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Association between polyphenol intake and adherence to the Mediterranean diet in Sicily, southern Italy.

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Abstract

Background. Mediterranean diet has been demonstrated to exert beneficial effects toward various health outcomes. Among the compounds that may be responsible for such benefits, polyphenols have been proposed as potential candidates. The aim of this study was to evaluate whether dietary polyphenols were associated with adherence to the Mediterranean diet in a Sicilian cohort.

Methods. A total of 1,937 adults were recruited in the urban area of Catania, southern Italy. Background characteristics and dietary habits were collected through validated questionnaires. Adherence to the Mediterranean diet was evaluated through application of a validated score (MEDI-LITE score). Dietary intake of polyphenols was estimated through the Phenol-explorer database. Differences in mean intake between quartiles of the MEDI-LITE score and association between quartiles of polyphenol intake and high adherence to the Mediterranean diet (highest quartile of the score) were calculated though logistic regression analyses.

Results. Mean intake of most polyphenols was significantly different between quartiles of the MEDI-LITE score, being generally higher in individuals more adherent to the Mediterranean diet. Only few compounds, such as lignans, anthocyanins, and flavanones, showed a linear positive association with high adherence to the Mediterranean diet, while other polyphenol classes were associated in a non-linear manner. Among individual polyphenols, apigenin, hesperetin, naringenin, lariciresinol, matairesinol, pinoresinol, secoisolariciresinol, and ferulic acid were associated with high adherence to Mediterranean diet in a linear manner, while all the others (except for myricetin) were associated in a non-linear way.

Conclusions. Mean polyphenol intake was higher in individuals more adherent to the Mediterranean diet compared to less adherent. However, dietary sources of polyphenols not included in the traditional foods comprised in the Mediterranean diet may contribute to total and specific classes of polyphenols irrespectively of their inclusion within the context of the Mediterranean diet.

Keywords. polyphenols; Mediterranean diet; flavonoids; phenolic acids; stilbenes; olive oil.

1. Introduction

Over the last 50 years, studies on the Mediterranean diet have shown a substantial beneficial effect of adherence to this dietary pattern for human health. The strongest evidence has been reached on its association with decreased risk of cardiovascular diseases [1, 2], metabolic disorders [3-6], and certain cancers [7-10]. This dietary pattern does not refer to strict dietary guidelines provided, rather stands for the diet commonly consumed in southern Italy during the ‘60s. Despite there is no univocal definition of the Mediterranean diet, the beneficial effects of this dietary pattern rely on some key features: daily consumption of fruit and vegetable; high consumption of fish and olive oil; limited intake of meat and sweets; moderate intake of red wine and dairy products [11]. Such dietary pattern is characterized by a low content in saturated and trans-fatty acids, as well as richness in anti-oxidant vitamins, mono- and poly-unsaturated fatty acids, and phytochemicals with anti-oxidant and anti-inflammatory properties, such as polyphenols [12].

Dietary polyphenols are a large family of molecules occurring in a variety of plant-derived foods; such compounds have different chemical structures characterizing their absorption, bioavailability, and bioactivity [13]. Dietary polyphenols are divided into five main classes depending on their chemical structure: flavonoids, phenolic acids, stilbenes, lignans, and others [14]. The recent scientific interest on polyphenol relies on their potential anti-oxidant effects and association with decreased risk of metabolic disorders, cardiovascular disease, and cancer [15-17]. All the aforementioned classes of polyphenols are commonly included in the diet, but their intake depends on type of foods consumed [18]. Several previous studies showed important differences between total and individual polyphenol intake between countries, including Europe [19-25], US [26, 27], Asia and South America [28, 29]. In the European context, a south-to-north gradient in the daily mean intake of total polyphenols has been reported; moreover, differences between Mediterranean and non-Mediterranean countries have been detected, being flavonoids the most abundant polyphenol class consumed in the former, while phenolic acids in the latter [30, 31]. Some of the benefits of the Mediterranean diet have been hypothesized to depend on the contribution of total or specific classes of polyphenol [32, 33]. Thus, the aim of this study was to assess the association between high adherence to the Mediterranean diet and intake of polyphenol.

2. Methods

2.1 Study population

Study sample was constituted of participants of the Mediterranean healthy Eating, Aging, and Lifestyles (MEAL) study, an observational investigation primarily focused on nutritional habits and their relation with a cluster of lifestyle behaviors characterizing the classical Mediterranean lifestyle. The study protocol with the rationale, design, and methods have been described in detail elsewhere [34]. Briefly, the cohort consisted of a random sample of 2,044 men and women (age 18+ y) recruited in the urban area of Catania, one of the largest cities in the east coast of Sicily, southern Italy during 2014-15. All the study procedures were carried out in accordance with the Declaration of Helsinki (1989) of the World Medical Association. Participants provided written informed consent and the study protocol was approved by the ethics committee of the referent health authority.

2.2 Data collection

Data regarding demographic (i.e., age, sex, educational and occupational level) and lifestyle characteristics (i.e., physical activity, smoking and drinking habits) were collected. Educational level was categorized as (i) low (primary/secondary), (ii) medium (high school), and (ii) high (university). Occupational level was categorized as (i) unemployed, (ii) low (unskilled workers), (iii) medium (partially skilled workers), and (iv) high (skilled workers). Physical activity level was evaluated through the International Physical Activity Questionnaires (IPAQ) [35], which comprised a set of questionnaires (5 domains) on time spent being physically active in the last 7 days that allow to categorize physical activity as (i) low, (ii) moderate, and (iii) high. Smoking status was categorized as (i) non-smoker, (ii) ex smoker, and (iii) current smoker. Alcohol consumption was categorized as (i) none, (ii) moderate drinker (0.1-12 g/d) and (ii) regular drinker (>12 g/d).

2.3 Dietary assessment

Dietary data was collected by using a long and a short food frequency questionnaires (FFQs) specifically developed and validated for the Sicilian population [34, 36]. The FFQs consisted of 110 food and drink items representative of the diet during the last 6 months. Participants were asked how often, on average, they had consumed foods and drinks included in the FFQ, with nine responses ranging from "never" to "4-5 times per day". Intake of food items characterized by seasonality referred to consumption during the period in which the food was available and then adjusted by its proportional intake in one year. After exclusion of 107 entries with unreliable intakes (<1,000 or >6,000 kcal/d, controlled case by case and validated due to missing food items or unreliable answers), a total of 1,937 individuals were included in the analyses for the present study.

2.4 Adherence to the Mediterranean diet

The Mediterranean diet adherence was assessed through the score developed by Sofi et al [37]: briefly, a scoring system (the MEDI-LITE score) was built based on existing literature weighting all the median (or mean) values for the sample size of each study population and then calculating a mean value of all the weighted medians; hence, two standard deviations were used to determine three different categories of consumption for each food group. For food groups typical of the Mediterranean diet (fruit, vegetables, cereals, legumes and fish), 2 points were given to the highest category of consumption, 1 point for the middle category and 0 point for the lowest category. Conversely, for food groups not typical of the Mediterranean diet (meat and meat products, dairy products), 2 points were given for the lowest category, 1 point for the middle category and 0 point for the highest category of consumption. For alcohol, categories related to the alcohol unit (1 alcohol unit = 12 g of alcohol) were used by giving 2 points to the middle category (1–2 alcohol units/d), 1 point to the lowest category (>1 alcohol unit/d) and 0 point to the highest category of consumption (>2 alcohol units/d). The final score comprised nine food categories (including olive oil) with a score ranging from 0 point (lowest adherence) to 18 points (highest adherence).

2.5 Estimation of polyphenol intake

Estimation of polyphenol intake was performed through a previously published process [19-21, 28, 38]. Briefly, data on the polyphenol content in foods was obtained from the Phenol-Explorer database (www.phenol-explorer.eu) [39]. A new module of the Phenol-Explorer database containing data on the effects of cooking and food processing on polyphenol contents was used whenever possible in order to apply polyphenol-specific retention factors [40]. All foods that contained no polyphenols were excluded from the calculation, leaving a total of 75 items included for the analyses. Weight loss or gain during cooking was corrected using yield factors [41]. The average food consumption was calculated (in g or ml) by following the standard portion sizes used in the study and then converted in 24-hour intake. Finally, a search was carried out in the Phenol-Explorer database to retrieve mean content values for all polyphenols contained in the foods obtained and polyphenol intake from each food was calculated by multiplying the content of each polyphenol by the daily consumption of each food. The polyphenol content of foods included in the FFQ that could correspond to several entries in the Phenol-Explorer database (i.e., jams and fruit juices containing fruit-derived polyphenols, street food/pizza containing wheat-derived polyphenols) was weighted based on data on 24-hour recalls available from the FFQ validation process (i.e., cherry, strawberry and apricot jams, orange, pear and peach juices, refined white flour, respectively). Data on reverse phase high performance liquid chromatography was used to calculate polyphenol intake for all phenolic compounds. For certain foods (i.e., cereals, beans, walnuts) for which polyphenol content cannot be released with normal extraction conditions, data corresponding to HPLC after hydrolysis was used. The main classes of polyphenols (flavonoids, phenolic acids, lignans, stilbenes, others) and the total polyphenol intake was estimated by the sum of the previous; additional subclass and selected individual polyphenols were also estimated. Finally, total and individual classes of polyphenol intake were adjusted for total energy intake (kcal/d) using the residual method [42].

2.6 Statistical analysis

Continuous variables are presented as means and standard deviations, categorical variables as frequencies and percentages. Differences of mean between groups were tested using Mann-Whitney U-test and Kruskall-Wallis test, as appropriate, differences between categorical variables were tested with Chi-squared test. The relation between polyphenol intake and adherence to the Mediterranean diet was tested through different approaches: (i) by testing for difference in mean intake of polyphenol intake among different quartiles of the MEDI-LITE score, and (ii) by testing, through logistic regression analysis, the association between quartiles of polyphenol intake and high adherence to the Mediterranean diet (highest quartile of the MEDI-LITE score) adjusted for total energy intake. All reported *P* values were based on two-sided tests and compared to a significance level of 5%. SPSS 17 (SPSS Inc., Chicago, IL, USA) software was used for all the statistical calculations.

3. Results

The general characteristics of the study population according the level of adherence to the Mediterranean diet are presented in Table 1. A total of 1,936 individuals with mean age of 48.5 years old (age range 18-92 years) were included in the final analysis; about 14% of men and women were high adherent to the Mediterranean diet (highest quartile of the score), with no specific association with sex, age, and smoking status; however, individuals more adherent to the Mediterranean diet were slightly more physically active.

Distribution of mean polyphenol consumption by quartiles of the MEDI-LITE score showed significant differences for total polyphenols and most of classes (Table 2) and subclasses (Table 3) with exception of flavanols (P = 0.242) and catechins (P = 0.129). The highest mean intake of total polyphenols was not in the highest quartile of the MEDI-LITE score (Table 2): a similar non-linear distribution was found for phenolic acids (and its subclass hydroxybenzoic acids), stilbenes, dihydroflavonols, hydroxyphenilacetic acids, hydroxybenzaldehydes, and tyrosols (Table 2), while among individual polyphenols was found for apigenin, myricetin, caffeic acid, cinnamic acid, and biochanin A (Table 3).

When testing the association between quartiles of polyphenol intake and high adherence to the Mediterranean diet (highest quartile of the MEDI-LITE score), only few classes and subclasses of polyphenols, such as lignans, anthocyanins, and flavanones, showed linear increasing trends of association while hydroxybenzoic acids showed linear inverse association (Table 4). Most of the other polyphenol classes were associated to high adherence to Mediterranean diet in a non-linear manner, with higher association to 2nd or 3rd quartile, with the exception of flavanols, dihydrolavonols, and hydroxybenzaldehydes, which showed decreasing association for higher intake (Table 4). Also among individual polyphenols, apigenin, hesperetin, naringenin, lariciresinol, matairesinol, pinoresinol, secoisolariciresinol, and ferulic acid were associated with high adherence to Mediterranean diet in a linear increasing manner, while all the others (except for myricetin and catechins) were associated in a non-linear way (Table 5).

4. Discussion

In this study we described the relation between high adherence to the Mediterranean diet and dietary polyphenol intake in a cohort of individuals living in Sicily, southern Italy. Overall, the majority of polyphenols consumed with the diet was associated with high adherence to Mediterranean diet (highest quartile of the MEDI-LITE score), despite (among flavonoids) only anthocyanins and flavanones showed a clear linear relation. In contrast, all other classes revealed a non-linear association, showing that highest adherence to the Mediterranean diet was not associated with greater consumption of polyphenols, rather with moderate-to-high intake.

Based on these results, flavonoids were the most consumed polyphenol class in individuals highly adherent to the Mediterranean diet. Flavonoid and flavonoid subclasses content vary between foods consumed, which may explain the observed difference in intake between countries. For instance, it has been reported that in US and Asian countries the main sources of polyphenols are tea and soy foods; in Mediterranean countries the main contributors to flavonoid intake are fruits, vegetables, and red wine; in Northern and Eastern European countries the most consumed polyphenol-rich foods/beverages are coffee and tea while in South America are coffee and legumes (beans) [19-28, 30, 31]. These differences may have certain implications on the effect of foods consumed across countries at global level. For instance, recent evidence suggested a significant decreased risk for total flavonoids intake and upper aero-digestive tract cancers, despite the association was stronger for flavones, flavanols, and theaflavins (mostly contained in tea) in a multicentric study conducted at European level, while regarding flavanones (which are mainly derived from citrus fruit) in studies conducted in Italy and Greece [17]. Overall, implications for dietary recommendations are multiple and a better understanding food content, effectiveness, and targets of flavonoids subclasses is of major interest for public health. The superior effectiveness of certain healthy dietary patterns may depend on a higher variety of foods consumed, which may provide a wider range of polyphenol classes and subclasses.

Flavonoids have been reported to be the most abundant polyphenol class consumed in Mediterranean countries [30]. Flavonoids are abundant in fruits, vegetables, and herbs, which may explain not only the favorable effects of plant-based dietary patterns, but also of certain beverages, such as tea [43]. In line with the major food sources of flavonoids, intake of all flavonoid classes was higher in individuals with higher adherence to the Mediterranean diet; in particular, a linear association with anthocyanins and flavanones may depend on the preference of fruit consumed in Sicily, such as (i) citrus fruits (including red orange, which is rich in both flavanones and anthocyanins [44]), prickly fruits [45], and red wine [46]. Regarding other classes and total flavonoids, the non-linear association may depend on other sources of flavonoids that may not be included into the score of the Mediterranean diet. For instance, tea is not considered part of the traditional Sicilian dietary pattern; however, tea is a major contributor of flavonoid intake [47, 48], and it has been suggested to improve metabolic status and decrease risk of chronic-degenerative diseases [49-51]. Also chocolate or cocoa products may modulate important health risk factors due to their contribution in flavanols [52]; however, such food items are not included in the index used to assess the adherence to the Mediterranean diet and this may be responsible for the non-linear association between intake of these subclasses of flavonoid high adherence to the dietary pattern.

Concerning phenolic acids, we found increasing association with high adherence to Mediterranean diet, mainly relying to hydroxycinnamic acids rather than hydroxybenzoic acids. The main differences depend on the food sources of such compounds. Hydroxycinnamic acids are contained in coffee, which is a major contributor to total polyphenol intake in non-Mediterranean cohorts; however, other dietary sources, such as artichokes and cherries, which are consumed by the Sicilian population, are important sources of such compounds. Hydroxybenzoic acids are also contained in nuts, which over the last year have been considered part of a Mediterranean dietary pattern but were not comprised in several Mediterranean diet scores, including the one used in the present study. Both coffee [53, 54] and nuts [55, 56] have been demonstrated to be key functional foods associated with important benefits on human health: compared to other studies, coffee intake only partially contributed to total polyphenol intake in our cohort, while the role of nuts was more important in relation to the phenolic acid content of the diet; further investigations are warrant in order to determine whether such food groups and polyphenol class are associated with health benefits.

Phytoestrogens, such as isoflavones and lignans, are polyphenols with weak estrogenic effects, which have been hypothesized to be potentially protective for cardiovascular disease and certain cancers [57, 58]. Major sources of isoflavones and lignans are soy products and seeds, respectively, which are not commonly consumed in Mediterranean countries. However, other food sources of phytoestrogens include citrus fruits, grain-derived foods, and olive oil, which are characteristic of the Mediterranean diet; in fact, we found that both isoflavones and lignan consumption was associated to high adherence to the Mediterranean diet. Among other features characterizing the Mediterranean diet, wines (red and white) exert beneficial effects on cardiovascular-related outcomes with a J-shaped association [59]. Moderate alcohol consumption is part of the Mediterranean dietary pattern [60], but only stilbenes were associated to high adherence to the dietary pattern, especially in moderate consumption, while other compounds (such as dihydroflavonols and hydroxybenzaldehydes) were inversely associated at higher intakes. Stilbenes are the most studied polyphenol group: the most known compounds, resveratrol, has been associated with improvements in cardiovascular risk factors [61]. Interestingly, less studied classes of polyphenols, such as those included in the group “others” and tyrosols, have demonstrated to be associated with high adherence to the Mediterranean diet. This is not surprising, as major food contributors of such polyphenol classes are foods commonly consumed in Mediterranean countries and part of the score used, such as olives and olive oil, but also wines, beer, and pasta. Polyphenols derived from olives and olive oil have been considered responsible for a number of effects on inflammation, endothelial function, and blood lipids [62, 63].

The present study should be considered in light of some limitations. First, the use of FFQ may result in overestimation of food intake; however, there is no perfect methodology to estimate food consumption and FFQs are widely used in nutritional epidemiology. Second, the FFQ may not include all food sources of polyphenol intake (i.e., spices) or lack of specificity for certain food items (i.e., fruit juices, jams). Third, due to the retrospective nature of the instrument, data may have been affected by recall bias.

In conclusion, polyphenol intake is generally higher in individuals more adherent to the Mediterranean diet than in non-adherent. The results of this study may confirm the hypothesis that the beneficial effects of the Mediterranean diet may be mediated by the high content in polyphenols of the diet. However, the highest intake of polyphenols was only partially associated with high adherence to this dietary pattern, suggesting that other food sources of polyphenols consumed in the context of a Mediterranean population but not considered in the scores of adherence may contribute to total and specific classes of polyphenol intake.

References

[1] Grosso G, Marventano S, Yang J, Micek A, et al., A Comprehensive Meta-analysis on Evidence of Mediterranean Diet and Cardiovascular Disease: Are Individual Components Equal?, Crit Rev Food Sci Nutr. (2015) 0.

[2] Martinez-Gonzalez MA, Bes-Rastrollo M, Dietary patterns, Mediterranean diet, and cardiovascular disease, Curr Opin Lipidol. 25 (2014) 20-6.

[3] Grosso G, Mistretta A, Marventano S, Purrello A, et al., Beneficial effects of the Mediterranean diet on metabolic syndrome, Curr Pharm Des. 20 (2014) 5039-44.

[4] Godos J, Federico A, Dallio M, Scazzina F, Mediterranean diet and nonalcoholic fatty liver disease: molecular mechanisms of protection, Int J Food Sci Nutr. (2016) 1-10.

[5] Godos J, Zappala G, Bernardini S, Giambini I, et al., Adherence to the Mediterranean diet is inversely associated with metabolic syndrome occurrence: a meta-analysis of observational studies, Int J Food Sci Nutr. (2016) 1-11.

[6] Esposito K, Kastorini CM, Panagiotakos DB, Giugliano D, Mediterranean diet and metabolic syndrome: an updated systematic review, Rev Endocr Metab Disord. 14 (2013) 255-63.

[7] Grosso G, Buscemi S, Galvano F, Mistretta A, et al., Mediterranean diet and cancer: epidemiological evidence and mechanism of selected aspects, BMC Surg. 13 Suppl 2 (2013) S14.

[8] D'Alessandro A, De Pergola G, Silvestris F, Mediterranean Diet and cancer risk: an open issue, Int J Food Sci Nutr. 67 (2016) 593-605.

[9] Schwingshackl L, Hoffmann G, Adherence to Mediterranean diet and risk of cancer: an updated systematic review and meta-analysis of observational studies, Cancer Med. 4 (2015) 1933-47.

[10] Giacosa A, Barale R, Bavaresco L, Gatenby P, et al., Cancer prevention in Europe: the Mediterranean diet as a protective choice, Eur J Cancer Prev. 22 (2013) 90-5.

[11] Bach-Faig A, Berry EM, Lairon D, Reguant J, et al., Mediterranean diet pyramid today. Science and cultural updates, Public Health Nutr. 14 (2011) 2274-84.

[12] Sofi F, The Mediterranean diet revisited: evidence of its effectiveness grows, Curr Opin Cardiol. 24 (2009) 442-6.

[13] Del Rio D, Rodriguez-Mateos A, Spencer JP, Tognolini M, et al., Dietary (poly)phenolics in human health: structures, bioavailability, and evidence of protective effects against chronic diseases, Antioxid Redox Signal. 18 (2013) 1818-92.

[14] Landete JM, Updated knowledge about polyphenols: functions, bioavailability, metabolism, and health, Crit Rev Food Sci Nutr. 52 (2012) 936-48.

[15] Hooper L, Kroon PA, Rimm EB, Cohn JS, et al., Flavonoids, flavonoid-rich foods, and cardiovascular risk: a meta-analysis of randomized controlled trials, Am J Clin Nutr. 88 (2008) 38-50.

[16] Liu YJ, Zhan J, Liu XL, Wang Y, et al., Dietary flavonoids intake and risk of type 2 diabetes: a meta-analysis of prospective cohort studies, Clin Nutr. 33 (2014) 59-63.

[17] Grosso G, Godos J, Lamuela-Raventos R, Ray S, et al., A comprehensive meta-analysis on dietary flavonoid and lignan intake and cancer risk: level of evidence and limitations, Mol Nutr Food Res. (2016).

[18] Del Rio D, Costa LG, Lean ME, Crozier A, Polyphenols and health: what compounds are involved?, Nutr Metab Cardiovasc Dis. 20 (2010) 1-6.

[19] Grosso G, Stepaniak U, Topor-Madry R, Szafraniec K, Pajak A, Estimated dietary intake and major food sources of polyphenols in the Polish arm of the HAPIEE study, Nutrition. 30 (2014) 1398-403.

[20] Perez-Jimenez J, Fezeu L, Touvier M, Arnault N, et al., Dietary intake of 337 polyphenols in French adults, Am J Clin Nutr. 93 (2011) 1220-8.

[21] Tresserra-Rimbau A, Medina-Remon A, Perez-Jimenez J, Martinez-Gonzalez MA, et al., Dietary intake and major food sources of polyphenols in a Spanish population at high cardiovascular risk: the PREDIMED study, Nutr Metab Cardiovasc Dis. 23 (2013) 953-9.

[22] Knekt P, Jarvinen R, Reunanen A, Maatela J, Flavonoid intake and coronary mortality in Finland: a cohort study, BMJ. 312 (1996) 478-81.

[23] Knekt P, Kumpulainen J, Jarvinen R, Rissanen H, et al., Flavonoid intake and risk of chronic diseases, Am J Clin Nutr. 76 (2002) 560-8.

[24] Dragsted LO, Strube M, Leth T, Dietary levels of plant phenols and other non-nutritive components: could they prevent cancer?, Eur J Cancer Prev. 6 (1997) 522-8.

[25] Hertog MG, Hollman PC, Katan MB, Kromhout D, Intake of potentially anticarcinogenic flavonoids and their determinants in adults in The Netherlands, Nutr Cancer. 20 (1993) 21-9.

[26] Chun OK, Chung SJ, Song WO, Estimated dietary flavonoid intake and major food sources of U.S. adults, J Nutr. 137 (2007) 1244-52.

[27] Bai W, Wang C, Ren C, Intakes of total and individual flavonoids by US adults, Int J Food Sci Nutr. 65 (2014) 9-20.

[28] Nascimento-Souza MA, de Paiva PG, Perez-Jimenez J, do Carmo Castro Franceschini S, Ribeiro AQ, Estimated dietary intake and major food sources of polyphenols in elderly of Vicosa, Brazil: a population-based study, Eur J Nutr. (2016).

[29] Taguchi C, Fukushima Y, Kishimoto Y, Suzuki-Sugihara N, et al., Estimated Dietary Polyphenol Intake and Major Food and Beverage Sources among Elderly Japanese, Nutrients. 7 (2015) 10269-81.

[30] Zamora-Ros R, Knaze V, Rothwell JA, Hemon B, et al., Dietary polyphenol intake in Europe: the European Prospective Investigation into Cancer and Nutrition (EPIC) study, Eur J Nutr. 55 (2016) 1359-75.

[31] Vogiatzoglou A, Mulligan AA, Lentjes MA, Luben RN, et al., Flavonoid intake in European adults (18 to 64 years), PLoS One. 10 (2015) e0128132.

[32] Bonaccio M, Pounis G, Cerletti C, Donati MB, et al., Mediterranean diet, dietary polyphenols and low grade inflammation: results from the MOLI-SANI study, Br J Clin Pharmacol. 83 (2017) 107-13.

[33] Medina-Remon A, Casas R, Tressserra-Rimbau A, Ros E, et al., Polyphenol intake from a Mediterranean diet decreases inflammatory biomarkers related to

atherosclerosis: a substudy of the PREDIMED trial, Br J Clin Pharmacol. 83 (2017) 114-28.

[34] Marventano S, Mistretta A, Platania A, Galvano F, Grosso G, Reliability and relative validity of a food frequency questionnaire for Italian adults living in Sicily, Southern Italy, Int J Food Sci Nutr. (2016) 1-8.

[35] Craig CL, Marshall AL, Sjostrom M, Bauman AE, et al., International physical activity questionnaire: 12-country reliability and validity, Med Sci Sports Exerc. 35 (2003) 1381-95.

[36] Buscemi S, Rosafio G, Vasto S, Massenti FM, et al., Validation of a food frequency questionnaire for use in Italian adults living in Sicily, Int J Food Sci Nutr. 66 (2015) 426-38.

[37] Sofi F, Macchi C, Abbate R, Gensini GF, Casini A, Mediterranean diet and health status: an updated meta-analysis and a proposal for a literature-based adherence score, Public Health Nutr. 17 (2014) 2769-82.

[38] Godos J, Marventano S, Mistretta A, Galvano F, Grosso G, Dietary sources of polyphenols in the Mediterranean healthy Eating, Aging and Lifestyle (MEAL) study cohort, Int J Food Sci Nutr. (2017) 1-7.

[39] Phenol-Explorer: an online comprehensive database on polyphenol contents in foods [Internet]. 2010. Available from: http://www.phenol-explorer.eu

[40] Rothwell JA, Perez-Jimenez J, Neveu V, Medina-Remon A, et al., Phenol-Explorer 3.0: a major update of the Phenol-Explorer database to incorporate data on the effects of food processing on polyphenol content, Database (Oxford). 2013 (2013) bat070.

[41] Bognar A. Tables on weight yield of food and retention factors of food constituents for the calculation of nutrient composition of cooked foods (dishes). BdBfr Eh, editor2002.

[42] Willett WC LE. Reproducibility and validity of food frequency questionnaire. In: Press OU, editor. Nutritional epidemiology. 2nd ed ed1998.

[43] Afzal M, Safer AM, Menon M, Green tea polyphenols and their potential role in health and disease, Inflammopharmacology. 23 (2015) 151-61.

[44] Grosso G, Galvano F, Mistretta A, Marventano S, et al., Red orange: experimental models and epidemiological evidence of its benefits on human health, Oxid Med Cell Longev. 2013 (2013) 157240.

[45] Maria Cova A, Crasci L, Panico A, Catalfo A, De Guidi G, Antioxidant capability and phytochemicals content of Sicilian prickly fruits, Int J Food Sci Nutr. 66 (2015) 881-6.

[46] Grosso G, Marventano S, Giorgianni G, Raciti T, et al., Mediterranean diet adherence rates in Sicily, southern Italy, Public Health Nutr. 17 (2014) 2001-9.

[47] Lee BH, Nam TG, Park NY, Chun OK, et al., Estimated daily intake of phenolics and antioxidants from green tea consumption in the Korean diet, Int J Food Sci Nutr. 67 (2016) 344-52.

[48] Zeng L, Luo L, Li H, Liu R, Phytochemical profiles and antioxidant activity of 27 cultivars of tea, Int J Food Sci Nutr. (2016) 1-13.

[49] Marventano S, Salomone F, Godos J, Pluchinotta F, et al., Coffee and tea consumption in relation with non-alcoholic fatty liver and metabolic syndrome: A systematic review and meta-analysis of observational studies, Clin Nutr. 35 (2016) 1269-81.

[50] Sohrab G, Hosseinpour-Niazi S, Hejazi J, Yuzbashian E, et al., Dietary polyphenols and metabolic syndrome among Iranian adults, Int J Food Sci Nutr. 64 (2013) 661-7.

[51] Momose Y, Maeda-Yamamoto M, Nabetani H, Systematic review of green tea epigallocatechin gallate in reducing low-density lipoprotein cholesterol levels of humans, Int J Food Sci Nutr. 67 (2016) 606-13.

[52] Shrime MG, Bauer SR, McDonald AC, Chowdhury NH, et al., Flavonoid-rich cocoa consumption affects multiple cardiovascular risk factors in a meta-analysis of short-term studies, J Nutr. 141 (2011) 1982-8.

[53] Crippa A, Discacciati A, Larsson SC, Wolk A, Orsini N, Coffee consumption and mortality from all causes, cardiovascular disease, and cancer: a dose-response meta-analysis, Am J Epidemiol. 180 (2014) 763-75.

[54] Grosso G, Micek A, Godos J, Sciacca S, et al., Coffee consumption and risk of all-cause, cardiovascular, and cancer mortality in smokers and non-smokers: a dose-response meta-analysis, Eur J Epidemiol. (2016).

[55] Grosso G, Yang J, Marventano S, Micek A, et al., Nut consumption on all-cause, cardiovascular, and cancer mortality risk: a systematic review and meta-analysis of epidemiologic studies, Am J Clin Nutr. 101 (2015) 783-93.

[56] van den Brandt PA, Schouten LJ, Relationship of tree nut, peanut and peanut butter intake with total and cause-specific mortality: a cohort study and meta-analysis, Int J Epidemiol. 44 (2015) 1038-49.

[57] Adlercreutz H, Lignans and human health, Crit Rev Clin Lab Sci. 44 (2007) 483-525.

[58] Peterson J, Dwyer J, Adlercreutz H, Scalbert A, et al., Dietary lignans: physiology and potential for cardiovascular disease risk reduction, Nutr Rev. 68 (2010) 571-603.

[59] Arranz S, Chiva-Blanch G, Valderas-Martinez P, Medina-Remon A, et al., Wine, beer, alcohol and polyphenols on cardiovascular disease and cancer, Nutrients. 4 (2012) 759-81.

[60] Giacosa A, Barale R, Bavaresco L, Faliva MA, et al., Mediterranean Way of Drinking and Longevity, Crit Rev Food Sci Nutr. 56 (2016) 635-40.

[61] Riccioni G, Gammone MA, Tettamanti G, Bergante S, et al., Resveratrol and anti-atherogenic effects, Int J Food Sci Nutr. 66 (2015) 603-10.

[62] Kabiri A, Hosseinzadeh-Attar MJ, Haghighatdoost F, Eshraghian M, Esmaillzadeh A, Impact of olive oil-rich diet on serum omentin and adiponectin levels: a randomized cross-over clinical trial among overweight women, Int J Food Sci Nutr. (2016) 1-9.

[63] EFSA Panel on Dietetic Products NaA, Scientific Opinion on the substantiation of health claims related to polyphenols in olive and protection of LDL particles from oxidative damage (ID 1333, 1638, 1639, 1696, 2865), maintenance of normal blood HDL-cholesterol concentrations (ID 1639), maintenance of normal blood pressure (ID 3781), "anti-inflammatory properties" (ID 1882), "contributes to the upper respiratory tract health" (ID 3468), "can help to maintain a normal function of

gastrointestinal tract" (3779), and "contributes to body defences against external agents" (ID 3467) pursuant to Article 13(1) of Regulation (EC) No 1924/20061., EFSA J. 9 (2011) 2033.

Table 1. Background characteristics of the study cohort according level of adherence to the Mediterranean diet.

	MEDI-LITE Score		
	Low-medium (Q1-Q3)	High (Q4)	P
Sex			0.771
Men	692 (41.7)	112 (40.7)	
Women	969 (58.3)	163 (59.3)	
Age groups			0.295
<30	308 (18.5)	42 (15.3)	
30-39	293 (17.6)	40 (14.5)	
40-49	311 (18.7)	59 (21.5)	
50-59	269 (16.2)	42 (15.3)	
60-69	260 (15.7)	54 (19.6)	
≥70	220 (13.2)	38 (13.8)	
Educational status			0.034
Low	605 (36.4)	92 (33.5)	
Medium	599 (36.1)	121 (44)	
High	457 (27.5)	62 (22.5)	
Occupational status			0.020
Unemployed	384 (27.3)	77 (30.8)	
Low	214 (15.2)	52 (20.8)	
Medium	376 (26.7)	64 (25.6)	
High	434 (30.8)	57 (22.8)	
Smoking status			0.060
Never smoker	1027 (61.8)	168 (61.1)	
Former smoker	387 (23.3)	78 (28.4)	
Current smoker	247 (14.9)	29 (10.5)	
Physical activity level			0.015
Low	296 (19.8)	33 (14.3)	
Moderate	748 (50.0)	108 (46.8)	
High	453 (30.3)	90 (39.0)	
Alcohol drinking habits			0.003
None	328 (19.7)	47 (17.1)	
Moderate drinker (0.1-12 g/d)	1011 (60.8)	195 (70.9)	
Regular drinker (>12 g/d)	323 (19.4)	33 (12.0)	

Table 2. Difference in mean polyphenol intake (total, classes and subclasses) between quartiles of the Mediterranean diet adherence score (MEDI-LITE score).

	MEDI-LITE score quartiles				
	Q1	Q2	Q3	Q4	P for trend
	Mean (SD), mg/d				
Total Polyphenols	532.4 (573.3)	714.2 (818.8)	692.7 (420.4)	710.9 (423.4)	
Flavonoids	199.0 (180.1)	251.1 (201.2)	280.3 (196.6)	327.7 (201.5)	<0.001
Flavonols	41.4 (42.8)	56.2 (46.8)	62.2 (40.1)	72.9 (50.6)	<0.001
Flavanols	86.8 (138.2)	90.7 (112.6)	99.3 (109.0)	100.3 (112.4)	0.050
Flavanones	23.1 (30.1)	37.4 (43.0)	40.4 (41.4)	58.1 (48.4)	<0.001
Flavones	5.4 (5.5)	8.2 (8.0)	9.6 (13.1)	11.0 (11.3)	<0.001
Anthocyanins	37.8 (33.8)	53.1 (55.4)	61.1 (59.1)	77.4 (64.9)	<0.001
Isoflavones	1.9 (7.1)	3.3 (10.4)	5.0 (17.8)	6.7 (20.4)	<0.001
Dihydroflavonols	2.3 (4.9)	1.9 (4.2)	2.4 (4.3)	1.2 (2.8)	0.052
Phenolic acids	303.0 (502.6)	422.2 (732.1)	367.9 (300.9)	322.3 (284.3)	0.704
Hydroxybenzoic acids	188.6 (497.5)	270.0 (721.6)	200.8 (278.6)	144.4 (255.9)	0.139
Hydroxycinnamic acids	113.8 (65.5)	151.3 (89.8)	166.4 (98.2)	177.0 (90.5)	<0.001
Stilbenes	2.0 (4.0)	1.7 (3.4)	2.2 (3.5)	1.3 (2.4)	0.239
Lignans	1.6 (1.9)	2.6 (2.7)	3.1 (2.3)	4.0 (3.0)	<0.001
Others	26.6 (51.6)	36.2 (52.7)	39.1 (31.3)	55.5 (59.4)	<0.001
Hydroxyphenilacetic acids	0.3 (1.0)	0.5 (1.4)	0.4 (0.5)	0.5 (1.3)	0.065
Hydroxybenzaldehydes	0.3 (0.6)	0.2 (0.5)	0.3 (0.5)	0.1 (0.3)	0.051
Tyrosols	11.4 (27.5)	16.0 (32.6)	15.4 (16.5)	17.9 (24.2)	0.002

Table 3. Difference in mean polyphenol intake (individual) between quartiles of the Mediterranean diet adherence score (MEDI-LITE score).

	MELI-LITE Score quartiles				P for trend
	Q1	Q2	Q3	Q4	
	Mean (SD), mg/d				
Flavonols					
Quercetin	0.6 (0.9)	0.7 (1.0)	0.7 (1.0)	0.8 (0.8)	0.004
Myricetin	0.3 (0.7)	0.2 (0.6)	0.3 (0.6)	0.1 (0.4)	0.033
Kaempferol	0.1 (0.2)	0.2 (0.3)	0.2 (0.2)	0.2 (0.1)	<0.001
Flavanols					
Catechins	54.2 (103.7)	58.7 (80.7)	62.8 (75.7)	68.5 (81.1)	0.018
Flavanones					
Hesperetin	16.4 (21.8)	26.9 (30.9)	29.1 (29.6)	42.0 (35.1)	<0.001
Naringenin	3.4 (5.5)	6.0 (7.6)	6.7 (6.5)	9.2 (8.7)	<0.001
Flavones					
Apigenin	0.008 (0.005)	0.008 (0.007)	0.009 (0.005)	0.010 (0.002)	<0.001
Luteolin	2.6 (3.2)	4.0 (4.2)	5.1 (8.5)	5.1 (7.4)	<0.001
Isoflavones					
Daidzein	0.05 (0.1)	0.1 (0.2)	0.1 (0.5)	0.1 (0.5)	<0.001
Genistein	0.0.5 (0.1)	0.1 (0.3)	0.1 (0.6)	0.2 (0.6)	<0.001
Biochanin A	0.001 (0.002)	0.001 (0.003)	0.001 (0.002)	0.0009 (0.001)	<0.001
Hydroxycinnamic acids					
Caffeic acid	1.4 (1.8)	1.6 (1.8)	1.8 (1.6)	1.7 (1.3)	<0.001
Cinnamic acid	0.2 (1.1)	0.5 (1.5)	0.4(0.5)	0.6 (1.5)	0.005
Ferulic acid	2.0 (2.2)	2.7 (3.0)	3.1 (2.6)	4.3 (3.6)	<0.001
Hydroxybenzoic acids					
Vanillic acid	0.3 (0.5)	0.3 (0.5)	0.4 (0.3)	0.4 (0.5)	<0.001
Lignans					
Lariciresinol	0.8 (1.2)	1.4 (1.6)	1.6 (1.4)	2.2 (1.8)	<0.001
Matairesinol	0.01 (0.02)	0.03 (0.03)	0.03 (0.02)	0.04 (0.03)	<0.001
Pinoresinol	0.5 (0.6)	0.9 (0.8)	1.0 (0.7)	1.3 (0.9)	<0.001
Secoisolariciresinol	0.07 (0.07)	0.1 (0.1)	0.1 (0.09)	0.1 (0.1)	<0.001

Table 4. Odds ratios (ORs) and 95% confidence intervals (CIs) of the association between quartiles of dietary polyphenol intake (total, classes and subclasses) and high adherence to the Mediterranean diet (highest quartile of the Mediterranean diet score).

	Polyphenol intake quartiles, OR (95% CI)*			
	Q1	Q2	Q3	Q4
Total Polyphenols	1	3.07 (1.83, 5.16)	5.4 (3.30, 8.94)	1.82 (1.07, 3.26)
Flavonoids	1	2.98 (1.61, 5.52)	8.39 (4.73, 14.90)	5.72 (3.15, 10.38)
Flavonols	1	5.07 (2.86, 8.99)	5.87 (3.33, 10.34)	5.39 (3.02, 9.56)
Flavanols	1	1.06 (0.68, 1.65)	0.44 (0.24, 0.83)	1.30 (0.63, 2.69)
Flavanones	1	1.85 (1.07, 3.19)	3.81 (2.31, 6.29)	5.82 (3.57, 9.50)
Flavones	1	1.31 (0.77, 2.23)	4.64 (2.93, 7.34)	3.35 (2.08, 5.39)
Anthocyanins	1	0.93 (0.58, 1.51)	1.99 (1.30, 3.03)	2.84 (1.89, 4.28)
Isoflavones	1	6.42 (3.14, 13.13)	12.70 (6.34, 25.44)	10.10 (4.98, 20.50)
Dihydroflavonols	1	1.35 (1.00, 1.83)	0.43 (0.30, 0.63)	-
Phenolic acids	1	2.30 (1.54, 3.43)	1.59 (1.06, 2.40)	0.52 (0.31, 0.86)
Hydroxybenzoic acids	1	0.91 (0.65, 1.28)	0.49 (0.33, 0.71)	0.33 (0.22, 0.50)
Hydroxycinnamic acids	1	1.72 (1.02, 2.89)	4.95 (3.09, 7.95)	2.53 (1.52, 4.21)
Stilbenes	1	2.38 (1.58, 3.58)	2.28 (1.51, 3.43)	0.98 (0.62, 1.53)
Lignans	1	1.39 (0.73, 2.62)	4.93 (2.82, 8.61)	8.59 (4.98, 14.81)
Others	1	4.14 (2.46, 6.96)	2.74 (1.60, 4.68)	4.54 (2.69, 7.67)
Hydroxyphenilacetic acids	1	1.64 (1.13, 2.39)	1.01 (0.67, 1.50)	0.81 (0.53, 1.22)
Hydroxybenzaldehydes	1	1.59 (1.10, 2.31)	1.46 (1.00, 2.13)	0.55 (0.36, 0.85)
Tyrosols	1	2.46 (1.58, 3.85)	2.25 (1.44, 3.51)	2.31 (1.48, 3.59)

*Analyses are adjusted for age, sex, and total energy intake.

Table 5. Odds ratios (ORs) and 95% confidence intervals (CIs) of the association between quartiles of dietary polyphenol intake (individual) and high adherence to the Mediterranean diet (highest quartile of the Mediterranean diet score).

	Polyphenol intake quartiles, OR (95% CI)*			
	Q1	Q2	Q3	Q4
Flavonols				
Quercetin	1	0.83 (0.54, 1.28)	1.57 (1.07, 2.28)	1.67 (1.15, 2.42)
Myricetin	1	1.27 (0.88, 1.84)	1.19 (0.81, 1.72)	0.56 (0.37, 0.85)
Kaempferol	1	4.70 (2.35, 9.38)	13.91 (7.19, 26.91)	5.83 (2.94, 11.57)
Flavanols				
Catechins	1	3.03 (1.96, 4.66)	2.09 (1.34, 3.26)	1.88 (1.18, 3.00)
Flavanones				
Hesperetin	1	1.73 (1.01, 2.96)	3.63 (2.22, 5.93)	5.60 (3.46, 9.07)
Naringenin	1	1.23 (0.67, 2.27)	4.82 (2.84, 8.17)	6.50 (3.86, 10.92)
Flavones				
Apigenin	1	1.51 (0.86, 2.65)	4.30 (2.61, 7.08)	6.34 (3.35, 8.50)
Luteolin	1	0.87 (0.56, 1.35)	1.81 (1.23, 2.67)	1.58 (1.06, 2.34)
Isoflavones				
Daidzein	1	9.47 (4.05,22.15)	16.01 (6.93, 36.96)	14.82 (6.38, 34.38)
Genistein	1	9.90 (4.23, 23.15)	17.75 (7.69, 41.03)	15.97 (6.90, 36.97)
Biochanin A	1	1.33 (0.90, 1.96)	1.45 (0.99, 2.13)	0.51 (0.32, 0.80)
Hydroxycinnamic acids				
Caffeic acid	1	4.17 (2.41, 7.22)	6.31 (3.70, 10.75)	2.50 (1.41, 4.45)
Cinnamic acid	1	1.58 (1.03, 2.41)	1.26 (0.81, 1.96)	2.14 (1.43, 3.19)
Ferulic acid	1	2.83 (1.67, 4.79)	4.04 (2.42, 6.72)	4.93 (2.94, 8.27)
Hydroxybenzoic acids				
Vanillic acid	1	1.63 (1.10, 2.41)	1.00 (0.66, 1.52)	1.40 (0.94, 2.08)
Lignans				
Lariciresinol	1	1.36 (0.75, 2.47)	4.68 (2.79, 7.85)	6.55 (3.94, 10.91)
Matairesinol	1	1.32 (0.71, 2.47)	5.24 (3.05, 8.98)	7.29 (4.27, 12.43)
Pinoresinol	1	1.18 (0.63, 2.21)	4.29 (2.52, 7.32)	8.24 (4.91, 13.80)
Secoisolariciresinol	1			

*Analyses are adjusted for age, sex, and total energy intake.