LONG ANTERIOR LENS ZONULES AND INTRAOCULAR PRESSURE

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Abstract

Purpose: To investigate the relation between intraocular pressure (IOP) and the idiopathic long anterior zonule (LAZ) trait.

Methods: Patients presenting for primary eye care were examined for LAZ, identified as radially-oriented zonular fibers with central extension >1.0 mm beyond the normal anterior lens insertion zone (estimated via slit lamp beam length). Ocular, systemic health, and lifestyle data were collected via comprehensive exam and questionnaire. Multivariate regression was used to assess the relationship between IOP (Goldmann) and LAZ.

Results: There were 2,169 non-LAZ and 129 LAZ subjects (mean age: 49.8 $\pm$ 15.0 vs. 62.6 $\pm$ 10.2 years; 63.6% vs. 76.0% female; 83.2% vs. 91.5% African-American). Right eyes with >trace LAZ (N=59 of 110) had higher unadjusted mean IOP than control eyes (16.4 $\pm$ 3.3 vs. 15.0 $\pm$ 3.3 mm Hg, P=0.005), and with control for numerous factors, LAZ eyes had average IOP about 1.3 $\pm$ 0.4 mm Hg higher (P=0.003) than non-LAZ eyes. Final model covariates included gender (P=0.001), spherical-equivalent refractive error (D) (P<0.0001), body mass index (kg/m^2) (P<0.001), presence of diabetes (P<0.001), having >high school education (P<0.001), systolic blood pressure (mm Hg) (P<0.0001), being an ever smoker (P=0.006), and having history of any site cancer (P=0.01).

Conclusions: The LAZ trait, with potential prevalence near 2%, was associated with a higher IOP. This observation is consistent with the hypothesis that the trait is a marker for underlying mechanisms that elevate glaucoma risk.

KEY WORDS: Crystalline lens, glaucoma, intraocular pressure, long anterior zonules, pigment dispersion

1

2 **Introduction**

3   Long anterior zonules (LAZ) are characterized by zonular fibers that extend more

4 central than usual on the anterior lens capsule.[1-4] They are observed following pupillary

5 dilation as radially-oriented fine lines, which often become pigmented due to rubbing

6 against the posterior iris pigment epithelium (Fig. 1 & 2).   Other pigment dispersal signs

7 may also be present, including Krukenberg spindles and trabecular meshwork

8 pigmentation,[5-7] and these signs may cause LAZ-associated pigment dispersion to be

9 confused with the more well-known "classic" variety pigment dispersion syndrome.[8,9]

10   Current understanding suggests that the LAZ trait may present with at least two

11 phenotypic varieties. One rare variety may be detected during young age, which occurs

12 with a serine to arginine (S163R) substitution in the complement 1q tumor necrosis factor-

13 related protein 5 (C1QTNF5) gene that causes late-onset retinal degeneration (L-

14 ORD).[10,11] Another, more common variety with unknown etiology and prevalence possibly

15 near 2%,[12] has association with age >50 years,[4,6,12] female gender,[4,6,12] hyperopia,[6,12,13]

16 shorter axial length,[14] and persistent pupillary membrane iris strands.[15] Only recently has

17 the literature begun to differentiate between these separate LAZ presentations, and it's

18 unknown what pathophysiology may produce LAZ in such different groups.

19   The LAZ trait has also drawn interest relative to cataract surgery because the

20 anomalous fibers reduce the size of the anterior capsule's zonule-free zone (ZFZ),

21 creating concern that zonular cutting during capsulorhexis may elevate risk of capsular

22 tearing and intraocular lens dislocation.[16-24] Furthermore, there has also been suggestion

23 that the LAZ trait could signal higher risk for both open- and narrow-angle

1 glaucoma.[5,7,10,14,25,26] In 1962, Stankovic and Stankovic[26] reported 14 subjects who had

2 LAZ and pigment dispersal signs, with 9 having heavy trabecular meshwork pigmentation

3 and elevated IOP. Similarly, Moroi et al.[5] described 15 LAZ subjects with pigment

4 dispersion signs, 7 of whom were being treated for glaucoma or ocular hypertension.

5 About half belonged to a four-generation pedigree (UM:H389)[7] that had many members

6 exhibiting LAZ alone or LAZ with the autosomal dominant retinal condition mentioned

7 earlier called L-ORD.[10,11] The C1QTNF5 gene, which has the S163R mutation causing

8 L-ORD, maps to chromosome 11q23 and influences wide-ranging processes that include

9 cellular adhesion and basement membrane functions.[27,28]

10 The question of increased risk of angle-closure glaucoma is perhaps not surprising

11 given that people with late-onset LAZ are more likely to be older, hyperopic, and female.

12 However, it's not clear that angle-closure risk is any higher among people with LAZ than

13 among similar people with similar refractive error who don't have LAZ.[29] There has also

14 been question though as to whether there is association between LAZ and plateau iris

15 configuration.[25] Should this be the case, potential angle-closure risk could be more

16 complex than any risk conveyed by basic axial dimensions of the eye.

17 Given the potential relationship between LAZ and glaucoma, there is need for further

18 inquiry, and as a step toward this, we investigated whether we could detect a relationship

19 between the LAZ trait and IOP level.

20

21 **Methods**

22 As part of a larger investigation of ocular and general health associations with the LAZ

23 trait, consecutive patients, presenting to six different practitioners for a regularly-

1 scheduled examination in an urban academic eye care facility in Chicago, IL, were

2 included as subjects if they were $\geq$18 years of age, having their pupils dilated, and if they

3 provided informed consent and completed a brief written questionnaire to supplement

4 other demographic, health and lifestyle information. Along with ocular/medical histories,

5 assessment included testing of Snellen visual acuities, pupils, motility and binocularity,

6 color vision, and confrontation visual fields. Also done were pre-dilation subjective

7 refraction, slit lamp exam, Goldmann applanation tonometry, and dilated retinal exam.

8 Student clinicians within the facility's Primary Eye Care Service performed initial

9 testing on subjects. Although tonometry was often checked by attending faculty

10 investigators, student measurements were used for analysis because faculty

11 measurements were not always done. Single measurements obtained on the day of

12 study were used and all were performed in a consistent fashion using slit lamp mounted

13 Goldmann tonometers, the standard in this clinical setting.

14 Immediately after instillation of pupil dilation drops, student clinicians provided

15 questionnaires for completion without assistance. Faculty investigators learned of subject

16 participation at time of final physical assessment and then examined for LAZ using bright

17 slit lamp illumination with 16-25x magnification. Investigators were experienced in LAZ

18 detection from prior investigations.[6,13,15,23,30]

19 The criterion for LAZ was presence of radially-oriented zonular fibers, pigmented or

20 non-pigmented, with anterior tips judged to extend substantially (>1.0 mm, estimated with

21 slit lamp beam length) central to the normal capsular zonular insertion zone, about 1.5

22 mm anterior to the lens equator.[31] From their anterior tips, LAZ fibers could extend

23 peripherally to the dilated pupil border where they became obscured, or the fibers could

1   be "segmental"[32] whereby their peripheral tips stopped abruptly along the anterior capsule

2   without detectable extension to the pupil border (Fig. 3). We included subjects with any

3   degree (number) of LAZ, but also distinguished between <5 LAZ fibers (trace LAZ) and 5

4   or more detectable fibers.[23]

5   In addition to LAZ, investigators examined eyes for Krukenberg spindles and

6   persistent pupillary iris strands.[6,12,15] We considered a Krukenberg spindle present when

7   there was any "fine pigment dusting" along the central posterior cornea, which we

8   considered present when individual pigment granules could not be "counted" because

9   they were too fine, numerous, and coalesced. Larger, coarse pigment flecks were not

10 considered sign of a Krukenberg spindle. We considered persistent pupillary membrane

11 iris strands (Fig. 1 & 3) present when there was at least one iris strand that bisected the

12 dilated pupil and had both ends attached to the iris collarette or one end to the collarette

13 and the other to the anterior lens capsule.[15]

14 We determined race using medical record notation and the questionnaire, and

15 assigned one of five categories, i.e., 1) Black / African-American, 2) Asian, 3) Hispanic,

16 Black or White, 4) Non-Hispanic White, and 5) other. Education level was determined via

17 questionnaire by asking: "*What is your highest level of education?* 1) *Less than high*

18 *school degree*, 2) *High school degree*, 3) *Vocational school or some college but no*

19 *degree*, 4) *College Associate's or Bachelor's degree*, 5) *College Master's, Professional,*

20 *or Doctoral degree.*"

21 We also used the questionnaire to categorize subjects as a "current smoker," "former

22 smoker," or "never smoker" by asking: *"Have you ever been a smoker? 1) Yes, currently,*

23 *2) Previously: quit <12 months ago, 3) Previously: quit >12 months ago, 4) Never or rarely:*

1 *smoked less than a total of 50 cigarettes (2 ½ packs) over my lifetime."* To improve

2 categorization, we asked subjects what they had smoked and how much, the age started,

3 and when they had stopped.

4   For alcohol use, we used the questionnaire to categorize subjects as a "current

5 drinker," "former drinker," or "never drinker" by asking: *"Do you drink alcohol? 1) Yes, I do*

6 *currently, 2) Previously: quit <12 months ago, 3) Previously: quit >12 months ago, 4)*

7 *Never or rarely because I have not drunk alcohol more than 10 times during my life."* To

8 improve categorization, we asked subjects how many days per week they drank, how

9 many years, and when they had stopped drinking.

10   For diabetes and hypertension, we considered subjects as having these conditions if

11 they were taking medication at the time of exam or if they had stopped against medical

12 advice.   In addition to assessing formal hypertension diagnosis, student clinicians

13 measured   blood   pressure   with   automated   wrist   cuffs   or   manual   arm

14 sphygmomanometers prior to eye drop instillation for pupillary dilation. Body mass index

15 (BMI) was derived using weight and height (kg/m^2) collected via the questionnaire, and it

16 was explored as a continuous variable and using standard BMI categories for adults.[33]

17 We explored cholesterol lowering medications using two approaches, i.e., via the

18 medication list in the health record and by asking about a history of high cholesterol and

19 medication use via the questionnaire.

20   To assess potential confounding, we also collected information on concurrent use of

21 oral beta-blockers, as well as oral, inhaled, or topical corticosteroids. Since subjects often

22 could not recall specific medication names, we conducted subanalyses that excluded

23 subjects with "unknown" hypertensive medications.

1   For refractive error, we used spherical-equivalent values based on the non-

2   cycloplegic, pre-dilation subjective refraction, and we excluded eyes with history of

3   refractive surgery or condition that could influence refractive error. Also, we excluded

4   eyes with history of trauma, uveitis, intraocular surgery, or other condition if there was

5   likely influence on IOP. Eyes treated with IOP lowering medications for glaucoma or

6   ocular hypertension were excluded to eliminate artificial influence on IOP.

7   After analysis of the current data, we also analyzed an older dataset (collected 1999-

8   2001) previously used to study LAZ.[6,12] Although the older dataset did not contain as

9   many variables as the current, we checked for trends similar to current data (See

10   Supplementary Material for further discussion).

11   Statistical analyses were conducted using the SAS® System, Release 9.3 for

12   Microsoft Windows® (SAS Institute Inc., Cary, NC). In addition to descriptive statistics,

13   multiple linear regression was used to model independent variables against the

14   dependent variable, IOP. Model building was aided by stepwise, forward, and backward

15   regression techniques, and variables were explored using varied continuous and

16   categorical formats as appropriate. Assumptions were met for analyses, and variables

17   were checked for correlation and interaction. The investigation received Institutional

18   Review Board approval, the research followed the tenets of the Declaration of Helsinki,

19   and subjects provided written informed consent prior to participation.

20

21   **Results**

22   Among 3,654 total potential subjects, 2,740 (75.0%) consented (Fig. 4). Gender

23   proportion was similar between those consenting and not (female: 64.2% vs. 65.0%;

1   P=0.65), but mean age of consenters was slightly younger (52.1 ± 15.8 vs. 55.0 ± 17.0

2   years; P<0.0001). Race distribution was heavily skewed toward African-Americans, and

3   a slightly higher percentage of African-Americans consented compared to non-African-

4   Americans (75.8% vs. 70.9%, P=0.009).

5   For final regression analyses, 442 (16.1%) of the 2,740 consenting subjects were

6   excluded due to one or more of the following: 1) both eyes had a history of ocular surgery,

7   injury, uveitis, or other condition that might influence IOP; 2) LAZ presence could not be

8   assessed in either eye because of pseudophakia, insufficient pupillary dilation, etc.; 3)

9   LAZ were absent in one eye, but couldn't be ruled out in the other eye because it couldn't

10   be assessed; 4) glaucoma medications were being taken; and/or 4) there was missing

11   information. This left 2,298 subjects.

12   Among consenters, 163 of 2,740 (5.9%) had LAZ of any degree (including trace LAZ,

13   i.e., <5 fibers) in at least one eye. Of these, 109 (66.8%) had bilateral LAZ, 27 (16.6%)

14   had only right eye LAZ, and 27 (16.6%) had only left eye LAZ. Mean age of the 163 LAZ

15   subjects was 63.7 ± 11.2 years (36-92 years), and 73.0% were female. Reflecting

16   institutional demographics, LAZ subjects were predominantly African-American (92.0%),

17   with some being Hispanic (3.7%), White (3.1%), and other (1.2%).

18   Of the 163 total LAZ subjects, we excluded 34 (61.8% female, mean age = 68.2 ±

19   13.8 years, 38-92 years) for the aforementioned reasons, leaving 129 inclusions (76.0%

20   female, mean age = 62.6 ± 10.2 years, 36-91 years) for final analyses. Race distribution

21   of the 129 LAZ inclusions was 118 (91.5%) African-Americans, 5 (3.9%) Hispanics, 4

22   (3.1%) Whites, and 2 (1.6%) subjects of other race. Of the 34 LAZ exclusions, there were

23   32 (94.1%) African-Americans, 1 (2.9%) Hispanic, and 1 (2.9%) White.

1   Composition of the 2,169 non-LAZ inclusions was 63.6% female (mean age = 49.8 $\pm$

2   15.0 years, 18-94 years), and race distribution was 83.2% African-American, 7.3%

3   Hispanic, 6.0% White, 1.7% Asian, and 1.8% other. Composition of the 408 non-LAZ

4   exclusions was 63.6% female (mean age = 59.8 $\pm$ 16.8 years, 18-95 years), and race

5   distribution was 83.4% African-American, 8.1% Hispanic, 5.1% White, 1.5% Asian, and

6   2.0% other.

7   Among all LAZ subjects, 18 of 163 (11.0%) were using IOP-lowering medication (95%

8   bilaterally) for diagnosed glaucoma or ocular hypertension. Of the non-LAZ subjects who

9   consented, 135 of 2,577 (5.2%) were using IOP medication (90% bilaterally). Therefore,

10   use of IOP medication was a frequent reason for exclusion among the 34 LAZ and 408

11   non-LAZ exclusions.

12   Prior to multivariate analysis, using just right eyes, we calculated unadjusted

13   relationships between LAZ and IOP and between IOP and other potential

14   confounding/explanatory variables. We also calculated unadjusted relationships between

15   LAZ and the other potential confounding/explanatory variables (Tables 1-4). To explore

16   whether relationships varied with degree of LAZ, we performed analyses with and without

17   eyes having only trace LAZ, i.e., <5 LAZ fibers. As shown in Tables 1-2, there were

18   numerous unadjusted relationships with the LAZ trait, which sometimes varied depending

19   on inclusion of the trace LAZ eyes. As indicated, those with trace LAZ were younger on

20   average compared to those with >trace LAZ, i.e., 60.8 vs. 65.1 years.

21   As shown in Tables 3-4, numerous variables, as well as having >trace LAZ, showed

22   significant relationship to IOP. Unadjusted mean IOP among eyes with >trace LAZ was

23   higher compared to eyes without LAZ, i.e., 16.4 $\pm$ 3.3 vs. 15.0 $\pm$ 3.3 mm Hg (P=0.005).

1 There was no significant difference between eyes with only trace LAZ and eyes without

2 LAZ, i.e., 14.7 $\pm$ 3.7 vs. 15.0 $\pm$ 3.3 mm Hg (P=0.55). Using multivariate modeling to

3 explore the LAZ-IOP relationship with control for other variables, a relationship between

4 >trace LAZ and IOP persisted (P=0.003) (Table 5), with the LAZ coefficient estimate

5 indicating that on average, IOP was about 1.3 $\pm$ 0.4 mm Hg higher in eyes with LAZ vs.

6 eyes without.

7   Table 6 shows how analyses varied with and without inclusion of the trace LAZ eyes.

8 As shown, the LAZ-IOP relationship was reduced with inclusion of trace LAZ eyes

9 (N=110, coefficient = 0.61 $\pm$ 0.32, P=0.06) and it disappeared when only trace LAZ eyes

10 were included (N=51, coefficient = -0.17 $\pm$ 0.46, P=0.71).

11   Along with primary analyses of right eyes, we also checked for stability and

12 consistency in the LAZ-IOP relationship using other groupings of LAZ eyes (Table 6).

13 Results remained consistent when the LAZ eyes included only left eyes with >trace LAZ

14 (N=59, coefficient = 1.07, P=0.008), as well as only African-American right eyes with

15 >trace LAZ (N=56, coefficient = 1.43, P=0.002). Finally, although numbers of eyes were

16 greatly reduced, we also assessed subjects presenting for first-time facility visits. Despite

17 fewer subjects, (>trace LAZ right eyes, N=8; control right eyes, N=870) and loss of

18 statistical power, results were consistent for a LAZ-IOP relationship (N=8 LAZ,

19 coefficient=2.1, P=0.08).

20   Similar to the current dataset, analysis of the older dataset[6,12] yielded results that also

21 supported a LAZ-IOP relationship while providing reasonable control for other variables

22 (See Supplementary Material).

23

1   **Discussion**

2   This analysis supports a relationship between IOP level and LAZ, and indicated that

3   IOP was about one mm Hg higher, or more, on average among eyes with LAZ compared

4   to non-LAZ eyes. Although this may seem a modest average amount, effect size could

5   be larger in individual subjects. Also, it should be kept in mind that lowering of IOP by

6   just one mm Hg yielded 10% risk reduction in visual field deterioration in the Early

7   Manifest Glaucoma Trial[34] as well as a 10% reduced risk of conversion to overt glaucoma

8   in the Ocular Hypertension Treatment Trial.[35] Given that LAZ subjects taking glaucoma

9   medications were excluded, the magnitude of association could be larger than estimated

10   herein.

11   It should be emphasized that our goal was not to perform an exhaustive analysis of

12   factors that might have association with IOP, but rather to explore the LAZ-IOP

13   relationship while providing reasonable control for other variables. In assessing the

14   control provided by our statistical models, it's also appropriate to gauge whether the

15   control factor relationships are compatible with previous investigations. Although reports

16   vary relative to populations studied, definition of variables, and other methodological

17   considerations, our data appear generally consistent with reported directional

18   relationships to IOP in terms of age,[36-38] gender,[37,38] myopia,[37-39] body mass index,[37,38,40-

19   42] systolic blood pressure,[36-38,43-45] diabetes,[44,46,47] and education level / socioeconomic

20   status.[48]

21   Although certain studies have noted a positive relationship between "current smoking"

22   and IOP,[49,50] others have not.[40-42] We found (Table 3) an unadjusted mean IOP = 14.9 $\pm$

23   3.3 mm Hg among both "current smokers" (32% of subjects) and "past smokers" (19% of

1 subjects). Whereas the dichotomous variable "current smoker vs. past/never smoker" did

2 not reach statistical significance in final models (P>0.05), "ever smoker vs. never smoker"

3 did reach significance (P=0.006, Table 5). Thus, selection of "ever smoker" instead of

4 "current smoker" may simply have added greater statistical power in final models. Factors

5 related to the negative association between smoking and IOP in our study may be related

6 to our clinic-based population demographics.

7   To our knowledge, the inverse association we measured between IOP and history of

8 any type cancer has not been previously reported,[51-55] and we could only speculate why

9 this relationship was present, especially since "cancer" represents a heterogenous

10 collection of diseases with varied treatments. Certainly, there could be a "survivor effect"

11 or some other selection bias influencing this observation.

12   It is not our intent in this report to conclude that the LAZ trait has a direct effect on

13 IOP, nor that it's absolutely a risk factor for glaucoma. Such conclusions are beyond the

14 scope of this cross-sectional study. Nonetheless, the findings herein are important

15 because they are consistent with anecdotal reports that a LAZ-IOP/glaucoma relationship

16 may exist.[5,7,10,26] Should the trait prove to be a risk factor for elevated IOP and glaucoma,

17 mechanisms are currently unknown. Although LAZ fibers can rub against the posterior

18 iris and lead to pigment dispersion,[2,4,5] it is not evident that pigment granule effects on

19 aqueous outflow are typically sufficient to influence IOP.

20   A weakness of this report is that subjects were not fully representative across multiple

21 race/ethnicities. It is a goal to broaden this inquiry for generalizability since it's clear that

22 LAZ prevalence may be similar across many racial/ethnicities.[6]

1   Also, in this study it was not possible to mask determination of LAZ status to IOP

2   because the faculty investigators had to review student exam findings prior to the post-

3   dilation lens assessment. However, it was not an initial goal of data collection to

4   specifically compare IOP between LAZ and non-LAZ subjects. Thus, it seems unlikely

5   that detection of LAZ was influenced by IOP status. Nonetheless, it is also a goal of future

6   study to further reduce potential bias in this regard.

7   Although we did not have central corneal thickness (CCT) measures, the corneal

8   thickness-LAZ relationship has been studied in our population. In that study, mean CCT

9   was similar between 61 African-Americans and controls matched on age, race, and

10   gender (LAZ vs. control right / left eyes: 535 $\pm$ 31 vs. 535 $\pm$ 36 µm / 526 $\pm$ 29 vs. 529 $\pm$

11   36 µm).[14] By definition for factor to be a confounder, it must have significant association

12   with the dependent (IOP) and independent variables of interest (LAZ). Thus, without

13   evidence that CCT has relationship with LAZ, it seems unlikely that the LAZ-IOP

14   association detected is confounded by CCT. Nonetheless, it is also a goal to establish

15   this further.

16   Since this work has investigated IOP, it would be ideal if gonioscopy had been done

17   on all eyes to absolutely rule out narrow angle and other anomalous contribution to IOP

18   level. However, gonioscopy was performed when van Herick estimation suggested need

19   to verify angle openness prior to proceeding with pupillary dilation. In addition,

20   gonioscopy was performed on subjects with IOP >21 mm Hg, and subjects identified with

21   partial angle-closure were excluded from analysis. It therefore seems unlikely that

22   undiscovered angle-closure mechanisms were responsible for the LAZ-IOP association

23   found in this current investigation.

1

Conclusions

In this analysis, the LAZ trait was associated with a higher IOP compared to eyes without LAZ. This is consistent with hypothesis that LAZ may be a marker for underlying mechanisms that elevate glaucoma risk. Given its potential prevalence, the idiopathic LAZ trait should be studied further.

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Precis

The idiopathic long anterior zonule (LAZ) trait, which could have prevalence near 2.0%, was found to have association with higher intraocular pressure, a finding consistent with hypothesis that LAZ is a clinical marker for underlying physiology that elevates glaucoma risk.

Acknowledgement

Figure Legends

Fig. 1.   Example of normal zonule insertion (top) and LAZ (bottom). Persistent pupillary membrane iris strand, common with LAZ, is also shown (bottom, asterisk).

Fig. 2.   Example of pigmented LAZ.

Fig. 3.   "Segmental" type LAZ, characterized by LAZ fibers that end abruptly without peripheral extension all the way to the dilated pupil border (arrows). Persistent pupillary membrane iris strand is also shown (asterisk).

Fig. 4.   Flow diagram summarizing selection of subjects.

TABLE 1

UNIVARIATE ASSOCIATIONS WITH LAZ[*] - CATEGORICAL VARIABLES

Variable	Control N=2,188	Trace LAZ [§]N=51	Any LAZ [§]N=110	>Trace LAZ [§]N=59
Gender, Female	64%	73% (0.19)	75% **(0.01)**[‡]	78% **(0.02)**
Race				
African-American	83%	88% (0.35)[†]	92% **(0.02)**	95% **(0.01)**
Asian	2%	0%	0%	0%
Hispanic	7%	8%	5%	2%
White	6%	4%	3%	2%
Other	2%	0%	1%	2%
Krukenberg's spindle	1%	12% **(<0.0001)**	15% **(<0.0001)**	17% **(<0.0001)**
Pupillary iris strands	15%	25% (0.06)	28% **(<0.001)**	31% **(0.001)**
Education >high school	60%	71% (0.13)	67% (0.14)	64% (0.51)
Diabetes	21%	20% (0.82)	27% (0.11)	34% **(0.02)**
Hypertension	46%	73% **(<0.001)**	71% **(<0.0001)**	69% **(<0.001)**
BMI (overweight or obese)	75%	78% (0.55)	83% (0.06)	86% **(0.04)**
Cancer history - any site	4%	10% (0.07)	8% (0.06)	7% (0.32)
Cholesterol med - current	15%	24% (0.09)	25% **(0.003)**	27% **(0.01)**
Cholesterol med - ever	27%	43% **(0.01)**	43% **(<0.001)**	42% **(0.01)**
Beta-blocker medication	10%	27% **(<0.0001)**	22% **(<0.0001)**	17% (0.07)
Corticosteroid medication	8%	6% (0.63)	7% (0.81)	8% (0.92)
Alcohol use				
Current	49%	51% (0.80)	46% (0.55)	42% (0.30)
Ever	39%	41% (0.75)	41% (0.69)	41% (0.79)
Smoking				
Current	32%	37% (0.43)	29% (0.51)	22% (0.10)
Ever	50%	61% (0.14)	60% (0.05)	59% (0.18)
IOP measured in AM	47%	64% **(0.02)**	64% **(<0.001)**	64% **(0.008)**
Time of year IOP measured				
Q1, January - March	26%	25% (0.23)	22% (0.09)	24% (0.41)
Q2, April - June	26%	37%	34%	34%
Q3, July - September	25%	20%	21%	19%
Q4, October - December	24%	18%	24%	24%

[*]**Abbreviations: IOP, intraocular pressure; LAZ, long anterior zonule trait; N, number of subjects; Q1-Q4, quarter 1-4;**
[†]**Statistical comparison is African-American vs. non-African-American**
[‡]**Bolded p-values significant at α=0.05 level**
[§]**Right eyes used in analysis**

TABLE 2

§UNIVARIATE ASSOCIATIONS WITH LAZ[*] - CONTINUOUS VARIABLES

	Control N=2,188	Trace LAZ ‡N=51	Any LAZ ‡N=110	>Trace LAZ ‡N=59
Variable		Mean (SD) P-value		
Age (years)	49.9 (15.0)	60.8 (9.1) **<0.0001†**	63.1 (10.5) **<0.0001**	65.1 (11.3) **<0.0001**
Refractive error (D)	-0.91 (2.9)	+0.55 (3.5) **<0.001**	+0.81 (2.6) **<0.0001**	+1.04 (1.6) **<0.0001**
Systolic BP (mm Hg)	128.2 (18.0)	133.0 (18.3) 0.06	134.7 (19.8) **0.001**	136.1 (21.0) **0.006**
Diastolic BP (mm Hg)	79.3 (11.0)	79.1 (11.2) 0.90	78.8 (11.4) 0.69	78.6 (11.6) 0.67
Body mass index (kg/m²)	30.5 (7.7)	30.8 (7.8) 0.78	30.7 (7.4) 0.75	30.7 (7.1) 0.85

[*]**Abbreviations: BP, blood pressure; D, diopters; kg/m², kilograms per meter-squared; LAZ, long anterior zonules; mm Hg, millimeters of mercury; SD, standard deviation**
[†]**Bolded p-values significant at α=0.05 level**
[‡]**Right eyes used in analysis**

TABLE 3

UNIVARIATE RELATIONSHIPS WITH IOP[*] - CATEGORICAL VARIABLES

Variable	Subject Distribution	Mean IOP (SD)	P-value
[§]LAZ, Trace only (N=51)			
Yes / No	2% / 98%	14.7 (3.7) / 15.0 (3.3)	0.55
LAZ, Any (N=110)			
Yes / No	5% / 95%	15.6 (3.6) / 15.0 (3.3)	0.10
LAZ, >Trace only (N=59)			
Yes / No	3% / 97%	16.4 (3.3) / 15.0 (3.3)	**0.005[†]**
Krukenberg's spindle			
Yes / No	2% / 98%	15.5 (3.5) / 15.1 (3.4)	0.43
Race			
African-American / Other	82% / 18%	15.2 (3.4) / 14.6 (3.2)	**0.003**
Gender			
Female / Male	64% / 36%	15.3 (3.4) / 14.7 (3.3)	**<0.001**
Education			
>High School / ≤High School	39% / 61%	14.9 (3.2) / 15.4 (3.6)	**<0.001**
Smoking (ever vs. never)	51% / 49%	14.9 (3.3) / 15.3 (3.4)	**0.008**
Current	32%	14.9 (3.3)	
Past	19%	14.9 (3.3)	
Never	49%	15.3 (3.4)	
Alcohol (ever vs. never)	61% / 39%	15.0 (3.3) / 15.1 (3.4)	0.32
Current	48%	15.0 (3.3)	
Past	12%	14.8 (3.5)	
Never	40%	15.1 (3.4)	
Diabetes			
Yes / No	21% / 79%	15.8 (3.6) / 14.9 (3.3)	**<0.0001**
Hypertension			
Yes / No	48% / 52%	15.3 (3.4) / 14.8 (3.3)	**0.001**
Body mass index (obese vs other)	46% / 54%	15.4 (3.4) / 14.8 (3.3)	**<0.0001**
Underweight (<18.5)	2%	14.4 (3.2)	
Normal weight (18.5 - 24.9)	23%	14.6 (3.1)	
Overweight (25.0 - 29.9)	29%	14.9 (3.5)	
Obese (≥30)	46%	15.4 (3.4)	
Beta-blocker medication			
Yes / No	10% / 90%	15.1 (2.9) / 15.0 (3.4)	0.67
Cholesterol - med (per record)			
Yes / No	16% / 84%	15.6 (3.9) / 15.1 (3.5)	**0.02**
Cholesterol - med ever (survey)			
Yes / No	29% / 71%	15.4 (3.7) / 15.1 (3.4)	0.06
Steroid medication	8% / 92%	15.1 (3.6) / 15.0 (3.3)	0.75
Cancer history - any site			
Yes / No	4% / 96%	14.0 (3.0) / 15.1 (3.4)	**0.001**
Time of day			
AM / PM	48% / 52%	15.2 (3.4) / 14.9 (3.4)	0.09
Time of Year			
Q1 (Jan-Mar)	25%	15.2 (3.3)	
Q2 (Apr-June)	26%	15.2 (3.5)	0.15
Q3 (July-Sept)	26%	14.8 (3.2)	
Q4 (Oct-Dec)	24%	15.0 (3.4)	

[*]**Abbreviations: D, diopters; SE, spherical equivalent; LAZ, long anterior zonule trait; N, number of subjects; Q1-Q4, Quarter1-Qaurter4; SD, standard deviation**
[†]**Bolded p-values significant at α=0.05 level**

TABLE 4

UNIVARIATE CORRELATIONS WITH IOP[*] - CONTINUOUS VARIABLES

Variable	Correlation with IOP (r)	P-value
Age (years)	0.04	0.07
Refractive Error (SE, diopters)	-0.07	**<0.001[†]**
Body mass index (kg/m^2)	0.13	**<0.0001**
Systolic blood pressure (mm Hg)	0.17	**<0.0001**
Diastolic blood pressure (mm Hg)	0.13	**<0.0001**
Pack years smoking	-0.01	0.36

[*]**Abbreviations: IOP, intraocular pressure; Kg/m^2, kilograms per meter-squared; mm Hg, millimeters of mercury; SE, spherical equivalent;**
[†]**Bolded p-values significant at α=0.05 level**

TABLE 5

MULTIVARIATE ANALYSIS OF LAZ RELATIONSHIP WITH IOP[*]

CONTROLLING FOR OTHER VARIABLES

Variable	Coefficient (SE)	P-value
Intercept	10.2 (0.59)	--
LAZ present (right eyes, >trace LAZ, N=59)	1.30 (0.43)	0.003
Gender (female)	0.49 (0.15)	0.001
[†]Refractive error (per diopter)	-0.10 (0.02)	<0.0001
Education >high school	-0.53 (0.14)	<0.001
[‡]History of cancer (any site)	-0.87 (0.34)	0.01
Body mass index (per 10 units, kg/m^2)	0.35 (0.09)	<0.001
Systolic blood pressure (per 10 mm Hg)	0.26 (0.04)	<0.0001
Diabetes	0.65 (0.17)	<0.001
Ever smoke	-0.39 (0.14)	0.006

[*]**Abbreviations: SE, spherical equivalent; IOP, intraocular pressure; kg/m^2, kilograms per meter-squared; LAZ, long anterior zonule trait; mm Hg, millimeters of mercury; N, number of subjects; SE, standard error**
[†]**Spherical equivalent value**
[‡]**Cancer sites (N=106 cases): breast = 42.4%, prostate = 13.2%, colon = 5.7%, lung = 4.7%; coefficient = -1.28 $\pm$ 0.49, P=0.009 when only breast cancer cases included; coefficient = -0.61 $\pm$ 0.44, P=0.16 when breast cancer cases excluded;**
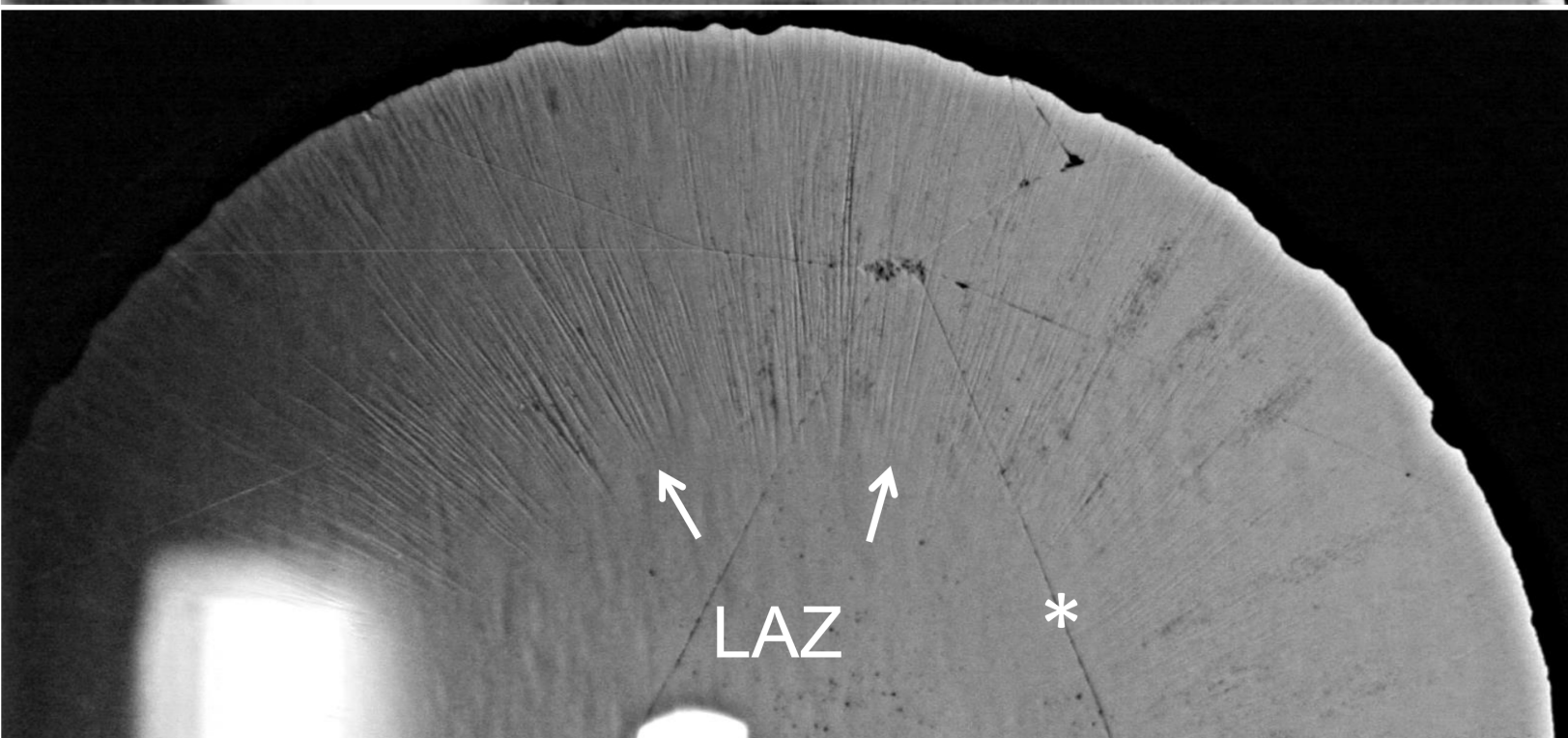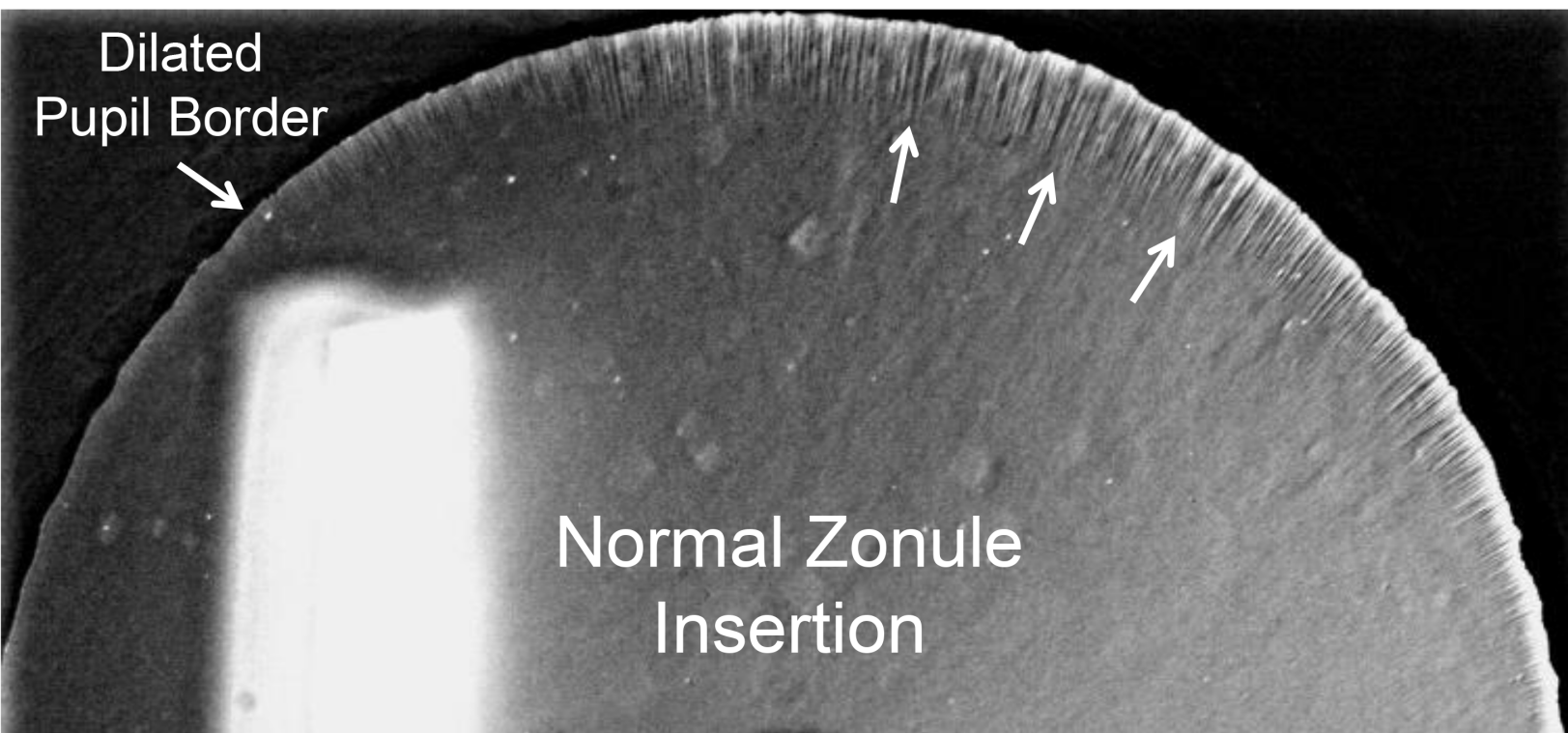
TABLE 6

MULTIVARIATE ANALYSIS OF LAZ WITH IOP[*] - CONTROLLING FOR OTHER VARIABLES

STABILITY OF COEFFICIENT ESTIMATES AMONG LAZ EYE SUBGROUPS
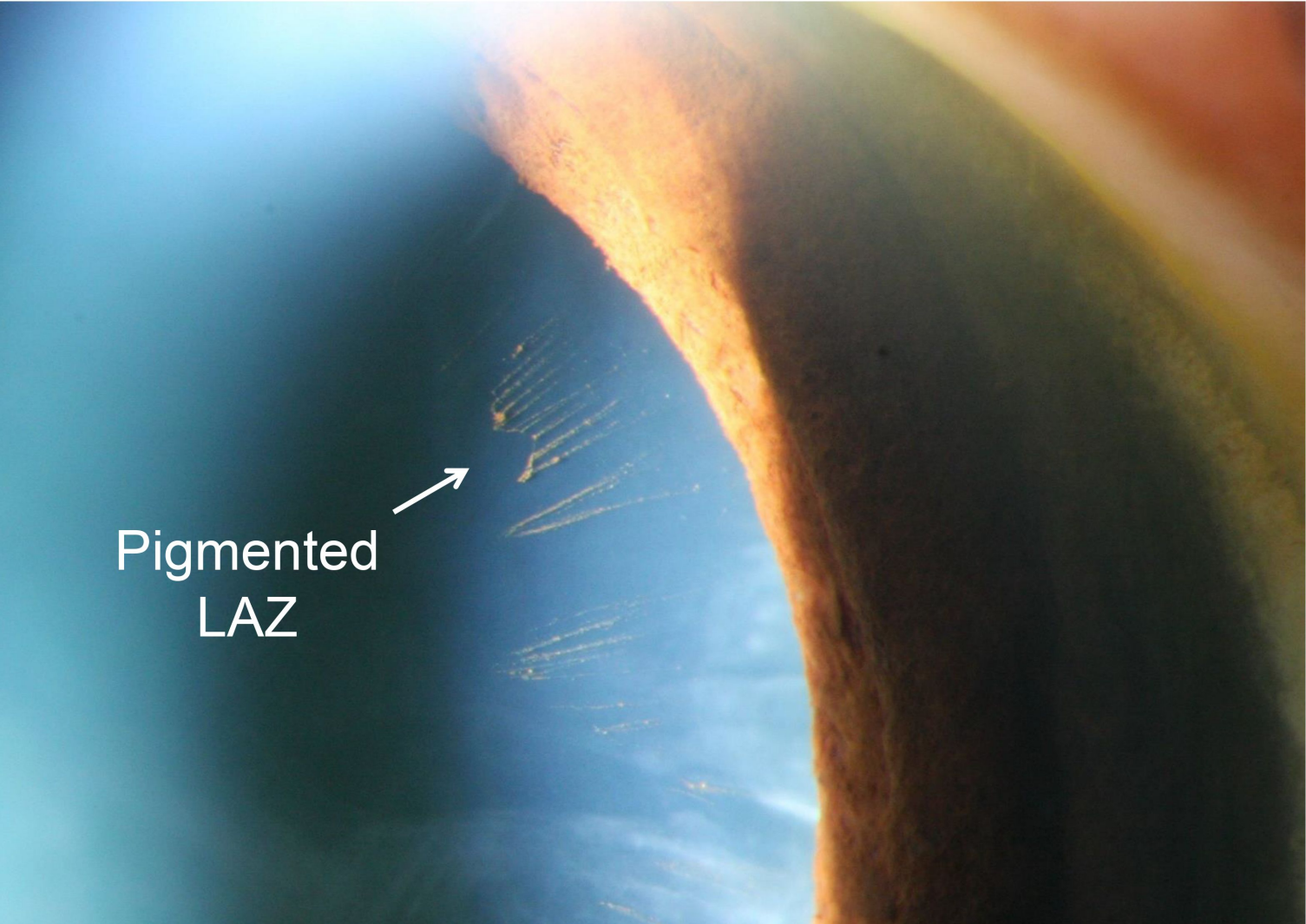
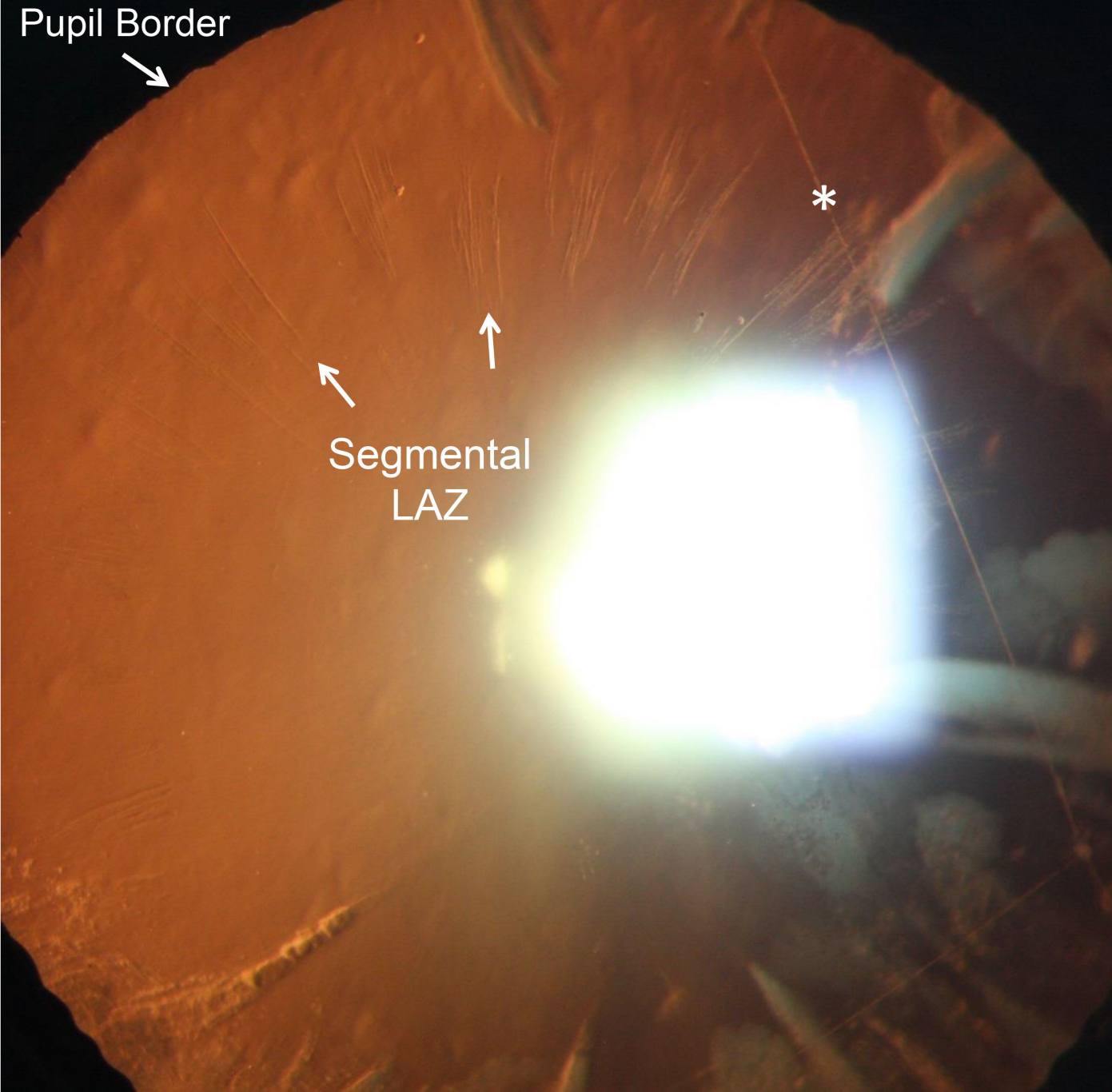| Variable	Right Eyes >Trace LAZ (N=59 LAZ)	Right Eyes Any LAZ (N=110)	Right Eyes Trace LAZ (N=51)	Left Eyes >Trace LAZ (N=59)	AA Only Right Eyes >Trace LAZ (N=56)	New Patients Right Eyes >Trace LAZ (N=8)
	Coefficients (P-values)					
Intercept	10.1	10.1	10.1	10.2	10.7	11.7
LAZ	1.30 (0.003)	0.61 (0.06)	-0.17 (0.71)	1.07 (0.008)	1.42 (0.002)	2.07 (0.08)
Gender (female)	0.49 (0.001)	0.46 (0.002)	0.45 (0.002)	0.52 (<0.001)	0.35 (0.04)	0.70 (0.002)
[†]Refractive error (per diopter)	-0.10 (<0.0001)	-0.10 (<0.0001)	-0.10 <0.0001)	-0.08 (0.002)	-0.11 (<0.0001)	-0.06 (0.18)
Education >high school	-0.53 (<0.001)	-0.56 (<0.0001)	-0.55 (<0.001)	-0.57 (<0.0001)	-0.60 (<0.001)	-0.25 (0.30)
History of cancer (any site)	-0.87 (0.01)	-0.92 (0.005)	-0.83 (0.01)	-0.94 (0.006)	-0.64 (0.07)	-1.42 (0.02)
BMI (per 10 units, kg/m^2)	0.35 (<0.001)	0.32 (<0.001)	0.32 (<0.001)	0.30 (0.002)	0.38 (<0.001)	0.27 (0.08)
Systolic BP (per 10 mm Hg)	0.26 (<0.0001)	0.28 (<0.0001)	0.27 (<0.0001)	0.27 <0.0001)	0.24 (<0.0001)	0.26 (<0.0001)
Diabetes	0.65 (<0.001)	0.64 (<0.001)	0.65 (<0.001)	0.61 (<0.001)	0.65 (<0.001)	0.72 (0.02)
Ever smoke	-0.39 (0.006)	-0.37 (0.007)	-0.37 (0.008)	-0.30 (0.03)	-0.50 (0.001)	-0.58 (0.01)

[*]Abbreviations: AA, African-American; BP, blood pressure; BMI, body mass index; IOP, intraocular pressure; kg/m^2, kilograms per meter-squared; LAZ, long anterior zonule trait; mm Hg, millimeters of mercury;
[†]Spherical equivalent

Dilated
Pupil Border

Normal Zonule
Insertion

LAZ

*

Pigmented LAZ