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Age variation in nerve fibre layer thickness in the optic nerve papilla

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Table of contents

Abstract	2
Populärvetenskaplig sammanfattning.....	3
Background.....	5
Glaucoma.....	5
Clinical diagnose and measurement methods	5
Optical Coherence Tomography OCT	7
The Pigment epithelium central limit - Inner limit of the retina Minimal Distance (PIMD).....	9
Aim.....	12
Hypothesis to be tested.....	12
Study design	12
Method	13
Subjects	13
Procedure	13
Data analysis.....	13
Statistical parameters.....	14
Results	15
PIMD loss rate.....	19
Discussion	22
Results	22
Method	22
Future	23
Conclusions.....	23
Acknowledgements	23
References.....	24

Abstract

Background: The nerve fibre layer thickness, or loss of thickness, in the papilla relates to the severity of the neuropathy of the retinal ganglion nerve cells and therefore the degree of glaucoma which is the clinical related disease. Glaucoma, that leads to visual field defects and stands for 8 % of the global blindness, is diagnosed and followed-up by computer aided perimetry, a method which is time consuming and whose result depends highly on the quality of the participation of the patient. OCT, optical coherence tomography, gives a non-subjective 3D-picture of the papilla. The OCT scan is instant with minor reliance of the participation of the patient. As of today, there is no consensus on what and how to measure the nerve fibre layer thickness in order to put forward a clinical usable measurement for diagnosing and evaluating glaucoma. Uppsala university has developed an application that automatically measures the Pigment epithelium central limit - Inner limit of the retina Minimal Distance (PIMD) for 500 radii around the optic nerve papilla with the information from an OCT scan as input. As a new measurement method there is a need to understand the natural variations and progression, e.g. to be able to determine reference ranges for different patient groups.

Purpose: To find an age variation in the nerve fibre layer thickness in the optic nerve papilla.

Method: In this cross-sectional study the PIMD for four age groups, 20 [30, 30 [45, 45 [65 and 65]85, with six subjects each, were compared in order to find any variations. The subjects were all healthy, with no retinal associated disease. Three OCT scans were taken for each subject at one occasion. The 500 radii were sorted in eight sectors of the papilla and compared.

Results: No significant, 95 % confidence interval, age dependent decrease of the overall nerve fibre layer thickness (PIMD- 2π) was found. Significant decrease was found for four sectors of the papilla; nasal inferior -1.55 $\mu\text{m}/\text{year}$ (+/- 1.53), inferior temporal -1.62 (+/- 1.06), temporal inferior -1.17 (+/- 0.74) and temporal superior -0.85 (+/- 0.76).

Conclusion: This study cannot verify an age dependent significant loss of overall thickness of the nerve fibre layer of the papilla. There is an age dependent decrease that affects sectors of the papilla, indicating the existence of an overall decline.

Populärvetenskaplig sammanfattning

OCT, optical coherence tomography, skulle man kunna kalla "ljus-ultraljud". Istället för ljudsignaler används ljus som liksom ljud reflekteras olika på olika ytor och material, reflektionsmönstret ger en bild av materialet som undersöks. Till skillnad från ultraljud har OCT mycket större upplösning och ger bättre bilder, dock är tekniken mycket känsligare och kräver ett orörligt material som, i någon mån, släpper igenom ljus. Dessa villkor uppfylls av ett stilla, fokuserande öga och OCT har således kommit att användas inom ögonkliniken, främst för att få en bild av näthinnan längst bak i ögongloben. Genom bilderna kan man upptäcka skador och anomalier som påverkar synen, diagnos kan ställas och behandling sättas in.

Glaukom är en ögonsjukdom som påverkar näthinnan och där man försöker att använda OCT för att ställa diagnos och följa upp patienter. Vid glaukom försämras synen genom att synfältet gradvis minskar på grund av att syncellernas nervtrådar dör, i värsta fall leder sjukdomen till blindhet. Behandlingen, i form av ögondroppar eller operation för att minska trycket i ögonen, syftar till att stoppa eller bromsa sjukdomsutvecklingen. Förlorad syn går inte att återställa. Det är viktigt att patienterna följs upp för att utvärdera behandlingen, justera medicineringen eller initiera operation. Uppföljningen görs m.h.a. standardiserad datorperimetri där patienten får trycka på en knapp när ett ljussken syns i synfältet. Denna undersökning tar tid och påverkas mycket av patientens kvaliteter och dagsform. En effektiv objektiv mätmetod är önskvärd både som komplement och som uppföljningsinstrument. Hoppet har satts till OCT.

Vid undersökning av ögat vid misstanke om glaukom tittar läkaren på ögonbotten med ett oftalmoskop, en typ av mikroskop, för att se hur papillen ser ut. Papillen, även kallad blinda fläcken, är det ställe där syncellernas nervtrådar lämnar ögat för att samsas i synnerven som går till hjärnan. Även ögonbottens blodkärl använder denna passage. Vid glaukom påverkas utseendet av papillen eftersom nervtrådarna har dött. Papillen kan ses som en golvbrunn som nervtrådarna rinner ned i. Ett friskt öga ger mycket vatten, alltså många nervtrådar och ett tjockt, stort flöde. Ett påverkat öga har litet tunt flöde. Flödet är inte lika runt hela brunnen utan beror av varifrån flödet kommer, störst flöde nedifrån och minst från ytter/kind-sidan.

OCT-scanning av papillen ger möjlighet att mäta tjockleken på flödet av nervtrådar. I Uppsala har man tagit fram ett program som automatiskt mäter tjockleken, kallad PIMD, i 500 radier runt papillen. Denna mätmetod är ny och etablerade referensvärden saknas, dvs man vet inte vad som är normal tjocklek för olika patientgrupper (unga, gamla, etc) och man vet heller inte hur tjockleken av nervtrådar normalt fördelas runt papillen.

Denna studie har haft som syfte att se om det finns naturliga åldersförändringar i nervtrådarnas tjocklek i papillen (PIMD).

Fyra åldersgrupper har studerats: 20 – 29 år, 30 – 44, 45 – 64 och 65 – 85 år. Sex ögonfriska personer i varje åldersgrupp har OCT-scannats och PIMD har tagits fram och studerats för att hitta statistiskt säkerställda skillnader mellan grupperna.

För medeltjockleken runt papillen kan studien inte visa någon säkerställd minskning med ålder. Däremot finns sektorer runt papillen som visar en nedgång, vilket indikerar att en minskning finns. Detta överensstämmer med liknande studier av papillen.

Studien är till sin form för liten för att visa något tillförlitligt resultat. För att kunna visa pålitliga resultat bör en uppföljande studie över ett flertal år/årtionden göras.

Background

Glaucoma

The eye disease glaucoma stands for 8 % of the global blindness, the second biggest cause next to cataract, and 2 % of the visual impairments, the third biggest cause next to refractive errors and cataract¹. Glaucoma, often divided into open-angle glaucoma and angle-closure glaucoma, affects the optic nerve, structurally damaging it, causing progressing vision impairment, mostly by a decreasing visual field, that is irreversible and may lead to blindness. The optic neuropathy associated with characteristic structural damage to the optic nerve and associated visual dysfunction may be caused by various pathological processes². One is an elevated intraocular pressure that affects the optic nerve as it leaves the optic globe through the lamina cribrosa. The elevated pressure damages the nerve cells as the lamina cribrosa is a weak spot in the stabilizing sclera surrounding the globe. The damage changes the appearance of the optical nerve head (ONH) as the nerve cells dies and the neural retinal rim width reduces.

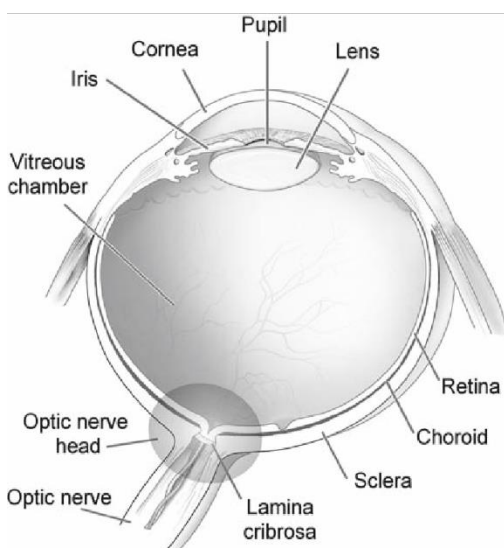


Figure 1 Schematic cross-section through a human eye.³

Treatment of glaucoma aims at stopping or slowing down the progression of the neuropathy and visual impairment, this is done by either medication or surgical intervention, commonly to lower the intraocular pressure. As treatment is preventing progression of an irreversible loss of vision an early diagnosis is important for the benefit of the patient.

Clinical diagnose and measurement methods

In the clinic the risk of glaucoma is assessed by measuring the intraocular pressure and inspecting the ONH. The damage to the optic nerve head is measured by the vertical cup:disc ratio ((V)CDR). Previous studies have found that a ratio over 0.5 suggests glaucomatous origin⁴. The examiner either uses an ophthalmoscope/slit lamp to inspect the optic disc (OD) and

estimate the ratio or calculate it from a retinal image. The inspection also verifies that the thickness of the rim depends on the location on the optic disc, following the “ISNT”-rule (inferior rim width>superior>nasal>temporal).

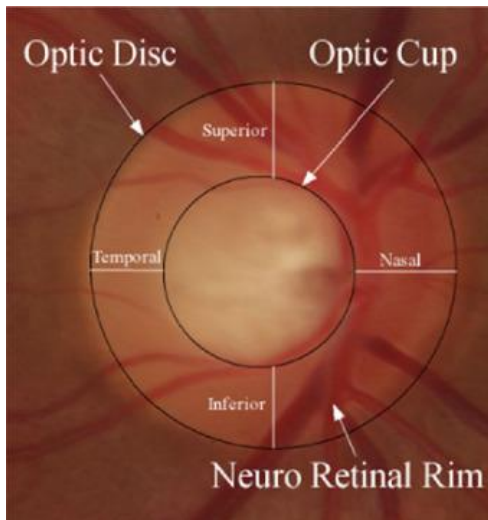


Figure 2 A Sample OD centric color retinal image with annotated OD and other retinal structures for the calculation of CDR and verification of ISNT rule.⁵

To diagnose and evaluate intervention of glaucoma the gold standard is computer aided visual field test, perimetry. In this test the patient pushes a button when a light is seen in the visual field and the result is calculated in a standardised way, reducing errors and deficiencies.



Figure 3 Visual field exam. Courtesy of aao.org

However, this method is associated with several uncertainties as it is highly dependent on the participation of the patient. Studies of the reliability and variability of the test have shown correlation to the severity of the visual impairment, time duration of the test⁶, mood and cognitive status of the test person^{7,8}. Moreover, visual field tests are time consuming and need to be repeated regularly in order to show reliable progression. Also, the neuropathy of the optic nerve in the papilla can be observed before the patient gets any symptoms and is diagnosed with

glaucoma after a visual field test⁹. Still visual field test is the standard, though continuously disputed and developed¹⁰.

The lack of a reliable acknowledged measurement method might contribute to that there is no exact comprehensive definition or diagnostic criteria for glaucoma today¹¹.

Optical Coherence Tomography OCT

OCT uses low-coherence light to create two and three-dimensional pictures of an optical scattering media. OCT measures the differences in echo time and intensity of backscattered and reflected light, i.e. in the eye globe¹². This is much like ultrasound although OCT has a much higher resolution and needs a stable translucent or opaque study object. In opaque biological tissue the imaging can reach two mm in depth. The exam is done in seconds and is performed using light in a wavelength not visible for the human eye (>800 nm).



Figure 4 OCT exam with a Topcon Triton OCT

Improvements of the technique since the 1990s have made it more reliable and fast¹³⁻¹⁵ as a method of imaging the retinal nerve fibre layer (RNFL) and the ONH.

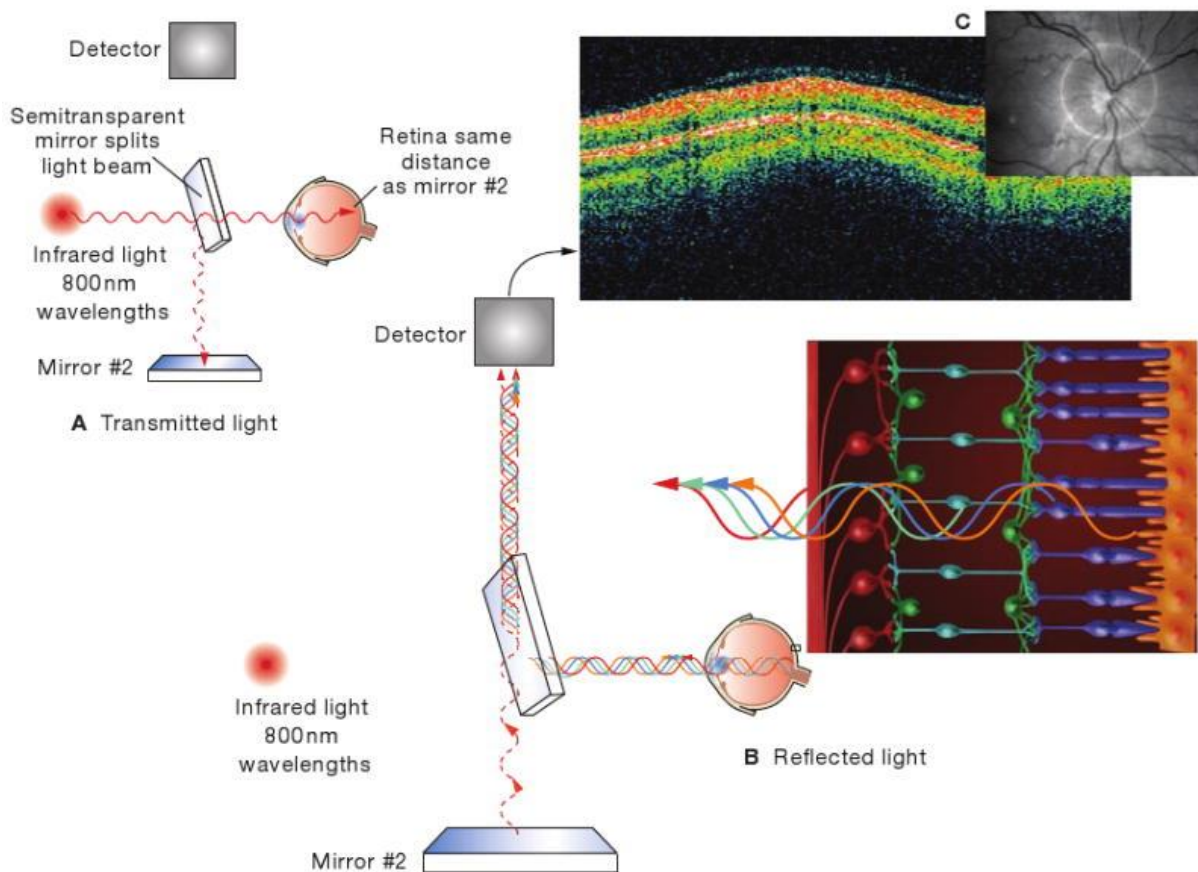


Figure 5 High-resolution images of the internal retinal structure taken with optical coherence tomography (OCT), demonstrating the processes involved in using this technology. (A) Low-coherence infrared light is transmitted into the eye through use of an interferometer. (B) The infrared light is transmitted through the pupil and then penetrates through the transparent nine layers of the retina. Subsequently, the light backscatters and returns through the pupil, where detectors can analyze the interference of light returning from the layers of the retina compared with light traveling a reference path (mirror #2). An algorithm mathematically uses this information to construct a gray-scale or false-color image representing the anatomy of the retina (shown in the upper right portion of the figure). (C) A fundus image from the OCT device, showing the optic disc appropriately centered and surrounded by the target image circumference marker for analysis of the retinal nerve fiber layer.¹⁶

OCT gives a quantitative picture of the optical disc (i.e. size and optical nerve layer thickness) whereas a clinical examination and estimation can be highly variable and observer dependent¹², but there is currently no consensus on which geometrical variables to measure for assessment of the ONH¹⁷.

Reis et al. introduced the Bruch's Membrane Opening-Minimum Rim Width (BMO-MRW)¹⁸ in 2012. BMO-MRW measures the minimum distance between Bruch's Membrane, which is the choroid's innermost layer, where it ends at the optic nerve entrance to the internal limiting membrane, which forms the border between the retina and the vitreous body. This is done for 48 radii of the papilla.

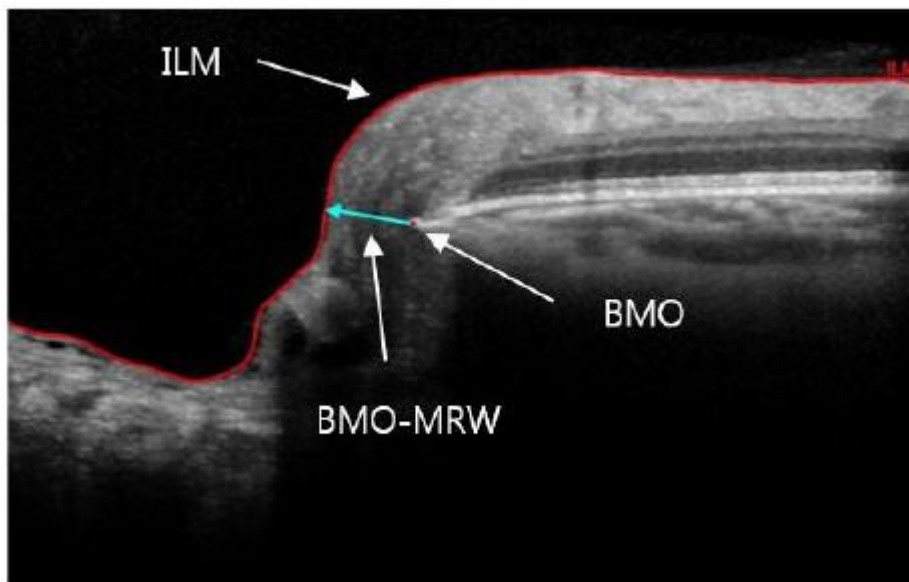


Figure 6 Neuroretinal rim parameters measured with Spectralis optical coherence tomography. B-scan illustrating Bruch membrane opening (BMO), and Bruch membrane opening-minimum rim width (BMO-MRW), the minimum distance from BMO to the internal limiting membrane (ILM).¹⁹

Studies of BMO-MRW have confirmed the ISNT-rule²⁰ and shown the benefits of BMO-MRW as a clinical tool²¹⁻²⁴. It has been found that the tipping point to clinically detect vision field impairment is at 25.9 % loss of the BMO-MRW from the normative value²⁰. Also to combine BMO-MRW and the peripapillary RNFL thickness has been suggested as a clinical decision-making index²⁵.

Studies have found that the RNFL thickness of the ONH varies with age, ethnicity, axial length, and optic disc area²⁶ and that BMO-MRW decreases with age in a healthy normal population²⁷⁻³⁰, at a loss rate of 1 to 2 $\mu\text{m}/\text{year}$.

The BMO method today needs manual input to be able to detect the Bruch's membrane. Also Bruch's membrane is 2-4 μm , whereas the OCT resolution at the sagittal axis is about 3 μm ¹⁷, making it hard to identify. However, the connected pigment epithelium is clearly visible in OCT scans due to the highly reflective melanin granula of the cells and can be used as a reference for ONH measurement.

[The Pigment epithelium central limit - Inner limit of the retina Minimal Distance \(PIMD\)](#)
PIMD is a new way of using the OCT information to form a clear picture of the ONH with clinical relevance. It was developed at Ophthalmology, Uppsala University, in 2019¹⁷. PIMD measures the thickness on the thinnest part, the Pigment epithelium central limit - Inner limit of the retina Minimal Distance, in 500 segmented radii of the ONH from information registered by OCT.

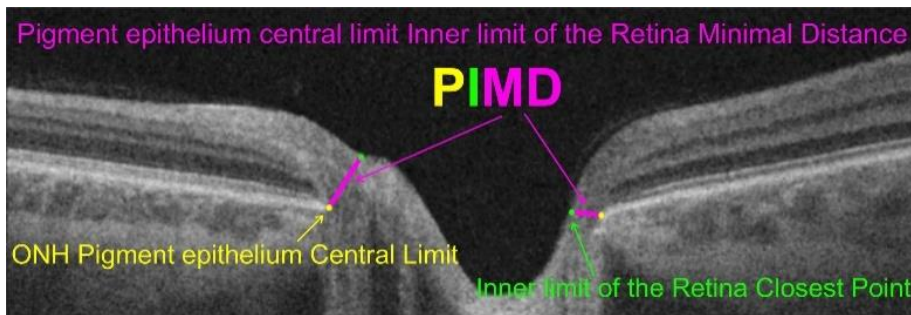


Figure 7 Definition of pigment epithelium central limit-inner limit of the retina minimal distance defined in a 2D-OCT B-scan.¹⁷

This is much like the BMO-MRW, the difference being identifying and naming the distinctly detectable pigment epithelium layer as the measurable starting point, rather than calling it the Bruch's membrane, and splitting the information into 500 radii instead of using 48. The result of the measurements can be presented as a graph showing the thinnest thickness as a variable to the angle of the radius (Figure 8).

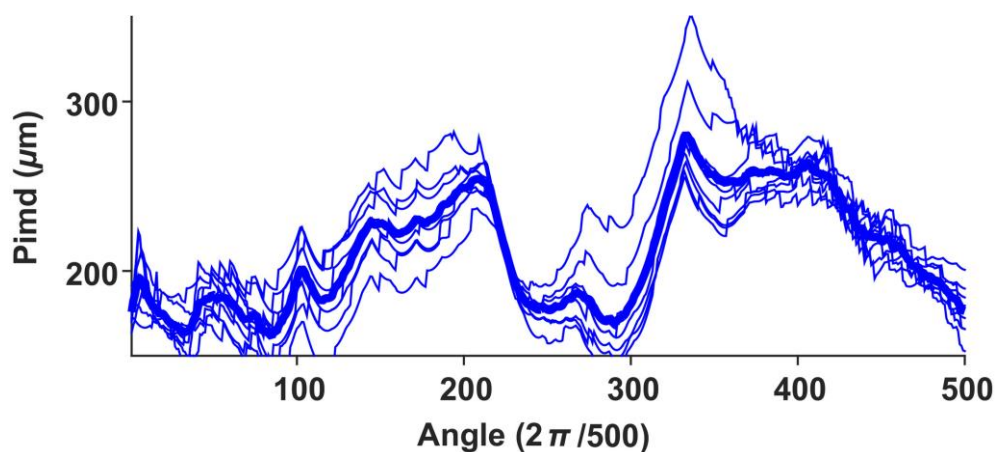


Figure 8 PIMD as a function of angle in eight iterated segmentations of one captured OCT volume of a healthy ONH. The bold line represents averaging of PIMD sequentially at each of the 500 angles.¹⁷

The graph showing a characteristic “M-shape” where the peaks are at 200 and 350 degrees, representing superior and inferior sectors respectively.

PIMD- 2π is the mean thickness of PIMD for all 500 radii and has been discussed as a clinical tool³¹. To detect glaucoma progression the mean thickness decrease may not be the best way, substantial loss of thickness at one sector of the ONH may only affect the mean value to a degree that can be interpreted as a normal finding.

An initial study at Ophthalmology, Uppsala University, has found no significant difference of the PIMD- 2π in gender³².

To calculate PIMD automatically a study at KTH Stockholm, has developed an algorithm that is using artificial intelligence (AI) to detect the pigment epithelium layer and the inner limit of the retina from the OCT information, and then assess the minimal distance in between.

Aim

The study means to find how the nerve fibre layer thickness in the papilla, PIMD, varies with age at non-glaucomatous persons.

Hypothesis to be tested

The nerve fibre layer thickness in the papilla, measured with PIMD, is presumed to decrease with age.

Study design

The study was conducted as a cross-sectional study, where the nerve fibre layer thickness was measured at one occasion for subjects of different ages.

Method

Subjects

The subjects in the study, aged 30-85, were, all but one, recruited at the eye clinic, Uppsala University Hospital. All met the inclusion criteria and gave informed consent in writing. The age group controlled were 20 – 29, 30 – 44, 45 – 64, 65 – 85. There were six subjects, three of each gender, in each age group, a total of 18 persons.

Inclusion criteria: not diagnosed with glaucoma, no retinopathy or abnormality of the retina, ability to perform OCT examination, age of ≥ 30 and < 85 .

Information from the study “PIMD- 2π , a new variable for measurement of glaucoma” by Sofia Eriksson 2017 was used to include subjects in the range 20 – 29 years of age. The information was taken randomly for six subjects, three of each gender.

No ethical approval was required as this student project is not intended for publication.

Procedure

The subjects were given dilating eye drops, tropicamide 5mg/ml, for the right eye. The subjects waited until proper response of the drops and then the right eye was scanned three times, each time after the subjects had removed and repositioned the head on the OCT scanner. The left eye was covered and the light in the test room was dimmed. The scans were repeated until three scans with seemingly adequate quality were obtained. The OCT scanner used was a Topcon 3D Optical Coherence Tomography DRI OCT Triton(plus) at the eye clinic, Uppsala University Hospital. The OCT scan was done according to the 3D Glaucoma disc 6*6 mm protocol of the OCT scanner using Topcon Imagenet i-base software, version 3.17.0, and the information was stored as Amir data-files.

For the age group 20 – 29 the Amir-data files from the study of 2017 were used.

Data analysis

PIMD was assessed by a custom-made algorithm version 191204, not yet published and under evaluation.

The algorithm gives the PIMD for 500 radii of the papilla in a csv-file. This file was processed in a MATHLAB-program that calculated the mean PIMD, both total and for eight sectors of the ONH, (Figure 9), for each OCT scan.

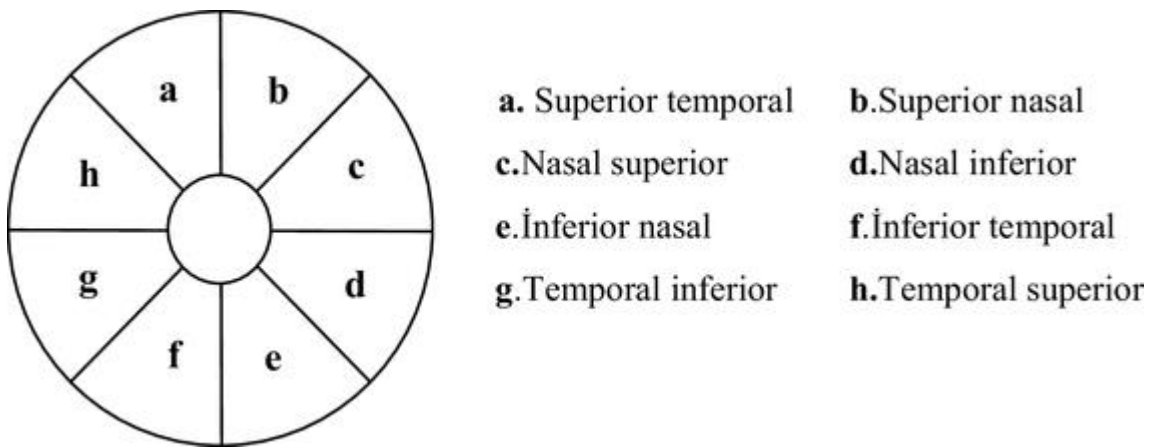


Figure 9 ONH sectors

The MATHLAB-program also gives the result as a csv-file. The data of the csv-file was further analysed using MS Excel for statistics and presentation graphs and tables.

For each subject all three approved OCT scans were included to calculate the group mean values of the ONH thickness (PIMD). This reduced the impact of errors and variance of the measurements. In the calculations Students t-distribution were used to evaluate confidence interval.

Statistical parameters

The confidence interval was set to 0.95.

Results

The age groups were named 0 = 20 – 29 years of age, 1 = 30 – 44, 2 = 45 – 64, 3 = 65 – 85. In total 24 subjects, six for each of the four age groups, were included, meaning that the total number of OCT-scans were 72.

During the OCT scan two subjects had irregular OCT scan results. This was confirmed when running the PIMD software. One subject had a severe cataract that dimmed all three scans and the other subject had one scan where eye movement during the scan made the OCT scanner restart the scan several times not finding the exact new starting point (Figure 10, Figure 11 and Figure 12).

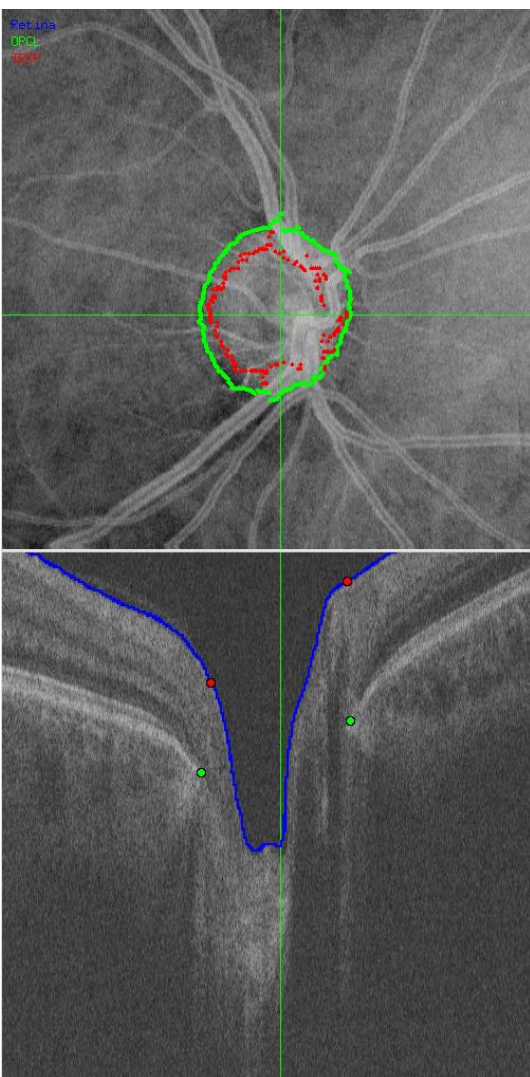


Figure 10 Good quality OCT scan as presented in the PIMD software. The upper picture showing the ONH frontal. The lower picture showing the ONH in cross section following the green line left-right on the upper picture. The green cross marks the centre of the ONH. The blue line shows the internal limiting membrane. The red dots showing points on the membrane where a PIMD is calculated. The green dots showing the pigment layers central limit. Note that they may not be the connected dots to the red dots in this 2D-picture.

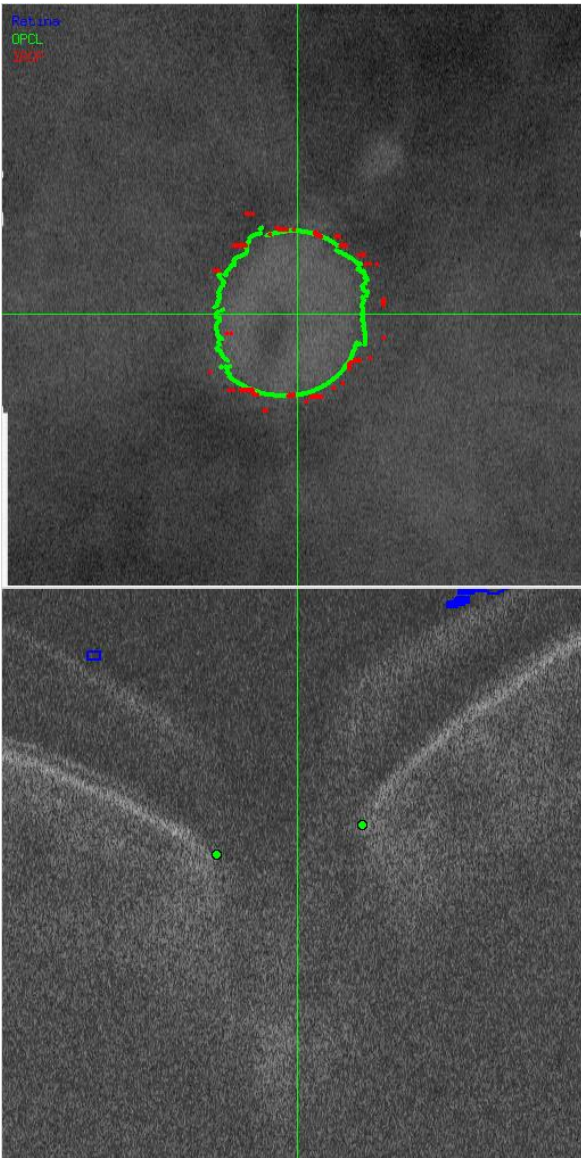


Figure 11 Low quality OCT scan. The software cannot identify the internal limiting membrane. This subject was not included in the study.

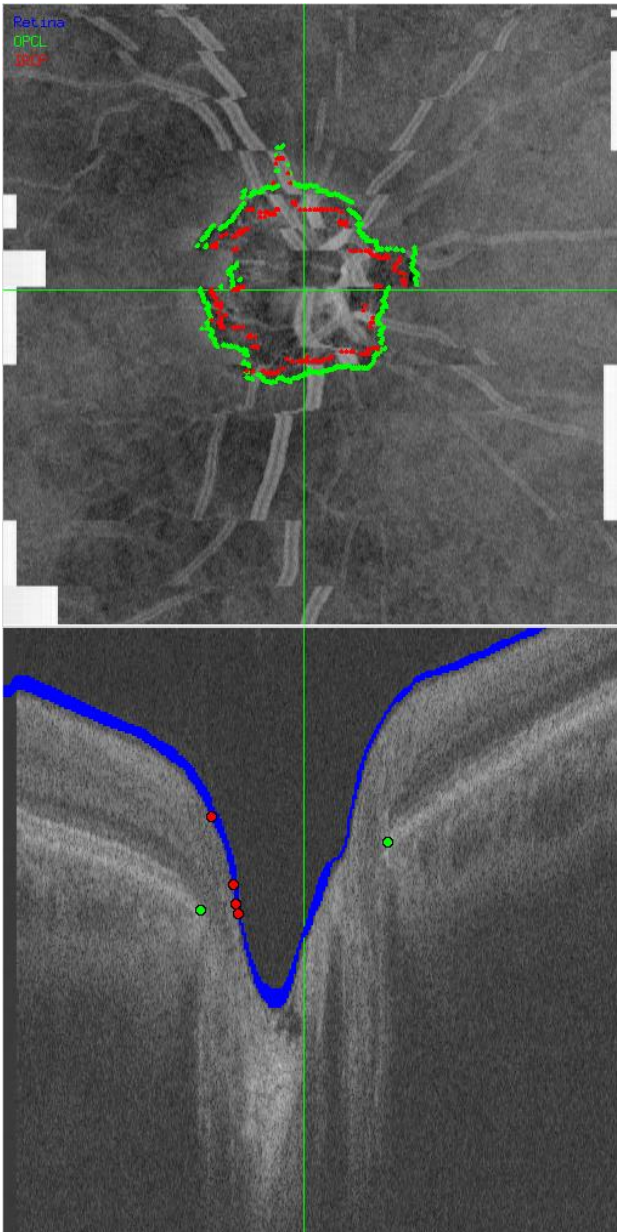


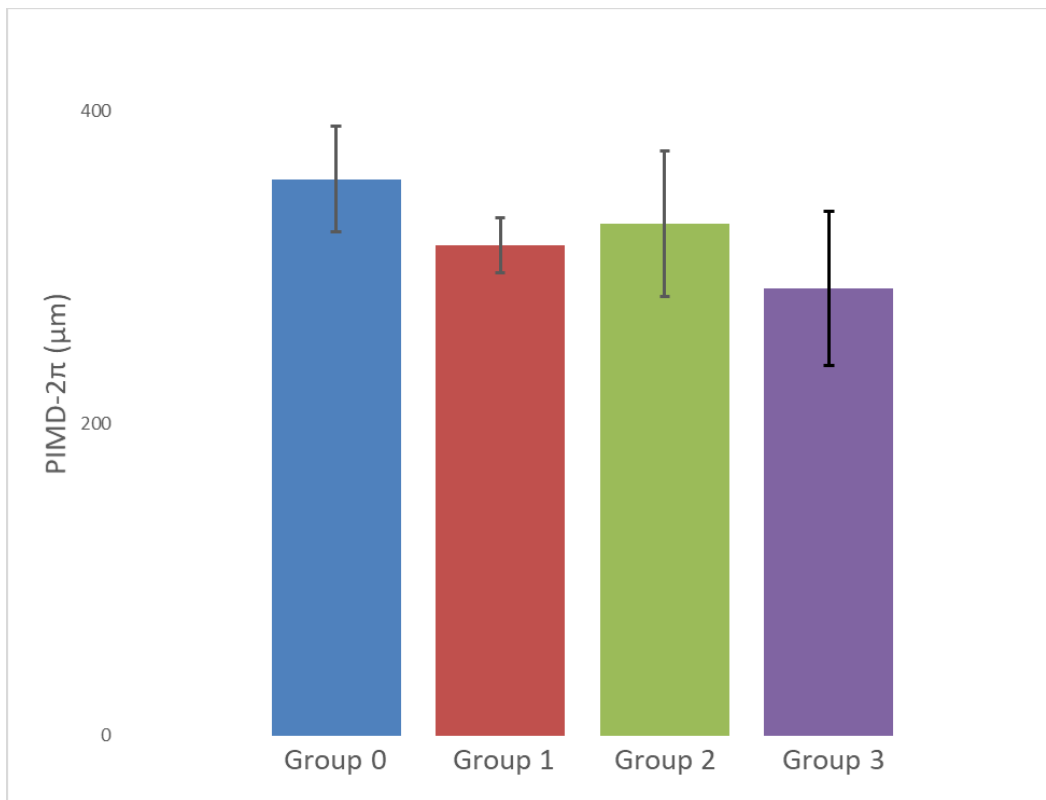
Figure 12 Low quality OCT scan. The scan has been interrupted several times and the restarts have been imprecise. This subject was not included in the study.

These subjects were not included in the study. As the irregular OCT scan results were found at an early stage, two other subjects were recruited during the normal recruiting process.

Average PIMD for the sectors show group 0 having the highest values for all sectors and group 3 the lowest for all but one, although the 95 % confidence interval range include all variations between the groups (Table 1 and Figure 13).

Table 1 PIMD for ONH sectors and age groups

ONH Sectors	20-29	30-44	45-64	64-85
	Mean±95%CI			
PIMD-2 π (μm)	357±44	314±23	328±61	287±64
Superior temporal	354±58	325±61	337±101	312±89
Superior nasal	390±50	324±30	355±51	330±89
Nasal superior	383±61	327±37	357±93	322±104
Nasal inferior	385±68	323±29	331±85	292±78
Inferior nasal	435±78	376±40	398±83	337±64
Inferior temporal	369±37	342±28	346±48	278±67
Temporal inferior	270±17	245±25	247±40	204±43
Temporal superior	264±19	253±27	253±47	218±39

Figure 13 PIMD-2 π per age group with 95 % confidence intervals

Illustrating the PIMD per sector and age group in a radar chart is shown in Figure 14.

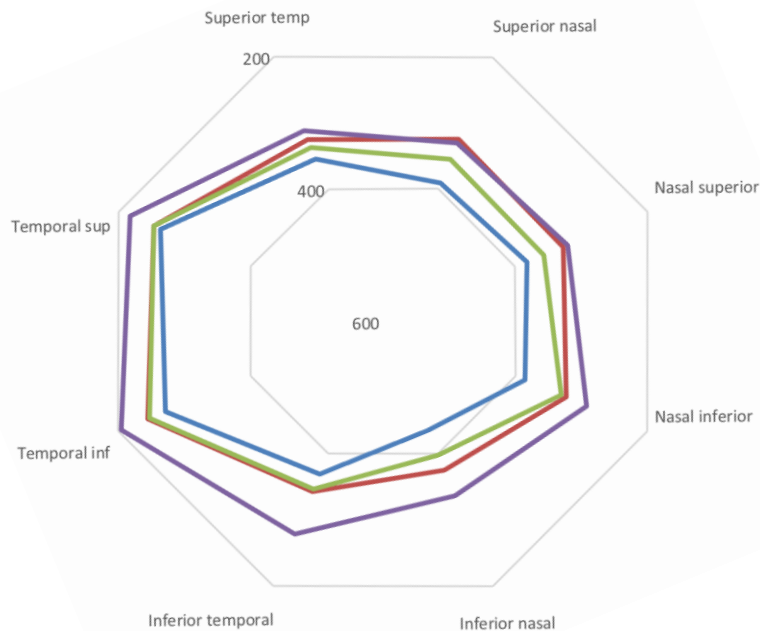


Figure 14 PIMD in micrometer for the eight sectors in a radar chart, highest value in the center. Blue representing group 0, red is group 1, green is group 2 and purple is group 3.

PIMD loss rate

Assuming and calculating linear trend lines for PIMD, setting the group median age as explanatory variable, gives a declination coefficient of $-1.14 \mu\text{m}/\text{year}$ for PIMD- 2π and values ranging from $-0.66 \mu\text{m}/\text{year}$ (superior temporal) to $-1.62 \mu\text{m}/\text{year}$ (inferior nasal) for the sectors. Significant loss is shown for sectors nasal inferior, inferior temporal, temporal inferior and temporal superior (Table 2).

Table 2 PIMD loss rate for ONH sectors

ONH Sectors	coeff.	95 % conf. int.
PIMD- 2π	-1.14	+/- 1.14
Superior temporal	-0.66	+/- 1.29
Superior nasal	-0.81	+/- 1.76
Nasal superior	-0.87	+/- 1.54
Nasal inferior	-1.55	+/- 1.53
Inferior nasal	-1.59	+/- 1.77
Inferior temporal	-1.62	+/- 1.06
Temporal inferior	-1.17	+/- 0.74
Temporal superior	-0.85	+/- 0.76

Scatter plot for PIMD- 2π with trend lines showing also the range of PIMD within the groups presents in Figure 15 and for ONH sectors in Figure 16.

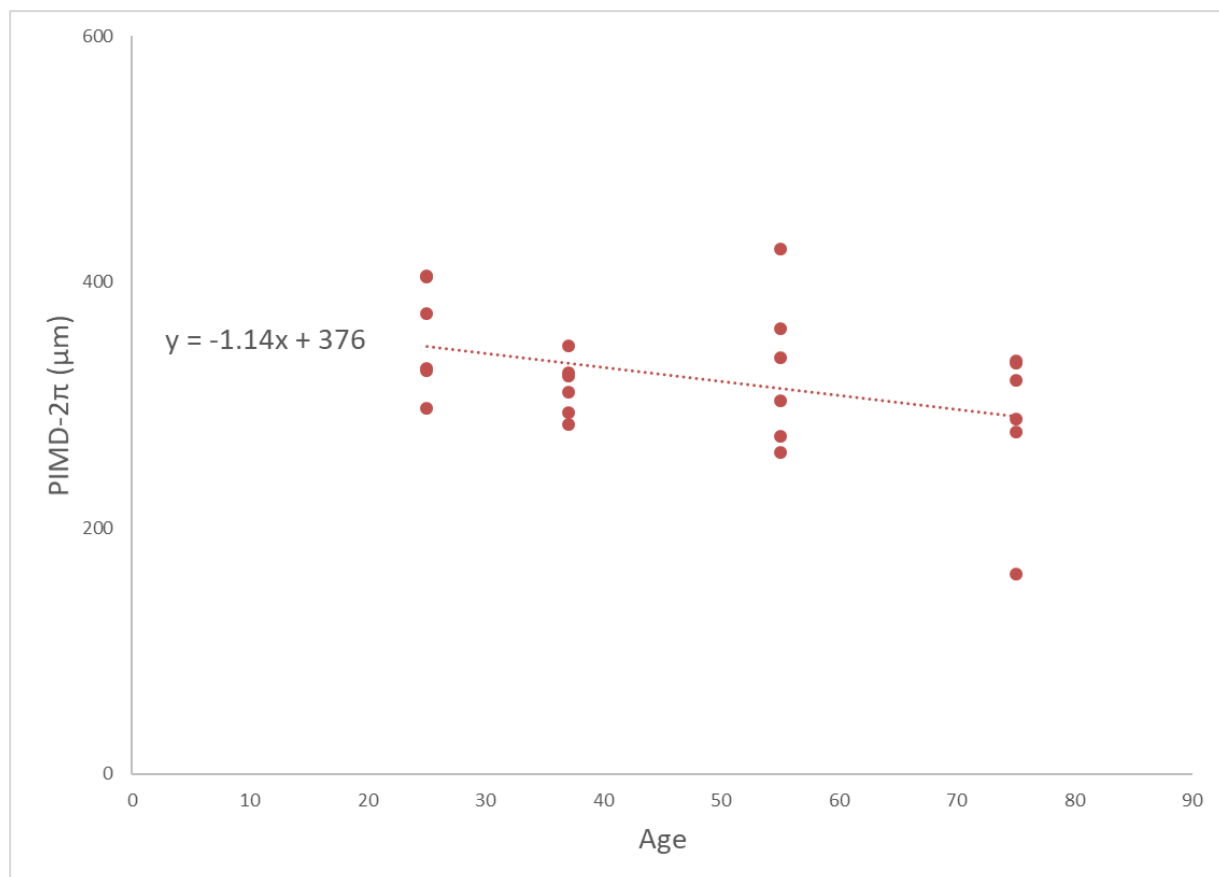


Figure 15 Scatter plot PIMD- 2π as a function of age. The red spots are mean PIMD- 2π of each subject. The dotted line is the regression line.

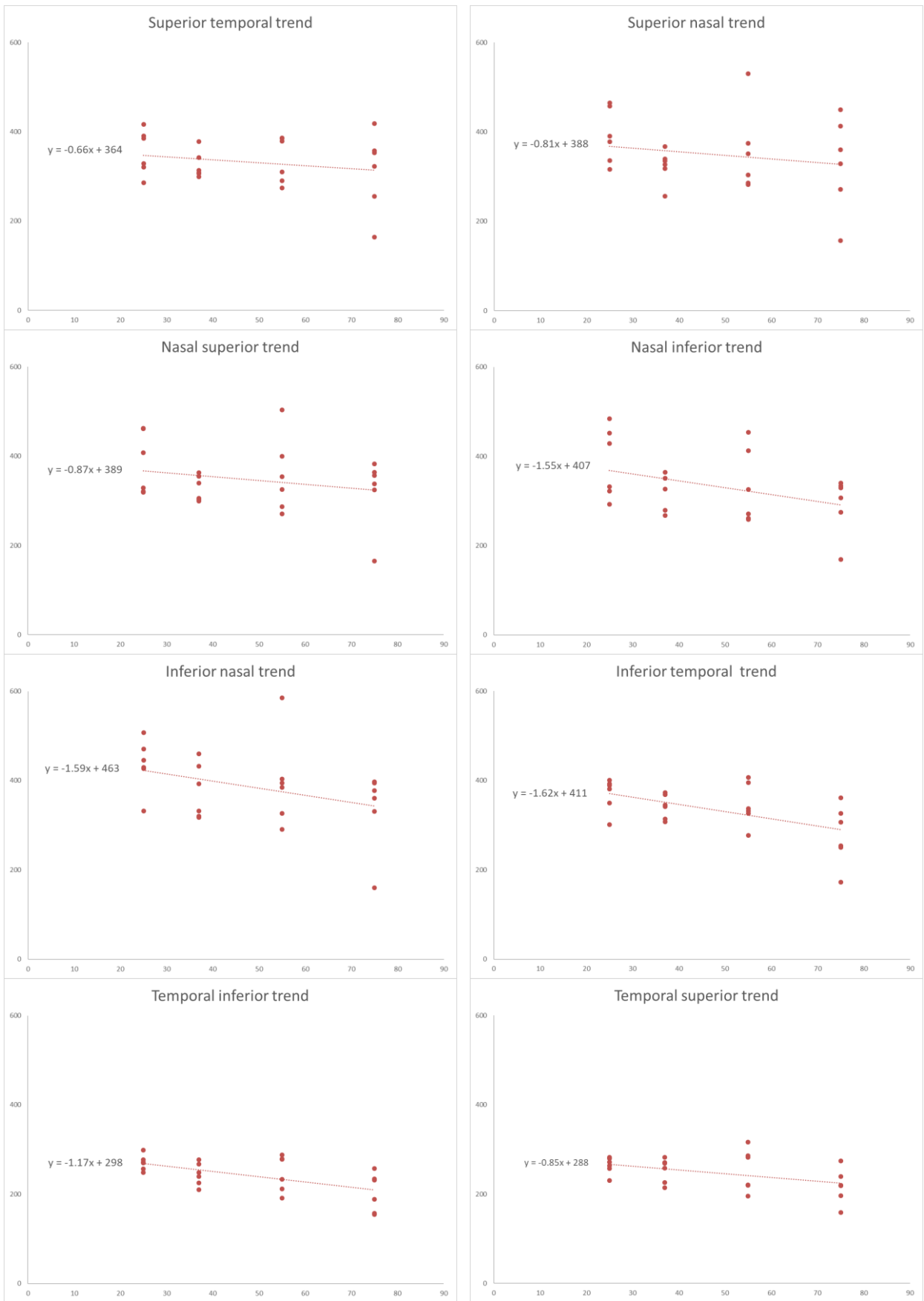


Figure 16 PIMD for the sectors in scatter plots with trend lines

Discussion

The purpose of this cross-sectional study was to find any age dependent variation of the nerve fibre layer of the optic papilla.

Results

Standing out studying the PIMD for the age groups is group 0 having the highest values and group 3 the lowest for all but one sector. Group 1 and 2 show similar figures. In this study trend lines are set as linear, but it could be discussed if there is a decline in PIMD stepwise affecting certain ages. A gradually, step by step decline of the ONH rim width or BMO-MRW has not been discussed in literature.

Looking at PIMD for the different sectors, inferior nasal is the thickest for all age group and the temporal sectors show the lowest PIMD, with the temporal inferior as the smallest for all groups save group 0 that has the temporal superior sector as the smallest. This is consistent with other studies^{27,28} as well as the ISNT rule.

The age dependent significant PIMD loss rate was found in sectors that also were found to have a comparatively small average PIMD. The temporal sectors have the lowest PIMD and show significant loss rate. Literature has suggested that the temporal sectors should be checked for glaucomatous changes for an early glaucoma diagnosis³³. This study implies that such a check also must take the age dependent loss rate in consideration. On the contrary, the vertical CDR, that is measured over the superior and inferior sectors is, based on this study, not affected by age variations.

Although the yearly loss of 1.14 μm for PIMD- 2π is not significant it is in line with studies of the BMR-MWO and also with studies of the optic nerve fibre amount that has found that the average rate of axon loss is about 5000 per year, 0.4 % of the 1.4 million at the start of our lives³⁴, this study's number would represent 0.3 % of the thickness as a child.

The subjects showed a great variation in PIMD, most notably in age group 3, proving that this study is too small to draw any conclusions about the possible age dependency of the PIMD.

Method

To determine the age dependent variation of the nerve fibre layer thickness in the papilla a prospective cohort study would be preferable. Obviously, such a study is not possible given the time frame of the thesis.

The subjects in the study, aged 30-85, were, all but one, recruited at at the eye clinic, Uppsala University Hospital. All met the inclusion criteria, but it can be disputed that the subjects, as they

were seeking care for problems with their eyes or reported for scheduled examination, represent a normal healthy population.

Although the OCT scanning procedure management is simple and straightforward there is a learning process connected to the evaluating of the quality of the scan. The OCT device has quality indexes that is helpful but the outcome of the scan in the PIMD algorithm may not only depend on those indexes. Learning the connection between the quality of the scan and the outcome of the algorithm will most likely improve the quality of the PIMD studies. In this study this matter was noted but no significant difference in evaluation was made over the study time.

The new unique algorithm that calculates the PIMD has not yet been fully developed and scrutinized. For the automatic identification of PIMD the vessels at the nasal side of the ONH may be one of the difficulties for the software to overcome. This study has not evaluated the quality of the algorithm and no cross-check has been done.

Future

The PIMD algorithm needs to be thoroughly evaluated to become fully reliant. The algorithm could then be integrated in the OCT device software. Today the OCT device automatically detects, measures and presents the retinal nerve fibre layer thickness in a circle some millimeters outside and around the papilla. This gives a rough picture of the thickness of the papilla and is used clinically as a diagnostic tool. A verified PIMD algorithm would improve the diagnose process and make future studies of the PIMD simple to extend in volume.

Conclusions

This study can not state but indicates that the nerve fibre layer thickness in the optic nerve papilla decreases with age and that this decrease is distributed unevenly around the papilla with a significant decline in the nasal inferior, inferior temporal and both temporal sectors.

Acknowledgements

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