



Optic Nerve Head Changes over 15 Years—From the Atropine Treatment Long-Term Assessment Study

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Purpose: To investigate optic nerve head (ONH) changes over 15 years from childhood to adulthood.

Design: A longitudinal study.

Participants: The Atropine Treatment Long-Term Assessment Study (ATLAS) included 148 myopic participants from the Atropine for the Treatment of Myopia 2 (ATOM2) trial.

Methods: During ATOM2, all participants were treated with daily atropine eye drops in concentrations of 0.01%, 0.1%, or 0.5%. The ATLAS recall visit was conducted in 2021–2022. At 3 study visits—ATOM2 baseline, last ATOM2 (5-year), and ATLAS recall (15-year)—participants underwent cycloplegic autorefractometry, biometry, and fundus photography. At recall, OCT centered on the optic disc was additionally performed. Fundus photographs were morphometrically examined for ONH ovality, torsion, parapapillary atrophy (PPA), disc–fovea distance, position of the central retinal vascular trunk (CRVT), angle kappa, and vertical distance between the arterial arcade. OCT images were analyzed for Bruch membrane opening distance, gamma zone, and Bruch membrane overhang.

Main Outcome Measures: Optic nerve head changes from childhood to young adulthood and associated factors.

Results: Optic nerve head characteristics were similar across atropine treatment groups. Myopic refractive error increased from -4.54 ± 1.64 diopters (D) at baseline to -6.35 ± 2.02 D at 5 years to -6.88 ± 2.4 D at 15 years ($P < 0.0001$). Axial length (AL) increased from a mean of 25.08 ± 0.89 mm to 26.31 ± 1.01 mm ($P < 0.0001$). Significant ONH changes after 15 years included PPA (beta zone/maximal disc diameter) increasing from 0.19 ± 0.11 to 0.31 ± 0.15 ($P < 0.0001$), and CRVT position ratio increasing from 1.62 ± 0.22 to 2.23 ± 0.5 ($P < 0.0001$). Multivariable mixed-effect models confirmed the association of age, AL, and spherical equivalent refraction (SER) with optic disc changes ($P < 0.0001$). Axial length, SER, and PPA were associated with the Bruch membrane opening distance area and the gamma zone (P values < 0.0001). Additionally, age ($P < 0.0001$), PPA ratio ($P = 0.002$), and disc–fovea distance ratio ($P = 0.030$) were found to be associated with myopic progression greater than -2 D over a 15-years period.

Conclusions: This long-term study suggests that myopic subjects showed increased PPA and nasal CRVT shift from childhood into young adulthood.

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Supplemental material available at www.ophtalmologyscience.org.

Axial myopia and its associated complications represent a significant yet often underestimated public health challenge worldwide.¹ Prevalence rates for myopia can reach up to 80%, with high myopia affecting approximately 30% of high school students in various East Asian regions.^{2–6} These trends have persisted for several decades, resulting in many myopic individuals who are now middle-aged and at an increased risk of developing myopia-related complications, including pathological myopia. Among these complications, glaucoma and pathological changes of the optic

nerve head (ONH) are particularly concerning due to their potential for significant and irreversible vision loss.

Previous cross-sectional studies have explored characteristics of the myopic ONH, for example, optic disc tilt and parapapillary atrophy (PPA) zones, in relation to the development and progression of glaucoma.^{7–11} However, research focusing on myopic ONH and parapapillary changes during childhood has remained limited. Given the established link between axial myopia and glaucoma, it is crucial to understand the myopia-related structural changes

of the ONH over time. This study aimed to assess myopia-related changes of the ONH in a longitudinal manner and to compare the findings with previously described changes in smaller cohorts with shorter observation period.¹² Particularly, it addresses the gap in knowledge about the changes of ONH characteristics occurring during the transition from childhood to adulthood.

This analysis draws on data from the cohort of the Atropine Treatment Long-Term Assessment Study (ATLAS)¹³, and aims to investigate optic disc changes over a 15-year period following atropine treatment during childhood to young adulthood. Specifically, we aimed to describe the longitudinal changes of various ONH parameters, such as optic disc ovality, PPA, and position of the central retinal vascular trunk (CRVT). Additionally, we assessed whether the various concentrations of atropine treatment in childhood are associated with changes in the optic nerve as myopia progresses.

Methods

Study Design and Participants

The ATLAS¹³ is a prospective observational cohort study that investigates the long-term effects of atropine treatment for myopia in participants who had previously been included in the Atropine for the Treatment of Myopia (ATOM) 1 and 2 randomized, double-masked, clinical trials. Further details on ATLAS and the long-term effects of short-term treatment of topical atropine during ATOM1 and 2 have been reported previously.¹³ Because the present analysis focused on longitudinal ONH changes, it included participants of the ATOM2 project for whom fundus photographs taken at baseline were available.

The ATOM2 study was conducted between 2006 and 2012, with baseline visits in 2006 to 2007 and final trial visits 5 years later, that is, from 2011 to 2012.^{14,15} It included 400 children aged 6 to 12 years with myopia of at least -2.0 D and a maximal astigmatism of -1.50 D. The children were randomly assigned in a 1:2:2 ratio to once-daily topical treatment with atropine eye drops in concentrations of 0.01%, 0.1%, or 0.5% over a 2-year period (treatment phase), after which the treatment was stopped for 1 year (washout phase). If a myopia progression of -0.5 D or more in ≥ 1 eye during the washout phase was noted, the study participants were offered an additional 2-year treatment with 0.01% atropine eye drops (retreatment phase).^{14,15}

Ten years after the final ATOM2 study visit, hence between 2021 and 2022, the former study participants were screened for their eligibility to be included in the present study and were recalled within the framework of the ATLAS project. It resulted in a follow-up time of approximately 15 years.

The ATLAS received approval from the Institutional Review Board of the Singapore Eye Research Institute (No. 2020/2249), ensuring compliance with ethical standards. Written informed consent was obtained from all participants before their inclusion in the study, aligning with the tenets of the Declaration of Helsinki.¹³

Ocular Examinations

Conducted during the ATOM2 study visits and the ATLAS recall,^{13–15} the ophthalmic examinations included measurement of best-corrected visual acuity, cycloplegic autorefractometry (to determine the spherical equivalent refraction [SER]) and ocular biometry to measure axial length (AL) at every study visit. In the

ATOM2 study, cycloplegic autorefractometry was performed using the Canon RK-F1 autorefractor after instillation of 3 drops of cyclopentolate 1% eye drops and waiting for 30 minutes. At the recall visit during the ATLAS trial, the participants received 1 drop of tropicamide 1% and 1 drop of cyclopentolate 1% to achieve cycloplegia, and the Topcon Auto Kerato-Refractometer was used for cycloplegic autorefractometry. Ocular biometry was conducted with different generations of Zeiss IOL Master biometers (Carl Zeiss Meditec) in both ATOM2 and ATLAS. Fundus photographs of the posterior pole taken in the ATOM2 were acquired with a Canon CR DGi Retinal Camera at every study visit. All ocular images, that is, fundus photographs and OCT during ATLAS recall, were acquired using the Topcon DRI OCT Triton device. OCT imaging centered on the optic disc was performed only at the 15-year ATLAS recall visit; therefore, OCT-derived metrics were measured only cross-sectionally at the end of the 15-year observation period.

ONH Measurements and Grading

Optic nerve head characteristics were manually assessed using ImageJ software¹⁶ and analyzed from serial fundus photographs taken at 3 time points: (1) at the ATOM2 baseline, (2) at the last study visit of ATOM2 (5-year), and (3) at the ATLAS recall (15-year). Two graders (J.C. and E.C.) measured the following optic disc characteristics (Fig 1):

- Vertical and horizontal disc diameter
- Minimal and maximal disc diameter
- Maximum width and location of parapapillary beta zone, defined as the area of visible sclera next to the disc without any retinal pigment epithelium^{8,11}
- Disc–fovea distance, defined as the distance between the foveola and the geometric optic disc center
- Vertical distance between the arterial arcade (VDA), measured on a vertical line running through the foveola
- Angle kappa, angle between the temporal arterial arcades with the optic disc as the angle vertex
- Distance between the temporal optic disc border to the location of the exit of the CRVT.^{8,17}

The serial posterior pole fundus photos were evaluated in sequence for each study participant.

Using these measurements, derived metrics were calculated: The ovality was defined as the ratio of maximal to minimal disc diameter.¹⁸ The PPA ratio was defined as the ratio between the maximal beta zone width and the maximal disc diameter.^{9,11} The disc torsion (or optic disc rotation around the sagittal axis) was determined as the absolute angle between the horizontal and the minimal diameter of the disc; there was no differentiation of direction. If the torsion changed direction over the course of the 3 evaluated images, this was additionally documented. The disc–fovea distance ratio was calculated as disc–fovea distance divided by the maximal disc diameter. The position of the CRVT was the ratio between the horizontal disc diameter and the CRVT exit distance from the temporal disc border.¹⁹ The VDA ratio described the ratio between the VDA distance and the maximal disc diameter.^{8,17}

Horizontal OCT B-scans centered on the optic disc and obtained during the ATLAS recall were analyzed using the manufacturer's proprietary software (IMAGENet 6) for the following parameters.^{9,11,18} One grader (J.C.) labeled and measured the Bruch membrane opening distance, defined as the distance between the temporal and nasal ends of Bruch membrane. If present, parapapillary gamma zone and the part of Bruch membrane overhanging into the intrapapillary compartment were

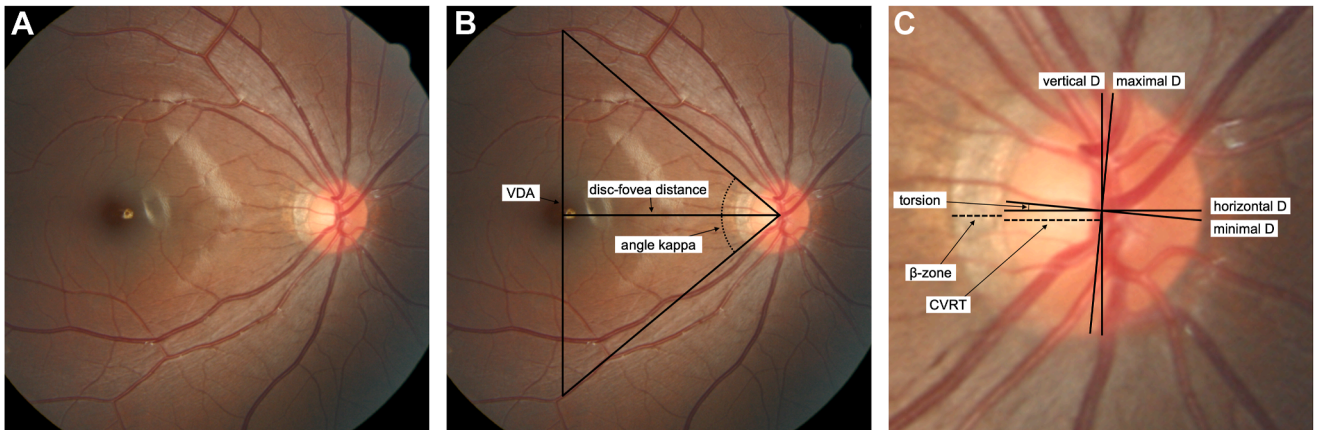


Figure 1. Optic nerve head characteristics. (A) Example fundus photograph acquired at the baseline ATOM2 visit with the Canon CR DGi retinal camera of a participant's right eye. (B) Measurements of the disc–fovea distance, VDA between the temporal superior and temporal inferior arterial arcade, and the resulting angle kappa between the temporal arterial arcades. (C) Optic disc parameters: horizontal and vertical diameter, minimal and maximal disc diameter, maximal width of β -zone parapapillary atrophy, and position of the CRVT. The position of the CRVT was calculated as the linear distance from the temporal rim of the optic disc to the point of vascular trunk exit, divided by the horizontal disc diameter, resulting in a dimensionless ratio. ATOM2 = Atropine for the Treatment of Myopia 2; CRVT = central retinal vascular trunk; VDA = vertical arcade distance.

measured. The gamma zone was defined as the parapapillary region devoid of Bruch membrane, that is, the region between the end of Bruch membrane and the optic disc border (Fig 2).

Data Analysis

Participant and optic disc characteristics were presented as absolute numbers and percentages for categorical data, while for continuous data, mean \pm SD was used.

Intergrader agreement was assessed using interclass correlation coefficients for the measured ONH characteristics. The mean of the 2 graders was used for the analysis of changes and

associations. Descriptive statistical analysis was performed using a 1-way analysis of variance test for normally distributed continuous variables across different groups, for example, atropine treatment groups. For categorical variables, chi-squared or Fisher exact tests were employed.

Both univariate and multivariable generalized linear and logit mixed-effect models were used to analyze the changes over time and to determine the associations between various factors and ONH parameters. The models allowed for consideration of intra-individual correlation between time points and between the 2 eyes of each participant, providing a robust analysis of the factors influencing changes in optic disc characteristics and refractive

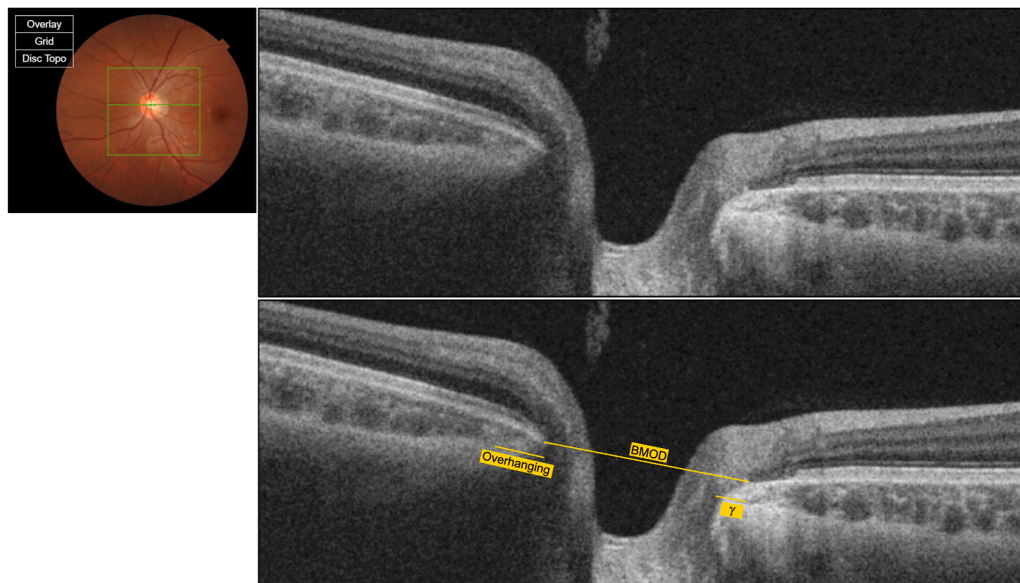


Figure 2. Optic nerve head parameter measurements in a horizontal OCT B-scan: the Bruch membrane opening distance (BMOD), the Bruch membrane overhanging, and the gamma (γ) zone are indicated.

Table 1. Comparison of Ocular Characteristics between Treatment Groups at Three Time Points: Baseline, Last ATOM2 Visit (5 Years), and ATLAS Recall (15 Years)

| Characteristics | Total | 0.01% Atropine in ATOM2 | 0.1% Atropine in ATOM2 | 0.5% Atropine in ATOM2 | P Value* |
|--|------------------|-------------------------|------------------------|------------------------|------------------|
| Participants' Characteristics | | | | | |
| Number of participants | 148 | 28 (18.9%) | 61 (41.2%) | 59 (39.9%) | |
| Age at baseline (ATOM2), years | 9.59 ± 1.41 | 9.59 ± 1.39 | 9.69 ± 1.44 | 9.49 ± 1.40 | 0.545 |
| Age at last (ATOM2), years | 14.58 ± 1.42 | 14.64 ± 1.38 | 14.68 ± 1.47 | 14.47 ± 1.40 | 0.508 |
| Age at recall (ATLAS), years | 24.30 ± 1.45 | 24.46 ± 1.39 | 24.39 ± 1.50 | 24.14 ± 1.41 | 0.254 |
| Gender, female | 71 (48%) | 12 (42.9%) | 27 (44.3%) | 32 (54.2%) | 0.500 |
| Ethnicity, Chinese | 134 (90.5%) | 27 (96.4%) | 54 (88.5%) | 53 (89.8%) | 0.500 |
| Ocular characteristics | | | | | |
| Number of eyes | 296 | 56 | 122 | 118 | |
| Laterality, right eyes | 148 (50.0%) | 28 (18.9%) | 61 (41.2%) | 59 (39.9%) | 1.000 |
| Spherical equivalent refraction, D | | | | | |
| Baseline | -4.54 ± 1.64 | -4.51 ± 1.41 | -4.49 ± 1.37 | -4.62 ± 1.98 | 0.811 |
| Last | -6.35 ± 2.02 | -5.97 ± 1.83 | -6.25 ± 1.64 | -6.63 ± 2.40 | 0.102 |
| Recall | -6.88 ± 2.40 | -6.40 ± 2.21 | -6.81 ± 1.92 | -7.19 ± 2.87 | 0.116 |
| Axial length, mm | | | | | |
| Baseline | 25.08 ± 0.89 | 25.20 ± 1.01 | 25.06 ± 0.79 | 25.04 ± 0.92 | 0.532 |
| Last | 25.93 ± 1.01 | 25.98 ± 1.13 | 25.89 ± 0.82 | 25.95 ± 1.12 | 0.827 |
| Recall | 26.31 ± 1.17 | 26.31 ± 1.29 | 26.28 ± 0.97 | 26.34 ± 1.30 | 0.935 |
| IOP at recall, mmHg | 17.14 ± 3.23 | 17.70 ± 3.32 | 17.02 ± 3.16 | 17.01 ± 3.26 | 0.363 |
| Myopic progression >2 D over 15 years | 154 (52.0%) | 25 | 58 | 71 | 0.068 |
| Myopic progression >1 D over first 5 years | 205 (69.3%) | 35 | 83 | 87 | 0.302 |
| Myopic progression >1 D over last 10 years | 82 (27.7%) | 9 | 38 | 35 | 0.094 |
| Retreatment with Atropine eye drops, yes | 174 (58.8%) | 14 | 74 | 86 | <0.001 |
| ONH characteristics | | | | | |
| Ovality | | | | | |
| Baseline | 1.26 ± 0.13 | 1.25 ± 0.12 | 1.26 ± 0.13 | 1.26 ± 0.14 | 0.834 |
| Last | 1.30 ± 0.14 | 1.32 ± 0.13 | 1.29 ± 0.14 | 1.29 ± 0.14 | 0.364 |
| Recall | 1.27 ± 0.14 | 1.27 ± 0.12 | 1.28 ± 0.13 | 1.28 ± 0.14 | 0.878 |
| PPA ratio | | | | | |
| Baseline | 0.19 ± 0.11 | 0.19 ± 0.10 | 0.20 ± 0.11 | 0.18 ± 0.10 | 0.127 |
| Last | 0.24 ± 0.13 | 0.25 ± 0.11 | 0.25 ± 0.11 | 0.23 ± 0.15 | 0.359 |
| Recall | 0.31 ± 0.15 | 0.30 ± 0.13 | 0.31 ± 0.13 | 0.30 ± 0.18 | 0.748 |
| Torsion angle, degree | | | | | |
| Baseline | 11.23 ± 11.42 | 14.74 ± 12.28 | 9.67 ± 10.67 | 11.18 ± 11.49 | 0.022 |
| Last | 11.39 ± 11.53 | 12.74 ± 9.83 | 11.39 ± 13.46 | 10.73 ± 10.02 | 0.566 |
| Recall | 12.2 ± 12.57 | 13.93 ± 10.25 | 12.46 ± 14.44 | 11.10 ± 11.43 | 0.367 |
| Disc-fovea distance ratio | | | | | |
| Baseline | 2.75 ± 0.33 | 2.73 ± 0.22 | 2.79 ± 0.34 | 2.73 ± 0.35 | 0.341 |
| Last | 2.75 ± 0.31 | 2.79 ± 0.23 | 2.76 ± 0.32 | 2.71 ± 0.34 | 0.250 |
| Recall | 2.78 ± 0.35 | 2.81 ± 0.24 | 2.79 ± 0.33 | 2.76 ± 0.41 | 0.652 |
| Position of CRVT | | | | | |
| Baseline | 1.62 ± 0.22 | 1.62 ± 0.20 | 1.63 ± 0.25 | 1.59 ± 0.19 | 0.383 |
| Last | 1.64 ± 0.36 | 1.77 ± 0.29 | 1.57 ± 0.42 | 1.64 ± 0.30 | 0.003 |
| Recall | 2.23 ± 0.5 | 2.25 ± 0.30 | 2.17 ± 0.55 | 2.29 ± 0.51 | 0.163 |
| VDA ratio | | | | | |
| Baseline | 3.73 ± 0.82 | 3.60 ± 0.89 | 3.82 ± 0.84 | 3.69 ± 0.76 | 0.193 |
| Last | 3.68 ± 0.8 | 3.57 ± 0.91 | 3.77 ± 0.81 | 3.65 ± 0.72 | 0.259 |
| Recall | 3.74 ± 0.85 | 3.61 ± 0.96 | 3.83 ± 0.86 | 3.70 ± 0.78 | 0.233 |
| Angle kappa, degree | | | | | |
| Baseline | 66.20 ± 10.68 | 64.66 ± 11.61 | 67.06 ± 10.65 | 66.05 ± 10.23 | 0.376 |
| Last | 65.75 ± 10.4 | 63.31 ± 11.56 | 66.71 ± 10.33 | 65.92 ± 9.76 | 0.124 |
| Recall | 65.81 ± 10.88 | 63.47 ± 11.96 | 66.84 ± 10.70 | 65.87 ± 10.45 | 0.158 |
| OCT measurements at recall | | | | | |
| Gamma zone, μm | 302.57 ± 201.79 | 279 ± 178.26 | 306.8 ± 159.4 | 309.44 ± 247.58 | 0.623 |
| Overhanging of Bruch membrane, μm | 178.54 ± 156.63 | 140.82 ± 138.62 | 203.94 ± 167.5 | 170.10 ± 149.55 | 0.033 |
| Bruch membrane opening, μm | 1729.47 ± 239.05 | 1711.54 ± 174.33 | 1729.73 ± 191.45 | 1737.79 ± 303.26 | 0.797 |

ATLAS = Atropine Treatment Long-Term Assessment Study; ATOM2 = Atropine for the Treatment of Myopia 2; CRVT = central retinal vascular trunk; D = diopters; IOP = intraocular pressure; ONH = optic nerve head; PPA = peripapillary atrophy; VDA = vertical arcade distance. Categorical, n (%); numeric, mean ± standard deviation. Bold values indicate statistical significant.

*Comparison performed using 1-way analysis of variance to compare the means of the 3 groups for numeric data, or the distributions using the chi-squared test for categorical data.

Table 2. Changes of Ocular and ONH Characteristics over Time, Generalized Linear Mixed-Effect Model Analysis

| Characteristics | Baseline | Last ATOM2 Visit | ATLAS Recall | Estimate | Standard Error | P Value |
|------------------------------------|-------------------|-------------------|-------------------|----------|----------------|-------------------|
| Ocular Characteristics | | | | | | |
| Spherical equivalent refraction, D | -4.54 ± 1.64 | -6.35 ± 2.02 | -6.88 ± 2.40 | -0.1413 | 0.006 | <0.0001 |
| Axial length, mm | 25.08 ± 0.89 | 25.93 ± 1.01 | 26.31 ± 1.17 | 0.076 | 0.002 | <0.0001 |
| ONH characteristics | | | | | | |
| Ovality | 1.26 ± 0.13 | 1.30 ± 0.14 | 1.27 ± 0.14 | 0.000 | 0.000 | 0.260 |
| PPA ratio | 0.19 ± 0.11 | 0.24 ± 0.13 | 0.31 ± 0.15 | 0.007 | 0.000 | <0.0001 |
| Torsion angle, degree | 11.23 ± 11.42 | 11.39 ± 11.53 | 12.2 ± 12.57 | 0.071 | 0.035 | 0.043 |
| Disc–fovea distance ratio | 2.75 ± 0.33 | 2.75 ± 0.31 | 2.78 ± 0.35 | 0.002 | 0.001 | 0.016 |
| Position of CRVT | 1.62 ± 0.22 | 1.64 ± 0.36 | 2.23 ± 0.5 | 0.044 | 0.002 | <0.0001 |
| VDA ratio | 3.73 ± 0.82 | 3.68 ± 0.8 | 3.74 ± 0.85 | 0.001 | 0.001 | 0.180 |
| Angle kappa, degree | 66.20 ± 10.68 | 65.75 ± 10.4 | 65.81 ± 10.88 | -0.016 | 0.011 | 0.150 |

ATLAS = Atropine Treatment Long-Term Assessment Study; ATOM2 = Atropine for the Treatment of Myopia 2; CRVT = central retinal vascular trunk; D = diopters; ONH = optic nerve head; PPA = peripapillary atrophy; VDA = vertical arcade distance.

Bold values indicate statistical significant.

measurements. We used R version 4.4.1 (R Core Team, 2023. R Foundation for Statistical Computing) for all statistical analyses. All statistical tests were performed at a significant level of 0.05.

Results

The ATLAS project included 158 participants (39.8%) of the 400 individuals who were primarily included in the ATOM2 study.¹³ Out of these 158 individuals, we excluded 10 because of discontinued atropine treatment within the first 2 years of the ATOM2 project, so that eventually the present statistical analysis was performed on a dataset of 148 participants (296 eyes). The 1:2:2 ratio random assignment of study participants to the 3 atropine concentration treatment groups in ATOM2 was similarly represented also in ATLAS: Out of the 148 participants, 28 individuals belonged to the 0.01% atropine concentration group, 61 persons to the 0.1% atropine concentration group, and 59 participants were found in the 0.5% atropine concentration group. The mean age of the study participants at baseline was 9.48 ± 1.41 years (median: 9.59 years; range: 6.27–12.93 years). As summarized in Table 1, the mean age at ATLAS recall was 24.30 ± 1.45 years. The study population included 71 (48%) women, and 134 (90.5%) participants were of Chinese ethnicity. The 3 atropine-treatment groups did not differ significantly in age ($P = 0.55$), sex distribution ($P = 0.21$), and ethnicity ($P = 0.23$).

Data were available for both eyes of all the participants at every visit. Intergrader agreement was tested for the manually measured ONH characteristics. The values for disc ovality, PPA ratio, and disc–fovea distance ratio demonstrated good reliability, with intraclass correlation coefficients (ICCs) of 0.822, 0.776, and 0.737, respectively (Supplementary Table S1, available at www.ophtalmologyscience.org). Subsequently, the average of both graders' values was used to investigate the changes of ONH characteristics over time.

Analyzed ocular and specifically ONH characteristics for the 3 time points, that is, baseline, last ATOM2 visit (5 years), and ATLAS recall (15 years), and across the

atropine treatment groups are listed and compared in Table 1. Overall, comparable distributions and values for all parameters were found between the 3 atropine groups at the 3 examined time points. The only exception was the mean value of the CRVT position at the 5-year visit (last ATOM2), which was significantly ($P = 0.003$) lower for the participants treated with 0.1% (1.57 ± 0.42), as compared with the 0.01% (1.77 ± 0.29) and the 0.5% (1.64 ± 0.30) atropine-treated participants.

The longitudinal changes of selected ocular and ONH characteristics are summarized in Table 2 and depicted in the plots in Figure 3. Changes over time of SER, AL, and the ONH characteristics collected from the fundus photographs obtained from all 148 participants ($n = 296$ eyes) at baseline, after 5 years (last ATOM2 visit), and after 15 years (ATLAS recall) were analyzed overall, independently of atropine treatment groups. Spherical equivalent refraction decreased from -4.54 ± 1.64 diopters (D) at baseline to -6.35 ± 2.02 D at 5 years (last ATOM2 visit) to -6.88 ± 2.40 D at 15 years after baseline (measured at ATLAS recall; $P < 0.0001$). Axial length increased from a mean of 25.08 ± 0.89 mm to 25.93 ± 1.01 mm to 26.31 ± 1.17 mm ($P < 0.0001$), respectively. All ONH characteristics, apart from the VDA ratio and angle kappa significantly changed over time; the disc ovality increased steeply in the first 5 years, from 1.26 ± 0.13 to 1.30 ± 0.14 , and decreased to 1.27 ± 0.14 in the following 10 years; consequently, overall no significant change was observed for disc ovality ($P = 0.26$). The maximal beta zone width to maximal disc diameter, that is, the PPA ratio, increased from 0.19 ± 0.11 to 0.24 ± 0.13 at 5 years and to 0.31 ± 0.15 at 15 years after baseline ($P < 0.0001$). Further, significant longitudinal changes were observed for the disc–fovea distance ratio ($P = 0.016$), and particularly for the position of the CRVT, which increased from 1.64 ± 0.36 at the last ATOM2 visit to 2.23 ± 0.5 at the ATLAS recall ($P < 0.0001$). Figure 4 shows fundus photographs of 2 different example study participants at each of the 3 analyzed time points.

According to the univariate and multivariable analyses using generalized linear mixed-effect models, ONH

Table 3. Univariate Generalized Linear Mixed-Effect Model Determination of Factors Associated with ONH Characteristics Changing over Time

| Univariate models | PPA Ratio | | | Torsion | | | Disc-Fovea Distance Ratio | | | Position of CRVT | | |
|---------------------------|-----------|----------------|---------|----------|----------------|--------------|---------------------------|----------------|---------|------------------|----------------|---------|
| | Estimate | Standard Error | P Value | Estimate | Standard Error | P Value | Estimate | Standard Error | P Value | Estimate | Standard Error | P Value |
| Age | 0.008 | 0.000 | <0.0001 | 0.072 | 0.036 | 0.046 | 0.002 | 0.001 | 0.014 | 0.044 | 0.002 | <0.0001 |
| AL | 0.081 | 0.003 | <0.0001 | -0.005 | 0.324 | 0.990 | 0.019 | 0.008 | 0.012 | 0.261 | 0.016 | <0.0001 |
| SER | -9.915 | 0.436 | <0.0001 | 0.085 | 0.160 | 0.600 | -0.010 | 0.004 | 0.008 | -0.109 | 0.008 | <0.0001 |
| PPA ratio | | | | -8.070 | 2.745 | 0.004 | 0.670 | 0.061 | <0.0001 | 2.160 | 0.123 | <0.0001 |
| Ovality | 0.493 | 0.032 | <0.0001 | -10.270 | 3.070 | 0.001 | 0.330 | 0.072 | <0.0001 | 0.798 | 0.138 | <0.0001 |
| Torsion | -0.002 | 0.000 | <0.0001 | | | | -0.003 | 0.001 | <0.0001 | -0.001 | 0.002 | 0.480 |
| Disc-fovea distance ratio | 0.174 | 0.015 | <0.0001 | -6.220 | 1.380 | <0.0001 | 0.077 | 0.013 | <0.0001 | 0.320 | 0.058 | <0.0001 |
| Position of CRVT | 0.125 | 0.006 | <0.0001 | -0.084 | 0.584 | 0.890 | | | 0.710 | | | |
| Atropine | | | | | | 0.350 | | | | | | |
| Atropine 0.1% | 0.007 | 0.026 | 0.670 | -2.630 | 2.090 | | 0.002 | 0.066 | | -0.087 | 0.066 | 0.370 |
| Atropine 0.5% | -0.011 | 0.026 | | -2.880 | 2.100 | | -0.038 | 0.066 | | -0.035 | 0.067 | |
| Retreatment, yes | 0.192 | 1.894 | 0.920 | 80.760 | 153.380 | 0.600 | -7.951 | 4.782 | 0.096 | -3.037 | 4.853 | 0.530 |

AL = axial length; CRVT = central retinal vascular trunk; ONH = optic nerve head; PPA = peripapillary atrophy; SER = spherical equivalent refraction. Bold values indicate statistical significant.

parameters derived from fundus photographs with multiple time points that had shown a statistically significant change over time, such as PPA ratio and position of CRVT, were most significantly ($P < 0.0001$) associated with increasing age, longer AL, and more myopic SER, as well as with one another. Differences in atropine treatments were not associated with any of the ONH characteristics. The estimates for their predictors are summarized in Table 3 for univariate and Table 4 for multivariate analyses.

Optic nerve head characteristics measured on OCT B-scans acquired exclusively at the time of the ATLAS recall served as outcome parameters for further univariate and multivariable mixed-effect models (Tables 5 and 6). In the univariate models, where each predictor was evaluated separately, AL, SER, PPA ratio, and disc-fovea distance ratio were significantly associated with the Bruch membrane opening distance area and the gamma zone ($P < 0.0001$). In multivariable models, taking interactions between associated parameters into account, AL and SER, as well as PPA ratio and position of CRVT, remained significantly associated with Bruch membrane opening distance (Table 6).

A supplementary analysis, including univariate and multivariable logistic regressions, showed that at baseline, besides age ($P < 0.0001$), the disc-fovea distance ratio ($P = 0.030$), and PPA ratio ($P = 0.002$) were significantly linked to myopic progression of ≥ 2 D or more over 15 years (Supplementary Table S2, available at www.opthalmologyscience.org). However, in the multivariable model including age at baseline as a predictor, the baseline ONH characteristics did not remain significantly associated with myopia progression. Similar results were found if myopia progression was defined as progression of ≥ 1 D in SER over the first 5 years of observation (Supplementary Table S3, available at www.opthalmologyscience.org).

Discussion

This analysis presents longitudinal evaluations of ONH and parapapillary structural changes during myopia progression from childhood to early adulthood over a 15-year observation period, utilizing fundus photographs. We extracted several parameters from fundus photographs and OCT images to track changes of the ONH over time and identify associated factors. We found that above all, the PPA, that is, the beta zone ratio and the position of the CRVT, changed the most. These changes were most significantly associated with older age and longer AL. None of the structural ONH changes were associated with the 3 different atropine concentrations applied during ATOM2.

The main findings of our study were that most of the ONH parameters, measured on the fundus photographs, changed over time. Most importantly, the PPA ratio and the location of the CRVT exit changed: the PPA ratio increased over time, reflecting the increase in the prevalence and size of the beta zone, usually in the temporal parapapillary area. The observed increase in the beta zone ratio occurred parallel to the increase in AL, with a more rapid increase in the

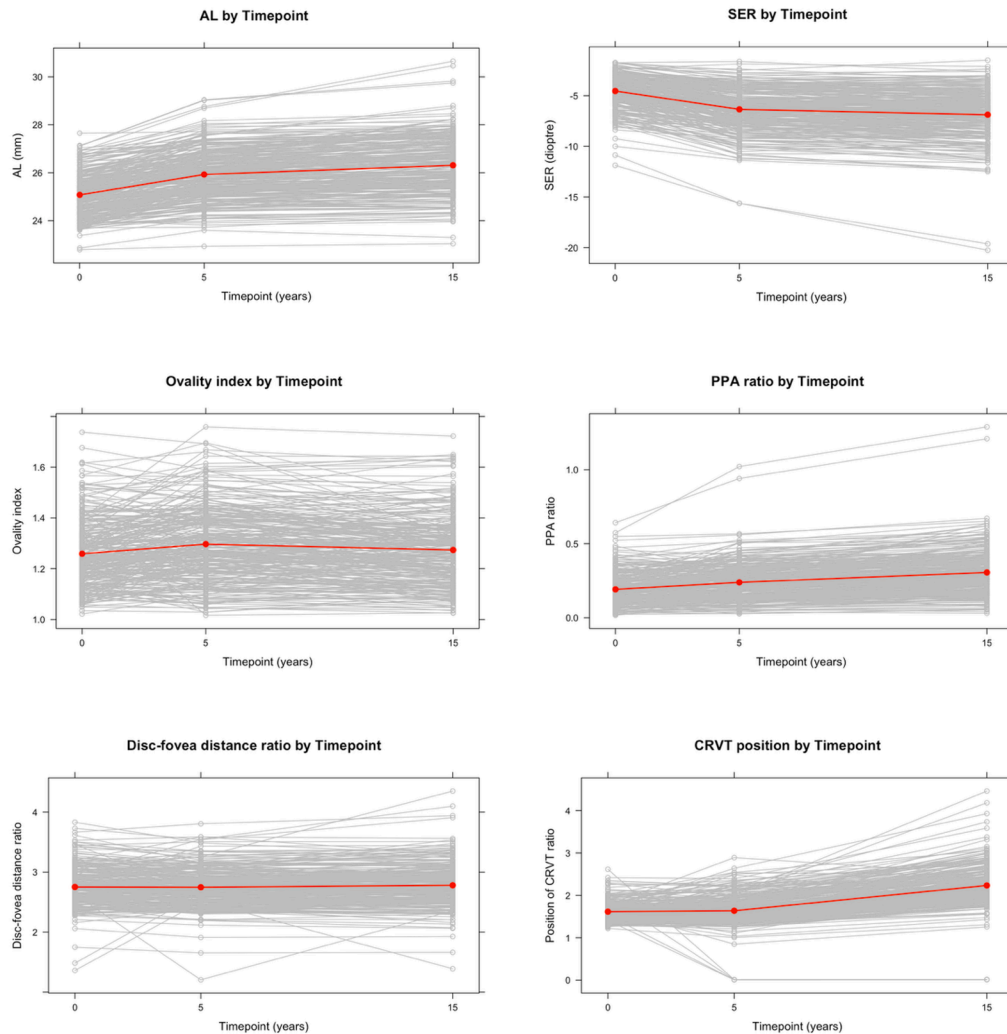


Figure 3. Longitudinal changes in ocular and ONH metrics. These plots illustrates the progression of ocular and ONH parameters, including SER, AL, disc ovality, beta zone ratio (PPA), disc–fovea distance ratio, and CRVT exit position across various timepoints (0, 5, and 15 years). Individual data trajectories are illustrated in gray, while the red points represent the mean values at each timepoint, allowing for visualization of trends and potential changes over time. AL = axial length; CRVT = central retinal vascular trunk; ONH = optic nerve head; PPA = peripapillary atrophy; SER = spherical equivalent refraction.

first 5 years of the observation period, when the participants were 9 to 14 years old, and then continued to augment, but with a flatter slope. The position of the CRVT exit showed a relative nasal shift. Interestingly, this shift was most pronounced in the second half of the observation period, from 14 to 24 years of age. Also, changes in the optic disc ovality, the disc torsion angle, and the disc–fovea distance ratio were observed. The measured disc torsion angle and the disc–fovea distance ratio increased over time, but the measured changes were smaller. Especially the torsion degree showed a very large variability and a moderate agreement between the 2 graders.

The main findings of our study may be contextualized within existing literature, particularly with the work of Kim et al and Guo et al.^{12,18,20} Kim et al investigated the changes in ONH parameters, such as PPA in relation to AL, over 2 years. Their results indicated that changes in

the ONH were most pronounced in eyes classified as having developed a parapapillary beta zone, with significant increases in gamma zone associated with axial elongation. This supports our findings of an increased beta zone ratio over time, reflecting a similar pattern of PPA. Notably, the association between axial elongation and ONH changes, such as the CRVT exit position observed in our study, is furthermore in line with Kim et al’s observation that myopic changes are linked to alterations in the ONH structure, such as the position of the CRVT exit.

Guo et al further contributed to these observations by examining the longitudinal changes in disc–fovea distance and the width of the parapapillary gamma zone among grade-1 children. They found a marked increase in zone width correlating with longer AL and longer disc–fovea distance, also suggesting that early myopic changes are

Table 4. Estimates of Fixed Effects by Multivariable Generalized Linear Mixed-Effect Models for the Factors Associated with Changing ONH Characteristics

| Multivariable Models | PPA Ratio | | | Torsion | | | Disc–Fovea Distance Ratio | | | Position of CRVT | | |
|---------------------------|-----------|----------------|-------------------|----------|----------------|-------------------|---------------------------|----------------|-------------------|------------------|----------------|-------------------|
| | Estimate | Standard Error | P Value | Estimate | Standard Error | P Value | Estimate | Standard Error | P Value | Estimate | Standard Error | P Value |
| Multivariable Model I* | | | | | | | | | | | | |
| Age | 0.002 | 0.000 | <0.0001 | 0.166 | 0.046 | <0.0001 | −0.004 | 0.001 | 0.005 | 0.041 | 0.002 | <0.0001 |
| AL | 0.015 | 0.007 | 0.045 | | | | −0.041 | 0.023 | 0.074 | −0.002 | 0.031 | 0.947 |
| SER | −0.014 | 0.003 | <0.0001 | | | | 0.003 | 0.010 | 0.783 | 0.015 | 0.014 | 0.320 |
| Ovality | 0.294 | 0.025 | <0.0001 | −4.192 | 3.561 | 0.243 | −0.106 | 0.079 | 0.185 | 0.460 | 0.124 | <0.0001 |
| PPA ratio | | | | −10.828 | 4.096 | 0.009 | 1.012 | 0.096 | <0.0001 | 0.685 | 0.156 | <0.0001 |
| Torsion | −0.001 | 0.000 | 0.011 | | | | −0.002 | 0.001 | 0.015 | | | |
| Disc–fovea distance ratio | 0.114 | 0.011 | <0.0001 | −4.679 | 1.470 | 0.002 | | | | 0.142 | 0.051 | 0.005 |
| Position of CRVT | 0.038 | 0.007 | <0.0001 | | | | 0.050 | 0.020 | 0.012 | | | |
| Multivariable Model II† | | | | | | | | | | | | |
| Age | | | <0.0001 | | | 0.001 | | | <0.0001 | | | <0.0001 |
| AL | | | <0.0001 | | | | | | <0.0001 | | | <0.0001 |
| SER | | | | | | | | | | | | |
| Ovality | | | 0.005 | | | 0.747 | | | 0.340 | | | 0.073 |
| PPA ratio | | | | | | | | | | | | |
| Torsion | | | | | | | | | | | | |
| Disc–fovea distance ratio | | | | | | | | | | | | |
| Position of CRVT | | | | | | | | | | | | |

AL = axial length; CRVT = central retinal vascular trunk; ONH = optic nerve head; PPA = peripapillary atrophy; SER = spherical equivalent refraction. Bold values indicate statistical significant.

*Interactions between the predictors are not considered.

†Interactions between AL and SE, between ovality index, PPA, torsion, disc–fovea distance ratio, and position of the CRVT.

Table 5. Univariate Generalized Linear Mixed-Effect Model Determination of Factors Associated with ONH Characteristics Measured on OCT Images at ATLAS Recall

| Univariate Models | Bruch Membrane Opening Distance (BMOD) | | | Gamma Zone | | | Bruch Membrane Overhanging | | |
|----------------------------|--|----------------|-------------------|------------|----------------|-------------------|----------------------------|----------------|--------------|
| | Estimate | Standard Error | P Value | Estimate | Standard Error | P Value | Estimate | Standard Error | P Value |
| Age | -17.400 | 14.700 | 0.240 | -5.960 | 11.690 | 0.610 | -10.960 | 7.350 | 0.130 |
| AL | 56.200 | 15.200 | <0.0001 | 68.700 | 12.900 | <0.0001 | 25.210 | 9.020 | 0.005 |
| SER | -29.700 | 7.000 | <0.0001 | -38.010 | 5.910 | <0.0001 | -11.820 | 4.450 | 0.008 |
| PPA ratio | 409.600 | 84.300 | <0.0001 | 1005.120 | 58.787 | <0.0001 | 93.500 | 67.400 | 0.160 |
| Position of CRVT | -8.720 | 27.830 | 0.760 | 60.900 | 25.800 | 0.019 | -14.500 | 20.400 | 0.480 |
| | | | | 0.551 | 0.041 | <0.0001 | -0.034 | 0.041 | 0.410 |
| Gamma zone | 0.642 | 0.051 | <0.0001 | | | | 0.084 | 0.048 | 0.081 |
| Bruch membrane overhanging | -0.086 | 0.058 | 0.140 | 0.177 | 0.059 | 0.003 | | | |
| Atropine | | | 0.740 | | | 0.670 | | | 0.078 |
| Atropine 0.1% | 18.200 | 59.400 | | 27.800 | 47.000 | | 63.100 | 29.300 | |
| Atropine 0.5% | 43.500 | 59.700 | | 42.200 | 47.300 | | 28.800 | 29.500 | |
| Retreatment, yes | 6267.000 | 4306.000 | 0.140 | 2360.300 | 3432.300 | 0.490 | 2112.100 | 2168.500 | 0.330 |

AL = axial length; ATLAS = Atropine Treatment Long-Term Assessment Study; CRVT = central retinal vascular trunk; ONH = optic nerve head; PPA = peripapillary atrophy; SER = spherical equivalent refraction. Bold values indicate statistical significant.

mainly driven by axial elongation. In our analysis, we observed that the increase in the PPA ratio was parallel to the increase in AL, particularly notable during the early years of observation from ages 9 to 14 years. This parallels Guo et al’s findings, highlighting the importance of axial elongation in shaping optic nerve morphology and risk factors associated with myopia.

Although our study does shed light on these significant structural changes in the ONH associated with myopia progression, it is essential to recognize that previous studies, such as those by Kim et al and Guo et al, have focused on shorter time frames or different childhood populations. Our long-term approach over 15 years provides a unique perspective, allowing for the observation of gradual changes

Table 6. Estimates of Fixed Effects by Multivariable Generalized Linear Mixed-Effect Model for the Factors Associated with ONH Characteristics Measured on OCT Images

| Multivariable Models | BMOD | | | Gamma Zone | | | Bruch Membrane Overhanging | | |
|----------------------------|----------|----------------|-------------------|------------|----------------|-------------------|----------------------------|----------------|--------------|
| | Estimate | Standard Error | P Value | Estimate | Standard Error | P Value | Estimate | Standard Error | P Value |
| Multivariable Model I* | | | | | | | | | |
| Age | | | | | | | | | |
| AL | 8.910 | 19.546 | 0.642 | -8.756 | 10.724 | 0.406 | 16.690 | 14.250 | 0.240 |
| SER | -6.909 | 9.444 | 0.461 | -6.056 | 5.369 | 0.253 | -5.300 | 7.020 | 0.450 |
| PPA ratio | -291.337 | 97.234 | 0.003 | 776.925 | 54.359 | <0.0001 | | | |
| Position of CRVT | | | | -6.238 | 15.261 | 0.669 | | | |
| BMOD | | | | 0.378 | 0.032 | <0.0001 | | | |
| Gamma zone | 0.752 | 0.069 | <0.0001 | | | | | | |
| Bruch membrane overhanging | | | | 0.123 | 0.039 | 0.003 | | | |
| Multivariable Model II† | | | | | | | | | |
| Age | | | | | | | | | |
| AL | | | <0.0001 | | | 0.390 | | | 0.002 |
| SER | | | | | | | | | |
| PPA ratio | | | 0.001 | | | 0.180 | | | |
| Position of CRVT | | | | | | | | | |
| BMOD | | | | | | 0.920 | | | |
| Gamma zone | | | <0.0001 | | | | | | |
| Bruch membrane overhanging | | | | | | | | | |

AL = axial length; BMOD = Bruch membrane opening distance; CRVT = central retinal vascular trunk; ONH = optic nerve head; PPA = peripapillary atrophy; SER = spherical equivalent refraction.

Bold values indicate statistical significant.

*Interactions between the predictors are not considered.

†Interactions between AL and SE, between PPA and the position of the CRVT, as well as between BMOD, gamma zone, and Bruch membrane overhanging.

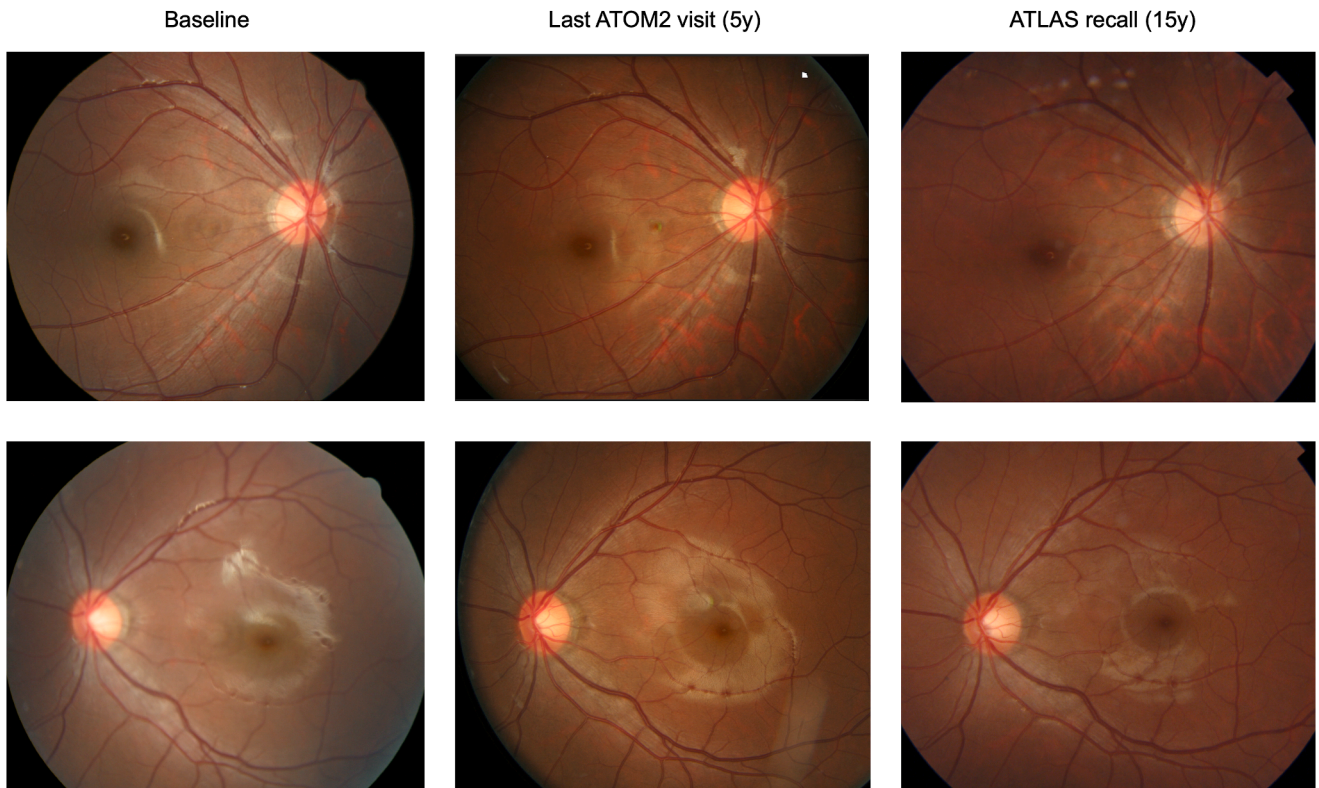


Figure 4. Examples of fundus photographs of a right (upper row) and a left (lower row) eye of 2 different study participants at the 3 timepoints analyzed. The second case illustrates how the ovality of the ONH could vary over time; with an increase followed by a decrease. ONH = optic nerve head.

in ONH parameters like disc–fovea distance ratio and position of the CRVT, which may not have been thoroughly examined in earlier studies.

Although we observed significant structural changes in the ONH associated with axial elongation during myopia progression, we only found the baseline PPA ratio and the disc–fovea distance ratio to be separately associated with an increase of myopia and a progression of -2 D or more over 15 years. However, in the multivariable model, only age was predictive for progression. It suggests that there is still a clear need for more detailed evaluations and targeted monitoring of those who demonstrate the most progression to better understand the underlying factors and improve management strategies.

The observed longitudinal changes in the ONH morphology might be explained by a speculative hypothesis that axial elongation is associated with a shift of Bruch membrane opening distance usually toward the direction of the macula, explaining the overhanging of Bruch membrane into the intrapapillary nasal compartment, the corresponding absence of Bruch membrane in the temporal parapapillary region (i.e., temporal gamma zone), and the ovalization of the optic disc shape due to the shortening of the horizontal optic disc diameter.⁷⁻⁹

Mostly because changes in ONH parameters had not previously been defined as outcomes of the ATOM1 and 2 studies, our study faced some limitations, including that the imaging techniques were not standardized across all

examination time points. Predominantly limiting was the fact that acquisition of OCT imaging was only conducted at the final ATLAS recall visit, preventing longitudinal analysis using this modality. Although 2 independent graders measured all the fundus photos, and their agreement was good for the majority of the measured ONH parameters, the reproducibility of some parameters (eg, VDA ratio and angle kappa) is questionable. This could be explained by the graders using different branches of the arterial arcades for measurements. Additionally, the relatively small sample size limits the statistical power to reliably compare the different atropine treatment groups. Furthermore, the absence of fundus photographs of an untreated myopic control group, as well as the lack of a nonmyopic comparator group, limits our ability to isolate the potential effects of atropine treatment from changes that may occur during the natural myopia progression. Although our analysis found no significant associations between atropine concentration and ONH morphology, the lack of a control group means that we cannot draw definitive conclusions about causality. This long-term longitudinal study suggests that subjects with myopia who received atropine treatment during the ATOM2 study and were followed up into young adulthood primarily exhibited changes of the ONH in the form of increased PPA and a nasal shift of the CRVT.

Despite this, the study's strengths are notable: The study involved a substantial cohort, which was observed over a long observation period of 15 years. The extensive data

collection allows for a more comprehensive understanding of ONH parameter changes over time. Also, the measurement and quantification of ONH parameters from fundus photographs and OCT images were conducted systematically, demonstrating a high intergrader agreement. This consistency in grading enhances the reliability of the collected data and the subsequent findings. Finally, the application of mixed-effects models, which account for both fixed effects and random effects, further supported the results by addressing the issue of intereye correlations and accommodating the longitudinal nature of the data.

Our findings emphasize that structural alterations in the ONH are predominantly associated with axial elongation and that the ONH morphology continues to change after the

peak increase in AL during childhood and early adolescence. This suggests that it may be clinically relevant to monitor the ONH into young adulthood, especially to better understand the factors that may cause further complications. Also, the presence of beta zone and gamma zone PPA, if observed early on, may be indicative of future progression and the need for a prompt clinical intervention to slow down ocular growth.

In summary, this study provides data on the progression of ONH changes in myopic children and young adults; however, further research is needed to explore the implications of these changes on long-term ocular health, including their relation to glaucoma and nonglaucomatous myopic optic disc changes.

Footnotes and Disclosures

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All authors have completed and submitted the ICMJE disclosures form.

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HUMAN SUBJECTS: Human subjects were included in this study. The ATLAS received approval from the Institutional Review Board of the Singapore Eye Research Institute (No. 2020/2249), ensuring compliance with ethical standards. Written informed consent was obtained from all participants prior to their inclusion in the study, aligning with the tenets of the Declaration of Helsinki.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Eppenberger, Chia, Schmetterer, Jonas, Ang

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Analysis and interpretation: Eppenberger, Wong, Chong, Jonas, Ang

Obtained funding: Ang

Overall responsibility: Eppenberger, Cheng, Wong, Chia, Wong, Chong, Schmetterer, Jonas, Ang

Data Availability

The participants of this study did not give written consent for their data to be shared publicly; hence, the research supporting data are not available.

Abbreviations and Acronyms:

AL = axial length; **ATLAS** = Atropine Treatment Long-Term Assessment Study; **ATOM** = Atropine for the Treatment of Myopia; **CRVT** = central retinal vascular trunk; **D** = diopters; **ONH** = optic nerve head; **PPA** = parapapillary atrophy; **SER** = spherical equivalent refraction; **VDA** = vertical distance between the arterial arcade.

Keywords:

Optic disc, Optic nerve head, Myopia progression, Parapapillary atrophy, Central retinal vascular trunk, Atropine.

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