

## Observational Study

**Dietary phytochemical consumption is inversely associated with liver alkaline phosphatase in Middle Eastern adults**

Zahra Darabi, Richard James Webb, Hassan Mozaffari-Khosravi, Masoud Mirzaei, Ian Glynn Davies, Sayyed Saeid Khayyat-zadeh, Mohsen Mazidi

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**Zahra Darabi, Sayyed Saeid Khayyat-zadeh**, Nutrition and Food Security Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

**Zahra Darabi, Hassan Mozaffari-Khosravi, Sayyed Saeid Khayyat-zadeh**, Department of Nutrition, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

**Richard James Webb**, School of Health Sciences, Liverpool Hope University, Liverpool L16 9JD, United Kingdom

**Hassan Mozaffari-Khosravi**, Nutrition and Food Security Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

**Masoud Mirzaei**, Yazd Cardiovascular Research Centre, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

**Ian Glynn Davies**, School of Sports and Exercise Sciences, Faculty of Science, Liverpool John Moores University, IM Marsh Campus, Barkhill Road, Liverpool L17 6AF, United Kingdom

**Mohsen Mazidi**, Medical Research Council Population Health Research Unit, Nuffield Department of Population Health, University of Oxford, Oxford OX3 7LF, United Kingdom

**Mohsen Mazidi**, Department of Twin Research & Genetic Epidemiology, King's college London, South Wing St Thomas', London SE1 7EH, United Kingdom

**Corresponding author:** Mohsen Mazidi, PhD, Research Scientist, Medical Research Council Population Health Research Unit, Nuffield Department of Population Health, University of Oxford, Richard Doll Building, Old Road Campus, Headington, Oxford OX3 7LF, United Kingdom. [mohsen.mazidi@ndph.ox.ac.uk](mailto:mohsen.mazidi@ndph.ox.ac.uk)

**Abstract****BACKGROUND**

The hepatoprotective effects of phytochemicals are controversial. A dietary phytochemical index (DPI) has been suggested as an alternative method for quantifying the phytochemical content of foods.

**AIM**

To assess the DPI in relation to liver function tests among a representative sample of Iranian adults.

## METHODS

A total of 5111 participants aged 35-70 years old were included in this cross-sectional study by a multistage cluster random sampling method. Dietary intakes were collected by a validated and reliable food frequency questionnaire with 121 items. DPI was calculated by the percent of daily energy intake taken from phytochemical-rich foods. Fasting serum concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT) were determined. Linear regression was used to investigate the association between DPI and levels of liver enzymes using crude and adjusted models.

## RESULTS

There was an inverse association between DPI score and serum ALP in the crude model ( $\beta = -0.05$ ;  $P < 0.001$ ). This association remained significant after adjustment for body mass index, age, smoking, energy intake, history of diabetes, and education ( $\beta = -0.03$ ;  $P = 0.01$ ). No significant associations were found between DPI score and serum levels of AST, ALT, and GGT. The individuals with the highest DPI scores consumed significantly higher amounts of fruits, vegetables, legumes, nuts, and cereals, yet were shown to have significantly higher serum total cholesterol and low-density lipoprotein cholesterol, as well as several other metabolic abnormalities.

## CONCLUSION

Higher adherence to phytochemical-rich foods was associated with lower levels of ALP, but no change in other liver enzymes. Those with higher DPI scores also consumed food items associated with a healthier overall dietary pattern; however, they also presented several unexpected metabolic derangements. Additional randomised trials are needed to better determine the effects of phytochemical-rich foods on liver function.

**Key Words:** Diet; Phytochemical; Liver; Dietary phytochemical index; Dietary pattern; Phytochemical index; Iran; Middle East; Nutrition

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**Core Tip:** It has been debated whether phytochemicals are hepatoprotective. Furthermore, to the authors knowledge, this has not previously been researched in an Iranian population. In our study we used a dietary phytochemical index to categorise participants in terms of their intake of dietary phytochemicals. We found that participants with higher intakes of phytochemicals had a healthier overall dietary pattern and lower levels of alanine aminotransferase, which may be suggestive of improved liver function. Despite this, several metabolic disturbances were also revealed in these participants.

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## INTRODUCTION

The hepatoprotective effects of phytochemicals have been the subject of recent debate. This has stemmed from increasing evidence concerning the ability of these plant-derived bioactive components to beneficially modulate metabolic processes. Favourable changes have been previously demonstrated in a variety of disease states, including Type 2 diabetes, obesity and cardiovascular and renal disease[1]. Given the links of these metabolic aberrations with liver pathology it is reasonable to suggest that phytochemicals might infer a degree of hepatoprotection[1].

More specifically, studies investigating potential links between dietary phytochemicals and liver function have shown that compounds such as polyphenols, flavonoids, carotenoid and terpenoids, contained in food items such as grapes, tea, olives, nuts and legumes, may favourably mediate liver function when consumed, especially in the context of a low-calorie diet[2,3]. Several proposed mechanisms responsible for these effects may include the ability of phytochemicals to act as natural ligands for peroxisome proliferator-activated receptors, as well as favourably impacting upon mitochondrial beta-oxidation[4]. Furthermore, the ability of phytochemicals to reduce oxidative stress

and decrease transaminase activity are also thought to be influencing factors[1,5].

The Iranian population has high rates of hepatic abnormalities, such as non-alcoholic fatty liver disease (NAFLD), which affects approximately 4.1% of the population[6]. It is thought that this is perpetuated by concurrent high rates of metabolic syndrome; a cluster of risk factors known to be strongly associated with the development of NAFLD[7]. In addition to this, recent findings have also revealed that NAFLD is more likely to be present in Iranians with a higher socioeconomic class and is exacerbated by a Western dietary pattern, whereas a healthier traditional Iranian dietary pattern, presumably richer in dietary phytochemical-containing foods, is likely to be more protective[8]. Although there is evidence concerning the beneficial impact of dietary phytochemicals upon cardiometabolic risk, there are no studies to date which focus specifically on liver function in Iranian adults[9].

We aimed to determine, for the first time, the association between dietary phytochemical index (DPI) and liver function in Iranian adults. We used data derived from the Prospective Epidemiological Research Studies in Iran (PERSIAN) Cohort Study to create a 'dietary phytochemical index' (DPI), based on the work of McCarty, which takes into account the health promoting properties of phytochemicals [10]. This enabled us to test the hypothesis that higher DPI scores would equate to improved liver function.

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## MATERIALS AND METHODS

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### **Study population**

The present cross-sectional study is reported based on the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guideline[11]. The study was conducted in the context of the baseline data of Shahedieh Cohort Study, which is a part of the PERSIAN multicenter cohort study which was conducted using a representative sample of the Iranian adult population aged 35-70 years old[12]. The Shahedieh cohort study recruited about 10000 adults older than 35 living in two municipal areas of Yazd city (Zarch and Shahedieh), Yazd province, Iran. The study protocol of the PERSIAN cohort is provided in detail elsewhere[12,13]. In brief, healthy participants were selected by a multistage cluster random sampling method after they provided written informed consent. The eligible participants were invited to give blood samples and provide data on general characteristics, demographic, dietary intake, smoking, and other lifestyle related data. Anthropometric and blood pressure measurements were also conducted for all attendants. All data were collected by trained interviewers[12,13]. Data on 10,113 adults were provided. Participants with a history of current pregnancy, ovary removal, cardiac ischemia, myocardial infarction, stroke, renal failure, hepatitis B and C, and different types of cancer such as skin cancer, breast cancer, stomach cancer, colorectal cancer, and bladder cancer along with the history of hematopoietic cancers were excluded from the current study because of the possibility of an adjustment in diet ( $n = 1189$ ). Data for participants with a history of alcohol consumption, fatty liver, and diabetes ( $n = 2241$ ) were also omitted. Furthermore, we excluded those who left > 70 items unanswered on the food frequency questionnaire (FFQ) and those who under and over reported their dietary intake (daily energy intake less than 800 kcal/d or more than 7000 kcal/d) ( $n = 1433$ ). The missing data consisted of  $n = 139$  participants who were also excluded from the study. After the mentioned exclusions, 5111 participants remained for the present analysis. The study was also approved by the ethics committee of Shahid Sadoughi University of Medical Sciences (approval code: IR.SSU.SPH.REC.1397.161).

### **Laboratory assessment**

Blood samples (25 mL) were taken when participants were in the fasted state (8 to 12 h before blood sampling). The blood was aliquoted into serum, buffy coat, and whole blood samples. Serum gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were determined from serum samples by an auto-analyser (Analyzer BT1500) using Pars Azmun standard kits.

### **Dietary intake assessment**

The study participants were interviewed by trained nutritionists to complete a semi-quantitative FFQ with 121 items, which asked about dietary intake over the past year[12]. To complete the information, two questions were asked from the participants about each food item: (1) The frequency of food consumption (number of times per month, week, or day the food was consumed) in the previous year, and (2) the amount of the food that was usually consumed every time (portion size based on the standard serving sizes commonly consumed by Iranians). All reported intakes were converted to g/day by using household portion sizes of consumed foods[14]. The USDA food database was used to calculate nutrient intakes[15].

### Dietary phytochemical index calculation

The DPI score was computed based on the method presented by McCarty as follows:  $\text{DPI} = [\text{daily energy derived from phytochemical-rich foods (kcal)} / \text{total daily energy intake (kcal)}] \times 100$ [10]. Fruits, vegetables, legumes, whole grains, nuts, soy products, seeds and olive oil were considered phytochemical-rich foods. The phytochemical content of potatoes is low and so potatoes were not included[16].

### Anthropometric measurement

Anthropometric parameters (weight, height) were measured by a trained investigator. Weight was measured while the participants were wearing minimum clothing and without shoes using a digital scale (SECA, model 755, Germany). Participants' height was measured using a stadiometer with a precision of 0.5 cm. Body mass index (BMI) was calculated by dividing weight (kg) by height (meters) squared.

### Assessment of other variables

Data on additional variables including marital status, smoking (never smoker/current smoker/ex-smoker), and multivitamin-mineral supplements use (yes/no) were obtained using questionnaires. People were asked about their usual physical activity in the last year and if they had seasonal jobs. The information gathered in the questionnaire was converted to the metabolic equivalent of task hours per week [metabolic equivalent of task (MET)-h/wk][17].

### Statistical methods

Continuous and categorical variables were compared across quartiles of DPI scores using analysis of variance (ANOVA) and chi-square tests, respectively. Linear regression was applied in crude and different multi-variable adjusted models to examine the linear association between DPI scores and serum liver enzyme levels. Age, sex (male/female) and the energy intake (kcal/day) were adjusted in the first model; the second model also included BMI (kg/m<sup>2</sup>). Additional adjustments were performed for physical activity, smoking and multivitamin supplement use in third model. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS, version 23.0 for Windows, 2006, SPSS, Inc, Chicago, IL, United States). *P* values less than 0.05 were considered statistically significant.

## RESULTS

General characteristics of the study participants across quartile scores of DPI are shown in [Table 1](#). There were no significant differences in BMI ( $P = 0.647$ ), multivitamin mineral supplement use ( $P = 0.211$ ) and gender ( $P = 0.071$ ). However, individuals in the first quartile of DPI scores were significantly younger than those in the fourth quartile of DPI scores ( $46.4 \pm 9.1$  and  $47.5 \pm 9.5$  y respectively ( $P < 0.001$ )) and had significantly lower systolic blood pressure ( $107.4 \pm 16.2$  and  $109.1 \pm 16.4$  mm/Hg respectively ( $P < 0.001$ )). Those in the first quartile of DPI score also had significantly lower MET than those in the fourth quartile of DPI score ( $41.3 \pm 6.8$  and  $42.0 \pm 6.5$  h/week respectively ( $P < 0.01$ )). [Table 2](#) shows that there were also no significant differences in the levels of serum ALT ( $P = 0.225$ ), AST ( $P = 0.562$ ) and GGT ( $P = 0.338$ ) between the quartiles of DPI scores. However, the participants in the first quartile of DPI scores had higher ALP levels compared to participants in the fourth quartile ( $185.7 \pm 59.3$  and  $176.8 \pm 52.7$  U/L respectively ( $P < 0.01$ )). There were also significant differences in serum total cholesterol and low-density lipoprotein cholesterol (LDL-C) concentrations between those with the lowest DPI scores compared to those with the highest ( $189.9 \pm 59.8$  and  $195.4 \pm 39.0$  mg/dL and  $106.7 \pm 55.1$  and  $111.4 \pm 31.2$  mg/dL respectively) (both  $P < 0.01$ ). Fasting blood sugar was also lower in those with the lowest DPI scores compared to those with higher scores ( $96.0 \pm 21.9$  and  $97.6 \pm 32.7$  mg/dL ( $P < 0.01$ )). Dietary intakes of study participants by quartile score of DPI is shown in [Supplementary Table 1](#). Participants with greater DPI scores had higher intakes of vegetable, fruits, legumes, nuts, olive oils and olives, dairy, and dietary cholesterol (all  $P < 0.001$ ). In addition, intakes of energy, carbohydrate, protein, fat, monounsaturated fatty acids (MUFA), saturated fatty acids (SFAs), and polyunsaturated fatty acids (PUFAs) were significantly lower among the subjects within the fourth quartile of DPI score compared to the first quartile (all  $P < 0.001$ ). Vitamin B12, vitamin A and vitamin C intake were significantly higher among individuals in the fourth quartile of DPI score in comparison to the first quartile (all  $P < 0.001$ ), but folate, magnesium, calcium, iron, vitamins B6, Niacin, Riboflavin and Thiamin intake were significantly higher among individuals in the first quartile of DPI score in comparison to the fourth quartile (all  $P < 0.001$ ). The relationships between score of DPI and levels of liver enzymes are presented in [Table 3](#). There was an inverse association between score of DPI and serum ALP levels in our unadjusted model ( $\beta = -0.05$ ; 95%CI (-0.43 to -0.15)  $P < 0.001$ ). Additionally, this inverse correlation remained significant after adjustment for confounding factors in Model I ( $\beta = -0.04$  95%CI (-0.39 to -0.07);  $P < 0.01$ ), Model II ( $\beta = -0.04$  95%CI (-0.39 to -0.08);  $P < 0.01$ ), Model III ( $\beta = -0.03$  95%CI (-0.34 to -0.03);  $P < 0.019$ ) and Model IV ( $\beta = -0.03$  95%CI (-0.35 to -0.04)  $P = 0.014$ ). No statistically significant

**Table 1** General characteristics of study participants by quartiles score of dietary phytochemical index

	Q4 (N = 1278)	Q3 (N = 1278)	Q2 (N = 1278)	Q1 (N = 1277)	P value <sup>1</sup>
Age (Yr)	47.5 ± 9.5	45.9 ± 8.8	45.5 ± 8.8	46.4 ± 9.1	< 0.001
BMI (kg/m <sup>2</sup> )	28.2 ± 4.9	28.3 ± 7.7	28.2 ± 10.9	27.9 ± 5.0	0.647
Waist circumference (cm)	94.1 ± 11.8	94.3 ± 11.5	94.2 ± 11.4	94.7 ± 12.1	0.668
WHR	0.9 ± 0.1	0.9 ± 0.1	0.9 ± 0.8	0.9 ± 0.3	0.021
Systolic blood pressure (mm/Hg)	109.1 ± 16.4	106.8 ± 15.8	106.7 ± 15.1	107.4 ± 16.2	< 0.001
Diastolic blood pressure (mm/Hg)	67.3 ± 11.0	66.8 ± 11.0	66.8 ± 10.3	67.2 ± 10.6	0.451
Metabolic equivalent of task (h/wk)	42.0 ± 6.5	41.0 ± 6.6	41.6 ± 7.2	41.3 ± 6.8	< 0.01
WSI	0.2 ± 0.7	0.2 ± 0.7	0.2 ± 0.7	0.1 ± 0.7	< 0.001
Gender men (%)	578 (45.2)	543 (42.5)	609 (47.7)	548 (45.7)	0.071
Smoking					< 0.01
Never smoker (%)	1086 (85.0)	1088 (85.1)	1045(81.8)	1052 (82.4)	
Current smoker (%)	106 (8.3)	128 (10.0)	161 (12.6)	140 (11.0)	
Ex_smoker (%)	86 (6.7)	62 (4.9)	72 (5.6)	85 (6.7)	
Education					< 0.001
Uneducated and elementary (%)	536 (41.9)	506 (39.6)	501 (39.2)	612 (48.0)	
Middle and high school	487 (38.2)	535 (38.2)	541 (42.3)	472 (37.0)	
University or college degree	224 (17.5)	212 (16.6)	195 (15.3)	168 (13.2)	
Postgraduate	31 (2.4)	25 (2.0)	40 (3.1)	24 (1.9)	
Multivitamin mineral use					0.211
Never (%)	1244 (97.4)	1242 (97.2)	1231 (96.5)	1245 (97.6)	
Daily (%)	1 (0.1)	0	2 (0.2)	1 (0.1)	
Weekly (%)	4 (0.3)	1 (0.1)	1 (0.1)	0	
Monthly (%)	1 (0.1)	4 (0.3)	2 (0.2)	0	
Yearly (%)	27 (2.1)	31(2.4)	39 (3.1)	30 (2.4)	
Metabolic syndrome	213 (16.7)	225 (17.6)	216 (16.9)	233 (18.2)	0.713

<sup>1</sup>Obtained from one way Anova or Chi-squared tests for continuous and categorical variables, respectively.

Values are means ± SDs or *n* (%).

DPI: Dietary phytochemical index; BMI: Body mass index; WHR: Waist-to-hip ratio; WSI: Wealth score index.

association was found between levels of ALT, AST, GGT and score of DPI in the crude mode, which remained non-significant after adjustment for potential confounders.

## DISCUSSION

In this study we aimed to determine if increased phytochemical consumption, consequently resulting in an increased 'dietary phytochemical index' (DPI) score, would be predictive of improved liver function in Iranian adults. Our principal finding was that DPI score was inversely related to ALP and that this relationship persisted, even after adjusting for multiple variables. No such relationship existed with the other liver enzymes, which were similar across the DPI quartile scores. Furthermore, perhaps unsurprisingly, there were also several differences in the overall dietary intake of the participants. Principally, those with higher DPI scores consumed more foods and nutrients suggestive of largely 'healthy' dietary patterns, as opposed to those with lower scores, who consumed greater quantities of foods and nutrients often associated with 'unhealthy' dietary patterns.

The homogeneity in levels of ALT, AST and GGT between those with varied DPI scores is a finding which is not in agreement with the literature. Previous studies have suggested that phytochemical consumption is associated with improvements in these particular liver enzymes[1]; however, this was

**Table 2 Biochemical parameters of study participants by quartiles score of dietary phytochemical index**

	Q4 (N = 1278)	Q3 (N = 1278)	Q2 (N = 1278)	Q1 (N = 1277)	P value <sup>1,2</sup>
ALT (U/L)	22.6 ± 15.4	22.3 ± 17.1	23.2 ± 17.3	21.9 ± 16.7	0.225
AST (U/L)	19.0 ± 7.4	19.0 ± 10.32	19.4 ± 8.5	19.1 ± 7.5	0.562
GGT (U/L)	27.9 ± 22.8	26.5 ± 23.5	27.2 ± 23.0	26.2 ± 27.7	0.338
ALP (U/L)	176.8 ± 52.7	180.5 ± 50.3	181.0 ± 49.7	185.7 ± 59.3	< 0.01
Cholesterol (mg/dL)	195.4 ± 39.0	191.9 ± 40.6	189.5 ± 38.8	189.9 ± 59.8	< 0.01
Triglyceride (mg/dL)	162.4 ± 96.4	155.0 ± 100.8	157.5 ± 99.8	152.5 ± 96.2	0.075
HDL-C (mg/dL)	53.6 ± 12.3	54.0 ± 12.1	52.9 ± 12.0	53.8 ± 12.4	0.116
LDL-C (mg/dL)	111.4 ± 31.2	107.9 ± 31.2	106.4 ± 30.9	106.7 ± 55.1	< 0.01
FBS (mg/dL)	97.6 ± 32.7	95.5 ± 20.0	94.4 ± 15.9	96.0 ± 21.8	< 0.01
BUN (mg/dL)	27.3 ± 7.6	27.0 ± 7.3	26.9 ± 7.1	27.4 ± 7.0	0.241
Creatinine (mg/dL)	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	1.1 ± 0.2	0.135

<sup>1</sup>Values are means ± SDs.

<sup>2</sup>Obtained from one way Anova.

DPI: Dietary phytochemical index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; ALP: Alkaline phosphatase; HDL: High-density lipoprotein; LDL: Low density lipoprotein; FBS: Fast blood sugar; BUN: Blood urea nitrogen.

not the case in the present study for reasons which are not entirely clear. This is also unexpected given the higher proportion of foods such as fruits, vegetables and nuts which were consumed by those with the highest DPI scores. Food items such as these have previously been associated with a more favourable overall dietary pattern; a feature associated with a decreased risk of NAFLD[18-21]. Furthermore, a reduction in calorie intake accompanied by a concomitant decrease in carbohydrate consumption, both factors which occurred in those with higher DPI scores in the present study, has also been previously associated with improvements in transaminase levels[20].

Despite the unexpected similarities in most liver enzymes, it is important to note that the concentration of ALP was significantly lower in those with higher DPI scores, even after adjusting for energy intake. This aligns with previous literature which also demonstrated that the consumption of phytochemicals is associated with improvements in ALP[22-27]. However, these studies have typically been carried out in animal models with the aim of alleviating hepatic damage resulting from aging and/or pharmacological agents *via* the delivery of phytochemical rich extracts as opposed to the dietary consumption of these compounds per se. Furthermore, as there is a dearth of human studies comparing the impact of dietary phytochemicals upon markers of liver damage it is difficult to make direct comparisons with the improvements in ALP shown by us. Despite this, it is noteworthy that this finding persisted after adjusting for a range of other variables, including metabolic syndrome. This is important, especially given the high rates of the disorder in Iran, its suspected role in NAFLD and because ALP is routinely utilised as a marker for liver disease[7,28]. More specifically, elevated ALP of hepatic origin is used as a marker of primary biliary cirrhosis which can indicate cholestatic liver disease[29]. This is possibly perpetuated by a decline in the tissue-specific environment, such as a deterioration of the HCO<sub>3</sub> umbrella; however, the exact mechanisms have yet to be fully elucidated[29]. As such, the driving factors underpinning the inverse association between DPI score and ALP found in the present study remain unknown.

While there are potentially hepatoprotective benefits of consuming a diet rich in dietary phytochemicals, it is noteworthy that those with higher DPI scores also had increased levels of serum cholesterol and LDL-C, as well as higher levels of fasting blood sugar and systolic blood pressure, even when these individuals were comprised of fewer current smokers and had similar rates of metabolic syndrome compared to those with lower DPI scores. These abnormalities associated with phytochemical consumption are not in agreement with previous research, with a recent review of the literature highlighting how these compounds are generally considered to infer positive effects upon a range of clinical markers including body weight, waist circumference and blood pressure and glucose[1]. Therefore, perhaps some of the observed cardiometabolic abnormalities may be related to other less favourable dietary factors. For example, those with higher DPI scores consumed a higher proportion of total dietary fats than those with lower scores and a smaller quantity of MUFA and PUFA per gram. Consumption of MUFA and PUFA are well known to favourably modulate both the concentration and size of LDL particles[30,31]. However, in the case of the current study it could be hypothesised that perhaps the reduced intake per gram of these fatty acids, along with the percentage increase in SFA intake may override any benefits normally attributed to MUFA and PUFA, leading to a net increase in

**Table 3** Linear regression analysis of the correlations between score of dietary phytochemical index and levels of liver enzymes.

	<b>P value</b>	<b>B (95%CI)</b>
<b>ALT</b>		
Crude	0.474	0.02 (-0.002 to 0.06)
Model I	0.063	0.02 (-0.002 to 0.09)
Model II	0.109	0.02 (-0.009 to 0.08)
Model III	0.1	0.02 (-0.008 to 0.08)
Model IV	0.097	0.02 (-0.007 to 0.08)
<b>AST</b>		
Crude	0.751	-0.004 (-0.02 to -0.01)
Model I	0.902	-0.002 (-0.02 to 0.02)
Model II	0.773	-0.005 (-0.02 to 0.02)
Model III	0.9	-0.002 (-0.02 to 0.02)
Model IV	0.917	-0.002 (-0.02 to 0.02)
<b>GGT</b>		
Crude	0.154	0.02 (-0.01 to 0.11)
Model I	0.328	0.01 (-0.03 to 0.10)
Model II	0.433	0.01 (-0.04 to 0.09)
Model III	0.366	0.01 (-0.03 to 0.10)
Model IV	0.365	0.01 (-0.03 to 0.10)
<b>ALP</b>		
Crude	< 0.001	-0.05 (-0.43 to -0.15)
Model I	< 0.01	-0.04 (-0.39 to -0.07)
Model II	< 0.01	-0.04 (-0.39 to -0.08)
Model III	0.019	-0.03 (-0.34 to -0.03)
Model IV	0.014	-0.03 (-0.35 to -0.04)

Model I: Adjusted for energy intake, age and gender; Model II: Additionally adjusted for body mass index; Model III: Additionally adjusted for physical activity, supplement or multivitamin use, smoking, education and wealth score index; Model IV: Additionally adjusted for metabolic syndrome. DPI: Dietary phytochemical index; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transferase; ALP: Alkaline phosphatase.

LDL-C.

### **Limitations and strengths**

This study has several strengths. These being that the study is the first of its kind to investigate the associations between DPI score and liver function in an Iranian adult population, using a large sample size. Despite this our study has several limitations. These being that the study design is cross-sectional in nature, meaning that the findings cannot detect changes across time, which is important since the impact of diet is often only detected through longitudinal measurements. Similarly, as the participants in the study resided in a single province it is unlikely that our findings are extrapolatable to the Iranian population. Furthermore, the DPI scoring technique only creates an approximate estimation of the consumption of dietary phytochemicals and excludes certain items, which have no calorific value, such as tea, which is consumed in high quantities in Iran[10,32]. Also, the scoring technique fails to consider that the ratio of phytochemicals to calories varies greatly in plant foods, as do the health promoting properties of individual phytochemicals[10]. In addition to this, the logistic regression analysis, although offering insights into the relationship between dietary phytochemical intake and liver function, can succumb to high intercorrelations as well as residual confounding, potentially leading to the production of spurious relationships. It is also important to remember that certain medications may also have impacted upon our findings and although a medication history was taken when the PERSIAN cohort study was conducted this data was not included in our analysis. Finally, as our study is

ecological in nature, the exact biological mechanisms underpinning our findings are subject to speculation and further research to elucidate these aspects is therefore warranted.

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## CONCLUSION

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To summarise, our findings reveal that an increased consumption of dietary phytochemicals is associated with beneficial reductions in serum ALP in an Iranian adult population. Furthermore, we also demonstrate that a higher DPI score is also accompanied with an overall increase in consumption of food items and nutrients associated with healthier dietary patterns. Despite these positive aspects, our findings also showed that those with higher DPI scores presented several metabolic disturbances compared to counterparts with lower scores. This suggests that there may be hepatoprotective effects associated with increased consumption of phytochemicals, but further research is required to determine the validity of these findings as well as any factors that may be driving unexpected metabolic abnormalities.

## ARTICLE HIGHLIGHTS

### **Research background**

Dietary phytochemicals are plant-derived bioactive compounds. It has been previously suggested that these compounds may be hepatoprotective; however, the existing literature concerning this is equivocal.

### **Research motivation**

In addition to the debatable hepatoprotective nature of dietary phytochemicals, there has been little research investigating this specifically in an Iranian population.

### **Research objectives**

To determine the if the intake of dietary phytochemicals is hepatoprotective.

### **Research methods**

Participants recruited to the PERSIAN cohort study were asked to complete a validated food frequency questionnaire. We applied a dietary phytochemical index to this data in order to categorise participants based upon their phytochemical intake. We then used linear regression to investigate the association between the dietary phytochemical index and levels of liver enzymes using both crude and adjusted models.

### **Research results**

We found significant and inverse associations between dietary phytochemical intake and alkaline phosphatase. This is possibly indicative of improved liver function. We also found that participants with higher intakes of dietary phytochemicals also had an overall healthier dietary pattern yet increased levels of serum cholesterol, low-density lipoprotein cholesterol, blood pressure and blood glucose.

### **Research conclusions**

Although there may be hepatoprotective effects associated with increased dietary phytochemical intake in addition to a healthier overall dietary pattern, these may be accompanied by a number of metabolic abnormalities.

### **Research perspectives**

Future research should seek to determine the validity of our findings and to elucidate any factors which may be responsible for any metabolic abnormalities associated with an increased intake of dietary phytochemicals.

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## FOOTNOTES

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**Author contributions:** Darabi Z, Mozaffari-Khosravi H, Mirzaei M, Khayyatzadeh SS, and Mazidi M conceived and designed the study, acquired and analysed the data; Darabi Z and Webb RJ interpreted the data and wrote the first draft of the manuscript; All authors critically revised the manuscript.

**Institutional review board statement:** The study was also approved by the ethics committee of Shahid Sadoughi University of Medical Sciences (approval code: IR.SSU.SPH.REC.1397.161).



**Informed consent statement:** All involved persons gave their informed consent prior to study inclusion.

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**Data sharing statement:** Technical appendix, statistical code, and dataset available from the corresponding author at [mohsen.mazidi@ndph.ox.ac.uk](mailto:mohsen.mazidi@ndph.ox.ac.uk).

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**Country/Territory of origin:** Iran

**ORCID number:** Zahra Darabi 0000-0001-7728-8506; Richard James Webb 0000-0001-9591-585X; Hassan Mozaffari-Khosravi 0000-0002-3513-1778; Masoud Mirzaei 0000-0001-6455-0747; Ian Glynn Davies 0000-0003-3722-8466; Sayyed Saied Khayatzadeh 0000-0002-9133-7340; Mohsen Mazidi 0000-0003-3059-229X.

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## REFERENCES

- 1 **Francini-Pesenti F**, Spinella P, Calò LA. Potential role of phytochemicals in metabolic syndrome prevention and therapy. *Diabetes Metab Syndr Obes* 2019; **12**: 1987-2002 [PMID: 31632110 DOI: 10.2147/DMSO.S214550]
- 2 **Basu A**, Basu P, Lyons TJ. Hepatic Biomarkers in Diabetes as Modulated by Dietary Phytochemicals. In: Patel VB, Preedy VR, editors. *Biomarkers in Liver Disease*. Dordrecht: Springer Netherlands 2017: 957-75
- 3 **Chakravarthy MV**, Waddell T, Banerjee R, Guess N. Nutrition and Nonalcoholic Fatty Liver Disease: Current Perspectives. *Gastroenterol Clin North Am* 2020; **49**: 63-94 [PMID: 32033765 DOI: 10.1016/j.gtc.2019.09.003]
- 4 **Ko JK**, Lee SS, Martin H. Phytochemicals as Modulators of PPARs and RXRs. *PPAR Res* 2010; **2010**: 407650 [PMID: 21629877 DOI: 10.1155/2010/407650]
- 5 **George ES**, Forsyth A, Itsiopoulos C, Nicoll AJ, Ryan M, Sood S, Roberts SK, Tierney AC. Practical Dietary Recommendations for the Prevention and Management of Nonalcoholic Fatty Liver Disease in Adults. *Adv Nutr* 2018; **9**: 30-40 [PMID: 29438460 DOI: 10.1093/advances/nmx007]
- 6 **Younossi ZM**. Non-alcoholic fatty liver disease - A global public health perspective. *J Hepatol* 2019; **70**: 531-544 [PMID: 30414863 DOI: 10.1016/j.jhep.2018.10.033]
- 7 **Adibi A**, Maleki S, Adibi P, Etmnani R, Hovsepian S. Prevalence of Nonalcoholic Fatty Liver Disease and its Related Metabolic Risk Factors in Isfahan, Iran. *Adv Biomed Res* 2017; **6**: 47 [PMID: 28503502 DOI: 10.4103/2277-9175.204590]
- 8 **Soleimani D**, Ranjbar G, Rezvani R, Goshayeshi L, Razmpour F, Nematy M. Dietary patterns in relation to hepatic fibrosis among patients with nonalcoholic fatty liver disease. *Diabetes Metab Syndr Obes* 2019; **12**: 315-324 [PMID: 30881075 DOI: 10.2147/DMSO.S198744]
- 9 **Bahadoran Z**, Golzarand M, Mirmiran P, Saadati N, Azizi F. The association of dietary phytochemical index and cardiometabolic risk factors in adults: Tehran Lipid and Glucose Study. *J Hum Nutr Diet* 2013; **26** Suppl 1: 145-153 [PMID: 23581519 DOI: 10.1111/jhn.12048]
- 10 **McCarty MF**. Proposal for a dietary "phytochemical index". *Med Hypotheses* 2004; **63**: 813-817 [PMID: 15488652 DOI: 10.1016/j.mehy.2002.11.004]
- 11 **von Elm E**, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008; **61**: 344-349 [PMID: 18313558 DOI: 10.1016/j.jclinepi.2007.11.008]
- 12 **Eghthesad S**, Mohammadi Z, Shayanrad A, Faramarzi E, Joukar F, Hamzeh B, Farjam M, Zare Sakhvidi MJ, Miri-Monjar M, Moosazadeh M, Hakimi H, Rahimi Kazerooni S, Cheraghian B, Ahmadi A, Nejatizadeh A, Mohebbi I, Pourfarzi F, Roozafzai F, Motamed-Gorji N, Montazeri SA, Masoudi S, Amin-Esmaili M, Danaei N, Mirhafez SR, Hashemi H, Poustchi H, Malekzadeh R. The PERSIAN Cohort: Providing the Evidence Needed for Healthcare Reform. *Arch Iran Med* 2017; **20**: 691-695 [PMID: 29480734]
- 13 **Poustchi H**, Eghthesad S, Kamangar F, Etemadi A, Keshkar AA, Hekmatdoost A, Mohammadi Z, Mahmoudi Z, Shayanrad A, Roozafzai F, Sheikh M, Jalaeikhoo A, Somi MH, Mansour-Ghanaei F, Najafi F, Bahramali E, Mehrparvar A, Ansari-Moghaddam A, Enayati AA, Esmaili Nadimi A, Rezaianzadeh A, Saki N, Alipour F, Kelishadi R, Rahimi-Movaghar A, Aminisani N, Boffetta P, Malekzadeh R. Prospective Epidemiological Research Studies in Iran (the PERSIAN Cohort Study): Rationale, Objectives, and Design. *Am J Epidemiol* 2018; **187**: 647-655 [PMID: 29145581 DOI: 10.1093/aje/kwz001]

- 10.1093/aje/kwx314]
- 14 **Ghaffarpour M**, Houshiar-Rad A, Kianfar H. The manual for household measures, cooking yields factors and edible portion of foods. Tehran: Nashre Olume Keshavarzy. 1999; 7: 42-58
  - 15 **Bodner-Montville J**, Ahuja JK, Ingwersen LA, Haggerty ES, Enns CW, Perloff BP. USDA food and nutrient database for dietary studies: released on the web. *J Food Compos Anal* 2006; **19**: S100-S7 [DOI: [10.1016/j.jfca.2006.02.002](https://doi.org/10.1016/j.jfca.2006.02.002)]
  - 16 **Farhangi MA**, Najafi M, Jafarabadi MA, Jahangiry L. Mediterranean dietary quality index and dietary phytochemical index among patients candidate for coronary artery bypass grafting (CABG) surgery. *BMC Cardiovasc Disord* 2017; **17**: 114 [PMID: [28482801](https://pubmed.ncbi.nlm.nih.gov/28482801/) DOI: [10.1186/s12872-017-0544-z](https://doi.org/10.1186/s12872-017-0544-z)]
  - 17 **Ainsworth BE**, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR Jr, Schmitz KH, Emplaincourt PO, Jacobs DR Jr, Leon AS. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* 2000; **32**: S498-S504 [PMID: [10993420](https://pubmed.ncbi.nlm.nih.gov/10993420/) DOI: [10.1097/00005768-200009001-00009](https://doi.org/10.1097/00005768-200009001-00009)]
  - 18 **Koch M**, Nöthlings U, Lieb W. Dietary patterns and fatty liver disease. *Curr Opin Lipidol* 2015; **26**: 35-41 [PMID: [25501880](https://pubmed.ncbi.nlm.nih.gov/25501880/) DOI: [10.1097/MOL.0000000000000141](https://doi.org/10.1097/MOL.0000000000000141)]
  - 19 **Salehi-Sahlabadi A**, Sadat S, Beigrezaei S, Pourmasomi M, Feizi A, Ghiasvand R, Hadi A, Clark CCT, Miraghajani M. Dietary patterns and risk of non-alcoholic fatty liver disease. *BMC Gastroenterol* 2021; **21**: 41 [PMID: [33509112](https://pubmed.ncbi.nlm.nih.gov/33509112/) DOI: [10.1186/s12876-021-01612-z](https://doi.org/10.1186/s12876-021-01612-z)]
  - 20 **Wei Y**, Zhang H, Zhang S, Li H. The influence of diet upon liver function indices of healthy volunteers resident in a Phase I clinical trail. *Am J Transl Res* 2019; **11**: 3187-3194 [PMID: [31217888](https://pubmed.ncbi.nlm.nih.gov/31217888/)]
  - 21 **Purkins L**, Love ER, Eve MD, Wooldridge CL, Cowan C, Smart TS, Johnson PJ, Rapeport WG. The influence of diet upon liver function tests and serum lipids in healthy male volunteers resident in a Phase I unit. *Br J Clin Pharmacol* 2004; **57**: 199-208 [PMID: [14748819](https://pubmed.ncbi.nlm.nih.gov/14748819/) DOI: [10.1046/j.1365-2125.2003.01969.x](https://doi.org/10.1046/j.1365-2125.2003.01969.x)]
  - 22 **Rahman S**, Jan G, Jan FG, Rahim HU. Phytochemical Screening and Antidiabetic, Antihyperlipidemic, and Antioxidant Effects of *Leptopus Cordifolius* Decne. In Diabetic Mice. *Front Pharmacol* 2021; **12**: 643242 [PMID: [33897432](https://pubmed.ncbi.nlm.nih.gov/33897432/) DOI: [10.3389/fphar.2021.643242](https://doi.org/10.3389/fphar.2021.643242)]
  - 23 **Nguyen V**, Huang J, Doan V, Lin X, Tang X, Huang Y, Tang A, Yang X, Huang R. Hepatoprotective effects of Yulangsan polysaccharide against nimesulide-induced liver injury in mice. *J Ethnopharmacol* 2015; **172**: 273-280 [PMID: [26144697](https://pubmed.ncbi.nlm.nih.gov/26144697/) DOI: [10.1016/j.jep.2015.06.048](https://doi.org/10.1016/j.jep.2015.06.048)]
  - 24 **Ghorbani A**, Hooshmand S. Protective Effects of *Morus nigra* and Its Phytochemicals against Hepatotoxicity: A Review of Preclinical Studies. *Pharmacology* 2021; **106**: 233-243 [PMID: [33849010](https://pubmed.ncbi.nlm.nih.gov/33849010/) DOI: [10.1159/000515032](https://doi.org/10.1159/000515032)]
  - 25 **Li S**, Tan HY, Wang N, Cheung F, Hong M, Feng Y. The Potential and Action Mechanism of Polyphenols in the Treatment of Liver Diseases. *Oxid Med Cell Longev* 2018; **2018**: 8394818 [PMID: [29507653](https://pubmed.ncbi.nlm.nih.gov/29507653/) DOI: [10.1155/2018/8394818](https://doi.org/10.1155/2018/8394818)]
  - 26 **Niu Y**, Na L, Feng R, Gong L, Zhao Y, Li Q, Li Y, Sun C. The phytochemical, EGCG, extends lifespan by reducing liver and kidney function damage and improving age-associated inflammation and oxidative stress in healthy rats. *Aging Cell* 2013; **12**: 1041-1049 [PMID: [23834676](https://pubmed.ncbi.nlm.nih.gov/23834676/) DOI: [10.1111/accel.12133](https://doi.org/10.1111/accel.12133)]
  - 27 **Nazir N**, Muhammad J, Ghaffar R, Nisar M, Zahoor M, Uddin F, Ullah R, Alotaibi A. Phytochemical profiling and antioxidant potential of *Daphne mucronata* Royle and action against paracetamol-induced hepatotoxicity and nephrotoxicity in rabbits. *Saudi J Biol Sci* 2021; **28**: 5290-5301 [PMID: [34466107](https://pubmed.ncbi.nlm.nih.gov/34466107/) DOI: [10.1016/j.sjbs.2021.05.051](https://doi.org/10.1016/j.sjbs.2021.05.051)]
  - 28 **Sharma U**, Pal D, Prasad R. Alkaline phosphatase: an overview. *Indian J Clin Biochem* 2014; **29**: 269-278 [PMID: [24966474](https://pubmed.ncbi.nlm.nih.gov/24966474/) DOI: [10.1007/s12291-013-0408-y](https://doi.org/10.1007/s12291-013-0408-y)]
  - 29 **Poupon R**. Liver alkaline phosphatase: a missing link between cholestasis and biliary inflammation. *Hepatology* 2015; **61**: 2080-2090 [PMID: [25603770](https://pubmed.ncbi.nlm.nih.gov/25603770/) DOI: [10.1002/hep.27715](https://doi.org/10.1002/hep.27715)]
  - 30 **Kris-Etherton PM**, Pearson TA, Wan Y, Hargrove RL, Moriarty K, Fishell V, Etherton TD. High-monounsaturated fatty acid diets lower both plasma cholesterol and triacylglycerol concentrations. *Am J Clin Nutr* 1999; **70**: 1009-1015 [PMID: [10584045](https://pubmed.ncbi.nlm.nih.gov/10584045/) DOI: [10.1093/ajcn/70.6.1009](https://doi.org/10.1093/ajcn/70.6.1009)]
  - 31 **Ander BP**, Dupasquier CM, Prociuk MA, Pierce GN. Polyunsaturated fatty acids and their effects on cardiovascular disease. *Exp Clin Cardiol* 2003; **8**: 164-172 [PMID: [19649216](https://pubmed.ncbi.nlm.nih.gov/19649216/)]
  - 32 **Rezaee E**, Mirlohi M, Hassanzadeh A, Fallah A. Factors affecting tea consumption pattern in an urban society in Isfahan, Iran. *J Educ Health Promot* 2016; **5**: 13 [PMID: [27500166](https://pubmed.ncbi.nlm.nih.gov/27500166/) DOI: [10.4103/2277-9531.184568](https://doi.org/10.4103/2277-9531.184568)]



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