

Original Article

The Association between Dietary Antioxidant Indices and Cardiac Disease: Baseline Data of Kharameh Cohort StudyParisa Keshani¹, Maryam Jalali¹, Masoumeh Ghodduji Johari^{2*}, Ramin Rezaeianzadeh³, Seyed Vahid Hosseini¹, Abbas Rezaianzadeh¹¹Colorectal Research Center, Shiraz University of Medical Sciences. Shiraz, Iran.²Breast Diseases Research Center, Shiraz University of Medical Sciences. Shiraz, Iran.³Experimental Medicine Program, Department of Medicine, Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada.

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ABSTRACT

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Introduction: Oxidative stress contributes to the development of cardiovascular disease. Tools for evaluating the anti-inflammatory and antioxidative characteristics of an individual's diet as a whole may be valuable for assessing the combined effects of dietary antioxidants on health. This population-based study aimed to investigate the association between dietary antioxidants and cardiac disease.

Methods: In this population-based cross-sectional study, 10439 individuals aged 40-70 years were recruited during 2014-2017 in Kherameh cohort study which is a part of the Prospective Epidemiological Research Studies in Iran (PERSIAN). The food frequency questionnaire (FFQ) with 130 food items was used to assess the dietary intakes. Vitamin A, E, C, selenium, zinc and Manganese intakes were used to compute dietary antioxidant index (DAI) and dietary antioxidant quality score (DAQs). Chi-square and independent sample T-test was used for comparing qualitative and quantitative variables between the groups respectively. Logistic regression analysis was applied for evaluating the association between cardiac disease, DAI and DAQS score after adjusting for covariates.

Results: The participants' mean age was 52.1±8.3 years. Among all, 4356 (41.7%) were overweight and 1892 (18.1%) were obese. According to the results, odds of cardiac diseases decreased by increasing DAI score (OR=0.80, P value<0.001), Odds of cardiac diseases increased by lower DAQS after adjusting for demographic variables including age, sex, BMI, Marital status and hypertension (OR=0.799, P value=0.002).

Conclusion: The role of anti-oxidants in reducing the odds of cardiovascular disease is very important. Our results highlighted that DAQS and DAI had protective effect on the odds of cardiovascular disease. Therefore, it is suggested that anti-oxidants as zinc, manganese, selenium, and vitamins A, E and C should be taken through food to reduce the risk of the disease.

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Introduction

Cardiovascular diseases (CVDs) account for almost a third of all deaths per year worldwide.¹ The prevalence of CVD cases reached 523 million in 2019, a figure almost twice as much as that reported in 1990.² Also, the frequency of deaths related to CVD reached 18.6 million in 2019, representing about 50% rise from the 12.1 million recorded in 1990.³ Most of the deaths from CVD occur in developing countries.⁴ In Iran, it is the main cause (46%) of death, accounting for roughly a fifth of the burden from diseases and causing a million disability-adjusted life years (DALYs).⁵ Fortunately, some risk factors for CVD are modifiable, the most notable of which being an unbalanced diet, lack of exercise, smoking, and alcohol consumption.¹

Oxidative stress contributes to the development of a wide range of diseases, among which CVDs can be mentioned.⁶ Thus, it is reasonable to say that preventing the formation of reactive oxygen species (ROS) can contribute to preventing and treating certain health disorders.⁶

Nutrients and other substances with free radical scavenging properties are known as antioxidants.⁷ Some examples are selenium, zinc, and vitamins A, C and E, which are known to reduce CVD and mortality, with a possible role in promoting endogenous antioxidative processes.⁸ So far, most researchers have looked at isolated nutrients when attempting to determine the possible links between antioxidants and health. However, antioxidant nutrients are consumed in different combinations as part of the meals that constitute an individual's diet.⁹ Hence, some tools including the Dietary Antioxidant Index (DAI) and Dietary Antioxidant Quality

Score (DAQS)¹⁰ have emerged for evaluating the anti-inflammatory and antioxidative characteristics of an individual's diet as a whole; These tools may be valuable for assessing the combined effects of dietary antioxidants on indices related to health.¹⁰ For example, the associations of the DAQS or the DAI with CVD mortality was investigated and confirmed among adults with diabetes in 2022.¹¹ Using these tools in this population-based study, we sought to investigate the association between dietary antioxidants and CVD risk.

Material and Method

Study population

This is a cross-sectional population-based study in which 10439 individuals aged 40-70 years were enrolled during 2014-2017 in Kherameh cohort study which is a part of the Prospective Epidemiological Research Studies in Iran (PERSIAN Cohort). Its aim and design had been previously published.¹² The primary aim of this cohort study was calculating the prevalence and risk factors of non-communicable diseases. All of the 10439 participants were investigated in present study through census.

The exclusion criteria in this study were unwillingness to cooperate in evaluation, intellectual disability, and lack of tendency to participate in the study. Additionally, participants with a total daily energy intake in the range of mean \pm 3SD were considered as over-report data and excluded from the analysis.^{13, 14}

CVD patients

The CVD patients in this study include those with heart failure, angina, and myocardial

infarction who were already diagnosed in Kherameh cohort. There were 1027 and 9412 subjects with and without CVD respectively.¹⁵

Measurements

Dietary and physical activity assessment

As a reliable and valid tool, food frequency questionnaire (FFQ) with 130 food items was applied to assess the participants' dietary intake.¹² The frequency of consumption of each food item was asked by expert dieticians through face-to-face interview. The participants reported their consumption of each food item in the past year on a monthly, weekly, or daily scale. After data gathering, all the findings were converted to the scale of daily intake. Finally, Nutritionist IV software modified for Iranian foods (version 7.0; N-Squared Computing, Salem, OR, USA) was used to analyze food items for their macro- and micro-nutrient content.¹⁶

physical activity was assessed using a questionnaire which included sports, occupation, and sleeping duration and eating in a day. Finally, the Metabolic Equivalent Task (MET) index was computed. Body Mass Index (BMI) was calculated by dividing weight (Kg) by squared height(meters).¹⁷

Measurement of dietary antioxidant quality score (DAQS)

Some minerals and vitamins with antioxidant functions such as selenium, zinc, Manganese, and vitamins A, E, C, were used to compute DAQs.¹⁸

For computing DAQS in this study, the first step was to compare the daily intake of nutrient to the recommended daily intake (RDI).¹⁹ We

applied the Tur et al.'s²⁰ method to allocate a value of 0 or 1 to every subject's antioxidant intake. In this method, when the intake was less than 2/3 of the RDI, the value of 0 was allocated to it, and if the intake was more than 2/3 of the RDI, the value of 1 was assigned to it. Total DAQS was calculated as the sum of these value intakes, so it ranged from 0 (very poor quality) to 6 (high quality).²¹ For estimating the risk of inadequate intake, the proportion of individuals with intakes less than 2/3 of the RDI was computed.²²

Assessment of Dietary Antioxidant Index (DAI)

In this study, DAI was calculated based on the Wright's method.¹⁸ For this purpose, vitamins A, C and E, selenium, manganese, and zinc were each standardized by subtracting the global mean and then dividing them by the global SD. Then, the DAI was obtained by summation of the standardized intakes; the formula is as follows:²³

$$DAI = \sum_{i=1}^{n=6} \frac{\text{individual intake} - \text{Mean}}{SD}$$

Statistical analysis

For quantitative variables, mean±SD and for qualitative one's frequency (%) are reported. The main outcome in our study was atherosclerosis disease. Chi-square and independent sample T-test was used for comparing qualitative and quantitative variables between the groups respectively. Logistic regression analysis was applied for evaluating the association between cardiac disease, DAI and DAQS score after adjusting for covariates like age, sex, BMI,

marital status, and hypertension. Odds ratio (OR) and confidence interval were estimated using the Statistical Package for Social Sciences (SPSS version 22; SPSS Inc., Chicago, IL, USA). We considered $p < 0.05$ as statistically significant.

Results

A total of 10439 participants with a mean age of 52.1 ± 8.3 years were included; of them, 43.4% and 56.6% were male and female, respectively. 419 subjects (40.1%) had normal BMI (18.5–24.9 kg/m²), 4356 (41.7%) were overweight (25–29.9 kg/m²), and 1892 (18.1%) were in the obese category (BMI ≥ 30 kg/m²).

Table 1 shows the demographic information of the participants. ORs and 95% CIs for the odds of cardiac diseases are shown in Table 2. According to the results, odds of cardiac diseases decrease by increasing DAI score (OR=0.80, P value<0.001).

Association between cardiac diseases and DAQs is also displayed in Table 3. DAQs is categorized based on median. When the analysis was done with dichotomous DAQs and adjustment of demographic variables including age, sex, BMI, marital status and hypertension, the odds of cardiac diseases were more in the category with lower DAQs intake (OR=0.799, P value=0.002).

Table 1. Demographic characteristics and dietary intake of nutrients for participants with or without cardiac disease

Characteristics		Total	Cardiac disease	No Cardiac disease	P value
Age		52.1±8.3	56.4±7.8	50.7±7.9	<0.001
Physical activity		38.44±6.08	36.9±6	38.6±6.1	<0.001
Gender	Male	4527 (43.4)	439 (9.7)	4088(90.3)	0.67
	Female	5912 (56.6)	588 (9.9)	5324 (90.1)	
Marital status	Single	1162 (11.1)	168 (14.5)	994 (85.5)	<0.001
	Married	9277 (88.9)	859 (9.3)	8418 (90.7)	
BMI	Normal	4191 (40.1)	338 (8.1)	3853 (91.9)	<0.001
	Overweight	4356 (41.7)	461 (10.6)	3895 (89.4)	
	Obese	1892 (18.1)	228 (12.1)	1664 (87.9)	
Employment	Yes	5325 (51)	393 (7.4)	4932 (92.6)	<0.001
	No	5114 (49)	634 (12.4)	4480 (87.6)	
Vitamin A intake (µg/day/1,000 kcal)		9663.1±5197.4	9460.8±5017.4	9685.2±5216.4	0.2
Vitamin C intake (mg/day/1,000 kcal)		119.5±61.8	116.4±59.1	119.9±62.1	0.07
Vitamin E intake (mg/day/1,000 kcal)		7.5±3	7.2±2.9	7.5±3	0.001
Zinc intake (mg/day/1,000 kcal)		9.8±3	9.2±3.2	9.9±3.3	<0.001
Selenium intake (µg/day/1,000 kcal)		107.5±41.6	99.4±41.4	108.4±41.6	<0.001
Manganese intake (mg/day/1,000 kcal)		4.8±2.1	4.6±2	4.8±2.1	<0.001
Energy intake		2395.27±714.43	2235.2±724.9	2412.7±711.1	<0.001

*Quantitative values are reported as mean±standard deviation. And qualitative values are reported as number (%).

**P values in bold indicate numbers that are significant (P value<0.05).

***BMI, body mass index; DAI, dietary antioxidant index; DAQ, dietary antioxidant quality

****Chi-square test and independent sample T-test was used to compare qualitative and quantitative variables between groups respectively.

Table 2. Association between cardiac disease and DAI after adjustment for covariates

Characteristics		OR	95% CI	P value
DAI		0.80	(0.78,0.83)	<0.001
Age		1.07	(1.06,1.08)	<0.001
Gender	Female	reference		<0.001
	Male	1.58	(1.34,1.58)	
BMI	Normal	Reference		0.002
	Overweight	1.24	(1.06,1.46)	0.007
	Obese	1.42	(1.16,1.74)	0.001
Hypertension	Yes	Reference		<0.001
	No	0.24	(0.18,0.25)	
Marital status	Married	Reference		0.11
	Single	1.19	(0.96,1.47)	

*BMI, body mass index; DAI, dietary antioxidant index

**values in bold indicate numbers that are significant (P value<0.05).

Table 3. Association between cardiac disease and DAQs after adjustment for covariates

characteristics		OR	95% CI	P value
DAQs	<Median	Reference		0.002
	>Median	0.80	(0.69,0.92)	
Age		1.07	(1.06,1.08)	<0.001
Gender	Female	Reference		<0.001
	Male	1.49	(1.27,1.75)	
BMI	Normal	Reference		0.004
	Overweight	1.23	(1.05,1.44)	0.01
	Obese	1.39	(1.16,1.74)	0.001
Hypertension	Yes	Reference		<0.001
	No	0.21	(0.19,0.25)	
Marital status	Married	Reference		0.1
	Single	1.19	(0.96,1.42)	

*BMI, body mass index; DAQ, dietary antioxidant quality

**values in bold indicate numbers that are significant (P value<0.05).

Discussion

This population-based study aimed to investigate the association of dietary antioxidants (measured by DAI and DAQ scores) and CVD risk. According to our findings, the risk of CVDs can be minimized by boosting the amount of antioxidants in an individual's diet.

Oxidative stress contributes to the development of a wide range of diseases, among which it can be mentioned those related to atherosclerosis.⁶ Atherosclerosis is a vascular disorder that develops as a result of chronic inflammation, with oxidized low-density lipoprotein (oxLDL) and endothelium dysfunction, which have vital roles in its pathogenesis. The progression of atherosclerosis is signaled by oxLDL

aggregation in the arterial wall.²² It is known that oxidative stress and inflammatory activity are associated with oxLDL accumulation and endothelial dysfunction.²⁴ Hence, it is plausible that by minimizing the generation of free radicals, CVDs like atherosclerosis can be prevented and treated.⁶

Various nutritional antioxidants work against atherosclerosis, either by promoting endogenous antioxidant activity or directly scavenging free radicals.²⁵ Some examples are selenium, zinc, vitamins C and E, manganese, flavonoids, and carotenoid compounds. While most studies have looked at the health-promoting effects of these nutrients in isolation,²⁶⁻³² few have investigated their combined impacts within different diets.¹⁸ When combined, dietary antioxidants may interact to provide various overall effects, which is why tools like the DAI and DAQ have been designed and implemented.³³ Some studies have assessed the relationship of the DAI with the Total Antioxidant Capacity and markers of inflammation.^{18, 33} Notably, scores related to dietary antioxidant content as evaluated by these tools were inversely related to the levels of inflammatory factors like IL-1 β and TNF- α , explaining the possible biochemical pathway through which an antioxidant-rich diet can lead to improved health outcomes like decreased mortality and CVD risk.¹⁸

Micronutrients and cardiovascular diseases

Although it is known that selenium acts as a cofactor of antioxidative enzymes like glutathione peroxidase (GSH-Px), its cardioprotective impact remains a matter of controversy. One study observed a 24% fall in CVD risk with a 50% rise in blood selenium levels.³⁴ Nonetheless, selenium

offers no significant protection against all-cause mortality, CVD mortality, or adverse cardiovascular events, according to meta-analyses and systematic reviews.³⁴⁻³⁶ Jenkins et al. concluded that the inclusion of this mineral in an antioxidative diet was important to promote cellular antioxidant activity and antioxidative supplements had health-promoting effects.⁸

Zinc is another nutritional element that may provide antioxidative activity. The presence or absence of zinc may affect oxidative stress-related atherosclerotic processes such as disturbed NO and NF- κ B-related signaling, impaired endothelial functioning, and oxidative low-density lipoprotein (LDL) modification.³⁷ A deficiency in zinc has been cited as a contributor to atherosclerosis in some studies, with an inverse relationship being found between atherosclerosis and the serum zinc/24-h urine zinc loss ratio.³⁸ A low intake of zinc has been associated with greater carotid intima-media thickness (CIMT) in some adults.³⁷ Another study proposed that zinc should be used as a biological marker of cardiovascular health due to its impacts on homeostasis.³⁹ In contrast, one of the latest meta-analyses on preventive interventional trials found that zinc exerted no remarkable impact on CVD prevention.⁴⁰

Manganese is another dietary mineral that may affect the course of atherosclerosis; however, limited data are available. One study reported that normal and atherosclerotic aortic tissues were similar in terms of manganese content.²⁴ On the other hand, epidemiologic research indicates increased serum manganese concentrations in individuals with atherosclerosis.^{41, 42} It appears that manganese is essential at trace levels, whereas excessive concentrations are toxic. In fact, some have suggested a U-shaped association of manganese with the generation

of reactive oxygen species, oxidative stress, and the associated diseases.^{24, 43} However, further biomolecular and population-based data are needed to confirm such theories.

According to a number of studies, vitamin C exerts a positive effect in minimizing CVD risk.³⁵ At doses above 500 mg/day, this vitamin was found to positively affect endothelial function, with its effect being more pronounced among individuals at greater risk of CVD (i.e., those with heart failure, diabetes mellitus, or atherosclerosis).⁴⁴ Furthermore, cardiovascular risk factors such as cigarette use and diabetes mellitus have been associated with low blood levels of vitamin C.⁴⁵

Vitamin E acts as a potent antioxidant and has eight stereoisomers. One of them, α -tocopherol, shows bioactivity in the human body. Supplementation with this vitamin for preventing CVDs remains a matter of controversy. A meta-analysis of 16 clinical trials found that vitamin E supplementation markedly reduced the rate of myocardial infarction in the treated subjects compared to controls.⁴⁶ In population-based studies, at similar blood cholesterol levels, increased dietary vitamin E has been consistently linked with greater plasma antioxidant levels and decreased CVD risk.²⁵ Nonetheless, a meta-analysis of 15 trials with 188,209 individuals revealed that vitamin E, β -carotene, and vitamin C supplementation revealed no protective effects against the occurrence of major cardiovascular events, myocardial infarction, cerebrovascular accidents, all-cause mortality, and cardiac mortality.³⁵

Retinoic acid or vitamin A1 is involved in cardiogenesis signaling, with some evidence also indicating an association between this vitamin and CVDs. A study in Finland on an

adult male population found that decreased levels of β -carotene, as a precursor to vitamin A, were linked with a higher rate of cardiovascular deaths, particularly in cigarette smokers.⁴⁷ Another study linked lower blood retinoic acid concentrations with a higher risk of death among coronary artery disease patients.⁴⁸ In contrast, the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) long-term (five to eight years) cohort study on 23,144 male smokers found that α -tocopherol (50 mg per day) and/or β -carotene (20 mg per day) supplementation exerted no impact on the occurrence of myocardial infarction or cardiovascular-related death.⁴⁹

Dietary antioxidant indices and risk of non-communicable diseases

The DAQ and DAI contain the six most potent dietary antioxidants. These antioxidants have been investigated alone and in combination with each other and with alternative micronutrients to determine their effects on CVD, but few studies have made use of the mentioned antioxidant indices. Here, we will briefly discuss our results in relation to the related literature.

According to a multi-adjusted model, the DAI had a significant effect on minimizing CVD risk.⁵⁰ Furthermore, one investigation examined the relationship of the DAQS with cardiovascular fitness and blood pressure, revealing a marked rise in maximum oxygen uptake when moving from the lower to upper DAQS tertiles with and without adjusting for confounding variables. It also showed a non-significant increase in blood pressure in the top DAQS tertile, after adjusting for confounders.⁵¹ Another investigation established a significant association between gastric neoplasms and

poor dietary antioxidant indices, highlighting the need for nutritional antioxidants.³³ Furthermore, another study found that the risk of multiple sclerosis was double in individuals with low DAI values. That study found an important dose-response pattern, concluding that adequate dietary antioxidant intake might reduce the risk of developing multiple sclerosis.⁵² Finally, lower odds of having non-alcoholic fatty liver disease were associated with higher DAI values with and without adjustments for confounding variables.⁵³ These results highlight the same pattern as that observed in our study, indicating that dietary antioxidants work together to reduce the risk of many non-communicable diseases.

Limitation

One limitation of our study is the indices; we did not consider some of non-nutritive antioxidant like carotenoids or polyphenols with antioxidant properties and just considered some major antioxidants. Another limitation was the cross-sectional design of the study of the baseline data collection for a population-based cohort, that cannot represent causal effects of the variables.

Conclusion

The role of anti-oxidants in reducing the odds of cardiovascular disease is very important. Our results highlighted the fact that DAQS and DAI had protective effects on the odds of atherosclerosis. Thus, it is suggested that dietary anti-oxidants as vitamins A, E and C, zinc, Manganese, and selenium should be taken to reduce the risk of cardiac disease. It will be advantageous to investigate the sensitivity and

specificity of DAI in different aspects in order to apply them in clinical works.

Declaration

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Availability of data and materials

The datasets used and analyzed during the current study are available by sending an email to the owner of data (Abbas Rezaianzadeh).

Consent for publication

Not Applicable.

Competing interests

The authors report no conflict of interest.

Authors' contributions

Study concept and design: PK; Acquisition of data: MGJ, AR, SVH, and RR; Analysis and interpretation of data: PK, and MJ; Drafting of the manuscript: PK, and MJ; Critical revision of the manuscript for important intellectual content: PK, MJ, and MGJ; Statistical analysis: MJ; Administrative, technical, and material support: MGJ, AR, SVH, and RR;

Study supervision: MGJ, AR, SVH, and RR. All authors have read and approved the final manuscript.

Ethical approval and consent to participate

informed consent was obtained from all subjects and/or their legal guardian(s). and all methods were carried out in accordance with relevant guidelines and regulations. The study was approved by ethics committee and confirmation were taken from Shiraz University of Medical Sciences (ethical code: IR.SUMS.REC.1401.116). Confidentiality of their personal data was emphasized.

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