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MEDITERRANEAN DIET AND HEPATOCELLULAR CARCINOMA

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Abbreviations

HCC, Hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; anti-HCV, antibodies against hepatitis C virus; MDS, Mediterranean diet score; Odds ratio, OR; CI, confidence interval; BMI, body mass index; RERI, excess risk due to interaction; S, synergy index.

Conflict of interest

Authors have no conflict of interest to declare.

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Abstract

**Background & Aims:** Hepatocellular carcinoma (HCC) has a very poor prognosis and any effort to identify additional risk factors, besides those already established, would be important for the prevention of the disease. Data on the role of diet on HCC risk are still controversial.

**Methods:** We have evaluated the association of adherence to the Mediterranean diet with HCC risk, as well as the interaction of this dietary pattern with chronic hepatitis infection, by combining two case-control studies undertaken in Italy and Greece, including overall 518 cases of HCC and 772 controls. Adherence to the traditional Mediterranean diet was assessed through the Mediterranean diet score (MDS), which ranges between 0 (lowest adherence) and 9 (highest adherence). Odds ratios (OR) for HCC were obtained through multiple logistic regression models, controlling for potentially confounding variables, including chronic infection with hepatitis B/C viruses.

**Results:** Compared to MDS of 0-3, the ORs for HCC were 0.66 (95% confidence interval (CI), 0.41-1.04) for MDS equal to 4 and 0.51 (95% CI, 0.34-0.75) for MDS≥5, with a significant trend (p<0.001). The detrimental effect of poor adherence to Mediterranean diet on HCC risk was disproportionately high among those chronically infected with hepatitis B and/or C viruses, with a suggestion of super-additivity additive interaction, albeit statistically non-significant.

**Conclusion:** Closer adherence to the Mediterranean diet appears to be protective against HCC. Our results also point to potential benefits from adhering to a Mediterranean dietary pattern for patients chronically infected with hepatitis viruses.

**Abstract word count:** 243

**Keywords:** Liver cancer, Case-control study, Risk factors, Dietary habits, Mediterranean diet.
Introduction

Hepatocellular carcinoma (HCC) is the most common histological type of primary liver cancer. The predominant role of chronic infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) in the aetiology of HCC is well documented [1]. Several other risk factors for HCC have been identified, including heavy alcohol intake, tobacco smoking, and obesity [2]. With the exception of aflatoxins, data on the role of diet on liver cancer are inconclusive. Some studies have shown a weak inverse association between fruit consumption and liver cancer risk, and a positive one with glycaemic load, but evidence is sparse and inconsistent [3, 4]. It has been reported that for certain diseases, notably coronary heart disease, no food, food group, or nutrient has been implicated as causal, but the evidence for a favorable role of the Mediterranean dietary pattern is convincing [5]. Data are much scantier on Mediterranean diet and cancer risk [6-9]. Because HCC is a disease with a very poor prognosis, with a 5-year survival rate of less than 10% [10], any effort to identify additional modifiable causes of liver cancer would be important in order to allow a more effective prevention of the disease.

We have therefore evaluated the association between the Mediterranean dietary pattern and liver cancer by combining two large case-control studies undertaken in Italy and Greece, two countries in which the traditional Mediterranean diet is still prevalent. Age-standardized mortality from primary liver cancer (mainly HCC) is around 3/100,000 population in these countries [11]. Thus, despite being more common than in most other high income countries, HCC is still a rare disease, with a lifelong cumulative incidence around 1% in the general population.

Materials and methods

Selection of cases and controls

The present data are derived from case-control studies of HCC in two Mediterranean countries.
The first study was conducted between 1999 and 2002, in the province of Pordenone (north-eastern Italy) and in the city of Naples (southern Italy) [12]. Cases were 258 patients under the age of 85 years with incident (newly diagnosed) HCC. Of the HCC cases, 29 cases did not provide a blood sample and 44 did not provide data on dietary habits, thus leaving 185 eligible cases for the present analysis. The cases excluded for these reasons were similar to those considered in the analyses in relation to major socio-demographic characteristics [13]. Histologic or cytologic confirmation was available for 78.2% of HCC cases, while for the remaining cases, the diagnosis was based on ultrasound, tomography, and elevated alpha-fetoprotein levels. Controls were patients <85 years of age admitted for a wide spectrum of acute conditions to the same hospitals as cases. Patients whose hospital admission was due to diseases related to tobacco smoking, alcohol abuse, hepatitis viruses (e.g., hepatitis, cirrhosis, and esophageal varices), or other chronic diseases were excluded from the comparison group. Blood samples were available for 431 of 462 controls; of these, 412 provided comprehensive questionnaire information on dietary habits and were included in the present analyses. Twenty-seven percent were admitted for trauma, 24% for nontraumatic orthopedic diseases, 25% for acute surgical conditions, 13% for eye diseases, and 11% for other miscellaneous illnesses. In this study, overall, there were 3 refusals in the case series (<1%) and 5 in the control one (<1%).

The second study was conducted between 1995 and 1998 in three teaching hospitals in Athens, Greece, and 374 subjects with incident (newly diagnosed) HCC were identified [14]. Forty-one (11%) of the HCC cases were not enrolled for various reasons (mainly refusals and difficulty in coordinating collection of blood samples in the context of standard medical care). For the 333 cases eventually included in the study, confirmation of their HCC diagnosis was based on biopsy (n=157), elevated alpha-fetoprotein level (n=159) or echotomography and/or other methods (n=14); for 3 cases, details concerning diagnostic confirmation were missing. Controls were 360 patients admitted to the same hospitals as the cases, for injuries, or eye, ear, nose or throat conditions. For each case with HCC, we attempted to select 1 control patient from the same hospital, matching for
gender and age. Overall there were 25 refusals in the control series (6%), and a properly matching control could not be identified for some HCC cases. Finally, 360 control subjects were enrolled. Thus, a total of 518 cases of HCC and 772 controls were considered in the present analysis. Both studies were approved by participating institutional review boards, and, in both the original case-control studies, written informed consent was obtained from each participant in accordance with the Declaration of Helsinki.

Data collection

In both component studies, information on socio-demographic characteristics, anthropometric measures, selected medical conditions, and lifetime tobacco smoking and alcohol drinking was collected. For dietary assessment, interviewer-administered semiquantitative food frequency questionnaires were used. In the Italian study, the average weekly frequency of consumption of 63 foods or food groups, as well as complex recipes, two years before cancer diagnosis or hospital admission (for controls) was recorded [15, 16]. Detailed information collected on history of alcohol drinking, including any change in alcohol beverage intake, allowed to compute maximal lifetime alcohol intake level. This variable, instead of average alcohol intake, was used in this analysis to take into account the strong tendency of HCC cases to diminish or stop alcohol drinking as a consequence of liver disease before cancer onset. Current and former drinkers were therefore combined on the basis of their maximal lifetime alcohol intake.

In the Greek study, cases and controls were asked to indicate the average frequency of consumption of 120 food items or beverage categories per month, per week or per day, over a period of 1 year preceding the recognition of symptoms or signs of the present disease. Concerning alcohol, the usual intake 1 year before enrolment was recorded.

We calculated energy intakes using country-specific food composition databases [17-19].
In both studies, biological samples were obtained from cases and controls and tests were conducted for hepatitis B surface antigen (HBsAg) and antibodies against HCV (anti-HCV) using third-generation assays.

**Mediterranean diet**

Adherence to the traditional Mediterranean diet was assessed through an *a priori* score, which is a slight variant of the score reported by Trichopoulou and colleagues [20]. The Mediterranean diet score (MDS) is based on 9 dietary components typical of the traditional Mediterranean diet. For each study subject, a value of 0 or 1 was assigned to each component of the score as follows: for components frequently consumed in the traditional Mediterranean diet (i.e., vegetables, legumes, fruit and nuts, cereals, fish and seafood, as well a high ratio of monounsaturated to saturated lipids), participants whose consumption was above or equal to the component study- and sex-specific median, calculated among controls, were assigned a value of 1, and 0 otherwise; for components less frequently consumed in the traditional Mediterranean diet (dairy, as well as meat and meat products), participants whose consumption was above or equal to the component study- and sex-specific median among controls were assigned a value of 0, and 1 otherwise. For alcohol, a value of 1 was assigned to moderate drinkers (that is, men who do drink but no more than 2 glasses per day, and women who do drink but no more than 1 glass every other day) and a value of 0 to those with consumption above these values, as well as to nondrinkers.

The MDS was then calculated by summing up the points for each of the nine components. Thus, the score ranged between 0 (lowest adherence) and 9 (highest adherence).

**Data analysis**

Odds ratios (OR) of HCC (as estimates of the respective incidence rate ratios) and the corresponding 95% confidence intervals (CI) according to the MDS (in categories, as well as for 1
point increment) were estimated through unconditional multiple logistic regression models, with terms for center, age (categorically, <60, 60-64, 65-70, ≥70 years), sex, education (categorically, <7, 7-11, ≥12 years), body mass index (BMI, categorically, <25, 25-24.9, ≥30 kg/m²), smoking (categorically, current versus never plus former smokers), history of diabetes, non-alcohol energy intake (categorically, in study-specific quartiles among controls), and HBsAg and/or anti-HCV positivity. Multiple logistic regression models with the same set of covariates were used to estimate alternately the associations of the individual components of the MDS with HCC. Missing values for adjusting covariates were included as dummy variables in the models.

We estimated ORs for categories of the MDS (i.e., 0-4 as an indicator of poor adherence and ≥5 as an indicator of close adherence to the Mediterranean diet) and chronic infection with HBV and/or HCV (presence of either or both versus absence of both).

We have evaluated interaction as a deviation from additivity rather than deviation from multiplicatively because the former is more relevant in the biological and clinical context [21, 22]. Moreover, multiplicative models typically involve logarithmic transformations and once the logarithm of the number of cases is taken, partitioning of subjects into causal subsets is no more interpretable [21, 22]. In order to estimate additive interaction we used the relative excess risk due to interaction (RERI) and the synergy index (S) [22]. RERI is the observed relative risk in the presence of both factors minus the relative risk that would have been expected in the presence of both factors if their effects were exactly additive; it ranges between –infinity to +infinity, with RERI=0 indicating no interaction (i.e., that the effects of the two exposures are exactly additive), RERI>0 positive interaction and RERI<0 negative interaction. S is the excess risk from both exposures when there is an additive interaction, relative to the risk from both exposures without additive interaction. S ranges from 0 to +infinity; S=1 means no additive interaction, S>1 means positive additive interaction and S<1 negative additive interaction. Confidence intervals for the indices were obtained using the delta method [23].

Statistical analyses were performed using SAS v.9.1 (SAS Institute, Cary, NC, USA).
Results

Table 1 presents the main characteristics of cases and controls in the Italian and Greek studies, separately, for descriptive purposes. The prevalence of current smokers is higher in the Greek study than in the Italian one; 79% of cases and 11% of controls in the Italian study and 75% of cases and 4% of controls in the Greek study had serological evidence of chronic infection with HBV and/or HCV.

With regard to the main recognized HCC risk factors, after mutual adjustment, the ORs were 1.33 (95% CI, 0.92-1.92) for current versus non smoking (never plus former smoking), 1.72 (95% CI, 1.04-2.87) for BMI ≥30 kg/m² versus BMI<25 kg/m², and 43.47 (95% CI, 30.11-62.75) for chronic infection with HBV and/or HCV (data not shown). Relevant results for each of the component studies have been reported in detail in earlier publication [12, 14, 24, 25].

The association of the MDS with HCC risk, controlling for center and potential confounders, is presented in Table 2. Compared to MDS of 0-3, the ORs for developing HCC were 0.66 (95% CI, 0.41-1.04) for MDS equal to 4 and 0.51 (95% CI, 0.34-0.75) for MDS ≥5, with a significant trend in risk (p<0.001). The OR per 1 point increment in the MDS was 0.86 (95% CI, 0.77-0.95). Relative risk estimates for MDS categories obtained from a sensitivity analysis with models increasingly adjusted for major confounders were very similar. Results were consistent in Italy (ORs for successive categories of the MDS, compared to MDS of 0-3: 0.73 and 0.39) and Greece (ORs: 0.57 and 0.61), and across strata of sex, age, education, and BMI. With regard to individual score components, the risk for HCC (for intakes over or equal to versus below the median) was inversely related to consumption of pulses (OR=0.66, 95% CI, 0.47-0.92) and cereals (OR=0.65, 95% CI, 0.46-0.91). No other components of the score were found to be significantly related to HCC: the ORs were 1.12 (95% CI, 0.76-1.64) for the ratio of monounsaturated to saturated lipids, 1.06 (95% CI, 0.74-1.51) for fruit and nuts, 1.01 (95% CI, 0.72-1.41) for vegetables, 0.77 (95% CI, 0.54-1.09) for fish and seafood, 1.23 (95% CI, 0.88-1.73) for meat and meat products, and 0.95 (95% CI, 0.67-
1.35) for dairy. For alcohol, compared to non drinkers, the ORs for HCC were 0.63 (95% CI, 0.39-1.02) for moderate drinkers and 1.40 (95% CI, 0.89-2.19) for heavier drinkers.

The joint effect of MDS and chronic infection with HBV and/or HCV on HCC risk, controlling for center and potential confounders, is shown in Table 3. Compared to the lowest risk category, that is hepatitis-free subjects with MDS≥5, the ORs for HCC were 1.64 (95% CI, 1.07–2.50) for hepatitis-free subjects with MDS of 0-4, 43.95 (95% CI, 25.93–74.49) for subjects chronically infected with HBV and/or HCV with MDS≥5, and 74.25 (95% CI, 42.84-128.67) for those chronically infected with HBV and/or HCV with MDS of 0-4. RERI was 29.65 (p=0.119) and S was 1.68 (p=0.082). The RERI and S estimates, although they do not reach statistical significance, are suggestive of positive additive interaction of poor adherence to Mediterranean diet with chronic hepatitis infection in the causation of HCC. Thus, the combined effect of chronic hepatitis infection and poor adherence to the Mediterranean diet could be associated with increased HCC risk over and beyond what would have been expected from the sum of the individual effects of these two exposures.

**Discussion**

Combining two large studies carried out in the Mediterranean region, we found that the degree of adherence to Mediterranean diet is significantly inversely related to HCC risk in a roughly monotonic way, so that the MDS ≥5 was associated with an about 50% reduction in HCC incidence in comparison to MDS of 3 or less. We also found that there is evidence, albeit statistically non significant, of super additivity in the risk implications of joint chronic hepatitis B and/or C infection and poor adherence to Mediterranean diet.

Several studies have shown a beneficial role of the traditional Mediterranean diet on health and longevity [20, 26-29]. The Mediterranean pattern has also been inversely related to cancer overall [8, 9, 30, 31], as well as specific forms of cancer [32-40]. Up to now, however, no study has investigated the association between Mediterranean diet and liver cancer risk.
We found a substantial and statistically significant reduction in HCC risk with closer adherence to the Mediterranean diet, even though, with respect to the individual components of the Mediterranean diet, relevant associations with HCC were generally statistically non-significant. A possible explanation is that the effects of the individual components of the score on HCC emerge only when these components are combined in an integrated unidimensional score, as the MDS is. Potential biologic interactions may also exist between the various dietary components of the Mediterranean pattern. Finally, the effects of individual components are evaluated against the background of average risk associated with other dietary factors, while the use of a score can account for extremes of cumulative exposure, in the absence of other major nutritional effects [20, 41].

The relative risk for the combined exposure to chronic hepatitis infection and low MDS was close to the product of the two relative risks. Consequently, our results indicate that adherence to the traditional Mediterranean diet may disproportionally reduce the excessively high relative risk to develop HCC among patients chronically infected with HBV and/or HCV from around 70 to around 40, although these results did not reach statistically significance. This observation, if confirmed in other studies, could have considerable clinical implications by leading to specific dietary recommendations for patients chronically infected with these viruses. This is a particularly innocuous recommendation, since Mediterranean diet has several beneficial health effects and it is not known to have any adverse side effects [8, 9, 28-30].

Among the possible limitations of the present study, there is the use of hospital controls, whose dietary habits may differ from those of the general population [42]. However, in both component studies, all diagnoses involving any long-term changes in diet were excluded from the control group. The comparable catchment areas for cases and controls, and the almost complete participation in both studies are reassuring against possible selection bias. Bias in the recall of food intake by cases should be small given the limited knowledge and attention paid in these populations to the possible relation between diet and liver cancer and reproducibility of food frequency data.
provided by hospital controls in Mediterranean populations was satisfactory [43]. Given the same
interview settings, information provided by hospital controls should have a good comparability with
that by cases. To reduce any possible dietary modification bias due to the recent cancer diagnosis,
we asked for habitual dietary habits before cancer diagnosis, although diet could have changed
before owing to subclinical disease. Another limitation is that alcohol consumption was evaluated
somewhat differently in the two studies. However, individual changes in alcohol consumption are
relatively infrequent in these Mediterranean populations [6, 44], and, in any case, unlikely to
substantially influence the definition of moderate drinking used in our Mediterranean diet score.
Further, the results were consistent in the two datasets.
Among the strengths of the present study are the relatively large sample size and the possibility to
adjust for the major known risk factors for HCC, including chronic infection with HBV and/or
HCV, tobacco smoking and BMI. The major strength of this study, however, is the application of an
a priori independently developed Mediterranean score [20] to populations with considerable
variability with respect to this score. Thus, any findings cannot be attributed to data dredging.
In conclusion, closer adherence to the Mediterranean diet appears to convey some protection against
HCC risk. Moreover, our findings, if independently confirmed, would point to potential benefits
from adhering to a Mediterranean dietary pattern for patients chronically infected with HBV and/or
HCV.

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References


Table 1. Distribution of cases of hepatocellular carcinoma and corresponding controls, according to

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<tbody>
<tr>
<td></td>
<td>Cases (%)</td>
<td>Controls (%)</td>
<td>Cases (%)</td>
</tr>
<tr>
<td></td>
<td>n=185</td>
<td>n=412</td>
<td>n=333</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
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<td></td>
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<tr>
<td>&lt;55</td>
<td>18 (9.7)</td>
<td>85 (20.6)</td>
<td>49 (14.7)</td>
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<tr>
<td>55-59</td>
<td>18 (9.7)</td>
<td>47 (11.4)</td>
<td>46 (13.8)</td>
</tr>
<tr>
<td>60-64</td>
<td>38 (20.5)</td>
<td>69 (16.8)</td>
<td>70 (21.0)</td>
</tr>
<tr>
<td>65-69</td>
<td>49 (26.5)</td>
<td>72 (17.5)</td>
<td>74 (22.2)</td>
</tr>
<tr>
<td>≥70</td>
<td>62 (33.5)</td>
<td>139 (33.7)</td>
<td>94 (28.2)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>149 (80.5)</td>
<td>281 (68.2)</td>
<td>283 (85.0)</td>
</tr>
<tr>
<td>Women</td>
<td>36 (19.5)</td>
<td>131 (31.8)</td>
<td>50 (15.0)</td>
</tr>
<tr>
<td>Education &lt;a&gt; (years)</td>
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<td></td>
<td></td>
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<tr>
<td>&lt;7</td>
<td>126 (68.1)</td>
<td>232 (56.3)</td>
<td>214 (64.9)</td>
</tr>
<tr>
<td>7-11</td>
<td>45 (24.3)</td>
<td>93 (22.6)</td>
<td>37 (11.2)</td>
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<td>≥12</td>
<td>14 (7.6)</td>
<td>87 (21.1)</td>
<td>79 (23.9)</td>
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<tr>
<td>Smoking habits</td>
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<tr>
<td>Never plus former</td>
<td>117 (63.2)</td>
<td>303 (73.5)</td>
<td>183 (55.0)</td>
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<td>Current</td>
<td>68 (36.8)</td>
<td>109 (26.5)</td>
<td>150 (45.0)</td>
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<tr>
<td>Body mass index (kg/m&lt;sup&gt;2&lt;/sup&gt;) &lt;a&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;25</td>
<td>71 (38.4)</td>
<td>147 (36.4)</td>
<td>139 (43.3)</td>
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<td>25-29.9</td>
<td>76 (41.1)</td>
<td>176 (43.6)</td>
<td>143 (44.5)</td>
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<td>≥30</td>
<td>38 (20.5)</td>
<td>81 (20.0)</td>
<td>39 (12.2)</td>
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<tr>
<td>Hepatitis &lt;a,b&gt;</td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>38 (20.5)</td>
<td>365 (88.6)</td>
<td>83 (24.9)</td>
</tr>
<tr>
<td>Yes</td>
<td>147 (79.5)</td>
<td>47 (11.4)</td>
<td>250 (75.1)</td>
</tr>
</tbody>
</table>

*The sum does not add up to the total because of some missing values.

*Hepatitis was defined as HBsAg and/or anti-HCV positivity.
Table 2. Odds ratios\(^a\) (OR) and 95\% confidence intervals (CI) for hepatocellular carcinoma (HCC), according to the Mediterranean diet score. Italy (1999-2002) and Greece (1995-1998).

<table>
<thead>
<tr>
<th>Mediterranean diet score(^b)</th>
<th>HCC Cases (%) N=518</th>
<th>Controls (%) N=772</th>
<th>OR(^a) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>198 (38.8)</td>
<td>223 (29.0)</td>
<td>1.00</td>
</tr>
<tr>
<td>4</td>
<td>113 (22.2)</td>
<td>166 (21.6)</td>
<td>0.66 (0.41-1.04)</td>
</tr>
<tr>
<td>≥5</td>
<td>199 (39.0)</td>
<td>379 (49.3)</td>
<td>0.51 (0.34-0.75)</td>
</tr>
<tr>
<td>(\chi^2) for trend=11.2; p&lt;0.001</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1 point increment</td>
<td></td>
<td>0.86 (0.77-0.95)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Estimated from unconditional logistic regression model adjusted for center, age, sex, education, body mass index, smoking, diabetes, non-alcohol energy intake, and HBsAg and/or anti-HCV positivity.

\(^b\) The sum does not add up to the total because of some missing values.

\(^c\) Reference category.
Table 3. Odds ratios\(^a\) (OR) and 95% confidence intervals (CI) for hepatocellular carcinoma according to the combination of the Mediterranean diet score and chronic infection with hepatitis B and/or hepatitis C viruses, and indexes of departure from additivity of effects. Italy (1999-2002) and Greece (1995-1998).

<table>
<thead>
<tr>
<th>Mediterranean diet score</th>
<th>≥5</th>
<th>0-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis(^b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>44:343(^c)</td>
<td>75:358</td>
</tr>
<tr>
<td></td>
<td>1(^d)</td>
<td>1.64 (1.07-2.50)</td>
</tr>
<tr>
<td>Yes</td>
<td>155:32</td>
<td>236:28</td>
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<tr>
<td></td>
<td>43.95 (25.93-74.49)</td>
<td>74.25 (42.84-128.67)</td>
</tr>
</tbody>
</table>

*Indices of departure from additivity of effects*
- Relative excess risk due to interaction (RERI)=29.65, p=0.119
- Synergy index (S)=1.68, p=0.082

\(^a\) Estimated from unconditional logistic regression model adjusted for center, age, sex, education, body mass index, smoking, diabetes, and non-alcohol energy intake.

\(^b\) Hepatitis was defined as HBsAg and/or anti-HCV positivity.

\(^c\) Cases: Controls. The sum does not add up to the total because of some missing values

\(^d\) Reference category.