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 (β = −0.0002, P = 0.01 and β = −0.001, P = 0.03, respectively), whereas manganese and intake of micronutrient supplements were protective against nuclear cataract at baseline only (β = −0.009, P = 0.03 and β = −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.

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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 supplementation6,10,14 on nuclear cataract formation often have given conflicting results. Case-control studies7,11,12,14 and some cohort studies6,9,10 have found protective effects. Other prospective cohort studies have found no effect overall8,13,15 or protective effects only in subgroups.8,15 Similarly to vitamin C, dietary6,9,11 and supplemental6,14,17 vitamin E intake and vitamin E blood concentrations6,13 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,7,20,21 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.
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), non-contactable (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: \( \Delta \text{NDS} = \text{NDS at follow-up} - \text{NDS at baseline} \). Both NDS and \( \Delta \text{NDS} \) 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/jg of each nutrient per person per day.32,34,35 We considered the following micronutrients in the analysis: sodium, potassium, calcium, magnesium, phosphorus, iron,
had nuclear cataract measured at follow-up. Baseline characteristics and nutrient and supplement intake are shown in Table 1, and an example of a lens image is available in Figure 2. The twins with follow-up data were on average 1.1 years younger at baseline (60.4 vs. 61.5 years) and, given their younger age, had less cataract (mean NDS scores of 55.3 and 60.4, respectively) compared with those with only cross-sectional data. In both cases, these differences were not statistically significant (P > 0.05). The MZ and DZ twins with follow-up data were similar in terms of age and NDS scores (P > 0.05). The MZ and DZ twins with cross-sectional data only were similar in terms of age, but the MZ twins had a slightly higher NDS score (61.6 vs. 59.3; P = 0.02).

There were also no statistically significant differences between groups in terms of micronutrient intake except for iron (P = 0.02), thiamine (P = 0.04), and biotin (P = 0.01). The twins with follow-up data had slightly lower iron and thiamine intake (mean of 12.6 and 1.7 mg, respectively) and slightly higher biotin intake (mean of 49.7 mg) compared with individuals without follow-up data. There were also no significant differences in supplement intake between the 2 groups (P > 0.05). There were no statistically significant differences between MZ and DZ twins in terms of nutrient or supplement intake (P > 0.05).

As expected, nuclear cataract scores progressed in all participants (Fig 3). The mean baseline central NDS was 55.1±11 (range, 32–99) with the score increasing by an average of 19.9±16.9 (range, 1–137) over the period of follow-up. The heritability analysis, conducted on 155 twin pairs (72 MZ and 83 DZ pairs), showed that the best-fitting model was one explained by additive genetic factors and the unique (individual) environment, with no significant effect of a common environment or nonadditive genetic factors. Calculations estimated the heritability to be 0.35, meaning that genetic factors explained 35% of variance (95% confidence interval [CI], 13–54) in progression of nuclear cataract, with individual environmental factors accounting for the remaining 65% (95% CI, 46–87).

To test associations between micronutrient intake and cataract progression, we used univariable regression (Table 2) followed by stepwise regression in 2054 female twins who had baseline data on nutrient intake. Seven micronutrients showed a significant association (P < 0.05) with NDS and were used in multivariable analysis: potassium, magnesium, manganese, phosphorus, vitamins C and E, and folate. After stepwise multivariable regression, 2 factors remained significantly associated with NDS at baseline: vitamin C (β = −0.0002; standard deviation [SD] = 6.3E-05; P = 0.01) and manganese (β = −0.009; SD = 0.04; P = 0.03). From these 2 nutrients, only vitamin C showed association with cataract progression (β = −0.001; SD = 0.001; P = 0.03). A sensitivity analysis excluding subjects with greatest progression (>100 units of change) did not alter the result. Comparing people in the highest and lowest tertiles of vitamin C intake was associated with a 19% risk reduction at baseline (RRR, 0.81; 95% CI, 0.68–0.96) and a 33% risk reduction of cataract progression (RRR, 0.66; 95% CI, 0.47–0.91) (Table 3). Manganese intake was associated with 20% risk reduction (RRR, 0.80; 95% CI, 0.67–0.95) at baseline (Table 3).

Two supplement groups, micronutrient supplements and minerals only, showed a significant association with NDS (P < 0.05) (Table 2), but only micronutrient supplements stayed significant in the multivariate model (β = −0.03; SD = 0.01; P = 0.01), and their intake led to an 18% risk reduction in people within the highest compared with the lowest tertile of nutrient intake (RRR, 0.82; 95% CI, 0.57–1.20) (Table 3). We found no statistically significant association between taking micronutrients in supplemental form and progression of nuclear cataract.
Discussion

This study found that progression of nuclear cataract over a 10-year period in a group of UK female twins is influenced by genetic factors that explain 35% of variance. The heritability estimate of cataract progression is lower than our previous cross-sectional estimates of susceptibility to development of nuclear cataract in this cohort, and it is also lower than the heritability estimated in the 324 individuals estimated from the nuclear score measurement at follow-up (61%; 95% CI, 45–72). This is consistent with previous studies showing that heritability generally is lower when examining change, compared with cross-sectional studies. In addition to early developmental differences and the body’s response to environmental factors in adulthood, environmentally driven processes or accumulated “errors” (e.g., somatic gene mutation and epigenetic remodeling) might play a greater role in determining change during aging than genetic factors.

This study also identified vitamin C as a micronutrient affecting nuclear cataract progression. We also replicate the previously found association between cross-sectional cataract and vitamin C intake. Vitamin C intake has long been studied in relation to age-related cataract because it is the L-ascorbate is present in the aqueous humor that bathes the eye. The many studies of the effects of ascorbate on cataract progression have used supplements, generally in combination (e.g., vitamin C only, vitamin D only, iron only, and ACD complex). The results are mixed; e.g., in one study, the data were consistent with the null hypothesis, and in another, there was a significant association. The conclusions of such studies are inconsistent and often conflicting.

Many of these have studied relatively well-nourished populations and are cross-sectional, although cross-sectional studies in India, where overall antioxidant levels may be lower, have found an inverse relationship between vitamin...
C and cataract. Our results are similar to those of the Carotenoids in Age-Related Eye Disease Study that showed vitamin C intake, assessed with an FFQ 10 years before cataract assessment, to be protective of nuclear cataract prevalence. The Blue Mountains Eye Study also found that vitamin C intake, through both diet and supplements together, resulted in a lower nuclear cataract incidence over 10 years. This study is the first, to our knowledge, to show that dietary vitamin C intake protects against progression of nuclear lens opacity.

We also found dietary manganese to be protective against cross-sectional nuclear cataract independent of vitamin C. We cannot exclude that this association was a type I error, given we did not find an association between dietary manganese and nuclear cataract progression and the lack of a dose response (Table 3), although factors associated with incidence and progression do not always overlap. Manganese is an important antioxidant present in the human lens, and its concentration has been reported to be lower in cataractous lenses in comparison with normal lenses. This study was not designed to elucidate the cause–effect relationship underlying the associations we found; therefore, we cannot distinguish whether manganese depletion is a cause or effect of cataractogenesis. Further studies are needed to answer this question. We also detected an association between supplemental intake of micronutrients and cross-sectional nuclear cataract but not between supplemental nutrients and cataract progression. These results are similar to those reported in the Blue Mountains Eye Study. Because only 10% or less of the participants in our study took any single supplement, we had to group supplements together; therefore, we could not draw conclusions on the effect of any single supplement or of components of supplements (e.g., supplemental vitamin C).

We used a highly quantitative measure of cataract from digital images (NDS), which essentially measures the nuclear opalescence (or “white scatter”) of the lens. The measure also was highly reproducible: the intraclass correlation coefficient for the worse eye in 30 subjects from our original study who came for repeat measurements was 0.93. The fact that every subject measured showed progression suggests that NDS is sensitive to change. Many epidemiologic studies have used the Lens Opacity Classification System (LOCS) grading scale, comparing phenotype with standardized photographs of 6 stages of lens opacification, which includes both nuclear opalescence and nuclear color or brunescence. The LOCS III
Table 2. Results from Univariable Regression Models

| Micronutrients | Beta  | Standard Error | P Value |
|----------------|-------|----------------|---------|
| Sodium (mg)    | 5.41E-06 | 9.58E-06      | 0.56    |
| Potassium (mg)*| -1.58E-05 | 7.54E-06      | 0.04    |
| Calcium (mg)   | -1.95E-05 | 1.52E-05      | 0.20    |
| Magnesium (mg)*| -0.010    | 0.004         | 0.01    |
| Phosphorus (mg)*| -4.01E-05 | 1.94E-05      | 0.04    |
| Iron (mg)      | -1.15E-04 | 0.002         | 0.95    |
| Copper (mg)    | 0.001    | 0.008         | 0.86    |
| Zinc (mg)      | -7.76E-04 | 0.003         | 0.77    |
| Chloride (mg)  | 3.79E-06  | 6.10E-06      | 0.53    |
| Manganese (mg)*| -0.010    | 0.004         | 0.01    |
| Iodine (mg)    | -1.10E-04 | 6.07E-05      | 0.07    |
| Retinol (µg)   | 2.36E-06  | 3.90E-06      | 0.55    |
| Carotene (µg)  | -1.67E-06 | 1.40E-06      | 0.23    |
| Vitamin D (µg) | -0.004    | 0.003         | 0.22    |
| Vitamin E (mg)*| -0.003    | 0.001         | 0.04    |
| Thiamine (mg)  | -0.013    | 0.013         | 0.31    |
| Riboflavin (mg)| -0.011    | 0.006         | 0.08    |
| Niacin (mg)    | -1.10E-04 | 8.26E-04      | 0.89    |
| Tryptophan (mg)| -0.001    | 0.001         | 0.27    |
| Vitamin B6 (mg)| -0.002    | 0.009         | 0.81    |
| Vitamin B12 (µg)| -0.001    | 0.001         | 0.50    |
| Folate (µg)*   | -9.91E-05 | 4.06E-05      | 0.02    |
| Pantothenate (mg)| -2.81E-05 | 1.87E-04      | 0.88    |
| Biotin (mg)    | -3.01E-04 | 4.17E-04      | 0.47    |
| Vitamin C (mg)*| -1.74E-04 | 6.19E-05      | 0.01    |

Supplement Groups

- Any supplement: -0.015, 0.029, 0.12
- Micronutrients*: -0.032, 0.013, 0.01
- Micronutrients excluding multivitamins: -0.023, 0.012, 0.06
- Minerals only*: -0.038, 0.016, 0.02
- Any other supplement: 0.005, 0.014, 0.72

The results of the unvariable linear regression analysis between nuclear cataract (natural logarithm-transformed NDS) and energy-adjusted micronutrient intakes and between nuclear cataract and supplement intake per supplement group are shown.

Denotes statistically significant associations at P < 0.05.

Denotes that in the case of supplement groups, supplement intake was coded binary (presence vs. absence of intake of at least 1 of the components in the group). All analyses were adjusted for age and family structure.

Table 3. Results of Multinomial Regression Analysis for Factors Associated with Cross-Sectional Nuclear Cataract and Nuclear Cataract Progression

| Cross-Sectional Results | Progression Results |
|-------------------------|---------------------|
| NDS Tertiles            | Vitamin C RRR 95% CI P Value | Vitamin C RRR 95% CI P Value |
| 34.5–53.2 reference     | 34.5–53.2 reference   |
| 53.3–54.5                | 53.3–54.5             |
| 54.6–229.2               | 54.6–229.2             |
| Manganese RRR 95% CI P Value | Vitamin C RRR 95% CI P Value |
| 1.02                     | 1.02                  |
| 0.96                     | 0.96                  |
| 0.95                     | 0.95                  |

ΔNDS Tertiles 1.0–12.6 12.7–19.3 19.4–137.1

CI = confidence interval; NDS = nuclear dip score; ΔNDS = NDS at follow-up − NDS at baseline; RRR = relative risk ratio.

The results from the multinomial regression analysis for factors associated with cross-sectional (vitamin C and manganese) and progression (vitamin C) are shown. The RRR with its 95% CIs for each tertile of NDS or progression (ΔNDS) is reported. The minimum and maximum NDS score per tertile are reported.

Significantly differ from the UK general population. Twin studies use the “equal environment assumption” that the degree of shared family environment is the same for both MZ and DZ twin pairs. This is generally found to be true, although there are few studies of elderly subjects that explore this assumption. In addition, the TwinsUK cohort is predominantly a female cohort, and we could not assess any gender differences in risk factors. The findings of this study can be generalizable only to Caucasian women of similar age because they reflect cataract progression in a group of white British women between, on average, the ages of 60 and 70 years, and so may not reflect other population groups or age ranges. In this article, we explored the effect of all micronutrients on nuclear cataract formation; however, we had no data on carotenoid (lutein and zeaxanthin) intake. We also lacked power to explore the effects of smoking on cataract progression because 85% of participants have never smoked.

Those participants with follow-up data collected were seen as part of the HATS study, which was not designed as a cataract follow-up study. This meant that the number of subjects decreased to 324 individuals, thus reducing the amount of data we could analyze and our power. The individuals who were lost to follow-up in HATS were in the group. All analyses were adjusted for age and family structure. The re-subjects decreased to 324 individuals, thus reducing the amount of data we could analyze and our power. The individuals who were lost to follow-up in HATS were in the group. All analyses were adjusted for age and family structure. The re-subjects decreased to 324 individuals, thus reducing the amount of data we could analyze and our power. The individuals who were lost to follow-up in HATS were in the group. All analyses were adjusted for age and family structure.

Study Limitations

A potential limitation is that our cohort is based on twin volunteers rather than a population study, but they are unselected and from across the United Kingdom and are unlikely to have reproducibility. Longitudinal studies using the LOC III scale show relatively little change: In the Longitudinal Study of Cataract, only 24% of participants had an increase in the degree of nuclear opalescence graded digitally or using a slit lamp. Digital image–derived NDSs using pixel density counts may be better suited for measuring progression and allowed our study the power to detect associations with a relatively small sample size.

CI = confidence interval; NDS = nuclear dip score; ΔNDS = NDS at follow-up − NDS at baseline; RRR = relative risk ratio.

The results from the multinomial regression analysis for factors associated with cross-sectional (vitamin C and manganese) and progression (vitamin C) are shown. The RRR with its 95% CIs for each tertile of NDS or progression (ΔNDS) is reported. The minimum and maximum NDS score per tertile are reported.
original cohort, but in general they were not significantly different in other respects or in nutrient or supplement intake, hopefully reducing potential selection bias in the progression data. As in any observational study, ours is potentially susceptible to residual confounding, missing data, or misspecification of variables.

In summary, this study has shown that progression of nuclear cataract over a 10-year period is influenced by genetic factors with a heritability of 35%. Dietary vitamin C and manganese, both factors related to oxidative stress, seem to influence cross-sectional nuclear cataract, and vitamin C intake also significantly influences nuclear cataract progression.

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References

1. Pascolini D, Mariotti SPM. Global estimates of visual impairment. 2010. Br J Ophthalmol 2012;96:614–8.
2. Klein BE, Klein R, Lee KE. Incidence of age-related cataract: the Beaver Dam Eye Study. Arch Ophthalmol 1998;116:219–25.
3. Kelly SP, Thornton J, Edwards R, et al. Smoking and cataract: review of causal association. J Cataract Refract Surg 2005;31:2395–404.
4. Truscott RJ. Age-related nuclear cataract–oxidation is the key. Exp Eye Res 2005;80:709–25.
5. Chiu CJ, Taylor A. Nutritional antioxidants and age-related cataract and maculopathy. Exp Eye Res 2007;84:229–45.
6. Jacques PF, Chylack LT Jr, Hankinson SE, et al. Long-term nutrient intake and early age-related nuclear lens opacities. Arch Ophthalmol 2001;119:1009–19.
7. Leske MC, Chylack LT Jr, Wu SY. The Lens Opacities Case-Control Study. Risk factors for cataract. Arch Ophthalmol 1991;109:244–51.
8. Lyle BJ, Mares-Perlman JA, Klein BE, et al. Antioxidant intake and risk of incident age-related nuclear cataracts in the Beaver Dam Eye Study. Am J Epidemiol 1999;149:801–9.
9. Ravindran RD, Vashist P, Gupta SK, et al. Inverse association of vitamin C with cataract in older people in India. Ophthalmology 2005;112:1439–52.
10. Tan AG, Mitchell P, Flood VM, et al. Antioxidant nutrient intake and the long-term incidence of age-related cataract: the Blue Mountains Eye Study. Am J Clin Nutr 2008;87:1899–905.
11. Valero MP, Fletcher AE, De Stavola BL, et al. Vitamin C is associated with reduced risk of cataract in a Mediterranean population. J Nutr 2002;132:1299–306.
12. Ferrigno L, Aldigeri R, Rosmini F, et al. Associations between plasma levels of vitamins and cataract in the Italian-American Clinical Trial of Nutritional Supplements and Age-Related Cataract (CTNS): CTNS Report #2. Ophthalmic Epidemiol 2005;12:71–80.
13. Vitale S, West S, Hallfrisch J, et al. Plasma antioxidants and risk of cortical and nuclear cataract. Epidemiology 1993;4:195–203.
14. Robertson JM, Donner AP, Trevithick JR. A possible role for vitamins C and E in cataract prevention. Am J Clin Nutr 1991;53(1 Suppl):546S–51S.
15. Mares JA, Voland R, Adler R, et al. Healthy diets and the subsequent prevalence of nuclear cataract in women. Arch Ophthalmol 2010;128:738–49.
16. Jacques PF, Taylor A, Moeller S, et al. Long-term nutrient intake and 5-year change in nuclear lens opacities. Arch Ophthalmol 2005;123:517–26.
17. Chasan-Taber L, Willett WC, Seddon JM, et al. A prospective study of vitamin supplement intake and cataract extraction among U.S. women. Epidemiology 1999;10:679–84.
18. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9. Arch Ophthalmol 2001;119:1439–52.
19. Christen WG, Glynn RJ, Sesso HD, et al. Age-related cataract in a randomized trial of vitamins E and C in men. Arch Ophthalmol 2010;128:1397–405.
20. Dherani M, Murthy GV, Gupta SK, et al. Blood levels of vitamin C, carotenoids and retinol are inversely associated with cataract in a North Indian population. Invest Ophthalmol Vis Sci 2008;49:3328–35.
21. Cumming RG, Mitchell P, Smith W. Diet and cataract: the Blue Mountains Eye Study. Ophthalmology 2000;107:450–6.
22. Delcourt C, Carriere I, Delage M, et al. Plasma lutein and zeaxanthin and other carotenoids as modifiable risk factors for age-related maculopathy and cataract: the POLA Study. Invest Ophthalmol Vis Sci 2006;47:2329–35.
23. Karppi J, Laukkanen JA, Kuri S. Plasma lutein and zeaxanthin and the risk of age-related nuclear cataract among the elderly Finnish population. Br J Nutr 2012;108:148–54.
24. Liu XH, Yu RB, Liu R, et al. Association between lutein and zeaxanthin status and the risk of cataract: a meta-analysis. Nutrients 2014;6:452–65.
25. Leske MC, Chylack LT Jr, He Q, et al. Antioxidant vitamins and nuclear opacities: the longitudinal study of cataract. Ophthalmology 1998;105:831–6.
26. Gritz DC, Srinivasan M, Smith SD, et al. The Antioxidants in Prevention of Cataracts Study: effects of antioxidant supplements on cataract progression in South India. Br J Ophthalmol 2006;90:847–51.
27. Mathew MC, Ervin AM, Tao J, Davis RM. Antioxidant vitamin supplementation for preventing and slowing the progression of age-related cataract. Cochrane Database Syst Rev 2012;6:CD004567.
28. Weikel KA, Garber C, Baburans A, Taylor A. Nutritional modulation of cataract. Nutr Rev 2014;72:30–47.
29. Hammond CJ, Snieder H, Spector TD, Gilbert CE. Genetic and environmental factors in age-related nuclear cataracts in monozigotic and dizygotic twins. N Engl J Med 2000;342:1786–90.
30. Liao J, Su X, Chen P, et al. Meta-analysis of genome-wide association studies in multiethnic Asians identifies two loci for age-related nuclear cataract. Hum Mol Genet 2014;23:6119–28.
31. Moayyeri A, Hammond CJ, Valdes AM, Spector TD. Cohort Profile: TwinsUK and healthy ageing twin study. Int J Epidemiol 2013;42:76–85.
32. Teucher B, Skinner J, Skidmore PM, et al. Dietary patterns and heritability of food choice in a UK female twin cohort. Twin Res Hum Genet 2007;10:734–48.
33. Bingham SA, Welch AA, McTaggart A, et al. Nutritional methods in the European Prospective Investigation of Cancer in Norfolk. Public Health Nutr 2001;4:847–58.
34. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. Am J Epidemiol 1986;124:17–27.
35. McCance RA, Holland B, Widdowson EM, et al. McCance and Widdowson’s The Composition of Foods. 5th revision and extended edition. Cambridge, UK: Royal Society of Chemistry; 1991:xiii, 462.
36. Christensen K, Gaist D, Vaupel JW, McGue M. Genetic contribution to rate of change in functional abilities among...
Danish twins aged 75 years or more. Am J Epidemiol 2002;155:132–9.

37. Gottlieb DJ, Wilk JB, Harmon M, et al. Heritability of longitudinal change in lung function. The Framingham study. Am J Respir Crit Care Med 2001;164:1655–9.

38. Steves CJ, Jackson SH, Spector TD. Cognitive change in older women using a computerised battery: a longitudinal quantitative genetic twin study. Behav Genet 2013;43:468–79.

39. Beebe DC, Holekamp NM, Shui YB. Oxidative damage and the prevention of age-related cataracts. Ophthalmic Res 2010;44:155–65.

40. Shui YB, Holekamp NM, Kramer BC, et al. The gel state of the vitreous and ascorbate-dependent oxygen consumption: relationship to the etiology of nuclear cataracts. Arch Ophthalmol 2009;127:475–82.

41. Reddy VN, Kasahara E, Hiraoka M, et al. Effects of variation in superoxide dismutases (SOD) on oxidative stress and apoptosis in lens epithelium. Exp Eye Res 2004;79:859–68.

42. Tarwadi K, Agte V. Linkages of antioxidant, micronutrient, and socioeconomic status with the degree of oxidative stress and lens opacity in Indian cataract patients. Nutrition 2004;20:261–7.

43. Cekic O, Bardak Y, Totan Y, et al. Nickel, chromium, manganese, iron and aluminum levels in human cataractous and normal lenses. Ophthalmic Res 1999;31:332–6.

44. Racz P, Ordogh M. Investigations on trace elements in normal and senile cataractous lenses. Activation analysis of copper, zinc, manganese, cobalt, rubidium, scandium, and nickel. Albrecht Von Graefes Arch Klin Exp Ophthalmol 1977;204:67–72.

45. Kuzniarz M, Mitchell P, Cumming RG, Flood VM. Use of vitamin supplements and cataract: the Blue Mountains Eye Study. Am J Ophthalmol 2001;132:19–26.

46. Chylack LT Jr, Wolfe JK, Singer DM, et al. The Lens Opacities Classification System III. The Longitudinal Study of Cataract Study Group. Arch Ophthalmol 1993;111:831–6.

47. Andrew T, Hart DJ, Snieder H, et al. Are twins and singletons comparable? A study of disease-related and lifestyle characteristics in adult women. Twin Res 2001;4:464–77.

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Abbreviations and Acronyms:
CI = confidence interval; DZ = dizygotic; FFQ = food frequency questionnaire; HATS = Healthy Ageing in Twins; LOCS = Lens Opacity Classification System; MZ = monozygotic; NDS = nuclear dip score; RRR = relative risk ratio; SD = standard deviation.

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