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Interaction between Mediterranean diet and statins on mortality risk in patients with cardiovascular disease: Findings from the Moli-sani Study

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ABSTRACT

Background: Statins are prescribed for patients with cardiovascular disease (CVD), along with the recommendation of adopting healthy diets. We evaluated the independent and the combined effect of statins and Mediterranean diet (MD) towards mortality risk in patients with previous CVD by using real-life data from a population-based prospective cohort.

Methods: Longitudinal analysis on 1180 subjects (mean age 67.7 ± 10) with prior CVD at enrollment in the Moli-sani Study and followed up for 7.9 y (median). Adherence to MD was appraised by a Mediterranean diet score. Hazard ratios (HR) with 95% confidence intervals (95% CI) were calculated by multivariable Cox regression and competing risk models.

Results: Multivariable risk estimates associated with a 2-point increase in MD score were 0.84 (95% CI 0.70–1.00), 0.77 (0.61–0.97) and 0.70 (0.52–0.93) for overall, cardiovascular and coronary artery disease (CAD)/cerebrovascular deaths, respectively. Statins were not associated with death risk. Subjects combining statins and average-high adherence to MD had much lower than expected risk of cardiovascular and CAD/cerebrovascular mortality (p for interaction = 0.045 and 0.0015, respectively) as compared to those neither using statins nor having average-high MD.

The combination of average-high MD and statins was associated in a likely synergistic way with reduced low-grade inflammation, but not with blood cholesterol.

Conclusions: MD lowered the risk of all-cause, cardiovascular and CAD/cerebrovascular mortality CVD patients, net of statins. In the same population, statins reduced CVD death risk only in combination with MD. Low-grade inflammation, rather than lipids, is likely to be on the pathway of the interaction between MD and statins towards mortality risk.

1. Introduction

Over the last decades, the number of individuals living with cardiovascular diseases (CVD) is rising due to factors including improved treatments that have resulted in people living longer with CVD [1].

Although the use of statin therapy for primary prevention of CVD is debated [2–7], their use for patients with prior CVD is largely supported by an appreciable number of intervention studies [8–10] and meta-analyses of randomized-controlled trials [2,11] showing reduced risk of mortality and recurrence of CVD.

Along with pharmacological treatments, health-promoting lifestyles are strongly advised for both primary and secondary prevention of CVD, with healthy diet being recommended as a cornerstone of CVD prevention in all individuals [12].

To date, there is a persuasive body of evidence on the long-term beneficial effects of the Mediterranean diet (MD) on a number of health outcomes, including cardiovascular and cerebrovascular diseases, cancer and mortality. Much of the evidence derives primarily from observational studies [13] although recent data from intervention trials have confirmed substantial health advantages after allocation to MD-like patterns both in primary [14] and secondary cardiovascular prevention [15,16].

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However, the favourable relationship between a Mediterranean-type pattern and risk of death or disease in subjects with prior CVD has been less extensively explored, especially within Mediterranean Countries, with few exceptions [17–19].

Yet there is a lack of evidence from epidemiological studies on a possible combined effect of statins and diet in modulating mortality risk in CVD subjects. In the ATTICA study, subjects who had a low adherence to MD and were on statin medication, had almost 50% higher CVD risk as compared with subjects on statin therapy who had healthier dietary habits [20]. Moreover, studies examining the combined effect of statins and MD on hard endpoints are lacking, while some limited evidence is only available in relation to CVD risk factors [21].

In light of this, a real-life approach may help clarify the actual independent and combined health impact of these two main prevention strategies for CVD subjects; despite a number of limitations, a real-life study has been indicated as a complementary of RCTs; the latter are useful to assess treatment efficacy, but their applicability is restricted to ideal conditions limiting their ability to portray what happens in the real world [22].

The main purpose of this study was threefold: first, we evaluated the overall and cardiovascular death risks in patients with CVD at time of recruitment associated with adherence to MD; second, to assess potential interactions between MD and statins in relation to mortality risk; finally, by using a real-life approach, we explored lipids and low-grade inflammation as two possible pathways between MD, statin use and mortality risk.

2. Methods

2.1. Study population

The Moli-sani Study is a prospective cohort study designed to investigate genetic and environmental risk factors in the onset of cardiovascular, cerebrovascular and tumour diseases. Methodological details have been published previously [23] and summarized in Supplementary material. Briefly, at the baseline survey performed between 2005 and 2010, 24,325 men and women (aged ≥35 y) were randomly recruited from the general population of a Southern Italian region. From the initial 24,325 participants, 1320 reported at enrolment a previous diagnosis of CVD. Among them, we excluded those subjects reporting implausible energy intakes (<800 kcal/day in men and 500 kcal/day in women or >4000 kcal/day in men and 3500 kcal/day in women; n = 66), unreliable medical/dietary questionnaires (n = 142), and individuals with missing information on the main variables of interest (n = 11). The final sample was of 1180 subjects.

2.2. Ascertainment of risk factors at baseline

CVD events at baseline were self-reported and included angina, myocardial infarction, revascularization procedures, peripheral artery disease and cerebrovascular events. Each self-reported CVD event was confirmed if at least one of the following criteria was fulfilled: a) reported the date of admission to the hospital; b) reported drug use for ischemic vascular disease; c) presented medical records of ischemic vascular disease diagnosis.

History of cancer, heart failure or atrial fibrillation at baseline was self-reported. Time since CVD diagnosis was categorized as a 6-level variable with missing values collapsed in the unascertained category. Family history of CVD was self-reported and set at before age 65 and 55 for women and men, respectively. The dataset of Moli-sani Study provides accurate information on the use (frequency, dose, compliance) of medication for any disease, collected during the recruitment. The questionnaire on drug usage was directly linked to the Italian National drug index. Antiplatelet drugs use is intended for primary or secondary CVD prevention. Statin use was dichotomized as no/yes.

Table 1
Baseline characteristics of the study population categorized by adherence to Mediterranean diet at baseline.

	Levels of adherence to the Mediterranean diet			
	Poor (0–3)	Average (4–5)	High (6–9)	p value
Mediterranean diet score*	2.47 (0.70)	4.55 (0.50)	6.57 (0.73)	–
N of subjects (%)	334 (28.3)	517 (43.8)	329 (27.9)	
Age groups, y				0.010
≤55	13.2	14.3	11.8	
56–64	23.6	25.1	33.7	
≥65	63.2	60.5	54.4	
Sex (men)	60.2	69.0	73.2	0.31
Postsecondary education	6.3	8.3	9.7	0.34
BMI*	29.6 (4.7)	29.5 (4.5)	28.9 (4.4)	0.10
Leisure-time PA (Met-h/day)*	2.9 (3.6)	3.4 (4.5)	3.7 (4.3)	0.050
Smokers	13.5	13.0	15.5	0.21
Heart failure	4.5	2.7	3.0	0.56
Atrial fibrillation	6.0	4.6	2.4	0.0003
Parental history of CVD before age 65 y**	9.3	9.3	12.5	0.64
Time since CVD diagnosis, y				0.0059
0–2	17.7	21.9	24.6	
>2–5	22.2	26.3	26.4	
>5–10	24.2	20.5	22.5	
>10–20	18.9	19.3	17.0	
>20	6.9	4.3	3.9	
Unascertained	10.2	7.7	5.5	
Drugs for diabetes	22.2	15.7	13.1	0.20
Drugs for hypertension	70.7	65.2	69.9	0.12
Drugs for hyperlipidaemia	42.8	47.4	53.8	0.0095
Statins	40.7	46.2	50.8	0.0074
Other lipid-lowering drugs	4.5	5.4	10.0	0.0056
Total cholesterol (mg/dL)*	198 (41)	197 (41)	195 (94)	0.66
HDL-cholesterol (mg/dL)*	54 (14)	55 (14)	53 (14)	0.31
LDL-cholesterol (mg/dL)*	115 (34)	115 (34)	112 (36)	0.45
LDL-cholesterol ≤ 70 mg/dL	9.6	9.1	11.5	0.28
LDL-cholesterol ≤ 100 mg/dL	35.3	38.7	40.4	0.16
Low-grade inflammation (INFLA-score)*	0.09 (0.99)	0.01 (0.99)	−0.11 (1.02)	0.06
History of cancer	6.3	6.0	3.3	0.040
Antiplatelet drugs	60.2	67.1	62.3	0.10
Energy intake (kcal/day)*	1749 (517)	1923 (534)	2109 (546)	<0.0001

Values are percentages unless otherwise stated.
Means and p values are adjusted for age groups, sex and energy intake.
* Means, SD.
** Before age 55 y for men.

Low-grade inflammation was assessed by an INFLA-score developed within the Moli-sani cohort [24] and including 10-tiles of C-reactive protein (CRP, mg/L), leukocyte (WBC, $\times 10^9$/L) and platelet counts ($\times 10^9$/L) and the granulocyte to lymphocyte ratio (G/L ratio). For all four components, being in the highest deciles (7 to 10) scored increasingly from 1 to 4, while being in the lowest deciles (1 to 4) was negatively scored from −4 to −1. Being in the deciles 5 or 6 got zero point. The INFLA-score ranged between −16 and 16 and came up as the sum of the four components. An increase in the score represented an increase in low-grade inflammation intensity. For analysis purposes, the INFLA-score was rescaled to have a mean of zero and a standard deviation of one.

2.3. Dietary assessment

Food intake during the year before enrolment was assessed by the validated Italian EPIC food frequency questionnaire [23]. Adherence to the traditional MD was defined according to the Mediterranean diet score (MDS) [25] which was obtained by assigning 1 point to healthy foods (fruits and nuts, vegetables, legumes, fish, cereals, monounsaturated to saturated fats ratio) whose consumption was above the sex-specific medians of intake of the population; foods presumed to be detrimental (meat and dairy products) were scored positively if the consumption was below the median. All other intakes received 0 points. For ethanol, men who consumed 10–50 g/d and women who consumed 5–25 g/d received 1 point; otherwise, the score was 0.

The MDS ranged from 0 to 9 (the latter reflecting maximal adherence) and was used either as continuous variable (2-point increase) or categorized into three levels ranging from poor (0–3 points), average (4–5), high (6–9) adherence.

2.4. Statistical analysis

Characteristics of the study population by degree of adherence to MD were presented as numbers and percentages, or mean values and standard deviation for continuous variables. Associations in Table 1 were calculated by using general linear models adjusted for age, sex and energy intake (PROC GENMOD and PROC GLM in SAS for categorical and continuous variables respectively).

Risk estimates for all-cause and cause-specific deaths were expressed as hazard ratios (HR) with 95% confidence intervals (95% CI) and calculated by using Cox regression models with time-on-study on the time scale and competing risk of dying for other causes.

To establish the association between MD and risk of mortality, three models were fitted: the first provided crude estimates (Model 1), the second (Model 2) was adjusted for age groups (≤55 y; 56–64 y; ≥65 y), sex and energy intake (continuous), the third as in model 2 further adjusted for educational level, BMI, leisure-time physical activity, smoking status, heart failure, atrial fibrillation and cancer at baseline, time since diagnosis of CVD, parental history of CVD before age 65 (before age 55 for men), aspirin, statins, lipid-lowering drugs other than statins, antihypertensive drugs, medication for diabetes, egg and potato consumption (g/d, continuous).

In order to evaluate the independent and the combined effect of statins and the MD towards the risk of mortality, we performed a second analysis by dividing the patients' population into four groups: average/high (MD score ≥ 5; above the median of the population)/low (MD score < 5; below the median) adherence to MD combined with use or not of statins; low MD/no statins served as the reference category. An appropriate term for testing interaction between MD and statins (average-high/low MD*yes/no use of statins) was included in the multivariable model 3 to test for a difference of effect (Table 3).

Tertiles of the INFLA-score were generated and associated with mortality risk in a multivariable model (Model 2).

Dummies variables for missing values were created. Two-sided p-value < 0.05 was considered as statistically significant.

The data analysis was generated using SAS/STAT software, Version 9.4 of the SAS System for Windows©2009. SAS Institute Inc. and SAS are registered trademarks of SAS Institute Inc., Cary, NC, USA.

3. Results

Among statin users, we found a prevalent use of simvastatin and atorvastatin (about 70%); of them, 69.2% and 83.2% used moderate-intensity simvastatin (20–40 mg) or atorvastatin (10–20 mg), respectively. The characteristics of the study participants at baseline according to levels of adherence to the MD are reported in Table 1. Subjects who had the highest adherence to the MD tended to be more physically active and reported greater energy intake, and had lower rates of atrial fibrillation and history of cancer. Higher adherence to the MD was also associated with a lower time interval since CVD diagnosis and with larger use of lipid-lowering drugs (including statins).

As compared to patients not using statins, individuals who did use them were more likely younger and reported higher prevalence of drugs for diabetes, high blood pressure, other lipid-lowering therapy and antiplatelet drugs and lower time interval since CVD diagnosis (Supplementary Table 1).

Over a median follow-up of 7.9 y (interquartile range 6.7 to 9.1 y; 8971 person-years), 235 all-cause deaths (131 cardiovascular, of which 88 CAD/cerebrovascular, 55 cancer and 49 other cause deaths) were ascertained. In the multivariable model, higher adherence to the MD was associated with 32% lower risk of all-cause death (HR = 0.68; 95% CI 0.47–0.99), while a trend of protection towards cause-specific deaths was observed (Table 2; Model 3). A 2-point increase in the MDS lowered the risk of all-cause, cardiovascular and CAD/cerebrovascular mortality by 16, 23, and 30%, respectively (Table 2; Model 3). A trend of reduction of CAD (n of events = 62) death risk of 28%

Table 2
Risk of overall and cause-specific death associated with Mediterranean diet in the CVD sample (n = 1180) of the Moli-sani cohort.

	Mediterranean diet score (MDS)			2-point increment in MDS
	Poor (0–3)	Average (4–5)	High (6–9)	
Overall mortality				
N of deaths/n of subjects	83/334	96/517	56/329	–
Rate of death, %	24.8	18.6	17.0	–
Person-years	2370	3920	2682	–
Model 1 (HR; 95% CI)	-1-	0.68 (0.51–0.92)	0.57 (0.40–0.80)	0.76 (0.65–0.89)
Model 2 (HR; 95% CI)	-1-	0.69 (0.51–0.93)	0.58 (0.40–0.83)	0.76 (0.65–0.90)
Model 3 (HR; 95% CI)	-1-	0.82 (0.60–1.12)	0.68 (0.47–0.99)	0.84 (0.70–1.00)*
Cardiovascular mortality				
N of deaths/n of subjects	48/334	51/517	32/329	–
Rate of death (%)	14.4	9.9	9.7	–
Model 1 (HR; 95% CI)	-1-	0.62 (0.42–0.93)	0.55 (0.35–0.87)	0.74 (0.60–0.91)
Model 2 (HR; 95% CI)	-1-	0.63 (0.42–0.94)	0.56 (0.35–0.91)	0.74 (0.59–0.93)
Model 3 (HR; 95% CI)	-1-	0.73 (0.48–1.12)	0.61 (0.37–1.01)	0.77 (0.61–0.97)
CAD/cerebrovascular mortality				
N of deaths/n of subjects	33/334	35/517	20/329	–
Rate of death (%)	9.9	6.8	6.1	–
Model 1 (HR; 95% CI)	-1-	0.63 (0.39–1.01)	0.51 (0.29–0.89)	0.68 (0.53–0.88)
Model 2 (HR; 95% CI)	-1-	0.63 (0.39–1.03)	0.51 (0.29–0.92)	0.67 (0.51–0.88)
Model 3 (HR; 95% CI)	-1-	0.75 (0.45–1.24)	0.56 (0.30–1.05)	0.70 (0.52–0.93)

Model 1: crude estimates.
Model 2: adjusted for age groups, sex and energy intake.
Model 3 as in Model 2 further controlled for education, smoking, leisure-time physical activity, BMI, atrial fibrillation, heart failure, cancer, time from diagnosis of CVD, parental history of CVD before age 65 y (before age 55 y for men), antiplatelet drugs, statins, lipid-lowering drugs other than statins, antihypertensive drugs, medication for diabetes, egg and potato consumption (g/d).
* p value = 0.045.

Table 3
Risk of all-cause and cause-specific death associated with a four-level combination of adherence to MD and use of statins.

	Low MD/NO statins	Low MD + statins	Average-high MD/NO statins	Average-high MD + statins	p for interaction
%	27.5	20.6	26.5	25.3	
Mediterranean diet score (means, SD)	3.04 (0.96)	3.18 (0.87)	5.79 (0.91)	5.89 (0.98)	–
All-cause mortality					
N of deaths/n of subjects	82/325	49/243	65/313	39/299	0.28
HR (95% CI)	-1-	0.90 (0.62–1.30)	0.78 (0.55–1.12)	0.52 (0.35–0.78)	
Cardiovascular mortality					
N of deaths/n of subjects	41/325	34/243	36/313	20/299	0.045
HR (95% CI)	-1-	1.29 (0.80–2.09)	0.83 (0.51–1.36)	0.50 (0.28–0.89)	
CAD/cerebrovascular mortality					
N of deaths/n of subjects	25/325	28/243	26/313	9/299	0.0015
HR (95% CI)	-1-	1.81 (1.02–3.20)	1.00 (0.55–1.84)	0.38 (0.17–0.85)	

Low MD = low adherence to the Mediterranean diet defined as Mediterranean diet score < 5.
Average-High MD = average-high adherence to the Mediterranean diet defined as Mediterranean diet score ≥ 5.
Use of statins is considered as yes/no.
Multivariable hazard ratios obtained from the model adjusted for age groups, sex, education, smoking, leisure-time physical activity, BMI, atrial fibrillation, heart failure, cancer, time from diagnosis of CVD, parental history of CVD before age 65 y (before age 55 y for men), antiplatelet drugs, lipid-lowering drugs other than statins, antihypertensive drugs, medication for diabetes, energy intake, egg and potato consumption (g/d).
P for interaction is obtained by including the interaction term MD (average-high/low) x use of statins (yes/no) in the multivariable model.

associated with 2-point increase in the Mediterranean diet score (HR = 0.72; 95% CI 0.51–1.01; p value = 0.054) was found. Mortality from stroke (n of events = 26) was lowered by 35% (HR = 0.65; 95% CI 0.37–1.15), but statistical significance was not reached.

Statin use was marginally associated with lower all-cause mortality risk (HR = 0.79; 0.60–1.05) but not with CVD and CAD/cerebrovascular deaths (HR = 0.96; 0.66–1.40 and HR = 1.04; 0.66–1.65, respectively).

Table 3 shows the risk estimates for mortality associated with a 4-level combination of MD and statins. The group reporting low adherence to MD and using statins did not substantially differ from the one with either average/high adherence to MD or under statin treatment, although in the latter group subjects were prevalently men, younger, and smokers and were more likely to report lower time interval since CVD diagnosis, higher use of other lipid-lowering drugs other than statins and lower prevalence of medications for diabetes and cancer at baseline (Supplementary Table 2).

As compared with either subjects neither on statins nor having good adherence to MD, or with patients with good adherence to MD but no statin use, individuals combining good adherence to MD and statin use had a significantly lower risk of all-cause, cardiovascular (Supplementary Fig. 1) and CAD/cerebrovascular death (p values for interaction = 0.28, p = 0.045 and p = 0.0015, respectively; Table 3).

Values of INFLA-score within combinations of MD and statins suggested a likely synergistic effect of MD and statins towards low-grade inflammation (p for interaction = 0.057; Fig. 1A), while no interaction was apparent for total blood cholesterol levels (p for interaction = 0.30; Fig. 1B).

The inclusion of INFLA-score in the Cox-regression analysis (multivariable model 2 as in Table 3) slightly modified the value of interaction between MD and statins in relation to CVD and CAD/cerebrovascular mortality risks (p value from 0.0045 to 0.084 and from 0.0015 to 0.0029, respectively).

Risk estimates associated with low-grade inflammation (highest vs lowest tertile of the INFLA-score) were HR = 1.70 (1.21–2.38), HR = 1.91 (1.21–3.01), HR = 1.98 (1.13–3.48) for all-cause, cardiovascular and CAD/cerebrovascular deaths, respectively.

4. Discussion

Adherence to a traditional MD was independently associated with reduced risk of all-cause, cardiovascular and CAD/cerebrovascular

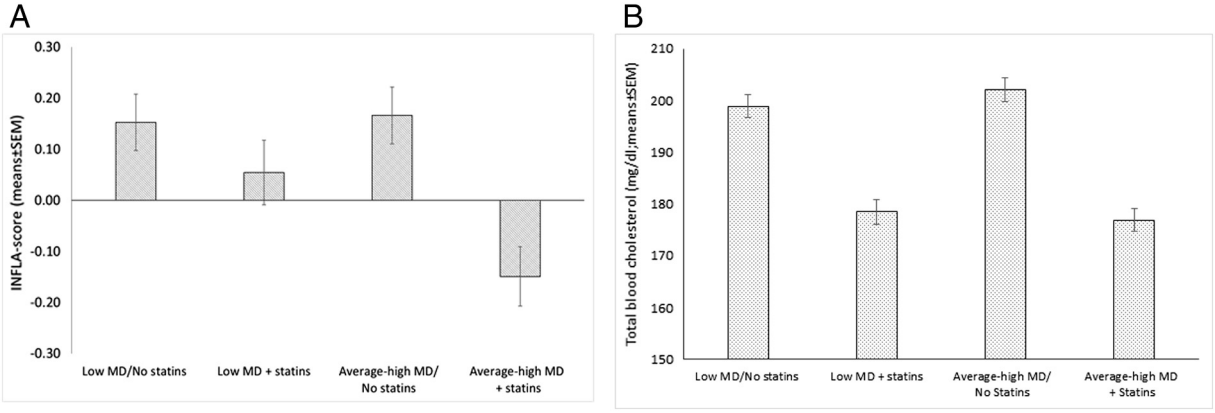

Fig. 1. A. Mean values (±SEM) of low-grade inflammation (measured by the INFLA-score) across 4-level combination of average-high adherence to MD and statin use. Means are adjusted for age groups, sex, education, smoking, leisure-time physical activity, BMI, atrial fibrillation, heart failure, cancer, time from diagnosis of CVD, parental history of CVD before age 65 y (before age 55 y for men), antiplatelet drugs, lipid-lowering drugs other than statins, antihypertensive drugs, medication for diabetes, energy intake, egg and potato consumption (g/d). B. Mean values (±SEM) of total blood cholesterol (mg/dL) across 4-level combination of average-high adherence to MD and statin use. Means are adjusted for age groups, sex, education, smoking, leisure-time physical activity, BMI, atrial fibrillation, heart failure, cancer, time from diagnosis of CVD, parental history of CVD before age 65 y (before age 55 y for men), antiplatelet drugs, lipid-lowering drugs other than statins, antihypertensive drugs, medication for diabetes, energy intake, egg and potato consumption (g/d).

mortality in a sample of CVD patients from the general population of the larger Moli-sani Study cohort.

Our results are in agreement with previous observational evidence that a MD was able to lower the risk of mortality in individuals with history of CVD net of use of drugs for hyperlipidaemia [17,18], as well as with findings from the Lyon Diet Heart Study, a randomized secondary prevention trial showing the effectiveness of the MD in reducing the risk of CVD recurrence [16].

Within our CVD subjects sample from a free living general population, (low dose) statin use was only marginally associated with lower risk of total mortality, but not related to CVD death risk, in apparent contrast with evidence from large randomized trials and meta-analyses of secondary CVD prevention [2,8–10]. More recently, a small but significant survival advantage associated with high-intensity statins, compared with moderate-intensity statins, in a large retrospective cohort of patients with established atherosclerotic cardiovascular disease was found [26]. A favourable association between statin treatment and non-fatal and fatal CVD outcomes has also been previously reported in different epidemiological studies [27–32].

Noticeably, the persistence with statins is likely to be very poor, indeed only about 45% after three years even in secondary prevention [33] and this may account for the weak effect of statins alone observed on death risk. Moreover, subjects from our study reported use of very low doses of statins, which may have led to small mortality benefits. However, the CVD death risk reduction associated with MD observed in our population, in respect to the poor response to statins, is not surprising, in view of the different, though not directly comparable effects, already reported in the Lyon study [16] (approximately 70% reduction of recurrent myocardial infarction or cardiac death in 4 y for the group allocated to MD) and 4S [8,34] (about 40% reduction of coronary death in 6 y, for statins vs placebo) trials and recently confirmed by a meta-analysis of randomized trials [35] showing a 20% reduction of CVD mortality for statin vs non statin users.

However, none of the aforementioned studies apparently accounted either for dietary behaviours or for a possible interaction between (Mediterranean) diet and statins in modulating cardiovascular risk.

Current recommendations for the prevention of cardiovascular disease emphasize that lifestyle modification, including a healthy diet, should be incorporated into any treatment plan, also for those on statins [36]. As recently pointed out [21], however, there is a paucity of data addressing the interaction between diet and statins with respect to additive, complementary or antagonistic effects. Available evidence seems to indicate a likely synergism between food and statins [37], but to date only few RCTs have addressed the effect of combining statins and Mediterranean diet on health outcomes, and all have only focused on modulation of traditional CVD risk factors rather than on hard clinical endpoints, such as mortality [38–40]; similarly, evidence from observational studies was limited to detect changes in traditional CVD biomarkers, such as serum cholesterol concentrations [41].

In order to assess a potential interaction between MD and statins, we performed a combined analysis by dividing the population according to a 4-level category in which adherence to MD and statin use were alternately combined.

Results showed a significant interaction between MD and statins towards the risk of cardiovascular or CAD/cerebrovascular death. Patients on statin treatment but poor adherence to MD did not appear to get any advantage towards cardiovascular death; the same applied to subjects reporting average/high adherence to MD but not using statins. On the contrary, CVD death risk was significantly reduced in the group using statins with a simultaneous average/high adherence to MD, as compared with those neither using statins nor having good adherence to MD: this suggests a possible synergistic effect of MD and pharmacological treatment in reducing the risk of mortality from vascular causes. Our findings appear in accordance with the ATTICA study [20] and the Alpha Omega Trial [42] and stress the opportunity to analyse the health effects of statins in the context of a healthy lifestyle, such as healthy dietary habits.

4.1. Possible pathways for the synergistic association of diet and statins towards mortality risk

We addressed two major pathways possibly accounting for the synergistic association of MD and statins with lower CVD mortality risk. There is solid evidence to date, mainly from clinical trials, on the lipid-lowering effect of statins [8] widely considered as the main biological pathway of statins to reduced disease risk [4]; a favourable modulation of the lipid profile has also been proposed as one of the mechanisms through which MD protects against cardiovascular disease [43].

On the other hand, many studies have highlighted the pleiotropic and anti-inflammatory effects of statins [44] and have discussed the anti-inflammatory properties of MD [45]. Our results showed that the best combination of MD and statins is associated with reduced low-grade inflammation with a magnitude greater than expected, although statistical significance was not fully reached (p for interaction = 0.057), and higher degree of low-grade inflammation was linked to increased risk of death, in line with our previous findings [24].

Conversely, no synergistic association of MD and statins in regulating lipids level was found.

These findings suggest that a favourable modulation of low-grade inflammation, rather than lipids, could be on the pathway of the interaction between MD and statins towards mortality risk.

Our data are supported by a number of publications mainly discussing the role of diet in the post-prandial state (including inflammation), rather than on fasting lipids [46,47], as well as those highlighting the role of red wine, one of the main components of the MD, in mitigating the postprandial increase of LDL susceptibility to oxidation [48].

More recently, findings from the CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study) trial demonstrated that among 10,000 patients with previous myocardial infarction, anti-inflammatory therapy led to a significantly lower rate of recurrent cardiovascular events than placebo, independent of lipid-level lowering [49].

Although it is still too early to speculate on the underlying mechanisms of the interaction between statins and a dietary regimen, due to paucity of data, prior evidence has provided some insight into the combined benefits of statins with some individual nutrients/foods typical of an MD.

For instance, dietary fibre, largely present in the MD, in conjunction with statins has been proven to reduce blood lipids levels significantly more than statins alone [50], while in the NHANES cohort study statin use was associated with healthier lipoprotein profiles when combined with higher whole-grain intake relative to low whole-grain intake [41].

4.2. Strengths and limitations

Strengths of the present study are represented by its prospective design, the relatively long-term follow-up and its real life setting of general population. Moreover, a large number of possible confounding factors have been considered in order to minimize confounding.

A limitation of our epidemiological approach in evaluating statin effects might rely on the observational, though prospective, nature of our investigation, as compared to the well-established randomized clinical trials. Accordingly, patients taking statins (at any dosage) or adhering to MD, as well as the control group of CVD patients who neither used statins nor adhered to MD, could not be randomized; MD was not controlled but only assessed by questionnaires, statin use was neither randomized nor controlled.

The findings here reported originate from epidemiological observations, thus causality cannot be inferred. We also acknowledge possible residual confounding due to unmeasured factors.

Another limitation is represented by the one-time measure of dietary and biological data (i.e. inflammatory status and lipids) that is unlikely to fully capture exposure over the follow-up course. We also acknowledge the problem, closely related to the one-time collection of drug-related information, of drug naïve patients and compliance over follow up.

The ascertainment of prior CVD event was self-reported (but supported by documented medical records) and consequently, we cannot exclude that some subjects could have had unnoticed previous CVD events. Finally, these data derive from an Italian Mediterranean population, thus caution is needed in extending the results to other contexts.

However, our general population-based, prospective cohort study offers an important evaluation of statins' effectiveness in real life, highlighting the potential advantage of combining a dietary and a pharmacological approach to overcome their relative limitations [22].

5. Conclusions

In this sample of subjects with CVD, at relatively low doses of statins, adherence to a traditional MD is independently associated with improved survival and lower CVD mortality risk.

Our data suggest that in some secondary prevention settings combining statin therapy with a traditional MD significantly reduces the risk of vascular and CAD/cerebrovascular death, as compared to those neither receiving statins nor reporting adequate adherence to the MD.

Conclusive evidence on the effectiveness of the combination of MD and statins will only be obtained by appropriate randomized clinical trials; however, to the best of our knowledge, our study is one of the few observational studies to show a possible favourable interaction between these two preventive strategies in relation to all-cause and CVD mortality risk.

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Authorship

LI, MB and ADiC contributed to the conception and design of the work, and interpretation of data; SC, MP, ADeC managed data collection; MB, ADiC analysed the data; MB wrote the paper; CC, MBD, GdG and LI originally inspired the research and critically reviewed the manuscript.

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Disclosures

None of the authors had a personal or financial conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.11.117.

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