Associations Between Regional Environment and Cornea-Related Morphology of the Eye in Young Adults: A Large-Scale Multicenter Cross-Sectional Study

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Purpose. To investigate environmental factors associated with corneal morphologic changes.

Methods. A cross-sectional study was conducted, which enrolled adults of the Han ethnicity aged 18 to 44 years from 20 cities. The cornea-related morphology was measured using an ocular anterior segment analysis system. The geographic indexes of each city and meteorological indexes of daily city-level data from the past 40 years (1980–2019) were obtained. Correlation analyses at the city level and multilevel model analyses at the eye level were performed.

Results. In total, 114,067 eyes were used for analysis. In the correlation analyses at the city level, the corneal thickness was positively correlated with the mean values of precip-

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itation (highest *r* [correlation coefficient]: >0.700), temperature, and relative humidity (RH), as well as the amount of annual variation in precipitation (*r*: 0.548 to 0.721), and negatively correlated with the mean daily difference in the temperature (DIF T), duration of sunshine, and variance in RH (*r*: −0.694 to 0.495). In contrast, the anterior chamber (AC) volume was negatively correlated with the mean values of precipitation, temperature, RH, and the amount of annual variation in precipitation (*r*: −0.672 to −0.448), and positively associated with the mean DIF T (*r* = 0.570) and variance in temperature (*r* = 0.507). In total 19,988 eyes were analyzed at the eye level. After adjusting for age, precipitation was the major explanatory factor among the environmental factors for the variability in corneal thickness and AC volume.

Conclusions. Individuals who were raised in warm and wet environments had thicker corneas and smaller AC volumes than those from cold and dry ambient environments. Our findings demonstrate the role of local environmental factors in corneal-related morphology.

Keywords: environment, climate, cornea, morphology

Corneal blindness is the fourth leading cause of blindness globally, accounting for 5.1% of the total blind population.[1,2] As the outermost layer of the eye, the cornea is highly sensitive to environmental stressors and vulnerable to external insults.[3] Diseases related to pathological changes in corneal morphology have been reported to be associated with environmental factors.[4–9] For example, keratoconus is a heterogeneous corneal disease with elusive pathogenesis, which is correlated with geographic differences, and has been attributed to a hot dry climate and greater ultraviolet light exposure.[4] Dry eye disease (DED), another multifactorial disorder of the ocular surface, with geographic variations in its prevalence, increased latitude, and high temperatures are found to be risk factors for DED.[5–9] Moreover, there are significant geographic differences in the prevalence of microbial keratitis and pathogens, influenced by the local climate.[10] Besides, the unusual thickness of cornea may be the pathological feature of higher intraocular pressure (IOP).[11] Therefore a better understanding of the relationship between corneal morphology and external environmental factors will facilitate our understanding of specific pathologies and better instruct the choice of therapeutic modality or interventions for corneal diseases.

Previous studies have reported the impact of geographic variance on the morphologic characteristics of the cornea related to physiological changes. For example, corneal thickness is an important parameter for the diagnosis of corneal disorders and for developing treatment plans in corneal refractive surgery. Population-based studies show differences in corneal thickness: 530.9 ± 31.5 μm in Korea, 540.9 ± 33.6 μm in Malaysia, 540.4 ± 33.6 μm in India, 521.0 ± 32.0 μm in Japan, 528.5 ± 35.8 μm in Iran, and 552.3 ± 33.4 μm in China.[12–15] However, such variations may only be partly explained by ethnicity; for instance, individuals of North African origin had thinner corneas compared with Europeans.[16] Significant differences in corneal thickness also exist between individuals from the same ethnicity: 547.2 ± 31.4 μm in Shanghai, 543.6 ± 29.4 μm in Tianjin, and 550.5 ± 30.0 μm in Wuhan, using the same measurement equipment.[17,18] The geographic differences in corneal morphology are likely to be attributed to external environmental factors in various areas. It has been speculated that corneal thickness tends to be thinner as latitudes become more equatorial, possibly due to increased ultraviolet exposure and high sunlight intensity.[19] Previous studies have focused on the effect of latitude on corneal morphology parameters, without considering the influence of other geographically related environmental factors on corneal morphology. In addition to latitude, other external environmental factors also need to be considered, because of the interaction between latitude and other environmental and climatic parameters, such as temperature, precipitation, and humidity.[20] How these environmental factors interact with each other and impact corneal morphology is poorly understood due to the lack of environmental parameter analyses. A multiregional study is valuable in understanding the impact of external environmental variations on cornea-related morphology.

China is one of the world's most populous countries with a relatively homogeneous ethnic group consisting of 90% Han Chinese. In addition, China has a land mass extending from the 3°51′N to the 53°33′N latitudes and features a wide range of climates.[21] Most parts of Southern China are of tropical or subtropical monsoon climate, with high temperature and ample rainfall, whereas the north is the opposite in climate. Therefore it is well suited to an investigation into the impact of environmental exposures, including geographic factors or climates, on cornea-related morphology.

This study collected large-scale, multidimensional data from multiple centers in different geographic locations and climates in China to investigate the association between environmental factors and cornea-related morphology. The elucidation of this relationship will greatly promote the exploration of the etiology of corneal diseases in different geographic areas and potentially facilitate diagnosis, treatment, and disease prevention.

Methods

Subjects

The study protocol was reviewed and approved by the Ethics Committee of Tianjin Eye Hospital (Tianjin Medical University, Tianjin, China) (201918) and adhered to the principles of the Declaration of Helsinki. All data of the eyes included in the study were de-identified before being accessed by the study investigators. Our study was part of the Corneal Morphology Analysis Trial, which is registered with ClinicalTrials.gov (Identifier NCT03010748).

This national cross-sectional study was carried out from January 1, 2010, to August 29, 2019, in 20 ophthalmic

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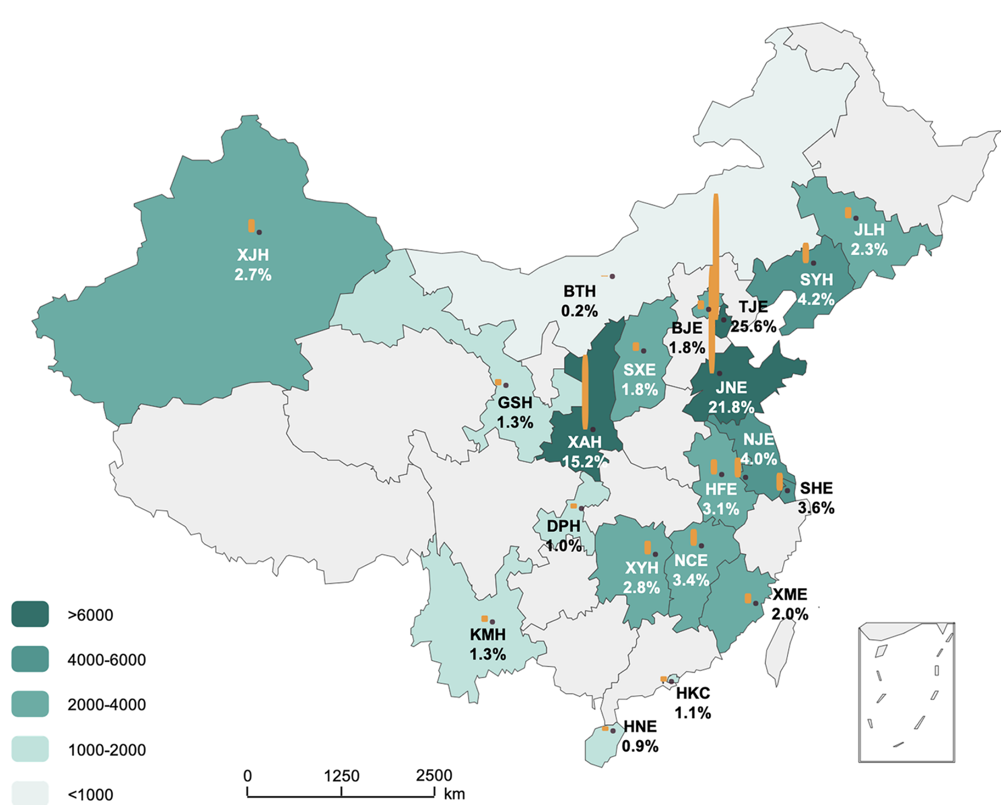

Figure 1. Distribution and sample size for each study site. The shade of the map background represents the sample size, and the height of the orange column represents the percentage of the sample size. Tianjin Eye Hospital (TJE, 29,223, 25.6%, Tianjin), Jinan Mingshui Eye Hospital (JNE, 24,893, 21.8%, Jinan), Xi'an No. 4 Hospital (XAH, 17,300, 15.2%, Xi'an), The 4th people's Hospital of Shenyang (SYH, 4,737, 4.2%, Shenyang), Nanjing Aier Eye Hospital (NJE, 4,582, 4.0%, Nanjing), Shanghai Aier Eye Hospital (SHE, 4,149, 3.6%, Shanghai), Nanchang Bright Eye Hospital (NCE, 3,883, 3.4%, Nanchang), Hefei Aier Eye Hospital (HFE, 3,535, 3.1%, Hefei), Xiangya Hospital of Central South University (XYH, 3,153, 2.8%, Changsha), The First Affiliated Hospital of Xinjiang Medical University (XJH, 3,045, 2.7%, Urumqi), The Second Hospital of Jilin University (JLH, 2,563, 2.3%, Changchun), Xiamen Eye Centre of Xiamen University (XME, 2,332, 2.0%, Xiamen), Beijing Huade Eye Hospital(BJE, 2,083, 1.8%, Beijing), Shanxi Eye Hospital (SXE, 2,016, 1.8%, Taiyuan), Yan'an Hospital of Kunming City (KMH, 1,488, 1.3%, Kunming), Gansu Provincial Hospital (GSH, 1,451, 1.3%, Lanzhou), Hong Kong Laser Eye Centre (HKC, 1,229, 1.1%, Hong Kong), Daping Hospital (DPH, 1,172, 1.0%, Chongqing), Hainan Eye Hospital (HNE, 1,052, 0.9%, Haikou), and Baotou Eighth Hospital (BTH, 181, 0.2%, Baotou).

centers that were participating in a multicenter clinical study designed to establish a database of corneal morphologies and associated parameters. The distribution of the study sites covered 58.8% of provincial-level administrative divisions in China (Fig. 1).

All subjects underwent an optometry examination with detailed measurement of the cornea. Considering the population mobility, we calculated the proportion of local residents in each study site. Data could provide additional clues to the potential impact of environmental exposures on cornea-related morphology if all the groups were of the same ethnicity, nationality, and age. Therefore, individuals aged 18 to 44 years were included as young people, which conforms to the latest United Nations World Health Organizations Global Burden of Diseases 2000[22] classifications of human age, and they were mainly local residents of each study center and were of Han Chinese descent. Individuals were excluded for the following reasons: (1) Individuals with a history of ocular surgery, trauma, or severe corneal disease, and (2) Individuals with keratoconus, suspected keratoconus, or subclinical keratoconus (diagnosis was based on the global consensus on keratoconus).[23]

Cornea-Related Morphology Measurement

An examiner-blinded method was used to measure each subject using a Pentacam ocular anterior segment analysis system with high resolution (HR) (OCULUS, Wetzlar, Germany). Detailed examination was shown in Supplementary Text. The above examinations were conducted by experienced optometrists with a standard protocol for collecting all measurements.

Among the collected data, 18 corneal morphologic parameters of more clinical concern were selected and further analyzed, including the corneal thickness (thickness at the corneal apex and pupil center [pachy apex and pachy pupil] and minimum corneal thickness [pachy min]), corneal keratometry (flat and steep keratometry in the front and back of the cornea [K1 F, K2 F, K1 B, and K2 B]), corneal astigmatism (flat axis within 0°–30° or 150°–180° [with the rule] measured on the anterior and posterior surfaces of the cornea [F AWR and B AWR, respectively]), and higher-order aberrations (HOAs) of the cornea (HOAs on the front, back and total corneal surface [HOA CF, HOA CB, and HOA cornea, respectively], corneal vertical and horizontal coma

[Z_3^1 cornea and Z_3^{-1} cornea, respectively], corneal spherical aberration [Z_4^0 cornea]), and the depth, volume, and angle of the anterior chamber (AC depth, AC volume, and AC angle, respectively). The value and definition of each parameter are summarized in Supplementary Table S1.

Environmental Data Collection

Climate characteristics are one of the external environmental factors most directly exposed to the human eye. According to the locations of the study sites, the corresponding 20 base stations were enrolled. For each station, the meteorological and geographic indexes of daily city-level data from the last 40 years (January 1980–September 2019, except Hong Kong data from January 1997–September 2019) were obtained from the National Meteorological Information Centre (http://data.cma.cn/) and the Hong Kong Observatory (https://www.hko.gov.hk/contentc.htm). The meteorological indexes included air pressure (AP, hPa); average temperature (T, °C); temperature difference (DIF T, the maximum temperature minus the minimum in one day, °C); precipitation (P, the depth of water that accumulates on a horizontal surface over a given period of time, mm); relative humidity (RH, %); wind speed (WS, m/s); and sunshine duration (SSD, h). Because of the changing and alternating use of the equipment to measure evaporation, the evaporation information obtained was only a rough estimate, and there is a possibility of inaccuracy. Therefore evaporation was excluded from the analysis. The geographic longitude (E), latitude (N), and altitude (m) and their average values were calculated as the indexes of each city. Annual mean and annual standard deviation (SD) statistics were calculated for each of the meteorological indexes of each city. Further analysis and description of meteorological indexes in the Methods and Results sections are based on annual mean and annual SD values.

Statistical Analysis

Data analysis was performed from November 1, 2019, to March 1, 2020. Only the right-eye data were chosen for analysis, considering the law of symmetry of our eyes[24] and the high correlation between both eyes.[25] The characteristics of our samples were reported using descriptive statistics (means and SDs for continuous variables and proportions for categorical variables).

To investigate the relationships between cornea-related and environmental parameters, we performed city-level and individual eye-level analyses. In the city-level analyses, all cornea-related parameters were averaged. The correlation analyses were performed using the Pearson method or Spearman method depending on the normality assumption, to investigate the relationship between each cornea-related parameter and each annual mean and SD of an environmental parameter.

In the eye-level analyses, multilevel models, including mixed-effects linear regression models for continuous cornea-related parameters and mixed-effects logistic regression models for categorical parameters with a random intercept and fixed slope, were constructed since eyes (level 1) were nested within cities (level 2). The random intercept term accounted for the dependency among eyes within each city (cluster), representing the variability among cities as a result of city-specific characteristics. The intraclass correlation coefficient, which is the ratio of the between-cluster error variance to the total error variance, can be interpreted as the proportion of variance in the outcome accounted for by the cluster and represents a measure of strength of association.[26] In this study, it was adopted to report the proportion of the overall unexplained variance within a cornea-related parameter that can be accounted for by the city in which each participant resided in the model results. In addition, due to the imbalanced data structure (high variances in the numbers of eyes across cities, Fig. 1), balanced data were imputed to improve the statistical power. The city with the smallest number of eyes (Baotou, 181 eyes) was excluded, and 1052 eyes (the smallest number of eyes in a city among the remaining 19 cities) were sampled randomly by computer from each of 19 cities. Therefore a balanced data structure (1052 eyes from each city) was obtained, and a total of 19,988 eyes were analyzed in the multilevel (two-level) models.

All data processing and statistical analyses were carried out using R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 24.0 (SPSS, Inc., Chicago, IL, USA). All tests were two-sided, and a P value < 0.05 was considered statistically significant.

Results

Between January 1, 2010, and August 29, 2019, data from 301,933 eyes (from 162,901 subjects) from 20 centers in China were collected for eligibility assessment in this study. A total of 255,049 (84.5%) eyes met the eligibility criteria. Of these, 29,105 (9.6%) eyes were excluded because of missing values and extreme outliers based on Tukey's method (three interquartile ranges). These outliers were due to poor subject cooperation or equipment errors during measurement or data collection process. Of the remaining 225,944 eyes (74.8%) (125,161 subjects), only the right eye of each subject was selected, resulting in 114,067 eyes (37.8%) (age_{mean} = 23.95 years, age_{sd} = 5.74 years) included in the final analysis (Fig. 2). Variables of cornea-related morphology of each site and environmental variables of each city are shown in the appendix (Supplementary Tables S2, S3). The details of the sample information for each study center are presented in Table 1 and Figure 1.

In the correlation analysis at the city level, we found significant correlations between ambient climate parameters and cornea-related parameters (Table 2). Among them, the corneal thickness was most influenced by climatic parameters (we only presented the results of the pachy apex since the three corneal thickness parameters were highly correlated, as presented in Supplementary Fig. S1). The results showed strong positive correlations between corneal thickness and mean precipitation ($r_{apex} = 0.721$, $P < 0.001$), as well as the amounts of variation in precipitation ($r_{apex} = 0.665$, $P = 0.001$), mean temperature ($r_{apex} = 0.600$, $P = 0.005$), and RH ($r_{apex} = 0.559$, $P = 0.010$). By contrast, there were strong negative correlations between corneal thickness and daily differences in temperature ($r_{apex} = -0.694$, $P < 0.001$), SSD ($r_{apex} = -0.504$, $P = 0.023$), and high variations in RH ($r_{apex} = -0.503$, $P = 0.024$) (Figs. 3 and 4).

The AC volume was also a strong indicator in relation to climatic parameters (Figs. 5 and 6). In contrast to the associations with corneal thickness, the AC volume was significantly negatively correlated with precipitation ($r = -0.672$, $P = 0.001$), temperature ($r = -0.484$, $P = 0.031$), and RH ($r = -0.448$, $P = 0.047$). Moreover, when the amount of variation in precipitation ($r = -0.502$, $P = 0.024$) was high, the

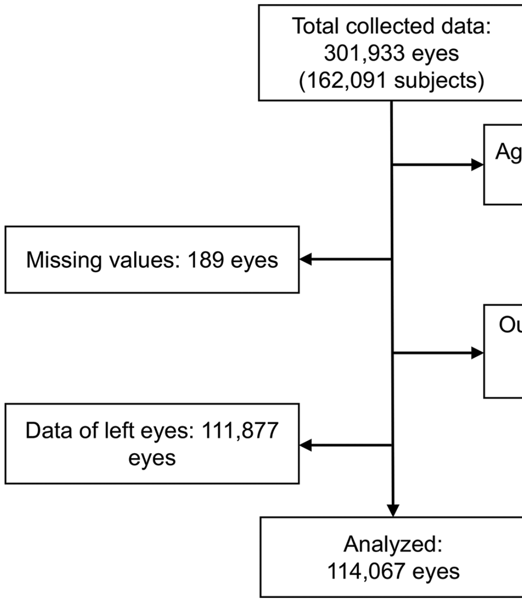

Figure 2. Flowchart of participants in the study. A total of 301,933 eyes from 162,091 subjects were included. Subjects aged <18 and >44 years and data with missing values and outliers based on Tukey's method (interquartile range) were excluded due to the subject's lack of cooperation or error during the measurement process or data collection by the equipment. A total of 114,067 right eyes were chosen for final analyses.

Table 1. Summary of Study Sites

Study Centers (City)	Age	Sample Size	Local Residents	Acquisition Time	Time Span (Days)
TJE (Tianjin)	23.942 (5.546)	29,223 (25.6%)	73%	2010.1.1–2019.1.28	3314
JNE (Jinan)	22.509 (5.487)	24,893 (21.8%)	89%	2011.4.23–2019.2.19	2859
XAH (Xi'an)	24.448 (5.221)	17,300 (15.2%)	85%	2010.7.7–2016.3.15	2078
SYH (Shenyang)	22.931 (5.408)	4,737 (4.2%)	90%	2015.5.2–2019.1.2	1341
NJE (Nanjing)	24.158 (5.813)	4,582 (4.0%)	90%	2013.9.29–2019.6.3	2073
SHE (Shanghai)	27.377 (6.221)	4,149 (3.6%)	80%	2011.1.2–2019.8.29	3161
NCE (Nanchang)	22.954 (5.470)	3,883 (3.4%)	95%	2014.10.31–2019.7.4	1707
HFE (Hefei)	22.788 (4.855)	3,535 (3.1%)	95%	2012.2.2–2019.8.22	2758
XYH (Changsha)	24.959 (5.852)	3,153 (2.8%)	90%	2017.1.1–2019.8.9	950
XJH (Urumqi)	27.225 (6.269)	3,045 (2.7%)	100%	2013.9.5–2019.1.11	1954
JLH (Changchun)	23.100 (5.401)	2,563 (2.3%)	95%	2015.4.9–2019.8.5	1579
XME (Xiamen)	23.539 (5.889)	2,332 (2.0%)	85%	2018.5.29–2019.8.5	433
BJE (Beijing)	26.791 (6.446)	2,083 (1.8%)	75%	2016.8.23–2019.7.23	1064
SXE (Taiyuan)	23.147 (5.386)	2,016 (1.8%)	95%	2018.6.15–2019.7.12	392
KMH (Kunming)	26.426 (6.922)	1,488 (1.3%)	98%	2013.6.18–2019.1.23	2045
GSH (Lanzhou)	25.196 (6.649)	1,451 (1.3%)	90%	2014.10.13–2019.4.29	1659
HKC (Hong Kong)	27.713 (5.734)	1,229 (1.1%)	99%	2013.8.3–2017.9.5	1494
DPH (Chongqing)	24.098 (5.526)	1,172 (1.0%)	95%	2016.1.5–2016.3.29	84
HNE (Haikou)	23.767 (5.506)	1,052 (0.9%)	95%	2015.5.27–2017.8.29	825
BTH (Baotou)	25.503 (6.323)	181 (0.2%)	98%	2017.4.12–2019.7.16	825

TJE: Tianjin Eye Hospital; JNE: Jinan Mingshui Eye Hospital; XAH: Xi·an No. 4 Hospital; SYH: The 4th People·s Hospital of Shenyang; NJE: Nanjing Aier Eye Hospital; SHE: Shanghai Aier Eye Hospital; NCE: Nanchang Bright Eye Hospital; HFE: Hefei Aier Eye Hospital; XYH: Xiangya Hospital of Central South University; XJH: The First Affiliated Hospital of Xinjiang Medical University; JLH: The Second Hospital of Jilin University; XME: Xiamen Eye Centre of Xiamen University; BJE: Beijing Huade Eye Hospital; SXE: Shanxi Eye Hospital; KMH: Yan·an Hospital of Kunming City; GSH: Gansu Provincial Hospital; HKC: Hong Kong Laser Eye Centre DPH: Daping Hospital; HNE: Hainan Eye Hospital; BTH: Baotou Eighth Hospital.

AC volume was small. However, when the amount of annual variation in temperature ($r = 0.507$, $P = 0.022$) or the daily difference in temperature ($r = 0.570$, $P = 0.009$) was high, the AC volume was large. The correlations between the AC depth and climate parameters were similar to those of the AC volume, although it was not statistically significant for all parameters. We did not find significant correlations between the AC angle and climate features.

Notably, temperature was the climatic parameter most associated with corneal aberrations, and there were significant negative correlations between them, especially for the HOA cornea ($r = -0.569$, $P = 0.009$) and Z_3^1 cornea

Table 2. Bivariate Correlations Between Cornea-Related Parameters and Environmental Variables at the City Level

	Latitude	Longitude	Altitude	Avg AP mean	P mean	Avg T mean	Dif T mean	Avg RH mean	Avg WS mean	SSD mean	Avg AP SD	P SD	Avg T SD	Dif T SD	Avg RH SD	Avg WS SD	SSD SD
AC depth	0.441	0.384	−0.002†	−0.021†	−0.524*	−0.400	0.510*	−0.430	−0.066†	0.316	0.292†	−0.296†	0.446*	0.251	0.201	−0.002†	−0.354†
AC volume	0.513*	0.106	0.068†	−0.084†	−0.672**	−0.484*	0.570**	−0.448*	−0.379†	0.183	0.365†	−0.502*,†	0.507*	0.403	0.223	−0.280†	−0.359†
AC angle	0.050	0.003	0.156†	−0.159†	−0.003	−0.149	0.101	−0.084	−0.029†	0.252	−0.152†	−0.063†	0.078	0.049	−0.002	0.036†	−0.213†
K1 F	0.180	−0.266	0.114†	−0.128†	−0.356	−0.094	0.225	−0.325	−0.358†	0.087	0.045†	−0.334†	0.061	0.446*	0.286	−0.147†	−0.023†
K2 F	−0.001	−0.101	0.032†	−0.008†	−0.044	0.006	0.141	−0.263	0.041†	0.243	−0.218†	−0.095†	−0.112	0.046	0.144	0.226†	−0.259†
K1 B	−0.316	0.150	−0.304†	0.234†	0.335	0.379	−0.420	0.419	0.443†	−0.324	0.113†	0.234†	−0.266	−0.438	−0.328	0.085†	0.216†
K2 B	−0.390	−0.068	−0.194†	0.126†	0.354	0.539*	−0.512*	0.400	0.114†	−0.472*	0.093†	0.288†	−0.361	−0.311	−0.247	−0.124†	0.504*,†
Pachy apex	−0.482*	0.376	−0.432†	0.420†	0.721***	0.600**	−0.694***	0.559*	0.459*,†	−0.504*	0.083†	0.665**,†	−0.432	−0.468*	−0.503*	0.024†	0.171†
Pachy pupil	−0.470*	0.383	−0.432†	0.420†	0.715***	0.590**	−0.686***	0.548*	0.459*,†	−0.495*	0.083†	0.665**,†	−0.419	−0.472*	−0.498*	0.024†	0.171†
Pachy min	−0.475*	0.406	−0.400†	0.395†	0.706***	0.597**	−0.685***	0.564**	0.403†	−0.513*	0.108†	0.629**,†	−0.422	−0.474*	−0.507*	0.027†	0.162†
HOA CF	0.233†	0.005†	0.233†	−0.233†	−0.277†	−0.413†	0.474*,†	−0.163†	−0.176†	0.295†	−0.114†	−0.223†	0.218†	0.327†	0.090†	−0.117†	−0.210†
HOA CB	0.079	0.044	0.037†	0.005†	0.030	−0.161	−0.039	0.062	0.003†	0.063	0.023†	0.000†	0.103	0.154	−0.063	−0.046†	−0.198†
HOA cornea	0.383†	−0.008†	0.308†	−0.295†	−0.393†	−0.569**,†	0.542*,†	−0.260†	−0.190†	0.380†	−0.137†	−0.346†	0.359†	0.423†	0.222†	0.007†	−0.255†
Z_3^1 Cornea	0.344	−0.103	0.446*,†	−0.420†	−0.406	−0.493*	0.434	−0.230	−0.329†	0.134	−0.087†	−0.350†	0.370	0.486*	0.169	−0.250†	−0.069†
Z_3^{-1} Cornea	0.283	0.099	−0.015†	−0.076†	−0.429	−0.291	0.477*	−0.366	0.085†	0.456*	−0.027†	−0.517*,†	0.207	0.087	0.250	0.200†	−0.507*,†
Z_4^0 Cornea	−0.428	−0.164	−0.092†	0.077†	0.332	0.351	−0.275	0.468*	−0.110†	−0.324	0.055†	0.337†	−0.365	−0.045	−0.307	−0.153†	0.397†
F AWR	−0.132	0.461*	−0.230†	0.237†	0.349	0.228	−0.271	0.123	0.468*,†	−0.020	−0.046†	0.124†	−0.081	−0.627**	−0.267	0.285†	−0.296†
B AWR	0.332	0.415	0.079†	−0.048†	−0.361	−0.421	0.353	−0.091	−0.057†	0.035	0.087†	−0.149†	0.375	0.156	−0.033	−0.308†	−0.404†

AC, anterior chamber; K1 F, flat keratometry in the front of the cornea; K2 F, steep keratometry in the front of the cornea; K1 B, flat keratometry in the back of the cornea; K2 B, steep keratometry in the back of the cornea; F AWR, astigmatism with the rule on the anterior surface of the cornea; B AWR, astigmatism with the rule on the posterior surface of the cornea; HOA CF, higher-order aberration on the front corneal surface; HOA CB, higher-order aberration on the back corneal surface; HOA cornea, higher-order aberration on the total corneal surface; Z_3^1 cornea, corneal vertical coma; Z_3^{-1} cornea, corneal horizontal coma; Z_4^0 cornea, corneal spherical aberration; E, evaporation; AP, air pressure; T, temperature; P, precipitation; RH, relative humidity; WS, wind speed, SSD: sunshine duration.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

† Spearman correlation coefficients, the rest are Pearson correlation coefficients.

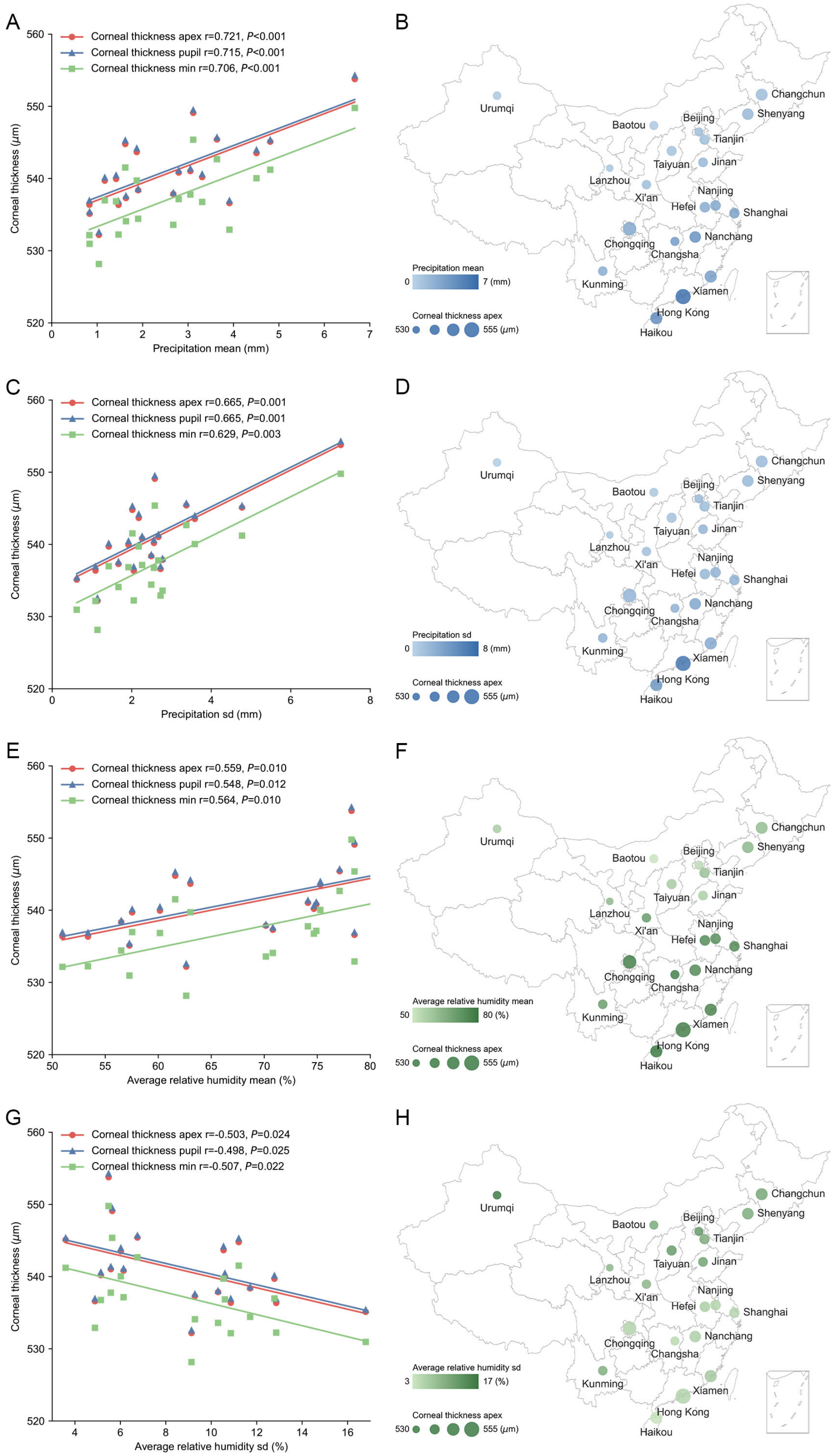

Figure 3. Relationships between corneal thickness and precipitation and relative humidity. Scatter plots and maps showing the correlations between corneal thickness and the mean (A and B) and standard deviation (C and D) of precipitation and the mean (E and F) and standard deviation (G and H) of relative humidity.

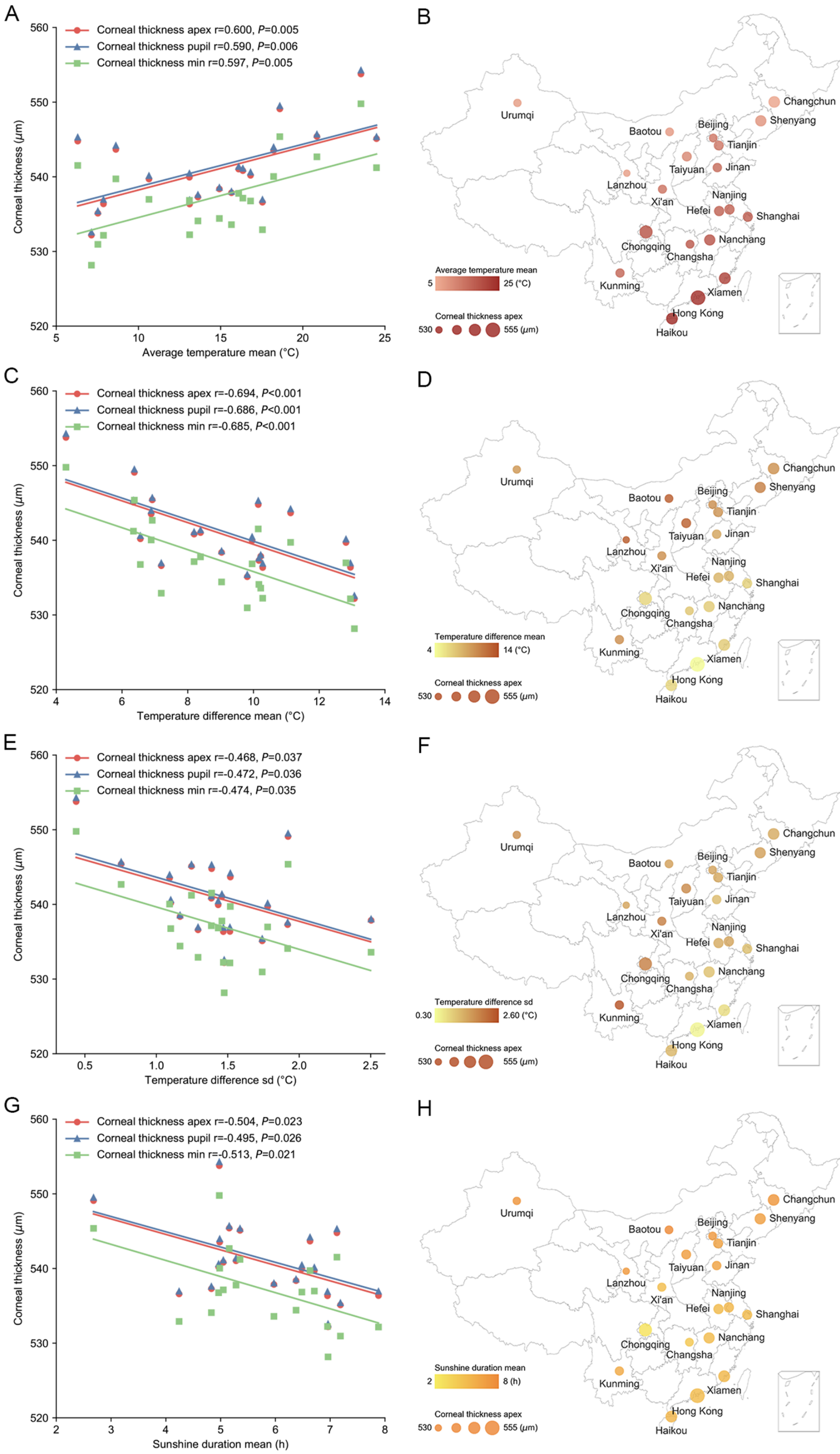

FIGURE 4. Relationships between corneal thickness and temperature and sunshine duration. Scatter plots and maps showing the correlations between corneal thickness and temperature (A and B), the mean (C and D) and standard deviation (E and F) of daily difference in temperature and sunshine duration (G and H).

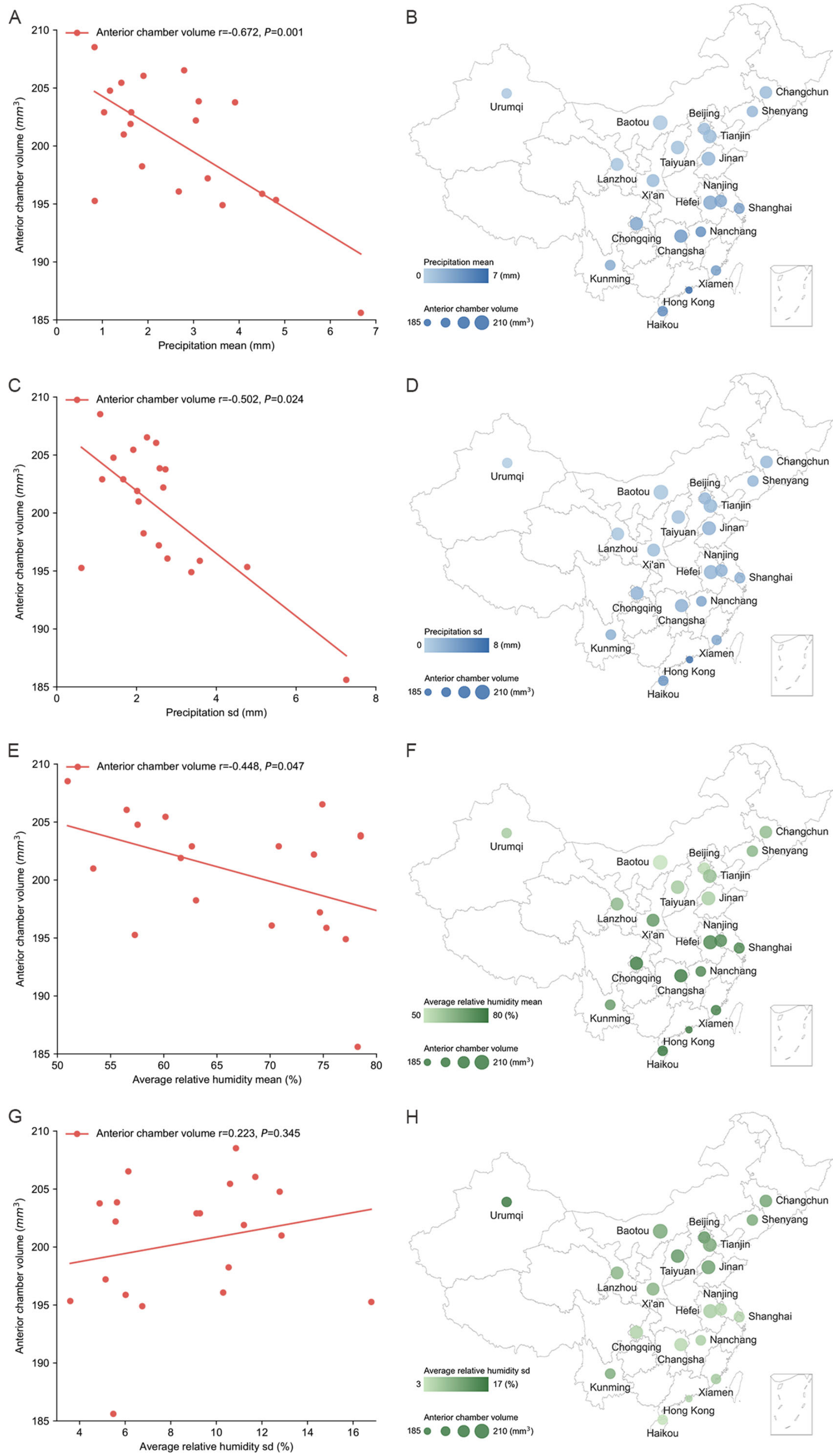

Figure 5. Relationships between anterior chamber volume and precipitation and relative humidity. Scatter plots and maps showing the correlations between anterior chamber volume and the mean (A and B) and standard deviation (C and D) of precipitation and the mean (E and F) and standard deviation (G and H) of relative humidity.

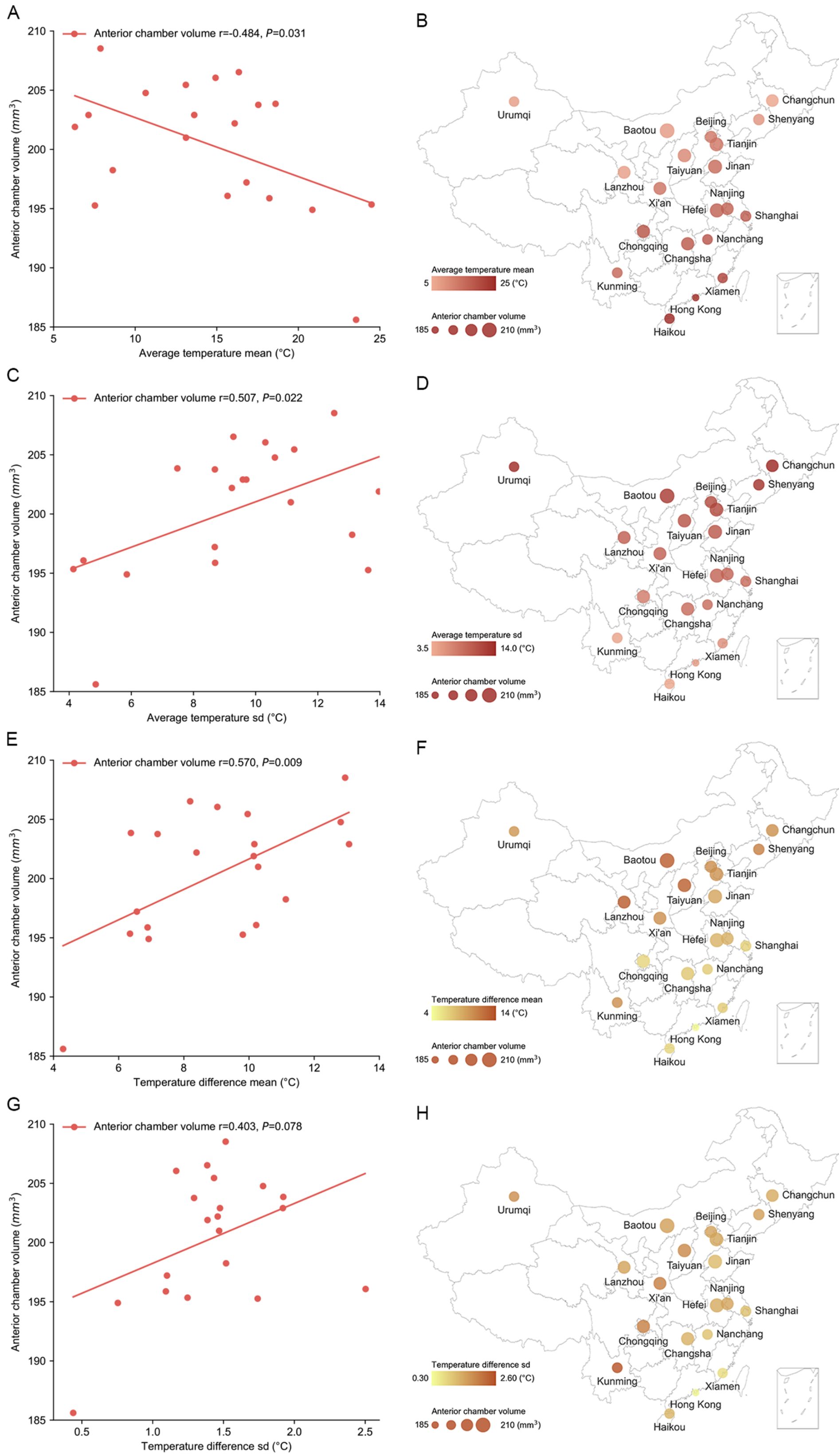

Figure 6. Relationships between anterior chamber volume and temperature. Scatter plots and maps showing the correlations between anterior chamber volume and the mean (A and B) and standard deviation (C and D) of temperature and the mean (E and F) and standard deviation (G and H) of daily difference in temperature.

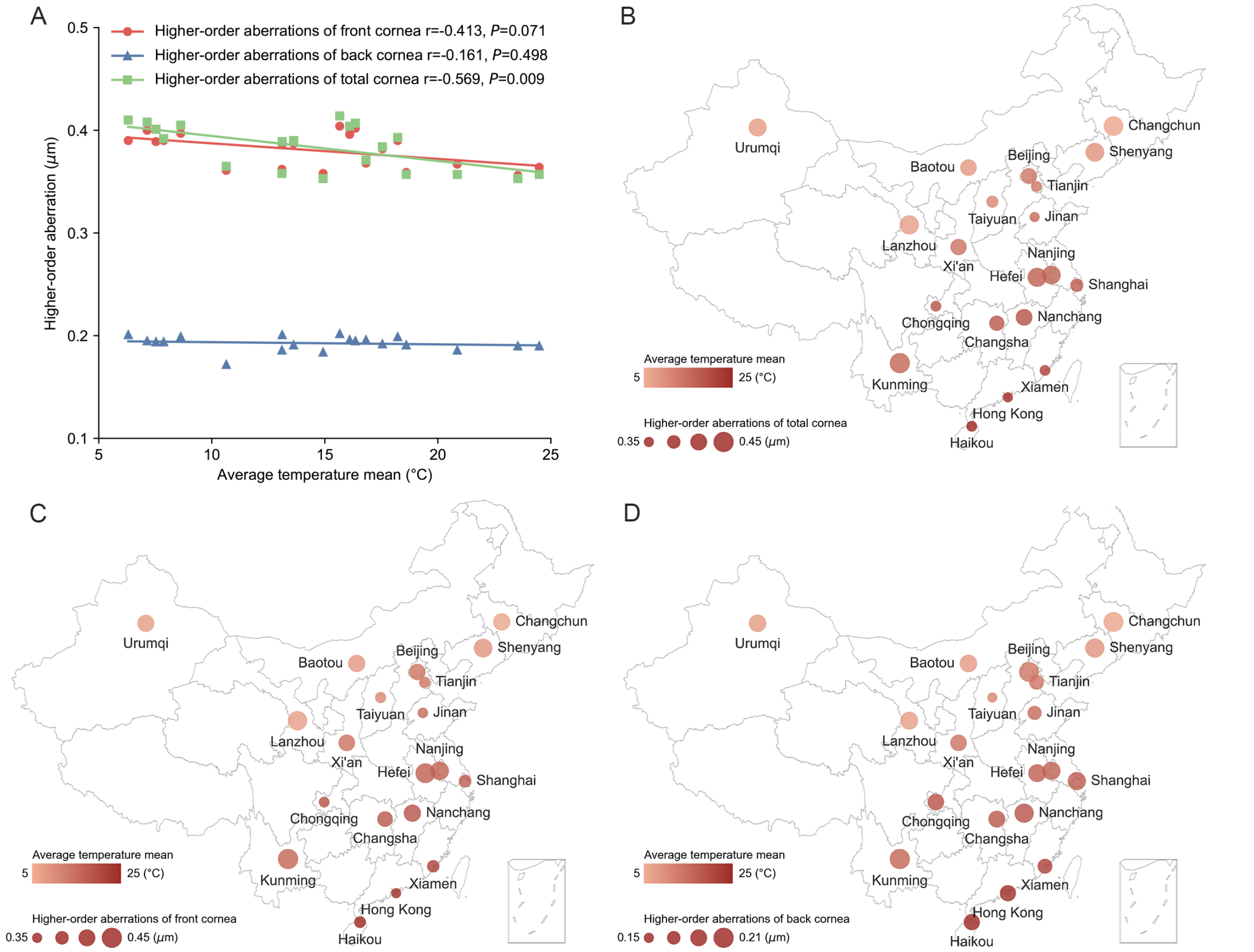

FIGURE 7. Relationships between corneal aberrations and temperature. Scatter plots (A) and maps (B-D) showing that several corneal parameters (higher-order abbreviations of total, front and back cornea) were negatively correlated with temperature.

(r = −0.493, P = 0.027) (Fig. 7). The Z_3^{-1} cornea was positively correlated with the daily differences in temperature (r = 0.477, P = 0.034) and SSD (r = 0.456, P = 0.044) and negatively correlated with the amounts of variation in precipitation (r = −0.517, P = 0.020) and SSD (r = −0.507, P = 0.023).

Furthermore, we analyzed the relationships between corneal morphologic parameters and latitude, longitude, and altitude. Latitude had the strongest correlation with cornea-related morphology. People who lived at high latitudes for a long time had thinner corneas (r_{apex} = −0.482, P = 0.031) and greater AC volumes (r = 0.513, P = 0.021) than those who lived at low latitudes (Fig. 8).

In the eye-level analysis, 19,988 eyes were analyzed in the multilevel models (Supplementary Table S4). Consistent with the results of the city-level analyses, the eye-level analyses reliably identified ambient climatic factors that were significantly related to each of the corneal morphologic parameters (Supplementary Tables S5–S22). After adjusting for age, the results showed that the mean precipitation (B_{apex} = 2.552, P < 0.001, and B_{ACV} = −2.104, P < 0.01), amount of variation in precipitation (B_{apex} = 2.887, P < 0.001, and B_{ACV} = −2.329, P < 0.001) and daily temperature difference (B_{apex} = −1.604, P < 0.001, and B_{ACV} = 1.086, P < 0.05) were associated with corneal thickness, along with the AC volume, according to the model fitting results. In addition, the wind speed exhibited associations with corneal thickness (B_{apex} = 3.007, P < 0.01) and AC volume (B_{ACV} = −2.561, P < 0.05). Moreover, high mean temperature was also an important factor of low HOA of the cornea.

DISCUSSION

This large multicenter study identified a correlation between the ambient environment and cornea-related morphology. Residents in warm and wet environments had thicker corneas and smaller AC volumes than those from cold and dry ambient climates. In comparison, individuals living in areas with a long sunshine duration and alternating dry and wet conditions had thinner corneas. High latitude was associated with a thinner cornea and a larger AC volume. Temperature was closely related to corneal higher-order aberrations. These effects were robust in population with the same ethnicity, age group, and the examination equipment.

We identified a group of interrelated factors, namely, precipitation, temperature, humidity, sunshine duration, and latitude, which were significantly associated with a number of morphologic characteristics of the human cornea. In contrast, there was no significant association with air pres-

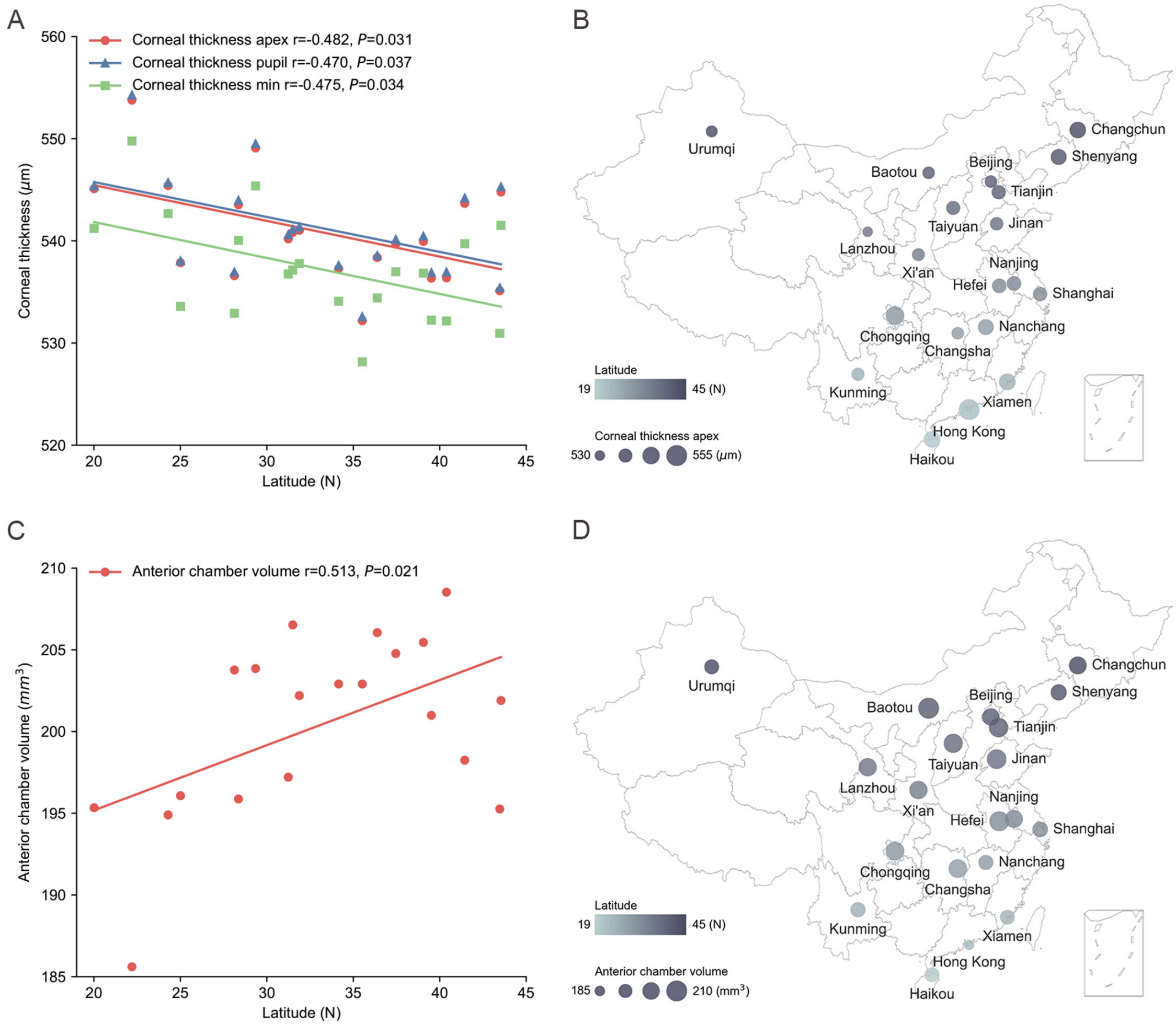

Figure 8. Relationships between latitude and corneal thickness and anterior chamber volume. Scatter plots (A and C) and maps (B and D) showing that latitude was negatively correlated with corneal thickness and positively correlated with anterior chamber volume.

sure or altitude. Our findings are consistent with the climate-morphology theory,[27] which proposes that environmental factors play an essential role in the evolution of human morphology, particularly in the body size and mid-facial morphology.[28–31] There have been a number of studies related to the environment and the development of ocular development.[32–36] It has been suggested that there is a relationship between the size of the human visual system and latitude,[32] although further study is still needed. The Chinese population has the same growth in orbital volume as the white population, and eyeball and orbital are positively correlated with latitude.[33–36] This may be due to an evolutionary mechanism with impaired light availability, which leads to enlarged eyes, and other factors associated with different geographic locations.[32] Furthermore, people from cold/dry climates tend to have a tall, narrow, and deep nasal cavity compared with those from warm/wet conditions, and this adaptation is likely driven by temperature and humidity.[29,30] We show that climatic conditions influence cornea-related morphology, indicating morphofunctional adaptability in relation to the ambient climate in humans.

Our findings indicate a significant correlation between water-related climatic factors and corneal morphology. Interestingly, people living in areas with a long sunshine duration, big difference in daily temperature, and cold, dry conditions had thinner corneas. The cornea has a water content of more than 80%.[37,38] Dry conditions or varied daily temperature differences accelerate the evaporation of water from the corneal surface, promote vertical and horizontal transport of water from the corneal stroma,[39,40] and eventually may result in a thinner cornea. Additionally, when the eye is exposed to long periods of sunshine, ultraviolet rays promote greater cross-linking of collagen fires within the corneal stroma,[41,42] causing a subsequent increase in collagen fiber diameter but a decrease in spacing between the collagen fibers and the number of collagen fibers per unit area, contributing to reduced corneal thickness.[43–45] Previous research has focused on the effect of sunlight on corneal thickness, whereas this study, by analyzing more environmental factors, found that people who lived in wet environments with abundant rainfall had thicker corneas, which is consistent with other reports that thicker corneas are in subjects from a location with many rainy days and less sunshine during the year.[46,47]

In our study, we found that people living at higher latitudes had thinner corneas. The mean epithelial thickness of the cornea has been reported to decrease with increasing geographic latitude,[48] which may play a role. And the effect of latitude on climate is reflected in temperature and areas at higher latitudes usually have lower temperatures. We also found temperature positively associated with corneal thickness. Additional studies based on animal models are needed to clarify the etiological basis for these observations and their relevance to corneal morphologic parameters.

Of note, we show that climatic factors have different influences on corneal morphology and AC volume. Individuals who lived in cold and dry environments had larger AC volumes than those living in moist and warm environments. The AC is filled with aqueous humor, and its volume is vital for maintaining intraocular pressure within a physiological range.[49] A cold and dry environment can stimulate the sympathetic nerves, causing pupil dilation.[50] The aqueous humor in the posterior chamber then flows into the AC, resulting in an increased AC volume.[49] It is particularly noteworthy that the pupils of patients with glaucoma are more prone to dilation when stimulated in a cold environment than in a warm environment.[51,52] This enhanced mechanism can lead to accumulation of aqueous humor in the AC, an increase of intraocular pressure, and a sudden onset of angle-closure glaucoma.[53] This is also consistent with previous reports that have found higher intraocular pressures in colder months than in warmer months in both longitudinal and cross-sectional populations.[54–56] A cold environment has been shown to promote acute angle-closure glaucoma attacks, as evidenced by a higher incidence of angle-closure glaucoma in the winter, and the number of hours without sunshine is positively correlated with the incidence of acute closed-angle glaucoma.[57,58] Our findings indicate that more attention needs to be focused on the ocular health of people living in cold regions or during cold seasons, and further evaluation is warranted to better determine patients at risk for glaucoma, and provide public health education.

Our study showed that compared with the mean annual temperature, the daily temperature difference had an opposite effect on the corneal thickness and AC volume. When the daily temperature difference was greater, the corneal thickness was thinner, and the AC volume was larger. The daily temperature difference is associated with the latitude, humidity, and land and sea location of a city.[59] If a city is located at a higher latitude, with lower humidity and inland far from the ocean, the daily temperatures tend to have greater fluctuations.[59] In our study, individuals from Lanzhou with the greatest daily temperature difference (high latitude, low humidity, and far from inland) exhibited thinner corneal thickness and larger AC volumes, whereas individuals from Hong Kong with the smallest daily temperature difference (low latitude, high humidity, proximity to the ocean) showed a thicker cornea and smaller AC volume. It indicated a complex correlation between climatic parameters and geographic location.[60] In addition, higher temperatures were related to lower corneal higher-order aberrations in the human eye, indicating that changes in corneal thickness associated with high temperature result in a thicker cornea and structural aberrations, which can have a significant impact on the finer aspects of visual perception.[61]

Because the majority of subjects included in this study lived in the local area, their age could represent the amount of time that they had lived there. By collecting the cornea-related parameters and climate data over the past 40 years and analyzing their correlations, we found subtle effects of environmental factors on morphologic characteristics over time. Understanding these influences may be beneficial for the development of normative ranges for cornea-related morphology and diagnostic criteria for related corneal pathology (e.g., keratoconus), as well as the individualization of surgical management plans (e.g., corneal refractive surgery) for individuals living in different environmental regions. It may also contribute to risk stratification in the diagnosis and management of glaucoma.

Our study has several limitations. First, in the data collected in real-world ophthalmic centers with ocular measurements being collected by different optometrists, there may be measurement bias, although a standard examination protocol was followed. Second, the climate data used were based on measurements at a meteorological base station in each city and cannot fully account for population mobility because of work, education, or medical service among the local population, which could potentially lead to bias, although more than 75% of the enrolled subjects were local residents in each study site. Third, other factors potentially affecting corneal morphology, such as heritage and regional dietary differences, were not included as covariates in the analysis in this study. For example, a high-sugar diet may contribute to the accumulation of nonenzymatic glycosylation of proteins and the formation of advanced glycosylation end products and result in morphologic changes in the corneal epithelium and endothelium.[62] The above biases may be minimized by increasing the sample size and optimizing sampling methods. Forth, the subjects in this study were candidates for refractive surgery, and our findings should be further evaluated in other healthy populations. Finally, gender probably should be adjusted for, because there may be some differences in cornea parameters between male and female. However, because of the lack of information collected by the equipment, there is an absence of gender information in the data of this study, and the gender-adjusted analysis cannot be performed. The potential impact of gender can be further explored in future studies.

In summary, the results of this multicenter study of a large Han Chinese population indicate that climatic conditions could have an important modulatory role in determining the ocular structure and influencing corneal morphology and its related parameters. Additional studies are warranted in other ethnic groups, and the wider implications in terms of the distribution and prevalence of specific ocular diseases in different regions of the world deserve further investigation.

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References

1. Flaxman SR, Bourne RRA, Resnikoff S, et al. Global causes of blindness and distance vision impairment 1990-2020: a systematic review and meta-analysis. *Lancet Glob Health*. 2017;5:e1221–e1234.
2. Bourne RR, Stevens GA, White RA, et al. Causes of vision loss worldwide, 1990–2010: a systematic analysis. *Lancet Glob Health*. 2013;1:e339–349.
3. DelMonte DW, Kim T. Anatomy and physiology of the cornea. *J Cataract Refract Surg*. 2011;37:588–598.
4. Kok YO, Tan GF, Loon SC. Review: keratoconus in Asia. *Cornea*. 2012;31:581–593.
5. Song P, Xia W, Wang M, et al. Variations of dry eye disease prevalence by age, sex and geographic characteristics in China: a systematic review and meta-analysis. *J Glob Health*. 2018;8:020503.
6. Osae AE, Gehlsen U, Horstmann J, et al. Epidemiology of dry eye disease in Africa: The sparse information, gaps and opportunities. *Ocul Surf*. 2017;15:159–168.
7. Um SB, Kim NH, Lee HK, Song JS, Kim HC. Spatial epidemiology of dry eye disease: findings from South Korea. *Int J Health Geogr*. 2014;13:31.
8. Uchiyama E, Aronowicz JD, Butovich IA, McCulley JP. Increased evaporative rates in laboratory testing conditions simulating airplane cabin relative humidity: an important factor for dry eye syndrome. *Eye Contact Lens*. 2007;33:174–176.
9. Lopez-Miguel A, Teson M, Martin-Montanez V, et al. Dry eye exacerbation in patients exposed to desiccating stress under controlled environmental conditions. *Am J Ophthalmol*. 2014;157:788–798.e782.
10. Bharathi J, Ramakrishanan R, Meenakshi R, Padmavathy S, Shivakumar C, Srinivasan M. Microbial keratitis in South India: influence of risk factors, climate, and geographical variation. *Ophthalmic epidemiology*. 2007;14:61–69.
11. Tomoyose E, Higa A, Sakai H, et al. Intraocular pressure and related systemic and ocular biometric factors in a population-based study in Japan: the Kumejima study. *Am J Ophthalmol*. 2010;150:279–286.
12. Hashemi H, Asgari S, Mehravaran S, Emamian MH, Shariati M, Fotouhi A. The distribution of corneal thickness in a 40- to 64-year-old population of Shahroud, Iran. *Cornea*. 2011;30:1409–1413.
13. Tomidokoro A, Araie M, Iwase A, Tajimi Study G. Corneal thickness and relating factors in a population-based study in Japan: the Tajimi study. *Am J Ophthalmol*. 2007;144:152–154.
14. Hwang YH, Kim HK, Sohn YH, Namil Study Group KGS. Central corneal thickness in a Korean population: the Namil Study. *Invest Ophthalmol Vis Sci*. 2012;53:6851–6855.
15. Chua J, Tham YC, Liao J, et al. Ethnic differences of intraocular pressure and central corneal thickness: the Singapore Epidemiology of Eye Diseases study. *Ophthalmology*. 2014;121:2013–2022.
16. Lifshitz T, Levy J, Rosen S, Belfair N, Levinger S. Central corneal thickness and its relationship to the patient's origin. *Eye (Lond)*. 2006;20:460–465.
17. Ma R, Liu Y, Zhang L, et al. Distribution and trends in corneal thickness parameters in a large population-based multicenter study of young Chinese adults. *Invest Ophthalmol Vis Sci*. 2018;59:3366–3374.
18. Zhou X, Wang L, Chu R, Yu Z. [Corneal thickness distribution and its relationship with corneal topography in ametropic population]. *Zhonghua Yan Ke Za Zhi*. 2014;50:658–664.
19. Schweitzer C, Korobelnik JF, Boniol M, et al. Associations of biomechanical properties of the cornea with environmental and metabolic factors in an elderly population: the ALIENOR Study. *Invest Ophthalmol Vis Sci*. 2016;57:2003–2011.
20. Dobson RBJ. Atmosphere, Climate and Environment Information Programme. *Geography*. 2000;85:288.
21. Clift P, Lee JI, Clark MK, Blusztajn J. Erosional response of South China to arc rifting and monsoonal strengthening; a record from the South China Sea. *Marine Geology*. 2002;184:207–226.
22. Organization WH. *World Health Day* 2012*: aging and health: toolkit for event organizers*. Geneva: World Health Organization; 2012.
23. Gomes JA, Tan D, Rapuano CJ, et al. Global consensus on keratoconus and ectatic diseases. *Cornea*. 2015;34:359.
24. Knapp H. The law of symmetry of our eyes, as manifested in the direction of their meridians: its rule and its exceptions. *Trans Am Ophthalmol Soc*. 1892;6:308–314.
25. Armstrong RA. Statistical guidelines for the analysis of data obtained from one or both eyes. *Ophthalmic Physiol Opt*. 2013;33:7–14.
26. Lorah J. Effect size measures for multilevel models: definition, interpretation, and TIMSS example. *Large Scale Assess Educ*. 2018;6:8.
27. Beall CM, Jablonski NG, Steegmann AT. Human adaptation to climate: temperature, ultraviolet radiation, and altitude. In: Stinson S, Bogin B, O'Rourke D , eds. *Human Biology An Evolutionary & Biocultural Perspective*. Hoboken, NJ: John Wiley and Sons, 2000;175–250.
28. Cui Y, Leclercq S. Environment-related variation in the human mid-face. *Anat Rec (Hoboken)*. 2017;300:238–250.
29. Evteev A, Cardini AL, Morozova I, O'Higgins P. Extreme climate, rather than population history, explains mid-facial morphology of Northern Asians. *Am J Phys Anthropol*. 2014;153:449–462.
30. Fukase H, Ito T, Ishida H. Geographic variation in nasal cavity form among three human groups from the Japanese Archipelago: Ecogeographic and functional implications. *Am J Hum Biol*. 2016;28:343–351.
31. Steegmann AT, Jr. Climate, racial category, and body proportions in the U.S. *Am J Hum Biol*. 2005;17:393–402.
32. Short Alice. The relationship between latitudinal light variation and orbit and cranial size in humans. *Anthropological Review*. 2016;79:143–149.
33. Todd TW, Beecher H, Williams GH, Todd AW. The Weight and Growth of the Human Eyeball. *Human Biology*. 1940;12:1–20.
34. Wei N, Bi H, Zhang B, Li X, Sun F, Qian X. Biphasic growth of orbital volume in Chinese children. *Br J Ophthalmol*. 2017;101:1162–1167.
35. Pearce E, Dunbar R. Latitudinal variation in light levels drives human visual system size. *Biol Lett*. 2012;8:90–93.
36. Pearce E, Bridge H. Is orbital volume associated with eyeball and visual cortex volume in humans? *Ann Hum Biol*. 2013;40:531–540.
37. Maurice DM. The structure and transparency of the cornea. *J Physiol*. 1957;136:263–286.

38. Birk DE, Trelstad RL. Extracellular compartments in matrix morphogenesis: collagen fibril, bundle, and lamellar formation by corneal fibroblasts. *J Cell Biol*. 1984;99:2024–2033.
39. Bonanno JA. Identity and regulation of ion transport mechanisms in the corneal endothelium. *Prog Retin Eye Res*. 2003;22:69–94.
40. Inoue T, Kobayashi T, Nakao S, et al. Horizontal intracorneal swirling water migration indicative of corneal endothelial function. *Invest Ophthalmol Vis Sci*. 2014;55:8006–8014.
41. Spoerl E, Huhle M, Seiler T. Induction of cross-links in corneal tissue. *Exp Eye Res*. 1998;66:97–103.
42. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol*. 2003;135:620–627.
43. Wollensak G, Wilsch M, Spoerl E, Seiler T. Collagen fiber diameter in the rabbit cornea after collagen crosslinking by riboflavin/UVA. *Cornea*. 2004;23:503–507.
44. Chang SH, Mohammadvali A, Chen KJ, et al. The relationship between mechanical properties, ultrastructural changes, and intrafibrillar bond formation in corneal UVA/riboflavin cross-linking treatment for keratoconus. *J Refract Surg*. 2018;34:264–272.
45. Akhtar S, Almubrad T, Paladini I, Mencucci R. Keratoconus corneal architecture after riboflavin/ultraviolet A cross-linking: ultrastructural studies. *Mol Vis*. 2013;19:1526–1537.
46. Hashemi H, Yekta A, Saatchi M, Moravej R, Aghamirsalim M, Khabazkhoob M. The distribution of corneal thickness in rural population. *Acta Medica Iranica*. 2017;3:320–328.
47. Mostafa EM. Central corneal thickness in southern Egypt. *Int Ophthalmol*. 2014;34:809–815.
48. Ringvold A, Anderssen E, Kjønniksen I. Impact of the environment on the mammalian corneal epithelium. *Invest Ophthalmol Vis Sci*. 2003;44:10–15.
49. Goel M, Picciani RG, Lee RK, Bhattacharya SK. Aqueous humor dynamics: a review. *Open Ophthalmol J*. 2010;4:52–59.
50. Rintamäki H. Human responses to cold. *Alaska Med*. 2007;49:29–31.
51. Lavanya R, Baskaran M, Kumar RS, et al. Risk of acute angle closure and changes in intraocular pressure after pupillary dilation in Asian subjects with narrow angles. *Ophthalmology*. 2012;119:474–480.
52. Quigley HA. Angle-closure glaucoma-simpler answers to complex mechanisms: LXVI Edward Jackson Memorial Lecture. *Am J Ophthalmol*. 2009;148:657–669.e651.
53. Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. *JAMA*. 2014;311:1901–1911.
54. Qureshi IA, Xi XR, Lu HJ, Wu XD, Huang YB, Shiarkar E. Effect of seasons upon intraocular pressure in healthy population of China. *Korean J Ophthalmol*. 1996;10:29–33.
55. Chan MP, Grossi CM, Khawaja AP, et al. Associations with intraocular pressure in a large cohort: results from the UK Biobank. *Ophthalmology*. 2016;123:771–782.
56. Gardiner SK, Demirel S, Gordon MO, Kass MA. Seasonal changes in visual field sensitivity and intraocular pressure in the ocular hypertension treatment study. *Ophthalmology*. 2013;120:724–730.
57. Zhu J, Xu Y, Wang H, Liu D, Zhu J, Wu H. The seasonality of acute attack of primary angle-closure glaucoma in Beijing, China. *Sci Rep*. 2018;8:4036.
58. Teikari JM, O'Donnell J, Nurminen M, Raivio I. Acute closed angle glaucoma and sunshine. *J Epidemiol Community Health*. 1991;45:291–293.
59. Gallo KP, Easterling DR, Peterson TC. The influence of land use/land cover on climatological values of the diurnal temperature range. *Journal of Climate*. 1996;9:2941–2944.
60. Sanderson M. The classification of climates from Pythagoras to Koeppen. *Bulletin of the American Meteorological Society*. 1999;80:669–674.
61. Touch B. Visual quality is mainly attributed to the development of higher-order aberrations. Available at: https://www.researchgate.net/publication/332818348_Visual_quality_is_mainly_attributed_to_the_development_of_higher-order_aberrations.
62. Bejarano E, Taylor A. Too sweet: problems of protein glycation in the eye. *Exp Eye Res*. 2019;178:255–262.