Adherence to Mediterranean Diet and Non-Alcoholic Fatty Liver Disease: Effect on Insulin Resistance

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OBJECTIVES: **The prevalence of cardiometabolic disorders, including non-alcoholic fatty liver disease (NAFLD), is increasing in western countries, because of changes in lifestyle and dietary habits. Mediterranean Diet (Med-Diet) is effective for cardiovascular prevention, but its relationship with NAFLD has been scarcely investigated.**

METHODS: **We included 584 consecutive outpatients presenting with one or more cardiovascular risk factor such as type 2 diabetes mellitus (T2DM), arterial hypertension, overweight/obesity, and dyslipidemia. Liver steatosis was assessed using ultrasonography. Med-Diet adherence was investigated by a validated semiquantitative nine-item dietary questionnaire; patients were divided into low, intermediate, and high adherence. Insulin resistance was defined by the 75th percentile of homeostasis model of insulin resistance (HOMA-IR; ≥3.8).**

RESULTS: **The mean age was 56.2±12.4 years and 38.2% were women. Liver steatosis was present in 82.7%, and its prevalence decreased from low to high adherence group (96.5% vs. 71.4%, *P*<0.001). In a multiple logistic regression analysis, hypertriglyceridemia (odds ratio (OR): 2.913; *P*=0.002), log (ALT) (OR: 6.186; *P*<0.001), Med-Diet adherence (intermediate vs. low OR: 0.115; *P*=0.041, high vs. low OR: 0.093; *P*=0.030), T2DM (OR: 3.940; *P*=0.003), and high waist circumference (OR: 3.012; *P*<0.001) were associated with NAFLD. Among single foods, low meat intake (OR: 0.178; *P*<0.001) was inversely significantly associated with NAFLD. In 334 non-diabetic NAFLD patients, age (OR: 1.035, *P*=0.025), high waist circumference (OR: 7.855, *P*<0.001), hypertriglyceridemia (OR: 2.152, *P*=0.011), and Log (ALT) (OR: 2.549, *P*=0.002) were directly associated with HOMA-IR, whereas Med-Diet score was inversely associated (OR: 0.801, *P*=0.018).**

CONCLUSIONS: **We found an inverse relationship between Med-Diet and NAFLD prevalence. Among NAFLD patients, good adherence to Med-Diet was associated with lower insulin resistance. Our findings suggest that Med-Diet may be a beneficial nutritional approach in NAFLD patients.**

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INTRODUCTION

The Mediterranean Diet (Med-Diet) was first described in 1960s by Ancel Keys (1), after the results of the epidemiological “Seven Countries’ Study”, which demonstrated that the populations bordering the Mediterranean Sea had a lower incidence of cardiovascular disease and cancer (2,3). In 2010, the United Nations Educational, Scientific and Cultural Organization (UNESCO) inscribed the Med-Diet in the Representative List of Intangible Cultural Heritage of Humanity, and described it as follows: “*The Mediterranean Diet […] is the set of skills, knowledge, rituals, symbols and traditions, ranging from the landscape to the table, which in the Mediterranean basin concerns the crops,*

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harvesting, picking, fishing, animal husbandry, conservation, processing, cooking and particularly sharing and consuming of food" (4) (available from: http://www.unesco.org/culture/ich/RL/00884).

The Med-Diet is characterized by an abundant consumption of fresh vegetables, fruits, wholegrain cereals, legumes, and olive oil (5). In addition, it includes a moderate intake of dairy products and wine, together with and a low intake of red and processed meats and foods containing high amounts of added sugar (5). The presence and the synergic combination of these foods, characterized by good nutritional and antioxidant properties, have beneficial effects on several metabolic pathways (6). Prior studies indicated that high adherence to Med-Diet is associated with a reduced incidence and prevalence of metabolic syndrome, obesity, and type 2 diabetes (T2DM) (7–9), and is effective in primary and secondary prevention of cardiovascular diseases (10). However, in the last decade a progressive "Westernization" of the dietary habits has been reported in many traditional Mediterranean countries (11).

Non-alcoholic fatty liver disease (NAFLD), defined as the presence of lipid droplets in almost 5% of hepatocytes in absence of alcohol abuse and hepatitis virus infection, is the most common chronic liver disease worldwide. The spread of NAFLD in Western countries is strongly associated with the increasing prevalence of obesity and T2DM due to the changing lifestyle and dietary habits (12,13). European Association for the Study of Liver guidelines on diagnosis and management of NAFLD (14), recommend to insert all NAFLD patients in a structured program aimed at lifestyle changes toward healthy diet and habitual physical activity (15). However, while weight loss is generally considered as an effective approach to reduce hepatic steatosis, the association between Med-Diet and liver steatosis has been investigated in few small studies (16).

Aim of the study was to investigate the relationship between NAFLD and adherence to Med-Diet in a large cohort of patients with cardiometabolic risk factors screened for the presence of liver steatosis.

METHODS

We enrolled 584 consecutive outpatients referring to the Day Service of Internal Medicine and Metabolic Disorders of the Policlinico Umberto I University Hospital in Rome presenting with ≥1 of the following cardiovascular risk factors: T2DM (17), arterial hypertension (18), overweight/obesity (19), dyslipidemia (20), and metabolic syndrome (ATP III criteria) (21).

Exclusion criteria were as follows: average daily consumption of alcohol >20 g in women and of >30 g in men (assessed by Alcohol Use Disorders Identification Test); presence of hepatitis B surface antigen and antibody to hepatitis C virus; positive tests for autoimmune hepatitis; cirrhosis and other chronic liver diseases; diagnosis of oncological diseases and concomitant therapy with drugs known to promote liver steatosis (e.g., amiodarone); and other chronic infectious or autoimmune disease.

Anthropometric data and medical history were collected at study entry, including a previous Major Adverse Cardiovascular and Cerebrovascular Event (MACCE); MACCE was defined as the presence of one of the following: myocardial infarction, cardiac and peripheral revascularization, transient ischemic attack, and stroke. Routine laboratory tests were carried out in fasting condition, including blood glucose, insulinemia, lipid profile, and liver function tests. The homeostasis model of insulin resistance (HOMA-IR) was calculated and used as a measure of IR. Given the lack of a standardized cutoff (22), insulin resistance was defined by the 75th percentile of HOMA-IR, corresponding to a value ≥3.8. This value is in accordance with previous study conducted in European population (23).

The study protocol was approved by the local ethical board of Sapienza—University of Rome (Ref. 2277 prot. 873/11) and was carried out according to the principles of the Declaration of Helsinki. All patients provided signed written informed consent at entry.

US examination

Liver ultrasound (US) scanning was performed to assess the presence of steatosis in all patients. All US were performed by the same operator who was blinded to laboratory values using a GE Vivid S6 apparatus equipped with a convex 3.5 MHz probe. Liver steatosis was defined according to Hamaguchi criteria (24) and patients were classified accordingly as having no steatosis, mild, moderate, and severe liver steatosis.

Med-Diet questionnaire

Adherence to the Med-Diet was investigated by a short nine-item validated dietary questionnaire, which was administered to each patient at study entry by a trained physician (F.B.) with a direct face-to-face interview, both to patients and controls (25). The physician was unaware of ultrasound results. For each food item, a commonly used portion size was specified, and participants were asked how often they had consumed that item on average in the previous year. This way of administration was already used in the original version of the questionnaire (26). Particular attention was paid to ensure that the answers were related to long-term dietary habits and not to recent changes in diet.

The questionnaire includes the most important cardioprotective foods and has been shown to correlate inversely with cardiovascular risk both in general population and in patients at high cardiovascular risk (27,28). It assigns 1 point for: (i) olive oil (≥1 spoon/day, i.e., tablespoon of 10 g of olive oil); (ii) fruit (≥1 serving/day); (iii) vegetables or salad (≥1 serving/day); (iv) both fruit (≥1 serving/day) and vegetables (≥1 serving/day); (v) legumes (≥2 servings/week); (vi) fish (≥3 servings/week); (vii) wine (≥1 glass/day, ≤20 g for women and ≤30 g for men, as for European Association for the Study of Liver position paper on NAFLD/NASH (29)); (viii) meat (<1 serving/day); (ix) (both white bread (<1/day) and rice (<1/week)) or whole-grain bread (>5/week). The Med-Diet score resulting from the questionnaire ranges from 0 to 9 points. Patients were divided into three groups according to the Med-Diet score: low, intermediate, and high adherence (0–2, 3–6, and 7–9 points, respectively).

Statistical analysis

Distribution of variables was assessed by the Kolmogorov–Smirnov test. Categorical variables were reported as counts/percentages, continuous variables as means±s.d. (or medians and interquartile ranges depending on their distribution). Independence of categorical variables was tested by χ^2-test. Student's unpaired *t*- and Mann–Whitney *U*-tests were used to compare means and medians, respectively. Group comparisons were performed by analysis of variance test with Bonferroni *post hoc* analysis and Kruskal–Wallis test as needed.

Continuous variables with non-normal distribution were log-transformed for multivariable analysis and dichotomized when possible. A multivariable logistic regression analysis was used to investigate independent predictors of NAFLD in the entire cohort. The following were entered covariates in the model: female sex, age (continuous), high waist circumference (>102 for men and >88 cm for women), hypertriglyceridemia (triglycerides ≥150 mg/dl), arterial hypertension (yes/no), statin use (yes/no), log (alt), previous MACCE (yes/no), type 2 diabetes (yes/no), intermediate vs. low adherence to Med-Diet, and high vs. low adherence to Med-Diet. A second model of logistic regression analysis was built using single foods instead of groups of Med-Diet adherence. In the group of patients with NAFLD, we also investigated with a multivariate logistic regression analysis, factors independently associated with insulin resistance defined as HOMA-IR ≥3.8, using the same covariates previously described. Only *P*-values <0.05 were considered as statistically significant. All tests were two-tailed and analyses were performed using computer software packages (SPSS-18.0, IBM, Armonk, NY).

RESULTS

The mean age was 56.2±12.4 years and 38.2% of patients were women. Most patients were overweight (92.3%) and obese (42.3%) with a mean body mass index 30.0 (±5.1) kg/m^2 and waist circumferences of 105.7 (±12.5) cm; arterial hypertension was present in 57.7% and type 2 diabetes mellitus (T2DM) in 27.1%. Liver steatosis was present in 82.7% of patients, and it was mild in 19.4%, moderate in 35.0%, and severe in 28.2% of patients.

Characteristics of patients according to adherence to Med-Diet

On the basis of dietary questionnaire, in the whole cohort, 57 (9.8%) patients had low, 436 (74,6%) intermediate, and 91 (15.6%) high adherence to Med-Diet. **Table 1** reports clinical and biochemical characteristics of patients among the three groups of Med-Diet adherence. Compared with patients with low adherence, those with high adherence to Med-Diet were older (*P*=0.012), with a lower body mass index (*P*=0.026), lower HOMA-IR (*P*=0.020), lower values of triglycerides (*P*=0.005), alanine aminotransferase (ALT) (*P*=0.012), and gamma-glutamyl transferase (GGT) (*P*=0.050). Prevalence of NAFLD decreased from subjects with low to those with high adherence to Med-Diet (from 96.5 to 71.4%, *P*<0.001).

When we investigated factors associated with the presence of NAFLD with a multiple logistic regression analysis, we found that hypertriglyceridemia (odds ratio (OR): 2.913; *P*=0.002), log (ALT) (OR: 6.186; *P*<0.001), Med-Diet adherence (intermediate vs. low OR: 0.115; *P*=0.041 and high vs. low OR: 0.093; *P*=0.030), type 2 diabetes (3.940; *P*=0.003), and high waist circumference (OR: 3.012; *P*<0.001) were independently associated with the presence of NAFLD (**Table 2**). Similar results were found when using Med-Diet score as continuous variable (OR: 0.804, 95% confidence interval (CI) 0.671–0.963; *P*=0.018). When we analyzed the relationship between individual food intakes and NAFLD, we found that low meat intake (OR: 0.178; *P*<0.001) was significantly associated with a lower prevalence of NAFLD (**Table 3**).

Med-Diet and HOMA-IR in non-diabetic patients with NAFLD

In 334 non-diabetic patients with NAFLD, Med-Diet score was inversely associated with HOMA-IR (*r*=−0.162, *P*=0.005). A multivariable logistic regression analysis exploring factors associated with insulin resistance (HOMA-IR ≥3.8, see Methods) showed that age (OR: 1.035, *P*=0.025), high waist circumference (OR: 7.855, *P*<0.001), hypertriglyceridemia (OR: 2.152, *P*=0.011), and Log (ALT) (OR: 2.549, *P*=0.002) were directly associated with insulin resistance, whereas Med-Diet score was inversely associated (OR for each point: 0.801, *P*=0.018; **Table 4**).

When we analyzed the association of single food intake with HOMA-IR, a direct association was found for olive oil consumption (OR: 3.922, 95% CI 1.381–11.139; *P*=0.010), whereas a negative association was found with wine (OR: 0.229, 95% CI 0.088–0.596; *P*=0.003). A positive trend was also found for bread intake (OR: 3.922, 95% CI 0.978–3.720; *P*=0.058) after adjusting for variables listed in **Table 4**.

DISCUSSION

Our results show an inverse relationship between the adherence to Med-Diet and the prevalence of NAFLD in a large cohort of consecutive patients with cardiometabolic risk factors. In the group of non-diabetic patients with NAFLD, adherence to Med-Diet was inversely associated with insulin resistance, the main pathophysiologic moment for the development of NAFLD.

The relationship between NAFLD and Med-Diet has been investigated by few interventional studies. Thus, in a randomized crossover study conducted in 12 diabetic patients with biopsy-proven NAFLD, Med-Diet reduced liver fat content independently from weight loss (30). In a further study, a reduction of US liver brightness after 6 months on Med-Diet in 90 non-diabetic NAFLD patients was observed (31). Indirect evidence of a beneficial effect of Med-Diet on liver comes from a *post hoc* analysis of 259 obese T2DM patients in whom Med-Diet improved serum liver enzymes (32). Another ongoing randomized interventional trial will assess the effect of a 3-month intervention with Med-Diet on 90 NAFLD patients (7). Similar results have been recently found in children, in whom adherence to Med-Diet reduced the risk of NAFLD and diabetes (33).

Thus, this represents the largest cross-sectional study showing that Med-Diet is associated with a lower prevalence of NAFLD. In particular, we found that, compared with those at low adherence to Med-Diet, patients with intermediate/high adherence had a progressive reduction of the risk of having NAFLD, along with a more favorable glycometabolic profile. The association between poor adherence with obesity and hypertriglyceridemia is in keeping with the Reus PREDIMED study, where a better adherence to a Med-Diet was associated with a lower OR of having metabolic syndrome in a population with a high cardiovascular risk (34).

Table 1. Characteristics of study cohort according to Mediterranean diet adherence

	Whole cohort (*n*=584)	Low adherence (0–2 points; *n*=57)	Intermediate adherence (3–6 points; *n*=436)	High adherence (7–9 points; *n*=91)	*P*
Age (years)	56.2±12.4	51.7±11.3	56.4±12.6	57.7±11.9	0.011[a] 0.01[b]2
Women (%)	38.2	33.3	40.4	30.8	0.168[a] 0.856[b]
BMI (kg/m^2)	30.0±5.1	31.1±5.7	30.0±5.2	28.9±3.9	0.029[a] 0.026[b]
Waist circumference (cm)	105.7±12.5	108.1±13.2	105.9±12.5	103.0±11.4	0.050[a] 0.056[b]
High waist circumference (%)	76.1	77.2	78.2	64.6	0.032[a] 0.135[b]
Blood glucose (mg/dl)	104.6±29.2	108.2±42.0	105.0±29.0	100.2±16.6	0.248[a] 0.347[b]
HOMA-IR	3.2 (2.2–5.3)	3.7 (2.5–7.7)	3.2 (2.2–5.2)	2.8 (1.9–4.8)	0.052[a] 0.020[b]
Total cholesterol (mg/dl)	199.9±40.9	206.0±40.4	199.9±40.4	196.2±42.0	0.389[a] 0.511[b]
HDL cholesterol (mg/dl)	49.3±14.1	46.6±10.7	49.7±14.8	49.1±12.3	0.307[a] 0.943[b]
LDL cholesterol (mg/dl)	121.6±35.3	120.5±38.0	122.0±34.2	120.5±38.7	0.919[a] 1.000[b]
Triglycerides (mg/dl)	135 (100/184)	158 (110/232)	135 (99/184)	120 (103/159)	0.013[a] 0.005[b]
Hypertriglyceridemia (triglycerides ≥150 mg/dl, %)	40.1	56.4	39.9	30.5	0.010[a] 0.004[b]
ALT (IU/l)	26 (18/40)	30 (21/40)	26 (18/42)	23 (17/31)	0.043[a] 0.012[b]
GGT (IU/l)	26 (18/41)	29 (21/44)	26 (18/42)	23 (16/34)	0.116[a] 0.050[b]
Type 2 diabetes (%)	27.1	26.3	28.5	20.9	0.358[a] 0.544[b]
Systolic blood pressure (mmHg)	130 (120/140)	130 (120/140)	130 (120/140)	130 (120/140)	0.600[a] 0.301[b]
Diastolic blood pressure (mmHg)	80 (75/85)	80 (79/85)	80 (75/85)	80 (75/90)	0.437[a] 0.622[b]
Arterial hypertension (%)	57.7	53.6	58.9	54.1	0.578[a] 1.000[b]
Previous MACCE (%)	10.9	14.0	10.1	12.8	0.549[a] 1.000[b]
Statin therapy (%)	39.5	39.6	38.9	42.2	0.856[a] 0.859[b]
Metabolic syndrome (%)	55.6	63.2	56.4	46.4	0.117[a] 0.060[b]
NAFLD (%)	82.7	96.5	83.3	71.4	<0.001[a] <0.001[b]

ALT, alanine aminotransferase; BMI, body mass index; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; HOMA-IR, homeostasis model of insulin resistance; LDL, low-density lipoprotein; MACCE, Major Adverse Cardiovascular and Cerebrovascular Event.
[a]Among groups.
[b]Low vs. high adherence.

Among foods, we found that low consumption of meat was associated with a lower prevalence of NAFLD, which is in keeping with previous evidence (35,36).

We also found that older patients were more likely to adhere to Med-Diet. This finding is in agreement with Pelucchi *et al.*, who found that among subjects screened in Milan area between

1991 and 2006 those in the 55–64-year age group showed a higher adherence as compared with younger people (37). In addition, young people are used to have lunch more often away from home because of work and to consume more frequently fast food, therefore showing a Westernization of the dietary habits (38). Besides, in a systematic review of 18 cross-sectional studies, modification of the dietary habits toward the abandonment of the traditional Mediterranean lifestyle was observed especially among young people (39).

Another interesting result of the study comes from the analysis of factors affecting insulin resistance in non-diabetic patients in whom NAFLD was diagnosed at ultrasonography. In particular, we found that age, obesity, high triglycerides, and ALT values were directly associated with HOMA-IR, whereas high adherence to Med-Diet showed a negative association. This finding is in keeping with a previous randomized interventional study demonstrating that, in 90 patients with metabolic syndrome, a Mediterranean-like diet reduced markers of inflammation and insulin resistance (40). Furthermore, a recent work (41), which analyzed the association between obesity, Med-Diet, and insulin resistance in 4,700 adults from the NHANES III cohort, showed that relationship between Med-Diet and insulin resistance may be mediated by abdominal adiposity.

In agreement with previous clinical and experimental results (34,42,43), we also found that high olive oil intake was associated with increased insulin resistance, whereas moderate wine intake was inversely associated, supporting the safety of moderate/low intake of wine in patients with NAFLD (44).

Several mechanisms may be responsible for the beneficial effects of Med-Diet in NAFLD, including the improvement of cardiometabolic profile (i.e., lowering of serum triglycerides and blood glycemia) (45) and the antioxidant effect (46), which is related to its content of antioxidant compounds such as polyphenols and vitamin E. This may turn particularly useful in NAFLD patients, considering that oxidative stress is one important factor implicated in the onset of NAFLD (47) and possibly in the development of its complications (48); moreover, the activation of oxidative stress pathways is involved in the onset of insulin resistance and impaired insulin secretion (49). In particular, the activity of Nox2, which is one of the most important extracellular sources

Table 2. Multivariable logistic regression analysis of clinical and biochemical factors associated with the presence of NAFLD

	P	Odd ratio	95% Confidence intervals	
Female sex	0.518	0.813	0.433	1.525
Age (continuous)	0.932	0.999	0.974	1.024
High waist circumference (>102 for men and >88 cm for women)	<0.001	3.012	1.635	5.546
Hypertriglyceridemia (triglycerides ≥150 mg/dl)	0.002	2.913	1.474	5.758
Arterial hypertension	0.138	1.579	0.864	2.889
Statin use	0.862	0.947	0.510	1.758
Log (ALT)	<0.001	6.186	3.188	12.005
Previous MACCE	0.647	0.782	0.273	2.242
Type 2 diabetes	0.003	3.940	1.594	9.734
Intermediate vs. low adherence to Med-Diet	0.041	0.115	0.014	0.913
High vs. low adherence to Med-Diet	0.030	0.093	0.011	0.792

ALT, alanine aminotransferase; MACCE, Major Adverse Cardiovascular and Cerebrovascular Event; Med-Diet, Mediterranean Diet; NAFLD, non-alcoholic fatty liver disease.

Table 3. Unadjusted and adjusted odd ratios of food intakes associated with the presence of NAFLD

	Unadjusted odd ratio (95% confidence intervals)	*P*	Adjusted odd ratio (95% confidence intervals)[a]	*P*
Olive oil (≥1 spoon/day)[b]	0.716 (0.377–1.358)	0.306	1.045 (0.432–2.529)	0.922
Fruit (≥1 serving/day)	0.686 (0.385–1.221)	0.200	0.919 (0.275–3.068)	0.891
Vegetables or salad (≥1 serving/day)	0.810 (0.465–1.410)	0.457	1.023 (0.315–3.323)	0.970
Both fruits (≥1 serving/day) and vegetables (≥1 serving/day)	0.700 (0.436–1.124)	0.140	0.722 (0.185–2.815)	0.639
Legumes (≥2 servings/week)	0.548 (0.355–0.847)	0.007	0.675 (0.370–1.230)	0.199
Fish (≥3 servings/week)	1.915 (1.082–3.391)	0.026	2.182 (0.986–4.827)	0.054
Wine (≥1 glass/day)[c]	0.559 (0.355–0.881)	0.012	0.872 (0.435–1.749)	0.700
Meat (<1 serving/day)	0.184 (0.109–0.309)	<0.001	0.178 (0.087–0.364)	<0.001
Bread (both white bread (<1/day) and rice (<1/week)) or whole-grain bread (>5/week)	0.881 (0.564–1.377)	0.578	0.999 (0.531–1.878)	0.997

NAFLD, non-alcoholic fatty liver disease.
[a]Adjusted for same variables listed in **Table 2**.
[b]Tablespoon with 10 g of olive oil.
[c]≤20 g for women and ≤30 g for men.

Table 4. Multivariable logistic regression analysis exploring factors associated with insulin resistance (75th percentile of HOMA-IR, ≥3.8) in 334 non-diabetic patients with NAFLD

	P	Odd ratio	95% Confidence intervals	
Female sex	0.855	1.060	0.567	1.982
Age (continuous)	0.025	1.035	1.004	1.067
High waist circumference (>102 for men and >88 cm for women)	<0.001	7.855	2.809	21.964
Hypertriglyceridemia (triglycerides ≥150 mg/dl)	0.011	2.152	1.196	3.872
Arterial hypertension	0.535	0.818	0.434	1.542
Statin use	0.167	0.629	0.326	1.214
Log (ALT)	0.002	2.549	1.397	4.649
Previous MACCE	0.394	1.705	0.500	5.814
Med-Diet score (for each point)	0.018	0.801	0.667	0.962

ALT, alanine aminotransferase; HOMA-IR, homeostasis model of insulin resistance; MACCE, Major Adverse Cardiovascular and Cerebrovascular Event; NAFLD, non-alcoholic fatty liver disease.

of reactive oxidant species, has been found to be upregulated in patients with NAFLD (50). This is of interest as we recently demonstrated that adherence to Med-Diet has been shown to be inversely associated with Nox2 activity in patients with atrial fibrillation (28). Thus, these data suggest the need for exploring the effect of Med-Diet on Nox2-related oxidative stress also in the setting of NAFLD.

Findings from this study have clinical implication. The association of poor adherence to Med-Diet with a higher prevalence of NAFLD and with insulin resistance suggests that nutritional habits should be always investigated in patients with cardiometabolic disorders, and that Med-Diet could be recommended in NAFLD patients, as it seems to have a beneficial effect on metabolic profile. However, it should be pointed out that in the group at high adherence to Med-Diet the prevalence of NAFLD was ~70%, suggesting that despite Med-Diet may favorably affect metabolic profile of NAFLD patients, its efficacy in preventing the onset of NAFLD in patients with cardiometabolic risk factors remains uncertain. Therefore, to assess whether Med-Diet may prevent NAFLD, a randomized dietary interventional trial comparing Med-Diet pattern with a control diet (i.e., low-fat diet according to the American Heart Association (51)) is needed.

This study has also limitations. Despite being performed on a large cohort of consecutive patients, this is a cross-sectional study, which allows only an association between adherence to Med-Diet and other variables.

Moreover, we used a semi-quantitative Med-Diet questionnaire, which does not estimate the exact intake of each food. However, as suggested by the American Heart Association Guideline on Lifestyle Management to Reduce Cardiovascular Risk (51), a greater emphasis should be put on dietary patterns (e.g., Dietary Approaches to Stop Hypertension or Med-Diet patterns) rather than individual dietary components. In this context, the questionnaire includes the most important cardioprotective foods, and has been previously validated in an Italian population, in whom the questionnaire was inversely associated with the incidence of cardiovascular disease (28). In addition, it is of simple administration, which makes it suitable to use in clinical practice to easily assess adherence to the Med-Diet in patients with NAFLD.

In conclusion, good adherence to Med-Diet is associated with a lower prevalence of NAFLD, and NAFLD patients with good compliance disclose lower insulin resistance. Therefore, Med-Diet may be a suitable nutritional approach in patients with NAFLD.

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CONFLICT OF INTEREST

Guarantor of the article: Daniele Pastori, MD.

Specific author contributions: Francesco Violi, Francesco Angelico, Maria Del Ben.: study concept and design; interpretation of data; drafting of the manuscript; critical revision of the manuscript. Daniele Pastori: study concept and design; analysis and interpretation of data; statistical analysis; drafting of the manuscript; critical revision of the manuscript. Francesco Baratta: acquisition of data (administration of dietary questionnaire); interpretation of data; drafting of the manuscript; critical revision of the manuscript. Tommaso Bucci, Licia Polimeni, Fabrizio Ceci, Cinzia Calabrese, Ilaria Ernesti: acquisition of data; drafting of the manuscript; critical revision of the manuscript. Licia Polimeni: acquisition of data (ultrasound evaluation of liver steatosis); drafting of the manuscript; critical revision of the manuscript. All authors read and approved the final version of the manuscript.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Mediterranean Diet (Med-Diet) is a healthy dietary pattern able to prevent some cardiometabolic disorders.
- ✓ Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide.
- ✓ Insulin resistance is a key pathophysiologic moment for the development of NAFLD.

WHAT IS NEW HERE

- ✓ Adherence to Med-Diet is associated with a lower prevalence of NAFLD in patients with cardiometabolic disorders.
- ✓ Med-Diet was inversely associated with insulin resistance in non-diabetic NAFLD patients.
- ✓ Evaluation of dietary habits is advisable in all NAFLD patients.

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