· Clinical Research ·

Nutrient patterns and risk of cataract: a case-control study

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Abstract

● AIM: To assess the relation between nutrient patterns and cataract risk.

● METHODS: This is a hospital-based case-control study with 97 cataract patients and 198 matched controls. Dietary consumption was collected through a valid food frequency questionnaire (FFQ). Nutrient patterns were detected by applying factor analysis. Unconditional logistic regression models were used to estimate odds ratio (ORs) and 95%CIs.

● RESULTS: We extracted 5 main nutrient patterns. Factor 1 included niacin, thiamin, carbohydrates, protein, zinc, vitamin B6 and sodium (sodium pattern). Factor 2 was characterized by oleic acid, monounsaturated fats, polyunsaturated fats, linoleic acid, trans fatty acid, linolenic acid, vitamin E and saturated fats (fatty acid pattern). The third factor represented high intake of vitamin B12, vitamin D, cholesterol and calcium (mixed pattern). The 4th pattern was high in intake of beta and alpha carotene, vitamin A and vitamin C (antioxidant pattern). Finally, the 5th pattern loaded heavily on docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) (omega-3 pattern). In crude and multivariate analysis, the sodium pattern was associated with increased risk of cataract (OR=1.97, 95%CI: 1.09-3.96). The fatty acid pattern elevated the risk of cataract (OR=1.94, 95%CI: 1.1-3.86). Antioxidant pattern was associated with a significant 79% reduced risk (2nd category compared with the 1st). Omega-3 pattern was significantly negatively associated with risk of cataract (*P*=0.04).

● CONCLUSION: These findings imply that nutrient patterns reflecting a combined consumption of nutrients might be important in the etiology of cataract. Additional studies with more efficient designs are warranted to confirm our findings.

● KEYWORDS: nutrient patterns; cataract; case-control study

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INTRODUCTION

Cataract is a opacification of eye lens which causes vision loss in over 80 million people and blinds 18 million worldwide[1]. In Iran 31.7% of blindness cases and 47.5% of severe and chronic visual diseases are due to this disease. In recent years, there was a significant increase in the rate of cataract surgery and many of these patients had applied for the second surgery[2]. The economic costs of major vision disorders is tremendous (>$138 billion annually, including direct costs and lost productivity) and are growing considerably[1]. Age-related cataract has multiple causes, including oxidative destruction of the lens[3]. Mounting evidence suggest that dietary antioxidants (by obviating oxidation of proteins or lipids within the lens) might prevent or delay the incidence of cataract[4].

Much of the early research on the role of diet in cataract focused on antioxidants, but this has since expanded to include macronutrients such as carbohydrates and fatty acids[5-12]. However, the results from observational studies[13] and randomized controlled trials[14] of the effects of antioxidant supplements on cataract risk have been inconclusive.

Based on Willett and Buzzard study, focusing overall nutrients as an exposure (rather than single nutrients) provides advantages, including an ability to detect cumulative effects which could be sufficiently large to be detectable[15]. Moreover, combining nutrients into composite "factors" (by applying factor analysis), provides an opportunity for taking into account interactions and synergic effects of nutrients, which probably is not detectable by traditional analysis of nutrients in isolation[16].

Therefore, the aim of current study was to evaluate the associations of major nutrient patterns with the risk of cataract in a hospital-based case-control study in Iran.

SUBJECTS AND METHODS

Subjects Details of the study are reported elsewhere[2]. Briefly 202 controls and 101 cases were selected using convenience sampling method from Farabi (ophthalmology teaching hospital, with 220 beds and 10 sections) and Shariati hospitals in Tehran considering the inclusion and exclusion criteria. Case definition for cataract: the progressive opacification of eye lens, resulting in blurred vision which was diagnosed by ophthalmologist (using slit lamps)[2,17].

The inclusion criteria for the case group were: it should not exceed one month since the diagnosis of the cataract; presence of a cataract in at least one eye; both eyes had no serious conditions that can cause vision loss except for cataract; the affected eye had visual acuity of 0.6 or worse[17]; aged above 40y. Meanwhile, controls were patients who had been referred to the same hospital for diseases not related to cataract, with good visual acuity and no lens opacities in either eye. Controls were excluded if they had any treatments or medical conditions which known to be associated to cataract or cause eye and vision problems (*e.g.* age-related macular degeneration, radiation therapy, diabetic retinopathy, glaucoma, previous ocular surgery or acute or chronic uveitis) and if they are being on a special diet one year before the interview. The control group was matched according to gender and age (with a five-year interval) with the case group. At the end of the study, eight persons from cases and controls with daily calories intake of less than 702 kcal or more than 5016 kcal, which perhaps demonstrate unconcerned completion of the dietary questionnaire (less or more than the "mean ±3 SD" for $\log_e$ transformed energy), were removed and excluded from the study.

Dietary Assessment Dietary information of cases (1y before diagnosis) and controls (1y before the interview) were gathered by trained dietitians applying a valid semi-quantitative food frequency questionnaire (FFQ). This FFQ includes 147 food items and has been indicated to be a valid and reproducible questionnaire for the measurements of nutrients and food groups intake among Iranian adults[18-19].

Participants were asked to recall their consumption frequency of a given serving of each food item during the past year (on a daily, weekly, monthly or yearly basis). Regular household measures (cups, spoons, palm of hand, *etc*.) were applied for better estimation of the real portion consumed by the participants[20]. Portion sizes consumed from each food item, were then converted to daily gram intake by using the household scales[20]. Daily energy, macronutrients and micronutrients consumption for participants were computed by Nutritionist IV software which was designed for evaluation of Iranian foods. Since Iranian food composition table (FCT) is not complete and comprehensive, analyses of energy and nutrients were done by using the United States Department of Agriculture (USDA) FCT. However, for some products (such as mint, sweet canned, kashk, cherry and sour cherry) that are not listed in the USDA FCT, Iranian FCT was run instead[19].

Assessment of Non-dietary Exposures The required information regarding age, family history of cataract, hypertension (defined as systolic blood pressure above 160 mm Hg or diastolic blood pressure above 100 mm Hg or the use of antihypertensive medication), heart disease, hyperlipidemia, arthritis, diabetes, physical activity, smoking, alcohol consumption, past consumption of vitamin C, omega-3 and multivitamin supplement, corticosteroids, oral contraceptives, estrogen therapy as well as the number of hours exposing to sunlight and using special equipment against the sun was gathered through face to face interviews. The weight of each subject was measured with minimum clothing, and 100 g sensitivity and height by a tape and the sensitivity of 0.1 cm and body mass index (BMI) was computed subsequently by the formula (weight in kg)/(height in meter)^2. All participants provided written informed consent prior to enrollment. The study was confirmed by the ethics committee at the National Nutrition and Food Technology Research Institute of Shahid Beheshti University of Medical Science.

Statistical Analysis All statistical analyses were run by applying the Statistical Package for Social Sciences software version 16 (SPSS Inc., Chicago, IL, USA), and a two-sided $P<0.05$ was regarded significant.

Factor analysis was run to explain the total variation in intake of 27 nutrients in terms of a few linear functions. In order to detect uncorrelated factors, factor scores were rotated by using varimax rotation.

We extracted 5 factors based on scree plot. By summing intakes of food groups weighted by their factor loadings, the factor score for each pattern was calculated and each patient received a factor score for each pattern. Then scores were used to assess the relation of each nutrient pattern with the risk of cataract.

We classified 5 pattern scores into two categories based on the medians. To evaluate the differences in distribution of categorical variables and continuous variables across the nutrient pattern score categories, Chi-square test and independent sample *t*-test were used respectively. The odds ratio (OR) with 95% confidence interval (CI) were calculated using conditional logistic regression. Regression models were adjusted for BMI, education, physical activity, hypertension, diabetes, and cataract family history as potential confounders.

RESULTS

General characteristics of cases (97) and controls (198) and distribution of selected risk factors are presented in Table 1. By desing, age and sex was similar in both case and control groups. In case group, male sex was less prevalent as compared to female sex (34% men *vs* 66% women). Compared to

Table 1 Baseline variables in Iranian case-control study of cataract (n=295)[1]

Characteristics	Cases (n=97)	Controls (n=198)	[2]*P*
Age (a)	57.9±9.4	57.4±9.2	0.69
BMI (kg/m^2)	28.0±4.6	26.3±4.8	0.003
Energy intake (kcal)	2850 (2354-3220)	2728 (1256-4291)	0.41
Sex (%)			0.86
M	34	33.8	
F	66	66.2	
Education (%)			<0.001
No formal education	43.3	14.6	
Primary school	23.7	34.8	
Secondary school	17.5	19.7	
Higher education	15.5	30.8	
Cataract family history (%)			0.001
Yes	54.6	40.9	
No	45.4	59.1	
Hypertension (%)[3]			0.001
Yes	54.6	40.9	
No	45.4	59.1	
Physical activity (%)[4]			0.04
Inactive	85.5	70.7	
Active	14.4	29.3	
Diabetes (%)[5]			<0.0001
Yes	27.8	11.6	
No	72.3	88.4	
Smoking status			0.28
Never	81 (83.5)	178 (80.9)	
Before	2 (2.1)	3 (0.5)	
Current	14 (14.4)	17 (8.6)	

[1]Data are presented as median (IQ: 25-75) or *n* (%); [2]*P* of the comparison between groups, using Wilcoxon or McNemar tests; [3]Hypertension defined as systolic to diastolic blood pressure over 160/100 mm Hg or the use of antihypertensive medication; [4]Fasting blood glucose >126 mg/dL was considered diabetes; [5]Physical activity more than 3 times/per week and each time >30min.

controls, cases reported higher physical inactivity and they had higher BMI (P<0.05). Cases were less educated and reported somewhat lower use of sun glasses or hats in front of the sun (P<0.05). However, controls reported less medical history of diabetes, hypertension, and family history of cataract.

Factor-loading matrix for the 5 extracted factors (major nutrients patterns) is shown in Table 2. These factors together accounted for 81.3% of the total variance. Factor 1 included 24.8% of the total variance and was highly correlated with thiamin, niacin, carbohydrates, protein, zinc, vitamin B6 and sodium (sodium pattern). The second factor reflected mainly consumption of oleic acid, monounsaturated fats, polyunsaturated fats, linoleic acid, trans fatty acids, linolenic acid, vitamin E and saturated fats (fatty acid pattern). The third factor was characterized by high intake of vitamin

Table 2 Factor-loading matrix for 5 factors representing major nutrient patterns in a case-control study of cataract in Iran n=295

Parameters	Component				
	1	2	3	4	5
Vitamin B1 (thiamine) (mg)	0.637				
Vitamin B3 (nicotinic acid) (mg)	0.614				
Carbohydrates (g)	0.893				
Proteins (g)	0.847		0.408		
Zinc (mg)	0.643		0.374		
Vitamin B6 (pyridoxine) (mg)	0.810			0.394	
Sodium (mg)	0.989				
Vitamin B2 (riboflavin) (mg)	0.688		0.651		
Vitamin H (Biotin) (mg)	0.576		0.373	0.421	
Oleic acid, 18:1		0.982			
Monounsaturated fats (g)		0.979			
Polyunsaturated fats (g)		0.966			
Linoleic acid, 18:2		0.962			
Trans fats (g)		0.949			
Linolenic acid, 18:3		0.877			
Vitamin E (mg)		0.759			
Saturated fats (g)		0.705	0.476		
Vitamin B12 (pyridoxine) (mg)			0.761		
Vitamin D (μg)			0.698		
Cholesterol (mg)	0.388		0.689		
Calcium (mg)	0.603		0.622		
Beta carotene (mg)				0.935	
Alfa carotene (mg)				0.811	
Vitamin A (mg)			0.484	0.763	
Vitamin C (mg)				0.651	
EPA 21:5 (g)					0.988
DHA 22:6 (g)					0.988

B12, vitamin D, cholesterol and calcium (mixed pattern). The 4th pattern was high in intake of beta and alpha carotene, vitamin A and vitamin C (antioxidant pattern). Finally, the 5th pattern loaded heavily on docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) (omega-3 pattern).

Table 3 shows participants' characteristics according to median categories of nutrient pattern scores. In high category of factor 1 and 2 scores compared with the low category, BMI values tended to be higher. BMI values in high category of factor 5 scores tended to be smaller compared with the low category. Total energy intakes of participants in the high category scores of first 3 factors relative to those in the low category was significantly higher (P<0.001).

The ORs and their 95% CI for cataract by the median of dietary pattern scores are displayed in Table 4. In crude and multivariate analysis, the sodium pattern tended to increase the risk of cataract (high: second median *vs* low: first median, OR=1.97, 95%CI: 1.09-3.96). Similarly, in crude and multivariate analysis, the fatty acid pattern increased the risk of

Table 3 Participants' characteristics according to median categories of nutrient pattern scores in a case-control study of cataract in Iran (*n*=295)[1]

Nutrient patterns	BMI (kg/m^2)	Energy intake (kcal/d)	University education (%)	Current smoking (%)
Factor 1				
Low	26.2±0.29	2437±40	35 (23.6)	12 (8.1)
High	27.4±0.47	3162±42	41(27.9)	19 (12.9)
P	0.02	0.00	0.28	0.37
Factor 2				
Low	26.2±0.30	2483±44	46 (31.1)	17 (11.5)
High	27.3±0.46	3115±44	30 (20.4)	14 (9.5)
P	0.04	<0.001	0.21	0.07
Factor 3				
Low	27.0±0.35	2661±48	32 (21.5)	13 (8.7)
High	26.5±0.43	2938±51	44 (30.1)	18 (12.3)
P	0.35	<0.001	0.29	0.52
Factor 4				
Low	27.0±0.43	2761±57	36 (24.3)	21 (14.2)
High	26.6±0.35	2836±43	40 (27.2)	10 (6.8)
P	0.36	0.30	0.04	0.10
Factor 5				
Low	27.5±0.43	2751±52	36 (24.3)	14 (9.5)
High	26.1±0.34	2846±49	40 (27.2)	17 (11.6)
P	0.01	0.18	0.35	0.35

[1]Categorical variables Chi-square test and for continuous variables independent sample *t*-test was applied. BMI: Body mass index.

Table 4 Unadjusted and adjusted OR and 95%CI for cataract risk by median categories of nutrient pattern in a case-control study in Iran *n*=295

Nutrient patterns	Control (*n*)	Case (*n*)	Crude OR	95%CI	Adjusted OR[1]	95%CI	*P*
[2]Factor 1							
Low	99	37	1.00 (ref.)		1.00 (ref.)		
High	99	60	1.62	1.05-2.66	1.97	1.09-3.96	0.051
Factor 2							
Low	99	35	1.00 (ref.)		1.00 (ref.)		
High	99	62	1.77	1.07-2.91	1.94	1.1-3.86	0.052
Factor 3							
Low	99	58	1.00 (ref.)		1.00 (ref.)		
High	99	39	0.67	0.41-1.10	0.73	0.41-1.29	0.28
Factor 4							
Low	99	76	1.00 (ref.)		1.00 (ref.)		
High	99	21	0.27	0.15-0.48	0.21	0.11-0.40	<0.001
Factor 5							
Low	100	63	1.00 (ref.)		1.00 (ref.)		
High	98	34	0.52	0.32-0.86	0.71	0.40-0.92	0.04

CI: Confidence interval; OR: Odds ratio. [1]Adjusted for BMI, physical activity, education, diabetes, hypertension and cataract family history; [2]Data are presented as median (IQ: 25-75).

cataract (high: second median *vs* low: first median, OR=1.94, 95%CI: 1.1-3.86). There were no significant association between mixed pattern and cataract (*P*=0.28). Antioxidant pattern was associated with a significant 79% lower risk for cataract in the 2nd category compared with the 1st (OR=0.21, 95%CI: 0.11-0.40). In both crude and multivariate analysis, omega-3 pattern was significantly negatively associated with risk of cataract (OR=0.71, 95%CI: 0.40-0.92).

DISCUSSION

The aim of the current study was to assess the relation between nutrient patterns and risk of cataract in Tehran. We identified five main nutrient patterns: factor 1 included thiamin, niacin, carbohydrates, protein, zinc, vitamin B6 and sodium (sodium pattern). Factor 2 was characterized by oleic acid, monounsaturated fats, polyunsaturated fats, linoleic acid, trans fatty acids, linolenic acid, vitamin E and saturated fats (fatty acid pattern). The third factor was characterized by high intake of vitamin B12, vitamin D, cholesterol and calcium (mixed pattern). The 4th pattern was high in intake of beta and alpha carotene, vitamin A and vitamin C (antioxidant pattern). Finally, the 5th pattern loaded heavily on DHA and EPA (omega-3 pattern). Sodium pattern and fatty acid pattern were positively associated with the risk of cataract. Moreover, antioxidant pattern and omega-3 pattern were negatively associated with the risk of cataract.

Although nutrients have always been shown to be an important determinant for cataract risk, the cumulative effect of nutrient intakes on incidence of cataract has never been assessed. To our knowledge, this is the first study to evaluate nutrient patterns (applying factor analysis) in relation to cataract risk. Our findings indicate that nutrient patterns may play an important role in the etiology of cataract. Several studies to date investigated the association between individual nutrients and cataract risk, and a positive relation has been found for sodium (loaded on factor 1) and fatty acids (loaded on factor 2). We know that excessive intake of sodium can cause hypertension and subsequent development of cataract[21]. Mirsamadi and Nourmohammadi[22] suggested a positive and significant correlation between the excessive sodium intake and cataract development. Recently, Bae *et al*[23] in a case-control study of 12693 participants mentioned that high sodium intake might affect the development of cataracts.

Na^+/K^+ electrolyte imbalance in the aqueous humor is another biological plausible mechanism of cataractogenesis[24]. In cataractous situation, higher levels of extracellular sodium would cause influx of Na^+ in the lens, attracts water ions. Thus, it would be difficult for sodium pumps to maintain the low levels of intracellular sodium needed for lens transparency[25].

Despite little evidence of significant associations between total fat intake and cataract, several studies suggested that high total fat and cholesterol intake will elevated the risk of cataract (overall and all subtypes)[26-27]. Tavani *et al*[28] in a case-control study (*n*=207 cases) found that diet might have an appreciable role in the risk of cataract extraction and among food items, higher intake of butter, total fat and salt accompanied by a significant increase in risk. Results from European Prospective Investigation into Cancer and Nutrition (EPIC-Oxford) (*n*= 27 670) revealed that elevated blood levels of saturated fat and cholesterol are associated with increased risk of “any” type of cataract[29]. By investigation into effects of fats separately, two studies reported a significant positive associations between nuclear opacity and high intakes of linoleic and linolenic acid[30-31]. In a hospital-based case-control study in China (*n*=360 cases), participants in the highest quartile had 2.7 times higher risk of nuclear cataract compare to participants in the lowest quartile of polyunsaturated fatty acids intake[32]. However, results regarding fat intake and cataract are inconsistent and in Beaver Dam cohort study (*n*=1919), there was no relation between prevalence of nuclear opacity and total fat intake[33].

In our study factor 4 (loaded heavily on carotenoids and vitamin C) was inversely related with risk of cataract. The eye lens is persistently exposed to oxidative stress related to radiation and other issues. When the level of pro-oxidants exceeds the cellular antioxidant defense, lens proteins become modified, denatured and aggregated, contributes to cataract formation[34]. The lens through several mechanisms protects its components against oxidative stress, such as antioxidant enzymes, micronutrients antioxidants and proteases[35]. According to the role of pro-oxidants in cataractogenesis, few epidemiologic studies have tried to assess which antioxidants are protective factors for cataract[36]. In accordance with our findings, carotenoids has been consistently associated with a reduced risk of cataract.

Cross-sectional analysis from a large cohort study (*n*=5638) reported a strong negative association between plasma and dietary vitamin C and cataract, the results revealed that those with the highest plasma levels of vitamin C compared with those with the lowest plasma levels had a 35% reduced risk of cortical cataract[36]. Also a large prospective study approved the negative relation between dietary vitamin C intake and the risk of age-related cataracts for both men and women[37], findings from two case-control studies strengthened the evidence for a protective role of vitamin C on the aging lens[27,38]. Furthermore, Theodoropoulou *et al*[26] findings provide additional support to this hypothesis that intake of antioxidants such as vitamins C and E and carotene is negatively associated with risk of cataract. However, some results have shown that vitamin C supplement use, particularly in higher dose and for longer duration, may increase the risk of age-related cataract[13]. One randomized controlled trial study shows that long-term intervention with high-dose vitamin E and vitamin C (either alone or in combination) has little effect on rates of cataract diagnosis and extraction[39].

In our study, factor 5 (loaded heavily on EPA and DHA) was negatively associated with risk of cataract. Two studies indicated the protective role of omega-3 in cataract[40-41]. The Blue Mountains Eye Study showed that in those who consumed 0.5-1.42 g/d of omega-3 fatty acids (found in flaxseed, walnuts, salmon, shrimp, and many other sea foods), omega-3 polyunsaturated fatty acids (n-3 PUFA) could reduce risk of nuclear cataract[41]. Based on the Nurses' Health Study, those with higher intake of omega-3 specifically, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) had a 17% and 12% decreased risk of cataract, respectively[42]. However, one study showed a 2.2 fold increased risk of "any" cataract in those with high intake of omega-3 fatty acids[30]. The protective mechanism provided by n-3 PUFA against cataract formation is not clear, but it might be explained by positive effects of n-3 PUFA on serum levels of high-density lipoprotein (HDL)[41,43]. HDL carries vitamin E molecules which are powerful antioxidants. Therefore, n-3 PUFA *via* increasing the availability of vitamin E indirectly could suppress the process of oxidation[44].

The careful selection of paricipants using slit lamp, participation rate of above 90%, using the validated questionnaires, low possibility of recall bias (only new cases were enrolled in the study) are the strengths of our study.

The major limitation of the current study is small sample size. Furthermore, since for running factor analysis we must have at least 5-10 subjects per variables (nutrients), therefore sub-analysis based on type of cataract (nuclear, posterior and mixed) was not possible due to small sample size. Moreover, one of the major drawbacks of convenience sampling method which we used in our study is the opportunity for bias to cloud the results of the study and undermines generalizability of results.

Our findings suggested that nutrient patterns (defined by factor analysis) might be important for the causation of cataract. Before any firm conclusion can be drawn, more results from large cohort studies are needed.

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