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Relationship between intraocular pressure and age: a population-based study in Nepal

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Abstract

Purpose: Few studies have assessed the distribution of intraocular pressure (IOP) from the Indian subcontinent, despite its large population and high burden of glaucoma. The objective of this study was to assess the distribution of IOP measurements from adults living in a lowland region of Nepal.

Methods: In a population-based cross-sectional study, all individuals aged 60 years and older from an area of lowland Nepal were invited for IOP assessment with a rebound tonometer.

Results: Of 160 communities (28,672 people aged ≥ 60 years) enrolled, 79 (13,808 people aged ≥ 60 years) were randomly selected for IOP testing. Of those eligible, 10,017 (72.5%) individuals underwent tonometry. Mean IOP decreased monotonically over 5-year age groups, from 14.1 mm Hg (SD 3.6) among the 60–64-year-olds to 13.0 mm Hg (SD 4.2) among those ≥ 80 years. The 97.5th percentile IOP measurement was 21.0 mm Hg for all age groups. In adjusted analyses,

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CONFLICT OF INTEREST
None of the authors has a conflict of interest to disclose.

younger age, self-reported diabetes, and higher population density were each associated with higher IOP and self-reported cataract surgery was associated with lower IOP.

Conclusions: Mean IOP was lower among older individuals in Nepal, consistent with many studies from East Asia and in contrast to many studies from western populations. These results suggest that ethnic background might be a consideration when diagnosing ocular hypertension.

PRÉCIS

Intraocular pressure decreased with age in a population-based study in Nepal, from a mean of 14.1 mm Hg among 60–64-year-olds to 13.0 mm Hg among ≥80-year-olds.

Keywords

intraocular pressure; epidemiology; diabetes mellitus; cataract extraction; population density

INTRODUCTION

Elevated intraocular pressure (IOP) is an established risk factor for glaucoma.[1, 2] Population-based studies demonstrating the IOP distribution in a given setting are important for establishing benchmarks, and should be age-stratified since studies have found the distribution of IOP to vary based on age. It is important to measure IOP in a diversity of settings, since IOP has been found to vary based on geographic region and ethnicity.[3, 4] For example, early studies from western populations typically found that IOP increases with age, but more recent studies from East Asia have found the inverse, reporting lower IOPs in older people.[5, 6]

Few studies have reported the IOP distribution on the Indian subcontinent, even though its burden of glaucoma is among the highest in the world due to the relatively high prevalence of undiagnosed disease as well as the extremely large population.[7–10] And those studies that have been done have found conflicting results regarding the association between IOP and age. An ongoing cluster-randomized trial in Nepal that is enrolling participants from the general population provided an opportunity to provide more data relevant for the Indian subcontinent.[11] Here, we report the age-stratified IOP distribution from a population-based sample of adults in a peri-urban region of Nepal. The main objective of this report was to assess the relationship between IOP across increasing age strata in a population-based sample of older adults from Nepal.

METHODS

Study Design.

The present study was conducted in a subset of communities enrolled in the Village Integrated Eye Worker Trial II (VIEW II), an ongoing NIH-funded cluster-randomized trial in Nepal that started April 21, 2019 (clinicaltrials.gov NCT03752840).[11] VIEW II takes place in peri-urban communities in the Chitwan and Nawalpur districts in Nepal that fall in the catchment area of Bharatpur Eye Hospital (BEH). In the trial, a door-to-door census is performed for all households in a contiguous geographic area surrounding Bharatpur, Nepal.

All household members are enumerated during the census, and the age and sex recorded. The geographic positioning system (GPS) coordinates are recorded for each household. As part of the trial, approximately half of the communities are subsequently randomized to a screening intervention and the other half are randomized to no intervention (permuted block randomization with block sizes of 6, 8, and 10). The unit of randomization is the subward. In this part of Nepal, government-defined municipalities are divided into wards. For study purposes each ward is further divided into subwards after the baseline census, with a target population of approximately 400 households. In the intervention communities all individuals 60 years or older are invited to receive IOP testing at a central location in the community. The screening team returns for additional visits, with a goal of 80% coverage.

Eligibility.

Study communities from 3 contiguous municipalities (Bharatpur, Ratnanagar, and Kalika) that had been randomized to eye screening examinations were included in the present study. All willing individuals 60 years and older were eligible to participate; mobilizers traveled door-to-door in the community to encourage participation. No exclusion criteria for participation were imposed.

IOP measurement.

Trained ophthalmic assistants assessed IOP of each eye with an iCare ic100 rebound tonometer (iCare Finland Oy, Vantaa, Finland), first on the participant's right eye and then on the left eye. The device takes six measurements in quick succession and does not require topical anesthesia. If the standard deviation (SD) is ≤ 2.5 mm Hg, the device displays an IOP that is the average of the four central measurements (i.e., the highest and the lowest readings are discarded). If the SD > 2.5 mm Hg, the device does not provide a result and instead prompts the user to repeat the test.

Risk factors.

The objective of the present study was descriptive. Neither the present study nor the underlying randomized trial was designed to determine risk factors associated with elevated IOP. However, the underlying trial data collected data on a limited number of factors previously found to be associated with IOP, and thus it seemed appropriate to explore the association of IOP with these factors for the present study. Specifically, study participants reported at the time of the census their age, whether they had a known diagnosis of diabetes, and whether they had undergone cataract surgery. GPS coordinates were taken of each household at the time of the census, and used to calculate population density. Other ocular and systemic factors associated with IOP were purposefully not collected for the underlying trial, which was designed as a large simple trial that collected a small number of data items from a large number of people.

Statistics.

Eyes with missing IOP data were excluded from descriptive analyses. Concordance of IOP measurements of two eyes from the same person was assessed with an intraclass correlation coefficient (ICC) using a two-way agreement-type model. For assessment of potential risk factors, IOP values from both eyes were modeled in eye-level, mixed effects linear regression models, with nested random intercepts for individual and study community to account for non-independence of two eyes from the same person as well as non-independence of participants from the same community. Both univariable and multivariable models included only those eyes with complete data for all risk factors. The association between IOP and age was explored in various ways (e.g. linear term, quadratic term, cubic spline for age) but analyses were similar and thus the linear term is reported here to simplify interpretation. Population density was estimated for each household by calculating the average distance to each of the 15 closest houses enumerated during the census (i.e., the mean distance to the nearest neighbor) and then categorized into quartiles. The significance level for the risk factor analysis was set at 0.01 given the 5 potential risk factors assessed in the study. All statistical analyses were performed with the statistical software R version 4 (R for Statistical Computing, Vienna Austria).

Human Subjects.

Ethical approval was obtained from the University of California, San Francisco Institutional Review Board and from the Nepali Health Research Council. Written informed consent was obtained from each participant prior to intraocular pressure testing. The research adhered to the Declaration of Helsinki.

RESULTS

A total of 28,672 people aged ≥ 60 years were enumerated on a door-to-door census in 41 wards of the 3 districts (Figure 1). Wards were subsequently divided into 160 subwards, of which 79 were randomly selected for IOP testing. Of 13,808 people aged 60 years or older eligible for screening, 10,017 (72.5%) presented for screening and had IOP successfully measured in at least one eye (10,000 right eyes and 9,992 left eyes). The mean age of participants undergoing IOP measurement was 70 years (range 60–103 years; standard deviation [SD] 7.8), and 5,033 (50.3%) were female. Of 9,772 people with complete questionnaire data, self-reported diabetes was documented for 906 (9.3%) and self-reported history of cataract surgery in either eye for 1,770 (18.1%) participants. Participants lived an average of 130 meters (SD=65) from their 15 nearest neighbors. The most notable difference between participants and nonparticipants was a relative lack of participation among the oldest individuals (Supplemental Table 1).

Overall, the mean IOP using data from both eyes for the 10,017 participants was 13.7 mm Hg (SD 3.6). IOP was moderately symmetric between eyes among the 9975 people with measurements of both eyes (within-person ICC 0.64, 95%CI 0.62 to 0.65). The distribution of IOP measurements was right-skewed (right eye: skew=1.4, kurtosis=13.2; left eye: skew=1.6, kurtosis=13.7; Supplemental Figure 1). Age- and sex-stratified descriptive statistics revealed a monotonic reduction in IOP over age ($P<0.001$), although the 97.5th percentile IOP measurement was 21.0 mm Hg for all age groups (Table 1). Descriptive statistics stratified by eye are provided in Supplemental Table 2. To investigate the possibility of biased IOP measurements due to nonparticipation, the mean IOP in each community was plotted against the participation rate for the community (Figure 2). Non-participation was not associated with mean IOP for most age strata, although estimates of mean IOP for the ≥ 80 year age group were slightly higher in communities with higher non-participation, suggesting the mean IOP for this oldest age group may have been slightly overestimated.

Exploratory analyses were performed to assess the strength of association between several risk factors previously found to be associated with IOP. The distribution of population density, gender, self-reported diabetes, and self-reported cataract is shown in Supplemental Table 3, stratified by age group. In a multivariable regression model including measurements of both eyes, IOP was significantly associated with age (0.5 mm Hg lower IOP per decade), self-reported diabetes (0.8 mm Hg higher relative to non-diabetics), previous cataract surgery (0.6 mm Hg lower among operated eyes) and higher population density (between 0.3 and 0.5 mm Hg higher in the highest-density quartile relative to the other 3 quartiles; Table 2).

DISCUSSION

This population-based study found a mean IOP of approximately 14 mmHg among individuals 60 years or older living in peri-urban communities in Nepal. Mean IOP decreased with increasing age stratum, although the 97.5th percentile IOP was 21 mm Hg across all age groups. The observed relationship between age and IOP was not likely due to increased non-participation among the oldest age strata since communities with higher non-participation generally had higher mean IOP. The findings have clinical implications. IOP is the only modifiable risk factor for glaucoma. Ocular hypertension is routinely treated to prevent glaucoma progression, and thus it is important for clinicians to be aware of the distribution of IOP in the population since they must decide when to treat. These findings are especially important given studies that have shown that glaucoma may occur at lower IOP in Asian populations.[12] It is also worth pointing out that although East Asians are at increased risk of angle closure glaucoma, primary open angle glaucoma remains the most prevalent type of glaucoma.[12] Although not designed to assess for risk factors for elevated IOP, the present study confirmed prior reports that have found higher IOP among those with diabetes and those living in more densely populated communities, and lower IOP in eyes with prior cataract surgery.

Numerous cross-sectional, population-based studies have collected data on IOP, many of which have published age-stratified estimates. We reviewed the literature to provide context for the results of the present study. We searched Pubmed from inception until March 25, 2022 using the following search terms: "(intraocular pressure[Title] OR intra-ocular pressure[Title]) AND ((population-based[Title/Abstract]) OR (random sample*[Title/Abstract]) OR (general population[Title/Abstract]) OR (defined population[Title/Abstract]))". Two authors (JDK and JTO) screened abstracts for studies of intraocular pressure assessment in cross-sectional population-based samples of adults and reviewed the full text for relevant articles, including only those papers whose methods described population-based sampling of the general population. From this search, we identified 30 studies reporting age-stratified IOP (36 of 143 manuscripts had relevant data; 6 had duplicate data). Besides the Pubmed search, 4 additional papers were found by reviewing the epidemiology chapter of the World Glaucoma Association's consensus document on intraocular pressure, and an additional 4 papers by reviewing the citations from all identified studies.[13] Finally, because of a relative paucity of studies from the Americas and Africa, we contacted the authors of population-based studies from these two regions if their papers did not include age-stratified IOP measurements, providing additional data for 2 of 8 studies. Thus, a grand total of 40 studies reporting age-stratified mean IOP were identified. Ultimately, this review revealed inconsistent findings with regards to the relationship between IOP and age among adults ≥ 50 years (Figure 3). Specifically, many of the studies from Western populations observed higher IOP among older age groups, whereas most studies from East Asia found lower IOP among older individuals. Two previous studies from South Asia had conflicting results.[10, 14] The present study's finding that mean IOP was lower in the older age groups was consistent with a previous study done in a different area of Nepal, suggesting that the population-level distribution of IOP on the Indian subcontinent may be more similar to that of East Asia than to western populations.[9]

It is not clear why IOP would be lower among older people in Asia but not elsewhere. Increased IOP has been found to be associated with diabetes, high blood pressure, hyperlipidemia, and obesity, all of which are more common in Western societies.[15–18] Cross-sectional studies are not ideal for assessment of longitudinal trends, since cohort effects (i.e., differential relationships in different birth cohorts) may alter the true longitudinal pattern—a phenomenon that may be especially problematic when comparing studies done in different geographic locations at different times. It is possible for example that the impact of survival bias in these cross-sectional studies could be differential by study site (i.e., that people with lower IOP are more likely to survive, but survival differs by site). Indeed, most longitudinal studies—both from Asia and the west—have found advancing age to be associated with a small increase in IOP.[19–26] Additional longitudinal studies in diverse patient populations would be helpful to more definitively determine whether the natural history of IOP differs based on ethnicity or geographic region.

Although this study was not designed to assess for risk factors of elevated IOP, the underlying trial did collect some data on factors previously found to be associated with IOP. In exploratory analyses, the present study found IOP to be associated with diabetes, prior cataract surgery, and higher population density. The association with diabetes is consistent with a meta-analysis that found IOP in diabetics to be on average 0.18 mm Hg higher than that of non-diabetics, although the mechanism remains unclear.[16] At least one prior population-based study found an association between IOP and cataract surgery, and similar to the present study reported a 0.6 mm Hg lower IOP among participants who had undergone cataract surgery.[27] These population-based studies suggest that the post-operative reduction in IOP seen in glaucoma patients undergoing cataract surgery most likely occurs in the general population as well.[28, 29] Moreover, in the present study the effect of age on IOP was slightly attenuated in multivariable models adjusted for prior cataract surgery. Cataract surgery is much more common among older individuals, raising the possibility that cataract surgery might be partially responsible for the lower IOPs observed among older people. Several previous population-based studies have found glaucoma to be more common in urban than rural areas.[30, 31] Other studies have found IOP to be higher in urban areas, consistent with the results of the present study.[32, 33] The underlying reasons for an association between IOP and higher population density is unclear, although it is worth noting that other factors associated with higher IOP, such as diabetes, high blood pressure, and obesity, tend to occur more frequently among urban populations.[34]

This study used a rebound tonometer. The iCare device was chosen because of its portability and ease of use, and because this tonometer displayed high agreement with Goldmann applanation tonometry (GAT) in a prior clinic-based study we conducted in India.[35] Other studies have also shown the iCare to provide reproducible results with reasonably high agreement with GAT.[36] Although GAT remains the gold standard for tonometry, this would not have been practical for our community-based study. Moreover, GAT is an imperfect gold standard due to its inherent subjectivity. For example, GAT measurements have been shown to be preferentially recorded as even as opposed to odd numbers, and the results of the first eye likely influences the measurement of the second eye, probably because of the belief that IOP should be symmetric between the two eyes.[35] Other recent population-based studies have also used rebound tonometry, and we anticipate others will opt for this method in the future.[37, 38]

This study has limitations. Although household visits were made to increase the response rate, the proportion of eligible people captured was about 72.5%, and non-participation was greater among the oldest age group. It is possible that IOP was different among non-participants, although no evidence for this was found in a community-level analysis that plotted the mean age-stratified IOP versus the participation rate in the community. The study was done in the context of a large simple trial of eye disease screening.[11] In exchange for the large sample size, the study minimizes the number of data points collected. Data was not collected on important biological factors such as corneal biomechanical properties that may have affected the IOP measurements, nor on the presence or severity of glaucoma. Data was not collected on many potential risk factors that could be associated with IOP, which limited the breadth of potential risk factors that could be analyzed, and also limited the ability to adjust for potential confounders. As discussed above, IOP was assessed with a rebound tonometer, chosen because of its portability for the mobile screening teams. Rebound tonometry may be systematically different from the current reference standard of GAT and also from newer tonometry methods that attempt to increase accuracy by accounting for corneal biomechanical properties.[35, 39] While the use of rebound tonometry could result in slightly different mean IOP measurements, this would not be expected to affect any of the associations found in the study. Finally, as demonstrated in Figure 3, the generalizability of these results to places outside Nepal is not clear.

In summary, this large population-based study reports age- and sex-stratified IOP measurements from a lowland area of Nepal, and confirmed previous studies that have found cross-sectional associations between IOP and age, diabetes, higher population density, and prior cataract surgery. Similar to other studies in Asia—and in contrast to studies of western populations—the mean IOP was slightly lower in oldest age groups. While the clinical relevance of this observation remains unclear, it may be important to consider ethnic background when diagnosing ocular hypertension in older individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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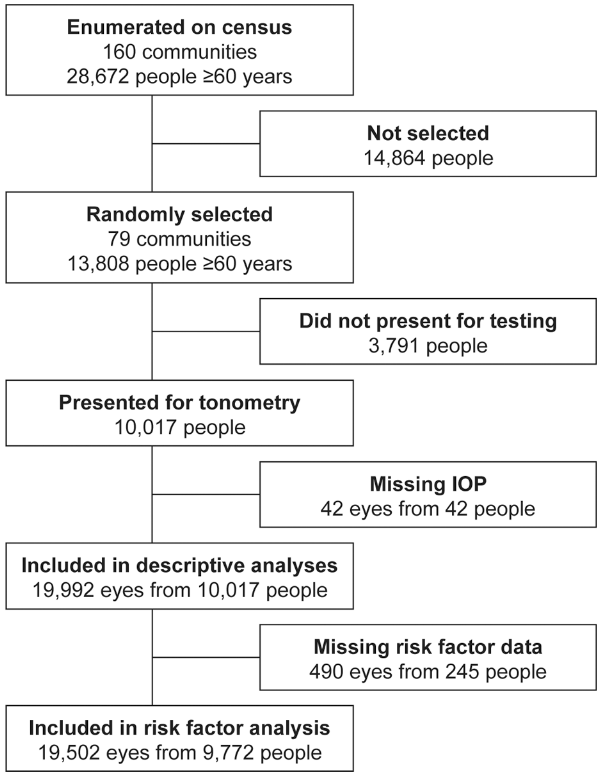

Figure 1. Participant flow.

Participants were drawn from 41 wards in Nepal.

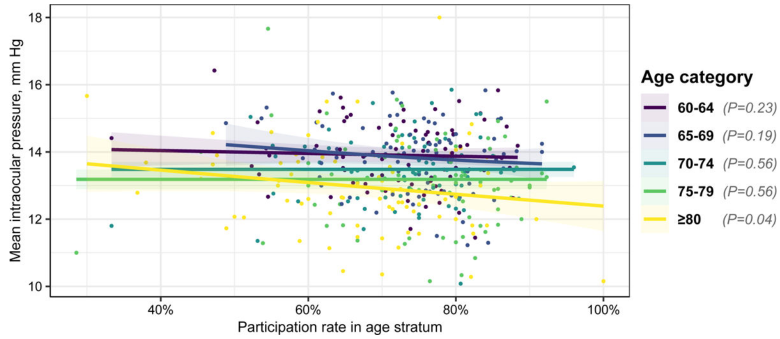

Figure 2. The relationship between non-participation and estimates of intraocular pressure, stratified by age.

Each dot represents an age stratum in one of the 79 study communities. The proportion of eligible participants in the age stratum participating in tonometry is plotted against the mean intraocular pressure in the age stratum. Generalized additive models were used to fit smoothed lines and 95% confidence bars, and to provide approximate *P*-values for the relationship between non-participation and mean IOP for each age stratum.

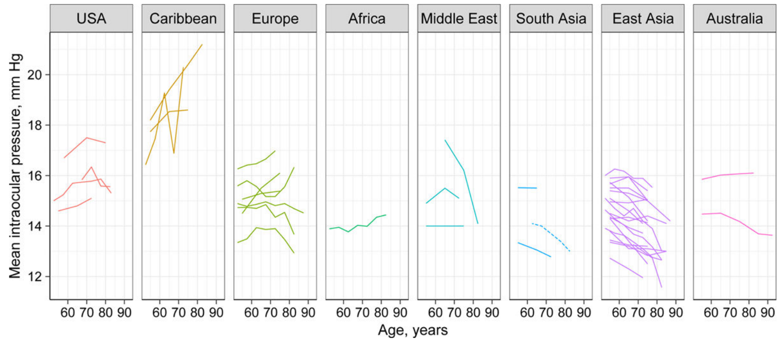

Figure 3. Mean intraocular pressure across age strata in cross-sectional population-based studies.

Age strata starting from 50 years are depicted, with lines connecting the mean IOP of successive age strata. The present study is depicted as a dashed line. The present study is depicted as a dashed line. Studies were found from the United States of America (USA), the Caribbean, Europe, Africa, the Middle East, South Asia, East Asia, and Australia (references provided in the online supplement). The relationship between IOP and age was significantly different for the Asian versus non-Asian studies (interaction $P<0.001$ in mixed effects linear regression), with a mean reduction in IOP of 0.4mmHg (95%CI −0.5 to −0.3) per decade of age among the Asian studies and a mean increase in IOP of 0.1mmHg (95%CI −0.05 to 0.2) per decade of age among the non-Asian studies.

Table 1.

Distribution of intraocular pressure, stratified by age and sex.

The analysis dataset included both eyes. The mean and standard deviation (SD) intraocular pressure are reported for each age stratum, along with the value at the 97.5th and 99.5th percentile of the distribution.

		Intraocular pressure, mm Hg		
Sex	**Eyes, n**	**Mean (SD)**	**97.5%**	**99.5%**
Female				
60–64 y	2974	13.9 (3.5)	21.0	22.0
65–69 y	2507	13.9 (3.6)	21.0	24.5
70–74 y	2105	13.7 (3.8)	21.0	27.0
75–79 y	1126	13.5 (3.9)	21.0	33.0
≥ 80 y	1336	13.0 (4.4)	20.0	33.3
Male				
60–64 y	2658	14.2 (3.8)	22.0	25.0
65–69 y	2562	14.2 (4.3)	22.0	35.0
70–74 y	1942	13.7 (3.9)	21.0	26.0
75–79 y	1332	13.4 (4.0)	21.7	26.7
≥ 80 y	1450	13.0 (4.0)	21.8	28.8
All				
60–64 y	5632	14.1 (3.6)	21.0	24.0
65–69 y	5069	14.0 (4.0)	21.0	27.0
70–74 y	4047	13.7 (3.8)	21.0	26.8
75–79 y	2458	13.4 (3.9)	21.0	30.0
≥ 80 y	2786	13.0 (4.2)	21.0	31.0

17 eyes had missing IOP data for the right eye and 25 eyes had missing IOP data for the left eye

Table 2.

Associations between variables and intraocular pressure.

All analyses were restricted to the 9,772 people with complete data for all covariates. Multivariable analyses were adjusted for all the other listed terms.

	Univariable[a]		Multivariable[a]	
Model term	Coefficient	p-value	Coefficient	p-value
Age, per 10 y	−0.5 (−0.6 to −0.4)	<0.001	−0.4 (−0.5 to −0.3)	<0.001
Male	0.2 (0 to 0.3)	0.03	0.2 (0 to 0.3)	0.02
Diabetes, self-reported	0.8 (0.6 to 1.0)	<0.001	0.8 (0.6 to 1.0)	<0.001
Cataract surgery, self-reported	−0.7 (−0.9 to −0.6)	<0.001	−0.6 (−0.8 to −0.4)	<0.001
Population density[b]				
Quartile 1	Reference		Reference	
Quartile 2	−0.3 (−0.5 to −0.1)	0.004	−0.3 (−0.5 to −0.1)	0.004
Quartile 3	−0.5 (−0.7 to −0.3)	<0.001	−0.5 (−0.7 to −0.3)	<0.001
Quartile 4	−0.4 (−0.7 to −0.2)	<0.001	−0.4 (−0.7 to −0.2)	<0.001

[a]Mixed effects linear regression models of eye-level data, incorporating nested random effects for person and study community

[b]Calculated as the average distance to the 15 nearest neighbors; quartile 1 is the highest population density and quartile 4 is the lowest population density.