Retinal layer thicknesses in early age-related macular degeneration: results from the German AugUR study

Caroline Brandl1,2,3*, Christiane Brücklmayer1, Felix Günther1,4, Martina E. Zimmermann1, Helmut Küchenhoff4, Horst Helbig2, Bernhard H. F. Weber3, Iris M. Heid1, Klaus J. Stark1

1) Department of Genetic Epidemiology, University of Regensburg, Regensburg, Germany
2) Department of Ophthalmology, University Hospital Regensburg, Regensburg, Germany
3) Institute of Human Genetics, University of Regensburg, Regensburg, Germany
4) Statistical Consulting Unit StaBLab, Department of Statistics, Ludwig-Maximilians-University Munich, Germany

*) Corresponding Author:
PD Dr. med. habil. Caroline Brandl, FEBO
Department of Ophthalmology,
Department of Genetic Epidemiology,
University of Regensburg
Franz-Josef-Strauss-Allee 11
93053 Regensburg, Germany
Tel.: +49 (0)941/944-5214
Fax: +49 (0)941/944-5212
Email: Caroline.Brandl@ukr.de
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**Supplementary Table 1. Comparison of SD-OCT-based retinal layer nomenclature.** This table contrasts the nomenclature for retinal layers on SD-OCT provided by the Heidelberg Eye Explorer software with the consensus nomenclature developed by the International Nomenclature for Optical Coherence Tomography Panel.\(^1\) Note that some layers are not segmented/provided by the Heidelberg Eye Explorer auto-segmentation tool, and that combinations of layers are given by the software (IRL, ORL, overall) that were not considered for the consensus nomenclature.

| Heidelberg Eye Explorer output | Consensus nomenclature                                      |
|-------------------------------|-------------------------------------------------------------|
| Retinal nerve fiber layer, RNFL| Nerve fiber layer                                            |
| Ganglion cell layer, GCL      | Ganglion cell layer                                          |
| Inner plexiform layer, IPL    | Inner plexiform layer                                        |
| Inner nuclear layer, INL      | Inner nuclear layer                                          |
| Outer plexiform layer, OPL    | Outer plexiform layer                                        |
| --                            | Henle fiber layer                                            |
| Outer nuclear layer, ONL      | Outer nuclear layer                                          |
| --                            | Myoid zone of photoreceptors                                 |
| Photoreceptors1, PR1\(^*\)    | Ellipsoid zone of photoreceptors                             |
| --                            | Outer segments of photoreceptors                             |
| Photoreceptors2, PR2\(^*\)    | Cone interdigitation with RPE (interdigitation zone)         |
| Retinal pigment epithelium, RPE| RPE/Bruch’s membrane complex (RPE/BrM complex)               |
| Inner retinal layers, IRL\(^\d\) | --                                                           |
| Outer retinal layers, ORL\(^\d\) | --                                                           |
| Overall\(^\d\)                | --                                                           |

\(\d\) Delineated by software but not included in retinal layer thickness output.

\(\d\) Ranging from inner limiting membrane to external limiting membrane; derived by software.

\(\d\) Ranging from external limiting membrane to Bruch’s membrane; derived by software.

\(\d\) Ranging from inner limiting membrane to Bruch’s membrane; derived by software.
Supplementary Figure 1. Exclusion of subjects/eyes in the first baseline survey from the AugUR OCT sub-study. Shown is the number of subjects/eyes after each exclusion step, also separated for right (OD) and left (OS) eyes.

AugUR Baseline  
\[ n = 1133 \text{ participants} \]

AugUR OCT sub-study  
\[ n = 510 \text{ participants}^a \]

At least one acquired 49 Raster macular cube  
\[ \begin{align*} 
\text{OD} & \quad n = 504 \\
\text{OS} & \quad n = 1004 \\
\end{align*} \]

At least one automatically segmentable 49 Raster macular cube  
\[ \begin{align*} 
\text{OD} & \quad n = 504 \\
\text{OS} & \quad n = 1004 \\
\end{align*} \]

Exclusion of 24 eyes from 22 persons due to:  
- mislocalized scans (n=7)  
- low-quality scans (n=10)  
- severe pathologies ineligible for manually distinguishing retinal layers (n=7)

Analyzed sample  

At least one manually correctable 49 Raster macular cube  
\[ \begin{align*} 
\text{OD} & \quad n = 489 \\
\text{OS} & \quad n = 980 \\
\end{align*} \]

Exclusion of:  
- eyes with late AMD

AMD association analysis$^b$  
\[ \begin{align*} 
\text{OD} & \quad n = 449 \\
\text{OS} & \quad n = 822 \\
\end{align*} \]

$^a$ Eligible for and agreeing to OCT sub-study.

$^b$ Performed in eyes with at least one manually correctable 49 Raster macular cube and no or mild/moderate/severe early AMD.
Supplementary Table 2A. Retinal layer thickness values in a population aged 70+ separated for right and left eyes. Shown are median thickness and interquartile range of the eight distinct retinal layers plus the combination of inner/outer and overall retinal layers as derived by the software. Results are given for the 495 analyzed participants (980 eyes, 489 right, 491 left) from the first AugUR baseline survey after manual correction of retinal layer segmentation. Results are separated for right and left eyes as well as central, inner and outer circles (as defined by the ETDRS grid, nasal/temporal/superior/inferior subfields combined).

| Retinal layers | Right eyes median thickness (IQR) [µm] | Left eyes median thickness (IQR) [µm] |
|---------------|--------------------------------------|--------------------------------------|
|               | Central circle (n=489)               | Inner circle (n=489)                 | Outer circle (n=489) | Central circle (n=491) | Inner circle (n=491) | Outer circle (n=491) |
| NFL           | 13.0 (11.0-15.0)                     | 21.8 (20.3-23.6)                     | 36.0 (32.8-39.6)     | 13.0 (11.0-15.0)       | 21.8 (20.3-23.8)     | 36.3 (32.8-40.3)     |
| GCL           | 14.0 (12.0-18.0)                     | 47.8 (43.8-50.9)                     | 33.0 (30.5-35.3)     | 15.0 (12.0-17.0)       | 47.3 (42.8-50.3)     | 32.8 (30.3-35.3)     |
| IPL           | 21.0 (19.0-24.0)                     | 40.0 (37.5-42.8)                     | 27.5 (25.8-29.5)     | 21.0 (19.0-24.0)       | 40.0 (37.0-42.3)     | 27.5 (25.8-29.5)     |
| INL           | 22.0 (17.0-27.0)                     | 40.3 (37.5-42.8)                     | 31.3 (29.8-33.0)     | 22.0 (17.0-26.0)       | 40.3 (37.8-43.0)     | 31.5 (30.0-33.3)     |
| OPL           | 26.0 (22.0-30.0)                     | 32.8 (30.3-36.0)                     | 27.0 (26.0-28.8)     | 26.0 (22.0-31.0)       | 32.8 (30.0-36.3)     | 27.3 (26.0-28.8)     |
| ONL           | 94.0 (86.0-103.0)                    | 69.3 (62.5-75.5)                     | 55.0 (50.8-59.7)     | 94.0 (85.5-102.0)      | 69.3 (62.3-75.0)     | 55.3 (50.0-59.5)     |
| PR-IS/OS*     | 68.0 (66.0-71.0)                     | 65.5 (64.3-66.0)                     | 65.0 (63.5-65.8)     | 68.0 (66.0-71.0)       | 65.5 (64.3-66.3)     | 64.8 (63.3-65.5)     |
| RPE/BrM       | 17.0 (15.0-18.0)                     | 15.5 (14.3-16.8)                     | 13.7 (12.8-14.8)     | 16.0 (15.0-18.0)       | 15.5 (14.5-16.8)     | 13.8 (12.8-14.8)     |
| IRL†          | 192.0 (175.0-208.0)                  | 251.9 (240.0-264.0)                  | 209.9 (200.0-220.9)  | 192.0 (174.0-209.0)    | 251.3 (239.3-262.3)  | 210.8 (200.5-220.0)  |
| ORL§          | 85.0 (83.0-90.0)                     | 81.0 (79.3-82.8)                     | 78.3 (76.5-80.0)     | 86.0 (83.0-89.0)       | 81.0 (79.3-83.0)     | 78.3 (76.5-80.0)     |
| Overall       | 279.0 (262.0-295.0)                  | 333.3 (321.6-344.9)                  | 288.3 (278.5-299.3)  | 278.0 (262.0-295.0)    | 333.0 (320.5-344.8)  | 289.0 (278.8-299.5)  |
Abbreviations: IQR = interquartile range (25th to 75th quartile); NFL = nerve fiber layer; GCL = ganglion cell layer; IPL = inner plexiform layer; INL = inner nuclear layer; OPL = outer plexiform layer; ONL = outer nuclear layer; PR-IS/OS = photoreceptor inner/outer segments+interdigitation zone; RPE/BrM = retinal pigment epithelium/Bruch’s membrane complex; IRL = inner retinal layers; ORL = outer retinal layers;
*) Ranging from external limiting membrane to retinal pigment epithelium; self-calculated.
†) Ranging from inner limiting membrane to external limiting membrane; derived by software.
§) Ranging from external limiting membrane to Bruch’s membrane; derived by software.
‖) Ranging from inner limiting membrane to Bruch’s membrane; derived by software.
Supplementary Table 2B. Retinal layer thickness values in a population aged 70+ separated for men and women. Shown are median thickness and interquartile range of the eight distinct retinal layers plus the combination of inner/outer and overall retinal layers as derived by the software. Results are given for the 495 analyzed participants (980 eyes, 479 male eyes, 501 female eyes) from the first AugUR baseline survey after manual correction of retinal layer segmentation. Results are separated for men and women as well as central, inner and outer circles (as defined by the ETDRS grid, nasal/temporal/superior/inferior subfields combined).

| Retinal layers | Male eyes median thickness (IQR) [µm] | Female eyes median thickness (IQR) [µm] |
|---------------|--------------------------------------|--------------------------------------|
|               | Central circle (n=479)               | Inner circle (n=479)                | Outer circle (n=479) | Central circle (n=501) | Inner circle (n=501) | Outer circle (n=501) |
| NFL           | 14.0 (12.0-15.5)                     | 22.0 (20.3-24.0)                    | 35.3 (32.3-39.3)    | 12.0 (10.5-14.0)       | 21.5 (20.3-23.3)     | 36.5 (33.3-40.5)       |
| GCL           | 16.0 (13.0-19.0)                     | 47.3 (42.8-50.8)                    | 32.5 (29.8-34.8)    | 14.0 (11.0-16.5)       | 47.8 (43.5-50.8)     | 33.3 (31.0-36.0)       |
| IPL           | 22.0 (20.0-25.0)                     | 40.0 (37.3-42.5)                    | 27.3 (25.3-29.0)    | 20.0 (18.0-23.0)       | 40.0 (37.5-42.8)     | 27.8 (26.0-30.0)       |
| INL           | 24.0 (20.0-29.0)                     | 40.5 (38.3-42.5)                    | 31.3 (29.8-32.8)    | 19.0 (15.0-23.0)       | 39.8 (37.0-42.3)     | 31.6 (30.1-33.3)       |
| OPL           | 27.0 (24.0-31.0)                     | 33.0 (30.3-35.5)                    | 27.0 (25.8-28.5)    | 25.0 (21.0-30.0)       | 32.5 (30.3-36.7)     | 27.3 (26.3-29.0)       |
| ONL†          | 95.0 (86.0-103.0)                    | 69.8 (62.8-77.0)                    | 55.5 (50.8-60.5)    | 93.0 (85.0-102.0)      | 68.5 (61.8-74.0)     | 54.5 (50.0-59.0)       |
| PR-IS/OS*     | 68.0 (66.0-71.0)                     | 65.8 (64.5-66.3)                    | 65.3 (64.0-65.8)    | 68.0 (67.0-71.0)       | 65.3 (64.0-66.0)     | 64.5 (63.0-65.5)       |
| RPE/BrM       | 17.0 (15.0-18.0)                     | 15.5 (14.3-16.8)                    | 13.5 (12.5-14.8)    | 16.0 (15.0-18.0)       | 15.5 (14.5-16.8)     | 13.8 (12.8-14.7)       |
| IRL‡          | 197.0 (183.0-213.0)                  | 252.3 (240.0-264.3)                 | 209.5 (199.0-219.3) | 184.0 (168.0-201.0)    | 250.9 (239.3-261.8)  | 211.3 (201.5-221.8)    |
| ORL§          | 86.0 (83.0-89.0)                     | 81.3 (79.3-83.3)                    | 78.5 (77.0-80.3)    | 85.0 (83.0-90.0)       | 80.8 (79.0-82.8)     | 78.3 (76.3-79.6)       |
| Overall‖      | 284.0 (270.0-302.0)                  | 333.8 (322.0-346.3)                 | 287.5 (278.0-298.3) | 274.0 (255.0-288.0)    | 332.0 (320.3-343.5)  | 289.3 (279.5-300.4)    |
Abbreviations: see Supplementary Table 2A;
*) Ranging from external limiting membrane to retinal pigment epithelium; self-calculated.
†) Ranging from inner limiting membrane to external limiting membrane; derived by software.
§) Ranging from external limiting membrane to Bruch’s membrane; derived by software.
‖) Ranging from inner limiting membrane to Bruch’s membrane; derived by software.
Supplementary Table 2C. Retinal layer thickness values in a population aged 70+ separated for “young” and “old”. Shown are median thickness and interquartile range of the eight distinct retinal layers plus the combination of inner/outer and overall retinal layers as derived by the software. Results are given for the 495 analyzed participants (980 eyes, 492 “young” eyes, 488 “old” eyes) from the first AugUR baseline survey after manual correction of retinal layer segmentation. Results are separated for participants younger and older than 76.5 years (= median) as well as central, inner and outer circles (as defined by the ETDRS grid, nasal/temporal/superior/inferior subfields combined).

| Retinal layers | Age participants ≤ 76.5 years median thickness (IQR) [µm] | Age participants ≥ 76.5 years median thickness (IQR) [µm] |
|----------------|----------------------------------------------------------|----------------------------------------------------------|
|                | Central circle (n=492) | Inner circle (n=492) | Outer circle (n=492) | Central circle (n=488) | Inner circle (n=488) | Outer circle (n=488) |
| NFL            | 13.0 (11.0-15.0)     | 21.5 (20.3-23.0)     | 35.8 (32.5-39.3)     | 13.0 (11.0-15.0)     | 21.8 (20.3-24.5)     | 36.3 (33.0-40.9)     |
| GCL            | 14.0 (12.0-17.0)     | 48.6 (44.5-51.3)     | 33.4 (31.3-36.0)     | 15.0 (12.0-18.0)     | 46.3 (42.0-50.0)     | 32.3 (29.5-34.8)     |
| IPL            | 21.0 (19.0-24.0)     | 40.8 (38.1-43.0)     | 27.8 (26.5-30.0)     | 21.0 (19.0-24.0)     | 39.3 (36.5-42.0)     | 27.1 (25.0-29.0)     |
| INL            | 21.0 (16.0-26.0)     | 40.3 (37.5-42.8)     | 31.5 (30.3-33.0)     | 22.0 (19.0-27.0)     | 40.0 (37.8-42.8)     | 31.3 (29.5-33.0)     |
| OPL            | 26.0 (22.0-31.0)     | 33.0 (30.3-35.8)     | 27.0 (26.0-28.8)     | 27.0 (23.0-31.0)     | 32.5 (30.3-36.3)     | 27.3 (26.0-28.8)     |
| ONL            | 94.0 (87.0-102.0)    | 69.5 (62.8-75.5)     | 55.5 (51.0-59.5)     | 94.0 (85.0-103.0)    | 69.0 (61.8-75.0)     | 55.1 (49.5-59.8)     |
| PR-IS/OS*      | 69.0 (67.0-72.0)     | 65.5 (64.5-66.3)     | 65.0 (63.5-65.8)     | 68.0 (66.0-70.0)     | 65.3 (63.8-66.0)     | 64.8 (63.3-65.5)     |
| RPE/BrM        | 17.0 (15.0-18.0)     | 15.5 (14.5-16.8)     | 13.8 (12.8-14.8)     | 16.0 (15.0-18.0)     | 15.5 (14.3-16.8)     | 13.8 (12.8-14.8)     |
| IRL†           | 189.0 (173.0-207.0)  | 252.8 (242.3-264.0)  | 211.5 (201.8-221.0)  | 194.0 (175.0-209.0)  | 249.8 (237.6-261.4)  | 209.3 (198.3-220.0)  |
| ORL§           | 86.0 (84.0-90.0)     | 81.3 (79.5-83.3)     | 78.5 (76.5-80.3)     | 85.0 (82.0-89.0)     | 80.8 (79.0-82.5)     | 78.3 (76.5-79.9)     |
| Overall††      | 277.0 (261.0-293.0)  | 334.6 (323.6-346.0)  | 289.3 (280.3-300.3)  | 280.5 (262.0-296.0)  | 330.8 (318.8-343.9)  | 287.4 (276.3-298.3)  |
Abbreviations: see Supplementary Table 2A;
*) Ranging from external limiting membrane to retinal pigment epithelium; self-calculated.
†) Ranging from inner limiting membrane to external limiting membrane; derived by software.
§) Ranging from external limiting membrane to Bruch’s membrane; derived by software.
‖) Ranging from inner limiting membrane to Bruch’s membrane; derived by software.
Supplementary Table 3. Retinal layer thicknesses in eyes of individuals aged 70+ revealing no pathologies on color fundus images. Shown are median thickness and interquartile range of the eight distinct retinal layers plus the combination of inner/outer and overall retinal layers as derived by the software. Results are given for 110 eyes (58 right, 52 left) from the first AugUR baseline survey after manual correction of retinal layer segmentation. Results are separated for central, inner and outer circles (as defined by the ETDRS grid, nasal/temporal/superior/inferior subfields combined).

| Retinal layer thicknesses [µm] | median (IQR) |
|--------------------------------|--------------|
| **Central circle** (n=110) | **Inner circle** (n=110) | **Outer circle** (n=110) |
| **NFL** | 13.0 (11.0-15.0) | 21.5 (20.3-22.8) | 36.3 (32.8-39.3) |
| **GCL** | 14.0 (11.0-17.0) | 48.0 (42.4-50.8) | 32.6 (30.2-34.8) |
| **IPL** | 21.0 (19.0-24.0) | 40.0 (37.5-42.3) | 27.3 (25.4-29.0) |
| **INL** | 20.5 (17.0-25.0) | 39.3 (37.3-41.8) | 31.0 (29.0-32.3) |
| **OPL** | 26.0 (22.0-30.0) | 33.0 (30.3-36.3) | 27.3 (26.0-28.8) |
| **ONL** | 94.0 (87.0-102.0) | 66.6 (61.5-74.0) | 51.9 (48.2-56.8) |
| **PR-IS/OS** | 69.0 (67.0-72.0) | 65.5 (64.5-66.0) | 65.0 (63.7-65.8) |
| **RPE/BrM** | 16.0 (15.0-17.0) | 15.0 (13.8-16.0) | 13.3 (12.3-13.8) |
| **IRL** | 189.5 (173.0-204.3) | 249.0 (237.7-259.9) | 206.5 (198.8-214.0) |
| **ORL** | 85.0 (82.0-89.0) | 80.5 (78.8-81.8) | 77.8 (76.3-79.5) |
| **Overall** | 275.5 (259.8-290.3) | 329.5 (318.7-338.3) | 282.8 (276.2-292.8) |

Abbreviations: see Supplementary Table 2A;
*) Ranging from external limiting membrane to retinal pigment epithelium; self-calculated.
†) Ranging from inner limiting membrane to external limiting membrane; derived by software.
‡) Ranging from external limiting membrane to Bruch’s membrane; derived by software.
§) Ranging from inner limiting membrane to Bruch’s membrane; derived by software.
Supplementary Figure 2. Overall retinal layer thickness in different AMD stages. Depicted are boxplots based on 876 eligible eyes from the first AugUR baseline survey with available AMD status and manually corrected retinal layer segmentation. Overall retinal layer thickness in the central circle demonstrates a marked thinning in geographic atrophy (GA) and a thickening in neovascular (NV) AMD.
Supplementary Figure 3. Model-based expected retinal layer thicknesses in early AMD from sensitivity analysis. Depicted are estimates of expected retinal layer thicknesses [µm] based on layer-specific linear mixed models of 255 eyes with either no AMD and no other pathologies on color fundus images (n=110), mild early (n=57), moderate early (n=40), or severe early AMD (n=48) from the first AugUR baseline survey after manual correction of retinal layer segmentation. Estimates by AMD status and central, inner, outer circles are derived from linear mixed models, adjusted for linear age and sex and nested random effects for within-person and within-eye correlation. 95% confidence intervals are derived from model-based parametric bootstrap.
Supplementary Text 1. Measurement error resulting from automated retinal layer segmentation in SD-OCT.

Automated segmentation software enables quantitative analyses of retinal layers and their thicknesses in SD-OCT scans via the delineation of optical reflectivity boundaries. The analyzed retinal layer thicknesses in this study correspond to the distance between the boundaries of each retinal layer. These boundaries result from an automated segmentation of the retina into eight distinct layers. However, this automated segmentation was found to be error-prone and was therefore, in several cases (Table 3), manually corrected.

In the present analysis, segmentation error leads to measurement error in the continuous response variable(s) of the statistical regression models: instead of the true response observations (retinal layer thicknesses), it is only possible to obtain potentially error-prone thickness measurements from the automated, uncorrected retinal layer segmentation. While it is known that unbiased, homoscedastic (non-differential) response measurement error induces additional variation, but no bias to estimates of (standard) linear regression models, biased measurements or measurement error that depends on covariates (differential measurement error) can induce substantial bias to estimates of regression coefficients.

Thus, we set out to assess the differences in retinal layer thicknesses derived from the automated (error-prone) and manually adjusted (assumed as correct) retinal layer segmentation: Table 3 shows the fraction of mean thickness measurements that required correction. Figure 3 shows boxplots of the differences between the (log) thicknesses from automated and manually corrected segmentation per circle and AMD disease stage in each retinal layer, that correspond to the response measurements in the estimated regression models. It can be seen that the layer thicknesses of the automated segmentation do not fluctuate randomly and with constant variance around the (true) measurements from the manually adjusted segmentation. Instead, the error resulting from automated segmentation appears to be, at least in some circles, related to AMD disease stage. Especially in the central and inner circle of the retinal pigment epithelium/Bruch’s membrane (RPE/BrM)
complex, we observed that several derived mean thickness measurements from the automated segmentation are heavily deflated. This matches the experience of the manual segmentation correction that the automated segmentation often fails to localize Bruch's membrane correctly, when e.g. drusen are present (Figure 4).

In consequence, the error resulting from automatic segmentation is differential by AMD stage and statistical models that would have been applied to data from the uncorrected auto-segmentation would lead to biased results. Figure 5 compares the results of the linear mixed models on the response data of the automated segmentation and the manually adjusted segmentation. We find that the thickness of the RPE/BrM complex in the central and inner circle is particularly underestimated for eyes with moderate or severe early AMD and the association between RPE/BrM complex thickness and the effects of these AMD stages would be underestimated accordingly. That this effects particularly central and inner RPE/BrM complex is plausible, as we did find the largest distortion of measurements towards lower values exactly in these groups.
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