Calidad de la dieta, adherencia dietética a largo plazo e incidencia de diabetes tipo 2 en pacientes coronarios: estudio CORDIOPREV

Diet quality, long-term dietary adherence and incidence of type 2 diabetes in coronary patients: the CORDIOPREV study

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<u>TÍTULO DE LA TESIS</u>: CALIDAD DE LA DIETA, ADHERENCIA ALIMENTARIA A LARGO PLAZO E INCIDENCIA DE DIABETES TIPO 2 EN PACIENTES CORONARIOS: ESTUDIO CORDIOPREV

<u>DOCTORANDA</u>: GRACIA MARÍA QUINTANA NAVARRO

INFORME RAZONADO DEL/DE LOS DIRECTOR/ES DE LA TESIS

(se hará mención a la evolución y desarrollo de la tesis, así como a trabajos y publicaciones derivados de la misma).

D. JAVIER DELGADO LISTA, PROFESOR TITULAR DEL DEPARTAMENTO DE MEDICINA DE LA UNIVERSIDAD DE CÓRDOBA Y D. JOSÉ LÓPEZ MIRANDA, CATEDRÁTICO DE MEDICINA DE LA UNIVERSIDAD DE CÓRDOBA,

HACEN CONSTAR:

Que el trabajo de tesis realizado por Dª. Gracia María Quintana Navarro, bajo nuestra dirección en la Unidad de Lípidos y Arteriosclerosis del Hospital Reina Sofía/ Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), ha conseguido un nivel científico de suficiente relevancia como para derivar en la publicación de un artículo en una revista internacional situada en Q1 de su categoría:

- Long-term dietary adherence and changes in dietary intake in coronary patients after intervention with a Mediterranean diet or a low-fat diet: the CORDIOPREV randomized trial. **Quintana-Navarro GM**, et al. Eur J Nutr. *2020 Aug;59(5):2099-2110. doi: 10.1007/s00394-019-02059-5. Epub 2019 Jul 24*. Impact Factor: 4.664; Science Edition - NUTRITION & DIETETICS, 16/89 (Q1).

Durante la realización de su programa de Doctorado la doctoranda ha participado en todas y cada una de las fases del protocolo de investigación. Ha sido responsable de coordinar la intervención dietética en el estudio CORDIOPREV, ha realizado el trabajo de campo sobre valoración dietética, estudio antropométrico, educación nutricional y

seguimiento de pacientes, ha desarrollado un método de derivación de nutrientes, alimentos y grupos de alimentos a partir de cuestionarios de frecuencia alimentaria, ha organizado las bases de datos dietéticas y ha realizado el análisis estadístico de los datos. Además, la doctoranda ha participado en varios congresos nacionales e internacionales con comunicaciones orales y tipo poster, dos de ellas premiadas con el Premio mención especial a la comunicación oral presentada en el congreso de la Sociedad Española de Arteriosclerosis (2017) y el Premio a la mejor comunicación en el congreso de la Sociedad Andaluza de Medicina Interna (2017), y ha participado como coautora en 22 trabajos publicados en revistas internacionales con alto índice de impacto.

A nuestro juicio, el trabajo realizado por la doctoranda reúne los méritos suficientes para poder optar al grado de Doctor por la Universidad de Córdoba. Por todo ello, se autoriza la presentación de la tesis doctoral.

Córdoba, 26 de Febrero de 2021

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Dedicado a mi maravillosa familia, y especialmente a mis padres y a Chema,
con todo mi amor y gratitud por su apoyo.

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ABBREVIATIONS

The most used abbreviations throughout the text are outlined below:

ADA	American Diabetes Association
AHA	American Heart Association
ANCOVA	Analysis of covariance
AUC	Area under the curve
BMI	Body mass index
CHD	Coronary heart disease
CI	Confidence interval
CORDIOPREV	Coronary Diet Intervention with Olive oil and cardiovascular Prevention study
CV	Coefficient of variation
CVD	Cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
EVOO	Extra-virgin olive oil
FFQ	Food frequency questionnaire
FPG	Fasting plasma glucose
HbA1c	Glycosylated hemoglobin
HDL	High-density lipoprotein
HOMA-IR	Homeostatic model assessment of insulin resistance
HR	Hazard ratios
ICC	Intra-class correlation coefficients
IDF	International Diabetes Federation
LDL	Low-density lipoprotein
LFDAS	9-point low-fat diet adherence screener

LFDAS-FFQ	LFDAS calculated from dietary data collected in the FFQ
LoA	Limits of agreement
Low-Fat DP	Low-fat dietary pattern identified by PCA
MDS-Trichopoulou	Mediterranean Dietary Score proposed by Trichopoulou et al.
MEDAS	14-point Mediterranean Diet Adherence Screener
MEDAS-FFQ	MEDAS calculated from dietary data collected in the FFQ
Mediterranean DP	Mediterranean dietary pattern identifies by PCA
METs	Metabolic equivalents
MUFA	Monounsaturated fatty acids
NCEP	National Cholesterol Education Program
OGTT	Oral glucose tolerance test
OR	Odd ratio
PCA	Principal components analysis
PCA-dietary patterns	Dietary patterns derived by principal components analysis
PREDIMED	PREvención con DIeta MEDiterránea study
PUFA	Polyunsaturated fatty acids
RCT	Randomized clinical trial
RDs	Registered dietitians
ROC	Receiver operating characteristic curves
RR	Relative risk
SFA	Saturated fatty acids
SSC beverages	Sugar-sweetened carbonated beverages
T2DM	Type 2 diabetes
Western DP	Western dietary pattern identified by PCA
WHO	World Health Organization

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ABSTRACT / RESUMEN

ABSTRACT

Introduction

Diet is a cornerstone in the secondary cardiovascular prevention, and the most efficient tool for preventing type 2 diabetes (T2DM). Dietary pattern analysis is widely used to examine the relationship between diet and the risk of chronic diseases, and two methods are commonly used for that purpose: *a priori*-defined dietary scores (based on diets with proven health benefits, like Mediterranean diet scores) and *a posteriori*-derived dietary patterns (obtained through statistical modelling of dietary intake data, such as principal components analysis, PCA). Several dietary pattern methods have been used to characterize the diet of patients with chronic diseases. However, to date, there is a lack of scientific data that compares them directly, in large and long-term trials, in their ability to detect future T2DM incident cases among coronary patients. We have analyzed three *a priori* and one *a posteriori* methods, and we have investigated whether any of these methods predicts better which patients will have incident T2DM at 5 years.

Hypothesis

Our hypothesis is to investigate whether a diabetes prediction model that includes an *a priori*-defined dietary pattern (dietary score) has similar predictive ability as a prediction model including an *a posteriori*-derived dietary pattern (empirically derived dietary pattern using PCA) after a period of 5 years of dietary intervention.

Objectives

Main objective: To determine if there is a method of dietary pattern analysis (i.e. *a priori*-defined dietary score or *a posteriori*-derived dietary pattern) which predicts with greater reliability the development of T2DM after 5 years of intervention with a Mediterranean diet or a low-fat diet in coronary patients.

Secondary objectives include:

1) To study the association between three *a priori*-defined dietary scores (MEDAS, 14-point Mediterranean Diet Adherence Screener; LFDAS, 9-point low-fat diet adherence screener; MDS-Trichopoulou, Mediterranean Dietary Score proposed by Trichopoulou et al.) assessed at baseline and after 1 year of intervention, and the incidence of T2DM after 5 years of follow-up.

2) To investigate the association between the *a posteriori*-derived dietary patterns using principal component analysis (PCA-dietary patterns) at baseline and after 1 year of intervention, and the incidence of T2DM after 5 years of follow-up.

3) To determine the relationship between these dietary pattern methods and multiple anthropometrical and biochemical parameters related to the development of T2DM.

4) To compare and assess the validity of the selected dietary scores and PCA-dietary patterns in our population.

5) To investigate the changes in dietary habits and address the level of adherence to the dietary intervention in the long-term in our population.

Methods

All analyses were conducted in the 462 patients without a clinical diagnosis of T2DM at baseline visit in the CORDIOPREV study (NTC00924937). Food intake was assessed with a validated food frequency questionnaire (FFQ). As dietary pattern methods we used three *a priori* (MEDAS, LFDAS and MDS-Trichopoulou) and one *a posteriori* (PCA-dietary patterns). To assess associations of dietary pattern methods with T2DM incidence, we used Cox regression, logistic regression or ROC curve analyses. We studied prospective associations of dietary pattern methods with anthropometric and biochemical variables using linear regression analyses. In all studies, we used dietary data of baseline (as raw baseline data information) and 1-year (as information after a stabilization period) visits. To assess the validity of the three dietary scores, we used

the dietary data reported on the FFQ as reference method, and we compared these results with those from the MEDAS, LFDAS and MDS-Trichopoulou. The consistency of PCA-dietary patterns was examined. To perform the study of adherence at long-term, dietary data of the 5-year follow-up of the total CORDIOPREV population (n=1002) were used and changes within and between groups (Mediterranean and low-fat diets) were assessed with paired t test and unpaired t test.

Results

Main results: *Identification of methods predicting T2DM at long-term:* The MEDAS (dietary score assessing Mediterranean diet adherence) at year 1 and the Western DP (PCA-dietary pattern characterized by higher loads of red/processed meats, highly-processed foods, canned fish, refined bread and sweets) at year 1 were the only methods showing significant associations with incident T2DM in our population. We then compared these two methods regarding their ability to predict the incidence of T2DM after a median follow-up of 60 months. The model including the MEDAS at year 1 together with classical clinical variables and lifestyle factors showed acceptable discrimination ability (AUC=0.733; 95% CI=0.665-0.801; p<0.001). The Western DP at year 1 together with the same potential confounders also showed acceptable discrimination ability (AUC=0.715; 95% CI=0.649-0.781; p<0.001). No statistically significant differences were found when compared both models (p=0.521).

When we assessed the impact of including these methods in the usual prediction models based only in clinical and lifestyle factors, the AUC of clinical variables and the model of clinical variables plus lifestyle improved when including the MEDAS at year 1 (p=0.022 and p=0.021, respectively) or the Western DP at year 1 (p=0.031 and p=0.032 respectively).

Secondary results:

1) *Association between a priori-defined dietary scores and risk of T2DM at 5 years:* Patients with the highest adherence to the MEDAS (10-14 points) at year 1

showed a significant 69% lower risk of developing T2DM (HR=0.31, 95% CI=0.16-0.60) compared with low-medium adherents (0-9 points), with one-point increment in the score being associated with a 17% reduction in the risk of T2DM (ExpB=0.83, 95% CI= 0.73-0.94). Neither the MDS-Trichopoulou nor the LFDAS at year 1 were associated with the incidence of T2DM. Baseline dietary scores were not associated with the development of T2DM.

2) *Association between a posteriori-derived dietary patterns and risk of T2DM at 5 years:* Using PCA, two dietary patterns (Western DP and Mediterranean DP) and three dietary patterns (Western DP, Mediterranean DP and Low-fat DP) were identified at baseline and at year 1, respectively. Patients with the highest adherence to the Western DP (third tertile) at year 1 had a 90% greater risk of developing T2DM (HR=1.90; 95% CI=1.05-3.46) than patients with low-medium adherence (first plus second tertiles). In the case of the Mediterranean DP and Low-fat DP at year 1, patients in the third tertile of each pattern had a non-significant reduction in the risk of developing T2DM of 25% (HR=0.75; 95% CI=0.41-1.39) and 35%, (HR=0.65; 95% CI=0.36-1.17), respectively. Baseline PCA-dietary patterns were not associated with the development of T2DM.

3) *Association between dietary pattern methods and variables linked to T2DM risk:* Linear regression analyses revealed that the MEDAS at year 1 was inversely associated to waist circumference, HbA1c, HOMA-IR, glucose, triglycerides, C-reactive protein, leucocytes and neutrophil-lymphocyte ratio (all $p<0.05$) at year 5, while the Western DP at year 1 was positively associated with BMI, waist circumference, glucose, triglycerides, total cholesterol, LDL cholesterol and C-reactive protein at year 5 (all $p<0.05$).

4) *Validation of the dietary pattern methods in patients with coronary heart disease in Spain:* The three dietary scores correlated in the expected direction with dietary data reported on the FFQ. A good correlation and agreement between the administered MEDAS and the MEDAS calculated from FFQ was found at baseline

(*r*=0.53, *p*<0.001; ICC=0.64, 95% CI 0.45-0.75, *p*<0.001), without consistent bias of one method versus the other (Bland-Altman plot mean±SD=0.94±1.82, 95% LoA -2.63 to 4.51). A moderate correlation and good reliability between the administered LFDAS and the LFDAS calculated from FFQ was observed at baseline (*r*=0.44, *p*<0.001; ICC=0.55, 95% CI 0.40 to 0.66, *p*<0.001), without consistent bias of one method versus the other (Bland-Altman plot=0.70±1.55; 95% LoA -2.35 to 3.73). All the analyses were repeated using the dietary information from 5-year visit and similar results were found for both the MEDAS and LFDAS. Moreover, all associations between PCA-dietary patterns and dietary scores were in the expected direction.

5) *Long-term dietary adherence with a Mediterranean or a Low-fat diet in patients with coronary heart disease:* From baseline to 5 years, significant increases were observed in overall dietary adherence (Mediterranean diet group from 8.9 to 11.4; low-fat diet group from 3.9 to 7.1) and in the percentage of patients considered *High Adherence* (Mediterranean diet group from 41 to 89%; low-fat diet group from 4 to 67%). When we evaluated the maintenance of adherence, patients considered *Low* and *Medium Adherence* at 1 year increased their adherence at the 5 years with both diets and patients considered *High Adherence* maintained their adherence with a Mediterranean diet, but decreased their adherence with a low-fat diet.

Conclusions

Main conclusion: The MEDAS (*a priori* analysis) and the PCA (*a posteriori* analysis) are the methods that captured the strongest relationship between the dietary intervention and long-term T2DM incidence (5 years) among all *a priori* and *a posteriori* methods evaluated in this thesis. When they are use after a stabilization period of one year, both methods provide reliable, accurate results, supported by internal validation.

Secondary conclusions:

- Our results also show that, in coronary patients participating in a dietary intervention trial, high adherence to a Mediterranean-type diet, reflected by the MEDAS and achieved after one year of intervention, was associated with an important reduction in the risk for T2DM and with healthier values of anthropometric and biochemical parameters related to T2DM risk.
- In our population, closer adherence to a Western-type dietary pattern after one year of intervention was associated with long-term increased risk of developing T2DM and with detrimental effects on waist circumference, BMI, glucose, lipid profile and inflammatory markers.
- We have validated the MEDAS and the LFDAS in coronary patients (the entire population of the CORDIOPREV study). This demonstrates that they are valid tools for rapidly assessing dietary adherence in coronary patients and that they could be used in clinical practice.
- Our findings show that a comprehensive dietary intervention results in an overall long-term improvement and maintenance of adherence to the Mediterranean and low-fat diets. In our population, the Mediterranean diet group achieved a higher level of adherence than the low-fat diet group at long-term.

RESUMEN

Introducción

La dieta es un pilar fundamental en la prevención secundaria cardiovascular y la herramienta más eficaz para prevenir la diabetes tipo 2 (DM2). El análisis de patrones dietéticos es ampliamente utilizado para estudiar la relación entre la dieta y el riesgo de enfermedades crónicas, siendo dos los métodos comúnmente utilizados para dicho propósito: índices dietéticos definidos *a priori* (basados en modelos dietéticos saludables, como los índices de dieta Mediterránea) y patrones dietéticos derivados *a posteriori* (identificados a través de métodos estadísticos basados en los datos de ingesta dietética de la propia población, como el análisis de componentes principales o PCA). Se han utilizado distintos métodos de análisis de patrones dietéticos para caracterizar la dieta de pacientes con enfermedades crónicas. Sin embargo, hasta la fecha, hay escasos datos científicos que los comparen directamente, en ensayos grandes y a largo plazo, en su capacidad para detectar futuros casos incidentes de DM2 en pacientes coronarios. Hemos analizado tres métodos *a priori* y uno *a posteriori*, y hemos investigado si alguno de estos métodos predice mejor qué pacientes desarrollarán DM2 a los 5 años.

Hipótesis

Nuestra hipótesis es investigar si un modelo de predicción de diabetes que incluye un patrón dietético definido *a priori* (índice dietético) tiene una capacidad predictiva similar a un modelo de predicción que incluye un patrón dietético derivado *a posteriori* (patrón dietético derivado de un PCA) tras un período de 5 años de intervención dietética.

Objetivos

Objetivo principal: Determinar si existe un método de análisis de patrones dietético (es decir, un índice dietético definido *a priori* o un patrón dietético derivado *a posteriori*)

que prediga con mayor fiabilidad el desarrollo de DM2 tras 5 años de intervención con una dieta Mediterránea o una dieta baja en grasas en pacientes coronarios.

Objetivos secundarios:

1) Estudiar la asociación entre tres índices dietéticos definidos *a priori* (MEDAS, cuestionario de adherencia a la dieta Mediterránea de 14 puntos; LFDAS, cuestionario de adherencia a la dieta baja en grasas de 9 puntos; MDS-Trichopoulou, índice de adherencia a dieta Mediterránea propuesto por Trichopoulou et al.), evaluados al inicio del estudio y después de 1 año de intervención, y la incidencia de DM2 tras 5 años de seguimiento.

2) Investigar la asociación entre los patrones dietéticos derivados *a posteriori* mediante el análisis de componentes principales (PCA-patrones dietéticos), al inicio y después de 1 año de intervención, y la incidencia de DM2 tras 5 años de seguimiento.

3) Determinar la relación entre los métodos de análisis de patrones dietéticos mencionados y múltiples parámetros antropométricos y bioquímicos relacionados con el desarrollo de DM2.

4) Comparar y evaluar la validez de los índices dietéticos y los PCA-patrones dietéticos en nuestra población.

5) Investigar los cambios en los hábitos alimentarios y abordar el nivel de adherencia a la intervención dietética a largo plazo en nuestra población.

Métodos

Todos los análisis se realizaron en los 462 pacientes sin diagnóstico clínico de DM2 al inicio del estudio CORDIOPREV (NTC00924937). La ingesta de alimentos se evaluó con un cuestionario de frecuencia de consumo de alimentos (FFQ) validado. Como métodos de análisis de patrones dietéticos utilizamos tres *a priori* (MEDAS, LFDAS y MDS-Trichopoulou) y uno *a posteriori* (PCA-patrones dietéticos). Para evaluar las asociaciones entre los métodos de análisis de patrones dietéticos y la incidencia de DM2, utilizamos análisis de regresión de Cox, regresión logística o análisis de curvas

ROC. Estudiamos asociaciones prospectivas de los métodos de análisis de patrones dietéticos con variables antropométricas y bioquímicas mediante análisis de regresión lineal. En todos los estudios, utilizamos los datos dietéticos de las visitas inicial (como información basal previa a la intervención) y de un año (como información después de un período de estabilización). Para evaluar la validez de los tres índices dietéticos, utilizamos los datos obtenidos del FFQ, como método de referencia, y comparamos estos resultados con los del MEDAS, LFDAS y MDS-Trichopoulou. Además, se examinó la consistencia de los PCA-patrones dietéticos. Para realizar el estudio de adherencia a largo plazo, se utilizaron los datos dietéticos de los 5 años de seguimiento de la población total del estudio CORDIOPREV (n=1002) y se evaluaron los cambios entre los grupos de intervención (dieta Mediterráneas y dieta baja en grasas) y dentro de dichos grupos con la prueba t pareada y prueba t no pareada.

Resultados

Resultados principales: *Identificación de métodos que predicen DM2 a largo plazo*: El MEDAS (índice dietético que evalúa la adherencia a la dieta Mediterránea) en el año 1 y el PD-Occidental (PCA-patrón dietético caracterizado por carnes rojas/procesadas, alimentos altamente procesados, conservas de pescado, pan blanco y dulces) en el año 1 fueron los únicos métodos que mostraron asociaciones significativas con la incidencia de DM2 en nuestra población. Estos dos métodos fueron comparados con respecto a su capacidad para predecir la incidencia de DM2 después de una mediana de seguimiento de 60 meses. El modelo que incluyó el MEDAS en el año 1 junto con las variables clínicas clásicas y los factores de estilo de vida mostró una capacidad discriminativa aceptable (AUC=0.733; IC 95%=0.665-0.801; p<0.001). El PD-Occidental en el año 1 junto con los mismos factores de confusión también mostró una capacidad discriminativa aceptable (AUC=0.715; IC 95%=0.649-0.781; p<0.001). No se encontraron diferencias estadísticamente significativas al comparar ambos modelos (p=0.521). Cuando evaluamos el impacto de

incluir estos métodos de análisis de patrones dietéticos en los modelos habituales de predicción basados únicamente en factores clínicos y de estilo de vida, las AUC de las variables clínicas y el modelo de variables clínicas más estilo de vida mejoraron al incluir el MEDAS en el año 1 (p=0.022 y p=0.021, respectivamente) o el Western DP en el año 1 (p=0.031 y p=0.032, respectivamente).

Resultados secundarios:

1) *Asociación entre los índices dietéticos definidos a priori y el riesgo de DM2 a los 5 años:* Los pacientes con la mayor adherencia al MEDAS (10-14 puntos) en el año 1 mostraron un 69% menos de riesgo de desarrollar DM2 (HR=0.31, IC 95%=0.16-0.60) en comparación con los pacientes con una adherencia baja-media (0-9 puntos). Por cada punto adicional en el MEDAS en el año 1, el riesgo de DM2 se redujo un 17% (ExpB=0.83, IC 95%=0.73-0.94). Ni el MDS-Trichopoulou ni el LFDAS en el año 1 se asociaron con la incidencia de DM2. Los índices dietéticos basales no se asociaron con el desarrollo de DM2.

2) *Asociación entre los patrones dietéticos derivados a posteriori y el riesgo de DM2 a los 5 años*: Utilizando el PCA, se identificaron dos patrones dietéticos (PD-Occidental y PD-Mediterráneo) y tres patrones dietéticos (PD-Occidental, DP-Mediterránea y DP-bajo en grasas) en tiempo basal y en el año 1, respectivamente. Los pacientes con mayor adherencia al PD-Occidental (tertil 3) en el año 1 mostraron un 90% más de riesgo de desarrollar DM2 (HR=1.90; 95% IC=1.05-3.46) que los pacientes con una adherencia baja-media (tertiles 1 y 2). En el caso del PD-Mediterráneo y PD-bajo en grasas en el año 1, los pacientes del tertile 3 de cada patrón tuvieron una reducción no significativa del riesgo de desarrollar DM2 del 25% (HR=0.75; IC 95%=0.41-1.39) y el 35% (HR=0.65; IC del 95%=0.36-1.17), respectivamente. Los PCA-patrones dietéticos en tiempo basal no se asociaron con el desarrollo de DM2.

3) *Asociación entre los métodos de análisis de patrones dietéticos y múltiples parámetros antropométricos/bioquímicos relacionados con el desarrollo de DM2*: Los análisis de regresión lineal revelaron que el MEDAS en el año 1 se asoció inversamente con la circunferencia de la cintura, la HbA1c, el HOMA-IR, la glucosa, los triglicéridos, la proteína C reactiva, los leucocitos y la proporción de neutrófilos/linfocitos en el año 5 (todos con $p<0.05$), mientras que el PD-Occidental en el año 1 se asoció positivamente con el IMC, la circunferencia de la cintura, la glucosa, los triglicéridos, el colesterol total, el colesterol LDL y la proteína C reactiva en el año 5 (todos $p< 0.05$).

4) *Validación de los métodos de análisis de patrones dietéticos en pacientes coronarios en España*: Los tres índices dietéticos correlacionaron en la dirección esperada con los datos dietéticos recogidos del FFQ. Se encontró una buena correlación y concordancia entre el MEDAS administrado y el MEDAS calculado a partir de FFQ al inicio del estudio ($r=0.53$, $p<0.001$; ICC=0.64, IC 95% 0.45-0.75, $p<0.001$), sin sesgo consistente de un método versus el otro (gráfico de Bland-Altman, media±DS=0.94±1.82, 95% LoA -2.63 a 4.51). Se observó una correlación moderada y buena concordancia entre el LFDAS administrado y el LFDAS calculado a partir del FFQ al inicio del estudio ($r=0.44$, $p<0.001$; ICC=0.55, IC 95% 0.40-0.66, $p<0.001$), sin un sesgo consistente de un método versus el otro (gráfico de Bland-Altman=0.70±1.55; 95% LoA -2.35 a 3.73). Todos los análisis se repitieron utilizando la información dietética de la visita de 5 años y se encontraron resultados similares tanto para el MEDAS como para el LFDAS. Además, todas las asociaciones entre los PCA-patrones dietéticos y los índices dietéticos fueron en la dirección esperada.

5) *Adherencia dietética a largo plazo con una dieta Mediterránea o una dieta baja en grasas en pacientes con enfermedad coronaria*: Desde el inicio del estudio hasta los 5 años, se observaron aumentos significativos en la adherencia dietética (grupo dieta Mediterránea: de 8.9 a 11.4; grupo dieta baja en grasas: de 3.9 a 7.1) y en el porcentaje de pacientes considerados como *Alta Adherencia* (grupo dieta

Mediterránea: del 41 al 89%; grupo dieta baja en grasas: del 4 al 67%). Cuando evaluamos el mantenimiento de la adherencia dietética, los pacientes considerados como *Baja* y *Media Adherencia* en el año 1 aumentaron su adherencia a los 5 años con ambas dietas y los pacientes considerados como *Alta Adherencia* mantuvieron su adherencia con una dieta Mediterránea, pero disminuyeron su adherencia con una dieta baja en grasas.

Conclusiones

Conclusión principal: El MEDAS (análisis *a priori*) y el PCA (*análisis a posteriori*) son los métodos que capturaron la relación más fuerte entre la intervención dietética y la incidencia de DM2 a largo plazo (5 años) entre todos los métodos *a priori* y *a posteriori* evaluados en esta tesis. Cuando se utilizan después de un período de estabilización de un año, ambos métodos proporcionan resultados fiables y precisos, respaldados por una validación interna.

Conclusiones secundarias:

- Nuestros resultados también muestran que, en pacientes coronarios que participaron en un ensayo de intervención dietética, la alta adherencia a una dieta de tipo Mediterránea, reflejada por el MEDAS y lograda después de un año de intervención, se asoció con una importante reducción del riesgo de DM2 y con valores más saludables de parámetros antropométricos y bioquímicos relacionados con el riesgo de DM2.
- En nuestra población, una mayor adherencia a un patrón dietético de tipo Occidental tras un año de intervención se asoció con un mayor riesgo a largo plazo de desarrollar DM2 y con efectos perjudiciales en la circunferencia de la cintura, el IMC, la glucosa, el perfil lipídico y los marcadores de inflamación.

- Hemos validado el MEDAS y el LFDAS en pacientes coronarios (toda la población del estudio CORDIOPREV). Esto demuestra que son herramientas válidas para evaluar rápidamente la adherencia dietética en pacientes coronarios y que podrían utilizarse en la práctica clínica.
- Nuestros hallazgos muestran que una intervención dietética integral da como resultado una mejora y un mantenimiento a largo plazo de la adherencia a las dietas Mediterránea y baja en grasas. En nuestra población, el grupo de dieta Mediterránea logró un mayor nivel de adherencia dietética a largo plazo que el grupo de dieta baja en grasas.

I. INTRODUCTION

I. INTRODUCTION

1.1. Diabetes and cardiovascular disease

1.1.1. Diabetes

Diabetes is one of the fastest growing diseases and a major cause of disability, of which type 2 diabetes (T2DM) constitutes the majority of cases [1]. This non-communicable disease has become an important health and socioeconomic problem due to its high prevalence across the world and the great impact of its chronic complications [2]. Despite this overwhelming scenario, there is strong evidence supporting that lifestyle changes can prevent or delay the onset of T2DM in high-risk subjects [3-6], and, in some cases, even reverse the disease.

1.1.1.1. Definition, classification and diagnosis of diabetes

Diabetes mellitus, more commonly called diabetes, is a complex metabolic disorder of glucose homeostasis characterized by a chronic hyperglycemia resulting from defects in insulin action, secretion, or both [7]. This chronic high blood glucose level is associated with long-term damage of various organs and the development of microvascular complications such as neuropathy, retinopathy and nephropathy; and macrovascular complications such as stroke, heart disease and peripheral arterial disease.

Diabetes can be classified into four broad categories according to the American Diabetes Association (ADA)[8]:

- Type 1 diabetes mellitus: It is characterized by the insufficient production of insulin due to autoimmune destruction of the pancreatic β-cells. This form of diabetes accounts for only 5–10% of all diabetes cases. Although it is usually diagnosed in children and adolescents, it can develop at any age.
- Type 2 diabetes mellitus: This form of diabetes is characterized by hyperglycemia, insulin resistance, and relative impairment in insulin secretion. It is the most common form of diabetes (>85% cases) and its incidence increases progressively with age.
- Gestational diabetes mellitus: It is characterized by hyperglycemia of variable severity with onset or first recognition during pregnancy.
- Other specific types of diabetes: Diabetes due to other causes, such as monogenic diabetes syndromes, diseases of the exocrine pancreas, drug and chemical-induced diabetes and uncommon specific forms of immune-mediated diabetes.

The diagnosis of diabetes has been the subject of debate and updates over decades. According to the last document of the ADA [8], diabetes can be diagnosed based on plasma glucose criteria, either the fasting plasma glucose (FPG) or the 2-h plasma glucose value during a 75-g oral glucose tolerance test (OGTT), or glycosylated hemoglobin (HbA1c) criteria. Table 1 summarizes the criteria proposed by the ADA according to the method used.

Generally, FGP, OGTT and HbA1c are equally appropriate for diagnostic testing but they do not necessarily detect diabetes in the same individuals. The concordance between the three methods is imperfect and more people with diabetes have been diagnosed with 2-h plasma glucose levels than with FPG or HbA1c.

Table 1. Criteria for the diagnosis of T2DM (cited from ADA 2021) [8]

FPG	≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8h.*
OR	
2-h PG during 75-g OGTT	≥ 200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by the WHO, using a glucose load containing equivalent of 75 g anhydrous glucose dissolved in water.*
OR	
HbA1c	≥ 6.5 % (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*
OR	
In patients with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).	

FPG, fasting plasma glucose; 2-h PG, 2 hours plasma glucose; OGTT, oral glucose tolerance test; WHO, World Health Organization; HbA1c, glycosylated hemoglobin NGSP, National Glycohemoglobin Standardization Program; DCCT, Diabetes Control and Complications Trial. *In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

HbA1c seems to provide several advantages over FPG and OGTT, such as providing a long-term analysis of the patient's average blood glucose, not requiring fasting, having a higher stability and being less susceptible to disturbances under stress and illness conditions. However, cost and availability are drawbacks to the HbA1c. Furthermore, it should be note that HbA1c is an indirect measure of average blood glucose levels.

Except when the diagnosis of diabetes is clear (e.g., patient with classic symptoms of hyperglycemia and a random plasma glucose ≥200 mg/dL [11.1 mmol/L]),

two abnormal test results are required to confirm the diagnosis. It is recommended that the same test be repeated or a different test be performed without delay.

A blood glucose level higher than normal, but not reaching the diagnostic criteria of diabetes, is a state of intermediate hyperglycemia and is called prediabetes. Depending on what test was used, impaired glucose tolerance and impaired fasting glucose are also used to refer to prediabetes. Table 2 summarizes criteria defining prediabetes according to the ADA. It is noteworthy that prediabetes should be viewed as an increased risk for diabetes and cardiovascular disease (CVD), rather than a clinical entity itself. Prediabetes is associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension.

Table 2. Criteria for the diagnosis of prediabetes (cited from ADA 2021) [8]

FPG	100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
	OR
2-h PG during 75-g OGTT	140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)
	OR
HbA1c	5.7–6.4% (39–47 mmol/mol)

FPG, fasting plasma glucose; IFG, impaired fasting glucose; 2-h PG, 2 hours plasma glucose; OGTT, oral glucose tolerance test; IGT, impaired glucose tolerance; HbA1c, glycosylated hemoglobin.

1.1.1.2. Epidemiology of type 2 diabetes

T2DM is currently one of the most common global forms of chronic disease globally, which represents >85% of all cases of diabetes. Its prevalence and incidence are steadily increasing worldwide in line with the increase in obesity, population ageing, economic development, unhealthy eating habits and sedentary lifestyles.

According to the recent 9th edition of the Diabetes Atlas of the International Diabetes Federation (IDF), about 463 million adults aged 20-79 years (9.3%) had diabetes globally in 2019 (Figure 1), which represents 1 in 11 adults. Reported data in adults in Spain show a prevalence of nearly 15% (diagnosed and undiagnosed) [9]. About 50% of diabetics are undiagnosed. The number of diabetics is projected to increase by 51% in 2045 reaching 700 million people [2].

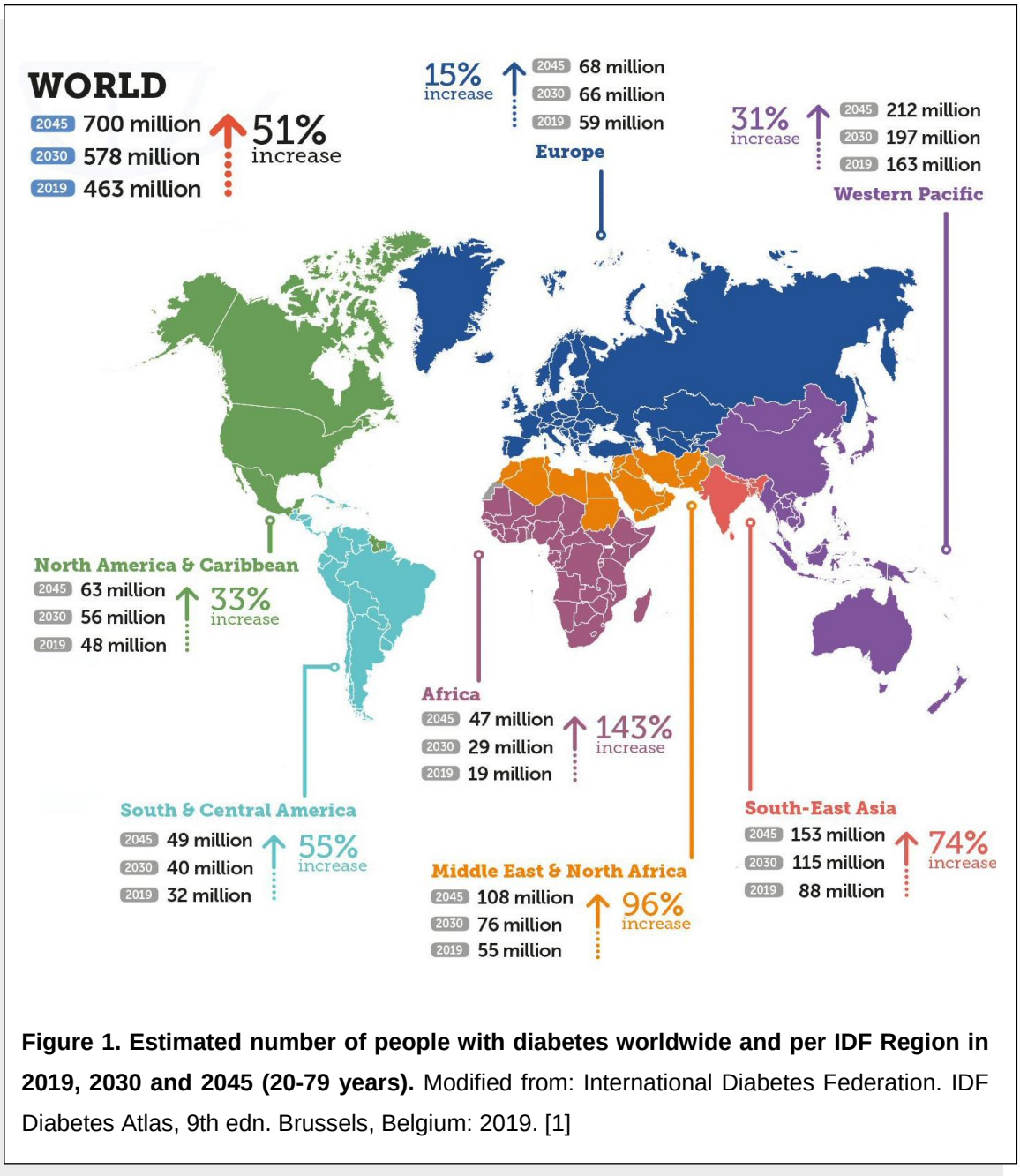

Figure 1. Estimated number of people with diabetes worldwide and per IDF Region in 2019, 2030 and 2045 (20-79 years). Modified from: International Diabetes Federation. IDF Diabetes Atlas, 9th edn. Brussels, Belgium: 2019. [1]

Prevalence of diabetes varies by age, gender and area of residence. In general, the prevalence of diabetes is slightly higher in men than in women (an estimated 9.6% in men compared to 9.0% in women in 2019). Prevalence of diabetes increases with age. Regarding the area of residence, the prevalence is higher in urban (10.8%) versus rural (7.2%) areas.

Across IDF regions, the Middle East and North Africa region has the highest age-adjusted comparative prevalence (12.2%) whereas the lowest is observed in the Africa Region (4.7%). Europe is the second region with the lowest age-adjusted prevalence of diabetes (6.3%), accounting for 59.5 million people being diabetic [2].

In Spain, the most recent available data are the results of the Di@bet.es study [9], showing a real prevalence of diabetes in people over 18 years old of 13.8%, and with a remarkably higher prevalence of T2DM. Of these, almost 6% has unknown diabetes. The prevalence increases with age and is higher in men than in women. The Di@bet.es study was the first national study in Spain to examine the prevalence and incidence of diabetes by OGTT in a representative sample of the Spanish population. This cross-sectional study was conducted between 2008 and 2010 including 5.072 adults randomly selected from the National Health System.

Although prevalence could potentially provide an insight into the global impact of diabetes, increasing prevalence can be partly related to improved medical care and the general increasing life expectancy trends. A more appropriate indicator of population risk is the incidence, which measures the proportion of people who develop diabetes over a period of time among the population at risk. In addition, the incidence is not affected by changes in survival. A recent systematic review of trends in diabetes showed that the incidence of clinically diagnosed T2DM has been stable or falling since 2006 and only one third of more recent studies suggested an increasing trend [10]. However, several limitations in this systematic review could compromise the interpretation of the reported trends. For example, the majority of the 100 populations

studied were from high-income countries and trends in diabetes incidence in low-middle income countries might be different. No adjustments were made for the different methods of diagnosis of diabetes and trends were not determined by different definitions of diabetes.

Recent data from the Di@bet.es study [11] indicate 386.000 new cases of T2DM annually in Spain (11.6 cases/1000 person-year). The incidence of diabetes is higher in men, increasing with age from the age of 18, with a maximum incidence in 75 years. In women, the incidence increases continuously with age.

In addition to its high prevalence and incidence, diabetes causes a high impact on healthcare expenditure and mortality. Diabetes caused at least USD 760 billion dollars in health expenditure in 2019, accounting for 10% of total spending on adults [1]. In terms of mortality, diabetes is among the top 10 causes of death globally. By the end of 2019, over 4 million people aged between 20 and 79 years died as a result of diabetes and its complications, and most of these cases were T2DM [2]. This is not surprising since patients with T2DM have 2 to 4 times greater risk for death and cardiovascular events compared to the general population [12].

1.1.1.3. Pathophysiology of type 2 diabetes

T2DM is a progressive disorder involving a complex pathophysiology. There is widespread agreement that three major metabolic disturbances contribute to hyperglycemia, leading to T2DM: increased hepatic glucose output, increased insulin resistance and impaired insulin secretion due to the progressive loss of β-cell function (Figure 2) [7]. Both insulin resistance and β-cell dysfunction occur early in the pathogenesis of T2DM and hyperglycemia is associated with these two abnormalities. Hyperglycemia develops gradually and asymptomatically and, therefore, T2DM remains undiagnosed for several years. Although the specific aetiology is currently

unknown, genetic and environmental factors are important determinants of insulin resistance and β-cell dysfunction.

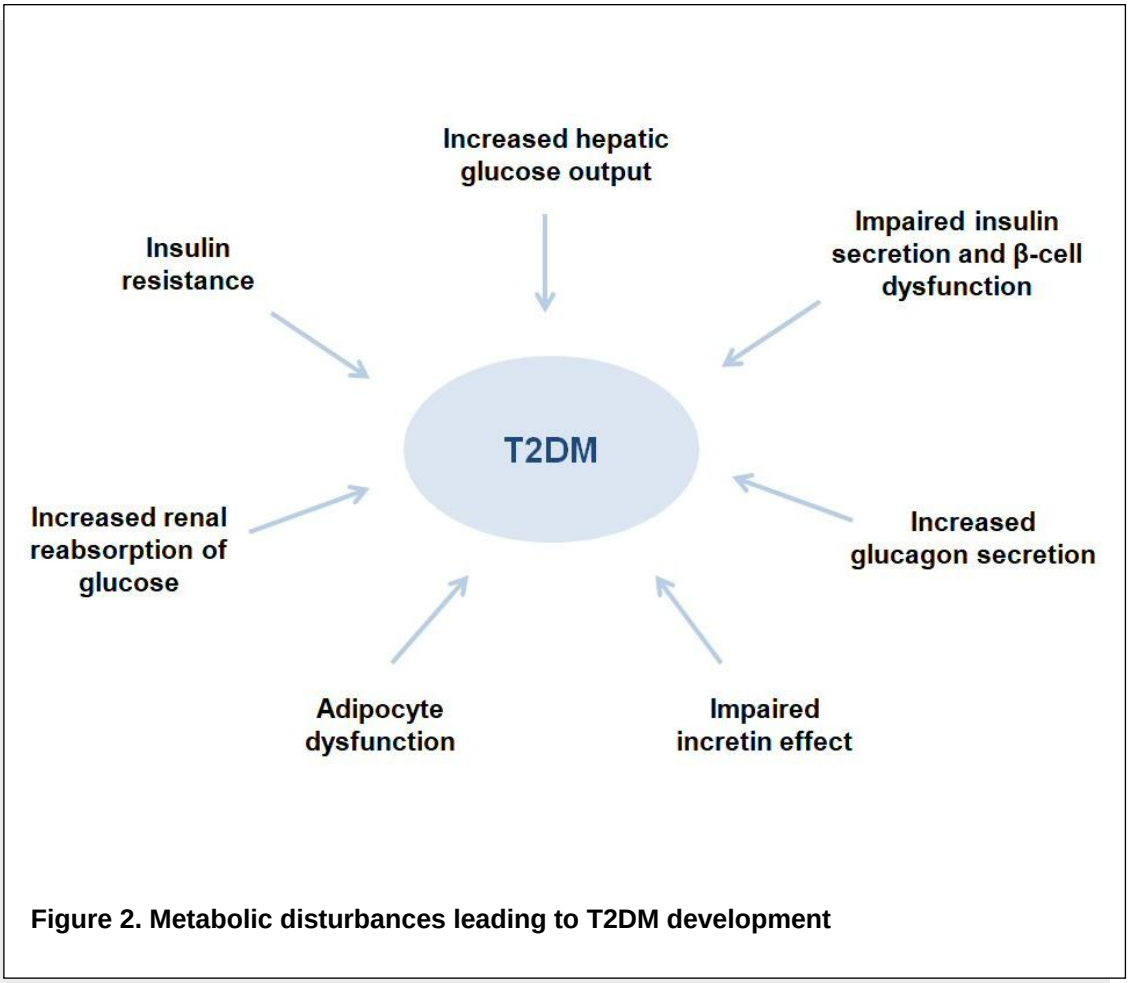

Figure 2. Metabolic disturbances leading to T2DM development

Insulin resistance

Insulin resistance is a pathological condition where insulin is unable to exert its normal effects in insulin-sensitive target tissues, predominantly in skeletal muscle, liver and adipose tissue [13]. On this basis, insulin is not capable to effectively stimulate glucose uptake by skeletal muscle, reduce glucose output by the liver or suppress fatty acid release from adipose tissue, resulting in increased circulating fatty acids and hyperglycemia [14]. Under this condition, pancreatic ß-cells compensate by increasing insulin secretion to maintain normoglycemia, leading to hyperinsulinemia and creating

a glucotoxic environment for β-cells which could compromise their function and ultimately causes T2DM [15].

The severity of insulin resistance varies from person to person and is usually progressive over time. The exact causes of insulin resistance is unclear, however it is commonly associated with obesity, visceral adiposity, hypertension, dyslipidemia, endothelial dysfunction and elevated levels of markers of inflammation. Although the mechanisms of insulin resistance have not been fully elucidated, mechanisms such as oxidative stress, inflammation, insulin receptor mutations, endoplasmic reticulum stress, and mitochondrial dysfunction play an important role in its development [16].

Impaired insulin secretion and β-cell dysfunction

Insulin secretion is a highly regulated process to provide stable concentrations of glucose in the blood during fasting and postprandial conditions. In healthy individuals, normoglycemia is maintained under a balance between insulin sensitivity and insulin secretion, and when there is a change in insulin sensitivity, an equivalent and complementary variation in insulin secretion occurs. A failure in this process leads to increasing glucose levels and finally, to the development of T2DM [17].

ß-cell dysfunction, which is clearly present when T2DM is diagnosed, gets progressively worse with disease duration. It is a sequential process that begins with the progressive decrease in insulin secretion, followed by a decrease in cell mass and finally cell apoptosis. Various mechanisms underlying β-cell failure have been proposed such as glucotoxicity [18], lipotoxicity [19], islet amyloid deposition [20] and oxidative and endoplasmic reticulum stress [21].

Other mechanisms

The growing understanding of the complexity of T2DM has shown that there are other important pathophysiological mechanisms in its development that involve and

affect other organs: adipose tissue (adipocyte dysfunction associated with insulin resistance), gastrointestinal tract (incretin deficiency/incretin resistance), pancreatic α-cells (hyperglucagonemia and increased hepatic sensitivity to glucagon), kidneys (increased glucose reabsorption) and brain/central nervous system (insulin resistance)[22].

Increased free fatty acid levels, inflammatory cytokines from fat, and oxidative factors have also been implicated in the pathogenesis of T2DM. Chronic elevated plasma levels of glucose, free fatty acids and other characteristic lipid metabolites of T2DM are associated with a glucolipotoxicity phenomenon that exacerbates the insulin resistance and β-cell dysfunction (induced by activation of the stress response, accelerated apoptosis, β-cell dedifferentiation and reduced proliferation) [23].

1.1.1.4. Risk factors for type 2 diabetes

T2DM is considered as a multifactorial disease resulting from a complex interaction between non-modifiable risk factors (e.g., age and genetic factors related to impaired insulin secretion and insulin resistance), as well as modifiable risk factors such as obesity, unhealthy diets, smoking and physical inactivity [24]. Changes in these modifiable risk factors, also called lifestyle factors, could reduce the risk of T2DM and influence the progression of the disease.

- **Non-modifiable risk factors**

Ethnicity, genetics and family history of T2DM

The prevalence of T2DM varies widely according to population. Moreover, we can find marked differences between different ethnic/race groups living in the same geographical area or in the same environment (e.g., African Americans, Hispanics, Asian Americans, Native Americans and Pima Indians have a higher prevalence of diabetes than Caucasian Americans) [25]. This shows that certain ethnic groups are at

increased risk for developing T2DM and support the idea of a genetic influence on the development of the disease.

The heritability of T2DM is estimated at 30-70% and more than 400 variants of genes associated with T2DM have been currently identified [26].

A positive family history of T2DM is a strong risk factor for the development of this condition. Individuals with an affected parent or sibling have a two to three fold increased risk of developing T2DM compared with the general population and when both parents have T2DM, this risk is even higher [27].

Age and sex

Increasing age confers higher risk of developing T2DM. According to the IDF, the prevalence of T2DM is low before the age of 30 years but increases rapidly and continuously with age. Similar trends are predicted for the year 2045 (Figure 3).

Evidence suggests that sex-differences may play a role in the epidemiology and pathophysiology of T2DM. The global diabetes prevalence is slightly higher in men than in women, with an estimated difference of 17.2 million in 2019 and which is expected to increase in both men and women by 2045 [2]. The sex difference in the prevalence of diabetes is reversed in older age maybe due to the greatest number of older women in most populations and the increasing prevalence of diabetes with age. Moreover, women with a history of gestational diabetes have an increased risk of developing T2DM in later years [28].

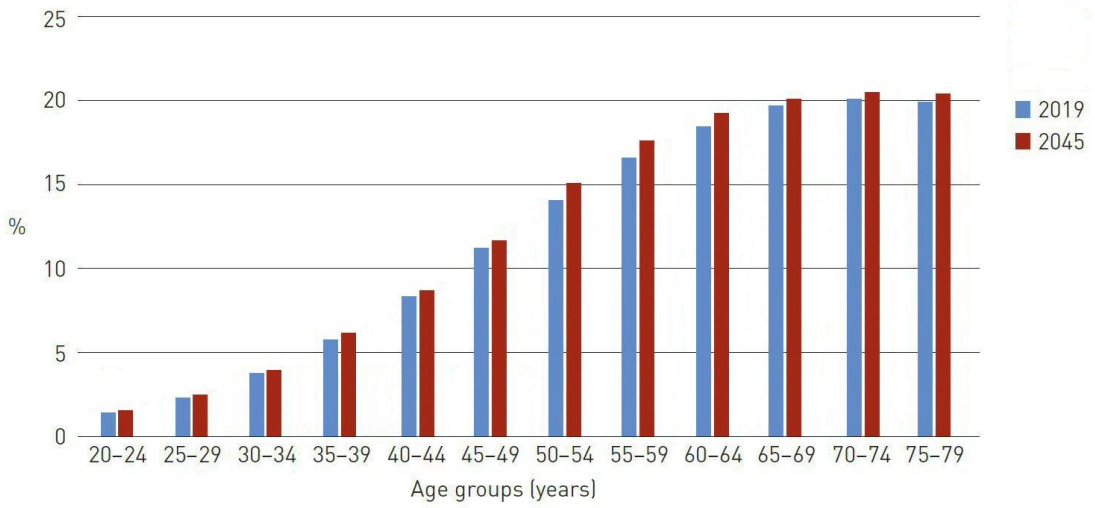

Figure 3. Worldwide prevalence of diabetes by age in adults (20-79 years) in 2019 and 2045. Modified from: International Diabetes Federation. IDF Diabetes Atlas, 9th edn. Brussels, Belgium: 2019. [1]

- **Modifiable risk factors.**

Overweight/ Obesity

Overweight and obesity are a major global public health problem, affecting both low and high-income countries indistinctly, with rates increasing dramatically over the last 40 years. According to the World Health Organization (WHO), more than 1.9 billion adults are overweight (39%) and, of these, 650 million are obese (13%) [29]. In Spain, it is estimated that 39.3% of the adult population is overweight and 21.6% suffers from obesity [30]. Moreover, childhood obesity has reached epidemic levels.

These figures are even more alarming if we consider that the prevalence of diabetes increases in parallel with obesity. In fact, excess of adiposity is the single strongest risk factor for T2DM [31] and is associated with several metabolic disturbances leading to insulin resistance. Although not all obese people have

diabetes, different studies have shown a strong association of body mass index (BMI) with T2DM risk. A meta-analysis including 18 prospective cohorts showed that overweight and obesity are associated with a nearly 3 and 7 times increased risk of T2DM, respectively [32]. Similarly, in the Nurses' Health Study, the relative risk of T2DM in women with BMI 30 to 34.9 kg/m^2 (obesity class I) was 20.1 and in women with BMI ≥ 35 kg/m^2 (obesity class II and III) was 38.8, compared to women with normal weight [31].

The age of onset and the duration of obesity also influence the risk of T2DM. Weight gain in early adulthood is related to a higher risk of T2DM than weight gain during middle-to-late adulthood [33,34]. Being overweight or obese for longer periods of time has also been associated with greater risk of type 2 diabetes, specifically, each 2 extra years of being overweight or obese is associated with 9% and 14% increased risk of developing T2DM, respectively [35].

Abdominal obesity, which is defined as a waist circumference >103 cm in men and >88 cm in women or as a waist-to-hip ratio > 0.90 for men and > 0.85 for women, is present in the majority of diabetics and is more strongly associated with insulin resistance than peripheral obesity [36]. Several studies indicate that waist circumference and waist-to-hip ratio are better than BMI in predicting T2DM risk [37,38], particularly in women [39]. However, both overall obesity and abdominal obesity predict or are independently associated with T2DM [40].

Evidence from studies in the USA, Finland, China and India shows the impact that weight loss has in the prevention and control of T2DM. In all of them, a lifestyle intervention (involving diet modification and exercise to promote weight-loss) significantly reduced the risk of developing T2DM among high risk patients with impaired glucose tolerance [3,4,41,42]. The beneficial effect of lifestyle modification has been confirmed in the long-term [43]. Moreover, a recent systematic review and

meta-analysis showed that lifestyle intervention is effective in reducing the risk of progression to T2DM in people with prediabetes [44].

Dietary habits

In the last decades and due to the globalization process, global dietary patterns have changed towards unhealthy diets with high energy content, high intake of highly refined carbohydrates, animal-source food, sugar-sweetened beverages, and unhealthy fats, with a reduced intake of legumes, vegetables and fruits [45]. These changes in diets along with lifestyles becoming more sedentary have largely contributed to the increase of non-communicable diseases, such as T2DM.

A large body of evidence from prospective observational studies and clinical trials supports the important role of diet in the prevention and management of T2DM. As the main focus of this thesis is the study of the diet as a dietary pattern, evidence on the associations between individual nutrients or foods and the risk of T2DM are not described here. Different dietary patterns have been related to T2DM risk, which fit into five main pattern types: the “Western pattern”, the “Prudent pattern”, the Mediterranean diet, the Dietary Approaches to Stop Hypertension (DASH) diet and the “plant-based dietary pattern”. Whereas the “Western pattern” seems to increase the risk of T2DM, the other dietary patterns are valuable in preventing this chronic disease [46].

Western-type patterns are mainly characterized by a higher intake of processed meat, red meat, butter, high-fat dairy products, eggs, refined grains, sweets/sugary drinks, and fried foods [47,48], and as a result, contain high amounts of saturated fatty acids (SFA), trans-fatty acids and refined carbohydrates. This pattern has been consistently associated with diabetes risk in several studies conducted in different countries [48-50]. In a meta-analysis of 9 prospective studies (309.430 participants) examining dietary patterns derived by factor analysis/principal component analysis and

incidence of T2DM risk, pooled results showed a 41% higher T2DM risk for participants in the highest category of unhealthy/Western dietary pattern compared to those in the lowest category (OR: 1.41; 95% CI: 1.32-1.52) [49]. In a more recent meta-analysis of 48 prospective studies on dietary patterns and T2DM considering different methodological approaches, unhealthy/Western patterns derived by principal component analysis or factor analysis were also related to a significant increase of T2DM risk by 44% (RR: 1.44; 95% CI: 1.27-1.62) without heterogeneity between studies (I^2 = 0%) [48].

On the other hand, the "Prudent pattern" is characterized by higher intakes of fruit, vegetables, whole grains, legumes and fish [47]. The relationship between the "Prudent pattern" and the risk for incident T2DM was first described in the Health Professionals Follow-up Study, where a higher score for this pattern was associated with a modestly lower risk for T2DM (RR for extreme quintiles: 0.84; 95% CI: 0.70-1.00) [51]. Similarly, in the Nurses' Health Study, women in the highest quintile of the prudent pattern had a slightly reduced risk of T2DM (RR for extreme quintiles: 0.80; 95% CI: 0.67-0.95) [52]. Moreover, in a cross-sectional study conducted in a middle-aged Irish population, high adherents to a Prudent diet showed the lowest homeostasis model assessment scores (HOMA) and levels of insulin resistance (OR: 0.53; 95% CI: 0.33-0.85) [53].

The scientific evidence regarding the association of the Mediterranean diet, the DASH diet and plant-based diets with T2DM is described in detail below.

Physical inactivity and sedentary behaviour

Physical inactivity is defined as an insufficient physical activity level to meet present physical activity recommendations (i.e. at least 150 minutes of moderate-intensity, or 75 minutes of vigorous-intensity physical activity per week, or any equivalent combination of the two). Whereas, sedentary behaviour implies any waking

behaviour with an energy expenditure ≤1.5 metabolic equivalents (METs), while in a sitting, reclining or lying posture [54]. Both physical inactivity and sedentary behaviour are independent risk factors for T2DM [55,56].

Results from recent meta-analysis showed that high levels of total physical activity or leisure-time physical activity lowered the relative risk for T2DM [57,58]. Similarly, a recent systematic review showed that higher levels of leisure-time physical activity of any intensity are associated with lower incidence of T2DM and that additional benefits can be obtained with levels of activity above the physical activity recommendations [59]. Moreover, results from the Action for Health in Diabetes (Look AHEAD) study showed that increasing physical activity in type 2 diabetics resulted in remission (partial or complete) of the disease in 11.5% and 7.3% of subjects after 1 and 4 years of intervention, respectively [60]. Most of the benefits of physical activity for both prevention and management of T2DM can be explained through improvement in uptake and utilization of glucose in muscle tissue, and increased insulin sensitivity by target tissues [61].

Prolonged sedentary time has been associated with insulin resistance [62] and with a greater risk of T2DM in the short [63] and long term [64], independent of physical activity. TV-viewing time is one of the most studied types of sedentary behaviour and has been positively associated with incidence of T2DM in healthy men [65] and women [66]. For example, men who on average spent more than 40 hours per week watching television had 3-fold increased risk of T2DM compared with those who spent less than 1 hour per week. Recently, in Spanish aged adults at high cardiovascular risk, fewer time spent on TV watching and greater on physical activity was inversely associated with prevalence of T2DM [67].

Therefore, strategies to reduce the risk of T2DM should be focused not only on increasing physical activity but also on reducing sedentary behaviour, especially watching TV for a long time.

Smoking habit

The strong association between smoking and the development T2DM is well documented. Active smokers have a 30-40% increased risk of T2DM compared with non-smokers [68]. The risk increases with the number of cigarettes smoked per day. Further, there is a significant association between smoking and increased central obesity, increased insulin resistance, impairment of β-cell function and increased risk of diabetic complications (microvascular and macrovascular) [69]. In former smokers, there is an increased risk of T2DM after smoking cessation (in the 3-5 years later) but it decreases as the time since quitting increases. Moreover, there is also evidence that passive smoking is positively and independently associated with the risk of T2DM.

Finally, it is important to highlight that lifestyle factors are strongly related to each other. Evidence also supports the positive impact of join adherence to lifestyle factors on T2DM. A recent systematic review and meta-analysis of prospective studies [70] shows that adhering to a healthy lifestyle, including normal weight, healthy diet, physical activity, and non-smoking, was associated with a 78% reduced relative risk for T2DM. Moreover, adherence to a healthy lifestyle in T2DM diabetics was associated with reduced relative risk of all-cause mortality by 57% compared with non-adherence.

1.1.2. Cardiovascular disease

1.1.2.1. An overview of cardiovascular disease

CVD is a broad term that includes a number of linked pathologies, commonly defined as coronary heart disease (CHD), cerebrovascular disease, peripheral arterial disease, and many other conditions. From the cluster of disorders that affect the cardiovascular system, CHD is one of the most common forms of presentation.

The importance of CVD lies in the immense human and economic burden that it poses worldwide. CVD remains the leading cause of global death, accounting for an estimated 17.8 million deaths globally in 2017 (31% of all deaths) [71]. Moreover, CVD is a major contributor to reduced quality of life expressed as disability-adjusted life years, which quantifies the number of years lost due to disability or premature death. In 2017, there were 366 million disability-adjusted life years lost due to CVD worldwide [72]. Importantly, CVD is a major cause of disability and death among people with T2DM, responsible for approximately half of all deaths [73]. Given the rapid growth of T2DM, the outlook for CVD becomes even more alarming.

In Spain, CVD causes more than 120.000 deaths annually (28.3% of total deaths), being the first cause of death among women and the second one among men behind cancer [74]. In addition, 2.5 million people are living with cardiovascular conditions and CVD-related healthcare costs amount to an estimated 9 billion Euros per year [75].

Several risk factors have been associated with an increased prevalence of CVD and mortality. Diabetes, dyslipidemia, hypertension, smoking and abdominal obesity are some of the well-established risk factors for CVD. Unhealthy dietary habits and physical inactivity are underlying causes of chronic conditions and therefore, play an important role in their prevention. High alcohol consumption is other contributor. Although there are some non-modifiable risk factors (i.e., age, sex, ethnicity and a positive family history), the majority of the risk factors associated with CVD can be modified by lifestyle changes and their reduction is effective for both primary and secondary cardiovascular prevention. Of all the modifiable risk factors, diet is a clear determinant of the risk of CVD mortality [75].

The major cause of CVD is atherosclerosis, a complex disease of the artery wall that results from a complex interplay between chronic inflammation and lipids [76]. Inflammation specially affects the endothelium inducing endothelial dysfunction and

triggering the initiation and progression of atherosclerosis. This chronic inflammation is related with the initiation and progression not only of CVD but also of other chronic diseases such as T2DM and obesity. Atherosclerosis involves not only endothelial dysfunction and inflammation but also oxidative stress, insulin resistance and dyslipidemia [77], and all of these processes are influenced by lifestyle and diet.

Evidence suggests that most of CVD and its related risk factors can be largely prevented and managed through effective and efficient preventive measures, highlighting the impact of a healthy dietary pattern. In this sense, diet modification is a key strategy that may prevent a large number of cardiovascular events and therefore, is critically important in primordial, primary and secondary prevention of CVD [78].

1.1.2.2. Secondary prevention of cardiovascular disease: the CORDIOPREV study

Individuals with established CVD have an increased risk of recurrent cardiovascular events and death. In Spain, approximately 1 in 4 survivors of acute coronary syndrome will suffer an acute myocardial infarction, stroke or cardiovascular death in the following 5 years, with an especially high risk of recurrence in the first year [79]. A retrospective study made in our clinical setting by the Cardiology Unit reported a total mortality rate of 20% after 6 years of follow-up in coronary patients [80]. Similarly, a study in 114.364 survivors of myocardial infarction from Sweden, England, France and USA showed that the risk of recurrent events is highest in the first year but remains elevated in subsequent years [81]. Consequently, providing a long-term comprehensive intervention for secondary prevention is critical in coronary patients.

Secondary cardiovascular prevention, which aims to prevent subsequent cardiac events, reduce early mortality and improve quality of life in patients who have manifest CVD, includes not only pharmacotherapy and revascularization procedures, but also lifestyle modifications for risk factor management [82,83]. These lifestyle

modification strategies, including regular physical activity, consuming a heart-healthy diet, smoking cessation and addressing psychosocial stressors, provide independent and additional benefits in reducing the risk of cardiovascular events [84].

Despite the well-known importance of secondary prevention, only a proportion of CHD patients achieve the recommended targets in terms of medication, lifestyle and cardiovascular risk factors [85]. Lack of adherence to dietary recommendations is commonly observed, especially in older patients with deeply rooted food habits. Thus, dietary changes in CHD patients are challenging and require a comprehensive, tailored and continuous intervention to achieve and maintain them in the long term.

The Mediterranean diet is probably one of the most extensively studied dietary patterns in relation to CVD prevention. Strong evidence on the effectiveness of this dietary pattern for managing cardiovascular risk factors in primary prevention is available, highlighting the results from the PREvención con DIeta MEDiterránea (PREDIMED) study. This landmark randomized primary prevention trial showed that the Mediterranean diet provides long-term high benefits on CVD compared with a low-fat diet [86]. However, no consensus about the best dietary pattern for the secondary prevention of CHD has been reached. The Coronary Diet Intervention with Olive oil and cardiovascular Prevention (CORDIOPREV) study is a dietary intervention trial comparing the rate of cardiovascular events of two healthy dietary patterns for secondary cardiovascular prevention [87]. One of them is low in fat and rich in complex carbohydrates, as proposed by the National Cholesterol Education Program (NCEP) and the American Heart Association (AHA) [88]. The other is a Mediterranean diet, rich in extra-virgin olive oil (EVOO), fruit and vegetables, whole grains, fish and nuts, and low in SFA, which has consistently demonstrated favourable effects on cardiovascular risk factors in patients in secondary prevention, but not consistently in cardiovascular events trials [89-93]. The CORDIOPREV study involves 1002 patients with CHD receiving a comprehensive dietary intervention for 7 years. The intervention phase was

completed in 2018. Data for the primary outcome measures, secondary outcome measures, and adverse events are currently being analyzed. Results from this large trial would offer a robust basis for secondary cardiovascular prevention guidelines.

1.2. Assessment of the relationship between diet and type 2 diabetes/cardiovascular disease

It is widely acknowledged that dietary habits have a strong influence on multiple cardiometabolic risk factors, including glucose-insulin homeostasis, blood pressure, lipoprotein concentrations and function, inflammation, endothelial function, oxidative stress, hepatic function, metabolic expenditure, adipocyte function, pathways of weight regulation, cardiac function, visceral adiposity, and the gut microbiota [94]. Consequently, diet is one of the main modifiable risk factors for chronic non-communicable diseases and plays a major role not only in their prevention but also in their management.

Poor dietary habits are one of the principal drivers of chronic diseases like T2DM, CVD and some cancers. According to a recent systematic analysis for the Global Burden of Disease study [95], a suboptimal diet (including inadequate intakes of whole grains, fruits and vegetables, and excess consumption of sodium, meat and sugar-sweetened drinks) was responsible for one-in-five deaths and 255 million disability-adjusted life years globally in 2017. CVD was the leading cause of diet-related deaths, followed by cancers and T2DM. Most importantly, poor dietary habits accounted for more deaths than any other risks globally. Moreover, obesity, dyslipidemia and hypertension, which confer an increased risk of T2DM and cardiovascular events, are also strongly related to diet.

Contrary, healthy eating patterns with an adequate calorie intake can help to maintain a healthy body weight, reduce the risk of chronic diseases and manage these

chronic conditions in those who already suffer them [78,94]. These patterns share several key common characteristics, including a high consumption of plant-based foods (fruits, vegetables, whole grains, legumes and nuts), a low intake of animal-based foods (particularly fatty and processed meats) and a very limited intake of refined grains, added sugar, sodium, SFA and trans-fatty acids [96].

1.2.1. The role of diet in type 2 diabetes and cardiovascular disease

The relationship of specific nutrients, foods and dietary patterns with T2DM has been extensively investigated [48,97]. Similarly, the study of the potential effects of dietary factors in the development of CVD and the possible mechanisms underlying these effects has been a major concern of the nutritional epidemiology research during the last decades. Considering that both chronic conditions and their risk factors are interrelated, targeting dietary factors for CVD may also help to prevent T2DM.

Diet is a particularly complex and dynamic exposure as we do not eat individual nutrients and foods in isolation but combinations of foods which contain many nutrients and other constituents that interact. The concept of dietary pattern summarises and captures the complexity of the diet, and therefore is most relevant for cardiometabolic health than individual nutrients or foods [94]. Considering that diet-disease relationship is the result of a long-term exposure and that each dietary factor can influence many cardiovascular and metabolic pathways, the dietary pattern approach is particularly appropriate in the context of chronic diseases like CVD and T2DM.

In agreement with current guidelines, and in the context of high-quality overall dietary patterns, the Mediterranean diet, the DASH diet, and healthy vegetarian diets have the most evidence for CVD prevention [82,98] and moderate evidence for T2DM prevention [99].

1.2.1.1. The Mediterranean diet

The Mediterranean diet is a widely used concept that describes a centuries-old eating pattern and lifestyle habits seen in Greece, Southern Italy, Spain and other olive tree-growing areas of the Mediterranean basin in the early 1960s [100]. Nutritional, socio-cultural, economic and environmental features, together with regular physical activity, are important parts of this concept. Thus, the Mediterranean diet is a whole healthy lifestyle pattern and reflects the diversity of Mediterranean food cultures, with their different food consumption and production patterns [101]. In this sense, it important to highlight that there is not one single Mediterranean diet but instead a number of versions of this eating pattern adapted to individual country's dietary practices and traditions.

The Mediterranean diet is a mainly plant-based dietary pattern that includes the abundant use of olive oil as the main culinary fat and a high consumption of vegetables, fruits, legumes, nuts, and unprocessed cereals. The diet also includes moderate consumption of wine (usually with meals), fish and dairy products (especially yoghurt and cheese), and low intake of red and processed meats and foods high in added sugars [102]. This translates to a diet with high content of dietary fiber, vitamins, minerals, monounsaturated fatty acids (MUFA) and omega 3 fatty acids, and other bioactive compounds, such as phytochemicals and polyphenols; and low content of SFA and trans-fatty acids, refined sugar, and carbohydrates of low glycemic load. Although healthy dietary patterns share similarities (Figure 4), the high intake of fat from olive oil and nuts, the moderate intake of wine, and the frequent use of *sofrito* (a homemade sauce with tomato, garlic, onion, aromatic herbs and olive oil, slow-cooked) are unique and differentiating components of the Mediterranean diet.

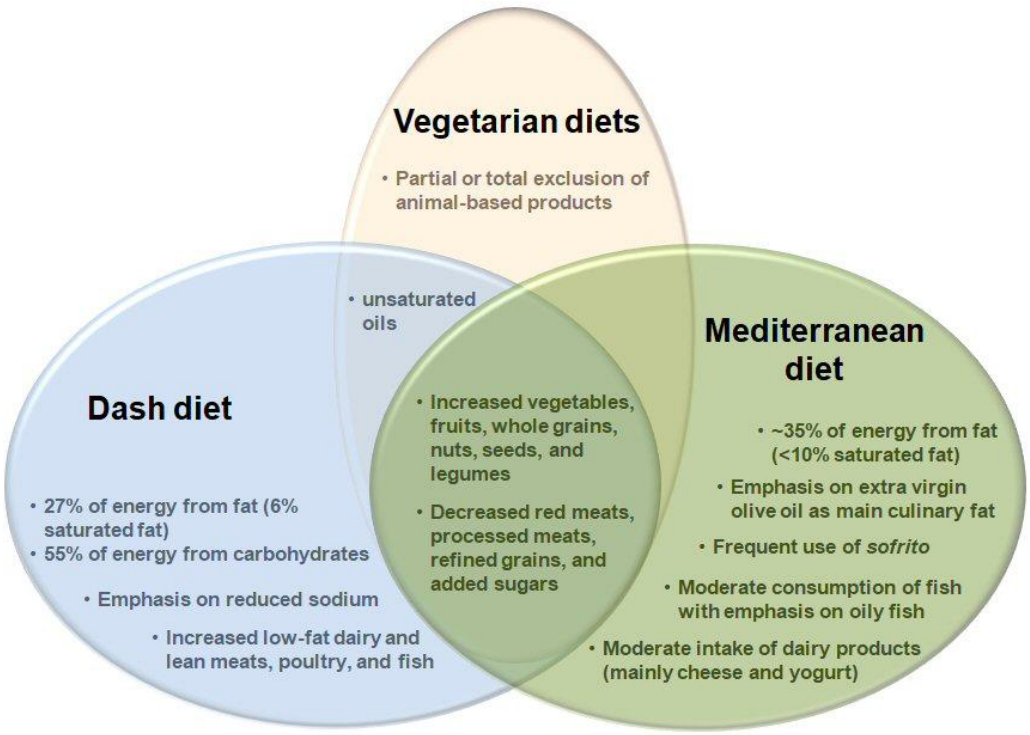

Figure 4. Commonalities and unique features of the Mediterranean diet, DASH diet, and vegetarian diets. Modified from Richter et al. [103]

CVD, and particularly CHD, has been the most analyzed disease outcome regarding the effects of the Mediterranean diet on chronic diseases. The first scientific evidence came from the Seven Countries Study, which suggested a link between local diets rich in MUFA and the low CHD mortality rates in the Mediterranean populations [104]. Since this ecological study conducted in the 1960s, a large number of prospective studies (observational studies and randomized clinical trials, RCT) and their meta-analyses have consistently shown the protective effect of the Mediterranean diet on CVD hard clinical endpoints [93,105,106]. For instance, a recent meta-analysis of 20 prospective studies and RCTs showed that participants with high Mediterranean diet adherence had lower incidence of (RR: 0.73; 95% CI: 0.66-0.80) and mortality from

CVD (RR: 0.71; 95% CI: 0.65-0.78) compared to those least adherent [93]. In this meta-analysis, an average 40% decreased risk of CVD incidence and mortality was found when pooling results of RCTs conducted on high CVD risk individuals. These results were further corroborated by Dinu et al. in an umbrella review of 13 meta-analyses of observational studies and 16 meta-analyses of RCTs, which included more than 12.800.000 individuals [105]. This latest review provides robust evidence supporting the effectiveness of the Mediterranean diet to reduce the risk of overall mortality, CVD, CHD, myocardial infarction and T2DM [105].

Two large, randomized trials of dietary intervention have been crucial to support causality regarding the protective role of the Mediterranean diet on cardiovascular health. The Lyon Diet Heart Study reported that a "Mediterranean diet enriched with α-linolenic acid" reduced recurrent cardiovascular events by 50%–70% among myocardial infarction patients, after 4 years of follow-up [107]. However, the addition of the canola oil as the source of fat makes that the result may not exactly be identified as "Mediterranean diet". Furthermore, its comparator was a "prudent Western-type diet", which is not an acceptable diet as a comparator in a secondary prevention environment. More recently, the PREDIMED study has confirmed these results also for primary cardiovascular prevention. In this trial, conducted in 7447 Spanish participants at high risk for CVD, a Mediterranean diet supplemented with EVOO or nuts was associated with 30% reduction in the rate of major cardiovascular events (a composite endpoint including myocardial infarction, stroke, and deaths) compared to a control low-fat diet, after a median follow-up of 4.8 years [86].

In terms of T2DM prevention, evidence from prospective cohort studies and RCTs supports that the Mediterranean diet is effective in reducing the risk of T2DM both in healthy and high-risk cardiovascular individuals [48,108-110]. For example, a meta-analysis conducted by Schwingshackl et al. (8 prospective studies and 1 RCT; >100.000 participants) found that a higher adherence to the Mediterranean diet was

associated with a 19% reduced risk of T2DM (RR: 0.81; 95% CI: 0.73-0.90) [109]. Similarly, Jannasch et al. showed in a recent meta-analysis that individuals highly adherents to the Mediterranean diet had a 13% lower risk of T2DM than those with low adherence (RR for comparing extreme quantiles: 0.87; 95% CI: 0.82-0.93) [48]. Furthermore, results from the PREDIMED study showed a 40% (HR: 0.60; 95% CI: 0.43-0.85) reduction in the incidence of T2DM in participants consuming a Mediterranean diet enriched with EVOO compared with those consuming a low-fat control diet [110].

The exact mechanisms by which the Mediterranean diet exerts its beneficial effects on preventing CVD and T2DM have not been fully elucidated. Potential mechanisms of action include its beneficial effects on traditional and non-traditional CVD risk factors [111], such as improvements in lipid profile and glucose metabolism, a reduction of oxidative stress, inflammation and platelet aggregation, a shortening of the duration of the postprandial lipemia, and an enhancement of endothelial function and metabolic health modulated by intestinal microbiota, among others [112,113]. These effects could be mainly attributed to the richness of the Mediterranean diet in natural bioactive compounds, such as polyphenols, carotenoids, phytosterols, dietary fiber, MUFA or polyunsaturated fatty acids (PUFA), which have powerful antioxidant, anti-inflammatory, and antithrombotic properties [114,115].

Taking into account the large, strong and consistent evidence that supports the protective effect of the Mediterranean diet on CVD and T2DM risk, it is clear that this high-quality and environmentally sustainable dietary pattern [116] is an ideal model for cardiovascular health.

1.2.1.2. The DASH diet

The DASH diet was originated in the 1990s and promoted by U.S. National Institutes of Health to prevent and control hypertension. The consumption of high amounts of fruits and vegetables, together with low-fat or fat free dairy, is the main characteristic of this healthy diet. It includes whole grains, lean fish, poultry, legumes, and nuts; and recommends reducing sodium intake, red meat, and sweets (in drinks and foods) [117]. The DASH diet also promotes the consumption of foods that are rich in potassium, calcium, and magnesium, while limiting SFA and trans-fatty acids.

Both the original DASH diet (27% fat, 15% protein and 58% carbohydrate, with high content of grains and starchy foods) and redesigned DASH diets (replacement of 10% energy of carbohydrate with protein or unsaturated fat from vegetable sources) have been demonstrated to significantly reduce blood pressure and improve blood lipids [118]. A recent umbrella review of the DASH dietary pattern and cardiometabolic outcomes showed that adherence to a DASH-type diet was also associated with a clinically meaningful reduction in HbA1C, fasting insulin, and body weight in RCTs, and a decreased incidence of CVD, CHD, stroke, and T2DM in prospective cohort studies [119]. The aforementioned benefits of this healthy dietary pattern may be attributable to its richness in dietary fiber, unsaturated fatty acids, potassium, calcium, magnesium and antioxidants components, and the synergy between them [120].

1.2.1.3. Plant-based diets and vegetarian diets

The term “plant-based diets” refers to a wide range of dietary patterns that include a low consumption of animal-derived products and a high intake of foods derived from plants. Among plant-based diets, vegetarian diets are defined by the partial or total exclusion of animal-based products [121]. Moreover, plant-based diets and vegetarian diets are also defined in terms of the quality of plant foods included and their potential effects on health [122]. Thus, healthy plant-based diets encourage a high

intake of whole grains, vegetables, fruits, legumes, and unsaturated oils, while unhealthy plant-based diets include a high consumption of refined grains, snacks, pastries or sugar-sweetened beverages.

Accumulating evidence from prospective studies supports the potential role of healthy plant-based diets in reducing cardio-metabolic risk and preventing CVD and T2DM [122-125]. For example, a recent meta-analysis of prospective cohort studies (197.737 participants) found that vegetarian dietary patterns were associated with a 28% reduced risk of CHD and 22% reduced CHD mortality [124]. In another recent meta-analysis totalling 307.099 participants with 23.544 cases of incident T2DM, closer adherence to a plant-based dietary pattern was inversely associated with the risk of T2DM (RR: 0.77; 95% CI: 0.71-0.84), and this association was strengthened when the dietary pattern included healthful plant-based foods (RR: 0.70; 95% CI: 0.62-0.79) [125]. Nutritional quality of healthy plant-based diets could explain these associations. Their richness on whole grains, fruits, legumes and nuts lead to a high content of unsaturated fats, dietary fiber, vitamins, minerals, antioxidants and phenolic compounds. These foods, individually and in combination, have been shown to improve insulin sensitivity [126], reduce blood pressure [127], promote weight loss and long-term weight maintenance, and decrease inflammation [128]. The substitution of red and processed meats by high quality plant foods lead to reduce the levels of sodium, heme iron, nitrates and nitrites, which have been associated with increased risk of CVD and T2DM [121,129].

1.2.2. Dietary adherence

Dietary intervention trials are an important tool to assess the relationship between diet and chronic diseases such as CVD and T2DM. However, large-scale dietary intervention trials are challenging. In these trials, beyond the choice of diet, the

most significant factor for the success of the intervention is the participants' adherence to the diet, especially in free-living settings and in long-term follow-up [130,131]. Thus, poor adherence and the difficulty of maintaining dietary changes are the main barriers to the long-term success of dietary intervention trials.

The WHO in their report *"Adherence to long-term therapy, evidence for action"* adopted a concept of adherence that includes numerous health-related behaviours and not just following medical instructions [132]. In the context of intervention trials, dietary adherence could be defined as the extent to which a participant's diet corresponds with the assigned dietary pattern in the trial. In this sense, dietary adherence measures the ability to achieve and maintain recommended dietary changes over time, implies active participant involvement and depends not only on the characteristics of the participant but also on the study features.

In dietary intervention trials, a good initial dietary adherence followed by gradual decreases over time is frequently observed when only dietary instructions are given [133]. However, the use of strategies to change dietary behaviour such as regular contact, negotiation, goal setting, monitoring of adherence and assistance, problem-solving and the free provision of key food items leads to enhanced dietary adherence [133-137]. Besides, involving family members in diet counselling visits are crucial considering that social support is one of the most important motivators to achieve adherence [132]. Moreover, the use of adherence diet screeners, simple tools which summarize the overall diet with a single score, not only allows to measure the level of dietary adherence easily but also provides immediate feedback to the participants, thus enhancing goal achievement and increasing the effectiveness of the intervention.

On the other hand, dietary adherence can also be measured in observational studies. In this context, dietary adherence is defined as the extent to which a participant's dietary habits corresponds with a pre-defined healthy dietary pattern which is studied in relation to a specific disease.

In both cases, dietary intervention trials and observational studies, an accurate and reliable measure of dietary adherence is crucial for the reliability of the results obtained.

1.2.2.1. Evidence on benefits of high dietary adherence on clinical outcomes: the case of Mediterranean diet adherence

Previous research has clearly revealed an important link between high dietary adherence and reaching pre-determined health-related goals. Focusing on dietary intervention trials, previous results have shown a strong correlation between high adherence to a Mediterranean diet intervention and improvement in cardiovascular risk factors [137,138], amelioration of atherothrombosis biomarkers [139], better quality of life [140], and prevention of CVD and T2DM in high CVD risk participants [86,110]. In all of these studies, dietary adherence was measured at each visit, was used to reinforce dietary changes and was included as covariate in all analyses.

Several large and well-characterized prospective cohort studies have estimated the risk of T2DM according to different levels of adherence to the Mediterranean diet [141-145]. These studies showed risk reductions ranging from 12% to 83% for participants with high adherence to the Mediterranean diet compared to those in the low adherence category. Only one prospective study has examined this association in patients with CVD, which found that high adherence to the Mediterranean diet reduced T2DM risk by 35% (HR: 0.65; 95% CI: 0.49-0.85) [146]. This study included 8.291 Italian patients with myocardial infarction participating in the GISSI-Prevenzione trial, with a mean follow-up of 3.2 years.

Closer adherence to the Mediterranean diet has been inversely associated with the risk of mortality from or incidence of CVD [93,106,147]. In a recent meta-analysis of prospective studies (25 observational cohorts and 2 trials), each 2-point increment in the Mediterranean diet score (0–9 points) was associated with 11% relative reduction

in the risk of CVD (Risk Ratio: 0.89; 95% CI: 0.86–0.91) [147]. In another recent meta-analysis of 29 observational studies, participants in the highest category of Mediterranean diet adherence had a 20% lower risk of CVD than those in the lowest category (RR: 0.81; 95% CI, 0.74-0.88) [106].

With respect to the metabolic syndrome, several prospective studies have reported and inverse association between Mediterranean diet adherence and the development of this chronic condition. A recent meta-analysis by Godos et al. [148]., which included 8 cross-sectional and 4 prospective studies with 33.847 individuals, indicated that participants with the highest adherence to the Mediterranean diet had 19% less risk of developing metabolic syndrome (RR: 0.81: 95%CI: 0.71-0.92) compared to lowest adherence. Regarding individual components of the metabolic syndrome, Godos et al. found that inverse associations were significant for waist circumference, blood pressure and low HDL cholesterol levels.

Adherence to the Mediterranean diet has also been related to lower risk of cancer and cognitive disorders. In a recent meta-analysis of 35 cohort studies and 21 case-control studies (1.784.404 subjects), Schwingshackl et al. reported that strongest adherence to a Mediterranean diet was inversely associated with cancer mortality and risk of colorectal, breast, gastric, liver, head and neck, gallbladder, and biliary tract cancer [149]. Wu et al. [150], in a meta-analysis of 9 cohort studies with 34.168 participants, found that participants in the category of high adherence had 21% less risk of developing cognitive disorders (RR:0.79; 95% CI: 0.70, 0.90) compared to those in the category of low adherence. A report of the Seguimiento Universidad Navarra (SUN) study, which included 15.093 Spanish university graduates with a median follow-up of 8.5 years, indicated that moderate-high adherence to the Mediterranean diet was associated with a reduced risk of depression (HR for fourth vs. first quintile: 0.80; 0.66–0.97) [151].

Finally, results of the Early Vascular Aging study showed that higher adherence to the Mediterranean diet reduced the probability of presenting early vascular aging (OR: 0.36; 95% CI: 0.16-0.82) [152].

1.2.2.2. Assessment of dietary adherence in dietary intervention studies

Considering that the best dietary intervention may be ineffective due to lack of adherence and that the findings of a dietary intervention trial may be compromised by poor adherence, the assessment of adherence and changes towards recommended diet is a critical element.

Dietary adherence can be measured through different indicators and each of these has its own advantages and drawbacks. One of them is attendance at nutritional counselling sessions (individual or group visits), which has been shown to be an important factor associated with dietary goals achievement [153]. In most studies, attendance is expressed as a rate (i.e. percent of the number of sessions attended out of the maximum number of sessions provided), where a high attendance rate would indicate high adherence to the intervention. However, attendance only reflects the capacity of participants to adhere to a behavioral component of the study but does not inform if participants follow the dietary recommendations or not [154]. Biochemical markers of compliance are also used as an indicator of adherence to the dietary intervention, especially in intervention trials that used diets supplemented with key foods. For example, urinary tyrosol and hydroxytyrosol are widely used as markers of olive oil intake. Although biochemical markers provide objective and accurate measurements of the intake of certain foods or nutrients, they are potentially influenced by numerous dietary and non dietary factors which can compromise their validity [155]. Moreover, biochemical markers are expensive, which makes them difficult to use in many studies. On the other hand, dietary adherence can be measured by several dietary assessment tools. One of them is the food frequency questionnaire (FFQ),

which provides estimates of usual dietary intake over time (typically 1 year) [155]. The basic principle behind their use is that differences in the total amount of food or nutrients consumed depend on the frequency of consumption rather than differences in the size of the servings served. This type of questionnaire provides extensive information on the consumption not only of food and food groups but also of energy and nutrients. FFQs including about 100 to 150 food items take 20-30 minutes to complete and then extra time is needed to process the information, which makes difficult a rapid assessment of dietary adherence. To overcome this limitation, most intervention studies use short questionnaires that quantitatively estimate the level of adherence to a specific diet, which are easy and quick to use and which allow to provide brief dietary feedback to participants in the study. These tools are usually called dietary indices or dietary scores and will be described in detail below.

1.2.3. Dietary pattern analysis

In the last two decades, nutritional epidemiologic research has moved from the traditional and reductionist single-nutrient/food approach to the more holistic approach of dietary patterns in relation to studying the association between diet and chronic diseases [156]. Examining and interpreting the effects of individual food or nutrients in T2DM or CVD is complicated and limited because humans do not consume specific foods or nutrients in isolation, but a combination of foods containing a variety of nutrients and other bio-active constituents that may act synergistically [155]. The intake of foods and nutrients is highly correlated (for example, diets rich in dietary fiber tend to be high in vitamin C, folic acid, carotenoids, magnesium and potassium) and when one component of the diet changes, it is usually replaced by another (for example, low-fat diets are usually high in carbohydrates). Therefore, it is difficult to investigate and interpret the effects of single foods or nutrients on health outcomes. Consequently, the study of dietary patterns has been recommended as a complementary approach to

examine the diet-disease relationship [156]. This approach accounts for both the complexity and the cumulative effects of dietary constituents on the overall disease risk, and may thus be a better predictor of disease risk than the study of single foods or nutrients [157]. This approach is particularly appropriate when many dietary components are relevant to a disease, such as in T2DM or in CVD [158]. Moreover, in terms of public health, the study of dietary patterns as a risk factor is particularly valuable because dietary patterns are easily translatable into dietary recommendations and public health messages [159].

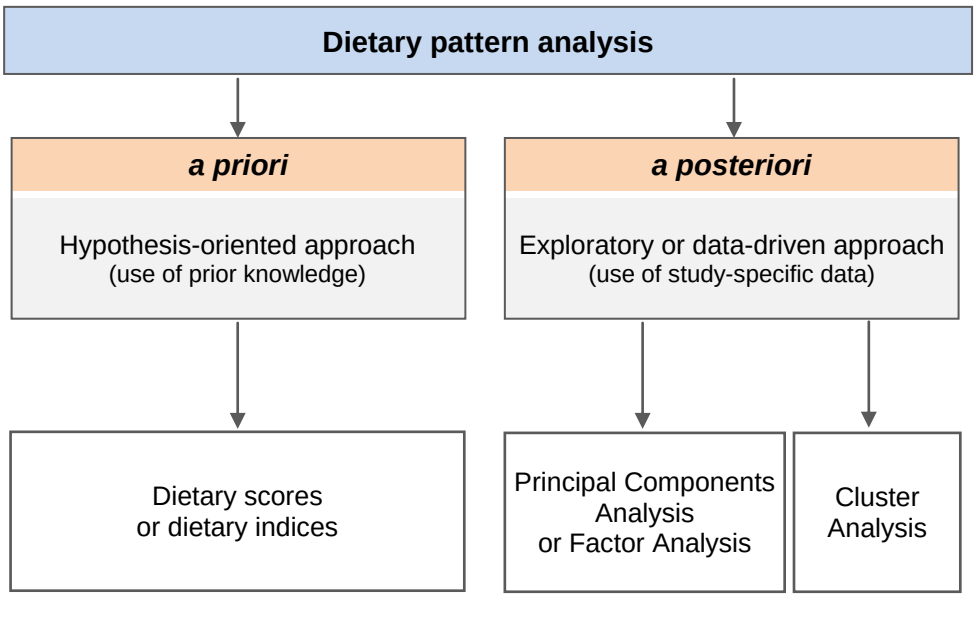

Figure 5. Methodological approaches to define dietary patterns. Modified from Schulze et al. [158]

Dietary patterns are defined as "the quantities, proportions, variety, or combination of different foods, drinks and nutrients in diets, and the frequency with which they are habitually consumed" [160]. Depending on the research question and study design, dietary patterns can be defined using two main approaches: *a priori* or hypothesis-driven approach and *a posteriori* or data-driven approach (Figure 5). The *a*

priori approach defines dietary patterns based on existing knowledge about the relationships between foods, nutrients, and specific diseases, while the *a posteriori* approach derives dietary patterns from the dietary data of the population of interest using statistical modelling. Thus, the *a priori* approach is useful to measure the compliance with specifics dietary recommendations whereas the *a posteriori* approach is useful to identify specifics dietary patterns in a population.

1.2.3.1. *A priori* dietary pattern analysis

In *a priori* analysis, scores or indices of the overall dietary quality are defined based on dietary guidelines, available scientific evidence regarding the association between diet and a specific disease, or a reference healthy diet (e.g. Mediterranean diet) [156], which conditions the type and number of components included in the dietary score. Each participant in the study receives a score in each component of the dietary score, depending on whether the criteria for each component are met or not. The components punctuations are then summed to a total score and participants are ranked from the minimum to maximum total score, wherein higher scores indicated high adherence to a dietary guideline or a specific healthy diet.

A priori-defined dietary scores are usually simple to compute and easily reproducible and comparable across populations. Moreover, they are usually related with health outcomes and therefore they are particularly useful for investigating associations between diet and disease endpoints [161]. However, this approach also has its limitations. Dietary scores focus on selected dietary aspects and thus the correlated structure of food and nutrient intakes is not considered [162]. Moreover, the accuracy of dietary scores is limited by the scientific evidence available at the time they are developed, as well as subjective decisions accompanying the dietary score construction process (i.e. choice and quantification of components).

There is a vast variety and quantity of dietary scores. A recent review of this topic identified a total of 57 dietary scores or their variations, of which 21 were Mediterranean diet scores [163]. These tools have been widely used in epidemiological and RCTs to measure adherence to the Mediterranean diet [164]. Two of the most relevant Mediterranean diet scores are the Mediterranean Dietary Score proposed by Trichopoulou et al. (MDS-Trichopoulou) [102] and the 14-point Mediterranean Diet Adherence Screener (MEDAS) [165]. A short description of these two Mediterranean diet scores, which are used within this thesis, is provided below.

The MDS-Trichopoulou is the most widely used in the literature and has several variants developed to assess different diet-heath relations [166]. This dietary score includes nine components (ratio of MUFA to SFA, vegetables, fruits and nuts, legumes, cereals, fish and seafood, meat and meats products, dairy products and moderate alcohol intake) and uses sex-specific medians of consumption of the study population as cut-off points to define a high or low consumption of each dietary component. Thus, one point is assigned to a person with a high consumption of six foods considered to be protective and with a low consumption of those components considered to be detrimental (Table 3). For alcohol intake, one point is given for moderate alcohol intake (5-25 g/day for women or 10-50 g/day for men). Therefore, the total score ranges from 0 to 9 points, with 9 points indicating the highest adherence to a Mediterranean diet.

The MEDAS was developed and used in the landmark PREDIMED study to measure compliance with the two Mediterranean diet interventions (one supplemented with EVOO and the other with mixed nuts) performed in this trial. This screener has been shown to be a valid tool for a rapid evaluation of Mediterranean diet adherence in both Mediterranean [165,167] and non-Mediterranean countries [168-170]. The MEDAS consist of 2 questions about eating habits and 12 questions about the frequency of consumption of different foods (Table 3). This screener uses pre-defined goals for each of the 14 components, assigning one or zero points depending on

whether the objective for each item is met or not. Therefore, the total score ranges from 0 to 14 point (14 points reflecting maximum adherence to the Mediterranean diet).

Table 3. Overview of the Mediterranean Diet Score proposed by Trichopoulou et al. (MDS-Trichopoulou) and the 14-point Mediterranean Diet Adherence Screener (MEDAS)

	MDS-Trichopoulou	MEDAS
Items	Beneficial foods: • Ratio of MUFA to SFA • Vegetables • Fruits and nuts • Legumes • Fish and seafood • Cereals • Moderate alcohol intake* Detrimental foods: • Meat and meat products • Dairy products	• Olive oil as main culinary fat • Olive oil ≥4 tablespoons/day • Vegetables ≥2 servings/day • Fruits ≥3 servings/day • Red/processed meats <1serving/day • Butter/margarine <1serving/day • Sugar-sweetened carbonated beverages <1serving/day • Wine ≥7 glasses/week • Legumes ≥3 servings/week • Fish/seafood ≥3 servings/week • Commercial bakery ≤2 servings/week • Nuts ≥3 servings/week • Preference for poultry instead of red meats • Use of *sofrito* ≥2 servings/week
Scoring system	Beneficial foods: 1 point for consumption at or above sex-specific medians (g/day). * 1 point for consumption of 5–25 g/day in women and 10–50 g/day in men. Detrimental foods: 1 point for consumption below sex-specific medians (g/day)	Positive responses= 1 point Negative responses= 0 points
Range	0-9 points	0-14 points

1.2.3.2. *A posteriori* dietary pattern analysis

A posteriori analysis describes the real diet consumed by the population under study, which means that these methods do not necessarily identify dietary patterns

related to a specific health outcome [156]. Unlike *a priori* analysis, this approach is not based on previous information and therefore it is not limited by available scientific knowledge. Rather, *a posteriori* approach analyzes dietary intake data through statistical methods such as principal components analysis (PCA), factor analysis, and cluster analysis [158]. Of them, PCA is the most widely used *a posteriori* method in nutritional epidemiology and the *a posteriori* method used within this thesis.

PCA reduces a large number of dietary variables, which are possibly correlated with each other, creating uncorrelated linear combinations (called components or patterns) that explain the greatest amount of variance in food intake. This method is based on the correlation matrices of the original variables (food groups). An orthogonal rotation procedure is usually applied to the extracted components, which leads to independent or uncorrelated components and improves their interpretation [171]. The number of components initially extracted is equal to the number of original variables (food groups) but only the first components account for a large quantity of the total variance. The final number of retained components is usually based on several parameters, including the eigenvalue-one criterion, the scree test and the interpretability criteria [171]. Each food group in each pattern has a weight named factor loading, where a positive factor loading indicates that the food group is positively correlated with the pattern and a negative value shows an inverse correlation. Finally, a factor score is calculated for each dietary pattern and each participant, where a higher value indicates a higher adherence to the corresponding dietary pattern.

Like other *a posteriori* methods, PCA has limitations related to the difficult of comparing the identified dietary patterns among populations (they are population-specific) or the subjective decisions made during the analytical process, which must be taken into account.

II. HYPOTHESIS

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T2DM and CVD are the most important causes of death and early disability by non-communicable diseases in developed countries, and together, they have prevalence higher than 25% in these countries, being also the most important causes of healthcare systems expenditure. In addition, coronary patients with coexisting T2DM have an additional increased risk of cardiovascular events.

Diet is a major modifiable risk factor for both conditions. The most common strategies for unveiling the underlying mechanisms by which diet influences CVD and T2DM have been using either *a priori*- or *a posteriori*-defined dietary patterns. However, to date, there are not clear arguments to say which dietary pattern method predicts better which patient will develop T2DM among patients with CVD.

Therefore, the hypothesis of this thesis is to investigate whether a diabetes prediction model that includes an *a priori*-defined dietary pattern (dietary score) has similar predictive ability as a prediction model including an *a posteriori*-derived dietary pattern (empirically derived dietary pattern, using PCA) after a period of dietary intervention.

The null hypothesis is that a diabetes prediction model including a dietary score has a different predictive capacity than another model that uses an empirically derived dietary pattern.

III. OBJECTIVES

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Main objective

To determine if there is a method of dietary pattern analysis (i.e. *a priori*-defined dietary score or *a posteriori*-derived dietary pattern) which predicts with greater reliability the development of T2DM after 5 years of intervention with a Mediterranean diet or a low-fat diet in coronary patients.

Secondary objectives

1. To study the association between three *a priori*-defined dietary scores (MEDAS, 14-point Mediterranean Diet Adherence Screener; LFDAS, 9-point low-fat diet adherence screener; MDS-Trichopoulou, Mediterranean Dietary Score proposed by Trichopoulou et al.) assessed at baseline and after 1 year of intervention, and the incidence of T2DM after 5 years of follow-up.
2. To investigate the association between the *a posteriori*-derived dietary patterns using PCA (PCA-dietary patterns) at baseline and after 1 year of intervention, and the incidence of T2DM after 5 years of follow-up.
3. To determine the relationship between the three dietary scores and PCA-dietary patterns and the following variables after 5 years of follow-up in our population:
    - Anthropometric variables: BMI, waist circumference.
    - Biochemical variables: HbA1c, HOMA-IR, C-reactive protein, leukocytes, neutrophil-lymphocyte ratio, triglycerides, and total, HDL and LDL cholesterol
4. To compare and assess the validity of the selected dietary scores and PCA-dietary patterns by their correlation with dietary data derived from food frequency questionnaires in our population.
5. To investigate the changes in dietary habits and address the level of adherence to the dietary intervention in the long-term in our population.

IV. METHODS

IV. METHODS

4.1. CORDIOPREV study design

This doctoral thesis has been conducted in the frame of the CORDIOPREV study, a randomized, single-blind, controlled, cardiovascular secondary prevention trial conducted in Spain between 2009 and 2018 with the objective to compare the effects of a Mediterranean-type diet and a low-fat diet on the risk of suffering new cardiovascular events.

The primary outcome comprised a composite of hard cardiovascular events (myocardial infarction, revascularization, ischemic stroke, documented peripheral artery disease or cardiovascular death) after a median follow-up of 7 years. In order to understand the role of dietary changes on clinical events, the study also included changes in intermediate outcomes such as fasting blood glucose, blood pressure, lipid profile, gut microbiota and markers of inflammation and oxidation. The incidence of T2DM is one of the prespecified secondary outcomes (Appendix I).

The study was registered at ClinicalTrials.gov (number NCT00924937). The study protocol was approved by the Human Investigation Review Committee of the Reina Sofia University Hospital following the Helsinki Declaration and Good Clinical Practice guidelines. Full details of the rationale and methods of the CORDIOPREV study have been reported by Delgado-Lista et al. [87].

The recruitment process of the CORDIOPREV study took place from July 2009 to February 2012. The intervention phase was ended in December 2018 with a median follow-up of 7 years. The data used in this thesis are from the first 5 years of follow-up.

Screening, baseline and follow-up visits were conducted at the Reina Sofia University Hospital and laboratory measurements were performed at the Instituto Maimonides de Investigacion Biomedica de Cordoba (IMIBIC).

4.2. CORDIOPREV study population

Almost of the CORDIOPREV participants were from Cordoba capital city and its province, but also patients from the province of Jaen were also admitted. The inclusion and exclusion criteria are detailed in Appendix II. To sum up, eligible participants were men and women (20 to 75 years old) with confirmed CHD and no clinical events in the last 6 months before screening, who were able to follow a long-term dietary intervention, and had no severe illnesses (e.g. psychiatric illnesses, chronic renal insufficiency or neoplasia under treatment). After recruitment, patients were assigned randomly to two intervention groups: Mediterranean diet or low-fat diet. All patients provided written informed consent before their inclusion in the study.

The CORDIOPREV study involved 1002 coronary patients, of which 462 were non-diabetics (patients without a clinical diagnosis of T2DM at baseline visit). For the main analysis of this thesis, the 462 non-diabetics patients were included. For secondary analyses of this thesis, including the validation of the dietary scores and the study of the long-term dietary adherence, the 1002 coronary patients were included.

4.3. CORDIOPREV dietary intervention

The dietary intervention was performed by a team of registered dietitians (RDs) who were previously trained to ensure uniformity and the quality of the intervention. The primary goal of the dietary intervention was to change the eating habits of the patients towards the randomized diet, focusing on the overall quality of the diet rather than on specific nutrients. No intervention to increase physical activity or lose weight was included.

Both study diets included foods from all major food groups, but no total calorie restriction was advised. The Mediterranean diet comprised a minimum of 35% of total calories from fat (22% MUFA, 6% PUFA, < 10% SFA), ≤ 50% from carbohydrates and

15% from protein. The low-fat diet included less than 30% of total calories from fat (12–14% MUFA, 6–8% PUFA, < 10% SFA), ≥ 55% from carbohydrates and 15% from protein.

The specific recommended diets are summarized in Appendix III. In the Mediterranean diet group, RDs gave personalized counseling to achieve the following goals progressively: abundant use of EVOO for cooking and dressing (≥4 tablespoons/day; 10–15 g/tablespoon); daily consumption of at least two servings of vegetables (200 g/serving; at least one serving raw or as salad) and three or more units of fresh fruit (125–150 g/unit); weekly consumption of at least three servings of legumes (150 g cooked weight/serving), three or more servings of fish or seafood (especially oily fish; 100–150 g/serving) and fresh nuts and seeds (three or more handfuls per week); cooking dishes seasoned with “sofrito” (a slow-cooked homemade sauce with tomato, garlic, onion, aromatic herbs, and olive oil) at least twice a week; a reduction in meat consumption, choosing (skinless) white meat instead of red meat or processed meat (<1 serving/day); and avoidance of additional fats (butter, margarine, seed oils, creams, etc.) and foods rich in sugar and unhealthy fats (commercial bakery products, chips, precooked food, sugared beverages, etc.). A moderate consumption of wine (seven glasses/week, during meals) was permitted only if the participant was previously a regular wine consumer. The patients allocated to the low-fat diet received personalized recommendations according to the American Heart Association (AHA) and the National Cholesterol Education Program (NCEP) dietary guidelines in use at the beginning of the study [88], focused on limiting all types of fat consumption (both animal and vegetable) and on increasing the intake of complex carbohydrates. Specifically, they were advised to minimize the amount of oil used for cooking and dressing (≤ 2 tablespoons/day); always remove visible fat from meats and soups; not to eat more than one serving of red meat per week; choosing low-fat dairy products; consumption of lean fish instead of oily fish or fish/seafood canned in oil (≤ 1

serving/week); avoidance of nuts and seeds (≤1 serving/week); to limit the consumption of commercial bakery goods, sweets, and pastries (≤1 serving/week) and to cook without the use of oil. There were no other differences in the dietary recommendations between groups.

The RDs conducted the dietary intervention with the same intensity in the two intervention groups. Table 4 shows an overview of dietary intervention performed yearly. At baseline and every 6 months, patients had an individual face-to-face visit with the RDs which included assessment of dietary intake and adherence, feedback, and reinforcement, as well as future directions. At each visit, RDs and patients worked together to identify dietary habits that needed to be changed, to set short-term goals and to work out how to make the changes. The achievements reached in the previous visits were used to increase patient motivation. Bimonthly telephone interviews were performed by the RDs to monitor compliance with the assigned diet, negotiate nutrition goals, and reinforce the dietary recommendations. In addition, group sessions of 20 participants were organized separately for each group every 3–4 months. These 2-h sessions included oral and written information (e.g., recipes, plans for meals, cooking tips, and shopping lists), group discussions, handouts, and reinforcement of dietary recommendations. To find social support, family members were encouraged to attend the individual and group sessions with the patient, especially if they shared the responsibility for food selection and the preparation of meals.

Written materials were designed and given to the patients at the individual and group sessions to enhance oral recommendations: leaflets summarizing the main food components and their frequency of consumption, and cooking recipes focused on increasing skills for preparing meals which complied with the assigned diet and meal plans. The patients also received free food to encourage dietary adherence: EVOO rich in polyphenols in the Mediterranean diet group (approximately 1 L per week) and food packets containing low-fat products in the low-fat diet group.

Table 4. Overview of dietary intervention performed yearly in the CORDIOPREV study. Summary of dietary measurements and activities performed in the first year of intervention which were repeated in each year of the study

	1ST YEAR OF INTERVENTION (month)											
	Baseline	2	3	4	5	6	7	8	9	10	11	12
Individual face-to-face interview (1hour)	X					X						X
Food Frequency Questionnaire (FFQ)	X											X
14-point Mediterranean Diet Adherence Screener (MEDAS)	X					X						X
9-point low-fat diet adherence screener (LFDAS)	X					X*						X*
Physical activity questionnaire	X											X
Quality of life questionnaire (SF36)	X											X
Anthropometric measurements**	X					X						X
Oral and writing dietary recommendations	X					X						X
Free food provision	X		X			X			X			X
Group session (2 hour)			X				X				X	
Reinforcement of the dietary recommendations			X				X				X	
Delivery of resource material			X				X				X	
Follow-up telephone call		X		X				X		X		

* Administered only in the low-fat diet group; ** Measurements of weight, height and waist circumference

Adherence to the dietary intervention performed in the CORDIOPREV study was assessed in all visits (individual, group and telephone; Table 4). The MEDAS was the tool used to measure adherence to the Mediterranean diet (Table 5), while the LFDAS was used to appraise adherence to the low-fat diet (Table 6). Both dietary scores were administered by RDs in the two intervention groups at baseline (before the randomization). At follow-up visits, the MEDAS was also administered in both groups, whereas the LFDAS was only administered in the low-fat diet group. The MEDAS was also conducted in the low-fat diet group to compare the deviation from the original values in the two arms of the study.

Table 5. Validated 14-point Mediterranean Diet Adherence Screener (MEDAS)

	Questions	Criteria for 1 point*
1	Do you use olive oil as the principal source of fat for cooking?	Yes
2	How much olive oil do you consume in a given day (including oil used for frying, salads, meals eaten away from home, etc.)?	≥ 4 tablespoons
3	How many servings of vegetables do you consume per day? (1 serving =200g- side dishes are considered as ½ serving)	≥ 2 (≥1 portion raw or as salad)
4	How many pieces of fruit (including fresh fruit juices) do you consume per day?	3 or more
5	How many servings of red meat, hamburger or meat products (ham, sausage, etc.) do you consume per day? (1 serving = 100-150g)	Less than 1
6	How many servings of butter, margarine or cream do you consume per day? (1 serving=12g)	Less than 1
7	How many sweet/carbonated beverages do you drink per day?	Less than 1
8	How much wine do you drink per week?	≥ 7 glasses
9	How many servings of pulses do you consume per week? (1 serving = 150g)	3 or more
10	How many servings of fish or shellfish/seafood do you consume per week? (1 serving= 100-150g fish, or 4-5 units or 200g shellfish)	Less than 3
11	How many times per week do you consume commercial sweets or pastries (not homemade), such as cakes, cookies, biscuits or custard?	Less than 2
12	How many serving of nuts do you consume per week? (1 serving=30g)	3 or more
13	Do you preferentially consume chicken, turkey or rabbit meat instead of veal, pork, hamburger or sausage?	Yes
14	How many times per week do you consume cooked vegetables, pasta, rice, or other dishes with a homemade sauce of tomato, garlic, onion, or leeks sautéed in olive oil (*sofrito)*?	2 or more

*0 points if these criteria are not met

Table 6. 9-point low-fat diet adherence screener (LFDAS)

	Questions	Criteria for 1 point*
1	How much oil do you consume in a given day (including oil used for frying, salads, meals eaten away from home, etc.)? (1 tablespoon = 10ml)	≤ 2 tablespoons
2	Do you remove the visible fat (or the skin) from chicken, duck, pork, lamb or veal meats before cooking and the fat from soups, broths and cooked meat dishes before consumption?	Yes
3	How many servings of fat-rich meat, hamburgers, commercial minced meat, sausage, cold meat, cured ham, bacon, salami or offal do you consume per week? (meat serving=100g; salami or bacon=30g)	1 or less
4	How many servings of butter, margarine, lard, mayonnaise, milk cream, or milk-based ice cream do you consume per week? (1 serving of fat spread= 12g; ice cream = 100g)	1 or less
5	Do you exclusively consume low-fat dairy products?	Yes (id. if no dairy consumption)
6	How many times per week do you prepare rice, pasta, potato, or legume dishes by using “sofrito” sauce (based on olive oil), bacon, salami, or fatty meats such as pork or lamb ribs?	2 or less
7	How many times per week do you consume oily fish or seafood canned in oil?	1 or less
8	How many servings of commercially-produced (not homemade) sweets or industrial bakery products such as cakes, cookies, biscuits, or custard do you consume per week? (1 serving of cake = 80g; 6 biscuits = 40g)	1 or less
9	How many times per week do you consume nuts, potato chips, French fries or commercial snacks?	1 or less

*0 points if these criteria are not met

4.4. General dietary assessment

Information on habitual dietary intake was collected at baseline and on a yearly basis during follow-up using a 146-item semi-quantitative FFQ, previously validated in the Spanish population [172,173]. The FFQ were administered by RDs in face-to-face visits, where participants were asked to report their average intake of different food and beverage items over the previous 12 months. 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". As nutrient intake may vary in response to the availability of seasonal foods, the consumption of these foods was recorded for the season and then adjusted by the proportional intake over 1 year. Energy and nutrient intake were calculated using the Spanish Food Composition Tables [174,175]. In order to present the consumption of nutrients and foods in a way that is uncorrelated with the total energy intake, foods and nutrients such as dietary fiber, cholesterol, minerals and vitamins were energy-adjusted by residual methods [176] and carbohydrates, proteins, total fat and types of fats (MUFA, PUFA and SFA) were expressed as percentage of total energy intake.

4.5. *A priori*-defined dietary scores

For the purpose of this thesis, we examined three dietary scores: the MEDAS and LFDAS, which were the monitoring adherence tools used in the CORDIOPREV study, and the MDS-Trichopoulou, which is the most widely used dietary score. The three dietary scores differ in the number of components and range of values used in their definition. They were evaluated at baseline (before starting the intervention) and at year 1 of follow-up (after completing the first year of dietary intervention) as follow:

MEDAS

Participants answered 2 questions about eating habits considered characteristic of the Spanish Mediterranean diet, 8 questions about the frequency of consumption of typical foods of the Mediterranean diet, and 4 questions about the consumption of foods not recommended in this diet [165]. Each question was scored with 0 (non-compliant) or 1 (compliant), and the total score (from a total of 14 questions) ranged from 0 to 14. A score of 14 points means maximum adherence. The level of adherence

to the MEDAS was categorized into low (0–5), medium (6–9), and high (10–14) adherence, as previously published [177].

LFDAS

This adherence screener was developed and used in the PREDIMED study [86] Participants answered 6 questions about the consumption of high-fat food, 1 question about the consumption of low-fat food, and 2 questions about dietary habits (scored 1 for yes, 0 for no). The total score ranged from 0 to 9, with 9 meaning maximum adherence. The level of adherence to the LFDAS was categorized as low (0–3), medium (4–6), and high (7–9) adherence.

Following the protocol of the CORDIOPREV study, this dietary score was administered at 1-year visit in 216 patients of the 462 non-diabetics (patients allocated to the low-fat diet group). For the 416 patients of the Mediterranean diet group, we calculated the LFDAS using dietary data from the FFQ and following the methodology explained in point 4.7 of this section.

MDS-Trichopoulou

This dietary score was calculated as indicated by Trichopoulou et al. [102]. The median of the intake of each of the 9 components included in the score was calculated separately for men and women. For each of the six protective components (vegetables, fruits and nuts, legumes, cereals, fish and the ratio of MUFA to SFA) participants received one points if their intake was equal to or above the median. For meat and dairy products one point was assigned if the intake was below the median. For alcohol one point was given if consumption was 10-50 g/day for men or 5-25 g/day for women. The total score range from 0 (minimum adherence) to 9 (points maximum adherence) and was categorized as low (0-3 points), medium (4-5 points) and high (6-9 points) adherence.

4.6. Identification of PCA-dietary patterns

Using dietary data from the FFQ, PCA-dietary patterns were derived. For that purpose, the 146 food items included in the FFQ were grouped into 36 predefined food groups according to their nutrient content and typical culinary use (Appendix IV). To identify major dietary patterns of patients, PCA was applied on the 36 foods groups using the PROC FACTOR procedure in SAS 9.4. This method identified a reduced number of factors that could explain the maximum proportion of the variance from the original groups. In the first step, principal components were retained based on the eigenvalue >1 criterion. Secondly, the Scree plot was visualized to identify an 'elbow' in the curve and principal components were retained above this inflection point as explaining the majority of variance. Principal components were then rotated with an orthogonal rotation procedure (varimax rotation) to ensure that they remained uncorrelated and to achieve a simpler structure with greater interpretability [178]. Finally, only those components with three or more food groups with absolute factor loadings ≥0.3 were finally retained.

For each pattern, each participant received a score coefficient. This score coefficient was calculated by summing up intakes of each food group weighted by its factor loadings, with a higher score coefficient indicating a higher adherence to the respective dietary pattern. Finally, we calculated tertiles of the pattern scores to categorize the level of adherence as low (first tertile), medium (second tertile) and high (third tertile).

PCA was performed with dietary intake data from baseline and 1-year visits in order to identify PCA-dietary patterns in both time points.

4.7. Calculation of the MEDAS and LFDAS from the FFQ

To perform the study of the validation of the MEDAS and LFDAS in the total CORDIOPREV population (n=1002), we calculated the two dietary scores from dietary data collected in the FFQ at baseline and at 5-year visit.

MEDAS-FFQ

Food intake data recorded by FFQ was grouped into the food-based dietary components of the MEDAS (Appendix V). To do this, the amounts of food consumed daily (expressed in grams) were converted to the number of servings per day or week according to the servings defined in the MEDAS and 1 point was assigned if participants met the criteria for each food group. The total score was obtained by summing the points and ranged from 0 to 14.

LFDAS-FFQ

To calculate the LFDAS from the FFQ, the dietary information obtained from the FFQ were collapsed into the food-based dietary components of the LFDAS (Appendix VI). The average number of servings per day or week of each food group was calculated and 1 point was given if participants met the criteria for each item. The total score was obtained by summing the points and ranged from 0 to 9.

4.8. Long-term dietary adherence maintenance

To perform the study of the long-term dietary adherence in the total CORDIOPREV population (n=1002), we evaluate whether the changes from year 1 to year 5 were representatives of the 5-year period of the intervention. For that purpose, we explored the consistency of the within-person variations in dietary adherence as the Coefficient of variation (CV, %), from the 1st year to the 5th year as follow:

$$CV_{1\text{-}5year} = \frac{SD}{(score_{1year} + score_{2year} + score_{3year} + score_{4year} + score_{5year}/5)} x100$$

SD= standard deviation
Score = MEDAS in the Mediterranean diet group; LFDAS in the Low-fat diet group

To study long-term maintenance of dietary adherence between the two intervention groups, we analyzed the change in adherence from the end of the first year of intervention to the 5th. Change in adherence to dietary treatment (*changeAdherence*, %) was calculated as follow: for the MEDAS, *changeAdherence*= [($MEDAS_{5\text{-}year}$ – $MEDAS_{1\text{-}year}$)/14*100]; for the LFDAS, *changeAdherence*= [($LFDAS_{5\text{-}year}$ – $LFDAS_{1\text{-}year}$)/9*100]. A positive value of percentage of change indicates that the adherence increased from 1-year to 5-year of follow-up, and a negative value indicates that the adherence decreased. We stratified this calculation based on the 1-year category of their dietary adherence (*Low*, *Medium*, and *High Adherence*).

4.9. Assessment of non-dietary variables

At baseline and at the annual visits, a collection of biological samples and several questionnaires on sociodemographic data and lifestyle variables were included. Physical activity and leisure-time activity were assessed by the validated Spanish version of the Minnesota Leisure-Time Physical Activity Questionnaire [179,180]. Weight and height were measured by trained RDs using calibrated scales (BF511 Body Composition Analyzer/Scale, OMROM, Japan) and a wall-mounted stadiometer (Seca 242, HealthCheck Systems, Brooklyn, NY, USA), respectively. Waist circumference was measured midway between the lowest rib and the iliac crest using an anthropometric tape. Body Mass Index (BMI) was calculated as weight per square meter (kg/m2). The incidence of T2DM was evaluated every year according to the ADA criteria [8].

4.10. Statistical analysis

Participants with extreme daily energy intake (<500 kcal/day or >3500 kcal/day for women and <800 kcal/day or >4000 kcal/day for men) were excluded from analyses [176]. Normal distribution was tested for all the measured variables, and log10 transformation was used to normalize skewed variables. Continuous variables were presented as mean ± standard error of the mean (SEM) and categorical variables as proportions. For continuous variables, differences in means were assessed using the Student's t-test. For nominal variables, the Chi-square test was used to assess differences between groups (i.e. intervention groups or categories of adherence to the dietary scores and PCA-dietary patterns). Differences were considered to be significant when $p<0.05$. All statistical analyses were performed using the SPSS (Statistical Package for the Social Sciences) and the statistical software SAS, version 9.4, and SAS Enterprise Guide, version 6.1 (SAS Institute, Cary, NC).

To perform the main analyses of this thesis, low and medium adherence categories of the three dietary scores and PCA-dietary patterns were merged into one category (low-medium adherence).

Study of the association between dietary scores, PCA-dietary patterns and the incidence of T2DM: COX proportional hazards regression analyses were performed to evaluate the association of dietary scores and PCA-dietary patterns, measured at baseline and after one year of intervention, with the incidence of T2DM after a median follow-up of 60 months. Hazard ratios (HR) with 95% confidence intervals (CI) for the high versus low-medium category of adherence to each dietary pattern method (reference category) were performed. Multivariate logistic regression, Receiver operating characteristic (ROC) curves and area under the curve (AUC) analyses were used to test the predictive ability of dietary scores, PCA-dietary patterns and other characteristics (clinical and lifestyle variables). The Hosmer-Lemeshow statistic was used to assess the goodness-of-fit of each model, with $p<0.05$ indicating poor fit [181].

Differences in ROC–AUCs were calculated by using the method as described by DeLong et al.[182]

Study of the association of dietary scores and PCA-dietary patterns with factors related to the development of T2DM: We performed linear regression analyses with the anthropometric/biochemical variables at year 5 as dependent variables and dietary scores or PCA-dietary patterns at year 1 as independent variables, and adjusted for age, sex and randomized group.

Analysis of the validity of the three dietary scores and PCA-dietary patterns in our population: In order to assess the construct validity of the three dietary scores, we calculated Pearson correlation analyses between each dietary score and the dietary data obtained from the FFQ. Analysis of covariance (ANCOVA) using age and sex as covariates, were used to estimate dietary intake derived from the FFQ according to the tertile distribution of the three dietary scores. All of these analyses were performed in the non-diabetics at baseline (n=462) and the total CORDIOPREV population (n=1002). To examine the consistency of PCA-dietary patterns, we calculated partial correlations of the PCA-dietary patterns with the three dietary scores at baseline, controlled for age and sex. We used ANCOVA adjusted for age and sex to estimate the level of adherence to the three dietary scores according to the tertile distribution of the PCA-dietary patterns. We examined the consistency of PCA-dietary patterns at baseline and at year 1.

Study of the validation of the MEDAS and LFDAS in the total CORDIOPREV population: The relative agreement between the MEDAS score and the MEDAS-FFQ score was established using Pearson's *r* correlation coefficient and intra-class correlation coefficients (ICC, two-way mixed effects model with average measures). Then, the absolute agreement in the total score between the two methods was examined using a Bland-Altman analysis. In this graphical method the x-axis is the average of the two methods (MEDAS + MEDAS-FFQ/2) and y-axis is the difference

between the two measurements (MEDAS − MEDAS-FFQ), in order to determine possible bias. A mean difference of 0 indicates complete agreement between the methods [183]. The 95% limits of agreement (LoA) lines, defined as the mean difference ±1.96 times the standard deviation of the differences, were also plotted. The LoA indicate that for an individual randomly selected from the population on which the results are expected to be inferred, the difference between the two evaluations is expected to be between the limits with a 95% probability. The interpretation of the LOA is done in relation to the research context. In a next step, the total score (MEDAS and MEDAS-FFQ) was categorized into tertiles and the percentage of participants classified into the same and opposite categories were determined (participants' cross-classification). A correctly classification was done when more than 50% were allocated to the same tertile [184]. Finally, the concordance between the answers to each item of the MEDAS and the MEDAS-FFQ was determined calculating the kappa (*k*) statistic and the percentage of absolute agreement. As reference, *k* values from 0 to 0.20 indicate poor agreement, 0.21 to 0.40 fair agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 good agreement and 0.81 to 1 very good agreement in validation studies of dietary assessment tools [185]. In order to prove whether the MEDAS is specific enough by measuring Mediterranean diet changes during the intervention, all of these analyses were repeated with dietary information from the 5-year follow-up visit.

The same methodology was used to assess the concurrent validity of the LFDAS at both baseline and 5-year visit.

Study of adherence at long-term in the total CORDIOPREV population: Within- and between-groups (Mediterranean and low-fat diets) changes in nutrient intake, food consumption, and adherence were analyzed on a yearly basis using paired t test and unpaired t test.

V. RESULTS

V. RESULTS

5.1. General characteristics of the sample studied

The 462 CORDIOPREV patients without T2DM at baseline were included in the present study (246 randomized to the Mediterranean diet group and 216 to the low-fat diet group).

Baseline socio-demographic, clinical and lifestyle characteristics of the 462 non-diabetics are shown in Table 7. Overall, the mean age was 57.7 years old (73.4% of patients were ≤65 years old) and there were more men (84.2%) than women, according to the usual distribution of the disease in the general population. Participants were predominantly retired (50.3%) and had primary education (54.6%). More than half of the patients were obese and abdominal obesity was present in 60.6%. The prevalence of hypertension was 65.2% and nearly 9% of patients were active smokers. The two groups of intervention were well balanced with respect to socio-demographic, clinical and lifestyle characteristics, indicating that the randomization process was well implemented. Moreover, baseline characteristics were not different in both arms when considering the 1002 CORDIOPREV patients (Appendix VII).

Dietary characteristics of the study population at baseline (before randomization) are displayed in Table 8 and Figure 6. Two patients in the low-fat diet group had extreme energy intake and were excluded from analysis [176]. Overall, there were no significant differences in energy and nutrient intake between the two intervention groups (Table 8). The habitual diet of patients was high in total fat (>35%), mainly consisting of MUFA, with 42.6% of the energy from carbohydrates and 18.1% from proteins. The dietary fiber intake was about 25g/day.

Table 7. Baseline characteristics of the 462 patients without T2DM at baseline according to randomized diet group

	All patients (n=462)	Med Diet (n=246)	Low-Fat Diet (n=216)	*p* value
Socio-demographic characteristics				
Sex (% male)	84.2	83.7	84.7	0.773
Age (years)	57.7 ± 0.4	57.8 ± 0.6	57.5 ± 0.6	0.673
Education level (%)[a]				
Higher education	10.5	12.6	8.1	0.428
Secondary education	21.3	20.6	22.0	
Primary education	54.6	52.5	56.9	
None	13.6	14.3	12.9	
Occupation (%)[a]				
Worker	32.7	34.0	31.3	0.781
Housewife	4.0	4.6	3.3	
Retired	50.3	49.2	51.7	
Unemployed	12.9	12.2	13.7	
Clinical and lifestyle characteristics				
BMI (kg/m^2)[b]	30.4 ± 0.2	30.3 ± 0.3	30.5 ± 0.3	0.604
Waist circumference (cm)	102.5 ± 0.5	102.1 ± 0.7	102.9 ± 0.8	0.390
Overweight (%)[b]	41.8	43.5	39.8	0.423
Obesity (%)[b]	50.2	48.4	52.3	0.398
Abdominal obesity (%)[c]	60.6	61.0	60.2	0.862
Hypertension (%)[d]	65.2	65.0	65.3	0.957
Fasting glucose (mg/dL)	93.4 ± 0.5	93.5 ± 0.7	93.3 ± 0.7	0.865
HbA1c (%)	5.9 ± 0.02	5.9 ± 0.02	5.9 ± 0.02	0.647
HOMA-IR	2.8 ± 0.1	2.8 ± 0.1	2.7 ± 0.1	0.717
HDL cholesterol (mg/dL)	44.3 ± 0.5	44.9 ± 0.7	43.7 ± 0.7	0.175
LDL cholesterol (mg/dL)	91.6 ± 1.2	92.2 ± 1.7	90.9 ± 1.7	0.728
Triglycerides (mg/dl)	122.5 ± 2.9	120.0 ± 3.9	125.2 ± 4.4	0.511
Treatment with statins (%)	85.1	84.1	86.1	0.554
Current smokers (%)	8.7	8.1	9.3	0.667
Physical Activity (METs-h/week)[e]	21.5 ± 1.0	20.5 ± 1.2	22.7 ± 1.5	0.053

Data are shown as mean ± SEM or percentage of participants, unless otherwise stated. We used unpaired *t* tests for quantitative variables and chi squared tests for categorical variables. T2DM, type 2 diabetes; Med Diet, Mediterranean diet group; Low-Fat Diet, low-fat diet group; BMI, body mass index; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment-insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein. [a]Data were available for 447 patients. [b]BMI was calculated as weight in kg divided by the square of height in m (kg/m^2). BMI ≥25 and <30: overweight. BMI ≥30: obese. [c]Abdominal obesity was defined as waist circumference >102 cm in men and >88 cm in women. [d]Hypertension was defined as a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or the use of antihypertensive therapy. [e]METs-h/week=metabolic equivalents of weekly leisure time physical activities.

As concerns the food intake (Figure 6), no significant differences were also found between randomized groups. The baseline dietary pattern of patients was characterised by a high intake of olive oil (3.4 servings/day), vegetables and fruit (2.7 and 2.4 servings/day, respectively), dairy products (2.4 servings/day), meat (1.9 servings/day), and commercial sweets and pastries (0.7 servings/day); a moderate consumption of fish (5 servings/week), and a moderate to low intake of legumes (2.6 servings/week) and nuts (2.1 servings/week). Processed meats were highly consumed (1.2 servings/day), whole grains accounted for less than a quarter of total grains intake (0.5 servings/day), and the consumption of low-fat dairy products was higher than that of whole-fat dairy products (1.4 vs. 0.9 servings/day). The average consumption of wine was about 4 glasses of wine per week.

Table 8. Daily energy and nutrients intake of participants by randomized groups (n=460)[a]

	All patients (n=460)	Med Diet (n=246)	Low-Fat Diet (n=214)	*p* value
Energy (kcal)	2296 ± 24	2300 ± 31	2292 ± 37	0.876
Total carbohydrate (%E)	42.6 ± 0.3	42.4 ± 0.4	42.8 ± 0.4	0.547
Total protein (%E)	18.1 ± 0.1	18.0 ± 0.2	18.1 ± 0.2	0.719
Total fat (%E)	36.2 ± 0.3	36.2 ± 0.3	36.1 ± 0.4	0.881
Monounsaturated fat (%E)	17.7 ± 0.2	17.7 ± 0.2	17.6 ± 0.2	0.765
Saturated fat (%E)	8.7 ± 0.1	8.7 ± 0.1	8.8 ± 0.1	0.451
Polyunsaturated fat (%E)	6.2 ± 0.1	6.3 ± 0.1	6.1 ± 0.1	0.190
Cholesterol (mg/day)[b]	327.1 ± 3.6	325.9 ± 5.1	328.6 ± 5.0	0.704
Dietary fiber (g/day)[b]	24.6 ± 0.3	24.7 ± 0.5	24.4 ± 0.5	0.730

Values are means ± SEM. $p<0.05$ based on unpaired *t* tests. Med Diet, Mediterranean diet group; Low-Fat Diet, low-fat diet group; %E, percentage of total energy intake; g/day, grams per day; mg/day, milligrams per day. [a]N=460 after excluding 2 patients with extreme energy intake. [b]Energy-adjusted by residual method.

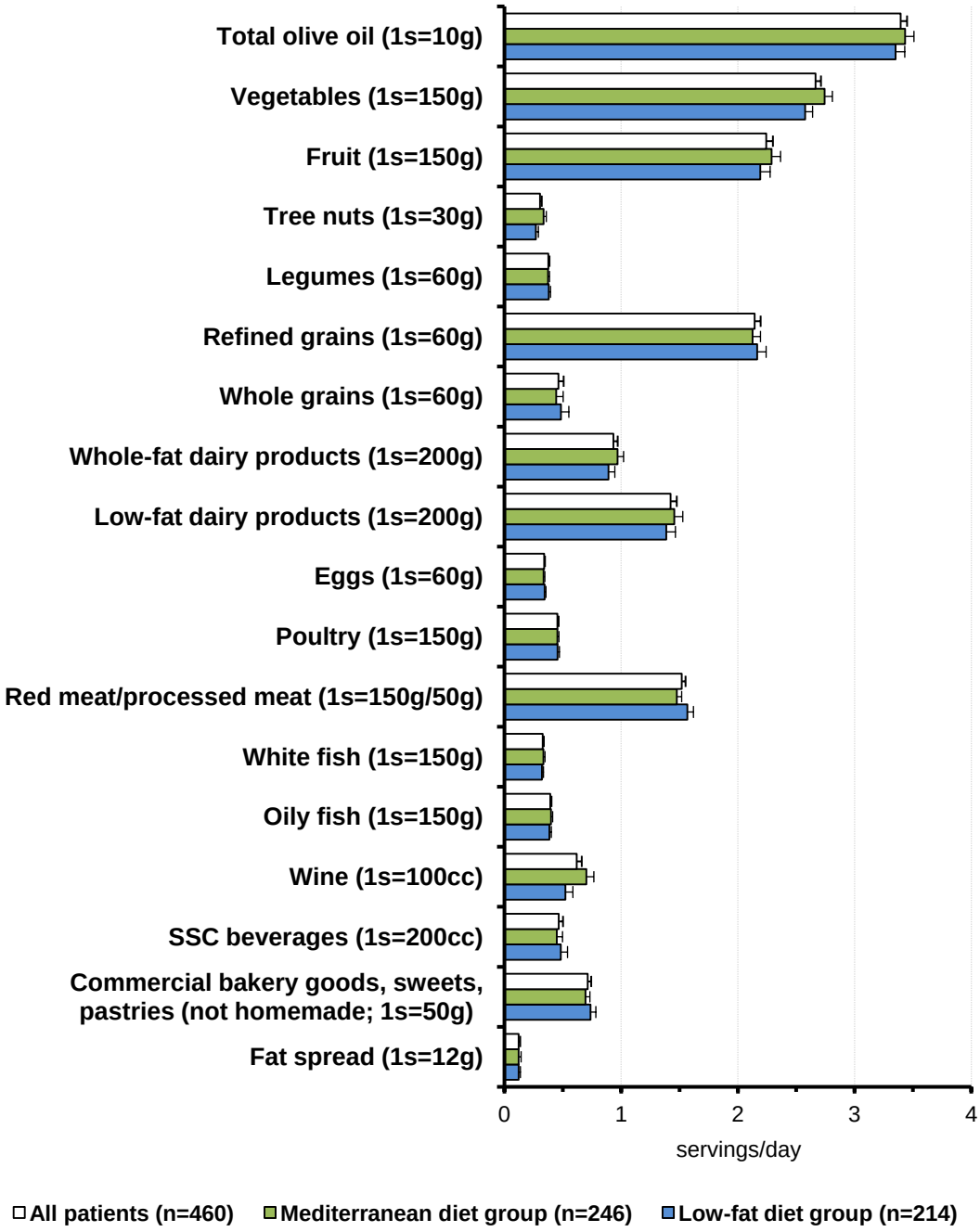


Figure 6. Baseline intake (servings/day) of major food groups in the study sample by randomized groups (n=460)[a]. Values are means ± SEM. **p*<0.05 between groups by Student's t-test. S denotes serving; g, grams; cc, cubic centimetres; SSC beverages, sugar-sweetened carbonated beverages. [a]N=460 after excluding 2 patients with extreme energy intake.

5.2. *A priori*-defined dietary scores

5.2.1. Dietary scores at baseline

Table 9 shows the punctuation at baseline of the participants of the study in the three dietary scores analyzed (MEDAS, MDS-Trichopoulou and LFDAS). The mean (±SEM) MEDAS and MDS-Trichopoulou scores for the total study sample were 8.7±0.1 and 4.5±0.1 points, respectively, which indicates moderate adherence to a Mediterranean-type diet. According to the mean LFDAS score (3.8±0.1 points), patients reported a moderate level of adherence to the low-fat diet.

Table 9. Mean total score obtained in the *a priori*-defined dietary scores at baseline according to intervention group (n=460)[a]

	All patients (n=460)	Med Diet (n=446)	Low-Fat Diet (n=412)	*p* value
MEDAS	8.7 ± 0.1	8.9 ± 0.1	8.5 ± 0.1	0.054
Low adherence (0-5 points)	7.6	6.9	8.4	
Medium adherence (6-9 points)	54.1	51.2	57.5	0.227
High adherence (10-14 points)	38.3	41.9	34.1	
MDS-Trichopoulou	4.5 ± 0.1	4.5 ± 0.1	4.4 ± 0.1	0.201
Low adherence (0-3 points)	25.0	23.2	27.1	
Medium adherence (4-5 points)	51.7	52.0	51.4	0.535
High adherence (6-9 points)	23.3	24.8	21.5	
LFDAS	3.8 ± 0.1	3.7 ± 0.1	3.8 ± 0.1	0.657
Low adherence (0-3 points)	45.4	45.5	45.3	
Medium adherence (4-6 points)	49.1	50.8	47.2	0.185
High adherence (7-9 points)	5.4	3.7	7.5	

Data are shown as mean ± SEM or percentage of participants, unless otherwise stated. $p<0.05$ based on unpaired *t* tests (quantitative variables) or chi squared tests (categorical variables). Med Diet, Mediterranean diet group; Low-Fat Diet, low-fat diet group; MEDAS, 14-point Mediterranean Diet Adherence Screener; MDS-Trichopoulou, Mediterranean Dietary Score proposed by Trichopoulou et al.; LFDAS, 9-point low-fat diet adherence screener. [a]N=460 after excluding 2 patients with extreme energy intake.

The percentages of patients in the high adherence category of the MEDAS (>9 points) and MDS-Trichopoulou (>5 points) were 38.3 and 23.3%, respectively, whereas only 5.4% of patients had high adherence to the LFDAS. Neither the total score nor the categories of adherence to the three dietary scores differed between the two groups.

Baseline characteristics according to categories of adherence to the three dietary scores are shown in Table 10. For all the three dietary scores, the prevalence of obesity and abdominal obesity was lower in patients with high adherence compared to those with low-medium adherence. For the MEDAS, patients with higher adherence were more likely to be men, retired, higher educated and physically active, and less likely to be current smokers that those in the low-medium category of adherence. They also showed significantly higher intakes of dietary fiber, probably due to a high consumption of vegetables, fruit, legumes and nuts, whereas they had a statistically significant lower consumption of SFA, red/processed meats, commercial bakery and sugar-sweetened carbonated beverages (SSC beverages). Moreover, patients with a higher score for the MEDAS presented a higher intake of olive oil, fish and wine. For the MDS-Trichopoulou, patients with high adherence showed a lower BMI. These patients had higher intakes of dietary fiber, vegetables, fruit, legumes, grains, fish and wine, and lower intakes of SFA, red/processed meats, dairy products and SSC beverages. On the other hand, patients with a total score >6 points in the LFDAS tended to be retired and showed a lower consumption of total energy. Their higher intakes of carbohydrates and dietary fiber were probably related to a higher consumption of grains, whereas their lower intakes of fat and SFA were probably due to lower consumptions of foods with high content of fat (olive oil, nuts, red/processed meats and commercial bakery).

Table 10. Baseline characteristics by categories of adherence to the 14-point Mediterranean Diet Adherence Screener, Mediterranean Dietary Score proposed by Trichopoulou et al. and the 9-point Low-Fat Diet Adherence Screener (n=460)[a]

	MEDAS		MDS-Trichopoulou		LFDAS	
	Low-medium adherence (0-9 points)	High adherence (10-14 points)	Low-medium adherence (0-5 points)	High adherence (6-9 points)	Low-medium adherence (0-6 points)	High adherence (7-9 points)
n	284	176	353	107	435	25
Sex (% male)	79.9	90.9*	82.4	89.7	83.9	88.0
Age (years)	57.4 ± 0.6	58.0 ± 0.7	57.8 ± 0.5	57.1 ± 0.9	57.8 ± 0.5	54.8 ± 1.7
Higher education (%)[b]	8.0	14.7*	10.8	9.8	10.2	17.4
Retired (%)[b]	46.7	56.7*	50.6	50.5	51.7	30.4*
BMI (kg/m^2)[c]	30.5 ± 0.2	30.0 ± 0.4	30.6 ± 0.2	29.6 ± 0.4*	30.4 ± 0.2	28.9 ± 0.9
Waist circumference (cm)	102.7 ± 0.6	102.2 ± 0.9	102.6 ± 0.6	102.2 ± 1.0	102.7 ± 0.5	98.7 ± 2.1
Obesity (%)[c]	53.9	43.8*	53.5	38.3*	51.0	32.0*
Abdominal obesity (%)[d]	64.4	54.0*	63.2	51.4*	61.6	40.0*
Current smokers (%)	10.9	5.1*	8.5	9.3	9.0	4.0
Physical activity (METs-h/week)[e]	20.0 ± 1.3	24.2 ± 1.5*	21.7 ± 1.1	21.2 ± 1.9	21.2 ± 1.0	28.2 ± 4.9
Energy	2249 ± 30	2372 ± 38*	2251 ± 28	2447 ± 45*	2317 ± 24	1934 ± 95*
Carbohydrates (%E)	42.5 ± 0.4	42.7 ± 0.5	42.4 ± 0.3	43.3 ± 0.5	42.5 ± 0.3	45.0 ± 1.5*
Proteins (%E)	18.0 ± 0.2	18.2 ± 0.2	18.2 ± 0.1	17.8 ± 0.2	18.1 ± 0.1	18.4 ± 0.5
Total fat (%E)	36.3 ± 0.3	36.0 ± 0.4	36.6 ± 0.3	35.3 ± 0.5*	36.3 ± 0.2	32.9 ± 1.6*
Monounsaturated fat (%E)	17.5 ± 0.2	17.6 ± 0.2	17.8 ± 0.2	17.4 ± 0.3	17.7 ± 0.2	17.2 ± 1.1
Polyunsaturated fat (%E)	6.0 ± 0.1	6.4 ± 0.1*	6.1 ± 0.1	6.3 ± 0.2	6.2 ± 0.1	5.8 ± 0.3
Saturated fat (%E)	9.1 ± 0.1	8.1 ± 0.1*	9.0 ± 0.1	7.9 ± 0.1*	8.8 ± 0.1	7.4 ± 0.4*
Dietary fiber (g/day)[f]	23.4 ± 0.4	26.4 ± 0.6*	23.7 ± 0.4	27.6 ± 0.7*	24.4 ± 0.3	27.8 ± 2.1*

Table 10. (Continued)

	MEDAS		MDS-Trichopoulou		LFDAS	
	Low-medium adherence (0-9 points)	High adherence (10-14 points)	Low-medium adherence (0-5 points)	High adherence (6-9 points)	Low-medium adherence (0-6 points)	High adherence (7-9 points)
n	284	176	353	107	435	25
Olive oil (g/day)[f]	33.0 ± 0.7	35.5 ± 1.0*	33.4 ± 0.6	35.7 ± 1.2	34.2 ± 0.6	28.8 ± 2.7*
Vegetables (g/day)[f]	244.4 ± 5.5	279.2 ± 7.7*	246.8 ± 5.2	294.1 ± 8.3*	256.5 ± 4.7	279.9 ± 21.1
Fruits (g/day)[f]	334.1 ± 11.4	393.4 ± 14.9*	336.5 ± 10.4	423.9 ± 17.8*	358.6 ± 9.5	325.2 ± 31.2
Nuts (g/day)[f]	7.1 ± 0.5	12.4 ± 0.9*	8.9 ± 0.5	9.9 ± 1.0	9.4 ± 0.5	4.4 ± 1.9*
Legumes (g/day)[f]	20.9 ± 0.7	25.4 ± 1.0*	21.8 ± 0.7	25.2 ± 1.0*	22.6 ± 0.6	22.1 ± 3.0
Grains (g/day)[f]	187.7 ± 3.7	189.4 ± 4.7	180.6 ± 4.5	213.8 ± 8.0*	186.2 ± 3.0	226.4 ± 12.6*
Fish and seafood (g/day)[f]	98.8 ± 2.7	115.8 ± 3.5*	99.6 ± 2.4	124.4 ± 4.2*	105.4 ± 2.2	105.2 ± 7.7
Poultry (g/day)[f]	66.3 ± 2.1	71.0 ± 2.4	69.2 ± 1.9	64.2 ± 2.6	68.7 ± 1.7	58.6 ± 5.8
Red/processed meat (g/day)[f]	91.0 ± 2.3	74.7 ± 2.7*	88.5 ± 2.1	72.4 ± 3.5*	85.7 ± 1.8	68.3 ± 8.3*
Dairy products (g/day)[f]	353.8 ± 10.7	374.2 ± 14.6	385.8 ± 9.9	281.7 ± 15.7*	360.3 ± 9.0	383.9 ± 30.1
Commercial bakery goods, sweets, and pastries (g/day)[f]	31.8 ± 1.5	24.3 ± 1.7*	29.7 ± 1.2	27.2 ± 2.6	29.5 ± 1.2	19.5 ± 4.2*
SSC beverages (g/day)[f]	110.6 ± 9.6	64.6 ± 11.8*	102.5 ± 9.1	61.5 ± 11.3*	94.2 ± 7.8	71.9 ± 23.0
Wine (g/day)[f]	49.6 ± 4.9	80.9 ± 8.1*	55.4 ± 4.8	82.0 ± 9.9*	60.8 ± 4.5	75.4 ± 18.7

Data are shown as mean ± SEM or percentage of participants, unless otherwise stated. *p<0.05 based on unpaired *t* tests (quantitative variables) or chi squared tests (categorical variables). MEDAS, 14-point Mediterranean Diet Adherence Screener; MDS-Trichopoulou, Mediterranean Dietary Score proposed by Trichopoulou et al.; LFDAS, 9-point low-fat diet adherence screener; BMI, body mass index; %E, percentage of total energy intake; g/day, grams per day; SSC, sugar-sweetened carbonated. [a]N=460 after excluding 2 patients with extreme energy intake . [b]Data were available for 447 patients. [c]BMI was calculated as weight in kg divided by the square of height in m (kg/m^2). BMI ≥30: obese. [d]Abdominal obesity was defined as waist circumference >102 cm in men and >88 cm in women. [e]METs-h/week=metabolic equivalents of weekly leisure time physical activities. [f]Energy-adjusted by residual method.

5.2.2. Dietary scores at 1-year visit

As it was mentioned above, levels of adherence to the MEDAS, MDS-Trichopoulou and the LFDAS at baseline were similar across the trial arms. After 1 year of dietary intervention, and following the expected course due to the intervention, the three dietary scores differed significantly both within and between groups (Figure 7). Patients in the Mediterranean diet group significantly increased their total scores on the MEDAS (from 8.9±0.1 points at baseline to 11.0±0.1 points (p<0.001)), and on the MDS-Trichopoulou, (from 4.4±0.1 baseline score to 4.9±0.1 points at 1-year visit (p<0.001)). In contrast, patients in the low-fat diet group showed significant decreases in the MEDAS and MDS-Trichopoulou (of 1.0±0.1 and 0.5±0.1 points, respectively (all p<0.001)), whereas they reported a significant increase in the LFDAS of 2.8±0.2 points.

After this first year of dietary intervention, the mean scores in the MEDAS and the MDS-Trichopoulou were significantly higher in the Mediterranean diet group than in the low-fat diet group (all p<0.001, Figure 7). Conversely, the mean score in the LFDAS was significantly higher in the low-fat diet group compared to the Mediterranean diet group (p<0.001). The greatest difference between the two groups was found for the MEDAS (3 points).

Importantly, the changes observed in the three dietary score from baseline to 1-year visit were maintained in each of the subsequent 4 years of follow-up as a result of the comprehensive and tailored dietary intervention (as described in detail in point 5.8 of the results section *"Long-term dietary adherence and changes in dietary intake in the CORDIOPREV population after dietary intervention"*).

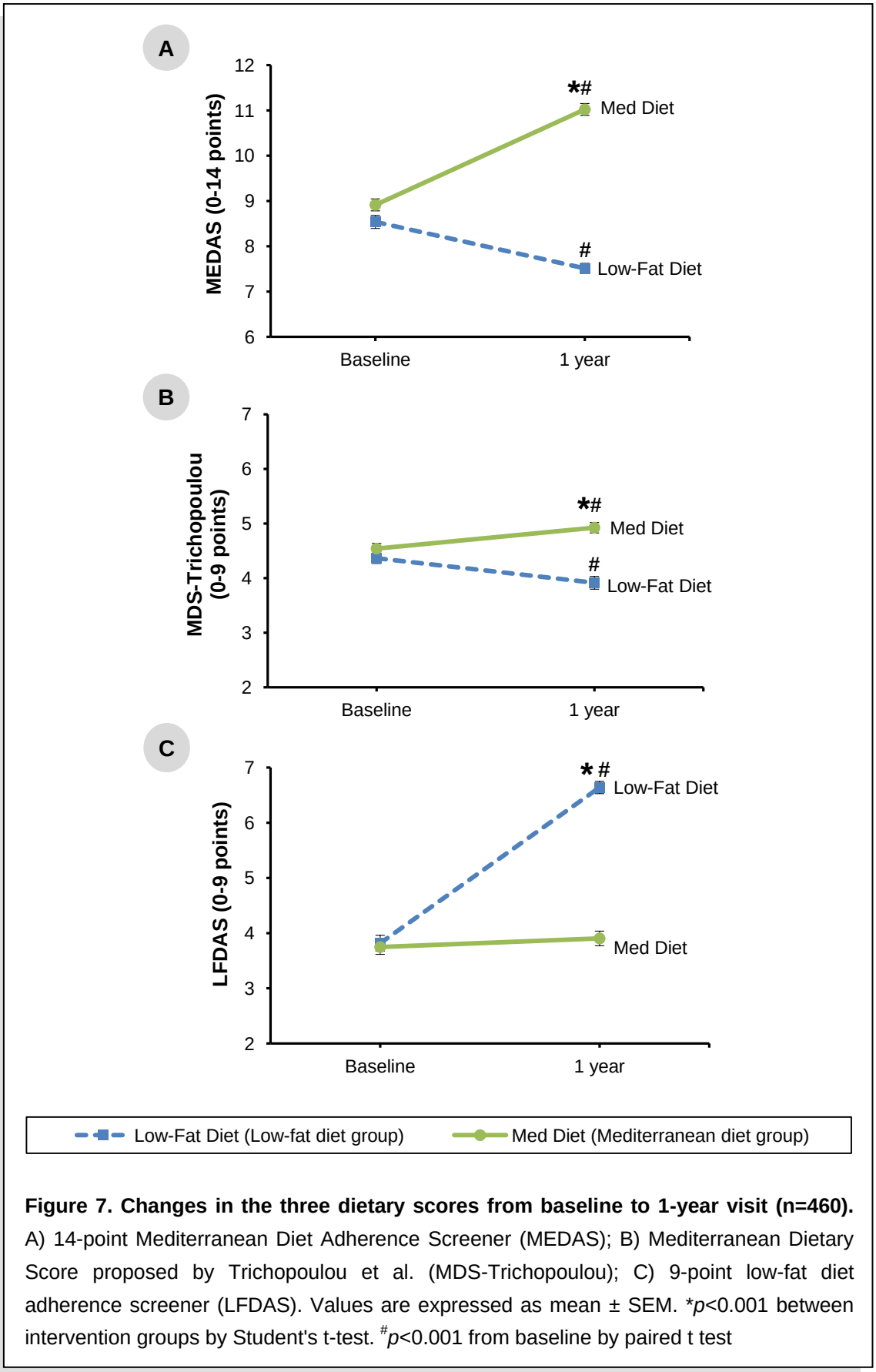


Figure 7. Changes in the three dietary scores from baseline to 1-year visit (n=460). A) 14-point Mediterranean Diet Adherence Screener (MEDAS); B) Mediterranean Dietary Score proposed by Trichopoulou et al. (MDS-Trichopoulou); C) 9-point low-fat diet adherence screener (LFDAS). Values are expressed as mean ± SEM. *p<0.001 between intervention groups by Student's t-test. $^{\#}p$<0.001 from baseline by paired t test

5.3. *A posteriori*-derived dietary patterns by principal components analysis (PCA-dietary patterns)

5.3.1. PCA-dietary patterns at baseline

Using the dietary data from baseline FFQs, a principal component analysis was performed to identify major dietary patterns of 460 non-diabetics (2 patients were excluded because their total daily energy intake was outside the range of 500-3500 kcal or 800-4000 kcal for women or men, respectively) [176]. Based on the visual examination of the Scree plot, an eigenvalue >1, and the plausibility of the factors, we identified two major dietary patterns explaining 14.4% of the total variance in basal food intake (Figure 8).

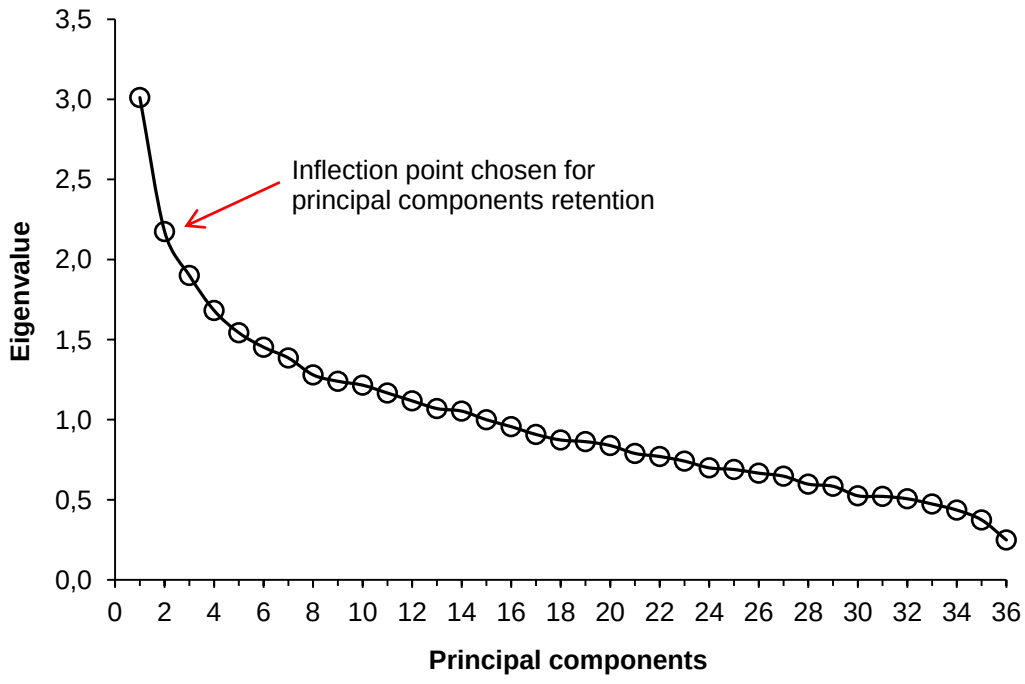


Figure 8. Scree plot of the principal component analysis to identify major dietary patterns at baseline of the 460 non-diabetic patients. Scree plot showing distribution of principal components by their eigenvalues. Red arrow shows an 'elbow' in the curve and principal components are retained above this inflection point as explaining the majority of variance. The two retained principal components had eigenvalues of 3.0 and 2.2 and accounted for 8.4 and 6.0% of the total variance, respectively.

Figure 9 displays the two identified dietary patterns at baseline and their rotated factor loadings as a spider web chart. According to the food groups considered as relevant components of each pattern (absolute rotated factor loadings ≥0.3), the first pattern was labelled as “Western dietary pattern (Western DP)” and the second pattern was named “Mediterranean-type dietary pattern (Mediterranean DP)”. The Western DP explained 8.4% of the total variance in food intake. It was characterized by high positive loadings of red meat, processed meats, eggs, refined bread, whole-fat dairy products, fried potatoes, sweets, sauces and processed meals, while fresh fruit and whole bread were negatively loaded. The Mediterranean DP accounted for 6.0% of the total variance in food intake and had high contributions of EVOO, vegetables, fresh fruit, legumes, seafood, white and oily fish, and low-fat dairy products. In addition, it was defined by a low consumption (negative loadings) of other olive oils different from EVOO.

Table 11 shows the baseline characteristics of patients by tertiles of the Western DP and Mediterranean DP at baseline. Patients with the highest adherence to the Western DP at baseline (third tertile) were more likely to be men, younger, and current smokers, had a higher BMI and waist circumference, were more likely to be active workers, and had less physical activity compared to those with low-medium adherence (first plus second tertiles). On the other hand, patients with the highest adherence to the Mediterranean DP (third tertile) were more likely men, more physically active and with a higher education level.

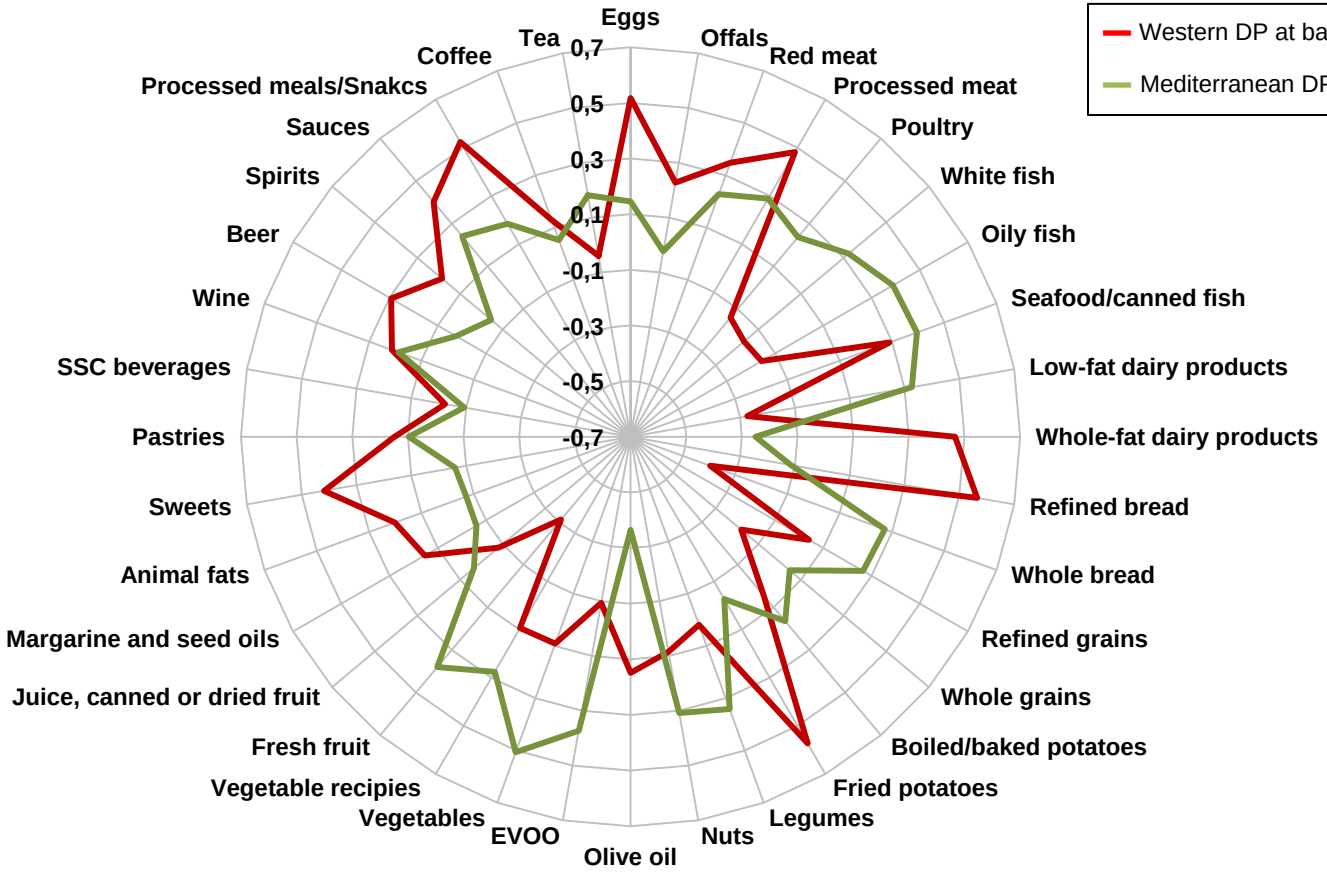


Figure 9. Baseline dietary patterns derived by principal components analysis in 460 non-diabetics. Rotated factor loadings (ranging from -0.7 to 0.7) of the 36 food groups on the two retained principal components are depicted in the spider graph. Red line denotes the Western dietary pattern (Western DP). Green line denotes the Mediterranean dietary pattern (Mediterranean DP). EVOO, extra-virgin olive oil; Olive oil, other olive oils different from EVOO; SSC, sugar-sweetened carbonated.

When we checked the baseline dietary habits of patients according to tertiles of adherence to each indentified dietary pattern at baseline (Table 11), all the results were in the expected direction. Patients in the third tertile of adherence to the Western DP at baseline showed higher intakes of energy and fat, mainly SFA, and a lower intake of dietary fiber. They had a higher consumption of refined grains, processed meats, whole-fat dairy products, sweets and pastries, and lower intakes of EVOO, fruit, nuts, fish, whole grains and low-fat dairy products. On the other hand, patients in the highest tertile of the Mediterranean DP at baseline presented a reduced intake of carbohydrates and increased intakes of dietary fiber, protein and fat, specifically MUFA and PUFA. They also showed higher consumptions of plant-source foods (EVOO, vegetables, fruit, legumes, nuts, whole grains), fish and seafood. Moreover, the intake of refined grains, processed meat, whole-fat dairy products, sweets and pastries was lower in these patients compared to those with low-medium adherence to the Mediterranean DP.

Table 11. Baseline characteristics of the 460[a] non-diabetics according to tertiles of baseline adherence to the Western dietary pattern and Mediterranean dietary pattern

	Western DP at baseline		Mediterranean DP at baseline	
	T1+T2 (low-medium adherence)	T3 (high adherence)	T1+T2 (low-medium adherence)	T3 (high adherence)
n	307	153	307	153
Sex (% male)	77.5	97.4*	80.8	90.8*
Age (years)	58.4 ± 0.5	56.1 ± 0.7*	57.9 ± 0.5	57.2 ± 0.8
Higher education (%)[b]	10.9	10.4	8.5	14.7*
Retired (%)[b]	51.2	49.3	49.7	55.0
Worker (%)[b]	29.4	39.2*	37.1	30.4
BMI (kg/m^2)	30.0 ± 0.2	30.9 ± 0.4*	30.2 ± 0.2	30.7 ± 0.4
Waist circumference (cm)	101.4 ± 0.6	104.6 ± 0.8*	102.2 ± 0.6	103.1 ± 1.0
Current smokers (%)	6.5	12.4*	8.8	7.8
Physical activity (METs-h/week)[c]	23.3 ± 1.2	18.3 ± 1.5*	20.0 ± 1.0	24.7 ± 2.1*

Table 11. (Continued)

	Western DP at baseline		Mediterranean DP at baseline	
	T1+T2 (low-medium adherence)	T3 (high adherence)	T1+T2 (low-medium adherence)	T3 (high adherence)
n	307	153	307	153
Energy	2123 ± 25	2644 ± 38*	2161 ± 28	2567 ± 37*
Carbohydrates (%E)	42.8 ± 0.4	42.2 ± 0.4	43.1 ± 0.4	41.6 ± 0.5*
Proteins (%E)	18.6 ± 0.2	17.0 ± 0.2*	17.6 ± 0.1	19.1 ± 0.2*
Total fat (%E)	35.7 ± 0.3	36.7 ± 0.4*	36.1 ± 0.3	36.3 ± 0.4
Monounsaturated fat (%E)	17.8 ± 0.2	17.4 ± 0.2	17.5 ± 0.2	18.1 ± 0.3*
Polyunsaturated fat (%E)	6.2 ± 0.1	6.0 ± 0.1	6.0 ± 0.1	6.4 ± 0.1*
Saturated fat (%E)	8.4 ± 0.1	9.4 ± 0.1*	8.9 ± 0.1	8.4 ± 0.1*
Dietary fiber (g/day)[c]	26.3 ± 0.4	21.0 ± 0.4*	22.5 ± 0.3	28.7 ± 0.6*
Extra-virgin olive oil (g/day)[c]	32.5 ± 0.8	24.8 ± 1.3*	28.5 ± 0.9	32.8 ± 1.1*
Other olive oils (g/day)[c]	3.1 ± 0.6	0.6 ± 1.0*	5.5 ± 0.7	1.2 ± 0.4*
Vegetables (g/day)[c]	372.9 ± 8.2	358.8 ± 10.5	336.0 ± 6.9	432.9 ± 12.2*
Fresh fruit (g/day)[c]	377.1 ± 10.9	260.5 ± 12.7*	301.3 ± 10.1	412.5 ± 15.3*
Nuts (g/day)[c]	9.8 ± 0.6	7.9 ± 0.8	8.3 ± 0.5	10.8 ± 0.9*
Legumes (g/day)[c]	23.6 ± 0.7	20.6 ± 0.9*	20.6 ± 0.7	26.6 ± 1.1*
Refined grains/bread (g/day)[c]	144.4 ± 4.8	176.1 ± 6.1*	176.2 ± 4.1	112.2 ± 7.0*
Whole grains/bread (g/day)[c]	47.1 ± 4.6	5.9 ± 2.3*	20.6 ± 3.1	59.1 ± 7.3*
Fish and seafood (g/day)[c]	110.8 ± 2.7	93.3 ± 3.4*	92.0 ± 2.3	130.9 ± 3.8*
Poultry (g/day)[c]	71.7 ± 1.9	61.0 ± 2.9*	64.7 ± 1.9	75.0 ± 3.0*
Red meats (g/day)[c]	40.4 ± 1.6	46.1 ± 2.9	40.8 ± 1.7	45.2 ± 2.6
Processed meats (g/day)[c]	37.9 ± 1.1	48.7 ± 2.1*	39.2 ± 1.1	46.0 ± 2.2*
Whole-fat dairy products (g/day)[c]	45.5 ± 2.9	120.1 ± 14.2*	90.3 ± 7.7	30.1 ± 6.0*
Low-fat dairy products (g/day)[c]	281.3 ± 11.8	172.1 ± 15.1*	208.5 ± 10.7	318.3 ± 18.2*
Sweets/pastries (g/day)[c]	37.8 ± 1.6	59.6 ± 3.0*	43.7 ± 1.8	47.6 ± 2.9*
SSC beverages (g/day)[c]	125.2 ± 11.2	141.5 ± 17.7	143.3 ± 11.8	105.1 ± 15.6
Wine (g/day)[c]	63.3 ± 4.8	58.8 ± 8.9	55.9 ± 4.9	73.7 ± 8.8

Data are shown as mean ± SEM or percentage of participants, unless otherwise stated. *p<0.05 based on unpaired *t* tests (quantitative variables) or chi squared tests (categorical variables). Western DP, Western dietary pattern; Mediterranean DP, Mediterranean dietary pattern; BMI, body mass index; %E, percentage of total energy intake; g/day, grams per day; SSC, sugar-sweetened carbonated. [a]N=460 after excluding 2 patients with extreme energy intake. [b]Data were available for 447 patients. [c]METs-h/week=metabolic equivalents of weekly leisure time physical activities. [d]Energy-adjusted by residual method.

5.3.2. PCA-dietary patterns at 1-year visit

To homogenise the data input of dietary intake in a controlled environment, to know the impact of the dietary intervention and to study the associations between derived dietary patterns and the risk of T2DM, a principal component analysis was performed after 1 year of intervention (data were available for 436 patients). In this case, three major dietary patterns were identified (Figure 10), accounting for 19.5% of the total variance in food intake at year 1, which means a relative increase of 35.4% in the explained variance. The first pattern explained 8.0% of the variance in food intake and was named “Western dietary pattern (Western DP)”. It was characterized by high factor loadings on red meats, processed meats, fried potatoes, sauces, processed meals, snacks, beer, canned fish, refined bread and sweets. The second pattern accounted for 6.2% of the variance in food intake and was labelled “Mediterranean-type dietary pattern (Mediterranean DP)”. It was characterized by high positive loadings on EVOO, oily fish, legumes, nuts, white fish and vegetables, while margarine, seed oils and commercial pastry products were negatively loaded. Finally, the third pattern, which was named “Low-fat dietary pattern (Low-Fat DP)”, explained 5.3% of the variance in food intake and showed high loadings for whole bread, low-fat dairy products, fresh fruits and poultry, while refined bread, whole-fat dairy products and fried potatoes loaded negatively. Importantly, the Mediterranean DP and the Low-Fat DP at year 1 were consistent with the two healthy diet models used in the dietary intervention.

Comparing the results of 1-year PCA with baseline PCA, we observed that although the Western DP at year 1 and Western DP at baseline showed a comparable structure, they differed in some high loading food groups. Similarly, the Mediterranean DP at year 1 and Mediterranean DP at baseline differed moderately in their pattern structure (Table 12). The higher variance explained by PCA-dietary patterns after one year of intervention suggests that data obtained from FFQs in a controlled dietary environment is more reliable than those obtained in a free living condition.

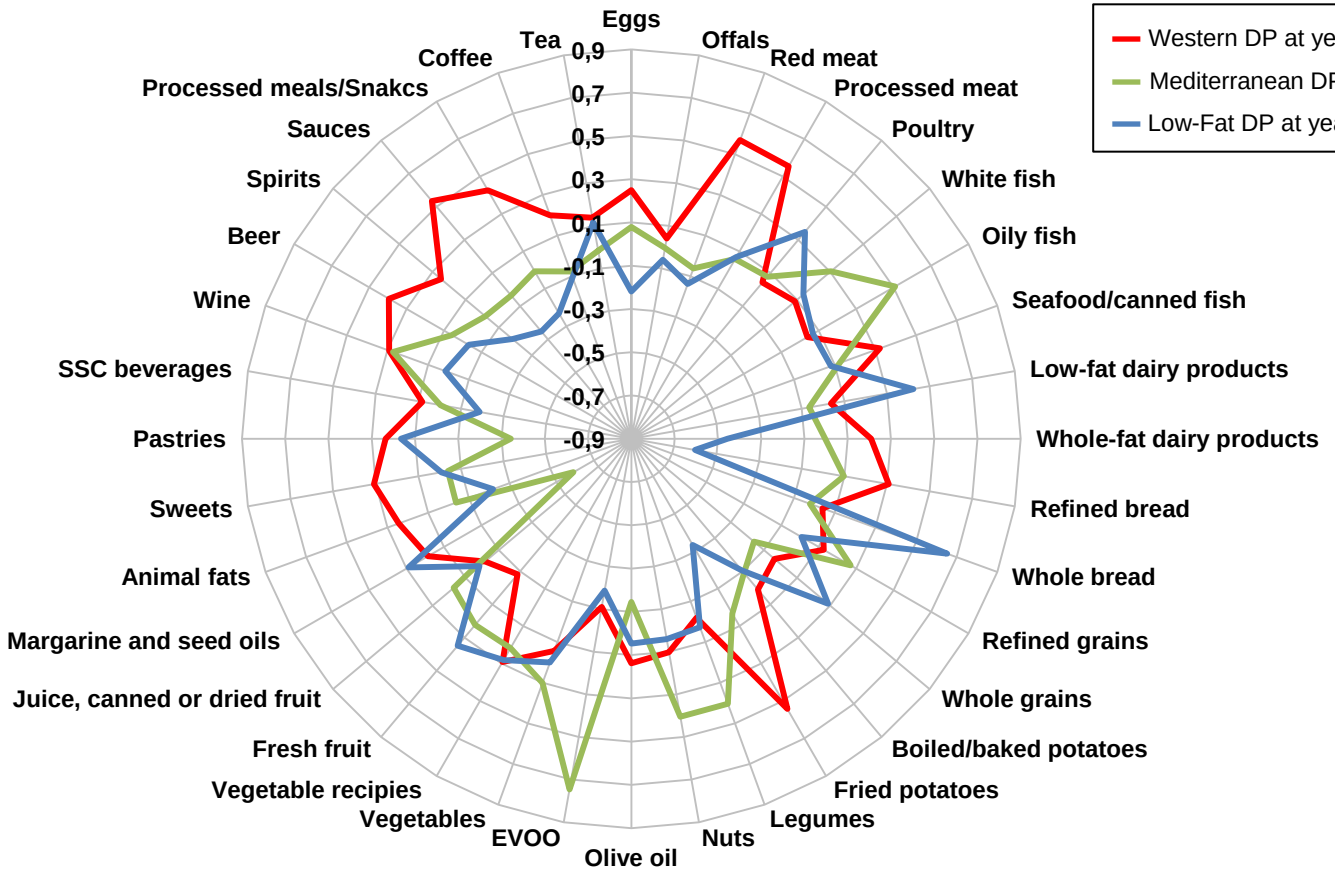


Figure 10. Dietary patterns derived after one year of intervention in the 436 non-diabetics. Rotated factor loadings (ranging from -0.9 to 0.9) of the 36 food groups on the three retained principal components are depicted in the spider graph. Red line shows the Western dietary pattern (Western DP). Green line denotes the Mediterranean dietary pattern (Mediterranean DP). Blue line shows the Low-fat dietary pattern (Low-Fat DP). EVOO, extra-virgin olive oil; Olive oil, other olive oils different from EVOO; SSC, sugar-sweetened carbonated.

Table 12. Rotated factor loadings[a] for the identified dietary patterns at baseline and after 1 year of dietary intervention

	Baseline (n=460)		1-year visit (n=436)		
	WDP	MDP	WDP	MDP	LFDP
Explained variance	8.4%	6.0%	8.0%	6.2%	5.3%
Eggs	0.52	–	–	–	–
Offals	–	–	–	–	–
Red meat	0.35	–	0.57	–	–
Processed meat	0.48	–	0.55	–	–
Poultry	–	–	–	–	0.35
White fish	–	0.32	–	0.30	–
Oily fish	–	0.39	–	0.51	–
Seafood/canned fish	–	0.40	0.32	–	–
Low-fat dairy products	–	0.33	–	–	0.42
Whole-fat dairy products	0.47	–	–	–	-0.46
Refined bread	0.57	–	0.31	–	-0.60
Whole bread	-0.40	–	–	–	0.65
Refined grains	–	–	–	–	–
Whole grains	–	–	–	–	–
Boiled/baked potatoes	–	–	–	–	–
Fried potatoes	0.57	–	0.54	–	-0.33
Legumes	–	0.34	–	0.40	–
Nuts	–	0.31	–	0.40	–
Olive oil (not extra-virgin)	–	-0.37	–	–	–
Extra-virgin olive oil	–	0.37	–	0.75	–
Vegetables	–	0.51	–	0.30	–
Vegetable recipes	–	–	–	–	–
Fresh fruit	-0.31	0.38	–	–	0.35
Juice, canned or dried fruit	–	–	–	–	–
Margarine and seed oils	–	–	–	-0.59	–
Animal fats	–	–	–	–	–
Sweets	0.42	–	0.31	–	–
Pastries	–	–	–	-0.34	–
SSC beverages	–	–	–	–	–
Wine	–	–	–	–	–
Beer	–	–	0.39	–	–
Spirits	–	–	–	–	–
Sauces	0.40	–	0.53	–	–
Processed meals/Snacks	0.52	–	0.43	–	–
Coffee	–	–	–	–	–

WDP, Western dietary pattern; MDP, Mediterranean dietary pattern; LFDP, Low-Fat dietary pattern. [a]Factor loadings correspond to correlation coefficients between food intake and the dietary pattern score. Food groups with absolute loading ≥0.30 were considered relevant components of the identified pattern patterns. Absolute factor loadings <0.30 are not shown.

5.4. Association of dietary scores and PCA-dietary patterns with the incidence of T2DM after a median follow-up of 5 years

After a median dietary intervention period of 60 months, a total of 107 patients (of the 462 non-diabetics at baseline) developed T2DM according to the ADA diagnosis criteria [8]. The incidence of T2DM in each year of follow-up is shown in Figure 11. The incidence of T2DM was 26.4% (65 new T2DM patients/246 patients in group) in the Mediterranean diet group and 19.4% (42 new T2DM patients/216 patients in group) in the low-fat diet group after a median follow-up of 60 months (Chi^2=3.147; *p*= 0.076).

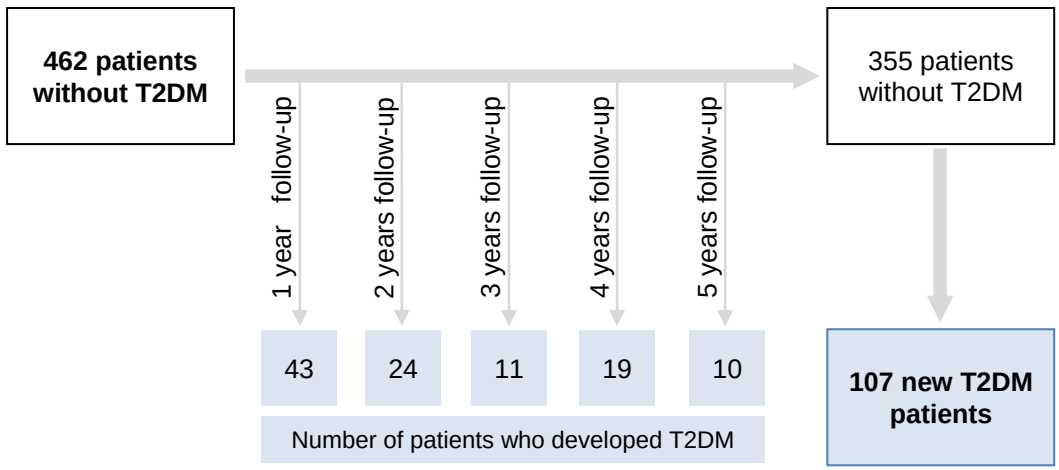


Figure 11. Number of patients who developed T2DM during the 5 years of follow-up. Modified from Camargo et al. [186]

When assessing the relationship of dietary scores and PCA-dietary patterns at baseline with incident T2DM events, the risk analysis excluded 39 patients (including 1 event) because of lost to follow-up (n=7), death before 5-year visit (n=17), implausible data on baseline energy intake (n=2), or missing data (n=13).

When assessing the relationship of dietary scores and PCA-dietary patterns at year 1 with incident T2DM events, the risk analysis excluded 90 patients (including 1 event) because of developing T2DM during the first year of follow-up (n=43), lost to follow-up (n=7), death before 5-year visit (n=17), implausible data on baseline energy intake (n=2), or missing data (n=21).

5.4.1. Association between dietary scores and incident T2DM

We performed COX proportional hazards regression analyses to evaluate the association of the MEDAS, MDS-Trichopoulou and LFDAS measured at baseline (at the entering on the study) and after one year of intervention (year 1) with the incidence of T2DM after a median follow-up of 60 months. We calculated multivariable-adjusted hazard ratios (HR) and 95% confidence intervals (CI) across categories of adherence to the three dietary scores, as well as considering the dietary scores as continuous variables.

5.4.1.1. Dietary scores at baseline (Time 0 years) and incident T2DM

Table 13 shows the associations observed between baseline dietary scores and incident T2DM. There were no significant associations between the MEDAS, MDS-Trichopoulou or the LFDAS at baseline and the incidence of T2DM after a median follow-up of 60 months (MEDAS: ExpB=1.06, 95% CI=0.96-1.17; MDS-Trichopoulou: ExpB=0.99, 95% CI=0.87-1.14; LFDAS: ExpB=1.01, 95% CI=0.89-1.14).

When we assessed the risk of developing T2DM according to categories of adherence to each of the three dietary scores at baseline, we found similar results (Table 14). There were no significant associations between the category of high adherence to the MEDAS, MDS-Trichopoulou or the LFDAS at baseline and the onset of T2DM after a median follow-up of 60 months (MEDAS: HR=0.95, 95% CI=0.62-1.44; MDS-Trichopoulou: HR=1.15, 95% CI=0.72-1.84; LFDAS: HR=0.88, 95% CI=0.32-2.45).

Table 13. Associations of baseline dietary scores with the incidence of T2DM after a median follow-up of 60 months[a]

Dietary scores at baseline (as continuous variables)	n=423[b]		
	Exp (B)	95% CI	*p*
MEDAS	1.06	0.96-1.17	0.237
MDS-Trichopoulou	0.99	0.87-1.14	0.943
LFDAS	1.01	0.89-1.14	0.917

T2DM, type 2 diabetes mellitus; CI, confidence intervals; MEDAS, 14-point Mediterranean Diet Adherence Screener; MDS-Trichopoulou, Mediterranean Dietary Score proposed by Trichopoulou et al.; LFDAS, 9-point low-fat diet adherence screener.

[a]Exp (B), 95% confidence intervals and *p* values were calculated by Cox regression analysis and were adjusted for age, sex, randomized group, BMI, waist circumference, HbA1c, triglycerides, HDL cholesterol, treatment with statins, smoking status, educational level, physical activity, and energy intake.

[b]Excluded were 39 patients (including 1 event) because of lost to follow-up, death before 5-year visit, implausible data on baseline energy intake, or missing data.

Table 14. Hazard ratios for incident T2DM according to categories of adherence to the three dietary scores at baseline[a]

Categories of adherence at baseline	n=423[b]				
	No. in group	No. of events	HR	95% CI	*p*
MEDAS					
Low-medium (0-9 points)	265	66	1	Referent	
High (10-14 points)	158	40	0.95	0.62-1.44	0.805
MDS-Trichopoulou					
Low-medium (0-5 points)	328	80	1	Referent	
High (6-9 points)	95	26	1.15	0.72-1.84	0.556
LFDAS					
Low-medium (0-6 points)	400	102	1	Referent	
High (7-9 points)	23	4	0.88	0.32-2.45	0.805

T2DM, type 2 diabetes mellitus; HR, hazard ratios; CI, confidence intervals; MEDAS, 14-point Mediterranean Diet Adherence Screener; MDS-Trichopoulou, Mediterranean Dietary Score proposed by Trichopoulou et al.; LFDAS, 9-point low-fat diet adherence screener.

[a]Hazard ratios, 95% confidence intervals and *p* values were calculated by Cox regression analysis and were adjusted for age, sex, randomized group, BMI, waist circumference, HbA1c, triglycerides, HDL cholesterol, treatment with statins, smoking status, educational level, physical activity, and energy intake.

[b]Excluded were 39 patients (including 1 event) because of lost to follow-up, death before 5-year visit, implausible data on baseline energy intake, or missing data.

5.4.1.2. Dietary scores at 1-year visit and incident T2DM

Table 15 displays the associations observed between dietary scores at 1-year visit (as continuous variables) and the incidence of T2DM after a median follow-up of 60 months. We observed that the MEDAS at year 1 was inversely and strongly associated with incident T2DM (*p*=0.003). Specifically, each one-point of increment in the MEDAS at year 1 (range: 0-14) was associated with a significant 17% reduction in incident T2DM (ExpB=0.83, 95% CI= 0.73-0.94). In contrast, no association between the MDS-Trichopoulou at year 1 and the incidence of T2DM was found (ExpB=0.99, 95% CI=0.83-1.17). Finally, we observed an inverse but not-statistically significant association between the LFDAS at year 1 and the incidence of T2DM (ExpB=0.88, 95% CI=0.75-1.02).

Table 15. Associations of dietary scores at 1-year visit with the incidence of T2DM after a median follow-up of 60 months[a]

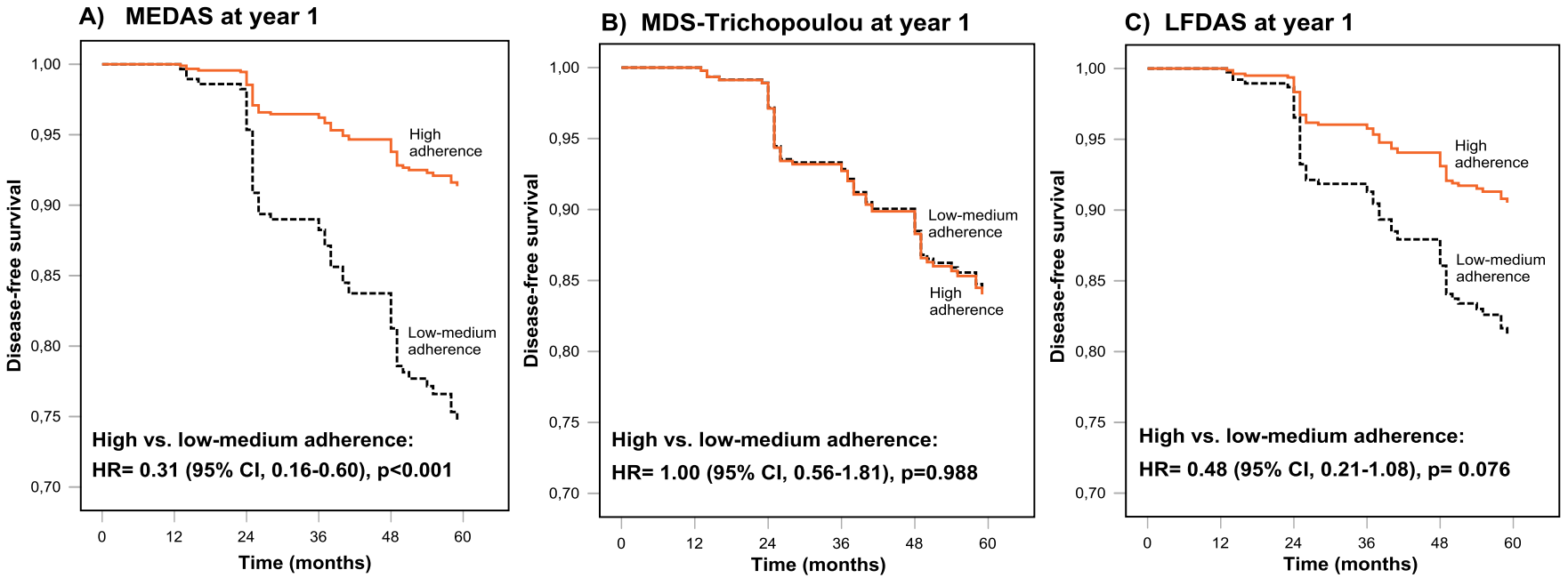
Dietary scores at year 1 (as continuous variables)	n=372[b]		
	Exp (B)	95% CI	*p*
MEDAS	0.83	0.73-0.94	0.003
MDS-Trichopoulou	0.99	0.83-1.17	0.867
LFDAS	0.88	0.75-1.02	0.098

T2DM, type 2 diabetes mellitus; CI, confidence intervals; MEDAS, 14-point Mediterranean Diet Adherence Screener; MDS-Trichopoulou, Mediterranean Dietary Score proposed by Trichopoulou et al.; LFDAS, 9-point low-fat diet adherence screener.

[a]Exp (B), 95% confidence intervals and *p* values were calculated by Cox regression analysis and were adjusted for age, sex, randomized group, BMI, waist circumference, HbA1c, triglycerides, HDL cholesterol, treatment with statins, smoking status, educational level, physical activity, and energy intake.

[b]Excluded were 90 patients (including 1 event) because of developing T2DM during the first year of follow-up, lost to follow-up, death before 5-year visit, implausible data on baseline energy intake, or missing data.

When we analyzed the risk of developing T2DM across categories of adherence to the three dietary scores at 1-year visit (Figure 12), we observed that patients in the highest adherence category of the MEDAS (10-14 points) at year 1 had a 69% less risk of developing T2DM than those patients in the low-medium adherence category (HR=0.31, 95% CI=0.16-0.60). However, no association was found between the category of high adherence to the MDS-Trichopoulou at year 1 and the risk of developing T2DM versus the low-medium adherence category (HR=1.00, 95% CI= 0.56-1.81). On the other hand, patients with the highest adherence to the LFDAS at year 1 had a HR of 0.48 (95% CI=0.21-1.08) for incident T2DM, compared to those patients in the low-medium adherence category, although the association did not reach statistical significance (p=0.076).



Categories of adherence at year 1	No. of events/ No. in group
Low-medium (0-9points)	36/188
High (10-14 points)	27/184

Categories of adherence at year 1	No. of events/ No. in group
Low-medium (0-5 points)	45/270
High (6-9 points)	18/102

Categories of adherence at year 1	No. of events/ No. in group
Low-medium (0-6 points)	53/267
High (7-9 points)	10/105

- - - - Low-medium adherence ——— High adherence

Figure 12. Diabetes-free survival by Cox analysis according to categories of adherence to dietary scores at year 1 (n=372). A) 14-point Mediterranean Diet Adherence Screener (MEDAS) at year 1; B) Mediterranean Dietary Score proposed by Trichopoulou et al. (MDS-Trichopoulou) at year 1; C) 9-point low-fat diet adherence screener (LFDAS) at year 1. All models were adjusted for age, sex, randomized group, BMI, waist circumference, HbA1c, triglycerides, HDL cholesterol, treatment with statins, smoking status, educational level, physical activity, and energy intake. The Hazard Ratios (HR) and 95% Confidence Intervals (CI) between high and low-medium adherence groups were calculated.

5.4.2. Association between PCA-dietary patterns and incident T2DM

In order to investigate the associations of PCA-dietary patterns (derived at baseline and at year 1) with the incidence of T2DM after a median follow-up of 60 months, we performed a similar statistical approach to that performed with the dietary scores. Therefore, COX proportional hazards regression analyses and HR with 95% CI for the upper tertile versus the lower plus middle tertiles of adherence to each dietary pattern (reference category) were performed.

5.4.2.1. PCA-dietary patterns at baseline and incident T2DM

HR and 95% CI for T2DM across tertiles of adherence to PCA-dietary patterns at baseline are shown in Table 16. No association between the highest tertile of the Western DP at baseline and incident T2DM was found (HR=1.06; 95% CI= 0.65-1.72). Similarly, there was no significant relationship between the highest tertile of the Mediterranean DP at baseline and incident T2DM (HR=0.92; 95% CI=0.58-1.45).

Table 16. Hazard ratios for incident T2DM according to tertiles of adherence to PCA-dietary patterns at baseline[a]

	n = 423[b]				
PCA-dietary patterns at baseline	No. in group	No. of events	HR	95% CI	*p*
Western dietary pattern					
T1+T2 (low-medium adherence)	285	70	1	Referent	
T3 (high adherence)	138	36	1.06	0.65-1.72	0.828
Mediterranean dietary pattern					
T1+T2 (low-medium adherence)	281	69	1	Referent	
T3 (high adherence)	142	37	0.92	0.58-1.45	0.714

T2DM, type 2 diabetes mellitus; HR, hazard ratios; CI, confidence intervals; PCA-dietary patterns, dietary patterns derived by principal components analysis; T1, tertile 1; T2, tertile 2; T3, tertile 3.

[a]Hazard ratios, 95% confidence intervals and *p* values were calculated by Cox regression analysis and were adjusted for age, sex, randomized group, BMI, waist circumference, HbA1c, triglycerides, HDL cholesterol, treatment with statins, smoking status, educational level, physical activity, and energy intake.

[b]Excluded were 39 patients (including 1 event) because of lost to follow-up, death before 5-year visit, implausible data on baseline energy intake, or missing data.

5.4.2.2. PCA-dietary patterns at 1-year visit and incident T2DM

When we assessed the risk of developing T2DM across tertiles of PCA-dietary patterns at 1-year visit (Figure 13), we observed that the Western DP at year 1 was positively associated with an increased risk of T2DM development (p=0.035). Specifically, patients in the third tertile of the Western DP at year 1 had a 90% greater risk of developing T2DM than patients in the first plus second tertiles (HR=1.90; 95% CI=1.05-3.46). In the case of the Mediterranean DP at year 1, patients with the highest adherence to this pattern (third tertile) had a non-significant reduction in the risk of developing T2DM of 25% (HR=0.75; 95% CI=0.41-1.39; p=0.368). Similarly, patients with the highest adherence to the Low-Fat DP at year 1 (third tertile) showed a non-significant trend for a lower risk of developing T2DM (HR=0.65; 95% CI=0.36-1.17; p=0.154) compared to those in the reference category (first plus second tertiles).

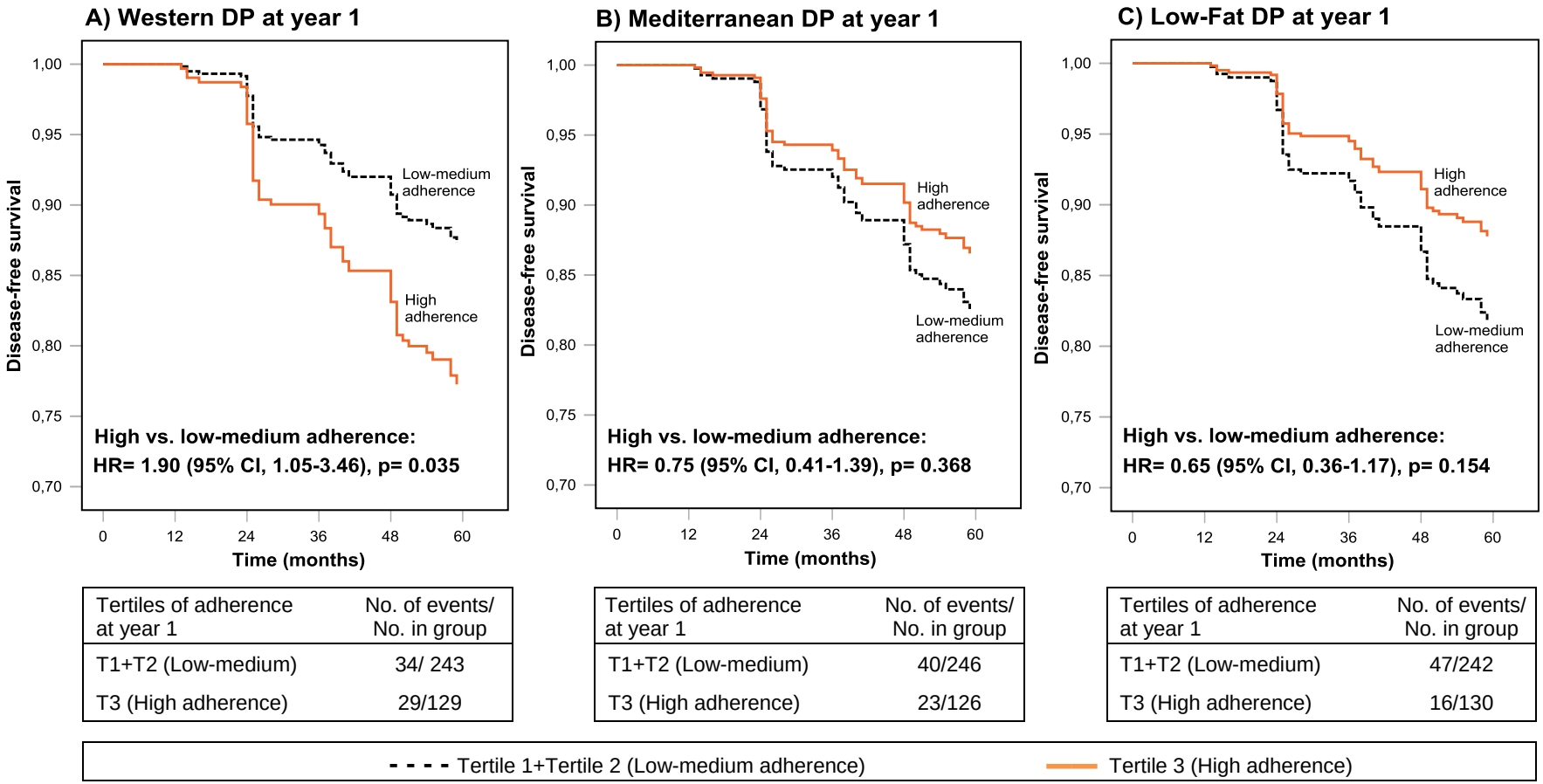


Figure 13. Diabetes-free survival by Cox analysis according to tertiles of adherence to PCA-dietary patterns at year 1 (n=372). A) Western dietary pattern (Western DP) at year 1; B) Mediterranean dietary pattern (Mediterranean DP) at year 1; C) Low-fat dietary pattern (Low-Fat DP) at year 1. All models were adjusted for age, sex, randomized group, BMI, waist circumference, HbA1c, triglycerides, HDL cholesterol, treatment with statins, smoking status, educational level, physical activity, and energy intake. The Hazard Ratio (HR) and 95% Confidence Intervals (CI) between high and low-medium adherence groups were calculated.

5.4.3. Comparison of the MEDAS at year 1 and Western DP at year 1 in predicting the incidence of T2DM after a median follow-up of 5 years

Based on the results presented above, the MEDAS (*a priori*-defined dietary pattern) at year 1 and the Western DP (*a posteriori*-derived dietary pattern) at year 1 were the only methods showing significant associations with incident T2DM in our population. Thus, in order to address the main objective of this thesis, the MEDAS at year 1 and Western DP at year 1 were compared regarding their ability to predict the incidence of T2DM after a median follow-up of 60 months. We performed logistic regression and ROC curve analyses to test the predictive ability of the two models: model 1, which included the MEDAS at year 1 and the potential confounders considered in the COX regression analyses (age, sex, randomized group, BMI, waist circumference, HbA1c, triglycerides, HDL cholesterol, statins use, smoking, educational level, physical activity and energy intake); model 2, which included the Western DP at year 1 and the same potential confounders.

The results of logistic regression analyses showed that in model 1, together with the MEDAS at year 1 ($OR_{High\ vs.\ low\text{-}medium\ adherence}$=0.28; 95% CI=0.13-0.62; p=0.002), randomized group ($OR_{Mediterranean\ diet\ group\ vs.\ low\text{-}fat\ diet\ group}$=4.03; 95% CI=1.79-9.07; p=0.001), waist circumference (OR=1.08; 95% CI=1.03-1.14) and energy intake (OR=1.00; 95% CI=1.00-1.01; p=0.043) appeared as significant predictors of incident T2DM among the 13 potential confounders initially included in the regression. Moreover, the Hosmer-Lemeshow statistic indicated an adequate good fit for the model (Chi^2=4.260; p=0.833). In model 2, together with the Western DP at year 1 ($OR_{High\ vs.\ low\text{-}medium\ adherence}$=2.02; 95% CI=1.02-3.98; p=0.043), randomized group ($OR_{Mediterranean\ diet\ group\ vs.\ low\text{-}fat\ diet\ group}$=1.92; 95% CI=1.04-3.55; p=0.036) and HbA1c (OR=2.63; 95% CI=1.07-6.44; p=0.034) appeared as significant predictors of incident T2DM among the 13 potential confounders tested. Likewise, the model well fitted the data as indicated by Hosmer-Lemeshow test (Chi^2=7.314; p=0.503).

Figure 14 shows the ROC curves and their respective areas under the curve (AUC) for T2DM incidence with the two models. We observed that both models showed significant areas under the ROC curve for predicting the incidence of T2DM after a median follow-up of 60 months (all $p<0.001$), with an acceptable discrimination ability (AUC range 0.7-0.8). The AUC for the model including the MEDAS at year 1 (AUC=0.733; 95% CI=0.665-0.801) was slightly higher than that for the model including the Western DP at year 1 (AUC=0.715; 95% CI=0.649-0.781). However, when areas under the ROC curves of the two models were compared by the method described by DeLong et al. [182], no statistically significant differences were found ($p=0.521$).

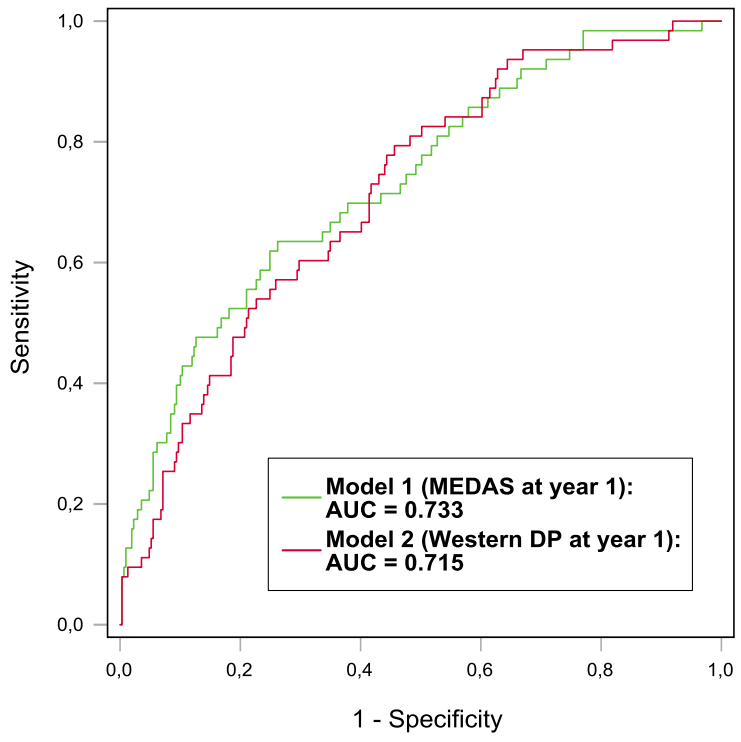


Figure 14. Receiver operating characteristic (ROC) curves and area under the curve (AUC) values for models including the MEDAS at year 1 and the Western DP at year 1 to predict incident T2DM. Model 1 (MEDAS at year 1): MEDAS at year 1, age, sex, randomized group, BMI, waist circumference, HbA1c, triglycerides, HDL cholesterol, statins use, smoking, educational level, physical activity, energy intake; Model 2 (Western DP at year 1): Western DP at year 1, age, sex, randomized group, BMI, waist circumference, HbA1c, triglycerides, HDL cholesterol, statins use, smoking, educational level, physical activity, energy intake.

Further, we compared the predictive value of both models to traditional clinical variables and lifestyle factors, in order to assess the added predictive value of the MEDAS at year 1 and the Western DP at year 1. Firstly, we performed ROC curves and their respective AUC to examine the ability of traditional clinical variables (model 3: age, sex, randomized group, BMI, waist circumference, HbA1c, triglycerides, HDL cholesterol and statins use) and clinical variables plus lifestyle factors (model 4: model 3, smoking status, educational level, physical activity, energy intake) to predict T2DM incidence. We observed an AUC of 0.654 (95% CI=0.580-0.728; $p<0.001$) when only traditional clinical variables were used (model 3) and an AUC of 0.661 (95% CI=0.583-0.738; $p<0.001$) when combining clinical variables with lifestyle factors (model 4). Then, we compared the ROC curves of the four models (Figure 15). Differences in AUC values between the four models were compared according to the method described by DeLong et al. [182]. We observed that including the MEDAS at year 1 improved AUC both of the model that included only clinical variables ($p=0.022$) and the model including clinical variables plus lifestyle factors ($p=0.021$) (Figure 15a). Similarly, the AUC of clinical variables and the model of clinical variables plus lifestyle improved when including the Western DP at year 1 ($p=0.031$ and $p=0.032$ respectively) (Figure 15b).

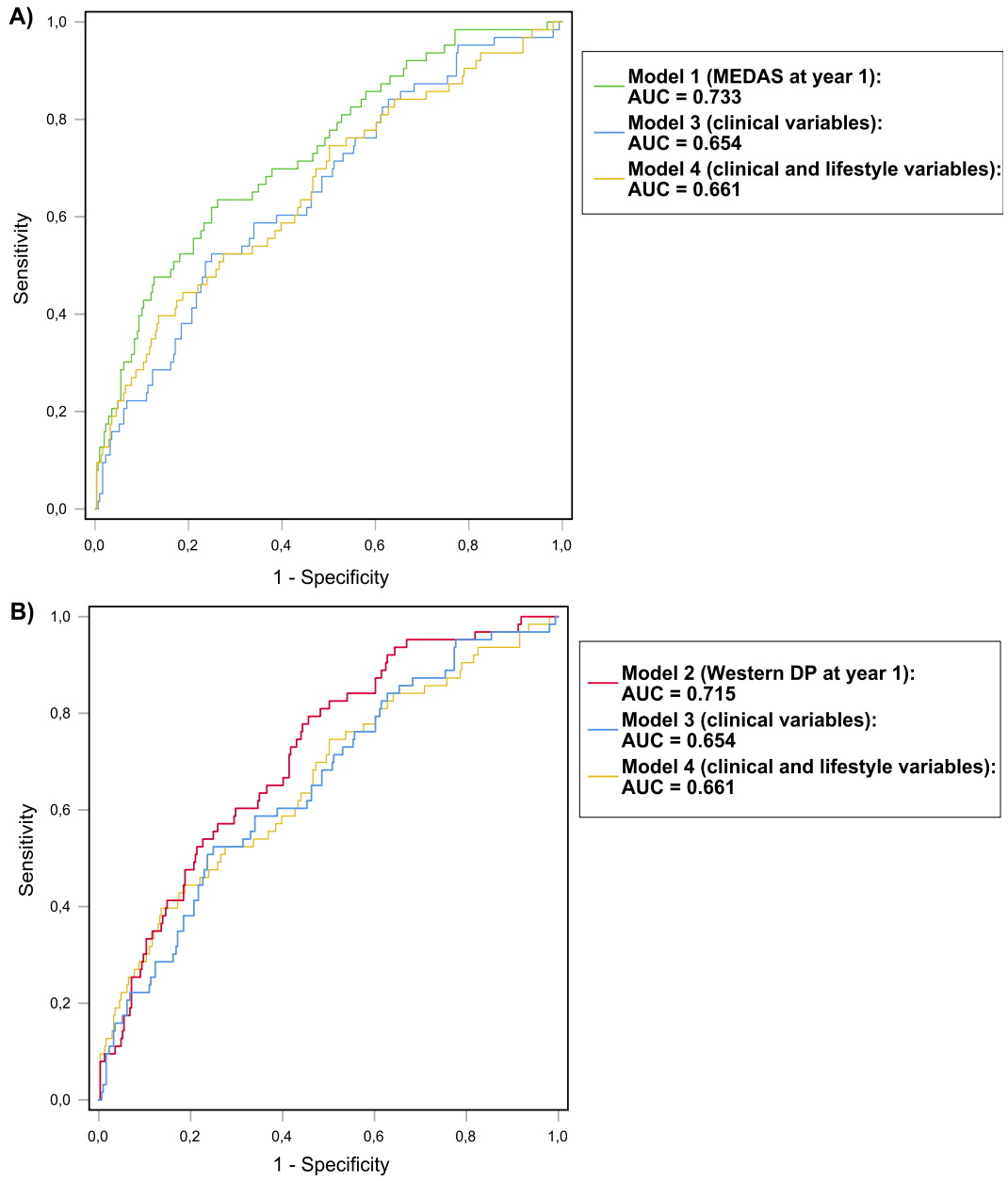


Figure 15. Comparison of Receiver Operating Characteristic (ROC) curves of the four models to predict incident T2DM. A) Model 1 (MEDAS at year 1) versus model 3 (clinical variables) and model 4 (clinical and lifestyle variables); B) Model 2 (Western DP at year 1) versus model 3 (clinical variables) and model 4 (clinical and lifestyle variables). Model 1: MEDAS at year 1+ traditional clinical variables+ lifestyle factors; Model 2: Western DP at year 1+ traditional clinical variables+ lifestyle factors; Model 3: traditional clinical variables; Model 4: traditional clinical variables+ lifestyle factors; Traditional clinical variables: age, sex, randomized group, BMI, waist circumference, HbA1c, triglycerides, HDL cholesterol, statins use; Lifestyle factors: smoking, educational level, physical activity, energy intake.

5.5. Association of dietary scores and PCA-dietary patterns with factors associated to the development of T2DM

Taking into account the importance of studying not only the incidence of T2DM but also factor associated to the development of T2DM, we further investigated the association of dietary scores and PCA-dietary patterns at year 1 with the following variables after 5 years of dietary intervention: BMI, waist circumference, HbA1c, homeostatic model assessment of insulin resistance (HOMA-IR), glucose, triglycerides, C-reactive protein, leukocytes and neutrophil-lymphocyte ratio, and total, HDL and LDL cholesterol.

5.5.1. Dietary scores at year 1 and anthropometric/biochemical variables at year 5

We performed linear regression analyses with the anthropometric/biochemical variables at year 5 as dependent variables and the three dietary scores at year 1 as independent variables, and adjusted for age, sex and randomized group. Table 17 summarises the results of the linear regression analyses. We observed that the MEDAS at year 1 was associated with most of the anthropometric/biochemical variables at year 5. Specifically, for every 1-point increase in the MEDAS at year 1, waist circumference decreased by 0.7 cm (95% CI=-1.36, -0.02), HbA1c decreased by 0.03% (95% CI=-0.05, -0.01), HOMA-IR decreased by 0.2 (95% CI=-0.38, -0.01), glucose decreased by 0.8 mg/dL (95% CI=-1.47, -0.13) and triglycerides decreased by 6.6 mg/dL (95% CI=-10.18, -3.07). Moreover, for each point of increase in this dietary score, there was a significant reduction in the inflammatory markers C-reactive protein, leukocytes and neutrophil-lymphocyte ratio of 0.21 mg/dL (95% CI=-0.40, -0.02), $0.09x10^3/\mu$ (95% CI=-0.19, -0.004) and 0.06 (95% CI=-0.11, -0.004), respectively.

Table 17. Results of linear regression analysis between dietary scores at year 1 and anthropometric/biochemical variables at year 5 in the study sample (n=372)[a]

Dependent variable	MEDAS at year 1			MDS-Trichopoulou at year 1			LFDAS at year 1		
	Regression coefficient[b]	95%CI	*p*	Regression coefficient[b]	95%CI	*p*	Regression coefficient[b]	95%CI	*p*
BMI, kg/m^2	-0.146	-0.425, 0.132	0.302	-0.172	-0.505, 0.161	0.310	-0.450	-0.746, -0.154	**0.003**
Waist circumference, cm	-0.689	-1.360, -0.017	**0.044**	-0.584	-1.388, 0.221	0.155	-1.297	-2.010, -0.584	**<0.001**
HbA1c,%	-0.029	-0.050, -0.007	**0.009**	-0.008	-0.035, 0.018	0.527	-0.011	-0.035, 0.012	0.345
HOMA-IR	-0.195	-0.384, -0.007	**0.042**	-0.133	-0.359, 0.093	0.246	-0.086	-0.289, 0.118	0.408
Glucose, mg/dL	-0.796	-1.465, -0.127	**0.020**	-0.042	-0.848, 0.763	0.918	-0.555	-1.277, 0.166	0.131
Triglycerides, mg/dL	-6.626	-10.183, -3.070	**<0.001**	-2.026	-6.349, 2.296	0.357	-5.225	-9.078, -1.373	**0.008**
Total Cholesterol, mg/dL	-1.108	-2.411, 0.195	0.095	-0.079	-2.262, 2.104	0.943	-1.582	-3.582, 0.418	0.121
HDL cholesterol, mg/dL	0.040	-0.380, 0.460	0.851	0.256	-0.428, 0.939	0.463	-0.032	-0.647, 0.582	0.918
LDL cholesterol, mg/dL	-0.736	-2.205, 0.733	0.325	-0.074	-1.832, 1.684	0.934	-1.223	-2.798, 0.352	0.128
C-reactive protein, mg/L	-0.208	-0.402, -0.015	**0.035**	-0.028	-0.260, 0.205	0.815	-0.164	-0.372, 0.045	0.123
Leukocytes, 10^3/µL	-0.094	-0.185, -0.004	**0.041**	-0.007	-0.116, 0.102	0.904	-0.089	-0.187, 0.009	0.074
Neutrophil-lymphocyte ratio	-0.055	-0.106, -0.004	**0.034**	0.057	-0.004, 0.118	0.065	-0.024	-0.079, 0.031	0.398

MEDAS, 14-point Mediterranean Diet Adherence Screener; MDS-Trichopoulou, Mediterranean Dietary Score proposed by Trichopoulou et al.; LFDAS, 9-point low-fat diet adherence screener; CI, confidence interval; BMI, body mass index; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein. [a]Excluded were 90 participants because of development of T2DM during the first year of follow-up (n=43), loss to follow-up (n=7), death before 5-year visit (n=17), implausible data on baseline energy intake (n=2), or missing data (n=21). [b]Adjusted for sex, age and randomized diet group.

In the case of the MDS-Trichopoulou at year 1, however, there were no significant associations with any of the investigated anthropometric/biochemical variables at year 5.

On the other hand, only for each point of increase in the LFDAS at year 1, the BMI, waist circumference and triglycerides at year 5 decreased by 0.5 kg/m^2 (95% CI=-0.75, -0.15), 1.3 cm (95% CI=-2.01, -0.58) and 5.2 mg/dL (95% CI=-9.08, -1.37), respectively.

5.5.2. PCA-dietary patterns at year 1 and anthropometric/biochemical variables at year 5

We performed a linear regression analyses with anthropometric/biochemical variables at year 5 as dependent variables and the PCA-dietary patterns at year 1 as independent variables (adjusted for age, sex and randomized group) (Table 18). As expected, the results showed a significant positive association between the Western DP at year 1 and BMI, waist circumference, glucose, triglycerides, total and LDL cholesterol, and C-reactive protein at year 5 (all $p<0.05$). No significant association was found between the Mediterranean DP at year 1 and any of the anthropometric/biochemical variables at year 5. Finally, we observed a significant inverse association between the Low-Fat DP at year 1 and waist circumference ($p=0.007$) and triglycerides ($p<0.001$) at year 5.

Table 18. Results of linear regression analysis between PCA-dietary patterns at year 1 and anthropometric/biochemical variables at year 5 in the study sample (n=372)[a]

Dependent variable	Western DP at year 1			Mediterranean DP at year 1			Low-Fat DP at year 1		
	Regression coefficient[b]	95%CI	*p*	Regression coefficient[b]	95%CI	*p*	Regression coefficient[b]	95%CI	*p*
BMI, kg/m^2	0.688	0.171, 1.204	**0.009**	0.236	-0.277, 0.748	0.367	-0.467	-0.977, 0.042	0.072
Waist circumference, cm	1.962	0.717, 3.208	**0.002**	0.138	-1.104, 1.380	0.828	-1.695	-2.922, -0.468	**0.007**
HbA1c,%	0.004	-0.037, 0.045	0.838	-0.011	-0.062, 0.039	0.657	-0.025	-0.065, 0.015	0.220
HOMA-IR	0.153	-0.201, 0.506	0.396	0.096	-0.342, 0.533	0.668	-0.208	-0.554, 0.139	0.240
Glucose, mg/dL	1.514	0.265, 2.763	**0.018**	0.611	-0.946, 2.168	0.441	-0.730	-1.964, 0.505	0.246
Triglycerides, mg/dL	10.240	3.559, 16.921	**0.003**	-2.563	-10.933, 5.806	0.547	-14.112	-20.597, -7.626	**<0.001**
Total Cholesterol, mg/dL	5.757	2.398, 9.117	**0.001**	2.360	-0.933, 5.652	0.160	-2.075	-5.490, 1.339	0.233
HDL cholesterol, mg/dL	-0.432	-1.481, 0.617	0.418	0.477	-0.846, 1.799	0.479	0.220	-0.830, 1.270	0.680
LDL cholesterol, mg/dL	3.498	0.774, 6.223	**0.012**	0.660	-2.046, 3.365	0.632	-2.110	-4.801, 0.581	0.124
C-reactive protein, mg/L	0.391	0.029, 0.752	**0.034**	-0.359	-0.807, 0.090	0.117	0.162	-0.283, 0.607	0.474
Leukocytes, 10^3/μL	0.102	-0.068, 0.272	0.239	-0.084	-0.294, 0.127	0.435	-0.086	-0.266, 0.093	0.343
Neutrophil-lymphocyte ratio	0.054	-0.041, 0.150	0.264	-0.052	-0.171, 0.066	0.386	0.004	-0.090, 0.098	0.935

Western DP, Western dietary pattern; Mediterranean DP, Mediterranean dietary pattern; Low-Fat DP, low-fat dietary pattern; CI, confidence interval; BMI, body mass index; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein. [a]Excluded were 90 participants because of development of T2DM during the first year of follow-up (n=43), loss to follow-up (n=7), death before 5-year visit (n=17), implausible data on baseline energy intake (n=2), or missing data (n=21). [b]Adjusted for sex, age and randomized diet group.

5.6. Assessment of the validity of the dietary scores in our population

As explained in the methodology section (pages 71 and 72), we firstly assessed the construct validity of the MEDAS, MDS-Trichopoulou and LFDAS in both the non-diabetics at baseline (n=462) and the total CORDIOPREV population (n=1002). Then, considering that the MEDAS and LFDAS were the monitoring adherence tools used in the CORDIOPREV study, we also evaluated the concurrent validity of both dietary scores in the 1002 coronary patients.

5.6.1. Construct validity of the three dietary scores (MEDAS, MDS-Trichopoulou and LFDAS) in our population

Construct validity of the MEDAS, MDS-Trichopoulou and LFDAS was determined by analysing the correlations of the three dietary scores with dietary data reported on FFQs at baseline using Pearson correlation analysis and analysis of covariance (ANCOVA).

5.6.1.1. Pearson correlation analysis

Pearson correlation coefficients between each dietary score and food intake at baseline in the non-diabetics are depicted in Table 19. As expected, the MEDAS correlated positively with olive oil, vegetables, fruits, nuts, legumes, fish and seafood, poultry and wine (all $p<0.05$), and negatively with red meat/processed meat ($p<0.001$), fats spread ($p=0.001$), SSC beverages ($p=0.002$), and commercial pastries ($p=0.001$). The magnitude of the correlation ranged from 0.315 for nuts to 0.115 for olive oil. Correlations between the MDS-Trichopolou and food groups were similar than those described above, except for poultry (non-significant correlation). Besides, the MDS-Trichopoulou showed significant positive correlation with grains ($p<0.001$ for total grains, $p=0.026$ for whole grains and $p=0.014$ for refined grains) and negative

correlation with dairy products (p<0.001). On the other hand, the LDFAS correlated positively with low-fat and high-carbohydrate foods like grains (p<0.001 for total grains and p=0.047 for whole grains) and vegetables (p=0.004), as well as with low-fat dairy products (p=0.003). As expected, this dietary score correlated negatively with fatty foods such as olive oil (p=0.023), nuts (p<0.001), oily fish (p=0.022), red meat/processed meat (p<0.001), commercial sweets and pastries (p<0.001), and fats spread (p=0.001).

Table 19. Correlation between the three dietary scores and food intake derived from food frequency questionnaires at baseline in the non-diabetic patients[a]

Food items	MEDAS	MDS-Trichopoulou	LFDAS
Olive oil	0.115 *	0.101 *	-0.106 *
Vegetables	0.208 **	0.344 **	0.134 *
Fruits	0.171 **	0.311 **	0.049
Nuts	0.315 **	0.134 *	-0.243 **
Legumes	0.186 **	0.207 **	0.087
Grains	0.014	0.221 **	0.172 **
Whole grains	0.020	0.104 *	0.085 *
Refined grains	-0.007	0.114 *	0.057
Fish and seafood	0.262 **	0.386 **	0.042
Oily fish	0.218 **	0.320 **	-0.107 *
White fish	0.168 **	0.274 **	0.028
Seafood	0.121 *	0.129 *	0.069
Poultry	0.139 *	-0.018	0.045
Red meat/processed meat	-0.221 **	-0.218 **	-0.246 **
Dairy products	0.048	-0.251 **	-0.013
Low-fat dairy products	0.044	-0.098 *	0.141 *
Commercial bakery goods, sweets, and pastries (not homemade)	-0.151 *	-0.071	-0.215 **
Fats spread	-0.148 *	-0.118 *	-0.161 *
SSC beverages	-0.144 *	-0.112 *	-0.052
Wine	0.200 **	0.171 **	-0.045

Data represent Person correlation coefficients. *p value <0.05 and **p<0.001 corresponding to the indicated Pearson correlation coefficient. MEDAS, 14-point Mediterranean Diet Adherence Screener; MDS-Trichopoulou, Mediterranean Dietary Score proposed by Trichopoulou et al.; LFDAS, 9-point low-fat diet adherence screener; SSC, sugar-sweetened carbonated. [a]N=460 after excluding 2 patients with extreme energy intake.

When we repeated Pearson correlation analyses including the total CORDIOPREV population, and not only the non-diabetic population evaluated in this thesis, we found similar results in terms of strength and direction of the relationship between each dietary score and food data from the FFQs (Table 20).

Table 20. Correlation between the three dietary scores and food intake derived from food frequency questionnaires at baseline in the total CORDIOPREV population[a]

Food items	MEDAS	MDS-Trichopoulou	LFDAS
Olive oil	0.101 *	0.128 **	-0.064 *
Vegetables	0.218 **	0.315 **	0.161 *
Fruits	0.209 **	0.321 **	0.080 *
Nuts	0.278 **	0.134 **	-0.243 **
Legumes	0.173 **	0.217 **	0.104 *
Grains	0.027	0.273 **	0.161 **
Whole grains	0.025	0.072 *	0.070 *
Refined grains	-0.005	0.177 **	0.062
Fish and seafood	0.248 **	0.320 **	0.014
Oily fish	0.189 **	0.242 **	-0.064 *
White fish	0.192 **	0.259 **	0.029
Seafood	0.088 *	0.107 *	0.046
Poultry	0.141 **	-0.053	0.013
Red meat/processed meat	-0.165 **	-0.107 *	-0.293 **
Dairy products	0.017	-0.325 **	0.002
Low-fat dairy products	0.068	-0.050	0.165 **
Commercial bakery goods, sweets, and pastries (not homemade)	-0.171 **	-0.046	-0.253 **
Fats spread	-0.156 **	-0.149 **	-0.183 **
SSC beverages	-0.175 **	-0.109 *	-0.057
Wine	0.179 **	0.172 **	-0.069

Data represent Person correlation coefficients. **p* value <0.05 and ***p*<0.001 corresponding to the indicated Pearson correlation coefficient. MEDAS, 14-point Mediterranean Diet Adherence Screener; MDS-Trichopoulou, Mediterranean Dietary Score proposed by Trichopoulou et al.; LFDAS, 9-point low-fat diet adherence screener; SSC, sugar-sweetened carbonated. [a]N=996 after excluding 6 patients with extreme energy intake.

5.6.1.2. Analysis of covariance (ANCOVA)

We also performed ANCOVA using age and sex as covariates to estimate baseline food and nutrient intake derived from the FFQ according to the tertile distribution of the MEDAS, MDS-Trichopoulou and LFDAS.

When the analysis was conducted among non-diabetics only, we observed that all the associations between the MEDAS and dietary intake from FFQs were in the expected direction (Table 21). Thus, patients with the highest adherence to the MEDAS (tertile 3) had a significant higher consumption of typical foods of the Mediterranean diet (i.e. olive oil, vegetables, fruits, nuts, legumes, fish and wine) and a significant lower intake of foods not recommended in this diet (i.e. red meat/processed meat, commercial pastries, fats spread and SSC beverages). These patients also showed higher intakes of proteins, dietary fiber, vitamins and magnesium, and lower intakes of total fat, SFA, cholesterol and sodium, which were probably related to reduced intakes of red meat/processed meat, fats spread and commercial pastries. In line with this, and although the intake of total MUFA was similar across tertiles of the MEDAS, high adherents to the MEDAS showed a higher intake of MUFA from olive oil and nuts (tertile 1=10.1±0.2, tertile 2=10.8±0.3, tertile 3=11.1±0.3; p=0.037) and a lower intake of MUFA from other sources like red meat/processed meat, seed oils or fats spread (tertile 1=4.2±0.1, tertile 2=3.3±0.1, tertile 3=0.2; p<0.001).

In the case of the MDS-Trichopoulou, associations between high adherents to this dietary score and food intake from the FFQ (Table 22) were similar than those found for the MEDAS, except for nuts, fats spread and SSC beverages (non-significant relationship). Moreover, and as expected, patients in the third tertile of the MDS-Trichopoulou had higher and lower consumptions of grains and dairy products, respectively. In relation to nutrient intake, these participants had higher intakes of dietary fiber, vitamins and magnesium, and lower intakes of total fat and SFA. They

also showed a higher ratio of MUFA to SFA, which is characteristic of this dietary score.

On the other hand, the distribution of food intake by tertiles of the LFDAS was also in the expected direction (Table 23). Participant with the highest adherence to the LFDAS showed reduced intakes of fatty foods (i.e. olive oil, nuts, red meat/processed meat, commercial pastries and fats spread) and increased intakes of vegetables, grains and low-fat dairy products. These patients also had a higher intake of carbohydrates and proteins, and lower intakes of total fat, MUFA, PUFA, SFA and cholesterol. They also showed higher intakes of dietary fiber and vitamin C, as well as of sodium probably due to a higher consumption of grains and low-fat dairy products.

Table 21. Food and nutrient intake recorded on the food frequency questionnaires according to the tertile distribution of the MEDAS at baseline in non-diabetic patients[a]

	MEDAS			
	Tertile 1 (score=0-8; n=204)	Tertile 2 (score=9-10; n=160)	Tertile 3 (score=11-14; n=96)	*p*-value
Foods				
Olive oil (g/day)[b]	32.1 ± 0.8	34.7 ± 0.9	36.7 ± 1.2	0.005
Vegetables (g/day)[b]	240.7 ± 6.8	266.5 ± 7.6	279.5 ± 9.9	0.002
Fruits (g/day)[b]	319.6 ± 13.2	388.1 ± 14.9	383.6 ± 19.3	0.001
Nuts (g/day)[b]	6.5 ± 0.7	9.5 ± 0.8	14.1 ± 1.0	<0.001
Legumes (g/day)[b]	19.8 ± 0.9	25.7 ± 1.0	23.4 ± 1.2	<0.001
Grains (g/day)[b]	188.6 ± 4.4	183.4 ± 4.9	196.0 ± 6.4	0.292
Fish and seafood (g/day)[b]	93.9 ± 3.2	113.9 ± 3.6	115.4 ± 4.6	<0.001
Poultry (g/day)[b]	63.0 ± 2.4	72.7 ± 2.7	71.4 ± 3.5	0.018
Red/processed meat (g/day)[b]	93.7 ± 2.6	82.5 ± 3.0	69.5 ± 3.8	<0.001
Dairy products (g/day)[b]	344.6 ± 12.9	378.9 ± 14.6	368.8 ± 18.8	0.197
Commercial sweets/pastries (g/day)[b]	33.8 ± 1.7	25.8 ± 1.9	23.9 ± 2.5	0.001
Fats spread (g/day)[b]	2.4 ± 0.3	1.1 ± 0.3	1.5 ± 0.4	0.003
SSC beverages (g/day)[b]	115.6 ± 11.2	86.6 ± 12.6	55.5 ± 16.3	0.009
Wine (g/day)[b]	48.8 ± 6.4	61.9 ± 7.2	88.2 ± 9.4	0.003
Nutrients				
Energy (kcal/day)	2273 ± 34	2286 ± 38	2363 ± 49	0.309
Carbohydrates (%E)	42.4 ± 0.4	42.7 ± 0.5	42.9 ± 0.6	0.753
Proteins (%E)	17.7 ± 0.2	18.6 ± 0.2	18.1 ± 0.3	0.007
Total fat (%E)	37.0 ± 0.4	35.7 ± 0.4	35.1 ± 0.5	0.006
Monounsaturated fat (%E)	18.0 ± 0.2	17.6 ± 0.3	17.2 ± 0.3	0.144
Polyunsaturated fat (%E)	6.0 ± 0.1	6.2 ± 0.1	6.5 ± 0.2	0.043
Saturated fat (%E)	9.3 ± 0.1	8.4 ± 0.1	8.0 ± 0.2	<0.001
Cholesterol (mg/day)[b]	339.6 ± 5.3	324.0 ± 6.0	306.0 ± 7.8	0.002
Dietary fiber (g/day)[b]	23.0 ± 0.5	25.4 ± 0.6	26.5 ± 0.7	<0.001
Vitamin C (mg/day)[b]	165.8 ± 4.6	188.1 ± 5.2	194.0 ± 6.7	<0.001
Vitamin E (mg/day)[b]	17.6 ± 0.3	18.6 ± 0.4	19.0 ± 0.5	0.027
Folic acid (µg/day)[b]	291.9 ± 5.6	325.9 ± 6.3	326.9 ± 8.2	<0.001
Carotenes (mg/day)[b]	2509.5 ± 74.3	2829.7 ± 83.7	2957.3 ± 108.2	0.001
Magnesium (mg/day)[b]	347.3 ± 4.8	372.4 ± 5.4	383.3 ± 7.0	<0.001
Sodium (mg/day)[b]	2760.9 ± 36.2	2632.5 ± 40.8	2641.7 ± 52.8	0.038

Values are means ± SEM. $p<0.05$ based on ANCOVA adjusted for sex and age. MEDAS, 14-point Mediterranean Diet Adherence Screener; E, energy intake; SSC, sugar-sweetened carbonated. [a]N=460 after excluding 2 patients with extreme energy intake. [b]Energy-adjusted by residual method.

Table 22. Food and nutrient intake recorded on the food frequency questionnaires according to the tertile distribution of the MDS-Trichopoulou in non-diabetic patients[a]

	MDS-Trichopoulou			
	Tertile 1 (score 0-4; n=238)	Tertile 2 (score 5; n=115)	Tertile 3 (score 6-9; n=107)	*p*-value
Foods				
Olive oil (g/day)[b]	32.4 ± 0.8	35.4 ± 1.1	35.7 ± 1.1	0.017
Vegetables (g/day)[b]	232.4 ± 6.1	275.7 ± 8.8	294.9 ± 9.1	<0.001
Fruits (g/day)[b]	307.1 ± 11.9	391.4 ± 17.2	430.2 ± 17.8	<0.001
Nuts (g/day)[b]	8.1 ± 0.7	10.4 ± 0.9	10.1 ± 1.0	0.073
Legumes (g/day)[b]	21.0 ± 0.8	23.7 ± 1.2	25.1 ± 1.2	0.010
Grains (g/day)[b]	175.0 ± 5.4	194.8 ± 7.7	211.1 ± 8.0	0.001
Fish and seafood (g/day)[b]	92.2 ± 2.9	115.1 ± 4.1	124.1 ± 4.3	<0.001
Poultry (g/day)[b]	67.3 ± 2.2	73.3 ± 3.2	64.4 ± 3.3	0.140
Red/processed meat (g/day)[b]	92.6 ± 2.4	80.5 ± 3.5	71.9 ± 3.7	<0.001
Dairy products (g/day)[b]	400.3 ± 11.6	352.1 ± 16.7	285.8 ± 17.3	<0.001
Commercial sweets/pastries (g/day)[b]	33.3 ± 1.5	21.8 ± 2.2	26.8 ± 2.3	<0.001
Fats spread (g/day)[b]	2.1 ± 0.2	1.5 ± 0.3	1.4 ± 0.3	0.202
SSC beverages (g/day)[b]	104.3 ± 10.4	99.8 ± 14.9	60.5 ± 15.5	0.057
Wine (g/day)[b]	52.3 ± 6.1	57.4 ± 8.7	86.8 ± 9.1	0.006
Nutrients				
Energy (kcal/day)	2231 ± 31	2316 ± 45	2422 ± 46	0.003
Carbohydrates (%E)	42.2 ± 0.4	42.7 ± 0.6	43.4 ± 0.6	0.247
Proteins (%E)	18.1 ± 0.2	18.5 ± 0.2	17.6 ± 0.3	0.059
Total fat (%E)	36.8 ± 0.3	36.1 ± 0.5	34.8 ± 0.5	0.007
Monounsaturated fat (%E)	17.8 ± 0.2	17.8 ± 0.3	17.2 ± 0.3	0.239
Polyunsaturated fat (%E)	6.1 ± 0.1	6.3 ± 0.1	6.3 ± 0.2	0.302
Saturated fat (%E)	9.2 ± 0.1	8.4 ± 0.2	7.9 ± 0.2	<0.001
MUFA/SFA ratio	1.97 ± 0.03	2.16 ± 0.04	2.22 ± 0.04	<0.001
Cholesterol (mg/day)[b]	335.9 ± 4.9	325.0 ± 7.1	309.9 ± 7.4	0.014
Dietary fiber (g/day)[b]	22.6 ± 0.4	25.7 ± 0.6	27.8 ± 0.7	<0.001
Vitamin C (mg/day)[b]	162.3 ± 4.2	192.0 ± 6.0	204.0 ± 6.2	<0.001
Vitamin E (mg/day)[b]	17.5 ± 0.3	19.6 ± 0.4	18.4 ± 0.5	0.001
Folic acid (µg/day)[b]	289.7 ± 5.1	330.5 ± 7.3	337.7 ± 7.6	<0.001
Carotenes (mg/day)[b]	2445.2 ± 67.3	2950.4 ± 96.7	3059.2 ± 100.4	<0.001
Magnesium (mg/day)[b]	352.2 ± 4.5	367.3 ± 6.4	384.7 ± 6.7	<0.001
Sodium (mg/day)[b]	2690.0 ± 33.7	2653.4 ± 48.4	2735.3 ± 50.2	0.501

Values are means ± SEM. $p<0.05$ based on ANCOVA adjusted for sex and age. MDS-Trichopoulou, Mediterranean Dietary Score proposed by Trichopoulou et al.; E, energy intake; SSC, sugar-sweetened carbonated; MUFA/SFA ratio, monounsaturated-to-saturated fat ratio. [a]N=460 after excluding 2 patients with extreme energy intake. [b]Energy-adjusted by residual method.

Table 23. Food and nutrient intake recorded on the food frequency questionnaires according to the tertile distribution of the LFDAS in non-diabetic patients[a]

	LFDAS			*p*-value
	Tertile 1 (score 0-3; n=209)	Tertile 2 (score 4; n=100)	Tertile 3 (score 5-9; n=151)	
Foods				
Olive oil (g/day)[b]	35.2 ± 0.8	34.2 ± 1.2	32.1 ± 1.0	0.047
Vegetables (g/day)[b]	244.7 ± 6.8	263.9 ± 9.8	271.8 ± 7.9	0.028
Fruits (g/day)[b]	349.9 ± 13.3	331.4 ± 19.2	383.2 ± 15.5	0.085
Nuts (g/day)[b]	11.0 ± 0.7	8.1 ± 1.0	7.3 ± 0.8	0.002
Legumes (g/day)[b]	22.8 ± 0.9	21.7 ± 1.0	23.5 ± 1.3	0.471
Grains (g/day)[b]	180.7 ± 4.3	183.8 ± 6.2	201.9 ± 5.0	0.004
Fish and seafood (g/day)[b]	103.8 ± 3.2	108.2 ± 4.7	105.6 ± 3.8	0.734
Oily fish (g/day)[b]	39.7 ± 1.7	34.7 ± 2.4	33.2 ± 1.9	0.032
Poultry (g/day)[b]	65.3 ± 2.4	69.9 ± 2.8	71.5 ± 3.5	0.261
Red/processed meat (g/day)[b]	89.1 ± 2.7	87.4 ± 3.9	77.0 ± 3.1	0.010
Dairy products (g/day)[b]	358.2 ± 12.8	347.2 ± 18.6	375.9 ± 15.0	0.454
Low-fat dairy products (g/day)[b]	211.7 ± 14.2	250.7 ± 20.5	287.3 ± 16.6	0.003
Commercial sweets/pastries (g/day)[b]	33.8 ± 1.8	27.0 ± 2.6	23.5 ± 2.1	0.001
Fats spread (g/day)[b]	2.3 ± 0.3	1.9 ± 0.4	1.1 ± 0.3	0.010
SSC beverages (g/day)[b]	87.1 ± 11.1	130.4 ± 16.1	76.3 ± 13.0	0.027
Wine (g/day)[b]	57.3 ± 6.6	78.1 ± 9.5	56.6 ± 7.7	0.149
Nutrients				
Energy (kcal/day)	2459 ± 32	2217 ± 46	2124 ± 37	<0.001
Carbohydrates (%E)	42.4 ± 0.4	41.3 ± 0.6	43.7 ± 0.5	0.009
Proteins (%E)	17.6 ± 0.2	18.4 ± 0.3	18.4 ± 0.2	0.008
Total fat (%E)	37.0 ± 0.4	36.4 ± 0.5	34.8 ± 0.4	0.001
Monounsaturated fat (%E)	18.0 ± 0.2	18.0 ± 0.3	17.1 ± 0.3	0.041
Polyunsaturated fat (%E)	6.4 ± 0.1	6.1 ± 0.2	5.9 ± 0.1	0.036
Saturated fat (%E)	9.2 ± 0.1	8.7 ± 0.2	8.0 ± 0.1	<0.001
Cholesterol (mg/day)[b]	333.1 ± 5.3	335.3 ± 7.7	313.5 ± 6.2	0.028
Dietary fiber (g/day)[b]	23.8 ± 0.5	24.3 ± 0.7	25.8 ± 0.6	0.033
Vitamin C (mg/day)[b]	172.6 ± 4.6	177.5 ± 6.7	190.2 ± 5.4	0.046
Vitamin E (mg/day)[b]	18.9 ± 0.4	17.8 ± 0.6	17.6 ± 0.5	0.051
Folic acid (µg/day)[b]	304.8 ± 5.7	313.1 ± 8.2	319.0 ± 6.6	0.266
Carotenes (mg/day)[b]	2605.1 ± 74.5	2805.0 ± 107.8	2805.4 ± 87.1	0.144
Magnesium (mg/day)[b]	357.7 ± 4.9	364.4 ± 7.1	371.0 ± 5.7	0.208
Sodium (mg/day)[b]	2620.4 ± 35.9	2714.3 ± 51.9	2774.3 ± 41.9	0.019

Values are means ± SEM. $p<0.05$ based on ANCOVA adjusted for sex and age. LFDAS, 9-point low-fat diet adherence screener; E, energy intake; SSC, sugar-sweetened carbonated. [a]N=460 after excluding 2 patients with extreme energy intake. [b]Energy-adjusted by residual method.

Similar results were found when the analysis was performed in the total CORDIOPREV population (n=1002). All associations between each dietary score and dietary intake recorded with FFQs were similar in direction, although generally of greater magnitude (almost all $p<0.001$), to those found in non-diabetics (Tables 24, 25 and 26).

All of these results confirmed the construct validity of the three dietary scores (MEDAS, MDS-Trichopoulou and LFDAS) not only in the non-diabetics but also in the total 1002 coronary patients included in the CORDIOPREV study.

Table 24. Food and nutrient intake recorded on the food frequency questionnaires according to the tertile distribution of the MEDAS at baseline in the total CORDIOPREV population[a]

	MEDAS			
	Tertile 1 (score=0-8; n=442)	Tertile 2 (score=9-10; n=367)	Tertile 3 (score=11-14; n=187)	*p*-value
Foods				
Olive oil (g/day)[b]	32.9 ± 0.6	34.8 ± 0.6	34.9 ± 0.9	0.041
Vegetables (g/day)[b]	239.2 ± 4.5	263.4 ± 4.9	286.4 ± 6.9	<0.001
Fruits (g/day)[b]	320.9 ± 8.8	386.6 ± 9.6	408.4 ± 13.5	<0.001
Nuts (g/day)[b]	6.2 ± 0.5	9.4 ± 0.5	13.4 ± 0.7	<0.001
Legumes (g/day)[b]	20.2 ± 0.7	25.8 ± 0.8	24.3 ± 1.1	<0.001
Grains (g/day)[b]	181.9 ± 3.0	172.8 ± 3.3	183.1 ± 4.7	0.075
Fish and seafood (g/day)[b]	91.9 ± 2.1	110.6 ± 2.3	114.3 ± 3.3	<0.001
Poultry (g/day)[b]	64.4 ± 1.7	74.2 ± 1.8	72.1 ± 2.5	0.001
Red/processed meat (g/day)[b]	92.1 ± 1.9	83.9 ± 2.0	74.0 ± 2.8	<0.001
Dairy products (g/day)[b]	367.6 ± 8.9	378.4 ± 9.7	368.4 ± 13.7	0.689
Commercial sweets/pastries (g/day)[b]	31.6 ± 1.1	24.2 ± 1.2	21.7 ± 1.7	<0.001
Fats spread (g/day)[b]	2.7 ± 2.2	1.3 ± 2.4	1.5 ± 0.3	<0.001
SSC beverages (g/day)[b]	116.3 ± 7.6	84.0 ± 8.3	51.6 ± 11.6	<0.001
Wine (g/day)[b]	45.4 ± 4.1	56.7 ± 4.5	83.2 ± 6.3	<0.001
Nutrients				
Energy (kcal/day)	2237 ± 23	2207 ± 25	2309 ± 35	0.057
Carbohydrates (%E)	41.6 ± 0.3	41.4 ± 0.3	41.8 ± 0.5	0.721
Proteins (%E)	18.0 ± 0.1	19.0 ± 0.1	18.6 ± 0.2	<0.001
Total fat (%E)	37.7 ± 0.3	36.9 ± 0.3	35.9 ± 0.4	0.003
Monounsaturated fat (%E)	18.3 ± 0.2	18.2 ± 0.2	17.6 ± 0.2	0.077
Polyunsaturated fat (%E)	6.1 ± 0.1	6.4 ± 0.1	6.6 ± 0.1	0.011
Saturated fat (%E)	9.4 ± 0.1	8.8 ± 0.1	8.2 ± 0.1	<0.001
Cholesterol (mg/day)[b]	335.4 ± 3.8	328.9 ± 4.2	312.1 ± 5.8	0.004
Dietary fiber (g/day)[b]	23.2 ± 0.3	25.6 ± 0.4	26.8 ± 0.5	<0.001
Vitamin C (mg/day)[b]	165.3 ± 3.1	187.9 ± 3.4	200.1 ± 4.8	<0.001
Vitamin E (mg/day)[b]	17.2 ± 0.2	18.6 ± 0.3	18.9 ± 0.4	<0.001
Folic acid (µg/day)[b]	291.0 ± 3.6	323.6 ± 3.9	335.8 ± 5.5	<0.001
Carotenes (mg/day)[b]	2482.3 ± 47.8	2785.1 ± 52.5	2931.6 ± 73.6	<0.001
Magnesium (mg/day)[b]	347.3 ± 3.2	370.9 ± 3.5	381.4 ± 5.0	<0.001
Sodium (mg/day)[b]	2738.9 ± 24.4	2610.3 ± 26.7	2626.2 ± 37.5	0.001

Values are means ± SEM. $p<0.05$ based on ANCOVA adjusted for sex and age. MEDAS, 14-point Mediterranean Diet Adherence Screener; E, energy intake; SSC, sugar-sweetened carbonated. [a]N=996 after excluding 6 patients with extreme energy intake. [b]Energy-adjusted by residual method.

Table 25. Food and nutrient intake recorded on the food frequency questionnaires according to the tertile distribution of the MDS-Trichopoulou at baseline in the total CORDIOPREV population[a]

	MDS-Trichopoulou			
	Tertile 1 (score=0-4;n=526)	Tertile 2 (score=5;n=229)	Tertile 3 (score=6-9;n=241)	*p*-value
Foods				
Olive oil (g/day)[b]	32.8 ± 0.5	34.3 ± 0.8	36.4 ± 0.8	0.001
Vegetables (g/day)[b]	236.8 ± 4.1	265.3 ± 6.2	293.2 ± 6.0	<0.001
Fruits (g/day)[b]	311.6 ± 7.8	393.2 ± 11.9	440.3 ± 11.6	<0.001
Nuts (g/day)[b]	8.0 ± 0.4	9.3 ± 0.7	9.8 ± 0.7	0.040
Legumes (g/day)[b]	21.7 ± 0.7	23.6 ± 1.0	25.6 ± 1.0	0.003
Grains (g/day)[b]	169.2 ± 2.7	189.1 ± 4.1	191.3 ± 4.0	<0.001
Fish and seafood (g/day)[b]	92.5 ± 1.9	111.7 ± 2.9	117.7 ± 2.9	<0.001
Poultry (g/day)[b]	71.6 ± 1.5	71.2 ± 2.3	63.1 ± 2.3	0.005
Red/processed meat (g/day)[b]	94.4 ± 1.7	79.7 ± 2.5	72.4 ± 2.5	<0.001
Dairy products (g/day)[b]	425.3 ± 7.7	345.1 ± 11.7	280.1 ± 11.4	<0.001
Commercial sweets/pastries (g/day)[b]	29.4 ± 1.0	24.8 ± 1.5	23.9 ± 1.5	0.003
Fats spread (g/day)[b]	2.5 ± 0.2	1.7 ± 0.3	1.1 ± 0.3	<0.001
SSC beverages (g/day)[b]	106.6 ± 7.0	88.5 ± 10.6	64.4 ± 10.3	0.003
Wine (g/day)[b]	50.9 ± 3.8	54.1 ± 5.7	71.7 ± 5.6	0.007
Nutrients				
Energy (kcal/day)	2161 ± 20	2266 ± 31	2386 ± 30	<0.001
Carbohydrates (%E)	40.5 ± 0.3	42.5 ± 0.4	42.9 ± 0.4	<0.001
Proteins (%E)	18.8 ± 0.1	18.5 ± 0.2	17.8 ± 0.2	<0.001
Total fat (%E)	37.8 ± 0.3	36.3 ± 0.4	36.3 ± 0.4	<0.001
Monounsaturated fat (%E)	18.4 ± 0.2	17.9 ± 0.2	17.9 ± 0.2	0.128
Polyunsaturated fat (%E)	6.3 ± 0.1	6.3 ± 0.1	6.3 ± 0.1	0.937
Saturated fat (%E)	9.6 ± 0.1	8.5 ± 0.1	8.1 ± 0.1	<0.001
MUFA/SFA ratio	1.96 ± 0.02	2.14 ± 0.03	2.23 ± 0.03	<0.001
Cholesterol (mg/day)[b]	347.0 ± 3.4	321.9 ± 5.2	306.9 ± 5.1	<0.001
Dietary fiber (g/day)[b]	22.9 ± 0.3	25.7 ± 0.4	28.0 ± 0.4	<0.001
Vitamin C (mg/day)[b]	162.1 ± 2.8	192.4 ± 4.2	207.9 ± 4.1	<0.001
Vitamin E (mg/day)[b]	17.4 ± 0.2	18.7 ± 0.3	18.8 ± 0.3	<0.001
Folic acid (µg/day)[b]	292.2 ± 3.3	324.7 ± 4.9	340.8 ± 4.8	<0.001
Carotenes (mg/day)[b]	2453.8 ± 43.3	2837.4 ± 65.6	3016.8 ± 64	<0.001
Magnesium (mg/day)[b]	354.7 ± 3.0	363.6 ± 4.5	377.9 ± 4.4	<0.001
Sodium (mg/day)[b]	2681.3 ± 22.5	2635.3 ± 34.1	2679.7 ± 33.3	0.504

Values are means ± SEM. $p<0.05$ based on ANCOVA adjusted for sex and age. MDS-Trichopoulou, Mediterranean Dietary Score proposed by Trichopoulou et al.; E, energy intake; SSC, sugar-sweetened carbonated; MUFA/SFA ratio, monounsaturated-to-saturated fat ratio. [a]N=996 after excluding 6 patients with extreme energy intake. [b]Energy-adjusted by residual method.

Table 26. Food and nutrient intake recorded on the food frequency questionnaires according to the tertile distribution of the LFDAS at baseline in the total CORDIOPREV population[a]

	LFDAS			*p*-value
	Tertile 1 (score=0-3;n=425)	Tertile 2 (score=4-5;n=422)	Tertile 3 (score=6-9;n=149)	
Foods				
Olive oil (g/day)[b]	35.0 ± 0.6	33.8 ± 0.6	31.9 ± 1.0	0.028
Vegetables (g/day)[b]	247.2 ± 4.7	260.9 ± 4.7	273.8 ± 7.8	0.008
Fruits (g/day)[b]	350.3 ± 9.1	369.8 ± 9.1	370.2 ± 15.3	0.267
Nuts (g/day)[b]	10.2 ± 0.5	7.8 ± 0.5	7.1 ± 0.8	<0.001
Legumes (g/day)[b]	23.4 ± 0.7	23.1 ± 0.7	21.9 ± 1.2	0.608
Grains (g/day)[b]	170.2 ± 3.1	181.8 ± 3.1	197.1 ± 5.1	<0.001
Fish and seafood (g/day)[b]	103.5 ± 2.2	104.7 ± 2.2	97.0 ± 3.7	0.198
Oily fish (g/day)[b]	38.2 ± 1.2	36.5 ± 1.2	30.9 ± 2.0	0.007
Poultry (g/day)[b]	66.3 ± 1.7	72.3 ± 1.7	70.2 ± 2.9	0.044
Red/processed meat (g/day)[b]	88.9 ± 1.9	86.1 ± 1.9	75.4 ± 3.2	0.002
Dairy products (g/day)[b]	357.7 ± 9.1	387.1 ± 9.1	368.2 ± 15.2	0.072
Low-fat dairy products (g/day)[b]	226.7 ± 9.9	274.9 ± 16.7	291.1 ± 10.0	<0.001
Commercial sweets/pastries (g/day)[b]	30.1 ± 1.1	25.0 ± 1.1	23.8 ± 1.9	0.001
Fats spread (g/day)[b]	2.5 ± 0.2	1.7 ± 0.2	1.4 ± 0.4	0.005
SSC beverages (g/day)[b]	88.8 ± 7.8	102.8 ± 7.8	72.2 ± 13.1	0.114
Wine (g/day)[b]	59.4 ± 4.3	54.3 ± 4.3	55.7 ± 7.2	0.704
Nutrients				
Energy (kcal/day)	2432 ± 21	2159 ± 21	1917 ± 36	<0.001
Carbohydrates (%E)	41.2 ± 0.3	41.5 ± 0.3	42.7 ± 0.5	0.043
Proteins (%E)	18.0 ± 0.1	18.9 ± 0.1	18.7 ± 0.2	<0.001
Total fat (%E)	37.9 ± 0.3	36.7 ± 0.3	35.5 ± 0.5	<0.001
Monounsaturated fat (%E)	18.2 ± 0.2	18.1 ± 0.2	18.1 ± 0.3	0.959
Polyunsaturated fat (%E)	6.6 ± 0.1	6.2 ± 0.1	5.9 ± 0.1	<0.001
Saturated fat (%E)	9.4 ± 0.1	8.8 ± 0.1	8.0 ± 0.1	<0.001
Cholesterol (mg/day)[b]	337.4 ± 3.9	324.6 ± 3.9	313.0 ± 6.5	0.003
Dietary fiber (g/day)[b]	24.0 ± 0.3	25.1 ± 0.3	25.9 ± 0.6	0.005
Vitamin C (mg/day)[b]	173.7 ± 3.2	183.5 ± 3.2	188.8 ± 5.4	0.022
Vitamin E (mg/day)[b]	19.1 ± 0.3	17.4 ± 0.3	16.9 ± 0.5	<0.001
Folic acid (µg/day)[b]	303.0 ± 3.8	317.3 ± 3.8	318.7 ± 6.3	0.013
Carotenes (mg/day)[b]	2570.1 ± 49.5	2767.1 ± 49.6	2734.8 ± 83.2	0.016
Magnesium (mg/day)[b]	354.9 ± 3.3	367.6 ± 3.4	369.0 ± 5.6	0.013
Sodium (mg/day)[b]	2614.2 ± 24.9	2688.0 ± 25.0	2780.2 ± 41.9	0.002

Values are means ± SEM. $p<0.05$ based on ANCOVA adjusted for sex and age. LFDAS, 9-point low-fat diet adherence screener; E, energy intake; SSC, sugar-sweetened carbonated. [a]N=996 after excluding 6 patients with extreme energy intake. [b]Energy-adjusted by residual method.

5.6.2. Concurrent validity of the MEDAS and LFDAS in the CORDIOPREV population

The concurrent validity of the MEDAS and LFDAS in the CORDIOPREV study was assessed by comparing the dietary adherence data retrieved from the face-to-face-administered screeners (MEDAS and LFDAS) with the data gathered from the FFQ (MEDAS-FFQ, MEDAS derived from FFQ; LFDAS-FFQ, LFDAS derived from FFQ) at baseline and at 5-year visit.

5.6.2.1. Concurrent validity of the MEDAS in the CORDIOPREV population

The MEDAS estimated a higher mean total score (mean ± SEM) compared to MEDAS-FFQ (8.78±0.06 vs. 7.84±0.06, $p<0.001$). Pearson correlation coefficient ($r=0.53$, $p<0.001$) showed a moderate correlation between the MEDAS total score and the MEDAS-FFQ total score. The ICC, which is preferable than Pearson correlation coefficient since it measures concordance between methods, indicated a good reliability (ICC=0.64, 95% CI 0.45-0.75, $p<0.001$).

Results from cross-classification showed that the percentage of patients correctly classified into the same tertile of total score by the MEDAS and the MEDAS-FFQ was 56.1%, whereas 4.2% was classified into opposite tertiles and 39.6% was classified into adjacent tertiles (20.3% and 19.3% into higher and lower adjacent tertiles, respectively). Cohen's Kappa value was 0.30 (95% CI=0.25-0.35; $p<0.001$) indicating sufficient agreement across tertiles between the MEDAS and MEDAS-FFQ.

The Bland–Altman plot showed the mean difference between the two methods as 0.94 with a standard deviation of 1.82, and the limits of agreement (LoA) were -2.63 and 4.51 (Figure 16). The visual examination of the Bland-Altman plot showed that the mean bias line was close to zero and the points were scattered all over the place, above and below zero, suggesting that there was no consistent bias of one method versus the other.

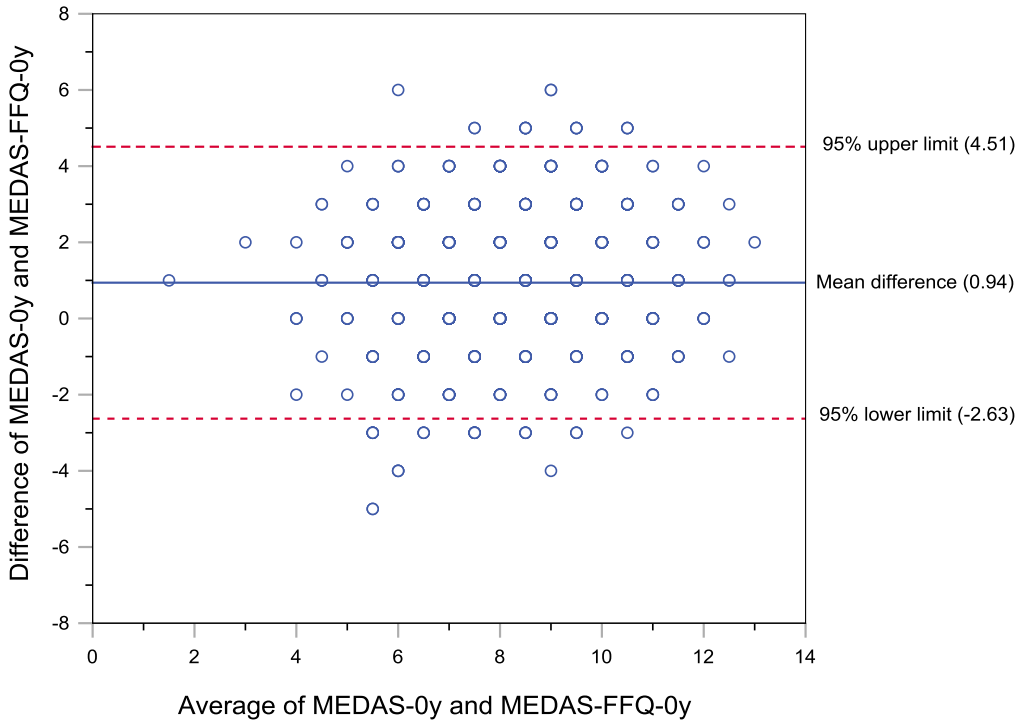


Figure 16. Bland-Altman plot and limits of agreement for the total score as estimated by the MEDAS and the MEDAS-FFQ (baseline measurements)[a]. The unbroken line represents the mean difference, and the dashed lines indicate the limits of agreement. MEDAS-0y, face-to-face administered 14-point Mediterranean Diet Adherence Screener; MEDAS-FFQ-0y, 14-point Mediterranean Diet Adherence Screener derived food frequency questionnaire. [a]N=996 after excluding 6 patients with extreme energy intake.

Item by item absolute and relative agreement between MEDAS and MEDAS-FFQ are shown in Table 27. Good (*k*=0.61-0.80), moderate (*k*=0.41-0.60), fair (*k*=0.21-0.40) and poor concordance (*k*<0.21) was found for 21.4, 28.6, 35.7 and 14.3% of the components of the score, respectively. Generally, a higher percentage of participants achieved a score of 1 via the MEDAS compared to the MEDAS-FFQ, except for items 6 (butter, margarine, cream <1 serving/day), 7 (sugar-sweetened carbonated beverages <1 serving/day) and 10 (fish or seafood ≥3 servings/week).

Table 27. Percentage of patients scoring 1 point on each of the 14 components of the MEDAS and MEDAS-FFQ (baseline measurements), and agreement between the two dietary assessment methods (n=996)[a]

Items	MEDAS	MEDAS-FFQ	AA	κ (95% CIs)
1. Olive oil as main culinary fat	98.2	97.7	97.5	0.38 (0.16, 0.56)
2. Olive oil ≥4 tablespoons/day	62.9	36.2	68.8	0.42 (0.37, 0.46)
3. Vegetables ≥2 s/d	75.4	36.4	52.2	0.16 (0.12, 0.20)
4. Fruits ≥3 s/d	53.6	28.8	62.6	0.27 (0.23, 0.32)
5. Red or processed meats <1 s/d	60.6	54.7	65.8	0.30 (0.24, 0.36)
6. Butter, margarine, cream <1 s/d	92.2	96.8	93.6	0.39 (0.26, 0.51)
7. SSC beverages <1 s/d	73.6	79.0	86.3	0.62 (0.57, 0.68)
8. Wine ≥ 7 glasses/week	27.8	25.5	91.5	0.78 (0.74, 0.82)
9. Legumes ≥3 s/w	39.8	36.4	79.2	0.56 (0.51, 0.62)
10. Fish or seafood ≥3 s/w	57.9	81.2	71.5	0.37 (0.31, 0.42)
11. Commercial bakery ≤2 s/w	42.5	38.4	79.6	0.58 (0.52, 0.63)
12. Nuts ≥3 s/w	33.6	33.3	88.7	0.75 (0.70, 0.79)
13. Poultry more than red meats	74.1	65.2	78.2	0.49 (0.43, 0.54)
14. Use of “sofrito” sauce ≥2 times/week	85.4	74.3	68.2	0.13 (0.06, 0.19)

AA = percentage of absolute agreement; κ = Cohen’s Kappa with the confidence intervals in brackets; s/d, servings per day; s/w, servings per week; SSC, sugar-sweetened carbonated.

[a]N=996 after excluding 6 patients with extreme energy intake.

κ: ≤0.20, poor agreement; 0.21-0.40, fair agreement; 0.41-0.60 moderate agreement; 0.61-0.80, good agreement; 0.81-1, very good agreement.

When we repeated all the analyses using the dietary information from 5-year follow-up visit (n=853), similar results were found. The MEDAS significantly overestimated the total score by 0.92 points compared to the MEDAS-FFQ (mean ± SEM, 9.62±0.08 vs. 8.70±0.08, $p<0.001$). Pearson correlation coefficient and ICC where higher than those found in baseline and showed a good correlation and agreement between the MEDAS and the MEDAS-FFQ ($r=0.83$, $p<0.001$; ICC=0.87, 95% CI=0.68–0.93, $p<0.001$). In the cross-classification of the total score into tertiles, 68.7% of patients were grouped into the same tertile on both instruments, whereas only 0.3% was grouped into opposite tertiles (9.6% and 21.3% were classified into higher and lower adjacent tertiles, respectively). Cohen's Kappa value was 0.53 (95% CI=0.48-0.57; $p<0.001$) showing moderate agreement across tertiles between the MEDAS and MEDAS-FFQ.

The Bland-Altman analysis showed a positive mean difference between the two methods of 0.92 with a standard deviation of 1.39, and the LoA were -1.80 and 3.64 (Figure 17), confirming that the MEDAS slightly overestimated the total score compared to the MEDAS-FFQ. The visual examination of the Bland-Altman plot showed that the scatter of differences was uniform and points lie relatively close to the mean bias line, indicating that there was no consistent bias between the two methods.

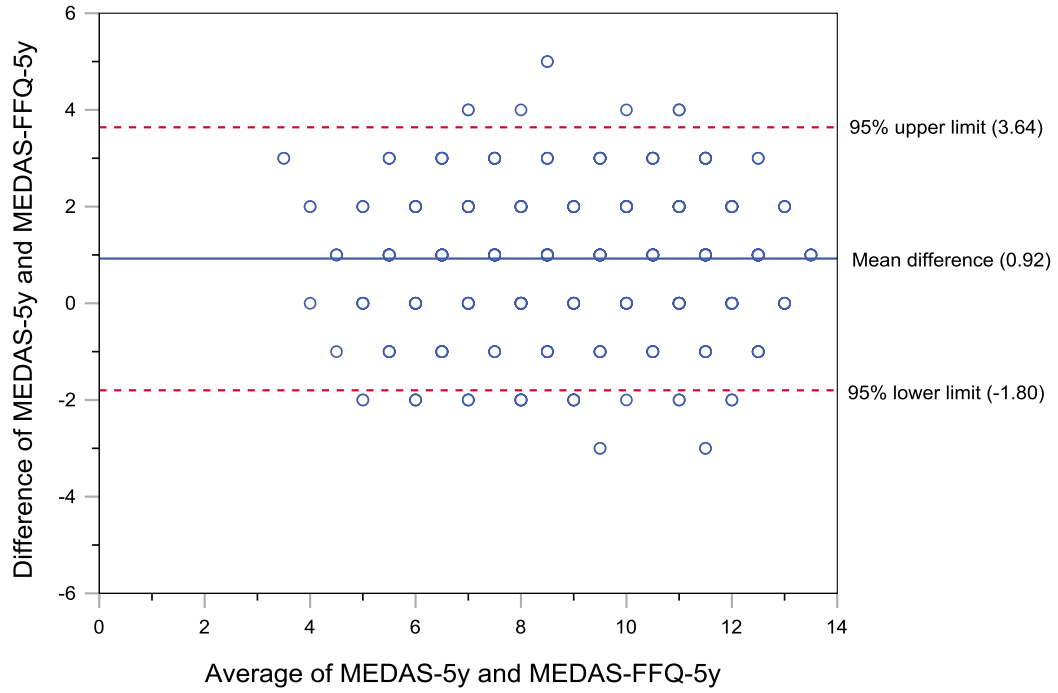


Figure 17. Bland-Altman plot and limits of agreement for the total score as estimated by the MEDAS and the MEDAS-FFQ (5-year measurements)[a]. The unbroken line represents mean of differences or bias, and the dashed lines indicate the limits of agreement. MEDAS-5y, face-to-face administered 14-point Mediterranean Diet Adherence Screener at 5-year visit; MEDAS-FFQ-5y, 14-point Mediterranean Diet Adherence Screener derived food frequency questionnaire at 5-year visit. [a]N=853 patients with complete dietary information at 5-year follow-up visit.

Absolute agreement of individual component scoring between the MEDAS and the MEDAS-FFQ was also determined (Table 28). Overall, very good, good, moderate, fair and poor concordance was found for 7.1, 21.4, 35.7, 28.6 and 7.1% of the components of the score, respectively. In this case, a higher percentage of patients achieved 1 point via the MEDAS-FFQ, compared to the MEDAS, in 6 of the 14 items.

Table 28. Percentage of patients scoring 1 point on each of the 14 components of the MEDAS and MEDAS-FFQ (5-year measurements), and agreement between the two dietary assessment methods (n= 853)[a]

Items	MEDAS	MEDAS-FFQ	AA	κ (95% CIs)
1. Olive oil as main culinary fat	83.2	83.4	93.8	0.78 (0.72, 0.83)
2. Olive oil ≥4 tablespoons/day	46.2	46.5	98.0	0.96 (0.94, 0.98)
3. Vegetables ≥2 s/d	86.5	48.2	61.7	0.25 (0.21 0.30)
4. Fruits ≥3 s/d	66.5	26.8	59.2	0.29 (0.25, 0.33)
5. Red or processed meats <1 s/d	81.9	94.7	87.0	0.39 (0.31, 0.47)
6. Butter, margarine, cream <1 s/d	97.0	99.6	97.3	0.20 (0.06, 0.40)
7. SSC beverages <1 s/d	84.2	88.9	88.7	0.52 (0.43, 0.60)
8. Wine ≥ 7 glasses/week	32.8	28.4	89.2	0.75 (0.70, 0.79)
9. Legumes ≥3 s/w	61.5	44.7	76.3	0.54 (0.49, 0.59)
10. Fish or seafood ≥3 s/w	50.8	74.7	72.8	0.45 (0.40, 0.50)
11. Commercial bakery ≤2 s/w	76.1	57.7	76.0	0.48 (0.42, 0.54)
12. Nuts ≥3 s/w	39.9	30.5	87.3	0.73 (0.67, 0.77)
13. Poultry more than red meats	95.0	87.3	88.6	0.31 (0.21, 0.41)
14. Use of "sofrito" sauce ≥2 times/week	60.4	58.1	82.8	0.46 (0.39, 0.49)

AA = percentage of absolute agreement; κ = Cohen's Kappa with the confidence intervals in brackets; s/d, servings per day; s/w, servings per week; SSC, sugar-sweetened carbonated.

[a]N=853 patients with complete dietary information at 5-year follow-up visit.

κ: ≤0.20, poor agreement; 0.21-0.40, fair agreement; 0.41-0.60 moderate agreement; 0.61-0.80, good agreement; 0.81-1, very good agreement.

5.6.2.2. Concurrent validity of the LFDAS in the CORDIOPREV population

The mean LFDAS score were higher than the LFDA-FFQ score at baseline (3.84±0.05 vs. 3.15±0.04, p<0.001) and at 5-year visit (7.05±0.08 vs. 5.03±0.08, p<0.001), with the mean total score being higher in 0.69 points at baseline and 2.02 points at 5-year visit. Pearson correlation coefficients showed a moderate correlation between the LFDAS total score and the LFDAS-FFQ total score both at baseline (r=0.44, p<0.001) and at 5-year visit (r=0.59, p<0.001). Moreover, the ICC values were 0.55 (95% CI=0.40, 0.66; p<0.001) and 0.50 (95% CI=-0.21, 0.77; p<0.001) at baseline

and at 5-year visit, respectively, showing good reliability between the LFDAS and LFDAS-FFQ.

Results of baseline cross-classification showed that 49.9% of patients were correctly categorised into the same tertile of the total mean score by the LFDAS and the LFDAS-FFQ, and only 3.9% was classified into opposite tertiles. At 5-year visit, percentages of subjects classified into the same and opposite tertiles were 45.4 and 9.5%, respectively. Cohen's kappa values were 0.21 (95% CI=0.16, 0.26; p<0.001) and 0.31 (95% CI=0.24, 0.38; p<0.001) at baseline and at 5-year visit, respectively, showing sufficient agreement across tertiles between the LFDAS and LFDAS-FFQ.

Bland-Altman plots of the agreement between the LFDAS and LFDAS-FFQ in the two time points evaluated are shown in Figure 18. The calculation of the difference between the two methods at baseline (mean±SD=0.70±1.55; 95% LoA=-2.35, 3.73) and at 5-year visit (mean±SD=2.02±1.46; 95% LoA=-0.82, 4.88) confirmed that the LFDAS overestimated the adherence to the low-fat diet with higher score points in comparison with the LFDA-FFQ. The visual examination of the plots did not suggest a systematic deviation of the difference between the two methods either at baseline or at 5-year visit (most of the points were around zero in a random manner).

Absolute agreement of individual component scoring between the LFDAS and the LFDAS-FFQ was also determined (Table 29). At baseline, good, moderate, fair and poor concordance was found for 11.1, 22.2, 44.4 and 22.2% of the components of the score, respectively. At 5-year visit, good concordance was found for a higher percentage (22.2%) of the components of the score and moderate and poor concordance for similar percentages. Items 3 (fatty/processed meats ≤1 serving/week) and 6 (use of sofrito≤2 times/week) had the lowest concordance in both time points.

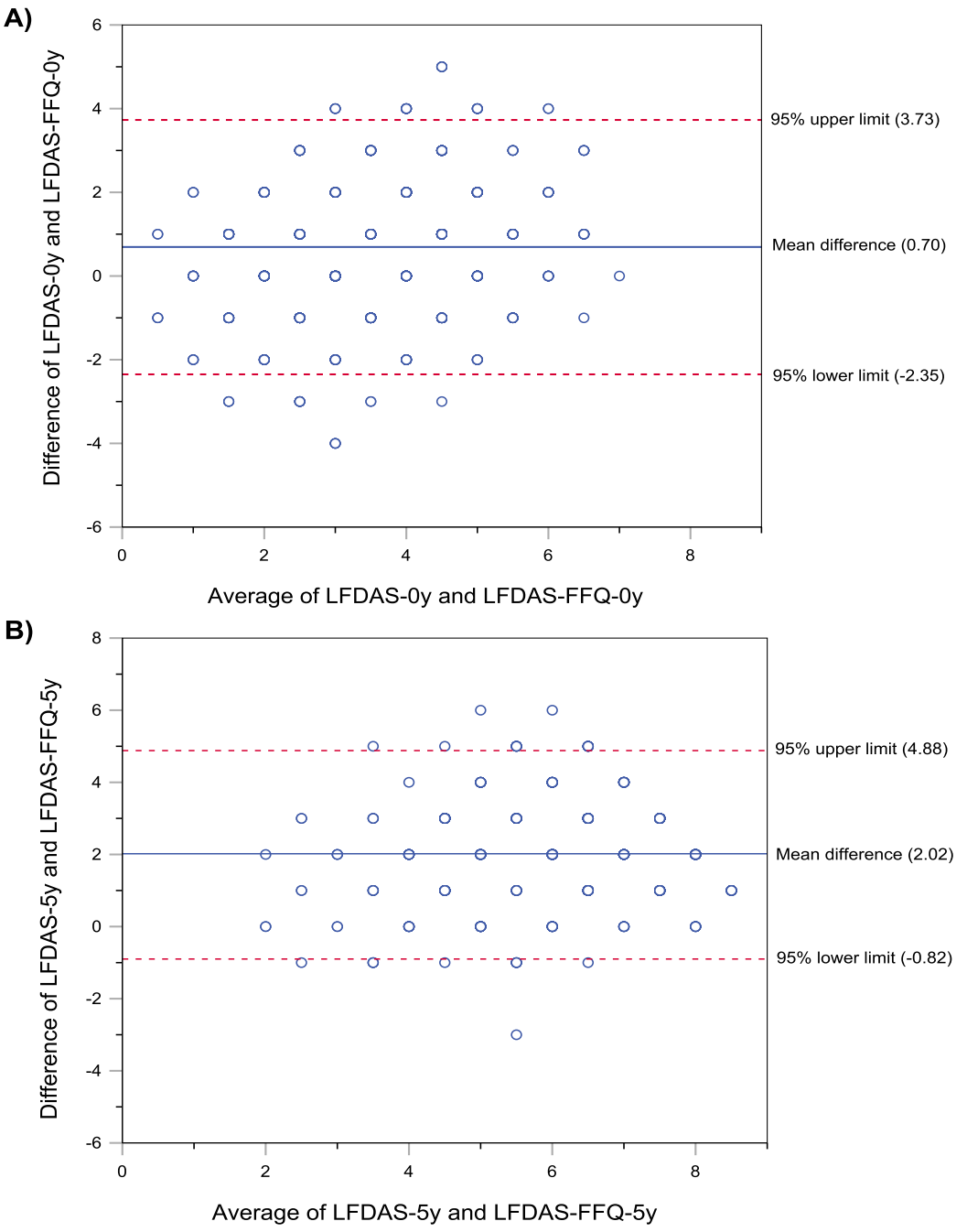


Figure 18. Bland-Altman plot and limits of agreement for the total score as estimated by the LFDAS and the LFDAS-FFQ at baseline (A) and at 5-year visit (B)
The unbroken line represents mean of differences or bias, and the dashed lines indicate the limits of agreement. LFDAS, face-to-face administered 9-point low-fat diet adherence screener at baseline; LFDAS-FFQ, 9-point low-fat diet adherence screener derived from food frequency questionnaire at baseline; LFDAS-5y, face-to-face administered 9-point low-fat diet adherence screener at 5-year visit; LFDAS-FFQ-5y, 9-point low-fat diet adherence screener derived from food frequency questionnaire at 5-year visit. N at baseline=996 patients; n at 5-year visit=406 patients.

Table 29. Percentage of patients scoring 1 point on each of the 9 components of the LFDAS and LFDAS-FFQ (baseline and 5-year measurements) and agreement between the two dietary assessment methods

	Baseline (n=996)[a]				5-year (n=406)[b]			
Items	LFDAS	LFDAS-FFQ	AA	κ (95% CIs)	LFDAS	LFDAS-FFQ	AA	κ (95% CIs)
1. Total daily oil ≤20ml	2.2	1.3	97.1	0.26 (0.10, 0.34)	52.2	39.4	80.9	0.62 (0.54, 0.69)
2. Remove visible fat or the skin of meats	79.3	90.2	80.3	0.26 (0.18, 0.32)	94.6	98.0	94.6	0.25 (0.05, 0.47)
3. Fatty/processed meats ≤1 s/w	13.2	6.6	85.6	0.20 (0.11, 0.29)	80.3	24.9	43.1	0.13 (0.09, 0.17)
4. Spread fat, mayonnaise, ice cream ≤1 s/w	78.2	68.9	77.6	0.43 (0.36, 0.49)	89.9	86.7	90.9	0.56 (0.43, 0.68)
5. Low-fat dairy products	49.1	17.0	61.8	0.23 (0.18, 0.28)	80.3	46.8	61.1	0.25 (0.18, 0.33)
6. “Sofrito” ≤2 times/week	36.6	26.2	58.4	0.05 (-0.01, 0.11)	79.1	21.4	33.5	0.05 (-0.05, 0.05)
7. Oily fish or seafood canned in oil ≤1 s/w	40.1	22.3	70.2	0.33 (0.27, 0.39)	82.5	21.4	66.7	0.27 (0.19, 0.35)
8. Commercial bakery products ≤1 s/w	34.9	32.7	80.1	0.56 (0.50, 0.61)	68.2	53.7	79.1	0.57 (0.49, 0.65)
9. Nuts and commercial snacks ≤1 s/w	50.8	49.9	81.8	0.64 (0.59, 0.69)	78.1	75.6	91.1	0.75 (0.67, 0.83)

AA = percentage of absolute agreement; κ = Cohen’s Kappa with the confidence intervals in brackets; s/w, servings per week.

[a]N=996 after excluding 6 patients with extreme energy intake.

[b]The LFDAS at 5-year visit was only administered in patients allocated to the low-fat diet group and 406 of those patients completed the 5-year follow-up visit.

κ: ≤0.20, poor agreement; 0.21-0.40, fair agreement; 0.41-0.60 moderate agreement; 0.61-0.80, good agreement; 0.81-1, very good agreement.

5.7. Assessment of the validity of PCA-dietary patterns in our population

Ideally, the validity of the PCA-dietary patterns is determined comparing PCA-dietary patterns from a FFQ as study instrument with those from a 3-days dietary record or repeated 24-h dietary recalls as referent instruments. In our case, it was not possible as the FFQ was the only dietary assessment tool used in the CORDIOPREV study. Instead, the consistency of PCA-dietary patterns at baseline and at year 1 was examined by analysing the relationship between PCA-dietary patterns and the three dietary scores in both time points.

5.7.1. Consistency of PCA-dietary patterns at baseline

Figure 19 shows the partial correlations of the Western DP and Mediterranean DP with the MEDAS, MDS-Trichopoulou and LFDAS at baseline, controlled for age and sex. As expected, the Western DP correlated negatively with the three dietary scores although the correlation with the MDS-Trichopoulou was non-significant (r=-0.08, p=0.074). Conversely, the Mediterranean DP showed a moderate positive correlation with the MEDAS (r=0.45, p<0.001) and the MDS-Trichopoulou (r=0.40, p<0.001), but a negative correlation with the LFDAS (r=-0.11, p=0.16).

Further, we estimated the level of adherence to the three dietary scores according to the tertile distribution of the Western DP and Mediterranean DP at baseline (Table 30). The results confirmed the consistency of PCA-dietary patterns. Patients with the highest adherence to the Western DP scored significantly lower in the MEDAS (p=0.001) and the LFDAS (p<0.001). In contrast, high adherents to the Mediterranean DP showed higher scores in the MEDAS and MDS-Trichopouolu (all p<0.001).

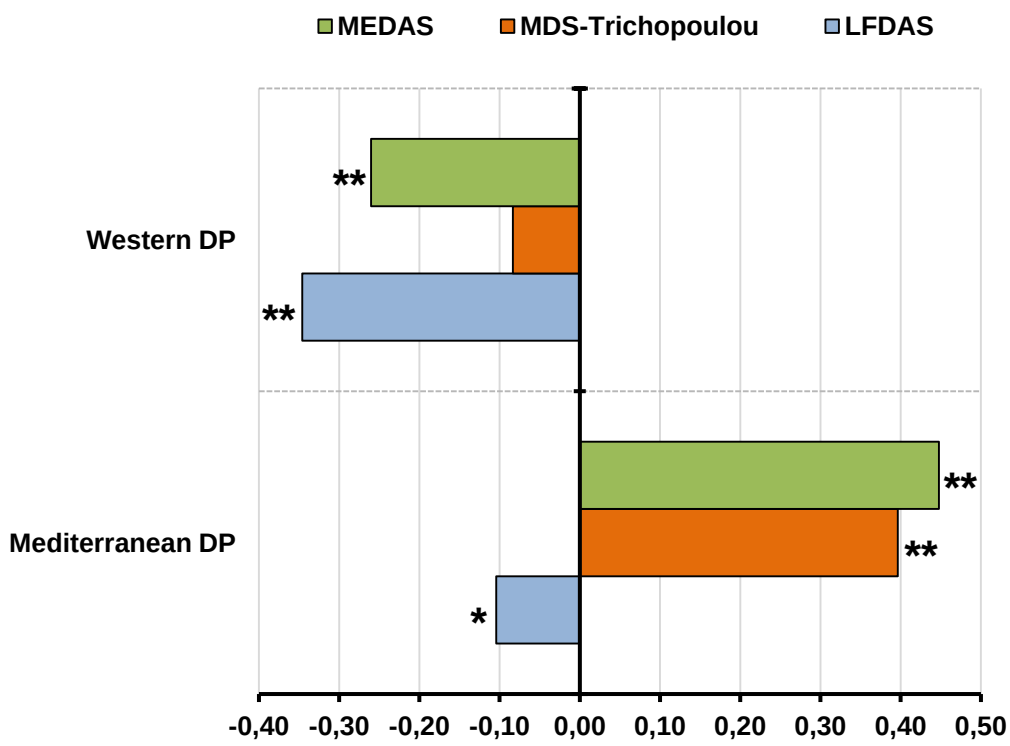


Figure 19. Partial correlations of the two PCA-dietary patterns with the three dietary scores at baseline (n=460)[a]. Correlations were adjusted for age and sex. Significant correlations are indicated with *p<0.05 and **p<0.001. PCA-dietary patterns, dietary patterns derived by principal components analysis; Western DP, Western dietary pattern; Mediterranean DP, Mediterranean dietary pattern; MEDAS, 14-point Mediterranean Diet Adherence Screener; MDS-Trichopoulou, Mediterranean Dietary Score proposed by Trichopoulou et al.; LFDAS, 9-point low-fat diet adherence screener. [a]N=460 after excluding 2 patients with extreme energy intake.

Table 30. Level of adherence to the three dietary scores according to tertiles of the Western DP and Mediterranean DP at baseline (n=460)[a]

	Western DP			
	Tertile 1 (low adherence)	Tertile 2 (medium adherence)	Tertile 3 (high adherence)	*p*-value
MEDAS (max score=14 points)	9.2 ± 0.2	8.8 ± 0.2	8.2 ± 0.2	0.001
MDS-Trichopoulou (max score=9 points)	4.6 ± 0.1	4.6 ± 0.1	4.3 ± 0.1	0.137
LFDAS (max score=9 points)	4.5 ± 0.1	3.9 ± 0.1	3.0 ± 0.1	<0.001
	Mediterranean DP			
	Tertile 1 (low adherence)	Tertile 2 (medium adherence)	Tertile 3 (high adherence)	*p*-value
MEDAS (max score=14 points)	8.0 ± 0.2	8.7 ± 0.2	9.5 ± 0.2	<0.001
MDS-Trichopoulou (max score=9 points)	3.7 ± 0.1	4.6 ± 0.1	5.1 ± 0.1	<0.001
LFDAS (max score=9 points)	3.8 ± 0.1	3.8 ± 0.1	3.7 ± 0.1	0.919

Values are means ± SEM. $p<0.05$ based on ANCOVA adjusted for sex and age. Western DP, Western dietary pattern; Mediterranean DP, Mediterranean dietary pattern; MEDAS, 14-point Mediterranean Diet Adherence Screener; MDS-Trichopoulou, Mediterranean Dietary Score proposed by Trichopoulou et al.; LFDAS, 9-point low-fat diet adherence screener. [a]N=460 after excluding 2 patients with extreme energy intake.

5.7.2. Consistency of PCA-dietary patterns at year 1

Figure 20 shows the partial correlations of the three PCA-dietary patterns (Western DP, Mediterranean DP and Low-Fat DP) with the three dietary scores at year 1. Similarly that observed at baseline, the Western DP at year 1 correlated negatively with all the dietary scores, although this correlation was non-significant for the MDS-Trichopoulou (r=-0.04, p=0.406). For the Mediterranean DP, we observed a strong positive association with the MEDAS (r=0.66, p<0.001), a moderate positive association with the MDS-Trichopoulou (r=0.48, p<0.001) and a moderate negative association with the LFDAS (r=-0.50, p<0.001). On the other hand and as expected, the Low-Fat DP correlated positively with the LFDAS (r=0.22, p<0.001). Moreover, the Low-Fat DP showed a negative correlation with the MEDAS (r=-0.02, p=0.745) and MDS-Trichopoulou (r=-0.03, p=0.537), although the correlation coefficients did not achieve statistical significance.

Furthermore, all associations between PCA-dietary patterns and dietary scores at year 1 were in the expected direction (Table 31). Patients with the highest adherence to the Western DP had lower scores in the MEDAS (p=0.003) and LFDAS (p<0.001). Conversely, high adherents to the Mediterranean DP scored significantly higher in the MEDAS and the MDS-Trichopoulou (all p<0.001). These patients also showed a significant lower score in the LFDAS (p<0.001). Finally and as expected, patients with the highest adherence to the Low-Fat DP scored significantly higher in the LFDAS compared to those patients with lower adherence to the Low-Fat DP (p<0.001).

All of these results, together with those found in the baseline analysis, confirm the consistency of PCA-dietary patterns and provide a validation of the PCA-results at both baseline and year 1.

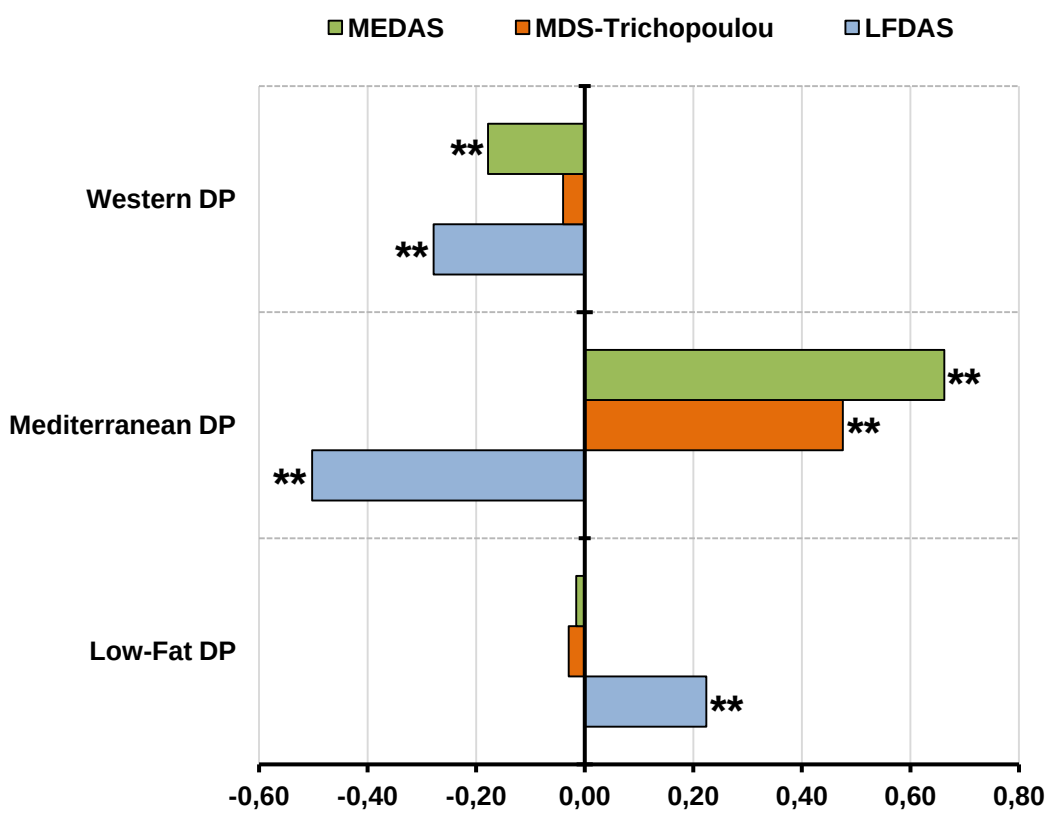


Figure 20. Partial correlations of the PCA-dietary patterns with the three dietary scores at year 1 (n=436)[a]. Correlations were adjusted for age and sex. Significant correlations are indicated with *p<0.05 and **p<0.001. PCA-dietary patterns, dietary patterns derived by principal components analysis; Western DP, Western dietary pattern; Mediterranean DP, Mediterranean dietary pattern; Low-Fat DP, low-fat dietary pattern; MEDAS, 14-point Mediterranean Diet Adherence Screener; MDS-Trichopoulou, Mediterranean Dietary Score proposed by Trichopoulou et al.; LFDAS, 9-point low-fat diet adherence screener. [a]Of the 462 non-diabetics at baseline, 436 patients completed the 1-year follow-up visit.

Table 31. Level of adherence to the three dietary scores according to tertiles of the Western DP, Mediterranean DP and Low-Fat DP at year 1 (n=436)[a]

	Western DP			
	Tertile 1 (low adherence)	Tertile 2 (medium adherence)	Tertile 3 (high adherence)	*p*-value
MEDAS (max score=14 points)	9.7 ± 0.2	9.7 ± 0.2	8.8 ± 0.2	0.003
MDS-Trichopoulou (max score=9 points)	4.3 ± 0.1	4.6 ± 0.1	4.4 ± 0.1	0.344
LFDAS (max score=9 points)	5.8 ± 0.2	5.2 ± 0.2	4.6 ± 0.2	<0.001
	Mediterranean DP			
	Tertile 1 (low adherence)	Tertile 2 (medium adherence)	Tertile 3 (high adherence)	*p*-value
MEDAS (max score=14 points)	7.2 ± 0.2	9.6 ± 0.2	11.4 ± 0.2	<0.001
MDS-Trichopoulou (max score=9 points)	3.6 ± 0.1	4.5 ± 0.1	5.3 ± 0.1	<0.001
LFDAS (max score=9 points)	6.6 ± 0.2	5.2 ± 0.2	3.9 ± 0.2	<0.001
	Low-Fat DP			
	Tertile 1 (low adherence)	Tertile 2 (medium adherence)	Tertile 3 (high adherence)	*p*-value
MEDAS (max score=14 points)	9.5 ± 0.2	9.4 ± 0.2	9.4 ± 0.2	0.775
MDS-Trichopoulou (max score=9 points)	4.5 ± 0.1	4.4 ± 0.1	4.4 ± 0.1	0.871
LFDAS (max score=9 points)	4.6 ± 0.2	5.6 ± 0.2	5.5 ± 0.2	<0.001

Values are means ± SEM. $p<0.05$ based on ANCOVA adjusted for sex and age. Western DP, Western dietary pattern; Mediterranean DP, Mediterranean dietary pattern; Low-Fat DP, low-fat dietary pattern; MEDAS, 14-point Mediterranean Diet Adherence Screener; MDS-Trichopoulou, Mediterranean Dietary Score proposed by Trichopoulou et al.; LFDAS, 9-point low-fat diet adherence screener. [a]Of the 462 non-diabetics at baseline, 436 patients completed the 1-year follow-up visit.

5.8. Long-term dietary adherence and changes in dietary intake in the CORDIOPREV population after dietary intervention

The results included in this section derived from the original article *"Long-term dietary adherence and changes in dietary intake in coronary patients after intervention with a Mediterranean diet or a low-fat diet: the CORDIOPREV randomized trial",* in which we investigated if long-term dietary adherence is possible. In this analysis, we included the 853 patients who completed the 5-year follow-up.

5.8.1. Dietary intake in the CORDIOPREV population during 5 years of dietary intervention

5.8.1.1. Energy and nutrients intake

The mean nutrient intake of the patients at baseline and 5 years after randomization are summarised in Table 32. No significant differences were found between the two groups at baseline. The usual diet of the patients was high in total fat (>35%), mainly consisting of MUFA, with 41% of the energy from carbohydrates and 18.5% from proteins. After 5 years of dietary intervention, participants in the Mediterranean diet group increased their intake of dietary fiber and total fat due to a higher consumption of MUFA (from olive oil) and PUFA (from tree nuts and oily fish) and reduced their consumption of total carbohydrates, SFA and cholesterol (all $p<0.05$). The low-fat diet group showed an increase in the intake of total dietary fiber and carbohydrates, mainly complex-carbohydrates, and showed decreases in the intake of total fat, all types of fatty acids and cholesterol (all $p<0.05$).

The total energy intake decreased in the two groups, and it was more marked in the low-fat diet group. The same pattern of changes in nutrient profile after 1 and 3 years of intervention was observed in both groups (Table 33).

Table 32. Baseline and 5-year values and changes in the intake of energy and nutrients in the two intervention groups (n=853)[a]

	Baseline			5-year follow-up visit			Within-group mean changes after 5 years			
	Med Diet (n=447)	Low-Fat Diet (n= 406)	*p value**	Med Diet (n=447)	Low-Fat Diet (n= 406)	*p value**	Med Diet (n=447)	*p value*[#]	Low-Fat Diet (n= 406)	*p value*[#]
Energy (kcal)	2242 ± 24	2263 ± 26	0.528	2024 ± 18	1716 ± 18	<0.001	-218 ± 24	<0.001	-546 ± 25	<0.001
Total protein (%E)	18.5 ± 0.1	18.6 ± 0.1	0.863	17.3 ± 0.1	18.9 ± 0.1	<0.001	-1.3 ± 0.2	<0.001	0.3 ± 0.2	0.052
Total carbohydrate (%E)	41.4 ± 0.3	41.6 ± 0.3	0.702	38.5 ± 0.3	45.6 ± 0.3	<0.001	-2.9 ± 0.3	<0.001	4.1 ± 0.4	<0.001
Dietary fiber (g/1000kcal)	11.4 ± 0.2	11.4 ± 0.2	0.886	12.9 ± 0.2	14.1 ± 0.2	<0.001	1.6 ± 0.2	<0.001	2.7 ± 0.2	<0.001
Total fat (%E)	37.3 ± 0.3	36.7 ± 0.3	0.172	41.0 ± 0.3	31.7 ± 0.3	<0.001	3.8 ± 0.3	<0.001	-5.0 ± 0.4	<0.001
Monounsaturated fat (%E)	18.3 ± 0.2	17.9 ± 0.2	0.063	21.9 ± 0.2	14.3 ± 0.2	<0.001	3.6 ± 0.2	<0.001	-3.5 ± 0.2	<0.001
Oleic acid (%E)	17.0 ± 0.2	16.6 ± 0.2	0.060	20.7 ± 0.2	13.2 ± 0.2	<0.001	3.6 ± 0.2	<0.001	-3.4 ± 0.2	<0.001
Saturated fat (%E)	8.9 ± 0.1	8.9 ± 0.1	0.954	8.0 ± 0.1	7.1 ± 0.1	<0.001	-0.9 ± 0.1	<0.001	-1.8 ± 0.1	<0.001
Polyunsaturated fat (%E)	6.4 ± 0.1	6.3 ± 0.1	0.175	7.4 ± 0.1	7.1 ± 0.1	0.022	1.0 ± 0.1	<0.001	0.8 ± 0.1	<0.001
Linoleic acid (%E)	5.1 ± 0.1	5.0 ± 0.1	0.264	5.8 ± 0.1	5.9 ± 0.1	0.384	0.7 ± 0.1	<0.001	0.9 ± 0.1	<0.001
α-linolenic acid (%E)	0.44 ± 0.01	0.43 ± 0.01	0.373	0.59 ± 0.01	0.35 ± 0.01	<0.001	0.15 ± 0.01	<0.001	-0.07 ± 0.01	<0.001
EPA (%E)	0.10 ± 0.01	0.10 ± 0.01	0.372	0.13 ± 0.01	0.10 ± 0.01	<0.001	0.023 ± 0.004	<0.001	-0.003 ± 0.003	0.435
DHA (%E)	0.23 ± 0.01	0.22 ± 0.01	0.503	0.30 ± 0.01	0.21 ± 0.01	<0.001	0.07 ± 0.01	<0.001	-0.01 ± 0.01	0.286
Marine n-3 fatty acids (%E)	0.40 ± 0.01	0.39 ± 0.01	0.605	0.52 ± 0.01	0.37 ± 0.01	<0.001	0.11 ± 0.02	<0.001	-0.02 ± 0.01	0.136
Cholesterol (mg/day)	328.4 ± 4.5	332.8 ± 5.4	0.531	260.3 ± 3.2	248.9 ± 3.7	0.019	-68.1 ± 4.7	<0.001	-84.0 ± 5.5	<0.001

Data are means ± SEM. Med Diet, Mediterranean diet group; Low-Fat Diet, low-fat diet group; %E, percentage of total energy; g, grams; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; mg, milligrams. *Significant difference (p<0.05) between the Mediterranean diet and the low-fat diet group, analysed using an unpaired t test. [#]Significant difference (p<0.05) between baseline and 5-year follow-up visit in each variable (of each group), analysed using a paired t test; [a]Of the 1002 coronary patients included in the CORDIOPREV study, 853 patients completed the 5-year follow-up visit.

When we compared the nutrient intake of the two intervention groups after 5 years of dietary intervention (Table 32), we observed that the Mediterranean diet group had a higher intake of total fat, MUFA, oleic acid, PUFA, α-linolenic acid and marine n-3 fatty acids, and a lower intake of carbohydrates and proteins in comparison with the low-fat diet group (all $p<0.05$).

Table 33. Intake of energy and nutrients at 1-year and 3-year follow-up visits by intervention group (n=853)[a]

	Med Diet (n=447)		Low-Fat Diet (n=406)	
	1-year visit	3-year visit	1-year visit	3-year visit
Energy (kcal)	1960 ± 21	2017 ± 19	1822 ± 22	1771 ± 20
Total protein (%E)	17.9 ± 0.1	17.6 ± 0.2	18.9 ± 0.2	18.6 ± 0.2
Total carbohydrate (%E)	41.8 ± 0.3	41.5 ± 0.3	45.0 ± 0.4	46.3 ± 0.3
Dietary fiber (g/1000kcal)	13.4 ± 0.2	14.2 ± 0.2	14.0 ± 0.2	14.6 ± 0.2
Total fat (%E)	37.5 ± 0.3	38.2 ± 0.3	32.8 ± 0.3	31.8 ± 0.3
Monounsaturated fat (%E)	19.6 ± 0.2	20.3 ± 0.2	14.7 ± 0.2	14.3 ± 0.2
Oleic acid (%E)	18.5 ± 0.2	19.2 ± 0.2	13.6 ± 0.2	13.3 ± 0.2
Saturated fat (%E)	7.8 ± 0.1	7.6 ± 0.1	7.7 ± 0.1	7.2 ± 0.1
Polyunsaturated fat (%E)	6.5 ± 0.1	6.8 ± 0.1	7.3 ± 0.2	7.2 ± 0.2
Linoleic acid (%E)	5.1 ± 0.1	5.3 ± 0.1	6.2 ± 0.2	6.1 ± 0.1
α-linolenic acid (%E)	0.49 ± 0.01	0.54 ± 0.01	0.33 ± 0.01	0.34 ± 0.01
EPA (%E)	0.11 ± 0.01	0.12 ± 0.01	0.09 ± 0.01	0.08 ± 0.01
DHA (%E)	0.23 ± 0.01	0.27 ± 0.01	0.19 ± 0.01	0.18 ± 0.01
Marine n-3 fatty acids (%E)	0.41 ± 0.01	0.47 ± 0.01	0.33 ± 0.01	0.32 ± 0.01
Cholesterol (mg/day)	251.2 ± 3.7	247.4 ± 3.3	255.1 ± 4.8	241.7 ± 4.3

Data are means ± SEM. Med Diet, Mediterranean diet group; Low-Fat Diet, low-fat diet group; %E, percentage of total energy; g, grams; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; mg, milligrams. [a]N= 853 patients who completed the 5-year follow-up visit.

5.8.1.2. Food intake

Food intake was also analysed in terms of its contribution (%) to the daily energy intake at baseline and after 5 years of dietary intervention (Figure 21). At baseline, cereals were the primary source of energy (21.7 %E) for all the patients, followed by olive oil (14 %E), dairy products (10.4 %E) and red/processed meat (8.3 %E). Other foods contributed less, such as fruit (7.1 %E), fish or seafood (5.8 %E), vegetables (3.5 %E), legumes (3.4 %E) and tree nuts (2.3 %E). As intended, EVOO became the main source of energy in the Mediterranean diet group (from 12.1 to 21.6 %E) and cereals (with an increase of whole cereals from 4.6 to 7.1 %E) in the low-fat diet group after the 5-year intervention period. Significant increases in the consumption of fruit, vegetables and legumes ($p<0.001$), as well as decreases in the intake of red/processed meats ($p<0.001$), SSC beverages ($p<0.05$) and fat spreads ($p<0.05$) were observed in the two intervention groups. The consumption of tree nuts and oily fish increased only in the Mediterranean diet group ($p<0.05$). Moreover, the intake of commercial bakery products, sweets and pastries decreased significantly ($p<0.001$) in this group.

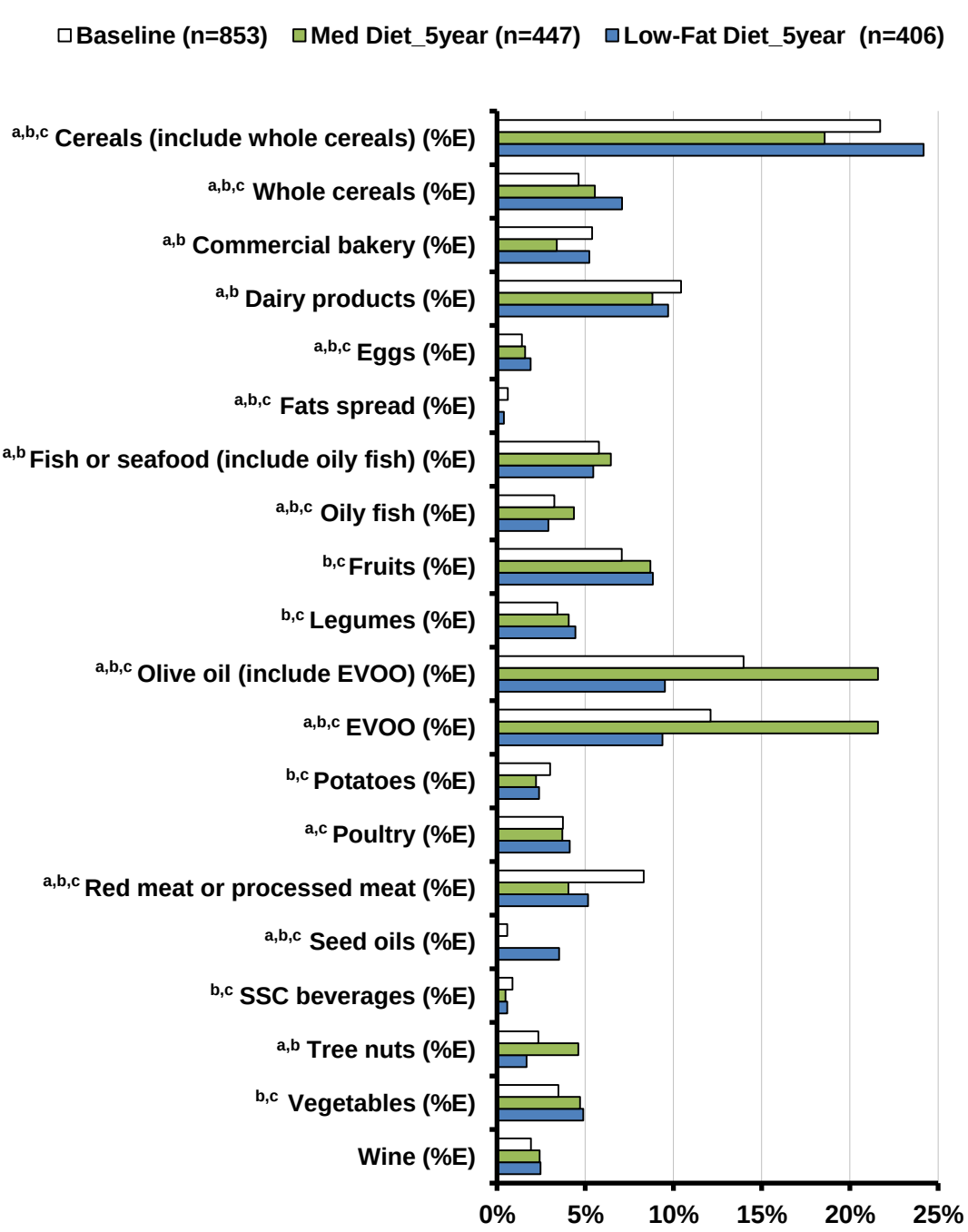


Figure 21. Dietary sources of energy from foods at baseline and after 5 years of intervention. The contribution (%) of foods to the daily energy intake, listed in alphabetical order, and categorized by intervention group. [a]*p*<0.05 for comparisons between groups in 5-year follow-up visit (unpaired *t* test); [b]*p*<0.05 from baseline by paired *t* test in the Mediterranean diet group; [c]*p*<0.05 from baseline by paired *t* test in the low-fat diet group. Med Diet, Mediterranean diet group; Low-Fat Diet, low-fat diet group; EVOO, extra-virgin olive oil; SSC beverages, sugar-sweetened carbonated beverages.

5.8.2. Dietary adherence achieved and its long-term maintenance in the CORDIOPREV population

Considering that the participants' adherence to the diet is one key element for the success of a dietary intervention, we addressed both the level of adherence and its maintenance in the total CORDIOPREV population during the 5 years of intervention.

5.8.2.1. Level of adherence to the dietary intervention

Figure 22 shows baseline and follow-up levels of adherence to the Mediterranean diet and the low-fat diet. At baseline, patients reported a moderate level of adherence to both diets based on the two dietary scores (the MEDAS and LFDAS) used in the CORDIOPREV study to monitor and assess the adherence. The mean MEDAS score was 8.9±0.1 and 8.7±0.1 points among the Mediterranean diet group and the low-fat diet group, respectively. The mean LFDAS was 3.9±0.1 points in both groups. These results were similar to those found in non-diabetics (as described in point 5.2 of the results section "*a priori*-defined dietary scores"). After the first year of dietary intervention, the mean scores in the MEDAS were significantly higher in the Mediterranean diet group than in the low-fat diet group (p<0.001 for all yearly comparisons from year 1 to 5 of follow-up), achieving a maximum difference of 3.8±0.1 points in the MEDAS at the 5-year visit (Figure 22a). Specifically, participants in the Mediterranean diet group showed a significant increase of 2.0±0.1, 2.4±0.1 and 2.5±0.1 points from their baseline MEDAS after 1, 3 and 5 years of intervention (p<0.001 for all comparisons), whereas the low-fat diet group reported a significant decrease in the MEDAS of 1.1±0.1, 1.0±0.1 and 1.1±0.1, respectively (p<0.001 for all comparisons). Participants in the low-fat diet group increased their score in the LFDAS in the expected direction, from 3.9±0.1 baseline score to 6.5±0.1, 6.4±0.1 and 7.1±0.1 after 1, 3 and 5 years of dietary intervention, respectively (p<0.001 for all comparisons) (Figure 22b).

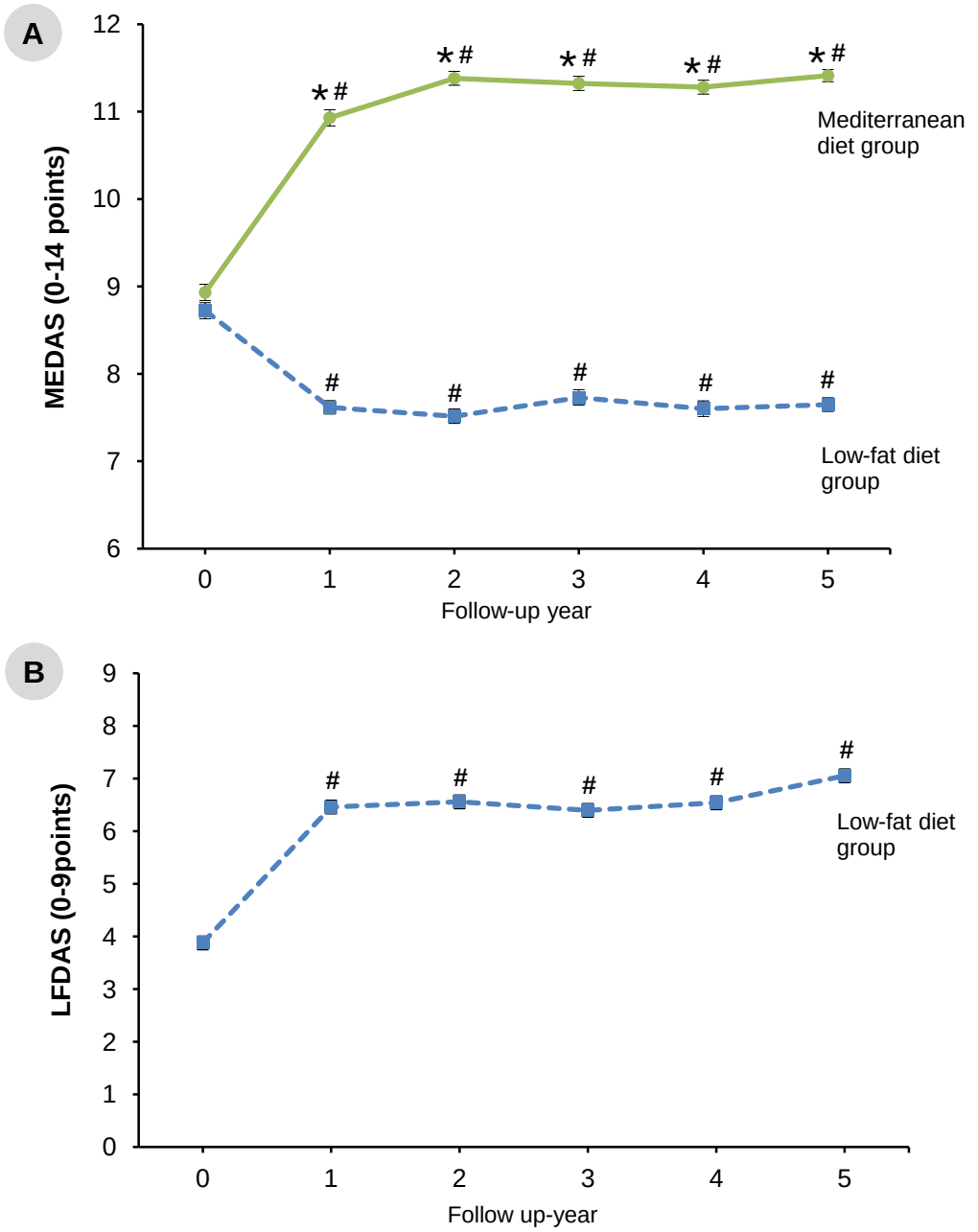


Figure 22. Changes in dietary scores during the 5 years of follow-up. A) Adherence to the 14-point Mediterranean Diet Adherence Screener (MEDAS) in the total population (both arms, *n*=853); B) Adherence to the 9-point low-fat diet adherence screener (LFDAS) in patients allocated to the low-fat diet (*n*=406). Values are expressed as mean ± SEM. **p*<0.001 between intervention groups by Student's t-test. $^{\#}$*p*<0.001 from baseline by paired t test.

As a robustness check, we also analysed the 5-year changes in dietary adherence based on the MEDAS-FFQ and LFDAS-FFQ (dietary scores derived from the FFQ). The results were similar than those obtained for administered MEDAS and LFDAS (Figure 23). Thus, significant between-group differences for the MEDAS-FFQ and LFDAS-FFQ were observed in the short- (1 year), medium- (3 years) and long-term (5 years) (all $p<0.001$). During follow-up, scores on the MEDAS-FFQ increased for the Mediterranean diet group (all $p<0.001$ from baseline) and decreased for the low-fat diet group (all $p<0.001$ from baseline). Conversely, scores on the LFDAS-FFQ increased for the low-fat diet group (all $p<0.001$ from baseline). Interesting, the analysis of the LFDAS-FFQ let us to know the level of adherence to the low-fat diet in those patients allocated to the Mediterranean diet group, which was not possible when analysing the administered LFDAS (following the protocol of the CORDIOPREV study, the LFDAS was only administered in this group at baseline visit). Patients in the Mediterranean diet group showed a mean score on the LFDAS-FFQ of less than 4 points during the 5 years of intervention, which would be related with the compliance of the 4 items compatible with a Mediterranean-type diet (item 2: remove visible fat and skin of meats; item 3: fatty/processed meats ≤1 serving/week; item 4: spread fats ≤1 serving/week; item 8: commercial pastry ≤1 serving/week).

Regarding the percentage of patients who fulfilled the MEDAS component targets (Table 34), the 5-year data showed significant differences between the intervention groups in 12 of the 14 items (all $p<0.05$). As intended, the Mediterranean diet group showed increases in their compliance with each of the 14 items in years 1, 3 and 5, whereas the low-fat diet group decreased their compliance with the 5 items of the MEDAS related to the consumption of fatty foods (olive oil, nuts, oily fish and “sofrito" sauce). In addition, this group raised the percentage of compliance with all the 9 items of the LFDAS (Table 35). These data were consistent with the food intake information derived from FFQ (Table 36).

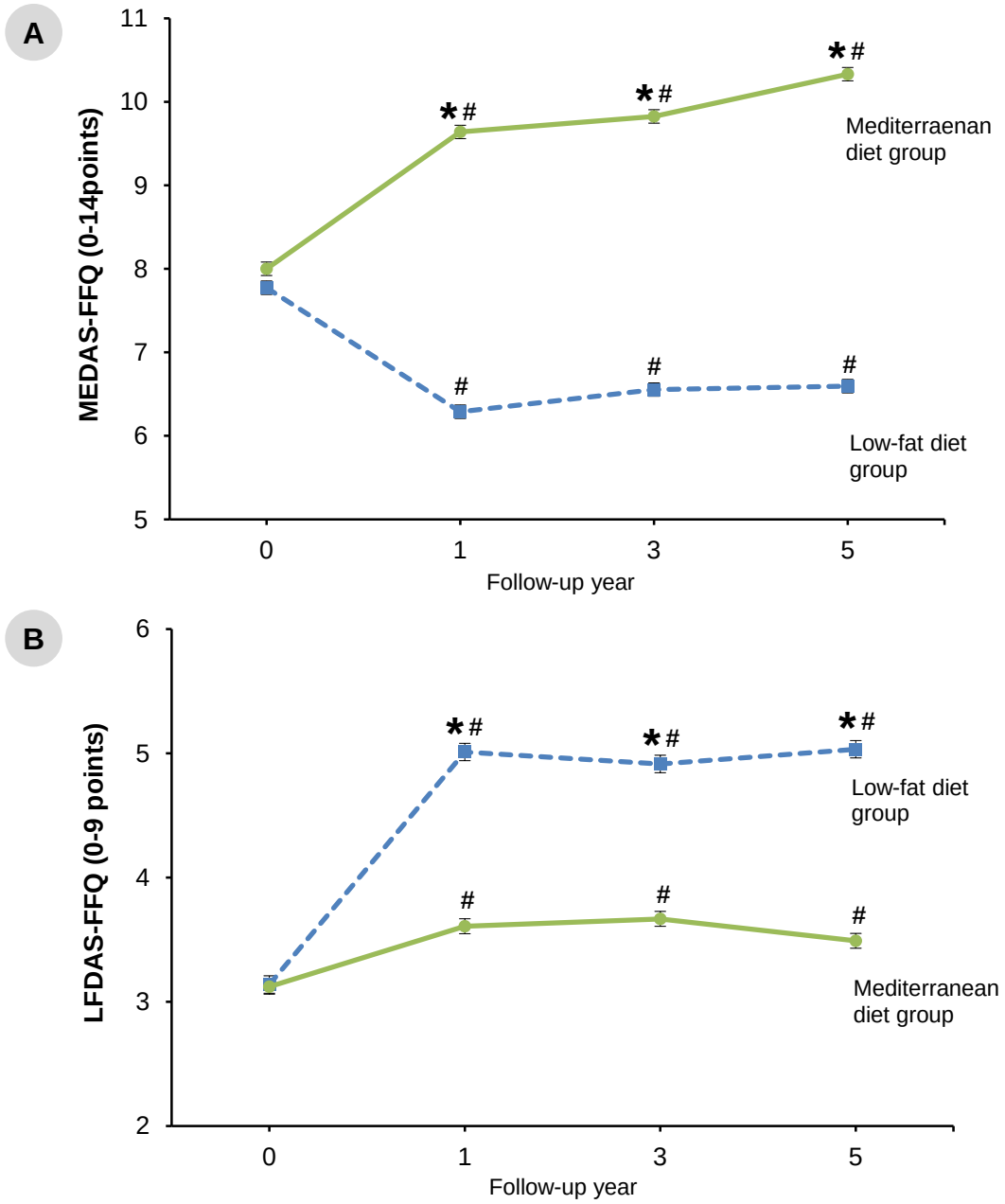


Figure 23. Changes in dietary scores calculated from the FFQ during the 5 years of follow-up (n=853)[a]. A) Adherence to the 14-point Mediterranean Diet Adherence Screener derived from the FFQ (MEDAS-FFQ); B) Adherence to the 9-point low-fat diet adherence screener derived from the FFQ (LFDAS-FFQ). Values are expressed as means ± SEM. *p<0.001 between intervention groups by Student's t-test. [#]p<0.001 from baseline by paired t test. [a]N=853 patients who completed the 5-year follow-up visit (447 patients in the Mediterranean diet group and 406 in the low-fat diet group).

Table 34. Percentage of patients with a positive answer to each item of the 14-point Mediterranean diet adherence screener (MEDAS) by intervention group during follow-up (n=853)[a]

	Baseline		1-year visit		3-year visit		5-year visit	
	Low-Fat Diet (n=406)	Med Diet (n=447)	Low-Fat Diet (n=406)	Med Diet (n=447)	Low-Fat Diet (n=406)	Med Diet (n=447)	Low-Fat Diet (n=406)	Med Diet (n=447)
1. Use of olive oil as main culinary fat	99.0	97.3	59.6	98.4**	60.8	99.3**	64.8	100.0**
2. Olive oil ≥4 tablespoons/day	60.1	65.8	9.6	80.8**	10.3	85.7**	1.7	86.6**
3. Vegetables ≥2 s/d	75.6	78.1	77.3	85.5*	62.3	85.9**	81.8	90.8**
4. Fruits ≥3 s/d	53.2	54.6	59.6	75.2**	53.9	76.5**	56.4	75.6**
5. Red or processed meats <1 s/d	58.1	61.1	87.7	86.4	89.9	91.3	79.8	83.9
6. Butter, margarine, cream <1 s/d	92.6	91.3	94.3	98.0*	95.8	99.1*	94.1	99.6**
7. Sweet/carbonated beverages <1 s/d	72.4	75.2	84.0	82.6	78.1	85.0*	80.3	87.7*
8. Wine ≥ 7 glasses/week	28.8	28.2	28.8	35.3*	30.3	37.1*	30.0	35.3
9. Legumes ≥3 s/w	37.4	42.1	40.4	64.4**	45.1	69.8**	45.8	75.8**
10. Fish or seafood ≥3 s/w	60.8	57.9	41.9	74.5**	37.9	72.7**	33.3	66.7**
11. Commercial bakery products ≤2 s/w	43.8	43.0	59.9	74.3**	62.1	75.4**	69.7	81.9**
12. Tree nuts ≥3 s/w	32.5	36.5	13.1	49.4**	17.0	59.3**	11.6	65.5**
13. Poultry more than red meats	72.9	76.3	88.2	92.2*	94.6	97.5*	93.3	96.4*
14. Use of “sofrito” ≥2 times/week	84.7	85.9	17.5	96.0**	34.7	97.5**	22.2	95.1**

Data are shown as percentage of participants. Med Diet denotes Mediterranean diet group; Low-Fat Diet, low fat diet group; s/d, servings per day; s/w, servings per week. Statistically significant comparisons between the Med Diet and the Low-Fat Diet for each year (Chi squared tests) were indicated with symbols *(p<0.05) and **(p<0.001). [a]N=853 patients who completed the 5-year follow-up visit (447 patients in the Mediterranean diet group and 406 in the low-fat diet group).

Table 35. Percentage of patients in the low-fat diet group with a positive answer to each item of the 9-point low-fat diet adherence screener (LFDAS)

Items	Low-fat diet group (n=406)[a]			
	Baseline	1-year visit	3-year visit	5-year visit
1. Vegetable oils (≤2 tablespoons/day)	2.5	44.8	44.1	52.2
2. Remove visible fat in meats and soups	78.8	84.5	92.6	94.6
3. Red and processed fatty meats (≤1 serving/week)	12.3	62.8	65.0	80.3
4. Fat spread (≤1 serving/week)	78.3	86.0	88.9	89.9
5. Low-fat dairy products	51.5	71.4	67.5	80.3
6. Use oil-free cooking techniques	36.9	79.6	77.3	79.1
7. Oily fish, seafood canned in oil (≤1 serving/week)	40.1	79.1	74.9	82.5
8. Commercial bakery products, sweets and pastries (≤1 serving/week)	36.9	58.6	54.2	68.2
9. Nuts and fried snacks (≤ 1 serving/week)	50.5	79.1	74.9	78.1

Values are expressed as percentage of participants. [a]N=406 patients randomized to the low-fat diet group who completed the 5-year follow-up visit.

Table 36. Food intake (servings/day) at baseline and after 5 years of dietary intervention by study group (n=853)[a]

	Mediterranean diet group (n=447)				Low-fat diet group (n=406)			
Food item	Baseline	1-year visit	3-year visit	5-year visit	Baseline	1-year visit	3-year visit	5-year visit
Total olive oil (1s=10g)	3.48 ± 0.06	3.99 ± 0.06	4.39 ± 0.06	4.47 ± 0.05	3.35 ± 0.06	1.94 ± 0.06	1.90 ± 0.05	1.80 ± 0.04
Extra-virgin olive oil (1s=10g)	3.08 ± 0.08	3.91 ± 0.07	4.32 ± 0.06	4.47 ± 0.05	2.85 ± 0.08	1.85 ± 0.04	1.83 ± 0.06	1.77 ± 0.04
Seed oils (1s=10g)	0.15 ± 0.02	0.02 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.14 ± 0.01	0.77 ± 0.04	0.82 ± 0.04	0.63 ± 0.03
Vegetables (1s=150g)	2.69 ± 0.05	2.64 ± 0.05	3.53 ± 0.06	3.42 ± 0.04	2.64 ± 0.05	2.76 ± 0.06	3.21 ± 0.06	2.92 ± 0.04
Fruit (1s=150g)	2.32 ± 0.06	2.68 ± 0.06	3.29 ± 0.07	2.76 ± 0.06	2.30 ± 0.06	2.51 ± 0.06	2.88 ± 0.07	2.36 ± 0.06
Red/processed meat (1s=150g)	1.54 ± 0.04	1.03 ± 0.03	0.85 ± 0.03	0.81 ± 0.02	1.60 ± 0.04	1.18 ± 0.04	0.94 ± 0.03	0.85 ± 0.02
Fat spread (1s=12g)	0.13 ± 0.02	0.02 ± 0.01	0.01 ± 0.01	0.01 ± 0.01	0.15 ± 0.02	0.12 ± 0.02	0.08 ± 0.01	0.07 ± 0.01
SSC beverages (1s=200cc)	0.47 ± 0.04	0.37 ± 0.03	0.35 ± 0.03	0.26 ± 0.02	0.48 ± 0.04	0.41 ± 0.03	0.35 ± 0.03	0.29 ± 0.02
Legumes (1s=60g)	0.38 ± 0.01	0.43 ± 0.01	0.44 ± 0.01	0.41 ± 0.01	0.40 ± 0.01	0.37 ± 0.01	0.38 ± 0.01	0.38 ± 0.01
Fish or seafood (1s=150g)	0.85 ± 0.02	0.72 ± 0.02	0.76 ± 0.02	0.82 ± 0.02	0.84 ± 0.02	0.63 ± 0.02	0.61 ± 0.01	0.66 ± 0.01
Oily fish (1s=150g)	0.40 ± 0.01	0.36 ± 0.01	0.44 ± 0.01	0.46 ± 0.01	0.40 ± 0.01	0.28 ± 0.01	0.30 ± 0.01	0.30 ± 0.01
Commercial bakery (1s=50g)	0.65 ± 0.03	0.41 ± 0.02	0.43 ± 0.02	0.36 ± 0.02	0.67 ± 0.03	0.62 ± 0.03	0.60 ± 0.03	0.47 ± 0.02
Tree nuts (1s=30g)	0.32 ± 0.02	0.38 ± 0.02	0.45 ± 0.02	0.53 ± 0.02	0.28 ± 0.02	0.16 ± 0.01	0.15 ± 0.01	0.17 ± 0.01
Wine (1s=100cc)	0.58 ± 0.04	0.60 ± 0.04	0.62 ± 0.04	0.66 ± 0.04	0.59 ± 0.05	0.57 ± 0.04	0.60 ± 0.04	0.56 ± 0.04
Poultry (1s=150g)	0.46 ± 0.01	0.43 ± 0.01	0.42 ± 0.01	0.43 ± 0.01	0.48 ± 0.01	0.42 ± 0.01	0.40 ± 0.01	0.40 ± 0.01
Dairy products (1s=200g)	2.52 ± 0.05	2.25 ± 0.05	2.23 ± 0.05	2.06 ± 0.05	2.33 ± 0.06	2.27 ± 0.06	2.17 ± 0.06	1.93 ± 0.05
Total grains (1s=60g)	2.44 ± 0.05	2.11 ± 0.05	2.03 ± 0.05	1.93 ± 0.04	2.54 ± 0.06	2.04 ± 0.05	1.97 ± 0.05	2.12 ± 0.05
Whole grains (1s=60g)	0.55 ± 0.05	0.85 ± 0.05	0.73 ± 0.05	0.62 ± 0.04	0.58 ± 0.05	0.84 ± 0.05	0.68 ± 0.04	0.64 ± 0.04

Data are mean±SEM. S, servings; g, grams; cc, cubic centimetres; SSC, sugar-sweetened carbonated. [a]N=853 patients who completed the 5-year follow-up visit (447 patients in the Mediterranean diet group and 406 in the low-fat diet group).

When dietary adherence was categorized, in the Mediterranean diet group, the percentage of patients in the *High Adherence* category increased from 40.9% at baseline to 88.8% at the 5-year visit (Figure 24), whereas in the low-fat diet group this percentage increased from 5.9% at baseline to 67% after 5 years (Figure 25).

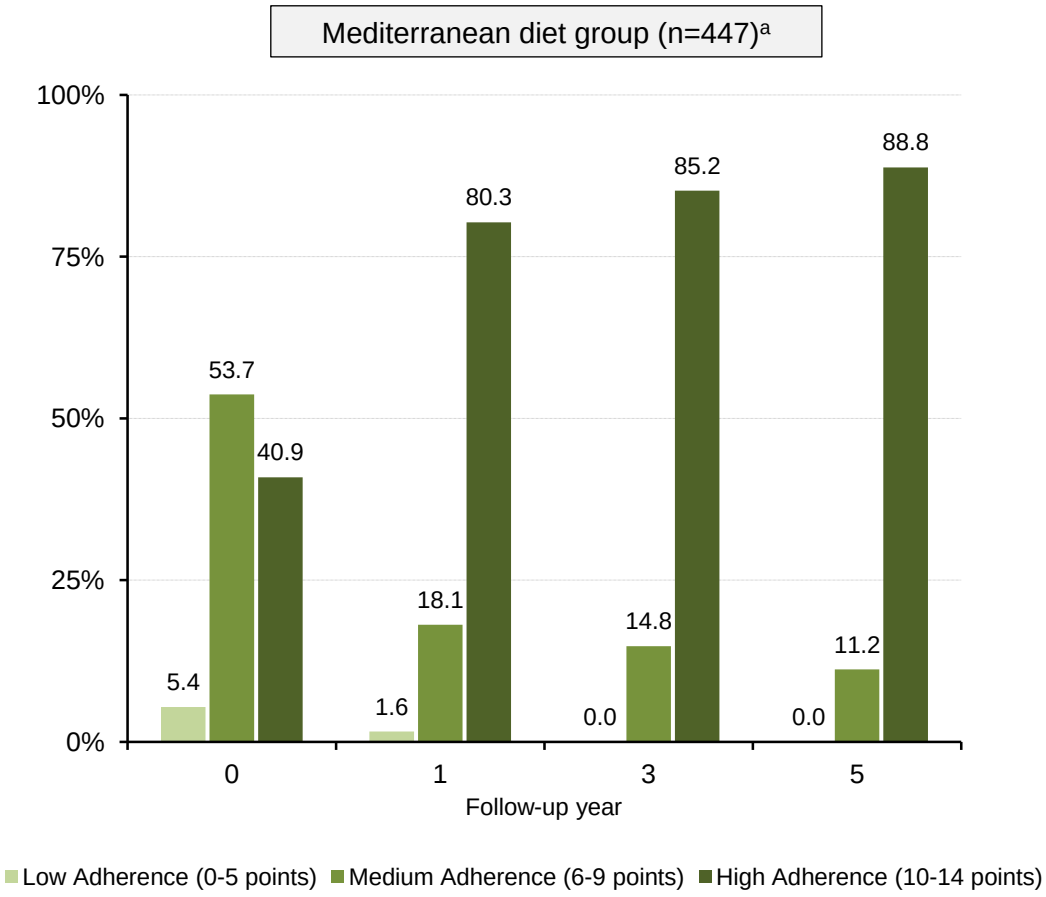


Figure 24. Categories of adherence to the Mediterranean diet during the 5 years of follow-up. Values are expressed as percentage of participants. Mediterranean diet adherence was categorized into low (0-5 points), medium (6-9 points) and high (10-14 points) in accordance with the score obtained on the 14-point Mediterranean Diet Adherence Screener (MEDAS).[a]N=447 patients in the Mediterranean diet group who completed the 5-year follow-up visit.

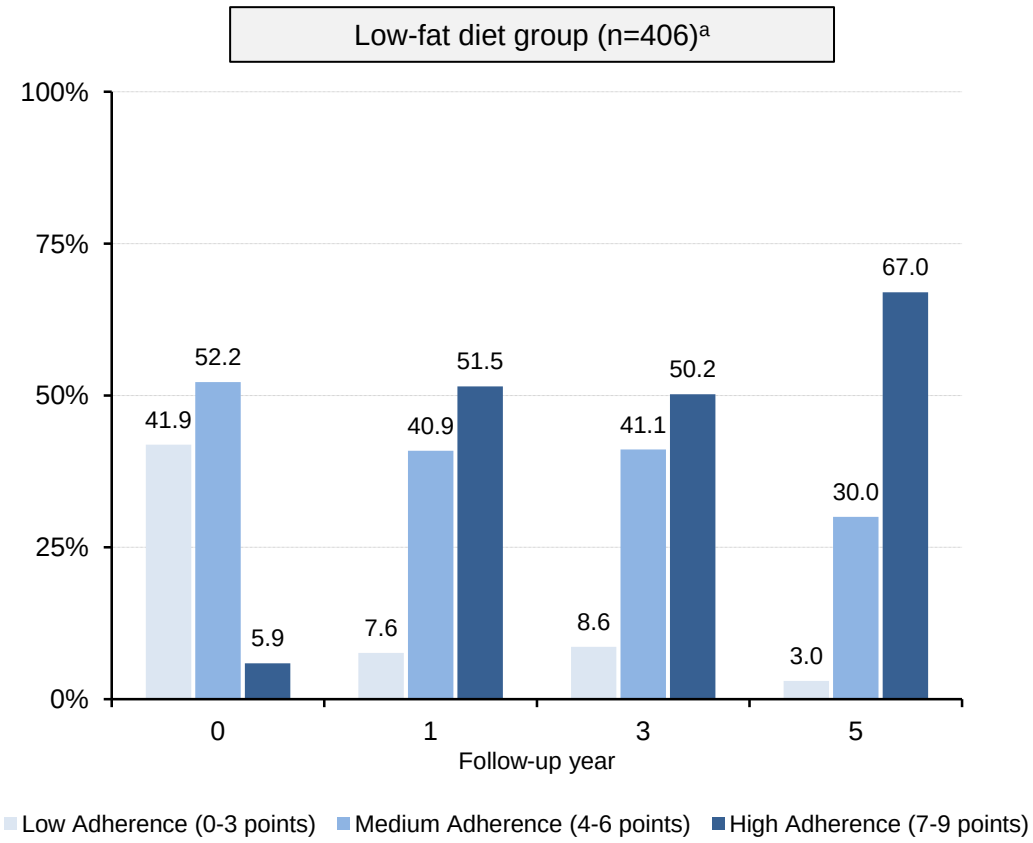


Figure 25. Categories of adherence to the low-fat diet during the 5 years of follow-up. Values are expressed as percentage of participants. Low-fat diet adherence was categorized as low (0-3 points), medium (4-6 points) and high (7-9 points) in accordance with the score obtained on the 9-point low-fat diet adherence screener (LFDAS). [a]N=406 patients in the low-fat diet group who completed the 5-year follow-up visit.

5.8.2.2. Long-term dietary adherence maintenance

Coefficients of variation in both groups during the first to fifth years of intervention were low (Mediterranean diet group, 11%; low-fat diet group, 23%), which supports the idea that the changes in the scores between the end of the first and fifth years were representative of the overall period.

Figure 26 shows the change in dietary adherence for each category of adherence (*Low*, *Medium* or *High Adherence*) between years 1 and 5, according to diet. In both groups, patients in the category of *Low Adherence* at year 1 showed the

greatest change over time (the Mediterranean diet group increased their adherence by 45.9±4.9% and the low-fat diet group increased by 41.2±3.8%, $p<0.001$ for all) with no significant differences between diets. Likewise, patients in the category of *Medium Adherence* also showed a positive percentage change in the two intervention groups. In the category of *High Adherence*, however, the Mediterranean diet group did not change their adherence over time, while there was a decrease in the adherence with the low-fat diet group (-8.2±1.2%, $p<0.001$). The difference between the Mediterranean versus low-fat diet groups was statistically significant *(*$p<0.001$).

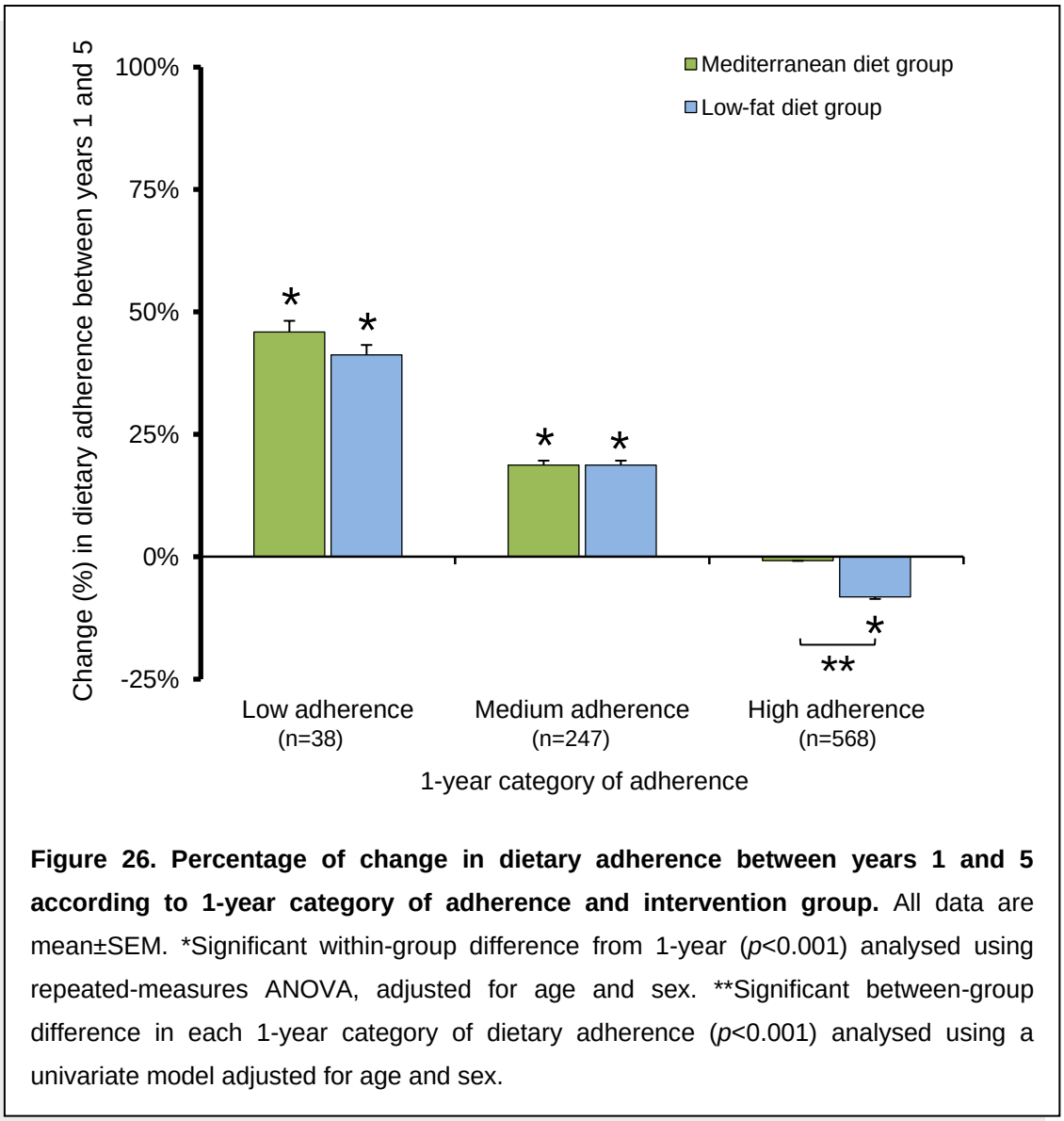


Figure 26. Percentage of change in dietary adherence between years 1 and 5 according to 1-year category of adherence and intervention group. All data are mean±SEM. *Significant within-group difference from 1-year ($p<0.001$) analysed using repeated-measures ANOVA, adjusted for age and sex. **Significant between-group difference in each 1-year category of dietary adherence ($p<0.001$) analysed using a univariate model adjusted for age and sex.

VI. DISCUSSION

VI. DISCUSSION

The realization of this thesis has allowed investigating in depth the relationship between diet and the incidence of T2DM in coronary patients, in which the development of this disease greatly increases the risk of suffering new coronary events and death. The novelty of the approach made in this work is the study of the diet as a whole concept using simultaneously *a priori* and *a posteriori* dietary pattern analysis and comparing their ability to predict incident T2DM after a long-term dietary intervention. The *a priori* approach (i.e. dietary scores) has allowed to know how the coronary patients' diet was close to two healthy dietary models and how this could predict the risk of developing T2DM. The *a posteriori* approach (i.e. PCA-dietary patterns) has allowed knowing how coronary patients were combining foods into main patterns and how these variances in food intake were related with a greater or lower risk of incident T2DM. Results of this research work have revealed that both approaches of dietary pattern analysis can be used to infer the incidence of T2DM after 5 years of dietary intervention.

In addition to our main results, we analysed the association of dietary scores and PCA-dietary patterns with several anthropometric and biochemical variables related to T2DM risk. Moreover, we examined the validity of both approaches of dietary pattern analysis in our population. Finally, in the total CORDIOPREV population, we assessed the long-term dietary adherence which is the major challenge of any dietary intervention trial.

The results of this doctoral thesis, as well as their research and clinical implications are discussed below. Finally, the main limitations found in this work are detailed and future lines of research are provided.

6.1. Association of dietary scores and PCA-dietary patterns with the incidence of T2DM after a median follow-up of 5 years

In non-diabetic coronary patients involved in a long-term dietary intervention trial, the present work shows that dietary habits before starting a dietary intervention are not related with the 5-year incidence of T2DM, whereas the level of dietary adherence achieved after one year of intervention is significantly predictive of the development of the disease. In our study, a high adherence to a Mediterranean diet assessed by the MEDAS was associated with a 69% reduction in the risk of incident T2DM, while high adherence to a Western-type dietary pattern increased the risk by 90%. Moreover, we have discovered which *a priori* and *a posteriori* dietary patterns have a higher efficacy to make these predictions, and that these two chosen methods have similar ability in predicting the 5-year incidence of T2DM.

Regardless the type of dietary pattern analysis used, baseline dietary adherence was not associated with the development of T2DM in our population. We hypothesized that this lack of association may be owing to a possible social desirability effect [187]. The fact of having recently suffered a coronary event may influence in a way the answers of the patients towards what they thought they should consume. Thus, coronary patients may tend to report a higher consumption of foods considered as “healthy” and a lower intake of those perceived as “unhealthy” in baseline visit. During the intervention, however, frequent contacts with the dietitian promote the dietitian-patient relationship which increases patient’s trust, honesty and willingness to communicate [188]. In addition, patients acquire tools and knowledge about nutrition, food, homemade measures and cooking techniques in face-to-face and group visits, which increase their ability to provide more accurate and detailed information on their dietary intake. In fact, we observed the greatest change in dietary intake and the

highest score in the three dietary screeners after one year of intervention, which supports that the first year of intervention in a long-term dietary intervention trial is crucial to gain patient's confidence, achieve the change in dietary habits, and thereby achieve maximum adherence [137]. Moreover, the higher percentage of variance explained by PCA-dietary patterns at one year in our population suggests that dietary data obtained during the intervention and in a more controlled environment is more reliable than dietary data at baseline prior to starting the intervention. Furthermore, in long-term dietary intervention trials, one-year time-point has been shown to be an important point to measure the impact of the intervention in dietary intake, dietary adherence and intermediates outcomes [137,138].

In the present work, we found that a high score on the MEDAS after one year of intervention was associated with a strikingly lower risk (about 70%) of developing T2DM, showing that increased adherence to a Mediterranean-type diet achieved and maintained in the long-term with comprehensive dietary intervention can substantially reduce the incidence of T2DM in coronary patients. Specifically, a one-point increment in the MEDAS was related to a 17% lower risk of T2DM in our population, suggesting that even a small change in dietary habits towards a Mediterranean diet can have a high impact on the prevention of T2DM in coronary patients. Our findings are aligned with a previous work of Mozaffarian et al. [146] showing a direct relationship between some components of the Mediterranean diet and a lower risk of new-onset T2DM in patients with CVD. Interestingly, the dietary screener used in that study did not really measure the adherence to a Mediterranean-type diet but rather to some components of this pattern (i.e. cooked/raw vegetables, fruit, fish and olive oil). This limitation is overcome in the current study using a valid tool for assessment of adherence to the Mediterranean diet [165]. Our findings are also consistent with those from dietary intervention trials examining the effect of the Mediterranean diet on T2DM, such as the PREDIMED study, which demonstrated that long-term adherence to a Mediterranean

diet reduced the risk of T2DM in high CVD risk patients [110]. In this landmark trial, the intensive Mediterranean diet intervention was similar to that of the CORDIOPREV study and the MEDAS was used to measure compliance with the intervention. Given that we analyzed the data by considering the level of adherence instead of randomization group and that diabetes risk reduction occurred in the absence of weight loss, we have a higher confidence that the beneficial effect observed in our analysis may be attributed to the Mediterranean diet. Taking into account that lifestyle modification trials including a dietary intervention have demonstrated that the beneficial effect on reducing T2DM persists after the intervention [4,189], the strong association between the MEDAS and incident T2DM found in our study may be of clinical relevance. Nevertheless, this concept may be investigated in the future, and the metabolic memory created by our intervention will be tested in the CORDIOPREV Long-term study, an observational cohort to assess future clinical events of the CORDIOPREV population.

Several factors may explain the strong association found in our study between the MEDAS at one year and the incidence of T2DM. We speculate that considering one-year dietary adherence instead baseline could be a key factor. The use of baseline adherence data and not considering the changes that might occur during the long period of follow-up, which could impact the results, has been a common limitation in previous prospective studies [141-146]. Using the MEDAS at year one allowed us to control for possible changes in dietary adherence since yearly measurement of the MEDAS showed that there were no significant changes between year one and each of the next four years of follow-up. Another factor could be the use of a Mediterranean diet score specifically designed to be used in a dietary intervention setting. Unlike other Mediterranean diet scores, the MEDAS was designed to allow for a quick assessment and immediate provision of feedback [165] and, therefore, is able to detect changes in Mediterranean diet adherence induced by the intervention [137]. It was developed and

used in the PREDIMED study, wherein changes in dietary adherence during the first year of intervention were similar than those found in our study [86]. Moreover, the MEDAS includes an essential characteristic of the Mediterranean diet which is the use of olive oil as main culinary fat [190], highlighting the EVOO as a source of polyphenols. Theses bioactive compounds contribute to the anti-inflammatory potential of the Mediterranean diet, one of the underlying mechanisms of protection of this dietary pattern against T2DM [115,191]. Indeed, the MEDAS has been demonstrated to be one of the dietary scores capturing the highest levels of dietary antioxidant intake [192]. In line with this, we found that the MEDAS was associated with increased intakes of protective nutrients such as dietary fiber, antioxidant vitamins (vitamins C and E, and carotenes), folic acid, magnesium, potassium, and MUFA, as well as with lower intakes of pro-inflammatory nutrients/foods, such as SFA, refined sugars and processed meats. Other potential mechanism by which the Mediterranean diet protects against T2DM, such as improvement in insulin sensitivity or beneficial effects on the beta-cell, are attributed to these nutritional characteristics [112,114].

Considering that the MEDAS and MDS-Trichopoulou measured the same concept, it would be expected to find a significant inverse association between the MDS-Trichopoulou at year 1 and incident T2DM [193]. However, we did not find such association. It could be explained by the fact that the MEDAS and MDS-Trichopoulou are based on different constructing algorithms and varied in the components included [194], and therefore, their association with the outcome may vary. For example, the intake of olive oil is specifically assessed in the MEDAS while it is indirectly measured by the ratio of MUFA to SFA in the MDS-Trichopoulou; red meats/processed meats are included as a specific item in the MEDAS while they are considered together with poultry in a same item in the MDS-Trichopoulou; SSC-beverages are not included in the MDS-Trichopoulou. These foods/food groups have been reported to be associated with the development of T2DM [97,195] and, therefore, a dietary score containing these

dietary factors may show a strong association with incident T2DM, especially in coronary patients. In this sense, most of the studies reporting an inverse relationship between incident T2DM and the dietary score proposed by Trichopoulou et al. were cohort studies conducted among individuals without CVD [141-145], and the only one involving patients with CVD was limited because only five of the nine items of the dietary score were assessed [146].

With respect to the LFDAS, we found a non-significant inverse association between adherence to the LFDAS after one year of intervention and incident T2DM at 5 years. Although there are no studies that specifically assessed this association, dietary intervention studies like the Women's Health Initiative Dietary Modification (WHI-DM) trial have tested the long-term effects of a low-fat diet in the incidence of T2DM. In agreement with our results, the WHI-DM trial showed that a low-fat dietary pattern did not significantly reduce T2DM risk [196]. However, the low-fat diet intervention of the CORDIOPREV study reduced fat intake to 30% of total energy intake, but maintained a healthy fat profile, and increased the intake of complex carbohydrates and dietary fiber from whole grains, vegetables, legumes and fruits. The high content of plant-based food rich in bioactive food constituents and the low content of SFA and refined carbohydrates of this dietary pattern could explain the trend towards lower T2DM risk with high adherence to the LFDAS in the current study.

In relation to the PCA-dietary patterns after one year of intervention, we found that the Western DP was consistently associated with an increased risk of incident T2DM. Specifically, patients with closer adherence to this unhealthy dietary pattern had almost the double the risk of developing T2DM that patients with low-medium adherence did. Although our results cannot be compared directly with those of other studies due to the highly heterogeneous nature of the a posteriori analysis and the lack of studies in coronary patients, a positive association between westernized dietary patterns and incident T2DM have already been reported in previous prospective

studies that used PCA and wherein the pattern composition was similar to that of the pattern derived in our study [51,52]. The foods that characterize this pattern, such as red meats, processed meats, refined grains and ultra-processed products, are sources of SFA and trans-fatty acids, sodium, high-glycemic carbohydrates and advanced glycation end products. The positive association between the Western DP and the risk of incident T2DM may be partly attributed to these dietary factors, which can promote oxidative stress, inflammatory process and insulin resistance [197-199].

With respect to the Mediterranean DP and Low-fat DP at year one, we found non-significant inverse associations between these healthy dietary patterns and the risk of incident T2DM. It is hard to compare our results directly, because previous studies examining the association between healthy overall dietary patterns and incident T2DM using PCA/factor analysis did not identify dietary patterns comparable to the current Mediterranean DP and Low-fat DP [48]. Most of these studies identified only one healthy dietary pattern per population/study, which was usually labelled “prudent” or “healthy” [51,52,200-202]. The foods that characterized the “prudent” pattern (i.e. vegetables, legumes, fruits, whole grains, poultry, and fish) differ across studies and in no study olive oil loaded positively in the “prudent” pattern. In addition, no study involved patient with CVD. Taken together, results of two studies showed that high adherence to a “prudent” pattern was related to lower risk of T2DM [51,201] and results of three studies [52,200,202] showed a non-significant inverse association, which was consistent with our findings. The lack of association between the Mediterranean DP, the Low-fat DP and T2DM risk in our study may be partly due to the interaction between foods having opposite effects on the outcome of interest within dietary patterns. For example, food groups with factor loadings close to 0.30 in the Mediterranean DP, such as refined grains, could have counteracted the effect of other food groups loaded on this pattern such as nuts, legumes or EVOO, which have been demonstrated to have a protective effect against T2DM [195,203].

To our knowledge, one study to date has directly compared the two methodological approaches of dietary pattern analysis in predicting the development of a chronic disease [204]. Here, Panagiotakos et al. found that a Mediterranean diet score and PCA-dietary patterns had equal discriminating ability in predicting the 5-year incidence of CVD in 3042 participants without CVD from the ATTICA study. In the current study, using models that also included classical clinical variables and lifestyle factors, we observed that the model including the MEDAS at year one (*a priori*-defined dietary score) had similar ability in predicting the five-year incidence of T2DM compared to the model that included the Western DP at year one (*a posteriori*-derived dietary pattern). These results suggest that both methodological approaches might are valid to infer T2DM risk assessment in coronary patients, and highlights the need to identify the focus of the investigation in each moment to choose the method. While dietary scores allow investigating whether or not adherence to a predefined healthy diet is related to risk, PCA-dietary patterns allow examining what explains the variation in food intakes and how well these variations relate to disease risk [205]. Thus, dietary scores are easily reproducible and comparable, and PCA-dietary patterns are population-specific. Nevertheless, the application of both approaches of dietary pattern analysis at the same time in epidemiological research may provide a more complete picture of the complex relationship between diet and T2DM.

6.2. Association of dietary scores and PCA-dietary patterns with factors associated to the development of diabetes

Some biological factors (biochemical and anthropometric variables) provide important information on the development and progression of chronic diseases such as T2DM and CVD, and the study of the effect of dietary patterns on these factors can help to better understand the relationship between dietary exposure and the

development of the disease. Thus, several analyses were performed in our population to examine the association of dietary scores and PCA-dietary patterns at year one with variables associated to the development of T2DM at year five. Overall, the MEDAS was the only dietary score that showed significant inverse associations with anthropometric variables, triglycerides and markers of glucose homeostasis and inflammation, suggesting a protective effect of a high adherence to a Mediterranean-type diet against these factors. In addition, the Western DP was associated with worse values of anthropometric variables, lipid profile, glucose and C-reactive protein, showing that a high adherence to this unhealthy dietary pattern has a deleterious effect on many factors implicated in the pathophysiology of T2DM.

Dietary scores at year 1 and anthropometric/biochemical variables at year 5

In the current analysis, high adherence to the MEDAS at year one was prospectively associated with lower waist circumference, HbA1c, HOMA-IR, glucose, triglycerides, C-reactive protein, leukocytes and neutrophil-lymphocyte ratio. These results are in line with previous studies reporting an inverse association between the MEDAS and the prevalence of abdominal obesity [177], and a direct association with improved lipid profile [165]. Evidence supports the benefits of the Mediterranean diet on glycemic control by reducing HbA1c [105,109]. Moreover, high adherence to this dietary pattern has been related to better fasting plasma glucose and HOMA-IR [206], which agree with the inverse association found in our study between the MEDAS and these markers of glucose homoeostasis. With regard to inflammation markers, our results are in agreement with a recent study carried out in a large Spanish cohort where C-reactive protein levels were inversely related to the MEDAS [207]. Several clinical trials have also described an inverse relationship between adherence to the Mediterranean diet and this marker of low-grade chronic inflammation [113,208], which is closely related to the development of T2DM and an independent predictor of cardiovascular events [209]. Although no studies have directly evaluated the

relationship between the MEDAS and leukocytes, results of the Moli-sani study linked high Mediterranean diet adherence to decreased leukocyte counts, which is in line with our results [210]. On the other hand, adherence to the Mediterranean diet via the MDS-Trichopoulou have been inversely associated with BMI, waist circumference, total cholesterol, C-reactive protein and leukocytes in previous studies [211-213]. In our study, we observed inverse associations between the MDS-Trichopoulou at year one and the aforementioned variables at year five, although they did not reach statistical significance.

When looking for hypothetical underlying mechanisms of our results, the richness in plant-based foods such as vegetables, fruits, nuts, legumes and EVOO, provide the Mediterranean diet with a high content of unsaturated fatty acids, dietary fiber, minerals (Ca, K, Mg), complex carbohydrates and highly bioactive compounds, which may act synergistically and beneficially by reducing oxidation and inflammation, decreasing adiposity and improving glycemic control [214,215]. This may explain the beneficial effect of high adherence to the Mediterranean diet on variables associated to the development of T2DM and the lower risk of incidence of T2DM associated with closer adherence to this dietary pattern that we observed in our population.

Finally, we found that the LFDAS at year one was inversely related with anthropometrical variables and triglycerides at year five. To our knowledge, three previous trials [86,216,217] have used the LFDAS to assess the level of adherence to a low-fat diet intervention but no one have reported results on the association of this dietary score with the aforementioned variables. Our findings may be partly explained by the quality of the low-fat diet. The reduction of total fat intake mainly from SFA, the high intake of plant-based foods (i.e. fruits, vegetables, legumes and whole grains) and replacing fatty/processed meats with lean meat and fish lead to a health dietary pattern that may have a small beneficial effect on body fatness.

PCA-dietary patterns at year 1 and anthropometric/biochemical variables at year 5

Our findings showed that the Western DP at year one was prospectively associated with deleterious effects on multiple anthropometric and biochemical parameters related to T2DM risk. In line with previous studies, we showed that this unhealthy dietary pattern was significantly associated with higher BMI and waist circumference, [218], glucose [219], triglycerides, LDL and total cholesterol [219,220], and C-reactive protein [209]. Several factors may explain the impact of the Western DP on variables associated to the development of T2DM. Western-type dietary patterns are high in refined grains, processed meats, sweets, sugar beverages and ultra-processed products and low in plant-based food, which may exacerbate inflammatory processes because of the combination of pro-inflammatory dietary elements and the relative lack of antioxidants [197]. Theses diets are also high in SFA and trans-fatty acids, mainly from processed foods, which negatively affect the blood lipid profile by increasing LDL and total cholesterol [221,222]. In addition, the high content of unhealthy fats along with refined carbohydrates tends to increase adiposity. The adverse effects of the Western DP on variables associated to the development of T2DM may thus contribute to explain our finding of increased incident T2DM risk with closer adherence to the Western DP.

In the current study, the Mediterranean DP and Low-fat DP at year one were found not associated with any of the anthropometric/biochemical variables related to T2DM risk at year five. As previously explained, it is possible that the presence in the pattern of foods with potentially deleterious effects on the outcome of interest could mask or reduce the beneficial effect of other foods. That is the case of refined grains in the Mediterranean DP and margarine/seed oils in the Low-fat DP, which had factor loadings closer to 0.30 in their respective patterns. Another factor that may contribute

to this lack of association is the amount consumed of each food and the cooking method applied to the foods, for which the PCA do not provide information.

6.3. Assessment of the validity of the dietary scores in our population

Dietary scores are useful and common tools largely used in nutritional research to evaluate diet-disease relationships, which require validation in the studied population to ensure they provide reliable and valid results. Although this seems obvious, this is not always followed in practice [223].

In this study, we compared and examined the construct validity of the MEDAS, the MDS-Trichopoulou and the LFDAS, as well as the concurrent validity of the MEDAS and LFDAS using a validated semi-quantitative FFQ as the reference method among coronary patients. Overall, the three dietary scores showed good construct validity in our context. Moreover, the MEDAS and the LFDAS displayed moderate-good concurrent validity and indicated that they are valid tools to assess adherence to the Mediterranean diet and the low-fat diet, respectively, in coronary patients.

Of all of the examined dietary scores, the MEDAS was the one with better construct and concurrent validity in our population. Although the MEDAS and the MDS-Trichopoulou showed similar and strong correlations with foods that characterize the Mediterranean diet, the latter also correlated with grains and dairy products, which can be explained by how this dietary score has been developed [102]. Unlike the MEDAS, the MSD-Trichopoulou includes all grains as a specific and single positive item, considering that both refined and whole grains have a protective health effect, perhaps because it was made reflecting the traditional Mediterranean diet wherein cereals were mainly unrefined. Dairy products are also included as specific item in the MDS-Trichopoulou but not in the MEDAS. In this sense, the great variability in the construction of Mediterranean diet scores is increasingly discussed, not only in terms of

the components included but also in the cut-offs used or the range of the score [194,224]. The MDS-Trichopoulou uses sex-specific medians as cut-off points which has the limitation of the potential lack of comparability between studies (medians are dependent on the sample characteristics). However, the MEDAS overcomes this possible limitation by using predefined goals for each of its items. The difference in the score range should also be mentioned considering that dietary scores with small range, such as the MDS-Trichopoulou, might not be sensitive enough to detect small changes in diet over time and not give good predictions when the outcome is a continuous variable [225].

In our population, the MEDAS and the LFDAS performed adequately in comparison with the scores derived from the FFQ (i.e. the MEDAS-FFQ and the LFDAS-FFQ) and our results are in line with the only study that has tested the validity of both dietary indices in the same population [226]. Nevertheless, this study included only 16 participants with heart and lung transplant in the UK and was a cross-sectional study with the impossibility to assess dietary adherence over time. We acknowledge, however, that the mean bias between the LFDAS and the LFDAS-FFQ at 5-year visit was greater than the one shown by the MEDAS and the MEDAS-FFQ at 5-year visit, indicating that the first was less accurate than the latter after dietary intervention.

The good reliability and moderate-good agreement found in our study between the MEDAS and the MEDAS-FFQ are comparable to those described in the first validation study conducted in the PREDIMED trial (r=0.52, p<0.001; ICC=0.51, p<0.001) [165] and in a subsequent validation study in an English population with high CVD risk (r=0.50, p<0.001; ICC=0.53, p<0.001) [168]. However, these studies showed worse results regarding the absolute agreement of individual component scoring between the MEDAS and the MEDAS-FFQ, with a 21.4% and 57.1% of components showing poor concordance in the PREDIMED and English validation studies, respectively. With regard to cross-classification, the MEDAS adequately ranked our

participants according to their score ratings before and after the dietary intervention. Moreover, misclassification rates in our population were lower compared to the PREDIMED study (4.2 vs. 8.6%) [165]. Concerning the Bland-Altman analysis, our results showed that the MEDAS overestimated the total score compared to the MEDAS-FFQ, confirming the results reported by Schröder et al. in the PREDIMED study [165]. This can be partly explained by the difficulty of properly estimating the two items on eating habits through the FFQ. In agreement with the other validation studies of the MEDAS mentioned above [165,168], a high level of adherence to the MEDAS was positively associated with higher intakes of nutrients and foods considered to be protective (including EVOO, vegetables, fruit, nuts, legumes, MUFA, dietary fiber and carotenes among others) and inversely associated with red meat/processed meat, commercial pastry, SSC beverages and SFA.

With respect to the LFDAS, our results showed a good reliability and moderate agreement between the administered dietary score and that calculated from the FFQ. These results are superior to those reported by Miura et al., which found a non-significant moderate correlation (r=0.42, p=0.11) and moderately good agreement (ICC= 0.44, 95% CI 0.12-0.79) between the administered and the calculated dietary scores [226]. The higher level of agreement found our study may be attributed to the large sample evaluated in our study compared to the only 16 participants assessed by Miura et al. In our study, the LFDAS adequately ranked participants according to their score ratings before and after the dietary intervention. As expected, we found that the LFDAS was positively associated with those foods that characterized a low-fat diet (i.e. low-fat dairy products, grains, vegetables and fruit) and negatively with high-fat foods.

6.4. Assessment of the validity of PCA-dietary patterns in our population

Studies reporting the relationship between empirically derived dietary patterns and different clinical outcomes, such as T2DM, have become increasingly common. However, the *a posteriori* approach is subject to several subjective decisions and therefore requires the validity of patterns.

In the present study, we identified major dietary patterns before and after a dietary intervention and addressed the validity of these patterns. Two major dietary patterns were identified at baseline using PCA. The prominent pattern, the Western DP, was characterized by processed foods and foods high in sugars and unhealthy fats. This finding is striking considering that the studied population consists of coronary patients who would have received nutritional counselling by cardiologists or primary care physicians, and highlights that many coronary patients are not able to adopt a healthier dietary pattern after suffering the coronary event [85], probably due to the lack of an effective dietary treatment with ongoing follow-up. However, the Mediterranean DP, which was characterized by the consumption of plant-based food, fish and EVOO, was the second major pattern. These two patterns identified in our population were consistent with those derived in previous studies in the Spanish population [227-229], where the two identified dietary patterns accounted for between 13 and 17% of total variance in food intake. More interesting, we were able to assess the effect of the dietary intervention in dietary habits through the PCA at year one. Two of the three identified dietary patterns were consistent with the two dietary models used in the intervention, which suggests that the comprehensive dietary intervention was effective in improving the diet quality of the coronary patients toward a more healthful dietary pattern.

In line with previous studies, we found that patients with high adherence to the Mediterranean DP also had a healthier lifestyle [228] and a higher education level [230], whereas those following the unhealthy Western DP also had an overall detrimental lifestyle characterised by decreased physical activity and smoking [231]. Moreover, younger participants were more compliant with the Western DP. A possible explanation could be that younger coronary patients are more likely to be active workers and the type of work may often condition the diet (e.g. eating away from home, shift work that alters meal times) and the attitudes and opportunities for physical activity. In this line of thought, these perceived barriers could make the change of dietary habits more difficult in coronary patients that are younger and active workers [232], which would explain the finding of a westernized dietary pattern after one year of intervention. Nevertheless, the other two identified dietary patterns were consistent with the Mediterranean and low-fat diet interventions of the CORDIOPREV study.

In the current analysis, the associations observed between PCA-dietary patterns and dietary scores provided a validation and an additional reliability of the results. The strong correlation and positive association of the Mediterranean DP with the MEDAS and MDS-Trichopoulou confirmed that they measured the same concept: the degree of adherence to a Mediterranean-type diet. As expected, the Western DP was found to be inversely associated with the three dietary scores showing that this pattern is a low-quality and not healthy dietary model. In line with our results, the study of Peñalvo et al. [233] showed an inverse association between a Western dietary pattern and four dietary scores, one of which was the MEDAS.

Finally, it is noteworthy that, through the a posteriori approach, we have been able to characterize the eating habits of coronary patients in greater detail. With the use of dietary scores, we were able to determine the level of adherence to a specific healthy dietary model but we couldn't know what type of diet had those patients with a low adherence to the dietary score. Moreover, we confirmed the consistency and

validity of PCA-dietary patterns at both baseline and after one year of intervention in our population.

6.5. Long-term dietary adherence and changes in dietary intake in the CORDIOPREV population after dietary intervention

It is well known that dietary adherence is critical to the success of a dietary intervention trial, but long-term adherence is difficult to maintain. In the present study, we evaluated 5-year changes in dietary habits, adherence achieved, and its maintenance in the total CORDIOPREV population. Our results can be summarized in two main findings: first, that it is possible to achieve and maintain a high adherence to two healthy dietary patterns in the long-term (5 years), when tailored, comprehensive dietary support is provided to patients, and second, that a high level of adherence to diet achieved after one year of intervention is easier to maintain in the long-term (5 years) with a Mediterranean diet than with a low-fat diet.

When evaluating the success of dietary intervention studies, the first step is analyzing the changes in the data from the dietary surveys (FFQs), taken from measurements of the daily intake of nutrients, food and food groups. In our study, we observed changes in the data from the FFQs of the patients in the expected direction for the assigned diet, which points to a good global adherence to the dietary models. In the low-fat diet group, it is noteworthy that although the participants live in a culture with a high consumption of olive oil and deeply-rooted dietary habits, they reduced their consumption of olive oil and adhered to a low-fat diet for 5 years. Furthermore, this group reduced their consumption of fat from 36.7±0.3% to 31.7±0.3%, which was higher than those reported in similar intervention studies. As an example, in the PREDIMED study, the low-fat diet group showed a reduction in fat intake from 39.0±0.2

to 37.0±0.2%. Moreover, extensive macro- and micronutrient analysis supports the good adherence of patients to their diets.

In our study, both the MEDAS and the LFDAS increased in the participants following the diets. Furthermore, and even more importantly, these changes were maintained in each subsequent year of follow-up and were not lost over time, doubling the number of people in the category of *High Adherence* for the Mediterranean diet group (41% to 89%) and achieving an impacting change (4% to 67%) in the low-fat diet group at 5 years of follow-up. The use of these dietary indices instead of foods or groups of foods have risen in importance, due to the accumulating evidence of their relationship to clinical data. Examples of this are two recent meta-analyses of observational and prospective studies investigating the association between adherence to the Mediterranean diet and health, which reported a 6-10% reduction in the risk of CVD (fatal or nonfatal clinical CVD event) per 2-points increase of adherence to the Mediterranean diet [92,106] Taking into account that the mean increase observed in our study was 2.5±0.1 points, our hypothesis is that it is likely to be clinically relevant.

Several factors can be linked to our results regarding the long-term maintenance of the changes in dietary adherence. A comprehensive, tailored and continuous support for lifestyle interventions, as provided in our case, has been shown to produce the best results [133]. After 1-year of intervention, our results indicate that a combination of regular contacts, group sessions, monitoring of adherence, goal setting, social support and the free provision of food was effective in changing dietary habits and increasing short-term adherence [137,234]. Furthermore, most of the changes observed at 1-year were maintained in those followed-up at 5 years, which suggests that the strategies used in our study were also useful for long-term adherence. On the other hand, the nutritional composition of the diet may influence dietary adherence. The two dietary patterns administered in our study presented the same protein content, which is described as the nutrient with the highest satiating properties. However, the

Mediterranean diet is relatively high in fat content, which makes it more palatable, satisfying and easy to maintain over time. In this sense, palatability can be one of the factors behind the 89% of participants who showed a high level of adherence to the Mediterranean diet after 5 years of dietary intervention, and the fact that those who were in the *High Adherence* at 1-year maintained this adherence at the 5-year mark. Less palatability in the low-fat diet could explain the fact that patients with high adherence at the end of the first year showed a 10% decrease in their long-term adherence.

As expected, those patients with baseline food habits which differ most from a healthy diet are likely to achieve greater dietary adherence changes. This same association has been described previously [235,236], and it would be a useful tool for quickly identifying which individuals will respond better to dietary intervention and for designing personalized intervention delivery strategies. In other words, our study shows that, in patients who have more difficulty to achieve adherence in the first year, continuing to receive dietary support can lead to a significant long-term improvement. Patients who were in the *Low Adherence* group in the first year showed the greatest improvement at 5 years, followed by those who were in the *Medium Adherence* group. It is remarkable that the participants belonging to the Mediterranean diet group who were in the *High Adherence* category in the first year were able to maintain it for another 4 years, whereas those who were in the *High Adherence* category after 1 year following the low-fat diet decreased their adherence at 5 years.

Finally, it is important to stress that the increase in adherence experienced by both intervention groups during the first year of study and the subsequent maintenance of adherence during the following 4 years of follow-up provide assurance that the intervention had a regular, measurable effect on diet and the incidence of T2DM.

6.6. Strengths of the research

Until now, limited research has been done to evaluate the relationship between diet and T2DM in patients with coronary disease. In our knowledge, this is the first study which analyzes the effect of dietary adherence in the development of T2DM in coronary patients using *a priori* and *a posteriori* dietary pattern analysis at the same time and which compares both approaches in predicting incident T2DM. The randomized design and the prospective nature of the study make possible to establish a causal association between the exposures (e.g. dietary scores and PCA-dietary patterns) and the outcomes (e.g. T2DM and anthropometric/biochemical variables related to T2DM risk). Added strengths of this analysis are the exhaustive yearly assessment of incident T2DM based on the ADA criteria [8], the detailed dietary data and the validation of the dietary scores and PCA-dietary patterns in our population. Furthermore, the large amount of socio-demographic and clinical data gathered in the CORDIOPREV study allows the consideration of many variables as potential confounders. Adjustment for a wide range of these factors makes it possible to avoid, at least in part, the possible bias attributable to confounding factors.

There are few prospective studies of diet quality and CVD outcomes in people with established CVD and these have limitations, such as being observational and measuring short-term adherence. For the first time, we address long-term adherence in a large population of patients with established CVD. Strengths of this analysis include the large number of patients (total CORDIOPREV population, n=1002) with an extended follow-up, the application of the same intensive dietary counselling in the two intervention groups, the small attrition rate and repeated measurements of dietary intake.

6.7. Limitations of the research

The research work presented in this thesis also has its limitations, which must be considered for a correct interpretation of the findings. These limitations can be placed into the following categories:

- Extrapolation of the obtained results to the general population

Our study included a population of CHD patients, who would probably be more receptive to the dietary intervention and motivated to comply with dietary counselling as they have suffered a cardiovascular event. Thus, it may not be suitable for extrapolating the results for the general population. Nevertheless, these patients are one of the populations in which dietary changes may have a higher impact on health, and, subsequently, it is worth having specific data on this population.

- Source of collection of dietary information

Although FFQs constitute to date the most practical and feasible tool to evaluate diet outcome in large epidemiological studies [237,238], they are known to contain measurement errors. However, we tried to limit this fact by using an FFQ which was validated in a Spanish population with the same characteristics as our study population [173]. Moreover, FFQs were administered by RDs who were well trained in their use and who applied a same protocol to minimize possible bias. Additionally, participants with energy intake outside of predefined limits were excluded and all analyses were adjusted for energy intake as proposed by experts in nutritional epidemiology [176].

- Reference method in the validation studies of the MEDAS and LFDAS

The only method of dietary assessment used in the CORDIOPREV study was the FFQ. Thus, it was used as the reference method to validate the MEDAS and LFDAS. FFQ has a similar design to the examined dietary scores and might result in

similar measurement errors [239]. However, there is no reference method without limitations and the long period of time evaluated by the FFQ allows capturing of habitual dietary habits and seasonal variation in food intake more accurately than other dietary assessment methods [240].

- Inherent limitations of *a priori* and *a posteriori* dietary pattern analysis

Dietary scores are based on available scientific knowledge at the moment of their development and, therefore, it may be possible that other more recent dietary scores include dietary components more appropriate for T2DM association. However, the dietary scores used in this thesis are widely used in nutritional research and have been consistently associated with decreased incident T2DM risk [109,193].

PCA is a data-driven analysis that involves arbitrary decision-making (e.g. the number and type of food groupings, numbers of factor to be retained, method of rotation and the labelling of the patterns), which can influence the patterns composition and their association with the outcome [241]. Moreover, PCA-dietary patterns are population-specific which limit their comparison among populations [48]. In order to reduce such subjectivity, foods from FFQ were grouped according to their food's nutrient profile and culinary use as made in previous studies [227,242] and establish criteria were used to derive the dietary patterns. In addition, PCA-dietary patterns in our population were consistent with those identified previously in the Spanish population. Additionally, the validity of PCA-dietary patterns in our population has been demonstrated through their comparison with dietary scores. Further, the whole process of learning and constructing dietary patterns using principal component analysis was guided and supervised by leading experts in this field [48,158,243] during the research stay at the German Institute of Human Nutrition Potsdam-Rehbruecke of the author of this thesis.

- Other factors

T2DM incidence was a secondary objective, not the primary endpoint of the CORDIOPREV study and, therefore, this work is a secondary analysis performed in a subpopulation of non-diabetics. However, the randomization process was effective in creating well-balanced and comparable intervention groups not only in the total CORDIOPREV population but also in the subgroup of non-diabetics, taking into account that baseline characteristics were similar in the two intervention group both when considering the total population and also when including only non-diabetics.

Although the analyses controlled for the main known risk factors for T2DM, residual confounding cannot be completely excluded.

6.8. Future lines of research

T2DM is a complex and chronic disease that can be prevented through lifestyle changes highlighting the role of a healthy dietary pattern. Results from the present research add further scientific evidence to understand the role that dietary adherence plays on the prevention of T2DM in coronary patients, highlighting that it is the most significant factor for long term success of any healthy dietary recommendation.

The research carried out during the doctoral period has generated a large volume of results and only part of them has been included in this doctoral thesis. As future work, we plan to continue working on those results and address the following aspects:

- Use of biomarkers of compliance to confirm the results obtained from the FFQs: the self-reported diet has been used in all the methods of dietary pattern analysis included in this thesis and we know that this is limited by a systematic measurement error. Thus, we are currently analysing the correlation between dietary data and

different biomarkers of compliance (plasma fatty acids and urinary hydroxytyrosol) in different time points of the follow-up.

- The relative importance of the individual components that comprise the MEDAS on T2DM risk: in light of the association between the MEDAS and the incidence of T2DM, investigation of the relative contribution of each item of the dietary score to this association is warranted.

- Major contributors to the Western DP and T2DM risk: to further explore the association between the Western dietary pattern and T2DM risk, we also plan to evaluate intakes of food groups that characterize this pattern in relation to T2DM risk.

- Analysis of the data adjusting for multiple medications: the population included in this work are coronary patient medicated with lipid-lowering drugs, diuretics and antiplatelets, among other medications. It is known that high-intensity statin doses have been linked with an increased risk development of T2DM, but other drugs or their doses could also influence our results. Although all of our analyses were adjusted for the use of statins, we plan to reanalyze our results controlling for different medications and doses as a covariate.

- Examining the prediction of the incidence of T2DM beyond the 5 years, and even beyond the dietary intervention: legacy studies (those examining the effects of a given intervention after its end) are a current hot topic in nutrition and metabolic studies. The creation of the Cordioprev-long term cohort will allow us to evaluate the legacy effects of the dietary intervention through the pass of time.

VII. CONCLUSIONS

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Main conclusion

The MEDAS (*a priori* analysis) and the PCA (*a posteriori* analysis) are the methods that captured the strongest relationship between the dietary intervention and long-term T2DM incidence (5 years) among all *a priori* and *a posteriori* methods evaluated in this Thesis. When they are use after a stabilization period of one year, both methods provide reliable, accurate results, supported by internal validation.

Secondary conclusions

1. Our results show that, in coronary patients participating in a dietary intervention trial, high adherence to a Mediterranean-type diet, reflected by the MEDAS and achieved after one year of intervention, was associated with an important reduction in the risk for T2DM and with healthier values of anthropometric and biochemical parameters related to T2DM risk.

2. In our population, closer adherence to a Western-type dietary pattern after one year of intervention was associated with long-term increased risk of developing T2DM and with detrimental effects on waist circumference, BMI, glucose, lipid profile and inflammatory markers.

3. We have validated the MEDAS and the LFDAS in coronary patients (the entire population of the CORDIOPREV study). This demonstrates that they are valid tools for rapidly assessing dietary adherence in coronary patients and that they could be used in clinical practice.

4. A comprehensive dietary intervention results in an overall long-term improvement and maintenance of adherence to the Mediterranean and low-fat diets. In our population, the Mediterranean diet group achieved a higher level of adherence than the low-fat diet group at long-term.

VIII. REFERENCES

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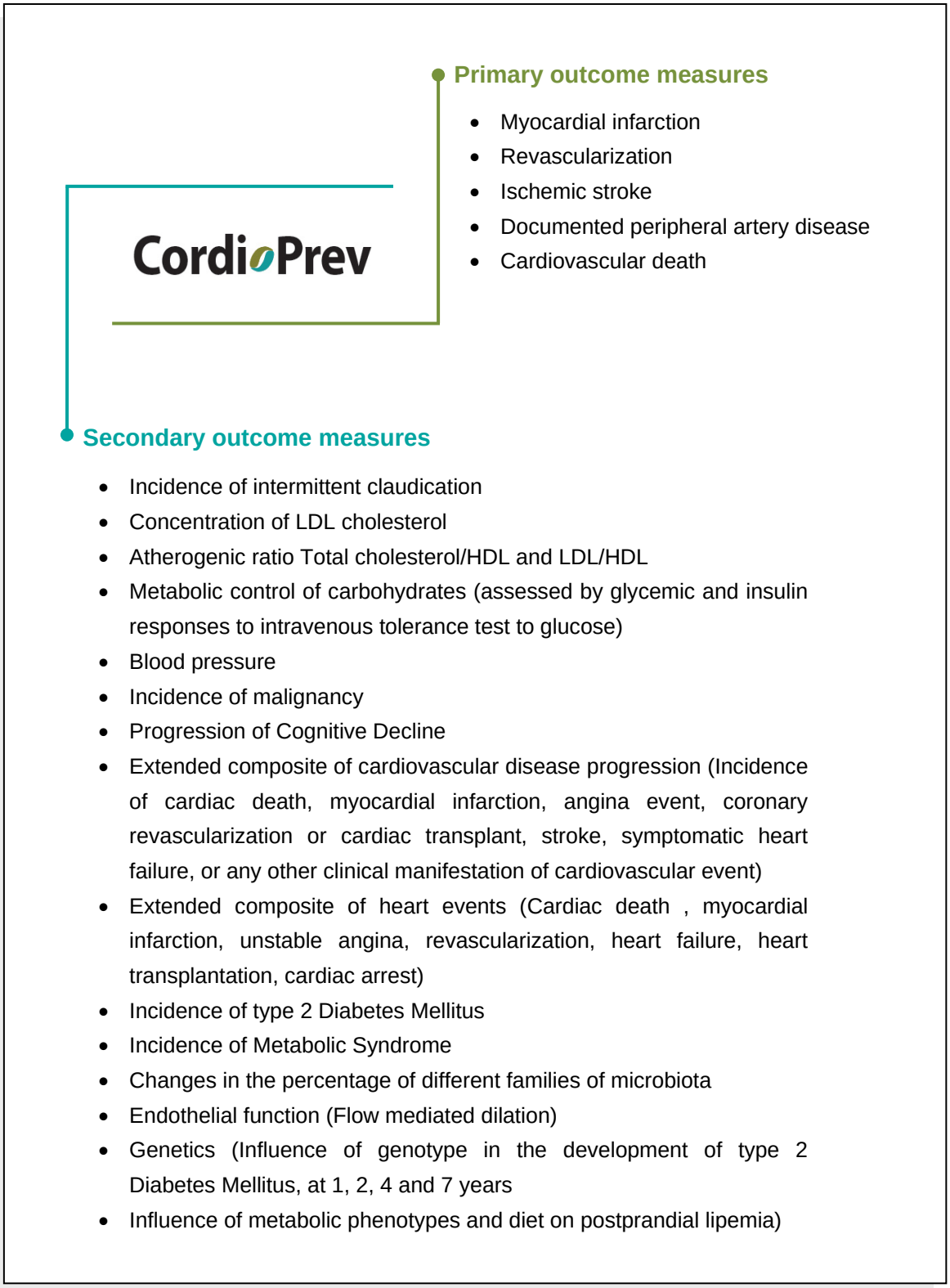
IX. APPENDICES

APPENDIX I

Primary and secondary outcomes of the CORDIOPREV study



APPENDIX II

Inclusion and exclusion criteria for CORDIOPREV study.

Adapted from Delgado-Lista J et al. [87]

Inclusion criteria

1. **Informed consent** → all participants will agree to being included in the study by signing the protocol approved by the Reina Sofia University Hospital Clinical Research Ethics Committee.
2. **Diagnostic criteria** → the patients were selected with acute coronary syndrome (unstable angina, acute myocardial infarction) and high-risk chronic CHD according to the following criteria:

   a) Acute myocardial infarction: The existence of at least 2 of the following 3 signs: angina-type chest pain (or anginal equivalents), typical ECG changes (appearance of new Q waves and/or changes in ST segments and/or T waves), and a rise in myocardial enzymes (creatine phosphokinase and/or creatine phosphokinase/MB more than twice the normal laboratory limits). The MB value criterion will prevail in case of discrepancies over the total creatine phosphokinase.

   b) Unstable angina: Admission to hospital for angina-type chest pains lasting at least 15 min, both at rest and after exercise, which have increased in frequency and duration in recent days or weeks. The latest episode must have occurred at least 48h before admission and must be accompanied by at least 1 of the following parameters: ST depression of at least 0.5 mm in 2 contiguous leads or ST elevation of at least 1 mm in 2 contiguous leads or T-wave inversion of at least 2 mm in 2 contiguous leads or positive troponin result.

   c) Chronic high-risk ischemic heart disease: patients who have been hospitalized for a coronary event and/or stable angina at least once in the past 2 years and who have undergone diagnostic coronary angiography with evidence of severe coronary disease (an epicardial vessel greater than 2.5 mm in diameter with stenosis of >50%).

Exclusion criteria

1. Patients younger than 20 years or older than 75 years old, or with a life expectancy <5 year.
2. Severe heart failure, NYHA functional class III or IV, with the exception of self-limited episodes of acute heart failure at the time of the acute ischemic event.
3. Severe left ventricular systolic dysfunction (with ejection fraction ≤35%).
4. Patients unable to follow the prescribed diet for whatever personal or family circumstances.
5. Hypertension and diabetes with organ involvement limiting survival (chronic renal failure with creatinine which is persistently >2.5 mg/dL) and disabling clinical manifestations of cerebral atherosclerosis.
6. Chronic diseases unrelated to coronary risk: severe psychiatric illnesses, chronic renal failure, chronic liver disease, neoplasia under treatment, chronic obstructive pulmonary disease involving respiratory pulmonary failure with home oxygen therapy, endocrine diseases susceptible to decompensation and diseases of the digestive tract that involve episodes of diarrhea).
7. Patients taking part in other studies at the time of selection or up to 30 days before.

APPENDIX III

Description of dietary recommendations to the CORDIOPREV patients in the two intervention groups

MEDITERRANEAN DIET GROUP		
Food	**Recommendations***	
Extra-virgin olive oil	≥4 tablespoons/day	1 tablespoons=10-15g The amount of olive oil includes oil used for cooking, dressing and out house meal
Fruit	≥3 servings/day	1 serving=150g Fresh fruit and natural fruit juices
Vegetables	≥2 servings/day	1 serving=200g At least 1 serving raw or as salad
Grains	6 servings/day	1 serving=1 slice of bread; ½ cup of cooked pasta, rice or oatmeal Preferably whole grains
Dairy	2 servings/day	1 serving= 1 cup of milk or yogurt or fresh cheese
Legumes	≥3 servings/week	1 serving of legumes=150g cooked
Tree nuts	≥3 servings/week	1 serving=30g Raw nuts, non-roasted or fried
Fish and seafood	≥3 servings/week	1 serving=150g Especially oily fish
White meat	≈2 servings/week	1 serving=100-150g Consume of white meat (chicken, turkey, rabbit) instead of red meat. Remove skin and visible fat
Red and processed meats	<1 servings/ week	Red meats: 1 serving=100-150g Processed meats: 1 serving=60g
Eggs	2-4 units/week	
Commercial bakery products, sweets and pastries	≤1 servings/week	1 serving=50g Commercial bakery, sweets and pastries (not homemade) included cakes, cookies, and custard
Fat spread	NO	Fat spread refers to butter and margarine
Wine	≥7 glasses/week	1 glass=100ml Optional consumption, only in case of habitual wine drinker (1glass/day for women, 2 glass/day for men)
Sweet/carbonated beverages	<1 drink/day	1 drink=200ml
Sofrito	≥2 times/week	*Sofrito* is a sauce made with tomato and onion, often including garlic and aromatic herbs, and slowly simmered with olive oil

LOW FAT DIET		
Food	**Recommendations***	
Vegetable oils	<2 tablespoons/day	1 tablespoons=10-15g Vegetable oils refers to sunflower oil and regular olive oil
Fruit	≥3 servings/day	1 serving=150g Fresh, frozen, canned, dried
Vegetables	≥2 servings/day	1 serving=200g Fresh, frozen, or canned, without added fat, sauce, or salt
Grains, legumes and potatoes	6-11 servings/day	1 serving=1 slice of bread; ½ cup of cooked pasta, rice or legumes; 1 medium boiled potato
Dairy	2-3 servings/day	1 serving= 1 cup of milk or yogurt or fresh cheese Choose low-fat or fat-free dairy products
Tree nuts	Occasional consumption	1 serving=30g Raw nuts, non-roasted or fried
Meat, poultry and fish	1 serving/day	1 serving=150g Choose skinless poultry and lean cuts loin, round; Choose white fish. Limit oily fish and seafood canned in oil (≤1serving/week)
Red and processed meats	≤1 servings/week	Red meats: 1 serving=100-150g Processed meats: 1 serving=60g
Eggs	2-4 units/week	≤2 egg yolks per week
Commercial bakery products, sweets and pastries	≤1 servings/week	1 serving=50g Commercial bakery, sweets and pastries (not homemade) included cakes, cookies, custard and skimmed ice cream
Fat spread	≤1 servings/week	Fat spread refers to butter and margarine
Wine	NO	
Sweet/carbonated beverages	<1 drink/day	1 drink=200ml
Culinary techniques	• Use low fat cooking methods (broiling, grilling, roasting, baking, microwaving, poaching and steaming), avoid frying and *sofrito* • Remove the visible fat (or the skin) of meats before cooking • Remove the fat beads that form on the top layer of soups and broths • Season food with herbs, spices, lemon juice or vinegar	

* Examples of amount of each food are presented for a 2.000 kcal diet. Amount of food was personalized and adjusted to patient's caloric intake

APPENDIX IV

Food groups used in the principal components analysis (PCA)

Food group	Food items included
1. Eggs	Chicken eggs
2. Offal	Beef, pork or chicken liver, brains, heart, and gizzard
3. Red meat	Beef/cow meat, pork loin/sirloin, pork chops/ribs, and lamb meat
4. Processed meat	Cured ham, cooked ham, salami, sausages, chorizo, pork liver pate, hamburgers, meatballs, and bacon
5. Poultry	Chicken/turkey with skin, chicken/turkey without skin, and rabbit
6. White fish	White fish (grouper, hake, whiting, cod and other similar fish)
7. Oily fish	Oily fish (sardine, tuna, albacore, mackerel, salmon and other similar fish), fish canned in water and fish canned in oil
8. Seafood/canned fish	Clams, oyster, mussel and similar; squid, octopus and baby squids; shrimp, prawn, lobster and similar
9. Low-fat dairy products	Semi-skimmed milk, skimmed milk, skimmed yogurt, curd and cottage, fresh cheeses, and skim-milk cheeses
10. Whole-fat dairy products	Whole milk, condensed milk, cream and single cream, whole yogurt, French cream cheese, melting cheese, hard and semi-hard cheeses
11. Refined bread	White bread
12. Whole bread	Whole wheat bread
13. Refined grains	White rice, white pasta, breakfast cereals
14. Whole grains	Brown rice, whole pasta, whole breakfast cereals
15. Boiled/baked potatoes	Boiled or baked potatoes
16. Fried potatoes	Home-made fried potatoes/French fries
17. Legumes	Green beans, lentils, white/red beans, chick-peas, broad beans and peas
18. Nuts	Walnuts , almonds, peanuts, hazelnuts, pistachios and pine nuts
19. OO	Other olive oils different from EVOO
20. EVOO	Extra- virgin olive oil
21. Vegetables	Spinach, chard, lettuce, endives, escarole, eggplant, zucchini, cucumber, tomato, peppers, carrot, pumpkin, cabbage, cauliflower, broccoli, onion, fresh garlic, asparagus, mushrooms, champignon, artichoke, leek, cardoon and celery
22. Vegetable recipes	Traditional Spanish recipes (*gazpacho, picadillo* and *salmorejo)*

23. Fresh fruits	Oranges, tangerines, banana, apple, pear, strawberries, cherries, plums, peach, apricot, nectarine, watermelon, melon, kiwi and grapes
24. Juice, canned or dried fruit	Canned fruits, dried fruits (dates, dried figs, raisins, dried plums), fresh orange juice and other fresh fruit juices
25. Margarine and seed oils	Margarine, corn oil, sunflower oil, soybean oil and mixture of oils
26. Animal fats	Butter, lard
27. Sweets	Sugar, jam, honey, nougat, marzipan and soluble cocoa
28. Pastries	Biscuits, whole-grain biscuits, chocolate cookies, croissant, ensaimada, tea cookies, pastries, donut, muffins, cakes and pies, churros and chocolate
29. Sweet/carbonated beverages	Sweet/carbonated beverages: Cola, soda and tonic drinks, light cola drinks and canned juices
30. Wines	Grape must, rosé wine, sweet wine, red wine, white wine and cava
31. Beer	Regular beer, alcohol-free beer
32. Spirits	Liquors, Whisky, vodka, gin and rum
33. Sauces	Mustard, mayonnaise, fried tomato sauce and ketchup
34. Processed meals/Snacks	Ready meals, dry soups, potatoes crisps/chips, popcorn, nachos, and honey roasted peanuts
35. Coffee	Coffee
36. Tea	Tea

APPENDIX V

MEDAS items and transfer of food intake data from the FFQ into its food groups

MEDAS item		Data from the FFQ used to calculate MEDAS food groups	
		FFQ items	How to calculate MEDAS food group
1.	Olive oil as main culinary fat	93. Olive oil 94. Extra-virgin olive oil (EVOO) 96. Corn oil 97. Sunflower oil 98. Soybean oil 99. Mixture of oils 100. Margarine 101. Butter 102. Lard 5. Cream	Total olive oil (g) = Olive oil (g) + EVOO (g) Total other fats (g) = corn oil (g) + sunflower oil (g) + soybean oil (g) + mixture of oils (g) + margarine (g) + butter (g) + lard (g) + cream (g) 1 point given: if total olive oil (g) > total other fats (g)
2.	Olive oil ≥ 4 tablespoons/day	93. Olive oil 94. Extra-virgin olive oil (EVOO)	Total olive oil (g) = olive oil (g) + EVOO (g) Total olive oil (tablespoons/day) = Total olive oil (g)/10 1 point given: if total olive oil ≥ 4 tablespoons/day
3.	Vegetables ≥ 2 servings/day	44. Chard, spinach 45. Cabbage, cauliflower, broccoli 46. Green beans 47. Eggplant, zucchini 48. Carrot, pumpkin 49. Lettuce, endives, escarole 50. Tomato 51. Peppers 52. Onion 53. Garlic 54. Asparagus 55. Mushrooms, champignon 56. Artichoke, leek, cardoon, celery 61. Gazpacho* 62. Sofrito* 63. Picadillo* 64. Salmorejo*	Total vegetables (g) = chard, spinach (g) + cabbage, cauliflower, broccoli (g) + green beans (g) + eggplant, zucchini (g) + carrot, pumpkin (g) + lettuce, endives, escarole (g) + tomato (g) + peppers (g) + onion (g) + garlic (g) + asparagus (g) + mushrooms, champignon (g) + artichoke, leek, cardoon, celery (g) + gazpacho (g) + sofrito (g) + picadillo (g) + salmorejo (g) Total vegetables (servings/day) = Total vegetables (g) /200 1 point given: if total vegetables ≥ 2 servings/day
4.	Fruits ≥ 3 servings/day	65. Oranges, tangerines 66. Banana 67. Apple, pear 68. Strawberries 69. Cherries, plums 70. Peach, apricot, nectarine 71. Watermelon 72. Melon 73. Kiwi 74. Grapes 130. Fresh orange juice 131. Fresh fruit juices	Total fruits (g) = oranges, tangerines (g) + banana (g) + apple, pear (g) + strawberries (g) + cherries, plums (g) + peach, apricot, nectarine (g) + watermelon (g) + melon (g) + kiwi (g) + grapes (g) + fresh orange juice (g) + fresh fruit juices (g) Total fruits (servings/day) = total fruit (g)/150 1 point given: if total fruits ≥3 servings/day

5.	Red meat, hamburger, or meat products <1serving/day	23. Beef, cow meat 24. Pork loin/sirloin 25. Pork chops/ribs 26. Lamb meat 30. Cured ham 31. Cooked ham 32. Processed meats: sausages, salami, chorizo 33. Pork liver pate 34. Hamburgers, meatballs 35. Bacon	Total red meat (g) = beef, cow meat (g) + pork (g) + lamb meat (g) Total red meat (servings/day) = total red meat (g)/125 Total processed meat products (g) = cured ham (g) + cooked ham (g) + processed meats (g) + pork liver pate (g) + hamburger, meatballs (g) + bacon (g) Total processed meat products (servings/day) = total processed meat products (g)/60 Total red/processed meat (servings/day) = total red meat (servings/day) + total processed meat products (servings/day) 1 point given: if total red/processed meat <1 serving/day
6.	Butter, margarine, or cream <1serving/day	100. Margarine 101. Butter 5. Cream	Butter, margarine, cream (g) = Butter (g) + margarine (g) + cream (g) Butter, margarine, cream (servings/day) = butter, margarine, cream (g)/12 1 point given: if butter, margarine, cream <1serving/day
7.	Sweet/carbonated beverages <1serving/day	128. Cola, soda, tonic drinks 129. Light cola drinks 130. Commercial juices	Total sweet/carbonated beverages (g) = cola, soda, tonic drinks (g) + light cola drinks (g) + commercial juices (g) Total sweet/carbonated beverages (servings/day) = total sweet/ carbonated beverages (g)/200 1 point given: if total sweet/carbonated beverages <1serving/day
8.	Wine ≥7glasses/week	137. Rosé wine 138. Sweet wine 139. Red wine “joven” 140. Red wine “crianza” 141. White wine	Total wine (ml) = rosé wine (ml) + sweet wine (ml) + red wine “joven” (ml) + red wine “crianza” (ml) + white wine (ml) Total wine (glasses/week) = total wine (ml)/100*7 1 point given: if total wine ≥7 glasses/week
9.	Legumes ≥3 servings/week	80. Lentils 81. White/red beans 82. Chick-peas 83. Broad beans	Total legumes (g) = lentils (g) + white/red beans (g) + chick-peas (g) + broad beans (g) Total legumes (servings/week) = total legumes (g)/60*7 1 point given: if total legumes ≥3 servings/week

10.	Fish or shellfish ≥3 servings/week	36. White fish: grouper, hake, whiting, cod 37. Oily fish: sardine, tuna, mackerel, salmon 38. Cured fish 39. Clams, oyster, mussel and similar 40. Squid, octopus, baby squids 41. Shrimp, prawn, lobster 42. Fish canned in water 43. Fish canned in oil	Total fish (g) = white fish (g) + oily fish (g) + cured fish (g) + canned fish (g) Total fish (servings/week) = total fish (g)/125*7 Total seafood (g) = clams, oyster, mussel (g) + squid, octopus (g) + shrimp, prawn, lobster (g) Total seafood (servings/week) = total seafood (g)/200*7 Total fish/seafood (servings/week) = total fish (servings/week)+ total seafood (servings/week) 1 point given: if total fish/seafood ≥3 servings/week
11.	Commercial (not homemade) pastry, such as cake, cookies, biscuits, or custard <2 servings/week	103. Biscuits 104. Whole-grain biscuits 105. Chocolate cookies 107. Croissant, tea cookies, pastries 108. Donut 109. Muffins 110. Cakes and pies 111. Churros 112. Chocolate 114. Nougat 115. Marzipan and Christmas sweets 15. Custard	Total commercial pastry (g) = biscuits (g) + whole-grain biscuits (g) + chocolate cookies (g) + pastries (g) + donut (g) + muffins (g) + cakes (g) + churros (g) + chocolate (g) + nougat (g) + marzipan (g) + custard (g) Total commercial pastry (servings/week) = total commercial pastry (g) /50*7 1 point given: if total commercial pastry <2 servings/week
12.	Nuts ≥3 servings/week	78. Almonds, peanuts, hazelnuts, pistachios, pine nuts 79. Walnuts	Total nuts (g) = almonds, peanuts, hazelnuts, pistachios, pine nuts (g) + walnuts (g) Total nuts (servings/week) = total nuts (g)/30*7 1 point given: if total nuts ≥3 servings/week
13.	Poultry more than red/processed meats	21. Chicken, turkey with skin 22. Chicken, turkey without skin 23. Beef, cow meat 24. Pork loin/sirloin 25. Pork chops/ribs 27. Rabbit 32. Processed meats: sausages, salami, chorizo 34. Hamburgers, meatballs	Total poultry (g) = chicken, turkey with skin (g) + chicken, turkey without skin + rabbit (g) Total red/processed meat (g) = beef, cow meat (g) + pork loin/sirloin (g) + pork chops/ribs (g) + sausages, salami, chorizo (g) + hamburger (g) 1 point given: if total poultry (g) > total red meat (g)
14.	Use of *sofrito* sauce ≥2 times/week	62. Sofrito*	Sofrito (servings/week) = sofrito (g) /75*7 1 point given: if *sofrito* ≥2 servings/week

g, grams/day

*_Gazpacho_* is a classic dish of Spanish cuisine originally from Andalusia. It is a cold soup made with tomato, green pepper, cucumber, garlic, olive oil, vinegar, water and salt; *Sofrito* is a homemade sauce with garlic, onion, aromatic herbs and tomato slow-cooked in olive oil. It is used as a base in Spanish cooking; *Picadillo* is a typical Andalusian dish, a salad of tomato, green pepper and onion, dressed with a good quality olive oil; *Salmorejo* is a classic Andalusian dish originally from Cordoba. It is a cold cream based on tomato, bread, garlic and good quality olive oil. We only considerer the vegetables ingredients of these dishes in calculating the total vegetable (item 3)

APPENDIX VI

LFDAS items and transfer of food intake data from the FFQ into its food groups

LFDAS item		Data from FFQs used to calculate LFDAS food groups	
		FFQ items	How to calculate LFDAS food group
1.	Total daily oil ≤20ml	95. Olive oil 96. Extra-virgin olive oil (EVOO) 103. Corn oil 104. Sunflower oil 105. Soybean oil 106. Mixture of oils	Total oil (ml) = Olive oil (ml) + EVOO (ml) + corn oil (ml) + sunflower oil (ml) + soybean oil (ml) + mixture of oils (ml) 1 point given: if total oil (ml) ≤20ml
2.	Remove visible fat or the skin of meats before cooking	26. Chicken, turkey with skin 27. Chicken, turkey without skin 28. Beef, cow meat 29. Pork loin/sirloin 30. Pork chops/ribs 31. Lamb meat 28. Rabbit	Total skinless meat and lean meat (g) = chicken, turkey without skin (g) + pork loin/sirloin (g) + rabbit (g) Total meat with skin and fatty meat (g) = chicken, turkey with skin (g) + beef, cow meat (g) + pork chops/ribs (g) + lamb meat (g) 1 point given: if total skinless meat and lean meat (g) > total meat with skin and fatty meat (g)
3.	Fatty/processed meats ≤1 serving/week	27. Beef, cow meat 25. Pork chops/ribs 26. Lamb meat 28. Liver (beef, pork, chicken) 29. Other offal (brains, heart, gizzard) 36. Cured ham 37. Cooked ham 38. Processed meats: sausages, salami, chorizo 39. Pork liver pate 40. Hamburgers, meatballs 57. Bacon	Total fatty meats (g) = beef, cow meat (g) + pork chops/ribs (g) + lamb meat (g) Total processed meats (g) = offal (g) + cured ham (g) + cooked ham (g) + processed meats (g) + pork liver pate (g) + hamburgers, meatballs (g) + bacon (g) Total fatty/processed meats (serving/week) = [total fatty meats (g)/100*7] +[total processed meats (g)/30*7] 1 point given: if total fatty/processed meats ≤1 serving/week
4.	Spread fat, mayonnaise and ice cream ≤1 serving/week	102. Margarine 103. Butter 104. Lard 119. Mayonnaise 5. Cream 16. Ice cream	Total spread fat, mayonnaise and ice cream (servings/week) = [margarine (g) + butter (g) + lard (g)/12*7] + [mayonnaise (g)/20*7] + [cream (g) + ice cream (g)/100*7] 1 point given: if total fruits ≥3 servings/day

5.	Low-fat dairy products	1. Whole milk 6. Milkshakes 7. Whole yogurt 11. Melting cheese 12. Hard and semi-hard cheeses	Total full-fat dairy products (g) = whole milk (g) + milkshakes (g) + whole yogurt (g) + melting cheese (g) + hard and semi-hard cheeses (g) 1 point given: if total full-fat dairy products = 0g
6.	Sofrito ≤2 times/week	62. Sofrito*	Sofrito (servings/week) = sofrito (g)/75*7 1 point given: if *sofrito* ≤2 servings/week
7.	Oily fish or seafood canned in oil ≤1 time/week	37. Oily fish: sardine, tuna, mackerel, salmon 43. Fish canned in oil	Total oily fish or seafood canned in oil (servings/week) = [oily fish (g)/125*7] + [fish canned in oil (g)/30*7] 1 point given: if total oily fish or seafood canned in oil ≤1 serving/week
8.	Total commercial sweets/pastries ≤1 serving/week	106. Biscuits 107. Whole-grain biscuits 108. Chocolate cookies 113. Croissant, tea cookies, pastries 114. Donut 115. Muffins 116. Cakes and pies 117. Churros 118. Chocolate 116. Nougat 117. Marzipan and Christmas sweets 15. Custard	Total commercial sweets/pastries (servings/week) = [biscuits (g) + whole-grain biscuits (g) + chocolate cookies (g) + chocolate (g) + nougat (g) + marzipan (g)/40*7] + [pastries (g) + donut (g) + muffins (g) + cakes (g) + churros (g)/80*7] + [custard (g)/130*7] 1 point given: if total commercial sweets/pastries <2 servings/week
9.	Nuts and commercial snacks ≤1 serving/week	80. Almonds, peanuts, hazelnuts, pistachios, pine nuts 84. Walnuts 58. Chips 127. Popcorn, honey roasted peanuts, nachos	Total nuts and commercial snacks (servings/week) = [almonds, peanuts, hazelnuts, pistachios, pine nuts (g) + walnuts (g)/30*7] + [chips (g) + popcorn, honey roasted peanuts, nachos (g)/50*7] 1 point given: if total nuts and commercial snacks ≤1 serving/week

g, grams/day

* *Sofrito* is a homemade sauce with garlic, onion, aromatic herbs and tomato slow-cooked in olive oil. It is used as a base in many Spanish dishes.

APPENDIX VII

Baseline characteristics of the 1002 patients of the CORDIOPREV study according to intervention group

	All patients (n=1002)	Mediterranean diet group (n=502)	Low-fat diet group (n=500)	*p* value
Socio-demographic characteristics				
Sex (% male)	82.5	82.5	82.6	0.957
Age (years)	59.5±0.2	59.7±0.4	59.5±0.4	0.696
Education level (%)[a]				
Higher education	8.2	9.3	7.0	0.556
Secondary education	20.4	20.7	20.1	
Primary education	55.3	53.7	57.0	
None	16.1	16.3	15.9	
Clinical and lifestyle characteristics				
BMI (kg/m^2)[b]	31.1±0.1	31.0±0.1	31.2±0.2	0.647
Waist circumference (cm)	105.1±0.3	104.9±0.5	105.4±0.5	0.579
Overweight (%)[b]	37.5	39.2	35.4	0.209
Obesity (%)[b]	56.5	54.4	58.0	0.249
Abdominal obesity (%)[c]	68.5	69.1	67.8	0.652
Diabetes (%)[d]	53.9	51.0	56.8	0.065
Hypertension (%)[e]	68.5	69.2	67.9	0.604
Fasting glucose (mg/dL)	113.7±1.2	114.7±1.8	112.8±1.6	0.431
HbA1c (%)	6.7±0.04	6.6±0.1	6.7±0.1	0.596
HDL cholesterol (mg/dL)	42.2±0.3	42.3±0.5	42.1±0.5	0.813
LDL cholesterol (mg/dL)	88.5±0.8	88.9±1.2	88.2±1.1	0.644
Triglycerides (mg/dl)	135.4±2.2	134.8±3.1	136.0±3.2	0.786
Treatment with statins (%)	85.6	84.9	86.4	0.487
Current smokers (%)	9.7	8.7	10.7	0.264
Physical Activity (METs-h/week)[f]	21.4±0.7	21.5±1.0	21.3±0.9	0.867

Data are shown as mean±SEM or percentage of participants, unless otherwise stated. We used unpaired *t* tests for quantitative variables and chi squared tests for categorical variables. T2DM, type 2 diabetes; BMI, body mass index; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment-insulin resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein. [a]Data were available for 447 patients. [b]BMI was calculated as weight in kg divided by the square of height in m (kg/m^2). BMI ≥25 and <30: overweight. BMI ≥30: obese. [c]Abdominal obesity was defined as waist circumference >102 cm in men and >88 cm in women. [d]Diabetes was defined as being diagnosed as diabetic before the start of the study (350, 34.9%) and those diagnosed by a fasting blood glucose level ≥126 mg/dL on two occasions, or a 2-hour plasma glucose level ≥200 mg/dL during a 75-g oral glucose-tolerance test, during the first procedures of the study. [e]Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg, a diastolic blood pressure ≥ 90 mm Hg, or the use of antihypertensive therapy. [f]METs-h/week=metabolic equivalents of weekly leisure time physical activities.

X.SCIENTIFIC CONTRIBUTIONS

Main publication derived from the present work

Long-term dietary adherence and changes in dietary intake in coronary patients after intervention with a Mediterranean diet or a low-fat diet: the CORDIOPREV randomized trial

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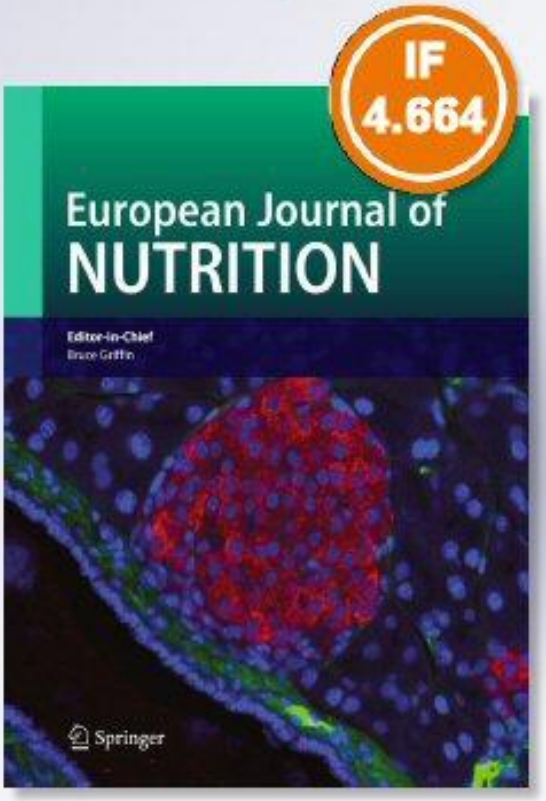

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ORIGINAL CONTRIBUTION

Long-term dietary adherence and changes in dietary intake in coronary patients after intervention with a Mediterranean diet or a low-fat diet: the CORDIOPREV randomized trial

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Abstract

Purpose Adherence to a healthy dietary pattern positively influences clinical outcomes in cardiovascular prevention, but long-term adherence is difficult to maintain. We evaluated 5-year changes in dietary habits, adherence achieved, and its maintenance in a cohort of coronary patients from the CORDIOPREV study.

Methods 1002 coronary patients were randomized to a Mediterranean diet ($n=502$) or a low-fat diet ($n=500$) and received individual-group-telephone visits and personalized dietary advice. A validated food-frequency questionnaire, a 14-point Mediterranean diet adherence screener, and a 9-point low-fat diet adherence score were used. Dietary adherence was categorized into *Low*, *Medium*, and *High Adherence*. Changes in nutrient intake, food consumption, and adherence were analyzed on a yearly basis. The maintenance of long-term dietary adherence was evaluated using data after the first year and fifth year.

Results From baseline to 5 years, significant increases were observed in overall dietary adherence (Mediterranean diet from 8.9 to 11.4; low-fat diet from 3.9 to 7.1) and in the percentage of patients considered *High Adherence* (Mediterranean diet from 41 to 89%; low-fat diet from 4 to 67%). When we evaluated the maintenance of adherence, patients considered *Low* and *Medium Adherence* at 1 year increased their adherence at the 5 years with both diets and patients considered *High Adherence* maintained their adherence with a Mediterranean diet, but decreased their adherence with a low-fat diet.

Conclusions A comprehensive dietary intervention results in an overall long-term improvement and maintenance of adherence to the Mediterranean and low-fat diets. In our population, the Mediterranean diet group achieved a high level of adherence in the short term which was maintained in the long term.

Keywords Dietary adherence · Long-term dietary adherence · Mediterranean diet · Low-fat diet · Secondary cardiovascular prevention · Dietary intervention

Background

Cardiovascular diseases (CVD) are the leading cause of global death, and coronary heart disease (CHD) is one of the commonest preventable forms of CVD [1]. Like other chronic diseases, CVD require lifelong treatment and lasting changes in lifestyle with a focus on diet management. A healthy diet, therefore, plays an important role both in the prevention and in the treatment of CVD.

Strong evidence on the effectiveness of the Mediterranean diet for managing cardiovascular risk factors in primary prevention is available, highlighting the results

Gracia Maria Quintana-Navarro and Juan Francisco Alcala-Diaz have contributed equally to this work.

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from the PREDIMED study. This landmark randomized primary prevention trial showed that the Mediterranean diet provides long-term high benefits on CVD compared with a low-fat diet [2]. However, no consensus about the best dietary pattern for the secondary prevention of CHD has been reached. The CORDIOPREV (CORonary Diet Intervention with Olive oil and cardiovascular PREVention) study is an ongoing dietary intervention trial comparing the rate of cardiovascular events of two healthy dietary patterns for secondary cardiovascular prevention [3]. One of them is low in fat and rich in complex carbohydrates, as proposed by the National Cholesterol Education Program and the American Heart Association [4]. The other is a Mediterranean diet, rich in extra-virgin olive oil, fruit and vegetables, whole grains, fish, and nuts, and low in saturated fats, which has consistently demonstrated favorable effects on cardiovascular risk factors in patients in secondary prevention, but not consistently in cardiovascular events trials [5–9].

Beyond the choice of diet, one key element for the success of interventions is the participants' adherence to the diet, especially in free-living settings and in long-term follow-up [10, 11]. Thus, poor adherence and the difficulty of maintaining dietary changes are the main barriers to the long-term success of dietary interventions.

Dietary adherence, defined as the extent to which a participant's diet corresponds with the assigned dietary pattern in the trial, implies active participant involvement [12] and depends not only on the characteristics of the participant but also on the study features. However, few studies have identified which factors are the best predictors of long-term adherence [13, 14].

A good initial dietary adherence followed by gradual decreases over time is frequently observed when only dietary instructions are given [15]. However, the use of strategies to change dietary behavior such as regular contact, negotiation, goal setting, monitoring of adherence and assistance, problem-solving, and the free provision of key food items leads to enhanced dietary adherence [15–19]. Besides, the use of adherence diet screeners, simple tools which summarize the overall diet with a single score, not only allows us to measure the level of dietary adherence easily but also provides immediate feedback to the participants, thus enhancing goal achievement and increasing the effectiveness of the intervention.

Data on long-term dietary changes and dietary adherence in coronary patients are scarce. Our aim, therefore, was to investigate the dietary changes and address both the level of adherence and its long-term maintenance in coronary patients following a Mediterranean diet versus a low-fat diet over a period of 5 years.

Methods

Study design

The present analysis was conducted within the frame of the CORDIOPREV study. Full details of the design and methods have been reported previously [3]. Briefly, the CORDIOPREV study is an ongoing randomized, single-blind, controlled, cardiovascular secondary prevention trial that aims to compare the effects of a Mediterranean-type diet and a low-fat diet on the risk of suffering new cardiovascular events. The primary outcome is a composite of cardiovascular events, including myocardial infarction, revascularization, ischemic stroke, documented peripheral artery disease, and cardiovascular death events. The data used in this study are from the first 5 years of follow-up.

The study was registered at ClinicalTrials.gov (number NCT00924937). The study protocol was approved by the Human Investigation Review Committee of the Reina Sofia University Hospital, according to institutional and Good Clinical Practice guidelines.

Study population

The baseline characteristics and inclusion/exclusion criteria have been described in detail elsewhere [3]. Briefly, eligible participants were men and women (20–75 years old) with confirmed CHD and no clinical events in the last 6 months before screening, who were able to follow a long-term dietary intervention, and had no severe illnesses (e.g., psychiatric illnesses, chronic renal insufficiency, or neoplasia under treatment). Patients were recruited from November 2009 to February 2012, mostly at Reina Sofia University Hospital (Cordoba, Spain) and were assigned randomly to two intervention groups: Mediterranean diet or low-fat diet. All subjects provided written informed consent before their inclusion in the study.

Out of the 1002 patients involved in the CORDIOPREV study, 853 patients had complete follow-up dietary information for 5 years and were included in the present analysis.

Dietary intervention

The dietary intervention was performed by a team of registered dietitians (RDs) who were previously trained to ensure uniformity and the quality of the intervention. The primary goal of the dietary intervention was to change the eating habits of the patients towards the randomized diet, focusing on the overall quality of the diet rather than

on specific nutrients. No intervention to increase physical activity or lose weight was included.

Both study diets included foods from all major food groups, but no total calorie restriction was advised. The Mediterranean diet comprised a minimum of 35% of total calories from fat (22% monounsaturated fatty acids-MUFAs, 6% polyunsaturated fatty acids-PUFAs, < 10% saturated fatty acids-SFAs), ≤ 50% from carbohydrates and 15% from protein. The low-fat diet included less than 30% of total calories from fat (12–14% MUFAs, 6–8% PUFAs, < 10% SFAs), ≥ 55% from carbohydrates and 15% from protein.

The specific recommended diets are summarized in Supplementary Table S1 and some examples of menus are included in Supplementary Table S2. In the Mediterranean diet group, RDs gave personalized counseling to achieve the following goals progressively: abundant use of virgin olive oil for cooking and dressing (≥ 4 tablespoons/day; 10–15 g/tablespoon); daily consumption of at least two servings of vegetables (200 g/serving; at least one serving raw or as salad) and three or more units of fresh fruit (125–150 g/unit); weekly consumption of at least three servings of legumes (150 g cooked weight/serving), three or more servings of fish or seafood (especially oily fish; 100–150 g/serving) and fresh nuts and seeds (three or more handfuls per week); cooking dishes seasoned with "sofrito" (a slow-cooked homemade sauce with tomato, garlic, onion, aromatic herbs, and olive oil) at least twice a week; a reduction in meat consumption, choosing (skinless) white meat instead of red meat or processed meat (< 1 serving/day); and avoidance of additional fats (butter, margarine, seed oils, creams, etc.) and foods rich in sugar and unhealthy fats (commercial bakery products, chips, precooked food, sugared beverages, etc.). A moderate consumption of wine (seven glasses/week, during meals) was permitted only if the participant was previously a regular wine consumer.

The patients allocated to the low-fat diet received personalized recommendations according to the American Heart Association (AHA) and the National Cholesterol Education Program (NCEP) dietary guidelines in use at the beginning of the study [4], focused on limiting all types of fat consumption (both animal and vegetable) and on increasing the intake of complex carbohydrates. Specifically, they were advised to minimize the amount of oil used for cooking and dressing (≤ 2 tablespoons/day); always remove visible fat from meats and soups; not to eat more than one serving of red meat per week; choosing low-fat dairy products; consumption of lean fish instead of oily fish or fish/seafood canned in oil (≤ 1 serving/week); avoidance of nuts and seeds (≤ 1 serving/week); to limit the consumption of commercial bakery goods, sweets, and pastries (≤ 1 serving/week) and to cook without the use of oil. There were no other differences in the dietary recommendations between groups.

The RDs conducted the dietary intervention with the same intensity in the two intervention groups. Supplementary Fig. S1 summarizes the frequency and type of visits performed every year during the intervention. At baseline and every 6 months, patients had an individual face-to-face visit with the RDs which included assessment of dietary intake and adherence, feedback, and reinforcement, as well as future directions. At each visit, RDs and patients worked together to identify dietary habits that needed to be changed, to set short-term goals and to work out how to make the changes. The achievements reached in the previous visits were used to increase patient motivation. Bimonthly telephone interviews were performed by the RDs to monitor compliance with the assigned diet, negotiate nutrition goals, and reinforce the dietary recommendations. In addition, group sessions of 20 participants were organized separately for each group every 3–4 months. These 2-h sessions included oral and written information (e.g., recipes, plans for meals, cooking tips, and shopping lists), group discussions, handouts, and reinforcement of dietary recommendations. To find social support, family members were encouraged to attend the individual and group sessions with the patient, especially if they shared the responsibility for food selection and the preparation of meals.

Written materials were designed and given to the patients at the individual and group sessions to enhance oral recommendations: leaflets summarizing the main food components and their frequency of consumption, and cooking recipes focused on increasing skills for preparing meals which complied with the assigned diet and meal plans. The patients also received free food to encourage dietary adherence: extra-virgin olive oil rich in polyphenols in the Mediterranean diet group (approximately 1 L per week) and food packets containing low-fat products in the low-fat diet group.

Dietary intake assessment

Information on habitual dietary intake was collected at baseline and on a yearly basis during follow-up using a 137-item semi-quantitative food-frequency questionnaire (FFQ), previously validated in the Spanish population [20, 21]. Participants were asked to report their average intake of different food and beverage items over the previous 12 months. 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". As nutrient intake may vary in response to the availability of seasonal foods, the consumption of these foods was recorded for the season and then adjusted by the proportional intake over 1 year. Energy and nutrient intake were calculated using the Spanish Food Composition Tables [22, 23]. To present the consumption of nutrients and foods in a way that is not correlated with the total energy intake, we also calculated the

percentage contribution of foods and nutrients to the mean daily energy intake.

Dietary adherence assessment

The 14-item MEditerranean Diet Adherence Screener (MEDAS) was used to measure adherence to the Mediterranean diet (Supplementary Fig. S2). This score is an extension of a 9-point score developed by Martinez-Gonzalez et al. [24] and consists of 2 questions about eating habits, 8 questions about the frequency of consumption of typical foods of the Mediterranean diet, and 4 questions about the consumption of foods not recommended in this diet. Each question was scored with 0 (non-compliant) or 1 (compliant), and the total score (from a total of 14 questions) ranged from 0 to 14, so a score of 14 points meant maximum adherence. Mediterranean diet adherence was categorized into *Low* (0–5), *Medium* (6–9), and *High* (10–14) *Adherence*, as previously published [25].

A 9-item dietary screener assessing adherence with the low-fat diet guidelines was also administered (Supplementary Fig. S3). This tool was developed and used in the PREDIMED study [2] and includes 6 questions about the consumption of high-fat food, 1 question about the consumption of low-fat food, and 2 questions about dietary habits (scored 1 for yes, 0 for no). The total score ranged from 0 to 9. Low-fat diet adherence was categorized as *Low* (0–3), *Medium* (4–6), and *High* (7–9) *Adherence*.

Dietary adherence was assessed in all visits (individual, group and telephone). The MEDAS and the 9-item dietary screener were performed in the two intervention groups at baseline (before the randomization). At follow-up visits, the MEDAS was also administered in both groups, whereas the 9-item dietary screener was only performed in the low-fat diet group. The MEDAS was also conducted in the low-fat diet to compare the deviation from the original values in the two arms of the study.

Long-term dietary adherence maintenance

To evaluate whether the changes from year 1 to year 5 were representatives of the 5-year period of the intervention, we explored the consistency of the within-person variations in dietary adherence as the Coefficient of variation (CV, %), from the 1st year to the 5th year (Supplementary data: Long-term dietary adherence). To study long-term maintenance of dietary adherence between the two intervention groups, we analyzed the change in adherence from the end of the first year of intervention to the 5th (Supplementary data: Long-term dietary adherence). We stratified this calculation based on the 1-year category of their dietary adherence (*Low*, *Medium*, and *High Adherence*).

Assessment of non-dietary variables

At baseline and at the annual visits, a collection of biological samples and several questionnaires on socio-demographic data and lifestyle variables were included. Physical activity and leisure-time activity were assessed by the validated Spanish version of the Minnesota Leisure-Time Physical Activity Questionnaire [26, 27]. Weight and height were measured by trained dietitians using calibrated scales (BF511 Body Composition Analyzer/Scale, OMROM, Japan) and a wall-mounted stadiometer (Seca 242, HealthCheck Systems, Brooklyn, NY, USA), respectively. Waist circumference was measured midway between the lowest rib and the iliac crest using an anthropometric tape. Body Mass Index (BMI) was calculated as weight per square meter (kg/m^2).

Statistical analysis

Participants whose 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) [28] were excluded from the present analysis. Normal distribution was tested for all the measured variables, and log10 transformation was used to normalize skewed variables. Baseline characteristics, dietary intake, and dietary adherence of the patients were presented as mean ± standard error of the mean (SEM) for continuous variables and proportions for categorical variables. Within- and between-group changes were assessed with a paired *t* test and unpaired *t* test, respectively. Differences were considered to be significant when $p < 0.05$.

All statistical analyses were performed using the SPSS (Statistical Package for the Social Sciences) version 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics

The baseline sample consisted of 1002 coronary patients (502 randomized to the Mediterranean diet group and 500 to the low-fat diet group). There were 83.5% males and the mean age was 59.5 ± 9.0 years (Table 1). After excluding subjects with missing dietary data, unrealistic baseline energy intakes, and those who did not complete the 5-year follow-up, the final sample size was 853 patients (Fig. 1). The two groups were balanced for socio-demographic and clinical characteristics, smoking habits, and physical activity level (Supplementary Table S3).

Table 1 Baseline characteristics of participants by randomized groups

	All patients ($n=1002$)	Med Diet ($n=502$)	Low-Fat Diet ($n=500$)	p value
Sex (% male)	82.5	82.5	82.6	0.957
Age (years)	59.5 ± 0.2	59.7 ± 0.4	59.5 ± 0.4	0.696
Age group (%)				
< 65 years	65.9	64.7	67.0	0.451
≥ 65 years	34.1	35.3	33.0	
Height (cm)	165.3 ± 0.3	165.2 ± 0.4	165.4 ± 0.3	0.822
Weight (kg)	85.1 ± 0.4	84.9 ± 0.6	85.4 ± 0.7	0.605
BMI (kg/m^2)[b]	31.1 ± 0.1	31.0 ± 0.1	31.2 ± 0.2	0.647
Waist circumference (cm)	105.1 ± 0.3	104.9 ± 0.5	105.4 ± 0.5	0.579
Overweight (%)[b]	37.5	39.2	35.4	0.209
Obesity (%)[b]	56.5	54.4	58.0	0.249
Abdominal obesity (%)[c]	68.5	69.1	67.8	0.652
Diabetes (%)[d]	53.9	51.0	56.8	0.065
Hypertension (%)[e]	68.5	69.2	67.9	0.604
Marital status (%)[a]				
Married	86.9	86.6	87.3	0.742
Single, widowed, divorced, others	13.1	13.4	12.7	
Education level (%)[a]				
Higher education	8.2	9.3	7.0	0.556
Secondary education	20.4	20.7	20.1	
Primary education	55.3	53.7	57.0	
None	16.1	16.3	15.9	
Occupation (%)[a]				
Worker	24.5	27.3	21.6	0.156
Housewife	4.1	4.5	3.6	
Retired	60.0	57.6	62.5	
Unemployed or others	11.4	10.5	12.3	
Income (Euros/month) (%)[a]				
< 900	30.0	28.5	31.6	
900–1800	51.8	52.7	50.8	0.579
> 1800	18.2	18.8	17.6	
Place of residence (%)[a]				
Rural area	56.9	55.4	58.5	0.333
Urban area	43.1	44.6	41.5	
Smoking habits (%)[a]				
Never smokers	25.7	27.4	24.1	0.351
Current smokers	9.7	8.7	10.7	
Former smokers	64.6	63.9	65.2	
Physical activity (METs-min/day)	183.6 ± 6.0	184.6 ± 8.0	182.5 ± 8.9	0.867
Adherence to Med diet (points)[f]	8.8 ± 0.1	8.9 ± 0.1	8.7 ± 0.1	0.055
Adherence to low-fat diet (points)[g]	3.8 ± 0.1	3.8 ± 0.1	3.8 ± 0.1	0.837

Data are shown as mean ± SEM or percentage of participants, unless otherwise stated. We used unpaired *t* tests for quantitative variables and Chi-squared tests for categorical variables

Med Diet Mediterranean diet group, *Low-Fat Diet* low-fat diet group

[a]Data were available for 956 patients

[b]Body mass index (BMI) was calculated as weight in kg divided by the square of height in m (kg/m2). BMI ≥ 25 and < 30: overweight; BMI ≥ 30: obese

[c]Abdominal obesity was defined as waist circumference > 102 cm in men and > 88 cm in women

[d]Diabetes was defined as being diagnosed as diabetic before the start of the study (350, 34.9%) and those diagnosed by a fasting blood glucose level ≥ 126 mg/dL on two occasions, or a 2-h plasma glucose level ≥ 200 mg/dL during a 75-g oral glucose-tolerance test, during the first procedures of the study

[e]Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg, a diastolic blood pressure ≥ 90 mm Hg, or the use of antihypertensive therapy

Table 1 (continued)

[f]Based on the 14-item MEditerranean Diet Adherence Screener, MEDAS (shown in Supplementary Fig. S2). The range was 0 (minimum)–14 (maximum) points

[g]Based on a 9-item low-fat diet adherence score (shown in Supplementary Fig. S3). The range was 0 (minimum)–9 (maximum) points

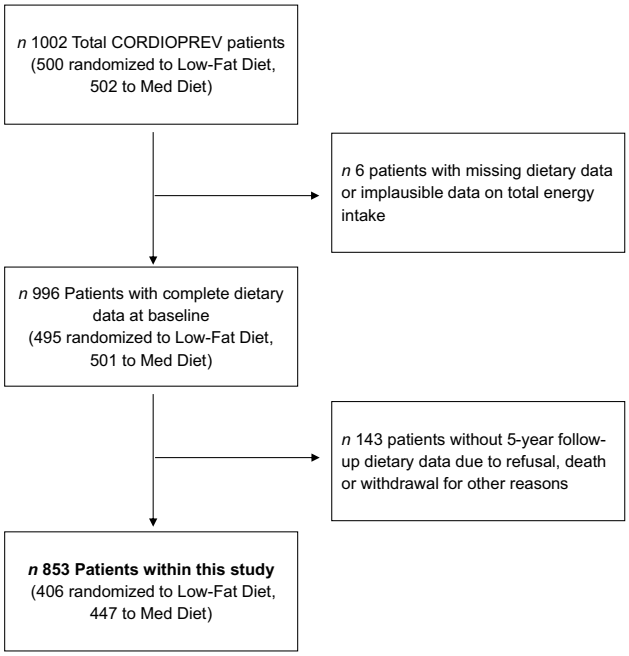

Fig. 1 Flowchart of participants from the CORDIOPREV study included in the present analysis. The exclusion of those patients with implausible data on total energy intake (< 500 or > 3500 kcal/day in women, or < 800 or > 4000 kcal/day in men) allowed us to control the normality. *Low-Fat Diet* low-fat diet group, *Med Diet* Mediterranean diet group

Energy and nutrients' intake

Table 2 summarizes the mean nutrient intake of the patients at baseline and 5 years after randomization. No significant differences were found between the two groups at baseline. The habitual diet of patients was high in total fat (> 35%), mainly consisting of MUFAs, with 41% of the energy from carbohydrates and 18.5% from proteins. After 5 years of dietary intervention, participants in the Mediterranean diet group increased their intake of fiber and total fat due to a higher consumption of MUFAs (from olive oil) and PUFAs (from tree nuts and oily fish) and reduced their consumption of total carbohydrates, SFAs, and cholesterol (all $p < 0.05$). The low-fat diet group showed an increase in the intake of total fiber and carbohydrates, mainly complex carbohydrates, and showed decreases in the intake of total fat, all types of fatty acids and cholesterol (all $p < 0.05$).

The total energy intake decreased in the two groups, and was more marked in the low-fat diet group. The same pattern of changes in nutrient profile after 1 and 3 years of intervention was observed in both groups (Supplementary Table S4).

Table 2 shows the changes in the nutrient intake after 5 years of dietary intervention. The Mediterranean diet group showed an increased intake of total fat, MUFAs, oleic acid, PUFAs, α-linolenic acid, and marine n-3 fatty acids, as well as a decreased consumption of carbohydrates compared to the low-fat diet group (all $p < 0.05$).

Food intake

Figure 2 shows the contribution (%) of foods to the daily energy intake at baseline and after 5 years of intervention. At baseline, cereals were the primary source of energy (21.7%E) for all the patients, followed by olive oil (14%E), dairy products (10.4%E), and red/processed meat (8.3%E). Other foods contributed less, such as fruit (7.1%E), fish or seafood (5.8%E), vegetables (3.5%E), legumes (3.4%E), and tree nuts (2.3%E). As intended, extra-virgin olive oil became the main source of energy in the Mediterranean diet group (from 12.1 to 21.6%E) and cereals (with an increase of whole cereals from 4.6 to 7.1%E) in the low-fat diet group after the 5-year intervention period. Significant increases in the consumption of fruit, vegetables, and legumes ($p < 0.001$), as well as decreases in the intake of red/processed meat ($p < 0.001$), sweet/carbonated beverages ($p < 0.05$), and fat spreads ($p < 0.05$) were observed in the two intervention groups. The consumption of tree nuts and oily fish increased only in the Mediterranean diet group ($p < 0.05$). The intake of commercial bakery products decreased significantly ($p < 0.001$) in this group.

Dietary adherence

Patients reported similar adherence to the Mediterranean diet and the low-fat diet at baseline (Table 1). After the first year of follow-up, the mean scores in the MEDAS were significantly higher in the Mediterranean diet group than in the low-fat diet group ($p < 0.001$ for all yearly comparisons from years 1 to 5 of follow-up), achieving a maximum difference of 3.8 ± 0.1 points in the MEDAS at the visit for the 5-year follow-up (Fig. 3a). Specifically, participants in the Mediterranean diet group showed a significant increase of 2.0 ± 0.1, 2.4 ± 0.1, and 2.5 ± 0.1 points from their baseline MEDAS (8.9 ± 0.1) after 1, 3, and 5 years of intervention (< 0.001 for all comparisons), whereas the low-fat diet group reported a significant decrease in the MEDAS of 1.1 ± 0.1, 1.0 ± 0.1,

Table 2 Mean baseline values and changes in energy and nutrient intake after 5 years of intervention with two healthy diets

	Baseline			5 years of follow-up			Within-group mean changes after 5 years			
	Med Diet ($n=447$)	Low-Fat Diet ($n=406$)	p value*	Med Diet ($n=447$)	Low-Fat Diet ($n=406$)	p value*	Med Diet ($n=447$)	p value#	Low-Fat Diet ($n=406$)	p value#
Energy (kcal)	2242 ± 24	2263 ± 26	0.528	2024 ± 18	1716 ± 18	< 0.001	− 218 ± 24	< 0.001	− 546 ± 25	< 0.001
Total protein (%E)	18.5 ± 0.1	18.6 ± 0.1	0.863	17.3 ± 0.1	18.9 ± 0.1	< 0.001	− 1.3 ± 0.2	< 0.001	0.3 ± 0.2	0.052
Total carbohydrate (%E)	41.4 ± 0.3	41.6 ± 0.3	0.702	38.5 ± 0.3	45.6 ± 0.3	< 0.001	− 2.9 ± 0.3	< 0.001	4.1 ± 0.4	< 0.001
Fiber (g/1000 kcal)	11.4 ± 0.2	11.4 ± 0.2	0.886	12.9 ± 0.2	14.1 ± 0.2	< 0.001	1.6 ± 0.2	< 0.001	2.7 ± 0.2	< 0.001
Total fat (%E)	37.3 ± 0.3	36.7 ± 0.3	0.172	41.0 ± 0.3	31.7 ± 0.3	< 0.001	3.8 ± 0.3	< 0.001	− 5.0 ± 0.4	< 0.001
MUFAs (%E)	18.3 ± 0.2	17.9 ± 0.2	0.063	21.9 ± 0.2	14.3 ± 0.2	< 0.001	3.6 ± 0.2	< 0.001	− 3.5 ± 0.2	< 0.001
Oleic acid (%E)	17.0 ± 0.2	16.6 ± 0.2	0.060	20.7 ± 0.2	13.2 ± 0.2	< 0.001	3.6 ± 0.2	< 0.001	− 3.4 ± 0.2	< 0.001
SFAs (%E)	8.9 ± 0.1	8.9 ± 0.1	0.954	8.0 ± 0.1	7.1 ± 0.1	< 0.001	− 0.9 ± 0.1	< 0.001	− 1.8 ± 0.1	< 0.001
PUFAs (%E)	6.4 ± 0.1	6.3 ± 0.1	0.175	7.4 ± 0.1	7.1 ± 0.1	0.022	1.0 ± 0.1	< 0.001	0.8 ± 0.1	< 0.001
Linolenic acid (%E)	5.1 ± 0.1	5.0 ± 0.1	0.264	5.8 ± 0.1	5.9 ± 0.1	0.384	0.7 ± 0.1	< 0.001	0.9 ± 0.1	< 0.001
α-linolenic acid (%E)	0.44 ± 0.01	0.43 ± 0.01	0.373	0.59 ± 0.01	0.35 ± 0.01	< 0.001	0.15 ± 0.01	< 0.001	− 0.07 ± 0.01	< 0.001
EPA (%E)	0.10 ± 0.01	0.10 ± 0.01	0.372	0.13 ± 0.01	0.10 ± 0.01	< 0.001	0.023 ± 0.004	< 0.001	− 0.003 ± 0.003	0.435
DHA (%E)	0.23 ± 0.01	0.22 ± 0.01	0.503	0.30 ± 0.01	0.21 ± 0.01	< 0.001	0.07 ± 0.01	< 0.001	− 0.01 ± 0.01	0.286
Marine n-3 fatty acids (%E)	0.40 ± 0.01	0.39 ± 0.01	0.605	0.52 ± 0.01	0.37 ± 0.01	< 0.001	0.11 ± 0.02	< 0.001	− 0.02 ± 0.01	0.136
Cholesterol (mg/day)	328.4 ± 4.5	332.8 ± 5.4	0.531	260.3 ± 3.2	248.9 ± 3.7	0.019	− 68.1 ± 4.7	< 0.001	− 84.0 ± 5.5	< 0.001

Data are mean ± SEM

Med Diet Mediterranean diet group, *Low-Fat Diet* low-fat diet group, *%E* percentage of total energy, *g* grams, *MUFAs* monounsaturated fatty acids, *SFAs* saturated fatty acids, *PUFAs* polyunsaturated fatty acids, *EPA* eicosapentaenoic acid, *DHA* docosahexaenoic acid, *mg* milligrams

*Significant difference ($p < 0.05$) between the Mediterranean diet and the low-fat diet group, analyzed using an unpaired t test

#Significant difference ($p < 0.05$) between baseline and after 5 years of follow-up in each variable (of each group), analyzed using a paired t test

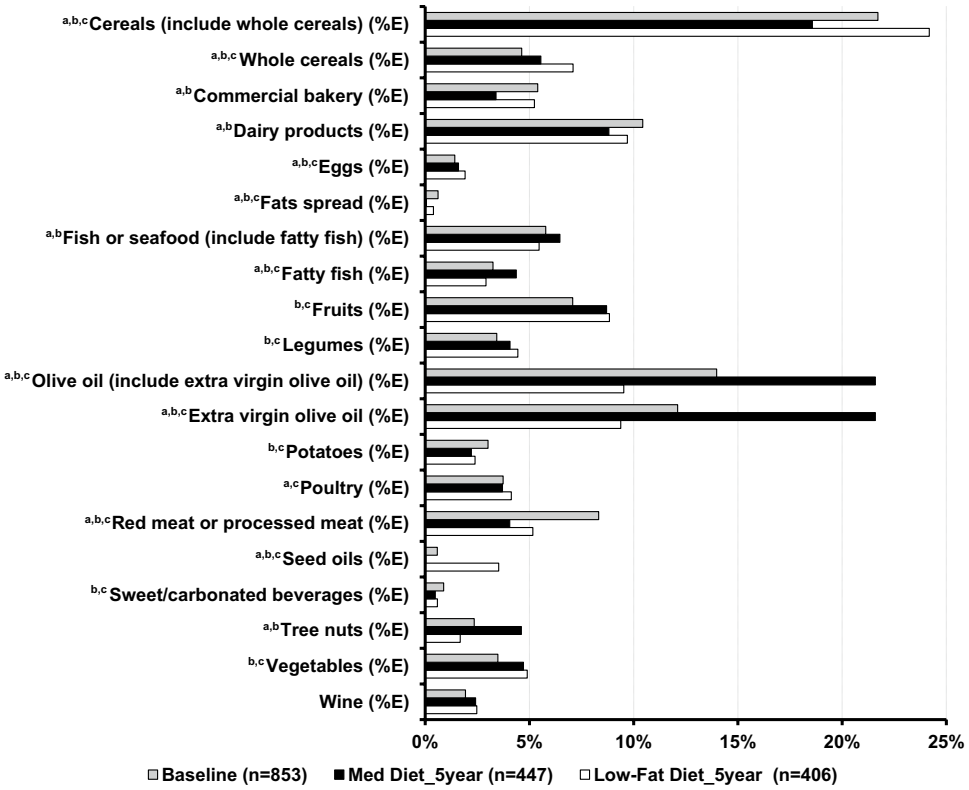

Fig. 2 Dietary sources of energy from foods at baseline and after 5 years of intervention. The contribution (%) of foods to the daily energy intake, listed in alphabetical order, and categorized by intervention group. $^{a}p < 0.05$ for comparisons between groups in 5-year follow-up visit (unpaired *t* test); $^{b}p < 0.05$ from baseline by paired *t* test in the Mediterranean diet group; $^{c}p < 0.05$ from baseline by paired *t* test in the low-fat diet group. *Med Diet* Mediterranean diet group, *Low-Fat Diet* low-fat diet group

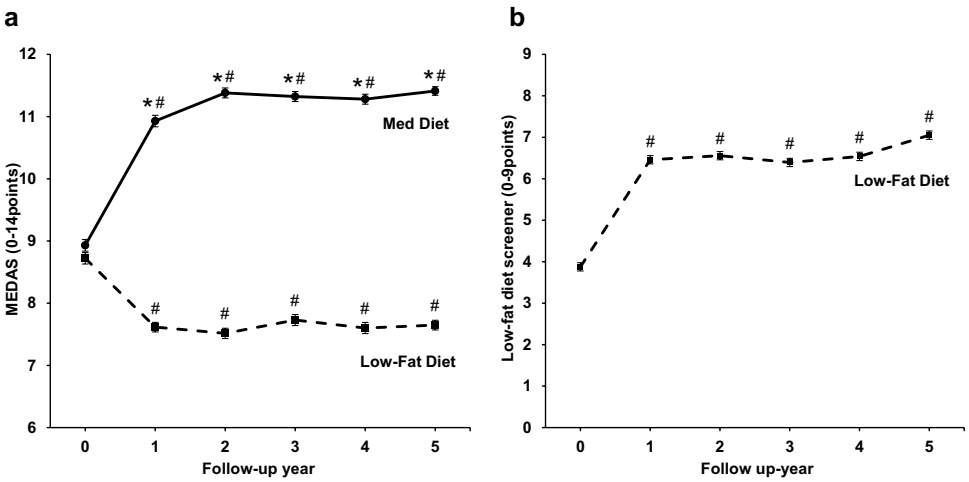

Fig. 3 Changes in dietary adherence during 5 years of follow-up. **a** Adherence to the Mediterranean diet of the CORDIOPREV population (both arms, $n = 853$) and **b** adherence to the low-fat diet in patients allocated to the low-fat diet ($n = 406$). Values are expressed as mean ± SEM. $^{*}p < 0.001$ for comparisons between groups at each visit. $^{\#}p < 0.001$ from baseline in each group. *Med Diet* Mediterranean diet group, *Low-Fat Diet* low-fat diet group

and 1.1 ± 0.1, respectively (< 0.001 for all comparisons). Participants in the low-fat diet group increased their score in the 9-item questionnaire on adherence to a low-fat diet in the expected direction, from 3.9 ± 0.1 baseline score to 6.5 ± 0.1, 6.4 ± 0.1, and 7.1 ± 0.1 after 1, 3, and 5 years of dietary intervention, respectively (< 0.001 for all comparisons) (Fig. 3b).

Regarding the percentage of patients who fulfilled the MEDAS component targets (Supplementary Table S5 and Supplementary Fig. S4), the 5-year data showed significant differences between the groups in 12 of the 14 items (all $p < 0.05$). As intended, the Mediterranean diet group showed increases in their compliance with each of the 14 items in years 1, 3, and 5, whereas the low-fat diet group decreased their compliance with the 5 items of the MEDAS related to the consumption of fatty foods (olive oil, nuts or seeds, fatty fish, and "sofrito" sauce). In addition, this group raised the percentage of compliance with all the nine items of the low-fat diet screener (Supplementary Table S6). These data were consistent with the food intake information derived from the FFQs (Supplementary Table S7).

When dietary adherence was categorized, in the Mediterranean diet group, the percentage of patients in the *High Adherence* category increased from 40.9% at baseline to 88.8% at the 5-year visit, and in the low-fat diet group, this percentage increased from 5.9% at baseline to 67% after 5 years (Supplementary Table S8).

Long-term dietary adherence maintenance

Coefficients of variation in both groups during the first to fifth years of intervention were low (Mediterranean diet group, 11%; low-fat diet group, 23%), which supports the idea that the changes in the scores between the end of the first and fifth years were representatives of the overall period.

Figure 4 shows the change in dietary adherence for each category of adherence (*Low*, *Medium* or *High Adherence*) between years 1 and 5, according to diet. In both groups, patients in the category of *Low Adherence* at year 1 showed the greatest change over time (the Mediterranean diet group increased their adherence by 45.9 ± 4.9% and the low-fat diet group increased by 41.2 ± 3.8%, $p < 0.001$ for all), with no significant differences between diets. Likewise, patients in the category of *Medium Adherence* also showed a positive percentage change in the two intervention groups. In the category of *High Adherence*, however, the Mediterranean diet group did not change their adherence over time, while there was a decrease in the adherence with the low-fat diet group (− 8.2 ± 1.2%, $p < 0.001$). The difference between the Mediterranean versus low-fat diet groups was statistically significant ($p < 0.001$).

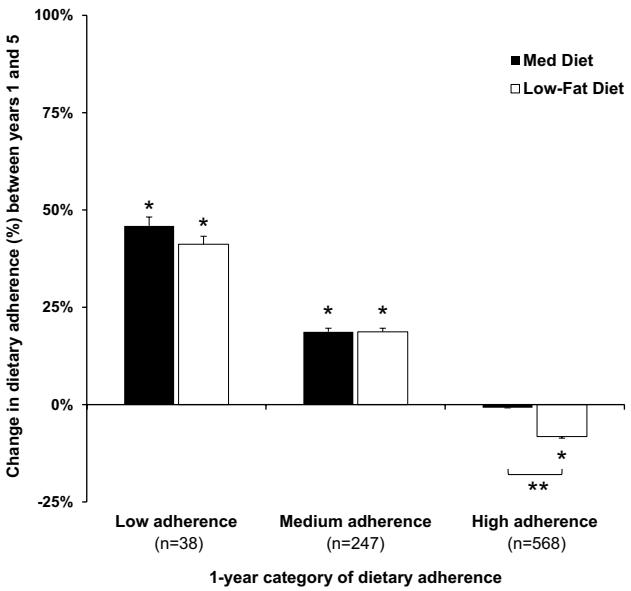

Fig. 4 Percentage of change in dietary adherence between years 1 and 5 according to 1-year category of adherence and intervention group. White bars represent the low-fat diet group, while black bars represent the Mediterranean diet group. All data are mean ± SEM. *Significant within-group difference from 1-year ($p < 0.001$) analyzed using repeated-measures ANOVA, adjusted for age and sex. **Significant between-group difference in each 1-year category of dietary adherence ($p < 0.001$) analyzed using a univariate model adjusted for age and sex

Discussion

In our study, there were two main findings: first, that it is possible to achieve and maintain a high adherence to two healthy dietary patterns in the long-term (5 years), when tailored, comprehensive dietary support is provided to patients, and second, that a high level of adherence to diet achieved after 1 year of intervention is easier to maintain in the long term (5 years) with a Mediterranean diet than with a low-fat diet.

When evaluating the success of dietary intervention studies, the first step is analyzing the changes in the data from the dietary surveys (FFQs), taken from measurements of the daily intake of nutrients, food, and food groups. In our study, we observed changes in the data from the FFQs of the patients in the expected direction for the assigned diet, which points to a good global adherence to the dietary models. In the low-fat diet group, it is noteworthy that although the participants live in a culture with a high consumption of olive oil and deeply rooted dietary habits, they reduced their consumption of olive oil and adhered to a low-fat diet for 5 years. Furthermore, this group reduced their consumption of fat from 36.7 ± 0.3 to 31.7 ± 0.3%, which was higher than those reported in similar intervention studies. As an example, in the PREDIMED study, the low-fat diet group showed a reduction in fat intake from 39.0 ± 0.2 to 37.0 ± 0.2%. Moreover, extensive macro- and micronutrient analyses support the good adherence of patients to their diets.

In our study, both the MEDAS and the low-fat adherence score increased in the participants following the diets. Furthermore, and even more importantly, these changes were maintained in each subsequent year of follow-up and were not lost over time, doubling the number of people in the category of *High Adherence* for the Mediterranean diet group (41–89%) and achieving an impacting change (4–67%) in the low-fat diet group at 5 years of follow-up. The use of these dietary scores or "screeners" instead of foods or groups of foods has risen in importance, due to the accumulating evidence of their relationship to clinical data. Examples of these are two recent meta-analyses of observational and prospective studies investigating the association between adherence to the Mediterranean diet and health, which reported a 6–10% reduction in the risk of CVD (fatal or nonfatal clinical CVD event) per two-point increase of adherence to the Mediterranean diet [8, 29]. Taking into account that the

mean increase observed in our study was 2.5 ± 0.1 points, our hypothesis is that it is likely to be clinically relevant.

Several factors can be linked to our results regarding the long-term maintenance of the changes in dietary adherence. A comprehensive, tailored, and continuous support for lifestyle interventions, as provided in our case, has been shown to produce the best results [15]. After 1 year of intervention, our results indicate that a combination of regular contacts, group sessions, monitoring of adherence, goal setting, social support, and the free provision of food was effective in changing dietary habits and increasing short-term adherence [19, 30]. Furthermore, most of the changes observed at 1 year were maintained in those followed up at 5 years, which suggests that the strategies used in our study were also useful for long-term adherence. On the other hand, the nutritional composition of the diet may influence dietary adherence. The two dietary patterns administered in our study presented the same protein content, which is described as the nutrient with the highest satiating properties. However, the Mediterranean diet is relatively high in fat content, which makes it more palatable, satisfying, and easy to maintain over time. In this sense, palatability can be one of the factors behind the 89% of participants who showed a high level of adherence to the Mediterranean diet after 5 years of dietary intervention, and the fact that those who were in the *High Adherence* at 1 year maintained this adherence at the 5-year mark. Less palatability in the low-fat diet could explain the fact that patients with high adherence at the end of the first year showed a 10% decrease in their long-term adherence.

As expected, those patients with baseline food habits which differ most from a healthy diet are likely to achieve greater dietary adherence changes. This same association has been described previously [13, 31], and it would be a useful tool for quickly identifying which individuals will respond better to dietary intervention and for designing personalized intervention delivery strategies. In other words, our study shows that, in patients who have more difficulty to achieve adherence in the first year, continuing to receive dietary support can lead to a significant long-term improvement. Patients who were in the *Low Adherence* group in the first year showed the greatest improvement at 5 years, followed by those who were in the *Medium Adherence* group. It is remarkable that the participants belonging to the Mediterranean diet group who were in the *High Adherence* category in the first year were able to maintain it for another 4 years, whereas those who were in the *High Adherence* category after 1 year following the low-fat diet decreased their adherence at 5 years.

There are few prospective studies of diet quality and CVD outcomes in people with established CVD and these have limitations, such as being observational and measuring short-term adherence. Our study is the first randomized trial to address long-term adherence in a large population of patients with established CVD. The large number of patients with an extended follow-up, the application of the same intensive dietary counseling in the two intervention groups, the small attrition rate, and adjustment for a wide range of confounding factors are added strengths. Our findings must be, however, interpreted in the context of the study's limitations. Although FFQs constitute to date the most practical and feasible tool to evaluate diet outcome in large epidemiological studies [32], they are known to contain measurement errors. However, we tried to limit this fact using an FFQ which was validated in a Spanish population with the same characteristics as our study population [21], and we, therefore, obtained the most trustworthy data possible. Another limitation of our study is that it is confined to CHD patients and may not be suitable for extrapolating the results for the general population. Nevertheless, these patients are one of the populations in which dietary changes may have a higher impact on health, and, subsequently, it is worth having specific data on this population.

Conclusions

Our study shows that, in coronary patients, comprehensive dietary intervention with two healthy diets (a Mediterranean-type diet and a low-fat diet) results in an overall improvement and maintenance of dietary adherence at 1 year. In this population, patients who were in the *Low* and *Medium Adherence* categories after 1 year of intervention maintain or increase this improvement at 5 years with both diets, while those who were in the *High Adherence* category after 1 year only maintain that adherence at 5 years with a Mediterranean diet, but not with a low-fat diet.

Our findings suggest, therefore, that long-term high adherence to diet is easier to maintain with the Mediterranean diet.

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Author contributions J Lopez-Miranda, PP-M, and JD-L conceived and designed the research. JFA-D, J Lopez-Moreno, AL-A, JDT-P, APAL, AG-R, PP-M, J Lopez-Miranda, and JD-L participated in the recruitment and carried out the clinical control of the volunteers. GMQ-N, IP-C, and A Corina carried out the nutritional control of the volunteers and GMQ-N drafted the nutritional approach for this paper. OAR-Z, A Camargo, EMY-S, and FR-C performed the lab tests. GMQ-N, JFA-D, and JD-L analyzed and interpreted the data. GMQ-N drafted the manuscript. RML, JMO, PP-M, J Lopez-Miranda, and JD-L provided critical revision of the paper for important intellectual content and edited the content of the draft. PP-M, J Lopez-Miranda, and JD-L had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All

the authors revised the manuscript, and read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest None of the authors has any conflict of interest that could affect the performance of the work or the interpretation of the data.

Ethical approval The study protocol was approved by the Human Investigation Review Committee of the Reina Sofia University Hospital, according to institutional and Good Clinical Practice guidelines.

Informed consent All participants provided written informed consent.

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ABSTRACT ONLY | VOLUME 275, E74, AUGUST 01, 2018

Long-term adherence to two healthy diets in coronary patients after five years of dietary intervention: Cordioprev study

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LONG-TERM ADHERENCE TO TWO HEALTHY DIETS IN CORONARY PATIENTS AFTER FIVE YEARS OF DIETARY INTERVENTION: CORDIOPREV STUDY

G.M. Quintana Navarro [1,2], J.F. Alcala-diaz [1,2], I. Perez-corral [1,2], J.D. Torres-peña [1,2], C. Fernandez-gandara [1,2], F. Perez-jimenez [1,2], J. delgado-lista [1,2], J. lopez-miranda [1,2]. [1] *Lipids and Atherosclerosis Unit, IMIBIC / Reina Sofía University Hospital / University of Cordoba, Cordoba, Spain;* [2] *Spanish Biomedical Research Centre in Physiopathology of Obesity and Nutrition (CIBEROBN)/ Institute of Health CarlosIII, Madrid, Spain*

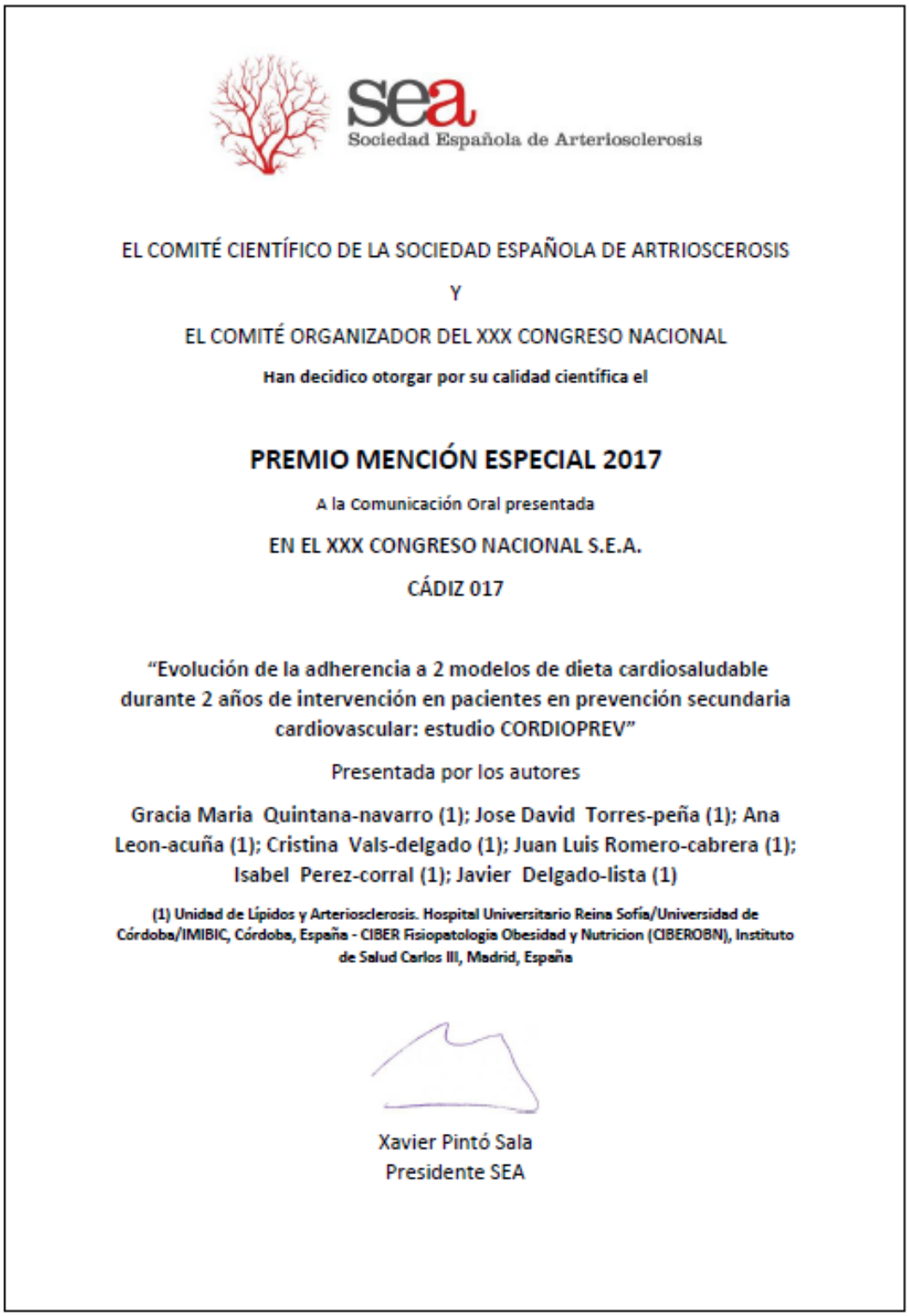
Aim: Adherence level to dietary advice may influence clinical outcomes in secondary prevention. Usually, dietary adherence decreases after some months when only dietary instructions are given. Our aim was to determine the long-term adherence (5-years) to two healthy diets with a comprehensive dietary advice intervention.

Methods: 853 patients from the CORDIOPREV study, 448 patients randomized to Mediterranean diet and 405 to low fat high carbohydrates diet (LFHCC), were included. Dietary intervention was performed by registered dietitians for 5 years. Dietary adherence was determined at 0, 1, 3 and 5 years follow-up. Mediterranean diet adherence was measured by MEDAS (scored 0-14) and categorized into low (0-7), medium (8-9) and high (>9). LFHCC was assessed with a 9-item questionnaire used in the Predimed study (scored 0-9) and categorized as low (0-3), medium (4-6) and high (>6).

Results: Baseline MEDAS score of Mediterranean diet group was 8.94±1.97 points, increasing to 10.94±1.95, 11.33±1.71 and 11.41±1.47 after 1, 3 and 5 years of intervention. The LFHCC group presented an initial score in the 9-item questionnaire of 3.87±1.60, increasing to 6.45±1.94, 6.40±1.90 and 7.05±1.68 after 1, 3 and 5 years of intervention. In both groups, the percentage of patients with high adherence increased after 5 years of intervention (Mediterranean diet: from 41.1 to 88.8%, LFHCC diet: from 5.9 to 67.4%).

Conclusions: Continuous dietary advice results in long-term improvement of adherence to two heart-healthy diets. Our results show that long-term adherence is possible with specialized dietary advice which is very relevant to evaluate the influence of the intervention on clinical outcomes.

Special mention award for the oral communication presented in the XXX Congreso Nacional Sociedad Española de Arteriosclerosis (SEA) (Cádiz, España, 31-2 junio 2017)



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EN EL XXX CONGRESO NACIONAL S.E.A.

CÁDIZ 017

"Evolución de la adherencia a 2 modelos de dieta cardiosaludable durante 2 años de intervención en pacientes en prevención secundaria cardiovascular: estudio CORDIOPREV"

Presentada por los autores

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Additional contributions achieved during the PhD program

The author of this thesis has participated as co-author in 22 papers during the realization of its doctoral program. Papers in which she is included among the top three authors are listed below:

1. Arroyo-Olivares R, Alonso R, **Quintana-Navarro G**. Adults with familial hypercholesterolaemia have healthier dietary and lifestyle habits compared with their non-affected relatives: the SAFEHEART study. Public Health Nutr. 2019

2. Lopez-Moreno J, **Quintana-Navarro GM**, Delgado-Lista J. Mediterranean Diet Supplemented With Coenzyme Q10 Modulates the Postprandial Metabolism of Advanced Glycation End Products in Elderly Men and Women. J Gerontol A Biol Sci Med Sc 2018.

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4. Lopez-Moreno J, **Quintana-Navarro GM**, Delgado-Lista J. Mediterranean Diet Reduces Serum Advanced Glycation End Products and Increases Antioxidant Defenses in Elderly Adults: A Randomized Controlled Trial. J Am Geriatr Soc. 2016.