AMERICAN ACADEMY™ OF OPHTHALMOLOGY

Associations with Intraocular Pressure in a Large Cohort

Results from the UK Biobank

*Michelle P.Y. Chan, FRCOphth,[1] Carlota M. Grossi, PhD,[1] Anthony P. Khawaja, PhD, FRCOphth,[2] Jennifer L.Y. Yip, PhD, MRCOphth,[2] Kay-Tee Khaw, MBBChir, FRCP,[2] Praveen J. Patel, FRCOphth, MD(Res),[1] Peng T. Khaw, PhD, FRCOphth,[1] James E. Morgan, DPhil, FRCOphth,[3] Stephen A. Vernon, DM, FRCOphth,[4] Paul J. Foster, PhD, FRCOphth,[1] on behalf of the UK Biobank Eye and Vision Consortium**

Purpose: To describe the associations of physical and demographic factors with Goldmann-correlated intraocular pressure (IOPg) and corneal-compensated intraocular pressure (IOPcc) in a British cohort.

Design: Cross-sectional study within the UK Biobank, a large-scale multisite cohort study in the United Kingdom.

Participants: We included 110 573 participants from the UK Biobank with intraocular pressure (IOP) measurements available. Their mean age was 57 years (range, 40–69 years); 54% were women, and 90% were white.

Methods: Participants had 1 IOP measurement made on each eye using the Ocular Response Analyzer noncontact tonometer. Linear regression models were used to assess the associations of IOP with physical and demographic factors.

Main Outcome Measures: The IOPg and IOPcc.

Results: The mean IOPg was 15.72 mmHg (95% confidence interval [CI], 15.70–15.74 mmHg), and the mean IOPcc was 15.95 mmHg (15.92–15.97 mmHg). After adjusting for covariates, IOPg and IOPcc were both significantly associated with older age, male sex, higher systolic blood pressure (SBP), faster heart rate, greater myopia, self-reported glaucoma, and colder season (all $P < 0.001$). The strongest determinants of both IOPg and IOPcc were SBP (partial R^2: IOPg 2.30%, IOPcc 2.26%), followed by refractive error (IOPg 0.60%, IOPcc 1.04%). The following variables had different directions of association with IOPg and IOPcc: height (−0.77 mmHg/m IOPg; 1.03 mmHg/m IOPcc), smoking (0.19 mmHg IOPg, −0.35 mmHg IOPcc), self-reported diabetes (0.41 mmHg IOPg, −0.05 mmHg IOPcc), and black ethnicity (−0.80 mmHg IOPg, 0.77 mmHg IOPcc). This suggests that height, smoking, diabetes, and ethnicity are related to corneal biomechanical properties. The increase in both IOPg and IOPcc with age was greatest among those of mixed ethnicities, followed by blacks and whites. The same set of covariates explained 7.4% of the variability of IOPcc but only 5.3% of the variability of IOPg.

Conclusions: This analysis of associations with IOP in a large cohort demonstrated that some variables clearly have different associations with IOPg and IOPcc, and that these 2 measurements may reflect different biological characteristics. *Ophthalmology 2016;123:771-782 © 2016 by the American Academy of Ophthalmology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).*

*Supplemental material is available at www.aaojournal.org.

Elevated intraocular pressure (IOP) is one of the most significant risk factors for the development[1] and progression[2] of open-angle glaucoma. Intraocular pressure is a multifactorial trait with a heritability of 29% to 62%.[3,4] Many epidemiologic studies have examined the association of IOP with physical and sociodemographic factors across different populations, and these factors have been shown to account for approximately 10% of IOP variability.[5–8] Although some associations with IOP have been demonstrated consistently, such as systolic blood pressure (SBP),[7–10] other factors such as age[7,8,11,12] and sex[7–9,11,13] have a less consistent effect. There is also growing evidence that corneal biomechanics influence IOP measurements.[14–16] The UK Biobank is one of the largest prospective cohort studies with ocular data globally and will lend statistical power to detecting weaker associations of IOP. In this study, we explore the associations of both Goldmann-correlated IOP (IOPg) and corneal-compensated IOP (IOPcc) measured by the Ocular Response Analyzer noncontact tonometer (ORA).

Methods

The UK Biobank is a large-scale multisite cohort study established by the Wellcome Trust medical charity, Medical Research Council, Department of Health, Scottish Government, and Northwest Regional Development Agency. The overall study

http://dx.doi.org/10.1016/j.ophtha.2015.11.031
ISSN 0161-6420/15

protocol (http://www.ukbiobank.ac.uk/resources/) and protocols for individual tests (http://biobank.ctsu.ox.ac.uk/crystal/docs.cgi) are available online. In brief, an extensive baseline questionnaire, physical measurements, and biological samples were undertaken in 22 assessment centers between 2006 and 2010. All UK residents aged 40 to 69 years who were registered with the National Health Service and living up to 25 miles from 1 of the 22 study assessment centers were invited to participate. The work was carried out with the approval of the North West Research Ethics Committee (reference number 06/MRE08/65), in accordance with the principles of the Declaration of Helsinki.

Ophthalmic data were collected in late 2009 in 6 assessment centers as an additional enhancement to the initial baseline assessment. These 6 centers are distributed widely across the United Kingdom, including Croydon and Hounslow in Greater London, Liverpool and Sheffield in Northern England, Birmingham in the Midlands, and Swansea in Wales. Participants completed a touch-screen self-administered questionnaire on their general health and socioeconomic status. The Townsend deprivation index was determined according to the participants' postcodes at recruitment and the corresponding output areas from the preceding national census. The index was calculated on the basis of the output area's employment status, home and car ownership, and household condition; the higher and more positive the index, the more deprived an area. The choices for ethnicity include white (English/Irish or other white background), Asian or British Asian (Indian/Pakistani/Bangladeshi or other Asian background), black or black British (Caribbean, African, or other black background), Chinese, mixed (white and black Caribbean or African, white and Asian, or other mixed background), or other ethnic group (not defined). Smoking status was determined by the participant's answer to "Do you smoke tobacco now?," from the selection of yes, on most or all days/only occasionally/no/prefer not to answer. Diabetes status was determined as those who answered yes to "Has a doctor ever told you that you have diabetes?" Glaucoma and macular degeneration statuses were determined as those who selected "glaucoma" or "macular degeneration" from a list of eye disorders to the question, "Has a doctor told you that you have any of the following problems with your eyes?"

Measurements

Blood pressure and heart rate were measured using the HEM-70151T digital blood pressure monitor (Omron, Hoofddorp, The Netherlands). Two measurements of each were taken, and the mean was used in subsequent analysis. Weight was measured with the BV-418 MA body composition analyzer (Tanita, Arlington Heights, IL). Height was measured using a Seca 202 height measure (Seca, Birmingham, UK). Body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Waist circumference at the level of the umbilicus was measured using a Wessex non-stretchable sprung tape measure. Autorefraction was performed using an RC5000 Auto Refkeratometer (Tomey, Nagoya, Japan), and refractive error (spherical equivalent) was calculated as sphere power + (cylinder power/2). The IOP was measured once for each eye (right eye first) using the ORA (Reichert Corp., Philadelphia, PA), and only 1 measurement per eye was taken. Participants who had eye surgery within the previous 4 weeks or those with possible eye infections were precluded from having IOP measured. The ORA flattens the cornea with a jet of air and uses an electro-optical system to measure the air pressures at which the cornea flattens both inward and outward. The average of the 2 ORA pressure values was calibrated against Goldmann applanation tonometer measures to derive IOPg. The IOPcc was derived using proprietary formulae to correct for the corneal biomechanical properties.[17]

Statistical Analysis

Left eye IOP values were chosen for the main analyses because they were measured after the right eye and were possibly less prone to artifacts with the participant more familiar with the test. Participants who reported having had laser refractive surgery or corneal graft surgery in the left eye were excluded from the analysis because corneal surgery would bias the relationship between IOPg and IOPcc. Body mass index was examined between 20 and 40 kg/m^2 (95% of the study population), because BMI outside this range showed a nonlinear relationship with IOP. Smoking status was dichotomized to regular (smokes on most or all days) and current nonsmokers (ex-smokers and never smokers) to maximize the potential to detect an effect. Season of IOP measurement was categorized into spring (March to May), summer (June to August), autumn (September to November), and winter (December to February).

The variables to be examined for associations with IOP were decided a priori on the basis of previous published studies. The possibility of clustering of IOP within each center of assessment was explored, but the intraclass correlation coefficients were very low (0.004 for IOPcc, 0.0005 for IOPg), which indicated that clustering accounted for a very small proportion of the variance in IOP. Therefore, we elected to proceed with multiple regression analysis using the center of assessment as a covariable to account for the potential underlying small differences in associations with IOP. Variations in characteristics between the centers were explored using multiple 1-way analysis of variance with Bonferroni correction for continuous variables and chi-square test for categoric variables.

Associations between IOP and continuous variables were first explored graphically. The relationship with sex, age, Townsend deprivation index, center of assessment, weight, height, waist circumference, SBP and diastolic blood pressure (DBP), BMI, refractive error, smoking status, diabetes, glaucoma, macular degeneration, and season of IOP measurement were explored with univariable linear regression. All examined variables were included in a multivariable regression model. All statistical analyses were performed using STATA (Stata/IC 12.0; StataCorp LP, College Station, TX). A more robust statistical significance threshold of $P < 0.001$ was used to avoid false-positives due to the large number of tests carried out. Further details of the derivation of the variables and missing data can be found on the UK Biobank online data showcase (http://biobank.ctsu.ox.ac.uk/crystal/label.cgi).

Results

Of the 502 656 participants in the whole UK Biobank cohort, 112 690 underwent IOP measurements, and 112 285 had valid measurements. Table 1 summarizes their mean IOP stratified by age, sex, and laterality. Mean IOP was slightly higher in the right eye than the left eye for both IOPg and IOPcc (mean difference, 0.14 mmHg IOPg; 95% confidence interval [CI], 0.12−0.16 mmHg, paired t test $P < 0.001$; 0.07 mmHg IOPcc; 95% CI, 0.05−0.09 mmHg; $P < 0.001$). Therefore, left eye values were used in all subsequent analyses because they were measured after the right eye and were possibly less prone to artifacts with the participant more familiar with the test. The mean left IOPg was 15.72 mmHg (95% CI, 15.70−15.74 mmHg), and the mean left IOPcc was 15.95 mmHg (95% CI, 15.92−15.97 mmHg). The IOPg and IOPcc increased linearly with age, SBP, DBP, pulse rate, and BMI (Fig 1A−D) and decreased linearly with refractive error (Fig 1E).