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ARTICLE

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Incremental monounsaturated to saturated fat ratio and fibre consumption is associated with a reduction in a composite score of modifiable cardiovascular risk factors: Prospective results from the Moli-sani study

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BACKGROUND/OBJECTIVES: Unsaturated fats, fibre-rich foods and polyphenols are distinctive features of a traditional Mediterranean diet and have pleiotropic properties possibly contributing to reduce the long-term risk of non-communicable diseases and mortality associated with this diet. We aimed to evaluate whether changes over time in dietary fats, fibre and polyphenols consumption are associated with modifications in cardiovascular disease (CVD) risk factors.
METHODS: The analytic sample consists of a sub-cohort of 2023 men and women enrolled in the Moli-sani Study ($n = 24{,}325$). Dietary and health data were obtained both at baseline (2005–2010) and at re-examination (2017–2020). The exposures were changes in dietary fats, fibre and polyphenols consumption measured after 12.7 years (median), and the outcome was change in a composite score including 13 modifiable CVD risk factors (*e.g.*, blood lipids, C-reactive protein), measured both at enrolment and after the 12.7 years period.
RESULTS: In multivariable-adjusted analysis including lifestyles, sociodemographic and clinical factors, an incremental intake of the ratio of monounsaturated to saturated fats or of fibre was associated with a reduction in the composite score of CVD risk factors ($\beta = -0.086$; 95%CI −0.150, −0.021 and $\beta = -0.051$; 95%CI −0.091, −0.012, respectively). Change in polyphenol intake was not associated with a substantial variation in the CVD risk score ($p = 0.15$).
CONCLUSIONS: An incremental consumption over time of monounsaturated versus saturated fats and of fibre was associated with an improvement in modifiable CVD risk factors as reflected by a composite score.

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INTRODUCTION

Improvement of overall diet quality is a key public health strategy to prevent chronic diseases [1], and is supported by a large body of evidence indicating that healthful diets are associated with lower risk of non-communicable diseases [2, 3] and premature death [4].

Studies evaluating whether improvement in overall diet quality might have long-term advantages on health are scarce [5, 6], and were mainly focused on changes in intermediate phenotypes that predispose to higher health risk [7, 8], while a few have related incremental improvement in the overall diet quality with disease occurrence or mortality [5, 9, 10].

The traditional Mediterranean diet (MD) has long been acknowledged as one of the healthiest diets, capable of reducing the risk of developing chronic diseases and improve survival in numerous cohorts [11, 12], possibly through a favourable modulation of several cardiovascular and cerebrovascular disease (CVD) risk factors [13] and inflammatory markers [14].

The MD emphasizes the consumption of plant-based foods that are natural sources of antioxidants and fibre, while limiting the intake of saturated fats (SFA) and trans fats, animal-derived proteins, and added/refined sugars [1]. By contrast, this eating model is characterized by the large use of dietary sources of unsaturated fats, i.e. monounsaturated (MUFA) and polyunsaturated (PUFA) fats, with energy from fat representing up to 40% of the total calories eaten daily [15], and extra-virgin olive oil being the main source of MUFA.

Unsaturated fats are likely one mechanism for reducing inflammation, optimizing cholesterol, and other risk factors, and diets rich in these fats were shown to reduce total and cause-specific mortality risk [16], whereas SFA were found to impact adversely on health [17].

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The health advantages deriving from a diet rich in fibre are well documented in a number of observational [18] and intervention studies [19]. Polyphenols are bioactive compounds largely present in in plant foods and plant-derived beverages [20], and there is robust evidence supporting their beneficial effects against type 2 diabetes, CVD and cancer [21–26], possibly through their well-recognized anti-inflammatory and antioxidative properties [27].

While the association of incremental diet quality changes, as measured by dietary indices, with intermediate phenotypes is well-documented, no prior investigations have seen whether improving adherence to main components of a healthy diet possibly associates with changes in modifiable CVD risk factors. Therefore, we sought to evaluate whether changes in some distinctive features of a traditional MD (i.e., dietary fats, fibre and polyphenols) are associated with modifications in several modifiable CVD risk factors, as reflected by a composite score of established CVD risk factors, in a sub-cohort of 2023 adults from the larger Moli-sani study in Italy.

METHODS

Study population

The Moli-sani Study is a large population-based cohort study that in 2005–2010 randomly recruited 24,325 men and women aged ≥ 35 years from the adult general population of the Molise region, a central-southern area of Italy with the aim of investigating genetic and environmental risk factors in the onset of cardiovascular, cerebrovascular and cancer diseases. Exclusion criteria were pregnancy at the time of recruitment, disturbances in mental or decision-making impairments, current poly-traumas or coma, or refusal to sign the informed consent. Details of the study are provided elsewhere [28]. In 2017–2020, the first 5438 residents in Campobasso (the chief town of the Molise region), previously recruited in the Moli-sani study, were re-contacted for a full re-examination, including dietary, lifestyle and psychological assessments, along with medical examination and blood collection. Of them, 3896 accepted (acceptance rate = 71.6%) and 2581 underwent the re-examination from May 2017 until the beginning of March 2020; the recruitment of the remaining 1315 participants was not completed since the COVID-19 outbreak. The final sample was of 2023 individuals (Supplementary Fig. 1). The Moli-sani Study complies with the Declaration of Helsinki and was approved by the Ethics Committee of the Catholic University Medical School in Rome, Italy. The re-examination of the cohort was granted the approval of the Ethics Committee of the IRCCS Neuromed, Pozzilli (IS), Italy. All participants provided written informed consent both at baseline and at re-examination.

Dietary assessment

Dietary intake during the year before enrolment was assessed at baseline (2005–2010) and follow-up (2017–2020) by an interviewer-administered semi-quantitative EPIC food frequency questionnaire (FFQ) validated and adapted to the Italian population [29].

The Nutrition Analysis of Food frequency questionnaire (NAF) [30] was used to convert questionnaire dietary data into frequencies of consumption and average daily quantities of foods (g/d) and energy intake (Kcal/d). The NAF software was linked to the Italian food composition tables for energy assessment [31].

The FFQ includes a total of 188-food items that were classified into 45 predefined food groups on the basis of similar nutrient characteristics or culinary usage.

Adherence to the traditional MD was defined according to the MD Score (MDS) developed by Trichopoulou et al. [32], ranging from 0 to 9 (the latter reflecting maximal adherence). Assessment of MDS at re-examination was made by using the sex-specific cut-offs for each food group as evaluated at baseline.

Intake of total and sub-types of fats (SFA, MUFA, and PUFA) was considered as percentage of the total energy intake or as the ratio of MUFA to SFA, used as a proxy of olive oil consumption. Total dietary fibre consumption from various food sources (e.g., bread, pasta, vegetables) was defined as g/d.

The Phenol-Explorer database [33] was used to estimate the total intake of polyphenols in the diet of participants. This is the most complete database currently available for polyphenol content. Both at baseline and follow-up, the individual polyphenol intake was calculated by multiplying the content of each polyphenol in a particular food item (mg/g) by the daily consumption of this food item (g/d) and then summing the product across all food items. Total polyphenol intake resulted as the sum of all individual polyphenol intakes.

Assessment of covariates

Data on socio-demographic, lifestyle and clinical variables were collected through an interviewer-administered questionnaire. Educational level was based on the highest qualification attained and was categorized as up to lower secondary (≤ 8 years), upper secondary (8–13 years) and post-secondary (>13 years). Housing tenure was defined as rented, 1 dwelling ownership or > 1 dwelling ownership. Present occupation was categorized as professional/managerial, skilled non-manual, skilled manual, semi-skilled/unskilled and unemployed/unclassified. Marital status was grouped as married/in couple, separated/divorced, single and widowed. Subjects were classified as never-smokers, current smokers, or former smokers (reported not having smoked at all over the previous 12 months or more) at baseline and at follow-up. Physical exercise was expressed as daily energy expenditure in metabolic equivalent task-hours (MET-h/d). Participants were considered to have diabetes, hypertension or dyslipidaemia if they were receiving disease-specific drugs. History of cardiovascular disease (angina, myocardial infarction, peripheral artery disease, revascularization procedures and cerebrovascular events) was self-reported and confirmed by medical records and therapy. History of cancer was self-reported and confirmed by medical records.

Blood collection and measurement of biomarkers

Serum lipids (total cholesterol, HDL-cholesterol, triglycerides) and blood glucose were assayed by enzymatic reaction methods using an automatic analyzer (ILab 350, Instrumentation Laboratory, Milan, Italy at baseline, and ILab Aries at re-examination). Quality control (high and low levels) for lipids was obtained by a commercial standard provided by IL and an in-house serum standard pool. Serum high sensitivity C-reactive protein (CRP) was measured by a particle-enhanced immunoturbidimetric assay (ILab 350, Instrumentation Laboratory, Milan, Italy at baseline, and ILab Aries at re-examination).

Hemochromocytometric analysis was performed by cell count (Coulter HMX, Beckman Coulter, IL Milan, Italy at baseline, and Siemens ADVIA 120 at re-examination) within 3 h from blood collection.

Blood pressure was measured by an automatic device (OMRON-HEM-705CP at baseline, and OMRON-HEM-FL31 at re-examination) three times on the non-dominant arm and the average of the last two values was taken as the BP. Measurements were made in a quiet room with comfortable temperature with the participants lying down for at least 5 min. Body weight and height were measured with a column mechanical scale with telescopic measuring rod (SECA 700, Hamburg, Germany), in subjects wearing no shoes and only light indoor clothing. Body mass index (BMI) was calculated as kg/m^2. Waist circumferences were measured according to the National Institutes of Health, Heart, Lung, and Blood Guidelines [34]. The same procedures were used for collecting data during the re-examination of the cohort.

Computation of the composite score of CVD risk factors

To appraise participants' CVD risk both at baseline and at re-examination, we derived a composite score that summarized levels of 13 modifiable risk factors reflecting different underlying pathways to CVD incidence and progression, that is systolic and diastolic blood pressure, heart rate, total serum cholesterol, HDL-cholesterol, triglycerides, blood glucose, BMI, waist-to-hip ratio, creatinine, CRP, white blood cell count, granulocyte-to lymphocyte ratio (GLR). Participants were categorized into sex-specific deciles of each marker level. For all components, higher levels (i.e., > Q6) scored increasing positively (from 1 to 4) while lower levels (i.e., < Q5) got negative scoring (from −1 to −4). Being in the deciles 5 or 6 got zero points. For HDL- cholesterol we reversed the scoring.

The composite CVD risk factors score resulted from summing the 13 individual scores and theoretically ranging from −52 to 52, with increased values reflecting worse cardiovascular health. For analyses purposes, this composite score was modelled as a continuous variable (1 standard deviation increase).

Statistical analysis

In this study, the exposures were changes in the intake of fats, fibre and polyphenols measured after a 12.7 years period, and the outcomes were

Table 1. Dietary intake and cardiovascular risk factors at baseline, during follow-up and change over 12.7 years.

	Moli-sani Study ($n = 2023$)			
	Baseline (2005–2010)	**Follow-up (2017–2010)**	**12.7 years change**	
	Means (SD)	**Means (SD)**	**Means (SD)**	***P*-value**
Dietary factors				
Energy intake (Kcal/d)	2156.7 (572.0)	1781.6 (458.9)	−375.2 (578.0)	<0.0001
Carbohydrate (% energy intake)	48.9 (6.8)	47.1 (6.6)	−1.8 (7.9)	<0.0001
Proteins (% energy intake)	16.1 (2.1)	14.3 (4.5)	−1.8 (4.3)	<0.0001
Total fats (% of total energy)	33.1 (5.6)	34.9 (5.3)	1.8 (6.1)	<0.0001
SFA (% of total energy)	11.8 (2.6)	12.5 (2.5)	0.6 (2.9)	<0.0001
MUFA (% of total energy)	15.9 (3.0)	16.4 (2.7)	0.5 (3.3)	<0.0001
PUFA (% of total energy)	3.5 (0.6)	3.9 (0.7)	0.4 (0.8)	<0.0001
MUFA-to-SFA ratio	1.38 (0.30)	1.35 (0.25)	−0.04 (0.32)	<0.0001
Fibre (g/d)	22.0 (7.0)	18.4 (4.9)	−3.5 (7.4)	<0.0001
Total polyphenol intake (mg/d)	701.8 (264.6)	564.3 (215.6)	−137.5 (258.5)	0.0014
CVD risk factors				
Systolic blood pressure (mm Hg)	141.0 (19.6)	136.7 (17.1)	−4.3 (18.2)	<0.0001
Diastolic blood pressure (mm Hg)	83.6 (9.5)	81.6 (8.9)	−2.0 (9.8)	<0.0001
Heart rate (bpm)	66.1 (9.5)	65.6 (10.0)	−0.6 (9.7)	<0.0001
Serum cholesterol (mg/dL)	213.6 (38.0)	206.2 (41.6)	−7.4 (45.8)	<0.0001
HDL-cholesterol (mg/dL)	58.0 (14.3)	60.2 (14.0)	2.3 (10.7)	0.0076
Triglycerides (mg/dL)	123.9 (63.7)	127.5 (60.4)	3.6 (63.6)	0.16
Blood glucose (mg/dL)	99.0 (19.8)	109.3 (25.0)	10.2 (23.4)	0.020
BMI (kg/m^2)	27.4 (4.3)	28.2 (4.7)	0.8 (2.5)	0.24
Waist-to-hip ratio	0.92 (0.07)	0.99 (0.05)	0.07 (0.06)	<0.0001
Creatinine (mg/dL)	0.80 (0.19)	0.88 (0.24)	0.07 (0.21)	0.013
C-reactive protein (mg/L)	2.3 (3.0)	2.9 (4.3)	0.6 (4.4)	0.45
White blood cells (x10^9/L)	6.1 (2.1)	5.7 (1.6)	−0.3 (2.0)	<0.0001
Granulocyte to lymphocyte ratio	1.97 (1.57)	2.07 (0.89)	0.10 (1.65)	<0.0001
CVD risk factors score	0.01 (13.8)	−0.05 (13.6)	−0.06 (11.4)	0.029

BMI Body mass index, *CVD* Cardiovascular disease, *SFA* Saturated fats, *MUFA* Monounsaturated fats, *PUFA* Polyunsaturated fats.
P-value for changes in dietary factors were obtained from a general linear model adjusted for duration of follow-up, baseline energy intake and changes in energy intake, and baseline consumption of each dietary factor.
P-value for changes in CVD risk factors and the CVD risk score were obtained from a general linear model adjusted for duration of follow-up and baseline levels of each risk factor or cardiovascular risk score.

changes in the composite score of CVD risk factors measured after the same 12.7 years period. We computed changes in the variables of exposure and outcome at individual level by subtracting values at baseline from those at 12.7 years follow-up.

Descriptive baseline characteristics are reported as mean and standard deviation (SD) or percentage.

Multivariable linear regression analysis (PROC REG in SAS) was used to estimate the relation between changes in the consumption of dietary fats, fibre and polyphenols (independent variables, standardised to one SD) with changes in the score of CVD risk factors (standardised to one SD) and results were expressed as regression coefficients (β) with 95% confidence interval (95%CI).

On the basis of previous literature and biological plausibility, the following 3 models were fitted: Model 1 was adjusted for age, sex, duration of follow-up, baseline energy intake and changes in energy intake, and baseline levels of each dietary exposure and the composite score of CVD risk factors; Model 2 was adjusted as in Model 1 and further controlled for baseline socioeconomic status (i.e. marital status, educational level, housing, occupational class), history of CVD (at baseline and follow-up), history of cancer (at baseline and follow-up), diabetes (at baseline and follow-up), hypertension (at baseline and follow-up), dyslipidaemia (at baseline and follow-up), baseline physical activity and changes in physical activity and smoking status (at baseline and follow-up); Model 3 was adjusted as in Model 2 and including changes in alcohol intake (g/d), energy from carbohydrates and protein, and all the listed dietary variables simultaneously.

Distribution of missing values was as follows: baseline CVD = 27; CVD at follow up = 43; baseline cancer = 4; cancer at follow up = 4; baseline diabetes = 24; diabetes at follow-up = 15; baseline hypertension = 21; hypertension at follow up = 5; baseline dyslipidaemia = 82; dyslipidaemia at follow up = 57; baseline smoking habit = 3; marital status = 1; baseline physical exercise = 1; physical exercise at follow up = 19.

We used a multiple imputation technique (SAS PROC MI, followed by PROC MIANALYZE) to maximize data availability for all variables, avoid bias introduced by not-at-random missing (MNAR) data patterns and achieve robust results over different simulations ($n = 10$ imputed datasets). Statistical tests were two-sided, and P values of less than 0.05 were considered to indicate statistical significance. Data analysis were generated using SAS/STAT software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

We analysed data on 2023 men and women with an average baseline age of 54.5 years (SD ± 8.8 years, range 35–79 years).

Distribution of baseline age and sex-standardized CVD risk factors in the Moli-sani participants was comparable to that from the Italian Health Examination Survey OEC/HES (2008–2012) [35], except for systolic blood pressure, that was higher in the Moli-sani study (Supplementary Table 1). Therefore, the median cut off of the individual CVD risk factors reflect neutral risk.

Table 2. Characteristics of the study participants at baseline and change over 12.7 years.

	Baseline (2005–2010)	Follow-up (2017–2020)	12.7 years change
N of subjects (%)	2023 (100.0)		-
Women	55.7		-
Age (y; means, SD)	54.5 (8.8)	67.2 (8.7)	12.8 (0.7)
Educational level			
Up to lower secondary	35.8	35.4	−0.4
Upper secondary	44.0	43.4	−0.6
Postsecondary	20.2	21.0	0.8
Missing data	0.0	0.2	0.2
Housing			
Rent	8.1	6.3	−1.8
1 dwelling ownership	74.5	68.3	−6.2
>1 dwelling ownership	17.2	25.0	7.8
Missing data	0.3	0.4	0.1
Occupational class			
Professional/Managerial	28.8	27.0	−1.8
Skilled Non-Manual	45.9	35.5	−10.4
Skilled Manual	10.8	7.9	−2.9
Semi-Skilled/Unskilled	10.7	7.5	−3.2
Unemployed/Unclassified	3.8	21.8	18
Missing data	0.0	0.3	0.3
Marital status			
Married/in couple	89.8	84.5	−5.3
Separated/divorced	2.3	3.0	0.7
Unmarried	4.0	3.5	−0.5
Widower	3.8	9.0	5.2
Missing data	0.1	0.0	−0.1
Smoking status			
Non-smoker	47.1	50.0	2.9
Smoker	23.0	13.3	−9.7
Former	29.7	36.7	7.0
Missing data	0.2	0.0	-
Physical exercise at baseline (MET-h/d)	42.2 (7.7)	40.8 (4.0)	−1.4 (7.9)
Cardiovascular disease	2.3	8.3	6.0
Cancer	3.0	9.4	6.4
Diabetes	3.0	10.0	7.0
Hypertension	22.5	49.4	26.9
Dyslipidaemia	6.0	22.3	16.3

Values are percentages, unless otherwise indicated.

Over 12.7 years of follow-up (interquartile range: 12.3–13.3 years), energy from fat increased from 33.1% (SD ± 5.6) to 34.9% (SD ± 5.3) and the same upward trend were observed for other subtypes of fat, with the exception of the MUFA-to-SFA ratio, that was otherwise decreased, as well as dietary fibre and total polyphenols (Table 1).

Overall, the composite score of CVD risk factors significantly lowered from 0.01 to −0.05 (Table 1).

Regarding individual biomarkers, relevant decreases were observed for total blood cholesterol and systolic and diastolic blood pressure, while major increases pertained to blood glucose levels, waist-to-hip ratio and the ratio of granulocytes to lymphocytes (Table 1).

Characteristics of the study participants at baseline and follow-up are reported in Table 2. Among lifestyles, data indicate lower prevalence of smokers and reduced levels of physical activity after 12.7 years as compared to baseline data; an increase in the prevalence of all chronic health conditions was also documented, likely as a consequence of aging.

In multivariable-adjusted analyses, an increase in the percentage of energy from total fat or SFA was directly associated with the composite score of CVD risk factors ($\beta = 0.104$; 95% CI 0.030, 0.179 and $\beta = 0.103$; 95%CI 0.034, 0.172, respectively; Table 3, Models 3).

Increases in the amount of MUFA on SFA inversely associated with the CVD risk factors score ($\beta = -0.086$; 95%CI −0.150, −0.021; Table 3, Model 3), while increases in energy from MUFA or PUFA taken individually were not associated with the outcome under study.

Higher intake of dietary fibre, but not polyphenols, was inversely associated with the composite score of CVD risk factors ($\beta = -0.051$; 95% CI −0.091, −0.012 and $\beta = -0.053$; 95%CI −0.124, 0.018; Table 3, Models 3; respectively). Similar results were

Table 3. Changes in the composite score of cardiovascular disease risk factors (1 SD-increment) associated with changes in the consumption of total fat, fat subtypes, fibre and polyphenols (1 SD-increment) over 12.7 years follow-up in the Moli-sani Study cohort ($n = 2023$).

	Δ Cardiovascular disease risk factors score			
	Regression coefficient *β*	**Lower 95%CI**	**Upper 95%CI**	***P*-value**
Δ Total fat (% of energy)				
Model 1	0.069	0.019	0.119	0.007
Model 2	0.074	0.021	0.126	0.006
Model 3	0.104	0.030	0.179	0.006
Δ MUFA (% of energy)				
Model 1	0.050	−0.003	0.102	0.062
Model 2	0.041	−0.013	0.095	0.139
Model 3	0.032	−0.046	0.109	0.426
Δ PUFA (% of energy)				
Model 1	0.023	−0.026	0.072	0.363
Model 2	0.019	−0.032	0.070	0.468
Model 3	0.012	−0.053	0.077	0.712
Δ MUFA-to-SFA				
Model 1	−0.062	−0.117	−0.006	0.029
Model 2	−0.085	−0.142	−0.028	0.004
Model 3	−0.086	−0.150	−0.021	0.009
Δ SFA (% of energy)				
Model 1	0.083	0.033	0.133	0.001
Model 2	0.099	0.047	0.150	0.0002
Model 3	0.103	0.034	0.172	0.003
Δ Fibre (g/d)				
Model 1	−0.072	−0.105	−0.040	<0.0001
Model 2	−0.073	−0.107	−0.040	<0.0001
Model 3	−0.051	−0.091	−0.012	0.011
Δ Total polyphenols (mg/d)				
Model 1	−0.041	−0.101	0.019	0.18
Model 2	−0.053	−0.115	0.009	0.096
Model 3	−0.053	−0.124	0.018	0.15

Model 1: Regression coefficient β with 95% confidence interval (95%CI) obtained from the linear regression analysis adjusted for age, sex, duration of follow-up, baseline energy intake and changes in energy intake, baseline levels of the dietary exposure and initial levels of the score of cardiovascular disease risk factors.
Model 2: As in model 1 and further controlled for baseline marital status, educational level, housing, occupational class, history of CVD (at baseline and follow-up), history of cancer (at baseline and follow-up), diabetes (at baseline and follow-up), hypertension (at baseline and follow-up), dyslipidaemia (at baseline and follow-up), baseline physical activity and changes in physical activity, smoking status (at baseline and follow-up), baseline levels of the dietary exposure and initial levels of the score of cardiovascular disease risk factors.
Models 3 were further controlled for changes in alcohol intake (g/d), energy from carbohydrates and protein, and includes all the listed dietary variables simultaneously.

observed when changes in dietary exposures were modelled as tertiles (Fig. 1).

DISCUSSION

The health advantages of an MD are well-documented in a variety of population cohorts [11, 12, 32] and also supported by RCTs [36, 37]; this diet is characterized by olive oil as a major source of unsaturated fat and high content of fibre and polyphenols, all acting on different, though complementary, health-promoting pathways.

In the present study, we sought to examine the associations of changes in key features of a traditional MD with concurrent changes in in modifiable CVD risk factors over a 12.7-year period.

The key findings of our analyses were that participants who have increased their optimal ratio of MUFA to SFA, that can be considered as a marker of olive oil consumption, were more likely to experience an improvement in a composite score of modifiable CVD risk factors; consistently, an incremental intake of energy from saturated fat was associated with an increase in this score.

A traditional MD has lipid-lowering effects that have been proposed among key biological mechanisms through which this diet likely exerts its favourable effects on health [38].

The role of dietary fats on health has been long studied as a modifiable factor in the prevention and treatment of several non-communicable diseases, as well as mortality risk [39, 40].

Extra-virgin olive oil is the major dietary source of MUFA in the Mediterranean diet and several studies showed its beneficial effects in the development and progression of diseases associated with chronic low-grade inflammation [36], as well as its positive association with survival [41].

A high ratio of MUFA to SFA, which is a proxy of olive oil consumption at least in Mediterranean populations, resulted in a significant risk reduction for all-cause and cardiovascular mortality in

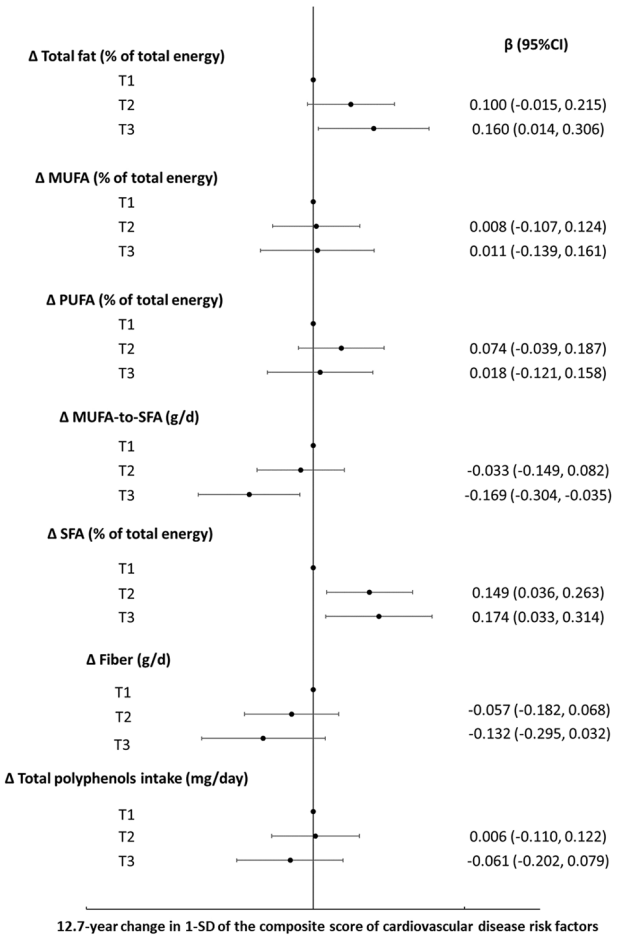

Fig. 1 Changes over time in the intake of fats, fibre and polyphenols (tertiles of) associated with 1-SD change of the composite score of cardiovascular disease risk factors over 12.7 years in the Moli-sani cohort ($n = 2023$). Regression coefficient β with 95% confidence interval (95%CI) obtained from the linear regression analysis adjusted for age, sex, duration of follow-up, baseline marital status, educational level, housing, occupational class, baseline energy intake and changes in energy intake, history of CVD (at baseline and follow-up), history of cancer (at baseline and follow-up), diabetes (at baseline and follow-up), hypertension (at baseline and follow-up), dyslipidaemia (at baseline and follow-up), baseline physical activity and changes in physical activity, smoking status (at baseline and follow-up), baseline levels of each the dietary exposure and initial levels of the score of cardiovascular disease risk factors, changes in alcohol intake (g/d), energy from carbohydrates and protein, and included all the listed dietary variables simultaneously.

numerous prospective cohorts worldwide [42], and was also found to be a top contributing factor to increased survival associated with an MD among a population of elderly Italians recruited in the same Moli-sani cohort [43]. In the last years, the PREDIMED dietary intervention trial on over 7000 Spanish individuals at high CVD risk showed that Mediterranean diets enriched with extra-virgin olive oil or nuts are effective in reducing the risk of developing CVD, cancer and diabetes compared to a standard low-fat diet [36, 44, 45]. Also, participants assigned to the MD arms of the trial experienced lower cellular and plasma concentrations of inflammatory markers related to atherosclerosis [46], as well as improvements in lipid profile and blood pressure [47].

Our findings on a direct association between increases in total or saturated fat intake with the CVD risk factors score support the notion that limiting SFA in the diet, also by preferring vegetable sources of cooking fat (e.g., olive oil over butter), should be prioritized for reduction of non-communicable disease risk [48].

Findings from our longitudinal analyses also point to an inverse association between an increase in dietary fibre and CVD risk factors; this is in line with several observational studies showing that a large dietary share of fibre is associated with lower long-term risk of developing CVD, diabetes and cancer, as well as reducing mortality risk [49].

Fibre can positively impact on cardiovascular health by exerting beneficial metabolic effects that include reduction of cholesterol levels, improved control of blood glucose levels, and better regulation of body weight [50].

Unexpectedly, in our analyses an increase in dietary polyphenols over time was not associated with an improvement in cardiovascular risk factors. This finding is in contrast with a large body of epidemiological evidence indicating that a diet rich in polyphenols is associated with reduced risk of non-communicable diseases [51, 52], especially cardiovascular disease [24, 53], possibly through a favourable modulation of intermediate phenotypes that ultimately translate into lower disease risk.

Yet, it is worth noting that our study used a limited number of blood markers of inflammation, and these may not necessarily reflect inflammation in tissue compartments or response to inflammatory challenges [54]; this possibly explains the lack of an association between increases in polyphenol intake and the CVD risk factors score in our population.

Strengths and limitations

To the best of our knowledge, this is the first study evaluating in an adult general population longitudinal changes in key components of a traditional MD, and subsequently assessing their association with changes in CVD risk factors.

The present study has several strengths which include a prospective design, a second dietary assessment over 12.7 years by a validated dietary questionnaire, and comprehensive information on a wide range of potential covariates.

However, there are several limitations that need to be considered. First, these are observational data which limit causal inference; second, although we have used Phenol-Explorer, which is the most comprehensive food composition database on polyphenols to date [33], measurement error in collecting and estimating dietary polyphenol intake remains an issue. Another critical point is represented by the effect of seasonality, storage and cooking process which is not always considered.

Also, we did not explore the different dietary sources of fats, that may have different effects on human health. A further weakness is the use of a limited number of inflammatory markers to evaluate low-grade inflammation, although a composite score based on these markers was found to be predictive of health outcomes [55].

Further investigations using biomarkers, such as human plasma or urine samples, may be necessary for better understanding of the role in human health of polyphenols, fibre and fats consumed within an MD.

Also, we acknowledge that the intake of total SFAs without considering specific types of SFAs and their food sources is insufficient, since food composition results in different physiological effects.

Finally, it might be that dietary changes observed in this cohort can be partly explained by regression to the mean [56] or changes in disease status, and this should be taken into account when interpreting our results.

CONCLUSIONS

In a prospective cohort of Italian adults, an incremental intake of monounsaturated fats and fibre over a 12.7-year period is

associated with improvement in modifiable CVD risk factors at the end of the subsequent 12.7 years. Findings from this longitudinal study shed light on the role of key components of a traditional MD acting on concurrent changes in established markers of cardiovascular risk, which possibly predispose to lower the long-term risk of developing chronic disease and mortality. Results from the present study may be used to plan novel strategies aimed to improve population health through dietary recommendations, namely by ensuring adequate consumption of fibre-rich foods and optimal food sources of unsaturated fats.

DATA AVAILABILITY

The data underlying this article will be shared on reasonable request to the corresponding author. The data are stored in an institutional repository (https://repository.neuromed.it) and access is restricted by the ethical approvals and the legislation of the European Union.

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AUTHOR CONTRIBUTIONS

MB and ER conceived the present study; LI, MB, ER, and ADiC contributed to its design and to interpretation of data; SC, SE and MP managed data collection; ADeC organized and performed laboratory tests; MB and ER analysed the data and drafted the manuscript; MBD, CC, GdG and LI originally inspired the Moli-sani study and critically reviewed this manuscript. All Authors have read and approved the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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