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The Etiology of Presbyopia, Contributing Factors, and Future Correction Methods



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# The Etiology of Presbyopia, Contributing Factors, and Future Correction Methods

By

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in the GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

and

UNIVERSITY OF CALIFORNIA, BERKELEY

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# Abstract

The Etiology of Presbyopia, Contributing Factors, and
Future Correction Methods

By

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Doctor of Philosophy in Bioengineering

University of California, San Francisco

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University of California, Berkeley

Professor Austin Roorda, Chair

## Introduction

Presbyopia has been a complicated problem for clinicians and researchers for centuries. Defining what constitutes presbyopia and what are its primary causes has been a struggle for the vision and scientific community. Considered to be a natural process of aging, presbyopia is not classified as a disease and therefore a search for a "cure" or a "treatment" would be considered by many to be fruitless. Something that is deemed normal can't be cured or treated.

Epidemiologists calculate the global burden caused by illnesses and diseases a variety of methods. Two methods that are commonly employed are by determining the disability-adjusted life years (DALY), the number of years lost due to ill-health, disability or early death, or by calculating the quality-adjusted life years (QALY), which includes not just the quantity but the quality of life. When calculating the burden of a disease on society, a common disease generally carries a much greater weight than a rare disease even when the rare disease is much more devastating. Unipolar depression, for example, is the most burdensome disease in middle and high income countries while a rare genetic disease such as Tay-Sachs, which results in premature death, would hardly register as a global burden in comparison even though its effects on a single individual are catastrophic.

If presbyopia were considered a disease, its burden would be enormous as it affects more than a billion people worldwide. Its health care cost has been calculated to be in the hundreds of billions of US dollars. Presbyopia correction is the "Holy Grail" for many eye research companies and the heartfelt wish of those affected by it. Although presbyopia is a normal aging process of the eye, the continuous and gradual loss of accommodation is often dreaded and

feared. Often the need to wear spectacle readers seems to come on suddenly to people in their 40's and comes as an undesirable sign of "old age". The causes of presbyopia are often misunderstood, especially among lay people, who inevitably attribute their loss of near vision to hundreds of possible causes.

**Methods**

In Chapter 1, we will begin by looking at the problem of aging and its effect on vision and the ocular anatomy to determine ultimately the benefits and possibilities of remaining ageless. Since presbyopia is considered to be a result of aging, it is important to consider the effects of aging on the entire ocular system. Next, in Chapter 2, we will explore the etiology of presbyopia and the many factors associated with it, including gender. We will then examine how depth of focus, accommodative amplitude, and preferred reading distance are inseparably connected to the onset of presbyopia. Then, we will evaluate the opportunity to use optical corrections to relieve presbyopia.

Determining an optical correction that can relieve presbyopia is complicated. There is an infinite selection of optical corrections that might provide a solution, but testing each on a human eye is impossibly time consuming, expensive and problematic from an experimental point of view. In Chapter 3, we will use a systematic approach to determine a workable solution. In order to simplify this problem we will examine the effects of wavefront aberrations on depth of focus using an ideal observer setup, which decouples the effects of size and blur. This method is a monitor-based test that measures the impact of different aberrations on depth of focus. We will analyze the data from this experiment to compute an image quality metric (based on the aberrations) that correlates best with visual performance. We will then use this metric to search further for an optimal aberration solution which relieves presbyopia by expanding the depth of focus.

Finally, in Chapter 4, having determined a set of possible optimal solutions, we will use an adaptive optics system to test those solutions on human participants in an experimental study. The adaptive optics system is capable of not only correcting the aberrations measured for a human participant but also bestowing a chosen set of aberrations upon the subject's vision. It can also implement an artificial pupil size by utilizing an aperture that is conjugate to the pupil plane. With these results we will conclude, in Chapter 5, by summarizing all of our findings and determining the ideal direction for presbyopia correction from a list of the current methods of presbyopia correction which include monovision, multifocality, small pupil, and accommodation restoration.

**Conclusion**

In Chapter 1, we concluded that while visual functions generally decrease with age, the speed of the decline is highly variable. Age itself is not an absolute predictor of vision and there are individuals of advanced age that maintain vision that is superior to individuals in much younger age categories.

It was determined in Chapter 2 that the onset of presbyopia is associated primarily with three factors; depth of focus, focusing ability, and habitual reading (or task) distance. If any of these three factors could be altered sufficiently, the onset of presbyopia could be delayed or prevented. In a meta-analysis that was performed, sex differences in the onset of presbyopia were found to be a result of habitual reading distance as a consequence of occupation, arm length, or refractive error.

In Chapter 3, we concluded that spherical aberration was the most efficient Zernike aberration in improving depth of focus and that an ideal amount of spherical aberration would depend on pupil size. A larger pupil size would require a greater magnitude of spherical aberration to produce an optimal depth of focus. Using a mean visual performance across a range of defocus values, we revealed the optimal amount of spherical aberration for various pupil sizes.

In Chapter 4, we discussed the effects that a changing pupil size or inadvertent optical errors would have on visual performance through an intended optical correction. We concluded that small pupil optical profiles were a better choice than spherical aberration profiles for presbyopia correction due to the expected accuracy, predictability, and visual performance across a larger range of defocus values.

Finally, in Chapter 5, we concluded that the future of presbyopia probably lies in the direction of accommodation restoration. Monovision has been found by some individuals to provide some relief from spectacle correction of presbyopia but comes at the expense of binocularity and is limited in its application. Both spherical aberration and small pupil profiles can provide some benefit as well but each has significant deficiencies in comparison to an ideal solution. Currently, there are no accommodation restoration methods that obtain consistent satisfactory results but future correction methods might be developed which provide the desired vision at all distances.

# Dedication

This work is dedicated to my loving wife, Natchaya, who supported me throughout this process. I also dedicate this to my 3 year old daughter, Arisa, who I have high hopes will pursue a quest for new scientific knowledge throughout her lifetime. I can't even imagine the advances she will see in her lifetime.

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## Education

**PhD Candidate in Bioengineering** Aug 2007-May 2012
**UC Berkeley/UC San Francisco**
GPA: 3.88

**Program in Clinical Research Conduct and Management** Aug 2011-Mar 2012
**UC Berkeley Extension**
GPA: 4.00

**Masters in Public Health** May 2010-May 2011
**University of California, Berkeley**
GPA: 3.84

**Doctoral Degree in Optometry** Aug 1999-May 2003
**University of California, Berkeley**
GPA: 3.60 Graduated with honors

**Bachelor's Degree in Psychology** Aug 1992-Aug 1995
**Brigham Young University**
GPA: 3.91 Graduated Magna Cum Laude, Dean's List

**Antelope Valley College, Lancaster, CA** 1999
Microbiology
4.0 GPA

**Utah Valley State College, Orem, UT** 1993
Physics
4.0 GPA

**Eldorado High School, Las Vegas, NV** 1989-1992
4.0 GPA, Valedictorian, High Honors

## Qualifications and Certifications

**Certificate Program in Clinical Research Conduct and Management –** University of California, Berkeley Extension –Instruction in clinical trial conduct and management, including clinical trial phases and design, planning, implementation, data analysis, regulatory and procedural guidelines, and ethical considerations.

**Berkeley Clinical Scientist Development Program –** University of California, Berkeley – 5 year training program in developing research skills for high-level, independent, patient-based, translational eye and vision research.

**Licensed Doctor of Optometry** – State of California (License number OPT 12423 T)

**Therapeutic Pharmaceutical Agent Certification** – State of California

**Diagnostic Pharmaceutical Agent Certification -** State of California

**Anterior Segment Laser Certification** – State of Oklahoma

**Certified ISO Internal Auditor** (International Organization of Standards)

## Work Experience

**Clinical Research Scientist**
**University of California, Berkeley**
May 2007-present

**Optometrist/Branch Marketing Manager**
**LaserVue Eye Center,** Walnut Creek, CA
Jan. 2012 – present

**Optometrist**
**Furlong Medical Corporation,** San Jose, CA
Oct. 2011-Jan. 2012

**Optometrist/Director of Marketing**
**Turner Eye Institute Medical Group,** San Leandro, CA
Sept. 2005 – Sept. 2011

**Optometrist/ Director of International Patient Care and Marketing**
**TRSC International LASIK Center**
Aug. 2003 – Aug.2005

**Branch Manager**
**TRSC International LASIK Center in Phuket, Thailand**
Nov. 2004 – May 2005

**Clinical and Physical Optics Research Assistant**
**University of California, Berkeley**
May 2000-Nov. 2002

**Research Assistant**

**Brigham Young University,** Provo, UT
Jan 1995 – May 1995

**Medical Assistant**
**Roy Optometric Inc.** - Walnut Creek, CA
Jun 2001 – June 2002

**International Translator - Thai and Lao Languages**
**Department of Homeland Security Transperfect Translations** - San Francisco, CA
June 2000 – July 2000

**Optometric Assistant**
**Matherly Optometry Clinic –** Lancaster, CA
Oct 1998 – Mar 1999

**Licensed Teacher**
**California, Los Angeles County**
Oct 1997– June 1999

## Research and Paper Publications

**Adam Hickenbotham**, Austin Roorda, Craig Steinmaus, and Adrian Glasser. **Meta-analysis of the Gender Differences in Presbyopia.** Invest. Ophthalmol. Vis. Sci. 2012;53 3215-3220
http://www.iovs.org/cgi/content/abstract/53/6/3215?ct
*While sex differences in presbyopia exist, they are likely due to other factors besides focusing ability, such as arm length, preferred reading distance, or uncorrected hyperopia.*

**Hickenbotham, A,** Roorda, A. **Comparing Visual Performance of Spherical Aberration and Small Pupil Aperture Profiles in Improving Measured Depth of Focus.** Journal of Cataract and Refractive Surgery. In Press.

**Hickenbotham, A**, Roorda, A. **Determining Wavefront Aberration Profiles that Maximize Subjective Visual Performance Through Focus**. Journal of Vision. In Press.

**The Effect of Wavefront Aberration Profiles on Visual Performance** May 2007 – present
Research into Objective Image Quality Metrics and their predictive ability for subjective visual performance when subject to wavefront aberration profiles

**Clinical Research into Zeiss Aspheric Laser Pattern for Presbyopic Correction**
Dec 2004 - May 2005

**Analysis of Clinical Results at TRSC International LASIK Center using Carl Zeiss MEL80 Wavefront and Prolate Treatment and Bausch and Lomb 217Z100 with Iris Recognition and Wavefront** Sept 2003 – Aug 2005

**Hickenbotham, A,** Vesper R, & Miles, T. **"Light Scatter and Contrast Sensitivity Measurements after Corneal Refractive Procedures with VDT Glare Testing" - Doctoral Thesis at University of California, Berkeley School of Optometry** May 2000 – May 2003

## Skills

**Language:** , English (Native), Thai (Fluent), Lao (Fluent), Spanish (Beginner), Mandarin (Beginner),
**Computer:** MS Office (Word, Powerpoint. Excel), Photoshop, Internet, SEO
**Medical Intruments:** VISX Star S4 Excimer Laser System with Wavefront Aberrometer, B&L Obscan, B&L Zyoptix 217 Excimer Laser (A, Z, Z100), B&L Wavescan, Zeiss Wavefront Analyzer, Slit Lamp, Zeiss MEL80 Excimer Laser System, Topography, Pachymetry, and all other standard ophthalmic and optometric equipment that is used in eye exams to diagnose and treat eye disorders, diseases, and all other vision related problems.

## Further Training

**Designing and Managing Clinical Trials in Eye Research -** May 2011

**Certified ISO (International Standards Organization) Internal Auditor** Jan 2005

**Medical Management 2004 -** Nov 2004

**Anterior Segment Laser Treatment at Northeastern State University -** May 2003

**Internship at the University of California, Meridith Morgan Eye Center** 2001 – 2003
**Honors Recognition** in contact lens and binocular vision rotations.

**Externship to Beijing, China** May 2002 – July 2002 **Honors Recognition**

**Externship to Sacramento Veterans Administration Hospital** Aug 2002 – Oct 2002 **Honors Recognition**

**Externship to Palo Alto Veterans Administration Hospital and Palo Alto Society for the Blind** Jan 2003 – Mar 2003 **Honors Recognition**

## Volunteer Work

**Volunteer Optometric Service for Humanity, Trip Coordinator**
Nov 2004-Jan 2005, Nov 2003-Jan 2004

**Volunteer Optometric Service for Humanity, Berkeley, VOSH Team Leader**
Aug 2001-Jan 2002

**Volunteer Optometric Clinician**

Mar 2001 Vision Screenings for Chinese Senior Center in San Francisco, CA
Apr 2000 Suitcase Clinic - Vision Screenings for underprivileged adults in Berkeley, CA

**Humanitarian Service** Dec 1995 – May 1997
Humanitarian Service in the provinces of Nakhorn Ratchasima, Chiang Rai, Udon Thani, Buriram, Lopburi, Sakorn Nakon and Bangkok. Voluntary service at hospitals, orphanages, retirement communities as well as duties as a Thai language trainer, translator, advisor and teacher, and English instructor.

**Intern Instructor** Apr 1994 – Aug 1994
Volunteer at Utah Valley State Hospital – Tutored child abuse victims

**American Red Cross Volunteer** May 1991 – June 1992 Nellis Air Force Base Hospital

## Seminars, Papers, Posters, and Lectures

**"Presbyopia: Many Causes, Many Solutions (Now and In the Future)"** May 2012 Continued Education lecture at Southern California College of Optometry and Western University of Health Sciences School of Optometry

**"Comparing Visual Performance of Spherical Aberration and Small Pupil Profiles in Improving Measured Depth of Focus"** February 2012 Presentation at Wavefront and Presbyopia Conference

**"Meta-analysis of the Factors Influencing Early Onset Presbyopia"** May 2011 Presented paper as thesis for MPH in Epidemiology

**"Vision and Aging: Pathology or Preventable"** April 2011 Presented paper regarding the effects of aging on vision and including a discussion of "normal" aging versus pathology

**"The Effect of Higher and Lower Order Aberrations on Best Mean Visual Acuity across a 2.5 Diopters Vergence Range"** May 2010 Presented Paper at ARVO describing efficient method for finding aberration profile providing an optimal depth of focus

**"Quantifying the Health Impacts of Climate Change: Comparing Two Approaches"** May 2010 Presentation in Global Burden of Disease Course providing instruction in the calculated effects of global warming

**"Managing Burnout in our Country's Emergency Care System"** April 2010 Analysis of psychological stress in emergency medicine to recommend managerial strategies to prevent and treat burnout

**"Weight of Cataracts in the Global Burden of Disease"** Feb 2010 Class Lecture in Global Burden of Disease Course estimating the weight of cataracts on global health

**"Image Quality Metrics for Predicting Optical Aberration Profiles that Enhance Depth of Focus"** Feb 2010 - Presentation at Wavefront and Presbyopia Conference

**"Using Power Fittings for Image Quality Metrics to Better Predict Visual Performance"** Nov. 2009
Discussed the use of better statistical fittings between objective image quality metrics and subjective visual performance to develop wavefront aberration profiles to treat presbyopia

**"Predicting Depth of Focus Using Image Quality Metrics" – ARVO** May 2009 Paper showing results of experiment which compared subjective visual performance with available image quality metrics and showed how combining metrics can increase predictability of data

**"Increasing Work Safety through Ergonomics Improvements at Lawrence Livermore National Laboratories"** May 2009 Developed Improved System for Sending/Receiving Department to Decrease Workplace Injuries and Improve Worker Satisfaction.

**"Incentivizing Private Sector to Improve Health Care"** April 2009 Presented methods for improving eyecare in Thailand through public/private sector cooperation on ocular health care

**"Optics in Optometric Equipment"** March 2009 Lecture for Optics Course for Optometry Students detailing calculations of the specific optical equipment used regularly by optometrists and ophthalmologists.

**"Neural MEMS Biosensor"** Dec. 2008 Developed plan for an innovative MEMS device which translates neural electrical signal into mechanical action to acts as a prosthetic limb replacement

**"Effects of Aberration on Depth of Focus"** Nov. 2008 Presentation at Annual Meeting of Center for Adaptive Optics reporting findings of Research into correlation between common vision quality metrics and subjective measurements for higher order aberrations

**"Biomimicry of Chromatic Reflectance Changes in the Iridophores of the Neon Tetra and Sand Goby"**
Nov 2007 Demonstrated theory behind device which imitates the effects of Chromatic Reflectance Changes in the Neon Tetra and Sand Goby that could be used for Stress Gauge or Light Frequency Translation

**"Near Vision LASIK"** March 2005 Introduced Presbyopic LASIK Correction to patients, including contact lens fitting or trial spectacle correction to simulate visual results

**"Marketing Medical Tourism"** Feb 2005 Introduced medical tourism to 50 IBAP members (International Business Association of Phuket)

**"Spherical Aberration and the Hubble Telescope"** Jan 2005 Lecture to team of 25 doctors and medical interns

**"TRSC Patient Care Expertise" Press Conference** Nov 2004 Press Conference (in Thai) announcing the opening of TRSC International LASIK Center in Phuket, Thailand

**"HospiMedica Presentation of LASIK Treatment** Nov 2004 Introduced benefits and details of LASIK treatment at Medical Convention in Singapore

**"LASIK Treatment at TRSC LASIK Center"** July 2004 LASIK Seminar at the US Embassy in Bangkok, Thailand to introduce the opportunity for LASIK surgery to correct refractive errors

**"Clinical and Technical Differences between Globally Available Brands of Excimer Lasers"** Jan 2004 Lecture to team of 25 doctors and doctoral interns at TRSC International LASIK Center

**"Introduction to LASIK Treatment: Contraindications and Side Effects"** Sept 2004 Lecture to team of Singaporean doctors given at TRSC International LASIK Center

**"Fitting of Corneal Refractive Therapy Contact Lenses"** May 2003 Contact lens clinic at UC Berkeley School of Optometry

**"Diabetes and Diabetic Retinopathy"** Aug 2002 – Sept 2002 Kaiser Permanente in Sacramento, once per week provided a series of four 1-hour lectures followed by diabetic screenings for 100+ patients per day

**"Refraction of Light Waves and Clinical Optics"** Aug 2002 Series of four lectures at Ramkamhaeng University in Bangkok, Thailand

**"Diagnosis and Treatment of Binocular Vision Dysfunctions"** July 2002 Lecture to Opthalmologists, Medical Interns, and nursing staff at Beijing Medical University in Beijing, China

**"Diagnosis and Treatment of Accommodative Dysfunctions"** June 2002 Lecture to Opthalmologists, Medical Interns, and nursing staff at Beijing Medical University in Beijing, China

**"Cranial Nerves and Methods of Evaluation and Testing"** April 2002 Presentation during Advanced Clinical Procedures Class, at UC Berkeley School of Optometry

**"Signs, Symptoms and Treatment of Grave's Disease"** Feb 2002 Primary Care Clinic at UC Berkeley School of Optometry

**"Complications of LASIK refractive surgery"** Oct 2001 Primary Care Clinic at UC Berkeley School of Optometry

**"Modern Advances in Neuroprotective Medications"** Mar 2001 Pharmacology lecture at UC Berkeley School of Optometry

# Chapter 1

## Presbyopia, “Old Eyes”:

## Pathology, Predetermined, or Preventable

Adam Hickenbotham, School of Bioengineering, University of California, Berkeley

**Abstract**

Declining vision is popularly considered to be a normal and immutable pattern for aging. Pathology and blindness are therefore often considered to be the final inevitable result of aging.

**Background/Objectives**

An attempt is made to separate visual loss that is caused by pathology from the decline caused by the normal aging process which will then be followed by a discussion of whether it is possible for an individual to retain good vision irrespective of advancing age.

**Methods:**

Vision will first be examined from an anatomical perspective as it relates to the biological and physiological changes that typically occur in the eye during aging. These factors will then be compared to the visual measurements that have been taken in various published reports in order to correlate vision lost to specific components of the visual system.

**Results:**

It was found that on average, measurements of vision declined regardless of the diagnosis of pathology although individuals with ocular pathology showed a strong tendency for greater vision decline than those without a diagnosed pathology. This decline in vision was not uniform among individuals and those scoring in the highest percentile among the most elderly showed minimal decline while the lowest percentiles often reached degrees of vision loss more than 10 times worse than those of the young groups, a level comparable to legal blindness. Due to the complexity of the visual system, it was impossible to correlate with certainty the loss of performance with a specific component of the eye but the form and location of a pathological condition or of anatomical changes does provide insight into likely deficits that might occur in vision.

**Conclusions:**

Variability in measurements among individuals of the same age group increases significantly with age despite a mean loss of vision with increasing age groups. It can therefore be concluded that while the probability of worse vision increase with age, age alone cannot be used as an absolute predictor of poor vision.

## INTRODUCTION

Presbyopia  comes from the greek word *presbys*, meaning "old man" or "elder", and the latin suffix –*opia*, meaning "sight" or "sightedness".[1] There is no universally accepted definition for presbyopia and the broadest definition would therefore cover all age-related processes and changes in the eye. Most people would consider aging to be unavoidable and the aging of the eye as one part in the natural aging process. It would therefore stand to reason that most people consider a slow steady loss of vision to be the natural result of a long lifespan.

In a recent news story, it was reported that an 81-year-old man in Hong Kong single-handedly fought off a gang of teenage muggers resulting in eight youth being arrested and requiring hospital treatment.[2] While this show of strength and vitality is certainly not the norm for individuals of advanced age, it is an example that some individuals are almost superhuman in their ability to avoid the regular deleterious effects of aging.

The elderly population is increasing at a faster rate than at any other time in the world's history. In the U.S. by 2030, one in five people who will be considered senior citizens. As the population ages, health care needs are expected to rise. While most elderly are considered healthy and independent, most do have at least one chronic health condition which requires regular care. Vision care needs are likewise expected to increase. One in four Americans is over fifty-five years of age. All can be diagnosed with presbyopia, requiring a near vision reading prescription. All will eventually develop or have already developed cataracts if they survive long enough. A large number will also be diagnosed with macular degeneration, glaucoma, or other age related vision problems.

As the proportion of elderly in the population increases, it becomes increasingly valuable to understand the effects that aging has on the visual system. While pathology and degeneration can often cause loss of vision, aging itself can often have marked effects on the human optical system. Oftentimes, such as with cataracts and presbyopia, it is difficult to separate the effects of normal aging on vision from those that are caused by pathology. It would be helpful therefore to discuss the normal process of aging on the various elements within the human optical system starting from the tear film and ending with the primary center for vision in the human brain, the visual cortex.

## AGING CHANGES IN OCULAR ANATOMY AND PHYSIOLOGY

A healthy tear film is necessary to create a clear image and to protect the anterior surfaces of the eye, including the cornea and conjunctiva. An uneven or dry surface will cause distortions in vision and could lead to discomfort or damage to the underlying tissues. Tear production has been shown to decrease with age. De Roeth found that tear production could decrease by as much as 75% to 80% throughout life.[3] Not only do tears decrease in quantity, but they also decrease in quality. Changes in the aqueous, lipid, and mucin layers of the tear film lead to decreases in tear stability over time.

The cornea also undergoes changes over time. Corneal sensitivity to touch has been measured to decrease over time, particularly over age 40.[4] Additionally, there are changes in the shape of the cornea which result in shifts in the magnitude and meridional direction of measured astigmatism.[5] While there is some loss in transparency due to light scatter over time, this can often be minimal in a healthy eye despite increasing age. Frequently, changes that occur in the appearance of the cornea over time are more cosmetic than functional in nature and do not significantly affect vision. The endothelium, the inner layer, of the cornea is responsible for maintaining proper levels of hydration. While this layer decreases over time, down to 900 cells/mm$^2$ by ninety years of age,[6] a critical count of 700 cells/mm$^2$ is what is considered required for adequate functioning.[7]

The anterior chamber of the eye, located behind the cornea, has been show to decrease in depth with age.[8] Since aqueous fluid is evacuated from the eye through the anterior chamber, this decreasing depth can cause angle blockage, decreased outflow, or possibly an acute angle closure event, which could all lead to glaucoma, a sight threatening disease more common among the elderly. While there are surgical and pharmaceutical interventions that can possibly prevent vision loss caused by narrow anterior angles, these treatments require sufficient access to ophthalmic medical care, which is frequently absent in many parts of the developing world.

One of the most significant changes in the eyes that occurs with age is a steady measurable decrease in pupil size.[9] As the eye ages, it is thought that atrophy of the iris dilator muscle causes pupil constriction. This results in less difference between measured pupil diameters in bright and dim light and allows less light to reach the retina. A smaller pupil can be advantageous, however, in that it prevents peripheral optical aberrations from distorting vision and can increase the depth of focus of the eye, which decreases the need for accurate focusing of the eye. This could result in improved visual acuity at both distance and near as a patient ages despite other less beneficial ocular changes that are occurring. The improved high contrast vision would come at a cost as decreasing light levels available to the retina would decrease vision when viewing low contrast targets and significantly worsen visual capabilities during poor illumination.

Another major change that occurs with time is the hardening, yellowing, and thickening of the lens which results in presbyopia and cataracts.[10] This inevitable change in the ocular media makes it nearly impossible to differentiate between those changes in vision that are due to pathology and those that are due to age. Every individual develops presbyopia and cataracts if they live long enough. While cataracts can generally be removed, this procedure can by itself result in increased ocular light scattering due to changes in ocular media clarity as an iatrogenic effect of the surgical intervention. Cataracts are the leading cause of blindness worldwide as a result of poor access to trained ophthalmologists that can perform the highly successful surgical procedure in developing countries.

Behind the lens, changes in the vitreous can also affect vision. Liquefaction and syneresis of the vitreous result in increased size and movement of floaters. These muscae volitantes can be distracting for tasks such as reading and are often very bothersome to older patients. The constant annoyance caused by floaters could also increase the difficulty of tasks that require a greater degree of attentional focus, such as driving. While subjective assessments of their vision are generally worse in patients with floaters, they rarely cause an objective measurable loss in vision on tests such as visual acuity since floaters rarely exactly intersect the line of sight to the fovea.

In addition to the ocular factors described, neural changes at the level of the retina, ocular nerve, and visual cortex have been described that are often unseen in a standard eye exam. When ocular media appears relatively transparent, neural changes are often implicated in the loss of vision. While macular degeneration is the most common cause of blindness in the United States, changes in the retina can decrease performance despite a lack of pathology. Dorey measured a decrease in retinal pigmented epithelial cells with age.[11] Similar finding occur at the level of the optic nerve with decreasing axons over time. Balazsi et al estimated a loss of twenty-five percent of all optical nerve axons by the age of seventy.[12] These neural losses would decrease input from the eye to visual centers of the brain located within the lateral geniculate nucleus and visual cortex. Devaney and Johnson reported a fifty percent loss in cells in the visual cortex between the ages of twenty and eighty.[13] This substantial loss could affect many aspects of vision that are the result of higher level forms of processing. Many of these neural losses, particular those within the brain, would be undetected during a standard eye exam and would require advance neural imaging techniques to be detectable.

Based on the previous description of the anatomical effects of aging, it can be assumed that vision loss will occur with age if accurate measurements can be obtained. While measurable declines in each of these ocular components might be inevitable there are likely some factors of vision that are predicated upon a baseline functional level and therefore remain stable and unaffected by age. Likewise, variability in visual performance between individuals is expected to increase over time and the visual performance for some particular individuals might be practically unaffected by age.

## EFFECT OF AGING ON MEASUREMENTS OF VISUAL PERFORMANCE

The standard measurement for visual performance is high contrast visual acuity. Most people understand that 20/20 vision represents “normal” human vision. High contrast visual acuity eye charts are ubiquitous for vision testing in doctor’s and nurse’s offices around the world. These are most often represented by the standard Snellen Acuity Charts that begin with a giant “E” and steadily decrease in size with letter rows until the letters become too tiny to read. It is certainly the most common measure of vision and the most recognizable. This is the measurement that is used by the Department of Motor Vehicles in order to qualify people for driving. The assumption is that if a person can read a letter that is sized “20/40” or smaller with appropriate spectacle correction than they are then safe to be allowed to operate a vehicle.

Most studies show that high contrast visual acuity is well maintained across age, with only mild loss among even the oldest age groups. Mean acuity scores are typically better than 20/40 even in populations over eighty years of age. One particular study by Elliott et al. found almost no decrease in high contrast visual acuity among older populations and reported mean visual acuity scores of 20/20 in an over seventy-five population.[14] It should be noted, however, that in an attempt to determine the extent that aging alone affects visual performance, Elliott excluded all participants from his study that were diagnosed with ocular pathology as well as disqualified participants who scored worse than 20/40 from qualifying for the assessment under the assumption that they had an undiagnosed and/or undetected pathology. This method of screening participants would certainly bias results towards higher visual acuity levels since an arbitrary cutoff value was chosen to disqualify individuals from participating. It also proves that poor vision can exist in the absence of diagnosed ocular pathology since participating individuals occasionally qualified as healthy due to an absence of diagnosed ocular pathology but were disqualified from being considered healthy due to a failure to read the 20/40 line on the eye chart.

While high contrast visual acuity testing provides valuable information regarding the spatial resolution that an individual can achieve visually under optimal conditions, it does not account for the fact that many daily vision tasks are performed under suboptimal conditions. Glare, low contrast, colors, and distractions are common in many situations and lead to decreased performance, particularly among the elderly.

Haegerstrom-Portnoy showed that while many elderly observers could pass a Department of Motor Vision vision screening, they might have severely reduced performance in less than ideal driving conditions, such as reduced contrast, presence of glare, poor lighting, poor weather conditions, high speeds, or tense traffic situations.[15] Unlike high visual acuity tests, tests such as low contrast visual acuity, glare recovery, vision in the presence of glare, and attentional field area showed much more marked decreases in performance with age. While even the oldest age group in the study, those over ninety years of age, showed only a two to three fold decrease in high contrast visual acuity when compared to young observers, this same group showed ten to eighteen times worse vision measurements than young groups when measured with tests that included glare, low contrast, or that required greater attentional focus. This level of decline would be comparable to the tenfold loss of high contrast visual acuity that is considered to qualify an individual as legally.

Despite the general trends toward lower mean visual performance scores that come with increasing age, it is important to note that older age groups also showed significantly greater variability than younger age groups for every method of measurement. Haegerstrom-Portnoy reported a constant increase in the standard deviation with increasing age groups for every method of measuring visual performance.[16] This would indicate that while there is a tendency towards decreasing visual performance with age, the amount of vision loss is highly unpredictable at an individual level.

Enoch reported that there are measurable vision functions that are unaffected by age: the Stiles Crawford Effect, Vernier Acuity, Color Constancies, Positional Acuity, Westheimer Function (a center-surround visual response function of receptive fields in the retina), and Modulation [Motion] Induced Sensitivity (a time-varying response mechanism associated with image rotation).[17] These functions are virtually age resistant despite the decrease that occurs with age in other vision functions. It is believed that these functions remain stable due to data processing mechanisms that do not change with age and are therefore less dependent on the visual stimulation that is obtained through the optics of the eye.

## DISCUSSION

Vision is a complex physiological ability with many different components. It begins as light carrying information from the outside world enters the eye. It passes through a series of refractive surfaces including the tear film, cornea, aqueous, lens, and vitreous and then passes through the retina to be absorbed by the photoreceptors. At each surface and with each structure, there exists the possibility for light to be reflected, refracted, absorbed, and/or scattered. Visual loss is, therefore, a composite of the total decrement of all the ocular components, starting at the tear film and ending in the visual cortex of the brain. As a result, it would be impossible to completely attribute a measured vision loss to only one location in the eye but there are certainly some structures that are more responsible than others for the loss of vision in a particular individual. Cataracts, for example, occur at the location of the lens and can cause rapid degeneration in visual performance if not treated. Another example, glaucoma, occurs with the death of the axons which pass into the optic nerve head. Loss of vision caused by glaucoma would therefore be caused by damage to the ocular system that is located primarily in the retina and optic nerve despite a healthy appearing anterior segment of the eye (although a blockage in the anterior chamber could have initiated a cascade of events leading to the destruction of the retinal ganglion cells).

Good vision relies upon more than just the health state of the eye. The condition and stability of the brain (particularly the lateral geniculate nucleus and visual cortex) and the ocular nerve are also requisite for quality vision. As a result, the absence of pathology or degeneration within the structures of the eye does not indicate a lack of visual deficits since a damaged visual cortex could cause significant vision loss just as easily as a damaged cornea. Vision must therefore be considered to be a sum total of the workings of the various components. Because of this degree of complexity, a single measurement cannot be expected to provide an accurate summary of a multifaceted issue such as vision.

No single vision test can be capable of providing all the necessary information to describe the vision of an individual. For one person, glare might be a significant problem due to light scatter at the cornea or lens. For another, distorted optics due to an inadequate tear film might lead to confusing images. Still another individual might have wide regions of lost vision from a degenerative condition of the retina or from a brain hemorrhage, resulting in a narrow field of view. Some of these conditions can be considered to occur normally due to age while others would be considered pathological.

Certainly, not all individuals age in exactly the same way, particularly in regards to vision. Some people retain high quality vision throughout life while others suffer a much more rapid loss as they age. Since the slope of vision loss is often unpredictable, regardless of the existence or absence of diagnosed pathology, mean measurement values for any one age group do not represent an accurate assessment of a random individual within that age group. Similarly the reaction of an individual to vision loss can be entirely unpredictable. Some individuals will struggle with even minute changes in vision while others will adapt well to marked deficits.

The medical community has most often employed diseased individuals as targets for study and examination. It is the abnormal structures and functions which have led to detailed descriptions and analysis. Perhaps this model is highly deficient in the aspect that it fails to recognize individuals who are the highest achievers and best performers in a group. Frequently, studies discuss the mean scores that were obtained on a given test for a normal population and then report the mean scores that were obtained from a diseased population. While this comparison can yield the magnitude of the average loss due to disease, it fails to recognize the variability within each groups and in particular fails to account for individuals within the normal group that are only mildly affected by age.

Perhaps careful studies performed on individuals that are considered “abnormal” due to exceptionally good scores on visual testing measurements could be equally beneficial. Rather than studying the bottom percentile to discover the effect of known pathologies, it could be equally valuable to study the highest percentile participants who have shown only slight decreases in visual performance with age. Certainly, precious insights can be obtained from both ends of a highly varied distribution.

## CONCLUSION

It has been found that most visual functions decrease with age regardless of the absence of pathology although the speed of the decline with age is highly variable. There are a few visual functions which have been reported to remain stable and age-independent. Further study of these ageless functions might provide exciting opportunities in the future. Perhaps new technologies can be developed which allow individuals to take advantage of the relative stability of these functions in order to offset the loss in other visual functions.

Standard clinical measurements may not detect significant losses in visual and neural functioning. High contrast visual acuity suffers only mild loss with normal healthy aging but can often misrepresent the actual vision of an individual since it only represents vision under ideal conditions. Contrary to current methods of determining eligibility for driving, vision should be assessed in ways to account for conditions that a driver would be likely to encounter. This could be combined with counseling or with limitations to allow older drivers to continue driving under conditions which could be managed successfully with low risk.

Neural and cognitive deficits must also be evaluated when considering complex tasks such as driving since they can cause significant loss in driving performance in addition to visual performance. Visual and neural functions might be critical to a number of activities of daily living in addition to driving. Once vision loss is detected, older individuals should be provided with sufficient resources in order to provide them the opportunity to act independently and at the highest functional level possible.

Regardless of the result of visual testing, each individual must be treated uniquely and with dignity and respect. Variability in visual performance increases with age so it is impossible to categorize an individual's capabilities based on the age group they belong to. While one specific ninety year old individual might be legally blind and incapable of performing most tasks which require a moderate quality of vision, another person of the exact same age might perform as well as someone many decades younger. It cannot be assumed that simply because someone is older that they have lost vision. Similarly, it cannot be assumed that due to advanced age, an individual should no longer qualify to drive.

Researchers should also consider developing focused studies which analyze individuals who are found to be in the upper percentile of individuals in their age group. These "super" humans might provide important discoveries into the degenerative aging process and offer clues into methods or practices which might be used to overcome the "normal" process of aging. While aging is a natural part of life, greater understanding of this process can provide greater opportunities for avoiding the inconveniences and disabilities that can often accompany old age.

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# Chapter 2

## The Etiology of Presbyopia and a Meta-analysis of Sex Differences

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## Abstract

**Purpose:**

We examine gender differences in near vision requirements and analyzed the factors relating to the onset of presbyopia and their direct or indirect association with gender.

**Methods:**

A meta-analysis was performed using nine cross-sectional studies that provided sufficient data to compare the prevalence and magnitude of presbyopia among men and women. This analysis was further subdivided into measurement methods to determine what differences in presbyopia might exist between men and women.

**Results:**

Studies of presbyopia including gender as a contributing factor were highly heterogenic ($p=0.01$) but overall found female gender to be statistically significant in predicting earlier onset for presbyopia with an adjusted confidence interval using the Shore method of 95% CI [1.02, 1.45]. When limited to studies only measuring accommodative amplitude, female gender was not associated with presbyopia in a fixed effects model with a 95% CI [0.49, 1.07].

**Conclusions:**

While an association between female gender and presbyopia for subjective measurements (near spectacle prescriptions and add powers) was indicated, measurements of accommodative amplitude show a weak tendency toward the opposite conclusion. This suggests that increased association of presbyopia for women is not due to a physiologic difference in accommodation but rather due to other gender differences, such as tasks performed and viewing distances. Age-based correction nomograms for presbyopia should therefore consider these gender differences when prescribing add powers for near tasks.

## INTRODUCTION

Presbyopia has been defined in a number of different ways. The generally understood definition among laymen is simply “old eyes” or the loss of vision that occurs due to age. Among clinicians it is more precisely understood as the age-related loss of accommodation that blurs near vision due to decreased focusing ability or a continuous but gradual loss of accommodation that occurs due to age. Accommodation is generally understood to be the process whereby an eye is able to change the point of focus from a distant target to a near target or vice versa.

Other definitions are used clinically in order to diagnose presbyopia. These include a classification that has been termed “functional presbyopia” which is defined as the need for a significant optical correction added to a “presenting” distance refraction correction, the vision correction that is currently worn by a patient, to achieve a near visual acuity criterion. This is separate from the standard “objective presbyopia” which is defined as needing a significant optical correction added to the best distance optical correction to achieve a given near vision criterion.[2] Neither of these definitions include accommodation as part of the criterion and could therefore lead to a diagnosis of presbyopia for any patients who meet the criterion regardless of age. A young hyperope would be diagnosed as a “functional presbyope” if a near prescription would aid his/her near vision.

It has been estimated that worldwide more than a billion adults are now affected by presbyopia. According to worldwide census data, one third of the population is over forty, an age when the effects of presbyopia become symptomatic enough that individuals begin using near vision spectacles. As the global population ages, the prevalence of presbyopia will increase. By 2030, the global population over forty is expected to rise to 41%.[1] Although estimates show uncorrected presbyopia as one of the leading causes of disability and worthy of attention as a significant contributor to the global burden of disease,[2] it is commonly overlooked as a major source of disability due to the ease of acquiring spectacle readers in wealthy countries.

With age, presbyopia eventually affects everyone, but is generally measured and diagnosed only when an individual becomes symptomatic and presents to an eye care provider with need for near vision correction. Due to the need for trained vision care providers, the burden of presbyopia is greatest among vulnerable populations with gender, race, ethnicity, climate, rurality and geographic locations considered to be contributing factors.[2,3,4,5] While presbyopia often manifests as a difficulty in reading small text, an inability to see clearly at near can have a substantial impact on the quality of life regardless of literacy or profession.[3]

In 1623, Benito Daza de Valdes noted that “women with blurred vision [presbyopia] cannot follow the same guidelines as men – they require eyeglasses possessing more degrees because they do more delicate work and because they have weaker vision.”[6] Recent studies confirm that women are indeed still being prescribed with higher near corrections than men of the same age.[7,8,9,10,11,12] The reason for this gender disparity is not immediately clear. Daza de Valdes made two different claims: women perform ‘more delicate work’ and women have naturally ‘weaker vision’. These claims would imply that there are biological, societal, and environmental components to the need for higher powered near prescriptions in women. Despite findings supporting the conclusion that women are given higher reading prescriptions than men of equal age, there is often no differentiation made between the biological, social, psychological, and cultural factors which could explain this difference.

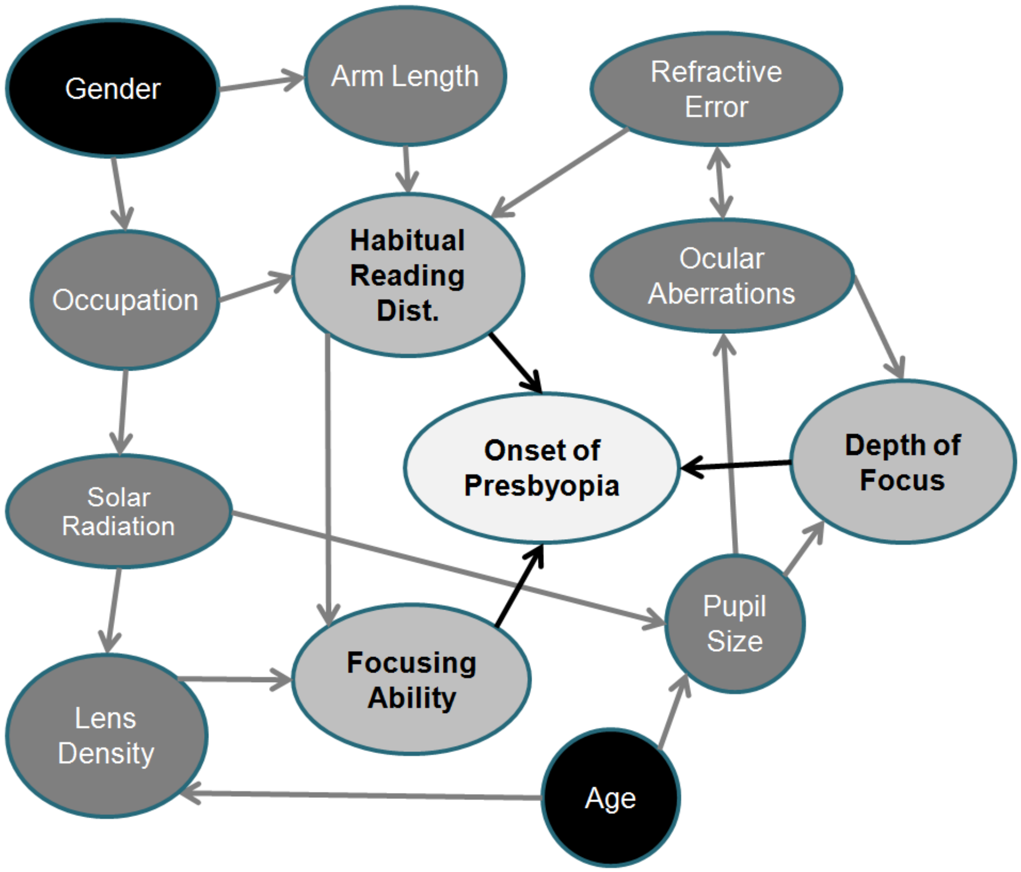


Figure 2-1: Directed acyclic graph of the causes of presbyopia. Onset of presbyopia is primarily determined by Habitual Reading Distance, Depth of Focus, and Focusing Ability. Gender could be associated with the onset of presbyopia through a variety of different pathways.

As illustrated in Figure 2-1, the onset of presbyopia is primarily influenced by three factors: focusing ability, habitual reading distance (or the preferred distance for near tasks), and depth of focus (the tolerance of an optical system such as the eye to defocus). Secondary factors that can influence the onset of presbyopia include occupation, refractive error and other ocular aberrations, arm length, pupil size, and possible differences in lens optical density. Other tertiary factors that could lead to differences in onset time of presbyopia, and therefore underlying gender differences, could include solar radiation, complexity of near tasks, indoor light levels, and/or other task specific conditions that could have a gender bias.

Loss of focusing ability, an underlying cause of presbyopia, occurs due to a loss of elasticity of the crystalline lens which makes it less effective at increasing optical power with attempts at accommodation. As the ciliary muscle contracts during accommodation, tension on the zonules decreases but a larger stiffer presbyopic lens fails to increase in optical power to the same magnitude as a younger more pliable crystalline lens.[13-20] While the onset, progression, and endpoint of the physiological focusing ability have been studied extensively,[19,21,22] the relationship between focusing ability and the subjective need for reading correction is less well understood. Measurements of focusing ability, such as accommodative amplitude, often reveal that women have greater focusing ability than men of the same age although these findings are often mixed.[23,24,25,26,27,28]

In addition to focusing ability, habitual reading distance and depth of focus are primary factors that influence the onset of presbyopia. There is evidence that adult women have a shorter measured habitual reading distance than adult men.[29] This could be one cause for the greater need for near correction in women. If women had a smaller depth of focus than men they would be more affected by near blur than men would be. There are no studies, however, that indicate a difference between men and women in terms of measured depth of focus. Pupil size and higher order aberrations can affect depth of focus but neither of these have been demonstrated to be different in women and men.[23,30,31,32,33]

There is evidence that refractive error, or the spectacle prescription needed to bring distant targets into focus, is different among men and women over forty.[34] Women over forty have higher rates of hyperopia than men over forty. While hyperopia and presbyopia have different etiologies, low amounts of undiagnosed hyperopia would manifest as an earlier need for near vision correction with the onset of presbyopia. By this definition, a ten year old +3.00 hyperope presenting with no distance correction could be described as a “functional presbyope” due to the need for near vision correction. Since “functional presbyopia” combines hyperopes and presbyopes into one group, it might be useful in describing the need for near vision correction but could add to the confusion due to grouping of vision problems with very different etiologies. Hyperopia is caused by either insufficient refractive power of the ocular structures or by reduced eye length while presbyopia is caused by loss of accommodative ability. It should be noted that any solution or correction that benefits “objective presbyopia”, could also benefit “functional presbyopia” although a full distance refractive correction would probably be the ideal solution.

In clinical practice, presbyopia is diagnosed by measurements of accommodative amplitude, near subjective refraction, and/or patient’s reported symptoms. Studies reporting presbyopia are therefore varied in their methods of diagnosis but for purposes of providing a more complete evaluation of the relationship between gender and presbyopia, this meta-analysis will consider the various methods to be equally valid.

**METHODS**

A literature search was performed for studies that reported data regarding presbyopia and gender that were published prior to 2012 (see Figure 2-2). Studies were excluded for which the data reported could not be interpreted to provide an odds ratio (OR) of the association between gender and presbyopia when controlling for age. OR was selected because it was the most commonly reported measure of association in the literature search. Studies which reported measures of presbyopia other than measures of prevalence were converted into an OR using methods described later in order to be included in the statistical analysis. A meta-analysis was then performed on included studies using the OR. No attempt was made to weight the studies based on quality of the measurements taken or on the manner used to determine the status of presbyopia since there was no objective way for determining such a method of weighting and a subjective method would not be defensible.

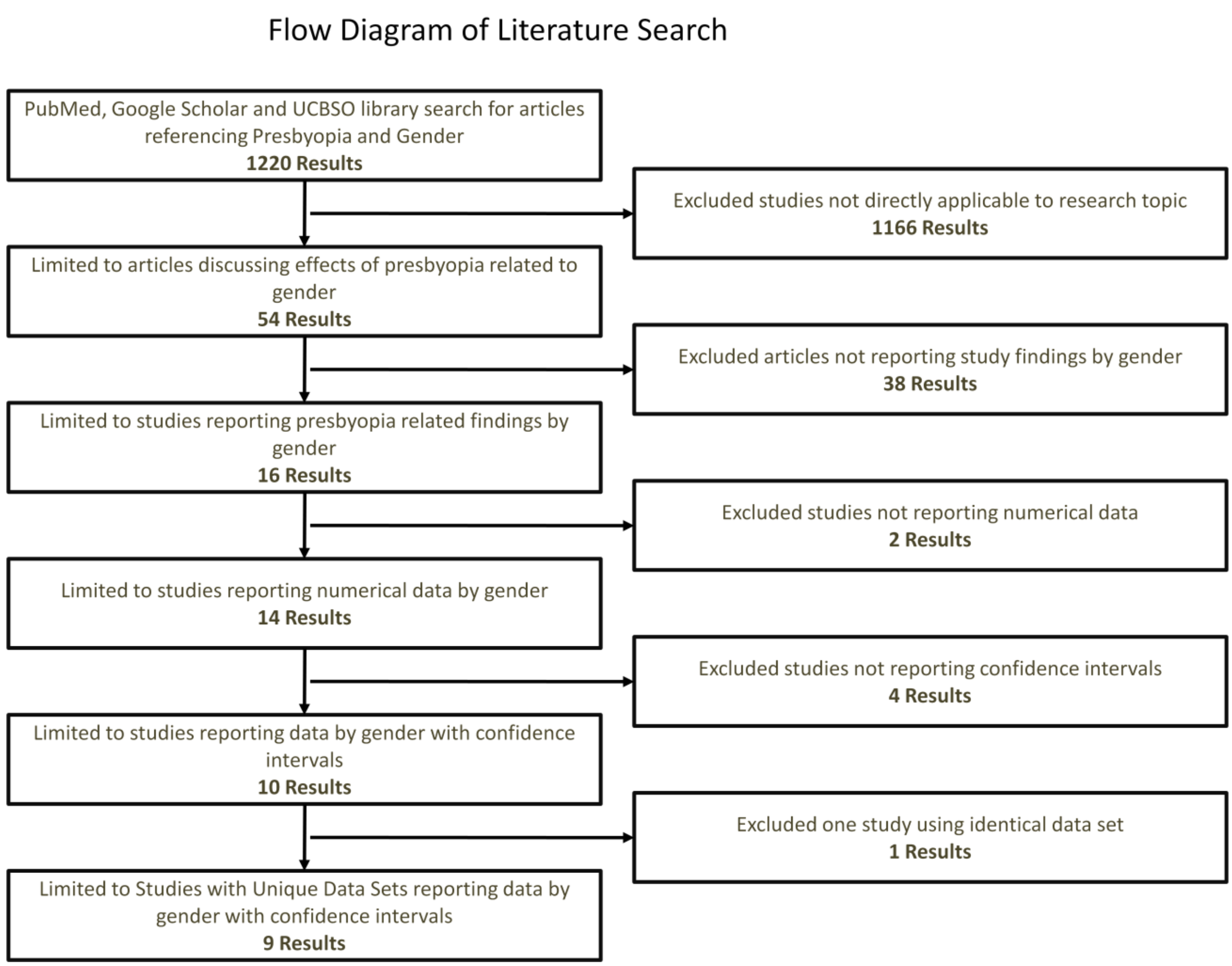


Figure 2-2: Flow Diagram of literature search

Each OR was weighted *(W,)* based on the inverse square of its standard error (SE) *(W;* = $1/SE^2$). SE were calculated by dividing the natural log of the ratio of the upper and lower 95 percent confidence intervals (CI) by 3.92 ($SE = \ln(CI_{up}/CI_{low})/3.92$). For each study, the weight was then multiplied by the natural log of the OR to calculate a summary measure. A pooled summary was determined by dividing the sum of the summary measures by the sum of the weights. A summary OR was produced by taking the exponential of the pooled summary.

Heterogeneity among studies was assessed using the chi-square statistic for heterogeneity.[35] When evidence of heterogeneity was present, the 95 percent CI of the fixed effects summary odds ratio was adjusted using the Shore method.[36] For a summary OR in which the chi-square test statistic was greater than the number of degrees of freedom, the variance of the log of the pooled relative risk was multiplied by the ratio of the heterogeneity chi-square statistic to its degrees of freedom. This adjusted variance was then used to adjust the 95 percent CI.

A total of 15 studies were found that reported presbyopia data with the gender of the participants. Of these studies, six were excluded for reasons that follow (see Table 1.1). Burke et al. (2006) and Patel et al. (2006) utilized the same data set of 1709 individuals in Tanzania so only the first was included.[9,11] Duarte et al. (2003) reported a 22% increased risk for women to develop presbyopia but did not include confidence intervals to allow inclusion into a meta-analysis.[12] Kragha et al. (1986) reported that women had 0.54 D greater accommodative amplitude than age-matched men but did not provide sufficient population demographics information (age and gender of participants) to convert this finding into a risk value for presbyopia based on age.[24] Carnevali et al. (2005) reported no significant differences for gender in accommodative amplitudes but did not provide the data used to arrive at this conclusion.[28] Millodot et al. (1989) found women to have greater accommodative amplitudes than men but found that for the overall study this value was not statistically significant.[29] The study did not provide standard deviation values for age groups which would allow inclusion into the meta-analysis.

| Excluded Studies | Finding | Reason for Exclusion |
|---|---|---|
| Patel et al., 2006 | OR 1.45 (95% CI [1.12, 1.87]) | Same data set as Burke et al. 2006 |
| Duarte et al., 2003 | 22% increased risk for women to develop presbyopia | Did not provide confidence intervals or standard errors |
| Kragha et al., 1985 | 0.54 D greater accommodative amplitude in women | Did not provide sufficient data about age and gender of participants to convert into odds ratio |
| Carnevali et al, 2005 | no significant difference between genders in accommodative amplitudes | Did not provide sufficient data about age and gender of participants to convert into odds ratio |
| Millodot et al., 1989 | Women greater accommodative amplitudes than men but did not reach statistical significance | Did not provide sufficient data about age and gender of participants to convert into odds ratio |

Table 2-1 Excluded Studies and reason for exclusion

Nine cross-sectional studies were found to meet inclusion criteria. From these, three studies [Burke et al. (2006), Nirmalan et al. (2006), and Morny et al. (1995)] reported the odds ratio of women being diagnosed with presbyopia compared to men when adjusted for age.[9,10,37] Two studies [Hofstetter (1949) and Pointer et al. (1995)] reported the values of prescribed near add powers for men and women of various ages.[7,8] The Hoffstetter study was converted into an odds ratio of women being diagnosed with presbyopia compared to men by using the need for a near add as a diagnosis of presbyopia. Because Pointer (1995) did not include data for patients who were found to have no need for a near vision add, a cutoff value of 1.00 Diopters (D) near add was used as the minimum value for a diagnosis of presbyopia. Ayrshire (1964), Miranda et al. (1979), and two studies by Koretz et al. (1989) were included.[23,25,27,38] For studies which measured subjective accommodative amplitudes, a cut off value of 3.75 D was chosen for the diagnosis of presbyopia (an amount reported in the study by Miranda et al., (1979)). For the Koretz study which measured objective accommodative amplitudes, a cutoff value of 2.5 D was chosen. This amount correlates with subjective values and it can be inferred that an individual with more than 2.5 D of measured objective focusing ability would not require a near correction for the standard reading distance of 40 cm. When individual data was not provided, a normal distribution of the metric value being measured was assumed to occur across a given age category.

The initial meta-analysis was performed combining all nine cross-sectional studies which met inclusion criteria. Subsequent smaller groups were analyzed based on three categories of methods in which the data was gathered: Near Vision Spectacles Prescribed, Near Add Power Measured, and Accommodative Amplitudes.

## RESULTS

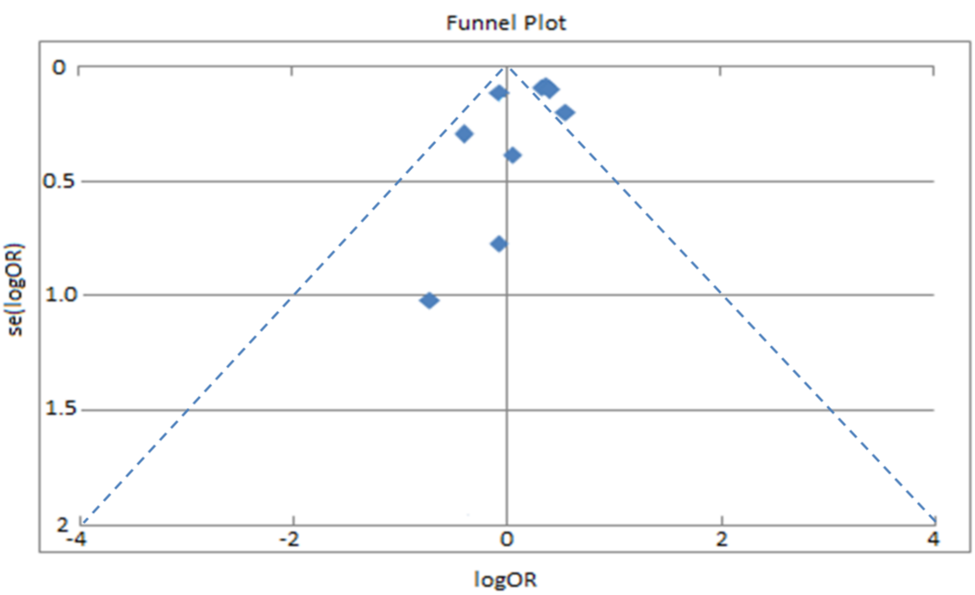


Figure 2-3 - Funnel plot depicting logORs of included studies

Using a funnel plot (Figure 2-3), no evidence of publication bias was found in the included studies.

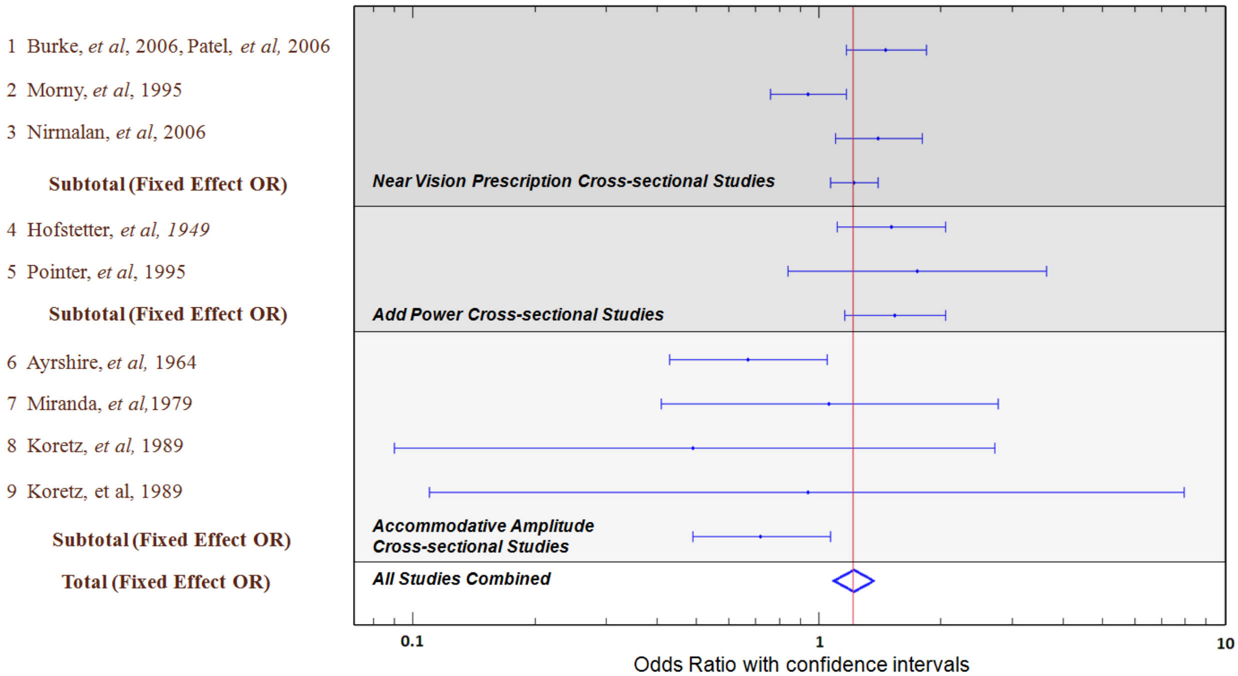


Figure 2-4: Forrest Plot of studies used in the meta-analysis of gender and presbyopia

With all nine studies included, gender was found to be a statistically significant predictor of presbyopia onset in the fixed effects model with females more likely than males to meet the study criterion for being diagnosed with presbyopia when controlling for age; Fixed Effect OR of 1.21 (95% CI [1.08, 1.36]), see Figure 2-4. The studies were found to be highly heterogenic with a probability value of 0.01. When controlling for heterogeneity across studies using a random effects model, a reduced OR of 1.19 (95% CI [0.95, 1.48]) was found (see Table 2-2).[39] When adjusting the confidence interval using the Shore method statistical significance was again achieved (95% CI [1.02, 1.45]). Two of the excluded studies (Carnevali et al. 2005, Millodot et al. 1989) reported no statistically significant difference between men and women for accommodative amplitudes. One excluded study reported an increased risk of presbyopia for women based on a self-assessment questionnaire (Duarte et al. 2003) and another excluded study reported that women had a greater accommodative amplitude than men (Kragha et al. 1985). These mixed results for the excluded studies would further increase the heterogeneity of the studies and could weaken the statistical significance of the meta-analysis reported here.

Table 2-2: Results of Meta-Analysis of Gender and Presbyopia

| | Author, Year of Publication | OR | $CI_{low}$ | $CI_{up}$ | N | Location | % $W_{all}$ | % $W_{subgroup}$ |
|---|---|---|---|---|---|---|---|---|
| *Near Vision Prescription Cross-sectional Studies* | | | | | | | | |
| 1 | Burke, *et al*, 2006 | 1.46 | 1.17 | 1.84 | 1709 | Tanzania | 25.5% | 33.9% |
| | Patel, *et al,* 2006 | " | " | " | " | " | | |
| 2 | Morny, *et al*, 1995 | 0.94 | 0.76 | 1.17 | 1884 | Ghana | 21.5% | 28.7% |
| 3 | Nirmalan, *et al*, 2006 | 1.40 | 1.10 | 1.80 | 5587 | South India | 28.2% | 37.4% |
| **Subtotal (Fixed Effect OR)** | | 1.22 | 1.07 | 1.4 | | | 75.2% | 100.0% |
| *Add Power Cross-sectional Studies* | | | | | | | | |
| 4 | Hofstetter, *et al, 1949* | 1.51 | 1.11 | 2.05 | 3917 | USA | 13.8% | 85.1% |
| 5 | Pointer, *et al*, 1995 | 1.75 | 0.84 | 3.64 | 600 | UK | 2.4% | 14.9% |
| **Subtotal (Fixed Effect OR)** | | 1.54 | 1.16 | 2.05 | | | 16.2% | 100.0% |
| *Accommodative Amplitude Cross-sectional Studies* | | | | | | | | |
| 6 | Ayrshire, *et al,* 1964 | 0.67 | 0.43 | 1.06 | 1307 | USA | 6.4% | 74.9% |
| 7 | Miranda, *et al,*1979 | 1.06 | 0.40 | 2.77 | 1000 | Puerto Rico | 1.4% | 16.5% |
| 8 | Koretz, *et al,* 1989 | 0.49 | 0.09 | 2.71 | 100 | USA | 0.5% | 5.3% |
| 9 | Koretz, et al, 1989 | 0.94 | 0.11 | 7.95 | 100 | USA | 0.3% | 3.3% |
| **Subtotal (Fixed Effect OR)** | | 0.72 | 0.49 | 1.07 | | | 8.5% | 100.0% |
| **Total (Fixed Effect OR)** | | 1.21 | 1.08 | 1.36 | | | 100.0% | |

OR = Odds Ratio, $CI_{low}$=lower bound of 95% confidence interval, $CI_{up}$= upper bound of 95% confidence interval, N = number of participants in study, % $W_{all}$ = percent weight of this study among all studies based on the inverse square of its standard error, % $W_{subgroup}$ = percent weight of this study among the subgroup of studies based on the inverse square of its standard error

Table 2-3: Results of Meta-Analysis of Gender and Presbyopia

| Category | N | Fixed Effects Odds Ratio | Fixed Effects $CI_{low}$ | Fixed Effects $CI_{up}$ | Random Effects Odds Ratio | Random Effects $CI_{low}$ | Random Effects $CI_{up}$ | Heterogeneity $\chi^2$ | Heterogeneity p |
|---|---|---|---|---|---|---|---|---|---|
| All Studies | 9 | 1.21 | 1.08 | 1.36 | 1.19 | 0.95 | 1.48 | 19.74 | 0.01 |
| Near Vision Prescription Studies | 3 | 1.22 | 1.07 | 1.40 | 1.24 | 0.93 | 1.64 | 9.12 | 0.01 |
| Add Power Studies | 2 | 1.54 | 1.16 | 2.05 | | | | 0.13 | 0.72 |
| Accommodative Amplitude Studies | 4 | 0.72 | 0.49 | 1.07 | | | | 0.95 | 0.81 |

| Category | N | Shore Adjusted CI Odds Ratio | $CI_{low}$ | $CI_{up}$ |
|---|---|---|---|---|
| All Studies | 9 | 1.19 | 1.02 | 1.45 |
| Near Vision Prescription Studies | 3 | 1.24 | 0.92 | 1.62 |

OR = Odds Ratio, $CI_{low}$=lower bound of 95% confidence interval, $CI_{up}$= upper bound of 95% confidence interval, N = number of studies
Random effects model only performed when $\chi^2$ > df, where df = number of studies minus one.

When evaluating the studies which measured presbyopia by using data for individuals who were given near vision spectacles, the fixed effect model showed that females were more likely than males to need a near vision correction when controlling for age (Fixed Effect OR of 1.22 (95% CI [1.07, 1.40]) though the studies remained heterogenous with a p-value of 0.01 (See Table 2-3). Controlling for heterogeneity through a random effects model resulted in a slightly increased OR of 1.24 (95% CI [0.93, 1.64]) which no longer achieved statistical significance even when adjusted using the Shore method (95% CI [0.92, 1.62]).

Hofstetter (1949) and Pointer(1995) compared females and males based on the add power that were prescribed by their eye doctor. They revealed a greater prevalence of presbyopia among females with a Fixed Effect OR of 1.54 (95% CI [1.16, 2.05]). Heterogeneity among these studies was much lower and did not reach statistical significance (p = 0.72).

Koretz (1989), Ayshire (1964), and Miranda (1979) found significantly greater subjective accommodative amplitudes for women than men of the same age, but when the data from these measures were converted into a predictive metric for presbyopia, the data predicted lower levels of presbyopia among women but not to a level of statistical significance. The Fixed effect OR was calculated at 0.72 (95% CI [0.49, 1.07]).

## DISCUSSION

Although presbyopia is commonly defined as the loss of focusing ability with age, the detection of presbyopia and need for near vision correction is dependent on not just the loss of focusing ability but also on the habitual reading distance and the depth of focus. Based on the findings of this analysis, there is no significant gender difference in accommodative amplitudes, a direct measure of focusing ability.

The tendency towards exclusion of studies which reported no statistically significant difference between men and women because those studies failed to report sufficient data could be problematic in the meta-analysis. While such a selective process would, of course, not bias results towards a specific gender, it would tend to decrease the likelihood of a meta-analysis revealing that there was no significant difference in presbyopia between genders.

While the overall meta-analysis did provide some evidence that females might have a greater risk for presbyopia in broad terms than males of equivalent age, the smaller group analysis of near add powers for presbyopic prescriptions showed that women have a need for higher power near adds than do men of an equivalent age. This finding is particularly important when combined with evidence that women in developing countries might often be underserved in receiving near vision spectacles.[4] This gender bias in receiving presbyopia correction would lead to an even greater disparity among men and women in terms of uncorrected presbyopia versus corrected presbyopia. Women, who have a greater need for presbyopia correction than men of equivalent age, may find themselves less likely to receive that aid. A five year update of their 2007 study by Ramke et. al. showed that improvements were being made in gender disparities in presbyopia correction through a National Spectacle Program as reported in 2012.[5]

The summary finding of a meta-analysis which combines the results of studies using differing methods for diagnosing presbyopia might be questionable since the weights of the various methods of measurement were not equal (a result of the number of participants in the studies not being equal). There were far more individuals in the cross-sectional studies that reported presbyopia based on the need for a near vision prescription by age and gender than in the studies which measured accommodative amplitude by age and gender. While both accommodative amplitude and the need for spectacle prescriptions are used clinically for determining the onset of presbyopia, they were not equally predictive of the differences between men and women. By using different measurements of presbyopia, the various studies also implicitly subscribed to slightly different definitions of the term presbyopia itself. Such an internal discrepancy could be rightly viewed as a limitation to the results of a meta-analysis that combined such a varied array of studies.

Due to the wide variety of primary, secondary, and tertiary factors that can be attributable to the onset of presbyopia it would be impossible to compare all the possible reasons for gender differences through a meta-analysis of previous research. The evidence presented supports the conclusion that gender differences are not due to differences in focusing ability but rather gender differences related to preferred reading distances, such as arm length, occupation, indoor light levels, and specific conditions related to desired tasks.

Following submission of this meta-analysis for review, a study performed by Hashemi et. al. (2012) was accepted for publication.[40] This study collected data from 5019 participants in Iran and the results agreed with the other cross-sectional studies already included in this meta-analysis by concluding that females require higher add powers than men of similar age. If included in the meta-analysis, this study would strengthen the conclusions already determined.

## CONCLUSION

Although there are no significant sex differences in presbyopia due to focusing ability when measured by accommodative amplitudes, there are significant gender differences in the add requirements for near vision spectacles for men and women of the same age. These differences are likely due to differences in preferred viewing distances (as a result of arm length or preferred near tasks) or due to uncorrected hyperopia. Measurements of accommodative amplitudes are therefore not sufficient to diagnose presbyopia without considerations of an individual's specific needs.

Presbyopia is a global challenge. More than a billion individuals require near vision aids to perform basic tasks of daily living. This number will continue to increase as the number of individuals over age forty increases. Global health policies that seek to overcome the disability caused by visual impairment should consider the specific needs that women have for near vision and adjust policies to meet these needs to provide equitable care for all individuals. In the future, more carefully performed studies should be executed which better isolate and measure the various factors that contribute to the development of presbyopia while controlling for age and gender. Metrics used to determine presbyopia must be carefully chosen. Future studies should also consider depth of focus as a factor in the development of presbyopia and should consider the potential for differences in depth of focus between men and women by looking at potential causes such as higher order aberrations and pupil size. Longitudinal studies which consider the interaction between the preferred reading distance and the change in accommodative amplitude across time for males and females could help determine to what extent biological factors or environmental factors play a role in the loss of focusing ability with increasing age.

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# Chapter 3

## Using Wavefront Aberration Profiles to Correct Presbyopia

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**Abstract**

**Purpose:**

We measured visual performance through a range of defocus values when affected by astigmatism, coma, trefoil, and 4$^{th}$, 6$^{th}$, and 8$^{th}$ order spherical aberration. We matched these results to objective image quality metrics to determine the ideal aberration profiles for maximizing depth of focus.

**Setting:**

University of California, Berkeley

**Methods:**

A random twenty alternative forced choice visual performance task was performed. Stimulus size was decoupled from blur in an ideal observer condition to minimize subject's own neural and optical limitations. Depth of focus was examined using mean visual performance through focus (meaning through a range of defocus values such as in plotting a defocus curve) and compared to image quality metrics. Ideal profiles were determined based on pupil sizes and range of focus values.

**Results:**

Of the tested aberrations, spherical aberration, Z (4,0), provided the best mean visual performance through focus. Of 31 image quality metrics, Equivalent Width (EW) provided the highest linear correlation with measured experimental values (r=0.84). Spherical aberration values for 2, 3, 4, and 5 mm pupils to optimize depth of focus were calculated as 0.065 µm, 0.115 µm, 0.19 µm, and 0.275 µm respectively for a 2 diopter range of defocus values.

**Conclusions:**

An optimal amount of spherical aberration to increase depth of focus would depend on pupil size and the desired range of defocus values. Since testing conditions utilized ideal observer conditions, actual visual performance would be reduced by neural and retinal limitations.

**Introduction:**

The human eye is an imperfect optical system. Light reaching the retina is distorted by aberrations in the cornea, lens, and other ocular materials before reaching the retina. Limitations such as the spacing of the photoreceptors, direction of the incoming light, and light absorption sensitivities to varying wavelengths can further decrease the image quality. Even after being imaged on the retina, the resulting neural transmission to the brain is further limited by the optic nerve. Although there are some 120 million rod photoreceptors and another 7 million cone photoreceptors in the retina, there are only approximately one million axons in the optic nerve. This inequity results in a decrease in the volume of information that is transmitted to the visual cortex. Although higher level neural processes may assist in reconfiguring the original image, its representative accuracy is invariably constrained by the quality of the input provided.

In addition to the optical and neural imperfections, a decrease in amplitude of accommodation with age leads to an inability to change focus, known as presbyopia. A greater depth of focus therefore becomes increasingly useful with age, since it allows an individual to retain adequate visual quality over a range of defocus distances despite decreased ability to change focus. Depth of focus is dependent on a variety of factors, including pupil size and optical aberrations.

Decreasing pupil size increases depth of focus by not only limiting stray light that passes through the aperture but also by reducing blur. The size of a blur circle on the retina (mrad) can be calculated directly from the product of the pupil diameter (mm) and the amount of defocus (diopters). The same amount of defocus results in less blur when passing through a smaller pupil.

Each eye is an optical system that can be represented by a wavefront aberration profile. This profile includes not only lower order aberrations, such as defocus and astigmatism, but also includes higher order aberrations, such as coma, trefoil, and spherical aberration. Similar to pupil size, aberrations can also affect the depth of focus. Using an adaptive optics simulator, Rocha et. al.[1] demonstrated that the presence of spherical aberration expands the depth of focus. Cheng et. al.[2] likewise showed that while increasing levels of spherical aberration caused the best achievable visual acuity to deteriorate, it also shifted the amount of defocus needed to produce the best visual acuity and increased depth of focus by decreasing the change in LogMAR produced by defocus.

Since image quality is dependent on the magnitude to which optical aberrations distort the wavefront, if optical aberrations can be selected to maximize image quality through a given range of defocus planes, the selected wavefront pattern would be considered ideal for that range. This ideal pattern of aberrations would be linked to the specific pupil size for which it was constructed and to the range of defocus values which were evaluated.

Objective image quality metrics are commonly utilized to predict the performance that a particular optical system would be expected to achieve. Various visual quality metrics have been introduced by researchers, including 31 metrics that were discussed by Thibos, Hong, Bradley, and Applegate.[3] It must be noted that a metric that is developed specifically for one visual performance task might potentially be less accurate when applied to other tasks so applicability must be considered. The amount that an objective image quality metric correlated with the actual measured performance of an individual when performing a visual task would reveal the potential accuracy in predicting future visual performances in similar tasks. An objective image quality metric could likewise be calculated across a range of defocus values and the performance of an optical system could then be evaluated for that range. The accuracy of this evaluation of depth of focus would be dependent on the accuracy of the metric in predicting visual performance at each defocus value.

For centuries, it has been possible to simulate ametropia using spectacle lenses. An emmetrope could simulate the vision of a myope by putting on glasses with converging lenses. Astigmatism could be simulated using toric lenses. With the emergence of adaptive optics technology using wavefront aberrometers and deformable mirrors, higher order aberrations can now be simulated as well. In an adaptive optics device, a wavefront sensor measures the aberrations of incoming light. This information can then be used to adjust a deformable mirror into a configuration that redirects the light into a focused image. A similar approach could be taken as well to create desired levels of chosen aberrations. Rather than shape the deformable mirror to produce zero aberrations, the surface could be constructed so as to produce specific aberration patterns, such as a desired magnitude of spherical aberration.

Measuring depth of focus requires a method that accurately relates the information that is most relevant to visual performance. A number of methods for calculating depth of focus exist in the literature so there is inconsistency in reported values. Some researchers use width at half maximum or half normal best corrected values.[4,5] Others utilize a percentage of the assumed maximum potential of a perfect optical system or the best set of performance results.[6] Dependence on a scale based on degradation of a peak performance value would always be problematic as well since individual levels of performance vary. A percentage value would fluctuate with changing peak values. In addition, image quality metrics are often not linear in scale in regards to decreasing quality, so a 50% value for one metric may have very little relationship to a 50% value of a second similar metric. These inconsistencies are problematic in making comparisons between reported values for depth of focus.

Rather than relate depth of focus to the width at half maximum value (or some other percentage), a better and more intuitive clinical metric might quantify the visual performance as a mean level measured across a range of defocus values with a calculated standard deviation from that mean. An example might be determining a mean visual performance on a Snellen high contrast visual acuity chart across a three diopter range of defocus along with the standard deviation of values from that mean.

In order to measure visual performance, it is also important to use a task that is repeatable and quantifiable on a quantifiable scale. While visual quality can be described by various subjective scales of vision (such as just objectionable, just bothersome, or just noticeable or detectable blur),[7,8] this might be confusing or inadequate for comparison purposes. Higher order aberrations can often cause minor fluctuations in various aspects of an image without causing actual degradation in visual performance. Measuring the amount of aberration required to obtain a just noticeable difference in vision could very well be determining the sensitivity to discriminating minute local changes in an image without quantifying any actual loss in visual performance. Similarly, measuring the just bothersome blur or just objectionable blur requires that each subject has equivalent subjective values established for such criteria.

Since depth of focus is influenced by a number of internal and external factors, such as luminance, contrast, spatial frequency, target detail, wavelength, visual acuity, pupil size, and refractive state,[9,10] determining an ideal optical aberration profile to optimize depth of focus would require an extremely complex system if efforts were not made to simplify the approach.

Our method was to devise a simple test which could isolate many of these factors in order to realistically compare optical systems. We did this by separating the blur produced by an optical system from its image size and retinal sampling. We also sought to identify an objective image quality metric that would best correlate with this specific vision test (although not necessarily all types of vision tests). This process would then allow for an efficient means of discovering an ideal optimal aberration profile for widening the depth of focus.

**Methods:**

All protocols adhered to the tenets of the Declaration of Helsinki. Participants reported good ocular health and no significant need for spectacle correction. Subjects were found to have 20/20 or better Best Corrected Visual Acuity at both near and distance.

Two subjects were tested using a 20 alternative forced choice Snellen letter visual performance test that was conducted binocularly using a high contrast stimulus presented on an 11-bit display monitor under mesopic lighting conditions. Each presentation consisted of a randomly chosen Snellen letter convolved with the point spread function (PSF) of one of the following Zernike aberrations: Z(2,2), Z(3,-1), Z(3,3), Z(4,0), Z(6,0), and Z(8,0). The PSF was calculated using 550 nm monochromatic light and a 5mm pupil diameter as given parameters and were varied systematically using 0.25μm steps for each Zernike aberration as well as measuring through focus using defocus [Z(2,0)] increments of 0.25 diopter steps.

Visual performance was measured in LogMAR units starting at 0.3 LogMAR (equivalent to 20/40 Snellen Acuity). Each series of presentations simulated decreasing letter sizes with 0.1 LogMAR steps (one line of standard Snellen Acuity). Five random letters were presented for each step size resulting in each presented letter stimulus as being equivalent to 0.02 LogMAR units. The series was ended when a subject failed to identify 3 out of 5 Snellen letters for the given step size.

The monitor chosen was a Totoku ME253i2 due to its resolution and gray scale range. It has a 1600x1200 pixel resolution with an 11 bit display for 2048 shades of gray. It came with default settings for calibration but we utilized a lookup table for images that were produced in order to linearize the gray scale and to take advantage of the full range of the gray scale. The monitor is capable of producing a luminance of 1800 cd/m$^2$.

While each stimulus simulated a Snellen letter of a given LogMAR, the actual letter stimulus was displayed on the monitor with a presentation size magnified to 7 mm (a size equivalent to 1.0 LogMAR or 20/200 Snellen letter size at 50cm). The aspect ratio of the blur and distortion of each image were held constant following magnification so as to provide no actual change in the legibility of the letter despite the increased size. A display size of 20/200 on the monitor was chosen to create an ideal observer situation and effectively decouple the size aspect from the blur aspect thereby minimizing the effects of a viewer's own aberrations and attempting to negate any biological limits of the eye, such as the photoreceptor spacing in the retina.[11] Since the LogMAR measurements that were taken are no longer indicative of the angle of resolution due to the magnified presentation, the values will in the future be referred to as $LogMAR_{sim}$ values rather than standard LogMAR.

Data obtained from the experiments was then used to compare the effectiveness of the tested Zernike aberrations, Z(2,2), Z(3,-1), Z(3,3), Z(4,0), Z(6,0), and Z(8,0), in improving depth of focus by calculating a mean visual performance through focus. Mean visual performance was also calculated for each 0.25µm step for the individual Zernike aberrations as well. Standard deviations for the mean performance values were determined to examine the spread of the through focus values.

Objective image quality metrics are useful methods for translating measurements of aberrations in the human eye into expected levels of visual performance. These metrics can be based on the quality of the measured wavefront at the pupil plane or upon the quality of the image produced by the optical system at the image plane (either a point object or a grating object). Experimental visual performance results were compared to 33 previously published objective image quality metrics using linear regression with the image metrics as independent variables in predicting visual performance as a dependent variable.[3,12] Objective image quality metrics were calculated using Get Metrics software that was developed by Larry Thibos, Ray Applegate, and Hope Queener. Experimental results were then further evaluated using power curve fittings to adjust for non-linearities within the 33 metrics.

The objective image quality which was determined to be most effective at predicting subject visual performance could then be used to calculate an ideal amount of aberration to improve depth of focus based on the effectiveness of the individual aberrations in expanding the depth of focus.

**Results:**

While visual performance results were found to be highly correlated between the two subjects (r=0.912), there was a small but statistically significant difference in mean visual performance values between the subjects ($p<0.001$) of 0.08 $LogMAR_{sim}$ units with a standard deviation of 0.1 $LogMAR_{sim}$ units (a difference equivalent to about one line of visual acuity).

Absent all aberrations, subjects showed a V-pattern in visual performance through focus. As seen in Figure 3-1, the rate of reduction in visual performance flattened out dramatically after the initial 0.5 diopters of added defocus, Z(2,0). Peak performance was found to be -0.89 $LogMAR_{sim}$ under ideal viewer conditions.

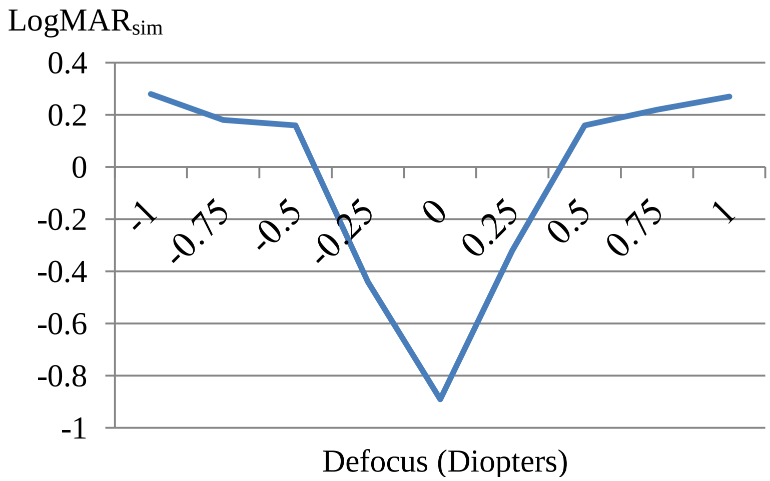

Figure 3-1: Mean LogMAR$_{sim}$ visual performance (y-axis) through focus (diopters, x-axis) for ideal viewing subjects with zero aberrations.

With a wavefront profile consisting of 0.25 µm of spherical aberration, Z(4,0), visual performance improved significantly across the entire range of defocus values except for the peak performance value. With positive spherical aberration, the more dramatic slope in measured acuity loss occurred in the direction of added negative defocus. Positive defocus created a more gradual loss of visual performance as seen in Figure 2. Peak performance of -0.78 LogMAR$_{sim}$ at -0.5 Diopters defocus was only 0.11 units less than the peak performance of the zero aberration condition.

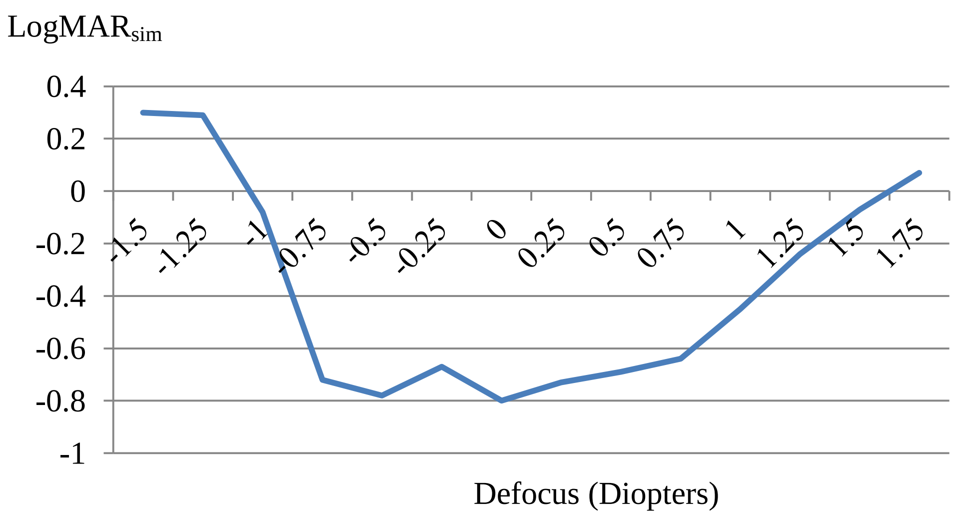


Figure 3-2: LogMAR$_{sim}$ visual performance (y-axis) through focus (diopters, x-axis) for ideal viewing subjects with a 5mm pupil profile and 0.25µm z(4,0).

In order to calculate a mean measurement of visual performance through focus, a range of defocus values must be chosen that will represent an acceptable depth of focus for an individual that is unable to accommodate. Peak visual performance through focus by ideal observers for a 5mm pupil with no aberrations was found to be -0.89 log MAR but beyond 1 diopter of defocus, visual performance dropped to worse 0.3 LogMAR$_{sim}$ (as seen in Figure 3-1). A mean visual performance across a 2 diopter range of focus would therefore be calculated to be -0.04 LogMAR$_{sim}$ with a standard deviation of 0.41 LogMAR$_{sim}$. A 2 diopter range of focus could be used to illustrate the range of an individual's visual quality from an object in the far distance up to an object 50 cm away (2 diopters of retinal defocus) in the absence of accommodation. Similarly, a 3 diopter range of focus would illustrate the overall vision that could be obtained up to 33 cm distance.

Of the 5 higher order aberrations tested (Z(3,-1), Z(3,3), Z(4,0), Z(6,0), and Z(8,0)), all except Z(3,3) were shown to increase depth of focus for a 0.25µm aberration profile relative to the zero aberration optical system as measured by a mean depth of focus across a 2 diopter range of defocus values (see Figure 3-3). One example of this, a mean visual performance across a 2 diopter range of defocus was calculated at -0.64 $LogMAR_{sim}$ with a standard deviation of 0.18 $LogMAR_{sim}$ (see Figures 3-2 and 3-3). A binocular peak visual performance of -0.80 log MAR was found on a magnified image of a spherical aberration profile for a 5mm pupil with 0.25µm z(4,0) (see Figure 3-2).

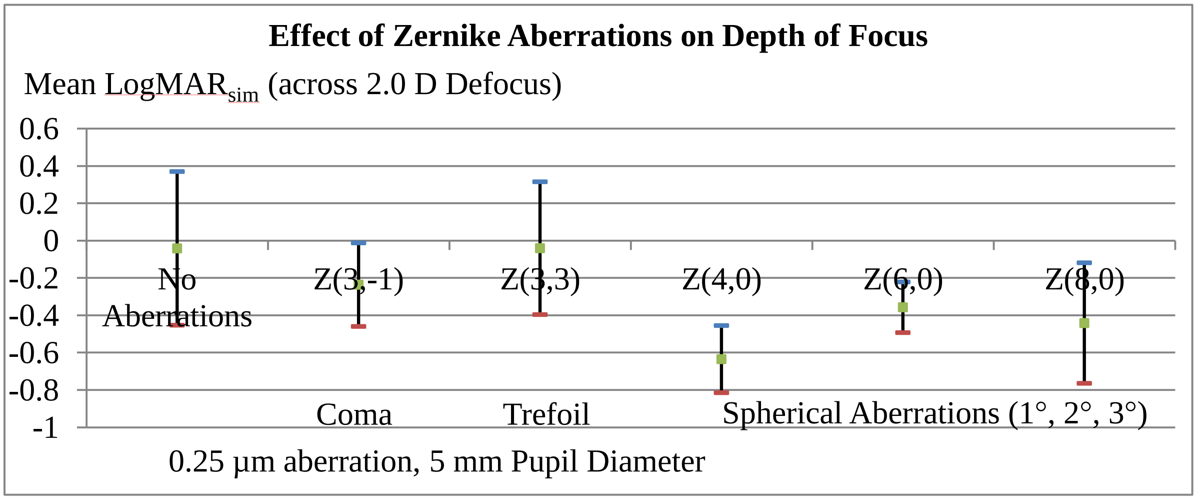


Figure 3-3: Mean $LogMAR_{sim}$ across a 2 diopter range of defocus values for no aberrations as well as 0.25µm of Coma, Z (3,-1), Trefoil, Z (3,3), Primary Spherical Aberration, Z (4,0), Secondary Spherical Aberration, Z (6,0), and Tertiary Spherical Aberration, Z (8,0). Error bars show the standard deviation across the 2 diopter range of defocus values.

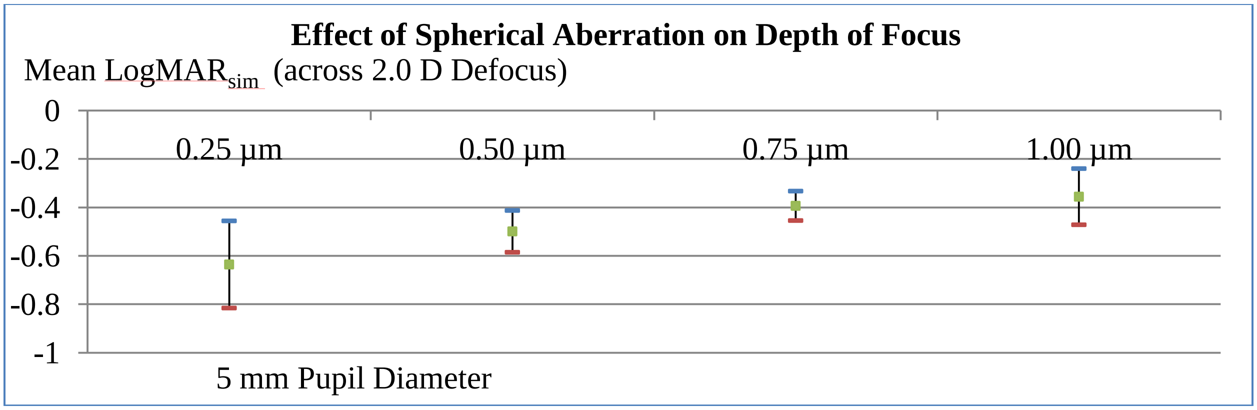


Figure 3-4: Mean $LogMAR_{sim}$ across a 2 diopter range of defocus values for 0.25µm steps of Z(4,0) spherical aberration profiles along with the standard deviation across the same range.

Of the 6 aberrations tested, spherical aberration Z(4,0) was most effective at providing a high mean visual performance (Figure 3-3). This level of effectiveness was highest at 0.25 µm (with a mean of -0.64 $LogMAR_{sim}$) and decreased with increase amounts of spherical aberration (Figure 3-4). Astigmatism, Z(2,2), was least effective at increasing the depth of focus and caused the greatest drop in visual performance when added. Of the higher order aberrations tested, trefoil was least effective at improving visual performance.

When correlating experimental results to the 33 objective visual quality metrics, linear correlation results showed that EW (r=0.84), SRX (r=0.82), SROTF (r=0.76), PeakPSF (r=0.76), and Strehl (r=0.75) were most predictive of subjective visual performance as seen in Table 3-1. Four of these five metrics represent the image quality for a point object at the image plane (EW, SRX (Strehl ratio computed in spatial domain), PeakPSF (Peak measurement of the PSF), and Strehl. Only one of them, SROTF (Strehl ratio computed in frequency domain), represents the image quality of a grating object at the image plane and none of the top five measured the quality of the wavefront at the pupil plane. EW, the highest correlated metric, is an acronym for Equivalent Width and is a measurement of the compactness of the point spread function.

Since neither visual performance nor the visual quality metrics are linear in nature, a variety of fittings were applied to each of the visual image quality metrics. A power fitting was reasoned to be most appropriate, since it matched the pattern of visual performance losses at the greatest range of metric values (see Appendix A). It was found that both SRX, the Strehl Ratio computed in the spatial domain, and EW were most highly correlated with visual performance (r=0.91) when using a power fitting. The power fitting also caused the two metrics to be effectively identical since pupil size was maintained at a constant value of 5 mm during repeated experiments, which negated the pupil variable that is part of calculations for the EW metric.

| **Metric** | **Corr.** |
|---|---|
| EW | 0.84 |
| SRX | 0.82 |
| SROTF | 0.76 |
| PeakPSF | 0.76 |
| Strehl | 0.75 |
| LIB | 0.59 |
| SRMTF | 0.52 |
| VSOTF | 0.52 |
| VSX | 0.51 |
| CW | 0.50 |
| VOTF | 0.43 |

| **Metric** | **Corr.** |
|---|---|
| PFSt | 0.38 |
| NS | 0.37 |
| VNOTF | 0.37 |
| HWHH | 0.33 |
| SFcMTF | 0.29 |
| STD | 0.25 |
| SFcOTF | 0.24 |
| VSMTF | 0.22 |
| AreaOTF | 0.16 |
| AreaMTF | 0.13 |
| PFWt | 0.13 |

| **Metric** | **Corr.** |
|---|---|
| PFWc | 0.11 |
| PFCt | 0.11 |
| RMSw | 0.09 |
| PFSc | 0.08 |
| PFCc | 0.07 |
| PV | 0.07 |
| ENT | 0.07 |
| D50 | 0.04 |
| Bave | 0.03 |
| SM | 0.02 |
| RMSs | 0.02 |

Table 3-1: Correlation of Objective Image Quality Metrics with measured $LogMAR_{sim}$ visual performance values during ideal viewer conditions

Data in Figure 3-5 demonstrates the effect that pupil size has on depth of focus by showing the mean EW metric across 2.0 diopters of defocus, Z(2,0). Smaller values of mean EW represent more compact Point Spread Functions across the range of defocus values. The graph shows that, for a 5 mm pupil, positive and negative spherical aberration of 0.275 µm provides the most compact PSF on average across a 2 diopter range of defocus. A more compact PSF over a range of defocus values would mean better visual performance over a larger range of focus. The smallest Mean EW would therefore be most ideal for increasing the depth of focus over the given range of defocus values. Similar ideal spherical aberration values can be found for 4, 3, and 2 mm pupils, which produce the most compact point spread functions on average across the range of defocus values. These are 0.19 µm, 0.115 µm, and 0.065 µm respectively. The optimal aberration measured in microns that would expand the depth of focus would therefore become smaller in as the pupil size was reduced.

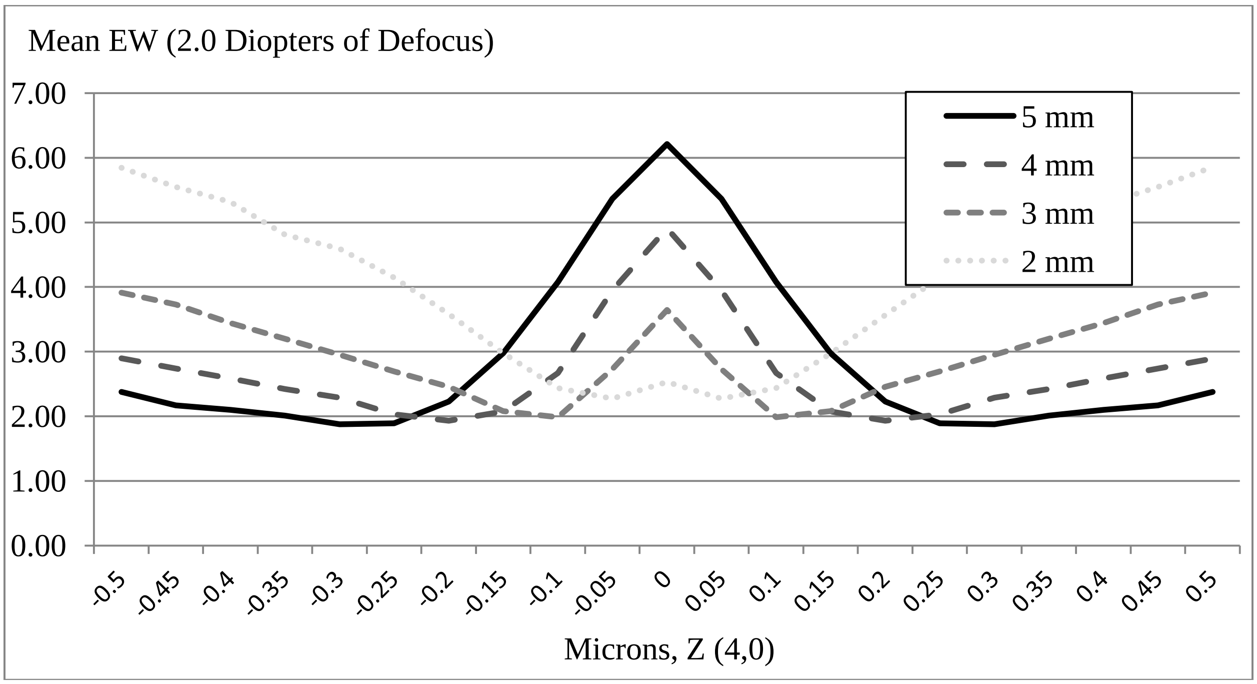


Figure 3-5: Graph showing the Mean EW metric across 2 Diopters of defocus (Y-axis) for 4 different pupil sizes (5, 4, 3, and 2 mm diameters). X-axis represents the microns of spherical aberration, Z (4,0).

Just as the EW metric can be used to calculate an ideal spherical aberration profile which produces the most compact Point Spread Function across 2 diopters of defocus, it is possible to calculate the ideal spherical aberration profile for smaller or larger ranges of defocus. Figure 3-6 shows the mean EW across a range of 3 diopters of defocus. For a 5 mm pupil, positive or negative spherical aberration, Z (4,0), equal to 0.45 µm produces the most compact Point Spread Function on average. 4, 3, and 2 mm pupils are maximized at 0.25 µm, 0.15 µm, and 0.1 µm respectively.

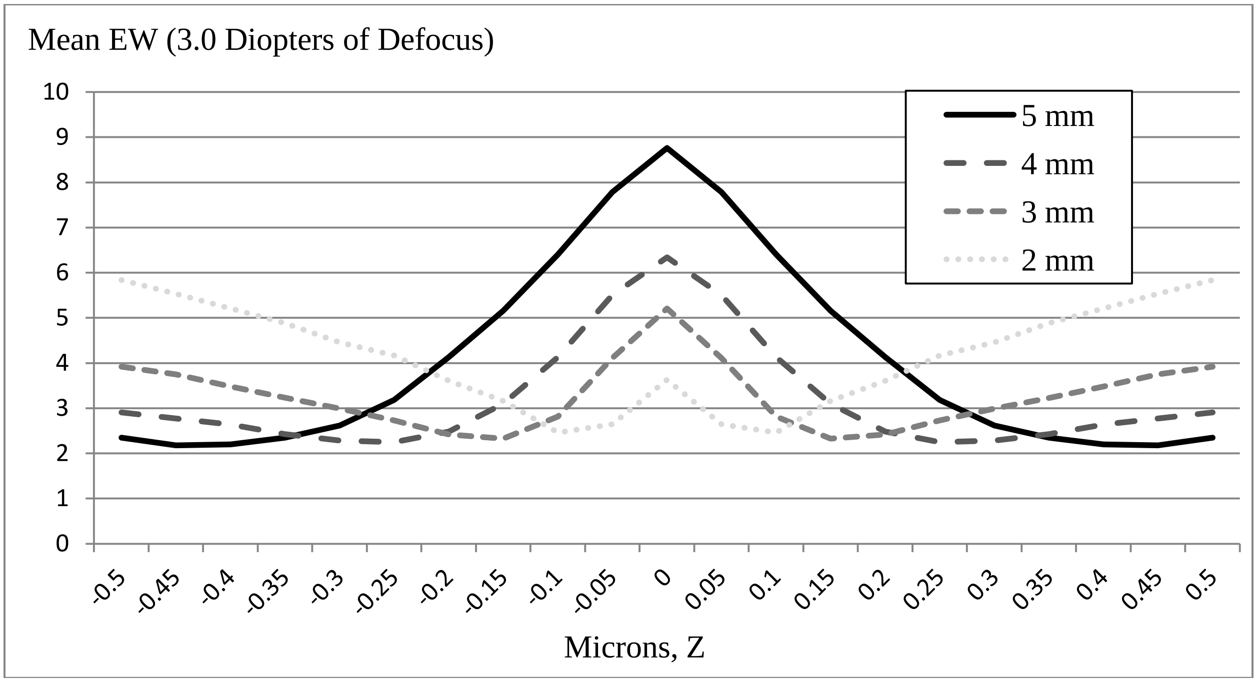

Figure 3-6: Graph showing the Mean EW metric across 3 Diopters of defocus (Y-axis) for 4 different pupil sizes (5, 4, 3, and 2 mm diameters). X-axis represents the microns of spherical aberration, Z (4,0).

**Discussion:**

Decoupling the size aspect from the blur aspect resulted in better angular resolution than standard visual acuity testing. This is due to an absence of neural and retinal limiting factors such as photoreceptor spacing. While standard visual acuity testing in healthy observers is occasionally better than -0.1 $LogMAR_{sim}$ (20/16 Snellen Acuity), it rarely exceeds -0.3 $LogMAR_{sim}$ (20/10 Snellen Acuity). In a study by Elliot, the mean of a normal healthy population of 25-29 year olds was found to be as low as –0.16 log MAR.[13] We can compare this to the results found by Rossi et. al. when measuring AO corrected emmetropes.[14] He found a mean $LogMAR_{sim}$ visual acuity of -0.31 when visual acuity measurements were taken with only 0.081 μm of mean residual RMS error remaining.

Using ideal binocular viewing observers with magnified images and a 5mm pupil diameter, we found a maximum mean visual performance of -0.89 $LogMAR_{sim}$ for a zero aberration profile. This value would indicate that retinal factors are quite significant at limiting visual performance since the best performance obtained using adaptive optics to correct optical aberration was much lower, as seen in the experiments by Rossi. Even when significant higher order aberrations were added, continued high performance was attainable without defocus. A mean visual performance of -0.62 $LogMAR_{sim}$ was measured with 0.5 μm of spherical aberration with an additional 1.25 diopters of defocus. With vertical coma of 0.5 μm, the mean visual performance was measured at -0.46 log MAR without additional defocus added.

Under normal viewing conditions, the photoreceptor spacing appears to be a major source of the limits to the visual acuity that can be obtained. Since visual performance under the ideal viewing conditions would not be limited by neurological or retinal limitations, it would be expected that continued improvement in visual performance would occur up to the diffraction limit. Objective image quality metrics based on the Point Spread Function would be particularly effective when they accurately indicated the compactness or the magnitude of the peak in relation to the surrounding spread.

Equivalent Width, EW, is defined as the equivalent width of a centered PSF (arcmin). This image quality metric is a measure of the compactness of the Point Spread Function and is calculated by dividing the total volume of the PSF by the peak value to determine the base area of the equivalent cylinder. The diameter can then be computed from the area and then scaled by the pixel size, which is determined by the given pupil size and wavelength.

```
EW = Pixelsize*sqrt(Volume(PSF)*4/pi)/Peak(PSF))
```

Because EW is calculated using the peak of the PSF, it will correlate exactly with Strehl Ratio for any given pupil size. Strehl Ratio is calculated from the peak of the aberrated PSF divided by the peak of a PSF for a diffraction limited pupil of the same size. All pupil sizes with similar aberration would therefore produce similar values. EW computes different values for different pupil sizes, which is more realistic. A 5 mm pupil with no aberrations will have a much different visual quality than a 2 mm pupil with no aberrations due to diffraction. Strehl Ratio would calculate both pupils to have a value of 1.0.

Within this study, Zernike polynomials were utilized independently. While aberrations such as defocus, astigmatism, coma, and spherical aberration effectively describe many conditions that occur within the human eye, they would never be considered as independent or occurring in the absence of other aberrations. This study determined that $4^{th}$ order spherical aberration was the most effective single Zernike aberration at increasing depth of focus based on mean performance values through a range of defocus values. This does not preclude the possibility of various combinations of Zernike aberrations in providing a wider depth of focus. These combinations were explored and various combinations of $4^{th}$, $6^{th}$, and $8^{th}$ order spherical aberration provided large depths of focus but these mixtures were not significantly more effective than an optimized amount of $4^{th}$ order spherical aberration alone.

Fourth order spherical aberration when combined with $3^{rd}$ order or $5^{th}$ order aberrations resulted in loss in visual performance through a range of defocus values. This could have important implications when considering the use of multifocal treatments for various modalities, such as refractive surgery or contact lens wear. It would not be possible under natural conditions to create a permanent optical system that retained only a solitary Zernike value at the exclusion of all others, it would therefore be expected that no treatment would produce the optimal depth of focus via multifocality. Additionally, since pupil size changes with lighting conditions and with age, a spherical aberration correction that was optimized for one pupil size, would offer varying results with different light levels and with aging.[15] Figure 3-7 shows the predicted mean visual performance of a -0.275 µm Z(4,0) 5 mm optical profile with changes in pupil size. Assuming that the EW metric remains equally valid across pupil sizes, this graph would indicate that depth of focus would worsen initially with pupils smaller or larger than 5 mm but eventually improve for very small pupils (although not reaching an ideal depth of focus for that pupil size).

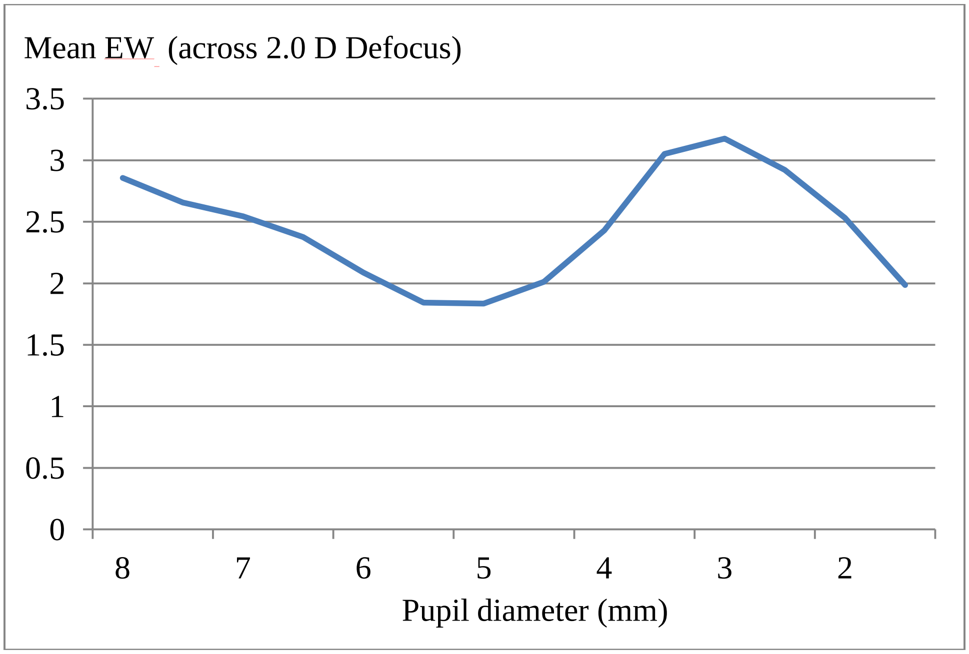


Figure 3-7: Graph showing the Mean EW metric across 2 Diopters of defocus (Y-axis) for a -0.275 µm Z(4,0) 5 mm optical profile with changing pupil sizes (2 to 8 mm diameters). X-axis represents the pupil diameter in millimeters.

**Conclusions:**

Under ideal observer conditions, by decoupling the size aspect of an image from the blur aspect, we measured the effects of individual Zernike aberrations on visual performance through focus. Mean visual performance through a range of defocus values was computed for each tested Zernike term and we compared the depths of focus of various aberration profiles. Primary spherical aberration, Z (4,0) was shown to be the most effective independent Zernike term at increasing depth of focus.

We then determined that the EW metric was most highly correlated with measured experimental data. Finally, we used the EW metric to determine several optimal wavefront aberration profiles which maximize depth of focus by calculating a mean EW value which represented the compactedness of the point spread function across a range of defocus values. A smaller mean EW value would correspond to better visual performance on average across a range of defocus values (due to reduced scatter of the point spread function). The smallest mean EW would therefore be ideal for that pupil size and that specific range of defocus values. Each optimized profile is inseparably bound to a specific pupil size and to a specific range of defocus values but would be ideal for that condition.

Since testing conditions utilized ideal observer conditions, actual visual performance would be reduced due to neural and retinal limitations. While spherical aberration can be used to enhance visual performance in the presence of defocus (such as caused by presbyopia while performing near tasks), improvements would be mitigated by changes in pupil size or in the presence of other aberrations.

An Adaptive Optics Scanning Laser Ophthalmoscope or similar adaptive optics system could be utilized to test optimized profiles further by measuring visual performance of individuals with the chosen aberration profiles and determined pupil sizes.[16] This testing system would need to accurately measure and correct for the inherent optical aberrations in the eye and then bestow the selected aberration profile.

Refractive surgery, new designs in ophthalmic lenses, specialized contact lenses, and adaptive optics hold the potential for improved corrected of higher order aberrations. It has been calculated that achieving diffraction limited performance for a 6 mm pupil would require the correction of the 14 largest Zernike modes.[17] If achievable, this level of performance would maximize visual acuity and be considered ideal under conditions where an individual could change focus freely. With the onset of presbyopia, however, this optimal focus at a single point in space would result in rapid loss of visual performance at all other defocus values. A more practical solution could therefore consist of balancing the visual needs at a variety of distance while considering the limitations of visual performance that are imposed by the neural limitations of the eye.

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Appendix A

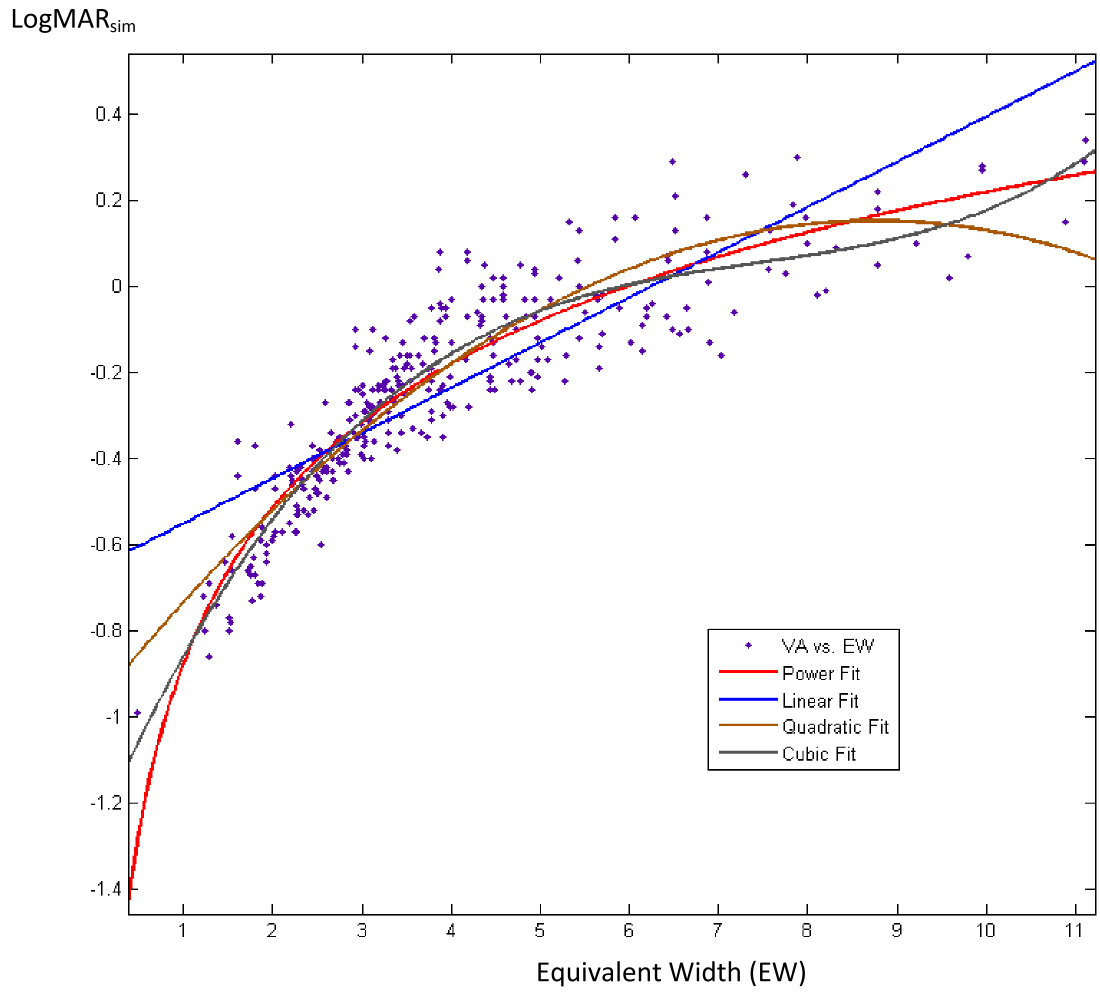


Figure 3-8: Graph showing the various fittings of data gathered with EW metric and $LogMAR_{sim}$ values measured. A linear correlation does not adequately represent the gradual loss in performance with an increase in the metric. Cubic and quadratic fits improve the accuracy of the matching but would not represent the extremes on either end well. A power fit best represents the steep loss in visual performance initially with increasing EW values followed by a more gradual change at higher values.

| 5mm pupil | Microns z(2,2) | 0 | 0.25 | 0.5 | 0.75 |
|---|---|---|---|---|---|
| Diopters z(2,0) | C5 | | | | |
| -1 | | 0.28 | | | |
| -0.75 | | 0.18 | | | -0.02 |
| -0.5 | | 0.16 | | -0.05 | -0.21 |
| -0.25 | | -0.44 | -0.37 | -0.12 | 0.16 |
| 0 | | -0.89 | -0.27 | 0.02 | 0.13 |
| 0.25 | | -0.32 | -0.47 | -0.15 | 0.08 |
| 0.5 | | 0.16 | -0.06 | -0.22 | -0.19 |
| 0.75 | | 0.22 | | | -0.11 |
| 1 | | 0.27 | | | |

Table 3-2: Mean $LogMAR_{sim}$ data for subjects tested with astigmatism, z(2,2), and defocus, z(2,0)

| 5mm pupil | Microns z(3,-1) | 0 | 0.25 | 0.5 | 0.75 | 1 |
|---|---|---|---|---|---|---|
| Diopters z(2,0) | C7 | | | | | |
| -1 | | 0.28 | 0.02 | -0.03 | -0.03 | 0 |
| -0.75 | | 0.18 | -0.05 | -0.08 | -0.16 | -0.17 |
| -0.5 | | 0.16 | -0.27 | -0.31 | -0.21 | -0.24 |
| -0.25 | | -0.44 | -0.44 | -0.45 | -0.37 | -0.3 |
| 0 | | -0.89 | -0.58 | -0.46 | -0.28 | -0.34 |
| 0.25 | | -0.32 | -0.47 | -0.45 | -0.34 | -0.35 |
| 0.5 | | 0.16 | -0.27 | -0.29 | -0.28 | -0.22 |
| 0.75 | | 0.22 | -0.07 | -0.24 | -0.13 | -0.12 |
| 1 | | 0.27 | 0 | 0.02 | 0.03 | -0.12 |

Table 3-3: Mean $LogMAR_{sim}$ data for subjects tested with coma, z(3,-1), and defocus, z(2,0)

| 5mm pupil | Microns z(3,-3) | 0 | 0.25 | 0.5 | 0.75 | 1 |
|---|---|---|---|---|---|---|
| Diopters z(2,0) | C9 | | | | | |
| -1 | | 0.28 | 0.34 | 0.16 | 0.04 | 0.13 |
| -0.75 | | 0.18 | 0.21 | 0.08 | -0.09 | -0.08 |
| -0.5 | | 0.16 | 0.08 | -0.14 | -0.3 | -0.34 |
| -0.25 | | -0.44 | -0.44 | -0.57 | -0.4 | -0.31 |
| 0 | | -0.89 | -0.66 | -0.44 | -0.38 | -0.28 |
| 0.25 | | -0.32 | -0.36 | -0.51 | -0.37 | -0.29 |
| 0.5 | | 0.16 | 0.04 | -0.1 | -0.35 | -0.34 |
| 0.75 | | 0.22 | 0.13 | 0.06 | -0.07 | -0.03 |
| 1 | | 0.27 | 0.29 | 0.11 | -0.07 | 0.06 |

Table 3-4: Mean $LogMAR_{sim}$ data for subjects tested with trefoil, z(3,-3), and defocus, z(2,0).

| 5mm pupil | Microns z(4,0) | 0 | 0.25 | 0.5 | 0.75 | 1 |
|---|---|---|---|---|---|---|
| Diopters z(2,0) | C12 | | | | | |
| -3.75 | | | | | | 0 |
| -3.5 | | | | | | -0.18 |
| -3.25 | | | | | | -0.13 |
| -3 | | | | | | -0.18 |
| -2.75 | | | | | -0.13 | -0.03 |
| -2.5 | | | | | -0.34 | -0.13 |
| -2.25 | | | | 0.26 | -0.38 | -0.23 |
| -2 | | | | -0.07 | -0.19 | -0.04 |
| -1.75 | | | | -0.28 | -0.19 | -0.12 |
| -1.5 | | | 0.3 | -0.38 | -0.3 | -0.16 |
| -1.25 | | | 0.29 | -0.49 | -0.21 | -0.16 |
| -1 | | 0.28 | -0.08 | -0.39 | -0.23 | -0.17 |
| -0.75 | | 0.18 | -0.72 | -0.45 | -0.24 | -0.27 |
| -0.5 | | 0.16 | -0.78 | -0.34 | -0.35 | -0.16 |
| -0.25 | | -0.44 | -0.67 | -0.52 | -0.35 | -0.25 |
| 0 | | -0.89 | -0.8 | -0.43 | -0.37 | -0.19 |
| 0.25 | | -0.32 | -0.73 | -0.57 | -0.25 | -0.24 |
| 0.5 | | 0.16 | -0.69 | -0.4 | -0.4 | -0.16 |
| 0.75 | | 0.22 | -0.64 | -0.57 | -0.39 | -0.24 |
| 1 | | 0.27 | -0.45 | -0.4 | -0.39 | -0.27 |
| 1.25 | | | -0.24 | -0.62 | -0.34 | -0.26 |
| 1.5 | | | -0.07 | -0.56 | -0.48 | -0.4 |
| 1.75 | | | 0.07 | -0.42 | -0.27 | -0.31 |
| 2 | | | | -0.36 | -0.4 | -0.28 |
| 2.25 | | | | -0.2 | -0.45 | -0.43 |
| 2.5 | | | | -0.06 | -0.42 | -0.24 |
| 2.75 | | | | 0.1 | -0.36 | -0.15 |
| 3 | | | | | -0.33 | -0.43 |
| 3.25 | | | | | -0.22 | -0.47 |
| 3.5 | | | | | -0.16 | -0.49 |
| 3.75 | | | | | | -0.35 |
| 4 | | | | | | -0.28 |
| 4.25 | | | | | | -0.19 |
| 4.5 | | | | | | -0.1 |
| 4.75 | | | | | | 0.02 |
| 5 | | | | | | 0.15 |

Table 3-5: Mean $LogMAR_{sim}$ data for subjects tested with spherical aberration, z(4,0), and defocus, z(2,0)

| 5mm pupil | Microns z(6,0) | 0 | 0.25 | 0.5 | 0.75 | 1 |
|---|---|---|---|---|---|---|
| Diopters z(2,0) | C24 | | | | | |
| -4.5 | | | | -0.15 | | |
| -4.25 | | | | -0.16 | | |
| -4 | | | | -0.31 | -0.07 | -0.11 |
| -3.75 | | | | -0.27 | -0.18 | 0.01 |
| -3.5 | | | | -0.35 | -0.24 | 0.03 |
| -3.25 | | | | -0.41 | -0.33 | 0.1 |
| -3 | | | | -0.47 | -0.23 | 0.04 |
| -2.75 | | | | -0.32 | -0.22 | -0.05 |
| -2.5 | | | -0.14 | -0.17 | -0.31 | -0.02 |
| -2.25 | | | -0.23 | -0.1 | -0.36 | -0.23 |
| -2 | | | -0.4 | -0.17 | -0.19 | -0.23 |
| -1.75 | | | -0.27 | -0.24 | -0.02 | -0.22 |
| -1.5 | | | -0.41 | -0.22 | -0.05 | -0.01 |
| -1.25 | | | -0.42 | -0.22 | -0.13 | -0.02 |
| -1 | | 0.28 | -0.59 | -0.45 | -0.27 | -0.22 |
| -0.75 | | 0.18 | -0.46 | -0.57 | -0.42 | -0.28 |
| -0.5 | | 0.16 | -0.3 | -0.19 | -0.12 | 0.09 |
| -0.25 | | -0.44 | 0.24 | -0.05 | -0.09 | -0.03 |
| 0 | | -0.89 | -0.05 | -0.59 | -0.53 | -0.37 |
| 0.25 | | -0.32 | -0.09 | -0.29 | -0.03 | 0.05 |
| 0.5 | | 0.16 | -0.06 | -0.52 | -0.35 | -0.29 |
| 0.75 | | 0.22 | -0.13 | -0.36 | -0.24 | -0.06 |
| 1 | | 0.27 | | -0.74 | -0.42 | -0.24 |
| 1.25 | | | | -0.58 | 0.15 | -0.05 |
| 1.5 | | | | | -0.66 | -0.43 |
| 1.75 | | | | | -0.63 | 0.16 |
| 2 | | | | | -0.29 | -0.55 |
| 2.25 | | | | | | -0.67 |
| 2.5 | | | | | | -0.48 |

Table 3-6: Mean $LogMAR_{sim}$ data for subjects tested with secondary spherical aberration, z(6,0), and defocus, z(2,0)

| 5mm pupil Diopters z(2,0) | Microns z(8,0) C40 | 0 | 0.25 | 0.5 |
|---|---|---|---|---|
| -2 | | | | -0.27 |
| -1.75 | | | | -0.52 |
| -1.5 | | | | -0.53 |
| -1.25 | | | | -0.53 |
| -1 | | 0.28 | -0.09 | -0.07 |
| -0.75 | | 0.18 | -0.6 | 0.05 |
| -0.5 | | 0.16 | -0.8 | -0.69 |
| -0.25 | | -0.44 | -0.12 | 0.06 |
| 0 | | -0.89 | -0.77 | -0.64 |
| 0.25 | | -0.32 | -0.1 | 0.07 |
| 0.5 | | 0.16 | -0.86 | -0.69 |
| 0.75 | | 0.22 | -0.43 | -0.03 |
| 1 | | 0.27 | -0.21 | -0.28 |
| 1.25 | | | 0.00 | -0.41 |
| 1.5 | | | -0.07 | -0.25 |
| 1.75 | | | -0.03 | -0.6 |
| 2 | | | -0.14 | -0.43 |
| 2.25 | | | -0.22 | 0.05 |
| 2.5 | | | -0.21 | 0.19 |
| 2.75 | | | -0.17 | |
| 3 | | | -0.2 | |
| 3.25 | | | -0.13 | |
| 3.5 | | | -0.1 | |
| 3.75 | | | -0.04 | |

Table 3-7: Mean $LogMAR_{sim}$ data for subjects tested with secondary spherical aberration, z(8,0), and defocus, z(2,0)

## Chapter 4

## Spherical Aberration vs. Small Pupil Profiles to Correct Presbyopia

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NIH Grant: K12 EY017269 (ALH)

## Abstract

**Purpose:**

We compared the validity and effectiveness of two methods for expanding depth of focus to correct for presbyopia: induction of spherical aberration and small pupil apertures.

**Setting:**

University of California, Berkeley

**Methods:**

A random four alternative forced choice acuity task was performed on 13 subjects. Visual performance and depth of focus was compared using best adaptive optics (AO) corrected visual acuity values (BCVA) and mean visual acuity over a 3 diopter range of defocus using 3 different AO corrected profiles: 2 mm pupil, 5 mm pupil, and 5 mm pupil with -0.274 microns of spherical aberration.

**Results:**

The 5 mm pupil profile had a BCVA of -0.218 LogMAR and a mean visual acuity through focus of 0.156 LogMAR. The 2 mm pupil profile had a worse BCVA of 0.012 LogMAR but an improved mean visual acuity of 0.061 LogMAR. The 5 mm pupil profile with -0.274 microns of spherical aberration measured a BCVA of -0.082 LogMAR and a mean visual acuity 0.103 LogMAR.

**Conclusions:**

Both spherical aberration and small pupil profiles improve the mean visual acuity across a 3 diopter range of defocus but result in decreased BCVA at the plane of best focus in comparison to an AO corrected 5 mm pupil. Small pupil profiles are a better choice than spherical aberration profiles for presbyopic corrections due to expected accuracy, predictability, and patient satisfaction.

**Introduction:**

With over 1 billion people worldwide requiring near vision correction for their age-related loss of focusing ability, the field of presbyopia research is an area of significant interest in vision care.[1] Bifocal and multifocal contact lenses can help alleviate the dependence on spectacles but are not without disadvantages in comfort and convenience and many people would prefer a one-time surgical procedure that would lead to a permanent solution to near vision blur. Multifocal contact lenses have been found in studies to increase depth of focus, thereby aiding in near vision tasks but this improvement in near vision has been found to cause a reduction in peak visual performance at distance.[2,3]

Both laser vision correction and cataract intraocular surgery can also improve near vision by utilizing multifocality. Laser vision correction can achieve this through the induction of spherical aberration through an ablation pattern using an excimer laser that differentially targets the central and mid-peripheral corneal stroma. Femtosecond treatments such as lamellar keratoplasty or intrastromal cylindrical rings could similarly create conditions of multifocality. Additionally, intraocular lenses allow for an even wider variety of multifocal solutions to loss of near vision.

Monovision is another method that has been used successfully with contact lenses as well as refractive surgery. The success of monovision would depend on the ability and willingness of a patient to both adapt to and accept using one eye for near vision and the other eye for distance vision to achieve a wider range of good vision. The resultant loss of good binocular vision, however, has remained a significant concern for many patients.

Perhaps as early as 1677, Descartes realized that human eye had spherical aberration. In 1801, Thomas Young described an instrument that could demonstrate its existence and now spherical aberration in the eye has been successfully measured and described in significant detail.[4,5,6] It is known that the natural human lens typically exhibits negative spherical aberration,[7] which could cause reduced vision quality if not counteracted by the positive spherical aberration generally measured in the cornea.[8,9] On average, the human population exhibits an overall small amount of positive spherical aberration.[10] There is some suggestion that perhaps the spherical aberration that is present could benefit our natural vision through improved depth of focus.[11] Gou et. al. suggested that spherical aberration would protect against the worsening of contrast sensitivity which occurs in the presence of defocus.[12]

Attempts have been made to apply this understanding of spherical aberration to surgical corrections for improving near vision. Multifocal LASIK ablation profiles create varying curvatures across the surface of the cornea to provide focused light at the retinal plane for both distant and near objects. This lack of a singular focus, however, would cause the image quality to be compromised at all distances but operates on the assumption that it is possible to expand the depth of focus using multifocality with only minor loss in visual performance at distance and near.[13] There is some evidence that these multifocal surface ablations can delay the near vision loss from presbyopia although there might be some loss of peak performance vision.[14,15] Multifocal IOLs function on a similar principle with multiple zones on the artificial implanted lens being designed to focus incoming light on the retina for both distant and near objects. There has been some discussion about whether there exists an amount of spherical aberration which could be placed in an IOL to optimize visual performance.[16,17] Most research, however, concludes that while multifocal IOLs can increase depth of focus, they also reduce contrast sensitivity as well as peak visual performance.[18,19]

Another area of research interest is the effect that small pupil apertures have on increasing depth of focus. It is known that while higher order aberrations increase with age, pupil size decreases.[20,21] Both of these age-related changes could result in a wider depth of focus, although any beneficial effect could be minimal if the resulting peak performance decreased as well. Small aperture corneal implants have been shown to improve near vision in patients by expanding the depth of focus. Some evidence also shows that this method might not produce the same loss in peak performance as is measured with induced spherical aberration.[22,23]

Since both spherical aberration profiles and small pupil aperture profiles are designed to improve near vision by expanding the depth of focus, this study was performed to compare, in the same experimental setting, the vision quality and performance that are obtained through these two methods.

**Methods:**

Participants were obtained through local volunteers and an online recruitment web site. Informed consent was obtained from all participants after written and oral explanations were given regarding possible complications. The experiment was approved by the University of California, Berkeley, Committee for the Protection of Human Subjects and all protocol adhered to the tenets of the Declaration of Helsinki.

Subjects were chosen from a pool of volunteers who reported good ocular health and no significant need for spectacle correction. All subjects were found to have 20/20 or better Best Corrected Visual Acuity. All included subjects were found to have less than 1.0 diopter of refractive error. 13 eyes from 13 subjects (7 males, 6 females) were included in the study with a mean age of 28.1 years (SD = 7.3 years). One subject had previously undergone LASIK refractive surgery but reported good results and had no reported complications. Testing results of the subject who had LASIK surgery were very similar to the other subjects and did not differ significantly in any category.

Each subject was dilated and cyclopleged using 1 drop of 1% tropicamide and 1 drop of 2.5% phenylephrine approximately 20 minutes prior to testing. Additional drops were added to maintain cycloplegia if testing lasted more than one hour. Subjects were tested monocularly with an eye patch covering the non-tested eye. Testing occurred over a period of 90 minutes or less for each subject.

Following dilation, pupil size was selected using an adjustable artificial aperture conjugate to the participant's pupil plane that was calibrated during each session to ensure accuracy. An Adaptive Optics Scanning Laser Ophthalmoscope was used to project a high contrast stimulus on the retina of each participant using an 840 nm infrared low coherence light source.[24,25] Prior to testing, the field size was calibrated using a calibration grid to ensure precise settings for image size. Optimization was performed on the central portion of the grid to prevent distortion of the aspect ratio for horizontal and vertical dimensions that could provide cues for determining letter orientation. Further calibration was performed as described by Rossi et. al. to overcome errors caused by the non-linear scanning velocity of the resonant scanner.[25]

Aberrations were measured using a Shack-Hartmann Wavefront Sensor (HSWS) and best spectacle correction was obtained using spherical and cylindrical trial lenses based on HSWS measurements.[26] A MEMS deformable mirror (140 actuator with 3.5 µm stroke; Boston Micromachines, Cambridge MA) was used to correct or control remaining lower and higher order aberrations and AO performance was gauged by computing the aberrations of the eye using Zernike terms up to the 10$^{th}$ order. Adaptive optics control of the optics was set prior to testing then fixed . It was reset whenever the subject sat out of the instrument or any other time it was deemed necessary. Custom aberration profiles were generated through a GUI menu system which allowed the operator to type in Zernike coefficients for the desired wave aberration. The reference offsets for the Shack-Hartmann spots were set accordingly and the AO system drove the mirror to the reference in closed-loop operation. As such, the desired aberration replaced, and was not added to, each subject's aberrations. To correct all aberrations, the reference was to a flat plane wavefront. The Shack-Hartman wavefront sensor displayed and logged the actual coefficients to allow the user to easily monitor AO performance.

For each trial, participants were presented with a random four alternative forced choice test using a tumbling E Snellen letter at a letter size initially determined to be slightly larger than the predicted threshold. Letters were adjusted in 5 pixel fixed step increments (1 pixel/letter line) in a 1-up, 2 down procedure with a value of 62.5% correct used to calculate threshold values. All visual acuity values were reported in LogMAR units (Logarithm of the Minimum Angle of Resolution, 0.3 LogMAR = 20/40 Snellen Acuity, 0.0 LogMAR = 20/20 Snellen Acuity, etc.).

Participants were shown 40 trials for each defocus value to establish threshold values. Between each series of 40 trials, defocus was added or subtracted in 0.5 D increments using trial lenses. Prior to each series of trials, a best adaptive optics correction was acquired before inserting trial lenses for providing defocus.

Participants were tested for visual acuity over a range of 3 diopters of defocus under 3 separate conditions: AO corrected 5 mm pupil, AO corrected 5 mm pupil with -0.275 µm of Z(4,0) spherical aberration, and AO corrected 2 mm pupil. Visual performance and depth of focus was evaluated using the best adaptive optics corrected visual acuity as well as mean visual acuity across the entire 3 diopter range of defocus values which was measured in 0.5 diopter increments (a mean of the means).

The AO corrected 5 mm pupil was chosen to represent an average pupil that achieved a "perfect" optical correction using a wavefront treatment. Originally, we had intended to use a 6 mm pupil but the deformable mirror was unstable and inconsistent at that size when trying to attach spherical aberration onto the corrected pupil. The AO corrected 5 mm pupil with -0.275 µm of Z(4,0) spherical aberration was chosen based on the above reason and due to results found in the previous chapter. As was noted, negative 0.275 microns of Z(4,0) spherical aberration provided the best mean visual performance across 2 diopters of defocus and negative 0.45 microns of Z(4,0) spherical aberration provided the best mean visual performance across 3 diopters of defocus. The deformable mirror was much more stable and consistent with 0.275 microns of Z(4,0) spherical aberration. A 2 mm pupil was chosen to represent a pinhole pupil due to computations using image quality metrics, limitations in the size range of the artificial pupil, and due to subjective visual performance feedback from participants.

**Results:**

Good optical correction was obtained under the initial condition of AO corrected 5 mm pupil with mean RMS = 0.061 µm (SD = 0.012 µm). Higher order aberrations (HOA) accounted for 85% of residual aberrations with mean RMS = 0.052 µm (SD = 0.010 µm). Under a 2 mm pupil condition, an optical system is near the diffraction limit. AO correction was obtained at 5 mm and was utilized to ensure that no residual defocus or astigmatism remained to interfere with testing. An artificial aperture conjugate to the participant's pupil was then reduced to 2 mm and checked for accuracy. Mean RMS was calculated to be 0.0002 µm (SD = 0.0002 µm) for the 2 mm pupil condition.

Under the Z(4,0) spherical aberration condition with a 5 mm pupil, mean RMS was measured at 0.302 µm (SD = 0.019 µm). Spherical aberration that was applied using the deformable mirror was measured by the HSWS at a mean of -0.274 µm for all participants with a standard deviation of 0.013 µm. This value was determined to be consistent across the 13 participants with only slight variability.

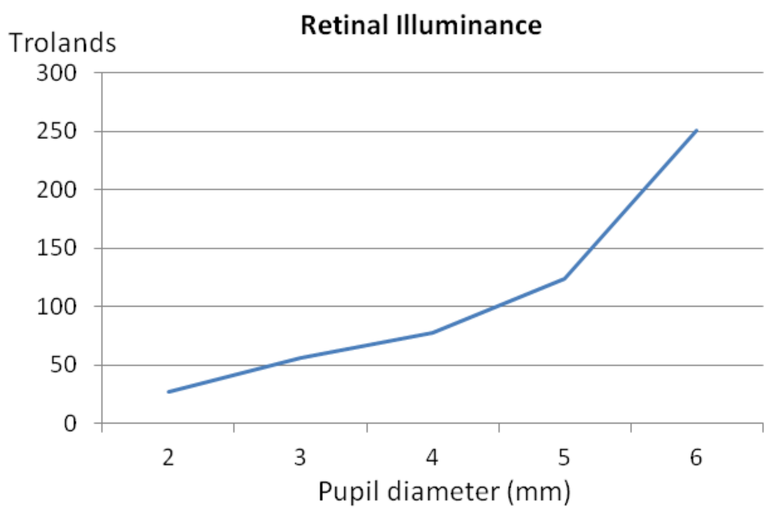



Figure 4-1: Measured retinal illuminance (trolands, y-axis) with change in pupil diameter (mm, x-axis)

Light source levels were held constant regardless of pupil size in order to realistically compare visual performance for each condition. A constant light source level, however, would result in decreased illumination on the retina for smaller pupil sizes. A change from a 5 mm pupil to a 2 mm pupil results in a 6 fold decrease in pupil area and, owing to the slightly Gaussian profile of the entrance beam, a measured 5 fold decrease in the retinal illuminance as measured by a powermeter at the level of the pupil plane (Figure 4-1).

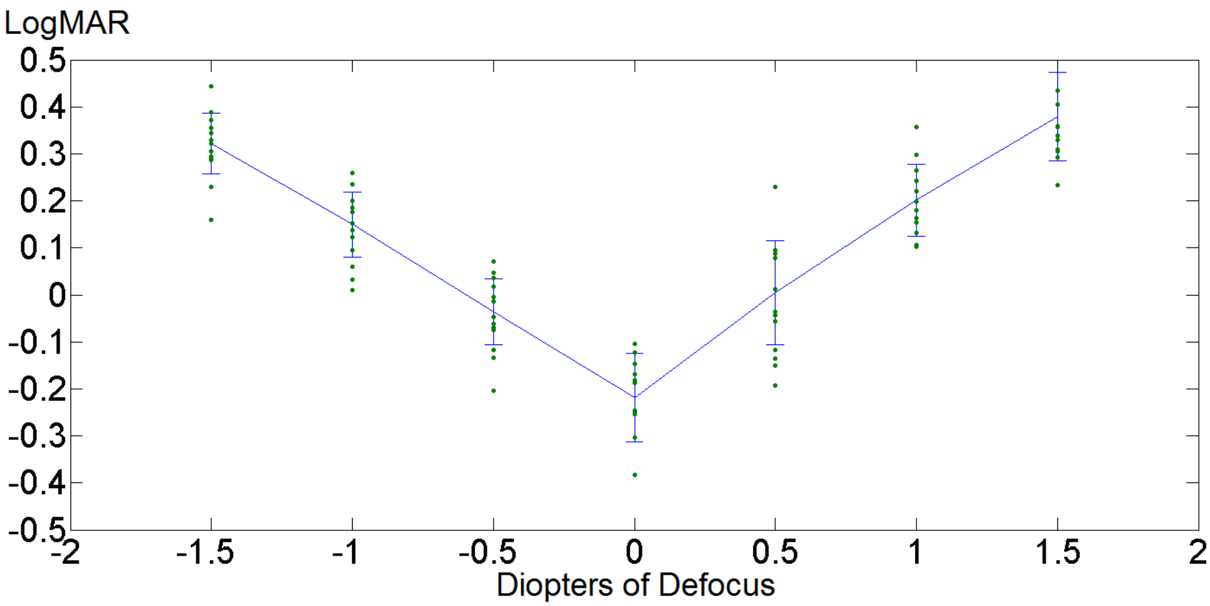



Figure 4-2: Mean visual acuity scores with standard deviations across 3 diopters of defocus along with data points for 13 participants with AO corrected 5 mm pupil, x-axis = diopters defocus, y-axis = LogMAR Visual Acuity

Through-focus visual acuities of participant's under the adaptive optics corrected 5 mm pupil condition adopted a V pattern with best visual acuity obtained at 0 diopters defocus (see Figure 4-2). Mean visual acuity for the 13 participants at best focus was -0.218 LogMAR (SD = 0.095). Mean visual acuity across the entire 3 diopter range of defocus values was 0.156 LogMAR (SD = 0.052).

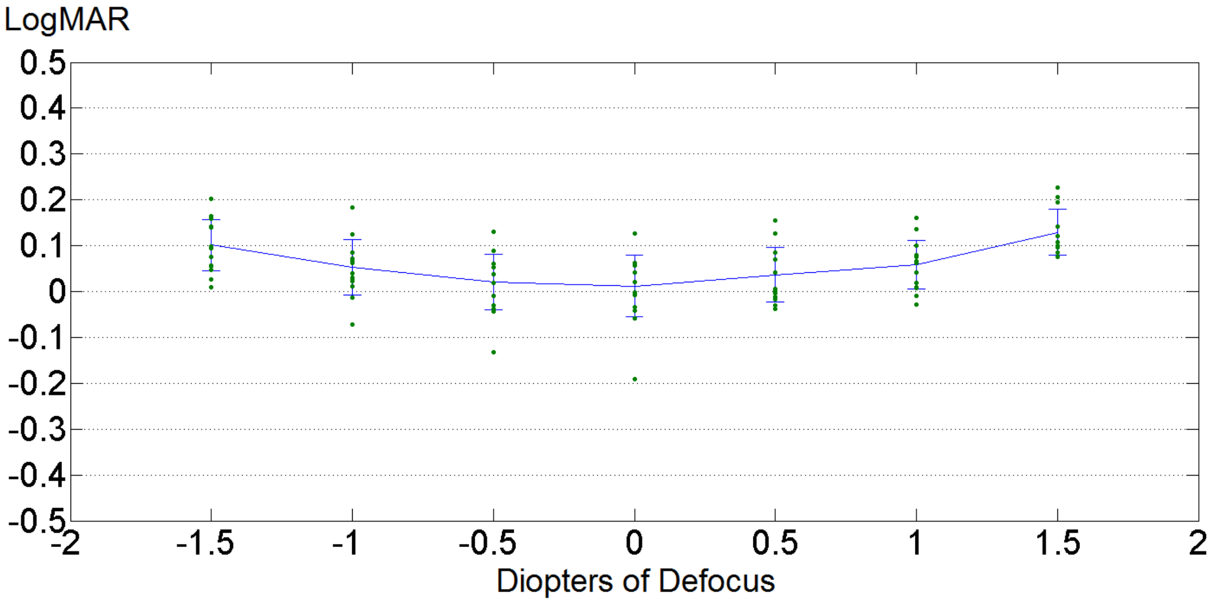



Figure 4-3: Mean visual acuity scores with standard deviations across 3 diopters of defocus along with data points for 13 participants with AO corrected 2 mm pupil, x-axis = diopters defocus, y-axis = LogMAR Visual Acuity

When pupil size was decreased to 2 mm, the through focus curve flattened considerably (see Figure 4-3). Mean visual acuity for the 13 participants at the plane of best focus was still obtained at 0 diopters defocus but worsened to 0.012 LogMAR (SD = 0.067), a two line drop in Snellen visual acuity compared to the 5 mm AO corrected condition. The visual performance remained much more stable through focus and the mean visual acuity across the entire 3 diopter range of defocus values improved to 0.061 LogMAR (SD = 0.041), averaging one line of Snellen acuity better through the entire range of defocus when compared to the 5 mm AO corrected condition.

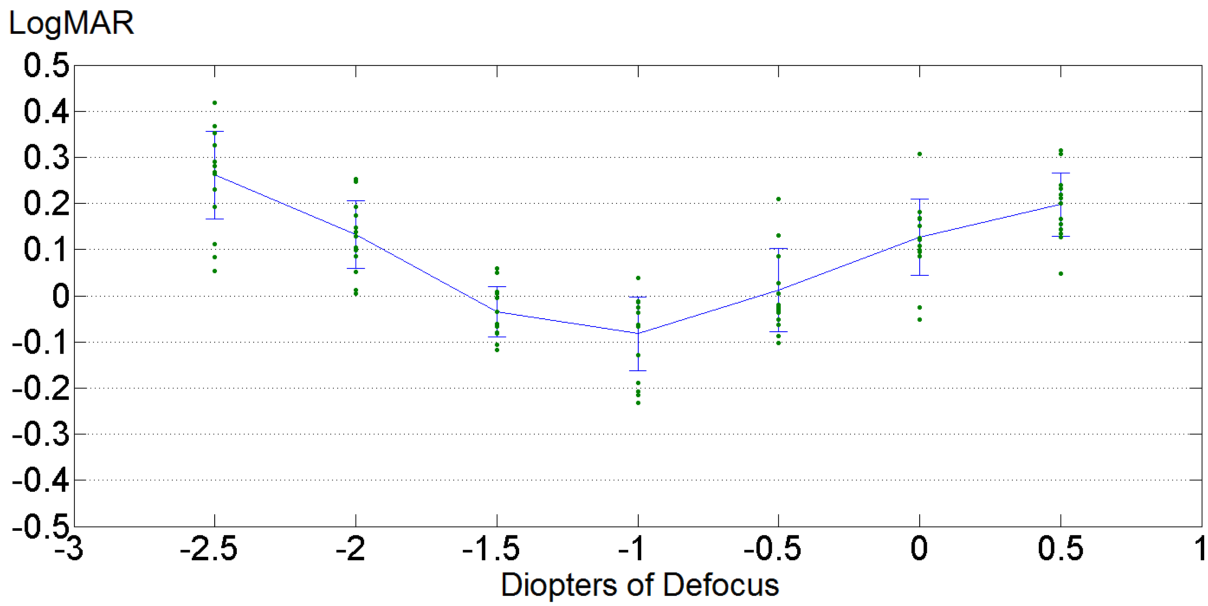



Figure 4-4: Mean visual acuity scores with standard deviations across 3 diopters of defocus along with data points for 13 participants with AO corrected 5 mm pupil with z(4,0) spherical aberration = -0.274 µm, x-axis = diopters defocus, y-axis = LogMAR Visual Acuity

For the AO corrected pupil with added negative spherical aberration Z(4,0) = -0.274 µm, the plane for the best mean visual acuity shifted to -1.0 diopters of defocus (see Figure 4-4). The best visual acuity was almost one line of Snellen acuity better than the 2 mm pupil AO corrected condition but at -0.082 LogMAR (SD = 0.080) was more than one line of Snellen visual acuity worse than without the induced spherical aberration. Mean visual acuity across the entire 3 diopter range of defocus values was improved by a half line of Snellen visual acuity over the AO corrected 5mm condition but a half line of Snellen visual acuity worse than the 2 mm pupil condition at 0.103 LogMAR (SD = 0.040).

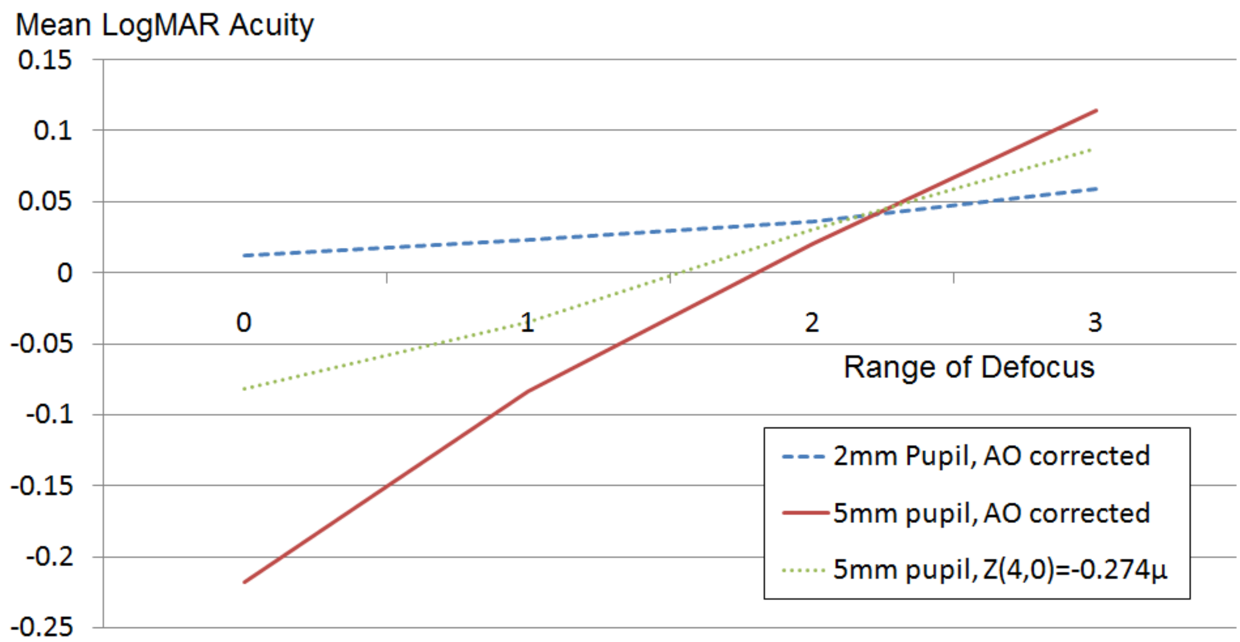



Figure 4-5: Comparison of mean visual acuity for 3 different optical profiles for varying ranges of defocus, x-axis = range of defocus in diopters, y-axis = mean visual acuity across given range of defocus in LogMAR units

While a 3 diopter range of defocus values was chosen to represent a satisfactory depth of focus for an individual wanting to see both distance and near, a smaller or larger range of defocus values could be selected arbitrarily as well. In Figure 4-5, it can be observed that an AO corrected 5 mm pupil (the solid line) provides the best mean visual acuity for all ranges of defocus values until approximately 2.25 diopters range. At that point, a 2 mm pupil (the dashed line) begins to provide a better mean visual acuity value. At no point on the graph does the spherical aberration profile (the dotted line) provide the best mean visual acuity for any range of defocus values.

T-tests revealed that the difference in the best AO corrected visual acuity scores were significantly different for all three groups at the plane of best focus. The AO corrected 5 mm pupil (LogMAR = -0.218) was better than the AO corrected 5 mm pupil with Z(4,0) = -0.274 (LogMAR = -0.082) with p=0.0014 and better than the AO corrected 2 mm pupil (LogMAR = 0.012) with p<0.00001. The AO corrected 5 mm pupil with Z(4,0) = -0.274 (LogMAR = -0.082) was better than AO corrected 2 mm pupil (LogMAR = 0.012) with p=0.006.

T-tests also revealed that the difference in mean visual acuity scores across 3 diopters of defocus were significantly different for all three groups as well. The AO corrected 2 mm pupil (LogMAR = 0.061) was better than the AO corrected 5 mm pupil with Z(4,0) = -0.274 (LogMAR = 0.103) with p=0.018 and better than the AO corrected 5 mm pupil (LogMAR = 0.156) with p=00013. The AO corrected 5 mm pupil with Z(4,0) = -0.274 (LogMAR = 0.103) was better than AO corrected 5 mm pupil (LogMAR = 0.156) with p=0.014.

**Discussion:**

The results of the experiment showed that the 2 mm pupil profile provided a significantly better mean visual acuity than either the 5 mm AO corrected pupil profile or the 5 mm pupil profile with -0.274 µm spherical aberration. The 5 mm spherical aberration profile did not offer an improvement in mean visual acuity over the AO corrected 5 mm pupil until the range of defocus was greater than 2.25 diopters. At no range of defocus values was the mean LogMAR acuity for spherical aberration profile superior to both the 2 mm AO corrected pupil and the 5 mm AO corrected pupil value (Figure 5).

While objective image quality metrics have shown accuracy in predicting subjective image quality, variability found in individual subjects and the added variability of changing pupil sizes and resulting light levels can decrease their predictive validity. Because of this, subjective testing remains an important step to compare the effects of spherical aberration and small pupil apertures on vision across a range of defocus values.[27,28,29]

In comparing different pupil sizes, it should be remembered that smaller pupils reduce the amount of light that enters the aperture and cause the stimulus to have reduced signal-to-noise compared to larger pupil sizes. A similar experiment could be performed in which perceived stimulus brightness was kept constant by increasing the laser light source. In this experiment, the 840 nm light source was already at maximum brightness in order to provide maximum contrast in the 5 mm pupil conditions. It was, therefore, not possible to increase illumination in the 2 mm pupil condition to match the perceived brightness of the 5 mm pupil conditions. It is expected that increasing the illumination for the 2 mm pupil conditions would increase visual performance for all defocus values by increasing contrast levels. Visual performance at the plane of best focus would still be expected to be would be worse than the AO corrected 5 mm pupil since the 2 mm pupil condition is more limited by diffraction. Clinically, with good illumination and a high contrast visual acuity chart it is possible to achieve Snellen visual acuities of 20/20 or even 20/16 when viewing through a 2 mm artificial aperture so it would be expected that a 2 mm pupil could achieve improved LogMAR acuity at the plane of best focus with increased luminance.

It should be noted that surgical or optical corrections that rely on small pupils to provide improved depth of focus could cause a worsening of visual function in areas of low lighting due to this significant decrease in retinal illuminance. This would be particularly debilitating for individuals who have cataracts or other optical media opacities. Since presbyopia onset is an early precursor to cataract formation, a surgical or pharmaceutical treatment which induces small pupils would require a careful ocular examination to determine if the patient would be an acceptable candidate for such a procedure. It might be added that while the contrast sensitivity loss that occurs with age worsens with higher spatial frequencies, there is evidence that the gradual miosis that occurs with age has a measurable positive effect on contrast sensitivity.[30]

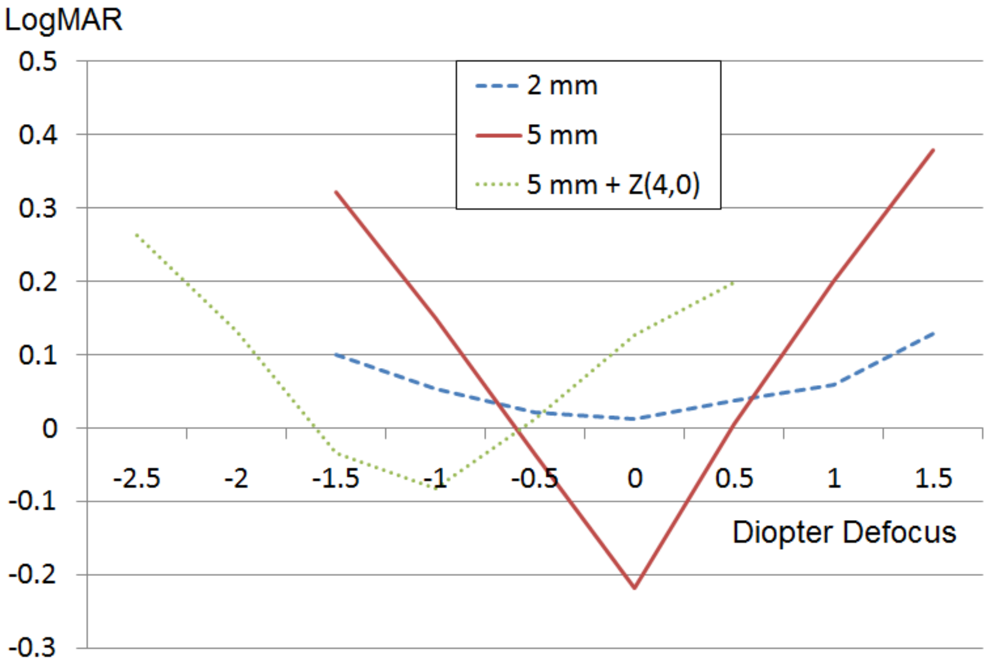



Figure 4-6: Comparison of mean visual acuities of 13 participants for all 3 tested conditions for 3 diopter range of defocus, x-axis = defocus in diopters, y-axis = visual acuity in LogMAR units

Although spherical aberration was shown to increase depth of focus, the amount of improvement may not be considered significant enough to justify the loss in best corrected visual acuity (see Figure 4-6). Measures of depth of focus (such as width at 50% threshold) often rely on the peak value, the maximum visual acuity level in this case. Spherical aberration lowers the peak value and would therefore artificially expand the depth of focus by changing the point at which the width is measured. Spherical aberration also causes a shift in the plane of best focus as seen in Figure 4-6. In this case, negative spherical aberration can be partially corrected with negative defocus.

A small pupil (2 mm in this case) would be the easier solution to implement and would be more predictable and uniform across a target population. The effect of a small pupil in reducing blur can be illustrated by a simple formula for the blur aspect ratio (BAR). Eq. BAR= p x D where p = pupil diameter in mm and D = defocus in diopters. The resulting blur is labeled in units of milliradians. The amount of blur caused by defocus would therefore decrease directly with the size of the pupil.

A small (2 mm) pupil will approach the diffraction limit and would virtually neutralize all inherent higher order aberrations except in extreme circumstances, such as keratoconus or other conditions causing high levels of wavefront distortions. In contrast, higher order aberrations have been extremely difficult to correct using wavefront-guided surgical corrections with either laser vision corrective procedures (such as LASIK) or intraocular implants. Despite the advancements in wavefront-guided technologies over the past decades, wavefront surgical corrections have failed to show evidence of a predictable and uniform reduction in higher order aberrations.[31,32] It follows that the ability to generate a specific level of aberration in the eye would be equally difficult.

Spherical aberration would be less effective in increasing depth of focus in the presence of other higher order aberrations and therefore requires the capacity to minimize other existing aberrations to be effective. Current surgical wavefront corrections continue to measure similar or greater levels of post-operative aberrations.

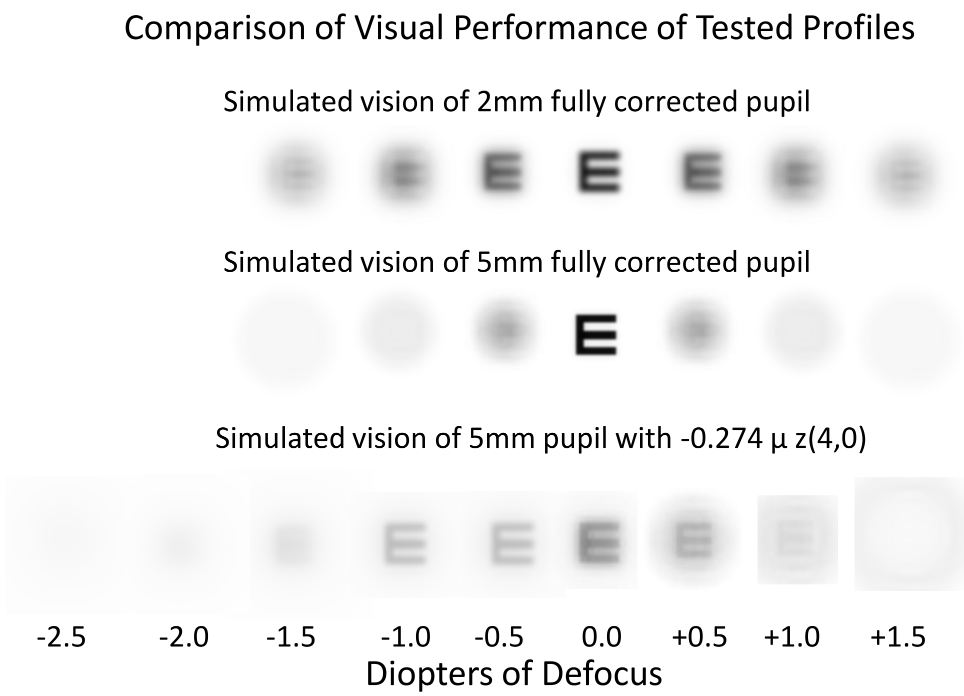
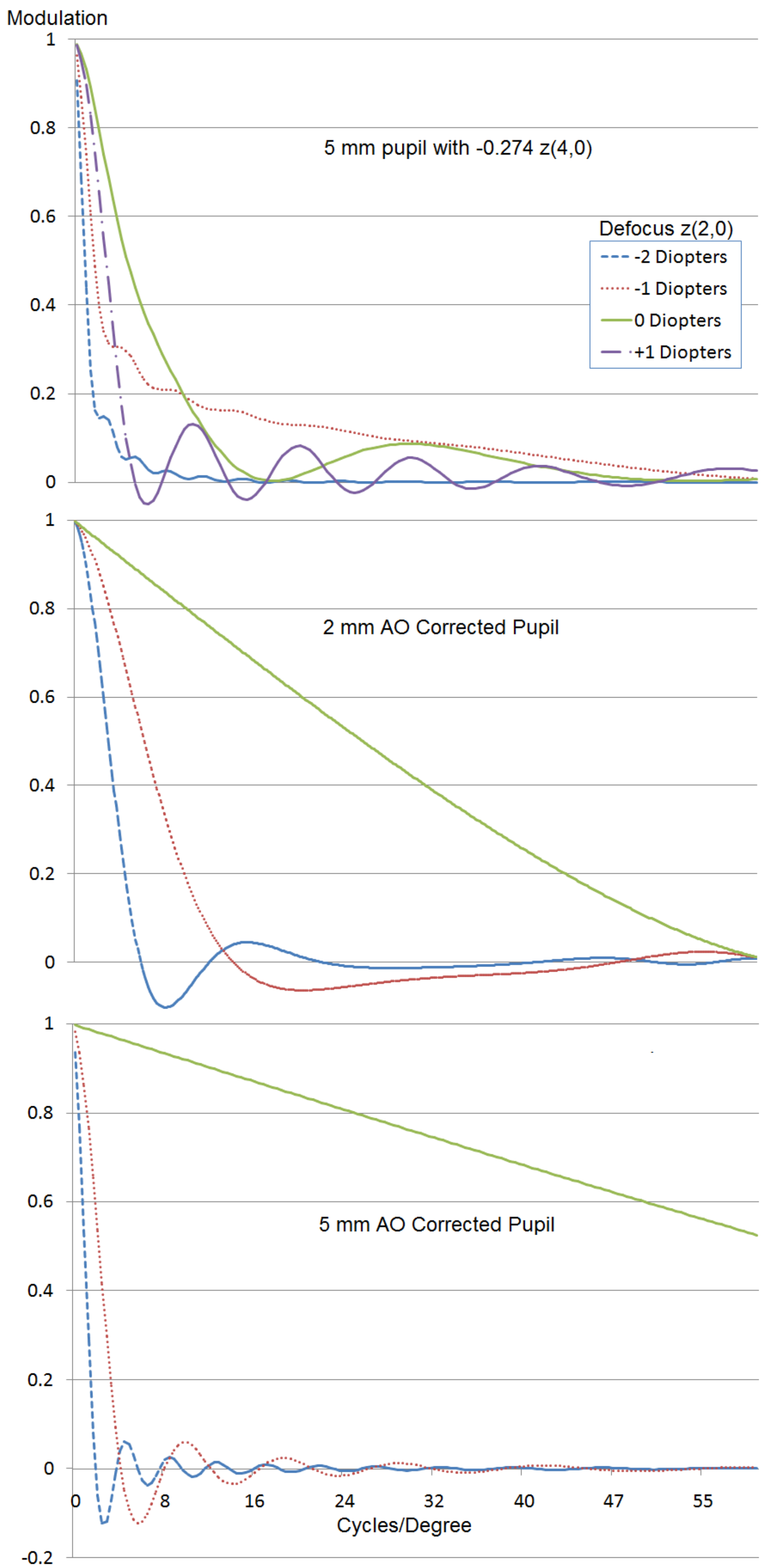



Figure 4-7: Simulated vision through 3 tested profiles. 20/20 Snellen E letter (0 LogMAR) was convolved with point spread function of each condition through focus.

Even if spherical aberration could be successfully applied to the human visual system in isolation, the blur from this specific aberration is asymmetrical, varying with positive and negative defocus. By comparison, the blur for a small pupil is symmetrical, identical with positive and negative defocus, and involves a simple reduction in contrast. Figure 4-7 shows the difference in legibility created by spherical aberration versus a small pupil for a 20/20 Snellen letter.



Modulation
1
0.8
0.6
0.4
0.2
0
5 mm pupil with -0.274 z(4,0)
Defocus z(2,0)
-2 Diopters
-1 Diopters
0 Diopters
+1 Diopters
1
0.8
0.6
0.4
0.2
0
2 mm AO Corrected Pupil
1
0.8
0.6
0.4
0.2
0
-0.2
5 mm AO Corrected Pupil
0
8
16
24
32
40
47
55
Cycles/Degree

Figure 4-8: Simulated Modulation Transfer Functions for 5 mm pupil, 5 mm pupil with negative spherical aberration (-0.274 µm), and 2 mm pupil. X-axis represents spatial frequencies in cycles/degree. Y-axis represents modulation for given spatial frequencies.

In our experiment, the majority of participants reported a subjective visual preference for the small pupil profile over the profile with induced spherical aberration although the reduction in illumination for the 2 mm pupil profile was described as problematic. There were a minority of subjects who reported a subjective visual preference for the brighter more distorted stimulus produced by the spherical aberration profile compared to the dimmer but more uniform stimulus of the 2 mm pupil. The uniformity of the stimulus across defocus levels and across spatial frequencies for the 2 mm pupil profile can be demonstrated by examining the Modulation Transfer Function (MTF). As seen in Figures 4-8, the MTF fluctuates much more dramatically over the range of defocus values for the profile with spherical aberration compared to the 2 mm pupil profiles. The MTF graphs demonstrate that the 2 mm profile shows very few contrast reversals across 1 or 2 diopters of defocus. In contrast, the 5 mm profile with negative spherical aberration shows frequent contrast reversals across spatial frequencies in the presence of defocus, exhibiting a lack of uniformity in vision across the range of defocus values which may not be satisfactory.

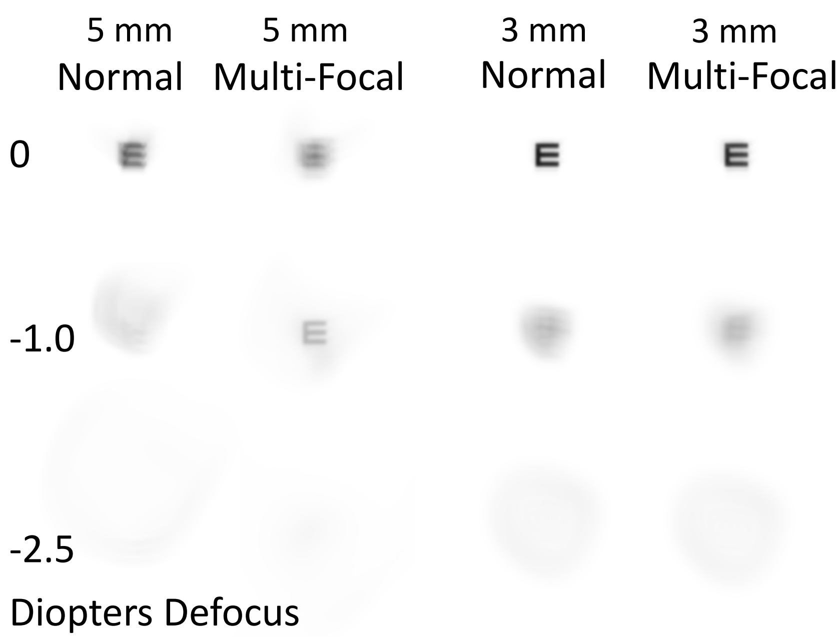



Figure 4-9: Simulated vision for a normal wavefront profile and a normal profile with added spherical aberration (-0.274µm for 5mm pupil). 20/20 Snellen E letter (0 LogMAR) was convolved with point spread function with 0, -1.0, and -2.5 diopters of defocus.

It should also be noted that while a 2 mm pupil provided inferior visual quality at the best focal plane when compared to an AO corrected 5 mm pupil (a 2 line difference in Snellen acuity), this comparison would be unlikely to occur in a clinical setting as the average eye has significant aberrations which can reduce vision quality in comparison to the more ideal AO corrected condition. In Figure 4-9, it is shown that for individuals with normal wavefront aberration profiles there is an improvement in distance vision (0 diopters defocus) when the pupil size decreases from 5 mm to 3 mm. It is also observable that when negative spherical aberration is added to a normal 5 mm wavefront profile, there is an improvement at the intermediate range of vision (-1.00 diopters defocus). This improvement is negated however if the pupil size is reduced down to 3 mm. This leads to two conclusions. First, individuals with large pupils and/or greater than normal levels of higher order aberrations could realistically expect to observe a significant improvement in BCVA with a 2 mm pupil. Second, multifocal wavefront profiles would not add significant value to intermediate or near vision for patients with smaller pupils (less than 4 mm). Since pupil size decreases with age[33], this would hinder efforts to correct presbyopia with a multifocal solution, particularly since higher order aberrations also tend increase with age.[34] Multifocal solutions which use diffractive corrections would be less influenced by pupil size but would not be unaffected.

**Conclusions:**

Both spherical aberration and small pupil profiles were shown to be valid methods of increasing depth of focus although both also resulted in decreased visual acuity at the plane of best focus compared to an AO corrected 5 mm profile. For presbyopia corrections that rely on an improved depth of focus to improve near vision, it would have to be considered whether the loss in best corrected visual acuity is an acceptable tradeoff for the improvement in near vision that is produced with the expanded depth of focus. In this study, no tested profile was able to achieve a mean visual acuity of 0 LogMAR (20/20 equivalent Snellen Acuity) across an entire 3 diopter range of defocus.

The 5 mm pupil profile with spherical aberration produced a better peak visual acuity but smaller depth of focus compared to the 2 mm pupil profile. The 2 mm profile decreased illumination levels resulting in decreased contrast but produced an image that was more uniform across spatial frequencies and less variable through-focus as demonstrated by the Modulation Transfer Function. Due to an inability to consistently and accurately change, correct, and/or induce desired levels of higher order aberrations in refractive surgery, it is concluded that small pupil profiles are a better choice than spherical aberration profiles for surgical presbyopic correction. A correction utilizing a small pupil profile would be more predictable and uniform in its vision results and would therefore provide greater patient satisfaction if expectations were managed appropriately.

**What Was Known:**

- Spherical aberration and small pupils have been shown to increase the depth of focus.

**What This Paper Adds:**

- Small pupils increase depth of focus more than spherical aberration.
- Small pupil apertures will be both more predictable and more effective in presbyopia correction than the application of spherical aberration.

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# Chapter 5

# The Future of Presbyopia Correction

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## Summary

Presbyopia correction is viewed by many as the "Holy Grail" of vision research. Over 1 billion people globally require near vision correction for their loss of focusing ability due to age. While bifocals, progressive lenses, and spectacle readers are the most common visual correction for presbyopia in use today, many people find the necessity to depend on glasses to be either inconvenient or bothersome. Bifocal and multifocal contact lenses are commonly prescribed as well, and have been found by many to aid in near vision tasks. Contact lenses are also not without disadvantages in comfort and convenience and many people would prefer a one-time surgical procedure that would lead to a permanent solution to near vision blur. Surgical presbyopia treatments are becoming more popular with the advent of laser surface ablation, most commonly LASIK, along with more advanced designs for intraocular lenses (IOLs) used in cataract surgeries.

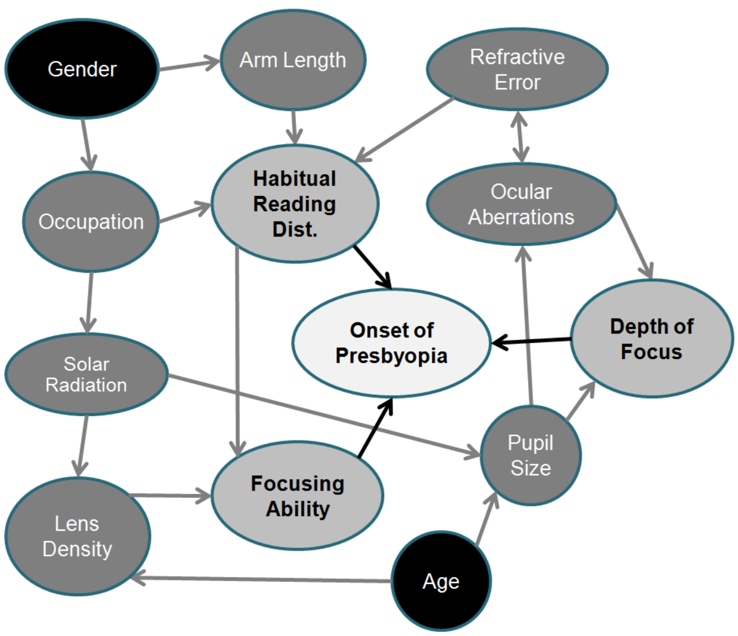


Figure 5.1: Directed acyclic graph of the causes of presbyopia.

In chapter 1, I presented an acyclic graph which represents the possible etiologies of presbyopia (repeated here as Figure 5.1). Three primary factors, focusing ability, habitual reading distance (or the preferred distance for near tasks), and depth of focus (the tolerance of an optical system such as the eye to defocus), contribute directly to the development and diagnosis of presbyopia. Secondary factors can also influence the onset of presbyopia include occupation, refractive error (and other ocular aberrations), arm length, pupil size, and possible differences in lens optical density. Other tertiary factors that could lead to differences in onset time of presbyopia include solar radiation, complexity of near tasks, indoor light levels, and/or other task specific conditions.

Current surgical methods for correcting presbyopia are generally accomplished through one of four possible methods: monovision, multifocality, small pupil, or accommodation restoration. Looking at the acyclic graph (Figure 6.1), monovision depends on the ability of a patient to adapt to using one eye for near vision and the other eye for distance vision and would correct presbyopia by adjusting the refractive error of one eye. This would adjust the focus of one eye towards the habitual task distance and allow the current depth of focus to be more effective in near vision. Both multifocality and small pupil act to correct presbyopia by increasing the depth of focus, one of the primary factors in the onset of presbyopia. The final method for correcting presbyopia that has been attempted surgically is to restore accommodation to increase focusing ability, another factor in the onset of presbyopia.

Monovision has been popular with patients over 40 who are willing to sacrifice binocularity to achieve greater freedom from spectacles. LASIK often utilizes the monovision option to achieve a wider range of good vision. Monovision can be similarly applied in cataract surgery by placing a slightly higher powered artificial lens in one eye that results in a low degree of myopia monocularly. Patients who have not yet developed cataracts can also undergo the same technique of monovision through refractive lens exchange.

Multifocality is another popular option, particularly in cataract surgery. Chapters 2 and 3 showed that multifocality can be successful in increasing the depth of focus but can be limited by pupil size. Since age and light levels directly affect pupil size, these factors must be considered. Another option for correcting presbyopia is the use of a small pupil aperture. Small pupils can correct for presbyopia by increasing the depth of focus although this would also cause a decrease in retinal illumination.

The final option for correcting presbyopia is through accommodation restoration to increase focusing ability. Various methods have been tried to achieve this. Scleral expansion attempted to surgically restore restoration by increasing the tension on the zonules. This method has not shown itself to be successful and has generally been abandoned. Eye exercises to increase the strength of the ciliary body and various pharmaceutical and homeopathic eye drops have also shown no success. Current research is exploring accommodative IOLs, femtosecond lentotomy (to increase malleability of the crystalline lens), and injectable fillers into the lens capsule following cataract removal in attempts to restore accommodation.

## Future Directions

An ideal solution to correct presbyopia would be permanent and provide excellent vision at distance, intermediate, and near. It would be convenient with no side effects and would allow full binocular vision. In effect, it would provide us with the vision that we had when we were in our teenage years. Currently, there are no options that provide this type of vision.

While both multifocality and small pupil can improve the depth of focus, this alone will not achieve the needed benefits for an ideal solution. In the future, both of these methods will be improved upon with better designs and more acceptable results but it is unlikely that either method will survive if a treatment is obtained that can restore accommodation.

Monovision has been successful with many patients who are satisfied with the results, having obtained greater freedom from spectacles. Will this form of treatment continue to be used? The future will most certainly include more 3-D movies and entertainment as technology in this medium improves. 3-D entertainment might be hindered by monovision in situations where each eye is presented with a different image to obtain a 3-D perspective. If one eye sees blurry at distance, it would be difficult to attend a 3-D movie and enjoy the display unless the viewer wore spectacles to correct the myopic eye in order to see distance.

The future of presbyopia correction most certainly lies in the direction of accommodation restoration although this might still be decades away. Current IOL technology often relies on the integrity of the capsular bag and the requirement that the ciliary body is still capable of producing changes in the capsule that will cause a refractive shift with an IOL that is designed to change powers. Current results show how difficult it is to translate changes in ciliary muscle contraction, into shifts in refractive power of an artificial lens.

Future corrections might change focus of the implementation of accommodation restoration onto direct reaction to the contraction of the ciliary muscle itself or onto the nerve impulses which caused the contraction. Presbyopia has been with us for as long as mankind has been on the earth yet we still are just beginning to understand its causes. Future studies of presbyopia should take a multi-factorial approach, gathering information such as higher order aberrations, pupil size, preferred task distances, and environmental exposures. The interaction between depth of focus, preferred reading distance, and accommodative amplitude is overlooked even by professional researchers.

**Appendix B**

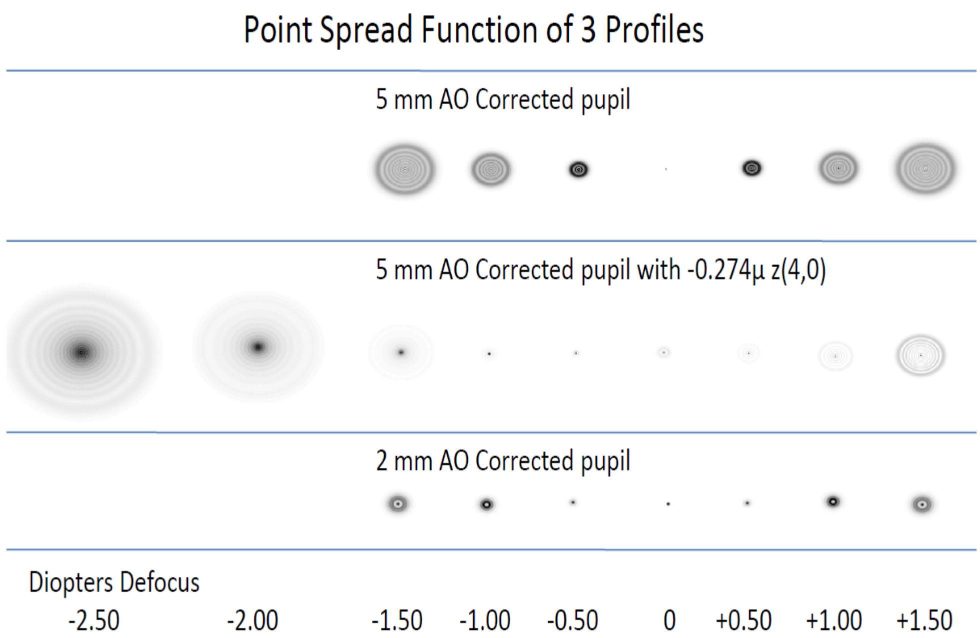


Figure 6-1: Point spread function of 3 optical profiles. 5 mm AO corrected pupil (top), 5 mm AO corrected pupil with -0.274 µm z(4,0) (middle), and 2 mm AO corrected pupil (bottom)

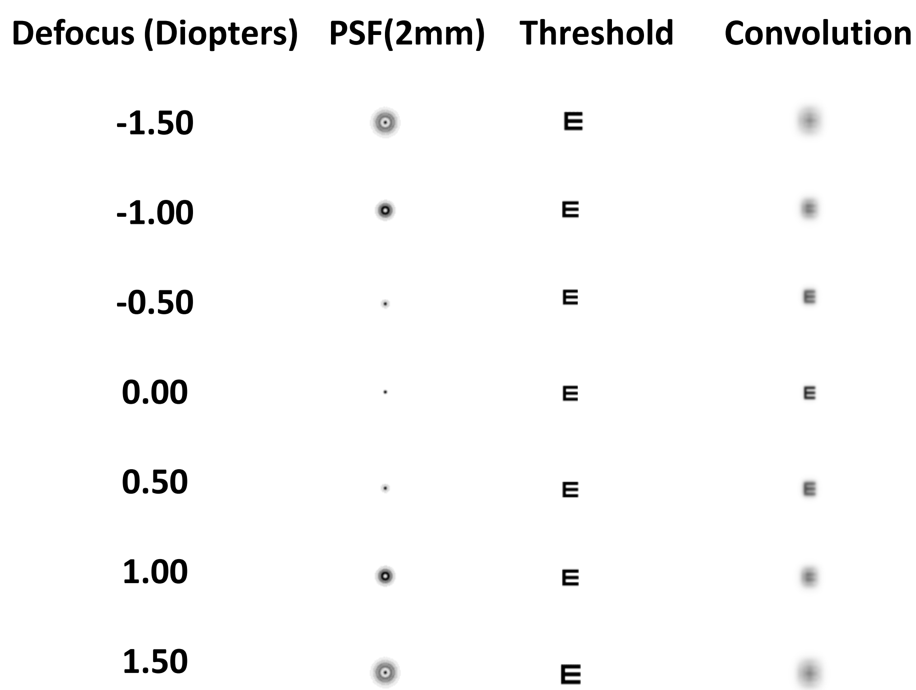


Figure 6-2: Point spread function (PSF) of 2 mm pupil with only defocus. Threshold letter size achieved in Adaptive optics testing. Convolution of PSF with threshold size letter. The amount of contrast that remains for these letters at threshold will not be reproduced well in this document. In the experiment, there was a greater depth of contrast.

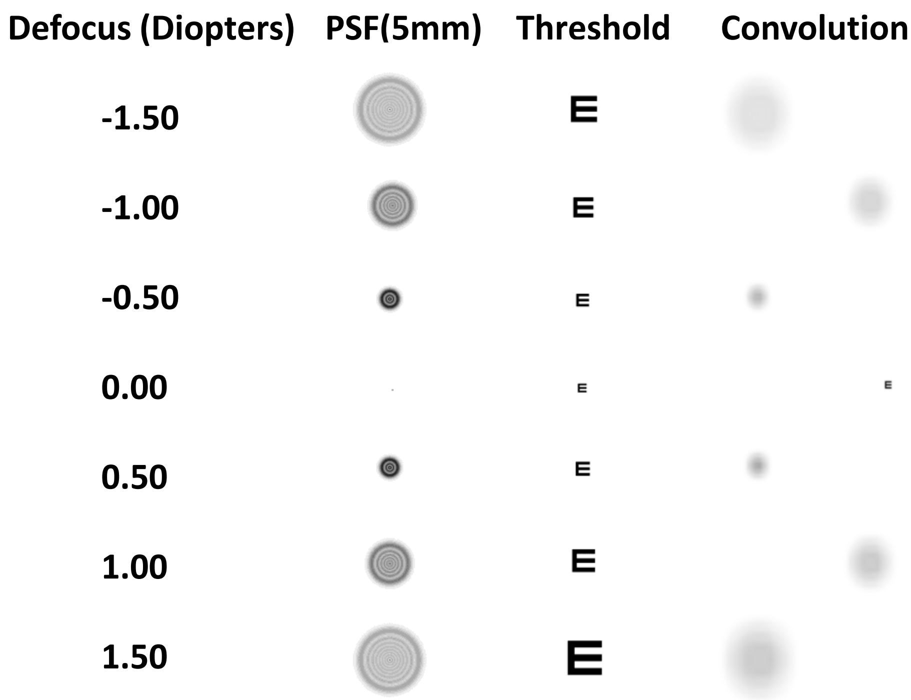


Figure 6-3: Point spread function (PSF) of 5 mm pupil with only defocus. Threshold letter size achieved in Adaptive optics testing. Convolution of PSF with threshold size letter.

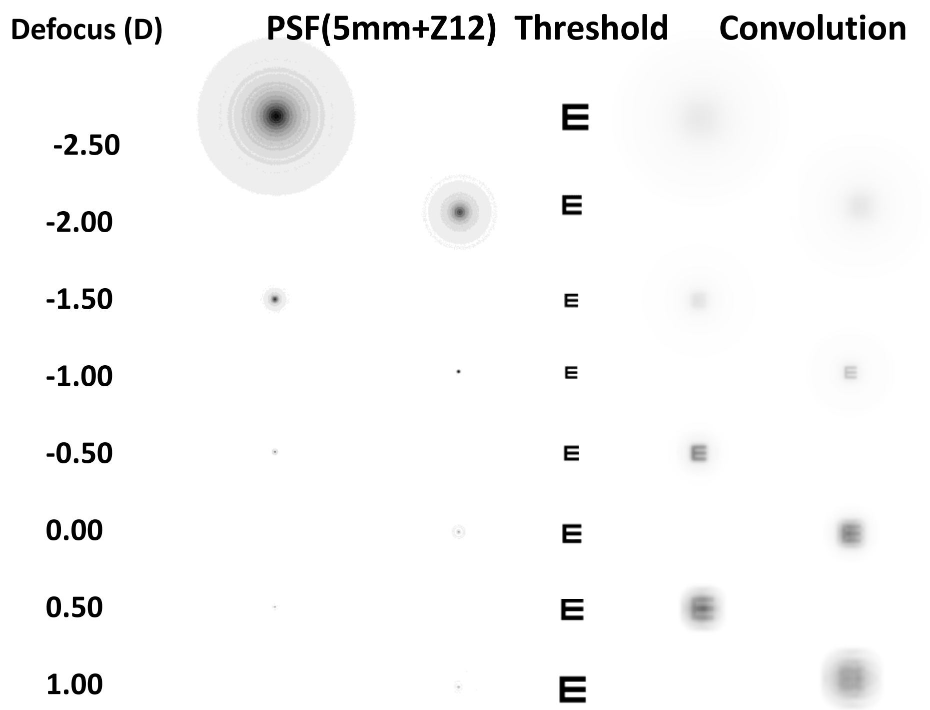


Figure 6-4: Point spread function (PSF) of 2 mm pupil with only defocus. Threshold letter size achieved in Adaptive optics testing. Convolution of PSF with threshold size letter.

**Appendix C**

## The Effect of Higher and Lower Order Aberrations on Best Mean Visual Acuity across a 2.5 Diopters Vergence Range

Paper Presented at ARVO 2010

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Austin Roorda, School of Optometry, University of California, Berkeley

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### Abstract

**Purpose:** We present an efficient and principled way to find the best aberration profiles that relieve focus problems with presbyopia. First, we define a specific task. Then, we find the aberration profile that will provide the best performance on that task. The specific task for presbyopia relief is to optimize vision from infinity to a 40 cm viewing distance (0 to 2.5 diopters vergence range) The metric we chose to optimize is the Best Mean Visual Acuity (BMVA) over that range, assessed experimentally and by computation.

**Methods:** A random choice visual performance experiment was performed using 20 Snellen letters presented on an 11-bit display monitor. Letters were convolved with the PSF of 0.25µm step Zernike aberrations (c5, c6, c7, c12, c24, and c40) and 0.25 diopter defocus steps for a 5 mm pupil. Visual performance for each PSF was measured for each Snellen Acuity letter size, which ranged from 20/40 and smaller but was magnified, after blurring, to 20/200 to decouple the size aspect (minimizing effects of viewer's aberrations and negating limits of photoreceptor spacing). A power fitting was used to correlate subjective performance with calculated Strehl Ratio of aberration profile (r=0.879). BMVA was computed as the highest average acuity value across a 2.5 diopters vergence range for each aberration profile.

**Results:** Decoupling size from blur resulted in higher acuities than standard testing due to an absence of limiting factors such as photoreceptor spacing. All aberrations tested increased BMVA scores across a 2.5 diopters vergence range. Correlation between experimental results and predicted values for BMVA across 2.5 diopters was r=0.932. Primary spherical aberration (c12) showed the highest BMVA values followed by secondary and tertiary spherical aberration (c24 and c40). Astigmatism (c5) and then Trefoil (c6) showed the lowest values for BMVA for the Zernike aberrations tested.

**Conclusion:** Using BMVA as a measurement of visual performance for a specific vergence range allows direct comparison of various aberration profiles. Using this metric for depth of focus provides an efficient way to compute the best aberration profile for a 2.5 diopters vergence range.

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