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CLINICAL STUDY

Risk factors for cataract subtypes waterclefts and retrodots: two case–control studies

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Abstract

Waterclefts and retrodots are independently associated with visual impairment, yet a review identified no data on risk factors.

Purpose **To investigate risk factors for these two human lens cataract subtypes.**

Method **Two nested case–control studies: The host study comprised 1078 subjects (≥55 years) attending the Somerset and Avon Eye Study (SAES). In total, 197 watercleft cases (≥Oxford grade 0.2 in either eye) and 199 retrodot cases (≥Oxford grade 1.0 in either eye) were individually age/gender matched to controls. Detailed ophthalmic and potential risk factor data were collected, including body mass index (BMI), smoking, alcohol, diabetes, hypertension, analgesics, vitamin supplementation, nutrition, sunlight exposure, dehydration, hormonal (women), blood lipids, glucose, urea, creatinine, uric acid, and vitamin levels.**

Results **For waterclefts, univariable analysis identified BMI, alcohol intake, vitamin status, sunlight, urea, creatinine, and uric acid as possible risk factors. Multivariable analysis identified two independent associations. Total number of 'any' analgesics in the previous year: adjusted $P<0.01$ (U-shaped risk profile, unadjusted high *vs* medium use (=reference) OR 2.39, 95% CI 1.35–4.26 with medium use *vs* none (=reference) OR 0.43, 95% CI 0.26–0.72); total sunlight: adjusted $P=0.03$ (unadjusted highest exposure *vs* lowest (=reference) OR 3.25, 95% CI 1.11–9.50). For retrodots, univariable analysis identified alcohol, HRT, and lipids. Multivariable analysis identified two independent associations. Mean number of alcohol units consumed per month, adjusted $P=0.02$ and HDL cholesterol levels, adjusted $P=0.02$ (unadjusted ORs NS both).**

Conclusion **This is the first available published information on risk factors for the human cataractous lens features waterclefts and retrodots.**

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Keywords: risk factors; case–control study; lens opacities; waterclefts; retrodots; cataract

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Introduction

Of the estimated 180 million people worldwide who are visually disabled, 40–45 million are blind and by definition cannot walk about unaided.[1] With half the blindness due to cataract and an increasingly ageing population, the World Health Organization has estimated that the number of people currently blind due to cataract alone could double to reach over 40 million by the year 2020.[1,2] Although the backlog of blinding cataract is a major problem for the developing world,[3] the problem for wealthier nations is that the provision of surgery for early cataract has become a major drain on resources.[4] It has been estimated that if the onset of cataract were delayed by 10 years, the number of cataract operations needed would decrease by 45%.[5] It is therefore important to identify modifiable risk factors in cataractogenesis. The prevalence of waterclefts and retrodots is fairly high, in an English population based survey of people aged 55–74 years of age waterclefts were present in 17% and retrodots in 11% of participants.[6] It had been suggested that waterclefts[7] and retrodots[8,9] have the potential to cause visual impairment, with symptoms including monocular diplopia,[10] but until recently their effects on vision remained largely speculative. Population-based data have now shown that waterclefts are independently associated with impaired visual acuity[11] and

retrodots are independently associated with both impaired visual acuity and impaired contrast sensitivity. Although waterclefts and retrodots may not cause blindness, they may cause significant visual symptoms in populations with high visual requirements and high expectations of visual performance.[11] With such high prevalence, strategies for prevention, as opposed to surgery, may be associated with cost-savings in countries that devote large expenditure to surgery for early cataract.

Waterclefts (Figure 1a) are fibre-based opacities that are usually situated in the anterior superficial cortical zone (52%), or both the anterior and posterior cortex (47%)[12,13] Shun-Shin *et al*[12] suggested that changes at the membrane of the lens fibre tip could set off activation of enzymes and inhibition of the Na^+K^+ ATP-ase pump resulting in a watercleft. Certain cortical cataracts and waterclefts might share a common aetiology, and it has been suggested that cortical cataract may be similarly caused following disruption of the Ca^{2+} ATP-ase pump. In addition, cortical spokes and waterclefts have been noted to coexist in mixed cortical cataract,[13,14] although some of this apparent association may be due to mis-classification, as in their more advanced stages of development waterclefts can become opaque and appear similar to cortical spokes.

Bron and Brown[8] defined retrodots (Figure 1b) as small (80–500 μm) round, oval or oblong birefringent features that can occur in the adult lens after the fifth decade. They are typically found in the perinuclear zones and their shape and development are independent of the lens fibre architecture.[10] Two studies have found a statistically significant relationship between the presence and grade of retrodots and nuclear scatter, suggesting a possible common aetiology.[14,15]

A literature review of cataract risk factors found no separate investigation into risk factors for waterclefts and retrodots. In view of the known associations between waterclefts and cortical cataract on the one hand, and retrodots and nuclear cataract on the other, findings from earlier studies on risk factors for cataract were consulted to decide which potential risk factors to investigate. The main putative risk factors considered at the time of designing the study included age (matched), gender (matched), body mass index (BMI), cardiovascular status and risks (various aspects of blood pressure, blood lipids), systemic comorbidities (treated hypertension, history of diabetes, blood glucose, gout—uric acid), smoking, alcohol intake, sunlight exposure (UV), nutrition (daily energy intake, vitamins A, C, and E, various supplements, blood levels for carotenoids and vitamins A and E), medications (various analgesics, antihypertensives) hormonal status (women), dehydration, and renal function (see West for review of information available at the time of study design[16]).

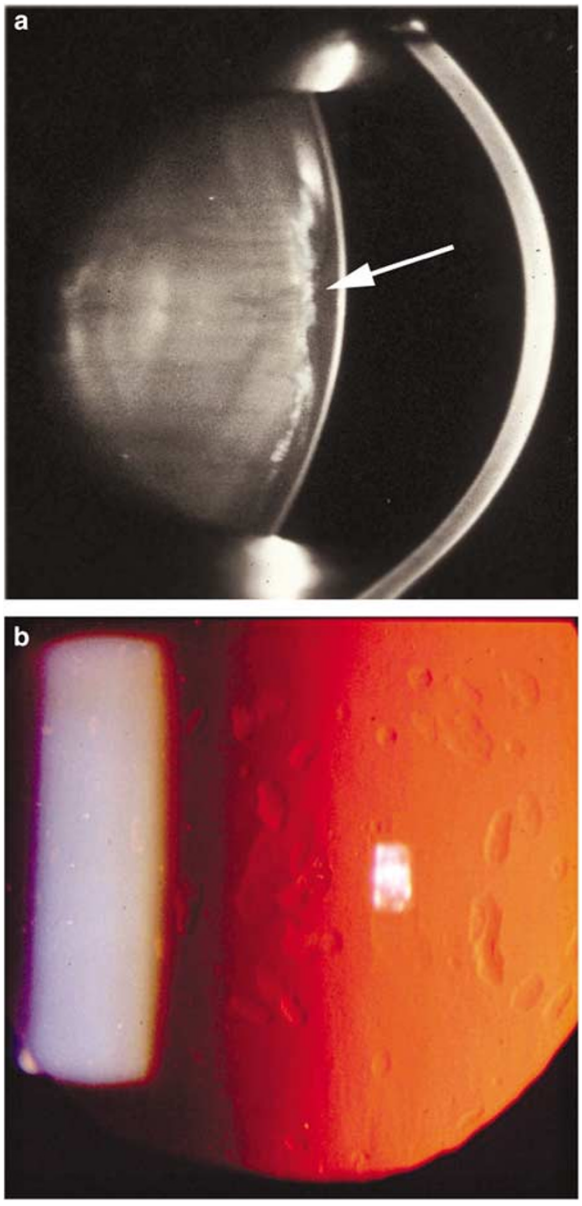

Figure 1 The cataract features of interest: waterclefts and retrodots. (a) Waterclefts in slit-beam illumination showing an 'optically empty' space (arrow) deep to the anterior lens capsule with opacification of the posterior wall of the watercleft and associated light scatter. (b) Retrodots in retro-illumination showing typical L/R reversal of the background illumination gradient within the retrodots.

Purpose

The aim of this study was to investigate the associations between suspected risk factors for cataract and the presence of waterclefts or retrodots in the human crystalline lens.

Two primary hypotheses were tested:

1. That some or all of the risk factors listed above are risk factors for the presence of waterclefts.
2. That some or all of the risk factors listed above are risk factors for the presence of retrodots.

Method

The study design consisted of two nested case–control studies, where the host study was the Somerset and Avon Eye Study (SAES).[17,18] The host study included 1078 subjects who attended the SAES research clinic, held at Bristol Eye Hospital and who provided a full data set. Somerset and Avon Eye Study was designed to investigate the population requirements for cataract surgery.[17] The source of potential subjects for the SAES was the Somerset and Avon Survey of Health (SASH), an age/gender stratified random sample of subjects aged at least 55 years registered at 40 general practices in Avon and Somerset.[19] The study was approved by the United Bristol Healthcare Trust Local Ethics Committee.

Abbreviated SAES clinic protocol

Once written consent had been obtained, subjects participated in the various clinic tests, in the order listed in Table 1.

Lens grading: the Oxford Clinical Cataract Classification and Grading System (OCCCGS)

The Decimalized Oxford Clinical Cataract Classification and Grading System[20,21] is designed for grading at the slit lamp and includes anterior subcapsular (ASC), posterior subcapsular (PSC), cortical spokes, fibre folds, vacuoles, focal dots, nuclear brunescence, white nuclear scatter, waterclefts, and retrodots (Figure 1). All features are scored from 0 to 5 on a decimalized scale. There is a linear relationship between most scales with logarithmic conversions for certain features where this is more appropriate, that is, vacuoles, retrodots, and focal dots.

Table 1 Abbreviated SAES clinic protocol

Order	*Procedure*
1	Vision questionnaire (Inc. VR-QoL = VCM1)
2	Height, weight, blood pressure measurements
3	Initial visual acuity/vision measurement, refraction and refracted visual acuity measurement (distance and near), Amsler test
4	Contrast sensitivity test and glare test
5	Visual field test (Henson 3200)
6	Anterior segment examination and pupil dilatation
7	Service utilization questionnaire (Su-Q) and comorbidity questionnaire (Co-MQ)
8	Fundus photography, lens imaging (CASE 2000 CCD camera), fundus examination, lens grading (OCCCGS and LOCS III), disc and macular grading, Goldmann tonometry
9	Blood tests
10	Additional questionnaires for self-completion at home, or in the clinic if possible (SF-36, domestic circumstances)

Case–control selection

Within the SAES, two nested case–control studies were constructed to investigate the two primary hypotheses (Figure 2). Cases for the two studies were respectively defined as those subjects with at least grade 0.2 waterclefts in either eye or at least grade 1.0 retrodots in either eye.[21] It was decided that these were the levels at which each feature could be said with confidence to be present. Case selection was irrespective of the presence of any other lens feature. Pupil diameters for all cases had to be at least 6.0 mm in the eye with the feature to minimize misclassification. No visual acuity criterion was used to determine case or control selection. The criteria for the controls for the two studies were absent or less than grade 0.2 waterclefts in both eyes, or absent or less than grade 1.0 retrodots in both eyes[21] with a pupil diameter of at least 6.0 mm in both eyes. The presence of any other cataract feature was not taken into account. Matched controls were selected for each case using a program written especially for this project using the programming language within Microsoft Access where the study database had been constructed. The program individually matched a control to each case, first by gender and then by age on the day of their clinic visit, to the nearest day.

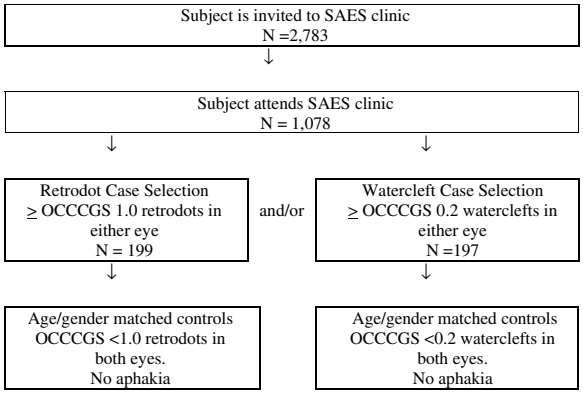

Figure 2 Flow chart of selection of cases and controls.

Risk factor information

The information gathered in the Host SAES[17] was supplemented with additional data. Three additional questionnaires were used to collect further information on the case–control study subjects. These covered possible risk factors including smoking, alcohol intake, nutrition (food frequency), sunlight exposure, dehydration, and hormonal history (women). The sunlight questionnaire was telephone administered by interviewers who were masked to the case–control status of the subjects, the other supplementary questionnaires were postal. A variety of analyses were performed on stored blood samples. A summary of data items and variable types is provided in Table 2.

Statistical analysis

All data were entered into an Access database, checked for errors, and transferred to the SPSS software package. All univariable and multivariable analyses were carried out using SPSS.

Statistical power

Post hoc power calculations were performed for all the variables of interest. For the vast majority of variables, the sample sizes and distributions were such that the standardized detectable effect size was 0.3 or 0.4 of an SD (small to medium effect) for at least 80% power at the 5% probability level for both waterclefts and retrodots.

Table 2 Risk factor information

Risk factor	*Available data*	*Variable*
Age[a]	Age in years at the time of clinic attendance	Age-matched case–control recruitment. Multivariable analysis: further age adjustment as continuous variable
Gender[a]	Male/female	Gender matched case–control recruitment. Multivariable: further male/female adjustment
Body mass index[a]	Calculated from the subject's height and weight	BMI = weight (kg)/height^2 (m^2); Categories: <22; 22–25; 26–29; 30; and above
Smoking[b]	If more than 100 cigarettes/cigars/pipes ever, then duration (years) and average each day used to calculate total pack-years smoked	'Cigarette' years smoked None; Light; Moderate; Heavy; (tertiles of smokers) Reference group: <100 cigarettes/cigars/pipes in their lives
Alcohol intake[b]	If consumption more than once a month, then how often and how much. Also asked if ever in habit of drinking more heavily in past and if so how much	Alcohol 'unit' = 10 ml pure alcohol (approx 1 glass wine, half pint beer, 'single' spirit measure) Never: none or <1 alcohol unit a month Light: 1–30 alcohol units a month (ie up to ~1 a day) Moderate: 31–80 alcohol units a month (ie up to ~2.5 a day) Heavy: 81 or more alcohol units a month (ie over ~2.5 a day) Analysed by intake over past 1 month (current), and average monthly intake over past year, and highest ever consumption. Reference group: Never (= None or <1 U a month)
Diabetes[b]	Co-MQ: Self reported diabetes 'Has a doctor *ever* said that you have diabetes?' If Yes, medication and duration	Diabetes absent/present Nonfasting blood glucose (below)
Hypertension[a]	Co-MQ: Self-reported hypertension 'Has a doctor *ever* said that you have high blood pressure?' If Yes, medication and duration Blood pressure (measured at clinic visit) Hypertension status	Yes/no If Yes, drug class and duration of use Systolic: <130 mmHg (Reference); 131–160 mmHg; 161–190 mmHg; >191 mmHg Diastolic: <80 mmHg (Reference); 81–90 mmHg; 91–100 mmHg; and >101 mmHg Hypertensive if Yes to self-report, or Systolic ≥160 or Diastolic ≥100
Analgesics[b]	SuQ: Analgesic use for past 12 months Aspirin, paracetamol or ibuprofen and frequency	Score for total yearly dose calculated for various combinations and 'any' analgesic use, for example 'any' analgesics: none; low use = 1–7; medium = 8–252; high = 253 or more (tertiles of users)
Vitamin supplements[b]	SuQ: Vitamins A, C, and E supplements or 'multivitamins' for past 12 months and frequency use	Score for total yearly dose calculated Analyses of continuous data and by quartiles

Table 2 (Continued)

Risk factor	*Available data*	*Variable*
Nutrition[b] (food frequency)	Semiquantitative Food Frequency Questionnaire, a modified version of the Cambridge EPIC questionnaire. Consumption of a 'normal portion' of a particular food multiplied by its nutrient content, as supplied by standard food tables	Daily energy intake Standard scoring used to calculate daily beta carotene, vitamin C, and vitamin E intake (milk intake included) Analyses of continuous data and by quartiles
Sunlight exposure[b]	Lifetime cumulative sunlight questionnaire estimated exposure for various 'life periods' based on work, recreation, and location	Adaptation of the Melbourne Visual Impairment Project sunlight exposure model[67] Categories: <1; 1 to <2; 2 to <3; 3 or more 'sun years'
Dehydration[b]	Episodes of diarrhoea or heat stroke severe enough to keep the subject in bed for 3 days or more (severity criterion in accordance with previous studies[68,69])	Never, one or more occasions Separate analyses for diarrhoea, heat-stroke, diarrhoea or heat-stroke, or 'dehydration', that is, at least one episode of severe diarrhoea, heat-stroke, or a blood transfusion
Hormonal history[b] (women)	Use of oral contraceptive pill and/or hormone replacement therapy (HRT) and duration (years); age of menarche; menopause; hysterectomy; completed pregnancies.	Analyses of dichotomous data or continuous and quartiles as appropriate
Lipids, glucose renal function, and uric acid[c]	Nonfasting total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, glucose, urea, creatinine, uric acid Glomerular filtration rate calculated for males and females using standard formula	Analyses of continuous data and by quartiles
Vitamin blood levels[c]	Total carotenoids, vitamin A, and vitamin E levels	Analyses of continuous data and by quartiles

SAES Co-MQ = Comorbidity questionnaire; SAES SuQ = Service utilization questionnaire; EPIC = European Prospective Investigation of Cancer.[70]
[a]Data available from the SAES Host Study.
[b]Additional questionnaire data collected on case/control study participants.
[c]Analysis of stored blood samples.

Where subgroup analyses examined only one gender (eg reproductive history for women), power was attenuated to detection of an effect size of 0.4 or 0.5 of an SD (medium effect).

Univariable analysis

Although the cases and controls had been individually matched for age and gender, the univariable analysis was carried out as if the cases and controls were unpaired. This was because for a number of the variables, subjects had missing data, which would have resulted in some case–control pairs being excluded. Other than being matched for age and gender, the samples were independent, hence the independent samples *t*-test, corrected for ties, was used for continuous data to test for differences between the cases and controls. Where numbers were too small or the data were too skewed, the Mann–Whitney Rank Sum *W* test, corrected for ties, was used instead. Paired analyses were performed *ad hoc* for certain variables. Continuous variables were also divided into four categories. Where there were '*a priori*' reasons for choice of cut points (eg compatibility with previous studies) then these were used, otherwise data were divided into quartiles, or where a natural zero 'first category' existed the nonzero values were divided into tertiles (Table 2). χ^2 tests were carried out on the categorical data and the Mantel–Haenszel test for linear association was used on categorical data where appropriate to test for trends. For initial hypothesis generation, the 10% level of significance was accepted; where a higher significance was found, this was noted. This relatively liberal level was chosen so as not to miss any significant results, which would be masked by negative confounding. Despite the use of a 10% threshold in the initial univariable analysis, the presentation of results reverts to standard format with probability values stated for continuous data and odds ratios with 95% confidence intervals given for categorical analyses. For the multivariable analysis, the more stringent 5% level of significance was used for inclusion/exclusion throughout.

Multivariable analysis

Variables significant at the 10% threshold from the univariable analysis were entered into a multivariable logistic regression model using backwards selection. Age

and gender were forced into the model and for all other variables probability levels for entry or removal from the model were 0.05. Where appropriate, significant variables within the same group, for example 'sunlight', were initially put into separate multivariable models to see which variable(s) from this group remained significant for inclusion in the final multivariable model.

Results: waterclefts

Prevalence of OCCCGS features in watercleft cases and controls

The study involved 197 watercleft cases and 197 age- and gender-matched controls. For cases, the mean OCCCGS watercleft score was 0.42 (SD 0.57) in the right eye, 0.47 (SD 0.46) in the left eye and 0.58 (SD 0.55) in the worse eye. The range of scores in the worse eye was from 0.2 to 4.0.

Univariable analysis: waterclefts

Separate univariable 'hypothesis generating' analysis at the 10% significance level suggested that the following variables might be important risk factors for waterclefts: BMI; alcohol consumption (highest ever level); analgesic use; mean annual sunlight exposure; mean plasma creatinine, urea; uric acid; vitamin A and vitamin E blood levels (see Table 3).

Body mass index

There was no significant difference in mean BMI between cases and controls. Univariable analysis however suggested a U-shaped risk profile with differences between four BMI categories. There was an increased risk for subjects with a BMI of more than 30 compared to those with a BMI of 26–29 (as reference category): OR 1.78 (95% CI 1.05–3.10). The odds ratios also suggested a protective effect for those with a BMI of 26–29 relative to those in the lowest category of less than 22 (as reference category): OR 0.52 (95% CI 0.32–0.86).

Alcohol consumption

In this study, 'highest ever' alcohol consumption showed a statistically reduced risk of having waterclefts for all three categories compared to 'never drinks alcohol'. This reduced risk was similar for all three categories of alcohol frequency, from OR 0.53 (95% CI 0.28–0.98) for 'heavy' *vs* 'never' to OR 0.47 (95% CI 0.25–0.91) for 'moderate' *vs* 'never' and 0.49 (95% CI 0.30–0.81) for 'light' *vs* 'never'. The Mantel–Haenszel test for linear association showed a significant trend between the four categories of alcohol consumption ($P = 0.02$). There was no association between the most recent 1 month's alcohol intake, that is, current intake and waterclefts or the mean

Table 3 Waterclefts: summary of significant (at 10% level) associations found in univariable hypothesis generation analyses (items selected to illustrate specific contrasts)

Risk factor for waterclefts	*Unpaired univariable analyses*
Body mass index	*U-shaped risk profile*
≥30 *vs* 26–29 (ref)	OR 1.78 (95% CI 1.05–3.10)
26–29 *vs* 22–25 (ref)	OR 0.50 (95% CI 0.32–0.86)
Alcohol consumption (highest ever)	*Linear trend P = 0.02*
'Heavy' *vs* 'Never' (ref)	OR 0.53 (95% CI 0.28–0.98)
'Moderate' *vs* 'never' (ref)	OR 0.47 (95% CI 0.25–0.91)
'Light' *vs* 'never' (ref)	OR 0.49 (95% CI 0.30–0.81)
'Any' analgesic use (in past year)	*U or J-shaped risk profile*
Mean no. of 'any' analgesics used	$P = 0.003$, cases used more
High use *vs* medium (ref)	OR 2.39 (95% CI 1.35–4.26)
Low use *vs* none (ref)	OR 0.43 (95% CI 0.26–0.72)
Sunlight exposure	*Linear trend P = 0.06*
Mean annual 'sun years'	$P = 0.07$, cases more exposed
Highest exposure *vs* lowest (ref)	OR 3.25 (95% CI 1.11–9.50)
Urea	*Linear trend P = 0.003*
Mean urea levels	$P = 0.001$, cases higher mean level
Highest *vs* lowest quartile (ref)	OR 2.44 (95% CI 1.31–4.56)
Highest *vs* second lowest quartile (ref)	OR 2.62 (95% CI 1.37–4.99)
Creatinine	*F: Linear trend P = 0.007*
F: Mean plasma level	F: $P = 0.01$, Cases higher mean level
F: Highest *vs* lowest quartile (ref)	F: OR 3.69 (95% CI 1.47–9.27)
F: Highest *vs* second lowest quartile (ref)	F: OR 3.28 (95% CI 1.25–8.59)
Uric acid	*F: Linear trend P = 0.03*
F: Mean plasma level	F: $P = 0.01$, Cases higher mean level
F: Highest *vs* lowest quartile (ref)	F: OR 2.57 (95% CI 1.14- 5.77)
F: Highest *vs* second lowest quartile (ref)	F: OR 2.94 (95% CI 1.35–6.40)
Vitamin A blood levels	*Linear trend P = 0.04*
Mean Vitamin A levels	$P = 0.02$, Cases had higher level
Highest *vs* lowest quartile (ref)	OR 1.70 (95% CI 0.91–3.16)
Vitamin E blood levels	*Linear trend P = 0.07*
Highest *vs* lowest quartile (ref)	OR 1.91 (95% CI 1.02–3.57)

monthly alcohol consumption over the past 1 year and watereclefts.

Analgesics

In total, 106 Watercleft cases and 125 controls reported use of paracetamol or a paracetamol containing products, aspirin, or ibuprofen in the past month. Cases were found to have taken a significantly greater number of paracetamol or paracetamol containing products in the past 12 months ($P = 0.04$).

'Any' analgesics referred to the total number of paracetamol, paracetamol containing products, aspirin, or ibuprofen. The cases had taken a highly significant greater total number of 'any' analgesics than the controls ($P = 0.003$). The odds ratios showed an increased risk for the highest use group (greater than 253 analgesics in the past year) compared to medium use (as reference, 8–252 analgesics in the past year) OR 2.39 (95% CI 1.35–4.26). Comparing the highest use group with both infrequent use (1–7 in past year) and no analgesic use, the results were in the same direction but the 95% CI for the odds ratios all overlapped 1.0, that is nonsignificant. The results suggested a U or J-shaped risk profile with a protective effect of medium and low total dose of 'any' analgesics compared to no analgesics at all. The odds ratio for the medium use group compared to using none (as reference category) was OR 0.43 (95% CI 0.26–0.72). The category with the lowest risk was the medium use group, and although further comparisons were in keeping with a U or J-shaped risk profile these did not yield significant differences, with 95% confidence intervals overlapping 1.0.

Sunlight

Watercleft cases appeared to have significantly higher mean annual sunlight exposure than controls ($P = 0.07$). The observed difference between the mean number of sun years for the cases and controls was 0.18 sun years. A three-fold increased risk was found for watercleft subjects in the highest exposure category compared to the lowest OR 3.25 (95% CI 1.11–9.50). The Mantel–Haenszel test for linear association showed a significant trend between the 4 sun year categories ($P = 0.06$).

Urea levels

Mean levels of plasma urea were within the 'normal' range for both cases and controls. The independent samples two-tailed *t*-test showed a significant difference between the mean level of urea with watercleft cases having higher levels ($P = 0.001$). Univariable results showed a significantly increased risk both for subjects in the highest quartile compared to those in the lowest OR 2.44 (95% CI 1.31–4.56) and also for subjects in the highest quartile compared to the second lowest OR 2.62 (95% CI 1.37–4.99). The Mantel–Haenszel test for linear association showed a significant trend across the quartiles ($P = 0.003$).

Creatinine

The independent samples two-tailed *t*-test showed a significant difference between the mean level of creatinine for the two groups, with cases having higher creatinine levels ($P = 0.02$). As 'normal' creatinine levels differ for males and females, a paired analysis was also performed and the unpaired analysis was repeated by gender. The paired analysis indicated a significantly higher mean creatinine level among cases ($P < 0.01$) with the Wilcoxon matched pairs ranked signs test showing a highly significant trend between the quartiles ($P < 0.001$). For female (but not male) subjects, there was a significant difference (unpaired) in mean creatinine with female cases having higher levels ($P = 0.01$). There was a significantly increased risk for female subjects in the highest quartile compared to the lowest OR 3.69 (95% CI 1.47–9.27), and also for the highest compared to the second lowest quartile OR 3.28 (95% CI 1.25–8.59). The Mantel–Haenszel test for linear association showed a highly significant trend between the quartiles ($P = 0.007$). The amounts of creatinine (and urea) excreted are closely related to the glomerular filtration rate (GFR). The independent samples two tailed *t*-test showed that the difference between the GFR for female cases and controls was not significant ($P = 0.15$). The risk associated with increased urea levels noted above in females was therefore not due to poor glomerular filtration.

Uric acid

The normal plasma uric acid level is approximately 240 μmol/l. In the SAES both watercleft cases and controls had higher mean levels of uric acid (347.48 and 327.26 μmol/l, respectively). Separate analysis, by gender, revealed that only for females was there a highly significant difference between the mean level of uric acid for the two groups, with cases having higher levels of uric acid than controls ($P = 0.01$). Categorical analysis revealed a significantly increased risk for female subjects in the highest quartile compared to the lowest OR 2.57 (95% CI 1.14–5.77) and also for those in the highest quartile compared to the second lowest OR 2.94 (95% CI 1.35–6.40). The Mantel–Haenszel test for linear association showed a significant trend between the quartiles for female subjects ($P = 0.03$).

Vitamin A levels

The daily beta-carotene dietary intake of the cases and controls (1998 and 2128 μg, respectively) did not differ significantly ($P = 0.75$). These equate to retinol equivalents of 333 and 355 μg. As the estimated average daily requirements for this age group are 500 μg retinol/day for males and 400 μg/day for females, this suggests that both cases and controls had a low vitamin A intake. There was a significant difference in the mean vitamin A levels of the cases and controls, as measured on the blood samples, with cases having higher levels than controls ($P = 0.02$). The Mantel–Haenszel test for linear association showed a significant trend between the four quartiles of vitamin A blood levels ($P = 0.04$). No significant risk was observed for subjects in the highest compared to those in the lowest quartile OR 1.70 (95% CI 0.91–3.16). No significant difference was observed between the total carotenoid levels of the blood samples of the cases and controls ($P = 0.30$).

Vitamin E levels

The mean daily vitamin E intake of the cases (7.81 mg) and controls (8.47 mg) did not differ significantly ($P = 0.24$). The approximate vitamin E requirement for men is 7 mg/day, and for women 5 mg/day,[22] so both cases and controls appeared to consume adequate dietary vitamin E. For blood levels, our results showed a significant risk for subjects in the highest compared to those in the lowest quartile of plasma vitamin E levels OR 1.91 (95% CI 1.02–3.57). The Mantel–Haenszel test for linear association also showed a significant trend between the four quartiles of vitamin E blood levels ($P = 0.07$).

Multivariable analysis: waterclefts

When all the significant variables from the univariable analysis were entered into the final multivariable model, two variables remained significant at the 5% level. The total number of 'any' analgesics used in the past year was highly significantly associated with waterclefts, with increased analgesic use being associated with a higher risk of waterclefts ($P < 0.01$). Total lifetime sunlight exposure was also significantly associated with waterclefts, with higher light exposure associated with a higher risk of having waterclefts ($P = 0.03$).

Results: retrodots

Prevalence of OCCCGS features in retrodot cases and controls

The study involved 199 retrodot cases and 199 age- and gender-matched controls.

For cases the mean OCCCGS retrodot grade was 1.59 (SD 0.89) in the right eye, 1.66 (SD 0.88) in the left eye, and 1.96 (SD 0.72) in the worse eye. The range of scores in the worse eye was from 1.0 to 4.0.

Univariable analysis: retrodots

Separate univariable 'hypothesis generating' analyses at the 10% significance level suggested that the following variables might be important risk factors for retrodots: alcohol consumption (mean number of alcohol units consumed per month); hormone replacement therapy (HRT); mean high density lipoprotein (HDL) cholesterol levels; mean triglyceride levels (see Table 4).

Alcohol consumption

Univariable results indicated a significant difference between the mean monthly alcohol intake over the past year of cases and controls ($P = 0.03$), with controls drinking a greater total number of alcohol units (30.9 U/month) than cases (20.6 U/month). However, although the odds ratios for 'heavy' alcohol consumption (as reference category) compared to 'never', 'light', and 'moderate' consumption were in a protective direction (eg OR 0.49 for 'heavy' *vs* 'never'), the 95% confidence intervals overlapped 1.0 in all cases (ie results not statistically significant at $P < 0.5$). There was no association between the most recent 1 month's alcohol

Table 4 Retrodots: summary of significant (at 10% level) associations found in univariable hypothesis generation analyses (items selected to illustrate specific contrasts)

Risk factor for retrodots	*Unpaired univariable analysis*
Alcohol consumption	
Mean no. of alcohol units/month (no significant differences between consumption categories)	$P = 0.03$, cases drank less
Hormone replacement therapy (HRT)	
Mean number of years HRT use (no significant differences between HRT categories)	$P = 0.05$, cases used for more years
Lipids	
High-density lipoprotein (HDL) cholesterol	$P = 0.10$, cases had higher HDL $P = 0.08$, cases had higher HDL : cholesterol ratios
Mean triglyceride level (no significant differences between lipid categories)	$P = 0.10$, cases had lower triglyceride

intake, that is, current intake and retrodots or the 'highest ever' category of alcohol consumption and retrodots.

Hormonal history

Only 14 cases and seven controls had reported HRT use. A borderline effect was observed for retrodot cases using HRT for more years than controls (Mann–Whitney rank sum W test $P = 0.05$). There was no significant difference between the mean number of years of *contraceptive pill* use for retrodot cases and controls. Neither was there any increased risk of retrodots associated with the number of completed pregnancies or the mean number of years of menstruation.

Cholesterol levels

A borderline significant difference was observed between the levels of HDL cholesterol ($P = 0.10$) with cases having higher levels of HDL cholesterol than controls. When odds ratios were calculated for the various quartiles of HDL values, no significantly increased risk was associated with any one category relative to any other. Also, a higher HDL : cholesterol ratio was found in cases than controls ($P = 0.08$).

Triglyceride levels

A borderline difference between the mean level of triglycerides for the two groups ($P = 0.10$) was found with cases having lower triglyceride levels than controls (1.99 and 2.17 mmol/l, respectively).

Multivariable analysis: retrodots

Multivariable analysis confirmed two of the variables as independent risk factors for retrodots: the mean number of alcohol units consumed per month over the past year, with higher alcohol consumption providing a protective effect ($P = 0.02$) and HDL cholesterol levels, with higher HDL associated with an increased risk of retrodots ($P = 0.02$).

Discussion

Case–control studies are well placed to identify risk factors for a condition of interest. Individual matching for age and gender followed by adjustment for these and other potential confounders strengthen the credibility of this observational methodology. Since we matched for age and gender, our study design does not permit any comment on the possible importance of either of these two variables as risk factors. A general expectation however would be that increasing age would be an important risk for both waterclefts and retrodots, hence the need for case–control matching. Our staged approach of univariable hypothesis generation at a liberal significance level (10%) followed by more stringent multivariable analyses has yielded a number of items for discussion. Quantification of exposures by more than one method has provided complimentary views for several factors of interest. For example, vitamin status was assessed in terms of nutritional intake based on food frequency questionnaires, supplement use, and vitamin levels from biochemical analysis of stored blood samples, and alcohol consumption was assessed in terms of the current intake over the previous 1 month, the average monthly intake over the past year, and the highest ever intake, to acknowledge that some individuals may have experienced important variations in intake at different times during their lives (see Table 2). While this staged and complimentary approach has certain advantages, it must be cautioned that multiple testing at the 10% level would have produced a number of chance associations in the initial results. Several factors however remained significant in the multivariable analyses conducted at the 5% level. The power of the study was sufficient to state with reasonable confidence that within the population studied a number of the hypothesized risk factors examined did not contribute medium to large effects, although small effects may have gone undetected.

Risk factors for waterclefts identified by univariable analysis included BMI, alcohol intake, vitamin status, sunlight exposure, indices of renal function, and uric acid levels (see Table 3). A U-shaped relationship was noted for BMI suggesting a lower risk for individuals with intermediate BMI. The obese subjects with a BMI of greater than 30 had a greater risk (OR = 1.78) compared to those with an intermediate BMI of between 26 and 29. Those with intermediate BMI had almost half the risk (OR = 0.52) of those subjects with a lower BMI of less than 22. Our finding is comparable with that of the Blue Mountains Eye Study[23] for cortical and PSC cataract, the Boston Nurses' Health Study cohort[24] for posterior subcapsular opacities, the Salisbury Eye Evaluation (SEE) project[25] for cortical opacity only with opposite effect for nuclear opacity, and the Framingham Eye Study cohort[26] for incident cortical and posterior subcapsular opacities.

For the variable 'highest ever alcohol consumption', we found that all levels of alcohol consumption had a protective effect for waterclefts. The risk was roughly halved for those who consumed alcohol at all three intake levels (OR = 0.53; 0.47; 0.49 highest to lowest), compared to those subjects who did not drink any alcohol. Similar protection was observed in the Boston Nurses' Health Study[27] for light to moderate wine consumption for cortical opacity. The Beaver Dam Eye

Study,[28] however, found no associations between alcohol and any form of incident cataract over a 10 year period. Earlier studies have found a protective effect for certain patterns of (light) alcohol consumption for cataract although mostly these studies have reported heavy alcohol consumption to be a risk, particularly for nuclear cataract.[16,29–33] In a number of these previous studies, heavy alcohol consumption has been defined as over four alcoholic drinks per day. In the case–control populations, we studied there were under 10% of participants who reported 'heavy' drinking, which we defined as greater than 80 alcohol units per month (approximately $>2\frac{1}{2}$U/day). This rate of alcohol consumption is lower than that reported for England as a whole (household survey data) where around 27% of men and 15% of women reported using this quantity of alcohol.[34]

A strongly significant excess in total number of 'any' analgesics was observed among cases, with a similar but statistically weaker effect seen for paracetamol (containing) products. For 'any' analgesics the risk between medium users (who took 8–252 analgesics a year as reference category) and those who took more (high use) was more than double (OR = 2.39). A U-shaped risk profile was observed with medium analgesic users showing a protective effect (risk halved, OR = 0.43) compared with those who took no analgesics at all. These findings suggest that complete avoidance of analgesics is associated with some increased watercleft risk, but the dominant effect appears to be an increased risk with high levels of use of these medications. The published literature is divided as to whether analgesic use, particularly aspirin, is a risk for cataract, protective or neither.[35–38] Interpretation of observational data related to drug use is fraught with difficulties. Conflicting results in different studies may be due to a range of confounders and biases. Different doses may produce different effects and reasons for the taking of 'over the counter medications' will vary widely, with the possibility that an underlying condition prompting the use of a drug may itself be associated with an increased risk of cataract.

Numerous published studies on sunlight and cataract provide evidence in support of an association between ultraviolet radiation (UVR) and cortical cataract (see McCarty and Taylor[39] for a review). In the present study, mean sunlight exposure was higher among watercleft cases than controls, with over a three-fold greater risk (OR = 3.25) in the highest exposure quartile compared with the lowest, and a significant trend across quartiles. The level of risk was similar to that found in the Maryland watermen study for cortical cataract.[40] These results suggest that even for subjects who had predominantly lived in the UK, there was a sufficient range of sunlight exposures to detect a possible three-fold excess risk of waterclefts in subjects with the greatest mean annual level of exposure.

The indices of renal function, urea, and creatinine levels, both indicated a higher risk of waterclefts associated with relatively worse renal function. There was a two and a half fold increase in risk for those in the highest urea quartile compared with both the lowest (OR = 2.44) and second lowest (OR = 2.62) quartiles. Creatinine levels among female (only) subjects indicated a similar pattern with a three and a half fold increase in risk for the highest quartile compared with the lowest (OR = 3.69) and second lowest (OR = 3.28) quartiles, and a strongly positive linear trend. The GFR did not reflect these patterns indicating that the variations in urea and creatinine levels were not due to poor glomerular filtration. The Beaver Dam Eye Study found blood urea nitrogen to be raised in association with cortical cataract over a 5 year period in univariable analysis, an association which disappeared after controlling for age.[41] A large case–control study of 1000 cases and 1000 individually matched controls in the UK found urea to be associated with PSC but not with cortical cataract.[42]

Uric acid plasma level appeared slightly elevated for both cases and controls. Female watercleft cases had a higher mean uric acid with a two and a half to three fold excess risk for those in the highest quartile compared with those in both the lowest (OR = 2.57) and second lowest (OR = 2.94) quartiles. A significant linear trend across categories was noted. This result accords with published associations between gout and cortical cataract,[43] gout medications and mixed cataract,[44] and higher uric acid and both mixed opacities[45] and PSC cataract.[46]

Previous studies have reported a variety of associations between risk of cataract or cataract extraction and antioxidant vitamin status (dietary intake, supplementation, or blood levels). In the present study, dietary beta-carotene intake was lower than expected for both cases and controls, with no group differences observed. Mean vitamin A blood levels were higher among cases than controls, with a significant linear association for trend across the quartiles, suggesting an increased risk of waterclefts with higher blood levels. No differences were observed however for total carotenoid levels. The Nutritional Factors in Eye Disease Study found use of multivitamin preparations to be associated with an increased risk of cortical opacities but a decreased risk of nuclear sclerosis.[47] In the Blue Mountains Eye Study, vitamin A supplements were protective against nuclear (but not cortical) cataract with folate and vitamin B_{12} supplements protective against cortical cataract[48] and vitamin A dietary intake protective for nuclear cataract.[49]

Mean dietary intake of vitamin E was adequate and similar among cases and controls. Univariable analysis of plasma vitamin E levels suggested an increase of almost twice the risk of waterclefts between lowest and highest quartiles (OR = 1.91). The observed effect was strengthened by a significant trend across quartiles supporting the notion of a dose response. A placebo-controlled double-masked randomized trial of vitamin E supplementation found no effect on incidence or progression of cortical, nuclear, or PSC cataract from 500 IU daily over 4 years.[50] A multicentered, prospective, double-masked, randomized, placebo-controlled, 3-year trial of a mixture of oral antioxidant micronutrients (mg/day) (beta-carotene (18), vitamin C (750), and vitamin E (600)) in 297 subjects was found to have a small but significant beneficial effect on cataract progression as measured by digital image analysis of retro-illumination lens images.[51] In the Beaver Dam Eye Study, the use of multivitamins or any supplement containing vitamin C or E for more than 10 years duration lowered the risk for nuclear and cortical cataracts.[52] In the Boston Nurses' Health Study, after adjustment for other nutrients vitamin C intake remained significantly protective against nuclear opacification as did duration of vitamin C supplement use and plasma measures of vitamins C and E.[53] In the Lens Opacities Case–control Study, the risk of nuclear opacities was reduced to less than one half in participants with higher levels of vitamin E.[45] In a Mediterranean case–control study of mixed cataract dietary intake of vitamins C, E and selenium were marginally associated with decreased risk, and blood levels of vitamin C above 49 μmol/l were associated with a 64% reduction of the odds for cataract.[54] In the present case–control studies we did not find associations with dietary vitamin C. In a study in the north of England the risk of nuclear cataract, after adjustment, was lowest in people with the highest plasma concentrations of alpha-carotene or beta-carotene; cortical cataract risk was lowest in people with the highest plasma concentrations of lycopene and PSC cataract risk was lowest in those with higher concentrations of lutein.[55]

In the present study, multivariable logistic regression incorporating all significant univariable results confirmed at a 5% probability level that the number of 'any' analgesics used in the past year and the total lifetime sunlight exposure were significant independent risk factors for waterclefts, with higher exposures to each conferring greater risk. While this concurs with an accepted risk of sunlight exposure for cortical cataract,[39] previous studies have been divided on the question of risk from analgesic use.[35–38]

Retrodot risk factors identified at the 10% significance level by univariable analysis included alcohol consumption, HRT, HDL cholesterol levels, and triglyceride levels (see Table 4). Controls consumed on average 50% more alcohol in an average month over the previous year than retrodot cases, with 'heavy' drinkers (over 2.5 units of alcohol per day) having around half the risk (OR = 0.49) of nondrinkers. The other self-reported estimates of alcohol consumption (past month or current and highest ever) were not found to be significant. These results are similar to those found for waterclefts in this study and as noted above accord with certain previous studies, which have found a protective effect of light alcohol consumption for cataract. In the Boston Nurses' Health Study cohort, wine drinking was found to be protective against cortical cataract, but conversely these authors reported that nuclear opacity increased by 30% per 10 g increase of total alcohol intake.[27] Although the Beaver Dam Eye Study found no associations between alcohol and any form of incident cataract at the 10 year review,[28] this study had previously reported a borderline effect of increased risk of incident nuclear cataract associated with increasing alcohol intake at the 5-year follow-up assessment.[56] Earlier studies have found a protective effect for certain patterns of (light) alcohol consumption for cataract although mostly these studies have reported heavy alcohol consumption to be a risk, particularly for nuclear cataract.[16,29–33] As noted above, our study population consisted mostly of relatively light drinkers, which could explain the absence of any observed harmful effects of 'heavy' alcohol use in our participants.

Among women using HRT retrodot cases reported significantly more years of HRT use than controls. This observation should be interpreted with caution due to the small numbers involved. None of the other elements of hormonal history were different between the groups. In the Blue Mountains Eye Study those who had ever used HRT had a decreased incidence of cortical cataract affecting any eye compared with those who had never used HRT. Older age at menarche was associated with an increased incidence of cataract surgery and of nuclear cataract. There was also a decreasing incidence of cataract surgery with increasing duration of reproductive years.[57] At the baseline examination, the Beaver Dam Eye Study found that current use of postmenopausal estrogens was associated with a decreased risk of more severe nuclear sclerosis and younger age at menarche was also associated with a protective effect regarding nuclear sclerosis. Older age at menopause was associated with a decreased risk of cortical opacities.[58] The 5 year review, however, did not confirm these observations, the only finding being a borderline trend suggesting a possible protective effect of increasing number of live births on incident PSC cataract.[59] The SEE study found that HRT was not associated with incident nuclear, cortical, or PSC opacities, or with progression of nuclear

or cortical opacification. Women who had an early menopause had a higher risk of nuclear progression, whereas those who had a later menopause had a lower risk.[60] Among the Boston area participants of the Nurses Health Study, the only aspect of hormonal history or HRT use associated with cataract was current use of oestrogen only preparations with a halving of the risk of nuclear opacities compared to women who had never used HRT.[61]

In terms of cardiovascular risk factors in this study, HDL cholesterol and the HDL : cholesterol ratio was higher among retrodot cases. Cases were also found to have lower triglyceride levels of borderline significance. In the Blue Mountains Eye Study, cortical cataract was associated at baseline with a history of myocardial infarction, higher plasma fibrinogen, and higher serum cholesterol. Nuclear cataract was associated with a higher platelet count but hypertension was associated with lower prevalence of nuclear cataract. Posterior subcapsular cataract was associated with higher plasma fibrinogen and lower BMI.[62] At baseline in the Beaver Dam Eye Study, for cortical cataract, higher serum HDL cholesterol was associated with decreased risk in women. For PSC cataract, men with higher ratios of total to HDL cholesterol were at increased risk. Associations were not found for nuclear cataract.[63] In a UK case–control study of 1000 cases and 1000 controls reduced levels of total cholesterol were associated with all forms of cataract.[42] In a South African clinic based population, a strong association was found between HDL cholesterol levels and lens opacities. Below an HDL-C level of 1.5 mmol/l subjects had a seven-fold higher calculated probability of falling in the lens opacity subgroup than those above this level. An association was also found between high (>5) LDL : HDL ratios and lens opacities.[64] There appears to be little consistency among these results from different studies.

Multivariable logistic regression confirmed that the mean number of units of alcohol consumed in a month and HDL cholesterol were each independently associated with retrodots at the 5% significance level. Higher mean alcohol intake was protective against retrodots. This relationship has been observed in previous studies for cortical cataract but not for nuclear opacification. The present finding of increased risk associated with higher HDL cholesterol is less in keeping with published results for other cataract morphologies.

Several previously identified risk factors for cataract were notable for their absence among the positive associations found in these case–control studies of waterclefts and retrodots. No associations with age and gender were expected because cases and controls were matched for these variables. The authors were however surprised that certain other documented risks, cigarette smoking[16,28,65] and blood glucose or diabetes[35,65,66] for example, did not feature among our identified risk factors. For most variables the power of the studies was sufficient to exclude, with some confidence, medium to large effects for the negative findings in our two study populations. Certain negative findings however might have occurred as a result of small numbers of participants being involved, for instance there were under 5% of subjects with diabetes in each of the case–control study samples.

The SAES is the first to report details on risk factors for the visually significant cataract features waterclefts and retrodots separately. The case–control methodology and sample size provide reasonable power for investigation of these factors. In addition to the identified associations, our two case–control studies were able to rule out medium to large effects in this population for certain of the hypothesised risk factors such as cigarette smoking. Although causal associations cannot be deduced or assumed on the basis of this methodology, this work suggests a need for investigation of the factors identified here in other populations.

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