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METHODOLOGICAL CONSIDERATIONS IN POPULATION-BASED STUDIES OF BLINDNESS AND LOW VISION

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ABSTRACT

In the past three decades, epidemiologic studies have made fundamental contributions to the understanding of the etiology , pathogenesis and management of age-related macular degeneration, diabetic retinopathy, glaucoma, retinal vessel occlusions, retinopathy of prematurity and cataract ; they have elucidated the role of a broad range of biological, social and economic risk factors in the development of sight-threatening complications ; they provided quantitative estimate of current practice outcomes , as well as the disparities in care and efficacy of new modalities in the prevention of blindness and visual impairment. This review summarized the key considerations in the selection of study design , the limitations of the most popular types and the innovative adjustments specific to the goals and social environment.

In the past three decades, epidemiologic studies have made fundamental contributions to the understanding of the etiology, pathogenesis and management of age-related macular degeneration, diabetic retinopathy, glaucoma, retinal vessel occlusions, retinopathy of prematurity and cataract; they have elucidated the role of a broad range of biological, social and economic risk factors in the development of sight-threatening complications; they provided quantitative estimate of current practice outcomes, as well as the disparities in care and efficacy of new modalities in the prevention of blindness and visual impairment. Among these have been population-based studies conducted in the United States among predominantly White (Framingham EyeStudy and Beaver Dam Eye Study), mixed White and African-American (Baltimore Eye Survey and SalisburyEye Evaluation Study), or Hispanic populations (ProyectoVER, Los Angeles Latino Eye Study), studies conductedin other countries, most notably Australia (BlueMountains Eye Study, Melbourne Visual ImpairmentProject), Europe (Rotterdam Eye Study, Copenhagen Eye Study), and the Caribbean (Barbados Eye Study). There are now a growing number of new population-based studies from Asia, including Taiwan (Shihpai Eye Study), Singapore (TanjongPagar Survey and Singapore Malay Eye Study), China(Beijing Eye Study), Japan (Hisayama study and Tajimi study) and India (Andhra Pradesh Eye Study and Aravind Comprehensive Eye Study) (1, 2, 3, 4, 5, 6) . The analysis of longitudinal data from blindness registries has provided a unique perspective of the dynamics in vision loss in Israel, Denmark, Germany and Australia (7, 8, 9, 10, 11). Behind the important findings of these diverse observational studies lay brilliant design, strict adherence to clinical and epidemiological methods of assessment and systematic control of data quality. This review summarized the key considerations in the selection of study design, the limitations of the most popular types and the innovative adjustments specific to the goals and social environment.

Cohort studies are often viewed as the gold standard in ophthalmic observational epidemiology as they allow for unrestricted choice of methods for clinical assessment and evaluation of the effect of genetics, non-ophthalmic comorbidity, social and

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environmental factors on development and progression of eye diseases, as well as psychometric tests measuring the deterioration in the quality of life .They have fundamental impact on the current concepts for the etiology and pathogenesis of key eye disorders. Studies in biracial and multiracial populations, such as the Baltimore Eye Study and the Singapore Eye study, have provided clear evidence of substantial racial/ethnic differences in the prevalence of major eye conditions, i.e. open-angle glaucoma in people of African origin (12, 13), exudative age-related macular degeneration (AMD) in White populations (14, 15, 16) and high myopia in Asian societies of Chinese, Japanese and Korean origin (17, 18). They have elucidated the role of environmental factors like exposure to ultraviolet light in the development of various types of cataract (19), and lifestyle determinants like cigarette smoking for AMD (16) and cataract (19).The importance of these surveys on the management of the leading ophthalmic pathology is profound. One of the landmark epidemiological studies, the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), first identified the importance of glycemic control and hypertension for diabetic retinopathy (20), and the Diabetic Retinopathy Study confirmed the efficacy of retinal photocoagulation in the prevention of vision loss from proliferative diabetic retinopathy. The implementation of the recommendations of Early Treatment for Retinopathy of Prematurity Study (23) has significantly reduced the prevalence of pediatric blindness in the industrialized societies. The Early Manifest Glaucoma Trial (24) demonstrated the efficacy of early intraocular pressure control within the target values in the prevention of glaucoma progression.

The long-term monitoring of the cohorts without significant loss of follow up require large groups of individuals settled at relatively confined areas, most often large cities like Rotterdam, Copenhagen and Singapore, usually within a specific age interval – premature neonates ,pre-school children or adults over 55 or 60 years. To compensate for the high mortality among the elderly participants, recruitment of three new cohorts was necessary both at Rotterdam and Copenhagen in order to complete the genomic evaluation. The comparisons in the course of the observation imply repetitive assessments using the same set of clinical tests as adopted at the start that by design have become stagnant and conceptually outdated while the survey is in progress. Successful cohort studies need large teams and substantial budget for long periods of time. A practical solution of the fiscal constraints is the inclusion of an ophthalmic module into the multidisciplinary evaluation of an already selected cohort, as in Copenhagen. The future cohort studies will have to describe the temporal patterns and changing incidence of major eye diseases (i.e. whether blindness has declined with earlier diagnosis and the introduction of new treatment modalities, or this has been counterbalanced by the increasing number of persons reaching older age) and new risk factors. Because epidemiological studies to determine gene-environment interactions for AMD or glaucoma are possible only with large samples, pooling data from multiple centers where the same methodologies and definitions has been used will be needed to achieve adequate statistical power(16).

As G. J. Johnson and A. Foster noted : “The only secure source of prevalence data (on visual impairment) are population-based cross-sectional surveys conducted according to strict criteria .”(25). This type of observational studies has been widely used for obtaining the point prevalence of blindness, visual function and major eye diseases among populations of all ages and geographic locations, as well as quantitative estimates of the efficacy of treatment and organization of ophthalmic care. Due the low prevalence of eye disorders and blindness these studies require large randomized samples distributed over the territory of interest. The contact with study participants is rather short which rules out lengthy interviews on the demographic, social and economic characteristics , time-consuming methods for instrumental assessment and clinical diagnosis, and extensive non-ophthalmic tests. These surveys typically necessitate more complex logistics, multidisciplinary teams, systematic control of data quality, and considerable budget. The majority are restricted to a specific age group – toddlers (26, 27), pre-schoolers (28), or adults over 50 or 60 years of age as in Australia and Oman (29, 30) , or by type of dwelling - urban (Baltimore, Barbados) or rural (China) populations (31). Often inclusion criterion is a predetermined level of visual acuity – below 0.1 or 0.05 (Oman and China). Some surveys are limited to evaluation for post-trachomatous

trichiasis , corneal opacities and cataract only as anterior segment examination is faster and more straightforward (Latin America,Nigeria, Pakistan) (32, 33, 34). The methods for rapid assessment of avoidable blindness (35) were developed for regions with difficult access, involved in armed conflicts or affected by humanitarian crisis – Rwanda, Kenya, Eritrea, Chiapas in Mexico, the Occupied Palestinian Territories. Even though the outcome lacks the precision of standard randomized sample studies, they provide a brief overview of the most urgent problems and needs of the population. A variety of sampling schemes have been utilized – simple randomized sampling – in Barbados and Roscommon Glaucoma Survey (36), and more often – cluster schemes with and without stratification. Usually a practical compromise is needed between the ideal design that yields unbiased prevalence estimates with the highest attainable statistical significance and the particular geographic features of the location, the cultural, socio-economic and demographic characteristics of the population at issue and available budget. Clusters are non-overlapping groups of individuals residing in city areas, villages, or household members, defined as blood relatives (Kuwait, 37) or sharing daily meals (Saudi Arabia, 38).One of the main reasons for adopting cluster sample design , as pointed by Tielsch J.M et al, is "…to minimize the distance between subjects' homes and our neighborhood screening centers and to enable the use of community leaders and the media to encourage participation."(13). These considerations are germane in the elimination of bias arising from non-response.

The system of data quality control has to be outlined during the planning stages of the survey. As specific components of the participants' evaluation are often delegated to other professionals in the team – socio-demographic interview – to social workers, visual acuity and refraction – to optometrists or ophthalmic assistants, primary eye evaluation – to ophthalmologists or trainees, individual instruction courses are held with each group, including methods of examination, classification of clinical signs and diagnoses, and documentation of findings. Instruments with automatic measurement and recording of refraction and intraocular pressure and contemporary fundus image analysis systems greatly reduce inaccuracy bias. Participants with conditions of interest with or without deteriorated vision are usually referred for further evaluation to the appropriate ophthalmic center and often final diagnoses are reached by consensus among the senior researchers. Recording of the findings into the database is usually associated with multitude of errors precluding reliable statistical analysis. Scrutiny of the contents of a randomized sample of the database files, usually 10% of the total sample, gives clear indications whether the information needs to be re-entered under stricter control.

In many countriesthe blind and partially sighted individuals eligible for practical and monetary social benefits register voluntarily in national and regional agencies. The records of these registers are based on the expert evaluation of the patients by qualified ophthalmologists, pertinent medical documents and instrumental tests that confirm the diagnosis and level of disability and usually are maintained for long periods of time. Thus the information collected at the registries has several valuable characteristics – low cost, high quality of the clinical examination and reliable diagnoses, availability for retrospection and consistent national criteria for legal blindness. Systematic analysis of the national and regional database reveals the trends in legal blindness by age groups and etiology over time thus demonstrating the impact of demographic changes in the population and the effects of ophthalmic care. There has been considerable interest towards blindness registries in Germany, Italy, UK, Ireland, Denmark, Israel and Australia resulting in numerous reviews (39, 40, 41, 42, 43, 44, 45, 46).These studies elucidated the sharp rise of blindness with age,the gradual increase of legal blindness incidence in aging populations and the key role of age-related macular degeneration, glaucoma, diabetic retinopathy and optic atrophy as leading causes. Ahead of other large-scale cross-sectional and cohort surveys these studies provided pivotal evidence for the efficacy of anti-VEGF agents in the treatment of exudative age-related macular degeneration and diabetic macular edema showing the decline of newly registered cases since 2006 – the year Avastin was introduced in mass practice. The registries are an important source of data on the magnitude and major causes of vision loss among children and adolescents - pigmentary retinitis in Kuwait, high myopia in Italy, perinatal and hereditary disorders in the UK ,

and outline number of affected children with treatable conditions like retinopathy of prematurity.

Incomplete registration of eligible individuals with blindness and low vision has always been a major obstacle for reliable statistical estimates – the female patients in the blindness register of Kuwait, for example, are twice less than the males (47, 48).Still, in countries with fuller registration of the blind, incidence rates derived from the registries' databases were used for prognosis of future needs of ophthalmic care on national level (49). Often the data on the social, ethnic and fiscal status of the registered persons are incomplete or lacking intentionally due to "political correctness" concerns which limits the evaluation of cardinal risk factors for avoidable blindness in multiethnic societies with educational and economic disparities. Non-ocular comorbidity is seldom described in detail hence it can hardly be of use in multifactorial analysis of blindness among these patients.

Practical steps in the statistical analysis of the data from the registries include appropriate selection of age intervals, computation of cumulative incidence rates instead of annual ones, and use of summary disorder classes for rare diseases.

Analysis of vision loss comparing the results from parallel observational studies and blindness registry database reviews - cohort and registry in Copenhagen, Denmark, cross-sectional random sample and registry in Kuwait, have significant advantages. They verify and corroborate their findings on the main causes, especially among the elder age groups and provide complementary data on the youngest ones, the unregistered and the individuals with visual acuity above, but close to the legal blindness levels.

Blindness is an unique and dynamic medico-social phenomenon. It will always attract the avid interest of the scientific community in its search for modifiable risk factors and potentially treatable conditions. An array of design concepts and practical solutions can be successfully applied and adapted to the specific environment and goals.

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