AMERICAN ACADEMY™ OF OPHTHALMOLOGY

Genetic and Dietary Factors Influencing the Progression of Nuclear Cataract

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Purpose: To determine the heritability of nuclear cataract progression and to explore prospectively the effect of dietary micronutrients on the progression of nuclear cataract.

Design: Prospective cohort study.

Participants: Cross-sectional nuclear cataract and dietary measurements were available for 2054 white female twins from the TwinsUK cohort. Follow-up cataract measurements were available for 324 of the twins (151 monozygotic and 173 dizygotic twins).

Methods: Nuclear cataract was measured using a quantitative measure of nuclear density obtained from digital Scheimpflug images. Dietary data were available from EPIC food frequency questionnaires. Heritability was modeled using maximum likelihood structural equation twin modeling. Association between nuclear cataract change and micronutrients was investigated using linear and multinomial regression analysis. The mean interval between baseline and follow-up examination was 9.4 years.

Main Outcome Measures: Nuclear cataract progression.

Results: The best-fitting model estimated that the heritability of nuclear cataract progression was 35% (95% confidence interval [CI], 13−54), and individual environmental factors explained the remaining 65% (95% CI, 46−87) of variance. Dietary vitamin C was protective against both nuclear cataract at baseline and nuclear cataract progression ($\beta = -0.0002$, $P = 0.01$ and $\beta = -0.001$, $P = 0.03$, respectively), whereas manganese and intake of micronutrient supplements were protective against nuclear cataract at baseline only ($\beta = -0.009$, $P = 0.03$ and $\beta = -0.03$, $P = 0.01$, respectively).

Conclusions: Genetic factors explained 35% of the variation in progression of nuclear cataract over a 10-year period. Environmental factors accounted for the remaining variance, and in particular, dietary vitamin C protected against cataract progression assessed approximately 10 years after baseline. *Ophthalmology 2016;123:1237-1244 © 2016 by the American Academy of Ophthalmology. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).*

Age-related cataract is the leading cause of blindness in the world, affecting approximately 20 million people, particularly in sub-Saharan Africa.[1] Its prevalence increases from 2.9% in the 43- to 54-year age group to 40% in those older than 75 years of age.[2] As the world's population ages, cataract will remain a serious healthcare and socioeconomic burden, in terms of both healthcare provision and blindness in less-developed countries.

Nuclear cataract is the most common form of age-related cataract.[2] Apart from age, other factors associated with nuclear cataract are smoking, oxidative stress, and dietary antioxidant intake.[3−5] However, studies of the effect of dietary vitamin C intake,[6−11] serum vitamin C concentrations,[6,9,11−13] and vitamin C supplementation[6,10,14] on nuclear cataract formation often have given conflicting results. Case-control studies[7,11,12,14] and some cohort studies[6,9,10] have found protective effects. Other prospective cohort studies have found no effect overall[8,13,15] or protective effects only in subgroups.[8,15] Similarly to vitamin C, dietary[6,16] and supplemental[14,17] vitamin E intake and vitamin E blood concentrations[6,13] have been shown to be related inversely with nuclear cataract. Randomized clinical trials of vitamins C and E supplementation alone or in combination with other vitamins failed to find an effect.[18,19] Vitamin A has been associated with a reduced risk of nuclear cataract,[9,20,21] as have lutein and zeaxanthin.[22−24] The studies exploring dietary nutrients and cataract progression have findings similar to those looking at prevalent cataract, with cohort studies finding a protective effect.[16,25] However, supplement trials largely have failed to find an effect.[18,26,27]

As opposed to vitamins and micronutrients,[28] the role of minerals in cataract formation in general and in nuclear cataract in particular is poorly studied. Together with epidemiologic factors, genetic factors also play a role in cataract formation. We previously reported that genetic factors explain 48% of cross-sectional variance in age-related nuclear cataract.[29] In a recent genome-wide meta-analysis, variants in 2 genes, *CRYAA* and *KCNAB1*, were found to be associated with nuclear cataract in Asian populations,[30] but no findings are available for populations of European origin. In comparison with epidemiologic factors, little is known about genetic susceptibility factors in age-related cataract.

http://dx.doi.org/10.1016/j.ophtha.2016.01.036
ISSN 0161-6420/16

Factors that lead to the development of a phenotype may be different from factors underlying change, such as progression of lens opacity. Therefore, we set out to establish the relative importance of genes on progression of nuclear cataract using a classic twin model with a highly quantitative measure of nuclear cataract. We also examined how intake of micronutrients and supplements associated with nuclear cataract at baseline affects nuclear cataract progression over a decade.

Methods

Subjects

Nuclear cataract data at baseline were available for 2515 white female twins (mean age, 62.3 years; range, 50.1−83.1 years) from the TwinsUK cohort, 2054 of whom had also completed a food frequency questionnaire (FFQ) around the time of their eye examination. The median time interval between an eye test taking place and a FFQ completion was 2 years. The 461 twins with cataract data but without FFQ data were 2.5 years younger on average and less affected by cataract. Cataract progression data were collected from 324 twins (151 monozygotic [MZ] and 173 dizygotic [DZ]) with a mean age at follow-up of 69.8±5.4 years (range, 58.3−83.6 years) as part of the Healthy Ageing in Twins (HATS) study between 2006 and 2010.[31] Individuals included in the follow-up were all part of our original cataract heritability study of 1012 twin participants assessed in 1998 and 1999.[29] The mean time between baseline and second visits was 9.4 years (range, 7−12 years). The smaller number of individuals with follow-up data is mainly due to the fact that the HATS study (in which the follow-up data were collected) was not designed specifically as a cataract follow-up study and had different selection criteria: Participants were aged more than 40 years and had to have previously attended clinical phenotyping irrespective of whether they had an eye examination or not (N = 4610) (Fig 1). The TwinsUK study started in 1992, but eye measures were performed only on subjects more than 50 years of age in 1998−1999, and subsequently from 2006. That meant that individuals (aged ≥50 years) who attended the HATS visit and who did not have eye examinations in 1989−1999 had their baseline cataract assessment during HATS (2006−2011; N = 1523). Reasons for having only longitudinal data for 324 of the original 1012 twins included death (N = 52), withdrawal of participation from the TwinsUK registry (N = 169), noncontactable (N = 30), refusal of further phenotyping (N = 82), cataract surgery (N = 11), and refusal of dilating drops or unavailability of ophthalmic testing at the HATS visit (N = 344).

Both the baseline study and the HATS study received local research ethics approval and were conducted according to the tenets of the Declaration of Helsinki. All the participants gave written informed consent.

Phenotyping

Nuclear Cataract Scores. Digital black and white lens photographs were taken using a Scheimpflug camera (Case 2000; Marcher Enterprises Ltd., Worcester, UK), and the same camera was used at both baseline and follow-up. Nuclear cataract was measured quantitatively by calculating the pixel density in the center of the lens nucleus, also known as the central nuclear dip score (NDS).[29] This score measures the amount of white scatter (opalescence), and more opacification results in higher pixel density. Because NDS uses black-and-white images, it does not assess the brunescence of the lens. Nuclear cataract progression was measured as the difference in measurements between the visits: ΔNDS = NDS at follow-up − NDS at baseline. Both NDS and ΔNDS were not normally distributed and therefore were transformed using natural logarithm before the analysis.

Nutrient Intake. Intake of micronutrients (vitamins and minerals) and supplements was estimated using the EPIC FFQ, which was self-administered at the baseline visit. This questionnaire explored the average frequency of intake of 131 foods and supplements over a 1-year period.[32,33] Nutrient intake was calculated using an established nutrient database, and the dietary variables were adjusted for calorie intake, yielding an energy-adjusted mg/μg of each nutrient per person per day.[32,34,35] We considered the following micronutrients in the analysis: sodium, potassium, calcium, magnesium, phosphorus, iron,

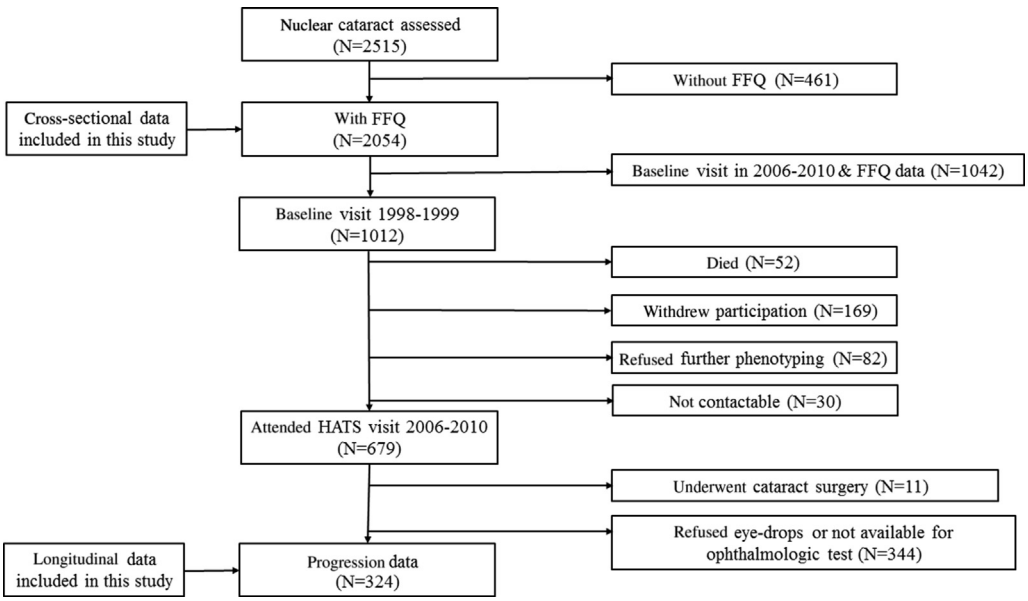

Figure 1. Consort diagram of the study showing the number of individuals who participated in the different parts of the study and reasons for no participation at follow-up. FFQ = food frequency questionnaire; HATS = Healthy Ageing in Twins.