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Age, ocular magnification, and circumpapillary retinal nerve fiber layer thickness

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Abstract. Optical coherence tomography (OCT) manufacturers graphically present circumpapillary retinal nerve fiber layer thickness (cpRNFLT) together with normative limits to support clinicians in diagnosing ophthalmic diseases. The impact of age on cpRNFLT is typically implemented by linear models. cpRNFLT is strongly location-specific, whereas previously published norms are typically restricted to coarse sectors and based on small populations. Furthermore, OCT devices neglect impacts of lens or eye size on the diameter of the cpRNFLT scan circle so that the diameter substantially varies over different eyes. We investigate the impact of age and scan diameter reported by Spectralis spectral-domain OCT on cpRNFLT in 5646 subjects with healthy eyes. We provide cpRNFLT by age and diameter at 768 angular locations. Age/diameter were significantly related to cpRNFLT on 89%/92% of the circle, respectively (pointwise linear regression), and to shifts in cpRNFLT peak locations. For subjects from age 42.1 onward but not below, increasing age significantly decreased scan diameter ($r = -0.28$, $p < 0.001$), which suggests that pathological cpRNFLT thinning over time may be underestimated in elderly compared to younger subjects, as scan diameter decrease correlated with cpRNFLT increase. Our detailed numerical results may help to generate various correction models to improve diagnosing and monitoring optic neuropathies. [DOI: 10.1117/1.JBO.22.12.121718]

Keywords: normative retinal nerve fiber layer profile; age-related thinning; ocular magnification; scan diameter; optical coherence tomography; glaucoma.

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1 Introduction

The normative profile of circumpapillary retinal nerve fiber layer thickness (cpRNFLT) is important to identify abnormal thinning of cpRNFLT, which is one of the hallmarks for glaucoma diagnosis and progression monitoring.[1,2] It is well known that the normative cpRNFLT decreases with increased age.[3,4] Moreover, studies have shown that the thinning of normative cpRNFLT with age is highly location-specific.[5,6] However, the location specificity of the age-related thinning varies among different studies. For example, Parikh et al.[5] have shown the age-related thinning rate of cpRNFLT in superior and inferior quadrants to be the maximum and minimum among the four quadrants, respectively. By contrast, Leung et al.[6] have shown the age-related thinning rate of cpRNFLT to be the maximum in inferior and minimum in nasal quadrants, respectively. The varying results of the quadrant specificity of age-related cpRNFLT thinning might be due to the relative small study populations in those studies, as all their results are based on less than 250 eyes. A second limitation of previously published cpRNFLT norms is their restriction on coarsely defined sectors, which neglects the large location specificity of cpRNFLT over the entire scan circle. One of the few studies that presented 12 instead of four to six sectors[7] demonstrates this location-specific variability.

Besides the correlation between the normative cpRNFLT and age, studies have also shown the cpRNFLT to be related to factors that represent the eye anatomy, including ocular axial length and the spherical equivalent (SE) of the refractive error.[8,9] More specifically, it has been shown that thinner cpRNFLT is associated with larger axial length and more myopia.[10–12] Ocular magnification formulas have been proposed to estimate the actual scan diameter from axial length and SE.[13,14] However, to our best knowledge, none of the clinical ophthalmic optical coherence tomography (OCT) devices takes the true scan diameter into account. Typically, manufacturers report to apply a fixed size of measurement/scan circle, for instance, for Cirrus HD-OCT (Carl Zeiss Meditec, Jena, Germany), the cpRNFLT on the standard measurement circle with 3.46-mm diameter is extracted from the volume scans without considering the variation of individual eye size.[15]

To our best knowledge, none of the clinical retinal OCT devices measures the true circle diameter on the retina. Heidelberg Spectralis internally estimates the circle size in mm based on the focus settings adjusted by the device operator prior to the scan.[14] This estimated diameter is not part of the printout and therefore not easily accessible to clinicians, but it can be electronically exported from the machine.

In this study, we will leverage a large population-based study to investigate the relationships between age, the scan diameter

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reported by the employed Spectralis OCT, and the full pointwise cpRNFLT profile in participants with healthy eyes.

2 Methods

This investigation is part of the Leipzig Research Centre for Civilization Diseases (LIFE) adult study.[16] The LIFE adult study was approved by the institutional ethics board of the Medical Faculty of Leipzig University and adheres to the Declaration of Helsinki. The written informed consent was obtained from all participants.

2.1 *Participants and Data Description*

The population-based LIFE adult study[16] involved an age and gender stratified random sample of the residents of the city of Leipzig, Germany. In total, 10,000 participants were recruited, with 514 participants in the age group between 18 and 39 years and 9486 participants between 40 and 79 years.

For 17,974 eyes of 9069 participants, Heidelberg Spectralis cpRNFLT OCT scans with a resolution of 768 measurement points around the optic nerve head (ONH) were available. In all of those eyes, nonmydriatic fundus imaging (Nidek AFC-230) and further OCT scans of the macular and papillary areas were additionally obtained.[16] On all images, degenerative changes and abnormalities were classified according to current ophthalmic standards.

Three sources of information were available for this step prior to analysis: (a) self-reported questionnaire including full list of diagnosed eye diseases, (b) all medications of the subject taken at time of test (all details/packages were brought in by the subject, the full list was coded and entered into the LIFE database using international classifications), and (c) ophthalmic examination of fundus and OCT images and resulting clinically significant diseases found. For the ophthalmic examination, two ophthalmologically trained readers graded all eyes separately based on macular and papillary OCT images and 45 deg color fundus photography and formed a consensus decision. The following categories were employed: "clinical" (i.e., eye disease present), "subclinical" and "free of subclinical or clinical signs" as well as "nongradable" (i.e., poor image quality). The exclusion criteria include manifestation of retina-related diseases defined by the following: (a) self-reported data on glaucoma diagnosis or status of prescribed glaucoma medication and (b) clinical findings at the papillary area, clinical findings at the macula, and clinical findings within the periphery (retinal area outside papillary and macular areas). This resulted in exclusion of any retinal or optic nerve disease objectively present. Cataract and anterior eye segment problems (granting the image was obtained in the first place) were not excluded. It is important for the current analysis to be strict on exclusion of retinal or optic nerve lesion as they potentially affect the cpRNFLT, and we aim to establish our model free from disease-based bias.

For the current analyses, subjects with manifestation of retina-related diseases or nongradable images in any of the two eyes were excluded. Furthermore, to ensure the reliability of the cpRNFLT measurements, only circle scans with image quality ≥20 dB, average number of B-scans ≥50, and no more than 5% missing or unreliable cpRNFLT segmentations among the 768 A-scans were included. Unreliable cpRNFLT segmentations were defined as measurements above 99.5% or below 0.5% quantiles among the cpRNFLT distribution for all measurement locations of all OCT scans. If both eyes of a participant met the aforementioned selection criteria, only one eye was randomly selected.

2.2 *Description of Scan Diameter*

The Heidelberg Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) device used in this study specifies a fixed circle diameter of 12 deg in the device settings, projected onto the retinal plane, as shown in Fig. 1(a), which corresponds to approximately a 3.5-mm diameter scan circle size on the retinal plane based on the standard eye model employed in the machine.[14,17] While the Spectralis machine always projects a fixed measurement circle into the eye, the size of the scan diameter on the retina varies with individual ocular parameters, particularly axial length and corneal curvature. For example, the actual scan diameter can be larger for eyes with larger axial length and smaller for eyes with shorter axial length, as illustrated in Fig. 1(a). Within the Spectralis OCT, conversion of this 12 deg circle scan into mm is achieved by calculations based on defocus correction and corneal curvature, as detailed in the work by Garway-Heath et al.[14]

Figure 1(b) illustrates the cpRNFLT circle, the coordinate system used in this study, and the effect of varying circle diameters. Superimposed on the ONH-centered infrared fundus image of the right eye of a 42-year old participant, a typical cpRNFLT measurement circle (solid circle) is depicted and an illustrative larger circle (dashed circle) is overlaid. In addition, the schematic trajectories of the cpRNFLT peaks are illustrated

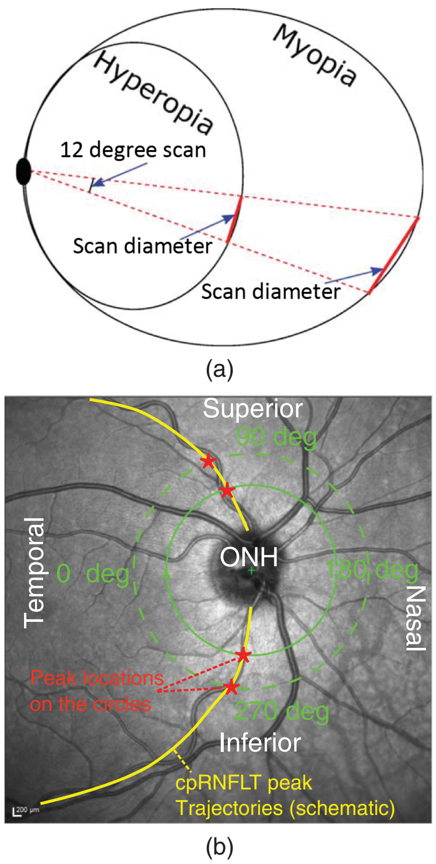

Fig. 1 (a) Schematic illustration of scan diameter variation with respect to axial length of the eye and (b) schematic illustration of the cpRNFLT measurement circle around the ONH including the effect of varying circle diameters.

(curves in superior/inferior temporal direction). These trajectories are correlated to the major temporal-superior/temporal-inferior arteries. As illustrated, the nonlinear curvy trajectories of the main nerve fiber bundles cause relative shifts of the angular positions of the cpRNFLT peak locations (illustrated by asterisks) if the measurement circle diameter changes. In addition, cpRNFLT is naturally thinner with increasing diameter for myopes due to ocular elongation.[10,11]

In this study, we employed the scan diameter as a measure of ocular magnification. The scan diameter in mm measured by Spectralis OCT is based on the scan focus parameters as a surrogate measure of refractive error and standard corneal curvature, as detailed in the work by Garway-Heath et al.[14] Within the current investigation, we deliberately employed only parameters routinely available from the Spectralis OCT device to ensure that our results can immediately be applied to all Spectralis OCT data without requiring additional tools or machines.

2.3 *Statistical Analyses*

All statistical analyses were performed by R platform.[18] First, the inter-relationships between age, scan diameter, and global cpRNFLT were evaluated. Segmented regression was performed to examine whether there are different relationships between age and scan diameter for different age groups. Second, multiple linear regressions were performed from age and scan diameter to global, quadrantal, and clock-hour cpRNFLTs, respectively, in comparison to the univariate regressions from age to global, quadrantal, and clock-hour cpRNFLTs. Third, we compared the spatial profiles of cpRNFLT between groups with younger and older ages with enforced no significant group difference of scan diameter, as well as between groups with smaller and larger scan diameters with enforced no significant group difference of age, in order to decouple the potential underlying interactive effects between age and scan diameter. Last, multivariate linear regressions were performed from age and scan diameter to pointwise cpRNFLT over all 768 measurement locations on the scan circle. The p values were adjusted for multiple comparisons.[19]

The context for our extensive linear regression analyses is that all ophthalmic OCT manufacturers and also many research scientists currently implement linear models to capture the influence of age. In a linear model, two parameters are required: First, a point estimate of cpRNFLT for a fixed age (or diameter) and second, an estimate for how cpRNFLT changes per year, which we call "slope" in this work. The current analysis provides point estimates for specific age groups and slopes separately in depicted figures. This allows device manufacturers to store only these two values for each of the 768 measurement locations to quantify the location-specific deviations of a patient's individual cpRNFLT from the norm. These individual deviations may be used by clinicians to support diagnostic statements. Furthermore, since optic neuropathies like glaucoma are progressive diseases, it is diagnostically important to compare the patients' individual age slope with the normative age slope for the respective measurement location (or sector), as provided in our study. For this purpose, diameter slopes are relevant as well.

3 Results

From 17,974 eyes of 9069 participants, 3329 participants were excluded in total due to any of the following exclusion criteria (or a combination of them): any clinically significant findings based on prior ophthalmic examination of fundus images and obtained OCT scans (2676 subjects), nongradable images due to poor image quality (2 subjects), a glaucoma diagnosis reported in the interview (613 subjects), the presence of glaucoma medication among all the medications the participant took at the time of the test (38 subjects). The 188 eyes from 94 participants were excluded due to unreliable measurements. After all data selection procedures, 5646 eyes from 5646 participants were selected for data analyses. The mean $\pm$ standard deviation of age was 54.9 ± 12.1 years. There were 2553 male and 3093 female participants.

The detailed ethnic proportion of the participants in LIFE study can be found in Table 1. The subjects of the current investigation are predominantly Caucasian (99.22%). The recruitment of participants in the LIFE study was performed by randomly selecting Leipzig residents from the city registration office. Citizens were sent invitation letters, and study participation depended on response. In the years of the data acquisition, the east German city of Leipzig had a low percentage of foreign residents (between 5% and 10%), most of them from European countries. Among the very small proportion of residents of non-European race, the response rate was extraordinarily low, particularly due to language issues. Therefore, the percentage of non-Caucasian participants in the current data sample is negligible (0.78%), and a race-specific data analysis was not feasible.

Figures 2(a) and 2(b) show the distributions of age and scan diameter over all subjects, respectively. Since the LIFE adult study focuses on the age group of 40 to 75 years, as detailed above, there were fewer subjects with age under 40 years. The trend that the number of subjects decreased with increasing age was due to excluding participants with clinical signs on OCT or fundus images or nongradable images, as described above, or due to excluding patients with diagnosed glaucoma or possible optic neuropathy, as shown in Fig. 2(a), since there was a higher proportion of those cases for older subjects. As shown in Fig. 2(b), the scan diameter was normally distributed with peak at the 3.5-mm diameter, which was the scan circle size for the standard eye model used on the machine with corneal radius set to be 7.8 mm and scan focus to be an individual measure of refractive error.

The scan diameter was mildly and inversely correlated to age ($r = -0.30$, $p < 0.001$). The results of segmented regression from age to scan diameter suggested that the scan diameter was differently related to age for age group younger/older than 42.1

Table 1 The ethnic proportion of the participants in LIFE study.

European Descent	Arabic/Middle Eastern Descent	Central Asian Descent	East Asian Descent	Latin American Descent	African Descent	Mixed Ethnicity
99.22%	0.22%	0.20%	0.12%	0.09%	0.06%	0.09%

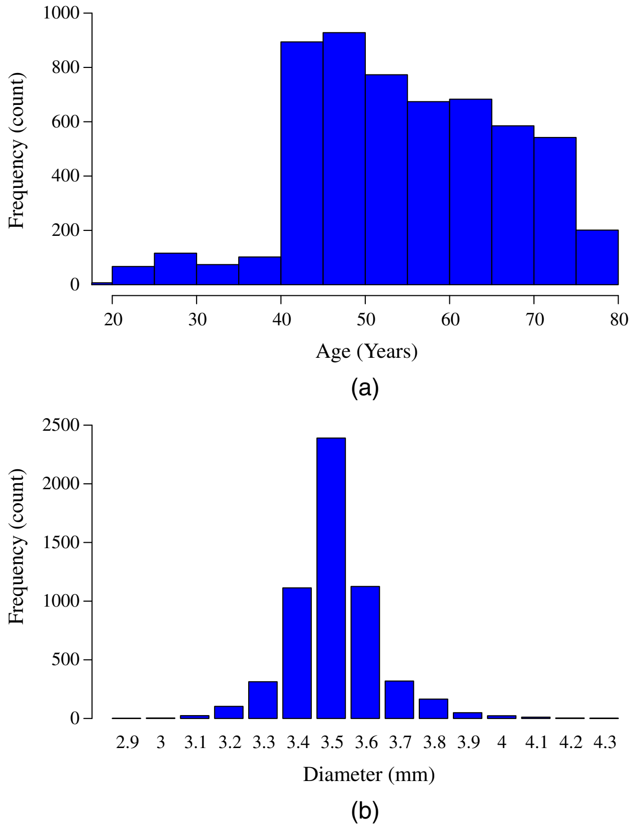

Fig. 2 The distribution of (a) age and (b) scan diameter over all subjects. The LIFE adult study focuses on the age range of 40 to 75 years. While the Spectralis machine projects a measurement circle with a fixed radius of 12 deg into the eye, the size of the scan diameter on the retina varies with individual ocular parameters, particularly axial length and corneal curvature.

years old, which was detected as a break point for age by the segmented regression. For subjects under 42.1 years, there was no significant correlation between age and scan diameter ($r = -0.04$, $p = 0.27$), whereas the correlation was -0.28 ($p < 0.001$) for subjects over 42.1 years. In addition, the global RNFLT was inversely correlated to scan diameter ($r = -0.25$, $p < 0.001$) as expected. In comparison, the global RNFLT was inversely correlated to age ($r = -0.12$, $p < 0.001$).

Table 2 shows the age slopes and p values obtained from (1) "univariate regression" from age to global and quadrant-specific cpRNFLTs compared to the slopes and p values of age and scan diameter obtained by (2) "multivariate regression" from age and diameter to global and quadrant-specific cpRNFLTs. Global cpRNFLT increased with decreasing scan diameter. Without considering the effect of scan diameter, the age slope was substantially underestimated (-0.09 μm/year) compared the age slope with adjusted effect of scan diameter (-0.17 μm/year). Sectoral cpRNFLT decreased with increasing scan diameter except for the temporal cpRNFLT. Accordingly, the age slopes were mostly underestimated when not including the effect of scan diameter except for temporal cpRNFLT, for which the age slope was overestimated without including the effect of scan diameter. In addition, for the nasal sector, the age slope shifted from insignificant thickening to significant thinning after adjusting for the scan diameter effect.

Table 3 shows the age slopes and p values obtained by univariate regression from age to clock-hour-specific RNFLTs compared to the slopes and p values of age and scan diameter obtained by multivariate regression. Mean cpRNFLT for clock-hour 8, 9, 10, and 11 increased with decreased scan diameter while the mean cpRNFLT for all other clock-hour sectors decreased. The sector with the strongest scan diameter effect was clock-hour 6. In addition, there were three clock-hour sectors (clock-hour 3, 4, and 6) with positive age slopes when not adjusting for the scan diameter effect, which were counter-intuitive if we assume that there is no age-related thickening. After adjusting the effect of scan diameter, all age slopes were negative, as expected. The fastest age-related thinning was in clock-hour 8 and 7 before and after adjusting the scan diameter effect.

Figure 3 shows the spatial profile of the mean cpRNFLT for (a) younger (35 to 45 years) and older (55 to 65 years) age groups and (b) larger ($\geq$3.7 mm) and smaller ($\leq$3.4 mm) scan diameter groups for subjects, respectively. To decouple the interactive effects between age and scan diameter on mean cpRNFLT: for age group comparison, we restricted the scan diameter to 3.5 mm, which was the most frequent diameter among the participants; for scan diameter group comparison, we restricted the subject age to be under 42.1 years, as we did not find a significant correlation between diameter and age for this age group (see above). Overall, the cpRNFLT peaks of the older group (555 subjects between 55-65 years) are more nasal than

Table 2 The age slopes and p values with (1) "univariate regression" from age to global and quadrant-specific cpRNFLTs in comparison to the slopes and p values of age and scan diameter with (2) "multivariate regression" from age and diameter to global and quadrant-specific cpRNFLTs. The table is to demonstrate how the ocular magnification can bias the estimation of age-related thinning rate of global and quadrant cpRNFLT as most previous works have not included ocular magnification in their cpRNFLT norm model.

	Univariate		Multivariate			
RNFLT	Age slope (μm/year)	p value for age	Age slope (μm/year)	p value for age	Diameter slope (μm/mm)	p value for diameter
Global	−0.09	<0.001	−0.17	<0.001	−22.47	<0.001
Temporal	−0.14	<0.001	−0.11	<0.001	6.65	<0.001
Superior	−0.14	<0.001	−0.23	<0.001	−27.6	<0.001
Nasal	0.03	0.09	−0.08	<0.001	−32.4	<0.001
Inferior	−0.13	<0.001	−0.24	<0.001	−36.62	<0.001

Table 3 The age slopes and p values with univariate regression from age to clock-hour-specific RNFLTs in comparison to the slopes and p values of age and scan diameter with multivariate regression from age and diameter to clock-hour-specific RNFLTs.

	Univariate		Multivariate			
RNFLT	Age slope (μm/year)	p value for age	Age slope (μm/year)	p value for age	Diameter slope (μm/mm)	p value for diameter
1 O'clock	−0.05	0.05	−0.16	<0.001	−33.53	<0.001
2 O'clock	−0.08	<0.001	−0.21	<0.001	−39.56	<0.001
3 O'clock	0.07	<0.001	−0.04	0.03	−35.58	<0.001
4 O'clock	0.05	0.001	−0.03	0.09	−22.46	<0.001
5 O'clock	−0.04	0.03	−0.17	<0.001	−38.17	<0.001
6 O'clock	0.02	0.54	−0.16	<0.001	−55.8	<0.001
7 O'clock	−0.19	<0.001	−0.31	<0.001	−38.71	<0.001
8 O'clock	−0.29	<0.001	−0.25	<0.001	13.22	<0.001
9 O'clock	−0.07	<0.001	−0.06	<0.001	5.19	<0.001
10 O'clock	−0.11	<0.001	−0.1	<0.001	3.34	0.005
11 O'clock	−0.28	<0.001	−0.26	<0.001	8.06	<0.001
12 O'clock	−0.13	<0.001	−0.24	<0.001	−35.76	<0.001

those of the younger group (454 subjects between 35 to 45 years). The superior and inferior peaks of the older group were located at 2.80 deg ($p = 0.01$) and 2.83 deg ($p < 0.001$) nasal to the younger group. The cpRNFLT peaks of the smaller scan diameter group were more nasal than the larger scan diameter group. The superior and inferior peaks of the smaller scan diameter group (97 subjects) were located at 9.77 deg ($p = 0.006$) and 7.83 deg ($p = 0.002$) nasal to the larger scan diameter group (194 subjects). There was no significant group age difference ($p = 0.41$) between the smaller (37.1 years) and larger (36.2 years) scan diameter groups.

Figures 4(a) and 4(b) show the spatial profile of age and scan diameter slopes to predict cpRNFLT in comparison to the spatial profile of mean RNFLT for all age subjects, respectively. The superior and inferior locations with largest age-related thinning rates were positioned at 9.76 deg and 3.78 deg ($p < 0.001$ for both, bootstrapping) temporal to the mean superior and inferior RNLFT peaks. Conversely, the superior and inferior locations with cpRNFLT, which presented with the steepest change for a decrease in scan diameter were positioned at 15.32 deg and 30.65 deg ($p < 0.001$ for both, bootstrapping) nasal to the mean superior and inferior RNLFT peaks.

This detailed cpRNFLT results based on over 5600 participants allow a comparison with the cpRNFLT norms of the Spectralis OCT device (based on only 201 eyes of 201 participants), which are employed for the standard clinical printout. Here, we illustratively perform this comparison for two cases. Figures 5(a) and 5(b) show the spatial profile of projected mean cpRNFLT norms based on our age and scan diameter model for a 47-year old subject with 3.5-mm scan diameter and a 75 years subject with 4.4-mm scan diameter in comparison to the Spectralis OCT machine norms, respectively. Those two exemplary cases were chosen to represent the variation of age and scan diameter. For the superior temporal region of the 47-year old participant with 3.5-mm scan diameter, our projected mean cpRNFLT was thinner than the machine norms, and the superior peak of our projected norms was more nasal than the machine norms, which might be explained by our findings in Fig. 4(a) that the fastest age-related thinning locations were temporal to the mean cpRNFLT peaks. The difference between our projected norms and machine norms might also be caused by the possibly higher resolution in our study, as we calculated pointwise models for all 768 measurement points. The considerably lower population size for the Spectralis norms might not have allowed such a pointwise approach. For the 75-year old subject with 4.4-mm scan diameter, our projected norms were substantially thinner than the machine norms and the mean cpRNFLT peak locations of our projected norms were more nasal compared to the machine norms, which might be mostly explained by the current findings in that larger scan diameter corresponding to thinner cpRNFLT and more temporal cpRNFLT peaks, as shown in Figs. 3(b) and 4(b).

To enhance comparisons with previously published age-specific cpRNFLT norms or the norms used by the different OCT machines, all of which ignored effects of scan diameter, we additionally provide the cpRNFLT quantiles of the study participants for different age decades, as shown in Fig. 6. Finally, this study provides the numerical coefficients for the multivariate regression models of all 768 measurement points in the Appendix, which may help scientists or manufacturers to apply both age and diameter corrections to cpRNFLT measurements.

4 Discussion

In this study, we not only verified the strong negative correlation between age and cpRNFLT at an unprecedented level of detail based on over 5600 participants of a population-based study but also demonstrated detailed location-specific effects of the scan diameter independent of as well as in relation to age. Our results

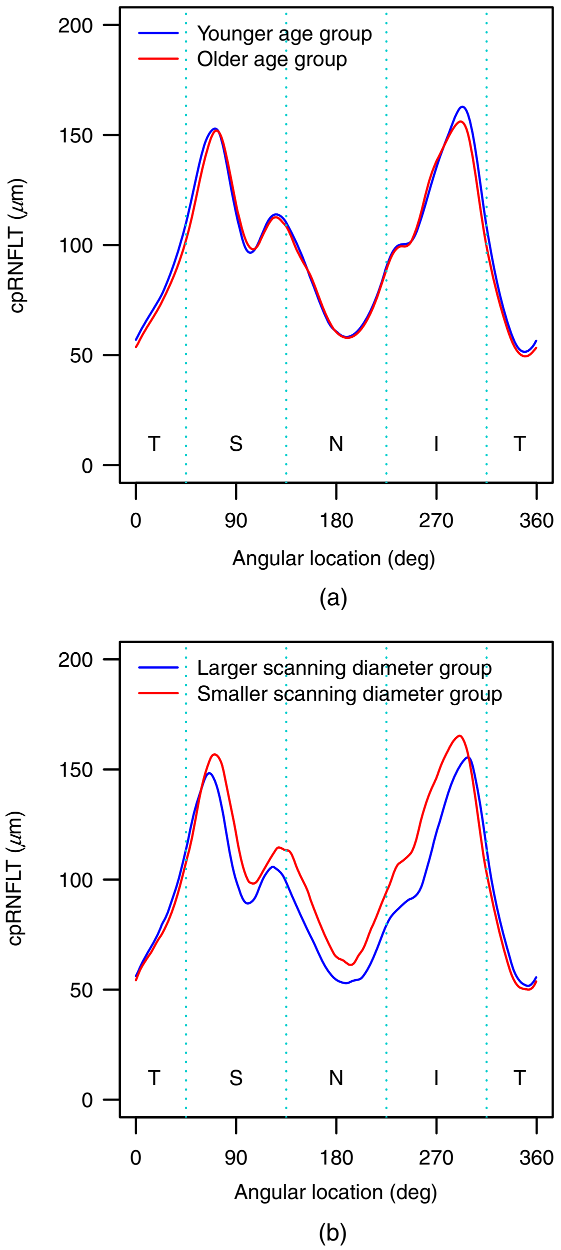

Fig. 3 The spatial profile of the mean cpRNFLT for (a) younger (454 subjects between 35 and 45 years) and older (555 subjects between 55 and 65 years) age groups for subjects with 3.5 mm scan diameter and (b) larger (≥3.7 mm) and smaller (≤3.4 mm) scan diameter groups for subjects under 42.1 years, respectively.

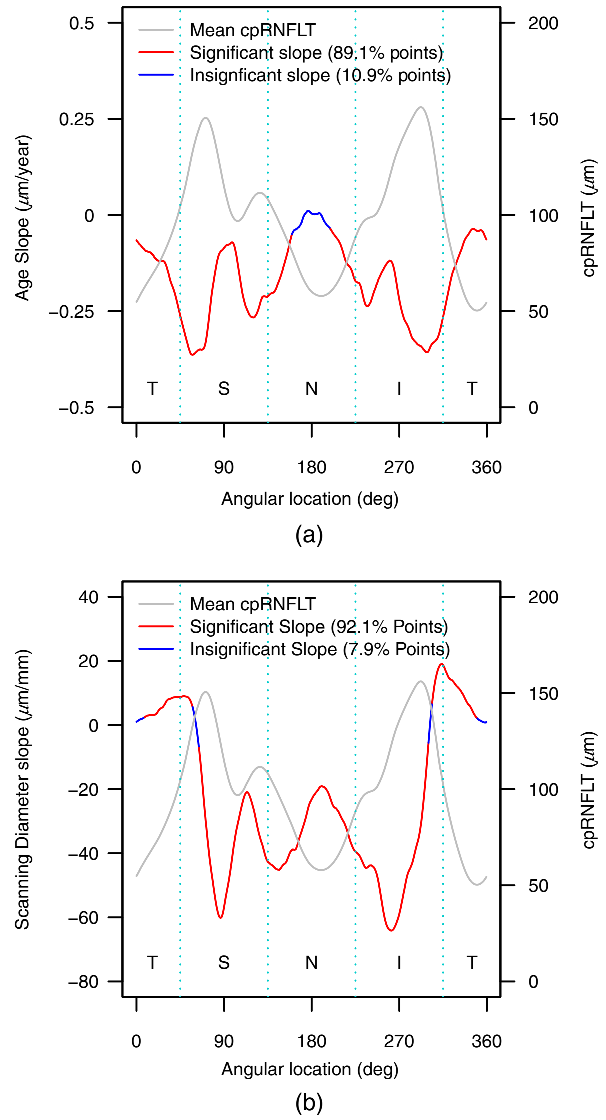

Fig. 4 The spatial profile of (a) age slope and (b) scan diameter slope to predict cpRNFLT in comparison to the spatial profile of mean cpRNFLT for all subjects. This figure is the visualization of our point-wise cpRNFLT model based on age and scan diameter, which is described in detail in Table 4 in the Appendix.

with a spatial resolution of 768 measurement points show that both parameters are strongly location-specific, which could not be sufficiently described by previous studies that focused on global averages or coarsely defined sectors. In particular, increasing age and decreasing scan diameter are related to cpRNFLT profiles with more nasalized superior and inferior peaks. The very detailed graphical and numerical presentation of our results in the Appendix may help researchers and manufacturers to improve their normative cpRNFLT models.

A further central finding of this study is the significant "correlation between age and scan diameter" for participants of age 42.1 or older. As cpRNFLT decreases with age as well as with increasing scan diameter commonly reported in literature, the systematic decrease of the diameter with age for participants older than 42.1 years implies that the true age-specific cpRNFLT thinning effect is underestimated for elderly individuals if the values are not corrected for diameter. In addition, there are implications for clinical practice, as current disease progression models for optic neuropathies like glaucoma are typically based on cpRNFLT slopes over time. Our results demonstrate, for instance, that in the absence of diameter correction, which is current clinical practice, a slope that indicates glaucomatous nerve fiber layer thinning in a young patient will be steeper than the slope for an elderly patient, even if both patients suffer from exactly the same level of thinning, because the elderly patient is additionally subject to a decrease of the scan diameter over time.

Previous works typically explained differences in scan diameter with axial ametropia.[10,11] For axial myopia, the extension in ocular length yields larger diameters of the projection of the circle on the retina, and cpRNFLT correction models have

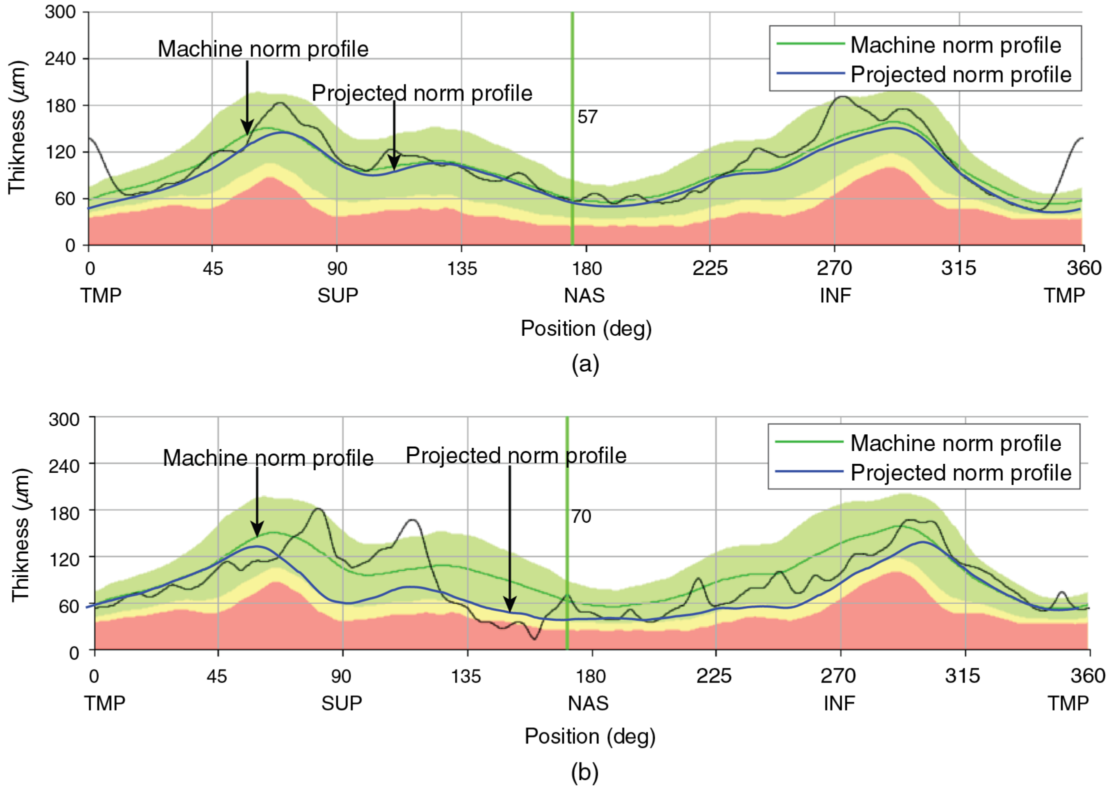

Fig. 5 The spatial profile of age-specific cpRNFLT norms for (a) a 47-year-old subject with 3.5-mm scan diameter and (b) a 75-year-old subject with 4.4-mm scan diameter. For this graphical comparison, our projected norms (thick blue lines) were overlaid on the printouts of the two example participants. The thin black lines denote the actual measurement values of the subjects and are ignored here. Instead, our comparison focuses on the dark green lines, which denote the medians of the machine norms for these two ages.

been proposed based on ocular axial length.[10] This effect, however, is unlikely to explain the relationship between diameter and age for elderly participants of the current study, as there are no indications that axial length systematically decreases at higher age. Instead, we assume this relationship to be caused by lens-related effects. Elderly individuals are not only subject to the well-known effect of presbyopia, which concerns near vision, but also to previously documented hyperopic shifts for distance vision.[20,21] These lens-related phenomena might explain the systematic decrease in scan diameter, which is otherwise typical for axial hyperopia in younger individuals.

Regarding the particular value of the results of the current investigation compared to the previous studies on ocular magnification and cpRNFLT,[10,11] two aspects need to be highlighted. First, our considerably larger sample size of over 5000 subjects substantially improves the reliability of the normative results and furthermore allows an unprecedented level of detail in terms of spatial resolution (measurements at 768 locations on the circle). In the previous studies, fewer than 300 subjects participated (e.g., 269 subjects in the work by Kang et al.[10] and 45 subjects in the work by Savini et al).[11] Our large age-stratified sample allows us to cover a wide age range from 19 to 80 years, whereas the age range in the work by Kang et al.[10] was restricted between 19 and 26 years. Note that optic neuropathies predominantly affect elderly people, which further stresses the additional benefit of the current results. Second, and more importantly, our study adjusts the effects of age and ocular magnification simultaneously. Only by this, we were able to show that age and scan diameter interact for elderly populations, so that adjusting the effects of axial length alone might not be sufficient for the generation of new cpRNFLT norms. This finding, which previous studies were unable to detect, is of special importance for scientists and OCT manufacturers alike.

As all participants who reported to have been diagnosed with glaucoma were excluded, regardless of whether they took glaucoma medication or had any clinically significant findings on their fundus/OCT images or nongradable images, participants who erroneously reported having glaucoma would have been excluded in our study as well. The strict exclusion criteria ensured to discard any subject with possible confounding diseases.

We did not exclude subjects based on cataract. First, cataract does not pathologically affect the cpRNFLT, and second, by excluding all cataract patients, we would unnecessarily bias our normative models. This is of particular importance, as due to the high cataract prevalence in elderly populations, a large proportion of patients presenting at clinical glaucoma services for cpRNFLT measurement will have cataracts, so that cpRNFLT norms should include cataract patients to account for the fact of its frequent occurrence in the total population to avert sampling bias.

This investigation also has limitations. First, the cross-sectional design of this study does not allow tracking changes of the scan diameter over age on an individual base. This will be made possible based on follow-up measurements on the same subjects in future. Second, the dataset contains an imbalanced

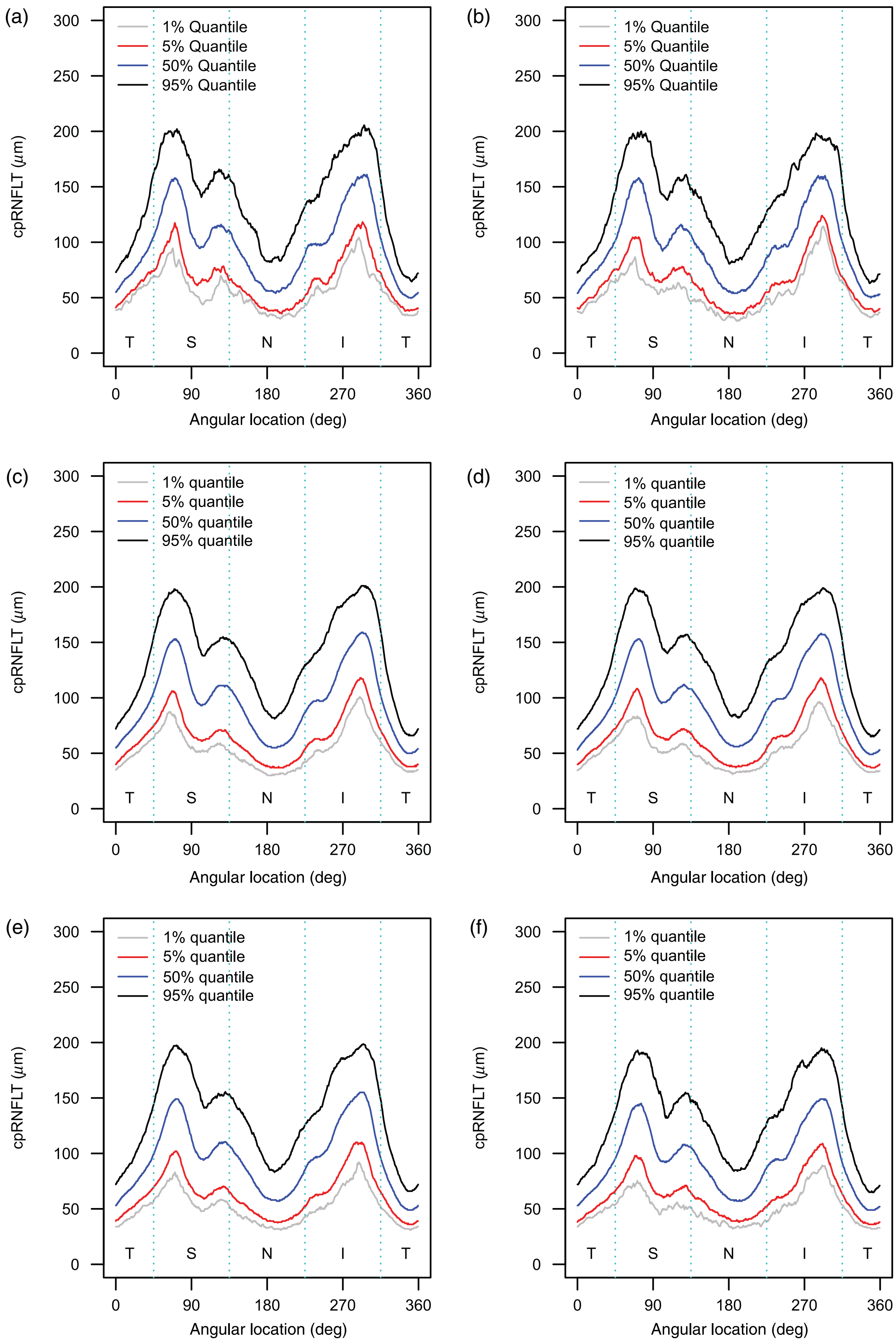

Fig. 6 The spatial profile of cpRNFLT at different quantiles for different age groups: (a) 19 to 30 years old, (b) 30 to 40 years old, (c) 40 to 50 years old, (d) 50 to 60 years old, (e) 60 to 70 years old, and (f) 70 to 80 years old.

gender ratio. Potential gender effects should be further investigated as part of future analyses. Third, the current study is based on subjects that are predominantly Caucasian, which restricts the applicability of extracted norms to Caucasian populations, and future studies are needed to investigate how generalizable the results are with respect to other ethnicities. However, it has to be noted that the current normative dataset of the Spectralis SD-OCT device approved by the US Food and Drug Administration is also solely based on a Caucasian population. Last, as the scan diameter reported by the Spectralis machine in mm for each subject is estimated based on the scan focus setting made by the operator and standard corneal curvature with a default value of 7.8 mm for mean anterior corneal radius, two further limitations of Spectralis scan diameter calculation also apply to the current dataset: (a) the manual setting of the focus is subjective and may vary between operators and (b) corneal radius is not measured on an individual basis in the current study.

Axial length was not measured in the course of the LIFE study due to capacity limitations, so it was not available for the current data analysis. The availability of axial length data would extend the scientific utility of the current work. However, none of the clinically used OCT machines currently measures axial length, so its inclusion, while interesting for the scientific community, would probably not be of immediate relevance to the improvement of cpRNFLT norms of current OCT devices. Instead, the current analysis employs scan diameter as the measure of ocular magnification, which is related to axial length and is immediately available from the OCT machine. This scan diameter is routinely calculated by the machine from the scan focus, based on a specific eye model.[14] While the major part of scan diameter variance is explained by axial length, it additionally contains lens-related aspects not covered by axial length, and the current investigation indeed found a significant relationship of scan diameter and age, which could not have been revealed by including axial length alone.

The current work is of immediate relevance for scientists, engineers, and OCT manufacturers. The investigation of the impact of age and ocular magnification (scan diameter) on a clinically very important measurement protocol (cpRNFLT) has an unprecedentedly high spatial resolution (768 measurement locations on the scan circle), which can be achieved due to this extraordinarily large sample size (5646 subjects). While this study clearly has clinical utility by demonstrating the considerable impact of these parameters, the main consequence of this work targets research into the engineering of the OCT device itself and its inherent norms. The current work clearly demonstrates that: (a) the location specificity of existing age norms used in the Spectralis OCT machine, based on only 201 subjects,[17] can be significantly improved by the presented detailed, high resolution model' (b) the location specificity and the quantitative effect of the scan diameter is at least as substantial as the effect of age. Diameter effects are currently entirely neglected by OCT machines, and while they have previously been discussed in the literature, although only indirectly in the context of axial length, a location-specific quantification of the effect and the introduction of detailed normative distributions (detailed in Table 4 in the Appendix) are novel, to our best knowledge; (c) we demonstrate that scan diameter decreases with age, which is also, to our best knowledge, an entirely novel finding. One of the conclusions of this newly reported relationship, particularly important for OCT manufacturers, is that it is insufficient to base personalized cpRNFLT norms on axial length, as suggested by numerous previous works. Axial length remains constant in elderly subjects, but the scan diameter nevertheless systematically decreases, which indicates lens-related explanations; and (d) normative models are of particular importance for medical device manufactures with a need to be integrated into OCT machines. The quantitative presentation of our results and the particular level of numerical and statistical details is aimed at research scientists of ophthalmic companies and allows not only the support of the generation of novel cpRNFLT norms, which is the main purpose of our study, but also subsequently the implementation of diagnostic models for disease progression by comparing these normative cpRNFLT slopes to individual slopes of patients, etc.

To summarize, in this work, we study the interrelationship between cpRNFLT, age, and scan diameter at an unprecedented level of detail. These results may help researchers and manufacturers to improve their normative cpRNFLT models. Besides, we reveal a systematic relationship between age and diameter, which is restricted to elderly people based on our results. This finding likely has clinical relevance, as current disease progression methods to quantify cpRNFLT thinning over time are based on slopes, which are assumed to be independent of the baseline age of patients. Therefore, pathological cpRNFLT thinning might be underestimated in elderly patients compared to younger patients.

Appendix

Table 4 provides the numerical coefficients of age slope, scan diameter slope, and intercept for the multivariate regression models of cpRNFLT for all 768 measurement points on the scan circle with starting point on the horizontal line towards the temporal direction. Table 4 may help scientists or manufacturers to apply both age and diameter corrections to cpRNFLT measurements.

Table 4 The age slope, scan diameter slope, and intercept of the multivariate regression model with accompanying *p* values for all 768 measurement points on the scan circle with starting point on the horizontal line towards the temporal direction, as illustrated in Fig. 1.

	Age slope	Age *p* value	Diameter slope	Diameter *p* value	Intercept	Intercept *p* value
Point 1	−0.07	<0.001	1.01	0.4	54.86	<0.001
Point 2	−0.07	<0.001	1.1	0.37	55.08	<0.001
Point 3	−0.07	<0.001	1.21	0.32	55.17	<0.001
Point 4	−0.07	<0.001	1.31	0.29	55.35	<0.001
Point 5	−0.07	<0.001	1.38	0.26	55.62	<0.001
Point 6	−0.07	<0.001	1.53	0.22	55.62	<0.001
Point 7	−0.08	<0.001	1.55	0.21	56.08	<0.001
Point 8	−0.08	<0.001	1.66	0.18	56.21	<0.001
Point 9	−0.08	<0.001	1.76	0.16	56.35	<0.001
Point 10	−0.08	<0.001	1.85	0.14	56.55	<0.001
Point 11	−0.08	<0.001	1.91	0.13	56.86	<0.001
Point 12	−0.08	<0.001	1.86	0.14	57.54	<0.001
Point 13	−0.08	<0.001	1.92	0.12	57.85	<0.001
Point 14	−0.08	<0.001	2.05	0.1	57.89	<0.001
Point 15	−0.09	<0.001	2.1	0.09	58.24	<0.001
Point 16	−0.09	<0.001	2.13	0.09	58.62	<0.001
Point 17	−0.09	<0.001	2.26	0.07	58.62	<0.001
Point 18	−0.09	<0.001	2.37	0.05	58.7	<0.001
Point 19	−0.09	<0.001	2.43	0.05	58.99	<0.001
Point 20	−0.09	<0.001	2.52	0.04	59.2	<0.001

Table 4 (*Continued*).

	Age slope	Age *p* value	Diameter slope	Diameter *p* value	Intercept	Intercept *p* value
Point 21	−0.09	<0.001	2.64	0.03	59.18	<0.001
Point 22	−0.09	<0.001	2.71	0.03	59.4	<0.001
Point 23	−0.09	<0.001	2.84	0.02	59.34	<0.001
Point 24	−0.09	<0.001	2.9	0.02	59.55	<0.001
Point 25	−0.09	<0.001	2.95	0.02	59.79	<0.001
Point 26	−0.1	<0.001	2.94	0.02	60.25	<0.001
Point 27	−0.1	<0.001	3.01	0.02	60.38	<0.001
Point 28	−0.1	<0.001	3.01	0.02	60.81	<0.001
Point 29	−0.1	<0.001	3.07	0.01	60.97	<0.001
Point 30	−0.1	<0.001	3.15	0.01	61.07	<0.001
Point 31	−0.1	<0.001	3.12	0.01	61.6	<0.001
Point 32	−0.1	<0.001	3.19	0.01	61.79	<0.001
Point 33	−0.1	<0.001	3.15	0.01	62.33	<0.001
Point 34	−0.1	<0.001	3.16	0.01	62.8	<0.001
Point 35	−0.1	<0.001	3.22	0.01	62.93	<0.001
Point 36	−0.1	<0.001	3.17	0.01	63.61	<0.001
Point 37	−0.1	<0.001	3.24	0.01	63.76	<0.001
Point 38	−0.11	<0.001	3.18	0.02	64.47	<0.001
Point 39	−0.11	<0.001	3.23	0.01	64.71	<0.001
Point 40	−0.11	<0.001	3.18	0.02	65.43	<0.001
Point 41	−0.11	<0.001	3.26	0.02	65.62	<0.001
Point 42	−0.11	<0.001	3.25	0.02	66.12	<0.001
Point 43	−0.11	<0.001	3.33	0.01	66.32	<0.001
Point 44	−0.11	<0.001	3.44	0.01	66.39	<0.001
Point 45	−0.12	<0.001	3.61	0.009	66.24	<0.001
Point 46	−0.12	<0.001	3.75	0.008	66.3	<0.001
Point 47	−0.12	<0.001	3.99	0.005	65.9	<0.001
Point 48	−0.12	<0.001	4.21	0.003	65.61	<0.001
Point 49	−0.12	<0.001	4.42	0.002	65.32	<0.001
Point 50	−0.12	<0.001	4.65	0.001	64.98	<0.001
Point 51	−0.12	<0.001	4.82	0.001	64.85	<0.001
Point 52	−0.12	<0.001	4.98	<0.001	64.77	<0.001
Point 53	−0.12	<0.001	5.14	<0.001	64.7	<0.001
Point 54	−0.12	<0.001	5.19	<0.001	64.99	<0.001
Point 55	−0.12	<0.001	5.27	<0.001	65.15	<0.001
Point 56	−0.12	<0.001	5.37	<0.001	65.3	<0.001
Point 57	−0.12	<0.001	5.43	<0.001	65.57	<0.001
Point 58	−0.12	<0.001	5.48	<0.001	65.93	<0.001
Point 59	−0.12	<0.001	5.64	<0.001	65.85	<0.001
Point 60	−0.12	<0.001	5.87	<0.001	65.59	<0.001
Point 61	−0.12	<0.001	6.07	<0.001	65.46	<0.001
Point 62	−0.12	<0.001	6.24	<0.001	65.43	<0.001
Point 63	−0.12	<0.001	6.49	<0.001	65.16	<0.001
Point 64	−0.13	<0.001	6.74	<0.001	65.01	<0.001
Point 65	−0.13	<0.001	7.03	<0.001	64.64	<0.001

Table 4 (*Continued*).

	Age slope	Age *p* value	Diameter slope	Diameter *p* value	Intercept	Intercept *p* value
Point 66	−0.13	<0.001	7.29	<0.001	64.47	<0.001
Point 67	−0.13	<0.001	7.55	<0.001	64.28	<0.001
Point 68	−0.14	<0.001	7.65	<0.001	64.7	<0.001
Point 69	−0.14	<0.001	7.83	<0.001	64.9	<0.001
Point 70	−0.15	<0.001	7.96	<0.001	65.22	<0.001
Point 71	−0.15	<0.001	8.03	<0.001	65.81	<0.001
Point 72	−0.16	<0.001	8.07	<0.001	66.51	<0.001
Point 73	−0.16	<0.001	8.13	<0.001	67.14	<0.001
Point 74	−0.17	<0.001	8.17	<0.001	67.86	<0.001
Point 75	−0.17	<0.001	8.2	<0.001	68.61	<0.001
Point 76	−0.17	<0.001	8.26	<0.001	69.21	<0.001
Point 77	−0.18	<0.001	8.3	<0.001	69.84	<0.001
Point 78	−0.18	<0.001	8.37	<0.001	70.45	<0.001
Point 79	−0.18	<0.001	8.45	<0.001	70.98	<0.001
Point 80	−0.19	<0.001	8.54	<0.001	71.46	<0.001
Point 81	−0.19	<0.001	8.56	<0.001	72.22	<0.001
Point 82	−0.19	<0.001	8.63	<0.001	72.86	<0.001
Point 83	−0.2	<0.001	8.63	<0.001	73.76	<0.001
Point 84	−0.2	<0.001	8.67	<0.001	74.54	<0.001
Point 85	−0.2	<0.001	8.64	<0.001	75.57	<0.001
Point 86	−0.21	<0.001	8.69	<0.001	76.36	<0.001
Point 87	−0.21	<0.001	8.72	<0.001	77.25	<0.001
Point 88	−0.22	<0.001	8.7	<0.001	78.35	<0.001
Point 89	−0.22	<0.001	8.71	<0.001	79.37	<0.001
Point 90	−0.23	<0.001	8.63	<0.001	80.73	<0.001
Point 91	−0.23	<0.001	8.7	<0.001	81.58	<0.001
Point 92	−0.24	<0.001	8.74	<0.001	82.56	<0.001
Point 93	−0.24	<0.001	8.65	<0.001	83.95	<0.001
Point 94	−0.25	<0.001	8.69	<0.001	84.97	<0.001
Point 95	−0.25	<0.001	8.65	<0.001	86.23	<0.001
Point 96	−0.26	<0.001	8.69	<0.001	87.23	<0.001
Point 97	−0.26	<0.001	8.68	<0.001	88.47	<0.001
Point 98	−0.27	<0.001	8.71	<0.001	89.52	<0.001
Point 99	−0.27	<0.001	8.77	<0.001	90.45	<0.001
Point 100	−0.28	<0.001	8.81	<0.001	91.53	<0.001
Point 101	−0.28	<0.001	8.9	<0.001	92.4	<0.001
Point 102	−0.29	<0.001	8.96	0.001	93.4	<0.001
Point 103	−0.29	<0.001	8.98	0.001	94.51	<0.001
Point 104	−0.3	<0.001	9	0.001	95.69	<0.001
Point 105	−0.3	<0.001	9.02	0.001	96.82	<0.001
Point 106	−0.3	<0.001	9.02	0.001	98.08	<0.001
Point 107	−0.31	<0.001	8.96	0.002	99.57	<0.001
Point 108	−0.31	<0.001	8.94	0.002	100.93	<0.001
Point 109	−0.32	<0.001	8.91	0.002	102.27	<0.001
Point 110	−0.32	<0.001	8.87	0.002	103.71	<0.001

Table 4 (*Continued*).

	Age slope	Age *p* value	Diameter slope	Diameter *p* value	Intercept	Intercept *p* value
Point 111	−0.33	<0.001	8.84	0.003	105.14	<0.001
Point 112	−0.33	<0.001	8.84	0.003	106.42	<0.001
Point 113	−0.34	<0.001	8.76	0.004	108.07	<0.001
Point 114	−0.34	<0.001	8.65	0.004	109.79	<0.001
Point 115	−0.34	<0.001	8.53	0.005	111.57	<0.001
Point 116	−0.35	<0.001	8.34	0.006	113.52	<0.001
Point 117	−0.35	<0.001	8.19	0.008	115.36	<0.001
Point 118	−0.36	<0.001	7.95	0.01	117.56	<0.001
Point 119	−0.36	<0.001	7.69	0.01	119.73	<0.001
Point 120	−0.36	<0.001	7.34	0.02	122.18	<0.001
Point 121	−0.36	<0.001	7	0.02	124.54	<0.001
Point 122	−0.36	<0.001	6.56	0.04	127.24	<0.001
Point 123	−0.36	<0.001	6.17	0.05	129.72	<0.001
Point 124	−0.36	<0.001	5.64	0.07	132.68	<0.001
Point 125	−0.36	<0.001	5.05	0.11	135.78	<0.001
Point 126	−0.36	<0.001	4.45	0.16	138.91	<0.001
Point 127	−0.36	<0.001	3.82	0.23	142.14	<0.001
Point 128	−0.36	<0.001	3.08	0.33	145.69	<0.001
Point 129	−0.36	<0.001	2.31	0.46	149.33	<0.001
Point 130	−0.36	<0.001	1.44	0.65	153.29	<0.001
Point 131	−0.36	<0.001	0.64	0.84	156.97	<0.001
Point 132	−0.36	<0.001	−0.31	0.92	161.17	<0.001
Point 133	−0.36	<0.001	−1.33	0.67	165.56	<0.001
Point 134	−0.35	<0.001	−2.38	0.45	170.04	<0.001
Point 135	−0.35	<0.001	−3.51	0.26	174.74	<0.001
Point 136	−0.35	<0.001	−4.68	0.13	179.55	<0.001
Point 137	−0.35	<0.001	−5.87	0.06	184.47	<0.001
Point 138	−0.35	<0.001	−7.15	0.02	189.63	<0.001
Point 139	−0.35	<0.001	−8.45	0.006	194.82	<0.001
Point 140	−0.35	<0.001	−9.78	0.002	200.1	<0.001
Point 141	−0.35	<0.001	−11.2	<0.001	205.68	<0.001
Point 142	−0.35	<0.001	−12.61	<0.001	211.17	<0.001
Point 143	−0.35	<0.001	−14.19	<0.001	217.23	<0.001
Point 144	−0.35	<0.001	−15.71	<0.001	222.97	<0.001
Point 145	−0.35	<0.001	−17.35	<0.001	229.14	<0.001
Point 146	−0.35	<0.001	−19.01	<0.001	235.28	<0.001
Point 147	−0.35	<0.001	−20.76	<0.001	241.69	<0.001
Point 148	−0.35	<0.001	−22.44	<0.001	247.82	<0.001
Point 149	−0.35	<0.001	−24.09	<0.001	253.62	<0.001
Point 150	−0.34	<0.001	−25.72	<0.001	259.42	<0.001
Point 151	−0.34	<0.001	−27.29	<0.001	264.78	<0.001
Point 152	−0.33	<0.001	−28.77	<0.001	269.83	<0.001
Point 153	−0.33	<0.001	−30.34	<0.001	275.04	<0.001
Point 154	−0.32	<0.001	−31.67	<0.001	279.25	<0.001
Point 155	−0.31	<0.001	−33.08	<0.001	283.66	<0.001

Table 4 (*Continued*).

	Age slope	Age *p* value	Diameter slope	Diameter *p* value	Intercept	Intercept *p* value
Point 156	−0.31	<0.001	−34.55	<0.001	288.17	<0.001
Point 157	−0.3	<0.001	−35.97	<0.001	292.4	<0.001
Point 158	−0.29	<0.001	−37.34	<0.001	296.42	<0.001
Point 159	−0.28	<0.001	−38.67	<0.001	300.17	<0.001
Point 160	−0.27	<0.001	−40.01	<0.001	303.88	<0.001
Point 161	−0.26	<0.001	−41.23	<0.001	307.11	<0.001
Point 162	−0.25	<0.001	−42.46	<0.001	310.27	<0.001
Point 163	−0.24	<0.001	−43.51	<0.001	312.8	<0.001
Point 164	−0.22	<0.001	−44.56	<0.001	315.23	<0.001
Point 165	−0.21	<0.001	−45.62	<0.001	317.64	<0.001
Point 166	−0.21	<0.001	−46.61	<0.001	319.85	<0.001
Point 167	−0.2	<0.001	−47.59	<0.001	322	<0.001
Point 168	−0.19	<0.001	−48.55	<0.001	324.08	<0.001
Point 169	−0.18	<0.001	−49.61	<0.001	326.42	<0.001
Point 170	−0.17	<0.001	−50.64	<0.001	328.71	<0.001
Point 171	−0.17	<0.001	−51.6	<0.001	330.66	<0.001
Point 172	−0.16	<0.001	−52.63	<0.001	332.85	<0.001
Point 173	−0.15	<0.001	−53.54	<0.001	334.58	<0.001
Point 174	−0.14	<0.001	−54.51	<0.001	336.5	<0.001
Point 175	−0.14	<0.001	−55.38	<0.001	338.08	<0.001
Point 176	−0.13	<0.001	−56.2	<0.001	339.45	<0.001
Point 177	−0.12	0.001	−56.97	<0.001	340.68	<0.001
Point 178	−0.12	0.002	−57.58	<0.001	341.34	<0.001
Point 179	−0.11	0.003	−58.27	<0.001	342.29	<0.001
Point 180	−0.11	0.005	−58.75	<0.001	342.53	<0.001
Point 181	−0.11	0.007	−59.27	<0.001	342.96	<0.001
Point 182	−0.1	0.009	−59.64	<0.001	342.82	<0.001
Point 183	−0.1	0.01	−59.88	<0.001	342.34	<0.001
Point 184	−0.1	0.01	−60.04	<0.001	341.54	<0.001
Point 185	−0.1	0.01	−60.15	<0.001	340.62	<0.001
Point 186	−0.09	0.02	−60.11	<0.001	339.16	<0.001
Point 187	−0.09	0.02	−59.99	<0.001	337.47	<0.001
Point 188	−0.09	0.02	−59.79	<0.001	335.49	<0.001
Point 189	−0.09	0.02	−59.39	<0.001	332.82	<0.001
Point 190	−0.09	0.02	−58.88	<0.001	329.78	<0.001
Point 191	−0.09	0.02	−58.32	<0.001	326.57	<0.001
Point 192	−0.09	0.02	−57.56	<0.001	322.64	<0.001
Point 193	−0.09	0.02	−56.73	<0.001	318.49	<0.001
Point 194	−0.08	0.03	−55.95	<0.001	314.54	<0.001
Point 195	−0.08	0.03	−55.14	<0.001	310.58	<0.001
Point 196	−0.08	0.03	−54.25	<0.001	306.28	<0.001
Point 197	−0.08	0.03	−53.44	<0.001	302.32	<0.001
Point 198	−0.08	0.03	−52.67	<0.001	298.55	<0.001
Point 199	−0.08	0.03	−51.86	<0.001	294.7	<0.001
Point 200	−0.08	0.03	−51.13	<0.001	291.18	<0.001

Table 4 (*Continued*).

	Age slope	Age *p* value	Diameter slope	Diameter *p* value	Intercept	Intercept *p* value
Point 201	−0.08	0.03	−50.4	<0.001	287.71	<0.001
Point 202	−0.08	0.03	−49.66	<0.001	284.22	<0.001
Point 203	−0.08	0.03	−48.82	<0.001	280.41	<0.001
Point 204	−0.08	0.02	−48.03	<0.001	276.83	<0.001
Point 205	−0.08	0.02	−47.1	<0.001	272.76	<0.001
Point 206	−0.07	0.02	−46.19	<0.001	268.81	<0.001
Point 207	−0.07	0.02	−45.21	<0.001	264.62	<0.001
Point 208	−0.07	0.03	−44.17	<0.001	260.3	<0.001
Point 209	−0.07	0.03	−43.16	<0.001	256.1	<0.001
Point 210	−0.07	0.03	−42.16	<0.001	252.03	<0.001
Point 211	−0.07	0.02	−41.07	<0.001	247.7	<0.001
Point 212	−0.07	0.02	−40.04	<0.001	243.66	<0.001
Point 213	−0.07	0.02	−38.98	<0.001	239.57	<0.001
Point 214	−0.08	0.01	−37.95	<0.001	235.74	<0.001
Point 215	−0.08	0.009	−37.02	<0.001	232.3	<0.001
Point 216	−0.08	0.005	−36.14	<0.001	229.13	<0.001
Point 217	−0.09	0.003	−35.18	<0.001	225.76	<0.001
Point 218	−0.09	0.001	−34.33	<0.001	222.88	<0.001
Point 219	−0.1	<0.001	−33.52	<0.001	220.21	<0.001
Point 220	−0.11	<0.001	−32.74	<0.001	217.66	<0.001
Point 221	−0.11	<0.001	−32.07	<0.001	215.6	<0.001
Point 222	−0.12	<0.001	−31.46	<0.001	213.86	<0.001
Point 223	−0.13	<0.001	−30.73	<0.001	211.63	<0.001
Point 224	−0.13	<0.001	−30.12	<0.001	209.96	<0.001
Point 225	−0.14	<0.001	−29.51	<0.001	208.3	<0.001
Point 226	−0.15	<0.001	−28.8	<0.001	206.34	<0.001
Point 227	−0.16	<0.001	−28.18	<0.001	204.7	<0.001
Point 228	−0.17	<0.001	−27.5	<0.001	202.9	<0.001
Point 229	−0.17	<0.001	−26.88	<0.001	201.35	<0.001
Point 230	−0.18	<0.001	−26.27	<0.001	199.89	<0.001
Point 231	−0.19	<0.001	−25.64	<0.001	198.3	<0.001
Point 232	−0.2	<0.001	−25.09	<0.001	197.08	<0.001
Point 233	−0.2	<0.001	−24.44	<0.001	195.52	<0.001
Point 234	−0.21	<0.001	−23.88	<0.001	194.27	<0.001
Point 235	−0.21	<0.001	−23.32	<0.001	192.99	<0.001
Point 236	−0.22	<0.001	−22.84	<0.001	191.97	<0.001
Point 237	−0.22	<0.001	−22.45	<0.001	191.33	<0.001
Point 238	−0.23	<0.001	−21.97	<0.001	190.32	<0.001
Point 239	−0.23	<0.001	−21.62	<0.001	189.81	<0.001
Point 240	−0.24	<0.001	−21.38	<0.001	189.69	<0.001
Point 241	−0.24	<0.001	−21.14	<0.001	189.52	<0.001
Point 242	−0.24	<0.001	−20.98	<0.001	189.55	<0.001
Point 243	−0.24	<0.001	−20.94	<0.001	190.04	<0.001
Point 244	−0.25	<0.001	−20.97	<0.001	190.79	<0.001
Point 245	−0.25	<0.001	−20.99	<0.001	191.46	<0.001

Table 4 (*Continued*).

	Age slope	Age *p* value	Diameter slope	Diameter *p* value	Intercept	Intercept *p* value
Point 246	−0.25	<0.001	−21.2	<0.001	192.81	<0.001
Point 247	−0.26	<0.001	−21.49	<0.001	194.43	<0.001
Point 248	−0.26	<0.001	−21.79	<0.001	196.07	<0.001
Point 249	−0.26	<0.001	−22.12	<0.001	197.76	<0.001
Point 250	−0.26	<0.001	−22.53	<0.001	199.69	<0.001
Point 251	−0.26	<0.001	−22.89	<0.001	201.47	<0.001
Point 252	−0.26	<0.001	−23.42	<0.001	203.79	<0.001
Point 253	−0.27	<0.001	−23.8	<0.001	205.57	<0.001
Point 254	−0.27	<0.001	−24.35	<0.001	207.91	<0.001
Point 255	−0.27	<0.001	−24.8	<0.001	209.86	<0.001
Point 256	−0.27	<0.001	−25.34	<0.001	212.18	<0.001
Point 257	−0.27	<0.001	−25.83	<0.001	214.24	<0.001
Point 258	−0.27	<0.001	−26.39	<0.001	216.56	<0.001
Point 259	−0.27	<0.001	−27	<0.001	219.03	<0.001
Point 260	−0.27	<0.001	−27.58	<0.001	221.31	<0.001
Point 261	−0.26	<0.001	−28.26	<0.001	223.88	<0.001
Point 262	−0.26	<0.001	−28.97	<0.001	226.51	<0.001
Point 263	−0.26	<0.001	−29.61	<0.001	228.89	<0.001
Point 264	−0.26	<0.001	−30.35	<0.001	231.58	<0.001
Point 265	−0.26	<0.001	−31.05	<0.001	234.03	<0.001
Point 266	−0.25	<0.001	−31.75	<0.001	236.48	<0.001
Point 267	−0.25	<0.001	−32.43	<0.001	238.81	<0.001
Point 268	−0.25	<0.001	−32.98	<0.001	240.68	<0.001
Point 269	−0.24	<0.001	−33.63	<0.001	242.79	<0.001
Point 270	−0.24	<0.001	−34.13	<0.001	244.37	<0.001
Point 271	−0.23	<0.001	−34.67	<0.001	246.04	<0.001
Point 272	−0.23	<0.001	−35.16	<0.001	247.5	<0.001
Point 273	−0.23	<0.001	−35.67	<0.001	249.03	<0.001
Point 274	−0.22	<0.001	−36.14	<0.001	250.44	<0.001
Point 275	−0.22	<0.001	−36.56	<0.001	251.69	<0.001
Point 276	−0.22	<0.001	−36.97	<0.001	252.87	<0.001
Point 277	−0.21	<0.001	−37.4	<0.001	254.1	<0.001
Point 278	−0.21	<0.001	−37.98	<0.001	255.94	<0.001
Point 279	−0.21	<0.001	−38.49	<0.001	257.59	<0.001
Point 280	−0.21	<0.001	−39.01	<0.001	259.2	<0.001
Point 281	−0.21	<0.001	−39.54	<0.001	260.84	<0.001
Point 282	−0.21	<0.001	−40.13	<0.001	262.72	<0.001
Point 283	−0.21	<0.001	−40.56	<0.001	263.97	<0.001
Point 284	−0.21	<0.001	−41.09	<0.001	265.56	<0.001
Point 285	−0.21	<0.001	−41.54	<0.001	266.89	<0.001
Point 286	−0.21	<0.001	−41.86	<0.001	267.67	<0.001
Point 287	−0.21	<0.001	−42.21	<0.001	268.62	<0.001
Point 288	−0.21	<0.001	−42.45	<0.001	269.09	<0.001
Point 289	−0.21	<0.001	−42.65	<0.001	269.33	<0.001
Point 290	−0.21	<0.001	−42.87	<0.001	269.71	<0.001

Table 4 (*Continued*).

	Age slope	Age *p* value	Diameter slope	Diameter *p* value	Intercept	Intercept *p* value
Point 291	−0.21	<0.001	−42.95	<0.001	269.5	<0.001
Point 292	−0.21	<0.001	−43	<0.001	269.2	<0.001
Point 293	−0.21	<0.001	−43.12	<0.001	269.13	<0.001
Point 294	−0.21	<0.001	−43.31	<0.001	269.31	<0.001
Point 295	−0.2	<0.001	−43.43	<0.001	269.21	<0.001
Point 296	−0.2	<0.001	−43.54	<0.001	269.08	<0.001
Point 297	−0.2	<0.001	−43.64	<0.001	268.95	<0.001
Point 298	−0.2	<0.001	−43.7	<0.001	268.63	<0.001
Point 299	−0.2	<0.001	−43.8	<0.001	268.48	<0.001
Point 300	−0.2	<0.001	−43.9	<0.001	268.38	<0.001
Point 301	−0.2	<0.001	−44.07	<0.001	268.41	<0.001
Point 302	−0.2	<0.001	−44.19	<0.001	268.26	<0.001
Point 303	−0.2	<0.001	−44.36	<0.001	268.32	<0.001
Point 304	−0.2	<0.001	−44.46	<0.001	268.09	<0.001
Point 305	−0.2	<0.001	−44.65	<0.001	268.16	<0.001
Point 306	−0.19	<0.001	−44.75	<0.001	267.9	<0.001
Point 307	−0.19	<0.001	−44.87	<0.001	267.71	<0.001
Point 308	−0.19	<0.001	−44.95	<0.001	267.31	<0.001
Point 309	−0.18	<0.001	−45	<0.001	266.81	<0.001
Point 310	−0.18	<0.001	−45.06	<0.001	266.37	<0.001
Point 311	−0.18	<0.001	−45.13	<0.001	265.93	<0.001
Point 312	−0.18	<0.001	−45.14	<0.001	265.28	<0.001
Point 313	−0.17	<0.001	−45.12	<0.001	264.55	<0.001
Point 314	−0.17	<0.001	−45.19	<0.001	264.11	<0.001
Point 315	−0.17	<0.001	−45.04	<0.001	262.87	<0.001
Point 316	−0.16	<0.001	−44.9	<0.001	261.69	<0.001
Point 317	−0.16	<0.001	−44.7	<0.001	260.24	<0.001
Point 318	−0.16	<0.001	−44.54	<0.001	259	<0.001
Point 319	−0.15	<0.001	−44.28	<0.001	257.3	<0.001
Point 320	−0.15	<0.001	−44.11	<0.001	255.96	<0.001
Point 321	−0.14	<0.001	−43.87	<0.001	254.38	<0.001
Point 322	−0.14	<0.001	−43.74	<0.001	253.13	<0.001
Point 323	−0.14	<0.001	−43.54	<0.001	251.63	<0.001
Point 324	−0.13	<0.001	−43.43	<0.001	250.51	<0.001
Point 325	−0.13	<0.001	−43.38	<0.001	249.54	<0.001
Point 326	−0.12	<0.001	−43.26	<0.001	248.36	<0.001
Point 327	−0.12	<0.001	−43.13	<0.001	247.13	<0.001
Point 328	−0.12	<0.001	−43.01	<0.001	245.92	<0.001
Point 329	−0.11	<0.001	−42.75	<0.001	244.25	<0.001
Point 330	−0.11	<0.001	−42.51	<0.001	242.6	<0.001
Point 331	−0.1	<0.001	−42.19	<0.001	240.72	<0.001
Point 332	−0.1	<0.001	−41.78	<0.001	238.48	<0.001
Point 333	−0.09	<0.001	−41.4	<0.001	236.32	<0.001
Point 334	−0.09	0.001	−41.07	<0.001	234.34	<0.001
Point 335	−0.08	0.002	−40.69	<0.001	232.18	<0.001

Table 4 (*Continued*).

	Age slope	Age *p* value	Diameter slope	Diameter *p* value	Intercept	Intercept *p* value
Point 336	−0.08	0.004	−40.31	<0.001	230.02	<0.001
Point 337	−0.07	0.007	−39.95	<0.001	227.91	<0.001
Point 338	−0.07	0.01	−39.68	<0.001	226.06	<0.001
Point 339	−0.06	0.02	−39.46	<0.001	224.55	<0.001
Point 340	−0.06	0.03	−39.23	<0.001	222.87	<0.001
Point 341	−0.05	0.04	−39.05	<0.001	221.4	<0.001
Point 342	−0.05	0.06	−38.86	<0.001	219.96	<0.001
Point 343	−0.05	0.07	−38.85	<0.001	219.21	<0.001
Point 344	−0.04	0.08	−38.79	<0.001	218.3	<0.001
Point 345	−0.04	0.1	−38.89	<0.001	217.89	<0.001
Point 346	−0.04	0.12	−38.88	<0.001	217.18	<0.001
Point 347	−0.04	0.12	−38.92	<0.001	216.67	<0.001
Point 348	−0.04	0.13	−38.9	<0.001	215.97	<0.001
Point 349	−0.04	0.13	−38.85	<0.001	215.17	<0.001
Point 350	−0.04	0.14	−38.76	<0.001	214.2	<0.001
Point 351	−0.04	0.13	−38.5	<0.001	212.69	<0.001
Point 352	−0.04	0.15	−38.09	<0.001	210.59	<0.001
Point 353	−0.04	0.15	−37.73	<0.001	208.7	<0.001
Point 354	−0.03	0.16	−37.27	<0.001	206.39	<0.001
Point 355	−0.03	0.17	−36.7	<0.001	203.75	<0.001
Point 356	−0.03	0.18	−36.18	<0.001	201.26	<0.001
Point 357	−0.03	0.18	−35.74	<0.001	199.11	<0.001
Point 358	−0.03	0.21	−35.26	<0.001	196.74	<0.001
Point 359	−0.03	0.23	−34.79	<0.001	194.4	<0.001
Point 360	−0.03	0.25	−34.4	<0.001	192.39	<0.001
Point 361	−0.02	0.29	−33.96	<0.001	190.13	<0.001
Point 362	−0.02	0.35	−33.56	<0.001	188.01	<0.001
Point 363	−0.02	0.39	−33.13	<0.001	185.87	<0.001
Point 364	−0.02	0.51	−32.76	<0.001	183.79	<0.001
Point 365	−0.01	0.61	−32.2	<0.001	181.1	<0.001
Point 366	−0.01	0.74	−31.83	<0.001	179.08	<0.001
Point 367	0	0.85	−31.34	<0.001	176.69	<0.001
Point 368	0	0.92	−30.93	<0.001	174.61	<0.001
Point 369	0	0.99	−30.42	<0.001	172.23	<0.001
Point 370	0	0.92	−29.97	<0.001	170.06	<0.001
Point 371	0	0.89	−29.47	<0.001	167.8	<0.001
Point 372	0.01	0.81	−28.97	<0.001	165.55	<0.001
Point 373	0.01	0.77	−28.4	<0.001	163.06	<0.001
Point 374	0.01	0.71	−27.82	<0.001	160.55	<0.001
Point 375	0.01	0.63	−27.33	<0.001	158.35	<0.001
Point 376	0.01	0.63	−26.61	<0.001	155.45	<0.001
Point 377	0.01	0.61	−26.1	<0.001	153.27	<0.001
Point 378	0.01	0.6	−25.54	<0.001	150.97	<0.001
Point 379	0.01	0.61	−25.11	<0.001	149.18	<0.001
Point 380	0.01	0.63	−24.62	<0.001	147.21	<0.001

Table 4 (*Continued*).

	Age slope	Age *p* value	Diameter slope	Diameter *p* value	Intercept	Intercept *p* value
Point 381	0.01	0.68	−24.3	<0.001	145.89	<0.001
Point 382	0.01	0.69	−23.93	<0.001	144.33	<0.001
Point 383	0.01	0.77	−23.72	<0.001	143.49	<0.001
Point 384	0.01	0.8	−23.44	<0.001	142.29	<0.001
Point 385	0	0.85	−23.11	<0.001	140.99	<0.001
Point 386	0	0.86	−22.92	<0.001	140.13	<0.001
Point 387	0	0.92	−22.63	<0.001	138.99	<0.001
Point 388	0	0.92	−22.36	<0.001	137.86	<0.001
Point 389	0	0.9	−22.09	<0.001	136.7	<0.001
Point 390	0	0.9	−21.91	<0.001	135.88	<0.001
Point 391	0	0.92	−21.74	<0.001	135.15	<0.001
Point 392	0	0.92	−21.54	<0.001	134.3	<0.001
Point 393	0	0.91	−21.31	<0.001	133.31	<0.001
Point 394	0	0.9	−21.1	<0.001	132.42	<0.001
Point 395	0	0.9	−20.97	<0.001	131.85	<0.001
Point 396	0	0.87	−20.76	<0.001	131.02	<0.001
Point 397	0	0.89	−20.62	<0.001	130.46	<0.001
Point 398	0	0.85	−20.37	<0.001	129.45	<0.001
Point 399	0	0.86	−20.26	<0.001	129.03	<0.001
Point 400	0	0.82	−19.99	<0.001	127.98	<0.001
Point 401	0.01	0.79	−19.75	<0.001	127.05	<0.001
Point 402	0	0.81	−19.52	<0.001	126.25	<0.001
Point 403	0	0.82	−19.34	<0.001	125.6	<0.001
Point 404	0	0.85	−19.22	<0.001	125.19	<0.001
Point 405	0	0.93	−19.16	<0.001	125.08	<0.001
Point 406	0	0.97	−19.11	<0.001	124.98	<0.001
Point 407	0	0.91	−19.06	<0.001	124.88	<0.001
Point 408	−0.01	0.78	−19.15	<0.001	125.38	<0.001
Point 409	−0.01	0.69	−19.14	<0.001	125.46	<0.001
Point 410	−0.01	0.56	−19.23	<0.001	125.98	<0.001
Point 411	−0.01	0.47	−19.25	<0.001	126.22	<0.001
Point 412	−0.02	0.37	−19.32	<0.001	126.66	<0.001
Point 413	−0.02	0.31	−19.37	<0.001	127.05	<0.001
Point 414	−0.02	0.26	−19.54	<0.001	127.82	<0.001
Point 415	−0.02	0.23	−19.65	<0.001	128.37	<0.001
Point 416	−0.02	0.18	−19.81	<0.001	129.19	<0.001
Point 417	−0.02	0.16	−20.07	<0.001	130.27	<0.001
Point 418	−0.03	0.13	−20.31	<0.001	131.35	<0.001
Point 419	−0.03	0.11	−20.49	<0.001	132.22	<0.001
Point 420	−0.03	0.1	−20.75	<0.001	133.32	<0.001
Point 421	−0.03	0.09	−21.05	<0.001	134.63	<0.001
Point 422	−0.03	0.08	−21.34	<0.001	135.85	<0.001
Point 423	−0.03	0.07	−21.75	<0.001	137.6	<0.001
Point 424	−0.03	0.06	−22.1	<0.001	139.07	<0.001
Point 425	−0.03	0.06	−22.5	<0.001	140.76	<0.001

Table 4 (*Continued*).

	Age slope	Age *p* value	Diameter slope	Diameter *p* value	Intercept	Intercept *p* value
Point 426	−0.04	0.04	−22.97	<0.001	142.75	<0.001
Point 427	−0.04	0.04	−23.31	<0.001	144.21	<0.001
Point 428	−0.04	0.03	−23.77	<0.001	146.22	<0.001
Point 429	−0.04	0.02	−24.17	<0.001	147.94	<0.001
Point 430	−0.04	0.02	−24.52	<0.001	149.56	<0.001
Point 431	−0.05	0.01	−24.9	<0.001	151.23	<0.001
Point 432	−0.05	0.01	−25.17	<0.001	152.58	<0.001
Point 433	−0.05	0.008	−25.41	<0.001	153.8	<0.001
Point 434	−0.05	0.007	−25.56	<0.001	154.72	<0.001
Point 435	−0.05	0.006	−25.65	<0.001	155.41	<0.001
Point 436	−0.05	0.005	−25.79	<0.001	156.32	<0.001
Point 437	−0.06	0.004	−25.91	<0.001	157.12	<0.001
Point 438	−0.06	0.004	−25.93	<0.001	157.65	<0.001
Point 439	−0.06	0.003	−26.09	<0.001	158.66	<0.001
Point 440	−0.06	0.003	−26.28	<0.001	159.76	<0.001
Point 441	−0.06	0.002	−26.46	<0.001	160.85	<0.001
Point 442	−0.06	0.002	−26.74	<0.001	162.33	<0.001
Point 443	−0.06	0.002	−26.85	<0.001	163.17	<0.001
Point 444	−0.07	0.002	−27.1	<0.001	164.58	<0.001
Point 445	−0.07	0.001	−27.41	<0.001	166.27	<0.001
Point 446	−0.07	<0.001	−27.71	<0.001	167.87	<0.001
Point 447	−0.07	<0.001	−28.05	<0.001	169.66	<0.001
Point 448	−0.08	<0.001	−28.3	<0.001	171.18	<0.001
Point 449	−0.08	<0.001	−28.62	<0.001	172.96	<0.001
Point 450	−0.08	<0.001	−28.88	<0.001	174.57	<0.001
Point 451	−0.09	<0.001	−29.18	<0.001	176.35	<0.001
Point 452	−0.09	<0.001	−29.41	<0.001	177.9	<0.001
Point 453	−0.09	<0.001	−29.67	<0.001	179.59	<0.001
Point 454	−0.1	<0.001	−29.92	<0.001	181.25	<0.001
Point 455	−0.1	<0.001	−30.15	<0.001	182.9	<0.001
Point 456	−0.11	<0.001	−30.41	<0.001	184.62	<0.001
Point 457	−0.11	<0.001	−30.69	<0.001	186.43	<0.001
Point 458	−0.11	<0.001	−31.08	<0.001	188.58	<0.001
Point 459	−0.12	<0.001	−31.44	<0.001	190.72	<0.001
Point 460	−0.12	<0.001	−31.79	<0.001	192.68	<0.001
Point 461	−0.12	<0.001	−32.22	<0.001	194.94	<0.001
Point 462	−0.13	<0.001	−32.63	<0.001	197.16	<0.001
Point 463	−0.13	<0.001	−33.11	<0.001	199.59	<0.001
Point 464	−0.13	<0.001	−33.52	<0.001	201.71	<0.001
Point 465	−0.13	<0.001	−34.02	<0.001	204.21	<0.001
Point 466	−0.13	<0.001	−34.49	<0.001	206.55	<0.001
Point 467	−0.13	<0.001	−35.07	<0.001	209.35	<0.001
Point 468	−0.13	<0.001	−35.5	<0.001	211.55	<0.001
Point 469	−0.14	<0.001	−35.98	<0.001	214	<0.001
Point 470	−0.14	<0.001	−36.41	<0.001	216.25	<0.001

Table 4 (*Continued*).

	Age slope	Age *p* value	Diameter slope	Diameter *p* value	Intercept	Intercept *p* value
Point 471	−0.14	<0.001	−36.76	<0.001	218.3	<0.001
Point 472	−0.14	<0.001	−37.14	<0.001	220.46	<0.001
Point 473	−0.14	<0.001	−37.45	<0.001	222.39	<0.001
Point 474	−0.15	<0.001	−37.87	<0.001	224.73	<0.001
Point 475	−0.15	<0.001	−38.17	<0.001	226.68	<0.001
Point 476	−0.16	<0.001	−38.53	<0.001	228.85	<0.001
Point 477	−0.16	<0.001	−38.75	<0.001	230.5	<0.001
Point 478	−0.16	<0.001	−38.98	<0.001	232.18	<0.001
Point 479	−0.17	<0.001	−39.19	<0.001	233.74	<0.001
Point 480	−0.17	<0.001	−39.36	<0.001	235.13	<0.001
Point 481	−0.17	<0.001	−39.48	<0.001	236.31	<0.001
Point 482	−0.17	<0.001	−39.65	<0.001	237.59	<0.001
Point 483	−0.17	<0.001	−39.73	<0.001	238.5	<0.001
Point 484	−0.17	<0.001	−39.85	<0.001	239.56	<0.001
Point 485	−0.18	<0.001	−40	<0.001	240.7	<0.001
Point 486	−0.18	<0.001	−40.1	<0.001	241.67	<0.001
Point 487	−0.18	<0.001	−40.26	<0.001	242.77	<0.001
Point 488	−0.18	<0.001	−40.44	<0.001	243.99	<0.001
Point 489	−0.18	<0.001	−40.58	<0.001	244.99	<0.001
Point 490	−0.18	<0.001	−40.82	<0.001	246.43	<0.001
Point 491	−0.18	<0.001	−41.03	<0.001	247.77	<0.001
Point 492	−0.18	<0.001	−41.32	<0.001	249.4	<0.001
Point 493	−0.19	<0.001	−41.62	<0.001	251.05	<0.001
Point 494	−0.19	<0.001	−41.97	<0.001	252.96	<0.001
Point 495	−0.2	<0.001	−42.28	<0.001	254.69	<0.001
Point 496	−0.2	<0.001	−42.6	<0.001	256.42	<0.001
Point 497	−0.21	<0.001	−42.9	<0.001	258.07	<0.001
Point 498	−0.21	<0.001	−43.24	<0.001	259.8	<0.001
Point 499	−0.22	<0.001	−43.57	<0.001	261.5	<0.001
Point 500	−0.22	<0.001	−43.85	<0.001	262.98	<0.001
Point 501	−0.23	<0.001	−44.15	<0.001	264.46	<0.001
Point 502	−0.23	<0.001	−44.34	<0.001	265.58	<0.001
Point 503	−0.23	<0.001	−44.52	<0.001	266.57	<0.001
Point 504	−0.24	<0.001	−44.51	<0.001	266.77	<0.001
Point 505	−0.24	<0.001	−44.58	<0.001	267.28	<0.001
Point 506	−0.24	<0.001	−44.53	<0.001	267.29	<0.001
Point 507	−0.24	<0.001	−44.43	<0.001	267.07	<0.001
Point 508	−0.24	<0.001	−44.35	<0.001	266.87	<0.001
Point 509	−0.24	<0.001	−44.16	<0.001	266.3	<0.001
Point 510	−0.24	<0.001	−44.12	<0.001	266.21	<0.001
Point 511	−0.23	<0.001	−43.96	<0.001	265.65	<0.001
Point 512	−0.23	<0.001	−43.82	<0.001	265.05	<0.001
Point 513	−0.23	<0.001	−43.81	<0.001	265.02	<0.001
Point 514	−0.23	<0.001	−43.8	<0.001	264.93	<0.001
Point 515	−0.22	<0.001	−43.76	<0.001	264.65	<0.001
Point 516	−0.22	<0.001	−43.79	<0.001	264.67	<0.001
Point 517	−0.22	<0.001	−43.87	<0.001	264.86	<0.001
Point 518	−0.21	<0.001	−44.03	<0.001	265.31	<0.001
Point 519	−0.21	<0.001	−44.09	<0.001	265.34	<0.001
Point 520	−0.2	<0.001	−44.26	<0.001	265.89	<0.001
Point 521	−0.2	<0.001	−44.36	<0.001	266.17	<0.001
Point 522	−0.2	<0.001	−44.55	<0.001	266.78	<0.001
Point 523	−0.2	<0.001	−44.83	<0.001	267.81	<0.001
Point 524	−0.19	<0.001	−45.1	<0.001	268.79	<0.001
Point 525	−0.19	<0.001	−45.45	<0.001	270.1	<0.001
Point 526	−0.19	<0.001	−45.85	<0.001	271.57	<0.001
Point 527	−0.18	<0.001	−46.27	<0.001	273.1	<0.001
Point 528	−0.18	<0.001	−46.81	<0.001	275.16	<0.001
Point 529	−0.18	<0.001	−47.37	<0.001	277.3	<0.001
Point 530	−0.17	<0.001	−47.97	<0.001	279.59	<0.001
Point 531	−0.17	<0.001	−48.71	<0.001	282.38	<0.001
Point 532	−0.17	<0.001	−49.41	<0.001	285.12	<0.001
Point 533	−0.16	<0.001	−50.23	<0.001	288.38	<0.001
Point 534	−0.16	<0.001	−51.1	<0.001	291.75	<0.001
Point 535	−0.16	<0.001	−51.93	<0.001	295.08	<0.001
Point 536	−0.16	<0.001	−52.83	<0.001	298.64	<0.001
Point 537	−0.15	<0.001	−53.74	<0.001	302.27	<0.001
Point 538	−0.15	<0.001	−54.59	<0.001	305.75	<0.001
Point 539	−0.15	<0.001	−55.49	<0.001	309.38	<0.001
Point 540	−0.15	<0.001	−56.4	<0.001	313.14	<0.001
Point 541	−0.14	<0.001	−57.2	<0.001	316.47	<0.001
Point 542	−0.14	<0.001	−58.1	<0.001	320.28	<0.001
Point 543	−0.14	<0.001	−58.81	<0.001	323.31	<0.001
Point 544	−0.14	<0.001	−59.54	<0.001	326.5	<0.001
Point 545	−0.13	<0.001	−60.26	<0.001	329.65	<0.001
Point 546	−0.13	<0.001	−60.87	<0.001	332.47	<0.001
Point 547	−0.13	<0.001	−61.39	<0.001	334.92	<0.001
Point 548	−0.13	<0.001	−61.95	<0.001	337.6	<0.001
Point 549	−0.13	<0.001	−62.34	<0.001	339.65	<0.001
Point 550	−0.13	<0.001	−62.69	<0.001	341.64	<0.001
Point 551	−0.12	<0.001	−62.99	<0.001	343.4	<0.001
Point 552	−0.12	<0.001	−63.27	<0.001	345.14	<0.001
Point 553	−0.12	<0.001	−63.51	<0.001	346.8	<0.001
Point 554	−0.12	<0.001	−63.69	<0.001	348.21	<0.001
Point 555	−0.12	<0.001	−63.8	<0.001	349.44	<0.001
Point 556	−0.12	<0.001	−63.95	<0.001	350.76	<0.001
Point 557	−0.12	<0.001	−64	<0.001	351.86	<0.001
Point 558	−0.12	<0.001	−64.06	<0.001	352.92	<0.001
Point 559	−0.12	<0.001	−64.15	<0.001	354.17	<0.001
Point 560	−0.12	<0.001	−64.12	<0.001	355.03	<0.001

Table 4 (*Continued*).

	Age slope	Age *p* value	Diameter slope	Diameter *p* value	Intercept	Intercept *p* value
Point 561	−0.12	<0.001	−64.09	<0.001	355.84	<0.001
Point 562	−0.13	<0.001	−64.01	<0.001	356.58	<0.001
Point 563	−0.13	<0.001	−63.87	<0.001	357.13	<0.001
Point 564	−0.13	<0.001	−63.74	<0.001	357.72	<0.001
Point 565	−0.14	<0.001	−63.54	<0.001	358.1	<0.001
Point 566	−0.14	<0.001	−63.29	<0.001	358.24	<0.001
Point 567	−0.15	<0.001	−62.99	<0.001	358.33	<0.001
Point 568	−0.16	<0.001	−62.71	<0.001	358.44	<0.001
Point 569	−0.16	<0.001	−62.37	<0.001	358.35	<0.001
Point 570	−0.17	<0.001	−62.01	<0.001	358.16	<0.001
Point 571	−0.18	<0.001	−61.69	<0.001	358.15	<0.001
Point 572	−0.19	<0.001	−61.2	<0.001	357.52	<0.001
Point 573	−0.19	<0.001	−60.85	<0.001	357.33	<0.001
Point 574	−0.2	<0.001	−60.45	<0.001	356.93	<0.001
Point 575	−0.21	<0.001	−60	<0.001	356.36	<0.001
Point 576	−0.21	<0.001	−59.49	<0.001	355.55	<0.001
Point 577	−0.22	<0.001	−58.94	<0.001	354.54	<0.001
Point 578	−0.23	<0.001	−58.35	<0.001	353.41	<0.001
Point 579	−0.23	<0.001	−57.71	<0.001	352.03	<0.001
Point 580	−0.24	<0.001	−57.09	<0.001	350.76	<0.001
Point 581	−0.24	<0.001	−56.33	<0.001	348.97	<0.001
Point 582	−0.25	<0.001	−55.63	<0.001	347.32	<0.001
Point 583	−0.25	<0.001	−55	<0.001	345.91	<0.001
Point 584	−0.26	<0.001	−54.25	<0.001	344.1	<0.001
Point 585	−0.26	<0.001	−53.55	<0.001	342.4	<0.001
Point 586	−0.26	<0.001	−52.75	<0.001	340.32	<0.001
Point 587	−0.27	<0.001	−52.06	<0.001	338.67	<0.001
Point 588	−0.27	<0.001	−51.39	<0.001	337	<0.001
Point 589	−0.27	<0.001	−50.61	<0.001	334.97	<0.001
Point 590	−0.28	<0.001	−49.87	<0.001	332.95	<0.001
Point 591	−0.28	<0.001	−49.13	<0.001	331.02	<0.001
Point 592	−0.28	<0.001	−48.46	<0.001	329.27	<0.001
Point 593	−0.28	<0.001	−47.77	<0.001	327.47	<0.001
Point 594	−0.28	<0.001	−47.19	<0.001	326.05	<0.001
Point 595	−0.29	<0.001	−46.67	<0.001	324.89	<0.001
Point 596	−0.29	<0.001	−46.2	<0.001	323.86	<0.001
Point 597	−0.29	<0.001	−45.84	<0.001	323.23	<0.001
Point 598	−0.3	<0.001	−45.54	<0.001	322.89	<0.001
Point 599	−0.3	<0.001	−45.19	<0.001	322.3	<0.001
Point 600	−0.3	<0.001	−44.93	<0.001	322.07	<0.001
Point 601	−0.31	<0.001	−44.66	<0.001	321.8	<0.001
Point 602	−0.31	<0.001	−44.3	<0.001	321.22	<0.001
Point 603	−0.31	<0.001	−43.95	<0.001	320.61	<0.001
Point 604	−0.32	<0.001	−43.6	<0.001	320.07	<0.001
Point 605	−0.32	<0.001	−43.22	<0.001	319.3	<0.001

Table 4 (*Continued*).

	Age slope	Age *p* value	Diameter slope	Diameter *p* value	Intercept	Intercept *p* value
Point 606	−0.32	<0.001	−42.76	<0.001	318.26	<0.001
Point 607	−0.32	<0.001	−42.24	<0.001	316.98	<0.001
Point 608	−0.32	<0.001	−41.67	<0.001	315.5	<0.001
Point 609	−0.33	<0.001	−41.13	<0.001	314.12	<0.001
Point 610	−0.33	<0.001	−40.47	<0.001	312.31	<0.001
Point 611	−0.33	<0.001	−39.88	<0.001	310.72	<0.001
Point 612	−0.33	<0.001	−39.3	<0.001	309.16	<0.001
Point 613	−0.33	<0.001	−38.68	<0.001	307.46	<0.001
Point 614	−0.33	<0.001	−38.13	<0.001	305.97	<0.001
Point 615	−0.33	<0.001	−37.59	<0.001	304.49	<0.001
Point 616	−0.33	<0.001	−37.13	<0.001	303.29	<0.001
Point 617	−0.34	<0.001	−36.57	<0.001	301.71	<0.001
Point 618	−0.34	<0.001	−36.12	<0.001	300.43	<0.001
Point 619	−0.34	<0.001	−35.52	<0.001	298.63	<0.001
Point 620	−0.34	<0.001	−34.82	<0.001	296.45	<0.001
Point 621	−0.34	<0.001	−34.07	<0.001	293.98	<0.001
Point 622	−0.34	<0.001	−33.32	<0.001	291.53	<0.001
Point 623	−0.34	<0.001	−32.45	<0.001	288.54	<0.001
Point 624	−0.34	<0.001	−31.4	<0.001	284.92	<0.001
Point 625	−0.34	<0.001	−30.42	<0.001	281.56	<0.001
Point 626	−0.34	<0.001	−29.3	<0.001	277.65	<0.001
Point 627	−0.34	<0.001	−28	<0.001	273.04	<0.001
Point 628	−0.35	<0.001	−26.68	<0.001	268.32	<0.001
Point 629	−0.35	<0.001	−25.33	<0.001	263.5	<0.001
Point 630	−0.35	<0.001	−23.89	<0.001	258.26	<0.001
Point 631	−0.35	<0.001	−22.33	<0.001	252.54	<0.001
Point 632	−0.35	<0.001	−20.83	<0.001	246.99	<0.001
Point 633	−0.35	<0.001	−19.28	<0.001	241.22	<0.001
Point 634	−0.35	<0.001	−17.67	<0.001	235.16	<0.001
Point 635	−0.36	<0.001	−16.01	<0.001	228.88	<0.001
Point 636	−0.36	<0.001	−14.37	<0.001	222.56	<0.001
Point 637	−0.36	<0.001	−12.63	<0.001	215.78	<0.001
Point 638	−0.36	<0.001	−10.84	<0.001	208.76	<0.001
Point 639	−0.36	<0.001	−9.13	0.004	201.94	<0.001
Point 640	−0.36	<0.001	−7.32	0.02	194.68	<0.001
Point 641	−0.35	<0.001	−5.54	0.08	187.38	<0.001
Point 642	−0.35	<0.001	−3.72	0.25	179.86	<0.001
Point 643	−0.35	<0.001	−1.98	0.54	172.58	<0.001
Point 644	−0.35	<0.001	−0.25	0.94	165.23	<0.001
Point 645	−0.34	<0.001	1.29	0.69	158.48	<0.001
Point 646	−0.34	<0.001	2.84	0.39	151.69	<0.001
Point 647	−0.34	<0.001	4.33	0.2	145.05	<0.001
Point 648	−0.34	<0.001	5.74	0.09	138.67	<0.001
Point 649	−0.33	<0.001	6.95	0.04	132.95	<0.001
Point 650	−0.33	<0.001	8.17	0.02	127.18	<0.001

Table 4 (*Continued*).

	Age slope	Age *p* value	Diameter slope	Diameter *p* value	Intercept	Intercept *p* value
Point 651	−0.33	<0.001	9.32	0.006	121.64	<0.001
Point 652	−0.33	<0.001	10.34	0.002	116.57	<0.001
Point 653	−0.33	<0.001	11.39	<0.001	111.3	<0.001
Point 654	−0.33	<0.001	12.34	<0.001	106.37	<0.001
Point 655	−0.33	<0.001	13.19	<0.001	101.8	<0.001
Point 656	−0.33	<0.001	13.94	<0.001	97.55	<0.001
Point 657	−0.33	<0.001	14.7	<0.001	93.2	<0.001
Point 658	−0.33	<0.001	15.31	<0.001	89.46	<0.001
Point 659	−0.32	<0.001	15.94	<0.001	85.52	<0.001
Point 660	−0.32	<0.001	16.45	<0.001	82.03	<0.001
Point 661	−0.32	<0.001	16.98	<0.001	78.44	<0.001
Point 662	−0.32	<0.001	17.4	<0.001	75.19	<0.001
Point 663	−0.31	<0.001	17.79	<0.001	72.08	<0.001
Point 664	−0.31	<0.001	18.09	<0.001	69.26	<0.001
Point 665	−0.31	<0.001	18.4	<0.001	66.38	<0.001
Point 666	−0.3	<0.001	18.66	<0.001	63.64	<0.001
Point 667	−0.3	<0.001	18.84	<0.001	61.25	<0.001
Point 668	−0.29	<0.001	18.92	<0.001	59.19	<0.001
Point 669	−0.29	<0.001	19.03	<0.001	57.04	<0.001
Point 670	−0.28	<0.001	19.1	<0.001	55.04	<0.001
Point 671	−0.28	<0.001	19.03	<0.001	53.55	<0.001
Point 672	−0.27	<0.001	18.89	<0.001	52.37	<0.001
Point 673	−0.27	<0.001	18.78	<0.001	51.08	<0.001
Point 674	−0.26	<0.001	18.45	<0.001	50.55	<0.001
Point 675	−0.25	<0.001	18.2	<0.001	49.86	<0.001
Point 676	−0.25	<0.001	17.89	<0.001	49.32	<0.001
Point 677	−0.24	<0.001	17.45	<0.001	49.3	<0.001
Point 678	−0.24	<0.001	17.14	<0.001	48.78	<0.001
Point 679	−0.23	<0.001	16.76	<0.001	48.6	<0.001
Point 680	−0.23	<0.001	16.47	<0.001	48.1	<0.001
Point 681	−0.22	<0.001	16.14	<0.001	47.75	<0.001
Point 682	−0.21	<0.001	15.86	<0.001	47.3	<0.001
Point 683	−0.21	<0.001	15.47	<0.001	47.19	<0.001
Point 684	−0.2	<0.001	15.14	<0.001	46.97	<0.001
Point 685	−0.2	<0.001	14.9	<0.001	46.39	<0.001
Point 686	−0.19	<0.001	14.71	<0.001	45.65	<0.001
Point 687	−0.18	<0.001	14.44	<0.001	45.26	<0.001
Point 688	−0.18	<0.001	14.39	<0.001	44.07	<0.001
Point 689	−0.17	<0.001	14.26	<0.001	43.23	<0.001
Point 690	−0.17	<0.001	14.18	<0.001	42.23	<0.001
Point 691	−0.16	<0.001	14.09	<0.001	41.29	<0.001
Point 692	−0.16	<0.001	14.01	<0.001	40.38	<0.001
Point 693	−0.15	<0.001	13.97	<0.001	39.3	<0.001
Point 694	−0.15	<0.001	13.75	<0.001	38.88	<0.001
Point 695	−0.15	<0.001	13.61	<0.001	38.3	<0.001

Table 4 (*Continued*).

	Age slope	Age *p* value	Diameter slope	Diameter *p* value	Intercept	Intercept *p* value
Point 696	−0.14	<0.001	13.43	<0.001	37.83	<0.001
Point 697	−0.14	<0.001	13.25	<0.001	37.35	<0.001
Point 698	−0.14	<0.001	13.06	<0.001	36.97	<0.001
Point 699	−0.13	<0.001	12.84	<0.001	36.65	<0.001
Point 700	−0.13	<0.001	12.62	<0.001	36.43	<0.001
Point 701	−0.13	<0.001	12.46	<0.001	35.93	<0.001
Point 702	−0.12	<0.001	12.25	<0.001	35.64	<0.001
Point 703	−0.12	<0.001	12.12	<0.001	35.08	<0.001
Point 704	−0.12	<0.001	11.96	<0.001	34.61	<0.001
Point 705	−0.11	<0.001	11.88	<0.001	33.86	<0.001
Point 706	−0.11	<0.001	11.63	<0.001	33.77	<0.001
Point 707	−0.11	<0.001	11.57	<0.001	33.03	<0.001
Point 708	−0.11	<0.001	11.38	<0.001	32.72	<0.001
Point 709	−0.1	<0.001	11.22	<0.001	32.33	<0.001
Point 710	−0.1	<0.001	11.05	<0.001	32.01	<0.001
Point 711	−0.1	<0.001	10.84	<0.001	31.78	<0.001
Point 712	−0.09	<0.001	10.61	<0.001	31.71	<0.001
Point 713	−0.09	<0.001	10.37	<0.001	31.65	<0.001
Point 714	−0.09	<0.001	10.15	<0.001	31.54	<0.001
Point 715	−0.08	<0.001	9.86	<0.001	31.69	<0.001
Point 716	−0.08	<0.001	9.73	<0.001	31.2	<0.001
Point 717	−0.08	<0.001	9.44	<0.001	31.37	<0.001
Point 718	−0.07	<0.001	9.21	<0.001	31.33	<0.001
Point 719	−0.07	<0.001	8.86	<0.001	31.73	<0.001
Point 720	−0.07	<0.001	8.57	<0.001	31.97	<0.001
Point 721	−0.06	<0.001	8.26	<0.001	32.3	<0.001
Point 722	−0.06	<0.001	7.99	<0.001	32.58	<0.001
Point 723	−0.06	<0.001	7.73	<0.001	32.77	<0.001
Point 724	−0.06	<0.001	7.42	<0.001	33.25	<0.001
Point 725	−0.06	<0.001	7.15	<0.001	33.6	<0.001
Point 726	−0.05	<0.001	6.94	<0.001	33.77	<0.001
Point 727	−0.05	<0.001	6.71	<0.001	34	<0.001
Point 728	−0.05	<0.001	6.47	<0.001	34.3	<0.001
Point 729	−0.05	<0.001	6.3	<0.001	34.41	<0.001
Point 730	−0.05	<0.001	6.2	<0.001	34.26	<0.001
Point 731	−0.05	<0.001	6.04	<0.001	34.36	<0.001
Point 732	−0.04	<0.001	5.89	<0.001	34.41	<0.001
Point 733	−0.04	<0.001	5.65	<0.001	34.84	<0.001
Point 734	−0.04	<0.001	5.43	<0.001	35.23	<0.001
Point 735	−0.04	<0.001	5.14	<0.001	35.9	<0.001
Point 736	−0.04	0.001	4.82	<0.001	36.7	<0.001
Point 737	−0.04	0.001	4.56	<0.001	37.34	<0.001
Point 738	−0.04	0.001	4.21	<0.001	38.37	<0.001
Point 739	−0.04	0.002	3.97	<0.001	39	<0.001
Point 740	−0.04	0.001	3.64	<0.001	40.02	<0.001

Table 4 (*Continued*).

	Age slope	Age *p* value	Diameter slope	Diameter *p* value	Intercept	Intercept *p* value
Point 741	−0.04	0.001	3.41	0.001	40.74	<0.001
Point 742	−0.04	0.001	3.2	0.002	41.4	<0.001
Point 743	−0.04	<0.001	2.93	0.005	42.29	<0.001
Point 744	−0.04	<0.001	2.77	0.008	42.85	<0.001
Point 745	−0.04	<0.001	2.5	0.02	43.8	<0.001
Point 746	−0.04	<0.001	2.38	0.02	44.23	<0.001
Point 747	−0.04	<0.001	2.17	0.04	44.98	<0.001
Point 748	−0.04	<0.001	2.07	0.05	45.37	<0.001
Point 749	−0.04	<0.001	1.9	0.08	45.97	<0.001
Point 750	−0.04	<0.001	1.78	0.1	46.43	<0.001
Point 751	−0.04	<0.001	1.69	0.12	46.73	<0.001
Point 752	−0.04	<0.001	1.57	0.15	47.25	<0.001
Point 753	−0.04	<0.001	1.49	0.18	47.56	<0.001
Point 754	−0.04	<0.001	1.44	0.19	47.86	<0.001
Point 755	−0.04	0.001	1.36	0.22	48.23	<0.001
Point 756	−0.04	0.001	1.29	0.25	48.6	<0.001
Point 757	−0.04	0.001	1.26	0.26	48.92	<0.001
Point 758	−0.04	0.001	1.13	0.32	49.59	<0.001
Point 759	−0.04	<0.001	1.03	0.37	50.21	<0.001
Point 760	−0.04	<0.001	1.01	0.38	50.61	<0.001
Point 761	−0.05	<0.001	0.99	0.39	51.06	<0.001
Point 762	−0.05	<0.001	0.87	0.45	51.89	<0.001
Point 763	−0.05	<0.001	0.82	0.48	52.54	<0.001
Point 764	−0.05	<0.001	0.81	0.49	53.05	<0.001
Point 765	−0.06	<0.001	0.77	0.51	53.66	<0.001
Point 766	−0.06	<0.001	0.81	0.5	54.06	<0.001
Point 767	−0.06	<0.001	0.79	0.51	54.62	<0.001
Point 768	−0.06	<0.001	0.93	0.44	54.64	<0.001

Disclosures

None of the authors has any conflict of interest to disclose.

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