Glaucoma

The Association Between Age and Systemic Variables and the Longitudinal Trend of Intraocular Pressure in a Large-Scale Health Examination Cohort

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PURPOSE. The detailed effects of age and systemic factors on intraocular pressure (IOP) have not been fully understood because of the lack of a large-scale longitudinal investigation. This study aimed to investigate the effect of various systemic factors on the longitudinal change of IOP.

METHODS. There were a total of 20,909 eyes of 10,471 subjects from a health checkup cohort that were followed up for systemic factors: (i) age at baseline, (ii) sex, (iii) time series body mass index (BMI), (iv) time series smoking habits, (v) time series systolic and diastolic blood pressures (SBP and DBP), and (vi) time series 19 blood examinations (all of the time series data was acquired at each annual visit), along with IOP annually for at least 8 years. Then the longitudinal effect of the systemic factors on the change of IOP was investigated.

RESULTS. IOP significantly decreased by −0.084 mm Hg/year. BMI, SBP, DBP, smoking habits, total triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and glycosylated hemoglobin A1c were not significantly associated with the change of IOP. Higher values of age, aspartate aminotransferase, hemoglobin, platelet, and calcium were suggested to be significantly associated with the decrease of IOP, whereas higher alanine aminotransferase, guanosine triphosphate, white blood cell count, red blood cell count, and female gender were significantly associated with the increase of IOP.

CONCLUSIONS. Age, aspartate aminotransferase, hemoglobin, platelet, calcium, alanine aminotransferase, guanosine triphosphate, white blood cell count, red blood cell count, and gender were the systemic variables significantly associated with the change of IOP.

Keywords: intraocular pressure, health examination cohort

Glaucoma is a leading cause of irreversible blindness in the world.[1,2] In 2013, the number of people aged 40 to 80 years with glaucoma worldwide was 64 million and is predicted to increase to 76 million by 2020 and 112 million by 2040, because the prevalence of glaucoma becomes higher with age.[3] Intraocular pressure (IOP) is one of the most representative ophthalmological measures, and an important clinical risk factor for many ophthalmological diseases, such as glaucoma. It is controversial whether IOP decreases or increases with age in previous cross-sectional studies from all over the world.[4–19] The analysis of the longitudinal trend of IOP, not only the cross-sectional observation, is clinically very important. For instance, longitudinal designs are appropriate to investigate individual changes caused by aging, whereas cross-sectional designs cannot distinguish aging and cohort effects.[20] The number of previous studies that investigated the longitudinal effect of age on IOP using a sufficiently large population is quite limited.

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Thus, the first purpose of the current study was to investigate the effect of age on IOP, using a large-scale longitudinal dataset.

IOP is the fluid pressure within an eye, and it is decided as the balance between the production of aqueous humor at the ciliary body and aqueous outflow from the eye. The aqueous humor flows out of the eye primarily through the conventional outflow pathway that includes the trabecular meshwork and Schlemm's canal, although a smaller portion of outflow can go via an unconventional pathway, which includes the ciliary muscle and supraciliary and suprachoroidal spaces. Thus, IOP is primarily regulated by the resistance at the local cites, including the trabecular meshwork or juxtacanalicular connective tissues[21–23]; however, the aqueous humor is further drained into the Schlemm's canal and ultimately the episcleral vein in the conventional pathway,[21] and, thus, the influence of exogenous (systemic) factors is non-negligible.[24] Indeed, many previous studies have suggested the effects of such systemic factors on IOP, metabolic variables, or obesity,[11,12,15] in addition to age[4–19]; however, most of the studies were conducted in a cross-sectional manner using a relatively small population, such as <10,000 subjects. The effect of various systemic factors on IOP would be more accurately analyzed in a longitudinal observation than in a cross-sectional investigation, because the measurements are repeated among the same individuals; however, a large-scale longitudinal study has not been conducted that comprehensively examined the effect of systemic parameters, including body mass index (BMI), blood pressure, and various blood examination values, on IOP.

Thus, the purpose of the current study was to investigate the association of age with IOP, using a large-scale longitudinal dataset, where the association of various systemic factors with IOP were analyzed in the comprehensive manner. Currently, IOP reduction is achieved through medications, laser treatment, or surgeries, which is an enormous burden worldwide. For instance, in the United States, it has been estimated that this treatment costs from $623 per year for patients with early-stage glaucoma to $2511 per year for patients with end-stage disease.[25] Such burden has been reported to be exaggerated in developing countries particularly.[26] It may be advantageous, if it is possible to reduce these burdens by controlling systemic parameters by changing life habits in particular.[27] In this study, 21,038 eyes of 10,536 subjects from a health checkup cohort were followed up for 8 years, and the longitudinal effect of systemic factors on IOP has been investigated in detail.

METHODS

Subjects

This is a health screening center-based cohort study in non-glaucomatous subjects. This study has been approved by the institutional review board of Seirei Hamamatsu General Hospital and Seirei Center for Health Promotion and Preventive Medicine (institutional review board [IRB] No. 3331), which has been conducted according to the tenets of the Declaration of Helsinki. A written informed consent had been obtained from all participants included in the study. The cohort database included 467,408 examinations from 64,636 subjects who participated in a health examination system in the Seirei Center for Health Promotion and Prevention Medicine from May 7, 2012, to March

31, 2021. Among the 64,636 subjects who attended the screening program at least once in the observation period, 37,989 subjects attended the program in the initial 3 years (otherwise they cannot take 8 annual measurements in the observed 10 years in theory). In the 37,989 subjects, 10,471 subjects (27.6 %) completed the 8 annual observations in 10 years, after excluding subjects with glaucoma. As a result, a total of 180,906 examinations from 20,909 eyes of 10,471 subjects have been selected from the database; all of these completed measurements of the following variables at least at 8 visits (the health examination was an annual program): age, sex, BMI, SBP, diastolic blood pressure (DBP), smoking habits, 19 blood examinations (white blood cell [WBC] count, red blood cell [RBC] count, hemoglobin [Hb], hematocrit [Ht], platelet [Plt] count, total protein [TP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], guanosine triphosphate [γGTP], alkaline phosphatase [ALP], triglyceride [TG], LDL-C, HDL-C, HbA1c, blood urea nitrogen [BUN], creatinine [Cre], calcium [Ca], uric acid [UA], and C-reactive protein [CRP]), and IOP. BMI was calculated as body weight (kg) divided by the square of the body height (m). There was a record of only one eye in 33 subjects, because IOP measurement was not measured or the subject had only one eye possibly due to trauma etc. Those who have been diagnosed with glaucoma or ocular hypertension were carefully excluded from the analysis to avoid the possible effect of IOP reduction treatment, based on the information obtained by the interview to the participants. Experienced laboratory technicians measured IOP using a noncontact tonometer (Full Auto Tonometer TX-F, Canon Incorporated, Tokyo, Japan) three times, and the average value was used in the analyses.

Statistical Analysis

The effect of age on IOP was investigated using the linear mixed model, whereby eyes were nested within each subject. The association among the time series IOP and (i) age at baseline, (ii) sex, (iii) time series BMI, (iv) time series smoking habits, (v) time series SBP and DBP, respectively, and (vi) time series of 19 blood examinations has been investigated using the random intercept and random slope two-level linear mixed model[28] (all of the time series data was acquired at each annual visit). The linear mixed model adjusts for the hierarchical structure of the data, modeling in a way in which measurements are grouped within subjects and eyes to reduce the possible bias derived from the nested structure of data.[29,30]

RESULTS

The characteristics of the 20,909 eyes of 10,471 subjects (6905 men, 65.9% and 3566 women, 34.1%) are summarized in Table 1. The mean age was 52.7 ± 9.6 (mean ± SD) years. The mean IOP was 12.7 ± 2.9 mm Hg. The number of visits was 8.7 ± 0.5 times in 7.8 ± 0.5 years.
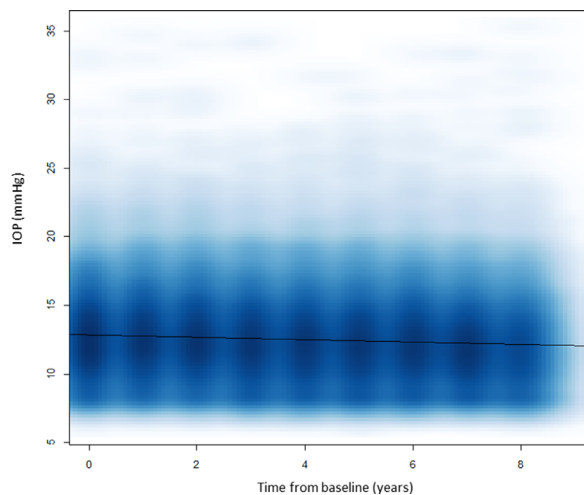
As shown in the Figure, IOP significantly decreased in the observation period by −0.084 mm Hg/year (standard error = 0.0019, $P < 1.0 \times 10^{-16}$, linear mixed model).

The results of multivariate analysis between various systemic parameters and IOP are summarized in Table 2. Among 27 parameters, 10 showed significant association with the change of IOP ($P < 0.05$); age, sex, AST, ALT, γGTP, WBC, RBC, Hb, Plt, and Ca.

TABLE 1. Subjects' Demographic Baseline Data

Parameters	Mean ± SD
IOP, mm Hg	12.7 ± 2.9
Age, y	52.7 ± 9.6
M/F	6945/3591
Height, cm	165.3 ± 8.5
BMI	22.6 ± 3.2
SBP, mm Hg	114.9 ± 14.8
DBP, mm Hg	70.9 ± 9.9
Smoking habits, yes/no	1773/8698
TP, g/dL	7.1 ± 0.4
Albumin, g/dL	4.3 ± 0.3
AST, IU/L	21.4 ± 8.3
ALT, IU/L	22.1 ± 15.1
γGTP, IU/L	35.8 ± 41.6
ALP, IU/L	205.4 ± 58.7
Total bilirubin, mg/dL	0.9 ± 0.4
TG, mg/dL	108.6 ± 70.6
HDL-C, mg/dL	66.7 ± 17.9
LDL-C, mg/dL	128.2 ± 30.0
HbA1c, %	5.6 ± 0.6
WBC, $\times 10^2/\mu L$	5419.1 ± 1558.4
RBC, $\times 10^4/\mu L$	473.1 ± 40.9
Hb, g/dL	14.4 ± 1.4
Ht, %	43.0 ± 3.7
Plt, $\times 10^4/\mu L$	22.9 ± 5.1
BUN, mg/dL	13.8 ± 3.4
Cre, mg/dL	0.8 ± 0.2
Ca, mg/dL	9.3 ± 0.4
UA, mg/dL	5.4 ± 1.3
CRP, mg/dL	0.1 ± 0.4

SD, standard deviation; IOP, intraocular pressure; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TP, total protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γGTP, guanosine triphosphate; ALP, alkaline phosphatase; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin A1c; WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; Ht, hematocrit; Plt, platelet; BUN, blood urea nitrogen; Cre, creatinine; Ca, calcium; UA, uric acid; CRP, C-reactive protein.

TABLE 2. Results of Multivariate Analysis Between IOP and Various Systemic Parameters

Parameters	Coefficient (Per 8 Years)	SE	*P* Value
Age at baseline (years)	**−0.00075**	**0.00025**	**0.0023**
Sex (for female)	**0.017**	**0.0060**	**0.0055**
BMI	−0.00044	0.00070	0.53
SBP (mmHg)	−0.00031	0.00016	0.055
DBP (mmHg)	−0.00033	0.00023	0.14
Smoking habits (for no)	−0.0056	0.0056	0.32
TP (g/dl)	0.0065	0.0055	0.24
Albumin (g/dl)	−0.0041	0.0085	0.63
AST (IU/l)	**−0.0015**	**0.00025**	**5.3×10^{-9}**
ALT (IU/l)	**0.00056**	**0.00017**	**0.0012**
γGTP (IU/l)	**0.00010**	**4.5×10^{-5}**	**0.020**
ALP (IU/l)	-3.7×10^{-5}	3.2×10^{-5}	0.24
Total bilirubin (mg/dl)	0.0081	0.0047	0.082
TG (mg/dl)	0.000022	2.6×10^{-5}	0.39
HDL-C (mg/dl)	−0.00020	0.00013	0.11
LDL-C (mg/dl)	-1.5×10^{-6}	6.0×10^{-5}	0.98
HbA1c (%)	−0.0058	0.0033	0.077
WBC (x10²/μl)	**0.00027**	**8.5×10^{-5}**	**0.0013**
RBC (x10⁴/μl)	**2.6×10^{-6}**	**9.1×10^{-7}**	**0.0037**
Hb (g/dl)	**−0.012**	**0.0043**	**0.0053**
Ht (%)	−0.00039	0.0017	0.82
Plt (x10⁴/μl)	**−0.0015**	**0.00036**	**2.9×10^{-5}**
BUN (mg/dl)	−0.00059	0.00049	0.23
Cre (mg/dl)	0.014	0.0090	0.11
Ca (mg/dl)	**−0.026**	**0.0052**	**1.1×10^{-6}**
UA (mg/dl)	0.0028	0.0017	0.093
CRP (mg/dl)	−0.0056	0.0039	0.16

All analyses were performed using the linear mixed model. Parameters in **bold** indicate $P < 0.05$.

SE, standard error; IOP, intraocular pressure; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TP, total protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γGTP, guanosine triphosphate; ALP, alkaline phosphatase; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin A1c; WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; Ht, hematocrit; Plt, platelet; BUN, blood urea nitrogen; Cre, creatinine, Ca, calcium; UA, uric acid, CRP, C-reactive protein.

FIGURE. IOP trend in the observation period. IOP significantly decreased in the observation period by −0.084 mm Hg/year. The results are plotted using the "smoothScatter" function in the statistical programming language R. The smoothScatter produces a smoothed color density representation of a scatterplot. IOP, intraocular pressure.

DISCUSSION

In this study, 20,909 eyes of 10,471 subjects from a health checkup cohort were followed up for systemic factors (BMI, SBP, DBP, and blood examinations) and IOP annually for 8 years, and the longitudinal effects of age and systemic factors on IOP have been investigated in detail. As a result, IOP significantly decreased in the observation period by −0.084 mm Hg/year. In addition, higher values of age, AST, Hb, Plt, and Ca were suggested to be significantly associated with the decrease of IOP ($P < 0.05$), ALT, WBC, RBC, and female gender were significantly associated with the increase of IOP.

The effect of age on IOP is controversial. Previous cross-sectional studies from Italy[4] and the United States[5,6] suggested a significant positive association between age and IOP; however, the inverse effect has also been reported in cross-sectional studies from Korea,[7–10] Taiwan,[11,12] China,[13] Japan,[14–16] and even Europe (only in female subjects).[19] This study also suggested a significant negative between older age and IOP; however, it may not be adequate to compare these results on the same ring, because the purpose of

this study was to investigate the longitudinal effect of age on IOP rather than the cross-sectional association between age and IOP. The number of previous studies that investigated the longitudinal effect of age on IOP using a sufficiently large population is quite limited. There is a large cross-sectional study conducted in Europe which reported the U-shaped association between age and IOP (IOP was peaked in the 60s) and suggested it as the reason of these contradicting results across studies.[18] To shed light on this issue, we applied the quadratic regression between IOP and observation period/age, however, the inflection point located outside the observation period (1.7 years before the initiation of the observation period) and age (22.2 years old), which suggested IOP consistently decreased within the observation period and age (data not shown in the Result section). A family-based longitudinal study from Korea and Mongolia in which 3096 subjects were followed up for >10 years suggested a negative association between older age and IOP, which is consistent with the current study.[17] IOP is a result of the balance between the production of aqueous fluid and resistance in the conventional and unconventional outflow pathways. The mechanism of the effect of aging on IOP may not be straightforward, because aging has been reported to cause a decrease in the aqueous humor production,[31–33] whereas resistance in outflow pathways, including trabecular meshwork resistance,[34] would be increased; our result suggested that the former effect is dominant than the latter one. The contradicting findings among studies may be attributed to the different nature of the eyes, such as the prevalence of myopia,[17,35–37] across regions (United States or Europe/Asia).

Cross-sectional reports regarding the association between sex and IOP have been contradicting: higher in female subjects,[38] no difference,[9,10,14,16] or higher in male subjects.[4,11,39] The entire reason of the significant association between the female gender and with the longitudinal increase of IOP is not clear; however, it may be because of the different tendency of various systemic parameters, including AST, ALT, γGTP, HDL-C, and Hb.

A number of previous studies have suggested the significant correlation between higher SBP and IOP,[8,10–12,14,16,17,40–44] between HbA1c and IOP,[7,8,10–12,14–16,42,44–46] between BMI and IOP,[6–8,10–12,14–16,42,45] between HDL-C and IOP,[47,48] and also between smoking habits and IOP.[49,50] Conversely, no significant correlation with these variables has been found in this study. These contradicting results would be attributed to the differences of the nature of the studies (cross-sectional or longitudinal) and also the sizes of the studied population. Most importantly, the correlation of systemic variables was comprehensively investigated in detail in this study, and none of the previous studies have investigated the correlation of each variable in conjunction with other variables. As the systemic variables investigated in this study are closely correlated, it is required to analyze their correlations simultaneously. The current results have suggested that age, AST, Hb, Plt, Ca, higher ALT, γGTP, WBC, RBC, and female gender were significantly associated with the longitudinal change of IOP; however, SBP, HbA1c, BMI, and smoking habits were not. Similarly, albumin has been reported to be associated with IOP,[38] and besides, previous cross-sectional studies have suggested the association between HDL-C and IOP,[47,48] being attributed to the association with the change of colloid osmotic pressure; however, such finding was not observed in this study.

In this study, hepatic and biliary enzymes were significantly associated with IOP change; the increase of AST was significantly associated with the decrease of IOP, whereas ALT and γGTP were significantly associated with the increase of IOP. Previous cross-sectional studies have suggested the increased IOP in subjects with hepatic steatosis in which ALT and γGTP are often elevated.[11,51] The entire mechanism of the IOP elevation remained unclear; however, it has been discussed in relation to metabolic syndrome.[11,51] For instance, in hepatic steatosis, free fatty acid molecule level increases due to the dysregulation in de novo lipogenesis,[52,53] which leads to oxidative stress. Consequently, various pro-inflammatory cytokines are released, including transforming growth factor (TGF)–β.[52,54] The accumulation of TGF-β2 at the trabecular meshwork (TM) causes the elevation of IOP by increasing the aqueous outflow resistance,[55–57] inducing epithelial-to-mesenchymal transition (EMT)-like changes in TM cells, including increased extracellular matrix (ECM) production, actin stress fiber formation, and alpha smooth muscle actin (α-SMA) expression.[57–60] Indeed, TGF-β2 is highly concentrated in the aqueous humor of primary open-angle glaucoma patients.[61–64] Our result suggested that none of the SBP, DBP, TG, LDL-C, HbA1c, and BMI were significantly associated with the longitudinal change of IOP. This would imply hepatic and biliary dysfunction causing the decrease of AST and increase of ALT, and γGTP induces the longitudinal increase of IOP, even independent from the apparent metabolic syndrome. Moreover, previous cross-sectional studies have suggested the association between HDL-C and IOP.[47,48] The mechanism has been discussed in conjunction with the association between metabolic syndrome and IOP elevation. For instance, hyper-triglyceridemia causes an increase in episcleral pressure owing to the accumulation of orbital adipose tissue[5,65]; elevated blood glucose resulted in the fluid shifts into the intraocular space from the osmotic gradient[43]; and an increased filtration fraction of the aqueous humor, through elevated ciliary artery pressure, increased serum corticoids, and also sympathetic tone results in elevated IOP when the blood pressure is high.[45,66] However, our results suggested that HDL-C has an effect on the IOP even without metabolic syndrome.

Calcium ion is a major cation that triggers a series of cascades and causes an impairment of the conventional pathway outflow, via various mechanisms.[67] In eyes with primary open-angle glaucoma (POAG), the mitochondrial function of TM cells is damaged and abnormally vulnerable to calcium ion stress, which causes the IOP elevation.[68] Additionally, in human TM cells, a central channel for calcium ion of the transient receptor potential vanilloid 4 (TRPV4) is activated by mechanical stress, including swelling and pressure. This causes an associated ECM remodeling, which leads to increased TM stiffness, contractility, and resistance.[69] Furthermore, a recent study identified a new gene of Cacna2d1, which encodes the voltage-dependent calcium channel complex in the TM and ciliary body and thus plays an important role in the elevation of IOP.[70] These mechanisms had been believed to be applied to calcium in the aqueous humor in eyes with glaucoma; however, a more recent study has revealed a clear association between serum calcium and IOP even in healthy subjects.[71] This was a result of a sufficiently large healthy population (14,037 subjects); however, the investigation was performed merely in the cross-sectional manner. The mechanism has been discussed with an association with cardiometabolic

conditions, including hypertension, diabetes, postprandial glucose, coronary atherosclerosis, and obesity.[71] In contrast, current results have suggested that calcium induces the longitudinal decrease of IOP, even independent from such conditions. Notably, calcium would be deemed to be most clinically relevant by comparing the coefficients and the *P* values of the significant blood parameters (see Table 2).

We know little regarding the association between blood cell components and IOP, because of the very limited number of previous studies shedding light on this issue. For instance, acute elevation of WBC count was not associated with the change of IOP,[72] in contrast to the current result, which suggested the significant association between WBC count and longitudinal change of IOP. Oxidative stress likely plays an important role in increasing IOP in glaucoma,[73,74] and RBCs are especially prone to oxidative stress[75] because they mainly carry out oxygen transport and are the first cells in the body to be exposed to these stressful stimuli. Blood viscosity may increase along with the increase in RBC count, hemoglobin and hematocrit levels, and consequently increased outflow resistance of episcleral veins in the obese population.[15] Plt has been reported to be higher in eyes with POAG than those in control subjects,[76] although a contradicting result has also been reported.[77] This study suggested that the blood cell components are influential on the longitudinal increase of IOP; higher Hb and Plt values were significantly associated with the decrease of IOP, whereas higher WBC and RBC counts were significantly associated with the increase of IOP. Lack of our knowledge regarding the mechanism of the association between blood cell components and IOP cannot fully explain the current results; thus, further investigation is expected in the future, as evoked by this study.

This study had several limitations: the first of which was the use of noncontact tonometry, which is generally believed to be less reliable than Goldmann applanation tonometry (the repeatability coefficient with non-contact tonometry has been reported as ± 3.2 mm Hg, whereas that with Goldmann applanation tonometry was between ± 2.2 and 2.5 mm Hg),[78,79] although IOP is usually measured using the noncontact tonometry in a health examination outside eye clinics. Furthermore, there was an absence of central corneal thickness measurements that are known to induce measurement errors during tonometry. Additionally, the study participants were all Japanese, and a further confirmatory investigation would be needed in different populations. The current results suggested that IOP might be suppressed by changing life habitat, such as increasing the intake of foods containing Ca and maintaining good biliary tract functions, however, these are not the results of intervention. A further study would be needed to investigate the effect of changing life habitat on IOP trend. Moreover, the currently analyzed 10,471 subjects were 27.6% among the 37,989 subjects who attended the screening program in the initial 3 years (otherwise they cannot take 8 annual measurements in the observed 10 years). The reasons are not clear, however, major reasons would be moving to other areas, they are deceased, or they simply forgot about taking the examinations. Significant differences were observed in age, gender, height, BMI, DBP, and smoking habitat between the two groups, although this was not the case for IOP and SBP. Despite the significance, the difference of the values was very small in general. More specifically, age, height, BMI, and DBP was differed only by 0.5 years, 0.9 cm, <0.01, and 2 mm Hg, respectively, in average, and hence these would have only a negligible effect on the results. Last, an important confounder in this analysis is systemic medication, especially systemic beta-blockers. They lower IOP and are related to many of the factors studied in this manuscript. There were 1494 in the 10,471 subjects who were taking systemic hypertension medication(s), although the contents of the medication (for example, beta-blockers) were not collected. In this group, IOP significantly decreased by −0.11 dB/Y (*P* < 0.001, linear mixed model). The significant decrease of IOP was also observed in the remaining 8977 subjects without such medications (−0.0072 dB/Y, *P* < 0.001, linear mixed model). Thus, IOP significantly decreased in both groups, however it was faster in eyes with such medications (−0.0027 mmHg/Y, *P* < 0.001, linear mixed model). A further investigation would be needed shedding light on this issue, analyzing the effect of systemic beta-blocker specifically in particular.

In conclusion, the current large-scale longitudinal study suggested that IOP significantly decreased with age. In addition, higher values of age, AST, Hb, Plt, and Ca were significantly associated with the decrease of IOP, whereas higher ALT, γGTP, WBC, and RBC values and female gender were significantly associated with the increase of IOP.

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