Adherence to a Mediterranean lifestyle improve the metabolic status among coronary heart disease patients: from the CORDIOPREV study

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ABSTRACT

Background and objectives

A Mediterranean lifestyle may prevent and mitigate cardiovascular and metabolic disorders. We explored whether greater adherence to a Mediterranean lifestyle was prospectively associated with a lower risk of metabolic syndrome (MetS) among coronary heart disease (CHD) patients.

Methods

The CORDIOPREV study was an interventional diet study to compare a Mediterranean diet with a low-fat diet, in 1,002 CHD patients. The Mediterranean lifestyle (MEDLIFE) index was used to assess adherence to a Mediterranean lifestyle at baseline and after 5 years. Subjects were classified as high (>13 points), moderate (12-13 points), and low (<12 points) according to tertiles of adherence to Mediterranean lifestyle. Multivariable logistic regression models were used to determine the association between the MEDLIFE adherence and the risk of MetS development or reversal.

Results

During 5 years of follow-up, CORDIOPREV participants with high adherence to the MEDLIFE had a lower risk of MetS development (odds ratio (OR) 0.37, 95% confidence interval (CI) 0.19-0.75, $p<0.01$) and a higher likelihood of reversing pre-existing MetS (OR 2.08 CI 95% 1.11-3.91, $p=0.02$) compared with participants in the low MEDLIFE adherence group. Each additional one-point increment in the MEDLIFE index was associated with a 24% lower risk of MetS development (OR 0.76, 95% CI 0.64-0.90, $p<0.01$) and 21% higher likelihood of reversing pre-existing MetS (OR 1.21 CI 95% 1.04-1.41, $p=0.01$).

Conclusions

Our results showed that greater adherence to a Mediterranean lifestyle reduced the risk of subsequent MetS development and increased the likelihood of reversing pre-existing MetS among patients with CHD at baseline.

Keywords: Mediterranean lifestyle, metabolic syndrome, coronary heart disease, secondary prevention

INTRODUCTION

Cardiometabolic diseases are the leading cause of death globally, despite continually improving evidence-based prevention and management strategies[1]. The Metabolic Syndrome (MetS) represents a common clinical condition associated with higher risk of cardiovascular disease[2-5], type 2 diabetes (T2DM)[6, 7], and non-alcoholic fatty liver disease[8, 9].

A healthy lifestyle has become a critical tool in the management of cardiometabolic disease, including for prevention/mitigation of MetS, T2DM, and cardiovascular disease[10]. We have recently demonstrated robust evidence that the Mediterranean diet can play a key role in secondary prevention among coronary heart disease (CHD) patients[11]. Additionally, the Mediterranean lifestyle encompasses not only healthy nutrition, but also other traits of the lifestyle such as adequate rest ("nap"), regular physical activity, conviviality and social interaction with friends[12]. Accordingly, the Mediterranean lifestyle (MEDLIFE) index was developed and validated in a Spanish cohort, and measures the synergistic health effects of all components of the Mediterranean lifestyle[13, 14]. Previous studies using this index have shown beneficial effects associated with higher scores for the primary prevention of cardiovascular and all-cause mortality[15, 16], depression[17], frailty[18], and chronic pain[19] in both Mediterranean and non-Mediterranean populations[20]. However, no previous evidence has assessed the MEDLIFE index for secondary prevention, specifically among patients with CHD and a high prevalence of MetS. Therefore, our aim was to explore whether the adherence to a Mediterranean lifestyle among CHD patients was associated with de novo development or reversal of pre-existing MetS after 5 years of follow-up among CHD patients in the

Coronary Diet Intervention with Olive Oil and Cardiovascular Prevention (CORDIOPREV) study.

MATERIAL AND METHODS

Study population

The CORDIOPREV study is a prospective, randomized, single-bind, controlled trial conducted among 1,002 patients with established CHD who had their last coronary event more than 6 months before their enrollment[21]. Participants were randomized to one of two dietary regimens: a Mediterranean diet or a low-fat diet. The primary objective was to evaluate the efficacy of the different diets for secondary prevention of clinical events and mortality in the long term. The study protocol was approved by the Ethics Committee for Clinical Investigations of the Reina Sofia University Hospital and is a registered Clinical Trial (NCT00924937).

For the present analysis, we excluded participants without adequate data to calculate the complete MEDLIFE index e.g. total energy intake was outside the prespecified range (< 500 kcal/day or >3500 kcal/day for women and <800 kcal/day or >4000 kcal/day for men[22]) or the dietary visits and questionnaires were not completed. Thus, the final sample size for the present analysis included 851 participants from the CORDIOPREV study using the data of the first 5 years of follow-up of the study **(Supplementary Figure 1).**

Dietary and lifestyle data collection

A 137-item semi-quantitative food-frequency questionnaire (FFQ) previously validated in the Spanish population, was collected at baseline and yearly during follow-up for the

information on habitual dietary intake[23, 24]. For each item, typical portion size was included, and consumption frequencies were registered in nine categories ranging from "never or hardly ever" to "≥ six times/day", over the previous 12 months. The consumption of seasonal foods was adjusted by the proportional intake over 1 year. The Spanish Food Composition Tables were used to calculate energy and nutrient intake[25, 26].

The validated Spanish version of the Minnesota Leisure Time Physical Activity Questionnaire was used to assess physical activity and leisure-time activity[27]. To calculate the physical activity we considered as light-intensity activities those with less than 3 of metabolic equivalent of task (MET) (gardening, walking slowly and yoga), moderate-intensity activities those with less than 6 METs (walking, bicycling slowly, swimming, dancing, hiking, sailing, weight lifting and spinning) and vigorous-intensity activities those with 6 or more METs (jogging, running, bicycling, tennis, football, basketball, aerobic, skiing, karate) based on a compendium of physical activities derived from the American College of Sports Medicine and the Physical Activity Guidelines for Americans (US Department of Health and Human Services)[28, 29].

The Mediterranean lifestyle (MEDLIFE) index

The MEDLIFE index is a validated score that assesses Mediterranean lifestyle globally based on the principles of the Mediterranean Diet Pyramid proposed by the Spanish Mediterranean Diet Foundation[12]. The original MEDLIFE was adapted with nine minor modifications to best fit with questionnaires included in the CORDIOPREV study, the available data and existing evidence (**Supplementary Table 1**). Thus, for this study, the MEDLIFE index was comprised of 27 items, divided into 3 blocks describing 1) food consumption (15 items); 2) other dietary habits such as consumption of coffee, sugar-sweetened beverages or limiting sodium intake (6 items); and 3) physical activity, rest,

social habits and conviviality (6 items)[13]. Each item was weighted equally with 0 or 1 point, if met the conditions. The final MEDLIFE index ranged from 0 (worst Mediterranean lifestyle) to 27 (best Mediterranean lifestyle). The MEDLIFE index was assessed at baseline, 3 years and 5 years of follow-up and a cumulative average was calculated of these three points[30].

to categorize the cohort into tertiles of adherence to MEDLIFE during the 5 years of follow-up: low-adherence (<12 points), moderate-adherence (12-13 points) and high-adherence (>13 points).

Metabolic Syndrome (MetS)

Biological samples were collected at baseline and during annual visits, including venous blood samples to measure glucose, high density lipoprotein cholesterol (HDL-C) and triglycerides (TGs) using an Architect c-16000 analyzer (Abbott®, Chicago, Illinois, USA) by spectrophotometric techniques. Blood pressure (BP) and waist circumference (WC) were measured using standardized procedures. The prevalence of MetS was determined at baseline and 5 years of follow-up using the joint diagnostic criteria for MetS[31]. MetS was prevalent at wither timepoint based on the presence of 3 or more metabolic component features: abdominal obesity as defined by WC (102 cm in men, 88 cm in women); elevated TGs (≥150 mg/dL (1.7 mmol/L)), low HDL-C (≤40 mg/dL (1.0 mmol/L) in men; ≤50 mg/dL (1.3 mmol/L) in women); elevated BP (Systolic ≥130 and/or diastolic ≥85 mm Hg); and elevated fasting glucose (≥100 mg/dL)[31].

Statistical analysis

To determine the differences in baseline characteristics according to adherence to Mediterranean lifestyle using the MEDLIFE index, we performed analysis of variance (ANOVA) or Kruskal Wallis test for non-normally distributed data. Furthermore, the Chi-

square test was used to compare frequencies between qualitative variables. Variables with quantitative values were expressed as means ± standard deviation (SD) and those characterized qualitatively as percentages.

Multivariable logistic regression was performed to examine the association between adherence to MEDLIFE index and MetS at 5 years of follow-up, as well as each MetS component (i.e., abdominal obesity, hyperglycaemia, hypertension, hypertriglyceridemia, and low HDL-C). Moreover, the evolution of MetS after 5 years of follow-up was evaluated with multivariable logistic regression models assessing reversal of pre-existing MetS and de novo development of MetS. Odds ratios (OR) were reported with 95% confidence intervals (CI) and p-values for each category of adherence to MEDLIFE index, as well as for each additional one-point increment of MEDLIFE Index. Potential confounding factors were sex, age, interventional dietary group of CORDIOPREV study, total energy intake, body mass index (BMI), smoking status, alcohol intake, lipid-lowering treatment (such as statins, fibrates or omega-3), antihypertensive drug therapy (such as angiotensin-converting enzyme inhibitor, angiotensin II receptor blockers, beta blocker, diuretics or calcium antagonist), antidiabetic treatment (such as oral antidiabetic treatment and insulin), education level, occupational status and income level.

Missing data enough to carry out an imputation (at least 70% of data completed during 5 years of study) were estimated using the MICE package in R as described by van Buuren and Groothuis-Oudshoorn[32].

The statistical analyses were carried out using SPSS version 24.0 for Windows (SPSS Inc, Chicago, IL) and R programs. All p-values were two-sided and considered statistically significant at $p < 0.05$.

RESULTS

Study population and classification

The CORDIOPREV study included 1,002 participants; their characteristics and details have been reported previously[21]. For the present study, 851 participants had sufficient data to calculate the MEDLIFE at baseline, 3 years and 5 years, and were included. No significant differences were found between the total population of the CORDIOPREV study (=1002) and the participants included in the present study (n=851) at baseline (**Supplementary Table 2**).

At study baseline, no significant differences in the MEDLIFE index were found between the two interventional dietary groups of the CORDIOPREV study (low-fat diet (n=406 participants) 11.1 points (95% CI, 10.9-11.3) *vs* Mediterranean diet (n=445 participants) 11.3 points (95% CI,11.0-11.5); *p*=0.28) (**Supplementary Table 3**).

Baseline characteristics for each tertile of MEDLIFE adherence: low MEDLIFE adherence (MEDLIFE index <7-12 points (n=267, 31.4%)), moderate MEDLIFE adherence (MEDLIFE index 12-13 points (n=253, 29.7%)) and high MEDLIFE adherence (MEDLIFE index >13-19 points (n=331, 38.9%)) are summarized in **Table 1**.

Prevalence of Metabolic Syndrome

At baseline, there were 363 participants without MetS and 488 participants with MetS (**Figure 1**). According to the degree of adherence to the MEDLIFE index, significant differences were found in the prevalence of MetS at 5 years of follow-up. Specifically, among those without MetS at baseline, 248 remained without MetS (45.6% in the high MEDLIFE adherence group vs 24.6% in the low MEDLIFE adherence p<0.05), while 115 developed MetS at 5 years (35.7% in the low MEDLIFE adherence group vs 31.3% in the high MEDLIFE adherence p<0.05) (*p*=0.02) (**Figure 1A**). Among 488 participants

with MetS at baseline in unadjusted analyses, although a clear trend was observed between MEDLIFE and MetS reversal, this was not significant (p=0.18) **(Figure 1B)**. Finally, according to the interventional dietary group of the CORDIOPREV study, the participants allocated to the Mediterranean diet showed similar results: those without MetS at baseline with high adherence to the MEDLIFE index remained without MetS (73.8% participants remained without MetS *vs* 26.2% participants developed MetS) compare to moderate adherence (58.1% *vs* 41.9% participants) and low adherence group (47.5% *vs* 52.5% participants) (p<0.01), while participants allocated to the low-fat diet did not show significant differences between MEDLIFE index groups for develop MetS. For reversal MetS both interventional dietary group of the CORDIOPREV study did not show significant differences between MEDLIFE index groups **(Supplementary Figure 2)**.

Metabolic syndrome prevalence, according to MEDLIFE index classification

Participants in the high MEDLIFE adherence group showed a lower risk for developing MetS at 5 years compared with those in the lowest adherence to the MEDLIFE (OR 0.37, 95% CI 0.19-0.75, p<0.01), while participants in the moderate MEDLIFE adherence group had a non-significantly lower risk (OR 0.71, 95% CI 0.37-1.40, p=0.33). In addition, the participants in the moderate MEDLIFE adherence group and in the high MEDLIFE adherence group had significantly higher likelihoods of MetS reversal compared with those in the low MEDLIFE adherence group (OR 1.96 CI 95% 1.04-3.69, p=0.04, and 2.08 CI 95% 1.11-3.91, p=0.02, respectively) **(Table 2)**.

The MEDLIFE index score and metabolic syndrome

For each additional one-point increment of the MEDLIFE index, there was a lower risk of MetS at 5 years. Furthermore, for each additional one-point increment of MEDLIFE

index, participants without MetS were 24% less likely to develop MetS (OR 0.76, 95% CI 0.64-0.90, $p<0.01$), while those with MetS were 21% more likely to reverse it (OR 1.21 CI 95% 1.04-1.41, p 0.01).

The MEDLIFE index and metabolic syndrome components

Participants in the high adherence group of MEDLIFE index had significantly lower likelihood of hypertriglyceridaemia and abdominal obesity at 5 years compared with those in the low adherence group **(Table 2)**. Indeed, higher MEDLIFE scores were associated with lower TGs levels (β -6.1, CI 95% -9.3- -2.9, $p<0.01$), higher HDL-C levels (β 0.43, CI 95% 0.01-0.9, $p<0.05$) and lower WC (β -0.8, CI 95% -1.1- -0.5, $p<0.01$). Furthermore, for one-point increments in the MEDLIFE index, there was a lower risk of hypertriglyceridemia (OR 0.74 CI 95% 0.66-0.83, $p<0.01$) and abdominal obesity (OR 0.72 CI 95% 0.63-0.82, $p<0.01$) (**Figure 2**).

The MEDLIFE blocks on metabolic syndrome

When we analysed separately the three blocks of the MEDLIFE index, we observed that block 1 (Mediterranean food consumption) and block 2 (Mediterranean dietary habits) were related to a lower risk of MetS at 5 years (OR 0.77, CI 95% 0.66-0.90, $p<0.01$ and OR 0.79, CI 95% 0.63-0.99, $p=0.04$ respectively) **(Figure 3).** However, this association was not observed for part 3 (physical activity, rest, social habits and conviviality).

DISCUSSION

Our findings showed that greater adherence to a Mediterranean lifestyle among CHD patients was associated with a lower risk of MetS, after 5 years of follow-up. These results provide additional evidence supporting that a healthy Mediterranean lifestyle, measured

by the MEDLIFE index, is related to an improvement of cardiometabolic health in a high-risk CHD population for secondary prevention.

MetS represents a common predisposing factor for cardiovascular disease, thus, as expected, there was a high prevalence of MetS among participants from the CORDIOPREV study. Similar results have been reported in other cohorts with cardiovascular disease[33, 34]. Therefore, our study highlights the importance of adherence to a healthy lifestyle to manage high-risk populations and the need of future community programs that encourage adherence to lifestyle measures for mitigating the increased cardiometabolic burden[35].

The MEDLIFE index measures the Mediterranean lifestyle globally: food consumption, other dietary habits, social habits, physical activity, rest and conviviality. While robust evidence supports the cardiometabolic health benefits of the Mediterranean diet[36-38], less information is available for the potential synergistic effects of a globally healthy Mediterranean lifestyle. Other individual components of the MEDLIFE index such as physical activity[39, 40], sedentary behaviour[41], sleep duration[42-44], naps[45] and limited salt intake[46] have been demonstrated to have beneficial effects on cardiometabolic health. In this study, our results showed that higher MEDLIFE index scores were linked to a lower MetS risk.

To the best of our knowledge, this is the first evidence showing the benefits of a healthy Mediterranean lifestyle using the MEDLIFE index in a large CHD patient cohort with a long follow-up. Previously, higher MEDLIFE index scores have been associated with various health benefits in a general population from Spain[15], a shift-working firefighters from a non-Mediterranean country[20] and in the large SUN cohort[16], comprising of university graduates.

Previously, other indexes or scores were used to assess the effect of a healthy lifestyle in cardiometabolic health, including biomarkers such as HDL-C, smoking habit or anthropometrics measures such as BMI[47-49]. Thus, our work demonstrates that assessment of the Mediterranean lifestyle, with the MEDLIFE index, a non-complex score, without anthropometrics or biological measures, could support recommendations for improved cardiometabolic health in CHD participants.

The Mediterranean diet has several health benefits such as cardiovascular diseases[37, 50, 51], metabolic disorders[52], cancer[53] or neurodegenerative disease[54]. Nutrients components representative of the Mediterranean diet such as olive oil, as the main source of fats, and a low-to-moderate red wine are rich in polyphenols, which have been linked to a reduction in inflammatory and oxidative stress markers[51, 55]. Diet is only one aspect of the overall Mediterranean lifestyle and synergistic effects have been demonstrated with physical activity[56, 57], sleep or social life[58]. Therefore, it could be more beneficial to recommend a Mediterranean lifestyle for the prevention of cardiovascular, metabolic and neurodegenerative diseases.

Recently, our group demonstrated the key role of the Mediterranean diet to prevent major cardiovascular events in secondary prevention compared with a low-fat diet, based on the results from the CORDIOPREV study[11]. These results highlighted the key role of the Mediterranean diet, as part of the Mediterranean lifestyle, in accordance with the results of the present study, where participants in the high adherence group of the MEDLIFE index had a better metabolic status. Furthermore, among the participants allocated to the Mediterranean diet, adherence to the MEDLIFE index significantly affected MetS development, whereas this link was not observed in participants allocated to the low-fat diet.

Finally, block 1 of the MEDLIFE index (Mediterranean food consumption) and block 2 (Mediterranean dietary habits) were significantly related to MetS prevalence at 5 years, whereas block 3 (including physical activity, rest, social habit, and conviviality) did not show any significant association. In contrast, previous observational studies using the MEDLIFE index showed that block 3 was associated with MetS, cardiovascular risk and mortality, while blocks 1 and 2 were not[15, 59]. These results could be due to the fact that the CORDIOPREV study is a dietary interventional trial including only dietary advice and not physical activity, rest, or social habit recommendations. Further clinical trials with educational programs on implementing Mediterranean lifestyle recommendations that include diet, physical activity, rest, and social habits, such as the E-DUCASS study[60] and the PREDIMED-plus study[57] could elucidate whether these interventions are effective for a better cardiometabolic status in CHD patients.

This study has some limitations. Firstly, some information was derived from self-reported questionnaires with risk of biases, despite the fact that all questionnaires have been previously validated. Secondly, residual confounding cannot be eliminated, despite the use of multivariable adjustments. In the CORDIOPREV study, CHD patients were randomized either to Mediterranean diet or a low-fat diet. Adherence to the MELIFE index was significantly differ between participants randomized to a Mediterranean diet and those following a low-fat diet, thus representing a confounding factor for the statistical analysis. We added the interventional diet group of the CORDIOPREV study as a covariate for the statistical analyses to eliminate this limitation. Some modifications were performed from the original MEDLIFE index to best fit with questionnaires included in the CORDIOPREV study, however these were based on previous evidence. Thus, for example, water consumption was substitute for coffee consumption based on the benefits demonstrated for health[61-63] or cut-offs for item of salt intake limit[64].

The present study also has strengths. Firstly, we performed a close follow-up of the participants from the CORDIOPREV study, determining the MEDLIFE index in three different times (at baseline, 3 years and 5 years) that allowed us to assess the adherence to the Mediterranean lifestyle during the length of the study. In addition, we assessed MetS development or reversal during the follow up of these CHD patients. Finally, the MEDLIFE index is a non-complex score to assess the adherence to a healthy lifestyle with benefits demonstrated in previous different populations.

In conclusion, we demonstrated that a greater adherence to a Mediterranean lifestyle in a high-risk population with established CHD was associated with a better metabolic status as defined by a lower risk of MetS development and a higher likelihood of MetS reversal. Therefore, a Mediterranean lifestyle should be recommended in CHD patients to prevent/treat MetS.

Declaration of interest

The authors have nothing to declare

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FIGURE LEGENDS

Figure 1. Metabolic Syndrome (MetS) prevalence during the 5 years of follow-up. A. Development of MetS among participants according to adherence to the MEDLIFE index. B. Reversal of MetS according to MEDLIFE index adherence.

Figure 2. Odds ratios (OR) and 95% confidence intervals for one-point increments in the Mediterranean lifestyle (MEDLIFE) index and the risk for metabolic syndrome and its five components after 5 years of follow-up.

Figure 3. Odds ratios (OR) and 95% confidence intervals for one-point increments in the Mediterranean lifestyle (MEDLIFE) index and its separated blocks 1, 2 and 3 on the risk of metabolic syndrome at 5 years of follow-up.

Table 1. Baseline characteristics of the Mediterranean lifestyle (MEDLIFE) index adherence groups based on cumulative average of MEDLIFE index at baseline, 3 years and 5 years from the CORDIOPREV study.

	Low adherence MEDLIFE (<12 points)	Moderate adherence MEDLIFE (12-13 points)	High adherence MEDLIFE (>13 points)	*p*
Number of participants	267	253	331	
MEDLIFE score at baseline (range 0-27)	9.7 ± 1.8	11.1 ± 1.8	12.6 ± 1.9	< 0.01
Gender, %				
- **Male**	82.4	82.6	83.4	0.94
- **Female**	17.6	17.4	16.6	
Age (years)	60 ± 8	59 ± 9	59 ± 9	0.23
Diet, %				
- **Low-fat**	67.8	49	30.5	<0.01
- **Mediterranean diet**	32.2	51	69.5	
Smoking status, %				
- **Never**	26.2	28.5	27.5	0.03
- **Former**	60.7	61.7	67.1	
- **Current**	13.1	9.9	5.4	
Alcohol Intake, %				
- **Non-drinkers**	17.2	15.8	18.4	0.04
- **<8 g/day**	34.5	39.1	43.8	
- **8-16 g/day**	17.6	20.6	19	
- **>16 g/day**	30.7	24.5	18.7	
Education Level, %				
- **None**	17.6	16.6	14.2	<0.01
- **Primary education**	58.8	61.7	47.4	
- **Secondary education**	18	17.8	24.2	
- **Higher education**	5.6	4	14.2	
Occupation status, %				
- **Unemployed**	16.5	12.6	8.2	<0.01
- **Retired**	64.4	56.1	57.1	
- **Worker**	16.1	26.9	30.5	
- **Housewife and others**	3	4.4	4.2	
Income Level, %				
- **<900 euros/month**	38.6	25.7	26.6	<0.01
- **900-1800 euros/month**	46.4	60.5	48.6	
- **>1800 euros/month**	15	13.8	24.8	
BMI, kg/m²	31.7 ± 4.6	31 ± 4.6	30.8 ± 4.2	0.03
Energy intake, kcal/day	2274 ± 531	2266 ± 480	2220 ± 505	0.37
Lipid-lowering treatments, %				
- **Statins**	89.9	81.8	86.4	0.03
- **Fibrates**	0.4	2.4	2.4	0.12
- **Others**[a]	4.1	5.1	5.1	0.81
Antihypertensive treatment, %				
- **ACEI/AIIRA**	83.9	81.8	84	0.75

- **Beta-blocker**	78.3	80.2	83.1	0.33
- **Diuretic**	49.4	53.8	53.8	0.50
- **Calcium antagonist**	33	29.2	24.5	0.07
Antidiabetic treatment, %				
- **Oral**	35.2	37.9	35	0.73
- **Insulin**	8.6	9.9	11.5	0.51
Metabolic Syndrome, %	61.8	55.7	55	0.20

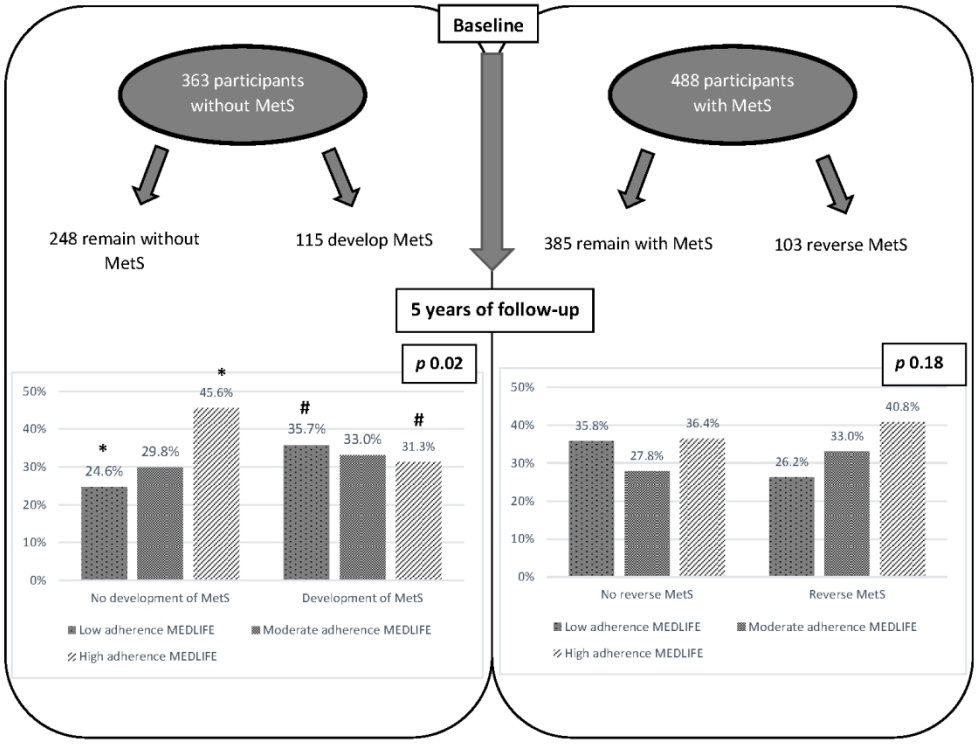
AIIRA, angiotensin II receptor blockers; ACEI, angiotensin-converting enzyme inhibitor;

BMI, body mass index

Table 2. Prevalence of the metabolic syndrome (MetS) and its components during the 5 years of follow-up, according to the Mediterranean lifestyle (MEDLIFE) index groups.

Odds ratio (95% CI)	Low adherence MEDLIFE	Moderate adherence MEDLIFE	*p*	High adherence MEDLIFE	*p*
MetS Development	Reference	0.71 (0.37-1.40)	0.33	0.37 (0.19-0.75)	<0.01
MetS Reversal	Reference	1.96 (1.04-3.69)	0.04	2.08 (1.11-3.91)	0.02
MetS Components at 5 years of the CORDIOPREV study	Reference	0.60 (0.39-0.91)	0.02	0.48 (0.31-0.73)	<0.01
- **Hypertension**		0.88 (0.59-1.31)	0.52	0.78 (0.52-1.17)	0.22
- **Hypertriglyceridaemia**		0.51 (0.34-0.78)	<0.01	0.38 (0.25-0.59)	<0.01
- **Hyperglycemia**		1.03 (0.68-1.57)	0.88	0.87 (0.58-1.33)	0.53
- **Low HDL cholesterol**		0.82 (0.56-1.20)	0.30	0.76 (0.52-1.12)	0.16
- **Abdominal Obesity**		0.55 (0.32-0.94)	0.03	0.38 (0.22-0.64)	<0.01

Figure 1. Metabolic Syndrome (MetS) prevalence during the 5 years of follow-up. A. Development of MetS among participants according to adherence to the MEDLIFE index. B. Reversal of MetS according to MEDLIFE index adherence.

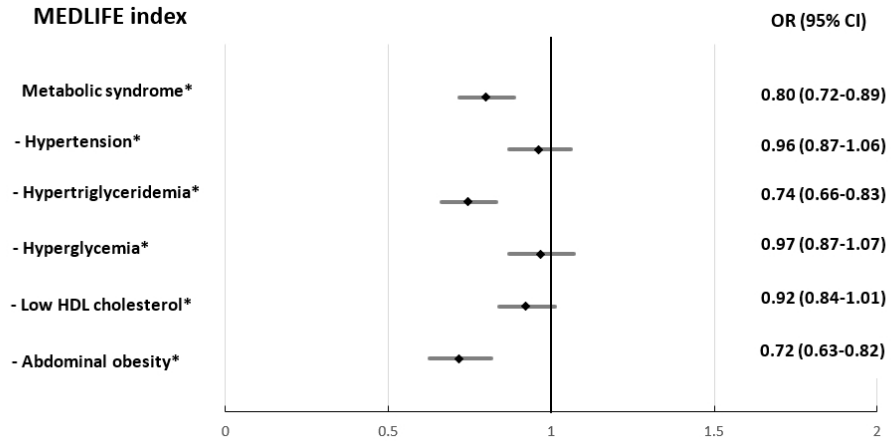


* # Between these groups significant differences ($p<0.05$) were found.

Figure 1. Metabolic Syndrome (MetS) prevalence during the 5 years of follow-up. A. Development of MetS among participants according to adherence to the MEDLIFE index. B. Reversal of MetS according to MEDLIFE index adherence.

207x210mm (200 x 200 DPI)

Figure 2. Odds ratios (OR) and 95% confidence intervals for one-point increments in the Mediterranean lifestyle (MEDLIFE) index and the risk for metabolic syndrome and its five components after 5 years of follow-up.

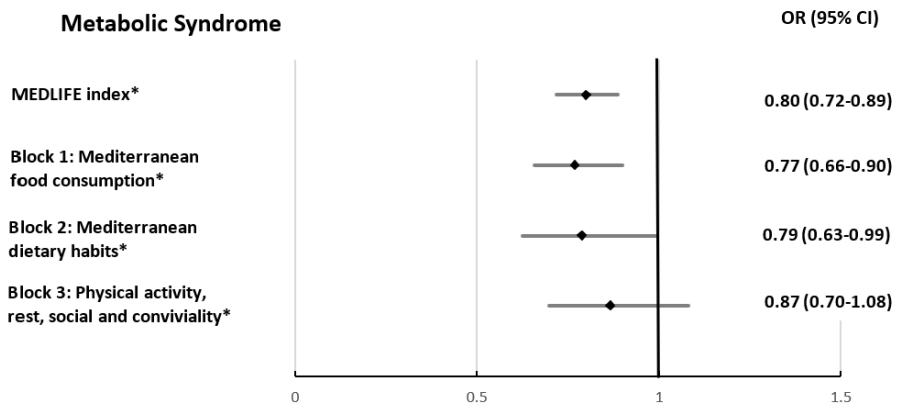


* Model was adjusted for sex, age, diet, total energy intake, BMI, smoking status, alcohol intake, lipid-lowering treatment, antihypertensive treatment, antidiabetic treatment, education level, occupation status and income level.

Figure 2. Odds ratios (OR) and 95% confidence intervals for one-point increments in the Mediterranean lifestyle (MEDLIFE) index and the risk for metabolic syndrome and its five components after 5 years of follow-up.

169x157mm (151 x 151 DPI)

Figure 3. Odds ratios (OR) and 95% confidence intervals for one-point increments in the Mediterranean lifestyle (MEDLIFE) index and its separated blocks 1, 2 and 3 on the risk of metabolic syndrome at 5 years of follow-up.

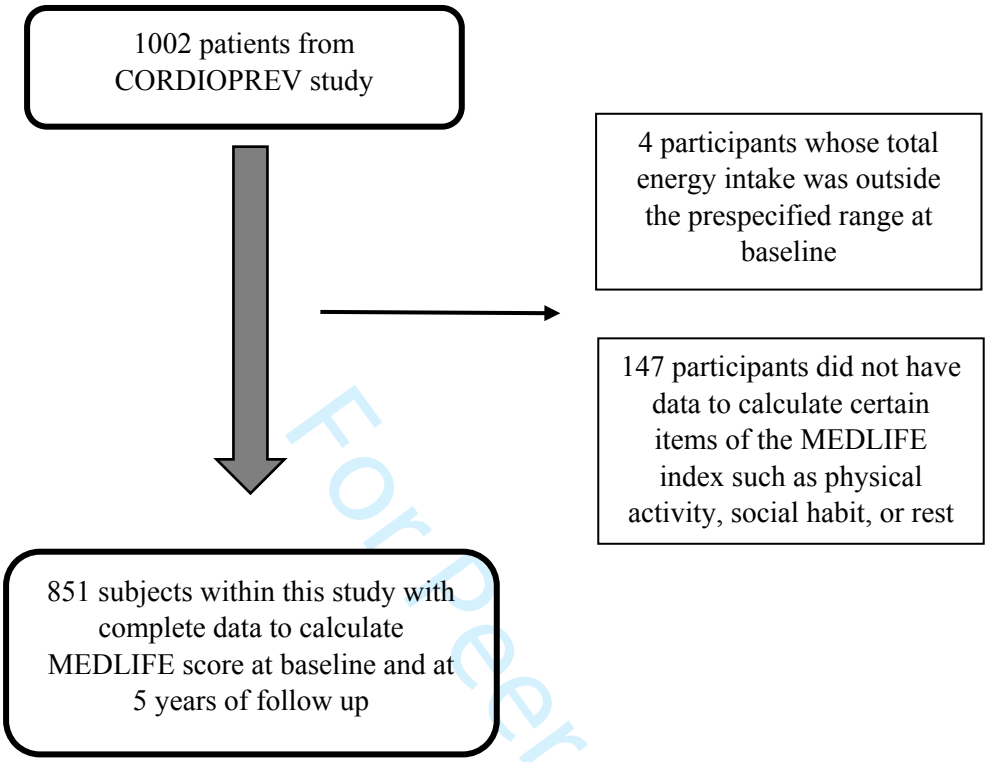


*Model was adjusted for sex, age, diet, total energy intake, BMI, smoking status, alcohol intake, lipid-lowering treatment, antihypertensive treatment, antidiabetic treatment, education level, occupation status, income level and the others blocks of MEDLIFE index.

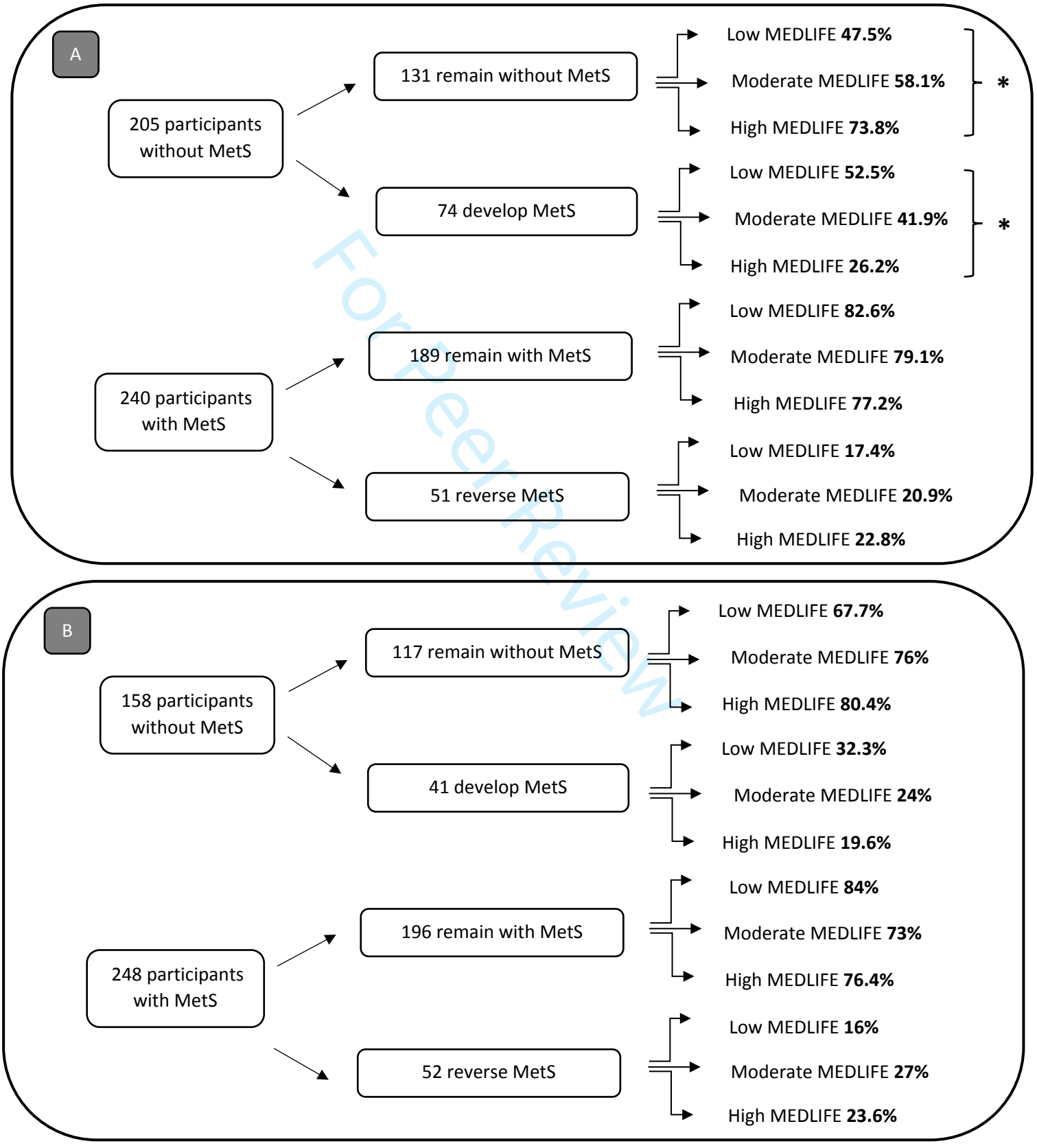
Figure 3. Odds ratios (OR) and 95% confidence intervals for one-point increments in the Mediterranean lifestyle (MEDLIFE) index and its separated blocks 1, 2 and 3 on the risk of metabolic syndrome at 5 years of follow-up.

164x167mm (168 x 168 DPI)

Supplementary Figure 1. Study flowgraph.



Supplementary Figure 2. Metabolic Syndrome (MetS) prevalence during 5 years of follow-up by the interventional dietary group of the CORDIOPREV study. A. Mediterranean diet. B. Low-fat diet. * Significant differences $p<0.05$



Supplementary Table 1. Description of the Mediterranean lifestyle (MEDLIFE) index in the CORDIOPREV study.

MEDLIFE CORDIOPREV		
	Description	Criteria for one point *
Block 1: Mediterranean food consumption		
1. Sweets	Biscuits and whole grain biscuits (4-6 units), chocolate biscuits (4 units, 50 g), bakery pastries (1 unit, 50g), donuts (1 unit), muffins (1-2 units), Spanish sweet fritters (100 g), chocolates (1 serving=30g), turron (1 serving 40 g), shortbreads (90g)	≤2 serving/week
2. Red Meat	Beef, pork, lamb (1 serving 100-150 g)	≤2 serving/week
3. Processed Meat	Cured Ham and Ham (1 serving=1slice or 30 g), sausage, soft spicy sausage, blood sausage, mortadella, bacon (1 serving=50 g), hamburger (1 serving=1unit, 50g), liver or similar (1serving=100-150g), pâte (1 serving=25 g)	≤1 serving/week
4. Eggs	Eggs (1 egg)	2-4 serving/week
5. Legumes	Lentils, beans, peas, chickpeas (1 serving=1plate or 150 g)	≥2 servings/week
6. White meat	Poultry, turkey and rabbit (1 serving=100-150g)	2 serving/week (≥1-<3 serving/week)
7. Fish/seafood	White/oily fish (1 serving=100-150g), canned fish (1 serving=1can or 50g), seafood (1serving=200g), smoked fish (60g)	≥2 serving/week
8. Potatoes	Roast/boiled potatoes, French fries (1 serving=150 g)	≤3serving/week
9. Low-fat dairy products	Skimmed dairy milk (1serving=1 cup or 200 ml), soft cheese (1 serving=50g), non-fat yogurt (1 serving=125g)	2serving/day (≥1-<3 serving/day)
10. Nuts and olives	Walnuts, almonds, hazelnuts, (1serving=1handful or 30g) olives (1serving= 10 units)	1-2 serving/day
11. Herbs, spices and garnish	Onion (50g), garlic (one clove), herbs (parsley, oregano)	≥1 serving/day
12. Fruit	All fruit (medium piece 150-200g, except for strawberries 6 units, watermelon and melon 200-250g and kiwi 100g and bunch grapes)	3-6 serving/day
13. Vegetables	All vegetables 1 serving=200g except for carrot (100g), pumpkin (100g), lettuce (100g), tomatoes (150g) and pepper (150g)	≥2 serving/day
14. Olive oil	Olive oil, virgin olive oil (1 serving= 1table spoon)	≥3 serving day
15. Cereals	White and whole grain bread (1 serving=75 gr), cereals (1 serving=30g), rice and whole rice (60g) and pasta and whole pasta (60g)	3-6 servings/day
Block 2: Mediterranean dietary habits		
16. Coffee or infusions	Coffee or infusions (1 serving=1 cup)	2-4 servings/day or ≥ 3 servings/week
17. Wine	White/red wine (1serving/cup)	Women ≤0.5 serving/d Men ≤1 serving/d
18. Limit sodium intake	Salt intake <5g/day (approximately sodium intake <2g/day)	Yes
19. Preference for whole grain products	Ratio consumption of whole cereals/consumption of refine cereals >1	Yes
20. Snacks	Potatoes chips, popcorn (1serving=1 bar or 50 g)	≤2servings/week
21. Limit sugar in beverages (including sugar-sweetened beverages)	No added sugar in beverages AND ≤1 sugar-sweetened beverages/week	Yes
Block 3: Physical activity, rest, social habit and conviviality		
22. Physical activity **	≥150 min/week moderate physical activity or ≥75 min/week vigorous physical activity	Yes
23. Siesta/nap	During weekends (less of 30 minutes)	Yes
24. Hours of sleep	During weekdays	6-8 hours/week
25. Watching TV	During weekdays	<1 hour/day

26. Socializing with friends	During weekends	≥2hours/weekends
27. Collective sports	During week (Football, basketball, dancing, aerobic, hiking, karate, yoga, spinning)	≥30min/week

* 0 points if these criteria are not met

** To calculate the physical activity we considered such as light-intensity activity activities with less than 3 of metabolic equivalent of task (MET) (gardening, walking slowly and yoga), moderate-intensity activity 3 to less than 6 METs (walking, bicycling slowly, swimming, dancing, hiking, sailing, weight lifting and spinning) and vigorous-intensity activity 6 or more METs (jogging, running, bicycling, tennis, football, basketball, aerobic, skiing, karate) based on compendium of physical activities from American College of Sports Medicine and Physical Activity Guidelines for Americans from Department of Health and Human Services.

Supplementary Table 2. Differences between total population of the CORDIOPREV study (n=1,002 participants) and participants included in the present analysis (n=851 participants).

	Total population CORDIOPREV study (n=1,002)	Participants included in the current analysis (n=851)	*p*
Gender, %			
- **Male**	82.5	82.8	0.86
- **Female**	17.5	17.2	
Age (years)	60 ± 9	59 ± 9	0.49
Diet, %			
- **Low-fat**	49.9	47.7	0.35
- **Mediterranean diet**	50.1	52.3	
Smoking status, %			
- **Never**	26.4	27.3	0.79
- **Former**	63.6	63.5	
- **Current**	10	9.2	
Alcohol Intake, %			
- **Non-drinkers**	17.5	17.3	0.99
- **<8 g/day**	39.5	39.5	
- **8-16 g/day**	18.8	19	
- **>16 g/day**	24.2	24.2	
Education Level, %			
- **None**	15.5	16	0.84
- **Primary education**	57.2	55.2	
- **Secondary education**	19.5	20.3	
- **Higher education**	7.8	8.5	
Occupation status, %			
- **Unemployed**	11	12.1	0.71
- **Retired**	61.6	59.1	
- **Worker**	23.4	24.9	
- **Housewife and others**	4	3.9	
Income Level, %			
- **<900 euros/month**	28.7	30.1	0.58
- **900-1800 euros/month**	53.9	51.5	
- **>1800 euros/month**	17.4	18.4	
BMI, kg/m^2	31.2 ± 4.5	31.1 ± 4.5	0.92
Energy intake, kcal/day	2247 ± 524	2251 ± 507	0.87
Lipid-lowering treatments, %			
- **Statins**	85.6	86.1	0.76
- **Fibrates**	1.6	1.8	0.78
- **Others**[a]	4.8	4.8	0.98
Antihypertensive treatment, %			
- **ACEI/AIIRA**	83.2	83.3	0.96
- **Beta-blocker**	80.1	80.7	0.75
- **Diuretic**	52.5	52.4	0.97
- **Calcium antagonist**	29.4	28.6	0.68
Antidiabetic treatment, %			
- **Oral**	35.9	36	0.99

-	**Insulin**	11.4	10.1	0.38

Supplementary Table 3. Score of Mediterranean lifestyle (MEDLIFE) index at baseline by the interventional dietary group of the CORDIOPREV study.

	Mediterranean diet (n=445 participants)	Low-fat diet (n=406 participants)	*p*
MEDLIFE index at baseline (0-27 points)	11.3 (95% CI 11.0-11.5)	11.1 (95% CI 10.9-11.3)	0.28

Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	n/a
Abstract	#1b	Provide in the abstract an informative and balanced	3-4

		summary of what was done and what was found	
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	#3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	#4	Present key elements of study design early in the paper	6
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-8
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up.	6
Eligibility criteria	#6b	For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-9
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for	6-9

		exposed and unexposed groups if applicable.	
Bias	#9	Describe any efforts to address potential sources of bias	8-9
Study size	#10	Explain how the study size was arrived at	6
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	6-9
			8-9
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding.	
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	8-9
Statistical methods	#12c	Explain how missing data were addressed	9
Statistical methods	#12d	If applicable, explain how loss to follow-up was addressed	n/a
Statistical methods	#12e	Describe any sensitivity analyses	
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility,	10

		confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable.	
Participants	#13b	Give reasons for non-participation at each stage	6
Participants	#13c	Consider use of a flow diagram **(Online Supplementary Data).**	
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for exposed and unexposed groups if applicable.	30-31
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	
Descriptive data	#14c	Summarise follow-up time (eg, average and total amount)	
6			
Outcome data	#15	Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable.	
10-12			
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95%	10-12

		confidence interval). Make clear which confounders were adjusted for and why they were included	
Main results	#16b	Report category boundaries when continuous variables were categorized	10-12
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	10-12
Other analyses	#17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10-12
Discussion			
Key results	#18	Summarise key results with reference to study objectives	12-13
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	15
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	12-16
Generalisability	#21	Discuss the generalisability (external validity) of the study results	12-16
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study	16

on which the present article is based