FACTORS ASSOCIATED WITH ARTERIAL STIFFNESS IN A GENERAL MEDITERRANEAN POPULATION AND IN A MEDITERRANEAN INTERMEDIATE CARDIOVASCULAR RISK POPULATION

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DOCTORAL THESIS

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Publications related to this thesis until now:

- Elosua-Bayés M, Martí-Lluch R, García-Gil M del M, Camós L, Comas-Cufí M, Blanch J, Ponjoan A, Alves-Cabratosa L, Elosua R, Grau M, Marrugat J and Ramos R. Association of Classic Cardiovascular Risk Factors and Lifestyles With the Cardio-ankle Vascular Index in a General Mediterranean Population. Rev Española Cardiol (English Ed) 2018; 71: 458–465.

- Martí-Lluch R, Garcia-Gil M del M, Camós L, Comas-Cufí M, Elosua-Bayés M, Blanch J, Ponjoan A, Alves-Cabratosa L, Elosua R, Grau M, Marrugat J and Ramos R. Differences in cardio-ankle vascular index in a general Mediterranean population depending on the presence or absence of metabolic cardiovascular risk factors. Atherosclerosis. 2017;264:29–35.

List of abbreviations

ABI	Ankle Brachial Index
AGE	Advanced glycation end-products
AIS	Athens Insomnia Scale
AMI	Acute myocardial infarction
ANOVA	Analysis of variance
AS-SIGN	Risk estimation model from the Scottish Intercollegiate Guidelines Network
BMI	Body mass index
BP	Blood Pressure
BSA	Body surface area
CABG	Coronary artery bypass graft
CAVI	Cardio-Ankle Vascular Index
CHD	Coronary heart disease
CI	Confidence interval
CKD	Chronic kidney disease
CV	Cardiovascular
CVD	Cardiovascular disease
DALY	Disability-adjusted life year
DBP	Diastolic Blood Pressure
DM	Diabetes mellitus
DQI	Diet Quality Index
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
EF	Ejection fraction
eGFR	Estimated glomerular filtration rate
ESC	European Society of Cardiology
ESH	European Society of Hypertension
EU	European Union
FCVRF	Free of cardiovascular risk factors
FPG	Fasting plasma glucose
HbA1c	Glycated haemoglobin
HDL-C	High-density lipoprotein cholesterol

HSD	Honest Significant Difference
HT	Hypertension
ICD	International Classification of Diseases
IFCC	International Federation of Clinical Chemistry
IMT	Intima media thickness
LDL-C	Low-density lipoprotein cholesterol
LTPA	Leisure time physical activity
LVH	Left ventricular hypertrophy
LVM	Left ventricular mass
MARK	Improving interMediAte RisK management
MET	Metabolic equivalent
MI	Myocardial infarction
MONICA	multinational MONItoring of trends and determinants in CArdiovascular disease
NCDs	Non-communicable diseases
OD	Organ damage
OGTT	Oral glucose tolerance test
OR	Odds ratio
PCI	Percutaneous coronary intervention
PP	Pulse pressure
PREDIMED	PREvención con DIeta MEDiterránea
PROCAM	Prospective Cardiovascular Munster Study
PWV	Pulse wave velocity
REGICOR	Registre Gironí del Cor
RF	Risk factors
SBP	Systolic Blood Pressure
SBRN	Sedentary Behaviour Research Network
SCORE	Systematic Coronary Risk Estimation
SD	Standard deviation
sDQS	Short dietary-quality screener
SDU	Standard drinking unit
SEP	Socioeconomic position
SES	Socioeconomic status

SPSS	Statistical Package for the Social Sciences
UNESCO	United Nations Educational, Scientific and Cultural Organization
VIF	Variance inflation factor
WC	Waist circumference
WCVRF	With cardiovascular risk factors
WHO	World Health Organisation
YLD	Years living with disability
YLL	Years of life lost

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Summary

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity worldwide, and accounts for one third of all deaths and nearly half of deaths from non-communicable diseases. Over 10% of the global disease burden is attributed to CVD. The underlying pathology of CVD is atherosclerosis, which tends to develop early in life and then continues progressing silently with age. Early detection of CVD requires screening measures aimed at detecting subclinical atherosclerosis, as increased arterial stiffness. Among the many non-invasive methods of assessment, the cardio-ankle vascular index (CAVI) is a relatively new indicator that, unlike pulse wave velocity (PWV), does not depend on blood pressure during the measuring time.

Although it would seem reasonable to expect that most coronary events would be concentrated in the high-risk population, in fact over 50% of cardiovascular (CV) events occur in the population at intermediate CV risk – that is, with a coronary risk in the range $\geq 5 - < 15\%$ according to the REGICOR equation – that represents about 30% of the population. This population, thus, has an important role to play in efforts to reduce CV events given that it provides more possibilities of reclassifying CV risk.

Since classical CV risk factors have been widely studied, we should focus on measures of subclinical atherosclerosis, as arterial stiffness. However, little evidence has been found to show which factors are related to pathological arterial stiffness (measured with CAVI) in a general Mediterranean population and in a Mediterranean intermediate CV risk population, partly because to date most studies of CAVI have been carried out on Asian populations. Considering that arterial stiffness is a good precursor of CVD, a good strategy in primary prevention could be to focus on lifestyles. Thus, to improve primary prevention of CVD we need to know which factors are related to arterial stiffness in the target population.

Objectives

1. In a general Mediterranean population:
   1.1. Estimate the prevalence of pathological arterial stiffness.
   1.2. Assess the association between arterial stiffness and lifestyles and classical CV risk factors.
   1.3. Describe differences in arterial stiffness between individuals with metabolic CV risk factors (WCVRF) and healthy individuals (FCVRF).
   1.4. Determine the distribution of arterial stiffness at different risk levels.
2. In a Mediterranean intermediate CV risk population:
   2.1. Describe the prevalence of pathological arterial stiffness.
   2.2. Analyse the association between arterial stiffness and lifestyles, socioeconomic status and CV risk factors.

Methods

To achieve these aims, three cross-sectional studies were performed on the two following populations:

a) A general Mediterranean population, which included 2,613 participants aged 35–79 from Girona (2007-2013).
b) A Mediterranean intermediate CV risk population, with 2,380 participants aged 35–74, from three different regions of Spain, recruited in 2011-2013.

The main variable assessed was arterial stiffness, which was measured with CAVI (using a VaSera VS-1500® device). To analyse the related factors, we studied different variables:

a) Lifestyle-related variables: diet (DQI – diet quality index – and adherence to a Mediterranean diet), physical activity, smoking habits, alcohol consumption, and sleep-related problems.
b) Cardiovascular risk factors: hypertension, diabetes, hypercholesterolemia and obesity (BMI).
c) Socioeconomic status: educational level and occupational class.

A logistic regression was used to perform the multivariate analyses to identify the factors associated with pathological arterial stiffness in both populations.

Results

In both populations, CAVI values were higher in men than in women and increased with age.

In the general Mediterranean population, the prevalence of pathological CAVI (≥9) was 41.1% (46.8% in men and 36.0% in women). The FCVRF (free of CV risk factors) group had a lower prevalence of pathological arterial stiffness (21.6% of men and 14.4% of women) than the WCVRF (with CV risk factors) group (57.9% of men and 51.8% of women).

In men CAVI ≥ 9 was positively associated with hypertension (OR: 2.70; 95% CI 1.90-3.87) and diabetes (OR: 2.38; 95% CI 1.52-3.78) but negatively associated with being overweight (BMI ≥ 25–<30 kg/m^2) (OR: 0.44; 95% CI 0.27–0.72), obesity (BMI ≥ 30 kg/m^2) (OR: 0.28; 95% CI 0.14–0.58) and physical activity (OR: 0.66; 95% CI 0.47–0.92). In women, CAVI ≥ 9 was positively associated with hypertension (OR: 2.22; 95% CI 1.59–3.09) and hypercholesterolemia (OR: 1.40; 95% CI 1.01–1.94) but inversely associated with BMI ≥ 30 kg/m^2 (OR: 0.38; 95% CI 0.20–0.71).

The prevalence of CAVI ≥ 9 was 48.6% (51.5% in men and 44.0% in women) in the intermediate CV risk population. In men, CAVI ≥ 9 was positively associated with hypertension (OR: 2.11; 95% CI 1.72–2.59), diabetes (OR: 1.83; 95% CI 1.50–2.23) and having completed only primary education (OR: 1.32; 95% CI 1.03–1.70), but negatively associated with BMI (OR: 0.89; 95% CI 0.87–0.91). In women, CAVI ≥ 9 was positively associated with hypertension (OR: 2.14; 95% CI 1.74–2.62) and diabetes (OR: 1.86; 95% CI 1.52–2.26), but inversely associated with BMI (OR: 0.89; 95% CI 0.87–0.91).

Conclusions

- CAVI is higher in the WCVRF than in the healthy group (FCVRF) and is also higher in the intermediate CV risk population.
- CV risk factors such as hypertension and diabetes are positively associated with pathological arterial stiffness, but BMI is inversely related.

- Apart from physical activity in men in the general population, no other lifestyles are associated with pathological arterial stiffness. Having completed only primary education (in men of the intermediate CV risk population) is also associated with CAVI ≥ 9.
- Our results support certain strategies to improve primary prevention of cardiovascular disease in primary healthcare. These strategies include early detection of arterial stiffness indicated by pathological CAVI, development of activities to promote control of diabetes and hypertension, and promotion of physical activity, especially in men. Particular attention should be paid to those men at intermediate cardiovascular risk with primary education level.

Resum

Introducció

Les malalties cardiovasculars són la primera causa de mortalitat i morbiditat al món, essent les responsables d'un terç de totes les morts i gairebé la meitat de les morts per malalties no transmissibles. A més, més d'un 10% de la càrrega de la malaltia total és atribuïda a les malalties cardiovasculars.

La patologia de base de les malalties cardiovasculars és l'aterosclerosi, que se sol iniciar a la joventut i que progressa silenciosament durant anys. La detecció precoç de les malalties cardiovasculars passa per la utilització d'eines que detectin l'aterosclerosi subclínica, com un augment de la rigidesa arterial. D'entre els mètodes no invasius per a mesurar-la, el relativament nou *cardio-ankle vascular index* (CAVI) és un mètode que no depèn de la pressió arterial en el moment de mesurar-lo, a diferència de la velocitat d'ona de pols (PWV).

Semblaria raonable esperar que la major part dels esdeveniments coronaris es produïssin en la població d'alt risc. Tot i això, més del 50% dels esdeveniments cardiovasculars (CV) ocorren a la població classificada com de risc entremig -risc coronari entre $\geq$ 5% i <15% segons l'equació de risc REGICOR- la qual engloba el 30% de la població. A l'hora de reduir els esdeveniments cardiovasculars, aquesta població és important, ja que té més possibilitats de ser reclassificada en un altre grup de risc cardiovascular.

Els factors clàssics de risc cardiovascular han estat llargament estudiats, per això ens hauríem de centrar en mesures d'aterosclerosi subclínica. Tanmateix, hi ha poca evidència de quins factors estan relacionats amb la rigidesa arterial patològica en una població general mediterrània i en una població mediterrània de risc entremig, ja que la majoria d'estudis amb CAVI han estat duts a terme en població asiàtica. Tenint en compte que la rigidesa arterial és una bona precursora de les malalties cardiovasculars, una bona estratègia a prevenció primària seria centrar-se en els estils de vida. Per tant, per millorar la prevenció primària de les malalties cardiovasculars, és important conèixer quins factors estan relacionats amb la rigidesa arterial en aquestes poblacions.

Objectius

1. En la població general mediterrània:
   1.1. Estimar la prevalença de la rigidesa arterial patològica.
   1.2. Avaluar l'associació de la rigidesa arterial amb els estils de vida i els factors de risc cardiovascular.
   1.3. Comparar les diferències en la rigidesa arterial en individus amb factors de risc cardiovascular (WCVRF) amb individus sans (FCVRF).
   1.4. Estudiar la distribució de la rigidesa arterial en tots els nivells de risc cardiovascular.
2. En la població mediterrània de risc cardiovascular entremig:
   2.1. Descriure la prevalença de rigidesa arterial patològica.
   2.2. Analitzar l'associació d'estils de vida, nivell socioeconòmic i factors de risc cardiovascular amb rigidesa arterial.

Mètodes

Es van dur a terme tres estudis transversals en dues poblacions diferents:

a) Una població mediterrània general, amb 2613 participants de Girona d'entre 35 i 79 anys (2007-2013)
b) Una població mediterrània de risc cardiovascular entremig, amb 2380 participants d'entre 35 i 74 anys de tres regions diferents d'Espanya (2011-2013).

La variable principal va ser la rigidesa arterial mesurada amb el CAVI (l'aparell utilitzat fou el VaSera VS-1500®). Per analitzar quins factors estaven associats a la rigidesa arterial patològica (CAVI $\geq$ 9) en ambdues poblacions es van dur a terme regressions logístiques considerant les següents variables:

a) Variables relacionades amb els estils de vida: dieta (DQI-*diet quality index*- i adherència a la dieta mediterrània), activitat física, hàbit tabàquic, consum d'alcohol i problemes amb el son.
b) Factors de risc cardiovascular: hipertensió, diabetis, hipercolesterolèmia i obesitat (index de massa corporal -IMC-).
c) Nivell socioeconòmic: nivell educatiu assolit i classe ocupacional.

Resultats

Els valors del CAVI van ser més alts en homes que en dones en ambdues poblacions i augmentaven amb l'edat.

En la població general mediterrània, la prevalença de CAVI patològic era de 41.1% (46.8% en homes i 36.0% en dones). El grup d'individus sans (FCVRF) tenia una prevalença menor (21.6% dels homes i 14.4% de les dones) que el grup amb factors de risc (WCVRF) (57.9% dels homes i 51.8% de les dones).

En els homes, CAVI $\geq$ 9 estava associat positivament a hipertensió (OR: 2.70; IC 95% 1.90-3.87) i diabetis (OR: 2.38; IC 95% 1.52-3.78), i negativament a sobrepès (IMC $\geq$ 25 - <30 kg/m^2) (OR: 0.44; IC 95% 0.27-0.72), obesitat (IMC $\geq$ 30 kg/m^2) (OR: 0.28; IC 95% 0.14-0.58) i activitat física (OR: 0.66; IC 95% 0.47-0.92).

En les dones, el CAVI $\geq$ 9 estava associat positivament a hipertensió (OR: 2.22; IC 95% 1.59-3.09) i hipercolesterolèmia (OR: 1.40; IC 95% 1.01-1.94), i inversament relacionat a obesitat (IMC $\geq$ 30 kg/m^2) (OR: 0.38; IC 95% 0.20-0.71).

A la població de risc entremig, la prevalença de CAVI $\geq$ 9 era de 48.6% (51.5% en els homes i 44.0% en les dones). En els homes, el CAVI $\geq$ 9 estava associat positivament a hipertensió (OR: 2.11; IC 95% 1.72-2.59), diabetis (OR: 1.83; IC 95% 1.50-2.23) i haver completat només educació primària (OR: 1.32; IC 95% 1.03-1.70), i estava inversament associat a IMC (OR: 0.89; IC 95% 0.87-0.91). En les dones, el CAVI $\geq$ 9 estava associat a hipertensió (OR: 2.14; IC 95% 1.74-2.62) i diabetis (OR: 1.86; IC 95% 1.52-2.26), i inversament associat a IMC (OR: 0.89; IC 95% 0.87-0.91).

Conclusions

- El CAVI és més alt en el grup amb factors de risc cardiovascular (WCVRF) que no en el grup d'individus sans (FCVRF) i també és més alt en la població de risc entremig.
- Els factors de risc cardiovascular com la hipertensió i la diabetis estan associats positivament a la rigidesa arterial patològica, i l'IMC està inversament associat.

- Els estils de vida no hi estan associats, excepte l'activitat física en els homes de la població general. En els homes de la població de risc entremig, el fet d'haver completat només l'educació primària també està associat al CAVI ≥ 9.
- Els nostres resultats fomenten certes estratègies per millorar la prevenció primària de les malalties cardiovasculars a atenció primària. Aquestes inclouen la detecció precoç de rigidesa arterial patològica (amb el CAVI), la realització d'activitats encaminades a controlar la diabetis i la hipertensió i la promoció d'activitat física sobretot en homes de la població general. A més, hauríem d'emfatitzar aquestes activitats preventives en homes que han assolit un nivell màxim d'educació primària en la població de risc entremig.

Resumen

Introducción

Las enfermedades cardiovasculares son la primera causa de mortalidad y morbilidad en el mundo, siendo responsables de un tercio de todas las muertes y casi la mitad de las muertes por enfermedades no transmisibles. Asimismo, más de un 10% de la carga total de enfermedad se atribuye a las enfermedades cardiovasculares.

La patología de base de las enfermedades cardiovasculares es la aterosclerosis, que suele iniciarse durante la juventud y que progresa silenciosamente a lo largo de los años. En la detección precoz de las enfermedades cardiovasculares es importante la detección de la aterosclerosis subclínica, con medidas como la rigidez arterial. Entre los métodos no invasivos para medirla está el *cardio-ankle vascular index* (CAVI), un método relativamente nuevo que no depende del valor de la tensión arterial en el momento de realizar la medida, a diferencia de la velocidad de onda de pulso (PWV).

Sería lógico encontrar la mayor parte de los eventos cardiovasculares en la población de alto riesgo. Sin embargo, más del 50% de los eventos cardiovasculares ocurren en la población de riesgo cardiovascular intermedio - riesgo coronario entre $\geq$ 5% to < 15% según la ecuación de riesgo REGICOR- que comprende el 30% de la población. Esta población es importante a la hora de reducir los eventos cardiovasculares, ya que es la que tiene más posibilidades de ser reclasificada en otro grupo de riesgo cardiovascular.

Dado que los factores clásicos de riesgo cardiovascular han sido ampliamente estudiados, tendríamos que centrarnos en medidas de aterosclerosis subclínica. Sin embargo, existe poca evidencia de los factores relacionados con la rigidez arterial patológica en una población general mediterránea y en una población de riesgo intermedio, ya que la mayor parte de los estudios con el CAVI han sido realizados en población asiática. Puesto que la rigidez arterial es una buena precursora de las enfermedades cardiovasculares, una buena estrategia en prevención primaria sería centrase en los estilos de vida. Con el objetivo de

mejorar la prevención primaria de las enfermedades cardiovasculares, es importante conocer que factores están relacionados con la rigidez arterial en estas poblaciones.

Objetivos

1. En la población general mediterránea:
   1.1. Estimar la prevalencia de la rigidez arterial patológica.
   1.2. Evaluar la asociación de la rigidez arterial con los estilos de vida y los factores de riesgo cardiovascular.
   1.3. Comparar las diferencias en la rigidez arterial en individuos con factores de riesgo cardiovascular (WCVRF) con individuos sanos (FCVRF).
   1.4. Estudiar la distribución de la rigidez arterial en todos los niveles de riesgo cardiovascular.
2. En la población mediterránea de riesgo cardiovascular intermedio:
   2.1. Describir la prevalencia de rigidez arterial patológica.
   2.2. Analizar la asociación de estilos de vida, nivel socioeconómico y factores de riesgo cardiovascular con rigidez arterial.

Métodos

Se realizaron tres estudios transversales en dos poblaciones distintas:

a) Una población mediterránea general, con 2613 participantes de Girona con edades comprendidas entre los 35 y los 79 años (2007-2013).
b) Una población mediterránea con riesgo cardiovascular intermedio, con 2380 participantes de entre 35 y 74 años de tres regiones diferentes de España (2011-2013).

La variable principal estudiada fue la rigidez arterial medida con el CAVI (se utilizó el VaSera VS-1500®). Para analizar cuáles eran los factores relacionados a la rigidez arterial patológica (CAVI $\geq$ 9) en las dos poblaciones, se realizaron regresiones logísticas considerando las siguientes variables:

a) Variables relacionadas con los estilos de vida: dieta (DQI -*diet quality index*- y adherencia a la dieta mediterránea), actividad física, hábito tabáquico, consumo de alcohol y problemas relacionados con el sueño.

b) Factores de riesgo cardiovascular: hipertensión, diabetes, hipercolesterolemia y obesidad (medido con el índice de masa corporal -IMC-).
c) Nivel socioeconómico: nivel educativo alcanzado y clase ocupacional.

Resultados

Los valores del CAVI fueron más altos en hombres que en mujeres en ambas poblaciones, aumentando con la edad.

En la población general mediterránea, la prevalencia del CAVI patológico era de 41.1% (46.8% en hombres y 36.0% en mujeres). El grupo de individuos sanos (FCVRF) tenia una prevalencia menor (21.6% de los hombres y 14.4% de las mujeres) que el grupo con factores de riesgo (WCVRF) (57.9% de los hombres y i 51.8% de las mujeres).

En los hombres, CAVI $\geq$ 9 estaba asociado positivamente a hipertensión (OR: 2.70; IC 95% 1.90-3.87) y diabetes (OR: 2.38; IC 95% 1.52-3.78), y negativamente a sobrepeso (IMC $\geq$ 25 - <30 kg/m^2) (OR: 0.44; IC 95% 0.27-0.72), obesidad (IMC $\geq$ 30 kg/m^2) (OR: 0.28; IC 95% 0.14-0.58) y actividad física (OR: 0.66; IC 95% 0.47-0.92). En las mujeres, el CAVI $\geq$ 9 estaba asociado positivamente a hipertensión (OR: 2.22; IC 95% 1.59-3.09) y hipercolesterolemia (OR: 1.40; IC 95% 1.01-1.94), y inversamente relacionado con obesidad (IMC $\geq$ 30 kg/m^2) (OR: 0.38; IC 95% 0.20-0.71).

En la población de riesgo intermedio, la prevalencia del CAVI $\geq$ 9 era de 48.6% (51.5% en los hombres y 44.0% en las mujeres). En los hombres, el CAVI $\geq$ 9 estaba asociado positivamente a hipertensión (OR: 2.11; IC 95% 1.72-2.59), diabetes (OR: 1.83; IC 95% 1.50-2.23) y haber completado solamente educación primaria (OR: 1.32; IC 95% 1.03-1.70), y estaba inversamente asociado a IMC (OR: 0.89; IC 95% 0.87-0.91). En las mujeres, el CAVI $\geq$ 9 estaba asociado a hipertensión (OR: 2.14; IC 95% 1.74-2.62) y diabetes (OR: 1.86; IC 95% 1.52-2.26), y inversamente asociado a IMC (OR: 0.89; IC 95% 0.87-0.91).

Conclusiones

- El CAVI es más alto en el grupo con factores de riesgo cardiovascular (WCVRF) que en el grupo de individuos sanos (FCVRF) y también es más alto en la población de riesgo intermedio.
- Los factores de riesgo cardiovascular como la hipertensión y la diabetes están asociados a la rigidez arterial patológica y el IMC está inversamente relacionado.
- Los estilos de vida no están asociados, excepto la actividad física en los hombres de la población general. En los hombres de la población de riesgo intermedio, habiendo completado solamente educación primaria también estaba asociado a CAVI ≥ 9.
- Teniendo en cuenta nuestros resultados, habría que promover estrategias para mejorar la prevención primaria de las enfermedades cardiovasculares en atención primaria, como la detección de rigidez arterial patológica (medida con el CAVI), la realización de actividades para controlar la diabetes y la hipertensión y la promoción de actividad física, principalmente en hombres de la población general. Tendríamos que prestar especial atención a aquellos hombres de la población de riesgo intermedio con una educación primaria.

1. INTRODUCTION

1.1. Context and rationale

'Health' was defined at the 1946 International Health Conference organized by the World Health Organisation (WHO) as a state of complete physical, mental and social well-being and not merely as the absence of disease or infirmity. Subsequently, the concept of 'health' has been broadened and it is now regarded as a multidimensional phenomenon embracing a combination of factors that affect individuals' health, which interact with different levels of organisation known as determinants of health.

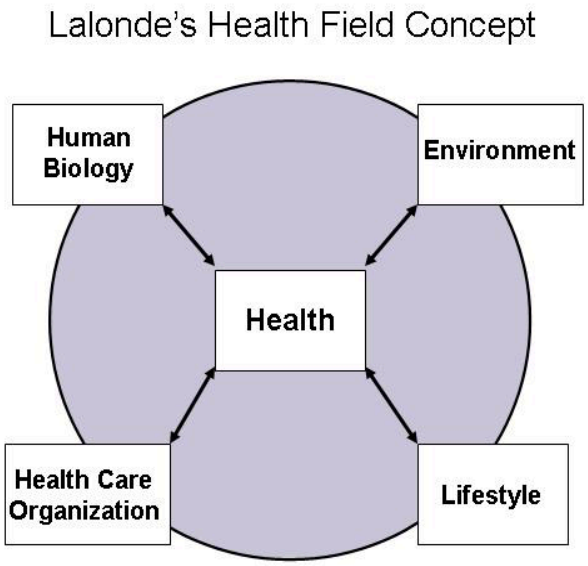


Figure 1. The four key determinants of health according to Lalonde's Health Field Concept[1].

Lalonde was one of the pioneers of the idea of determinants of health. He developed the Health Field Concept (Figure 1), which considered human biology, environment, lifestyle and health-care organisation as the major elements that underlie the concept of health. These four elements were identified through an

examination of the causes and underlying factors of sickness and death in Canada, and via an assessment of the role each element plays in affecting the level of health in that country[1]. In his report, he defined lifestyle as "the aggregation of decisions by individuals which affect their health and over which they more or less have control. Personal decisions and habits that are bad, from a health point of view, create self-imposed risks. When those risks result in illness or death, the victim's lifestyle can be said to have contributed to, or caused, his own illness or death".

Table 1. Comparison of health expenditure in the allocation of mortality in accordance with the epidemiological model for health policy analysis[2].

Epidemiological model for health policy analysis	Federal health expenditures 1974-76 (percentage)	Allocation of mortality to the epidemiological model (percentage)
System of Health Care Organisation	90.6	11
Lifestyle	1.2	43
Enviroment	1.5	19
Human biology	6.9	27
Total	100.2 [a]	100%

[a] Due to rounding

Dever extended this concept into an epidemiological model of health policy[2] that established a direct link between health determinants and the use of resources. This author identified the resources not being used according to the causes that actually determine the health of the population. His report showed how the US Government spent a disproportionate amount of money on the System of Health Care Organisation, when in fact this system only contributed minimally to reducing mortality and morbidity. Lifestyle, human biology and the environment, on the other hand, contributed greatly to mortality and morbidity but received little

investment (Table 1). He thus asked: "How do we change our model so that diseases resulting from lifestyles may be significantly reduced?"

Dahlgren and Whitehead widened the determinants of the field of health by introducing social health factors into a 'rainbow model' [3]. Individuals were placed at the centre together with those largely fixed characteristics that influence their health. Surrounding them were placed the various layers of influences on health (individual lifestyle factors, community influences, living and working conditions, and more general social conditions) that are potentially modifiable (Figure 2). This model emphasises the interactions between the different layers.

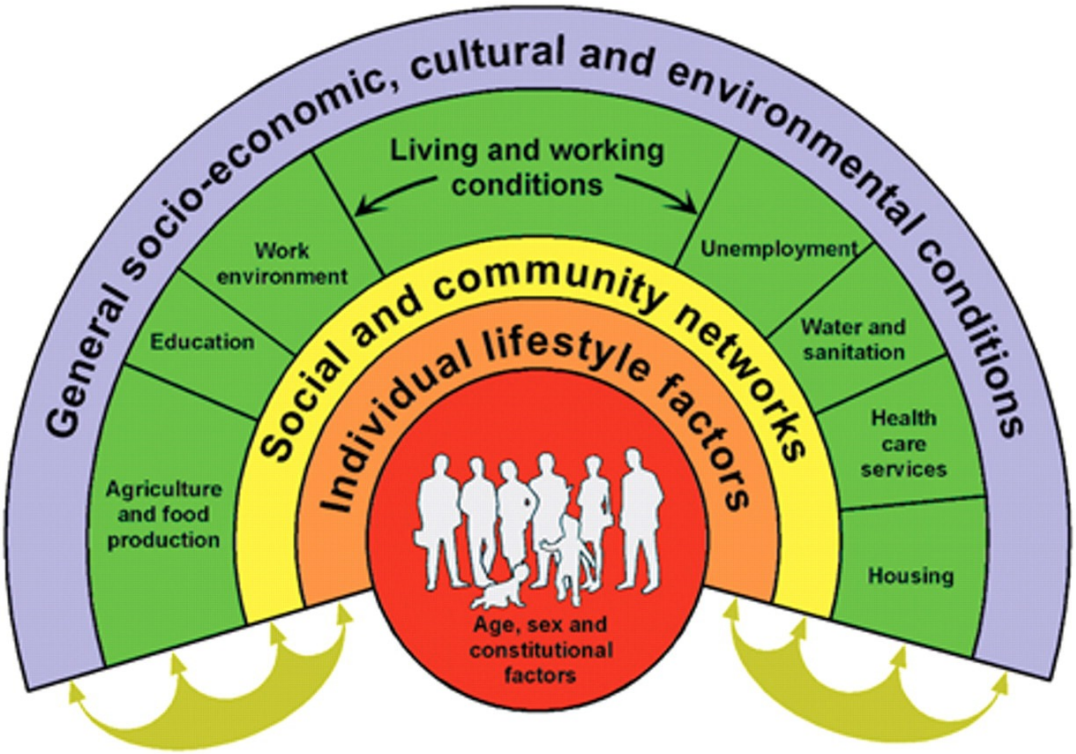


Figure 2. Main determinants of health. The Dahlgren-Whitehead rainbow model[3].

The International Conference on Primary Health Care held in Alma-Ata in 1978 underlined the importance of the determinants of health. Health care has since then been more focused towards prevention, keeping people healthy rather than focussing on caring for the sick.

Cardiovascular diseases (CVDs) remain the leading cause of morbidity and mortality worldwide, despite improvements in outcomes. They account for 31% of all deaths and 45% of all non-communicable disease deaths, more than twice of those caused by cancer. In Europe, 4 million people die from CVD every year, of which 1.4 million die prematurely before the age of 75 years[4]. More than 10% of the global disease burden, as measured in disability-adjusted life-years (DALY), is attributed to CVD, and there are growing inequalities in the occurrence and outcome of CVD between countries and social classes [5].

Most frequently, CVD baseline pathology is atherosclerosis[6]. Given that the classical risk factors of cardiovascular disease have already been widely studied, it now seems time to focus on measures of subclinical atherosclerosis such as arterial stiffness. Increased arterial stiffness is a marker of cardiovascular (CV) 'aging' and a predictor of adverse CV outcomes in both the general population and in patients with overt CVD[7]. Of measures of arterial stiffness, the Cardio-Ankle Vascular Index (CAVI) is a newly devised indicator that does not depend on blood pressure during the measuring time[8–10].

Given the role of arterial stiffness as a critical precursor of CVD, according to models of determinants of health (Figure 1 and 2, Table 1) a good strategy is to focus on lifestyles. Whereas it is evident that CVD are related to lifestyle[11], more evidence is needed for the association between arterial stiffness (measured as CAVI) and lifestyle in Mediterranean populations since CAVI to date has only been well studied in Asian populations[12,13].

Southern European countries have lower death rates from CVD than other western European countries[14]. Mediterranean populations are of special interest because of their relatively low incidence of acute myocardial infarction (AMI)

despite the high prevalence of risk factors; this is known as the 'Mediterranean paradox'[15]. The study of this population thus offers opportunities for exploring unmeasured factors that might be protecting it against CVD.

The aim of primary CV prevention is to reduce the incidence of CV events. One of the strategies used is to target high-risk individuals. In clinical practice, we use cardiovascular risk functions to identify high-risk individuals by estimating the probability of a coronary event occurring within the next 10 years. It seems reasonable to expect that most coronary events will be concentrated in the high-risk population. However, over 50% of CV events occur in the population with intermediate CV risk, which represents approximately 30% of the population aged 35–74[16]. This population is of particular interest in efforts designed to reduce CV events as it offers greater possibilities for reclassifying CV risk.

In the light of these ideas, this thesis aims to examine (i) the distribution of CAVI and the prevalence of pathological CAVI in both a general Mediterranean population and a Mediterranean population with intermediate CV risk, (ii) the differences of CAVI in healthy individuals compared to those with CV risk factors, and (iii) the factors that are associated with pathological arterial stiffness (measured with CAVI), in order to improve the primary prevention of CVDs and reclassify CV risk.

1.2. Cardiovascular disease

CVD include diseases of the heart, vascular diseases of the brain and diseases of blood vessels. There are different types of CVDs:

a) CVDs due to atherosclerosis: coronary heart disease (CHD) (such as angina and AMI), cerebrovascular disease (stroke) and peripheral artery disease.
b) Other CVDs: rheumatic heart disease, congenital heart disease, cardiomyopathies and cardiac arrhythmias, among others.

The main underlying pathology that leads to CHD and cerebrovascular diseases is atherosclerosis, an inflammatory process in which the artery wall thickens as a result of an accumulation of white blood cells, thereby creating an atheromatous plaque[17]. The process of atherosclerosis starts in childhood and adolescence due to the presence of risk factors, silently develops over a lifetime, and then finally manifests itself as a CHD or stroke in later life[6,18].

1.2.1. Mortality

Worldwide, CVD is the commonest cause of death and a major cause of morbidity: more people die annually from CVD than from any other cause. In 2016, CVD caused over 17.6 million deaths (31% of total deaths) (Figure 3), 8.93 million neoplasms, and 3.54 million chronic respiratory diseases. Of CVD, CHD and strokes account for 85.1% of all deaths[19].

Despite a decrease in mortality in Europe as a whole[a], CVD is still responsible for over 3.9 million deaths a year, that is, 45% of all deaths: it accounts for 1.8 million deaths in men (40% of all deaths) and 2.1 million deaths in women (49%). CVD is the main cause of death in all but 12 countries in men, and the main cause of

[a] European countries considered as the WHO European Region (53 countries) (Appendix 1)

death in all but two countries in women.

Deaths rates from CHD and strokes (the main forms of CVD) are higher in Central and Eastern European countries. CHD (the leading single cause of mortality in Europe) accounts for 1.8 million deaths, and strokes for one million. In men, CHD is responsible for 862,000 deaths a year (19% of all deaths) and strokes are responsible for 405,000 deaths (9%) (Figure 4). In women, CHD accounts for 877,000 deaths (20%) and strokes for 583,000 deaths a year (13%) (Figure 5)[4,20].

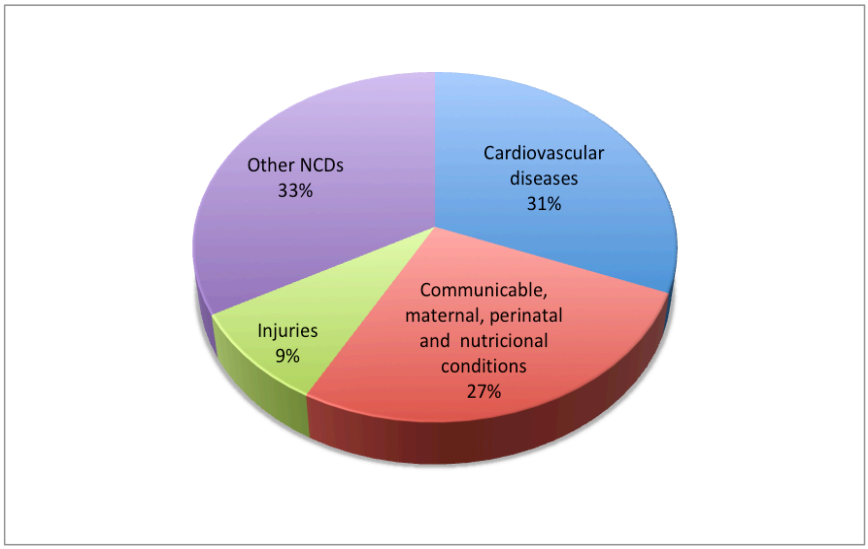


Figure 3. Distribution of the major causes of death worldwide[6].
NCDs: non-communicable diseases.

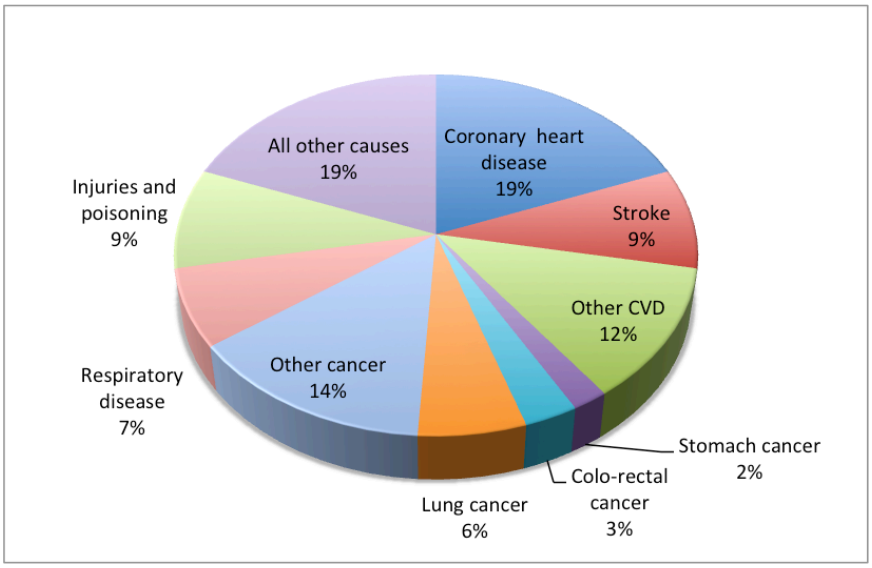


Figure 4. Distribution of deaths by cause in Europe in males (latest available year)[20]. CVD: Cardiovascular diseases.

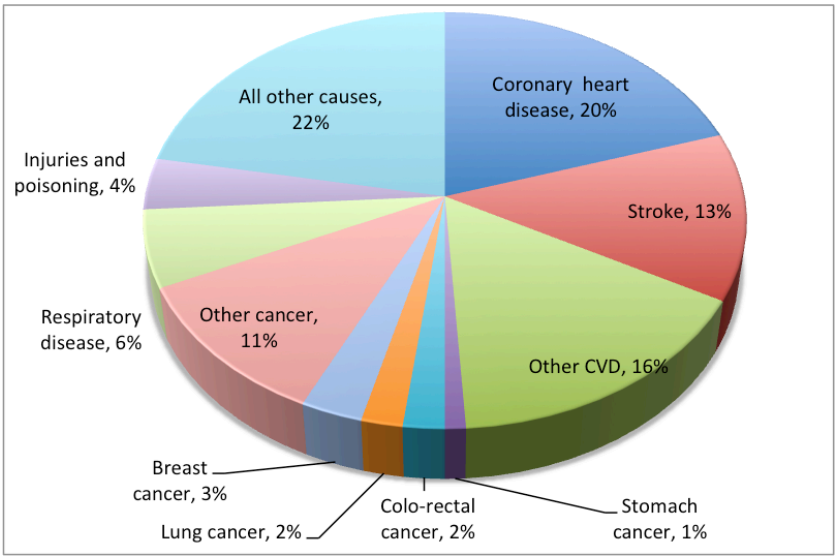


Figure 5. Distribution of deaths by cause in Europe in females (latest available year)[20]. CVD: Cardiovascular diseases.

In the European Union (EU)[b] countries, CVD is responsible for 1.8 million deaths (37% of all EU deaths): 800,000 deaths per year in men (34% of all deaths) and one million deaths (40%) in women. CHD is responsible for 335,000 deaths per year in men (14% of all deaths) and 297,000 deaths in women (12%). Strokes account for 176,000 deaths per year in men (7% of all deaths) and 250,000 deaths in women (10%) (Figures 6 and 7)[4,20].

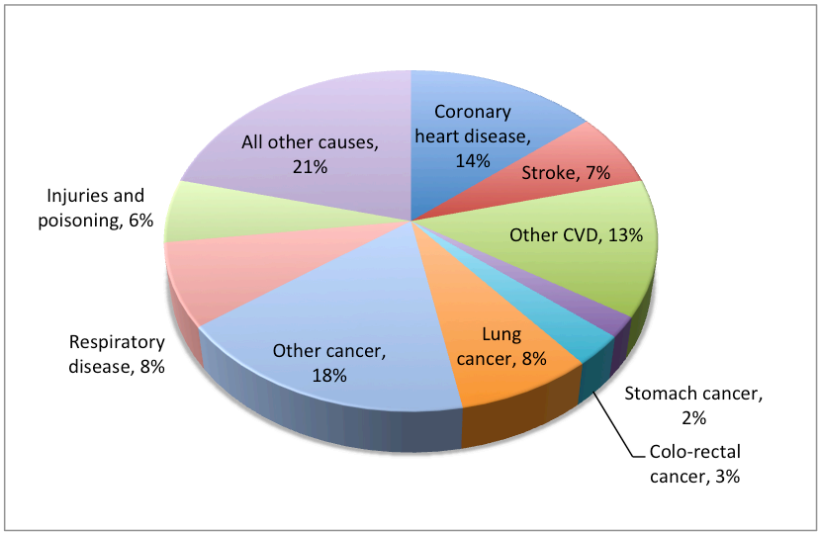


Figure 6. Distribution of deaths by cause in the EU in males (latest available year)[20]. CVD: Cardiovascular diseases.

[b] The 28 member states of the European Union (Appendix 1)

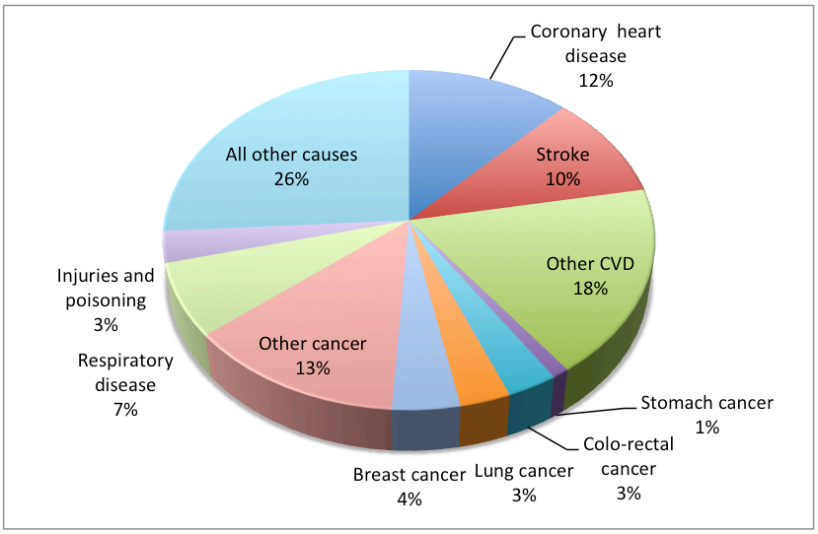


Figure 7. Distribution of deaths by cause in the EU in females (latest available year)[20]. CVD: Cardiovascular diseases.

Although mortality from CVD in Spain is one of the lowest in the world (Figure 8), CVD is still the leading cause of mortality. Of the total deaths, 31% were due to CVD in 2011 (27% in men and 34% in women); in all, 54% of those deaths were due to CHD or strokes[21]. In 2014, 120,000 people died of CVD[20].

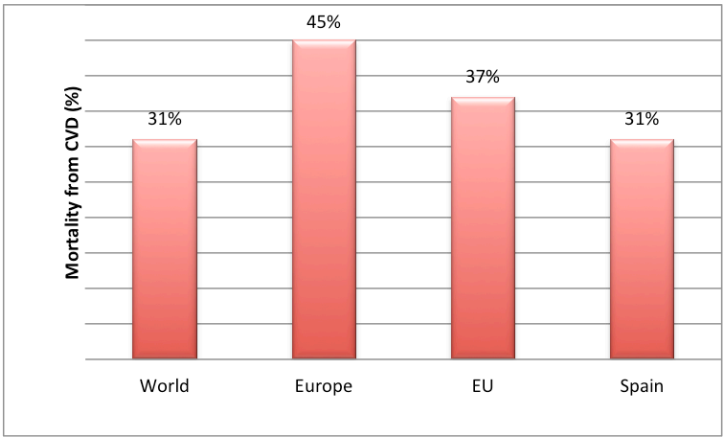


Figure 8. Comparison of mortality rates in different areas of the world.

1.2.1.1. Premature mortality

Globally, CVD causes 17 million premature deaths (counted as deaths before the age of 70) each year (37% of total deaths before 70)[19]. In Europe, CVD is the leading cause of mortality in people under 75. Of total deaths, 1.3 million are caused by CVD each year (35% of all deaths before 75). By contrast, in the EU, CVD is the second commonest cause of death in people under 75 (436,000 deaths, 26%), behind deaths due to cancer (681,000 deaths, 40%)[20].

1.2.2. Morbidity

Along with its burden of mortality, CVD contributes substantially to morbidity all over the world. Although statistics show that CVD mortality is decreasing in nearly all European countries, its incidence and prevalence are still significant. Over the last 25 years, most European countries have reported an increase in the number of new cases of CVD, as well as in the absolute numbers of CVD, due to an increase in the total population and, in particular, the number of older people.

1.2.2.1. Incidence

In 2016, there were more than 54 million new cases of CVD throughout the world, more than 20 million new cases of CHD, and around 13.6 million new cases of stroke[22]. In 2015, about 11.3 million new cases of CVD appeared in Europe, half of which were due to CHD, and around 14% due to strokes. In the EU, the incidence of CVD accounted for 6.1 million new cases, half of them due to CHD and around 10% due to strokes[20]. In Spain, there were more than 430,000 new cases of CVD in 2015, more than 40% due to CHD and about 10% due to strokes[20].

1.2.2.2. Prevalence

In 2016, nearly 470 million people throughout the world were living with CVD, of

which CHD is regarded as the most prevalent CV condition (33% of all CVD) followed by strokes (17%)[22]. In 2015 in Europe, more than 85 million people were living with CVD, with CHD affecting about 30 million people (35%). In the EU, there were almost 49 million people living with CVD, 27% of which (more than 13 million) were affected by CHD. In Spain, more than 4 million people suffer from CVD: more than 800,000 people live with CHD (20% of all CVD) and more than 270,000 with strokes (6.8%)[20].

1.2.2.3. Disability-adjusted life-years lost

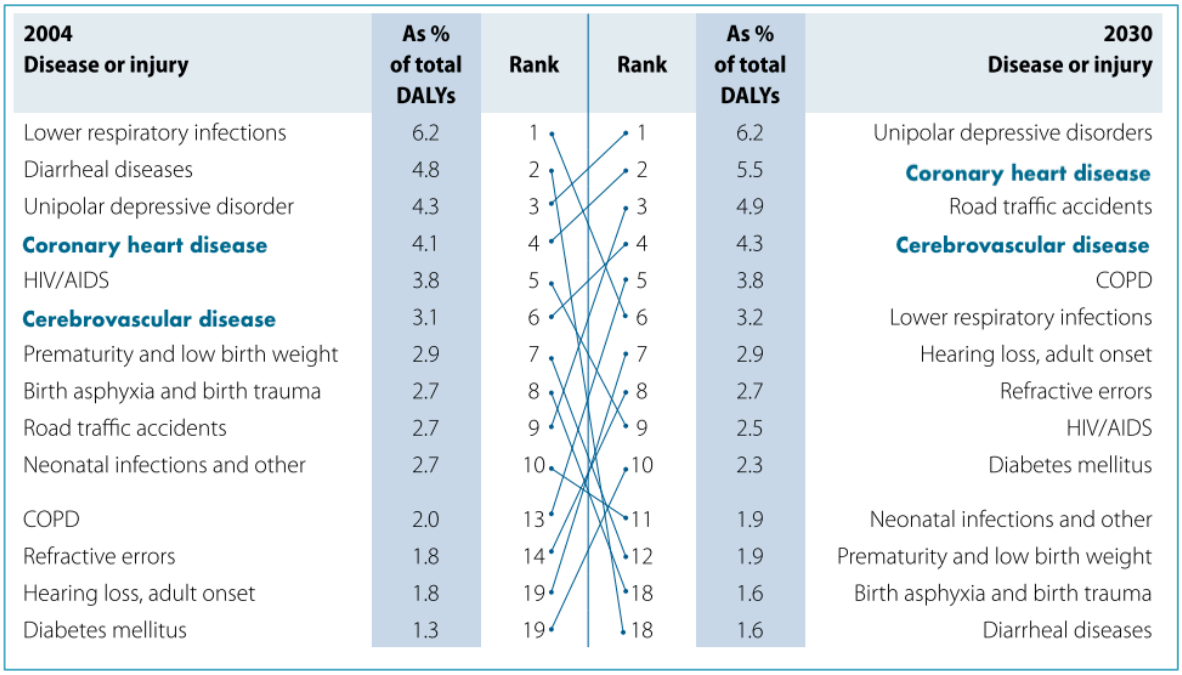
The burden of CVD is not confined to mortality. One measure of the overall disease burden is the disability-adjusted life-year (DALY), measured as a sum of the years of life lost (YLLs) due to a death from a condition and years lived with a disability (YLDs) due to a condition. One DALY is equivalent to one year of healthy life lost.

Worldwide, 10% of the global disease burden (as measured in DALYs) is attributed to CVD, which is estimated to be responsible for a 151 million DALYs annually, of which about 62 million are due to coronary heart disease and more than 46 million to cerebrovascular disease [6,23]. According to WHO[6], the burden of CVD is going to increase in the next few years and will become one of the most severe components of the global disease burden (Figure 9).

CVD was responsible for 64.7 million DALYs lost in Europe in 2015 (23% of the total) and was the main cause of all lost DALYs. CHD was the leading single cause of DALYs lost (35.6 million; 13% of the total), strokes being the second most frequent cause of lost DALYs (17.1 million; 6% of the total). In the EU, 26 million DALYs were lost in 2015 due to CVD (19% of the total), 13.3 million DALYs were lost due to CHD (10% of the total), and 6.5 million DALYs were lost due to strokes (5% of the total)[20].

In Spain, 15% of the DALYs lost were due to CVD in 2016 (over 1.5 million). CHD

was the second most frequent cause (nearly 7% of the total), while strokes were the seventh most frequent cause (more than 3%)[24].



2004 Disease or injury	As % of total DALYs	Rank	Rank	As % of total DALYs	2030 Disease or injury
Lower respiratory infections	6.2	1	1	6.2	Unipolar depressive disorders
Diarrheal diseases	4.8	2	2	5.5	**Coronary heart disease**
Unipolar depressive disorder	4.3	3	3	4.9	Road traffic accidents
Coronary heart disease	4.1	4	4	4.3	**Cerebrovascular disease**
HIV/AIDS	3.8	5	5	3.8	COPD
Cerebrovascular disease	3.1	6	6	3.2	Lower respiratory infections
Prematurity and low birth weight	2.9	7	7	2.9	Hearing loss, adult onset
Birth asphyxia and birth trauma	2.7	8	8	2.7	Refractive errors
Road traffic accidents	2.7	9	9	2.5	HIV/AIDS
Neonatal infections and other	2.7	10	10	2.3	Diabetes mellitus
COPD	2.0	13	11	1.9	Neonatal infections and other
Refractive errors	1.8	14	12	1.9	Prematurity and low birth weight
Hearing loss, adult onset	1.8	19	18	1.6	Birth asphyxia and birth trauma
Diabetes mellitus	1.3	19	18	1.6	Diarrheal diseases

Figure 9. Leading causes of the disease burden in the world (2004-2030)[6,23].
HIV: human immunodeficiency virus; AIDS: acquired immune deficiency syndrome; COPD: chronic obstructive pulmonary disease.

1.2.3. Economic costs

In addition to the great burdens of mortality and morbidity, CVD has significant economic costs that include direct health-care costs (i.e. hospitalisation, drugs and follow-ups) and indirect or non-health care costs (premature mortality, temporary or permanent absence from work, and informal care). In 2015, the total cost of CVD to the EU was 210 billion € (8% of total health care expenditure), of which 110 billion € (53% of the total cost of CVD) were due to health care costs, 45 billion € (21%) due to informal care costs, 31 billion € (15%) due to productivity loss caused by mortality, and 23 billion € (11%) due to productivity loss caused by morbidity[20].

Of the total economic costs of CVD in 2015 in Spain, 9% of the total health care expenditure (more than 16 billion €) was as a result of CVD. Around 55% of that cost (9 billion €) was due to health care costs, 24% (4 billion €) to informal care, 12% (2 billion €) to productivity loss due to morbidity, and 9% (more than 1 billion €) to productivity loss due to mortality[20].

1.3. Prediction of the CVD risk

The CV risk can be calculated as the sum of numerous interacting risk factors since, apart from familial hypercholesterolemia, no single factor on its own causes CVD[25]. In women, the CV risk is lower than in men and is delayed by up to 10 years [11].

CV risk prediction is used largely in clinical practice to stratify risk and to manage preventive strategies[11,26]. However, there are inherent limitations: they are short-term risk predictions (10 years), are highly age dependent, and do not take into account non-classical risk factors or pharmacological treatments[27,28].

1.3.1. Risk equations

Numerous CV risk assessment systems are used, including the Framingham, REGICOR (Registre Gironí del Cor), SCORE (Systematic Coronary Risk Estimation), AS-SIGN (CV risk estimation model from the Scottish Intercollegiate Guidelines Network), QRISK, PROCAM (Prospective Cardiovascular Munster Study) and CUORE systems. In this thesis we make use of the following risk equations:

1.3.1.1. Framingham

The Framingham risk score is the result of the combination of two studies: the Framingham Heart Study – an on-going cohort study set up in 1948 in Framingham (Massachusetts, USA) with 5,209 participants aiming to uncover the

determinants of coronary heart disease – and the Framingham offspring study. It calculates the 10-year risk of a CV event in the population aged 30–75 by assessing sex, age, total Cholesterol (mg/dL), HDL Cholesterol (HDL-C) (mg/dL), Systolic Blood Pressure (SBP) (mmHg), smoking status, diabetes mellitus (DM) and hypertensive treatment[11,25,29].

The risk is classified into three bands[30]:

- low (less than 10% CHD risk within the next 10 years)
- intermediate (10–20% risk)
- high (over 20%)

1.3.1.2. REGICOR (Registre Gironí del Cor)

In light of the fact that the Framingham risk equations overestimate the risk of coronary heart disease in the southern European countries[30], and the low incidence of CHD in Spain despite the high prevalence of CV risk factors (Mediterranean paradox)[15], a recalibrated Framingham equation (REGICOR) has been developed[31,32] that has been shown to be effective in predicting CVD [16,33].
The REGICOR (Registre Gironí del Cor) function is an adaptation of the Framingham equation to the low incidence of CHD in Spain, and has been validated in a sample from Spain[34]. It takes into account sex, age, total cholesterol, HDL-C, SBP, Diastolic Blood Pressure (DBP), DM, and smoking status, and the final function provides an estimate of the risk of having a coronary event (fatal or otherwise) within 10 years in the population aged 35–74.

The risk is classified into four bands[16] (REGICOR risk tables in Appendix 2) :

- low (<5%),
- moderate (5–9.9%)
- high (10–14.9%)
- very high (≥15%)

1.3.1.3. SCORE (Systematic Coronary Risk Evaluation)

The SCORE equation was developed using 12 European cohort studies from 11 European countries. The model estimates the 10-year risk of fatal CVD (not only coronary events) in the 40–65 age group. This narrow age range is, precisely, one of the limitations of SCORE since only 18% of all fatal CVD events occur in this age group[35]. It is based on age, gender, smoking habits, total cholesterol and SBP. There are different versions for use in high and low risk countries[36] (Appendix 3). In the 2003 European guidelines on cardiovascular disease prevention in clinical practice, a 10-year risk of CVD death ≥5% was considered to be a high risk[37,38].

1.3.1.4. European Society of Hypertension (ESH)/European Society of Cardiology (ESC) Guidelines

The 2013 ESH/ESC guidelines for the management of arterial hypertension[36] and the 2012 ESC prevention guidelines[38] classified CV risk using blood pressure (BP), CV risk factors, asymptomatic organ damage (OD), presence of diabetes mellitus, symptomatic CVD and/or chronic kidney disease (CKD) (Appendix 4, Table 25).

The 10-year CV mortality risk classified into four bands: (Appendix 4, Table 26):

- low risk (<1%)
- moderate (≥1–<5%)
- high (≥5–<10%)
- very high risk (≥10%)

1.3.2. Intermediate cardiovascular risk population

In the Mediterranean region, the incidence of cardiovascular disease (CVD) is low[15,16]. However, more than 50% of all cardiovascular (CV) events occur in the population at intermediate CV risk, which represents approximately 30% of the

total population[16,34]. Thus, measures to improve CV risk classification are greatly needed in this fraction of the population in order to reclassify the risk[15,16] and reduce CV events. Intermediate cardiovascular risk is defined by the following classifications from any of these three different 10-year risk equations:

1. Framingham-REGICOR-adapted coronary risk equation used due to the low CV incidence in our region, and validated in a Spanish population: a coronary risk in the range ≥5–<15% [9].
2. SCORE risk function: CV mortality risk in the range ≥1–<5% [40].
3. 2013 ESH/ESC guidelines for the management of arterial hypertension: moderate CV mortality risk category (≥1–<5%)[36].

1.4. Prevention of CVD

Despite improvements in outcomes, CVD is still a major cause of mortality and morbidity. A high proportion of the deaths occurring in people under the age of 60 could have been prevented[5,6]. Moreover, it is estimated than 80% of CVD is preventable if health-risk behaviour is eliminated[41–44]. Thus, it is clear that a greater focus on preventive strategies is required if the burden of CVD is to be reduced.

CVD prevention is a challenge for the general population, politicians and healthcare professionals, and is defined as a coordinated set of actions at population level or actions targeting an individual whose aim is to minimize the impact of CVD[45]. European guidelines on cardiovascular disease prevention[38], following Rose [41,46], consider that preventive strategies should consider:

a) A population strategy aimed at reducing CVD incidence at population level that promotes both lifestyle and environmental changes.

b) A high-risk strategy, including measures of both primary (individuals with high risk, but no established CVD) and secondary (individuals with

established CVD) prevention designed to reduce risk factors in individuals at greatest risk. These measures target unhealthy lifestyles such as poor-quality diets, physical inactivity, smoking and alcohol consumption.

In the latter strategy, the key element is identifying high-risk individuals via risk functions. Nevertheless, there are certain limitations as most events occur in non-high-risk categories[33,41]. Therefore, given that both strategies give the same estimated benefits[47], Rose[41,46] concluded that both approaches are complementary and important for reducing the CVD burden. He stated that the population strategy only gives a small benefit to each individual, which he enshrined in the prevention paradox: "A preventive measure which brings much benefit to the population, and offers little to each participating individual"[48].

1.5. Cardiovascular risk factors

Although chronic diseases such as CVD are usually the result of exposure to an alleged cause, disease can still sometimes appear in people who have not been exposed to it. Austin Bradford Hill described causality in 1965 in what is known as Hill's criteria of causation[49]. He stated that nine conditions were necessary to establish a causal relationship between two items:

1. Strength: the stronger the association between exposure and disease, the more likely it is to be causal. Even so, weak associations can still be causal.
2. Consistency across studies, countries and time.
3. Specificity, meaning the exposure causes only one disease (although this is rather uncommon in CVD).
4. Temporality: exposure always precedes the outcome. This is probably the only criterion that all epidemiologists agree on.
5. Biological gradient or dose-response curve: an increase in exposure increases the risk.
6. Plausibility: according to Bradford, this concept is satisfied if the relationship is consistent with the current body of knowledge regarding the aetiology

and mechanism of the disease.

7. Coherence: the cause-and-effect should be compatible with all knowledge available to the researcher. This principle is similar to biological plausibility.
8. Experimental studies: evidence from experimental studies is the strongest support for a causal relationship.
9. Analogy: even though there is good evidence for a causal relationship, other hypothesis should still be considered since a similar agent may cause a similar disease, despite weaker evidence for it.

These criteria are still a valuable tool for causal inference, even though specific interpretations of each criterion have evolved over time and have to be adapted to current knowledge[50].

CVD was highly prevalent during the first half of the twentieth century and gave rise to great interest in CV risk factors and determinants. The first population-based study of CVD was initiated in the US by Dawber[51] (the Framingham Heart Study project[52]), and was followed by the Seven Countries study[53]. Subsequently, many other studies have been undertaken, the most relevant of which was the WHO's MONICA project (multinational MONItoring of trends and determinants in CArdiovascular disease). This multinational project, which was carried out in 1979–1997 and involved 21 centres around the world, concluded that a reduction by about two-thirds in CHD mortality could be achieved via changes in risk factors[54].

Many factors are causally related to the development of CVD, of which the following eight are considered to be the most significant:

a) Behavioural factors: unhealthy diet, physical inactivity, smoking and harmful consumption of alcohol are the main behavioural risks in CVD and other major NCDs.
b) Metabolic risk factors: a continuous exposure to unhealthy lifestyles (behavioural risk factors) culminates in hypertension, diabetes mellitus, hypercholesterolemia and overweight and obesity.

Other cardiovascular risk factors include psychosocial factors (socioeconomic status, personality, chronic stress, anxiety, depression), insomnia, advanced age, sex and a history of family disease [5,6,11,55].

The causes of a disease follow an on-going chain of events, during which time certain risk factors interact. In the causal chain for CHD (Figure 10), the first risk factors (type 2 diabetes, cholesterol and blood pressure) act almost directly on the disease. The risk factors located in the second link of the chain act indirectly on CHD via intermediaries. Finally, there is less certainty about the causal relation between CHD and the most distant risk factors[55].

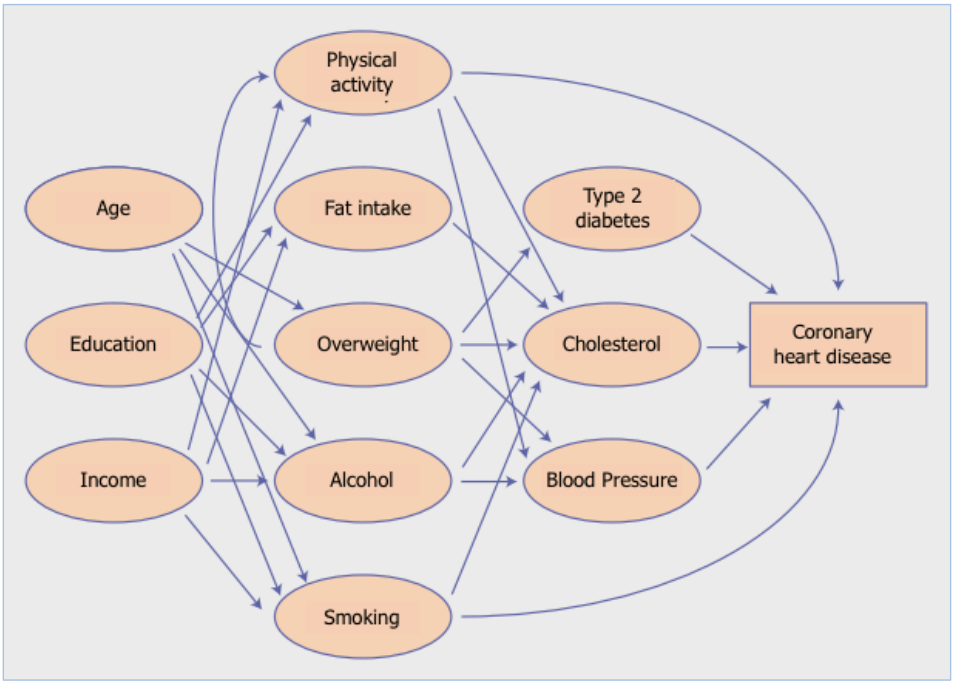


Figure 10. The causal chain for coronary heart disease (CHD) [55]. Arrows indicate some of the pathways along which causes interact.

According to WHO, globally, the five most important risk factors for mortality are hypertension (13% of deaths attributed globally), smoking (9%), diabetes (6%), physical inactivity (6%) and overweight and obesity (5%). All these risk factors are responsible for increasing the risk of chronic diseases such as CHD, type 2 diabetes and some cancers[55].

1.5.1. Hypertension

Hypertension is the leading risk factor in CVD mortality and causes around 7.5 million deaths a year worldwide[55–57], that is, approximately 13% of all deaths globally in any one year. Overall, the prevalence of hypertension in adults over 18 is around 30–45%, and increases with age[57,58]. In Europe, the mean SBP is higher in men, the highest levels being found in Central and Eastern European countries [20]. According to the 2013 ESH/ESC guidelines for the management of arterial hypertension[36], hypertension is defined as values of SBP ≥ 140 mmHg and/or values of DPB ≥ 90 mmHg. The definition and classification of different grades of hypertension are given in Table 2.

Table 2. Classification of office blood pressure levels (mmHg)[36].

Category	Systolic		Diastolic
Optimal	<120	and	<80
Normal	120-129	and/or	80-84
High normal	130-139	and/or	85-89
Grade 1 hypertension	140-159	and/or	90-99
Grade 2 hypertension	160-179	and/or	100-109
Grade 3 hypertension	≥ 180	and/or	≥ 110
Isolated systolic hypertension	≥ 140	and	< 90

High blood pressure is positively related to the incidence of several CV events[57,59–61]. Moreover, the risk of CVD is directly associated with both systolic and diastolic blood pressure levels: for every increase of 20 mmHg in the SBP above 115 mmHg, or in DBP above 75 mmHg, the CVD risk doubles[57,59,62].

Epidemiological studies have shown the benefits to health of lowering blood pressure and the efficacy of specific lifestyle or pharmacological interventions[59]. Although blood pressure can be controlled in most people, the control rates of blood pressure continue to be low since treatment is mostly lifelong and patients are usually asymptomatic[63,64]. High blood pressure can be lowered by lifestyle changes such as reduced salt and alcohol intake, increased physical activity, and weight loss, as well as by treatment with drugs[20,55].

In May 2013, the World Health Assembly recommended nine global targets for the prevention of non-communicable diseases (including CVD), one of which was a 25% relative reduction in the prevalence of high blood pressure[65]. The most effective means of reducing CVD would seem to involve restricting the hypertension control rate to 50%, reducing sodium intake by 30%, and eliminating artificial trans-fat from diets[57,63,66].

1.5.2. Diabetes

Diabetes is a major risk factor in CVD. Globally, increased blood glucose causes 6% of total deaths, 22% of CHD, and 16% of stroke deaths[55], and is associated with a more than two-fold risk of a CV event[67–69]. The prevalence of diabetes is 5.4% worldwide[24], 3.8% in Europe, and 5.1% in EU countries[20].

Diabetes mellitus is diagnosed by high levels of blood glucose, although individuals with high blood sugar that are not classified as having diabetes also have greater CVD risks[70]. The current diagnostic criteria for diabetes are shown in Table 3[71]: along with a cut-off point of 126 mg/dL for fasting plasma glucose (FPG) or oral glucose tolerance test (OGTT) levels ≥ 200 mg/dL, glycated haemoglobin ($HbA1_c$) is recommended as a test for diagnosing diabetes[72]. It expresses the average blood glucose levels over the past 2–3 months, with a threshold of ≥ 6.5%[71]. Recently, the International Federation of Clinical Chemistry (IFCC) recommended the use of millimoles per mol (mmol/mol) instead of a percentage

for assessing $HbA1_c$ levels (equivalences are shown in Table 4)[73].

Table 3. Criteria for the diagnosis of diabetes (according to American Diabetes Association).

1. HbA1c ≥ 6.5%
   OR
2. FPG* ≥ 126 mg/dL (7.0mmol/L)
   OR
3. 2-h plasma glucose ≥ 200 mg/dL (11.1 mmol/L) during an OGTT
   OR
4. In a patient with classic symptoms of hyperglycaemia or a hyperglycaemia crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L)

FPG: fasting plasma glucose; HbA1c: glycated haemoglobin; OGTT: oral glucose tolerance test.
*Fasting is defined as no caloric intake for at least 8h.

Table 4. Equivalences between millimoles per mole (mmol / mol) and percentage (%) for $HbA1_c$ values.

HbA1c% (old units)	HbA1c mmol/mol (new units)
6	42
6.5	48
7	53
7.5	58
8	64
9	75
10	86
11	97
12	108
13	119
14	130
15	140
16	151

A number of meta-analyses of randomised controlled trials and systemic reviews have examined the effects of intensive glucose control on CVD. Results were similar, showing a reduction in CVD events but no effect in reducing CV or total mortality[68,74]. A HbA1c reduction of 0.9% significantly decreased non-fatal myocardial infarction by 17% and CHD events by 15% in one of the meta-analysis[75]. To reduce the risk of microvascular complications and CVD, the multifactorial approach is very important in patients with type 2 DM, and dietary changes and physical activity are key elements in the management of these patients[11].

1.5.3. Obesity

Overweight and obesity are the fifth most important CV risk factors in terms of attributable deaths (5% of global deaths)[6,55,76–78]. Today, 65% of the world's population live in a country where overweight and obesity cause more deaths than underweight (all high-income countries and most middle-income countries)[55].

The prevalence of overweight and obesity has increased in recent decades[79,80] and has nearly tripled since 1975 worldwide. In 2016, 1.9 billion adults (aged 18 or over) were overweight (39% of the total population; 38% of men and 40% of women), while 650 million adults were regarded as obese (13%; 11% of men and 15% of women). Every year, more than 2.8 million people die as a consequence of being overweight or obese[81]. In 2014 in Europe, 62% of males and 55% of females were overweight or obese, while 21% of men and 25% of women were simply obese. Similarly, in 2014 in the EU countries, 65% of men and 53% of women were overweight or obese, and 23% of men and women were obese[20].

Overweight and obesity are closely linked to diet and physical inactivity, and result from a positive energy balance, that is, the person's energy expenditure is less than his/her energy intake[79]. High consumption of processed foods with high fat and sugar contents, and a reduction in physical activity lead to obesity[6,82].

Body mass index (BMI) – defined as a person's weight (in kg) divided by the square of his/her height (in meters) – is used to classify obesity in adults. The international accepted cut-off points for being overweight is BMI ≥25 kg/m^2, and for obesity BMI ≥30 kg/m^2 [77,81]. The current BMI cut-off points for excess weight and obesity compared to normal weight (BMI 18.5 to <25 kg/m^2) are associated with an elevated risk of fatal CHD in both sexes[76]. The risk of comorbidities increases with a BMI of 25.0–29.9 kg/m^2, and the risk is moderate to very severe with a BMI ≥30.0 kg/m^2 (Table 5) [83].

Table 5. Classification of adult weight according to BMI[83].

Classification	BMI	Risk of comorbidities
Underweight	<18.5	Low for CVD
Normal range	18.5-24.99	Average
Overweight	≥25	
Preobese	25-29.99	Increased
Obese class I	30-34.99	Moderate
Obese class II	35-39.99	Severe
Obese class III	≥ 40	Very severe

BMI: body mass index; CVD: cardiovascular diseases

Waist circumference (WC) provides a measure of abdominal fat distribution but, unlike BMI, is unrelated to height. A waist circumference ≥102 cm in men and ≥88 cm in women substantially increases the risk of metabolic complications associated with obesity (Table 6)[83].

Table 6. Risk of metabolic complications associated with waist circumference[83].

Risk of metabolic complications	Waist circumference (cm)	
	Men	Women
Increased	≥94	≥80
Substancially increased	≥102	≥88

Whether or not excess global adiposity (BMI) and regional adiposity (waist circumference) contribute to the prediction of CVD is the subject of debate[84]. Whereas some studies have found that BMI and WC are similarly closely associated with the CVD risk[85,86], one meta-analysis found that only measures of abdominal adiposity (e.g. WC) but not of BMI were related to an increase in CVD mortality[80].

Even though obesity remains a major risk factor in CVD, the negative consequences of obesity on cardiovascular health are attenuated in obese people who are relatively fit. This is known as the 'fat-but-fit' paradigm, which describes people who, despite being obese, have relatively good cardiorespiratory fitness levels. This suggests that improving fitness levels – even without losing weight – could have important positive benefits for CVD[87].

Overweight and obesity are preventable, mainly by choosing a healthy diet and taking regular physical activity. Within dietary choices, obese people should limit their energy intake of fats and sugars and increase their consumption of fruit and vegetables[81].

1.5.4. Hypercholesterolemia

Hypercholesterolemia is a major cardiovascular risk factor[88]. According to WHO[89], there is evidence that in developed countries about 8% of the whole disease burden, 60% of CHD and about 40% of strokes are caused by increased blood cholesterol. Overall, high blood cholesterol is estimated to cause 2.6 million deaths (4.5% of total) and 29.7 million DALYs (2.0% of total)[56]. In 2008, the prevalence of total blood cholesterol ≥ 6.2 mmol/L (240mg/dL) worldwide was 9.7% (8.5% for men and 10.7% for women), although if the threshold is reduced to ≥ 5.0 mmol/L (190mg/dl), prevalence increases to 39% (37% for men and 40% for women)[56]. In the same year, the prevalence of high blood cholesterol in the EU – with a threshold of ≥ 6.2 mmol/L – was in the range 12.1%–25.6% (depending on the country). If we consider ≥ 5.0 mmol/L, prevalence was 45.8–66.9%; prevalence in

the whole of Europe was 4.6–29.1% (≥ 6.2 mmol/L) or 24–69.8% (≥ 5.0 mmol/L)[20].

There is a positive association between total cholesterol and low-density-lipoprotein cholesterol (LDL-C) and the risk of CVD[11]; HDL-C has a strong negative association with CHD events[90]. Likewise, hypertriglyceridemia is a significant CVD risk factor, although the association is weaker than with hypercholesterolemia[91]. A reduction of 1.0 mmol/L in total cholesterol has been reported to lead to a 50% reduction in CHD mortality within five years (people aged 40–49), and in a 17% reduction in people between 70–79 years[92]. A reduction of 1.0 mmol/L in LDL-C is associated with a reduction of 20%–25% in CVD mortality and non-fatal AMI [93,94].

High total cholesterol and LDL-C are of great importance in CVD prevention as they can be modified by lifestyle changes and drug therapies. There is evidence that a reduction in total cholesterol and LDL-C can prevent CVD and so they constitute the primary targets of much therapy[95]. The Joint European Societies lowered the total cholesterol target in 2007 to less than 4.0mmol/L, wherever feasible[96]. Target levels for LDL-C according to CV risk are shown in Table 7. Many studies have demonstrated that the benefits of cholesterol-lowering therapy depend on the initial level of CV risk: the higher the total risk, the greater the benefit[82,95].

Table 7. Recommendations for treatment targets for LDL-C depending on individual CV risk[11].

	Low or moderate risk	High risk	Very high risk
LDL-C	<3mmol/L (<115mg/dL)	<2.6 mmol/L (<100mg/dL)	<1.8mmol/L (<70mg/dL) or a reduction of 50% of baseline LDL-C

CV: cardiovascular; LDL-C: low-density lipoprotein cholesterol.

Statins can reduce LDL-C by an average of 1.8 mmol/L (depending on drug, dose and adherence), which reduces the risk of CHD events by 60% and of strokes by 17%[97]. The effectiveness of statins has been proven in people with high adherence to the treatment. Even though patients at high CV risk should be treated with statins, it is not clear as yet whether or not treatment with statins is effective in patients with other CV risk levels[98].

1.5.5. Diet

Diet is one of the major modifiable risk factors in CVD[20]. Dietary habits influence the CV risk via by affecting factors such as cholesterol, blood pressure, body weight and diabetes[99]. The high consumption of dietary saturated fat is one of the main determinants of increased blood lipid levels; salt intake likewise plays a major role in increasing the risk of hypertension[100,101]. Certain dietary habits such as greater consumption of fruit and vegetables, wholegrains, nuts and fish, and lower consumption of refined carbohydrates, sugars, salt, saturated fatty acids and processed meats[101–103] are known to have cardiometabolic benefits.

The WHO recommends eating more than 400 g of fruit and vegetables per day (at least five servings), less than 5 g of salt every day, limiting dietary fat and sugar intake, and balancing energy expenditure with the total energy intake[104] (Table 8). A higher adherence to these recommendations can reduce by 20–30% the CVD burden and add an extra year of life for a 40-year-old person[105].

1.5.5.1. Mediterranean diet

The Mediterranean diet is the traditional dietary pattern followed in several countries around the Mediterranean Sea, and includes many of the nutrients and foods that are recommended as part of a healthy diet. Even though there is no “one” Mediterranean diet since diets in the Mediterranean vary from one country to another[106–109], in general this diet is characterised by[110,111]:

- High consumption of fruits, vegetables, grains (mainly wholegrain), nuts and legumes
- Moderate consumption of fish, milk and dairy products
- Low-to-moderate consumption of wine (mainly at meals)
- Low consumption of meat and meat products
- Use of olive oil as a main fat (with the resulting improvement in the monounsaturated/saturated fat ratio)

Table 8. Healthy diet recommendations[11].

•Saturated fatty acids to account for <10% of total energy intake, through replacement by polyunsaturated fatty acids.
•Trans unsaturated fatty acids: as little as possible, preferably no intake from processed food, and <1% of total energy intake from natural origin.
•< 5 g of salt per day.
•30-45 g of fibre per day, preferably from wholegrain products.
•≥ 200 g of fruit per day (2-3 servings).
•≥ 200 g of vegetables per day (2-3 servings).
•Fish 1-2 times per week, once of which to be oily fish.
•30 grams unsalted nuts per day.
•Consumption of alcoholic beverages should be limited to 2 glasses per day (20g/d of alcohol) for men and 1 glass per day (10 g/d of alcohol) for women.
•Sugar-sweetened soft drinks and alcoholic beverages consumption must be discouraged.

UNESCO (United Nations Educational, Scientific, and Cultural Organization) declared the Mediterranean diet as an Intangible Cultural Heritage of Humanity in 2010 due to its interest for the world in general. The Mediterranean Diet Foundation Expert Group presented a new Mediterranean diet pyramid, conceived as a tool for helping to adhere to this dietary pattern[112] (Figure 11).

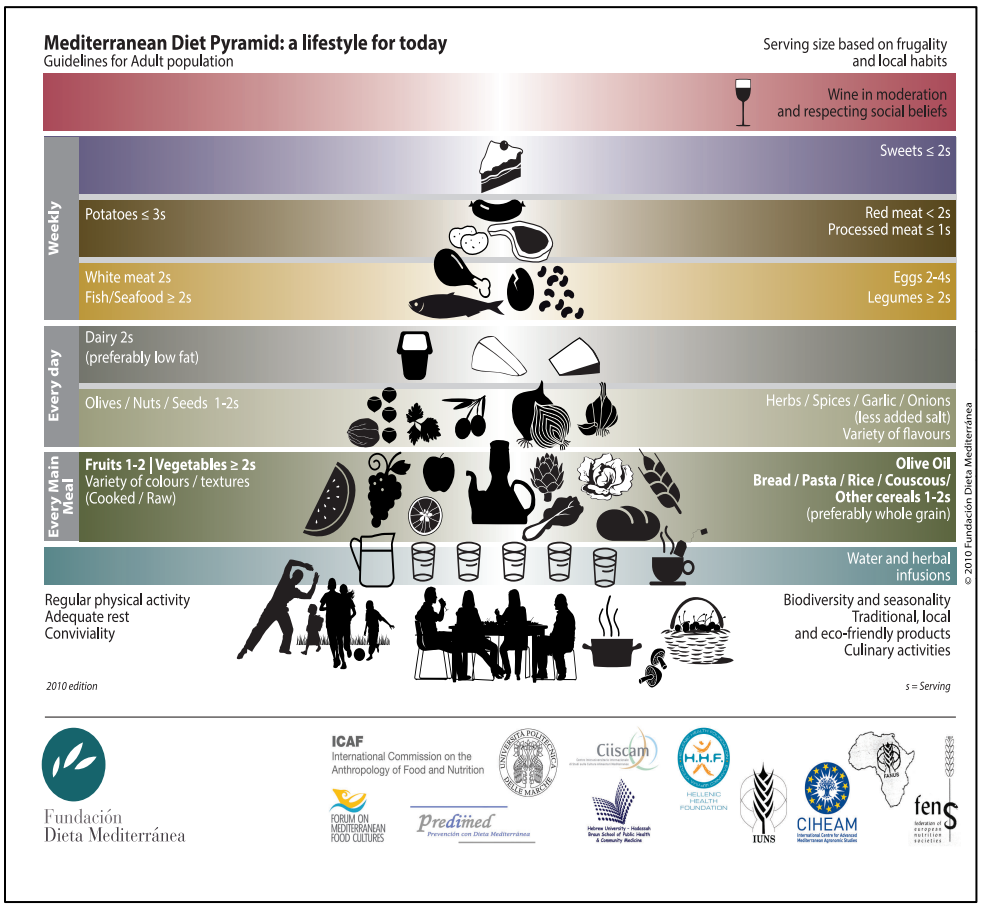


Figure 11. Mediterranean diet pyramid[112].

The Mediterranean diet is the best-studied and most evidence-based diet recommended for preventing and reducing the burden of not only CVD but also other chronic diseases. The term first appeared in the 1950s. One of the first studies of this diet was the Seven Countries Study[53], conducted in the middle of the previous century, which compared dietary habits in seven different countries with their CVD risk. It revealed lower CHD incidence and mortality in Mediterranean countries. Another important study, the MONICA survey[113], reported similar results, which were attributed to the cardioprotective effect of the Mediterranean diet.

The Spanish five-year PREDIMED trial (PREvención con DIeta MEDiterránea) demonstrated a reduction in the relative risk of CV events by approximately 30% when high-risk participants were recommended to supplement their Mediterranean diets with foods that were rich in healthy fats (extra-virgin oil and nuts)[114]. An

increasing number of studies now support the role of the Mediterranean diet in protecting against CVD and other non-communicable diseases[108,110,115,116].

The potential benefits of the Mediterranean diet have also been studied in non-Mediterranean countries, although in these cases the evidence is less consistent: while in the UK the Mediterranean diet was found to be inversely associated with incident CVD and all-cause mortality[117], an association between a strict adherence to a Mediterranean diet and lower CV mortality was observed only in women in Sweden[118] and in men in Australia[119].

Recent studies have found that certain Mediterranean populations are giving up their traditional diet and are adopting more westernised food patterns. The people most likely to quit a Mediterranean diet are generally less-well educated, overweight, less physically active, smokers, single, divorced or separated, and suffer from diabetes[120].

1.5.6. Physical activity

Physical inactivity is the fourth leading risk factor for non-communicable diseases[121] and contributes to 3.2 million deaths a year (6% of the total), and in 2010 to 69.3 million DALYs (2.8% of the total)[78].

Although the terms physical activity, exercise, physical fitness and sport are sometimes used interchangeably, in truth they describe different concepts[122].

a) *Physical activity*: any bodily movement produced by skeletal muscles that results in energy expenditure.
b) *Exercise:* a subset of physical activity that is planned, structured and repetitive, and has as a final or intermediate objective the improvement or maintenance of physical fitness.
c) *Physical fitness:* a set of attributes that is either health- or skill-related.
d) *Sport:* exercise practiced according to established rules and practiced in a competitive spirit.

In the EU, 42% of the respondents of the Eurobarometer survey[123] never undertake any exercise, the highest percentages being found in southern European countries (in Spain it was 44%); 30% of adults never engage in any physical activity (49% in Spain)[124].

Physical activity can be defined and measured in terms of four dimensions[125]:

a) *Settings or domains:* the place where the activity is performed, including leisure time physical activity (LTPA), occupational activity, a domestic setting, and active commuting.
b) *Frequency*: how often physical activity is undertaken. Measures of frequency are usually expressed within a defined time frame: the past week, last month, a usual week or weekday…
c) *Duration*: expressed as total time (in hours or minutes) per day or per the chosen time frame.
d) *Intensity*: the absolute intensity is the amount of energy expended per minute of activity assessed as a metabolic equivalent (MET). One MET is the metabolic cost of resting quietly[126] (approximately 1 kcal/min); while 10 METs is the equivalent to a task that requires ten times the energy expenditure associated with sitting quietly. MET values range from 0.9 (sleeping) to 23 (running at 22.5 km/h). Table 9 shows the classification of physical activity intensity.

Participation in regular physical activity is associated with a marked decrease in CVD prevalence and all-cause mortality[127–131]. Data show that, in healthy individuals, moving from sedentariness to an active lifestyle can reduce CVD mortality by 20–30% in a dose-response trend[130,132,133]. Some of the benefits of physical activity on the prevention of CVD are attributed to positive modifications of traditional risk factors such as hypertension, type 2 diabetes, body weight and LDL-C[134,135]. There is evidence that LTPA is more beneficial than occupational physical activity for reducing the CVD risk [136,137], which is known as the health paradox.

Table 9. Classification and examples of physical activity intensity.

Intensity	MET	Examples
Light	< 4	Walking 4.7 km/h, light household work
Moderate	4-5.5	Walking briskly (4.8-6.5 km/h), slow cycling (15 km/h), gardening (mowing lawn), ballroom dancing, water aerobics
Vigorous	≥ 6	Jogging or running, race-walking, cycling > 15 km/h, heavy gardening, swimming laps

MET: metabolic equivalent. Modified from Piepoli[11].

To promote and maintain health, the minimum amount of activity recommended in adults (18–64 years) according to WHO is[131]:

- 30 minutes of moderate-intensity physical activity five days a week (150 minutes/week), or
- 20 minutes of vigorous-intensity activity three days a week (75 minutes/week), or
- an equivalent combination of moderate- and vigorous- intensity physical activity accumulating at least 600 MET minutes/week

The activity can be accumulated in 10 minutes bouts [131,134,138–140] and should be added on to the routine activities involved in daily living.

According to the Sedentary Behaviour Research Network (SBRN), physical inactivity is defined as an activity level that does not meet the current physical activity recommendations, whereas sedentary behaviour is any waking behaviour characterized by an energy expenditure ≤1.5 metabolic equivalents (METs) while in a sitting, reclining or lying posture[141]. Globally, in 2010, 20% of men and 27% of women did not meet the WHO recommendations[77]. While women are generally less active than men[142], as people get older, the intensity of PA decreases, although light intensity PA (such as walking) does increase.

1.5.7. Alcohol consumption

In 2012, about 3.3 million deaths (5.9% of all global deaths) and 139 million DALYs (5.1% of the total disease burden) were attributable to alcohol consumption[143].

Alcohol consumption can be described as[144]:

- *Hazardous alcohol consumption*: a level of consumption that is likely to result in harm should it persist as a habit[145]. WHO describes a regular daily average consumption of 20g–40g of alcohol per day for women and 40g–60g for men[146] as hazardous.
- *Harmful drinking:* a pattern of drinking that causes damage to health, either physical or mental[145]. According to WHO, harmful drinking consists of regular average daily consumption of more than 40g of alcohol for women and more than 60g for men[146].
- *Binge drinking (or heavy episodic drinking):* defined as a consumption of at least 60g of alcohol on one drinking occasion at least once a month, which can be particularly damaging[143].

At a scientific level, total grams of alcohol are used to establish international comparisons. However, at a primary health-care level it is more manageable to use standard drinking units (SDU), which is the volume of alcoholic beverage (a glass of wine, a can of beer, or a mixed drink containing distilled spirits) that contains approximately the same amount (in grams) of ethanol regardless of the type of beverage[145]. In Europe, 1 SDU contains about 10g of pure alcohol[147].
WHO proposed a SDU to be the equivalent of [148]:

- 330 ml of beer at 5% strength
- 140 ml of wine at 12% strength
- 90 ml of fortified wine at 18% strength
- 70 ml of a liqueur or aperitif at 25% strength
- 40 ml of spirits at 40% strength

High alcohol consumption, especially binge drinking, increases the risk of CVD[149]. The relationship has been described as “J-shaped”, with the greatest risks at high alcohol consumption and zero consumption, and lower risk for moderate intake[150–152]. Even though drinking at low levels involving no episodes of heavy drinking is associated with lower risk of multiple CV outcomes[55,153], other evidence suggests that the lowest risks for CV outcomes are in abstainers[154]. However, overall, the most important factor is the pattern of drinking: moderate intake seems to be protective[146,155–157], while binge drinking leads to a greater risk of CVD[55,158]. It has also been shown that a reduction of alcohol intake by 2.5–14.9 grams per day is associated with a diminution in the CVD mortality risk of about 14–35% [159].

1.5.8. Smoking

Smoking is the second most important risk factor for CVD and globally is responsible for about 9% of all deaths and approximately 10% of CVD events[55] .
In the EU, 27% of men and 18.5% of women were smokers in 2014, a similar proportion to Spain. In Europe as a whole, under 38% of men and 17% of women smoked in 2006[20].

A lifetime smoker has a 50% probability of dying due to smoking and will have 10 years less life expectancy on average[160]. The risks associated with smoking show a dose- and duration-response relationship with no lower limits for harmful effects; it is clear that even low levels of smoking engender vascular risk[161,162] and all types of tobacco are unsafe[163].One of the most common ways of studying tobacco use is to divide subjects into the following categories: ‘never’, ‘former’ and ‘current’ smokers. Compared to ‘never’ smokers, ‘current’ smokers are associated with increased CVD risk; the evidence is not as clear for past smokers[164–166].
Some studies suggest that there is increased risk of CHD death with greater smoking intensity (assessed by cigarettes/day)[160,165]. Passive smoking also increases the risk of CVD[167–170]: a second-hand smoker has a CVD risk that increases by an estimated 30%[11,171].

There is a large body of evidence that demonstrates the beneficial effects of stopping smoking on CHD mortality[82,172–175], which reveal it as the most effective way of preventing CVD[11].

1.5.9. Sleep-related problems

Like other health-related behaviour, sleep problems play an important role in preventing CVD. However, they have been less studied than other behaviour[176]. Sleeping fewer hours than is recommended may be a voluntary decision or a sleep disorder such as insomnia or obstructive sleep apnea[177].

Insomnia is defined as a subjective feeling of difficulty in falling asleep or staying sleep (frequent awakenings, difficulty in returning to sleep after awakening, or awakening too early and unable to get back to sleep), accompanied by irritability or fatigue during wakefulness[178]. The factors associated with the greatest severity of insomnia or lowest sleep quality are poorer educational levels, more than three hours a day watching TV or using a computer or mobile, depressive symptoms and severe stress[179].

Sleep problems are frequent in the general population, especially in women[180,181]. The prevalence of insomnia lies in the range 6–33% – with approximately 50% of cases being chronic – depending on the assessment measures used[182]:

- When assessing insomnia symptoms using the insomnia criteria defined in the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition), the prevalence of at least one symptom is about 30%;
- if we also consider daytime effects, the prevalence is 9–15%;
- if we only assess dissatisfaction with sleep quality or quantity, then prevalence is 8–18%;
- finally, if we take the diagnoses of insomnia as per the DSM-IV classification, prevalence is around 6%.

Currently available research evidence shows that there is a recognisable association between sleep disorders and CVD in the general population:

- Insomnia and poor sleep are related to a high risk of CVD[183–186].
- Short (< 7h) and long (>9 h) sleep times are also associated with an increase in CVD[176,187–191].

Sleep duration and mortality are associated in a U-shaped trend: the lowest risk is in those who sleep for 7–8 hours but the risk of mortality increases with greater deviation at either end of the range[192,193]. The mechanisms involved in this association are still not clear, although it is thought that sleep may influence CVD through certain risk factors including obesity, hypertension, hypercholesterolemia and diabetes since too-short sleep times have also been related to these CV risk factors[194,195].

The American Academy of Sleep Medicine and the Sleep Research Society highlights the importance for adults of adequate sleep patterns, and recommends that adults should get at least seven hours of sleep on a typical night in order to stay in good health[196].

1.5.10. Socioeconomic status

The World Health Organization defines the social determinants of health as “the societal conditions in which people are born, grow, live, work and age” [197]. Socioeconomic status (SES) is a complex construct commonly used in health research that depends on many factors (Figure 12)[198]. It can be described and measured in several ways and as such there is no one good indicator of SES since each indicator stresses one aspect or another of social stratification[199].

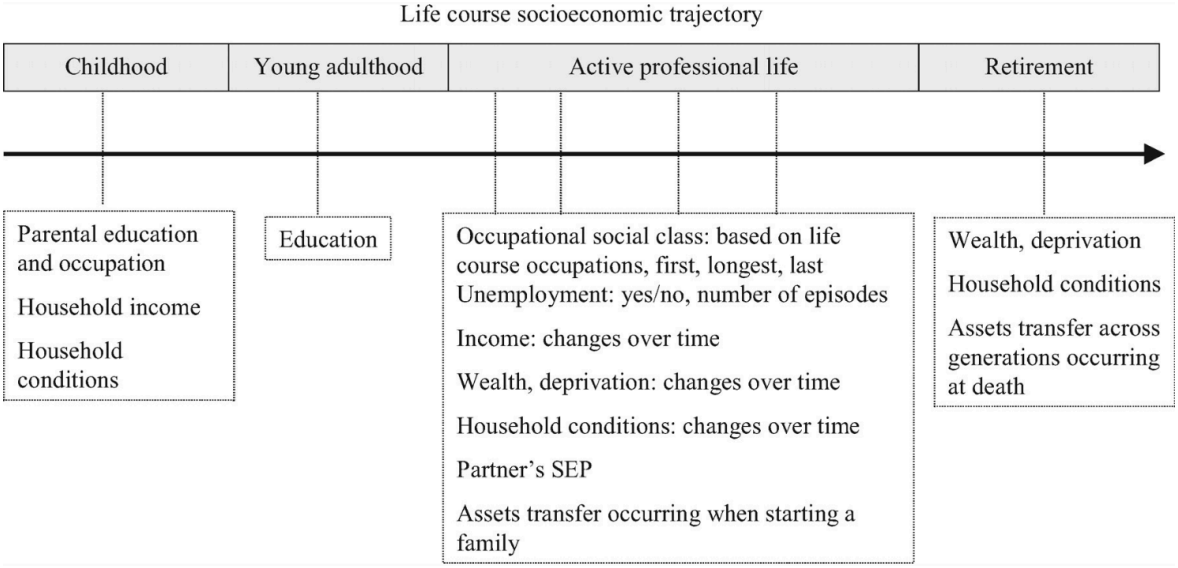


Figure 12: Indicators measuring life-course socioeconomic status, taken from Galobardes[198]. SEP: socioeconomic position.

The most used individual-level indicators of SES are educational level, occupational social class and income:

a) *Education* reflects the transition from a person's parent's socioeconomic status to his/her own resources as an adult, and its ability to act as a determinant of future employment and income[198]. The educational level of an individual provides much information about certain aspects of social opportunities for education, and parental choices and limitations on how they can influence their children's socioeconomic circumstances[199].

b) *Occupational social class* indicates a person's place in society relative to their social standing, income and intellectual level. This aspect may be related to health outcomes due to certain privileges such as easier access to better health care and healthier residential facilities[198].

c) *Income* is the indicator of SES that most directly measures material resources. Like the other indicators, income has a ''dose-response' association with health and can influence a wide range of material circumstances that have direct implications for health[198].

In western countries, there is a large amount of evidence suggesting that lower SES (especially lower educational attainment) is associated with greater risk of CVD or greater incidence of CVD events [11,200–206]. Educational level, which is probably the most used indicator of SES, provides the most consistent results in relation to CVD outcomes[204]. However, the association between occupational social class and CVD is less evident than it is for education[207]. The mechanisms by which SES is related to CVD are still unclear, although some authors have analysed the mediating role of classical CV risk factors and lifestyle factors[208–210], and report that a 26% of the association was mediated by risk factors such as DM, hypertension and BMI[202].

1.6. Arterial stiffness

The pathology underlying CVD is atherosclerosis, a chronic and progressive vascular disease whereby arteries become clogged with fatty substances (plaque) or atheroma (Figure 13), which predisposes people to CHD, cerebrovascular disease and peripheral arterial disease. Atherosclerosis tends to develop early in life and continues silently with age. This largely asymptomatic stage is one of the foundations of primary prevention, during which time we can modify the course of the CVD with specific interventions[18]. The early detection of CVDs requires screening measures that can detect subclinical atherosclerosis. Unfortunately, current CV-risk screening tools are not perfect (especially in intermediate-risk populations).

One of the measures used to detect subclinical atherosclerosis is the Ankle Brachial Index (ABI), which is the ratio of systolic pressure at the ankle to that in the arm. It is quick and easy to measure, and has been used for many years in vascular practice as an indicator of generalised atherosclerosis due to the fact that lower ABI levels are associated with higher rates of CVD[211]. A low ABI (≤ 0.9) is related to an increased risk of total mortality, cardiovascular mortality or major coronary events[30].

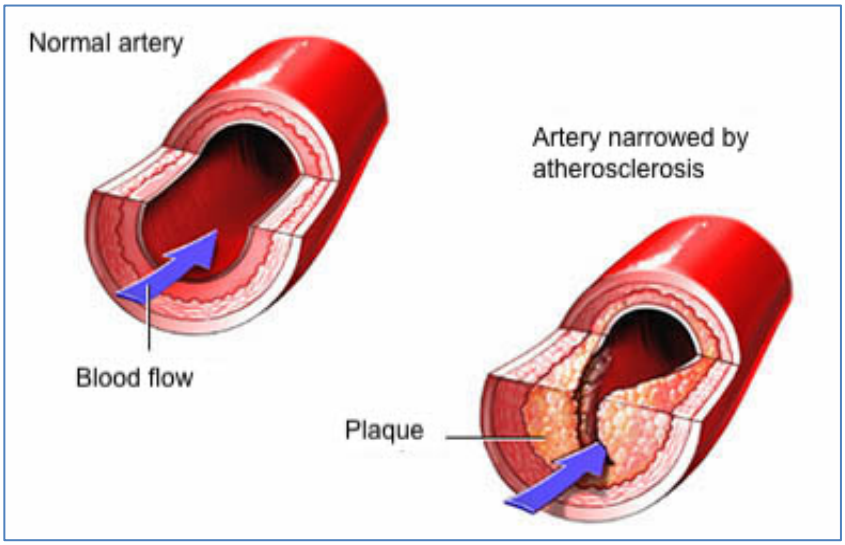


Figure 13: Difference between a normal artery with normal blood flow and an artery with plaque build-up.

Increased arterial stiffness is another measure of subclinical atherosclerosis and also a predictor of CV events[7]. It reflects the loss of elasticity and collagen that depend on the basic properties of the arteries: the diameter of arterial light, and the thickness and composition of its wall. The elasticity of an artery is not constant, with more elastic proximal arteries and stiffer distal arteries. This heterogeneity is caused by the molecular, cellular and histological structure of the arterial wall, which differs between the various parts of the arterial tree[212,213].

Arterial stiffness is mainly determined by age[214] and sex (it is greater in men)[215] but is also strongly related to classical CV risk factors and lifestyle patterns[13,216]. Its incorporation into coronary risk functions has been proposed as a means of improving their discrimination capacity, risk prediction and effectiveness in ensuring medical prevention for those who need it[217,218].

1.6.1. Measuring arterial stiffness

Systemic arterial stiffness can only be estimated using models of circulation. By contrast, regional and local arterial stiffness can be measured directly and non-

invasively at various places along the arterial tree. A major advantage of regional and local evaluations of arterial stiffness is that they are based on direct measurements of parameters closely linked to wall stiffness[212]. Of the many non-invasive methods of assessing this indicator, some of the most common include pulse wave velocity (PWV) and the cardio-ankle vascular index (CAVI), along with – albeit to a lesser extent – the augmentation index (Aix) and stiffness parameter β.

1.6.1.1. Pulse Wave Velocity (PWV)

PWV is a direct measure corresponding to the propagation model in the circulatory system that has emerged as the gold-standard measurement of arterial stiffness[212]. The results of PWV depend on physiological aspects such as blood pressure, heart rate and age, and also on the system of measurement used. The most commonly used systems are Complior® and the SphygmoCor®.

The theoretical basis of PWV as a measure of arterial stiffness is described by the Moens–Korteweg equation:

$$PWV = \sqrt{(Eh/2r\rho)}$$

where E is the slope of the stress-strain relationship for a given vessel (Young's modulus), h the wall thickness, *r* the radius, and ρ the density of fluid[212]. The unit of measurement is meters/second.

Increased PWV is associated with the development of CVD[219], and some meta-analysis have concluded that aortic PWV is an independent predictive factor for CV events and mortality in certain populations[220,221]. The drawback of PWV is that it depends on the patient's blood pressure at the moment measures are taken[222,223] and so the effects of mean blood pressure must be adjusted before estimating the independent influence of arterial stiffness on the outcomes of interest[7].

1.6.1.2. Cardio-ankle vascular index (CAVI)

CAVI is a new indicator of arterial stiffness that describes the stiffness of the arteries between the heart and the ankles (aortic, femoral and tibial). As atherosclerosis progresses, the CAVI value grows: the cut-off point of the index is 9. Figure 14 shows images of the differences in the abdominal aorta in a person without atheroma (with a normal CAVI) and a person who died in advanced stages of atherosclerosis (with a CAVI $\geq$ 9.0)[8].

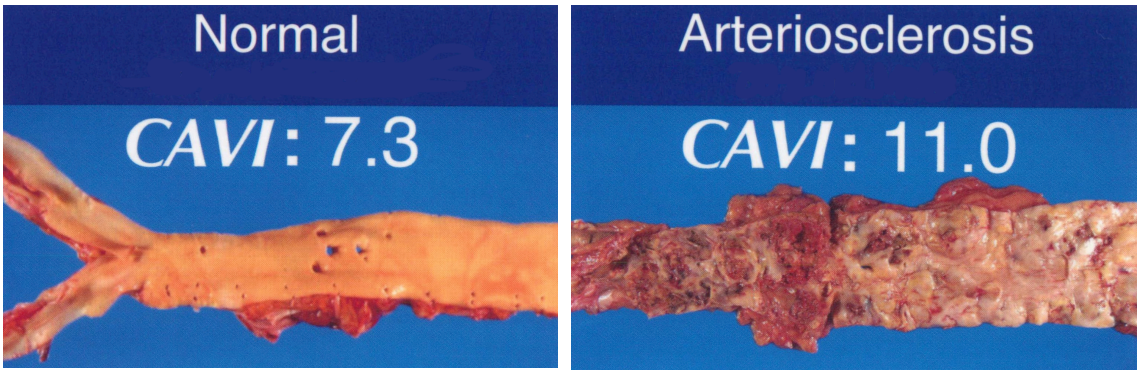


Figure 14: Image of the abdominal aorta in a person without atheroma (CAVI=7.3) and in a person with advanced stages of atherosclerosis (CAVI=11.0). From Shirai[8]. CAVI: cardio-ankle vascular index.

The CAVI, which is based on a β parameter, is not affected by blood pressure at the measuring time[8–10], and is a unit-less index determined using the following equation:

$$CAVI = a \{(2\rho / \Delta P) \times \ln (Ps/Pd) PWV^2 \} + b$$

where PWV is the pulse wave velocity from valve orifice to ankle, Ps the systolic blood pressure, Pd the diastolic blood pressure, ΔP the change in blood pressure, and ρ the blood density.

Some assessments of arterial stiffness using the CAVI method in various populations have shown higher values for men than for women[8,216,224], for older

people, for participants with diagnosed cardiovascular disease[225–227], and for the presence of cardiovascular risk factors[228–230]. However, CAVI has mainly been studied in Asian populations[216] and to data there are few data available for non-Asian countries [231].

The CAVI assessment is non-invasive, reliable, has good reproducibility, and takes just a few minutes to carry out[222,232,233], which makes it suitable for use in primary care.

1.6.2. Determinants of arterial stiffness

Classical CV risk factors such as aging[234], hypertension[235], diabetes mellitus[236] and hypercholesterolemia[237] are associated with increased arterial stiffness[7,212]. Together with the structural alterations caused by reiterated periods of arterial distension and recoil, with aging the accumulation of advanced glycation end-products (AGE) in the arterial wall plays an important role in the development of arterial stiffness[7]. The determinants and treatment of arterial stiffness are shown in Figure 15.

Given that arterial stiffness is a critical precursor of CVD, and that current medical therapy is unlikely to completely restore arterial function, it is important to know the effects that lifestyle modifications can have on the prevention and treatment of arterial stiffness. A number of publications provide evidence of the relationship between lifestyles and arterial stiffness, and conclude that lifestyle modifications can prevent and even reverse this process[238].

- *Diet* is associated with increased arterial stiffness[105]: diets low in alcohol and processed meat[239], low in sodium[7,238,240], high in fruit and vegetables[241,242], high in fish[238,243], and with a high intake of dairy food[244] are shown to be effective in reducing arterial stiffness.
- *Physical activity* has been shown by many studies to play a role in preventing and reversing arterial stiffness [238,245–249].

- *Alcohol:* it has also been demonstrated that a high consumption of alcohol is a risk factor in increased arterial stiffness, but that moderate consumption is a protective factor[250–255].
- *Smoking* is also determinant for the development of arterial stiffness[238,256–258].
- *Poor-quality sleep* or sleeping less than seven hours has also been related to greater arterial stiffness[219,259–262].

Low educational levels have also been associated with increased arterial stiffness in both women[263] and men[264].

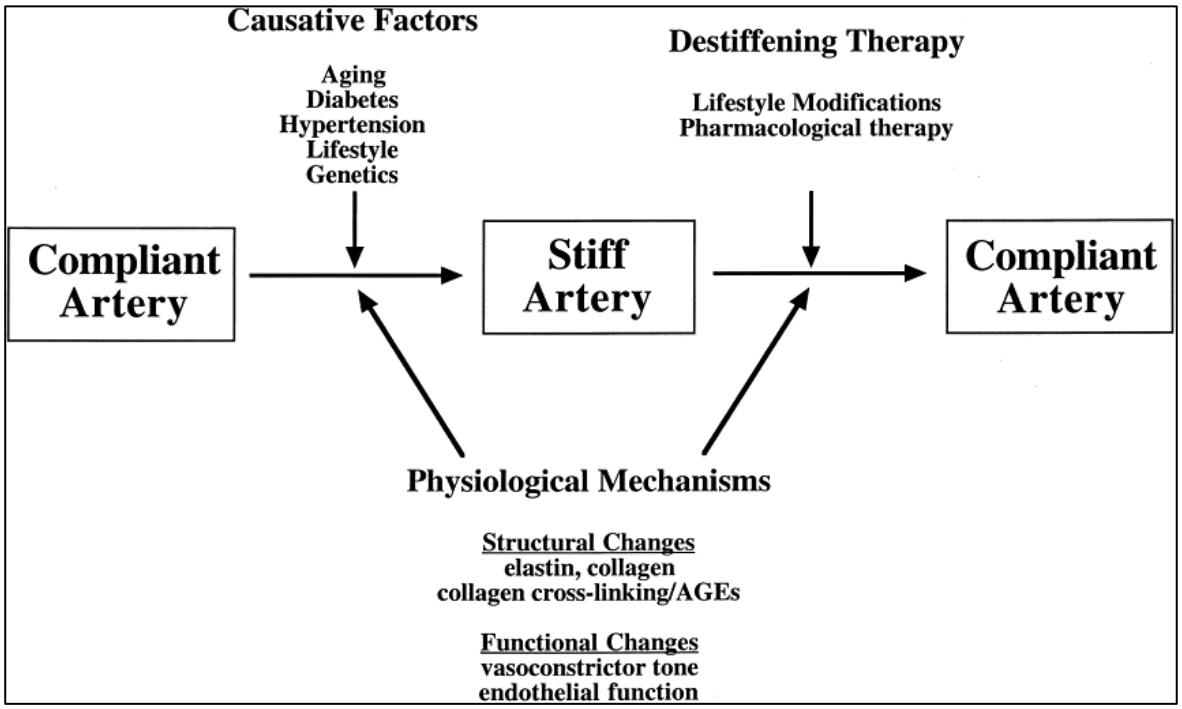


Figure 15: Processes of arterial stiffening and destiffening[238]. AGEs: advanced glycation end-products.

In the light of the above, we thus need to focus on the prevention of arterial stiffening before alterations in the arterial wall become irreversible. However, little evidence has been found to show which factors are related to pathological arterial stiffness (measured with CAVI) in a general Mediterranean population and in a Mediterranean intermediate CV risk population, partly because to date most studies of CAVI have been carried out on Asian populations. Considering that arterial stiffness is a good precursor of CVD, and since classical CV risk factors have been widely studied, a good strategy in primary prevention could be to focus on lifestyles. Lifestyle modifications may play an important role in changes[7] and nurses would have significant responsibilities in helping people manage risk factors and in promoting healthy lifestyles.

Thus, to improve primary prevention of CVD we need to know which factors are related to arterial stiffness in the target population.

2. HYPOTHESIS

Hypothesis

1. In a general Mediterranean population,

    1.1. The prevalence of arterial stiffness is low.
    1.2. Arterial stiffness values are positively associated with cardiovascular risk factors but negatively associated with lifestyles.
    1.3. The prevalence of arterial stiffness is greater in people with higher levels of cardiovascular risk.
    1.4. The prevalence of arterial stiffness in individuals with metabolic cardiovascular risk factors is greater than in healthy individuals.

2. In a Mediterranean intermediate cardiovascular risk population,

    2.1. Arterial stiffness is positively associated with cardiovascular risk factors but negatively associated with lifestyles and socioeconomic status.
    2.2. The prevalence of arterial stiffness is higher than in the general Mediterranean population.

3. OBJECTIVES

Objectives

The main objectives of this thesis are:

1. Assess in a general Mediterranean population the association between arterial stiffness values, on the one hand, and lifestyles and classical CV risk factors, on the other.

2. Analyse in a Mediterranean intermediate CV risk population the association between arterial stiffness, on the one hand, and, lifestyles, socioeconomic status and CV risk factors, on the other.

The secondary objectives are:

1. In a general Mediterranean population,

    1.1. Estimate the prevalence of arterial stiffness.
    1.2. Determine the distribution of arterial stiffness at different CV risk levels.
    1.3. Describe differences in arterial stiffness between individuals with metabolic CV risk factors (hypertension, diabetes mellitus and hypercholesterolemia) and healthy individuals (free from risk factors).

2. In a Mediterranean intermediate CV risk population,

    2.1. Describe the prevalence of arterial stiffness.

4. METHODS

4.1. Study design

Three descriptive, cross-sectional studies were conducted[c]:

1) Association between classic cardiovascular risk factors and lifestyles, and the cardio-ankle vascular index (CAVI) in a general Mediterranean population study.

2) Differences in CAVI in a general Mediterranean population in relation to the presence or absence of metabolic cardiovascular risk factors study.

3) Association between lifestyles, socioeconomic status and cardiovascular risk factors, and arterial stiffness in an intermediate cardiovascular risk population study.

4.2. Study population

4.2.1. *Association between CV risk factors and lifestyles, and CAVI in a general Mediterranean population* study

Differences in *CAVI in a general Mediterranean population in relation to the presence or absence of metabolic CV risk factors* study

In 2003–2006, a population-based cohort of 6,556 participants aged 35–79 was recruited in Girona (Catalonia, SW Europe) as part of the *Registre Gironí del Cor* (RECIGOR) study[265,266]. The objectives of this study were:

- to measure classical CV risk factors.
- to determine the roles played by physical activity and diet in this risk.

[c] Unless otherwise stated, all the definitions and methods are applicable to all of the objectives. When there are different approximations, these are fully explained.

- to define a long-term function for estimating the risk of CHD, cerebrovascular disease and/or peripheral artery disease.
- to study the risk or protection of a CV event associated with physical activity, diet, social class and/or biochemical markers.

The sample used in these two studies corresponds to a random subsample of a follow-up survey carried out in September 2007–November 2013: 4,280 participants aged 41–90 responded to a follow-up visit (Figure 16). The population used in these studies were participants who underwent a VaSera exploration. The participation rate, both in the initial and follow-up surveys, was >70%.

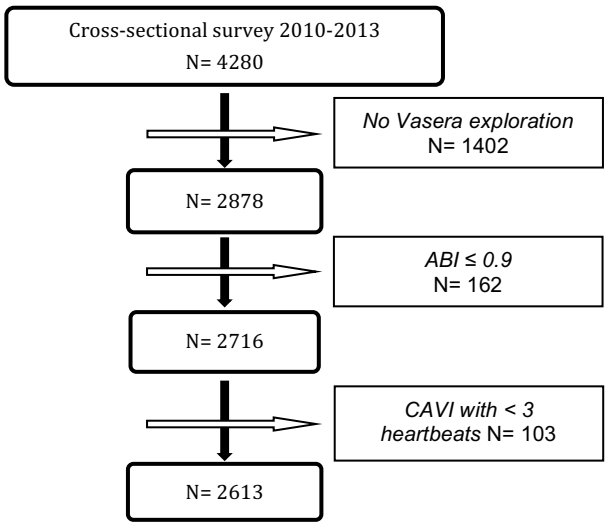


Figure 16: Flow chart showing the patients included in the two studies conducted in the general Mediterranean population. ABI: ankle-brachial index; CAVI: cardio-ankle vascular index.

4.2.2. *Association between lifestyles, SES and CV risk factors, and arterial stiffness in an intermediate CV risk population* study

The data for this study were obtained from a baseline survey carried out in June 2011–December 2013 corresponding to the recruitment period of an on-going multicentre study, *Improving interMediAte RisK management* (MARK)[267]. The purpose of MARK was to analyse whether knowledge of variables other than the

classical CV risk factors could improve the predictive capacity of current CV risk equations in the intermediate risk population. Intermediate CV risk participants aged 35–74 (n=2495) were randomly selected from three different regions in Spain (Girona, Balearic Islands and Salamanca), with a participation rate of about 70%.

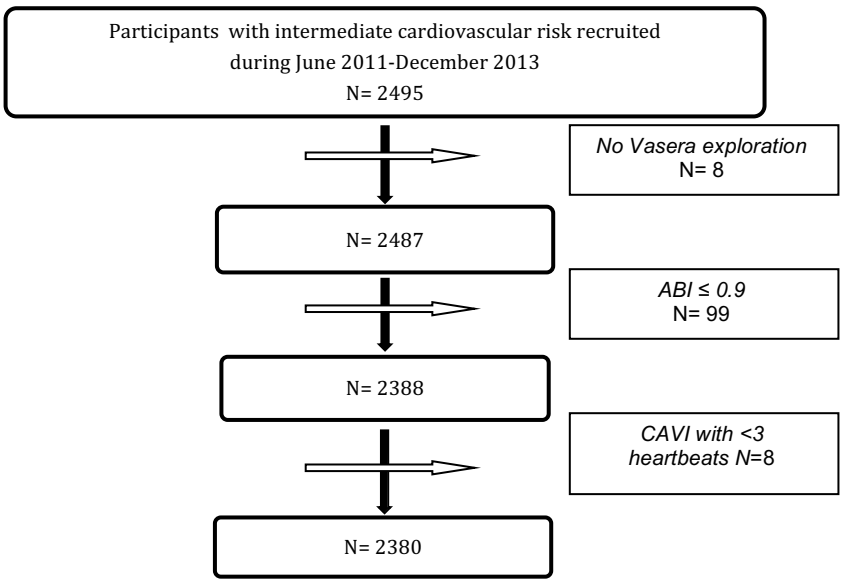


Figure 17: Flow chart showing the patients included in the intermediate CV risk Mediterranean population study. ABI: ankle-brachial index; CAVI: cardio-ankle vascular index.

4.2.3. Inclusion criteria

In the study carried out on the intermediate CV risk population, the intermediate CV risk was determined using the criteria of any of the three 10-year risk equations employed in everyday clinical practice in the three study areas:

1) Framingham-REGICOR-adapted coronary risk equation, validated in the Spanish population (coronary risk of ≥5%–<15%)[16,34].

2) SCORE risk function (CV mortality risk of ≥1%–<5%)[40].
3) European Society of Cardiology, 2013 Risk Stratification Guidelines[36]: moderate CV mortality risk category.

4.2.4. Exclusion criteria

We excluded participants with an ankle brachial index (ABI) ≤ 0.9 since the presence of peripheral arterial disease can give false low CAVI values[222] (Figures 16 and 17). The other exclusion criteria were:

- history of atherosclerotic disease.
- terminal illness.
- institutionalization at the time of recruitment.

4.3. Measurements

Nurses trained in the study protocols carried out physical examinations and interviews following standardized methods; homologated devices and validated questionnaires were used[265,267].

4.3.1. Main outcome: arterial stiffness

Arterial stiffness on both right and left sides was measured with a VaSera VS-1500® device (Fukuda Denshi Co, Ltd, Tokyo, Japan), following the manufacturer's instructions to guarantee accurate CAVI measurements. Participants refrained from exercising, smoking or consuming caffeine for 30 minutes, and remained in supine position for 10 minutes with a small cushion under their heads and dressed in light clothes. They were asked to keep still and silent for the five minutes that the exploration lasts. A nurse fitted the cuffs for size and tightly wrapped them around the participants' arms and ankles. Electrodes were attached to the right and left arms and ankles, and a heart sound microphone was fixed with double-sided tape on the sternum over the second intercostal space. Only CAVI measurements obtained during at least three consecutive

heartbeats were considered valid (Fig. 16 and 17).

CAVI values ranged from 3 to 18. According to the manufacturer's protocol[268], the highest CAVI value of the two measures taken on each side was classified as either 'normal' (CAVI<8), 'borderline' (8≤CAVI<9), or 'pathological' or 'suspected atherosclerosis' (CAVI≥9), subsequently classified as 9≤CAVI<10 or CAVI≥10 (CAVI scores of 10 or higher have been associated with higher incidences of cardiovascular events)[269].

Evidence of the validity of the CAVI has been provided by Takaki, who reported a positive correlation between aortic stiffness parameter β and CAVI ($r = 0.67$, $p < 0.01$)[232]. Reproducibility has been shown in Japanese[222] and European populations[233], with an average coefficient of variation of 3.8% and 4.4%, respectively.

4.3.2. Lifestyles

4.3.2.1. Diet

Association between CV risk factors and lifestyles, and CAVI in a general Mediterranean population; and
Association between lifestyles, SES and CV risk factors, and arterial stiffness in an intermediate CV risk population

Diet quality was assessed using a validated short dietary-quality screener (sDQS)[270]. The diet quality index (DQI) is derived from the short diet-quality screener and is used to estimate the overall diet quality. It includes three food groups (Table 10): the first category assesses the daily intake of certain number of different foods; the second the weekly consumption of harmful foods, and the third the weekly consumption of beneficial food items. The total possible score ranges from 18 to 54.

Table 10. Scoring method for the Diet Quality Index (DQI).

1. Daily frequency consumption of the following foods during the last 12 months				
Food	Amount	<1 time/d	1 time/d	≥2 times/d
Bread	1–2 slices	1	2	3
Vegetable/salad	1 serving	1	2	3
Fruit	1 piece or serving	1	2	3
Yoghurt or milk	1 tub/1 glass	1	2	3
Pasta or rice	1 serving	1	2	3
Oil (olive or sunflower)	1 tablespoon	1	2	3
Alcoholic beverages	1 drink	1	3	1
Breakfast flakes	1 bowl	1	2	3
2. Weekly frequency consumption of the following foods during the last 12 months				
Food	Amount	<4 times/week	4–6 times/week	≥7 times/week
Meat	1 serving	3	2	1
Sausages	1–3 slices	3	2	1
Cheese	1 serving	3	2	1
Pastry or sweets	1 piece or serving	3	2	1
Butter or lard	1 teaspoon	3	2	1
Other vegetable oils	1 tablespoon	3	2	1
Fast food	1 serving	3	2	1
3. Weekly frequency consumption of the following foods during the last 12 months				
Food	Amount	<2 times/week	2–3 times/week	≥4 times/week
Fish	1 serving	1	2	3
Legumes	1 serving	1	2	3
Nuts	1 handful	1	2	3

Association between lifestyles, SES and CV risk factors, and arterial stiffness in an intermediate CV risk population

As previously stated, the Mediterranean diet is associated with protection against CVD. We used a short dietary intake questionnaire to quantitatively estimate adherence to the Mediterranean diet[271], which in turn is derived from a validated food-frequency questionnaire with 136 items[272]. This questionnaire assesses the extent to which the recommended consumption of a typical serving of nine Mediterranean foods – olive oil, fruit, vegetables, legumes, fish, wine, meat, white bread and rice (Table 11) – is fulfilled.

The resulting composite score ranges from 0 to 9 points, and adherence is classified as low (0–2), moderate (3–6) or high (7–9).

Table 11. Dietary items included in the short questionnaire to estimate the adherence to the Mediterranean diet.

	Yes
1. Olive oil (≥ 1 spoon/day)	1
2. Fruit (≥ 1 serving/day)	1
3. Vegetables or salad (≥ 1 serving/day)	1
4. Fruit (≥ 1 serving/day) and vegetables (≥ 1 serving/day) (a)	1
5. Legumes (≥ 2 servings/week)	1
6. Fish (≥ 3 servings/week)	1
7. Wine (≥ 1 glass/day)	1
8. Meat (< 1 serving/day)	1
9. [White bread (<1/day) and rice (<1/week)] or whole-grain bread (>5/week) (b)	1

(a) One point is added when ≥ 1 serving/day of both fruits and vegetables is consumed.
(b) One point is added when either consumption of both white bread and rice is low or when consumption of whole-grain is high.

4.3.2.2. Physical activity

Association between CV risk factors and lifestyles, and CAVI in a general Mediterranean population; and
Association between lifestyles, SES, CV risk factors, and arterial stiffness in an intermediate CV risk population

Physical activity was assessed using the validated REGICOR short questionnaire[273] (Appendix 5), adapted from the *Minnesota Leisure Time Physical Activity Questionnaire*, previously validated for a Spanish population[274,275]. This questionnaire covers the four dimensions of physical activity (type of activity, frequency, duration and intensity) and two of the four domains (occupational and leisure time). Participants were asked about their daily physical activity during a normal month and their METs in minutes per week were calculated following Ainsworth[126]. This gave a physical activity score classified as of either 'vigorous' (>6.0 MET), 'moderate' (3.0-6.0 MET) or 'light' (<3.0 MET) intensity. We defined

physical inactivity as per the Sedentary Behaviour Research Network (SBRN)[141]: less than 30 minutes of moderate activity five days a week (energy expenditure < 675 Kcal/week) or less than 20 minutes of intense activity three days a week (energy expenditure < 420 Kcal/week).

4.3.2.3. Smoking

Smoking was evaluated using a questionnaire following the WHO MONICA study[276]. We established three categories: *smokers* (current smokers or persons who had quit in the past year), *former smokers* (persons who had quit smoking over a year ago), and *non-smokers* (people who had never smoked). Smoking intensity was calculated in the intermediate CV risk population in smokers and former smokers who had quit smoking within the previous five years, and was expressed as a pack-year index (number of cigarettes smoked per day multiplied by the number of years of smoking and divided by 20).

4.3.2.4. Alcohol consumption

Association between lifestyles, SES and CV risk factors, and arterial stiffness in an intermediate CV risk population

We recorded the type and amount of alcohol consumed in the preceding seven days, measured in standard drinking units (SDU). Individuals were classified according to their consumption of alcohol, as per the WHO working definition: no consumption, *low risk* (<28 SDU/week in men and <14 SDU/week in women), *hazardous consumption* (28-42 SDU/week in men and 14–28 SDU/week in women), and *harmful consumption* (>42 SDU/week in men and >28 SDU/week in women)[144].

4.3.2.5. Sleep-related problems

Association between lifestyles, SES and CV risk factors, and arterial stiffness in an intermediate CV risk population

The Spanish validated version[277] of the Athens Insomnia Scale (AIS)[180] was used to assess sleeping habits. This self-administered questionnaire includes eight items: the first five (assessing difficulty with falling sleep, awakening during the night, early morning awakening, total sleep time, and overall sleep quality) correspond to the insomnia criteria defined by the ICD-10[278]. To be valid, the habits in question should have occurred at least three times a week during the previous month. The final three items refer to the next-day consequences of insomnia (problems regarding the sense of well-being, functioning and sleepiness during the day). Each item is rated from 0 to 3 (with 0 being *no problem at all* and 3 *very serious problem*s). The total score ranges from 0 (absence of any sleep-related problem) to 24 (the most severe degree of insomnia). Insomnia is defined as a total score ≥ 6 [279].

4.3.3. Socioeconomic status

Association between lifestyles, SES and CV risk factors, and arterial stiffness in an intermediate CV risk population

To assess SES we determined people's educational achievement since it is a strong determinant of social status[198] and occupational social class. Educational level was categorized as *primary school*, *secondary school* or *university studies*. Occupational social class was classified into three categories: *high-level non-manual workers*, *low-level non-manual workers* and *manual workers*[280].

4.3.4. Cardiovascular risk factors

In the *Differences in CAVI in a general Mediterranean population in relation to the presence or absence of metabolic CV risk factors study*, participants were categorised into two CV risk-factors groups:

1) WCVRF group: participants with metabolic CV risk factors (hypertension, diabetes or hypercholesterolemia) or a previous history of vascular

diseases (myocardial infarction, angina pectoris, stroke or revascularization).

2) FCVRF group: participants free of metabolic CV risk factors and with no history of vascular disease.

4.3.4.1. Hypertension

Hypertension was defined to exist if:

a) participants had reported a previous diagnosis of hypertension;
b) participants had received antihypertensive treatment (β-blocking agents, calcium-channel blockers, agents acting on the renin-angiotensin system, diuretics or any other antihypertensive), or
c) participants' SBP or DBP were ≥ 140 mmHg or ≥ 90 mmHg, respectively, at recruitment time.

Blood pressure was measured twice, firstly with the participant seated and then after five minutes of rest, with a calibrated oscillometric sphygmomanometer (OMRON M6, HEM-7001-E). The mean value was taken; however, if the two measurements differed by more than 5 mmHg, a third was taken and the mean of the second two measurements was taken. Brachial pulse pressure (PP) was calculated by subtracting the mean DBP from the mean SBP.

4.3.4.2. Diabetes

Diabetes was defined to exist if:

a) participants had reported a previous diagnosis;
b) participants had received treatment for diabetes (insulin or oral antidiabetics), or
c) participants' fasting glucose concentration was ≥ 126 mg/dL.

4.3.4.3. Obesity

General obesity was defined as having a body mass index (BMI) ≥ 30kg/m^2 (calculated as weight divided by the square of height).

4.3.4.4. Hypercholesterolemia

Hypercholesterolemia was considered to exist when:

a) participants were taking lipid-lowering drugs, or
b) participants' total blood cholesterol concentration at baseline was ≥ 250 mg/dL.

4.3.5. Other variables

The following variables were also recorded:

- age
- sex
- weight and height (using a precision scale for easy calibration, with participants in underwear and barefoot).
- waist circumference: measured between the lowest rib and the iliac crest.
- Medication being taken:
    - antihypertensive
    - lipid-lowering
    - antiplatelet
- a blood sample was taken after 10–14 h fasting. Laboratory tests applied included:
    - Determined by direct methodology (Roche Diagnostics, Basel, Switzerland):
        - Fasting glucose
        - total cholesterol
        - high-density lipoprotein cholesterol (HDL-C)
        - triglycerides

- low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald equation when triglyceride levels were < 300 mg/dL.

4.4. Statistical analysis

As assessment of arterial stiffness using the CAVI method in various populations gives higher values in men than in women[8,281], the results of the three different studies were stratified by sex. A p-value < 0.05 was considered as significant. Continuous variables were expressed as mean and standard deviation (SD) with a 95% confidence interval (CI), or median and 25th and 75th percentiles for non-normally distributed variables. Categorical variables were expressed as proportions.

For bivariate and multivariate analyses, we used a dichotomous CAVI score, namely, CAVI < 9 or CAVI ≥9. A T-test for independent samples, ANOVA or Mann-Whitney test were used in the bivariate analyses for continuous variables; a Chi-square was used for categorical variables.

4.4.1. Association of CV risk factors and lifestyles with CAVI in a general Mediterranean population

The 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles of the CAVI scores were estimated across age groups and by sex. A Bonferroni correction was applied to correct for multiple comparisons (total of five comparisons; statistical significance threshold P < 0.01). A test for trend in the proportions was carried out to determine the prevalence of CAVI ≥ 9; the 95%CI was calculated. Correlations between CAVI and 10-year coronary heart disease risk score (estimated with REGICOR) by sex were performed. A logistic regression was used to identify the cardiovascular risk factors and lifestyles associated with CAVI ≥ 9. The variables included in the model were those that were significant in the bivariate analysis or were clinically relevant. We analysed the possible interactions between variables and no

significant interactions were found. The discrimination ability of the models was assessed by means of the area under the curve, while the goodness-of-fit was assessed using the Hosmer-Lemeshow test. Linearity assumptions were tested for age, waist circumference and BMI. The statistical analyses were carried out with the R-studio software (R Foundation for Statistical Computing, Vienna, Austria; Version 2.13.1)[282].

4.4.2. CAVI in a general Mediterranean population in relation to the presence or absence of metabolic CV risk factors

Apart from stratifying by sex, analyses were also stratified by CV risk factor groups. The Bonferroni correction was applied when comparing CAVI between sexes within each age category, and, overall, 10 comparisons were considered. ANOVA models were performed to compare CAVI values using the combination of sex, age and CV risk factor groups. Statistical analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) for Windows, version 21.

4.4.3. Association between lifestyles, SES, and CV risk factors, and arterial stiffness in an intermediate CV risk population

Logistic regression was used to perform the multivariate analysis, with CAVI ≥ 9 as the dependent variable, adjusted for all the variables that were significant in the bivariate analysis or clinically relevant. We analysed the interactions between the variables and no significant interactions were found. Even though waist circumference was statistically significant, we suspect that BMI and waist circumference were strongly correlated and that there could be multicollinearity in the models. The variance inflation factor (VIF) was measured to quantify the severity of multicollinearity. A scatter plot was performed and R^2 was calculated to determine whether or not there was multicollinearity in the models. Given that multicollinearity was detected, we removed waist circumference from the model but left BMI in the model since:

- this variable was more associated with CAVI in our analysis,

- in the bivariate analysis, waist circumference was only associated in women,
- other studies in the literature have also related BMI with CAVI[13,283].

IBM SPSS for Windows, version 21, was used in all the analyses.

4.5. Ethics information

The MARK protocol (*Association between lifestyles, SES CV risk factors, and arterial stiffness in an intermediate CV risk population*) received approval from the three participating Spanish autonomous communities. The local ethics committee approved the other two studies. All participants were informed about the studies and gave written consent before participating. Afterwards, a report was sent to each one with the results of the exploration and the interview. The investigation conformed to the principles of experimentation in humans outlined in the Declaration of Helsinki.

5. RESULTS

5.1. Association between CV risk factors and lifestyles, and CAVI in a general Mediterranean population

5.1.1. Participant characteristics

The sample consisted of 2,613 participants (Figure 16) and was representative of the original cohort (Tables 12 and 13); 47.26% were men with a mean age of 60.12 years (11.09 SD).

Table 12. Main characteristics of the participants and distribution of risk factors in men from the whole sample vs. the subset assessed.

	Follow up sample	Subsample	P-value
Number of participants	1962	1235	
Age, years	61.51 (11.75)	60.19 (10.74)	0.001
Systolic BP, mmHg	134.36 (18.57)	135.49 (18.12)	0.090
Diastolic BP, mmHg	78.69 (10.08)	80.19 (9.95)	<0.001
Pulse pressure, mmHg	55.68 (16.07)	55.31 (15.34)	0.512
Hypertension, %	56.42	57.00	0.774
Total cholesterol, mg/dL	195.17 (36.2)	196.71 (35.09)	0.233
LDL-C, mg/dL	126.57 (31.7)	128.48 (30.34)	0.091
HDL-C, mg/dL	47.40 (10.54)	46.84 (10.28)	0.141
Hypercholesterolemia , %	30.08	28.84	0.478
Glucose, mg/dL	101.73 (26.27)	101.46 (25.86)	0.771
Diabetes Mellitus, %	19.31	19.72	0.812
Triglycerides, mg/dL	92 [68-127]	92 [68-128]	0.675
BMI, kg/m^2	27.74 (3.81)	27.97 (3.91)	0.094
Waist circumference, cm	99.80 (10.53)	100.55 (10.65)	0.054
REGICOR coronary risk	4.26 [2.59-6.88]	4.72 [2.76-7.31]	0.096
Diet Quality Index	38.99 (2.99)	38.88 (2.98)	0.366
Smoking, %			0.633
Current	19.45	20.60	
Former	47.46	45.93	
Never	33.09	33.47	
EEPA, MET·min/week			
Total	2098 [1007-3898]	2150 [969-3935]	0.957
Light	336 [0-839]	280 [0-839]	0.004
Moderate	280 [0-1399]	280 [0-1678]	0.420
Vigorous	325 [49-1441]	336 [73-1605]	0.651
Active, %	67.41	69.26	0.315

Unless otherwise indicated, data are expressed as mean (standard deviation) or median [25th percentile-75th percentile]. BP: blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; BMI: body mass index; CAVI: cardio-ankle vascular index; EEPA: energy expenditure of physical activity; MET: metabolic equivalent.

Table 13. Main characteristics of the participants and distribution of risk factors in women from the whole sample vs. the subset assessed.

	Follow up sample	Subsample	P-value
Number of participants	2317	1378	
Age, years	60.74 (11.69)	60.04 (11.40)	0.074
Systolic BP, mmHg	126.11 (20.29)	126.49 (19.84)	0.573
Diastolic BP, mmHg	74.51 (9.51)	74.99 (9.68)	0.144
Pulse pressure, mmHg	51.60 (16.50)	51.50 (15.92)	0.864
Hypertension, %	41.91	42.09	0.941
Total cholesterol, mg/dL	206.82 (35.31)	204.26 (34.83)	0.033
LDL-C, mg/dL	132.05 (30.52)	130.99 (30.28)	0.312
HDL-C, mg/dL	56.32 (11.57)	55.15 (11.00)	0.002
Hypercholesterolemia, %	28.15	27.85	0.876
Glucose, mg/dL	92.95 (18.15)	92.02 (17.89)	0.133
Diabetes Mellitus, %	10.45	10.47	1
Triglycerides, mg/dL	81 [60-111]	80 [59-110]	0.420
BMI, kg/m^2	26.88 (5.03)	26.90 (4.93)	0.901
Waist circumference, cm	91.43 (12.83)	92.26 (12.66)	0.055
REGICOR coronary risk	2.28 [1.35-3.75]	2.41 [1.39-3.99]	0.052
Diet Quality Index	39.22 (2.84)	39.26 (2.84)	0.683
Smoking, %			0.702
Current	13.23	13.60	
Former	16.48	17.38	
Never	70.29	69.02	
EEPA, MET·min/week			
Total	1504 [706-2545]	1538 [743-2558]	0.565
Light	336 [0-839]	252 [0-839]	0.382
Moderate	0 [0-839]	70 [0-839]	0.725
Vigorous	294 [49-1143]	339 [73-1185]	0.349
Active, %	57.80	59.23	0.420

Unless otherwise indicated, data are expressed as mean (standard deviation) or median [25th percentile-75th percentile]. BP: blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; BMI: body mass index; CAVI: cardio-ankle vascular index; EEPA: energy expenditure of physical activity; MET: metabolic equivalent.

The main clinical characteristics and lifestyles by sex are shown in Table 14. Men had higher values for blood pressure, fasting glucose, BMI, waist circumference and REGICOR coronary risk than women but lower levels of total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol. Men also had higher CAVI values, as well as a higher proportion of individuals with CAVI $\geq$ 9. In terms of lifestyles, men were more active and smoked more, while women had a higher-quality diet.

Table 14. Main sociodemographic and clinical characteristics of the participants by sex.

	All	Men	Women	*p*-value
Number of participants	2613	1235	1378	
Age, years	60.12(11.09)	60.19 (10.74)	60.04 (11.40)	0.724
Systolic BP, mmHg	130.75(19.57)	135.49 (18.12)	126.49 (19.84)	<0.001
Diastolic BP, mmHg	77.45(10.15)	80.19 (9.95)	74.99 (9.68)	<0.001
Pulse pressure, mmHg	53.30(15.76)	55.31 (15.34)	51.50 (15.92)	<0.001
Hypertension, %	49.14	57.00	42.09	<0.001
Hypertension treatment, %	30.46	33.93	27.36	<0.001
Total cholesterol, mg/dL	200.66(35.15)	196.71 (35.09)	204.26 (34.83)	<0.001
LDL-C, mg/dL	129.80(30.33)	128.48 (30.34)	130.99 (30.28)	0.038
HDL-C, mg/dL	51.19(11.44)	46.84 (10.28)	55.15 (11.00)	<0.001
Hypercholesterolemia, %	28.32	28.84	27.85	0.609
Hypercholesterolemia treatment, %	21.01	22.83	19.38	0.034
Glucose, mg/dL	96.52(22.55)	101.46 (25.86)	92.02 (17.89)	<0.001
Diabetes mellitus, %	14.88	19.72	10.47	<0.001
Diabetes mellitus treatment, %	8.84	11.50	6.46	<0.001
Triglycerides, mg/dL	86 [63-118]	92 [68-128]	80 [59-110]	<0.001
BMI, kg/m^2	27.41(4.51)	27.97 (3.91)	26.90 (4.93)	<0.001
Waist circumference, cm	96.17(12.46)	100.55 (10.65)	92.26 (12.66)	<0.001
REGICOR coronary risk	3.36 [1.87-5.69]	4.72 [2.76-7.31]	2.41 [1.39-3.99]	<0.001
CAVI	8.76(1.35)	8.97 (1.38)	8.57 (1.29)	<0.001
CAVI, %				<0.001
CAVI<8	31.08	25.55	36.07	
CAVI>8 and <9	27.82	27.69	27.94	
CAVI≥9 and <10	24.38	27.13	21.92	
CAVI≥10	16.72	19.68	14.08	
CAVI ≥ 9, %	41.10	46.80	35.99	<0.001
Diet Quality Index	39.08 (2.92)	38.88 (2.98)	39.26 (2.84)	0.002
Smoking, %				<0.001
Current	16.90	20.60	13.60	
Former	30.85	45.93	17.38	
Never	52.25	33.47	69.02	
EEPA, MET·min/week				
Total	1776 [839-3119]	2150 [969-3935]	1538 [743-2558]	<0.001
Light	261 [0-839]	280 [0-839]	252 [0-839]	0.734
Moderate	140 [0-1119]	280 [0-1678]	70 [0-839]	<0.001
Vigorous	339 [73-1311]	336 [73-1605]	339 [73-1185]	<0.001
Active, %	63.87	69.26	59.23	<0.001

Unless otherwise indicated, data are expressed as mean (standard deviation) or median [25th percentile-75th percentile]. BP: blood pressure;LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; BMI: body mass index; CAVI: cardio-ankle vascular index; EEPA: energy expenditure of physical activity; MET: metabolic equivalent.

5.1.2. CAVI distribution by sex and age

The percentile distribution of CAVI across ages and by sex is shown in Figure 18. Variability in CAVI (difference between the minimum [5th] and the maximal [95th] percentiles) tends to stay even across the age categories in both sexes. CAVI increased with age in both sexes and was significantly higher in men across all age categories (post hoc Tukey HSD P-values < 0.05). The mean value of CAVI in men and women by 10-year age groups is shown in Figure 19.

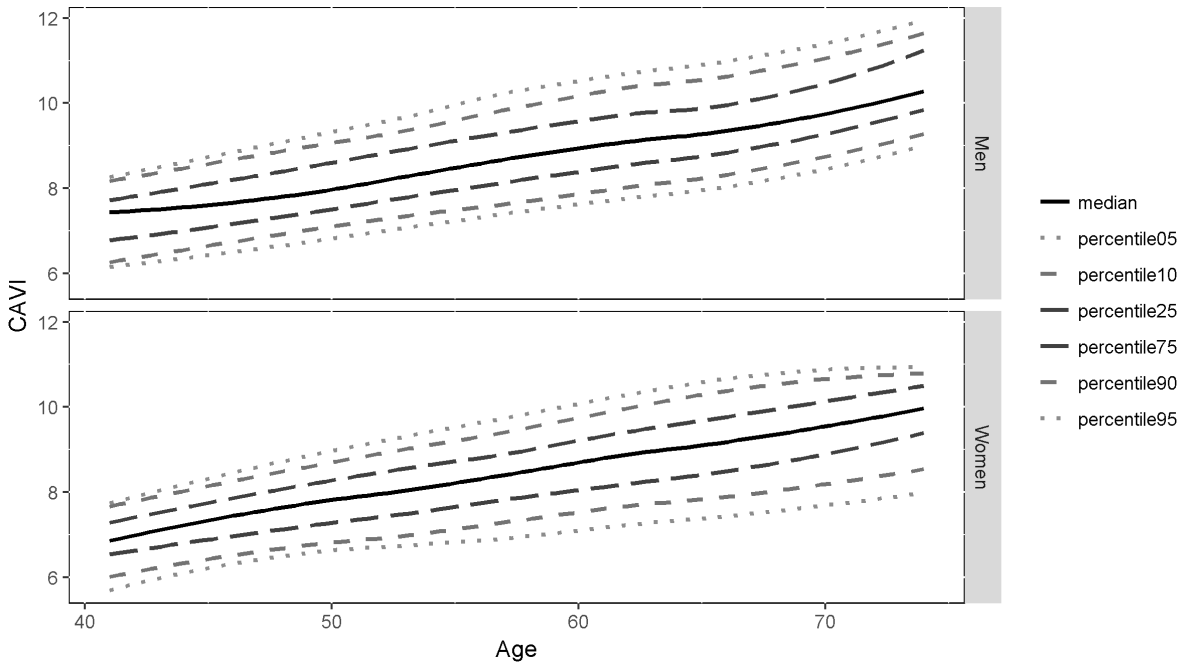


Figure 18. Cardio-ankle vascular index (CAVI) percentiles (5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, 95^{th}) by sex and age.

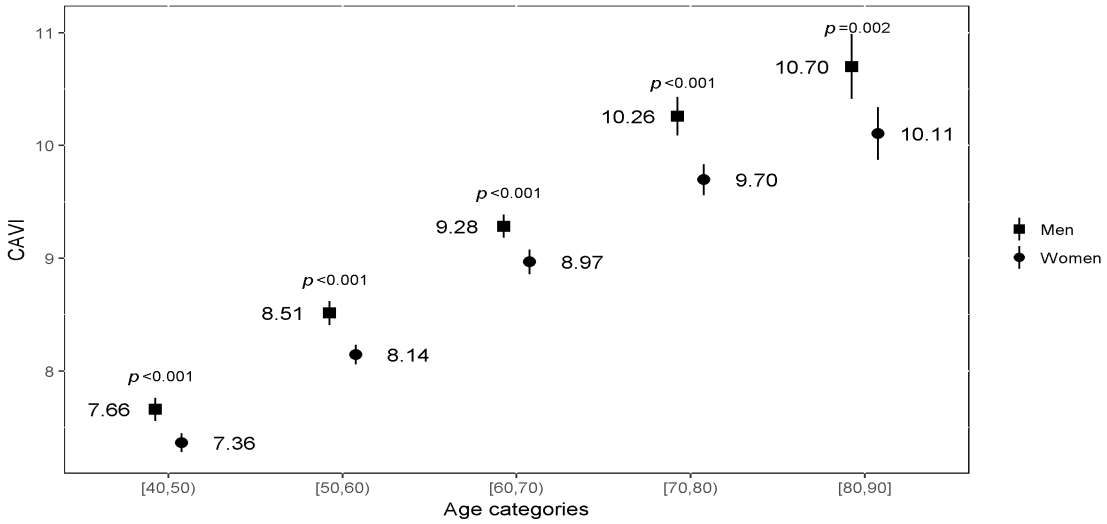


Figure 19. Mean CAVI (cardio-ankle vascular index) by 10-year age categories and sex. P-value indicates the difference in mean CAVI values for men and women in each age group.

5.1.3. CAVI and CV risk factors and lifestyles

The prevalence of CAVI ≥ 9 was 41.1% (95%CI, 39.2–43.0). Regardless of sex, participants with CAVI ≥ 9 were 10 years older, had higher blood pressure, a higher prevalence of hypertension, and higher levels of fasting glucose and triglycerides. Women with CAVI ≥ 9 had higher levels of cholesterol, as well as a

Table 15. Sociodemographic and clinical characteristics of the participants by sex and presence of CAVI ≥ 9 .

	Men			***Women***		
	CAVI < 9	*CAVI ≥ 9*	*P-value*	*CAVI < 9*	*CAVI ≥ 9*	*P-value*
Number of participants	660	575		885	493	
Age, years	54.08(8.16)	67.22(8.89)	<0.001	54.71(8.94)	69.61(8.80)	<0.001
Systolic BP, mmHg	129.56(15.20)	142.30(18.81)	<0.001	120.27(17.78)	137.66(18.41)	<0.001
Diastolic BP, mmHg	80.27(9.69)	80.10(10.25)	0.764	74.54(9.68)	75.80(9.64)	0.021
Pulse pressure, mmHg	49.30(11.69)	62.21 (16.11)	<0.001	45.74(12.30)	61.86(16.43)	<0.001
Hypertension, %	40.91	75.48	<0.001	28.36	66.73	<0.001
Total cholesterol, mg/dL	198.87(33.93)	194.23(36.25)	0.021	202.62(34.46)	207.17(35.33)	0.022
LDL-C, mg/dL	130.74(29.64)	125.91(30.95)	0.006	130.41(29.72)	132.02(31.27)	0.356
HDL-C, mg/dL	46.66(9.94)	47.05(10.67)	0.510	55.28(10.87)	54.93(11.23)	0.573
Hypercholesterolemia,%	21.61	37.11	<0.001	20.57	40.82	<0.001
Glucose, mg/dL	96.70(18.06)	106.93(31.76)	<0.001	89.92(14.74)	95.77(21.95)	<0.001
Diabetes Mellitus, %	11.42	29.14	<0.001	7.40	15.90	<0.001
Triglycerides, mg/dL	90[67-128]	95[70-127]	0.981	75[55-102]	90[68-118.3]	<0.001
BMI, kg/m^2	28.23(4.13)	27.68(3.62)	0.012	26.82 (5.31)	27.04 (4.16)	0.403
Waist circumference, cm	100.18(11.15)	100.97(10.05)	0.191	91.32(13.31)	93.95(11.23)	<0.001
REGICOR coronary risk	3.44 [2.20-5.41]	6.81 [4.80-10.20]	<0.001	1.95 [1.15-3.34]	3.63 [2.51-5.10]	<0.001
CAVI	7.96(0.71)	10.12 (1.02)	<0.001	7.79(0.80)	9.95(0.74)	<0.001
Diet Quality Index	38.62(3.05)	39.22(2.89)	<0.001	39.00(2.74)	39.74(2.97)	<0.001
Smoking, %			<0.001			<0.001
Current	25.46	15.03		17.76	6.11	
Former	40.70	51.92		22.28	8.55	
Never	33.84	33.04		59.95	85.34	
EEPA, MET·min/week						
Total	2004 [937-3509]	2293 [1057-4255]	0.003	1456 [740-2431]	1681 [797-3077]	0.017
Light	224[0-559]	420[0-979]	<0.001	224[0-671]	448[0-1119]	<0.001
Moderate	280[0-1119]	559[0-2098]	<0.001	105[0-699]	0[0-1049]	0.004
Vigorous	671[98-1800]	171[24-1136]	<0.001	392[98-1170]	245[33-1192]	0.196
Active, %	73.00	64.78	0.003	60.82	56.34	0.121

Unless otherwise indicated, data are expressed as mean (standard deviation) or median [25th percentile-75th percentile]. BP: blood pressure; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; BMI: body mass index; CAVI: cardio-ankle vascular index; EEPA: energy expenditure of physical activity; MET: metabolic equivalent.

higher BMI. In men, CAVI ≥ 9 was associated with lower levels of total cholesterol and low-density lipoprotein cholesterol, as well as higher high-density lipoprotein cholesterol levels. Men and women with CAVI ≥ 9 had greater diet quality and better smoking habits but were less active than their healthier counterparts (Table 15).

The prevalence of CAVI ≥ 9 increased as the coronary risk increased (Figure 20), being 21.1% in men and 24.8% in women categorised as of low coronary risk, 58.3% and 44.6%, respectively, in the moderate-risk category, and 76.7% and 61.9% in the high-risk category. The correlation between CAVI and the 10-year coronary heart disease risk was significant, although moderate, in both men (Pearson's r = 0.471, P < 0.001) and women (Pearson's r = 0.359, P < 0.001).

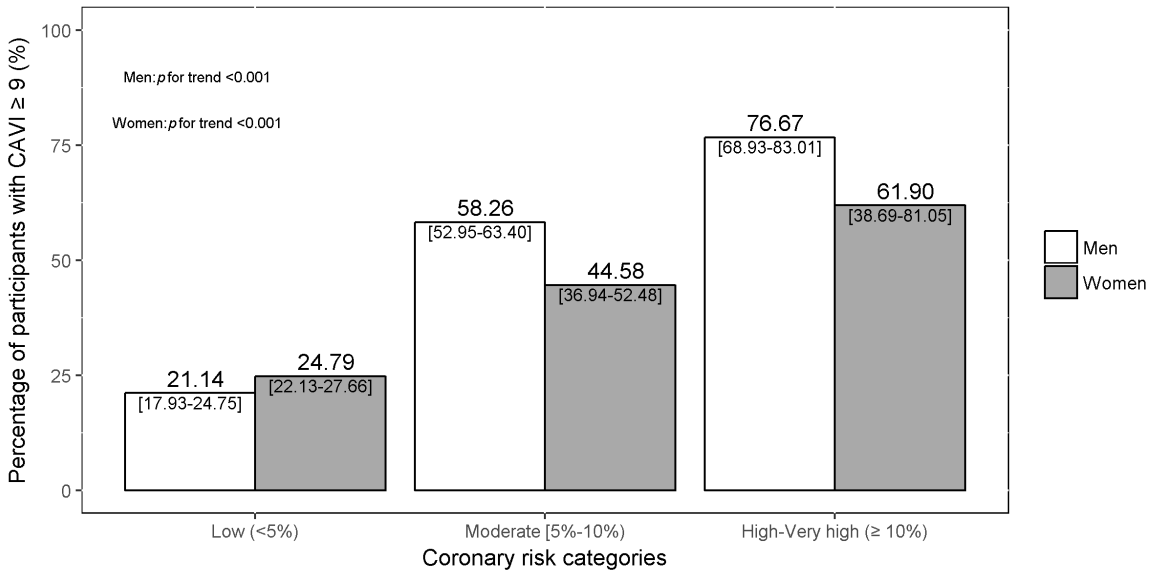


Figure 20. Percentage [95% confidence interval] of participants with CAVI ≥ 9 by sex within each REGICOR risk category: low (risk < 5%), moderate (risk ≥ 5% to < 10%) high–very high (risk ≥ 10%). CAVI: cardio-ankle vascular index.

The multivariate logistic regression results (Figure 21) indicate that age, hypertension and diabetes were associated with a higher prevalence of CAVI ≥ 9 in men, whereas a higher BMI and an active lifestyle were associated with a lower prevalence of CAVI ≥ 9. In women, CAVI ≥ 9 prevalence was directly associated with age, hypertension and hypercholesterolemia but inversely associated with

BMI values. The multivariate models showed a good capacity for discriminating for the presence of CAVI ≥ 9, as well as good goodness-of-fit, both in men and women. The area under the curve was 88.2 (95%CI, 86.3-90.1) in men and 88.8 (95%CI, 87.1-90.6) in women. The goodness-of-fit was also assessed using the Hosmer-Lemeshow statistic and was not significant in either men (P = 0.302) or women (P = 0.176). Age and waist circumference met the linearity assumption; however, BMI did not comply with this assumption and was thus categorised.

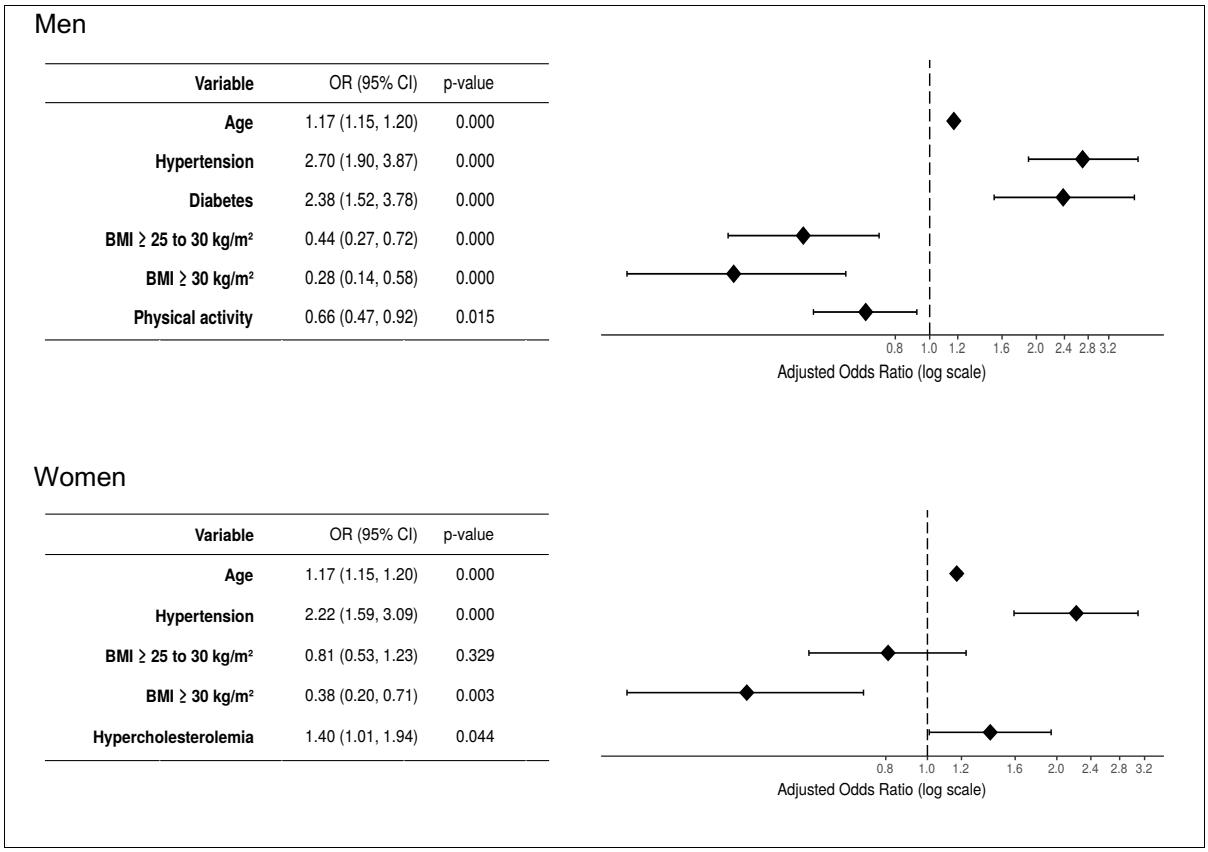


Figure 21. Forest plot showing the effect of physical activity, risk factors (hypertension, diabetes, hypercholesterolemia and body mass index (BMI)), and age on CAVI (cardio-ankle vascular index) ≥ 9 in men and women. Reference categories are not having diabetes, not having hypertension, not having hypercholesterolemia, and BMI < 25 kg/m^2.

5.2. Differences in CAVI in a general Mediterranean population in relation to the presence or absence of metabolic CV risk factors

5.2.1. Characteristics of participants

A total of 2,613 participants aged 41–90 years took part in the study (Figure 16). Of all the participants, 52.7% were women and 63.2% belonged to the WCVRF group. The mean CAVI was significantly higher in the WCVRF group than in the FCVRF group in men [9.3 (1.4) vs. 8.2 (1.0)] and women [9.0 (1.2) vs. 7.9 (1.1)]. As shown in Figure 22, CAVI values in the WCVRF group were more dispersed throughout the sample and its median CAVI was higher than in the FCVRF group. Furthermore, in the WCVRF group, the proportion of CAVI ≥ 9 was 51.8% and 57.9% in women and men, respectively, while in the FCVRF group, it was 14.4% and 21.6%, respectively.

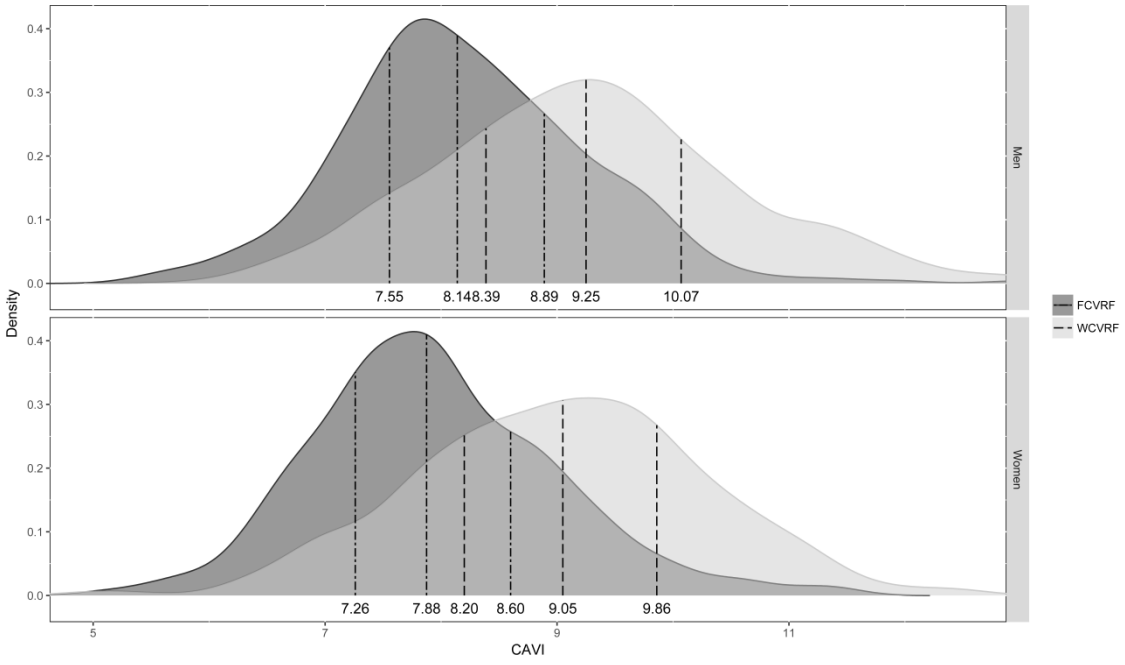


Figure 22. Density distribution of cardio-ankle vascular index (CAVI) by sex and presence or absence of metabolic risk factors. Discontinuous lines represent quartiles (Q_1, Q_2, Q_3) in each group.

The baseline characteristics of participants by sex and CV risk factors groups are shown in Table 16. WCVRF participants were older and had higher mean values for Systolic BP, Diastolic BP, pulse pressure, triglycerides, glucose, BMI, body fat, waist circumference and coronary risk than FCVRF participants in both men and women. Smoking was less frequent in WCVRF than in FCVRF. Men were more likely to suffer from diabetes and hypertension, and to have a history of previous CV events, whilst women were more likely to be under treatment with antihypertensive drugs.

Table 16. Participant characteristics by sex and presence of metabolic cardiovascular risk factors or cardiovascular disease.

	Men			***Women***		
	FCVRF[c]	WCVRF[d]	P-value	FCVRF[c]	WCVRF[d]	P-value
Number of participants	379	856		582	796	
Age, years	53.8 (8.9)	63.0 (10.2)	<0.001	53.8 (9.5)	64.6 (10.5)	<0.001
Systolic BP, mmHg	121.1 (9.5)	141.9 (17.4)	<0.001	113.0 (12.1)	136.3 (18.6)	<0.001
Diastolic BP, mmHg	75.7 (7.1)	82.2 (10.4)	<0.001	71.1 (7.6)	77.8 (10.1)	<0.001
Pulse pressure, mmHg	45.4 (8.4)	59.7 (15.7)	<0.001	41.9 (8.8)	58.5 (16.3)	<0.001
Total cholesterol, mg/dL	197.7 (27.9)	196.3 (37.8)	0.462	196.3 (28.6)	210.0 (37.7)	<0.001
Total cholesterol ≥ 250 mg/dL, %		9.5			15.3	<0.001
HDL-C, mg/dL	47.5 (9.7)	46.5 (10.5)	0.108	56.4 (10.6)	54.2 (11.2)	<0.001
LDL-C, mg/dL	131.9 (24.8)	127.0 (32.4)	0.004	125.8 (25.5)	134.8 (32.9)	<0.001
Triglycerides, mg/dL	82 [61-108]	97 [72-137]	<0.001	63 [51-82]	95 [72-126]	<0.001
Lipid lowering treatment, %		32.9			33.5	0.837
Glucose, mg/dL	90.5 (8.0)	106.3 (29.3)	<0.001	85.8 (8.4)	96.6 (21.3)	<0.001
Diabetes mellitus, %		28.37			18.1	<0.001
Diabetes treament[a], %		58.7			63.1	0.002
Hypertension, %		87.0			80.4	<0.001
Hypertension treatment[b], %		56.24			58.9	0.344
BMI, kg/m^2	26.4 (3.4)	28.7 (3.9)	<0.001	24.8 (3.9)	28.4 (5.0)	<0.001
Obesity (BMI≥30), %	11.6	32.2	<0.001	10.5	32.8	<0.001
Percentage of body fat	23.3 (5.7)	27.9 (5.2)	<0.001	33.0 (6.3)	37.8 (6.4)	<0.001
Waist circumference, cm	95.7 (9.8)	102.7 (10.3)	<0.001	86.9 (10.7)	96.2 (12.5)	<0.001
Waist (≥102 cm in men, ≥88 cm in women), %	23.8	49.1	<0.001	42.5	73.0	<0.001
CAVI	8.22(1.05)	9.30(1.38)	<0.001	7.94(1.06)	9.02(1.26)	<0.001
Smoking, %						
Current	24.7	18.8	<0.001	18.4	10.1	<0.001
Former	35.4	50.6		22.7	13.5	
Never	39.9	30.6		58.8	76.4	
REGICOR coronary risk	2.7 [1.8-3.9]	6.0 [4.0-9.0]	<0.001	1.5 [0.9-2.3]	3.6 [2.4-5.2]	<0.001
REGICOR, %						
Low (<5%)	87.2	36.3	<0.001	98.1	71.3	<0.001
Moderate (5-9%)	11.9	43.4		1.9	25.3	
High (10-14%)	0.56	16.6		0	3.1	
Very high (≥15%)	0.28	3.7		0	0.3	
History of CV diseases, %		4.8			2.5	0.020

Unless otherwise indicated, data are expressed as mean (standard deviation) or median [25th percentile - 75th percentile].
BP: Blood pressure; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; BMI: Body mass index; CAVI: cardio-ankle vascular index; CV: cardiovascular.

[a] Among participants with diabetes.

[b] Among participants with hypertension.

[c] FCVRF: participants free of any of the three cardiovascular risk factors: hypertension, diabetes or hypercholesterolemia and without personal history of vascular events (myocardial infarction, angina pectoris or stroke).

[d] WCVRF: participants with at least one of the three risk factors: hypertension, diabetes or hypercholesterolemia or with personal history of vascular disease (myocardial infarction, angina pectoris or stroke).

5.2.2. CAVI patterns by sex, 10-year age categories and CVRF groups

Mean CAVI values between CV risk factors groups sorted by sex and 10-year age categories are shown in Figure 23. The mean CAVI was significantly higher in the WCVRF group than in the FCVRF group in both sexes ($p < 0.001$). ANOVA results showed that CAVI increased significantly with age in both men ($p < 0.001$) and women ($p < 0.001$). Post-hoc Tukey HSD age comparisons were $p < 0.001$ except in the 70–79 and 80–89 age groups. The interaction between age and CV risk factors was not significant in either men ($p = 0.326$) or women ($p = 0.344$). Moreover, the mean CAVI was higher in the WCVRF group than in the FCVRF group for all ages, and was significant in all groups except in men aged 80–89 and in women aged 70–79 or older.

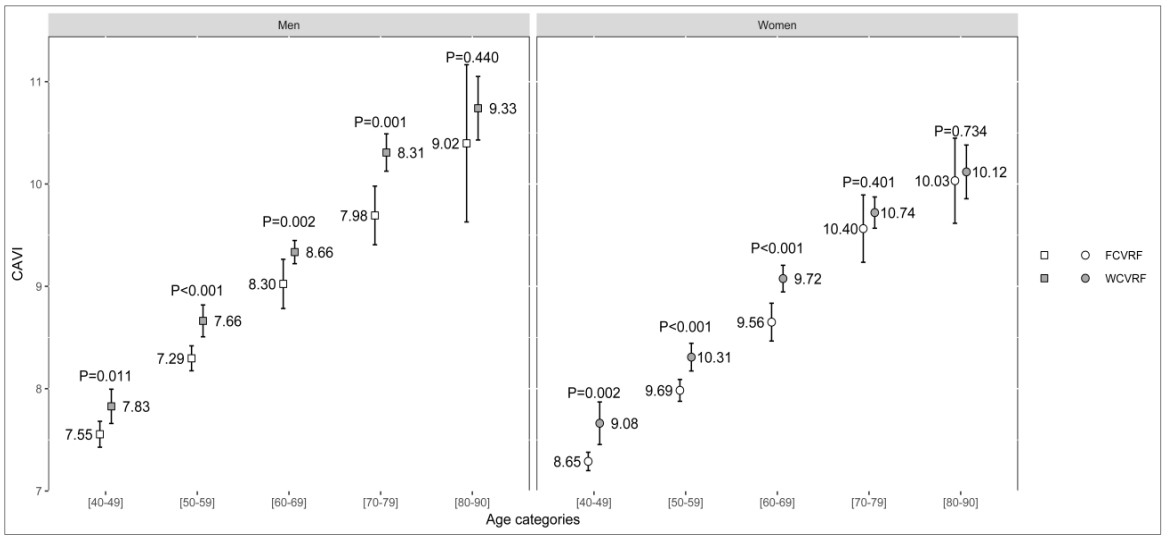


Figure 23. Mean cardio-ankle vascular index (CAVI) in participants free of any of the three cardiovascular risk factors: hypertension, diabetes and hypercholesterolemia (FCVRF); and participants with at least one of the three risk factors or with a personal history of vascular disease (myocardial infarction, angina pectoris or stroke) (WCVRF), by age categories in men and women.

The proportion of participants in the defined CAVI groups stratified by CV risk factors groups and sorted by 10-year age categories and sex, is shown in Table 17. The proportion of individuals with CAVI ≥ 9 increased with age in both men and women, and was higher in men than in women.

Table 17. Proportion of men and women in each category of cardio-ankle vascular index score, by age categories and presence or absence of metabolic cardiovascular risk factors.

	Age	N	CAVI<8	8≤CAVI<9	9≤CAVI <10	CAVI≥10
Men		1235	25.5	27.7	27.1	19.7
FCVRF[a]	40-49	149	75.2	20.8	4.0	0
	50-59	147	38.1	42.9	18.4	0.7
	60-69	60	11.7	41.7	38.3	8.3
	70-79	16	0	12.5	56.3	31.3
	80-89	7	0	14.3	28.6	57.1
WCVRF[b]	40-49	94	59.6	34.0	6.4	0
	50-59	217	26.7	37.8	27.2	8.3
	60-69	302	7.3	27.4	42.4	22.8
	70-79	191	1.6	11	33.0	54.5
	80-89	52	1.9	3.8	23.1	71.2
Women		1378	36.1	28.0	21.9	14.1
FCVRF[a]	40-49	238	84.5	14.7	0.4	0
	50-59	200	52.4	40.3	6.8	0.5
	60-69	91	22.0	42.9	29.7	5.5
	70-79	36	8.3	22.2	38.9	30.6
	80-89	11	0	0	54.5	45.5
WCVRF[b]	40-49	60	65	31.7	1.7	1.7
	50-59	203	37.4	40.0	19.7	2.96
	60-69	269	13.0	30.9	39.0	17.1
	70-79	193	6.2	16.6	34.2	43.0
	80-89	71	2.8	7.0	39.4	50.7

[a] FCVRF: participants free of any of the three cardiovascular risk factors: hypertension, diabetes or hypercholesterolemia and without personal history of vascular events (myocardial infarction, angina pectoris or stroke).

[b] WCVRF: participants with at least one of the three cardiovascular risk factors: hypertension, diabetes or hypercholesterolemia or with personal history of vascular disease (myocardial infarction, angina pectoris or stroke).

5.2.3. CAVI and coronary risk

REGICOR coronary risk scores were calculated for participants up to 74 years of age with no previous history of cardiovascular disease (N=2111). Figure 24 shows that the proportion of participants, regardless of the CV risk factors group, with CAVI ≥ 9 within each coronary risk category differs between the sexes (Pearson's Chi-square test; $p < 0.001$ in each sex) and increases as risk also increases. Overall, for the FCVRF group, 13.4% of men and 11.0% of women with low coronary risk (<5%) and 55.8% of men and 10.0% of women with moderate coronary risk (≥ 5% to < 10%) had CAVI ≥ 9. For the WCVRF group, the prevalence was higher, with 30.4% in men and 41.4% in women with low coronary

risk, and 58.6% in men and 46.8% in women with moderate coronary risk. In the high coronary risk category, more than three quarters of men (76.19%) in the WCVRF group had CAVI ≥ 9, while in women this percentage was lower (61.9%).

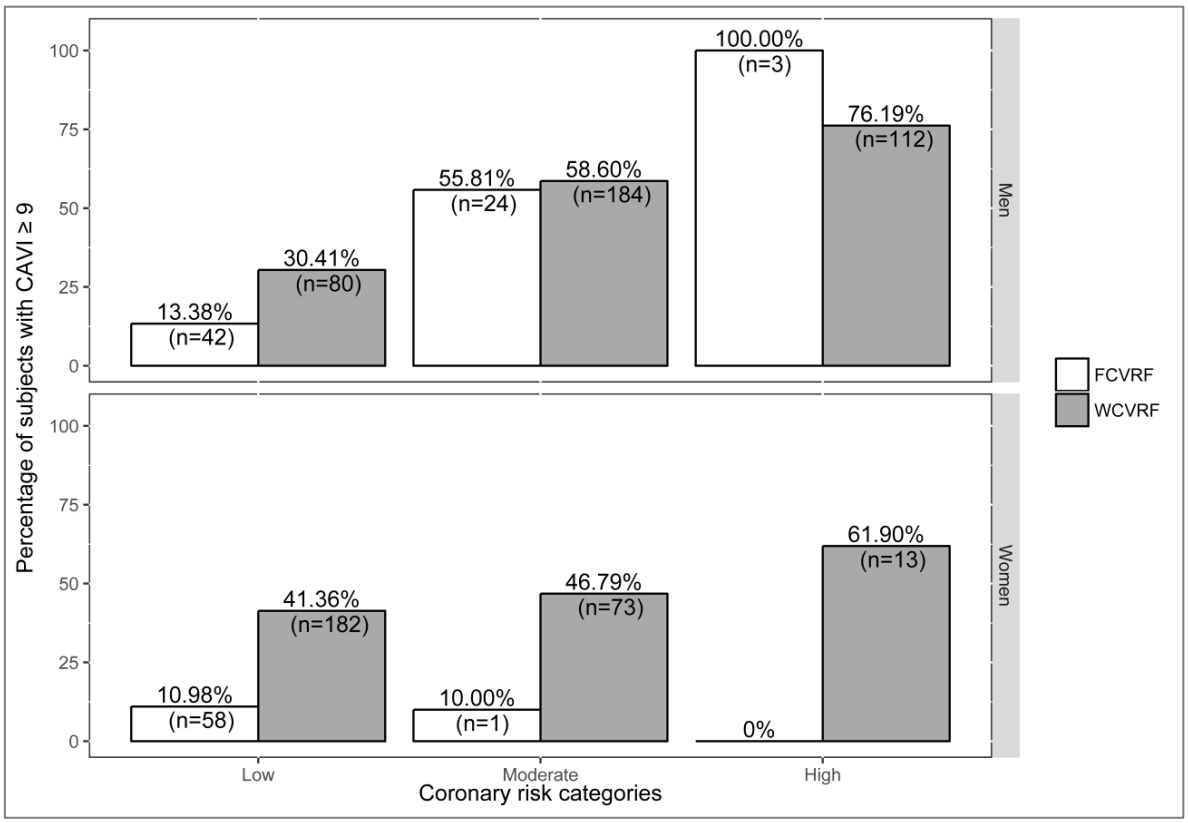


Figure 24. Percentage and number of participants with cardio-ankle vascular index (CAVI) ≥ 9 within each REGICOR risk category: Low (<5%), Moderate (≥ 5%–< 10%) and High (≥10%) in participants free of any of the three cardiovascular risk factors: hypertension, diabetes or hypercholesterolemia (FCVRC); and participants with at least one of the three risk factors or with personal history of vascular disease (myocardial infarction, angina pectoris or stroke) (WCVRF).

5.3. Association between lifestyles, socioeconomic status, cardiovascular risk factors, and arterial stiffness in an intermediate cardiovascular risk population

5.3.1. Characteristics of participants

A total of 2,380 participants aged 35–74 years took part in the study. The study flowchart is shown in Figure 17. The baseline characteristics of the participants, comparing lifestyles, socioeconomic status, the presence of CV risk factors, and arterial stiffness by sex, are summarized in Table 18. Men had higher levels of systolic BP, diastolic BP, pulse pressure, triglycerides and arterial stiffness (measured as CAVI ≥ 9), and a higher prevalence of hypertension than women. Diabetes, obesity, hypercholesterolemia, sedentary lifestyle, and insomnia were more frequent in women. Women adhered better to the Mediterranean diet and, overall, had better diet quality, smoked less, consumed less alcohol, had lower educational levels and were of lower occupational classes than men. CAVI ≥ 9 was observed in 48.6% of all participants, in 51.5% of men and in 44.0% women.

5.3.2. CAVI distribution by sex and age

The median CAVI score was 8.9 (9.01 for men and 8.87 for women), with an interquartile range of 1.59 (Figure 25). Men had a higher percentage of CAVI ≥ 9 than women, especially in participants over 65 years (75% vs. 62.2%, respectively) (Figure 26).

Table 18. Baseline characteristics of the participants by sex.

	Total	Men	Women	P-value
Sex, n (%)	2380	1468 (61.7)	912 (38.3)	
Age, years	61.3 (7.7)	61.0 (8.1)	61.7 (7.0)	0.037
SBP, mmHg	137.1 (17.3)	138.8 (17.0)	134.2 (17.5)	<0.001
DBP, mmHg	84.5 (10.2)	85.6 (10.4)	82.7 (9.7)	<0.001
Pulse Pressure, mmHg	52.6 (14.0)	53.3 (14.1)	51.5 (13.8)	0.002
Waist circumference, cm	100.9 (11.6)	102.9 (10.5)	97.6 (12.5)	<0.001
Total cholesterol, mg/dL	225.7 (40.8)	220.8 (39.0)	233.5 (42.5)	<0.001
HDL-C, mg/dL	49.8 (12.9)	48.0 (12.0)	52.9 (13.7)	<0.001
LDL-C, mg/dL	140.4 (34.9)	138.9 (34.2)	142.6 (35.8)	0.012
Triglycerides, mg/dL	123.0 [91.0-172.8]	125.0 [91.0-177.3]	121.0 [91.0-164.0]	0.026
Fasting glucose, mg/dL	107.5 (34.3)	107.2 (33.3)	108.0 (35.8)	0.582
Diet Quality Index	38.7 (3.1)	38.6 (3.1)	38.9 (2.9)	0.039
Adherence to Mediterranean Diet, %				
Low	7.7	9.0	5.7	0.011
Moderate	68.1	67.6	68.9	
High	24.2	23.4	25.4	
Physical inactivity, %	43.5	37.0	54.1	<0.001
Smoking status, %				
Current	27.9	31.4	22.3	<0.001
Former	34.8	46.5	16.0	
Never	37.3	22.1	61.7	
Pack/year index	24.0 [9.9-40.0]	25.5 [8.7-43.0]	22.8 [11.2-36.0]	0.001
Alcohol consumption, %				
No consumption	31.6	18.9	51.9	<0.001
Low risk	61.6	72.0	44.7	
Hazardous consumption	4.7	5.7	3.2	
Harmful consumption	2.1	3.3	0.2	
Insomnia, %	24.6	17.9	35.4	<0.001
Educational attainment, %				
University	17.4	21.2	11.3	<0.001
Secondary school	25.1	27.0	22.1	
Primary school	57.5	51.8	66.6	
Occupational social class, %				
Higher-level non-manual workers	17.0	20.8	9.2	<0.001
Lower-level non-manual workers	21.6	19.9	25.1	
Manual workers	61.4	59.3	65.7	
Diabetes, %	31.8	30.2	34.5	0.026
Hypertension, %	72.6	76.9	65.6	<0.001
Hypercholesterolemia, %	67.2	63.6	73.0	<0.001
Obesity, %	36.2	33.5	40.6	<0.001
BMI, kg/m^2	29.2 (4.4)	29.1 (3.9)	29.5 (5.1)	0.017
CAVI	8.9 (1.2)	9.0 (1.2)	8.8 (1.1)	<0.001
CAVI, %				
CAVI < 8	21,5	19,5	24,7	<0.001
8 ≤ CAVI < 9	30,1	28,7	32,2	
CAVI ≥ 9	48,4	51,8	43,1	

Data are expressed as mean (Standard Deviation) or median [25th percentile-75th percentile], unless otherwise indicated. BMI: body mass index; CAVI: Cardio-Ankle Vascular Index; DBP: diastolic blood pressure; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; TGL: triglycerides.

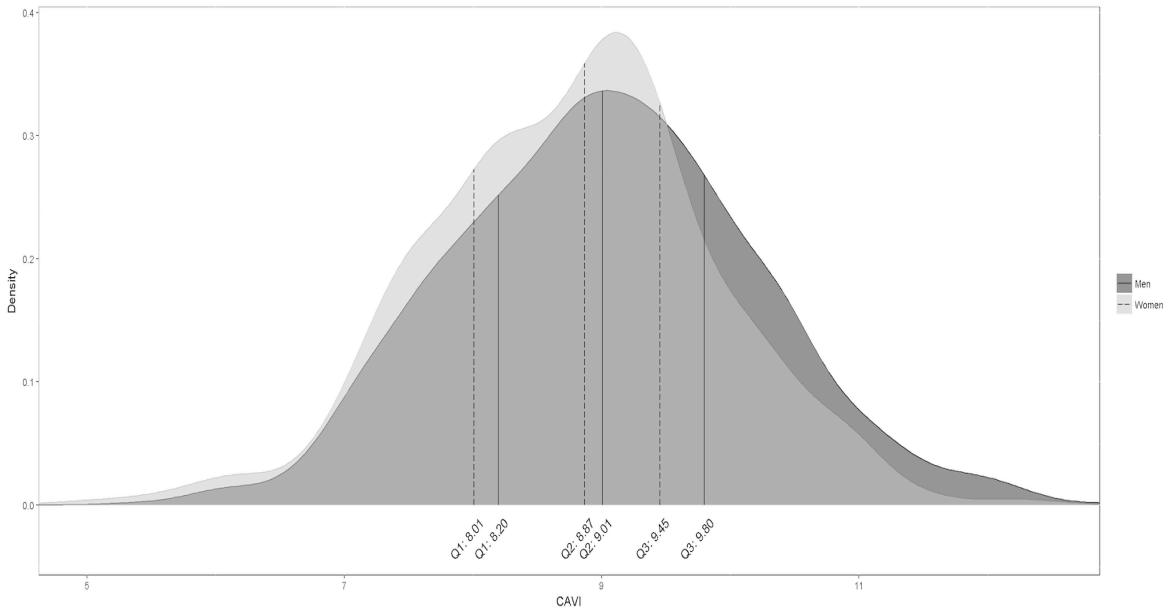


Figure 25. Density distribution of CAVI values by sex. CAVI: cardio-ankle vascular index; Q1: first quartile; Q2: median or second quartile; Q3: third quartile.

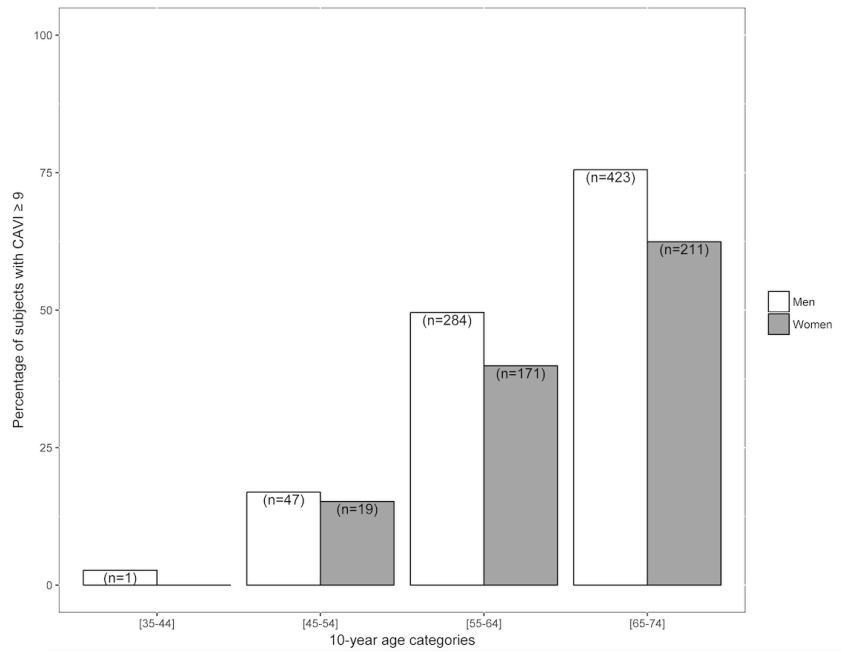


Figure 26. Distribution of participants with CAVI (cardio-ankle vascular index) ≥ 9 by age categories and sex.

5.3.3. CAVI and CV risk factors, lifestyles and SES

Table 19 compares CV risk factors, lifestyles and socioeconomic status in individuals with and without CAVI≥9 stratified by sex. Overall, participants with CAVI≥9 were older, more often hypertensive, were less obese, had lower educational levels and smoked less. In men, hypertension, hypercholesterolemia, obesity, current smoking habits, and sedentary lifestyle differed significantly between the groups with and without CAVI ≥ 9. In women, differences between CAVI groups were observed for hypertension, diabetes, obesity, waist circumference, diet quality index, educational level, and hypertensive and lipid-lowering medication.

Table 19. Characteristics of the participants according to CAVI values by sex.

	Men			***Women***		
	CAVI < 9	*CAVI ≥ 9*	*P-value*	*CAVI < 9*	*CAVI ≥ 9*	*P-value*
SBP, mmHg	135.5 (15.5)	142.2 (17.8)	<0.001	130.4 (15.7)	139.3 (18.6)	<0.001
Pulse Pressure, mmHg	49.8 (12.3)	56.8 (15.0)	<0.001	48.0 (11.8)	56.2 (15.0)	<0.001
Waist circumference, cm	103.4 (11.2)	102.4 (9.7)	0.080	98.6 (13.1)	96.2 (11.5)	0.004
Total cholesterol, mg/dL	225.4 (39.4)	216.3 (38.1)	<0.001	234.0 (42.5)	232.8 (42.5)	0.671
HDL-C, mg/dL	46.4 (10.8)	49.5 (12.7)	<0.001	52.1 (13.9)	53.9 (13.5)	0.054
LDL-C, mg/dL	142.4 (34.4)	135.6 (33.7)	<0.001	144.0 (35.8)	140.7 (35.8)	0.167
Triglycerides, mg/dL	132 [96.0-188.0]	119 [88.0-170.0]	0.026	121 [89.2-168.0]	122 [95.0-160.0]	0.779
Fasting glucose, mg/dL	105.4 (32.0)	109.0 (34.5)	0.039	104.6 (35.2)	112.6 (36.1)	0.001
Diet Quality Index	38.5 (3.2)	38.7 (3.1)	0.172	38.7 (3.1)	39.1 (2.8)	0.035
Physical inactivity, %	39.6	34.4	0.021	56.1	51.3	0.088
Smoking status, %						
Current	39.2	23.6	<0.001	26.7	16.1	<0.001
Former	40.6	52.4		18.4	12.8	
Never	20.2	23.9		54.9	71.1	
Educational attainment, %						
University	24.5	17.9	<0.001	13.4	8.3	0.001
Secondary school	31.6	22.4		24.8	18.5	
Primary school	44.0	59.6		61.7	73.2	
Diabetes, %	28.3	32.1	0.064	28.6	42.7	<0.001
Hypertension, %	72.5	81.3	<0.001	59.3	74.2	<0.001
Hypercholesterolemia, %	67.9	59.4	<0.001	72.2	74.2	0.269
Obesity, %	39.5	27.6	<0.001	47.5	31.0	<0.001
BMI, kg/m^2	29.6 (4.3)	28.5 (3.3)	<0.001	30.3 (5.5)	28.3 (4.2)	<0.001
Hypertensive medication, %	46	54.5	0.001	49.8	57.9	0.016
Lipid lowering medication, %	26.2	27.9	0.454	26.4	36.6	0.001
Age, %						
34-44	5.2	0.1	<0.001	2.8	0.0	<0.001
45-54	33.3	6.0		20.3	4.7	
55-64	41.4	37.2		50.8	43.0	
65-74	20.1	56.7		26.1	52.3	

We display only statistically significant results in one or both sexes.

Data are expressed as mean (Standard Deviation) or median [25th percentile-75th percentile], unless otherwise indicated.

BMI: body mass index; CAVI: Cardio-Ankle Vascular Index; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; TGL: triglycerides.

Results of the logistical regression analysing the relation between lifestyles, SES, and CV risk factors, and CAVI are shown in Figure 27. In both men and women, age, hypertension and diabetes were positively associated with arterial stiffness (CAVI≥9), while BMI was inversely related. Men who only finished primary education were also associated with arterial stiffness.

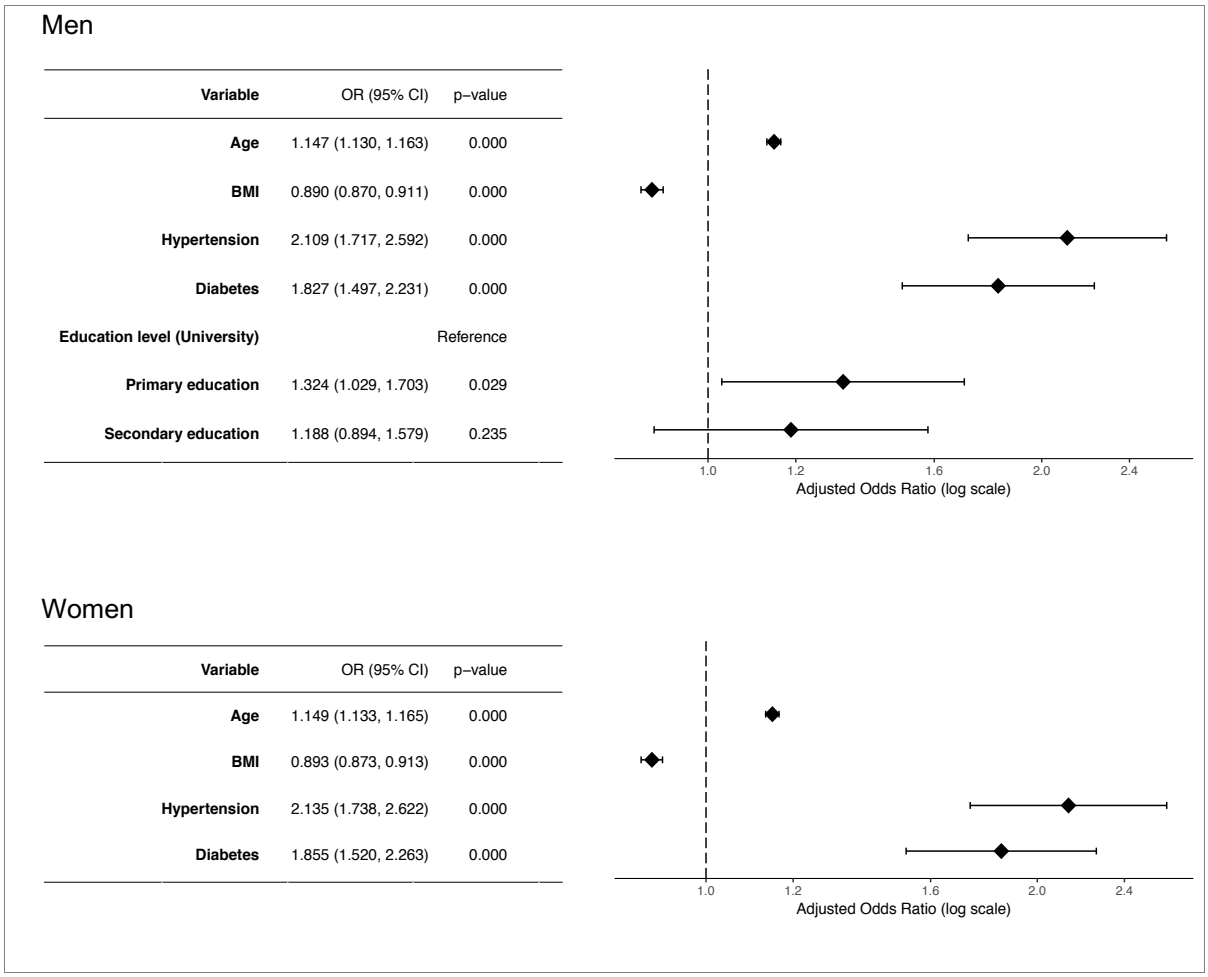


Figure 27. Forest plot showing the effect of educational level, risk factors (hypertension, diabetes and body mass index (BMI)), and age on CAVI (cardio-ankle vascular index) ≥ 9 in men and women. Reference categories are not having diabetes, not having hypertension, and university education.

6. DISCUSSION

In these studies, CAVI values and the relation of CAVI with CV risk factors and lifestyles in Mediterranean populations are presented for the first time.

According to objectives 1.1 and 2.1, we found that pathological arterial stiffness (CAVI ≥ 9) was present in a significant proportion of the population (more than 40%) and that its prevalence increased markedly with age, whichever population was considered: general or intermediate CV risk Mediterranean population, men or women, FCVRF or WCVRF. This high prevalence is remarkable since it is known that CAVI scores of ≥ 9 are associated with coronary artery disease[226] but does not agree with hypothesis 1.1, in which we presumed that the prevalence of arterial stiffness in the general Mediterranean population would be lower than in other studies[226].

Additionally, we estimated the prevalence of pathological arterial stiffness across coronary risk levels in the general Mediterranean population (objective 1.2) and found that CAVI ≥ 9 also increased with CV risk levels, in accordance with hypothesis 1.3. A further interesting result was the discovery of a significant proportion of individuals with low or moderate coronary risk, regardless of their CVRF group, with CAVI ≥ 9. The prevalence of CAVI ≥ 9 was also higher in the intermediate CV risk population than in the general population (48.6% vs. 41.1%), in line with hypothesis 2.2. Therefore, as a marker of subclinical atherosclerosis, CAVI scores ≥ 9 could be used to detect high-risk individuals that would otherwise not be identified using classical risk functions, which therefore represents an improvement on the current CV risk classification.

The results indicate that in Mediterranean populations CAVI values were higher in men than in women, as other studies have reported[231,284], even though the differences between the sexes in the intermediate CV risk population were less pronounced. In accordance with objective 1.3, we determined the CAVI values in the FCVRF and WCVRF groups in order to uncover any differences between them: the values of the index were higher in participants in the WCVRF group than in the FCVRF group, as predicted by hypothesis 1.4.

The mean CAVI values obtained in our study showed the same patterns for age and sex groups as in general Asian populations[285]. However, the mean CAVI values were higher in all age categories than those reported in Asian populations[12,13,286,287], probably due to the high prevalence of cardiovascular risk factors in our populations. CAVI values in healthy Japanese [216,286], Chinese[286] and Korean populations[288] were lower than those in our FCVRF (healthy) group. However, a typical problem when comparing healthy populations is the definition of 'healthy'. A common characteristic is that healthy individuals are not affected by impaired arterial pressure or glucose metabolism alteration, and do not have an impaired cholesterol profile or past history of cardiovascular disease, all factors that have a higher association with arterial stiffness. On the contrary, the mean CAVI values obtained in the WCVRF group were higher than those reported by the Japanese population with risk factors[216], in all age categories and in both sexes.
We presented the reference ranges of CAVI values in a general Mediterranean population aged 35-79 by sex and age (Figure 18). The availability of reference CAVI ranges could be helpful to assess the atherosclerosis burden in clinical practice.

As stated in our main objectives, we also assessed the relationship between arterial stiffness and lifestyles, CV risk factors and socioeconomic status in both Mediterranean populations (the latter only in the intermediate CV risk population). All the participants with CAVI ≥ 9 were older and had a higher prevalence of cardiovascular risk factors and a higher coronary risk score than participants with CAVI < 9. Not surprisingly, most CV risk factors increased the probability of a CAVI ≥ 9 score in both men and women (mainly hypertension and diabetes, and hypercholesterolemia in women in the general population), in line with hypotheses 1.2 and 2.1. However, of all lifestyle factors, only physical inactivity in men of the general population was found to increase the probability of a CAVI ≥ 9 score, which does not agree with our hypotheses. In turn, BMI was inversely related to CAVI ≥ 9. In men in the intermediate CV risk population, having completed only primary education was associated with arterial stiffness. Our results are similar to some studies performed with PWV that found an association between arterial stiffness, high blood pressure, diabetes mellitus, and gender[235,289].

6.1. CAVI and cardiovascular risk factors

As expected, CV risk factors were more prevalent in the intermediate CV risk population than in the general population. In both, hypertension was more frequent in men. However, whereas in the general population diabetes and BMI were higher in men, in the intermediate CV risk population hypercholesterolemia, diabetes and obesity were more prevalent in women.

In our analyses, all CV risk factors behaved as expected except BMI, which seemed to be inversely related: the odds of having CAVI ≥ 9 significantly decreased with overweight and obesity, in line with other studies[281,283,290]. These unexpected results could be explained by a decrease in arterial stiffness due to systemic accumulation of adiposity tissue as opposed to increased arterial stiffness associated with visceral accumulation of adiposity, as suggested by Nagayama[283]. Accordingly, waist circumference could be a more accurate measure of noxious fat than BMI, which takes into account both subcutaneous and visceral fat. Waist circumference has been shown to be a good indicator of visceral adiposity[291], despite not being identified as significantly associated in these studies.

Hypertension was positively associated with the risk of pathological arterial stiffness in men and women in both populations, as has previously been reported[13]. Diabetes was also associated with higher odds of CAVI ≥ 9 in the intermediate CV risk population, as other studies have indicated[9,292]. In the general population, however, despite a lack of significance, a tendency can be observed in women, probably due to the small sample size since there were only 64 diabetic women in the CAVI < 9 group and 77 in the CAVI ≥ 9 group. Hypercholesterolemia was associated with CAVI ≥ 9 in women in the general population but not in men or in the intermediate CV risk population. Other studies that define hypercholesterolemia using different guidelines have found an association between CAVI and hypercholesterolemia in both men and women[293].

In summary, in the general population hypertension and hypercholesterolemia (the

latter only in women) were positively associated with CAVI, but negatively associated with BMI. In the intermediate CV risk population, hypertension and diabetes were positively related in both men and women, but BMI was inversely related.

6.2. CAVI and lifestyles

We found that only physical activity in men in the general population was significantly associated with CAVI $\geq$ 9 in the multivariate analysis. No other lifestyles were related to pathological arterial stiffness, either positively or negatively. Men were significantly more active than women, even though the participants of the intermediate CV risk population were less active than the ones in the general population. Even though some authors failed to find a relationship with physical activity and arterial stiffness, as in our intermediate CV risk population[249], physical activity has been shown to have a positive effect on cardiovascular health and, specifically, is related to lower central arterial stiffness[294,295]. This beneficial effect was present in our general Mediterranean population in both men and women but is only significant in men. These results highlight the importance of current strategies including the promotion of healthier lifestyles as means of preventing the onset of CVD.

In both populations, participants had similar quality diets (DQI around 39, which is moderately good); no significant differences were observed between DQI and CAVI. In the intermediate CV risk population, we also assessed the adherence to a Mediterranean diet, and found that over two thirds of the population adhered moderately. The percentage of the population with a high adherence to a Mediterranean diet was lower than reported by other studies[107,120], perhaps because the questionnaires we used were different and the populations surveyed had different characteristics (the respondents in these studies were older and were part of a general population with no intermediate CV risk).

No significant differences were observed in the bivariate analysis. Our results do not coincide with other studies that found that following a Mediterranean dietary pattern during adolescence and early adulthood can prevent arterial stiffness in

adulthood[296]; these other studies use different questionnaires to assess Mediterranean dietary patterns.

The participants in the intermediate CV risk population that smoked more than in the general population (30% vs. 17%) were mainly men, and there was a lower proportion of people in this population that had never smoked (the proportion was higher in women in both populations). Smoking has long been established as an unhealthy lifestyle factor because it is a major CV risk factor and one of the main preventable causes of death in developed countries[297]; it has been associated with an increase in arterial stiffness measured using both CAVI and PWV[257]. However, in some previous studies no association between smoking and pathological arterial stiffness was found [298,299], possibly due to the cross-sectional design of studies and the fact that pack-years of exposure may not have been taken into consideration (in the general population). Since smoking is a modifiable lifestyle factor, follow-up studies would be useful for assessing whether there is indeed a causal relationship. Perhaps those individuals with modifiable risk factors have been encouraged to make lifestyle changes and have done so that recently that the discernible benefits are not yet evident.

In the Intermediate CV risk population, we also assessed the risk of alcohol consumption. We found that men drank more than women, albeit mainly low-risk consumption (<28 SDU/week in men and <14 SDU/week in women), and that women were more frequently non-consumers of alcohol. A J-shaped association between alcohol consumption and arterial stiffness has been reported by other studies, in which light-to-moderate alcohol consumption is associated with lower arterial stiffness, although these studies used PWV as a measure and only studied the relationship in men [251,254].

Despite the fact that half the participants in the intermediate CV risk population reported good-quality sleep, women suffered more from insomnia than men. Although poor sleep quality has been associated with increased arterial stiffness (measured with PWV) in participants with type 2 diabetes mellitus[261], we found no associations between insomnia and pathological CAVI.

6.3. CAVI and socioeconomic status

Education was used as a socioeconomic status indicator since it reflects the transition from parents' socioeconomic status to an adult's own resources (employment status and income).[198] In our study, the fact of only having completed primary education was associated with higher arterial stiffness in men, which agrees with other studies that have assessed arterial stiffness or CVD.[202,264] No such relationship has been reported in women. As lifestyles are established before employment age, the relationship between arterial stiffness and education (and not with type of employment) could reflect an early onset of an unhealthy lifestyle[264].

One interpretation of this finding is that it is important to consider both social backgrounds and educational levels when designing individualized strategies for CVD prevention, as education could be a vital factor in the decision to adopt or avoid risk behaviour. As CV risk factors are potentially modifiable by health counselling, our results suggest that primary-care policies and the design of health promotion activities should take into account strategies for targeting individuals with only primary education.

6.4. Limitations and strengths

Several weaknesses or limitations regarding the methods and analyses used in this study must be acknowledged. Firstly, the cross-sectional design of the three studies precluded establishing causal relationships. This is particularly important in the case of hypertension since there is much disagreement regarding which comes first; indeed, it is most likely that there is bidirectional association[213,235].

Secondly, the respondents in our population (above all in the intermediate CV risk population) could have changed their lifestyles shortly before our survey due to their CV risk. As the questionnaires asked about activities over the last month or week, answers would not necessarily reflect long-term habits. Questionnaires assessing alcohol and smoking may have an additional limitation: people could have underestimated their consumption since assessing lifestyles is a highly

sensitive issue and questionnaires based on self-reported data tend to be subjective.

Another limitation is the determination of the CAVI itself. It cannot be assessed with enough accuracy in individuals with ABI $\leq$ 0.9 because the presence of peripheral arterial disease can result in false, too-low CAVI values [222]. As a result, we excluded participants with pathological ABI. An ABI $\leq$ 0.9 reflects an arteriosclerotic femoral artery, and lower ABI values indicate more severe peripheral artery disease and higher CV risk factors.

Lastly, the definition of 'healthy' participants when considering comparative purposes is another possible limitation. In our study *Differences in cardio-ankle vascular index in a general Mediterranean population in relation to the presence or absence of metabolic cardiovascular risk factors*[300], we took to be healthy those participants free of any of the following three cardiovascular risk factors: hypertension, diabetes or hypercholesterolemia, and with no personal history of vascular events (myocardial infarction, angina pectoris or stroke).

The three studies have several strengths that support the conclusions obtained:

- the large sample size.
- the use of validated questionnaires.
- the representativeness of the samples that ensure the external validity of the findings.
- the assessment of arterial stiffness using the CAVI score, an indicator that does not depend on blood pressure at measuring time, is easy to assess and is highly accurate.[8] Therefore, CAVI offers some advantages over PWV, that is highly correlated with SBP and DBP[10].
- the specific training for nurses in charge of participant recruitment and data collection.

6.5. Impact of this research

Some facts support the idea that CAVI could be used to complement the classical risk factors to improve coronary risk stratification. Firstly, CAVI is related to classical CV risk factors and to lifestyles that promote CV health[221]. Secondly, in our research the prevalence of CAVI ≥ 9 increases with risk, suggesting that those individuals with CAVI ≥ 9 – but not at high risk – may be reclassified into higher risk groups. Finally, CAVI has been shown to have a good predictive value for the onset of CVD.

All these data, together with the high prevalence of pathological CAVI in the low and moderate risk categories, regardless of the CV risk factors, makes this index a plausible tool in the struggle to improve the detection of asymptomatic atherosclerosis. Moreover, CAVI has good reproducibility and can be performed by nurses in a primary healthcare setting. Accordingly, CAVI should be assessed by follow-up studies as a means of determining its validity as an indicator of asymptomatic atherosclerosis, as well as its ability to help strengthen risk stratification.

This research will also be useful for nursing practitioners in primary healthcare who play a prominent role in strategies designed to improve CVD prevention. Evidence exists of the effectiveness of nurses in CVD prevention in primary care: programmes conducted in six European countries[301], as well as the Netherlands[302] and the USA[303], have shown that practice nurses can help obtain significant improvements in CV risk factors (blood pressure, cholesterol and diabetes mellitus) in high-risk individuals.

Our results support certain strategies to improve primary prevention of CVD in primary healthcare. These strategies include early detection of arterial stiffness indicated by pathological CAVI, development of activities to promote control of diabetes and hypertension, and promotion of physical activity, especially in men. Particular attention should be paid to those men at intermediate cardiovascular risk with primary education level.

7. CONCLUSIONS

The main conclusions of the thesis are:

- The prevalence of pathological arterial stiffness (measured as CAVI ≥ 9) increases with coronary risk and reaches 60% in groups not classified as being at high risk.

- The CV risk factors (mainly hypertension and diabetes) are positively associated with pathological arterial stiffness, but BMI is negatively related.

- Physical activity is associated with pathological arterial stiffness in men in the general population; however, no other specific lifestyles are associated with arterial stiffness.

- In the intermediate CV risk population, the fact of having completed only primary education is related to CAVI ≥ 9.

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9. APPENDIXES

Appendix 1. European countries as considered in the WHO European Region

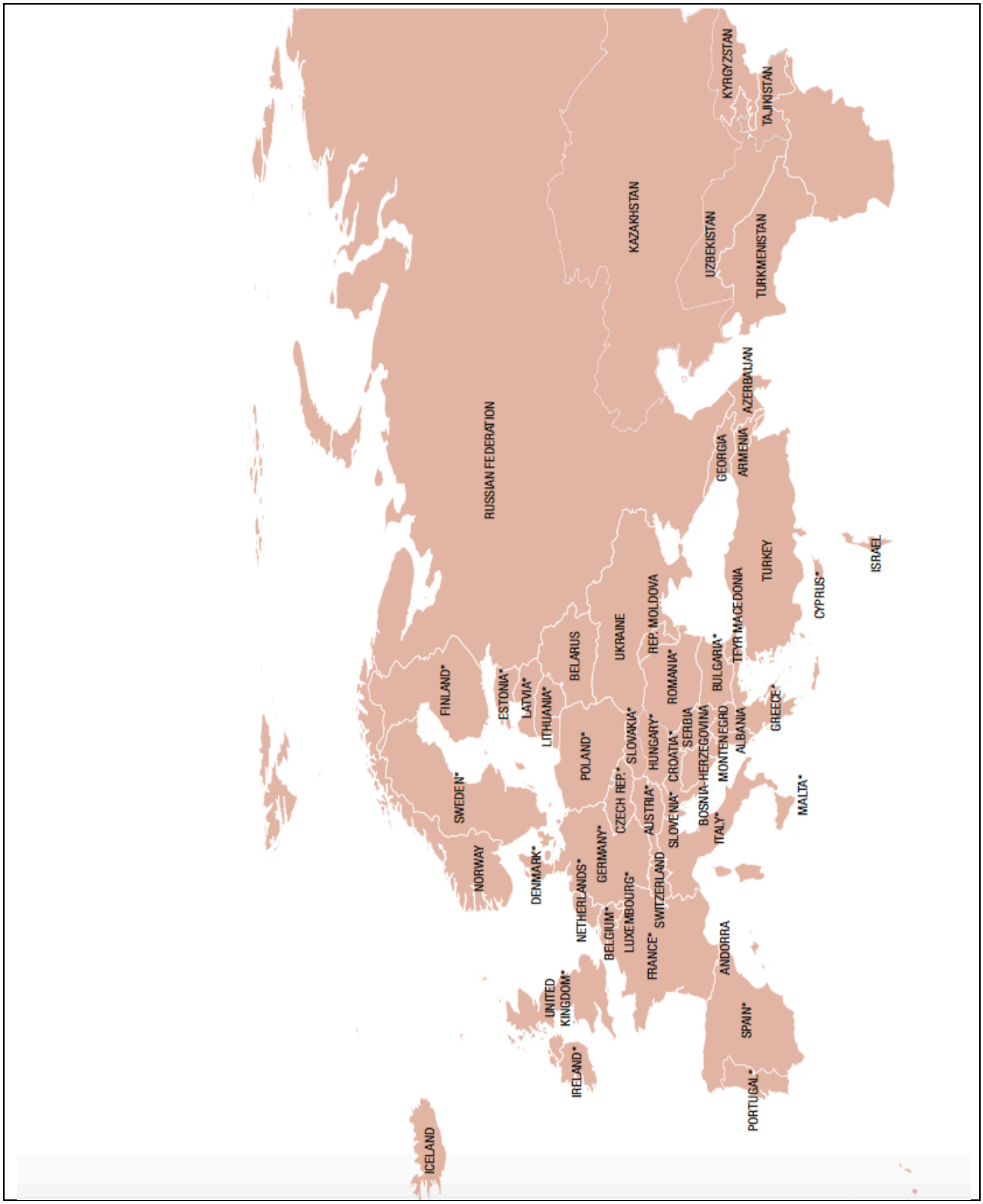


Figure 28. Member states of the WHO European Region. * Member of the EU[20].

Appendix 2. REGICOR risk tables

Table 20. Ten-year risk of a coronary event (fatal or non-fatal) in men. HDL cholesterol: high-density lipoprotein cholesterol[16].

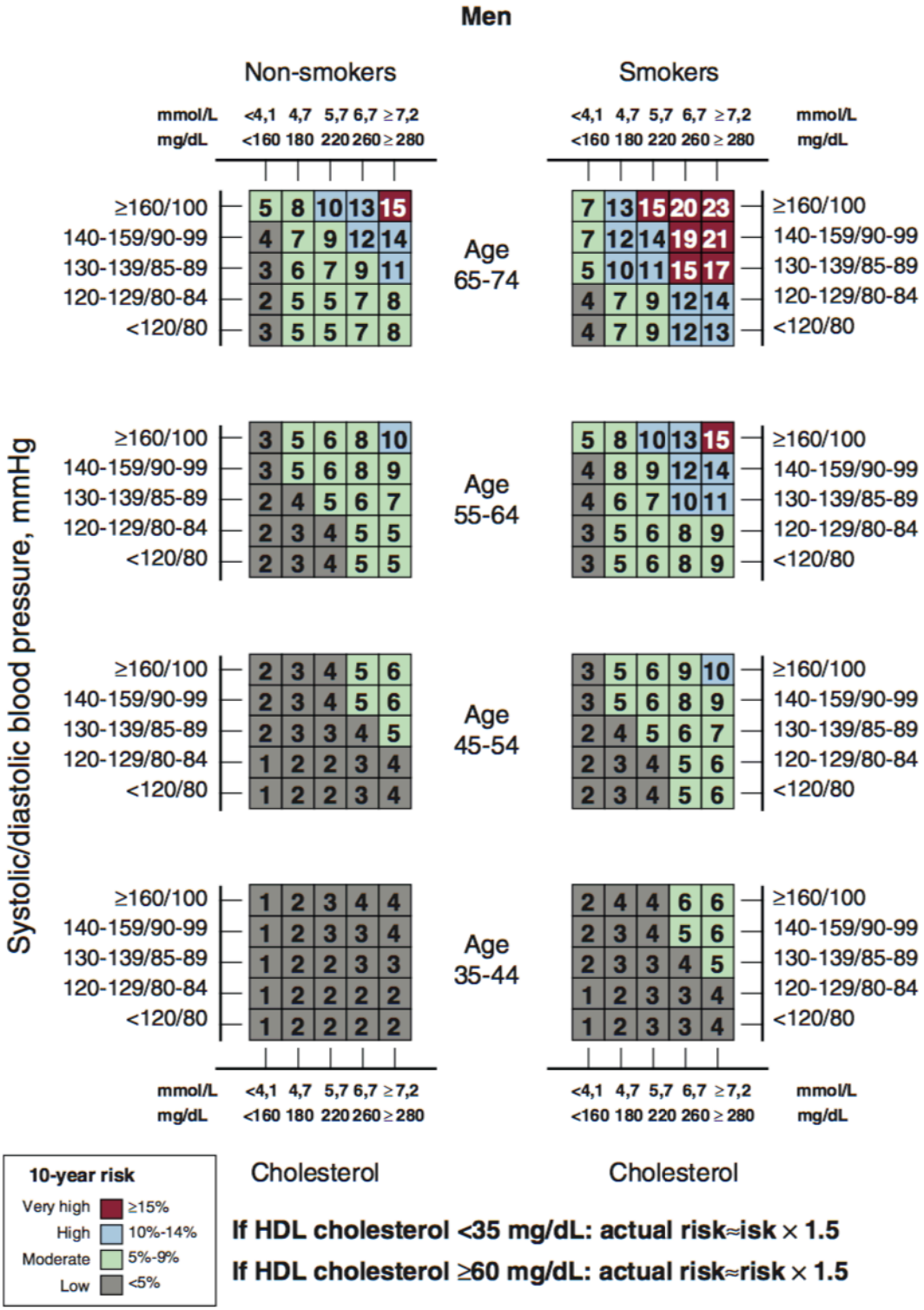


Table 21. Ten-year risk of a coronary event (fatal or non-fatal) in diabetic men. HDL cholesterol: high-density lipoprotein cholesterol[16].

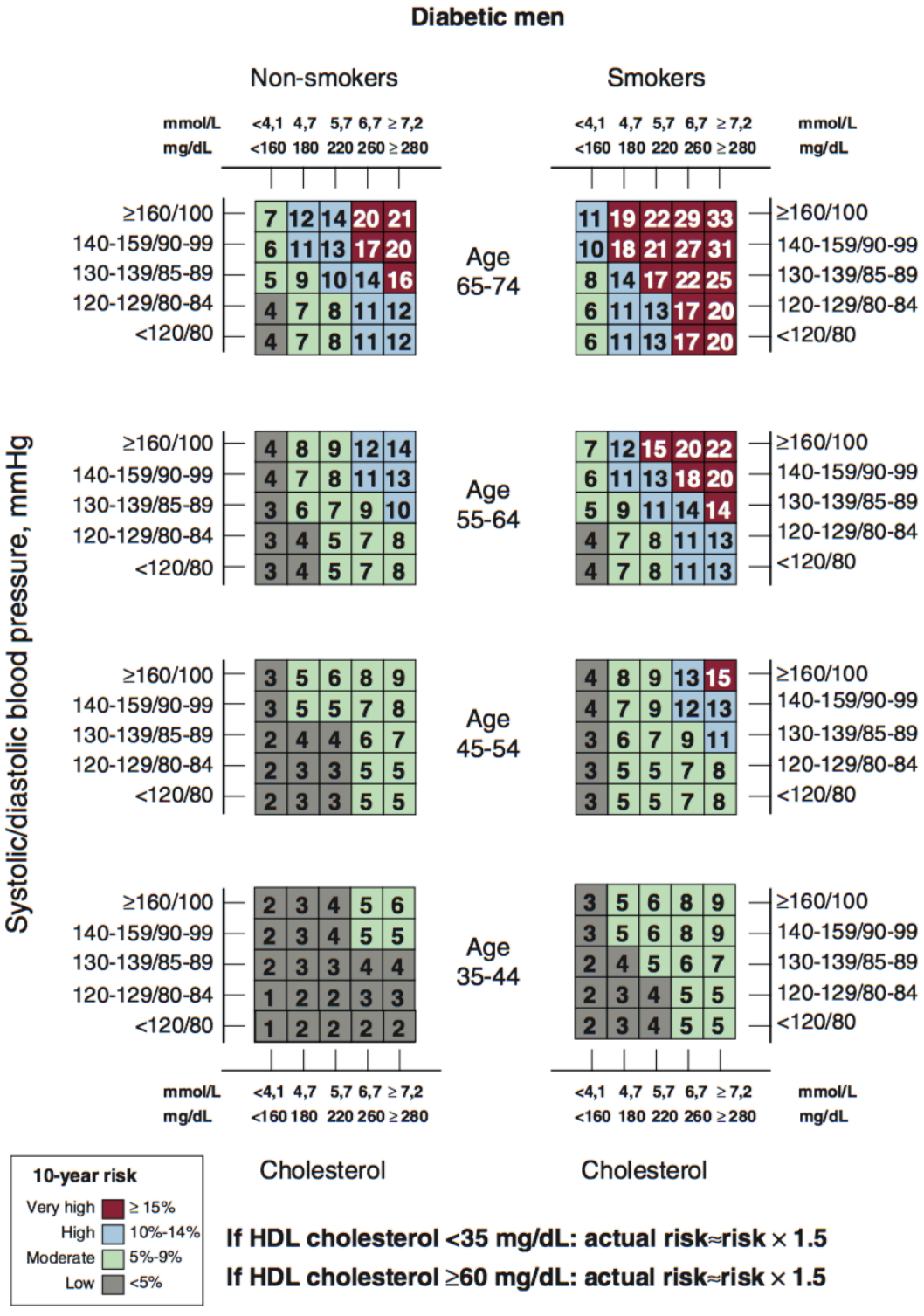


Table 22. Ten-year risk of a coronary event (fatal or non-fatal) in women. HDL cholesterol: high-density lipoprotein cholesterol[16].

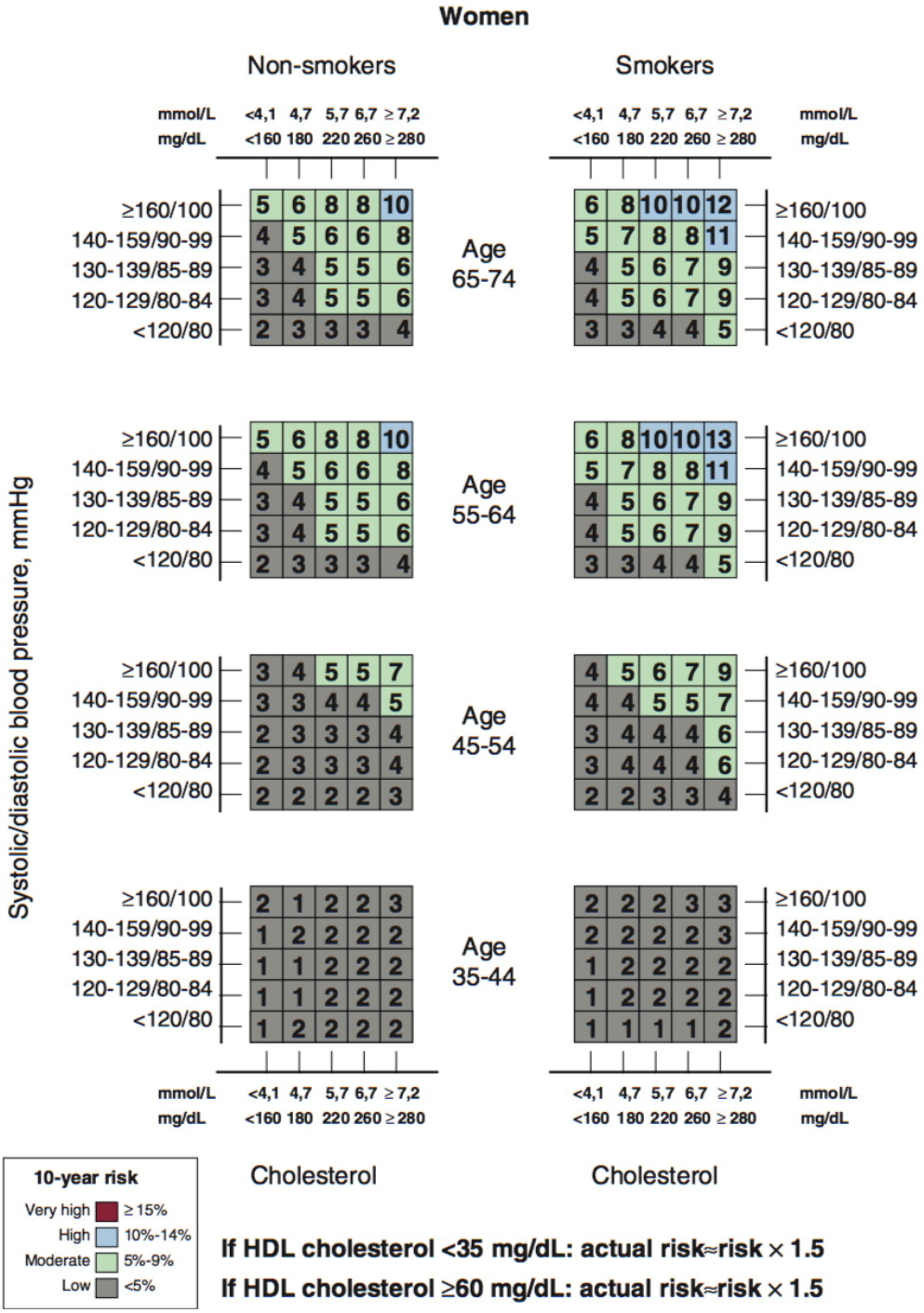
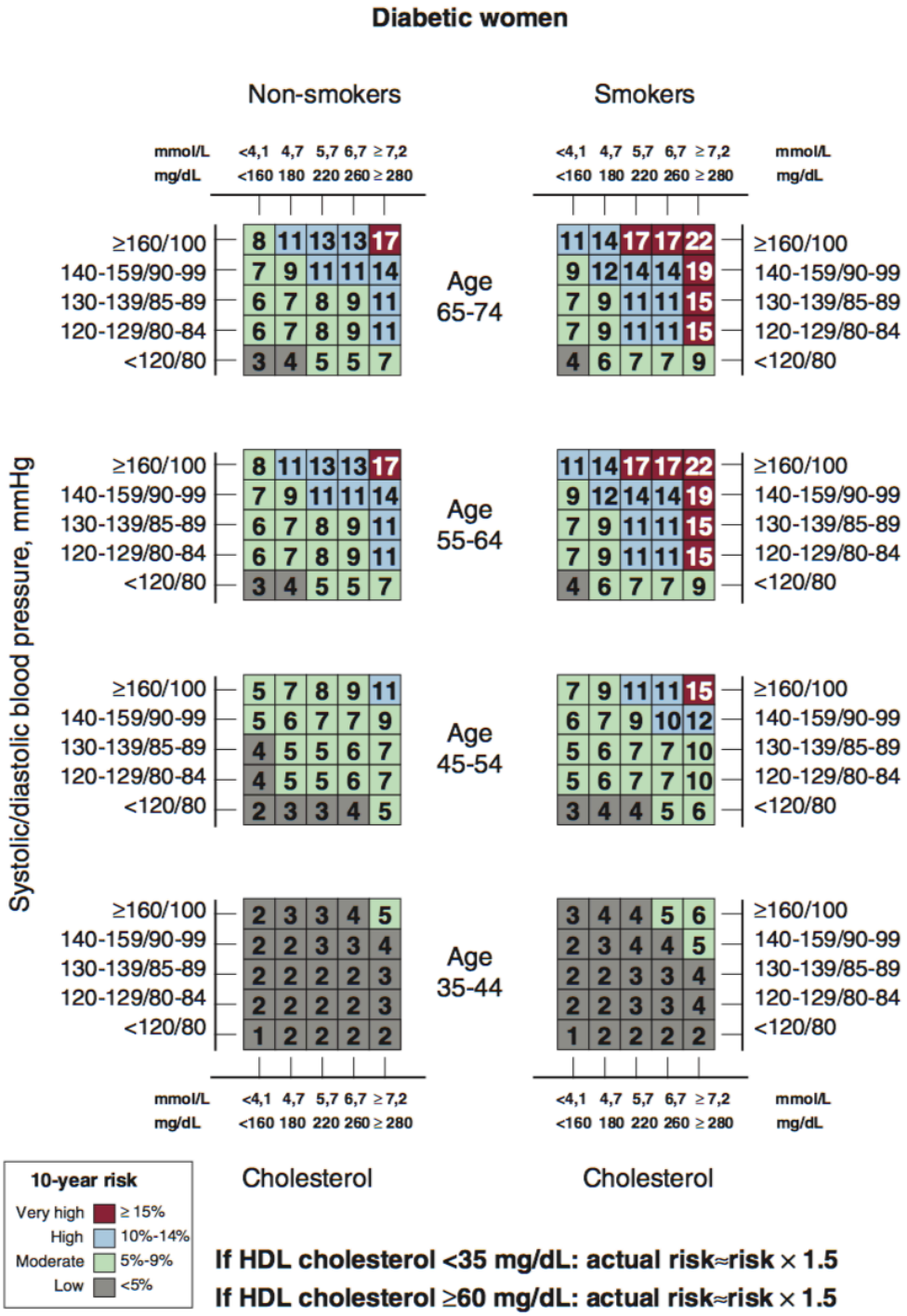


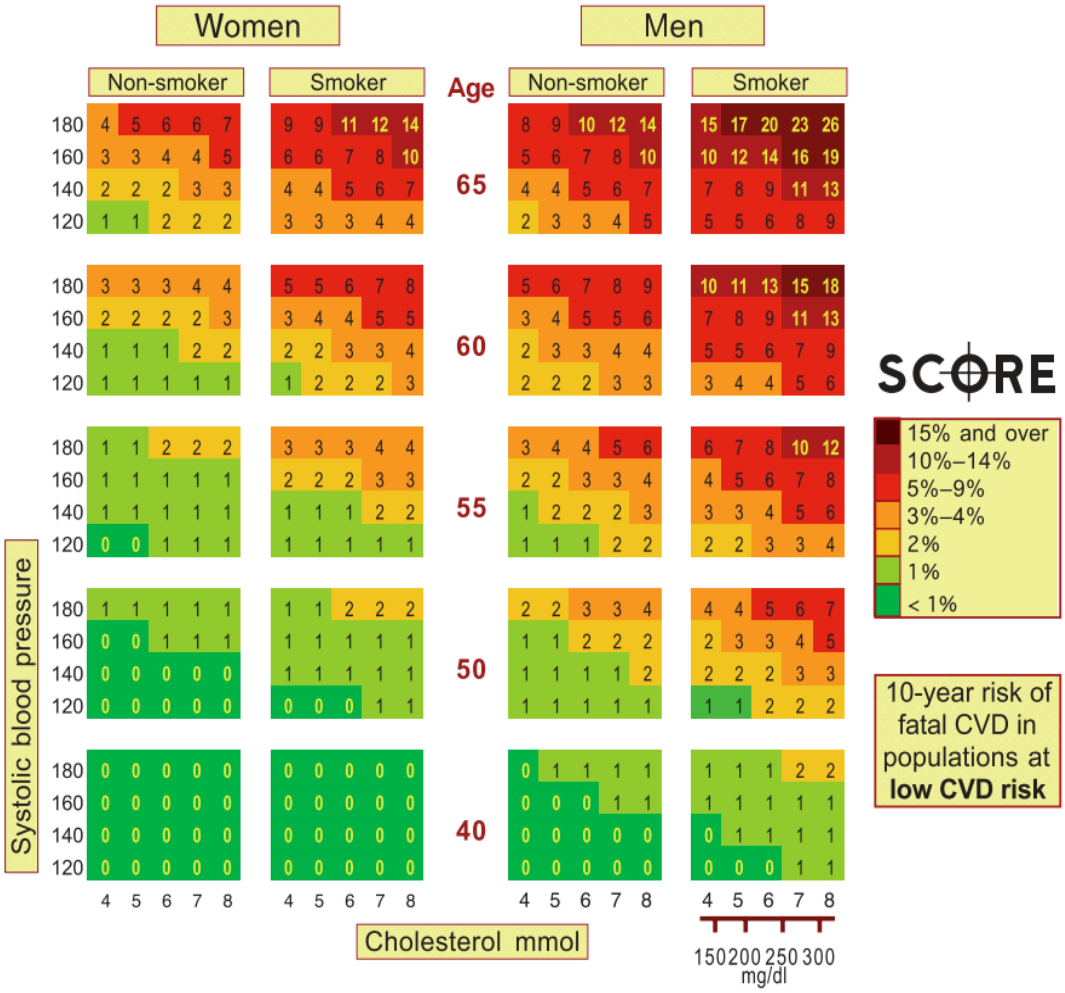
Table 23. Ten-year risk of a coronary event (fatal or non-fatal) in diabetic women. HDL cholesterol: high-density lipoprotein cholesterol[16].



Appendix 3. SCORE risk table.

Table 24. Ten-year risk of fatal cardiovascular disease (CVD) in countries at low cardiovascular disease risk[40].

Low CVD countries: Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, The Netherlands, Norway, Portugal, San Marino, Slovenia, Spain, Sweden, Switzerland and the United Kingdom.



Appendix 4. Risk stratification proposed in the 2013 European Society of Cardiology (ESC) Guidelines.

Table 25. Factors used for stratification of total CV risk[36](apart from BP).

Risk factors
Male sex
Age (men ≥55 years; women ≥65 years)
Smoking
Dyslipidaemia
Total cholesterol >4.9 mmol/L (190 mg/dL), and/or
Low-density lipoprotein cholesterol >3.0 mmol/L (115 mg/dL), and/or
High-density lipoprotein cholesterol: men <1.0 mmol/L (40 mg/dL), women <1.2 mmol/L (46 mg/dL), and/or
Triglycerides >1.7 mmol/L (150 mg/dL)
Fasting plasma glucose 5.6–6.9 mmol/L (102–125 mg/dL)
Abnormal glucose tolerance test
Obesity [BMI ≥30 kg/m^2 (height^2)]
Abdominal obesity (waist circumference: men ≥102 cm; women ≥88 cm) (in Caucasians)
Family history of premature CVD (men aged <55 years; women aged <65 years)
Asymptomatic organ damage
Pulse pressure (in the elderly) ≥60 mmHg
Electrocardiographic LVH (Sokolow–Lyon index >3.5 mV; RaVL >1.1 mV; Cornell voltage duration product >244 mV*ms), or
Echocardiographic LVH [LVM index: men >115 g/m^2; women >95 g/m^2 (BSA)][a]
Carotid wall thickening (IMT >0.9 mm) or plaque
Carotid–femoral PWV >10 m/s
Ankle-brachial index <0.9
CKD with eGFR 30–60 mL/min/1.73 m^2 (BSA)
Microalbuminuria (30–300 mg/24 h), or albumin–creatinine ratio (30–300 mg/g; 3.4–34 mg/mmol) (preferentially on morning spot urine)
Diabetes mellitus
Fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) on two repeated measurements, and/or
HbA_{1c} >7% (53 mmol/mol), and/or
Post-load plasma glucose >11.0 mmol/L (198 mg/dL)
Established CV or renal disease
Cerebrovascular disease: ischaemic stroke; cerebral haemorrhage; transient ischaemic attack
CHD: myocardial infarction; angina; myocardial revascularization with PCI or CABG
Heart failure, including heart failure with preserved EF
Symptomatic lower extremities peripheral artery disease
CKD with eGFR <30 mL/min/1.73m^2 (BSA); proteinuria (>300 mg/24 h).
Advanced retinopathy: haemorrhages or exudates, papilloedema

BMI: body mass index; BP: blood pressure; BSA: body surface area; CABG: coronary artery bypass graft; CHD: coronary heart disease; CKD: chronic kidney disease; CV: cardiovascular; CVD: cardiovascular disease; EF: ejection fraction; eGFR: estimated glomerular filtration rate; HbA_{1c}: Glycated haemoglobin; IMT: intima-media thickness; LVH: left ventricular hypertrophy; LVM: left ventricular mass; PCI: percutaneous coronary intervention; PWV: pulse wave velocity.

[a]Risk maximal for concentric LVH: increased LVM index with a wall thickness/radius ratio of 0.42.

Table 26. Stratification of CV risk in different categories (low, moderate, high and very high)[36].

Other risk factors, asymptomatic organ damage or disease	Blood Pressure (mmHg)			
	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other RF		Low risk	Moderate risk	High risk
1–2 RF	Low risk	Moderate risk	Moderate to high risk	High risk
≥3 RF	Low to Moderate risk	Moderate to high risk	High Risk	High risk
OD, CKD stage 3 or diabetes	Moderate to high risk	High risk	High risk	High to very high risk
Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs	Very high risk	Very high risk	Very high risk	Very high risk

BP: blood pressure; CKD: chronic kidney disease; CV: cardiovascular; CVD: cardiovascular disease; DBP: diastolic blood pressure; HT: hypertension; OD: organ damage; RF: risk factor; SBP: systolic blood pressure.

Appendix 5. English version of the developed and validated REGICOR short questionnaire for physical activity[273].

Leisure time physical activity

I am going to ask you some questions about your physical activity during a typical month.

In a typical month:

1.a. How many days do you go for a walk at a slow or normal pace? † |__|__| days

1.b. On average, how many minutes each day? |__|__|__| min/day

2.a. How many days do you walk fast (brisk walking)? |__|__| days

2.b. On average, how many minutes each day? |__|__|__| min/day

3.a. How many days do you walk in the countryside or in the mountains? |__|__| days

3.b. On average, how many minutes each day? |__|__|__| min/day

4.a. How many days do you climb stairs? |__|__| days

4.b. On average, how many floors each day? |__|__|__| floors/day

5.a. How many days do you work in the yard or garden? |__|__| days

5.b. On average, how many minutes each day? |__|__|__| min/day

6.a. How many days do you exercise or play sports at home, outdoors,

or in a gym? |__|__| days

6.b. On average, how many minutes each day? |__|__|__| min/day

† NOTE: Walking for commuting to work is included. Bicycling for commuting to work or for pleasure could also be included in this item.

Sedentary behavior

On average during a typical work-day and excluding work time, how many hours do you watch TV or sit at a computer or play video games? |__|__| hours/day

On average during a non-working day, how many hours do you watch TV or sit at a computer or play video games? |__|__| hours/day

How many days per week do you work? |__| days

Occupational physical activity

What type of physical activity do you perform in your occupation (or in your daily life)?

a.- Basically, I'm seated and I walk very little (administrative, ...)

b.- I am seated but I very often perform moderate intensity efforts (cashier...)

c.- Basically, I am standing and I walk very little

d.- I walk a lot but I do not perform vigorous effort (salesperson, shopkeeper...)

e.- I walk a lot and I perform vigorous effort (mail carrier, delivery person...)

f.- Basically, I perform vigorous effort (construction worker...)