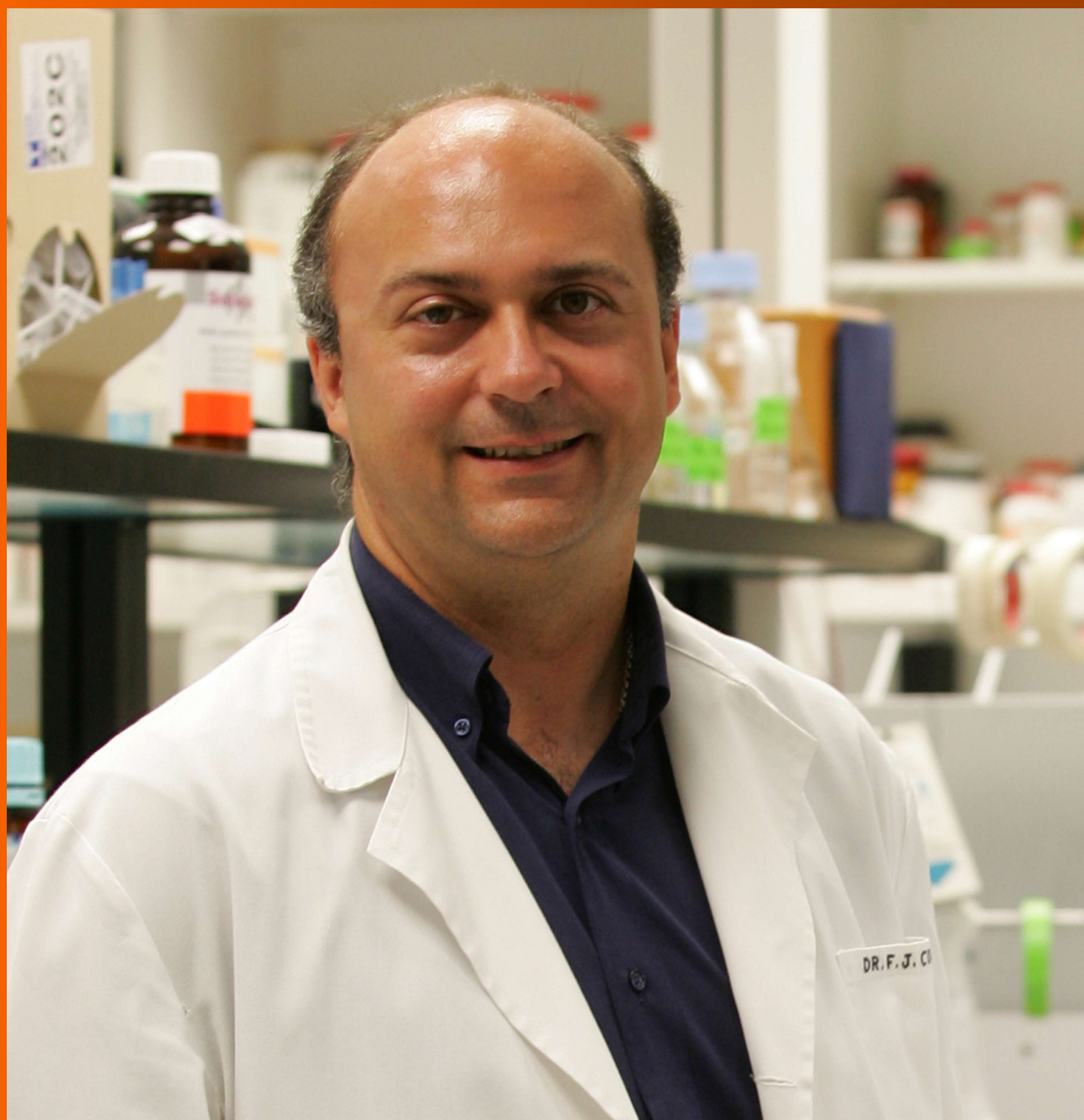


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## Case Control Study

# Mediterranean dietary components are inversely associated with advanced colorectal polyps: A case-control study

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## Abstract

### AIM

To evaluate the association between the Mediterranean diet (MD) pattern and its components, and advanced colorectal polyps (adenoma and serrated adenoma).

### METHODS

A case-control study among patients undergoing screening, diagnostic or surveillance colonoscopies during 2010-2015 at the Tel-Aviv Medical Center, Gastroenterology Department. Cases with advanced polyps were defined as: Advanced adenoma [ $> 10$  mm, with features of high grade dysplasia (HGD) or villous histology], advanced serrated adenoma ( $> 10$  mm or with dysplasia) or multiple ( $\geq 3$ ) non-advanced adenomas or serrated adenomas. Cases of non-advanced adenomas were defined as adenomas  $< 10$  mm, without features of HGD or villous histology. Controls were defined as those



without polyps at the current colonoscopy and without a history of colorectal polyps. Data collection included: anthropometrics measured according to a standardized protocol, fasting blood tests performed at the same lab, medical history recorded by a structured interview and dietary intake evaluated by a 116-item food frequency questionnaire. Adherence to the MD components was evaluated according to intake above/below the sample median, for potentially beneficial/detrimental components respectively, as accepted.

## RESULTS

We recruited 206 cases with advanced polyps, 192 cases with non-advanced adenoma and 385 controls. The number of adhered MD components was inversely associated with a diagnosis of advanced polyps in a dose-response manner (OR = 0.34, 95%CI: 0.17-0.65; OR = 0.22, 95%CI: 0.11-0.43; and OR = 0.18, 95%CI: 0.07-0.47 for 3-4, 5-7 and 8-10 components, respectively), but not with non-advanced adenomas (OR = 0.54, 95%CI: 0.25-1.13; OR = 0.48, 95%CI: 0.23-0.99; and OR = 0.43, 95%CI: 0.16-1.12 for 3-4, 5-7 and 8-10 components, respectively). Low intake of sugar-sweetened beverages and red meat, as well as high intake of fish, were inversely associated with advanced polyps (OR = 0.56, 95%CI: 0.36-0.87; OR = 0.63, 95%CI: 0.42-0.95; and OR = 0.66, 95%CI: 0.44-0.99, respectively), while only low intake of red meat was inversely associated with non-advanced adenomas (OR = 0.71, 95%CI: 0.49-0.97).

## CONCLUSION

A better adherence to the MD, specifically low intake of sugar-sweetened beverages and red meat as well as high intake of fish, is related to lower odds for advanced polyps.

**Key words:** Fish intake; Sugar-sweetened beverages; Red meat intake; Dietary adherence; Cancer

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**Core tip:** Adherence to the Mediterranean diet is inversely associated with advanced colorectal polyps in a dose-response manner. Low intake of sugar-sweetened beverages and red meat, as well as high intake of fish, were associated with lower odds of advanced colorectal polyps. Importantly, these protective associations were independent of other important risk factors such as medical background and other lifestyle parameters. Therefore, a healthy diet may have a significant preventive role in colorectal neoplasia.

Fliss-Isakov N, Kariv R, Webb M, Ivancovsky D, Margalit D, Zelber-Sagi S. Mediterranean dietary components are inversely associated with advanced colorectal polyps: A case-control study. *World J Gastroenterol* 2018; 24(24): 2617-2627 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v24/i24/2617.htm> DOI: <http://dx.doi.org/10.3748/wjg.v24.i24.2617>

## INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide, and the fourth most common cause of death from cancer, in both men and women<sup>[1]</sup>. The annual age-adjusted incidence rates for CRC in Israeli Jews are 46.7 for males and 35.5 for females per 100000 people<sup>[2]</sup>. The association between diet and CRC and adenomas has been extensively investigated<sup>[3,4]</sup>, indicating an association with CRC incidence<sup>[5]</sup> and survival<sup>[6]</sup>. High intake of red or processed meat and alcohol, and low intake of dietary fiber from fruit, vegetables, whole grains and legumes have been identified as risk factors for CRC<sup>[7]</sup>. Recently, a negative association between nut and fish intake and colorectal neoplasia was suggested<sup>[8,9]</sup>. Mechanisms include the protective anti-inflammatory effects of omega-3 fatty acids<sup>[10]</sup>, fiber, antioxidants and other phytochemicals<sup>[11,12]</sup>. Plant-based dietary patterns as pesco-vegetarian<sup>[13]</sup>, anti-inflammatory<sup>[14]</sup> and Mediterranean diet (MD)<sup>[15,16]</sup>, were described to be inversely associated with CRC. The MD is a dietary regimen based on plant foods, olive oil as the principal source of fat, moderate consumption of fish, poultry, dairy, and wine, and low amounts of red meat<sup>[17]</sup>. Epidemiological studies have shown that the MD is associated with a lower incidence of cardiovascular diseases, metabolic disorders, and several types of cancer<sup>[18-20]</sup>. Specifically, an inverse association between the MD and colorectal neoplasia has been documented<sup>[21-24]</sup>. Therefore, the MD is considered as one of the most evidence-based dietary pattern related to the prevention of chronic diseases<sup>[19,25]</sup>, increased life expectancy<sup>[26]</sup>, and indeed has recently become the standard recommendation for healthy eating<sup>[27]</sup>. It has been suggested that the MD exerts anti-neoplastic properties since it combines a plant-based diet, low in calorie-dense foods and favors fish over red meat<sup>[16,28]</sup>. Therefore, it is rich in dietary fiber, a variety of antioxidants and polyphenols. These are proposed to have strong anti-inflammatory and anti-carcinogenic effects<sup>[29]</sup>. On the other hand, the MD is low in sugar, saturated fat cholesterol, and sodium<sup>[30,31]</sup>. Taken together, these dietary characteristics are hypothesized to exert their favorable effects through several mechanisms which include: a lipid-lowering effect, protection against oxidative stress and inflammation, maintenance of normal weight, modification of growth factors involved in the pathogenesis of cancer, and gut microbiota-mediated production of metabolites influencing metabolic and colonic health<sup>[32-34]</sup>.

Given the high prevalence of CRC in the western world<sup>[35]</sup>, and the preventive potential of lifestyle<sup>[36]</sup>, the aim of this study was to evaluate the association between the MD pattern and its components, and advanced colorectal polyps (adenoma and serrated adenoma).

## MATERIALS AND METHODS

A case-control study, among consecutive subjects aged

40-70 years, undergoing colonoscopy at the Department of Gastroenterology and Hepatology at the Tel-Aviv Medical center (TLVMC) during 2010-2015. Participant indications for colonoscopy were categorized as screening, diagnostic (indicated by alarming symptoms such as anemia, unexplained weight loss, rectal bleeding, abdominal pain or change in bowel habits) or surveillance (familial or personal history of colorectal polyps). We aimed to look for an association between diet and colorectal polyps, by gathering a study population with minimal risk for genetic predisposition for colorectal neoplasia. Exclusion criteria for both cases and controls were: familial hereditary CRC syndromes (such as Lynch and Familial Adenomatous Polyposis syndrome), personal history of CRC, first degree family history of CRC, inflammatory bowel disease (IBD), celiac disease, solid malignancy, hyperthyroidism, past colectomy, recent hospitalization or surgery (within one year), pregnancy, chronic liver disease, or grade 4-5 chronic kidney disease. Cases were further excluded for personal history of colorectal polyps before the age of 40, or diagnosis of > 5 colorectal polyps (ever). In addition, controls were excluded for any past colonic polyps. Participants with an incomplete food frequency questionnaire (FFQ) (total calories did not reach 500 or 800 kcal, or exceeded 3500 or 4000 kcal for women/men, respectively) were also excluded. The study protocol was approved by the Institutional Review Board of the TLVMC, and all participants provided informed consent prior to the study enrollment.

### Definition of cases and controls

For the definition of cases, polyps were reviewed by a gastro-intestinal (GI) pathologist, and classified as adenomatous polyps, hyperplastic polyps, sessile serrated adenomas, traditional serrated adenomas, or serrated adenomas with dysplasia). Furthermore, we classified polyps as advanced polyps or non-advanced adenomas according to the guidelines of the United States Multi-Society Task Force on CRC, the American Cancer Society CRC Advisory Group, United States Multi-Society Task Force and American College of Radiology CRC Committee<sup>[37,38]</sup>. Cases with advanced polyps were defined as: Advanced adenoma [ $> 10$  mm, with features of high grade dysplasia (HGD) or villous histology], advanced serrated adenoma ( $> 10$  mm or with dysplasia) or multiple ( $\geq 3$ ) non-advanced adenomas or serrated adenomas. Cases of non-advanced adenomas were defined as adenomas  $< 10$  mm, without features of high grade dysplasia (HGD) or villous histology. Cases with more than one polyp were defined according to the polyp of highest neoplastic potential. Controls were defined as patients with no colorectal polyps detected in their current or past colonoscopy examinations. Cases with solitary serrated adenomas  $< 10$  mm, serrated adenomas without dysplasia, hyperplastic polyps  $< 10$  mm or hyperplastic polyps in the left colon were not included in this analysis.

### Data collection

Within two months after their colonoscopy, eligible

cases of colorectal polyps and controls were invited to participate in the study. Blood tests were obtained following a 12-h fast, all analyzed at a single lab of the TLVMC. Weight, height, hip and waist circumference were measured using a uniform protocol. Participants were face-to-face interviewed for their medical history, current medications and indication for colonoscopy, lifestyle, demographic characteristics and dietary intake according to a structured questionnaire, which was assembled by the Israeli Center for Disease Control<sup>[39]</sup>. This questionnaire included a detailed semi-quantitative FFQ, adapted to the Israeli population and to the needs of this study, assembled by the Food and Nutrition Administration of the Israeli Ministry of Health. The FFQ was composed of 116 food items with specified serving sizes. For each food item, participants indicated their average frequency of consumption over the past year. Mean daily and weekly intake was calculated for each food and food group (whole and refined grains, legumes, nuts and seeds, vegetables, fruit, cooking oils, fish, eggs, dairy, poultry, red meat, desserts, sugar-sweetened beverages, alcoholic beverages).

### Definition of adherence to the MD

Adherence to the MD was evaluated based on a score reported by Rosato *et al.*<sup>[16]</sup>, and adjusted to the Israeli eating habits. In the Israeli population intake of red and processed meat, high-fat dairy products and alcoholic beverages is relatively low, as opposed to poultry and sugared-drink intake, which is relatively high. Therefore, we adjusted the MD score by assessing the intake of 10 MD components, with high relevance to the common Israeli eating habits. For beneficial components, consumption at or above the group median was considered as adherence, while for components presumed to be detrimental, consumption below the group median was considered as adherence.

The MD score was calculated by assessing the intake of 10 components: (1) Vegetables and legumes (fresh/cooked  $\geq 2.60$  servings/day), (2) Fruit (fresh whole fruit  $\geq 1.51$  servings/day), (3) Nuts and seeds (natural unsalted nuts and seeds or paste products  $\geq 0.38$  servings/day), (4) Whole grains (bread, cooked grains, breakfast cereal  $\geq 1.00$  servings/day), (5) Fish (fresh, canned and cooked  $\geq 2.43$  servings/week), (6) Ratio of mono-unsaturated fatty-acids to saturated fatty-acids (MUFA/SFA  $\geq 0.97$ ), (7) Poultry (chicken and turkey products  $\geq 5.00$  servings/week), (8) Red meat (beef, veal, pork products and internal organs  $< 1.17$  servings/week), (9) Alcohol (beer, wine, liquor  $< 0.75$  servings/week), and (10) Sugar-sweetened beverages (fruit juice, iced tea, non-diet soft drinks  $< 0.21$  servings/day). The number of adhered MD components of 0 represents no adherence, and 10 represents the highest adherence to the MD.

### Statistical analysis

All statistical analyses were performed using SPSS version 22.0 for Windows (SPSS Inc., Chicago, IL, United States) during the years 2015-2017. Continuous variables were presented as means  $\pm$  SD and dichotomous variables as

proportions. The normality of distribution of continuous variables was tested by the Kolmogorov-Smirnov test. Univariate analysis was used to compare variable's distribution between study groups. Pearson Chi-Square test was used to test the association between categorical variables. Since all continuous variables were distributed normally, continuous variables were compared between study groups using the independent samples *t*-test or One-Way ANOVA test. The Fisher's Least Significant Difference (LSD) post-hoc analysis was used to address multiple comparisons. A linear-trend was assessed using the linear polynomial analysis in One-Way ANOVA for continuous variables or the linear-by-linear Chi-square test for categorical variables. Multivariate logistic regression analysis was used to test the association between dietary components and advanced colorectal polyps, controlling for potential confounders. Adjustments were made for variables, which were distributed differently between cases and controls and may be related with nutritional habits.  $P < 0.05$  was considered statistically significant for all analyses. All statistical methods of this study were reviewed by Professor Shira Zelber-Sagi from the Department of Gastroenterology in the TLVMC.

## RESULTS

### *Characteristics of the study population and comparison between cases and controls*

A total of 2628 out of 5774 potentially eligible patients who underwent colonoscopy at the Tel-Aviv medical center and were contacted agreed to participate in the study, representing 45% response rate. Of those, we excluded patients for multiple polyps or polyps at a young age ( $n = 352$ ), IBD ( $n = 326$ ), chronic liver or kidney disease ( $n = 202$ ), family history of CRC  $< 70$  years ( $n = 218$ ), personal history of CRC ( $n = 124$ ), past colectomy ( $n = 83$ ), incomplete colonoscopy ( $n = 67$ ), past colorectal polyps among controls ( $n = 343$ ) and an incomplete FFQ ( $n = 85$ ).

A total of 783 subjects completed the study protocol and were analyzed: 385 controls, 206 cases with advanced polyps (advanced adenoma  $n = 165$ , advanced serrated adenoma  $n = 11$ , multiple non-advanced adenomatous or serrated adenomas  $n = 30$ ), and 192 cases of non-advanced adenomas.

The demographic and clinical characteristics and comparison between cases and controls is depicted in Table 1. Cases (both with non-advanced adenomas and advanced polyps) were older, had higher BMI and a higher percent of men, smokers, and users of some medications, compared to controls. As anticipated, only cases underwent surveillance colonoscopies, whereas controls showed significantly higher proportions of screening colonoscopies.

### *The association between the MD score and different types of polyps*

The mean number of adhered MD components was

significantly lower among cases with advanced polyps as compared to controls (Table 1).

In multivariate analysis, adjusting for age, gender, smoking, BMI ( $\text{kg/m}^2$ ), use of aspirin, NSAIDs, statin and antidiabetic medication, daily caloric intake (kcal) and colonoscopy indication (screening, diagnostic or surveillance), each additional component of the MD to which participants adhered was inversely associated with advanced polyps (OR = 0.80, 95%CI: 0.72-0.89,  $P < 0.001$ ), but not with non-advanced adenomas (OR = 0.93, 95%CI: 0.83-1.05,  $P = 0.279$ ) (Table 2). Sensitivity analysis including only patients attending screening/diagnostic colonoscopies (not surveillance colonoscopies) showed similar results (OR = 0.82, 95%CI: 0.73-0.91,  $P = 0.001$  and OR = 0.97, 95%CI: 0.85-1.11,  $P = 0.711$  for advanced polyps and non-advanced adenomas, respectively).

This association remained significant when categorizing the number of adhered MD components by the median ( $\geq 5$  components) for advanced polyps, and remained non-significant for non-advanced adenomas (Table 2).

Categories of adhered MD components were negatively associated with the proportion of cases with advanced polyps and with odds of advanced polyps in multivariate analysis in a dose-response manner (Figure 1A). The MD score categories were not significantly associated with non-advanced adenomas (Figure 1B). Sensitivity analysis including only patients attending screening/diagnostic colonoscopies (not surveillance colonoscopies) showed similar results (Supplementary Figure 1).

### *The association between the individual components of the MD and different types of polyps*

In multivariate analysis, adjusting for age, gender and BMI, low intake of red meat and sugar-sweetened beverages, and high MUFA/SFA ratio, intake of fruit, fish and whole grains were negatively associated with advanced polyps. Low intake of red meat, and high intake of nuts and seeds were negatively associated with non-advanced adenomas. With additional adjustment for smoking, use of aspirin, NSAIDs, statin and antidiabetic medication, daily caloric intake (kcal) and colonoscopy indication (screening, diagnostic or surveillance), high consumption of whole grains, fruit and fish, and low consumption of sugar-sweetened beverages and red meat were inversely associated with advanced polyps, whereas only low consumption of red meat was inversely associated with non-advanced adenomas. With further adjustment for one another, the dietary components, which remained inversely associated with advanced polyps, were high consumption of fish, and low consumption of sugar-sweetened beverages and red meat, whereas only low consumption of red meat was inversely associated with non-advanced adenomas (Table 2).

## DISCUSSION

Diet is a complex exposure, which has been linked

**Table 1 Comparison between cases of advanced polyps and non-advanced adenomas versus controls in demographic, clinical and dietary parameters**

	Controls ( <i>n</i> = 385)	Cases with non-advanced adenomas ( <i>n</i> = 192)	<i>P</i> value	Cases with advanced polyps ( <i>n</i> = 206)	<i>P</i> value
Age (yr)	58.2 ± 6.6	58.8 ± 6.6	0.069	59.7 ± 6.0	0.022
Gender (% male)	47.9	56.2	0.061	58.1	0.010
Low socio-economic status <sup>1</sup> (%)	7.2	8.6	0.410	8.6	0.846
1 <sup>st</sup> degree Family history of CRC (%)	7.6	12.0	0.097	5.8	0.451
Physical inactivity <sup>2</sup> (%)	44.3	45.2	0.988	50.3	0.171
Smoking (ever) (%)	48.4	62.5	0.017	60.7	0.002
BMI (kg/m <sup>2</sup> )	27.0 ± 5.1	29.1 ± 5.2	0.009	29.2 ± 6.1	0.004
Total calories (Kcal)	2013 ± 688	2063 ± 1045	0.652	2006 ± 724	0.804
Colonoscopy indication					
Screening (%)	59.5	34.4	< 0.001	37.9	< 0.001
Diagnostic <sup>3</sup> (%)	35.6	33.3	0.491	37.9	0.583
Surveillance <sup>4</sup> (%)	0.0	32.3	< 0.001	24.3	< 0.001
Medication use					
Statins (%)	41.1	47.4	0.046	49.7	0.091
Aspirin (%)	28.2	37.0	0.006	38.2	0.019
NSAIDs (%)	1.0	0.5	0.112	0.5	0.923
Antidiabetic medication (%)	10.8	9.9	0.923	13.1	0.654
Dietary intake					
Number of MD components	5.1 ± 1.7	5.0 ± 1.9	0.620	4.5 ± 1.9	< 0.001
Beneficial components					
Whole grains (servings/d)	2.2 ± 2.2	2.1 ± 1.9	0.884	1.7 ± 2.0	0.027
Vegetables and legumes (servings/d)	3.3 ± 2.0	3.4 ± 2.4	0.378	3.1 ± 2.1	0.185
Fruit (servings/d)	2.7 ± 2.3	2.2 ± 2.2	0.122	2.3 ± 2.4	0.227
Nuts and seeds (servings/d)	1.5 ± 1.6	1.5 ± 1.5	0.358	1.5 ± 1.7	0.355
MUFA/SFA ratio (per day)	1.4 ± 0.5	1.3 ± 0.5	0.298	1.3 ± 0.4	0.098
Fish (servings/wk)	3.9 ± 3.6	3.5 ± 3.8	0.378	3.4 ± 3.1	0.177
Poultry (servings/wk)	6.7 ± 5.1	6.8 ± 5.3	0.688	6.6 ± 4.5	0.462
Detrimental components					
Alcoholic beverage (servings/d)	1.1 ± 0.5	1.1 ± 0.7	0.925	1.1 ± 0.6	0.179
Sugar sweetened beverages (servings/d)	3.1 ± 3.2	3.0 ± 3.4	0.827	3.3 ± 3.6	0.277
Red meat (servings/wk)	2.6 ± 4.1	3.2 ± 4.1	0.039	3.4 ± 4.1	0.036

<sup>1</sup>Low socio-economic status - categorized as the lowest quartiles of education or income; <sup>2</sup>Physical inactivity - categorized as reported physical activity of less than 20 min per week; <sup>3</sup>Diagnostic colonoscopy - indicated by alarming symptoms such as anemia, unexplained weight loss, rectal bleeding, abdominal pain or change in bowel habits; <sup>4</sup>Surveillance colonoscopy - indicated by familial or personal history of colorectal polyps. Continuous variables are presented as mean ± SD, and categorical variables as proportions. CRC: Colorectal cancer; BMI: Body mass index; NSAIDs: Non-steroidal anti-inflammatory drugs; MD: Mediterranean diet.

to multiple chronic diseases, including cancer<sup>[40]</sup>. The current study suggested that adherence to the MD was lower among cases with advanced colorectal polyps compared to controls, and was inversely associated with advanced colorectal polyps in a dose-response manner. Interestingly, the associations were weaker or absent with non-advanced adenomas, implying that the MD may be more strongly linked to neoplastic progression.

These results are in agreement with previous studies demonstrating an inverse association between the MD and colorectal adenoma incidence and recurrence<sup>[4,21]</sup>, and with CRC<sup>[41-43]</sup>. As in the present study, the MD score was negatively associated with colorectal adenomas in a dose response manner, in a large case-control study of a hospital-based population. Strong negative association with the MD score was observed for multiple adenomas and for tubovillous/villous adenomas<sup>[22]</sup>. In a cancer screening trial, a negative dose-response association between the number of adhered components of the MD and colorectal adenomas was detected. In contrast to the present study, similar associations were seen between

the MD score and both advanced and non-advanced adenomas<sup>[23]</sup>. A pooled analyses of primary prevention cohort studies showed that high adherence to the MD score was associated with a reduction in the incidence of total cancer and CRC<sup>[44]</sup>. Furthermore, a recent meta-analysis found an inverse association between adherence to a MD and CRC mortality<sup>[45]</sup>. Altogether, previous studies, as well as the current study, support a negative association between adherence to the MD and colorectal adenomas, specifically advanced adenomas and CRC.

High consumption of fish, and low consumption of sugar-sweetened beverages and red meat were independently inversely associated with advanced colorectal polyps controlling for important potential confounders, including BMI, caloric intake and medical history (cardiovascular disease, diabetes, familial and personal history of colorectal neoplasia).

Red meat is an established risk factor for CRC, shown repeatedly to increase CRC incidence and associated mortality rates<sup>[46-48]</sup>. In fact, the International Agency for Research on Cancer (IARC) declared red meat as



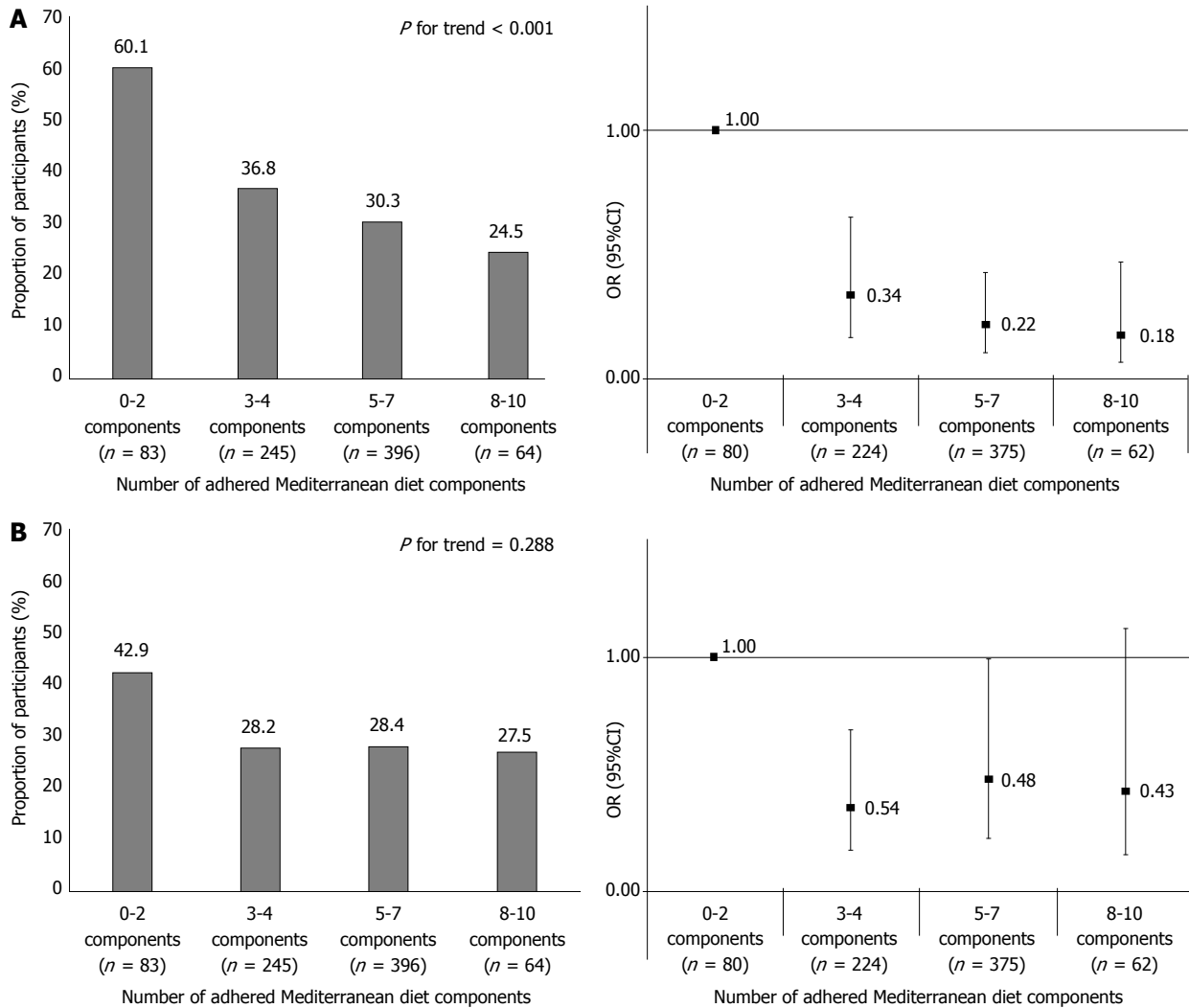
**Table 2** Adjusted association between the Mediterranean dietary pattern score and its components and non-advanced or advanced colorectal polyps

<sup>1</sup> Dietary parameter	Non Advanced adenomas (n = 192)			Advanced colorectal polyps (n = 206)		
	Model 1 OR (95%CI) P value	Model 2 OR (95%CI) P value	Model 3 OR (95%CI) P value	Model 1 OR (95%CI) P value	Model 2 OR (95%CI) P value	Model 3 OR (95%CI) P value
MD score (per 1 point increase)	0.96 (0.87-1.07) 0.833	0.93 (0.83-1.05) 0.279	-	0.82 (0.75-0.91) < 0.001	0.80 (0.72-0.89) < 0.001	-
MD score						
> 5	1 (ref)	1 (ref)	-	1 (ref)	1 (ref)	-
≤ 5	1.14 (0.78-1.67) 0.492	1.08 (0.70-1.64) 0.72		0.62 (0.43-0.90) 0.012	0.56 (0.39-0.87) 0.009	
Whole grains (servings/d)						
≤ 1.00	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
> 1.00	1.08 (0.74-1.58) 0.656	1.10 (0.74-1.64) 0.628	0.91 (0.58-1.40) 0.673	0.64 (0.45-0.91) 0.014	0.59 (0.40-0.85) 0.005	0.72 (0.48-1.09) 0.122
Vegetables and legumes (servings/d)						
≤ 2.60	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
> 2.60	1.03 (0.71-1.50) 0.866	1.13 (0.73-1.73) 0.578	1.12 (0.69-1.80) 0.64	0.83 (0.58-1.17) 0.301	0.88 (0.59-1.31) 0.544	1.08 (0.69-1.69) 0.716
Fruit (servings/d)						
≤ 1.50	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
> 1.50	0.79 (0.54-1.15) 0.225	0.77 (0.50-1.17) 0.229	0.93 (0.59-1.46) 0.751	0.61 (0.43-0.87) 0.007	0.60 (0.40-0.90) 0.013	0.70 (0.57-1.30) 0.107
Nuts and seeds (servings/d)						
≤ 0.37	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
> 0.37	1.52 (1.04-2.24) 0.031	1.44 (0.96-2.18) 0.077	1.53 (0.96-2.44) 0.068	0.88 (0.62-1.25) 0.489	0.86 (0.59-1.25) 0.445	0.94 (0.62-1.43) 0.798
MUFA/SFA ratio (per day)						
≤ 0.96	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
> 0.97	NA	0.82 (0.55-1.22) 0.337	0.73 (0.47-1.14) 0.171	1.04 (1.00-1.07) 0.017	0.81 (0.56-1.17) 0.263	0.86 (0.57-1.30) 0.478
Fish (servings/wk)						
≤ 2.42	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
> 2.42	0.80 (0.53-1.17) 0.258	0.80 (0.53-1.20) 0.294	0.70 (0.45-1.09) 0.117	0.69 (0.48-0.98) 0.039	0.65 (0.44-0.94) 0.025	0.66 (0.44-0.99) 0.047
Poultry (servings/wk)						
≤ 5.00	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
> 5.00	1.20 (0.82-1.76) 0.343	1.06 (0.70-1.61) 0.767	1.07 (0.69-1.65) 0.759	0.90 (0.63-1.27) 0.559	0.85 (0.59-1.25) 0.428	0.75 (0.50-1.11) 0.157
Alcoholic beverage (servings/d)						
> 0.75	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
≤ 0.75	0.81 (0.55-1.20) 0.304	0.78 (0.51-1.17) 0.235	0.83 (0.53-1.29) 0.411	1.18 (0.82-1.69) 0.357	1.18 (0.81-1.74) 0.377	1.17 (0.78-1.76) 0.438
Sugar sweetened beverages (servings/d)						
> 0.20	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
≤ 0.20	1.14 (0.78-1.67) 0.474	1.04 (0.68-1.58) 0.856	1.12 (0.70-1.77) 0.622	0.63 (0.44-0.90) 0.012	0.56 (0.37-0.83) 0.005	0.56 (0.36-0.87) 0.010
Red meat (servings/wk)						
> 1.17	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
≤ 1.17	0.63 (0.42-0.93) 0.021	0.60 (0.40-0.91) 0.017	0.56 (0.35-0.88) 0.013	0.71 (0.49-0.97) 0.039	0.66 (0.45-0.96) 0.033	0.63 (0.42-0.95) 0.031

Model 1 - OR are adjusted for age (years), gender and BMI (kg/m<sup>2</sup>); Model 2 - OR are adjusted for: parameters of Model 1 and smoking (ever), use of aspirin, NSAIDs, statin and antidiabetic medication, daily caloric intake (kcal) and colonoscopy indication (screening, diagnostic or surveillance); Model 3 - OR are adjusted for: parameters of Model 2 and for all other dietary components. <sup>1</sup>The cutoffs for the MD and for each dietary factor was based on the sample median, with the exception of the MD score (per 1 point increase) which ranged from zero to ten. Vegetables and legumes: Fresh/cooked; Fruit: Fresh whole fruit; Nuts and seeds: Natural unsalted nuts and seeds or paste products; Whole grains: Bread, cooked grains, breakfast cereal; Fish: Fresh, canned and cooked. Ratio of mono-unsaturated fatty-acids to saturated fatty-acids (MUFA/SFA); Poultry: Chicken and turkey products; Red meat: Beef, veal, pork products and internal organs; Alcohol: Beer, wine, liquor; Sugar-sweetened beverages: Fruit juice, iced tea, non-diet soft drinks. BMI: Body mass index; NSAIDs: Non-steroidal anti-inflammatory drugs; MD: Mediterranean diet.

a „probable carcinogen to humans“, owing to strong mechanistic evidence linking red meat intake with CRC including N-nitroso compounds (NOC) heterocyclic aromatic amines, and the endogenous compound, heme iron<sup>[49]</sup>.

Fish intake has been associated with CRC risk reduction in other epidemiological studies<sup>[50,51]</sup>. In the Adventist Health Study II, the adjusted hazard ratio (HR) for CRC in pesco-vegetarians was HR = 0.57 (95%CI: 0.40-0.82) compared with non-vegetarians. Pesco-vegetarians



**Figure 1** Dose response univariate and multivariate association between the number of adhered Mediterranean dietary components and (A) advanced colorectal polyps or (B) non-advanced adenomas. Association between the number of adhered Mediterranean dietary components and (A) advanced polyps, univariate (left panel) and multivariate (right panel) or (B) non-advanced adenomas, univariate (left panel) and multivariate (right panel). Univariate *P*-values are calculated by Chi-Square test. OR adjusted for: Age (years), gender, smoking (ever), BMI (kg/m<sup>2</sup>), use of aspirin, NSAIDs, statin and antidiabetic medication, daily caloric intake (kcal) and colonoscopy indication (screening, diagnostic or surveillance), and 95%CI are calculated by logistic regression. BMI: Body mass index; NSAIDs: Non-steroidal anti-inflammatory drugs.

were at the lowest risk compared to all other forms of vegetarianism<sup>[52]</sup>, perhaps due to fish consumption, which best distinguishes pesco-vegetarians from other vegetarian dietary patterns. Indeed, experimental studies have shown that fish intake is associated with increased apoptosis rates in the colonic mucosa<sup>[53]</sup>, which may be explained by immunomodulatory activities of omega-3 PUFAs<sup>[10]</sup>. It may be argued that the protective association seen between increased fish intake and lower odds of advanced polyps is confounded by the accompanied lower red meat intake. However, in this study, the significant association with high fish intake was maintained with adjustment for low red meat and for poultry intake.

It has been previously reported that sugar-sweetened beverage consumption is associated with CRC<sup>[54]</sup>. High sugar consumption, is associated with abdominal obesity and the activation of the insulin and insulin growth-factor

(IGF) system<sup>[55]</sup>, which have been shown to play a pivotal role in the pathogenesis, progression, and prognosis of CRC<sup>[56]</sup>. In this study, the protective association between low sugar-sweetened beverages intake and colorectal advanced polyps remained significant after adjustment for other dietary factors, total calories and BMI, and is therefore assumed to be independent of these potentially confounding or mediating factors.

Notably, we found that high intake of whole grains and fruit, were significantly associated with lower odds of advanced colorectal polyps with adjustment for many potentially confounding factors. With additional adjustment for the other components of the MD, these associations were no longer significant. This may be explained by multicollinearity between different food groups of the MD. Both fruit and whole grains are major factors of the MD plant-based compartment, contributing dietary fiber and polyphenols<sup>[57]</sup>, and both have been

negatively associated with colorectal inflammation and neoplasia<sup>[12,58,59]</sup>. Other MD factors, distributed similarly between cases and controls, were vegetables and legumes, nuts and seeds, poultry and alcoholic beverages. These results contradict previous reports of vegetables being negatively associated<sup>[60]</sup>, and alcohol being positively associated<sup>[61]</sup> with colorectal neoplasia. This can be attributed to the low diversity in the intake of these food groups in the Israeli population, characterized by high intake of vegetables and poultry, and low intake of alcohol<sup>[62,63]</sup>.

The limitations of this study include the lack of temporal sequence, which does not permit a causal inference. In terms of external validity, this study population was intentionally selected to represent low to medium risk for colorectal polyps. Despite the reasonable response rate, we had a low proportion of patients with a low socio-economic status, thus we may not represent the full spectrum of patients undergoing colonoscopy. The prevalence of several variables potentially affecting the risk of colorectal adenomas differed between cases and controls. Specifically, there was a higher use of statins and aspirin in the cases, which may stem from the more altered metabolic state of these patients. Although adjustments were made, residual confounding may still exist. Information bias on dietary intake may exist, specifically report and recall bias, leading to under-reporting of certain foods<sup>[64,65]</sup>, and social desirability bias<sup>[66]</sup>. This bias was minimized by a standardized structured dietary questionnaire, which was assessed in the same manner, in consecutive cases and controls, and blinding of study participants to the study hypothesis. Thus, this potential report bias is most probably non-differential, and may only weaken the strength of the observed associations.

In conclusion, the MD is inversely associated with advanced colorectal polyps in a dose-response manner. MD components, which are independently associated with advanced polyps, are low intake of sugar-sweetened beverages, and high intake of fish. Therefore, these foods should be in the focus of lifestyle interventions aimed for primary prevention of CRC.

## ARTICLE HIGHLIGHTS

### Research background

Colorectal cancer (CRC) is a common disease with considerable mortality rates in the western world. The association between diet and CRC and adenomas has been investigated, and risk factors, which have been identified, include high intake of red or processed meat and alcohol, and low intake of fruit, vegetables, whole grains and legumes. The Mediterranean diet (MD) is a plant based dietary pattern, previously associated with a lower incidence of several chronic diseases, including several types of cancer, and specifically CRC and colonic adenomas. It has been suggested that the anti-neoplastic properties of the MD are due to a high fiber and phytochemical content, typically low amounts of calorie-dense foods such as sweets, and red meat.

### Research motivation

Given the high prevalence of CRC in the western world there is need for

evidence-based means of prevention. Nowadays, the recommended strategies for prevention of CRC include screening for early detection, and reduction of CRC risk through lifestyle and certain dietary regimens, although a specific dietary pattern has not been identified.

### Research objectives

The aim of this study was to evaluate the association between the MD dietary pattern, and advanced colorectal polyps (adenoma and serrated adenoma). As these are the main precursor lesions of CRC, elucidating this association may imply a dietary strategy in lowering colorectal neoplasia risk. If the hypothesis of this study is confirmed, larger prospective studies will be able to further elucidate the temporal association and strengthen a causal link between the adherence to the MD diet and CRC prevention.

### Research methods

We collected detailed information of 783 subjects who underwent colonoscopy at the Tel Aviv medical center, including 385 controls, 192 cases on non-advanced adenomas and 206 cases with advanced polyps (advanced adenoma  $n = 165$ , advanced serrated adenoma  $n = 11$ , multiple non-advanced adenomatous or serrated adenomas  $n = 30$ ). Within two months after their colonoscopy, patients underwent blood tests, anthropometric measurements, demographic characteristics and medical history, current medications and indication for colonoscopy were documented, lifestyle, and dietary intake were assessed with a structured questionnaire. Mean daily and weekly intake was calculated for each food group: whole grains, vegetables and legumes, nuts and seeds, fruit, fish, poultry, red and processed meat, sugar-sweetened beverages, alcoholic beverages, and the ratio of mono-unsaturated fatty-acids to saturated fatty-acids (MUFA/SFA). For beneficial components (whole grains, vegetables and legumes, nuts and seeds, fruit, fish, poultry, and MUFA/SFA), consumption at or above the group median was considered as adherence, while for components presumed to be detrimental (red and processed meat, sugar-sweetened beverages, and alcoholic beverages), consumption below the group median was considered as adherence. The MD score was calculated as the sum of all adhered components.

### Research results

Main findings include a significant negative association between the MD score and advanced colorectal polyps, which demonstrated a dose response relationship. Of all MD components, the ones most highly associated with lower odds of advanced polyps were low intake of sugar-sweetened beverages and red meat, as well as high intake of fish. We conclude that adherence to the MD dietary pattern is associated with lower odds of advanced colorectal polyps. As this is an observational case-control study, further prospective studies are needed to confirm this association.

### Research conclusions

In this study we show that the MD score is negatively associated with colorectal polyps, and specifically advanced polyps. A significant dose response association was detected with categories of the number of adhered MD components. Also, from all the components of the MD, low intake of sugar-sweetened beverages, red meat and high intake of fish were independently associated with lower odds of advanced polyps. The findings of this study imply that adherence to the MD diet may have a role in colorectal neoplasia progression, and should further be studied as a means of colorectal polyp prevention. This study confirms previous reports regarding the MD and colorectal cancer and adenomas, and adds to the knowledge regarding the specific components of the MD independently associated with lower odds of advanced colorectal polyp. The strengths of this study include the large sample-size case control study design, which enabled testing the association between diet and the rare finding of advanced polyps, in a population which is not at high risk of CRC. Furthermore, we had a meticulous nutritional data collection as well as data on important potential confounders, which we adjusted for.

### Research perspectives

Future prospective research in the field of dietary CRC prevention should focus on elucidating the temporality and the strength of the association between diet and colorectal polyps. Also, it is advised that future studies elucidate this

association within the context of serrated polyps, which our study sample was unable to provide.

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