Design, methodology, and preliminary results of the follow-up of a population-based cohort study in rural area of northern China: Handan Eye Study

Kai Cao[1], Jie Hao[2], Ye Zhang[3], Ai-Lian Hu[1], Xiao-Hui Yang[1], Si-Zhen Li[4], Bing-Song Wang[1], Qing Zhang[1], Jian-Ping Hu[1], Cai-Xia Lin[3], Mayinuer Yusufu[1], Ning-Li Wang[1], the Handan Eye Study Group

[1]Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, China;
[2]Clinical Research Center, Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, China;
[3]Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing 100730, China;
[4]Nanjing Aier Eye Hospital, Nanjing, Jiangsu 210000, China.

Abstract

Background: Handan Eye Study (HES), a large population-based cohort study in rural area of northern China, was one of the few studies focusing on the major eye diseases of rural Chinese population. The aim of this study was to introduce the design, methodology and to assess the data quality of the follow-up phase of HES.

Methods: All participants were recruited in Yongnian county of Handan city between 2012 and 2013. Main outcomes were measured by visual quality scales and ocular examinations. We performed the Chi-square test to make comparison of categorical data among groups, One-way analysis of variance and Kruskal-Wallis test was applied to make comparison of continuous data among groups, a *post-hoc* test was done to make further pairwise comparison. Inter-class correlation coefficients (ICCs) and Kappa coefficients were used to evaluate the consistency between different operators. Logistic regression was used to explore the influence factors of death, odds ratio (OR) and 95% confidence interval (CI) were used to estimate the effect size of each influence factor.

Results: The follow-up rate was 85.3%. Subjects were classified into three groups: the follow-up group ($n = 5394$), the loss to follow-up group ($n = 929$), and the dead group ($n = 507$), comparison of their baseline information was done. Compared with the other two groups, age of the dead group (66.52 ± 10.31 years) was the oldest ($Z = 651.293$, $P < 0.001$), male proportion was the highest (59.0%) ($\chi^2 = 42.351$, $P < 0.001$), only 65.9% of the dead finished middle school education ($Z = 205.354$, $P < 0.001$). The marriage percentage, body mass index (BMI), best-corrected visual acuity (BCVA), and intra-ocular pressure of the dead group was the lowest either. Spherical equivalent error (SER) of the dead group was the highest. Besides, history of smoking, hypertension, diabetes, and heart disease were more common in the dead group. Multivariate analysis showed that age (OR = 1.901, 95% CI: 1.074–1.108), gender (OR = 0.317, 95% CI: 0.224–0.448), and BCVA (OR = 0.282, 95% CI: 0.158–0.503) were associated with death. While between the follow-up group and the loss to follow-up group, there was only difference on age, gender, BMI, systolic blood pressure and SER. The Cronbach coefficients of all scales used in the follow-up were ≥0.63 and the cumulative variances were ≥0.61, indicating good reliability and validity. The ICCs and Kappa coefficients between different operators were ≥0.69.

Conclusions: HES has a high follow-up rate and a low risk of loss to follow-up bias. Age, gender, and BCVA are influence factors of death. Specifically, male subjects are at a higher risk of death than female, age is a risk factor of death while BCVA is a protective factor for death.

Keywords: Cohort study; Rural population; Methodology; Follow-up; Bias

Introduction

China has the largest population in the world, with rural residents accounting for more than half of its population. Although some studies had revealed the epidemiological characteristics of ocular disorders, most of them focused on urban residents.[1-3] Few studies had shed light on the incidence of major eye diseases among rural population, as well as the impact factors or the cause and effect associations. Epidemiology study focusing on rural Chinese population is needed, especially a well-designed population-based cohort study.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000000418

Kai Cao, Jie Hao, and Ye Zhang contributed equally to this study.

Correspondence to: Prof. Ning-Li Wang, Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing Key Laboratory of Ophthalmology and Visual Sciences, Beijing 100730, China
E-Mail: wningli@vip.163.com

Chinese Medical Journal 2019;132(18)

Received: 28-04-2019 **Edited by:** Li-Min Chen

Back in 2006, the baseline survey of Handan Eye Study (HES) was conducted, the subjects were rural population aged 30 years or above from Handan city, Hebei province, China. HES baseline had provided abundant information on the prevalence of major eye diseases including glaucoma, cataract, refractive error, age-related macular degeneration (AMD), diabetic retinopathy (DR), retinal vein occlusion, and so on for rural population, as well as the risk factors of visual impairment or eye diseases.[4-12] Moreover, HES baseline had demonstrated the effect of eye diseases on visual function and healthcare.[13,14]

To make the investigation into a further step, the follow-up phase of HES was implemented between 2012 and 2013, the participants were all from baseline. The follow-up phase was aimed at investigating the cumulative 6-year incidence, progression, and the impact of vision-threatening ocular diseases in rural Chinese population. To help better understand HES and to build a reference for all subsequent studies, we intend to give a brief introduction of the design and methodology of the follow-up of HES. We will also assess the reliability and validity of scales used, as well as the consistency on same measurements by different operators, which is a reflection of the data quality. Besides, given that loss to follow-up is very common for cohort studies, we must evaluate whether there is bias caused by the subjects lost to follow-up, thus we will outline the preliminary comparison results among the subjects followed-up, the subjects lost to follow-up, and the dead subjects in this study.

Methods

Registration and ethic approval of HES

HES was registered in Chinese Clinical Trial Registry website "http://www.chictr.org.cn/," the registry number was ChiCTR-EOC-17013214. The study was conducted in accordance with the *Declaration of Helsinki* and the study was approved by the Ethical Committee of Beijing Tongren Hospital, Capital University of Medical Sciences (Ethical approval number TREC2006-22). The informed consents from the subjects were obtained in this study.

Study design

HES was a population-based cohort study. The methodology and design of HES baseline were described elsewhere,[15] specifically, at the baseline of HES, 6830 adults aged 30 years or above were included from 13 villages in Yongnian county, Handan city, Hebei province, northern China. In this paper we aimed at describing the methodology and the data quality of HES follow-up.

Why did we choose Handan?

Handan city was chosen carefully for two main reasons, firstly, according to data from National Bureau of Statistics of China, per capita net income of people in rural area of Hebei was at the medium level compared to other rural areas in northern China. We considered that the rural area of Hebei was of good representation to the rural area of northern China. We were supported by the government of Handan city, which was very helpful to the subject recruitment and the implement of the HES follow-up.

Characteristics of Handan

Handan city, between 114°03′–40′ east longitude and 36°20′–44′ north latitude, is located at the southern end of Hebei province. Handan has a complex terrain, the west of Handan is hilly landform, and the east of Handan is plain. The highest altitude of Handan is 1898.7 meters and the lowest is 32.7 meters. In Handan, there is a large steel factory: HBIS Group Hansteel Company, as well as lots of township enterprise doing leather business. What's more, Handan villagers' average income is around the median level of the rural area in northern China, thus Handan is an appropriate sample site.

How were the 13 villages selected?

Based on our baseline sample size estimation, it was expected that 8354 subjects[15] should be recruited. Besides, our basic sampling unit (BSU) was controlled at around 1500. If the number of residents in a village was less than 1500, the village would be merged with another neighboring village. At the same time, according to the 2010 census data, Chinese population over 30 years old accounted for about 51.7%, so it was expected that we could recruit 750 subjects from each BSU. For conservative consideration, we decreased this number to be 650, thus 13 villages were needed, and all the villages were randomly selected through a clustered sampling method.

Similarity of samples compared to the whole rural population of China

We compared the similarity of subjects from the investigation site, the Yongnian county, with the whole rural population of China.[15] The male proportion of Yongnian county was 50.6%, and it was 51.7% of the whole rural area population of China. In terms of age, the proportions of 0 to 9 years, 10 to 19 years, 20 to 29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years, 60 to 69 years, 70 to 79 years, and 80 years or above were 14.5%, 24.3%, 15.8, 16.0%, 12.8%, 8.2%, 4.9%, 2.8%, and 0.7%, respectively, while for the whole rural area population of China, the proportions were 14.1%, 19.2%, 15.6%, 18.1%, 13.0%, 9.1%, 6.3%, 3.6%, and 1.0%, respectively. Yongnian county and the whole rural area of China was relatively close in gender and age distribution.

Inclusion and exclusion criteria

Inclusion criterias were: (1) subjects of 30 years or above. (2) the household registration was in the local area. (3) the household registration was not in the local area but subjects had lived in the local area for more than half a year. (4) voluntarily participate in the study.

Exclusion criterias were: (1) subjects whose age was under 30 years. (2) the household registration was not in the local

area and the residence time was less than half a year. (3) subjects who refused to participate in this research.

What's new for the follow-up?

HES baseline was aimed at probing the prevalence, as well as the risk factors of major ocular diseases, visual impairment, and blindness. HES follow-up would focus on the incidence of ocular diseases, visual impairment, and blindness. What's more, the follow-up stage of HES would reveal a cause-and-effect relationship between the risk factors and the ocular diseases.

Recruitment strategy for the follow-up

For better recruitment of the subjects, village group leaders /local doctors made explanations to the villagers by social media (television and radio broadcast), as well as communications by face-to-face. Otherwise, local doctors carried out home visits to make further explanation to the subjects who had not understood the follow-up well.

For residents who were unable to attend the examination in central clinic, the examinations were conducted in the village clinic, including abbreviated examinations for subjects disabled at home.

Follow-up rate

Generally, 5394 subjects aged 36 years or above participated in the follow-up phase of HES. 929 subjects were lost to follow-up, another 507 subjects died and were excluded, the follow-up rate was 85.3% (5394/6323).

Data collection

The questionnaires and ocular examinations were performed by trained interviewers and experienced doctors who participated in the baseline survey of HES.

What questionnaires and scales were used?

(1) Socio-demographic information. (2) Internal medicine diseases. (3) Cognitive function (mini-mental state examination [MMSE][16]). (4) General quality of life (EuroQol-5D[17]). (5) Eye diseases and corresponding symptoms. (6) Refractive error. (7) Medical history. (8) Behavior information. (9) Family history. (10) Gynecology and fertility questions for female.

Except for the above questionnaires and scales that used for HES baseline, information of the following aspects was added in the follow-up: (1) the 8-item short-form health survey (SF-8).[18,19] (2) 12-item quality of life related with near vision (NVR-QOL). (3) 15-item visual quality questionnaire.[20]

What examinations were performed?

Examinations covered the following information. (1) Anthropometry. (2) Autorefraction and visual acuity (VA) measurement.[21] (3) intra-ocular pressure (IOP) measurement.[22] (4) Anterior segment optical coherence tomography. (5) Slit-lamp examination. (6) Optic disc imaging. (7) Retinal nerve fiber layer imaging. (8) Visual field testing. (9) Gonioscopy. (10) Ocular biometry. (11) Fundus photography. (12) Other measurements of physical function. (13) Blood collection. (14) Urine collection.

Except for the above examinations that performed at the baseline of HES, we added color vision measurement, near vision measurement, and trachoma screening. The whole examination procedure was shown in Figure 1.

Definitions of ocular disease and progression

Definitions of visual impairment

Blindness was defined as BCVA <20/400 in the better-seeing eye. Low vision was defined as BCVA <20/60 and ≥20/400 in the better-seeing eye. If the visual acuity was presented in the above categories during the follow-up without appearance at baseline, the visual acuity was taken as deterioration into blindness or low vision.

Definitions of glaucoma

Diagnosis of glaucoma was based on three aspects: the eye fundus, the visual field results, and the IOP. At the beginning, subjects were categorized as definite, probable, possible, or no glaucoma based on eye fundus. Subsequently, for the probable and possible subjects, if there were glaucomatous visual field defects and if the IOP was >21 mmHg, they would be diagnosed as glaucoma.

Glaucomatous visual field defects had at least two of the following characteristics: (1) a cluster of three points with a probability less than 1% on a pattern deviation map in at least one hemifield, including at least one point with a probability less than 1%; or a cluster of two points with a probability less than 1%. (2) glaucoma hemifield test results outside 99% of the age-specific normal limits. (3) pattern standard deviation outside 95% of the normal limits.

Specifically, the eye fundus reading followed the following process. Firstly, four ophthalmologists from Beijing Tongren Hospital (YZ, JH, QZ, and ZG) reviewed disc photographs for vertical cup/disc ratios, rim of optic disc, nerve fiber layer defect, and optic disk hemorrhage. Secondly, independent review of the finding was carried out by three senior glaucoma specialists (TR, BSW, and YBL), classified the patients according to the same definitions. If the results differed among three specialists, a third independent reading was conducted by another glaucoma specialist (DSF). The final diagnosis was determined by another glaucoma specialist (NLW) if some confused diagnosis still existed in the third step.

Glaucoma was also diagnosed as present in cases where the optic nerve was not visible due to media opacity and the VA was <20/400 and the IOP was >99.5th percentile, or the VA was <20/400 and the eye had evidence of prior glaucoma filtering surgery, or medical records were available confirming glaucomatous visual morbidity.

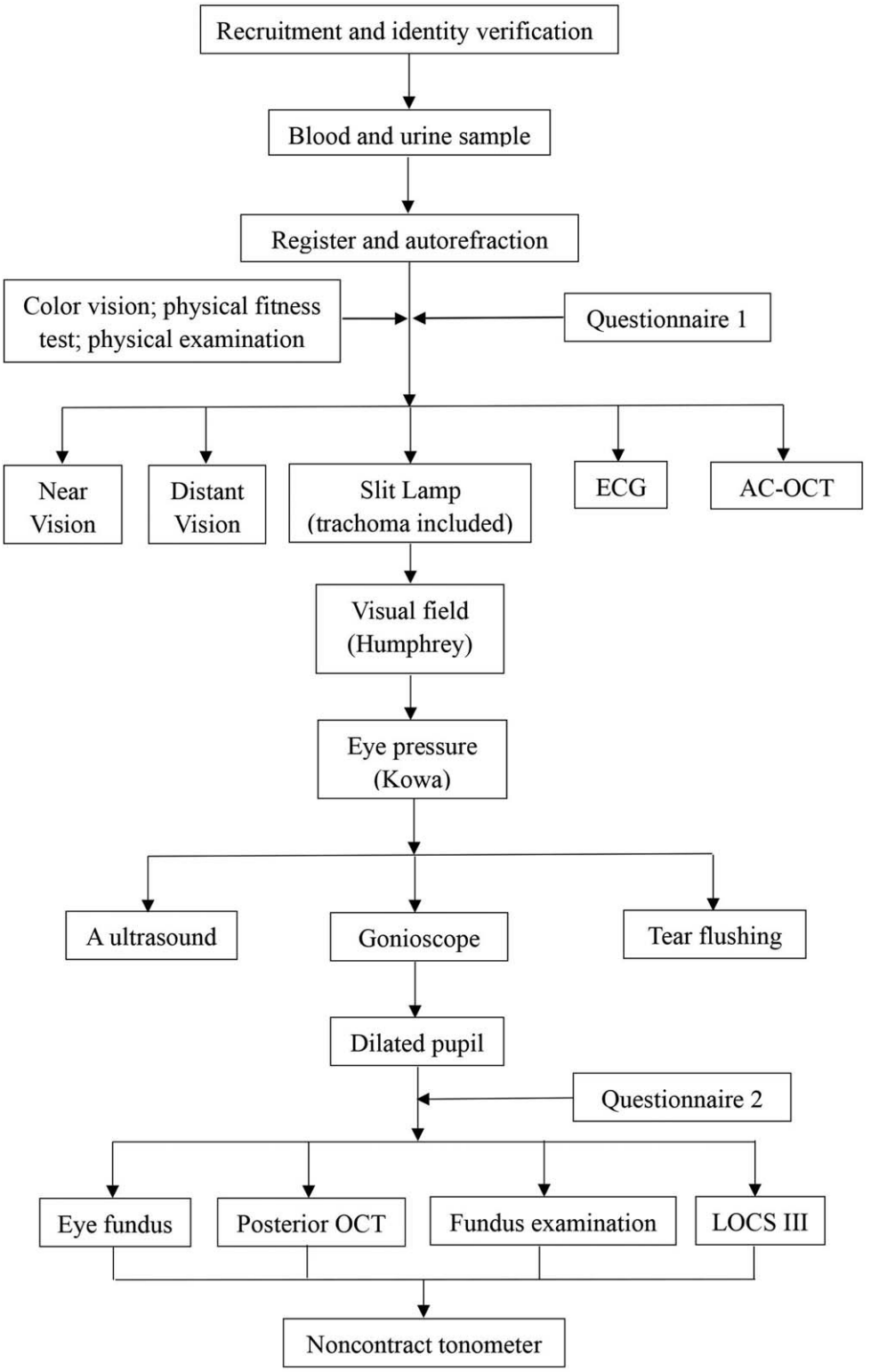

Figure 1: Flow chart of examination. ECG: electrocardiogram; OCT: optical coherence tomography; AC-OCT: anterior chamber optical coherence tomography; LOCS: lens opacities classification system.

Definitions of cataract

Cataract was defined based on the examination of slit lamp reference to standard grading photos. Lens opacities classification system (LOCS) III grade[23] was used as same as baseline study: nuclear opacity or nuclear color >4 or cortical opacity >2 or posterior subcapsular opacity >2 in at least one eye. If the opacity was worse in the follow-up, it would be considered as progression.

Definitions of AMD

AMD was defined as early and late stage. Macular-centered photographs were graded in both the baseline and the follow-up, following the definition used in the blue mountain eye study (BMES) for comparison. Early AMD was defined as absence of late AMD and presence of either: (1) large in distinct soft or reticular drusen, or (2) both large distinct soft drusen and retinal pigmentary abnormalities. If indistinct/reticular drusen or distinct soft drusen combined with retinal pigmentary abnormalities were presented, incident of early AMD would be considered in subjects without early or late AMD at baseline. Late AMD was defined as the presence of geographic atrophy (GA) or neurovascular AMD. If the neurovascular AMD or GA involved the macular area in either eye, incident of late AMD would be calculated in subjects without late AMD at baseline. Neovascular AMD was diagnosed if there was serous or hemorrhagic detachment of the retinal pigment epithelium or sensory retina, with the presence of sub-retinal or sub-RPE hemorrhages or sub-retinal fibrous scar tissue.

Definitions of refraction changes

Refraction changes would be calculated by subtracting the spherical equivalent error (SER) of the follow-up and the SER of the baseline. Emmetropia, myopia, and hyperopia were considered as SER (sphere +1/2 cylinder) of between −0.5 and 0.5 diopters (D), less than −0.5D and greater than +0.5D, respectively. A positive change was called a hyperopic shift, whereas a negative change was called myopic shift.[24] Myopic shift was defined as change in SER ≤−0.5D, and hyperopic shift as change in SER ≥0.5D.

Definitions of myopic maculopathy

Progression of myopic maculopathy would be defined under any of the following circumstances. (1) New signs of myopic maculopathy lesions showed up (diffuse chorioretinal atrophy, patchy chorioretinal atrophy, macular atrophy, lacquer cracks, and choroidal neovascularization. (2) Enlargement of the area of diffuse chorioretinal atrophy, patchy chorioretinal atrophy, and macular atrophy. (3) Increase in the number of lacquer cracks in participants who already had myopic maculopathy at baseline.

Definitions of DR

DR would be diagnosed among diabetes patients: diabetes mellitus (fasting plasma glucose ≥7.0 mmol/L) or medical history of diabetes. With five standard field photos, lesions would be graded based on the following criterias (No DR: levels 10 through 13. Any DR: levels 14 through 80. Minimal non-proliferative diabetic retinopathy (NPDR): levels 14–20. Mild-moderate NPDR: levels 31 to 41. Severe NPDR to proliferative retinopathy: levels 51–80). The progression of DR would be defined as one level grade to the further deterioration.

Definition of general diseases

Diagnosis of diabetes, high blood pressure and other general diseases was not made by ophthalmologists. These diagnoses were based on the patient's medical history (whether there was a doctor's diagnosis of hypertension or diabetes), as well as patients' drug using status (the patients were asked whether they used oral hypotension, hypoglycemic drugs, insulin, and so on). We also measured patients' blood pressure and blood glucose to help make confirmation. We believe that the data was credible and of high quality.

Statistical analysis

In this study, mean value and standard deviation, as well as median value and interquartile range (IQR), were used for basic statistical description for continuous data. Frequency and percentage were used to make basic statistical description for categorical data. Chi-square test was applied to make comparison on categorical data between groups, One-way analysis of variance (ANOVA) and Kruskal-Wallis test were applied to make comparison on continuous data, a *post-hoc* test was done. Inter-class correlation coefficients (ICCs) and Kappa coefficients were used to evaluate the consistency between different operators. Logistic regression was used to explore the influence factors of death, odds ratio (OR) and 95% confidence intervals (CIs) were used to estimate the effect size of each influence factor.

In the future analysis, age and gender standardized 6-year cumulative incidence rate would be calculated for ocular diseases. The relationship between risk factors of disease onset, progression, regression or disappearance, and 6-year death would be evaluated by risk ratios and 95% CIs. These would be calculated by fitting cox proportional hazard models, in multivariable analysis. Generalized estimating equation methods would be incorporated to allow for correlations between paired eyes. For continuous traits obeying normal distribution, *t*-tests, ANOVA, analysis of covariance, and linear regression models would be used. For continuous traits disobeying normal distribution, Wilcoxon rank-sum test, Kruskal-Wallis test, and mixed-effect model would be applied. In addition, both person-specific and eye-specific analyses would be conducted.

For the imbalanced data, synthetic minority over-sampling technique (SMOTE)[25] had been adopted in a published study.[26] The reason was that ocular diseases like myopic maculopathy usually had a very low incidence, there would be very few cases, leading to extremely large or small ORs, the results would not be robust. SMOTE algorithm used a statistical technique that build new cases from existing features rather than simply replicating existing cases, which could effectively balance data and avoid overfitting situation.[27]

The open-source statistical computing software R (Version 3.4.1) was used. The significant level was set to be 0.05.

Data management and quality control

Quality control procedures were implemented following the protocol of HES baseline. The clinicians and ophthalmologists were trained and certified for performing

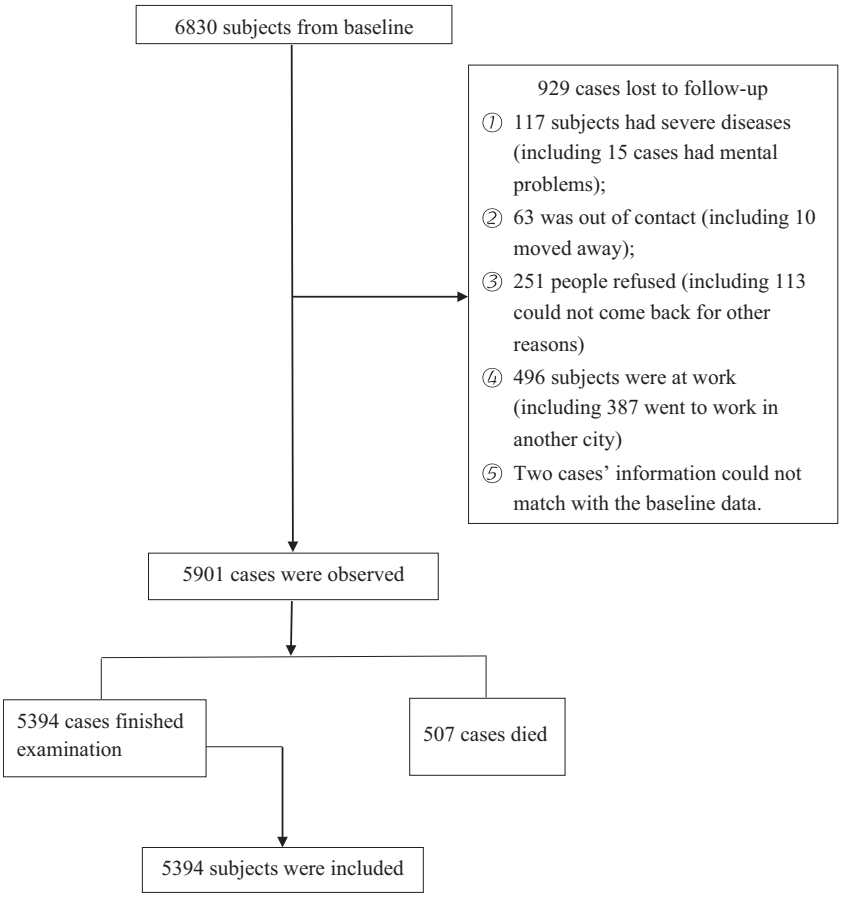

Figure 2: Flow chart of followed subjects screening.

visual acuity measurement, IOP measurement, LOCS III grading, cup-to-disc ratio estimation, and gonioscopy examination in pilot study.

Two clinicians examined the same subjects and results of 30 cases were recorded for each item to ensure the consistency of data measured by different operators. The consistency was assessed using ICC or Kappa coefficient according to data type through the pilot study and was reassessed at the intermediate stage of the study. In this study, the ICCs of quantitative measurements between different operators were all above 0.80, and the Kappa coefficients of categorical indicators (such as the diagnosis result of eye diseases) between different ophthalmologists were 0.69 or above, indicating a high consistency.

Data of the questionnaires, as well as data of the ocular examinations including color vision, physical fitness test, physical examination, near vision, distant vision, slit lamp, eye pressure, and LOCS III, was recorded on the clinical research form (CRF) first, and then was transformed into electronic database using the Epidata software. Subjects' autorefraction data would be printed automatically on thermo-sensitive paper and pasted to the CRF, also, autorefraction data would be typed into the Epidata database later on. Two staff finished the data entry job independently, and comparison between the two copies of data entry was done, if there were any inconformity of any variable of any subject, revision job would then be done according to the original paper material (the CRF) of this subject. The revision process would not be finished until the two databases were completely the same. As for urine and blood sample, the data would be generated automatically by the examination machine and exported to excel sheet. As for diagnosis of ocular diseases including glaucoma, age-related macular degeneration, and so on, the diagnosis of both eyes would be recorded in excel files directly by one researcher; meanwhile, another researcher monitored the recording process to make sure there was no mistake.

Subsequently, data from different sources would be merged together using statistical analysis system (SAS) software according to patients' ID, which was unique for each subject.

At last, there would be a data cleaning process done by a data manager, the outliers, the missing data, and logical mistakes would be checked. For example, age below 36 years would be considered as a logical error, because the inclusion criteria of HES baseline was 30 years old or above, thus 6 years later, at the follow-up period, all subjects should be 36 years or older. For logical errors, the revision job would be done carefully by tracing this subjects' all information, the outliers would be replaced with the upper limits or lower limits of this variable unless

the subject was diagnosed of some diseases, the missing data would be replaced using a multiple imputation statistical method.

Results

Reasons of loss to follow-up

Total 5394 subjects finished the follow-up (the follow-up group), 507 subjects died (the dead group) and 929 subjects were lost to follow-up (the loss to follow-up group), the follow-up rate (85.3%) of HES was calculated by excluding the dead group. Among the 929 subjects that were lost to follow-up, 117 (12.6%) had severe physical or mental diseases, 496 (53.4%) were at work, 251 (27.0%) refused to attend, 63 (6.8%) were out of contact, and two were documented with wrong information [Figure 2].

Assessment of loss to follow-up bias

Loss to follow-up bias could be reflected by the difference on measurements between the subjects followed-up and the subjects lost to follow-up, the more the difference was, the higher the risk of loss to follow-up bias would be. To explore whether a large bias would be caused by the subjects lost to follow-up, comparison among the three groups was done.

The average ages of the follow-up group, the loss to follow-up group and the dead group were 51.37 ± 11.07 years (IQR: 42–58), 50.21 ± 14.00 years (IQR: 38–59), and 66.52 ± 10.31 years (IQR: 59–74), respectively [Table 1], age of the dead group was the oldest ($Z = 651.293$, $P < 0.001$). Male accounted for 44.6%, 49.3%, and 59.0%, respectively of the follow-up group, the loss to follow-up group, and the dead group, male proportion of the dead group was significantly higher than the other two groups ($\chi^2 = 42.351$, $P < 0.001$). Those who finished middle school or above accounted for 85.5%, 84.8%, and 65.9%, respectively in the follow-up group, loss to follow-up group, and the dead group, the education level of the dead was the lowest ($\chi^2 = 205.354$, $P < 0.001$). Besides, marriage percentage of the dead group was 75.5%, while the percentages of the follow-up group and loss to follow-up group were 91.8% and 90.2%, there was no statistical difference between the loss to follow-up group and the follow-up group, but they were both statistically higher than that of the dead group. BMI of the dead group, follow-up group and the loss to follow-up group was 24.05 ± 4.07, 24.55 ± 3.61, and 24.40 ± 4.47 kg/m^2, respectively, BMI of the dead was the lowest ($Z = 18.789$, $P = 0.005$. There was no statistical difference on waist-to-hip ratio among three groups.

For hypertension history, diabetic history, heart disease history, and hyperlipidemia history, there was no statistical difference between the loss to follow-up group and the follow-up group. Yet for the dead group, the proportion of hypertension history, diabetic history, and heart disease history was statistically higher than that of the other two groups. 36.7% of the dead group had a hypertension history while the percentage was only 20.2% and 16.0% for the other two groups. 8.2% of the dead subjects had a diabetic history while the percentage was only 1.8% and 1.5% for the other two groups. 10.9% of the dead group reported the heart disease history while the percentage was only 5.2% and 4.8% for the other two groups.

Besides, there was no statistical difference on BCVA, IOP, central cornea thickness (CCT), and axial length (AL) between the follow-up group and the loss to follow-up group either. BCVA (logMAR unit) of the dead group was 0.37 ± 0.57, while it was 0.08 ± 0.28 and 0.12 ± 0.38 in the follow-up group and loss to follow-up group; BCVA of the dead group was the lowest. IOP of the dead group was statistically lower than that of the other two groups; the mean IOP of the dead group, the follow-up group, and the loss to the follow-up group was 14.36 ± 2.93, 15.04 ± 2.98, and 15.15 ± 2.95 mmHg, respectively. The average SER of the dead subjects, subjects followed-up and subjects lost to follow-up were 0.18 ± 0.63, 0.05 ± 1.71, and -0.17 ± 1.17 D, respectively. SER of the dead group was statistically higher than other two groups. SER of the loss to follow-up group was statistically lower than the other two groups.

There was no statistical difference in smoking history and drinking history between the loss to follow-up group and the follow-up group. 38.4% of the dead group had a smoking history, which was statistically higher than that of the follow-up group (31.2%) and the loss to follow-up group (34.1%).

The average total scores of MMSE of the dead group, loss to follow-up group and follow-up group were 19.04 ± 6.45, 21.28 ± 5.22, and 21.49 ± 5.58 points, respectively. The MMSE score of the dead group was statistically lower than that of the other two groups ($Z = 40.095$, $P < 0.001$). However, there was no statistical difference between the loss to follow-up group and the follow-up group. The average total scores of visual quality of the dead group, loss to follow-up, and follow-up group were 20.29 ± 4.73, 18.72 ± 2.80, and 18.63 ± 2.98 points, respectively. Visual quality score of the dead group was the highest ($Z = 96.432$, $P < 0.001$). And it was worth mentioning that the higher the visual quality score was, the worse the visual quality would be, meaning that the visual quality of the dead was the worst. However, there was no statistical difference between the loss to follow-up group and the follow-up group. The proportions of narrow-angle of the dead group, loss to follow-up, and follow-up group were 9.5%, 4.0%, and 6.0%, respectively. Proportion of narrow-angle of the dead group was higher than that of the other two groups ($\chi^2 = 6.798$, $P < 0.033$). However, there was no statistical difference between the loss to follow-up group and the follow-up group. There was no statistical difference in visual field testing among the three groups.

Given that the dead group was different from the other two groups in many aspects, multivariate analysis was further done to explore the influence factors of death, results of logistic regression [Table 2] showed that age (OR = 1.901, 95% CI: 1.074–1.108), gender (OR = 0.317, 95% CI: 0.224–0.448), and BCVA (OR = 0.282, 95% CI: 0.158–0.503) were associated with death.

Table 1: Comparison of baseline demographic characteristics, medical history, behavior, and ocular parameters among three groups.

Variables	Dead ($n = 507$)	Follow-up ($n = 5394$)	Loss to follow-up ($n = 929$)	Statistics	Values	*P*
Age (years)	66.52 ± 10.31†,‡	51.37 ± 11.07	50.21 ± 14.00*	Kruskal-Wallis	651.293	<0.001
Gender				CHISQ	42.351	<0.001
Male	299 (59.0)†,‡	2406 (44.6)	458 (49.3)*			
Female	208 (41.0)	2988 (55.4)	471 (50.7)			
Education				CHISQ	205.354	<0.001
Primary school or below	173 (34.1)	783 (14.5)	141 (15.2)			
Middle school and above	334 (65.9) †,‡	4611 (85.5)	788 (84.8)			
Marriage status				CHISQ	165.095	<0.001
Single/widow/divorced	124 (24.5)	440 (8.2)	91 (9.8)			
Married	383 (75.5)†,‡	4954 (91.8)	838 (90.2)			
BMI (kg/m^2)	24.05 ± 4.07†,‡	24.55 ± 3.61	24.40 ± 4.47*	Kruskal-Wallis	18.789	<0.001
Waist-to-hip ratio	0.91 ± 0.05	0.90 ± 0.08	0.90 ± 0.07	*F* test	1.818	0.162
SBP (mmHg)	151.87 ± 26.08†,‡	138.24 ± 21.83	134.45 ± 22.06*	Kruskal-Wallis	165.660	<0.001
Hypertension history				CHISQ	76.350	<0.001
No	260 (63.3)	4140 (79.8)	718 (84.0)			
Yes	151 (36.7)†,‡	1051 (20.2)	137 (16.0)*			
Diabetic history				CHISQ	75.639	<0.001
No	381 (91.8)	5063 (98.2)	845 (98.5)			
Yes	34 (8.2)†,‡	93 (1.8)	13 (1.5)			
Heart disease history				CHISQ	25.009	<0.001
No	360 (89.1)	4821 (94.8)	800 (95.2)			
Yes	44 (10.9)†,‡	263 (5.2)	40 (4.8)			
Hyperlipidemia history				CHISQ	1.775	0.412
No	367 (97.4)	4623 (97.6)	774 (98.4)			
Yes	10 (2.6)	112 (2.4)	13 (1.6)			
BCVA (logMAR)	0.37 ± 0.57†,‡	0.08 ± 0.28	0.12 ± 0.38	Kruskal-Wallis	460.983	<0.001
IOP (mmHg)	14.36 ± 2.93†,‡	15.04 ± 2.98	15.15 ± 2.95	*F* test	10.156	<0.001
SER (D)	0.18 ± 1.63‡	0.05 ± 1.71	−0.17 ± 1.17*	Kruskal-Wallis	48.356	<0.001
CCT (mm)	549.97 ± 34.02	547.72 ± 34.20	546.31 ± 39.71	*F* test	0.332	0.717
AL (mm)	22.78 ± 0.99	22.80 ± 0.86	22.88 ± 0.87	*F* test	2.745	0.064
Smoke history				CHISQ	11.570	0.003
Yes	164 (38.4)†,‡	1656 (31.2)	299 (34.1)			
No	263 (61.6)	3662 (68.8)	579 (65.9)			
Drink history				CHISQ	3.908	0.142
Yes	89 (20.9)	1129 (21.2)	212 (24.2)			
No	337 (79.1)	4188 (78.8)	666 (75.8)			
MMSE	19.04 ± 6.45†,‡	21.28 ± 5.22	21.49 ± 5.58	Kruskal-Wallis	40.095	<0.001
Visual quality	20.29 ± 4.73†,‡	18.72 ± 2.80	18.63 ± 2.98	Kruskal-Wallis	96.432	<0.001
Narrow angle				CHISQ	6.798	0.033
No	161 (90.5)	382 (96.0)	2235 (94.0)			
Yes	17 (9.5)†,‡	16 (4.0)	142 (6.0)			
Visual field OD				CHISQ	7.367	0.118
Abnormal	1 (3.3)	16 (23.6)	96 (18.7)			
Normal	18 (60.0)	26 (38.2)	213 (41.4)			
Uncertain	11 (36.7)	26 (38.2)	205 (39.9)			
Visual field OS				CHISQ	5.498	0.240
Abnormal	4 (13.3)	21 (31.8)	126 (24.6)			
Normal	13 (43.4)	26 (39.4)	237 (46.3)			
Uncertain	13 (43.3)	19 (28.8)	149 (29.1)			

All data were shown as mean ± SD or *n* (%). If *P* were below 0.05, then *post-hoc* test would be done. * Statistical difference between the loss to follow-up group and follow-up group. † Statistical difference between the dead and follow-up group. ‡ Statistical difference between the dead and loss to follow up group. BMI: Body mass index; SBP: Systolic blood pressure; BCVA: Best-corrected visual acuity; IOP: Intra-ocular pressure; SER: Spherical equivalent error; CCT: Central corneal thickness; AL: Axial length; MMSE: Mini-mental state examination; OD: Right eye; OS: Left eye. CHISQ: Chi-square test.

Table 2: Multivariate analysis of influence factors of death.

Variables	β	SE	*P*	OR (95% CI)
Age	0.087	0.008	<0.001	1.091 (1.074, 1.108)
Gender (male *vs*. female)	−0.574	0.088	<0.001	0.317 (0.224, 0.448)
Education	−0.049	0.069	0.479	0.953 (0.833, 1.090)
Marital status	0.100	0.059	0.090	1.105 (0.984, 1.241)
Smoking history	0.077	0.089	0.385	1.080 (0.908, 1.286)
Drinking history	0.033	0.091	0.721	1.033 (0.864, 1.236)
BMI	−0.011	0.018	0.539	0.989 (0.955, 1.024)
BCVA	−1.267	0.296	<0.001	0.282 (0.158, 0.503)
IOP	−0.014	0.020	0.469	0.986 (0.948, 1.025)
SER	0.057	0.030	0.058	1.059 (0.998, 1.123)

SE: Standard error; OR: Odds ratio; CI: Confidence interval; BMI: Body mass index; BCVA: Best-corrected visual acuity; IOP: Intra-ocular pressure; SER: Spherical equivalent error.

Table 3: Reliability and validity of the scales used in the follow-up of Handan Eye study.

Scale	Items	Cronbach coefficients	Cumulative variance
Life quality (EuroQol-5D scale)	8	0.63	0.69
Life quality (SF-8 scale)	8	0.90	0.72
NVR-QOL scale	12	0.64	0.61
Visual quality scale	15	0.79	0.66
MMSE	20	0.78	0.62

EuroQol-5D: General quality of life; SF-8: The 8-item short-form health survey; NVR-QOL: 12-Item quality of life related with near vision; MMSE: Mini-mental state examination.

Analysis of reliability and validity of questionnaires and scales

We assessed the reliability and validity of the scales used in the follow-up of HES, as shown in Table 3. The Cronbach coefficients of EuroQol-5D scale, SF-8 scale, NVR-QOL scale, visual quality scale, and MMSE scale were 0.63, 0.90, 0.64, 0.79, and 0.78, respectively. The cumulative variances of EuroQol-5D scale, SF-8 scale, NVR-QOL scale, visual quality scale, and MMSE scale were 0.69, 0.72, 0.61, 0.66, and 0.62, respectively. All Cronbach coefficients were 0.63 or above and all cumulative variances were 0.61 or above, indicating that these five scales used in HES were of good reliability and validity.

Analysis of consistency between different operators/ ophthalmologists

We also assessed the consistency of ocular parameters measurements by different operators and the consistency of diagnosis of main ocular diseases by different ophthalmologists, as shown in Table 4. Specifically, IOP measurement, visual acuity measurement, and subjective refraction measurement were done by more than two operators, thus there were more than one pair of ICCs for each ocular parameter. However, all ICCs were 0.80 or above. Besides, the diagnosis of main ocular diseases including glaucoma, AMD, and DR achieved good consistency between ophthalmologists too, the Kappa coefficients were 0.69 or above.

In conclusion, on almost every aspect, the dead group were statistically different from the loss to follow-up group and the follow-up group. However, between the loss to follow-up group and the follow-up group, there was only difference on age, gender, BMI, systolic blood pressure (SBP), and SER, we believed that there was a low-risk of large loss to follow-up bias. Besides, we believed that the data of HES was of good quality, which was qualified for subsequent studies.

Discussion

HES was an epidemiological cohort study for the rural Chinese population in northern China. It would provide data on the incidence and risk factors of blindness, low vision and major eye diseases. Various normative data for the rural Chinese adult population would also be obtained from this study.

Comparison among three groups on demographic information, medical history, anthropometric indicators, behaviors, and ocular parameters was done in this study. Difference between the subjects lost to follow-up and the subjects followed-up might cause bias to the study, sadly there was indeed difference in age, gender, BMI, SBP, and hypertension history. However, it was explainable because in our study there were 929 subjects lost to follow-up in total, among which 496 (53.4%) were at work. Obviously, younger and male villagers were more easily to find a physical job. As to BMI, although there was a statistical difference between the subjects followed-up and the subjects lost to follow-up, the difference between 24.55 and 24.40 kg/m^2 was quite small in clinic. A lower SBP and a lower proportion of hypertension history of the subjects

Table 4: The consistency of ocular parameters measurements by different operators and the consistency of diagnosis of main ocular diseases by different ophthalmologists.

Measurements	Statistics	Values
IOP	ICC	>0.85
Visual acuity	ICC	>0.80
Subjective refraction	ICC	>0.82
Diagnose of glaucoma	Kappa	0.80
Diagnose of AMD	Kappa	0.73
Diagnose of DR	Kappa	0.69

IOP: Intra-ocular pressure; AMD: Age related macular degeneration; DR: Diabetic retinopathy; ICC: Inter-class correlation coefficient.

lost to follow-up was also reasonable, after all, more than half of the subjects lost to follow-up went out for work, they tended to have a healthier body. SER was an important ocular parameter, and the reason why SER of the subjects lost to follow-up were statistically lower than that of the subjects followed-up was unclear.

In conclusion, for HES, a higher incidence of age-related ocular diseases like cataract, AMD, and so on would be calculated due to that there was a higher proportion of young people in the subjects lost to follow-up. However, since that there was no statistical difference in BCVA, IOP, CCT, and AL, which were very important ocular parameters, we believed there was a low-risk of loss to follow-up bias. Subsequently, HES would reveal the cumulative 6-year incidence, progression, risk factors of major ocular diseases and 6-year death risk of rural Chinese adults.

We admitted that there were some limitations of the HES follow-up. Firstly, the subjects were all aged 36 years or above, thus there would be no finding on young adults. Secondly, the gonioscope examination was not performed for all subjects, thus we could not distinguish angle-closure glaucoma and open angle-closure glaucoma. What's more, given that the sample size estimation was based on a prevalence of 2% of main ocular diseases,[15] for some low-prevalence or low-incidence ocular diseases such as macular retinoschisis and so on, the sample size was not enough to carry out a research. However, HES achieved a high follow-up rate, the questionnaires and scales were of good reliability and validity, measurements between different operators, as well as the diagnosis made by different ophthalmologists, were of good consistency, we believed that data of the scales and ocular examinations were of good quality.

Funding

This study was supported by the grants from the Ministry of Science and Technology of China (No. 2007CB512201), and from the Key Technologies R&D Program.

Conflicts of interest

None.

References

1. Jie R, Xu L, Wang YX, Zhang L, You QS, Yang H, *et al*. Ten-year incidence of retinal nerve fiber layer defects: the beijing eye study 2001/2011. Invest Ophthalmol Vis Sci 2015;56:5118–5124. doi: 10.1167/iovs.15-16682.
2. Wang L, Huang W, He M, Zheng Y, Huang S, Liu B, *et al*. Causes and five-year incidence of blindness and visual impairment in urban Southern China: the Liwan eye study. Invest Ophthalmol Vis Sci 2013;54:4117–4121. doi: 10.1167/iovs.13-11911.
3. Ye H, Zhang Q, Liu X, Cai X, Yu W, Yu S, *et al*. Prevalence of age-related macular degeneration in an elderly urban Chinese population in China: the Jiangning eye study. Invest Ophthalmol Vis Sci 2014;55:6374–6380. doi: 10.1167/iovs.14-14899.
4. Zhang Y, Li SZ, Li L, He MG, Thomas R, Wang NL, *et al*. Dynamic iris changes as a risk factor in primary angle closure disease. Invest Ophthalmol Vis Sci 2016;57:218–226. doi: 10.1167/iovs.15-17651.
5. Lin Z, Gao TY, Vasudevan B, Ciuffreda KJ, Liang YB, Jhanji V, *et al*. Near work, outdoor activity, and myopia in children in rural China: the Handan offspring myopia study. BMC Ophthalmol 2017;17:203. doi: 10.1186/s12886-017-0598-9.
6. Duan XR, Liang YB, Wang NL, Wong TY, Sun LP, Yang XH, *et al*. Prevalence and associations of cataract in a rural Chinese adult population: the Handan eye study. Graefes Arch Clin Exp Ophthalmol 2013;251:203–212. doi: 10.1007/s00417-012-2012-x.
7. Shen Z, Duan X, Wang F, Wang N, Peng Y, Liu DT, *et al*. Prevalence and risk factors of posterior vitreous detachment in a Chinese adult population: the Handan eye study. BMC Ophthalmol 2013;13:33. doi: 10.1186/1471-2415-13-33.
8. Yang K, Liang YB, Gao LQ, Peng Y, Shen R, Duan XR, *et al*. Prevalence of age-related macular degeneration in a rural Chinese population: the Handan eye study. Ophthalmology 2011;118:1395–1401. doi: 10.1016/j.ophtha.2010.12.030.
9. Wang FH, Liang YB, Zhang F, Wang JJ, Wei WB, Tao QS, *et al*. Prevalence of diabetic retinopathy in rural China: the Handan eye study. Ophthalmology 2009;116:461–467. doi: 10.1016/j.ophtha.2008.10.003.
10. Liang YB, Friedman DS, Zhou Q, Yang X, Sun LP, Guo LX, *et al*. Prevalence of primary open angle glaucoma in a rural adult Chinese population: the Handan eye study. Invest Ophthalmol Vis Sci 2011;52:8250–8257. doi: 10.1167/iovs.11-7472.
11. Gao J, Liang Y, Wang F, Shen R, Wong T, Peng Y, *et al*. Retinal vessels change in primary angle-closure glaucoma: the Handan eye study. Sci Rep 2015;5:9585. doi: 10.1038/srep09585.
12. Wang FH, Liang YB, Peng XY, Wang JJ, Zhang F, Wei WB, *et al*. Risk factors for diabetic retinopathy in a rural Chinese population with type 2 diabetes: the Handan eye study. Acta Ophthalmol 2011;89:e336–e343. doi: 10.1111/j.1755-3768.2010.02062.x.
13. Peng Y, Tao QS, Liang YB, Friedman DS, Yang XH, Jhanji V, *et al*. Eye care use among rural adults in China: the Handan eye study. Ophthalmic Epidemiol 2013;20:274–280. doi: 10.3109/09286586.2013.823216.
14. Liang YB, Friedman DS, Wong TY, Zhan SY, Sun LP, Wang JJ, *et al*. Prevalence and causes of low vision and blindness in a rural Chinese adult population: the Handan eye study. Ophthalmology 2008;115:1965–1972. doi: 10.1016/j.ophtha.2008.05.030.
15. Liang YB, Friedman DS, Wong TY, Wang FH, Duan XR, Yang XH, *et al*. Rationale, design, methodology, and baseline data of a population-based study in rural China: the Handan eye study. Ophthalmic Epidemiol 2009;16:115–127. doi: 10.1080/09286580902738159.
16. Xue J, Chiu H, Liang J, Zhu T, Jiang Y, Chen S. Validation of the six-item screener to screen for cognitive impairment in primary care settings in China. Aging Ment Health 2018;22:453–457. doi: 10.1080/13607863.2017.1280768.
17. Wu C, Gong Y, Wu J, Zhang S, Yin X, Dong X, *et al*. Chinese version of the EQ-5D preference weights: applicability in a Chinese general population. PLoS One 2016;11:e164334. doi: 10.1371/journal.pone.0164334.
18. Bost JE, Williams BA, Bottegal MT, Dang Q, Rubio DM. The 8-item short-form health survey and the physical comfort composite score of the quality of recovery 40-item scale provide the most responsive assessments of pain, physical function, and mental function during the first 4 days after ambulatory knee surgery with regional anesthesia. Anesth Analg 2007;105:1693–1700. doi: 10.1213/01.ane.0000287659.14893.65.

19. Lang L, Zhang L, Zhang P, Li Q, Bian J, Guo Y. Evaluating the reliability and validity of SF-8 with a large representative sample of urban Chinese. Health Qual Life Outcomes 2018;16:55. doi: 10.1186/s12955-018-0880-4.
20. Wang Y, Alnwisi S, Ke M. The impact of mild, moderate, and severe visual field loss in glaucoma on patients' quality of life measured via the Glaucoma Quality of Life-15 Questionnaire: a meta-analysis. Medicine (Baltimore) 2017;96:e8019. doi: 10.1097/MD.0000000000008019.
21. Liang YB, Wong TY, Sun LP, Tao QS, Wang JJ, Yang XH, *et al*. Refractive errors in a rural Chinese adult population the Handan eye study. Ophthalmology 2009;116:2119–2127. doi: 10.1016/j.ophtha.2009.04.040.
22. Troost A, Yun SH, Specht K, Krummenauer F, Schwenn O. Transpalpebral tonometry: reliability and comparison with Goldmann applanation tonometry and palpation in healthy volunteers. Br J Ophthalmol 2005;89:280–283. doi: 10.1136/bjo.2004.050211.
23. Chylack LJ, Wolfe JK, Singer DM, Leske MC, Bullimore MA, Bailey IL, *et al*. The lens opacities classification system III. The longitudinal study of cataract study group. Arch Ophthalmol 1993;111:831–836. doi: 10.1001/archopht.1993.01090060119035.
24. Gudmundsdottir E, Arnarsson A, Jonasson F. Five-year refractive changes in an adult population: Reykjavik Eye Study. Ophthalmology 2005;112:672–677. doi: 10.1016/j.ophtha.2004.11.039.
25. Nakamura M, Kajiwara Y, Otsuka A, Kimura H. LVQ-SMOTE – learning vector quantization based synthetic minority over-sampling technique for biomedical data. BioData Min 2013;6:16. doi: 10.1186/1756-0381-6-16.
26. Lin C, Li SM, Ohno-Matsui K, Wang BS, Fang YX, Cao K. Five-year incidence and progression of myopic maculopathy in a rural Chinese adult population: the Handan eye study. Ophthalmic Physiol Opt 2018;3:337–345. doi: 10.1111/opo.12456.
27. Blagus R, Lusa L. SMOTE for high-dimensional class-imbalanced data. BMC Bioinformatics 2013;22:106. doi: 10.1186/1471-2105-14-106.

How to cite this article: Cao K, Hao J, Zhang Y, Hu AL, Yang XH, Li SZ, Wang BS, Zhang Q, Hu JP, Lin CX, Yusufu M, Wang NL. Design, methodology, and preliminary results of the follow-up of a population-based cohort study in rural area of northern China: Handan Eye Study. Chin Med J 2019;132:2157–2167. doi: 10.1097/CM9.0000000000000418