straylight value increased (ΔSL = 0.42 log units) less than that of Bal et al.'s PSC group. The mean visual acuity deteriorated the least in Nischler et al.'s nuclear and cortical groups.

4.3.6. Ratio between straylight and age and visual acuity

The ratios between straylight and age, and between straylight and visual acuity are illustrated using box-and-whisker plots (Figure 4.7). The median of straylight parameter [s]/age [year] had the lowest value in nuclear cataract group and the highest value in PSC group, albeit with a rather more skewed distribution comparing the two other cataract groups. The median of log(s)/logMAR showed similarly lower values in nuclear and cortical groups in comparison to that of PSC group. In both cases, the differences in medians of the nuclear and cortical groups were statistically significantly higher than those of the PSC group.

4.4. Discussion

The application of the findings of this literature review is limited by the restricted range of the severity of cataracts and the difference in age between the studies. However, it is a good place to start studying the distinctive relationship between cataract morphology and visual functions. There is a strong correlation between cataract morphology, the intensity of lens opacification and impairment of visual functions (*i.e.* straylight and visual acuity). From the results, we found that PSC population was generally younger, which is in agreement with the literature [24–27] reporting that the average age of the population developing or undergoing surgery for PSC is younger that for other types of cataract.

In the present study, the log(s)-age dependencies were obtained for cataracts of different morphologies. Among five published articles used in this literature review, four could be used for the nuclear, three for the PSC, and two for the cortical log(s)-age dependency equations (Table 4.1).

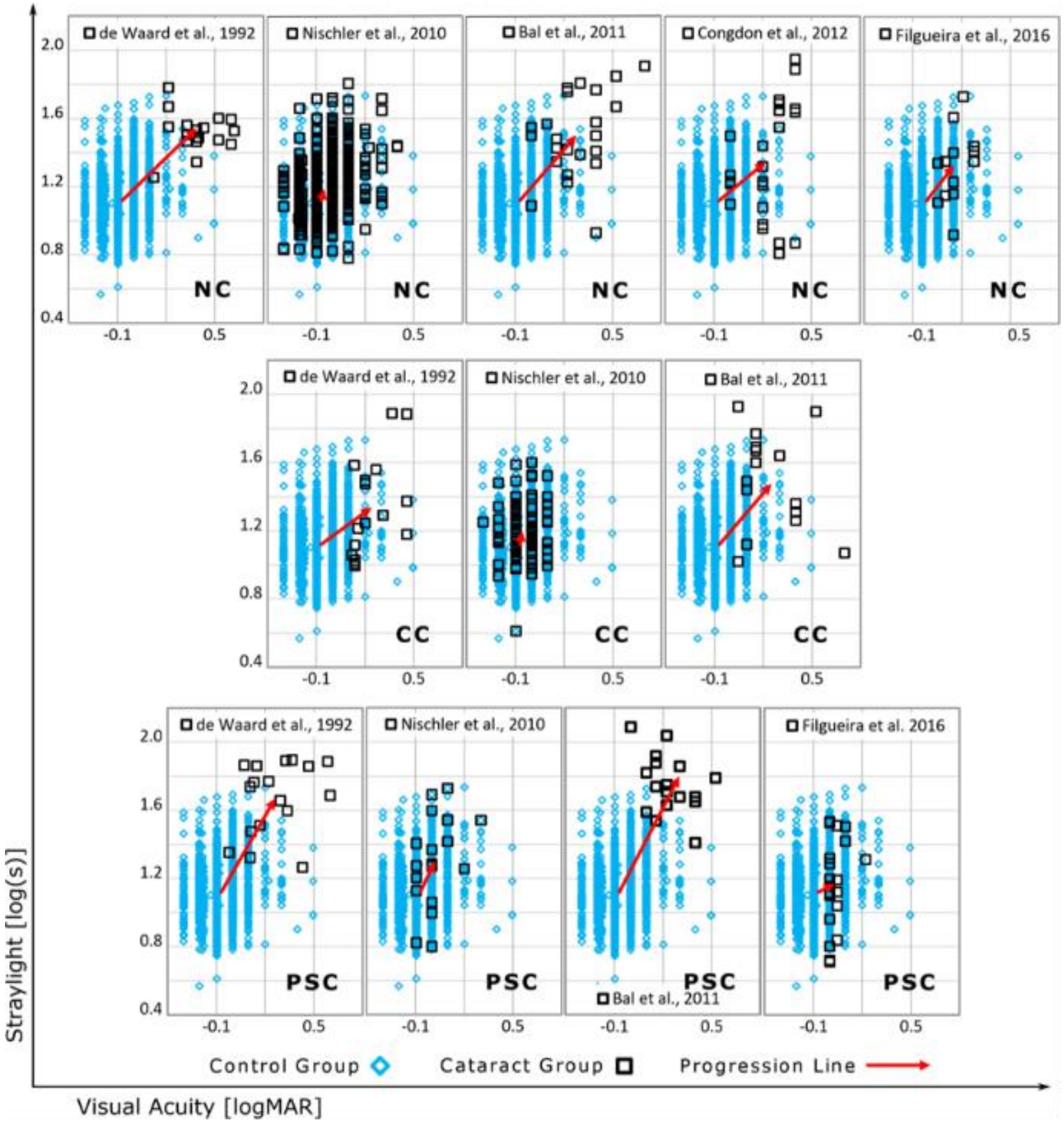

Figure 4.6. Progression of cataracts from control group is illustrated by arrows originating from mean straylight and mean visual acuity of the control group towards those of each type of cataract in each individual study. (NC: nuclear cataract, CC: cortical cataract, and PSC: posterior-subcapsular cataract)

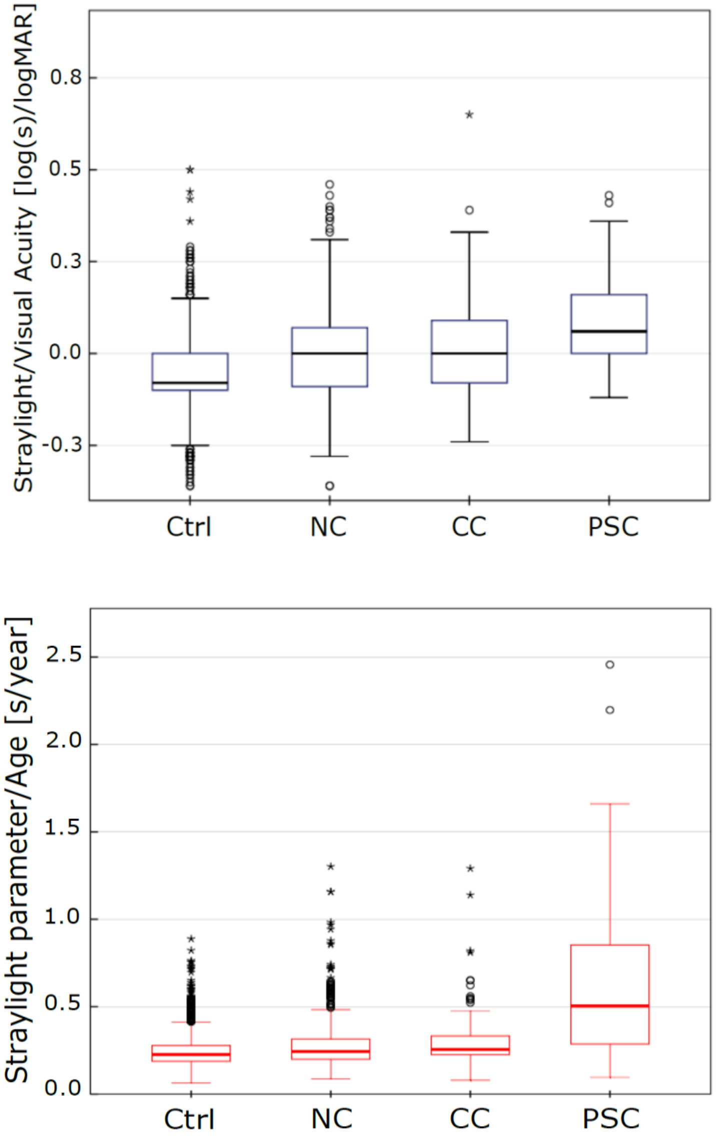

Figure 4.7. *Above.* Ratio between straylight and age for each type of cataract: The median of such ratio is significantly higher in PSC group. *Below.* The same is valid for straylight-visual acuity ratio. Both cases suggest that straylight is the highest in patients with PSC group albeit lower and/or similar age and visual acuity than/as the other cataracts. (Ctrl: control group, NC: nuclear cataract, CC: cortical cataract, and PSC: posterior-subcapsular cataract)

These equations cannot be considered normative reference curves, because the different studies made a severity selection of the cataract populations. This must have influenced (weakened) the dependencies. The slopes of the dependency equations varied from one cataract group to another, but the differences were not statistically significant. The slope of the dependency function of the nuclear cataract was close to that of the control group. The reason is that Nischler et al.'s nuclear group with patients with rather good vision, was remarkably larger than the rest. The differences between cataracts and control groups, as mentioned earlier, were small, with large overlap between the cataract and control populations. This points at limited validity of the LOCS cataract grading. Although LOCS serves to improve the grading and classifying slit-lamp observation, it is not precise for assessing function. As mentioned in the introduction, there is a weak relation between backscatter and forward scatter, therefore a slit-lamp-based measurement cannot be a reliable means to quantify forward scatter. The correlation between log(s) and age also varied between cataract groups and control group; it was the highest in cortical cataract and the lowest in PSC.

In each cataract group, the difference in the mean straylight values of individual studies and the respective dependency function was significant. This can be explained by different levels of cataract severity and significant difference in the number of eyes of the largest study and the rest. Such difference was not observed between the slopes of each study and the respective dependency functions. It appeared that the mean straylight values of the reference curves were moderately closer to those of Nischler et al.'s nuclear and cortical groups. Nischler et al. covered the major part of the overall data in these two groups, therefore it is no surprise that it leads the outcomes. The reason Nischler et al. had the lowest mean values in straylight and visual acuity may be due to the fact that the patients were active drivers, therefore they had comparatively better vision than their age-equivalent peers in other studies. The lowest straylight belonged to Filgueira et al.'s PSC. This is a deviant behavior as PSC in every other study had the highest straylight value. This group's visual acuity was almost as low as that of Nischler et al. Recruiting patients with eyes at the early stage of cataract in these two studies can explain these results (Table

4.2). When we left out data from Nischler et al. and Filgueira et al., the difference in means of cataract groups became very small, whereas the mean straylight of PSC was approximately 0.3 log units higher than that of other cataracts. This is in agreement with the finding by Elliott et al. [28][29] that in the advanced stages of cataracts, for patients with PSC, visual acuity alone is not an adequate assessment of visual performance and cataract management. The straylight curve established for normal phakic eyes [23] shows that straylight increases strongly with age with a logarithmic relation (to the power of 4). The change in straylight shows stable behavior in young eyes and considerably increases over 50 years of age. However, our findings showed rather linear relationship between log(s) and age. This may be related to the selection based on severity. We also found that the control group in Figure 4.4 shows the phakic reference norm works very well.

The correlation between log(s) and logMAR visual acuity varied from none to a moderate one in individual studies and within cataract types, but it never was strong. Overall, no type of cataract showed strong log(s)-logMAR correlation. In clinical practice, this means straylight cannot be predicted on the basis of visual acuity for any type of cataract. Figure 4.6 shows that, overall, in PSC group straylight deteriorated faster than visual acuity. Some studies [30–31] found that with increasing the severity of posterior capsule opacification (PCO), visual acuity and straylight deteriorate, albeit with different rates; the PCO severity-log(s) relation is linear, whereas the PCO severity-logMAR is curvilinear [31]. Therefore, straylight is more sensitive to the changes in PCO severity than visual acuity. Kruijt et al [32] also discussed this difference for localized processes.

Regardless of severity of cataracts, the present study supports the notion that the straylight is the highest in PSC. Fluctuations in density and discontinuous refractive index can be responsible for such amplification [33][34]. The difference between log(s)-logMAR dependency slopes of cataracts of different morphologies and their correlation coefficients are notable. The distinction between PSC and non-cataract eyes is especially remarkable. The log(s)-logMAR progression of cataracts from a control group in our study, also showed that PSC deteriorated the most in terms of visual functions. Therefore, it can be inferred that patients with this type of cataract would benefit the most from surgery. However, to draw definite conclusion, further studies on the improvement of visual functions after cataract surgery considering cataract morphologies are necessary. The results presented in Figure 4.4 show that the age-corrected mean straylight values of Bal et al. in every cataract groups are higher than those of other studies. Unlike patients recruited in the other studies, these patients were listed for cataract surgery. When Bal et al.'s patients were excluded from analysis, PSC had the worst visual acuity; the change in visual acuity in all cataract groups was in average 0.03 log units. The changes in straylight of nuclear and cortical groups were negligible, but it decreased about 0.11 log units in PSC. Therefore, the difference in mean straylight of PSC remained remarkably higher than the other cataracts and the correlation with age decreased ($R^2 = 0.04$, $P = 0.22$). The slopes of the new reference curves remained almost unchanged. We observed no change in the new log(s)-logMAR correlation in any cataract group, whereas the slopes changed, albeit insignificantly, with the average change of 0.06. Although the effect of excluding Bal et al.'s data on our analysis was unimportant, one needs to recognize the relatively small size of this study as an effective factor in this context.

It should be noted that correlations that were significant in one or some studies and were not in the other(s), were in fact significant in the whole cataract group. However, this cannot be said about the whole data (different types of cataracts combined), because of different morphologies and eventually different optical dynamics.

4.5. Conclusion

We confirm that straylight in cataract eyes varies rather independently from age and best-corrected visual acuity. The independence of these two aspects of crystalline lens was speculated to be caused by different optical processes of remarkably different scales [3]. We found that, in accordance to the literature, to assess visual functions of cataracts, the analysis should consider cataract morphology. This becomes more crucial in PSC, where the general visual acuity might not show severe loss, but a remarkable increase of straylight above the cut-off value of 1.40 log units [35] can have negative effect on the quality of life. The norm curves obtained in this literature review serve to distinguish the particular effect of each type of cataract, from early-stage to mild, on visual impairment. However to generalize our results, scrutinize their validity in more severe cataracts and to develop post-operative straylight improvement references, further studies are needed.

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Chapter 5

Straylight in pulverulent congenital cataract

5.1. Introduction

Cataract is a clouding of the lens and may be divided into early onset or congenital cataract [1][2], and age-related cataract. Congenital cataract is less prevalent, but it is responsible for approximately one tenth of childhood blindness on a global scale [3]. The most common causes of this type of cataract are genetic mutation and infection during pregnancy [4][5]. Congenital cataract is prevalent with 2 cases per 10,000 births in the United States [6][7] and with approximately 5 cases per 10,000 births in China [8][9]. This form of cataract in adults may cause visual issues such as lack of depth perception or poor retinal development due to *stimulus deprivation amblyopia* [10]. The congenital cataract can involve the entire lens, have a profound impact on visual prognosis, and lead to an urgent need for early surgery. Pulverulent congenital cataracts are composed of pulverous opacities, hence the name. They are non-progressive, usually bilateral, symmetrical, familial [11], and rarely affect acuity [12][13].

Cataract is a multifactorial optical defect, affecting the point spread function (PSF) of the eye in different ways. A cataractous lens may have several ultrastructural light scatterers causing various amounts of backward and forward light scattering. However, the important central part of the PSF, is associated with optical aberrations, and is formed by part of the entering light which is not disturbed by the scatterers in the eye media [14][15]. This fraction of the PSF is clinically assessed by visual acuity and contrast sensitivity. Merely a few percent of the entering light is affected by the scattering irregularities in the media [16], and projects a veil of unwanted light over the retinal image. This veil is called straylight, and corresponds to the skirt of the PSF covering visual angles beyond 1°. It has been established that straylight intensity decreases greatly with angle (θ), with an approximately quadratic dependence [17]. The straylight parameter defined as θ^2 x PSF, changes slightly from 2.5° to 25.4° with a parabolic behavior with a minimum in proximity to 7° in healthy as well as cataract eyes. Straylight is the scientific definition of disability glare according international agreement (Commission Internationale d'Éclairage), and an important reason for patient complaints in early age-related cataracts [18]. Also in the pulverulent type of congenital cataract it has been noted that vision can be strongly disturbed without much acuity loss. Recently, we came across one dramatic case where a high-level professional threatened to lose his job because of strongly elevated glare, whereas acuity was normal, and we decided to study the straylight effects of this condition.

The primary interest of the present work was to study the degree to which straylight is elevated. The secondary interest was to test whether the angular-dependency corresponds to what is typical for cataracts as mentioned above. Three cases are included, all three showing remarkably elevated straylight levels. One case could be studied in more detail, *i.e.* cataract morphology, multi-angle straylight, visual acuity, and wavefront aberrations (visual Strehl ratio calculated in the frequency domain called VSMTF) [19][20]. Results will be compared with those from previously conducted studies on non-cataract and age-related cataract groups.

5.2. Case 1

5.2.1. Methods and Materials

A 30-year-old white male volunteered as subject for more extensive testing. He had no history of eye surgery, trauma, or ocular/retinal diseases. The tenets of the Helsinki Agreement were adhered to and an informed consent was signed by the subject. Uncorrected visual acuity (UCVA) and best-corrected visual acuity (BCVA) were assessed by the ETDRS chart. Retro-illumination images as well as slit-lamp images were taken from both eyes. To dilate the pupils, 1% tropicamide was instilled into both eyes.

5.2.1.a. Straylight: To evaluate straylight at 7°, we used the standard C-Quant (Oculus optikgeräte GmbH) which measures the amount of ocular light scattering using the *compensation comparison* method and renders the straylight parameter in logarithmic units, log(s). An elongated version of the straylight meter was used for measuring straylight at a scatter angle of 2.5° [21]. The straylight measurement at these two angles was repeated twice. The straylight was measured with the *direct compensation* method for three more angular distances of 3.5°, 10°, and 28°. Those measurements were repeated eight times, because they are much quicker, but less accurate. Because of differences between the two methods, we employed bias correction to calculate the mean straylight value at each angle.

For details of the procedures for measuring straylight at different scatter angles please see the respective literature [22][23].

The same set of measurements was also performed in a 68-year-old white male with non-cataract blue eyes. The results are compared with the CIE age-dependent norm functions [15]. To compare the forward scatter of Case 1 with that of normal eyes, we compared our results with those of two previous studies: one, in 33 blue-eyed Caucasians with no cataract [24], and the other, in 65 patients with cortical, nuclear and posterior subcapsular cataracts [25].

5.2.1.b. Visual Strehl ratio: As another means to evaluate the severity of the cataract, we utilized a visual Strehl-based image quality metric derived from wavefront aberrations called visual Strehl ratio computed in the frequency domain using modulation transfer function (VSMTF). Studies [19][26] showed that VSMTF along with two other metrics of the same family were the best metrics for predicting the impact of uncorrected aberrations on visual acuity in (non-cataract) eyes. We concluded in a separate study that VSMTF is also a good predictor of visual acuity in cataract eyes for corrected as well as uncorrected aberrations (paper in preparation). The ocular wavefront analyzer ORK (SCHWIND, eye-tech-resolutions) was used to analyze the total wavefront aberrations of both eyes. To allow natural pupil dilation, the room was dimly lit (mesopic), *i.e.* ~ 10 cd/m^2.

5.2.2. Results

5.2.2.a. Cataract Morphology

The cataract was a central pulverulent congenital type, bilateral, static, and perfectly symmetrical in both eyes. It can be described best as a granular floriform cataract with 3-petal shaped lamellar structures inscribed in two concentric circular punctuate opacities in the nucleus (Figure 5.1). We estimated diameters of around 20−30 μm for the particles. The average size of the petals was 1.6 mm, whereas the average diameter of the inner circle was 4.2 mm (with a band size of circ. 0.1 mm) and that of the outer circle was 5.6 mm. The cataract was large enough to cover an average mesopic pupil (~4−6 mm), however the rest of the lens and the central part with an average diameter of 1.2 mm remained largely unaffected.

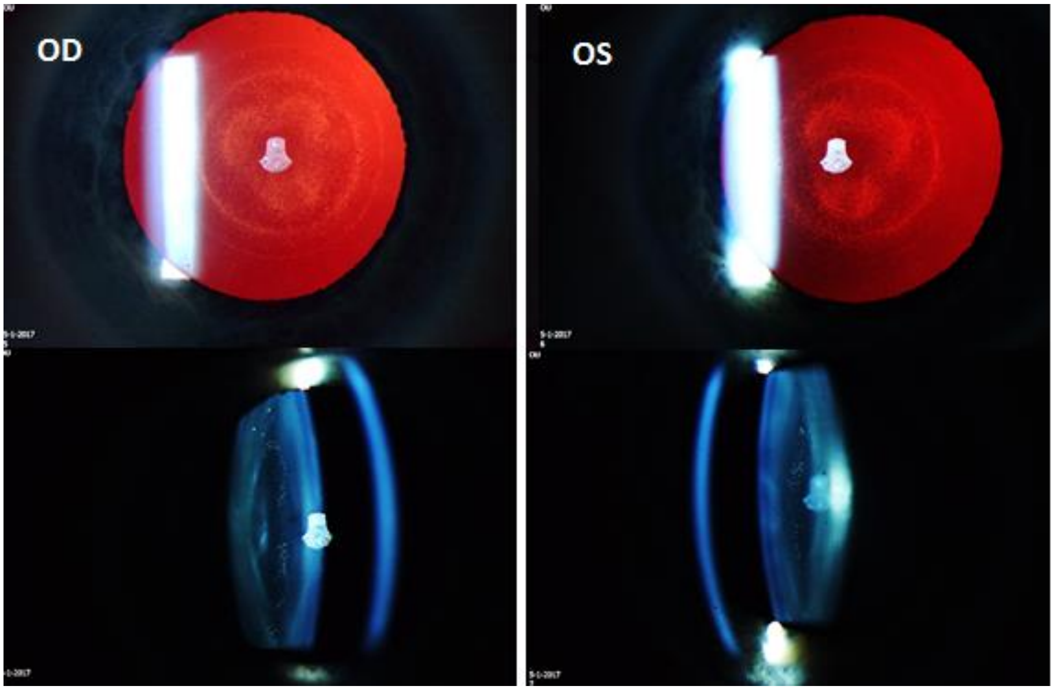

Figure 5.1. Case 1. *Top*: retro-illumination images show granular floriform cataract with 3-petal shaped lamellar structures inscribed in two concentric circular punctuate opacities in both eyes. The cataract is bilateral and symmetrical. *Bottom*: slit-lamp side-view images show a rather lamellar structure in the nucleus in both lenses.

5.2.2.b. Straylight

Figure 5.2 compares the straylight results as function of angle (green symbols) to data for normal eyes. The data collected from the 68-year-old heathy subject, shows good agreement with the prediction model [17], whereas significant deviation from the prediction model was observed in the pulverulent congenital cataract eyes. Figure 5.3 shows a comparison between our results with those of a young non-cataract group (average age 33.5 years) [24], and three groups with the most common types of cataract (*i.e.* nuclear, cortical and subcapsular posterior) from a published study [25]. At 3.5° his straylight is 0.86 log units (a factor of 7) higher than that of the non-cataract group. The difference decreases to nearly 0.20 log units at 25.4°. Comparing the present results with the cataract groups, again a difference in angular dependence is seen. Straylight at 3.5° is comparable with that of the posterior-subcapsular group (Δlog(s) ~ 0.06 log units), whereas straylight at 25.4° is close to that of the cortical group (Δlog(s) ~ 0.03 log units).

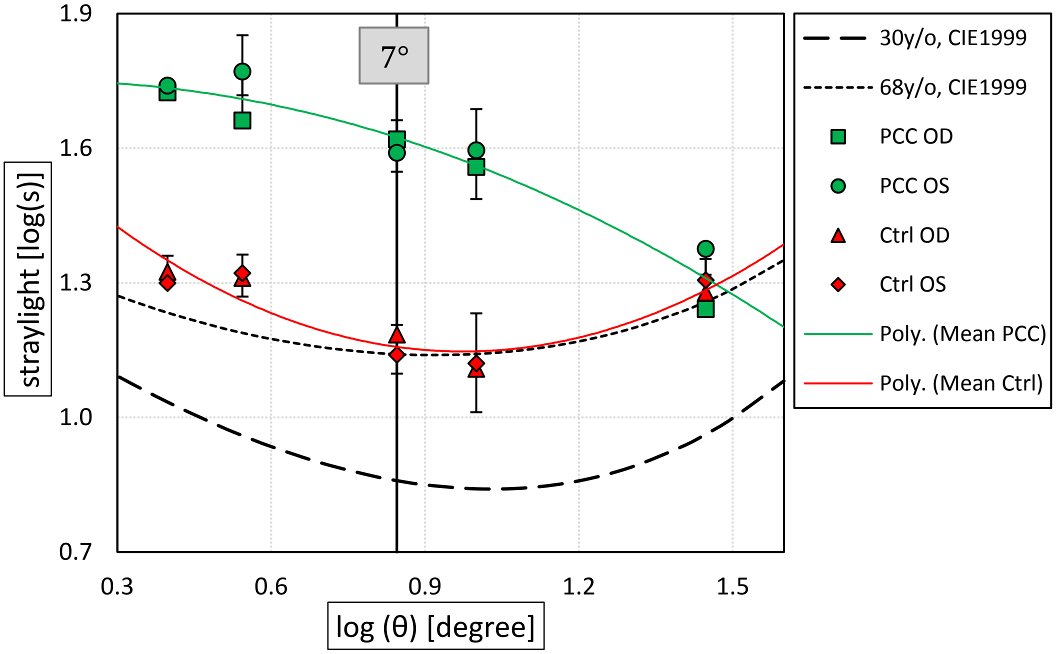

Figure 5.2. Straylight at 5 angles for a 30-year-old male subject with pulverulent congenital cataract (PCC) eyes and a 68-year-old male with heathy eyes as control (Ctrl) subject. The green and red lines are the respective quadratic fitting lines. The dashed line refers to straylight according the CIE standard at the age of 30 years, and the dotted line at the age of 68 years.

5.2.2.c. Visual acuity

The UCVA of the right eye was 0.04 logMAR and that of the left eye was −0.30 logMAR. The BCVA of the right eye was −0.24 logMAR with a refraction of −0.25 −1.50 x 77° and that of the left eye was −0.30 logMAR with a refraction of −0.25 −0.25 x 73°.

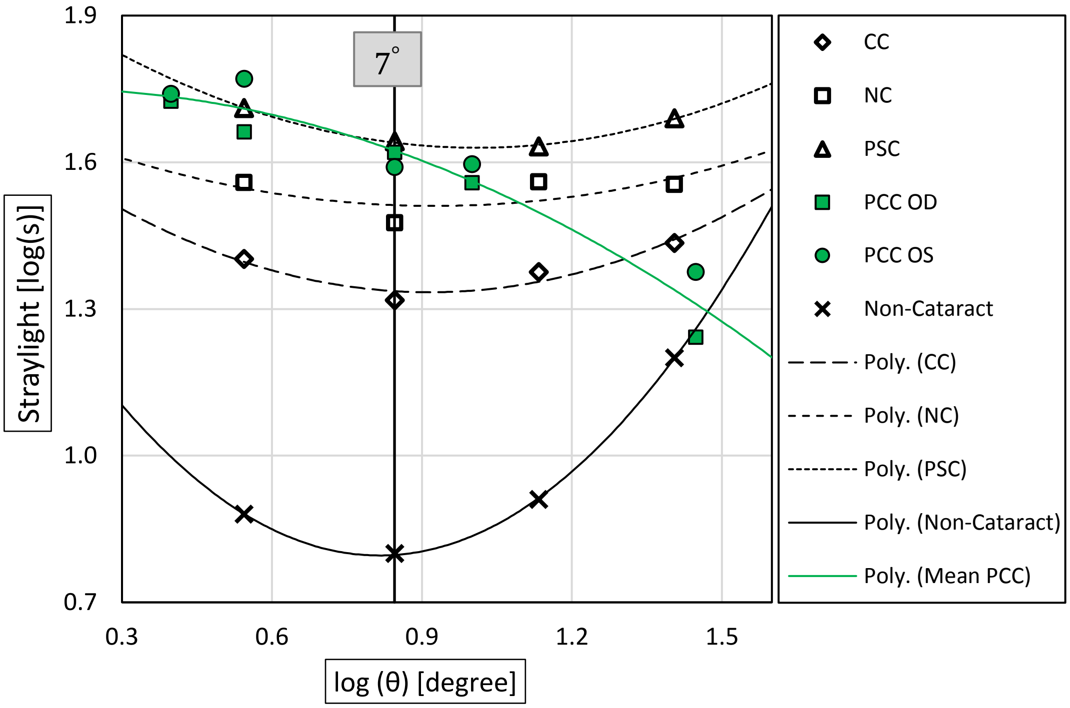

Figure 5.3. Straylight change with scatter angle in Case 1 (PCC) was compared with the same change in a group of 33 subjects with non-cataract eyes and three cataract groups (cortical (CC), 16 eyes; nuclear (NC) 19 eyes; posterior subcapsular (PSC), 17 eyes).

5.2.2.d. Visual Strehl ratio

To calculate the VSMTF, we rescaled the Zernike coefficients for a 3-mm pupil. This made it possible to compare the result of this study with that of a group of subjects with non-cataract eyes and a group of cataract patients in a separate study (paper in preparation). The log(VSMTF) of the uncorrected eyes was −1.018 for the right eye and −0.625 for the left eye. After correcting the lower order aberrations, log(VSMTF) was −0.512 for the right eye and −0.402 for the left eye. The Zernike components were within normal limits, as were the log(VSMTF) values.

5.3. Cases 2 and 3

Case 2 was a 23-year-old white male and Case 3 was an 18-year-old white male who had been experiencing disabling glare. Both cases were involved in visually demanding careers. Straylight at a scatter angle of 7° was measured by using the standard C-Quant. The measurement was repeated twice on each eye. Remarkably high straylight values were noted for both cases. The results are reported in Table 5.1.

	Iteration	Case 2		Case 3	
		OD	*OS*	*OD*	*OS*
Straylight [log(s)]	1	1.80	1.81	1.48	1.35
	2	1.74	1.79	1.46	1.49

Table 5.1. Standard straylight measured at 7° for Cases 2 and 3. The measurement was repeated twice on each eye.

A slit-lamp image of Case 3’s lens was taken (Figure 5.4). The cataract has a ring shape and is located in the fetal nucleus. The granules, with an approximate size of the order of 20 μm, are deposited in a band with outer diameter of 2.7 mm and inner diameter of 1.9 mm. Neither of these cases consented to participate in the other optical and visual assessments. Case 2 had cataract surgery, which brought straylight down to normal levels, and relieved him from the problems he had experienced in fulfilling his profession.

Figure 5.4. Case2: A slit-lamp side-view image of right eye. The grainy opacities formed a ring structure in the center of the lens.

5.4. Discussion

The present study is a report of three young cases with pulverulent congenital cataract. The cataracts are composed of tiny dotty opacities. The morphology of cataract in each case and the location of the opaque grains were different. However, they all appeared to be opalescent white. This form of congenital cataract is linked to genetic issues of chromosome 16 [27] and caused by mutation in the gamma-crystallin genes [28][29].

The finding that straylight was substantially high in the three pairs of pulverulent congenital cataract eyes is not surprising. It is a widely-accepted notion that cataract can significantly elevate forward light scatter which leads to visual problems [28][30–34]. However, the angular dependence does not agree with the findings of previous studies [24][25][33][34]. Two previous studies [24][25] found angular dependency of straylight to differ not much between healthy (non-cataract) eyes and the three cataract groups, albeit with shifts in the level of the straylight values; with posterior subcapsular cataract having the highest straylight and the non-cataract group having the lowest straylight. A juxtaposition of these results with that of Case 1, showed that at low angle (3.5°), the mean straylight of his eyes was higher than that of the posterior subcapsular group, whereas at high angle (28°), straylight was lower than that of the cortical group (See Figure 5.3). The downtrend of straylight with scatter angle is an atypical behavior, compared to what is common in non-cataract eyes, and more interestingly, to what is common in age-related cataracts. The dependence of straylight on particle size has been discussed before [35][36]. For young and aged human eye lenses it was found that particles with average diameter of approximately 1.4 μm dominate straylight. Scattering at large angles (30°−180°) is dominated by particles much smaller than the wavelength of the incident light. In contrast, when the particle size is much larger than the wavelength of the incident light, as it is in Case 1, diffraction causes scattering patterns with a stronger distribution in the forward direction and smaller angles. This explains the difference in angular dependence as reported here. However, for a precise theoretical underpinning, one needs to establish the detailed nature of the particles involved. Details needed would be their refractive index, and potential internal structure. This would require rather difficult to achieve goals, such as extraction of these lenses with no disturbance to them.

The very good visual acuities of these cases, despite elevated light scattering, can be explained by different spatial positions of optical aberrations (assessed by visual acuity) and straylight on the PSF as well as the different provenances [37]. Recently, the independence between the two aspects of quality of vision has been studied from three different points of view, *i.e.* methodological, optical, and statistical [15]. In all 3 aspects straylight and visual acuity are quite independent, as they belong to two separate angular domains of the functional PSF. From the optical standpoint, this lack of relation, has been explained by showing that the process of light scatter which results in straylight, has little impact on the central region of the PSF, which is associated with visual acuity, regardless of the level of straylight [15].

Comparing the wavefront analysis of Case 1 with those of a yet-to-be-published study by the authors of this work on a group of 18 non-cataract (normal) eyes, has shown that log(VSMTF) of Case 1 was either similar or better than that of almost all subjects, except for two cases. The same comparison with a group of 15 cataract patients from the same study, showed that the log(VSMTF) of Case 1 was better than almost all cataract eyes. In any case, the BCVA of both eyes of Case 1 were exceptionally good, and better than those of the cataract eyes, except for one case.

Straylight is a measure of visual quality that deteriorates with age and optical irregularities such as cataract. In this contribution, we studied cases with a special form of congenital cataract, called pulverulent congenital cataract. Similar to age-related cataracts, it elevated the amount of light scattering in the eye. However, it had a different angular-dependence caused by the existence of particles much larger than those found in normal lenses and age-related cataracts.

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Chapter 6

General conclusions and future work

Cataract, a multifactorial optical defect occurring in the crystalline lens, remains the leading cause of blindness on a global scale. The lens is susceptible to oxidation and, with ageing, protein aggregation and protein crosslinking which increase in fourth decade of life, may lead to intralenticular changes in refractive indices and an increase in light scatter. Growing throughout life, the human lens is exposed to such effects and damages for a longer period. Some congenital disorders, however, can also cause premature forms of cataract in younger individuals. With declining lens transparency, vision becomes more affected by an increase in glare. Glare not only happens on the road at night, but anywhere there is a relatively bright light in the visual field, leading to a reduction in contrast of the retinal image. An example could be when one is facing a computer screen with a daylight window at the background. A continuous attenuation of visual performance because of increased glare may need to be resolved, at some point, by a cataract operation.

In this doctoral thesis, we aimed to study two main areas; first, the changes in *in vivo* ocular straylight with age, particularly in eyes developing age-related cataract with regard to the type of cataract. We also studied cases of premature ageing of the eye in the form of a congenital cataract. Second, we sought to identify the competence of certain optical functions as suitable predictors for cataract operation. We also studied the eligibility of cataract morphology in aiding judgment and cataract decision-making process. Together, these elements may have the potential for being used in an algorithm to determine the threshold for a cataract operation for an individual patient.

6.1. Summaries and conclusions

To serve the purpose of this thesis, several studies were conducted. The summaries and conclusions of these studies presented in this doctoral thesis are as follows:

In **Chapter 2**, we aimed to find out the pupillary conditions during straylight measurement with the C-Quant, and the potential effect this might have on straylight for normal aging eyes. The outcomes lead to a conclusion that the illuminance of the examination room during straylight assessment does not affect the outcome. Under both mesopic and scotopic conditions, the luminance of the test field is so much higher than that of the room, that it is the brightness of the test field that determines the pupil size. Regardless of the lighting level, straylight measured in a laboratory, applies to photopic pupils at an adaptation level corresponding with a daylight-illuminated room. It seems probable that the same applies irrespective of eye condition, such as cataract.

Chapter 3 tested the usability of the ocular VSR derived from wavefront aberrations, computed in the frequency domain using the modulation transfer function (VSMTF), for quantifying the severity of age-related cataract in terms of visual acuity. Thus, we sought to study the following objectives: first, correlation between the VSMTF and visual acuity in cataract eyes with uncorrected vision and compared the result with that of normal eyes; second, correlation between the two variables in corrected cataract eyes in terms of higher-order aberrations. High correlations were found between the VSMTF and visual acuity in both uncorrected non-cataract and cataract eyes. This suggests that VSMTF may act as a surrogate for testing visual acuity in eyes with normal-functioning retina and cerebrum, regardless of their cataract status. The results of the cataract group after correction also corresponded with the earlier data. Therefore, we gathered that the VSMTF is a suitable metric for predicting visual acuity in both healthy and cataract eyes. Perhaps more interestingly, VSMTF can be used as an objective and independent measure for the severity of a cataract in terms of visual acuity.

In clinical practice, a surgical decision made merely on visual acuity tests, can result in no change or even an increase in straylight [reference]. To establish a reference, stratified to cataract morphology, which can predict the outcome of operation in terms of straylight, we conducted a literature survey. In **Chapter 4**, a meta-analysis on relevant published studies, resulted in concluding that taking cataract morphology into account for weighing the dependency of straylight on age and visual acuity, will provide a more accurate insight into the visual dysfunction of cataract eyes. This is especially evident in eyes with posterior-subcapsular cataract, where a remarkably elevated straylight might not be accompanied by a notable loss in visual acuity.

A 3-case study in **Chapter 5**, on six pulverulent congenital cataract eyes, a form of early onset cataract, endorsed the notion that regardless of the provenance of cataract, it may strongly elevate the amount of light scatter in the eye. However, near perfect visual acuity was noted in these eyes. A lack of relation between the two separate domains of the point spread function, associated with straylight and visual acuity, explains this disparity. In non-cataract and age-related cataract eyes, straylight is weakly dependent on angle with a parabolic shape and a minimum in proximity to 7°. Angular-dependence of straylight was studied in one subject whose eyes were studied in more details. The results showed a clearly different angular dependence, that is to say, straylight almost continually decreased with angle. This phenomenon was explained by the larger-than-wavelength size of the particles causing this type of cataract. Particles in non-cataract and age-related cataracts, on average, are 1.4 μm in diameter, whereas in the case of pulverulent cataract, the particles were estimated to be 20−30 μm in diameter. Diffraction is known to cause scattering patterns with a stronger distribution in the forward direction and smaller angles for such large particles (*Mie scattering*).

6.2. Future work

Several opportunities for expanding the scope of this thesis remain. Some of these directions are as follows:

- To study the potential effect of the pupillary response on straylight in cataract eyes. For a more precise conclusion, considering cataract morphology as a discriminator could be interesting.
- Further studies on the liability of the VSMTF in predicting visual performance in larger groups of cataract eyes. In this respect, considering cataract morphology as a discriminator can avail us of more comprehensive information.
- To continue investigations for identifying more suitable optical and visual parameters in predicting visual performance in cataract eyes
- Eventually, to develop a multi-variable algorithm to predict the optimal timing for cataract operation. This algorithm can enjoy key optical-visual variables as well as quality of life factors and the morphology of the cataract.

- To enroll more congenital cataract patients with more diverse types of optical scattering defects, for exploring the peculiar changes in straylight with angle. This can assist rationalizing our assumption on this matter.

Appendix

Publications and presentations of the content of this Thesis

A1. This doctoral thesis has resulted in the following peer- reviewed publications:

- S. Gholami, NJ. Reus, TJTP. van den Berg. The significance of changes in pupil size and straylight value of human eye with slight changes in environmental light intensity. Submitted (*under peer-review*)

- S. Gholami, NJ. Reus, TJTP. van den Berg. Visual Strehl ratio metric derived from wave aberrations to predict visual performance in cataract eyes. Submitted (*under peer-review*)

- S. Gholami, NJ. Reus, TJTP. van den Berg. Ocular straylight and visual acuity changes with age in different cataract types: A review. Submitted (*under peer-review*)

- S. Gholami, NJ. Reus, TJTP. van den Berg. Straylight in pulverulent congenital cataract. Submitted (*under peer-review*)

A2. Parts of the present thesis have been presented as oral or poster communications at the following international scientific congresses:

- **Authors**: S. Gholami S, TJTP van den Berg, and N. Reus. **Title**: Cataract and visual function: a prospective observational study of surgical selection **(oral presentation). Congress**: OC'15 Ageing Eye Annual Meeting. Valencia, Spain. 7-8 March 2015.

- **Authors**: S. Gholami S, TJTP van den Berg, and N. Reus. **Title**: Cataract and visual function: a prospective observational study of surgical selection **(oral presentation). Congress**: XXXII European Society Cataract & Refractive Surgeons (ESCRS) Annual Congress. Barcelona, Spain. September 5-9, 2015. Link:http://escrs.org/barcelona2015/programme/posters-details.asp?id=22943

- **Authors**: S. Gholami S, TJTP van den Berg, and N. Reus. **Title**: Intraocular scattering changes with age **(oral presentation). Congress**: OC'15 Ageing Eye Annual Meeting. Valencia, Spain. 7-8 March 2015.

- **Authors**: S. Gholami S, TJTP van den Berg, and N. Reus. **Title**: Visual Strehl Ratio to predict visual performance in the healthy and cataract eyes **(oral presentation). Congress**: The VIII European Meeting on Visual and Physiological Optics. Antwerp (Belgium). 2016. Proceedings of VPO 2016; pp: 217-219.

- **Authors**: S. Gholami S, TJTP van den Berg, and N. Reus. **Title**: Cataract and visual function: a prospective observational study of surgical selection **(oral presentation). Congress**: XXXIV European Society of Cataract & Refractive Surgeons (ESCRS). Copenhagen, Denmark. September 10-14, 2016. Link:http://www.escrs.org/Copenhagen2016/programme/posters-details.asp?id=25420