European Journal of Clinical Nutrition (2018) 72, 161–167

www.nature.com/ejcn

ORIGINAL ARTICLE

Associations between fruits, vegetables, vitamin A, β-carotene and flavonol dietary intake, and age-related macular degeneration in elderly women in Korea: the Fifth Korea National Health and Nutrition Examination Survey

E-k Kim, H Kim, O Kwon and N Chang

BACKGROUND/OBJECTIVES: Age-related macular degeneration (AMD) is one of the principal causes of blindness. This study investigated the association between diet and the prevalence of AMD in elderly Korean women.
SUBJECTS/METHODS: Study subjects were women aged ⩾65 years ($n = 1008$) from the Korea National Health and Nutrition Examination Survey (2010–2012). The presence of early- and late-onset AMD was determined on the basis of a fundus photograph from a health examination survey. Food intake was estimated using 24 h recall.
RESULTS: The prevalence of AMD was 18.8% in elderly women in Korea. Multiple logistic regression analysis showed a significant negative association between vegetable intake and AMD (odds ratio (OR) 0.44, 95% confidence interval (CI) 0.25, 0.77, *P* for trend = 0.002) after adjusting for age, body mass index, postmenopausal period, duration of hormone replacement therapy, residential area, education level, family income, smoking status, alcohol consumption, dietary supplement use and total energy intake. After adjusting for potential confounders, the ORs between extreme quartiles were 0.55 (95% CI 0.29, 1.05, *P* for trend = 0.070) for fruit and vegetable intake, 0.38 (95% CI 0.21, 0.68, *P* for trend = 0.001) for vitamin A, 0.36 (95% CI 0.19, 0.67, *P* for trend < 0.001) for β-carotene and 0.45 (95% CI 0.25, 0.82, *P* for trend = 0.008) for flavonols.
CONCLUSIONS: These results suggest that higher consumption of fruits and vegetables containing antioxidant nutrients and phytochemicals may provide some protection against AMD.

European Journal of Clinical Nutrition (2018) 72, 161–167; doi:10.1038/ejcn.2017.152; published online 27 September 2017

INTRODUCTION

Age-related macular degeneration (AMD) is one of the principal causes of blindness, comprising an estimated 5% of all cases of blindness.[1] Worldwide, the estimated prevalence of early and late AMD varies from 4.4 to 16.8% and 0.6 to 3.7%, respectively, depending on the study population.[2–6] Numerous studies have identified age,[7,8] female gender,[9] smoking,[7,8] blood cadmium level,[10] diabetes mellitus,[7,11] alcohol consumption,[12] liver cancer[7] and family history[13] as risk factors for AMD.

Observational studies[14–16] have also investigated the relationship between AMD and dietary factors, and suggested that fruits, vegetables, vitamin C, vitamin E, β-carotene and other carotenoids and flavonoids may have an important role in the onset and progression of AMD. Recently, studies have shown associations between AMD and dietary patterns,[17–19] the Healthy Eating Index Score[20] and the Mediterranean diet.[21] Healthier diets including high fruit and vegetable intake were associated with lower AMD risk.

Among carotenoids, lutein and zeaxanthin, the main pigment in the macular area in human retina are particularly effective for protecting the macular from oxidative damage by eliminating harmful reactive oxygen species.[22,23] β-Carotene accumulates in retinal pigment epithelium (RPE) cells and provides some protection against light-induced retinal damage.[24] Flavonoids assist with blocking the accumulation of reactive oxygen species and upregulating the expression of proteins, which could protect against oxidative stress in human RPE cells.[25] However, interventional studies assessing the effect of dietary supplementation on AMD progression are inconsistent.[26–28]

Most previous studies on the association between AMD and dietary factors have been performed in the American[14,15,26] and European regions.[2,16,29] Some studies have also been conducted in Japan, China and India.[11,30,31] The prevalence of AMD in Korea is estimated to be 16.9% for early AMD and 1.8% for late AMD in the elderly.[8] With an increasing elderly population, age-related health problems are becoming more important in Korea. In addition, female gender has been associated with a higher risk of AMD in many studies.[5,9] Identification of risk factors for female AMD need to understand the pathogenesis of the AMD and reduce the risk. However, there has been little research associated with AMD and the relationship between dietary intake and AMD has never been studied in the Korean population.

Thus, this study was conducted to investigate the association between AMD and dietary factors, including the consumption of fruits, vegetables, carotenoids and flavonoids in the Korean elderly women, using the Korea National Health and Nutrition Examination Survey (KNHANES) data.

Department of Nutritional Science and Food Management, Ewha Womans University, Seoul, Republic of Korea. Correspondence: Professor N Chang, Department of Nutritional Science and Food Management, Ewha Womans University, 11-1 Daehyun-Dong, Seodaemun-Gu, Seoul 120-750, Republic of Korea.
E-mail: nschang@ewha.ac.kr
Received 5 September 2016; revised 18 July 2017; accepted 19 July 2017; published online 27 September 2017

SUBJECTS AND METHODS

Study population

This study used data from the fifth KNHANES, a cross-sectional and nationally representative survey conducted by the Korean Ministry of Health and Welfare from 2010–2012. KNHANES comprises a series of cross-sectional, stratified and multistage probability surveys of the civilian, non-institutionalized Korean population. The survey consists of a health interview survey, a health examination survey and a nutrition survey. The response rate of these surveys was 81.9, 80.4 and 80.0% in 2010–2012, respectively. Detailed information of each survey is available on the website (http://knhanes.cdc.go.kr).[32]

This study included all women aged ⩾65 years ($n=2711$) in the database. We excluded 159 participants without 24 h dietary recall data; 559 without fundus photograph; 366 diagnosed with diabetes mellitus or diabetic retinopathy, or reported taking medications for diabetes; 33 reported a history of liver, stomach, colorectal, uterine or cervical cancer; 573 had undergone ocular surgery; and 13 with implausible energy intakes (< 500 or > 5000 kcal). Thus, a total of 1008 participants were eligible for further analysis.

This study was approved by the Institutional Review Board of the Korea Centers for Disease Control and Prevention (2010-02CON-21-C, 2011-02CON-06-C, 2012-01EXP-01-2C). All subjects in the study participated voluntarily and provided informed consent.

General characteristics and other covariates

The general questionnaire and health interview data were used to obtain the demographic and socioeconomic characteristics of the participants, including age, body mass index (BMI), reproductive (number of pregnancies and duration of oral contraceptive pills) and menopausal (menopausal age, postmenopausal period and duration of hormone replacement therapy) factors, residential area, education level, family income, smoking status, alcohol consumption and dietary supplement use.

BMI was calculated as weight (kg)/(height (m))^2. Residential area was categorized as urban or rural. Education level was categorized as less than high school or high school and above. Family income was assessed with 4 categories (low, middle-low, middle-high or high). Smoking status was assessed with three categories (current smoker, ex-smoker or non-smoker). Alcohol consumption was assessed with five categories (never, < 1 drink/mo, 1 drink/mo, 2–4 drink/mo or ⩾4 drink/mo within the last year). Dietary supplement use was assessed with two categories (yes or no).

Assessment of AMD

The presence of early and late onset AMD was determined on the basis of the fundus photograph.[5,33] All fundus photographs were graded twice using the International Age-related Maculopathy Epidemiological Study Group grading system.[34] Preliminary grading was performed on the site by trained ophthalmologist. Detailed grading was later done by nine retina specialists having experience in grading early and late AMD. Any inconsistencies between the preliminary and detailed grading was decided by an independent reading specialist. When the fundus photograph for a participant's eyes were different in severity, the grade was defined based on the more advanced grade. When the fundus photograph for only one eye was assessed, the grade was evaluated by that eye. Participants were diagnosed with early AMD if they met one of the following criteria: the presence of soft, indistinct drusen or reticular drusen; the presence of soft or hard distinct drusen with pigmentary abnormalities in the absence of signs of late AMD. Late AMD was defined as the presence of neovascular AMD or geographic atrophy. Neovascular AMD was identified by the detachment of RPE or neurosensory retina, or the presence of hemorrhages in sub-RPE or subretinal spaces. Geographic atrophy was defined as the presence of a circular discrete depigmented area ⩾175 μm in choroidal vessel diameter. The presence of any AMD was defined as either early ($n=180$) or late ($n=10$) AMD in this study.

Dietary assessment and estimation of dietary intake of carotenoids and flavonoids

We used the dietary intake data obtained from a single 24 h recall in the KNHANES data. Participants reported all foods and drinks consumed for the previous day during face-to-face interviews.

To estimate the intake of carotenoid and flavonoid, we merged individual food files from KNHANES with carotenoid and flavonoid databases. The carotenoid database included 2191 food items and was constructed using the food items of KNHANES[35] and the Carotenoid Content Database from the United States Department of Agriculture.[36] The flavonoid database was developed based on a systematic review and comprised 649 food items based on their analytic values and 900 items replaced with adaptations or calculations from similar items,[37] where we used data for the closest food item based on species and nutrients. The carotenoid and flavonoid databases included 68.7 and 68.9% of all plant foods reported in the 24 h dietary recall method, respectively.

Statistical analysis

Differences in the distribution of general characteristics between the group without AMD and the group with AMD were investigated using the SURVEY FREQ procedure. We calculated the crude weighted mean and s.e. of continuous variables using the SURVEY MEAN procedure. Significant difference according to the presence of AMD was analyzed using the SURVEY REG procedure. SURVEY LOGISTIC analysis was performed to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for AMD across quartiles of fruit, vegetable, vitamin A, β-carotene and flavonols intake, where the lowest quartile was set as the reference. The objectives of the fourth Health Plan for Korea include increasing the percentage of Koreans who eat ⩾500 g of fruits and vegetables daily.[38] Therefore, we estimated the ORs and CIs by comparing participants who consumed < 500 g of fruits and vegetables with those that consumed 500 g or more. For dietary intake, we conducted analyses adjusted for age and then further controlled for potential confounding factors: BMI, postmenopausal period, duration of hormone replacement therapy,[39] residential area, education level, family income, smoking status, alcohol consumption, dietary supplement use and total energy intake. All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

RESULTS

Of the 1008 eligible subjects, the prevalence of AMD was 18.8% (data not shown). The mean age was not statistically significantly different between subjects without and with AMD (without 71.6 years, with 72.0 years). The proportion of subjects with AMD was higher in those with education level of high school and above. Except for the educational level, the general characteristics were not significantly different between subjects without and with AMD (Table 1). General demographic and socioeconomic factors were not significantly different between included and excluded subjects (data not shown).

The subjects with AMD consumed less vegetable (274.1 g/day in subjects without AMD vs 237.0 g/day in subjects with AMD, P-value = 0.006), and fruit and vegetable (424.3 g/day in subjects without AMD vs 367.0 g/day in subjects with AMD, P-value = 0.009) than those without AMD after adjusting for age, BMI, postmenopausal period, duration of hormone replacement therapy, residential area, education level, family income, smoking status, alcohol consumption, dietary supplement use and total energy intake (Table 2). Sugar and oil/fat consumption of subjects without AMD are higher than those with AMD in our subjects. However, the mean percentages of daily calories from sugar (5.1 g) and oil/fat (3.8 g) were 1.3 and 1.9%, respectively. Therefore, it is difficult to estimate AMD prevalence according to sugar and oil/fat intake.

We found that subjects with AMD consumed fewer antioxidant nutrients including vitamin A (P-value = 0.019), β-carotene (P-value = 0.006) and flavonols (P-value = 0.031) than those without AMD after adjusting for confounding factors. Energy intake and other nutrients were not significantly different between the groups after adjusting for confounding factors (Table 3).

After adjustment for confounding factors, women with higher fruit and vegetable intakes had ORs < 1.0, but there was no statistically significant decreasing risk across intake quartiles. OR for the highest vegetable intake quartile category compared with the lowest quartile category was 0.44 (95% CI 0.25, 0.77, P for trend = 0.002). Subjects in the highest quartiles showed significantly decreased prevalence of AMD by 62% for vitamin A (OR (95% CI) 0.38 (0.21–0.68), P for trend = 0.001), 64% for β-carotene

Table 1. General characteristics of participants with or without AMD

	AMD[a]		
	Without (n = 818)	With (n = 190)	P-value[b]
Age (years)	71.6 ± 0.3	72.0 ± 0.4	0.439
BMI (kg/m^2)	24.4 ± 0.2	24.0 ± 0.3	0.305
Reproductive factors			
Number of pregnancies	5.7 ± 0.1	5.6 ± 0.2	0.443
Duration of OCP (months)	0.3 ± 0.0	0.3 ± 0.1	0.947
Menopausal factors			
Menopausal age (years)	49.2 ± 0.2	48.7 ± 0.5	0.375
Postmenopausal period (years)	22.3 ± 0.4	23.3 ± 0.7	0.375
Duration of HRT (months)	0.1 ± 0.0	0.1 ± 0.1	0.293
Residential area			
Urban	550 (67.3)	122 (64.2)	0.531
Rural	268 (32.7)	68 (35.8)	
Education			
Less than high school	699 (92.5)	153 (86.3)	0.013
High school and more	87 (7.5)	31 (13.7)	
Family income			
Low	432 (56.7)	104 (53.3)	0.870
Middle–low	194 (23.4)	43 (26.0)	
Middle–high	106 (11.9)	23 (11.4)	
High	74 (7.9)	16 (9.3)	
Smoking status			
Current smoker	24 (3.0)	4 (1.1)	0.417
Ex-smoker	33 (5.4)	8 (5.2)	
Nonsmoker	730 (91.6)	173 (93.7)	
Alcohol consumption			
Never	484 (62.4)	118 (62.2)	0.204
< 1 Months	159 (18.6)	29 (14.6)	
1 Months	44 (5.7)	13 (11.2)	
2–4 Months	66 (8.1)	16 (8.0)	
⩾ 4 Months	34 (5.2)	8 (4.0)	
Dietary supplement use			
Yes	396 (45.4)	98 (51.5)	0.248
No	422 (54.6)	92 (49.0)	

Abbreviations: AMD, age-related macular degeneration; BMI, body mass index; OCP, oral contraceptive pills; HRT, hormone replacement therapy. [a]The presence of any AMD was defined as either early or late AMD. [b]Differences between the group without AMD and the group with AMD were analyzed using the χ^2 test.

(OR (95% CI) 0.36 (0.19–0.67), *P* for trend < 0.001) and 55% for flavonols (OR (95% CI) 0.45 (0.25–0.82), *P* for trend = 0.008) after adjusting for confounding factors (Table 4).

Although fish consumption has been associated with AMD,[40] there was no a significant association between fish consumption and AMD in this study. The associations between fruit, vegetable, and nutrient intake and AMD were not significantly different after adjustment for fish consumption (data not shown).

Multiple logistic regression analysis showed a significant negative association between fruit and vegetable intake and the prevalence of AMD (OR (95% CI) for subjects consuming ⩾ 500 g = 0.61 (0.38–0.97) compared with those consuming < 500 g) after adjusting for age, BMI, postmenopausal period, duration of hormone replacement therapy, residential area, education level, family income, smoking status, alcohol consumption, dietary supplement use and total energy intake (Table 5).

DISCUSSION

This study investigated the association between dietary intake and the prevalence of AMD. We found a significant negative association between fruit and vegetable intake and AMD. The highest quartiles of vitamin A, β-carotene and flavonols intake had significantly decreased odds ratios for AMD compared with the lowest quartiles. In contrast to previous studies, we did not find a significant relationship between lutein/zeaxanthin and AMD.

This is the first study identifying an inverse relationship between fruit and vegetable consumption and AMD in elderly Korean women. High fruit and vegetable intake was inversely associated with the prevalence of AMD, which is consistent with other (non-Korean) studies. A prospective cohort study of postmenopausal women in the United States showed that the OR of AMD for participants who consumed 14 servings per week of vegetables was 0.49 (95% CI 0.27–0.91) compared with those who consumed 6.2 servings per week.[41] In the Nurses' Health Study and Health Professionals Follow-up Study, the pooled multivariate relative risk of neovascular age-related maculopathy for participants who consumed three or more servings of fruit per day was 0.64 (*P* for trend = 0.004), compared with those who consumed < 1.5 servings per day.[15] Recently, healthy dietary patterns including high intake of fruits and vegetables have been shown to be associated with lower risk of AMD. In the Age-Related Eye Disease Study, subjects in the fifth quintile group of the oriental pattern score consuming high fruits, tomatoes, vegetables and whole grains had lower risk of early AMD by 26% and advanced AMD by 62% compared with those in the first quintile group.[19]

Beneficial effects from fruit and vegetable intake may derive from the nutrients and phytochemicals, such as fibers, vitamins, minerals, flavonoids and carotenoids.[42] In this study, fruit and vegetable intake were significantly positively correlated with β-carotene, lutein+zeaxanthin and β-cryptoxanthin (data not shown). There was a significant inverse relationship between β-carotene intake and AMD, which is consistent with earlier studies in Western and Asian populations. A case–control study conducted in Japan showed that subjects in the highest quintile of β-carotene exhibited a low prevalence of neovascular AMD (OR (95% CI) 0.2 (0.1–0.4)).[31] A hospital-based study in India showed that higher levels of dietary β-carotene consumption were associated with reduced AMD risk (OR (95% CI) 0.65 (0.42–0.86)).[11] In prospective cohort studies from Nurses' Health Study and Health Professionals Follow-up Study, subjects in the highest intake quintile for β-carotene had 32% less risk of advanced AMD including neovascular AMD and central geographic atrophy (pooled relative risk (95% CI) = 0.68 (0.55–0.85)).[43]

Carotenoids, which constitute the main pigments of photoreceptors in the eye, help protect against damage and toxins.[44] They act as biological sunglasses,[45–47] absorbing and filtering blue light, which appears to be dangerous for RPE cells.[48,49] They also act as antioxidants and oxidative damage in RPE cells is known to contribute to macular degeneration.[50] The RPE accumulates α-tocopherol and carotenoids (lutein, zeaxanthin and β-carotene), which serve as antioxidants.[45,46,51] Chichili *et al.*[51] showed the uptake and protective effects of β-carotene from tomatoes on oxidative stress in human RPE cell lines.

We did not find a relationship between xanthophyll carotenoids, such as lutein, zeaxanthin and β-cryptoxanthin, and AMD. Similarly, epidemiological studies on the association between lutein and zeaxanthin intake and AMD are inconclusive and differ according to the type of AMD. A cross-sectional population-based study showed no relationship between lutein/zeaxanthin and either early or late AMD.[14] A recent prospective cohort study in the United States showed a relationship between lutein/zeaxanthin and advanced AMD (primarily neovascular AMD), but no relationship with intermediate AMD.[43] Another cohort study

Table 2. Daily food intake of participants with or without AMD

	AMD[a]		P-value[b]	
	Without (n = 818)	*With (n = 190)*	*Age-adjusted*	*Multiple adjusted*[c]
Cereal and cereal products (g)	288.8 ± 5.5	277.9 ± 9.9	0.358	0.767
Potatoes and starch products (g)	31.2 ± 5.6	23.4 ± 7.3	0.437	0.474
Sugar and sugar products (g)	5.5 ± 0.4	3.4 ± 0.5	0.001	0.006
Beans and bean products (g)	32.5 ± 2.6	33.2 ± 4.9	0.900	0.734
Nuts and seeds products (g)	3.8 ± 0.6	4.8 ± 1.6	0.514	0.316
Mushrooms (g)	3.0 ± 1.3	3.4 ± 1.4	0.808	0.711
Seaweeds (g)	3.7 ± 0.6	4.0 ± 1.6	0.852	0.853
Fruit and vegetable (g)	424.3 ± 15.4	367.0 ± 18.5	0.022	0.009
Fruits (g)	150.3 ± 11.4	130.0 ± 12.3	0.272	0.232
Vegetables (g)	274.1 ± 9.1	237.0 ± 12.8	0.023	0.006
Meat and meat products (g)	37.2 ± 5.3	29.4 ± 4.7	0.264	0.703
Eggs and egg products (g)	8.4 ± 0.9	6.3 ± 1.6	0.272	0.600
Fish and shellfish (g)	32.1 ± 3.1	24.2 ± 4.0	0.137	0.426
Milk and dairy products (g)	39.8 ± 3.8	56.9 ± 9.6	0.080	0.290
Oil and fat (g)	4.1 ± 0.3	2.6 ± 0.3	< 0.001	0.003
Beverages (g)	47.1 ± 6.1	67.5 ± 14.7	0.192	0.199
Seasoning (g)	21.8 ± 1.0	22.5 ± 2.0	0.747	0.334
Other (g)	0.40 ± 0.24	0.01 ± 0.01	0.101	0.136
Total food intake (g)	983.7 ± 23.0	926.4 ± 32.4	0.197	0.200

Abbreviations: AMD, age-related macular degeneration; BMI, body mass index. [a]The presence of any AMD was defined as either early or late AMD. [b]Significant difference according to the presence of AMD was analyzed using the SURVEY REG procedure. [c]The multiple model was adjusted for age, BMI, postmenopausal period, duration of hormone replacement therapy, residential area, education level, family income, smoking status, alcohol consumption, dietary supplement use and total energy intake.

Table 3. Daily nutrients, carotenoids and flavonoids intake of participants with or without AMD

	AMD[a]		P-value[b]	
	Without (n = 818)	*With (n = 190)*	*Age-adjusted*	*Multiple adjusted*[c]
Energy (kcal)	1498.5 ± 23.6	1437.5 ± 46.6	0.284	0.246
Carbohydrate (g)	287.4 ± 4.3	271.6 ± 8.9	0.129	0.113
Protein (g)	47.2 ± 1.1	44.3 ± 1.8	0.199	0.566
Fat (g)	18.5 ± 0.7	19.1 ± 1.2	0.566	0.153
Calcium (mg)	368.0 ± 11.8	336.2 ± 20.7	0.226	0.200
Iron (mg)	12.3 ± 0.6	10.5 ± 0.6	0.055	0.161
Thiamin (mg)	0.9 ± 0.0	0.9 ± 0.0	0.305	0.124
Riboflavin (mg)	0.8 ± 0.0	0.7 ± 0.0	0.129	0.087
Niacin (mg)	11.4 ± 0.3	10.8 ± 0.5	0.271	0.512
Vitamin C (mg)	80.7 ± 3.7	70.6 ± 4.9	0.125	0.171
Vitamin A (μgRE)	614.0 ± 35.1	460.9 ± 43.1	0.008	0.019
Carotenoids				
β-Carotene (mg)	3.4 ± 2.0	2.4 ± 2.4	0.003	0.006
β-Cryptoxanthin (mg)	0.5 ± 0.1	0.3 ± 0.1	0.046	0.177
Lutein+zeaxanthin (mg)	2.0 ± 0.1	1.8 ± 0.3	0.729	0.848
Lycopene (mg)	1.2 ± 0.2	0.8 ± 0.2	0.128	0.225
Flavonoids				
Total flavonoids (mg)	89.1 ± 5.3	80.5 ± 7.2	0.418	0.382
Anthocyanidins (mg)	28.0 ± 2.7	19.6 ± 2.6	0.023	0.096
Flavan-3-ols (mg)	10.9 ± 3.6	12.3 ± 5.3	0.750	0.985
Flavanones (mg)	5.4 ± 0.7	4.8 ± 1.2	0.737	0.865
Flavones (mg)	0.7 ± 0.0	0.7 ± 0.1	0.550	0.611
Flavonols (mg)	23.1 ± 1.7	19.3 ± 2.7	0.260	0.031
Isoflavones (mg)	21.3 ± 1.2	24.1 ± 3.5	0.465	0.288

Abbreviations: AMD, age-related macular degeneration; BMI, body mass index. [a]The presence of any AMD was defined as either early or late AMD. [b]Significant difference according to the presence of AMD was analyzed using the SURVEY REG procedure. [c]The multiple model was adjusted for age, BMI, postmenopausal period, duration of hormone replacement therapy, residential area, education level, family income, smoking status, alcohol consumption, dietary supplement use and total energy intake.

Table 4. ORs and 95% CIs of intakes of fruit and vegetable and the prevalence of AMD

	Quartile 1	*Quartile 2*	*Quartile 3*	*Quartile 4*	*P for trend*[a]
Fruit and vegetable					
Participants, *n*	252	252	252	252	
Median (g/day)	118.5	267.5	445.7	814.9	
Age-adjusted	Ref	0.82 (0.50–1.35)	0.87 (0.51–1.49)	0.69 (0.41–1.15)	0.166
Multiple adjusted[b]	Ref	0.80 (0.47–1.37)	0.71 (0.39–1.28)	0.55 (0.29–1.05)	0.070
Fruits					
Participants, *n*	390	114	252	252	
Median (g/day)	0	22.6	139.7	399.8	
Age-adjusted	Ref	1.15 (0.58–2.26)	1.51 (0.93–2.47)	1.22 (0.77–1.93)	0.571
Multiple adjusted[b]	Ref	1.30 (0.64–2.64)	1.64 (0.95–2.81)	1.21 (0.69–2.13)	0.508
Vegetables					
Participants, *n*	252	252	252	252	
Median (g/day)	79.3	124.9	277.7	496.1	
Age-adjusted	Ref	0.77 (0.47–1.28)	0.84 (0.49–1.44)	0.57 (0.33–0.97)	0.042
Multiple adjusted[b]	Ref	0.84 (0.63–1.20)	0.73 (0.41–1.31)	0.44 (0.25–0.77)	0.002
Vitamin A					
Participants, *n*	252	252	252	252	
Median (μgRE/day)	101.2	272.5	552.0	1181.1	
Age-adjusted	Ref	1.00 (0.58–1.61)	0.82 (0.50–1.34)	0.48 (0.28–0.84)	0.003
Multiple adjusted[b]	Ref	0.84 (0.50–1.43)	0.71 (0.41–1.21)	0.38 (0.21–0.68)	0.001
β-carotene					
Participants, *n*	252	252	252	252	
Median (mg/day)	0.5	1.4	3.0	6.4	
Age-adjusted	Ref	0.99 (0.61–1.62)	0.76 (0.47–1.25)	0.45 (0.25–0.84)	0.002
Multiple adjusted[b]	Ref	0.92 (0.56–1.54)	0.69 (0.41–1.15)	0.36 (0.19–0.67)	< 0.001
Flavonols					
Participants, *n*	252	252	252	252	
Median (mg/day)	2.5	7.9	16.4	49.4	
Age-adjusted	Ref	0.77 (0.45–1.32)	0.75 (0.45–1.27)	0.59 (0.34–1.01)	0.069
Multiple adjusted[b]	Ref	0.75 (0.41–1.39)	0.68 (0.38–1.21)	0.45 (0.25–0.82)	0.008

Abbreviations: AMD, age-related macular degeneration; BMI, body mass index; CI, confidence interval; OR, odds ratio. [a]Test for linear trends used the median value in each quartile as a continuous variable in linear regression. [b]The multiple model was adjusted for age, BMI, postmenopausal period, duration of hormone replacement therapy, residential area, education level, family income, smoking status, alcohol consumption, dietary supplement use and total energy intake.

Table 5. ORs and 95% CIs of AMD according to fruit and vegetable intake

	< 500 g/day	⩾500 g/day
Participants, *n*	686	322
Median (g/day)	244.6	697.3
Age-adjusted	Ref	0.71 (0.48–1.06)
Multiple adjusted[a]	Ref	0.61 (0.38–0.97)

Abbreviations: AMD, age-related macular degeneration; BMI, body mass index; CI, confidence interval; OR, odds ratio. [a]The multiple model was adjusted for age, BMI, postmenopausal period, duration of hormone replacement therapy, residential area, education level, family income, smoking status, alcohol consumption, dietary supplement use and total energy intake.

conducted in the United States suggested that diets rich in lutein and zeaxanthin may have protective effects against intermediate AMD in women aged 50–74 years.[41] Although lutein and zeaxanthin may be effective in preventing AMD, the effect may differ according to the development and progression of AMD. In this study, subjects with late AMD were 10% of the total AMD. Therefore, we could not confirm associations between lutein/ zeaxanthin intake and each different type of AMD.

We observed for the first time that the highest quartile of flavonols intake had significantly decreased ORs for AMD compared with the lowest quartile. Subjects with AMD consumed significantly less quercetin than those without AMD after adjusting for confounding factors ($P = 0.02$) (data not shown). The flavonol quercetin occurs abundantly in apples, onions and berries.[52] Several previous studies have identified the protective effects of quercetin on human RPE. Kook *et al.*[53] showed that quercetin protects human RPE cells *in vitro* from oxidative stress-induced cell death and cellular senescence. Saviranta *et al.*[54] showed that quercetin may have protective effects on cells by inhibiting pro-inflammatory products, such as interleukin-6.

In this study, we determined that subjects with AMD consumed fewer anthocyanidins than those without AMD. However, no significant association between anthocyanidins and AMD was found. Association between dietary anthocyanin and AMD has not been reported in a cross-sectional study design, although a recent *in vitro* cell culture study demonstrated possible mechanisms related to the protective effects of anthocyanin in the eye.[55] The study showed that blueberry anthocyanin extract suppressed senescence and ameliorated cell viability against light-induced cellular stress in RPE cells. Blueberry anthocyanin extract is beneficial to RPE cells by suppressing aging and apoptosis, and downregulating overexpressed vascular endothelial growth factor.

The prevalence of AMD among our participants was 18.8% (17.9% for early AMD and 1.0% for late AMD). The prevalence of AMD differ considerably according to age group. For the elderly women aged ⩾65 years, the prevalence of AMD was comparable to the rate from the Shihpai Eye Study conducted in Taiwan (9.5% for early AMD and 1.0% for late AMD). The prevalence for late AMD was 1.0%, which is similar several population based-studies including The Shihpai Eye Study[56] and The Coimbra Eye Study.[57]

We identified an association between dietary intake and AMD in elderly women. The role of female sex hormones in AMD have been reported[58] and menopause, accompanied by a decline in circulating estrogen levels, was associated with increased production of reactive oxygen species and lipid peroxidation products.[59] Estrogen also helps induce the expression of antioxidant enzymes, such as manganese superoxide dismutase and glutathione peroxidase.[60] Therefore, the anti-inflammatory properties of estrogen have a role in AMD pathogenesis.[58]

The present study has several limitations. First, as KNHANES is a cross-sectional study, we could not confirm the causal relationship between dietary factors and AMD. Second, we used a single 24 h dietary recall, which may not be sufficient to estimate the usual dietary intake. However, variations between a single day 24 h dietary recall and data obtained over 2–10 days were not much different (0.8% for energy, 8.1% for vitamin A and 3.4% for vitamin C) in the 2009 Korea National Health and Nutrition Examination Survey.[61] Furthermore, the within-person variation for vitamin A is much lower rate than the difference (33%) in vitamin A intake between with and without AMD. We examined dietary intake of carotenoids, flavonoids and other nutrients, but not dietary supplement intake. There was limited data on antioxidant nutrient intakes from dietary supplements (19.6%) and these data existed only for 2010 and 2011 years but not 2012. Therefore, we were unable to estimate nutrient intakes from foods and supplements. Third, only 10 subjects had late AMD in this study, 9 with neovascular AMD and 1 with geographic atrophy. Therefore, we have insufficient data to identify if dietary intakes differed according to AMD type. Lastly, the carotenoids and flavonoids databases used in this study did not include all foods consumed.

Nevertheless, this study had several strengths. The trial subjects comprise a nationally representative sample of elderly Korean women and this is the first study showing an inverse relationship between dietary factors and AMD for a Korean population.

In conclusion, we found significant associations between fruit, vegetable, vitamin A, β-carotene and flavonols intake and AMD in elderly Korean women. The current results suggest that higher consumption of fruits, vegetables and foods containing multi-functional phytochemicals may help protect against AMD. This study strengthens existing evidence indicating that high fruit and vegetable consumption is beneficial for health.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This study was supported by the Brain Korea 21 PLUS and the Ministry of Science, ICT, and Future Planning through the National Research Foundation (Bio-synergy Research Project NRF2012M3A9C4048761).

REFERENCES

1 Pascolini D, Mariotti SP. Global estimates of visual impairment: 2010. *Br J Ophthalmol* 2012; **96**: 614–618.
2 Gale CR, Hall NF, Phillips DI, Martyn CN. Lutein and zeaxanthin status and risk of age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2003; **44**: 2461–2465.
3 Michikawa T, Ishida S, Nishiwaki Y, Kikuchi Y, Tsuboi T, Hosoda K *et al.* Serum antioxidants and age-related macular degeneration among older Japanese. *Asia Pac J Clin Nutr* 2009; **18**: 1–7.
4 Park SJ, Lee JH, Woo SJ, Ahn J, Shin JP, Song SJ *et al.* Age-related macular degeneration: prevalence and risk factors from Korean National Health and Nutrition Examination Survey, 2008 through 2011. *Ophthalmology* 2014; **121**: 1756–1765.
5 Cho BJ, Heo JW, Shin JP, Ahn J, Kim TW, Chung H. Association between reproductive factors and age-related macular degeneration in postmenopausal women: the Korea National Health and Nutrition Examination Survey 2010-2012. *PLoS One* 2014; **9**: e102816.
6 Klein R, Chou CF, Klein BE, Zhang X, Meuer SM, Saaddine JB. Prevalence of age-related macular degeneration in the US population. *Arch Ophthalmol* 2011; **129**: 75–80.
7 Cho BJ, Heo JW, Shin JP, Ahn J, Kim TW, Chung H. Epidemiological association between systemic diseases and age-related macular degeneration: the Korea National Health and Nutrition Examination Survey 2008-2011. *Invest Ophthalmol Vis Sci* 2014; **55**: 4430–4437.
8 Cho BJ, Heo JW, Kim TW, Ahn J, Chung H. Prevalence and risk factors of age-related macular degeneration in Korea: the Korea National Health and Nutrition Examination Survey 2010-2011. *Invest Ophthalmol Vis Sci* 2014; **55**: 1101–1108.
9 Rudnicka AR, Jarrar Z, Wormald R, Cook DG, Fletcher A, Owen CG. Age and gender variations in age-related macular degeneration prevalence in populations of European ancestry: a meta-analysis. *Ophthalmology* 2012; **119**: 571–580.
10 Kim EC, Cho E, Jee D. Association between blood cadmium level and age-related macular degeneration in a representative Korean population. *Invest Ophthalmol Vis Sci* 2014; **55**: 5702–5710.
11 Nidhi B, Mamatha BS, Padmaprabhu CA, Pallavi P, Vallikannan B. Dietary and lifestyle risk factors associated with age-related macular degeneration: a hospital based study. *Indian J Ophthalmol* 2013; **61**: 722–727.
12 Piermarocchi S, Tognetto D, Piermarocchi R, Masetto M, Monterosso G, Segato T *et al.* Risk factors and age-related macular degeneration in a Mediterranean-Basin Population: The PAMDI (Prevalence of Age-Related Macular Degeneration in Italy) Study - Report 2. *Ophthalmic Res* 2016; **55**: 111–118.
13 Shahid H, Khan JC, Cipriani V, Sepp T, Matharu BK, Bunce C *et al.* Age-related macular degeneration: the importance of family history as a risk factor. *Br J Ophthalmol* 2012; **96**: 427–431.
14 Mares-Perlman JA, Fisher AI, Klein R, Palta M, Block G, Millen AE *et al.* Lutein and zeaxanthin in the diet and serum and their relation to age-related maculopathy in the third national health and nutrition examination survey. *Am J Epidemiol* 2001; **153**: 424–432.
15 Cho E, Seddon JM, Rosner B, Willett WC, Hankinson SE. Prospective study of intake of fruits, vegetables, vitamins, and carotenoids and risk of age-related maculopathy. *Arch Ophthalmol* 2004; **122**: 883–892.
16 van Leeuwen R, Boekhoorn S, Vingerling JR, Witteman JC, Klaver CC, Hofman A *et al.* Dietary intake of antioxidants and risk of age-related macular degeneration. *JAMA* 2005; **294**: 3101–3107.
17 Chiu CJ, Chang ML, Zhang FF, Li T, Gensler G, Schleicher M *et al.* The relationship of major American dietary patterns to age-related macular degeneration. *Am J Ophthalmol* 2014; **158**: 118–127.e111.
18 Amirul Islam FM, Chong EW, Hodge AM, Guymer RH, Aung KZ, Makeyeva GA *et al.* Dietary patterns and their associations with age-related macular degeneration: the Melbourne collaborative cohort study. *Ophthalmology* 2014; **121**: 1428–1434.e1422.
19 Chiu C-J, Chang M-L, Li T, Gensler G, Taylor A. Visualization of dietary patterns and their associations with age-related macular degenerationvisualized dietary patterns and AMD. *Invest Ophthalmol Vis Sci* 2017; **58**: 1404–1410.
20 Mares JA, Voland RP, Sondel SA, Millen AE, Larowe T, Moeller SM *et al.* Healthy lifestyles related to subsequent prevalence of age-related macular degeneration. *Arch Ophthalmol* 2011; **129**: 470–480.
21 Merle BM, Silver RE, Rosner B, Seddon JM. Adherence to a Mediterranean diet, genetic susceptibility, and progression to advanced macular degeneration: a prospective cohort study. *Am J Clin Nutr* 2015; **102**: 1196–1206.
22 Abdel-Aal el SM, Akhtar H, Zaheer K, Ali R. Dietary sources of lutein and zeaxanthin carotenoids and their role in eye health. *Nutrients* 2013; **5**: 1169–1185.
23 Salguero A, de la Morena B, Vigara J, Vega JM, Vilchez C, Leon R. Carotenoids as protective response against oxidative damage in Dunaliella bardawil. *Biomol Eng* 2003; **20**: 249–253.
24 Tso MO. Experiments on visual cells by nature and man: in search of treatment for photoreceptor degeneration. Friedenwald lecture. *Invest Ophthalmol Vis Sci* 1989; **30**: 2430–2454.
25 Hanneken A, Lin FF, Johnson J, Maher P. Flavonoids protect human retinal pigment epithelial cells from oxidative-stress-induced death. *Invest Ophthalmol Vis Sci* 2006; **47**: 3164–3177.
26 Chew EY, Clemons TE, Sangiovanni JP, Danis RP, Ferris FL 3rd, Elman MJ *et al.* Secondary analyses of the effects of lutein/zeaxanthin on age-related macular degeneration progression: AREDS2 report No. 3. *JAMA Ophthalmol* 2014; **132**: 142–149.

27 Weigert G, Kaya S, Pemp B, Sacu S, Lasta M, Werkmeister RM *et al*. Effects of lutein supplementation on macular pigment optical density and visual acuity in patients with age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2011; **52**: 8174–8178.

28 Johnson LV, Leitner WP, Staples MK, Anderson DH. Complement activation and inflammatory processes in Drusen formation and age related macular degeneration. *Exp Eye Res* 2001; **73**: 887–896.

29 Snellen EL, Verbeek AL, Van Den Hoogen GW, Cruysberg JR, Hoyng CB. Neovascular age-related macular degeneration and its relationship to antioxidant intake. *Acta Ophthalmol Scand* 2002; **80**: 368–371.

30 Ma L, Yan SF, Huang YM, Lu XR, Qian F, Pang HL *et al*. Effect of lutein and zeaxanthin on macular pigment and visual function in patients with early age-related macular degeneration. *Ophthalmology* 2012; **119**: 2290–2297.

31 Aoki A, Inoue M, Nguyen E, Obata R, Kadonosono K, Shinkai S *et al*. Dietary n-3 fatty acid, alpha-tocopherol, zinc, vitamin D, vitamin C, and beta-carotene are associated with age-related macular degeneration in Japan. *Sci Rep* 2016; **6**: 20723.

32 Korea Centers for Disease Control and Prevention, Ministry of Health & Welfare. An instruction for the fifth Korea National Health and Nutrition Examination Survey. 2014. Available from https://knhanes.cdc.go.kr/knhanes/index.do/ (accessed 17 July 2017).

33 Yoon K-C, Mun G-H, Kim S-D, Kim S-H, Kim CY, Park KH *et al*. Prevalence of eye diseases in South Korea: data from the Korea national health and nutrition examination survey 2008-2009. *Korean J Ophthalmol* 2011; **25**: 421–433.

34 Bird AC, Bressler NM, Bressler SB, Chisholm IH, Coscas G, Davis MD *et al*. An international classification and grading system for age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group. *Surv Ophthalmol* 1995; **39**: 367–374.

35 Korea Centers for Disease Control and Prevention. The Fifth Korea National Health and Nutrition Examination Survey (KNHANES V). Korea Centers for Disease Control and Prevention, Ministry of Health and Welfare: Seoul, Korea, 2013.

36 US Department of Agriculture, Agricultural Research Service, Nutrient Data Laboratory. USDA National Nutrient Database. 2015. Available from https://ndb.nal.usda.gov/ndb/nutrients/index (assessed 20 August 2016).

37 Yang YK, Kim JY, Kwon O. Development of flavonoid database for commonly consumed foods by Koreans. *Korean J Nutr* 2012; **45**: 283–292.

38 Welfare MoHa. *National Health Plan 2020*. Ministry of Health and Welfare: Sejong, 2011.

39 Snow KK, Cote J, Yang W, Davis NJ, Seddon JM. Association between reproductive and hormonal factors and age-related maculopathy in postmenopausal women. *Am J Ophthalmol* 2002; **134**: 842–848.

40 Christen WG, Schaumberg DA, Glynn RJ, Buring JE. Dietary ω-3 fatty acid and fish intake and incident age-related macular degeneration in women. *Arch Ophthalmol* 2011; **129**: 921–929.

41 Moeller SM, Parekh N, Tinker L, Ritenbaugh C, Blodi B, Wallace RB *et al*. Associations between intermediate age-related macular degeneration and lutein and zeaxanthin in the Carotenoids in Age-related Eye Disease Study (CAREDS): ancillary study of the Women's Health Initiative. *Arch Ophthalmol* 2006; **124**: 1151–1162.

42 Padayachee A, Day L, Howell K, Gidley MJ. Complexity and health functionality of plant cell wall fibers from fruits and vegetables. *Crit Rev Food Sci Nutr* 2017; **57**: 59–81.

43 Wu J, Cho E, Willett WC, Sastry SM, Schaumberg DA. Intakes of lutein, zeaxanthin, and other carotenoids and age-related macular degeneration during 2 decades of prospective follow-up. *JAMA Ophthalmol* 2015; **133**: 1415–1424.

44 Stahl W, Sies H. Antioxidant activity of carotenoids. *Mol Aspects Med* 2003; **24**: 345–351.

45 Beatty S, Murray IJ, Henson DB, Carden D, Koh H, Boulton ME. Macular pigment and risk for age-related macular degeneration in subjects from a Northern European population. *Invest Ophthalmol Vis Sci* 2001; **42**: 439–446.

46 Beatty S, Koh H, Phil M, Henson D, Boulton M. The role of oxidative stress in the pathogenesis of age-related macular degeneration. *Surv Ophthalmol* 2000; **45**: 115–134.

47 Beatty S, Boulton M, Henson D, Koh HH, Murray IJ. Macular pigment and age related macular degeneration. *Br J Ophthalmol* 1999; **83**: 867–877.

48 Sparrow JR, Cai B. Blue light-induced apoptosis of A2E-containing RPE: involvement of caspase-3 and protection by Bcl-2. *Invest Ophthalmol Vis Sci* 2001; **42**: 1356–1362.

49 Sparrow JR, Nakanishi K, Parish CA. The lipofuscin fluorophore A2E mediates blue light-induced damage to retinal pigmented epithelial cells. *Invest Ophthalmol Vis Sci* 2000; **41**: 1981–1989.

50 Imamura Y, Noda S, Hashizume K, Shinoda K, Yamaguchi M, Uchiyama S *et al*. Drusen, choroidal neovascularization, and retinal pigment epithelium dysfunction in SOD1-deficient mice: a model of age-related macular degeneration. *Proc Natl Acad Sci USA* 2006; **103**: 11282–11287.

51 Chichili GR, Nohr D, Frank J, Flaccus A, Fraser PD, Enfissi EM *et al*. Protective effects of tomato extract with elevated beta-carotene levels on oxidative stress in ARPE-19 cells. *Br J Nutr* 2006; **96**: 643–649.

52 Sultana B, Anwar F. Flavonols (kaempeferol, quercetin, myricetin) contents of selected fruits, vegetables and medicinal plants. *Food Chem* 2008; **108**: 879–884.

53 Kook D, Wolf AH, Yu AL, Neubauer AS, Priglinger SG, Kampik A *et al*. The protective effect of quercetin against oxidative stress in the human RPE in vitro. *Invest Ophthalmol Vis Sci* 2008; **49**: 1712–1720.

54 Saviranta NM, Veeroos L, Granlund LJ, Hassinen VH, Kaarniranta K, Karjalainen RO. Plant flavonol quercetin and isoflavone biochanin A differentially induce protection against oxidative stress and inflammation in ARPE-19 cells. *Food Res Int* 2011; **44**: 109–113.

55 Liu Y, Song X, Zhang D, Zhou F, Wang D, Wei Y *et al*. Blueberry anthocyanins: protection against ageing and light-induced damage in retinal pigment epithelial cells. *Br J Nutr* 2012; **108**: 16–27.

56 Chen SJ, Cheng CY, Peng KL, Li AF, Hsu WM, Liu JH *et al*. Prevalence and associated risk factors of age-related macular degeneration in an elderly Chinese population in Taiwan: the Shihpai Eye Study. *Invest Ophthalmol Vis Sci* 2008; **49**: 3126–3133.

57 Cachulo MdL, Laíns I, Lobo C, Figueira J, Ribeiro L, Marques JP *et al*. Age-related macular degeneration in Portugal: prevalence and risk factors in a coastal and an inland town. The Coimbra Eye Study–Report 2. *Acta Ophthalmol* 2016; **94**: 442–453.

58 Kaarniranta K, Machalinska A, Vereb Z, Salminen A, Petrovski G, Kauppinen A. Estrogen signalling in the pathogenesis of age-related macular degeneration. *Curr Eye Res* 2015; **40**: 226–233.

59 Pfeilschifter J, Koditz R, Pfohl M, Schatz H. Changes in proinflammatory cytokine activity after menopause. *Endocrine Rev* 2002; **23**: 90–119.

60 Vina J, Sastre J, Pallardo FV, Gambini J, Borras C. Role of mitochondrial oxidative stress to explain the different longevity between genders: protective effect of estrogens. *Free Radic Res* 2006; **40**: 1359–1365.

61 Korea Centers for Disease Control and Prevention. Report presentation of Korea National Health and Nutrition Examination Survey IV, 2009. Korea Centers for Disease Control and Prevention, Ministry of Health and Welfare: Seoul, Korea, 2010.