Long Anterior Lens Zonules and Intraocular Pressure

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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 2169 non-LAZ and 129 LAZ subjects (mean age: 49.8 ± 15.0 vs. 62.6 ± 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 ± 3.3 vs. 15.0 ± 3.3 mm Hg, $P = 0.005$), and with control for numerous factors, LAZ eyes had an average IOP of approximately 1.3 ± 0.4 mm Hg higher ($P = 0.003$) than non-LAZ eyes. Final model covariates included sex ($P = 0.001$); 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.

Keywords: crystalline lens, glaucoma, intraocular pressure, long anterior zonules, pigment dispersion

Long anterior zonules (LAZ) are characterized by zonular fibers that extend more central than usual on the anterior lens capsule.[1–4] They are observed following pupillary dilation as radially oriented fine lines, which often become pigmented due to rubbing against the posterior iris pigment epithelium (Figs. 1, 2). Other pigment dispersal signs may also be present, including Krukenberg spindles and trabecular meshwork pigmentation,[5–7] and these signs may cause LAZ-associated pigment dispersion to be confused with the more well-known "classic" variety pigment dispersion syndrome.[8,9]

Current understanding suggests that the LAZ trait may present with at least two phenotypic varieties. One rare variety may be detected during a young age, which occurs with a serine to arginine (S163R) substitution in the complement 1q tumor necrosis factor-related protein 5 (C1QTNF5) gene that causes late-onset retinal degeneration (L-ORD).[10,11] Another, more common variety with unknown etiology and prevalence possibly near 2%,[12] has association with age >50 years,[4,6,12] female sex,[4,6,12] hyperopia,[6,12,13] shorter axial length,[14] and persistent pupillary membrane iris strands.[15] Only recently has the literature begun to differentiate between these separate LAZ presentations, and it's unknown what pathophysiology may produce LAZ in such different groups.

The LAZ trait has also drawn interest relative to cataract surgery because the anomalous fibers reduce the size of the anterior capsule's zonule-free zone (ZFZ), creating concern that zonular cutting during capsulorhexis may elevate risk of capsular tearing and intraocular lens dislocation.[16–24] Furthermore, there has also been suggestion that the LAZ trait could signal higher risk for both open- and narrow-angle glaucoma.[5,7,10,14,25,26] In 1962, Stankovic and Stankovic[26] reported 14 subjects who had LAZ and pigment dispersal signs, with nine having heavy trabecular meshwork pigmentation and elevated IOP. Similarly, Moroi et al.[5] described 15 LAZ subjects with pigment dispersion signs, seven of whom were being treated for glaucoma or ocular hypertension. About half belonged to a four-generation pedigree (UM:H389)[7] that had many members exhibiting LAZ alone or LAZ with the autosomal dominant retinal condition mentioned earlier called L-ORD.[10,11] The C1QTNF5 gene, which has the S163R mutation causing L-ORD, maps to chromosome 11q23 and influences wide-ranging processes that include cellular adhesion and basement membrane functions.[27,28]

The question of increased risk of angle-closure glaucoma is perhaps not surprising given that people with late-onset LAZ are more likely to be older, hyperopic, and female. However, it's not clear that angle-closure risk is any higher among people with LAZ than among similar people with similar refractive error who don't have LAZ.[29] There has also been question though as to whether there is association between LAZ and

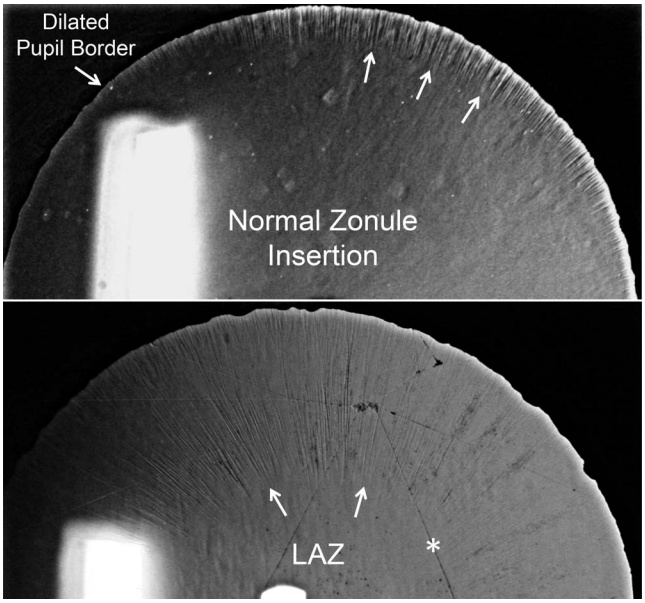

FIGURE 1. Example of normal zonule insertion (*top*) and LAZ (*bottom*). Persistent pupillary membrane iris strand, common with LAZ, is also shown (*bottom*, *asterisk*).

plateau iris configuration.[25] Should this be the case, potential angle-closure risk could be more complex than any risk conveyed by basic axial dimensions of the eye.

Given the potential relationship between LAZ and glaucoma, there is need for further inquiry, and as a step toward this, we investigated whether we could detect a relationship between the LAZ trait and IOP level.

METHODS

As part of a larger investigation of ocular and general health associations with the LAZ trait, consecutive patients, presenting to six different practitioners for a regularly scheduled examination in an urban academic eye care facility in Chicago, Illinois, were included as subjects if they were aged ≥18 years, having their pupils dilated, and if they provided informed consent and completed a brief written questionnaire to supplement other demographic, health, and lifestyle information. Along with ocular/medical histories, assessment included testing of Snellen visual acuities, pupils, motility and binocularity, color vision, and confrontation visual fields. Also done were predilation subjective refraction, slit lamp exam, Goldmann applanation tonometry, and dilated retinal exam.

Student clinicians within the facility's Primary Eye Care Service performed initial testing on subjects. Although tonometry was often checked by attending faculty investigators, student measurements were used for analysis because faculty measurements were not always done. Single measurements obtained on the day of study were used and all were performed in a consistent fashion using slit lamp mounted Goldmann tonometers, the standard in this clinical setting.

Immediately after instillation of pupil dilation drops, student clinicians provided questionnaires for completion without assistance. Faculty investigators learned of subject participation at time of final physical assessment and then examined for LAZ using bright slit-lamp illumination with ×16 to ×25 magnification. Investigators were experienced in LAZ detection from prior investigations.[6,13,15,23,30]

The criterion for LAZ was presence of radially oriented zonular fibers, pigmented or nonpigmented, with anterior tips judged to extend substantially (>1.0 mm, estimated with slit-lamp beam length) central to the normal capsular zonular insertion zone, about 1.5 mm anterior to the lens equator.[31] From their anterior tips, LAZ fibers could extend peripherally to the dilated pupil border where they became obscured, or the fibers could be "segmental"[32] whereby their peripheral tips stopped abruptly along the anterior capsule without detectable extension to the pupil border (Fig. 3). We included subjects with any degree (number) of LAZ, but also distinguished between <5 LAZ fibers (trace LAZ) and five or more detectable fibers.[23]

In addition to LAZ, investigators examined eyes for Krukenberg spindles and persistent pupillary iris strands.[6,12,15] We considered a Krukenberg spindle present when there was any "fine pigment dusting" along the central posterior cornea, which we considered present when individual pigment granules could not be "counted" because they were too fine, numerous, and coalesced. Larger, coarse pigment flecks were

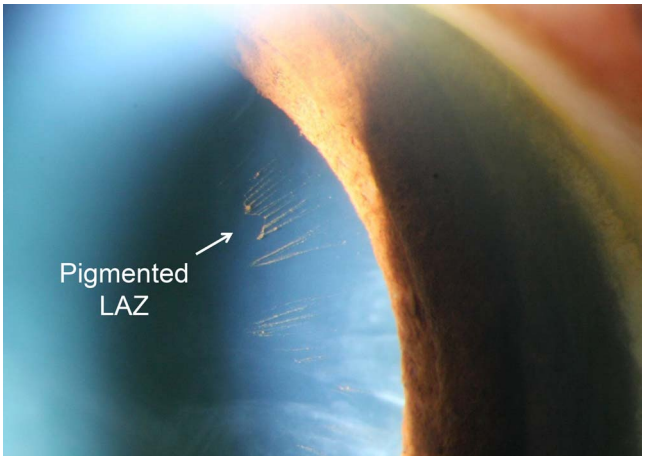

FIGURE 2. Example of pigmented LAZ.

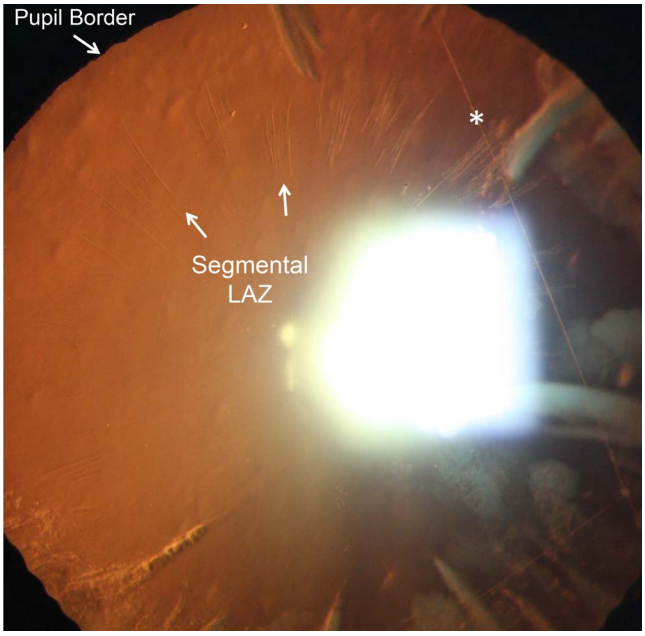

FIGURE 3. "Segmental" type LAZ, characterized by LAZ fibers that end abruptly without peripheral extension all the way to the dilated pupil border (*arrows*). Persistent pupillary membrane iris strand is also shown (*asterisk*).

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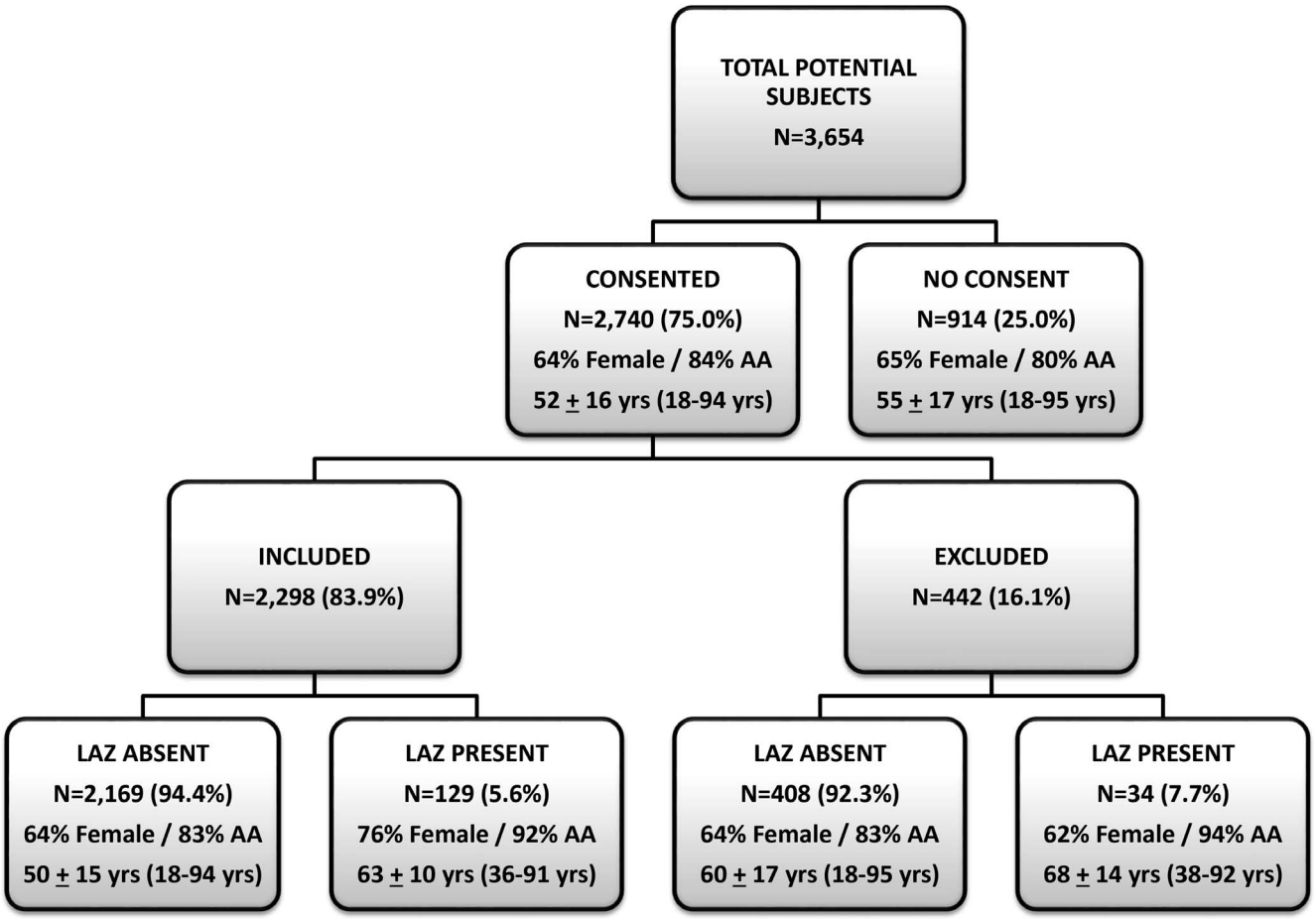

Figure 4. Flow diagram summarizing selection of subjects.

not considered a sign of a Krukenberg spindle. We considered persistent pupillary membrane iris strands (Figs. 1, 3) present when there was at least one iris strand that bisected the dilated pupil and had both ends attached to the iris collarette or one end to the collarette and the other to the anterior lens capsule.[15]

We determined race using medical record notation and the questionnaire, and assigned one of five categories: (1) black/African American, (2) Asian, (3) Hispanic, black or white, (4) Non-Hispanic white, and (5) Other. Education level was determined via questionnaire by asking: "What is your highest level of education? (1) Less than high school degree, (2) High school degree, (3) Vocational school or some college but no degree, (4) College Associate's or Bachelor's degree, (5) College Master's, Professional, or Doctoral degree."

We also used the questionnaire to categorize subjects as a "current smoker," "former smoker," or "never smoker" by asking: "Have you ever been a smoker? (1) Yes, currently, (2) Previously: quit <12 months ago, (3) Previously: quit >12 months ago, (4) Never or rarely: smoked less than a total of 50 cigarettes (2½ packs) over my lifetime." To improve categorization, we asked subjects what they had smoked and how much, the age started, and when they had stopped.

For alcohol use, we used the questionnaire to categorize subjects as a "current drinker," "former drinker," or "never drinker" by asking: "Do you drink alcohol? (1) Yes, I do currently, (2) Previously: quit <12 months ago, (3) Previously: quit >12 months ago, (4) Never or rarely because I have not drunk alcohol more than 10 times during my life." To improve categorization, we asked subjects how many days per week they drank, how many years, and when they had stopped drinking.

For diabetes and hypertension, we considered subjects as having these conditions if they were taking medication at the time of exam or if they had stopped against medical advice. In addition to assessing formal hypertension diagnosis, student clinicians measured blood pressure with automated wrist cuffs or manual arm sphygmomanometers prior to eye drop instillation for pupillary dilation. Body mass index (BMI) was derived using weight and height (kg/m^2) collected via the questionnaire, and it was explored as a continuous variable and using standard BMI categories for adults.[33] We explored cholesterol lowering medications using two approaches: via the medication list in the health record and by asking about a history of high cholesterol and medication use via the questionnaire.

To assess potential confounding, we also collected information on concurrent use of oral beta-blockers, as well as oral, inhaled, or topical corticosteroids. Since subjects often could not recall specific medication names, we conducted subanalyses that excluded subjects with "unknown" hypertensive medications.

For refractive error, we used spherical-equivalent (SE) values based on the noncycloplegic, predilation subjective refraction, and we excluded eyes with history of refractive surgery or condition that could influence refractive error. Also, we excluded eyes with history of trauma, uveitis, intraocular surgery, or other condition if there was likely influence on IOP. Eyes treated with IOP-lowering medications for glaucoma or

Table 1. Univariate Associations With LAZ, Categorical Variables

Variable	Control, $n = 2188$†	Trace LAZ, $n = 51$†	Any LAZ, $n = 110$†	>Trace LAZ, $n = 59$†
Sex, 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 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				
Quarter (Q)1, 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%

Bolded P values (in parentheses) are significant at $\alpha = 0.05$ level.
* Statistical comparison is African American versus non-African American.
† Right eyes used in analysis.

ocular hypertension were excluded to eliminate artificial influence on IOP.

After analysis of the current data, we also analyzed an older dataset (collected 1999–2001) previously used to study LAZ.[6,12] Although the older dataset did not contain as many variables as the current, we checked for trends similar to current data (see Supplementary Material for further discussion).

Statistical analyses were conducted using a commercial system (SAS Release 9.3 for Microsoft Windows; SAS Institute, Inc., Cary, NC, USA). In addition to descriptive statistics, multiple linear regression was used to model independent variables against the dependent variable, IOP. Model building was aided by stepwise, forward, and backward regression techniques, and variables were explored using varied continuous and categorical formats as appropriate. Assumptions were met for analyses, and variables were checked for correlation and interaction. The investigation received Institutional Review Board approval, the research followed the tenets of the Declaration of Helsinki, and subjects provided written informed consent prior to participation.

Results

Among 3654 total potential subjects, 2740 (75.0%) consented (Fig. 4). Sex proportion was similar between those consenting and not (female: 64.2% vs. 65.0%; $P = 0.65$), but mean age of consenters was slightly younger (52.1 ± 15.8 vs. 55.0 ± 17.0 years; $P < 0.0001$). Race distribution was heavily skewed toward African Americans, and a slightly higher percentage of African Americans consented compared to non-African Americans (75.8% vs. 70.9%, $P = 0.009$).

For final regression analyses, 442 (16.1%) of the 2740 consenting subjects were excluded due to one or more of the following: (1) both eyes had a history of ocular surgery, injury, uveitis, or other condition that might influence IOP; (2) LAZ presence could not be assessed in either eye because of pseudophakia, insufficient pupillary dilation, etc.; (3) LAZ were absent in one eye, but couldn't be ruled out in the other eye because it couldn't be assessed; (4) glaucoma medications were being taken; and/or (5) there was missing information. This left 2298 subjects.

Among consenters, 163 of 2740 (5.9%) had LAZ of any degree (including trace LAZ, i.e., <5 fibers) in at least one eye. Of these, 109 (66.8%) had bilateral LAZ, 27 (16.6%) had only right eye LAZ, and 27 (16.6%) had only left eye LAZ. Mean age of the 163 LAZ subjects was 63.7 ± 11.2 years (36–92 years), and 73.0% were female. Reflecting institutional demographics, LAZ subjects were predominantly African American (92.0%), with some being Hispanic (3.7%), white (3.1%), and other (1.2%).

Of the 163 total LAZ subjects, we excluded 34 (61.8% female, mean age = 68.2 ± 13.8 years, 38–92 years) for the aforementioned reasons, leaving 129 inclusions (76.0% female, mean age = 62.6 ± 10.2 years, 36–91 years) for final analyses. Race distribution of the 129 LAZ inclusions was 118 (91.5%) African Americans; 5 (3.9%) Hispanics; 4 (3.1%) whites; and 2 (1.6%) subjects of other race. Of the 34 LAZ exclusions, there were 32 (94.1%) African Americans; 1 (2.9%) Hispanic; and 1 (2.9%) white.

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Table 2. Univariate Associations With LAZ, Continuous Variables

Variable	Mean (SD) *P* Value			
	Control, $n = 2188$†	Trace LAZ, $n = 51$*	Any LAZ, $n = 110$*	>Trace LAZ, $n = 59$*
Age, y	49.9 (15.0)	60.8 (9.1)	63.1 (10.5)	65.1 (11.3)
		<0.0001	**<0.0001**	**<0.0001**
Refractive error, diopter (D)	0.91 (2.9)	±0.55 (3.5)	±0.81 (2.6)	±1.04 (1.6)
		<0.001	**<0.0001**	**<0.0001**
Systolic blood pressure (BP), mm Hg	128.2 (18.0)	133.0 (18.3)	134.7 (19.8)	136.1 (21.0)
		0.06	**0.001**	**0.006**
Diastolic BP, mm Hg	79.3 (11.0)	79.1 (11.2)	78.8 (11.4)	78.6 (11.6)
		0.90	0.69	0.67
Body mass index, kg/m^2	30.5 (7.7)	30.8 (7.8)	30.7 (7.4)	30.7 (7.1)
		0.78	0.75	0.85

Bolded *P* values are significant at $\alpha = 0.05$ level.
* Right eyes used in analysis.

Composition of the 2169 non-LAZ inclusions was 63.6% female (mean age = 49.8 ± 15.0 years, 18–94 years), and race distribution was 83.2% African American, 7.3% Hispanic, 6.0% white, 1.7% Asian, and 1.8% other. Composition of the 408 non-LAZ exclusions was 63.6% female (mean age = 59.8 ± 16.8 years, 18–95 years), and race distribution was 83.4% African American, 8.1% Hispanic, 5.1% white, 1.5% Asian, and 2.0% other.

Among all LAZ subjects, 18 of 163 (11.0%) were using IOP-lowering medication (95% bilaterally) for diagnosed glaucoma or ocular hypertension. Of the non-LAZ subjects who consented, 135 of 2577 (5.2%) were using IOP medication (90% bilaterally). Therefore, use of IOP medication was a frequent reason for exclusion among the 34 LAZ and 408 non-LAZ exclusions.

Prior to multivariate analysis, using just right eyes, we calculated unadjusted relationships between LAZ and IOP and between IOP and other potential confounding/explanatory variables. We also calculated unadjusted relationships between

Table 3. Univariate Relationships With IOP, Categorical Variables

Variable	Subject Distribution, %	Mean IOP (SD), mm Hg	*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 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**
Sex, 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/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/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/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 medication (per record), yes/no	16/84	15.6 (3.9)/15.1 (3.5)	**0.02**
Cholesterol medication ever (survey), yes/no	29/71	15.4 (3.7)/15.1 (3.4)	0.06
Steroid medication, yes/no	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			0.15
Q1, January–March	25	15.2 (3.3)	
Q2, April–June	26	15.2 (3.5)	
Q3, July–September	26	14.8 (3.2)	
Q4, October–December	24	15.0 (3.4)	

Bolded *P* values are significant at $\alpha = 0.05$ level.

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Table 4. Univariate Correlations With IOP, Continuous Variables

Variable	Correlation With IOP, *r*	*P* Value
Age, y	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

Bolded *P* values are significant at $\alpha = 0.05$ level.

LAZ and the other potential confounding/explanatory variables (Tables 1–4). To explore whether relationships varied with degree of LAZ, we performed analyses with and without eyes having only trace LAZ (i.e., <5 LAZ fibers). As shown in Tables 1 and 2, there were numerous unadjusted relationships with the LAZ trait, which sometimes varied depending on inclusion of the trace LAZ eyes. As indicated, those with trace LAZ were younger on average compared to those with >trace LAZ (i.e., 60.8 vs. 65.1 years).

As shown in Tables 3 and 4, numerous variables, as well as having >trace LAZ, showed significant relationship to IOP. Unadjusted mean IOP among eyes with >trace LAZ was higher compared to eyes without LAZ (i.e., 16.4 ± 3.3 vs. 15.0 ± 3.3 mm Hg; $P = 0.005$). There was no significant difference between eyes with only trace LAZ and eyes without LAZ (i.e., 14.7 ± 3.7 vs. 15.0 ± 3.3 mm Hg; $P = 0.55$). Using multivariate modeling to explore the LAZ-IOP relationship with control for other variables, a relationship between >trace LAZ and IOP persisted ($P = 0.003$; Table 5), with the LAZ coefficient estimate indicating that on average, IOP was about 1.3 ± 0.4 mm Hg higher in eyes with LAZ versus eyes without.

Table 6 shows how analyses varied with and without inclusion of the trace LAZ eyes. As shown, the LAZ-IOP relationship was reduced with inclusion of trace LAZ eyes ($n = 110$, coefficient = 0.61 ± 0.32, $P = 0.06$) and it disappeared when only trace LAZ eyes were included ($n = 51$, coefficient = −0.17 ± 0.46, $P = 0.71$).

Along with primary analyses of right eyes, we also checked for stability and consistency in the LAZ-IOP relationship using other groupings of LAZ eyes (Table 6). Results remained consistent when the LAZ eyes included only left eyes with >trace LAZ ($n = 59$, coefficient = 1.07, $P = 0.008$), as well as only African American right eyes with >trace LAZ ($n = 56$, coefficient = 1.43, $P = 0.002$). Finally, although numbers of eyes were greatly reduced, we also assessed subjects presenting for first-time facility visits. Despite fewer subjects, (>trace LAZ right eyes, $n = 8$; control right eyes, $n = 870$) and loss of statistical power, results were consistent for a LAZ-IOP relationship ($n = 8$ LAZ, coefficient = 2.1, $P = 0.08$).

Similar to the current dataset, analysis of the older dataset[6,12] yielded results that also supported a LAZ-IOP relationship while providing reasonable control for other variables (see Supplementary Material).

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
Sex, 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 BP, 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

* Spherical equivalent.

† Cancer sites ($n = 106$ cases): breast = 42.4%; prostate = 13.2%; colon = 5.7%; lung = 4.7%; coefficient = −1.28 ± 0.49, $P = 0.009$ when only breast cancer cases included; coefficient = −0.61 ± 0.44, $P = 0.16$ when breast cancer cases excluded.

Discussion

This analysis supports a relationship between IOP level and LAZ, and indicated that IOP was about one mm Hg higher, or more, on average among eyes with LAZ compared to non-LAZ eyes. Although this may seem a modest average amount, effect size could be larger in individual subjects. Also, it should be kept in mind that lowering of IOP by just 1 mm Hg yielded 10% risk reduction in visual field deterioration in the Early Manifest Glaucoma Trial[34] as well as a 10% reduced risk of conversion to

Table 6. Multivariate Analysis of LAZ With IOP, Controlling for Other Variables; Stability of Coefficient Estimates Among LAZ Eye Subgroups

	Coefficients (*P* Values)					
Variable	Right Eyes >Trace LAZ, $n = 59$	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, $n = 8$
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)
Sex, 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)

AA, African American.

* Spherical equivalent.

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overt glaucoma in the Ocular Hypertension Treatment Trial.[35] Given that LAZ subjects taking glaucoma medications were excluded, the magnitude of association could be larger than estimated herein.

It should be emphasized that our goal was not to perform an exhaustive analysis of factors that might have association with IOP, but rather to explore the LAZ-IOP relationship while providing reasonable control for other variables. In assessing the control provided by our statistical models, it's also appropriate to gauge whether the control factor relationships are compatible with previous investigations. Although reports vary relative to populations studied, definition of variables, and other methodologic considerations, our data appear generally consistent with reported directional relationships to IOP in terms of age,[36–38] sex,[37,38] myopia,[37–39] body mass index,[37,38,40–42] systolic blood pressure,[36–38,43–45] diabetes,[44,46,47] and education level/socioeconomic status.[48]

Although certain studies have noted a positive relationship between "current smoking" and IOP,[49,50] others have not.[40–42] We found (Table 3) an unadjusted mean IOP = 14.9 ± 3.3 mm Hg among both "current smokers" (32% of subjects) and "past smokers" (19% of subjects). Whereas the dichotomous variable "current smoker versus past/never smoker" did not reach statistical significance in final models ($P > 0.05$), "ever smoker versus never smoker" did reach significance ($P = 0.006$, Table 5). Thus, selection of "ever smoker" instead of "current smoker" may simply have added greater statistical power in final models. Factors related to the negative association between smoking and IOP in our study may be related to our clinic-based population demographics.

To our knowledge, the inverse association we measured between IOP and history of any type cancer has not been previously reported,[51–55] and we could only speculate why this relationship was present, especially since "cancer" represents a heterogenous collection of diseases with varied treatments. Certainly, there could be a "survivor effect" or some other selection bias influencing this observation.

It is not our intent in this report to conclude that the LAZ trait has a direct effect on IOP, nor that it's absolutely a risk factor for glaucoma. Such conclusions are beyond the scope of this cross-sectional study. Nonetheless, the findings herein are important because they are consistent with anecdotal reports that a LAZ-IOP/glaucoma relationship may exist.[5,7,10,26] Should the trait prove to be a risk factor for elevated IOP and glaucoma, mechanisms are currently unknown. Although LAZ fibers can rub against the posterior iris and lead to pigment dispersion,[2,4,5] it is not evident that pigment granule effects on aqueous outflow are typically sufficient to influence IOP.

A weakness of this report is that subjects were not fully representative across multiple race/ethnicities. It is a goal to broaden this inquiry for generalizability since it's clear that LAZ prevalence may be similar across many racial/ethnicities.[6]

Also, in this study it was not possible to mask determination of LAZ status to IOP because the faculty investigators had to review student exam findings prior to the postdilation lens assessment. However, it was not an initial goal of data collection to specifically compare IOP between LAZ and non-LAZ subjects. Thus, it seems unlikely that detection of LAZ was influenced by IOP status. Nonetheless, it is also a goal of future studies to further reduce potential bias in this regard.

Although we did not have central corneal thickness (CCT) measures, the corneal thickness-LAZ relationship has been studied in our population. In that study, mean CCT was similar between 61 African Americans and controls matched on age, race, and sex (LAZ versus control right/left eyes: 535 ± 31 vs. 535 ± 36 μm/526 ± 29 vs. 529 ± 36 μm).[14] By definition, for a factor to be a confounder, it must have significant association with the dependent (IOP) and independent variables of interest (LAZ). Thus, without evidence that CCT has relationship with LAZ, it seems unlikely that the LAZ-IOP association detected is confounded by CCT. Nonetheless, it is also a goal to establish this further.

Since this work has investigated IOP, it would be ideal if gonioscopy had been done on all eyes to absolutely rule out narrow angle and other anomalous contribution to IOP level. However, gonioscopy was performed when van Herick estimation suggested the need to verify angle openness prior to proceeding with pupillary dilation. In addition, gonioscopy was performed on subjects with IOP >21 mm Hg, and subjects identified with partial angle-closure were excluded from analysis. It therefore seems unlikely that undiscovered angle-closure mechanisms were responsible for the LAZ-IOP association found in this current investigation.

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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