DOCTORAL THESIS

Impact of Psychological and Social Factors on Cardiovascular Risk in an Adult Population at High Cardiovascular Risk

Author: Cília Mejía Lancheros

Director: Miguel Ángel Muñoz Pérez

Department of Paediatrics, Obstetrics, Gynaecology, and Preventive Medicine

SCHOOL OF MEDICINE
UNIVERSITAT AUTÒNOMA DE BARCELONA

Barcelona, February 2015

Universitat Autònoma de Barcelona

School of Medicine

Department of Paediatrics, Obstetrics, Gynaecology, and Preventive Medicine

Impact of Psychological and Social Factors on Cardiovascular Risk in an Adult Population at High Cardiovascular Risk

Thesis Submitted in Partial Fulfilment of the Requirements for the Degree of Doctor of Philosophy
Doctoral Programme in Paediatrics, Obstetrics, Gynaecology, Preventive Medicine and Public Health

Presented by

Cília Mejía Lancheros

Under the direction of Doctor

Miguel Ángel Muñoz Pérez

Barcelona, February 2015

Certification of thesis supervision

Miguel Ángel Muñoz, PhD, MD and associated professor of the Department of Paediatrics, Obstetrics and Gynaecology, Preventive Medicine, Universitat Autònoma de Barcelona; Barcelona, Spain,

Certifies

That the present doctoral thesis presented by **Cília Mejía Lancheros**, entitled **"Impact of Psychological and Social Factors on Cardiovascular Risk in an Adult Population at High Cardiovascular Risk"** has been carried out under my direction and supervision.

Barcelona, February 2015

Dr. Miguel Ángel Muñoz
Thesis Director

Cília Mejía Lancheros
PhD Candidate

Acknowledgements

The patience of sharing knowledge, facing obstacles and joining forces, resources and support, make it possible that a doctorate candidate does not lose the horizon on the challenging path of scientific research; therefore, I express my sincere thanks to all those people who made possible the development and culmination of my thesis work.

Especially Thanks:

To Dr. Miguel Angel Muñoz who apart from sharing his knowledge and research experience, taught me the art of patience and supporting me in all professional and personal moments experienced during the development of this thesis.

To the PREDIMED study committee and researchers for giving me the invaluable opportunity and experience of developing this research and giving me their priceless scientific expertise.

To PREDIMED study participants for participating in the growth of the scientific knowledge in cardiovascular health in Spain.

To the Institute for Research in Primary Care IDIAP Jordi Gol and the Institut Catala de la Salut for putting at my disposal all necessary human, logistical and economical resources to make my research work possible.

To Jordi Real, my supporting Statistician for dedicating a lot of his time to share with me his knowledge and statistical experience and for encouraging me during those more taxing moments of my research work.

To the School of Social and Community Medicine, University of Bristol and particularly to Dr. Bruna Galobardes for giving me the opportunity to have an invaluable international research experience and particularly for inspiring me to progress in my research career.

I especially thank my friends Nelly Gomez Chiquillo for giving me a hand in those most challenging personal moments experienced during my doctoral studies and being a ray of light on the horizon, and to Giorgetta Ciuraro for supporting me with her unconditional friendship and affection.

To my mother:

Flor Celmira Lancheros

"For her courage to give me life alone under the stars"

To my father:

Luis Eduardo Mejía

“For instilling in me the courage and sprit of survival”

To my godfather:

Alessandro Gaggianese

“For believing and supporting my every step and choices made over time”

“Observing the socioeconomic injustices in the eyes of people and being indifferent, makes us all complicit in them”

Cilia Mejia-Lancheros

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

AMI: Acute myocardial infarction

BMI: Body mass index

BP: Blood pressure

CHD: Coronary heart disease

CSDH: Commission on Social Determinant of Health

CVDs: Cardiovascular diseases

DALYs: Disability-adjusted life years

DBP: Diastolic Blood Pressure

GPs: Primary care physicians /general practitioner

HDL: High-density lipoprotein cholesterol

Hs-CRP: High-Sensitive C-reactive protein

IHD: Ischemic heart disease

LDL: Low-density lipoprotein cholesterol

NCDs: Noncommunicable diseases

PC: Primary care

PCCs: Primary care centres

SBP: Systolic Blood Pressure

SEP: Socioeconomic position/socioeconomic status/social class

WHO: World Health Organization

Summary

Impact of Psychological and Social Factors on Cardiovascular Risk in an Adult Population at High Cardiovascular Risk

Cardiovascular diseases (CVDs) remain the leading cause of morbimortality and disability in high income countries, and with an alarming growth in those with lower income economies. Spain however has one of the lowest cardiovascular morbimortality rates worldwide; CVDs continue to be the main cause of death, especially derived from ischemic heath diseases, stroke and heart failure. Likewise, in the last decades the prevalence of classic cardiovascular risk factors such as hypertension, diabetes, dyslipidaemia and obesity in the general population and the smoking prevalence among young adult women have significantly increased. For the next 40 years, there is expected to be a negative demographic growth tendency, when people over 64 years old will account for more than 30% of the total Spanish population.

On the other hand, causes leading to cardiovascular diseases are multifactorial and several modifiable and non-modifiable risk factors and unhealthy lifestyles are involved; however, these risks and behaviours cannot completely explain the incidence of cardiovascular events (about 75%). In the last three decades, the scientific evidence has shown the existence of cardiovascular health disparities among different social population groups. Socioeconomic and psychological disadvantaged conditions at individual, ecological and macro levels have been found to be directly and indirectly related with prevalence of unhealthy lifestyles, poor cardiovascular profile, and incidence and worsening progression of CVDs. However, the mechanisms or pathways through which these conditions lead to adverse cardiovascular outcomes are not completely clear. In addition, much of the existing evidence is based on Anglo Saxon or Northern countries, while in other contexts with different socioeconomic, cultural and political circumstances such evidence is scarce. In Spain, few studies have addressed the effect of socioeconomic and psychological circumstances at individual level regarding cardiovascular risk.

The present thesis is aimed at studying the impact of socioeconomic position (educational level as indicator), depression (medical diagnosis) and social support (number of people living in the household) on different cardiovascular risk aspects. These aspects include: the treatment received in primary cardiovascular prevention; the degree of control and the values of blood pressure; and the increased risk of suffering primary major cardiovascular events (acute myocardial infarction, stroke and cardiovascular death) in an adult population with high cardiovascular risk (PREDIMED study participants), living in Spain.

This thesis is composed of three research studies. The main results have been presented in three articles published in international and indexed scientific journals.

Overall, our 7447 research participants were more frequently women (57.5%), older (average age 67 years), with a low percentage of high education level (7.2%). Most of them were living with others (around 90%) and less than a fifth of our population had depression (17.9%). As relates to cardiovascular risk factors and behaviours, 14% of our participants were current smokers and around 21% alcohol drinkers. Less than half of our population had low adherence to the Mediterranean diet pattern (46%) and more than one third had sedentary behaviour (36.2%). Likewise, the majority of the participants were overweight (average BMI: 30.2), suffering from hypertension (81.1%), and dyslipidaemia (71.0%) while about half had diabetes (47.7%) and a fifth had (22.4%) family history of premature coronary heart diseases.

Regarding the impact of the psychological and socioeconomic factors on the three aspect of cardiovascular risk considered, we found: (1) socioeconomic differences did not affect the treatment prescribed for primary cardiovascular prevention; (2) among hypertensive patients at high cardiovascular risk, the control of blood pressure was better in those diagnosed with depression compared to those without depression; and (3) participants with low educational level had a higher risk of stroke. Depression and low social support were not associated with CVD incidence.

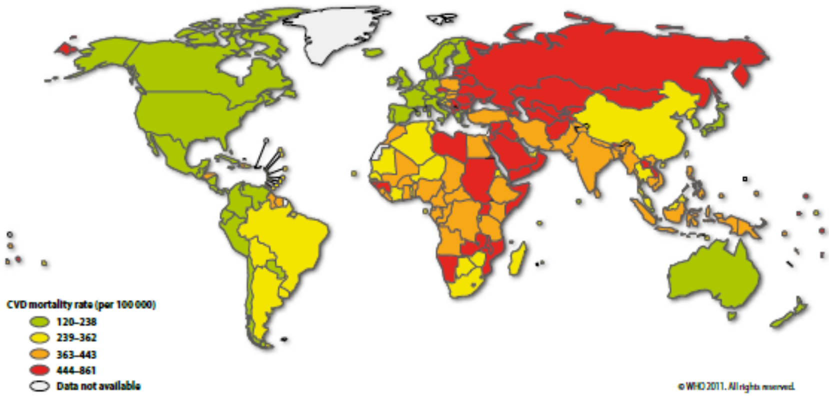
Part I: Introduction

Chapter 1: Background

1.1. Overview of cardiovascular disease burden

In the last few decades, the mortality rates as a consequence of cardiovascular diseases (CVDs) have declined in some western and high income regions, however they remain the leading cause of death and disability in most of the industrialized societies, and with a significant rise in low-and middle-income countries (1-4). According to the World Health Organization (WHO) Global Atlas on Cardiovascular Disease Prevention and Control (2010)(1), CVDs are responsible for around 17.3 million deaths every year in both males and females across the world (1) (Figure 1). From the total deaths in 2008 worldwide (57 million), around 63% were due to noncommunicable diseases (NCDs), especially from CVDs, diabetes, cancer and chronic respiratory diseases (5).

Panel A. Global distribution of CVD mortality rates in males (age standardized, per 100 000)



Panel B. Global distribution of CVD mortality rates in females (age standardized, per 100 000)

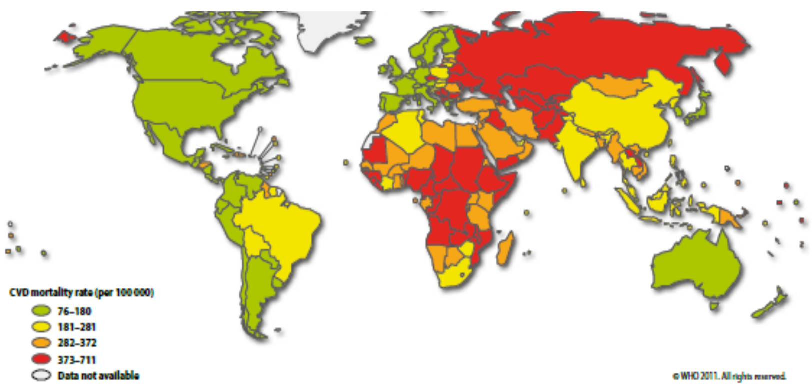


Figure 1. World map showing the global distribution of CVD mortality rates (males and females), World Health Organization (1)

It is estimated that around 80% of the NCDs deaths happen in low and middle-income countries except in African regions where communicable infections, maternal and perinatal diseases and malnutrition are still the main cause of death; however by 2030, it is estimated that NCDs will become the primary global cause of death (5).

According to the latest systematic analysis of the Global Burden of Disease Study 2010, NCDs accounted for 54% of all DALYs (disability-adjusted life years) compared with 35% due to communicable, maternal, neonatal and nutritional disorders, and with 11% due to injuries (6). Cardiovascular and circulatory diseases as a serious cause of disability, accounted for around 11.8% of global DALYs (2.490 billions), of which, 5.2% of DALYs were due to ischemic heart disease (IHD), while 2.5% and 1.6% were due to haemorrhagic and ischemic stroke respectively (6). Even though the volume of DALYs produced by all causes has shown a slight reduction during 1990 to 2010 (2.503 billion in 1990 to 2.490 billion in 2010), that due to NCDs has shown a significant increase (1.075 billion in 1990 to 1.344 billion in 2010), this tendency observed is explained by the significant increase in the number of people and the ageing of the population worldwide (6).

Spain is one of the Western and European countries with the lowest rates of morbid-mortality due to CVDs (7,8). However, according to the latest available data, CVDs continue to be the main cause of death, accounting for around 30.3% (122 097) of all deaths in 2012 (402 950), particularly remarkable in the over 65 population. Ischemic heart disease (IHD), cerebrovascular diseases and heart failure were the most common type of CVDs accounting for the largest number of deaths (34 751; 29 520; and 18 453 deaths respectively). IHD was the main source of CDV deaths among men with cerebrovascular diseases and heart failure for women (figure 2.) (9).

1.2. Cardiovascular diseases

Cardiovascular diseases (CVDs) are considered multifactorial conditions that especially affect the essential components of the circulatory system of the human body such as heart, blood vessels, and blood itself (1,10). CVDs can be congenital or acquired throughout people’s lifespan. Atherosclerosis, rheumatic heart disease and cardiovascular inflammation are the main and more prevalent cardiovascular acquired problems (10).

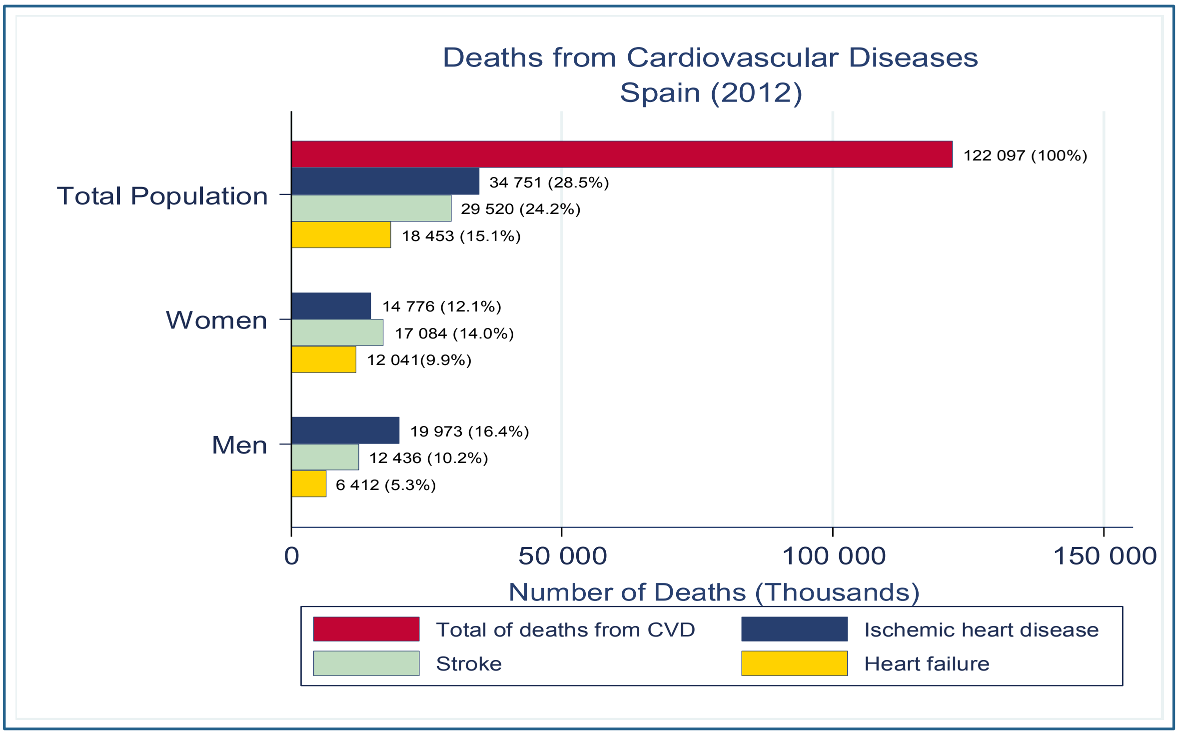


Figure 2. Deaths from the most common cardiovascular diseases in Spain, year 2012. (Adapted from reference (9)).

1.2.1. Atherosclerosis

Atherosclerosis is defined as a chronic condition occurring in the blood vessels. It is characterised by the decrease in elasticity as a result of the narrowing and rigidity of the blood vessels' walls caused by deposition of fats, cholesterol, calcium and other substances (minerals and cellular debris among others) in the inner layer of medium and large-sized arteries (1,10). Arteriosclerosis increases blood pressure, diminishes the good blood flow to different body structures and produces serious tissue damage. Additionally, the plaque formed in the blood vessels walls may break and result in the formation of blood clots (thrombus) which in turn can produce serious blockages *in situ* or elsewhere (1,10)**.** **Ischemic heart disease** or coronary heart disease (CHD) (inadequate supply of oxygen-rich blood to the heart muscle) and **stroke** (reduction in blood flow to the brain tissue by blood vessel blockage or intracranial bleeding) are the most serious health consequences of arteriosclerosis disease (1,10).

1.2.2. Rheumatic heart disease

This is an inflammation of the heart lining and muscle occurring during rheumatic fever episodes (systemic disease affecting the peri-arteriolar connective tissue of the different body organs) following a streptococcal infection (1,10).

1.2.3. Congenital heart diseases

These relate to heart structure damage present at birth. They may be a consequence of multifactorial factors such as infection, alcohol and drugs use and poor nutrition patterns of the mother during the pregnancy (1,10). Other congenital heart diseases are inherited and may be transmitted as autosomal or as sex-linked traits; however, many other causes of the common congenital anomalies are still unknown (1,10). Septal defects (hole in the heart septal), valves and chamber abnormalities are the most common types of congenital heart pathologies (1,10).

1.2.4. Other cardiovascular disease

Heart failure (heart is unable to pump the blood through the body), disorders of the heart muscle (cardiomyopathy) and alterations in the heart rhythm (arrhythmias) are also considered types of CVDs; however, they are less frequent than IHD and stroke (1).

1.3. Cardiovascular risk factors and behaviours

There are different factors which have been identified to be related to the aetiology of atherosclerosis disease and to the CVDs themselves (1,10). Most of these cardiovascular risk factors are a result of people's lifestyles and behaviours; therefore, they could be modifiable and avoidable. In 1976, Thomas Mackeown indicated that most of the disease states could be determined by human behaviour such as harmful lifestyles (e.g. smoking, sedentary, consumption of excessive refined food); likewise, he also considered that many of the illnesses were determined by the economic conditions rather than by the choices of individuals themselves(11).

CVDs are considered caused by multiple risk factors (12). Many risk factors can have both a direct relationship (causation) or can only be involved or act as an indirect predictor or intermediate factor for specific or multiple health diseases (12). The concept of cardiovascular risk factor was introduced for the first time by Dr. W. Kannel in the context of the Framingham Heart Study (1961) (13). Hypertension, dyslipidaemia diabetes, and tobacco were the first cardiovascular risk conditions to be established (13-15). In the last few decades, new factors such as those related to inflammatory and metabolic processes as well as people's behaviours and psychological and socioeconomic conditions have been linked to CVDs (16-19).

Figure 3 shows a summary of the most significant cardiovascular risk factors.

1.3.1. Sex and age

Sex and age differences in CVDs and cardiovascular risk factor profile have been well documented (20,21). Women tend to experience negative cardiovascular events later in life than men; however, recent studies have been showing an increased prevalence of acute myocardial infarction (AMI) and IHD death in women in their midlife compared with men (no midlife acceleration of CVD) (22,23). This evidence suggests that cardiovascular risk between women and men tends to pair up. Cardiovascular profile and health behaviour patterns can contribute to explain some of the sex and age differences in cardiovascular risk observed in some studies (24). Menopause has also been considered as a main possible factor to explain differences in the cardiovascular profile and cardiovascular risk between women and men (20); however, with the new scientific evidence, its role is still under debate (22,23,25). Other women-specific factors such as those related with ovary, gestational and reproductive function, and those related to clinical testing and chest pain syndromes might contribute to the observed cardiovascular risk gap between women and men (20,26).

1.3.2. Family history of premature cardiovascular disease

Having parent and/or sibling history of premature CHD is strongly associated with high risk for developing CHD events (27,28) as well as for incidence and progression of subclinical atherosclerosis (29,30).

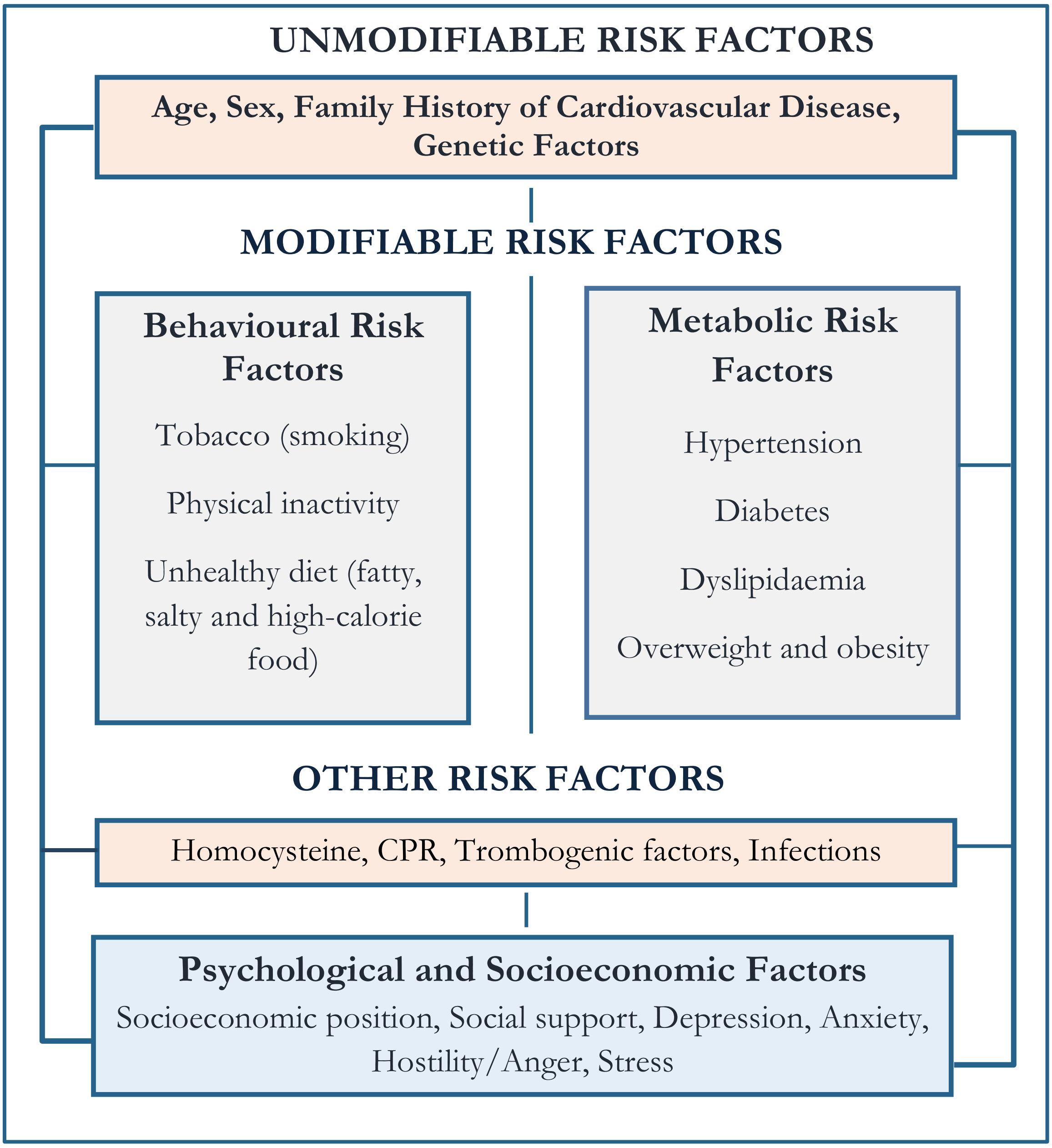


Figure 3. Risk factors associated with cardiovascular diseases. (Adapted from reference (1,10).

1.3.3. Hypertension

Hypertension or raised values in both systolic and diastolic blood pressure, is one of the key risk factors for development of CVD such as CHD and stroke as well as mortality and disability (1,13). High blood pressure is responsible for about 13% (7.5 million) of the total annual deaths and 3.7% of total DALYs (57 million) worldwide (1,31). In 2008, approximately 40% of hypertension prevalence in the global population aged over 25 was estimated, where around one billion people had uncontrolled blood pressure values (1,10). In the latest health statistics in a US context, they reported that only 52.2% of the hypertensive population (77.9 million) presented optimal control of their hypertension (32). In addition, in low and middle countries, high prevalence rates of hypertension close to those in industrialized countries but with more inadequate control and treatment have also been observed (33). In Spain, in spite of the intensive treatment and health care follow up performed in hypertensive populations, the grade of control is suboptimal. Approximately 67% of the hypertensive patients showed blood pressure (BP) values over 140/90 mmHg, and 87% had BP ≥130/80-85 mmHg (34).

Studies have shown that hypertensive populations and those with history of hypertension have a higher risk of suffering a heart attack compared with those without hypertension (17). High BP values also trigger the incidence of other cardiovascular diseases such as stroke (both ischemic and haemorrhagic), unheralded coronary death, angina, heart failure, peripheral arterial disease among others (35). Furthermore, it is estimated that there is a 17.2% difference in the lifetime risk for total cardiovascular diseases at 30 years of age between hypertensive people and those with normal BP values (63.3% in hypertensive people vs 46.1% in those without hypertension)(35). This scenario suggests that effective health care approaches at individual and population level as well as health policies need to be set to achieve an optimal control and management of hypertension worldwide. Lifestyle modification (e.g. reducing tobacco, unhealthy diet, salt intake, high alcohol intake and sedentary, among others), early and aggressive BP lowering treatment by choosing the appropriate drugs as well as the promotion of patient adherence to the therapy are considered essential strategies to reduce CVD risk in hypertensive populations (36).

1.3.4. Diabetes (Type 2 Diabetes)

Globally, around 382 million people (8.3%) suffer from diabetes, where 175 million, most of whom live in low and middle-income countries (80%), have undiagnosed diabetes (37). It is also expected that the diabetes will affect approximately 592 million over the next 25 years (37). In Spain, according to the latest estimations, 13.8% (5.3 million approximately) of the Spanish population over 18 years old suffer from diabetes (38). Many people with diabetes are unaware of their condition due to the fact that its clinical manifestations tend to appear later over time. During that "silent time" irreversible damage to the body has already happened (37). Obesity, unhealthy diet, sedentary behaviour, family history of diabetes, ethnicity, aging and economic growth among others, are factors that can contribute to developing diabetes (37).

Diabetes is well-recognised as one of the major and independent CVD risk factors (39). People with diabetes have a high risk of developing cardiovascular problems such as heart attack, stroke, peripheral artery disease, angina, heart failure (15,37). For example diabetic people have three times more risk of suffering a heart attack compared to those without (17). Likewise, diabetic people or those with high blood glycaemic values present a higher probability of cerebrovascular diseases, stroke related deaths, and worse health prognostics after a cerebrovascular event (40). Although there are contrasting findings in relation to the optimal control of diabetes and other CVD risks, some evidence shows that improving glycaemic control in the diabetic population can contribute significantly to reducing any cardiovascular event (e.g. myocardial infarction, stroke, or death from CVD)(41). Hence, joint efforts to prevent, diagnose, treat and control diabetes alongside other cardiovascular risk factors can have a positive impact on cardiovascular health.

1.3.5. Dyslipidaemia

Alteration in the essential lipid profile components (blood lipoproteins) such as low-density lipoprotein cholesterol (LDL), triglycerides as well as in the high-density lipoprotein cholesterol (HDL) has been found to be linked with CVDs (16,42).

Although total blood cholesterol figures have decreased between 1980 and 2008 particularly in high-income regions (among both women and men), their hypercholesterolemia rates continue to be the highest (43). Globally, approximately 39% of the adult population have high cholesterol (≥240 mg/dl) (43). Moreover, 2.6 million deaths and 2.0% (29.7 million) of DALYs are due to high cholesterol (31). In Spain (2012), around 50% of the population over 18 years old have reported blood cholesterol values >200mg/dl, where only 50% of these were aware of its existence, and only 13% presented optimal control (44).

Different components of lipid profile both as an individual element and in combination have been found to be directly linked with different cardiovascular outcomes (45-47). For example, in the context of Framingham's study (pioneer in the study of cardiovascular diseases), the incidence of CHD was found to be directly related to total cholesterol, being double in people over 70 years (42). Hypertriglyceridemia is considered an independent risk factor for developing CDVs. After adjusting for other lipoproteins and risk factors, a rise of 1 mmol/L in plasma triglyceride showed a 14% and a 37% increase in risk for developing fatal and non-fatal cardiovascular events in both men and women (45). Regarding HDL, high blood HDL levels have shown an inverse relationship to atherosclerosis disease (48); however, its role as a protective factor for cardiovascular events is still controversial (49,50). Dyslipidaemia can be partially due to genetic factors (51), but by improving lifestyles and receiving pharmacological treatment it is likely to reduce significantly the risk of CVDs due to this condition (50,52,53).

1.3.6. Smoking

Smoking is an important well-known harmful factor for several adverse health conditions, especially for cancer and cardiovascular disease morbi-mortality (e.g. CHD, stroke and cardiovascular death) (14,54,55). Smoking has a direct relation with the genesis of arteriosclerosis and hemodynamic changes due to its chemical components such as nicotine, carbon monoxide and free radicals (54,56). These substances produce a significant increase in the cardiovascular vessel walls, vasomotor dysfunction, inflammation, and alteration in the lipoproteins profile and antithrombotic and prothrombotic factors (56).

The linear relationship between cigarette smoking dose and CVDs is unclear; heavy as well as light active smokers and passive smokers present a risk of suffering cardiovascular damage (56).

Scientific evidence supports that both cardiovascular risk and the risk for all causes of mortality decrease with smoking cessation (57-59). Age has an important role in the lifelong probability after quitting smoking. A smoker who quits at an earlier age has more chance of living longer than those who continue to smoke (60); for example, stopping smoking between 35-44 years old gives a similar chance of living longer as someone that has never smoked, or gain around 10 years of life expectancy, compared to someone who continues to smoke (60). Quitting smoking can reduce 36% of all causes of death in people with CHD (58).

Overall, in 2013, an estimated one billion people were current smokers, with the European region having the highest rates (31%) and African region the lowest ones (10%)(1). Smoking leads to approximately 10% of CVDs, and approximately 6 million people die from both tobacco use and exposure each year (6% females and 12% males) (31). By 2030 it is expected that more than 8 million tobacco-related deaths will occur every year, accounting for 10% of all deaths worldwide (5).

Cost-effective measures and policies to reduce the global tobacco epidemic such as preventing and monitoring tobacco use and exposure, helping smokers to quit tobacco, warning the population about the damages of tobacco, banning tobacco advertising and sponsorship, and increasing taxes on tobacco products are being adopted by different countries (Framework Convention on Tobacco Control) (61). In Spain, after the first and second smoke-free legislations settled in 2005 and 2010 respectively, a significant reduction in second-hand smoke exposure has been observed (62).

1.3.7. Obesity

Obesity (excessive body fat accumulation) (63) is becoming a serious public health concern, affecting children and adults, men and women. It has reached the level of pandemic (simultaneous increase in obesity in almost all countries) (64).

Globally, in 2013, 36.9% of men and 38.0% of women had a body mass index of ≥ 25kg/m^2 (65).There was also a significant increase in prevalence of overweight or obesity among children and adolescents in higher income countries (23.8% in boys and 22.6% in girls) as well as in lower income states (12.9% in boys and 13.4% in girls) (65). In some countries, more than 50% of the population are obese (65). In Spain, around 20.0 % of adults (women and men) over 20 years old are obese (BMI: ≥30 kg/m^2), and 62.3% of men and 46.5% of women are overweight (65).

Obesity is a strong risk for multiple and serious health disorders such as diabetes, metabolic syndrome (co-ocurrency of several risk factors: type 2 diabetes, dislipidemia, obesity and hypertension), cancer and CVDs (66-69). Nevertheless, obesity is considered an independent CVD factor (70), the "obesity paradox" (obese individuals with established CHD seem to have similar mortality rates than non obese people) has also been documented (71,72). Obesity produces many alterations in the cardiovascular structures, leading to atheroclerosis process, inflamation, elevation of ST-segment, myocardial damage and dysfuction, among others (69).

Multiple factors such as genetic, environmental, poor lifestyles and socioeconomic conditions are possible causes of obesity (73). The alarming rise worldwide without any effective reversed health measure is a serious global public health concern, thus, urgent efforts and effective policies, resources and health population interventions at all population levels are called to control its spread (64,65,74).

1.3.8. Physical activity and diet

Phyiscal activity and diet patterns have changed substantially as a result of the main socioeconomic and technological transformations which have been happening in society such as the increase in energy-food, type and characteristics of jobs, increase in the means of transport and urbanization, and the availability and access to new technologies (75-79). Socioeconomic disparities have been reported among populations with sedentary behaviour and unhealthy diets (75). Physical inactivity, poor nutrition and other harmful lifestyles tend to be more prevalent among low socioeconomic groups (75).

According to the latest data, 10.0% of global DALYs in 2010 were a consequence of both physical inactivity and dietary risk factors, especially diets based on low fruit, nuts, seeds, and high sodium intake (80). Physical inactivity contributes to 31% of IHD-DALYs while diets low in nuts and seed, and poor in fruits contribute to 40% and 30% of IHD-DALYs respectively (80).

The lack of physical exercise or physical inactivity level less than that needed for optimal health and prevention of premature death is an important risk for many chronic diseases such as obesity, diabetes, dyslipidaemia and CVDs (e.g. CHD, stroke, peripheral arterial disease, heart failure), psychological and neurology disorders (depression, anxiety), as well as premature death and disability (81).

On the other hand, the intake of saturated fat and trans fat is associated with high cardiovascular risk while the consumption of monounsaturated fatty acids, N-3 fatty acids, higher intake of fruit and vegetables and grains seems to have a protective role in CVDs, especially in CHD (82). Different combinations of nutrients are also involved in cardiovascular health (82). The Mediterranean diet pattern (rich in daily intake of unrefined cereals, vegetables, fruits, olive oil, fish, olives, nuts and less consumption of red meat products, and 1 or 2 glasses of wine) is associated with a lower risk of cardiovascular morbid-mortality and several risk factors (e.g. high blood pressure, inflammation, high blood lipids, among others)(83-86). Other diet patterns such Dietary Approaches to Stop Hypertension, (DASH) and those recommended by well-established health dietary guidelines have also been shown to be beneficial for cardiovascular health (82). The dramatic increase in adoption of Western dietary patterns (high consumption of animal products and refined carbohydrates and salty foods, low intake of fruits, vegetables and grains) are negatively impacting the health status of populations worldwide (87).

Regarding alcohol consumption, some studies have shown that consumption of low-to moderate amounts of alcohol (one to two drinks per day, or 10-30g alcohol) especially wine and beer (rich in polyphenols) may have a “protective effect” on CVDs (88,89). This apparent protective role can be due to the effect of some alcoholic beverage substances on the antioxidant and anti-inflammatory function, blood vessel cells adhesion reduction and rise in HDLc concentration and decrease in the procoagulant process (88,89).

In contrast, the latest evidence suggests that reducing any alcohol consumption even in light to moderate amounts can diminish the risk of developing CHD and stroke and associated risk factors (90). It is expected that health institutions and health professionals should be cautious and ethical when making recommendations about drinking alcohol, especially because it is strongly associated with many different types of cancers even when consumed at low levels (91,92).

Lifestyle intervention programs including promotion of exercise and reducing dietary fat intake have shown benefits on cardiovascular conditions and people's well-being (82, 93). Promoting adherence to the regular practice of physical activity at individual and population level, in local, national and international contexts needs to be endorsed as a key strategy to obtain better and multiple health benefits, including the reduction of cardiovascular risk (94). Setting health policies, effective regulations on the production and distributions of healthy food along with encouraging healthy diet patterning at the individual level is an urgent call to impact the population's health status positively (87).

1.3.9. Other cardiovascular risk factors

Homocysteine: blood metabolism of amino acid methionine may promote atherosclerosis; however, its role as a cardiovascular risk factor is still unclear (16,95). Low folic acid and B vitamins are linked to higher homocysteine levels (95). Evidence about the benefit of some treatments such as daily folic acid supplements on reducing homocysteine concentration, and therefore the risk and course of CVDs, is contradictory (95).

High-Sensitive C-reactive protein (Hs-CRP): increased levels of Hs-CRP (Bio-protein sensitive to inflammation process and tissue damage) have been found associated with high risk from suffering CHD and stroke, worsening health course of cardiac patients and carotid arteriosclerosis (16,96,97). Evidence suggests that Hs-CRP may be a strong predictor for assessing cardiovascular risk and a maker for setting a proper primary and secondary cardiovascular treatment (98,99).

Trombogenic/haemostatic factors: Elevated levels of some thrombotic factors such as fibrinogen, von Wilebrand factor (vWF) and tissue plasminogen activator antigen (tPA) have been found in patients who have suffered major cardiovascular events and those with a poorer cardiovascular risk profile (100-102).

Higher blood platelet agreeability has also been found to be associated with higher cardiovascular risk (100). On the other hand, lower levels of some haemostatic factors such as FVIII seem to be linked to a lower cardiovascular risk (101). The relationship between reduction in the fibrinolytic response and high lipoprotein a (Lpa) has been suggested as a possible pathway that links thrombotic factors and atherosclerosis (100,101).

Infections: in the last few decades, supporting evidence about the role of infections in CVDs aetiology has been increasing (103,104). Inflammatory response is considered a possible linkage factor between infections and atherosclerosis process and cardiovascular outcomes (103,104). Recent studies suggest a positive relation between influenza infection and major cardiovascular events (e.g. AMI, IHD death) (105,106). In addition, a recent Meta-Analysis evidenced a positive association between influenza vaccination and lower risk of major adverse cardiovascular events (107), suggesting a potential protective role of influenza vaccination against CVDs, especially in elderly people.

1.4. Psychological and social determinants of cardiovascular health

1.4.1. Overview of social determinants of health

In the latest decades, scientific researchers, health organizations and scientific institutions have been studying and trying to understand the role of human conditions on health and disease of individuals and populations. In the modern era, Thomas McKeown was one of the pioneers in considering the hypothesis of the socioeconomic factors as a fundamental cause of disease (108). However, there are contrasting opinions around McKeown's thesis (109,110). Scientific studies carried out in different contexts have demonstrated that socioeconomic conditions are indirectly and directly related with different health outcomes and population health disparities (111-113).

According to WHO, social determinants of health are the conditions in which people are born, grow, live, work and age (114). These social conditions are influenced by the distribution of money, power and resources as well as by political actions and policies at global, national and local levels (114,115). In 2005, WHO set up the Commission on Social Determinants of Health (CSDH) to address socioeconomic disparities in health across the world. This Commission has collected evidence and knowledge on the influence of social determinants on population health. It has also made recommendations, actions, policies and technical approaches to tackle health disparities, particularly among the most disadvantaged and vulnerable people and social groups. CSDH emphasizes the need to involve civil society organizations, research institutions and governments at international, national and local contexts in the process of reducing socioeconomic health inequalities because these exist within and between population groups, societies and countries worldwide (111,113,115).

Many disadvantaged socioeconomic situations at individual as well as ecological level within and between countries have shown to affect many people's health outcomes during their lifetime (75,111-113,116,117). For example, people at the bottom of the social structure have more risk of suffering illness, premature death and adopting hazardous life styles, long–term stress status together with social isolation and low social support, having no control over work (112). These conditions increase the vulnerability of people to have worse mental and physical health (112). Poor socioeconomic and psychological circumstances during their early life, social exclusion (e.g. racism, unemployment, social, ethnic and gender discrimination and stigmatization, among others), adverse environmental conditions in the place of residence and work, job insecurity among others have also been found to negatively affect the health and life of people (112,113).

Different theoretical approaches, pathways and elements have been proposed to explain the influence of social conditions on health inequalities. *Link and Phelan* (1995, 2010) suggest that health inequalities tend to persist over time regardless of the effort made and strategies adopted to reduce them (118,119). This can be explained by following reasons:

1) SEP may influence multiple diseases and it is not only linked to one health issue (118,119).

2) The effect of social inequalities on health might occur through multiple health risk factors or disease/death causes (e.g. unhealthy behaviours, stressful life conditions, deprived living circumstances etc.) (118,119).
3) SEP is closely related not only with income but social knowledge, prestige, power, social networks or support, which can avoid, prevent and reduce health risks and health deterioration once the illness appears (118,119).
4) Socioeconomic differences on health persist over time due to the fact that new sources of health disparities emerge. For example, if individuals with a higher SEP tend to have more accessibility to the new diagnostics and treatments than those with lower SEP, this fact can become a new font or path for socioeconomic health disparities (118,119).

The CSDH, based on the existing theoretical and scientific approaches, has developed a conceptual framework scheme to explain and tackle social-economic health inequalities. It summaries the main social determinants of health, the possible pathways and relationships among themselves and in relation to the health and wellbeing of people as well as the essential level/areas for addressing intervention, actions and policies (120) (figure 4).

1.4.2. Socioeconomic and psychological factors on cardiovascular risk

Scientific evidence suggests that major well-established cardiovascular risk factors (hypertension, hypercholesterolemia and cigarette smoking) explain around 75% of incidences of CVDs where the causes of the other 25% remain unestablished (121). Some disadvantaged social and psychological conditions at individual and ecological/macro level seem to have an essential role in the aetiology and course of cardiovascular outcomes and the associated risk factors and behaviours (18,19,122-124).

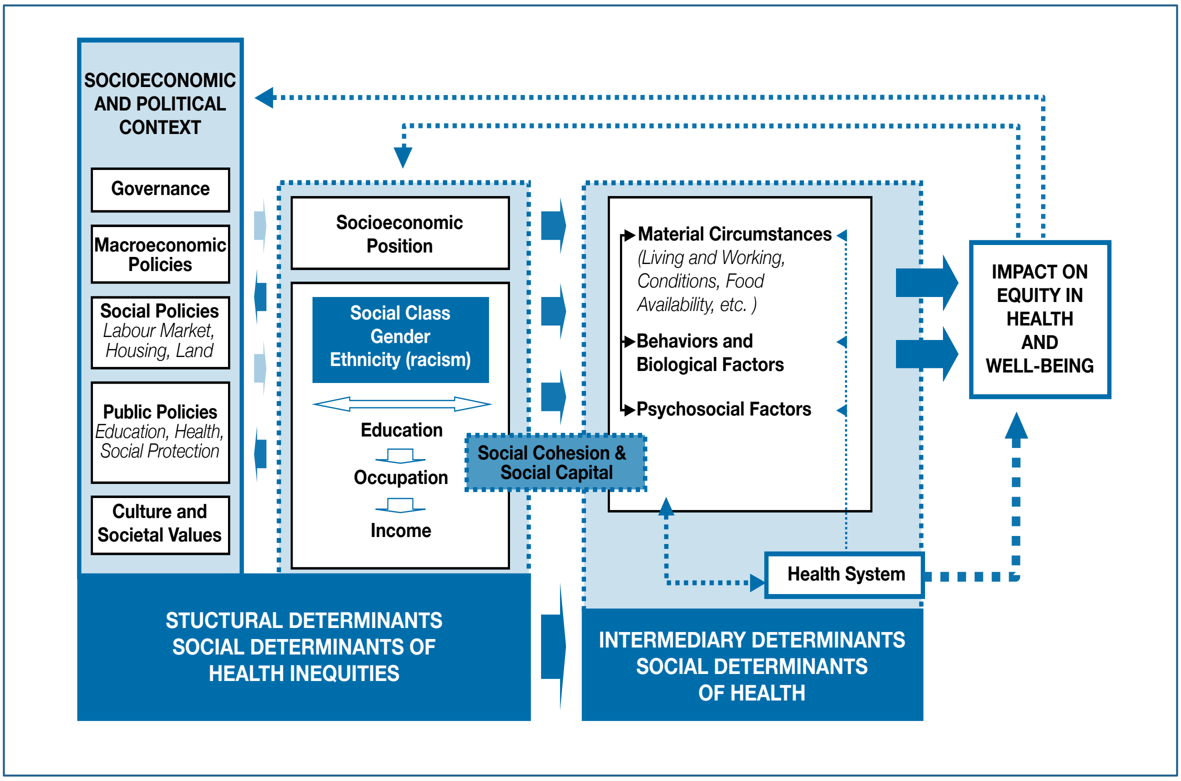


Figure 4. Conceptual framework of social determinants of health. CSDH, World Health Organization (120).

1.4.2.1. Socioeconomic and psychosocial factors at individual level

Socioeconomic position

There are different conceptualizations and approaches to measure socioeconomic class (also called socioeconomic status (SES) or socioeconomic position (SEP)) in epidemiological studies. Webern and Max's sociological approaches have influenced the concept of social class and social stratification widely. The Weberian approach considerers the influence of both subjective and objective dimensions (e.g. education, income, gender, etc.) in the stratification of society where social groups share common elements, while the Marxist approach is more focused on factors such as production process, control and ownership power, and social class relationship (125,126).

Based on Weberian and Marxist notions, Goldthorpe and Wright proposed the social class classification models frequently used in social and health research (126). However, those classifications do not always represent the empirical realities of the social stratification of individuals and the associated socioeconomic, political and cultural forces.

The remarkable scientific evidence related to cardiovascular health and some SEP indicators are summarised below.

Education: one of the most used indicators of SEP in epidemiological studies. Once maximum education level is reach, it continues to be stable during the individual life course. Education not only may influence cognitive skills, but also may condition employment and income opportunities, as well as comprehension and following of medical advice and adoption of lifestyles (127).

Educational level has been associated with traditional cardiovascular risk factors and lifestyles such as hypertension, diabetes, dyslipidaemia, smoking, sedentary as well as incidence of CHD, stroke and death from cardiovascular causes, and health prognosis after suffering a CVD event (128-132). For example, people with less education tend to have a poorer cardiovascular risk profile (128,129), a higher risk of suffering CHD, heart failure and stroke (130-132). Education level can influence access to health preventive care and following medical recommendations (133,134).

Income: individual and family income is a strong indicator of material resources/circumstances. It is also a relative indicator of poverty that can vary over time (127). It may influence access to goods, social and health services and therefore influence the health profile of people (127,135). Evidence, especially that coming from high-income contexts showed that women and men in the lowest income level have more risk of having ischemic stroke than those at the highest levels (136). People with constantly low income over their adulthood presented an increased risk of CVD mortality compared with those with increasing income over their lifetime (137). In addition, income has also found to contribute to higher CVD mortality when race/ethnicity cardiovascular disparities have been studied (138).

Having financial problems can also worsen the prognosis of patients with established CVD (139). Likewise, the economic capability of individuals and/or households accessing treatment and medical services for CVD has also great importance, since in many contexts the cost of health care and treatments is paid by individuals and families rather than by health systems or health assurances (140).

Occupation: This may categorise the social status/rank or prestige of an individual in the society depending on his/her occupation or the occupied working position (127,135). Occupation is directly/indirectly linked to socioeconomic factors (e.g. income, education, living spaces, material assets and social and health services), psychological and social elements (e.g. autonomy, work stress/pressure, social networks) and work environment (e.g. job characteristic, exposition to hazards and work control) (127,135).

People with a lower employment position tend to have poorer cardiovascular risk profile unhealthy lifestyles, and a higher risk of dying from CVD (141,142). Job environment conditions such as high job strain and job insecurity may also contribute significantly to developing CHD (143,144).

Social support

Social networks/interactions not only give psychological support but can also provide material assistance helping individuals to maintain wellbeing and face adverse experiences over their lifetime, including physical and mental illnesses (145). Social support can influence people's health status through emotional, neuroendocrine, cardiovascular and immune-inflammatory pathways, or by influencing the adoption of lifestyle patterns and balance of physiological process when individuals face stressful or harmful experiences/events (e.g. prevention of stress appraisal or inhibition, reduction or adjusting of physiological response) (145,146). **Esteemed support** (emotional, expressive or close support), **informational support** (advice, appraisal support or cognitive guidance), **social companionship** (spending time and sharing leisure activities with others), and **instrumental/tangible support** (having material assistance such as financial help, material resources and needed services or facilities) are the main types of hypothesised social support that people can have available (145). It is important to highlight that these kinds of social support resources are usually strongly correlated.

Weak social support situations such as living alone have been found to be an important risk factor for some cardiovascular outcomes such as higher cardiovascular mortality rates (147), and worsened prognosis and survival after suffering an AMI (148, 149). Marital status has also shown to have an important role in cardiovascular health. Unmarried individuals had less probability of survival after a first AMI (150) and more risk of hypertension (151); widowed patients presented poorer cardiovascular profile and outcomes (152). Despite evidence suggesting that structural social support tends to be more linked with the aetiology of CHD and perceived or emotional support with cardiovascular health prognosis (153), the effect of improving the networks and resources of social support on cardiovascular outcomes and treatment is still unclear. It can be due to the fact that there are multiple factors involved in the conceptualization, operationalisation and perception of social support resources (153).

Psychological factors

Psychological factors/states can impact physiological process directly and indirectly and therefore, they can determine health status or illness conditions of individuals, with the existence of a bidirectional relationship between them plausible (154). Taking into account that psychological/emotional factors and social conditions or social environment are likely to cluster or interrelate, some health researchers refer to them as a "psychosocial factor" or "psychosocial determinants" (155,156). Many mechanisms through psychological and psychosocial factors might impact adversely on physical health (154,156,157).

Regarding specifically to CVDs, some authors consider that negative psychological conditions can lead to adverse cardiovascular outcomes and a poor cardiovascular profile (18, 19). The hypothesised ways are the adoption of unhealthy behaviour patterns (e.g. smoking, diet, alcohol consumption and physical activity), acute or long-term changes in the body's physiological functions (e.g. neuro-endocrine system, inflammatory and immune response), and the accessibility to health care services (18,19).

Depression: considered an independent causal risk factor for CHD (158,159). It has even been suggested that the more serious the depression the higher the risk of developing CHD (158). Clinical depression is also considered a possible good predictor of mortality in patients with established CHD (160).

Though the role of depression in the aetiology of CHD seems to be clear, its role in the control and management of major cardiovascular risk factors such as hypertension is still uncertain (161). Although the contribution of anti-depressive pharmacological treatment to reduce the cardiovascular risk is still under study (159), scientists and health institutions recommend the clinical assessment and treatment of depression in patients with high cardiovascular risk (159,162).

Anxiety: this mental disorder has been found to be related to both incidences of cardiovascular endpoints (CHD and cardiovascular mortality), and with risk factors such as hypertension (163,164). For example, anxiety in young Swedish men has been shown to predict CHD outcome in their adulthood independent of the traditional cardiovascular risk factors and unhealthy behaviours (165) High risk of developing hypertension at one year has been found in Canadian people having anxiety disorders (166). As with other mental disorders, there might be a reverse relation between anxiety and CVD outcomes and risk factors such as hypertension (164).

Hostility/Anger: experiencing negative emotions/feelings may adversely influence the health of people. People who reported hostility or anger behaviour patterns (cynical attitudes about others, irritation, annoyance, antipathy, frustration, etc.) are more likely to develop hypertension and to suffer cardiovascular events (fatal and non-fatal AMI) in both healthy individuals and those with known CHD (167,168). Research studies also suggest that the effect of anger/hostility traits on cardiovascular health is more harmful among men than among women (168,169). The role of anger/hostility in subclinical biomarkers such as carotid arterial wall thickness is still uncertain (170,171). Hostility/anger behaviours could impact cardiovascular health through affecting different cardiovascular functions and related risk factors such as health and social lifestyle patterns (e.g. smoking, alcohol consumption, dyslipidaemia, hyperglycaemia, hypertension, obesity, poor SEP, among others), stressful expositions (e.g. social isolation, stressful job environment) and physiological function (e.g. cardiovascular reactivity, inflammation and neuroendocrine reposes)(167,172).

Stress: emotional stress over the individual's life can lead to several health outcomes. People who experienced intensive acute and long-term stressful experiences in different dimensions and stages in their life course (e.g. child and adulthood) have more likelihood to suffer CHD and bad heart disease prognosis (173,174). Stressed people also seem to have a tendency to adopt unhealthy lifestyles (e.g. smoking, alcohol consumption, low physical activity, and unhealthy diet) which turn into higher risk of suffering major traditional cardiovascular risk factors (e.g. hypertension, dyslipidaemia, diabetes and obesity), increasing in this way their risk of suffering negative cardiovascular endpoints (173,175).

Stressors in the workplace (e.g. job strain, low work control, shift work, workload and harmful work environment) have also shown an essential role in triggering adverse cardiovascular results, risk factors and lifestyles (143,176). On the other hand, despite the real benefit of interventions at the emotional, physical and pharmacological level to reduce and manage stress in reducing cardiovascular risk profile is still unclear, it should be considered in the daily clinical practice (173,177).

1.4.2.2. Socioeconomic and psychosocial factors at ecological level.

Socioeconomic and cultural circumstances as well as policies at local and macro ecological levels are considered to be involved in health results beyond the own individual's health risk profiles and socioeconomic conditions (111,113,178). These local and macro-structural factors are also considered as fundamental determinants of illness and health disparities within and between countries (120).

In the cardiovascular field, different socioeconomic and psychological/psychosocial characteristics at the ecological level (e.g. country income level, and both physical and social residential environment) have been related with diverse cardiovascular health aspects such as poor cardiovascular risk profile and incidence of major cardiovascular event (e.g. CHD, stroke)(123,124,179-183).

However, more evidence is needed to have better knowledge about the possible mechanisms linking macro and local ecological environment characteristics and negative cardiovascular endpoints. It is suggested that socioeconomic and cultural circumstances and policies at the macro level (e.g. income level, political and administrative related factors, welfare system, cultural background) as well as at the local level (e.g. neighbourhood sociodemographic structures and social interactions, physical environment and public services) directly influence emotional, cognitive, and social dimensions of individuals, for finally impacting people behaviours and health risk profiles that lead to developing negative cardiovascular outcomes (e.g. atherosclerosis progression, incidence of clinical events, and poor survival) (184).

Residential area factors

Living in more disadvantaged socioeconomic neighbourhoods/areas appears to be an important hazard for having a poor cardiovascular risk profile (e.g. smoking, sedentary lifestyle and obesity)(179), several cardiovascular endpoints (e.g. CHD, health failure, peripheral arterial disease)(180,181), worse cardiovascular prognosis (185), and high cardiovascular mortality (186). In addition, residing in neighbourhoods with a high level of psychosocial hazard (high violence and crime, street problems, high selling of alcohol. among others) has also been shown to be linked with an increased CVD risk (187).

Although deprived psychosocial and socioeconomic conditions at residence area level seem to trigger CVDs, few tools for assessing the cardiovascular risk have considered them amongst their predictive risk factors (188).

Macro level factors

Few studies have addressed the role of some socioeconomic indictors at a more macroeconomic and global level (country level) on CVDs. Recent studies have revealed that aspects such as income, health expenditure, health systems or urbanization at country level are associated with higher incidence of stroke morbid-mortality (124), and poor metabolic risk profile (182,183). In addition, global issues linked to globalization and westernisation phenomena seem to play an important role in the adoption of harmful cardiovascular behaviours such as unhealthy diet and physical activity patterns (87,189,190).

1.5. Cardiovascular disease prevention

CVDs are considered highly preventable. The INTERHEART study found that around 90% of AMI risk in women and men, young people and adults, and in all regions across the world can be attributed to nine potentially modifiable risk factors (191). Likewise, this study also revealed that up to 33% of IMA risk could be attributable to adverse psychosocial conditions (192). Thus, cardiovascular risk and adverse outcomes can be reduced if harmful behaviours such as smoking, unhealthy diet patterns, sedentary behaviour, and psychological and socioeconomic conditions are taken into account (19, 193, 194). In addition, acting at an early age by promoting healthy lifestyle changes and proper prevention and management of traditional risk factors (e.g. hypertension, hyperlipidaemia and obesity) contribute to a significant cardiovascular risk reduction in both middle and late adulthood (195,196).

Primary cardiovascular prevention (avoiding cardiovascular outcomes) and secondary cardiovascular prevention (avoiding worsening the CVD course when it is already present) remain key to avoiding, reducing and minimizing the burden of CVD worldwide (197,198). Thus, scientific and medical institutions systematically work to join solid scientific knowledge to develop updated clinical practice recommendations that aim to assess, reduce, treat and control cardiovascular risk (199).

Some cardiovascular prevention guidelines are not only focused on the evaluation and management of traditional cardiovascular risk factors and behaviours, but also on psychological and socioeconomic conditions in the daily clinical cardiovascular risk assessment and treatment (199).

The major challenge of cardiovascular prevention consists of setting up multidisciplinary approaches that combine interventions oriented towards reducing cardiovascular risk such as promoting lifestyle changes, optimal medical treatment and care services, health education as well as improvements to the environmental and social conditions in which individuals live during their lifetime (197,198).

1.6. Current state of the role of psychological and socioeconomic factors on cardiovascular risk in Spain

Evidence about the psychological and socioeconomic role on cardiovascular risk and CVD has been substantially growing especially in Anglo-Saxon countries. In Spain, however the number of studies that have analysed their effect on CVD is low. A recent systematic review, which evaluated the cardiovascular epidemiology in Spain during 1980–2010, revealed that only about 3.8% of the published cardiovascular disease studies performed on the general population had analysed the relationship between social and psychosocial factors and CVD (200).

The systematic study of the role of psychological and socioeconomic circumstances at individual, local and macro level is essential to understand the possible aetiological role of these conditions on CVD, and therefore, to implement effective strategies and actions to reduce the CVD burden in Spain.

1.6.1. Psychological and social conditions and cardiovascular risk factors and behaviours

Regarding traditional cardiovascular risk factors, people with low SEP tend to be more hypertensive (201-203), and have obesity and be overweight (particularly women) (201,203,204). Controversial results have been found between diabetes and socioeconomic factors (203,205,206).

In some southern Spanish regions, no differences in diabetes regarding SEP have been observed (203) while in northern ones, socioeconomic deprivation was found to be related to more prevalence, less control and worse prognosis of type 2 diabetes (205,206). Moreover, a large population study using information from Spanish National Health survey revealed the existence of SEP-related inequalities in the prevalence of diabetes, markedly among women during 1987-2006 (207).

Regarding dyslipidaemia, evidence of the influences of social conditions is scarce and ambiguous (208, 209).

Although the optimal control and management of the main cardiovascular risk factors once they are detected or diagnosed is the cornerstone to prevent adverse cardiovascular outcomes, the study of the contribution of socioeconomic and psychological conditions on the grade of control and values of these risk factors is limited (206).

Regarding lifestyles, the evidence is contradictory; some research has found that those people with higher SEP tend to practice more physical leisure activity (201,203) while others did not find any socioeconomic pattern (210). Considering dietary quality patterns and alcohol intake in some Spanish regions such as Catalonia, there were found to be no differences for socioeconomic level (210). Regarding smoking habit, in Spain, it is still possible to observe the tobacco transition from the higher socioeconomic groups to those at the socioeconomic bottom. Thus, some groups with better socioeconomic conditions tend to be smokers, especially women (201,210) while in other population groups, smoking is more prevalent amongst less educated individuals (203).

1.6.2. Psychological and social conditions and adverse cardiovascular outcomes

Although it has been noticed that people in the lowest socio economic position of the Spanish social ladder have a higher risk of AMI (211), no studies addressing the incidence of stroke related to psychological or socioeconomic characteristics have been carried out in Spain. The influence of socioeconomic condition at the individual level regarding mortality seems to be more evident for strokes than for IHD (212-214).

On the other hand, evidence from ecological studies carried out in some Spanish towns/regions, have found that the higher the psycho-socioeconomic deprivation the greater the cardiovascular mortality (215,216).

1.6.3. Psychological and social conditions and cardiovascular prevention

A recent study has shown that in spite of the economic crises, primary cardiovascular prevention strategies (e.g. promotion of health lifestyle, prevention of smoking and the use of cardiovascular risk therapy for controlling traditional cardiovascular risk) set up in Spain in the past few years, have effectively contributed to reducing the IHD hospitalizations (217).

Evidence about the role of socioeconomic conditions on different aspects of primary and secondary cardiovascular prevention in Spain is scarce. A study addressed to analyse the influence of SEP in secondary cardiovascular prevention in Catalonia Spain, did not find social inequalities in the treatment received and the cardiovascular risk control achieved (218).

In relation to the cardiovascular risk estimation, evidence has shown that SEP may modify the cardiovascular risk when it is introduced in the cardiovascular evaluation tables (219). When patient SEP (using education level as indicator) was introduced along with other risk factors in the cardiovascular risk estimation tables, it revealed that Spanish people with low educational level have 27% more cardiovascular risk for having CHD while those with high education present a 50% less high risk probability (219).

SEP is not considered in any cardiovascular risk estimation tool or cardiovascular guide used in Spain; however, the latest European guide of cardiovascular prevention clearly invites all medical professionals to take into account the psychological and socioeconomic factors at the individual level in the prevention, assessment and treatment of CVD in daily clinical practice (199).

1.7. Genesis of the present research thesis

First, CVDs are multifactorial disorders that are in a great part preventable and reducible. Their aetiology and course is not only a result of the genetic and family heritage, poor risk profile or unhealthy lifestyles, but also a result of disadvantaged psychological and socioeconomic conditions in which individuals are born, grow, work, live and age.

Second, despite growing evidence (mostly from Anglo-Saxon countries) showing that adverse psychological and socioeconomic circumstances can lead to poor cardiovascular health, the mechanisms and pathways are not clearly established.

Third, even though Spain is one of the Western countries with the lowest cardiovascular morbid-mortality rates (7,8), CVDs continue to be the leading cause of death (9) and the prevalence of traditional cardiovascular risk factors is significantly high (221).

Fourth, in the Spanish context, the role of psychological and socioeconomic factors at individual, ecological and macro level is still scarce, particularly in relation to the control of classic cardiovascular risks factors, incidence of major cardiovascular outcomes and primary cardiovascular prevention.

Fifth, the type of health care model and health care coverage adopted for a country may become a crucial driver in reducing or increasing the gap in socioeconomic health inequalities.

Hence, the aim of the present thesis is to analyse the role of some psychological and socioeconomic factors (socioeconomic position, social support and depression) on three aspects of cardiovascular risk: i) primary cardiovascular prevention treatment; ii) optimal control and values of hypertension (as one of the main traditional cardiovascular risk factors); and iii) the incidence of primary major cardiovascular events in an adult population at high cardiovascular risk and living in Spain.

The acquired knowledge will contribute to understand the influence of psychological and socioeconomic conditions on the prevention, control and genesis of CVDs in a country with different cultural, political and economic contexts compared with Anglo-Saxon countries where most of the evidence come from. In addition, the results can contribute to understand the importance of the universal and free coverage system in reducing socioeconomic differences in cardiovascular health.

The results of this thesis may encourage health professionals to consider the assessment of socioeconomic and psychological circumstances in the daily health care practice to prevent and reduce the burden of CVDs in the Spanish context.

Chapter 2: Hypotheses and Objectives

2.1. Research hypotheses

1_. There are socioeconomic differences in receiving primary cardiovascular preventive treatment for the main cardiovascular risk factors (hypertension, type 2 diabetes and dyslipidaemia) in an adult population with a high cardiovascular risk within the context of a universal health care system.

2_. Depression may affect the degree of control and values of blood pressure in a hypertensive adult population with a high cardiovascular risk.

3_. Low socioeconomic position, low social support and depression may contribute to increase the risk of developing cardiovascular events (acute myocardial infarction stroke and death from cardiovascular disease) in an adult population with high cardiovascular risk.

2.2. General objective

To determine the effect of specific psychological and social conditions at the individual level on different aspects of cardiovascular risk in an adult population with high cardiovascular risk, in Spain.

2.3. Specific objectives

1_. To assess the relationship between the socioeconomic status of an elderly population at high cardiovascular risk and inequalities in receiving primary cardiovascular treatment, within the context of a universal health care system.

2_. To determinate whether depression may influence the control of blood pressure in hypertensive individuals at high cardiovascular risk.

3_. To determine whether adverse psychological and socioeconomic conditions such as depression, lower educational level and weak social support contribute to increase the risk of cardiovascular events (myocardial infarction and stroke) and death from CVD in an adult population at high cardiovascular risk.

Part II:
Methods

Chapter 3:
Study population

3.1. Study population

This thesis has been made in the framework of the PREDIMED study, which is a randomised clinical trial carried out on 7447 adults between October 2003 and 31 December 2010, in Spain. It was aimed at analysing the effect of three Mediterranean diet patterns on cardiovascular prevention.

For the purpose of this thesis, three papers have been published. In order to answer objectives 1 and 2, a cross-sectional design was performed and for objective 3, a cohort study embedded in the clinical trial was carried out.

Regarding the study population, women and men aged over 60 and 55 respectively, with high cardiovascular risk, free of cardiovascular diseases at baseline, living in Spain and participating in the PREDIMED study (Prevention with Mediterranean diet) (83,220) were included.

3.1.1. Inclusion criteria

Participants must be between 55 and 80 years (men) and 60 to 80 years (women), and meet at least one of the following criteria for inclusion (**a or b**):

- **a.** Type 2 diabetes: defined by the well-established medical diagnosis of type 2 diabetes, or receiving insulin or oral hypoglycaemic treatment, or fasting blood glucose levels >126mg/dl, or casual blood glucose levels >200mg/dl with presence of polydipsia or polyuria or unexplained weight loss, or casual blood glucose levels >200mg/dl in two measurements after an oral glucose tolerance test.
- **b.** Having at least three of the following cardiovascular risk factors: smoking (>1 cig/day during the last month), hypertension (systolic blood pressure >=140 mm Hg or diastolic blood pressure >=90mmHg or being under antihypertensive medication), elevated LDL (>=160 mg/dl), low LHD levels (<=40 mg/dl), overweight (BMI>=25 kg/m2), a family history of premature CHD (defined as myocardial infarction or sudden death before 55 years in father or male 1st- degree relative, or before 65 years in mother or female 1st-degree relative).

If the HDL-cholesterol level was >=60 mg/dl, one risk factor was subtracted degree relative, or before 65 years in mother or female 1st-degree relative). If the HDL-cholesterol level was >=60 mg/dl, one risk factor was subtracted.

3.1.2. Exclusion criteria

a. Documented history of previous cardiovascular disease: AMI, angina, coronary revascularization, Abnormal Q in the electrocardiogram, stroke (ischemic, haemorrhagic or transient ischemic attack), or peripheral artery diseases with intermittent claudication.

b. Severe medical conditions: digestive disease with fat intolerance, advanced malignancy, major neurological, psychiatric or endocrine disease, or Immunodeficiency condition.

c. Illegal drug use, problematic alcohol intake (chronic alcoholism or total daily alcohol intake >80 g/d).

d. BMI > 40 kg/m2.

e. Difficulties or major inconvenience to change dietary habits, impossibility to follow a Mediterranean-type diet or to understand the recommendations of the protocol, and patients who lacked autonomy.

3.1.3. Data collection

The 7447 participants came from seven regions of Spain (Navarra, Basque Country, Catalonia, Valencia, the Balearic Islands, Andalusia and the Canary Islands) and were recruited between June 2003 and June 2009 for the PREDIMED study. The selection of participants was based on their medical history in the primary care centres (PCCs). Each individual medical record was reviewed to exclude those who did not meet the inclusion criteria. Once a potential participant was identified, he/she was invited to participate in the study. The objectives, characteristics and interventions of the PREDIMED study were then explained during the invited visit carried out in their PCCs.

Patients interested in participating in the study and with confirmed inclusion criteria, followed up two medical visits in the PCCs, where they underwent face-to-face interviews and administration of validated questionnaires (socio-demographic and medical history questionnaires (221), a 137-item food frequency questionnaire (222,223), 14-item questionnaire of adherence to the Mediterranean (224), and Minnesota leisure-time physical activity questionnaire (225,226).

In addition, they also underwent physical medical evaluations (anthropometrical and blood pressure measurements, determining the ankle-arm blood pressure index, and an electrocardiogram) and biomarkers tests (blood and tissue samples) using calibrated medical devices.

3.1.4. Ethical considerations

All participants gave written informed consent to participate in the PREDIMED study as well as for collecting biomarkers samples, all under the current ethical principles for medical research involving human subjects. The PREDIMED Study PROTOCOL was approved by the Institutional Review Board of Hospital Clinic (Hospital Clínic de Barcelona, Spain) and was registered in the Current Controlled Trials (number: ISRCTN35739639, http://www.controlled-trials.com/ISRCTN35739639). The Steering Committee of PREDIMED Study approved all the studies carried out in the present thesis.

Chapter 4: Study variables

4.1. End points

4.4.1. Objetive 1:

To assess the relationship between the socioeconomic status of an elderly population at high cardiovascular risk and inequalities in receiving primary cardiovascular treatment, within the context of a universal health care system.

Cardiovascular prevention treatment was considered when:

Hypertensive participants (medical diagnosis of hypertension): to be receiving at least some of the following medications for hypertension status: Angiotensin-converting-enzyme inhibitor (ACE inhibitors), diuretics, calcium channel blockers, angiotensin II receptor antagonists, ß-blockers, α-blockers, or other antihypertensive drugs.

Diabetic participants (medical diagnosis of type 2 diabetes): to be receiving insulin or/and hypoglycaemic agents (biguanides, sulphonamides, thiazolidinediones, alpha glucosidase inhibitors, other oral lowering-glucose medication).

Dyslipidemic participants (medical diagnosis of dyslipidaemia): to be getting statins or fibrates.

4.1.2. Objective 2

To analyse whether depression may influence the control of blood pressure in hypertensive individuals at high cardiovascular risk.

Optimal control of blood pressure values: following the recommendations of the European guidelines on cardiovascular disease prevention in clinical practice (version 2012), blood pressure was considered to be optimally controlled when the value of systolic blood pressure (SBP) was below 140 mmHg and diastolic blood pressure (DBP) was below 90 mmHg. The blood pressure values for both SBP and DBP were calculated using the mean of four measurements at baseline.

Blood pressure values: the SBP and DBP values were also considered as continuous variables (mmHg).

4.1.3. Objective 3

To determine whether adverse psychological and socioeconomic conditions such as depression, lower educational level and weak social support contribute to increase the risk of cardiovascular events (myocardial infarction and stroke) and death from CVD in an adult population at high cardiovascular risk..

Myocardial Infarction

AMI: defined by at least one of the two following conditions:

a. Rising or gradual falling of typical biochemical markers of myocardial necrosis (troponin, CK-MB) with at least one of the following situations: Ischemic symptoms (chest, epigastric, arm, wrist or jaw discomfort with exertion or rest, lasting at least for 20 minutes and may be associated with unexplained nausea and vomiting, persistent shortness of breath, weakness, dizziness, lightheadedness or syncope, or a combination of them). Pathologic Q waves in the electrocardiogram (ECG, any Q waves in leads V1 through V3, or Q wave higher or equal to 30 ms (0.03 s) in leads I, II, aVL, aVF, V4, V5 or V6. The Q wave changes must be present in any two contiguous leads, and be above or equal to 1 mm in depth). ECG indicative of ischemia by the ST segment elevation or depression (New or presumed new ST segment elevation at the J point in two or more contiguous leads with the cut-off points > 0.2 mV in leads V1, V2 or V3 and > 0.1mV in other leads). ST segment depression in at least two contiguous leads. T wave inversion > 0.1 mV in at least two contiguous leads. Underwent coronary artery intervention.

b. Findings of acute myocardial infarction (MI) at pathological examination**.**

Established MI: defined by myocardial necrosis or clinically established MI in the standard 12-lead ECG criteria as follows:

a. Any Q waves in leads V1 through V3**.**

b. Q wave higher or equal to 30 ms (0.03 s) in leads I, II, aVL, aVF, V4, V5 or V6. The Q wave observed changes must be present in any two contiguous leads, and be higher or equal to 1 mm in depth. Bundle branch block, left ventricular hypertrophy or Wolff-Parkinson-White syndrome were excluded.

Stroke

Defined by the presence of an acute neurological deficit for more than 24 hours caused by an abrupt impairment of brain function due to blockage of brain blood flow (especially the arteries supplying blood to the brain) or cerebral haemorrhage. The transit ischemic attack was excluded. Computed tomography (CT) or magnetic resonance imaging (MRI) was used to confirm the stroke diagnosis.

Cardiovascular death

Death from any of the following causes: coronary heart disease (AMI, unstable angina), stroke, arrhythmias, congestive heart failure, pulmonary edema, pulmonary embolisms, and ruptured aortic aneurysm.

All the above endpoint criteria definitions are also available in a supplementary appendix of the published article about the main PREDIMED study findings (83).

Cardiovascular endpoints were identified by systematic contact with the study participants and/or their close relatives, and by annual revisions of participant medical records and consultation of the Spanish National Death Index. In addition, all cardiovascular outcomes considered in the study were revised, confirmed and proven (accepting consensus) by the Adjudication Committee of the PREDIMED study which was integrated by a specialized team of cardiologists, endocrinologists, neurologists, and ophthalmologists.

4.2. Psychological and socioeconomic factors

4.2.1. Depression

The self-reported diagnosis of depression (further confirmed in medical records at baseline) was considered. Depression has strongly been found linked with both adverse cardiovascular outcomes and related risk factors (158-161).

In Spain, the medical diagnosis of depression is carried out by the family doctor or psychiatrists, based on the criteria of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) of the American Psychiatric Association and in the Mental and behavioural disorder of the international classification of diseases of WHO, or by using validated mental health scales such as the Beck Depression Inventory which are included in the Spanish health guidelines.

4.2.2. Education attainment

Education attainment achieved by participants was used as an indicator of SEP, because it remains stable over the lifetime. Since a reverse causation is scarcely probable, education level is widely used as SEP in epidemiological studies. Education level may condition the cognitive capabilities to identify and change health risk circumstances, seek health care, understand and follow medical advice and indications, and may act as a strong driver to accessing better employment opportunities and therefore to higher income levels and well-being during the people's life course (127). In addition, education level has been demonstrated to be highly correlated with many cardiovascular aspects (128,129,131,132).

The main basic categories of education attainment considered were the following: **low education level** (up to primary school), **middle education level** (secondary education, up to 16–18 years) and **high education level** (university or similar studies). Due to the low percentage of university studies and the number of cardiovascular events among our population, in the final adjusted analyses for properly answering objective 3, the education attainment was also grouped in two categories: **high education level** (university and secondary education) and **primary education** (up to primary studies).

4.2.1. Social support

Living alone or living with others was used as a proxy of social support. Living alone, or living with others has been previously considered a strong proxy to evaluate the effect of social support on cardiovascular risk and prognosis (147-149,151).

4.3. Other co-variables

The following participant characteristics and /or conditions were also considered as they could be closely related to both cardiovascular risk and psychological or socioeconomic factors.

4.3.1. Socio-demographic factors

Age (expressed in years) and sex (women and men)

4.3.2. Risk behaviours

Smoking status: the following basic categories were considered: **non-smoker** (Never smoked), **former smoker** (quit smoking more than 1 year ago), **current smoker** (current smoker or quit smoking less than 1 year ago) in the analysis of objective 3. In the analyses of objectives 1 and 2, the smoking condition was placed in two categories: **non-smoker** (never smoked plus former smoker) and **smoker** (current smoker)

Leisure-time physical activity: based on the information collected in the Minnesota leisure-time physical activity questionnaire (225,226) and the recommendations from the physical activity from the American College of Sports Medicine and the American Heart Association (227), it was considered as: Sedentary behaviour or low physical activity (< 1000 kcal/week) and active physical activity (≥1000 Kcal/week).

Alcohol intake: following the previous cardiovascular indications for risky alcohol intake, in some analyses high alcohol intake was considered as 280g/week and 170 g/week for men and women respectively (objective 1).

For the subsequent analysis (objective 2 and 3), based on the update of alcoholic drinking assessment recommendations of the European guidelines on cardiovascular disease prevention version 2012(199), the high alcohol intake cut-off was set at >20gr/daily in men and 10gr/daily women.

Adherence to Mediterranean diet pattern: low adherence was considered when it was less than nine points (median) on a scale (0-14) validated for that purpose (224) in objective 1 and 2. For the 3rd objective, the three interventions of the Mediterranean diet pattern carried out in the PREDIMED study (83) were considered (low fat Mediterranean diet, Mediterranean diet enriched with olive oil and Mediterranean diet enriched with olive mix nuts) as an adjusted factor.

4.3.3. Cardiovascular risk factors

Hypertension: to answer objective 1 and 2 the self-reported diagnosis of hypertension was considered. To answer objective 3, both receiving any antihypertensive therapy and having medical diagnosis of hypertension were considered as criteria to definite hypertension.

Diabetes (Type 2 diabetes): to answer objective 1 and 2 the self-reported diagnosis of diabetes was considered. To answer objective 3, both receiving any antidiabetic drug and having medical diagnosis of diabetes were considered as criteria to definite diabetes

Dyslipidaemia: to answer objective 1 and 2 the self-reported diagnosis of dyslipidaemia was considered. To answer objective 3, both receiving any lowering-lipid therapy and having medical diagnosis of dyslipidaemia were considered as criteria to definite dyslipidaemia.

Family history of premature CHD: having a father or male 1st-degree relative, or before 65 years in mother or female 1st-degree relative who had suffered myocardial infarction or sudden death was taken into account when the probability of suffering major cardiovascular events was analysed (objective 3).

BMI: it was considered as an indicator to evaluate overweight and obesity. It was categorised by three levels (normal weight: BMI ≤ 25, overweight: BMI >25 30, obesity: BMI >30), or considered as a continuous variable.

4.3.4. Mental disorders pharmacological treatment

Antidepressant treatment: taking at least one of the following antidepressant agents: selective serotonin reuptake inhibitors, non-selective monoamine reuptake inhibitors, monoamine oxidase A inhibitors, antidepressants in combination with psycholeptics or other antidepressant agents.

Anti-anxiety or sedative treatment: taking at least one of the following drugs: benzodiazepine derivatives, azaspirodecanedione derivatives, GABA (gamma-aminobutyric acid) analogues, natural antianxiety agents, ethanolamine derivatives, other anxiolytics, hypnotics and sedatives agents). It was taken into account in the analysis carried out to answer objective 2 as an important covariable of depression.

Chapter 5:
Studies design and statistical analyses

5.1. Studies design and statistical analysis

Although the respective study designs and statistical methods performed to meet the objectives outlined in the present thesis are specified in each of the articles included in the result section (part III), a summary of them is presented below.

5.1.1. Objective 1

To assess the relationship between the socioeconomic status of an elderly population at high cardiovascular risk and inequalities in receiving primary cardiovascular treatment, within the context of a universal health care system.

A cross-sectional study based on the demographic and socioeconomic characteristics, medical treatments, cardiovascular risks and lifestyles of study population at baseline (N=7447 people).

Univariate and bivariate descriptive analyses of characteristics of participants were assessed. In the bivariate analyse, Chi square tests was used to evaluate correlation between categorical variables while variance F-test to compare means of continuous variables among two or more groups, The crude and adjusted associations between educational attainment (SEP) and main outcomes (receiving treatment for hypertension, type 2 diabetes and dyslipidaemia) were performed by using binomial logistic regression (logit regression) probability function. All population characteristics that could have clinical or epidemiological relationships to the outcomes and predictable variables were included in the adjusted multivariate models to control the confounding effect. The adjusted analyses were also stratified by sex. The Hosmer-Lemeshow test was used to assess the goodness of fit for multivariate models.

5.1.2. Objective 2

To analyse whether depression may influence the control of blood pressure in hypertensive individuals at high cardiovascular risk.

A cross-sectional study carried out on a population with hypertension at baseline (N=5954 people). Besides the depression conditions (diagnosis of depression and receiving antidepressant treatment) and the blood pressure values, other characteristics such as sex, age, SEP (education), BMI, cardiovascular comorbidity (diabetes and dyslipidaemia), behaviour patterns, and anxiolytics and sedative medication at study baseline were also taken into account.

The description of the study population was performed by using univariate and bivariate analyses. Bivariate analyses included chi square tests and ANOVA F-test. To assess the relationship between depression condition and the optimal control of BP (multivariate model), the binomial logistic regression probability function was used. To evaluate the specific effect of depression condition on both SBP and DBP values (multivariate models), the log-linear regression function was also used. All final models of both logistic and linear regressions were adjusted by the remaining populations' characteristics (age, sex, education, anxiolytic or sedative treatment, BMI, lifestyles, hypertension co-morbidity, and antihypertensive treatment). The goodness-of-fit logistic models were performed using the Homer and Lemeshow test, and for linear model residual validation using the Kolmogorov test.

5.1.3. Objective 3

To determine whether adverse psychological and socioeconomic conditions such as depression, lower educational level and weak social support contribute to increase the risk of cardiovascular events (myocardial infarction and stroke) and death from CVD in an adult population at high cardiovascular risk.

A prospective cohort study was carried out in 7263 participants (with complete data regarding psychological socioeconomic factors) from our study population between October 2003 and December 2010 (average follow up of 4.8 years).

Psychological and socioeconomic conditions (depression, educational level, and social support), demographic characteristic, BMI, lifestyles, and cardiovascular profile of participants at baseline were considered.

Univariate and bivariate analyses were used for describing the study population. In the bivariate analysis, Chi-square test for analysing differences among proportions, and t-student or one-way ANOVA F-test for differences among means were used. The crude incidence rate of cardiovascular endpoints was calculated per 1000 person-years. The hazard of developing a cardiovascular event according psychological and socioeconomic conditions was calculated using Cox proportional regression function. All final multivariate hazard rates (HR) were adjusted for the other demographic (sex, age), clinical and behavioural conditions of our population (cardiovascular risks, BMI, type of Mediterranean diet pattern, alcohol consumption and smoking). The adjusted analyses were also performed separately for both men and women. The proportional HR assumption from the final multivariate Cox models was validated with time-varying tests (Schoenfeld residuals approach).

Part III:
Results

Chapter 6:
General description of the study population

6.1. Baseline characteristics of the study population

Our study population was 7447 women (57.5%) and men (42.5%) with an average age of 67.0 (SD 6.2) at high cardiovascular risk, residing in seven Autonomous regions of Spain (Navarra, Basque Country, Catalonia, Valencia, the Balearic Islands, Andalusia and the Canary Islands), and participing in the Predimed Study (figure 5).

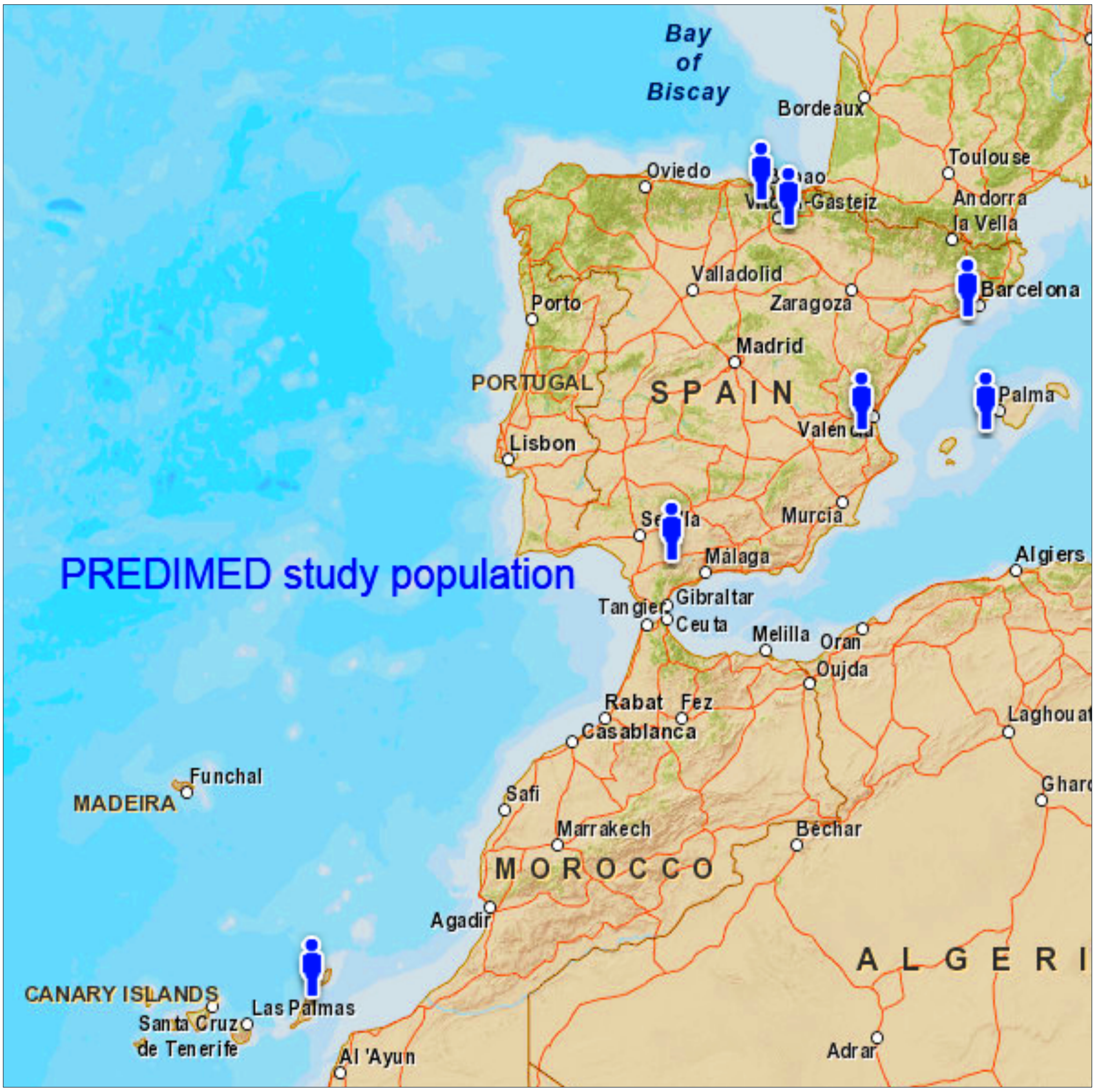


Figure 5. Geographical recruitment of the research participants (PREDIMED Study).

With regard to the psychological and socioeconomic situations, the majority of our participants attained only primary education, less than 10% lived alone and around 18% had depression. Related with cardiovascular risk factors and lifestyles, most of our population was overweight, presented high prevalence of hypertension and dyslipidaemia, but was less smoker and alcoholic drinker. Nearly one third of participants had sedentary behaviour while less than half of them showed a low pattern of adherence to Mediterranean diet and suffered from diabetes (table 1).

Table 1. Main characteristics of the research population at baseline.

Main characteristic of participants	N	%
	7447	**100**
Age , years (Mean ± SD)	7447	67.0(6.2)
Sex (women)	4282	57.5
Educational attainment		
High education	534	7.2
Middle education	1121	15.1
Low education	5657	76.0
Social support		
Living alone in the household	730	9.8
Diagnosis Depression	1330	17.9
BMI (Kg/m^2) (Mean ± SD)	7447	30.2(3.8)
Lifestyles		
Smoking		
Never	4564	61.3
Former (>1 year)	1836	24.7
Current (current smoker or < 1 year quitted)	1047	14.01
Low adherence to Mediterranean diet pattern	3434	46.1
Sedentary behaviour (<1000 kcal/week)	2699	36.2
High alcohol intake (> 20gr in men and >10gr in women daily)	1515	21.0
Cardiovascular risk factors		
Hypertension	6163	82.8
Diabetes	3614	48.5
Dyslipidaemia	5384	72.3
Family history of premature CHD	1668	22.4

Chapter 7:

Article 1: "Socioeconomic status and health inequalities for cardiovascular prevention among elderly Spaniards"

Mejía-Lancheros C, et al. Socioeconomic status and health inequalities
for cardiovascular prevention among elderly Spaniards.
Rev Esp Cardiol (Engl Ed). 2013;66(10):803–811
doi: 10.1016/j.rec.2013.05.025

Rev Esp Cardiol. 2013;66(10):803–811

Original article

Socioeconomic Status and Health Inequalities for Cardiovascular Prevention Among Elderly Spaniards

Cília Mejía-Lancheros,[a] Ramón Estruch,[b,c] Miguel A. Martínez-González,[d] Jordi Salas-Salvadó,[c,e] Dolores Corella,[c,f] Enrique Gómez-Gracia,[g] Miquel Fiol,[c,h] José Lapetra,[c,i] Maria I. Covas,[c,j] Fernando Arós,[k] Lluís Serra-Majem,[l] Xavier Pintó,[m] Josep Basora,[c,n] José V. Sorlí,[c,o,p] and Miguel A. Muñoz[a,q,*], on behalf of the PREDIMED Study Investigators

[a] *Departamento de Pediatría, Obstetricia, Ginecología y Medicina Preventiva, Universitat Autònoma de Barcelona, Barcelona, Spain*
[b] *Departamento de Medicina Interna, IDIBAPS, Hospital Clínic, Universidad de Barcelona, Barcelona, Spain*
[c] *CIBER Fisiopatología de la Obesidad y Nutrición (CIBERobn), Instituto de Salud Carlos III (ISCIII), Madrid, Spain*
[d] *Departamento de Medicina Preventiva y Salud Pública, Universidad de Navarra, Pamplona, Navarra, Spain*
[e] *Departamento de Nutrición Humana, IISPV, Universitat Rovira i Virgili, Reus, Tarragona, Spain*
[f] *Departamento de Medicina Preventiva, Universidad de Valencia, Valencia, Spain*
[g] *Departamento de Medicina Preventiva, Universidad de Málaga, Málaga, Spain*
[h] *Instituto de Ciencias de la Salud (IUNICS), Universidad de las Islas Baleares, Palma de Mallorca, Baleares, Spain*
[i] *Departamento de Medicina de Familia, División de Atención Primaria de Sevilla, Centro de Salud Bellavista, Sevilla, Spain*
[j] *Unidad de Lípidos e Investigación en Epidemiología Cardiovascular, Institut Municipal d'Investigació Mèdica (IMIM), Barcelona, Spain*
[k] *Departamento de Cardiología, Hospital Universitario Txagorritxu, Vitoria, Álava, Spain*
[l] *Departamento de Ciencias Clínicas, Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain*
[m] *Unidad de Lípidos y Riesgo Vascular, Medicina Interna, Hospital Universitario de Bellvitge, Hospitalet de Llobregat, Barcelona, Spain*
[n] *Unidad de Investigación en Atención Primaria de Tarragona, Institut Català de la Salut e IDIAP-Jordi Gol, Tarragona, Spain*
[o] *Departamento de Medicina Preventiva, Facultad de Medicina, Universidad de Valencia, Valencia, Spain*
[p] *División de Atención Primaria, Instituto de la Salud de Valencia, Valencia, Spain*
[q] *Unitat de Suport a la Recerca, División de Atención Primaria de Salud, Institut Català de la Salut e IDIAP-Jordi Gol, Barcelona, Spain*

Article history:
Received 12 April 2013
Accepted 22 May 2013
Available online 30 August 2013

Keywords:
Cardiovascular disease
Cardiovascular risk factor
Pharmacological treatment
Socioeconomic inequalities
Life styles

A B S T R A C T

Introduction and objectives: Although it is known that social factors may introduce inequalities in cardiovascular health, data on the role of socioeconomic differences in the prescription of preventive treatment are scarce. We aimed to assess the relationship between the socioeconomic status of an elderly population at high cardiovascular risk and inequalities in receiving primary cardiovascular treatment, within the context of a universal health care system.
Methods: Cross-sectional study of 7447 individuals with high cardiovascular risk (57.5% women, mean age 67 years) who participated in the PREDIMED study, a clinical trial of nutritional interventions for cardiovascular prevention. Educational attainment was used as the indicator of socioeconomic status to evaluate differences in pharmacological treatment received for hypertension, diabetes, and dyslipidemia.
Results: Participants with the lowest socioeconomic status were more frequently women, older, overweight, sedentary, and less adherent to the Mediterranean dietary pattern. They were, however, less likely to smoke and drink alcohol. This socioeconomic subgroup had a higher proportion of coexisting cardiovascular risk factors. Multivariate analysis of the whole population found no differences between participants with middle and low levels of education in the drug treatment prescribed for 3 major cardiovascular risk factors (odds ratio [95% confidence interval]): hypertension (0.75 [0.56-1.00] vs 0.85 [0.65-1.10]); diabetic participants (0.86 [0.61-1.22] vs 0.90 [0.67-1.22]); and dyslipidemia (0.93 [0.75-1.15] vs 0.99 [0.82-1.19], respectively).
Conclusions: In our analysis, socioeconomic differences did not affect the treatment prescribed for primary cardiovascular prevention in elderly patients in Spain. Free, universal health care based on a primary care model can be effective in reducing health inequalities related to socioeconomic status.

* Corresponding author: Unitat de Suport a la Recerca, Àmbit Atenció Primària Barcelona-Ciutat, ICS-IDIAP-Jordi Gol, Sardenya 375, 08025 Barcelona, Spain.
E-mail address: mamunoz.bcn.ics@gencat.cat (M.A. Muñoz).

1885-5857/$ – see front matter © 2013 Sociedad Española de Cardiología. Published by Elsevier España, S.L. All rights reserved.
http://dx.doi.org/10.1016/j.rec.2013.05.025

804 C. Mejía-Lancheros et al. / Rev Esp Cardiol. 2013;66(10):803–811

Nivel socioeconómico y desigualdades de salud en la prevención cardiovascular de la población española de edad avanzada

Palabras clave:
Enfermedad cardiovascular
Factor de riesgo cardiovascular
Tratamiento farmacológico
Desigualdades socioeconómicas
Estilos de vida

R E S U M E N

Introducción y objetivos: Aunque se sabe que los determinantes sociales pueden ser causa de desigualdades en la salud, se ha evaluado escasamente si hay diferencias socioeconómicas relacionadas con el tratamiento preventivo. El objetivo de este estudio es analizar la relación entre el nivel socioeconómico de una población con alto riesgo cardiovascular y las desigualdades en el tratamiento cardiovascular recibido en un sistema sanitario gratuito y universal.

Métodos: Estudio transversal de 7.447 pacientes con alto riesgo cardiovascular (el 57,5% mujeres; media de edad, 67 años) procedentes del estudio PREDIMED, un ensayo clínico de intervención nutricional para la prevención cardiovascular. El nivel educativo alcanzado se usó como indicador del nivel socioeconómico para evaluar las diferencias en el tratamiento farmacológico contra la hipertensión, la diabetes mellitus y la dislipemia.

Resultados: Los participantes que con mayor frecuencia se encontraban en niveles socioeconómicos inferiores eran mujeres, ancianos, pacientes con sobrepeso y sedentarios y aquellos con peor patrón de adherencia a la dieta mediterránea; sin embargo, eran menos fumadores y consumidores habituales de alcohol. Asimismo, este subgrupo mostró mayor proporción de factores de riesgo cardiovascular. El análisis multivariable ajustado en la población general no mostró diferencias en el tratamiento de fármacos preventivos prescritos para los principales factores de riesgo cardiovascular en relación con el nivel socioeconómico (*odds ratio* [intervalo de confianza del 95%]): participantes hipertensos (0,75 [0,56-1,00] frente a 0,85 [0,65-1,10]); participantes diabéticos (0,86 [0,61-1,22] frente a 0,90 [0,67-1,22]); participantes con dislipemia (0,93 [0,75-1,15] frente a 0,99 [0,82-1,19]).

Conclusiones: No se observaron diferencias en el tratamiento recibido en prevención cardiovascular primaria por los pacientes de edad avanzada en relación con el nivel socioeconómico. Un sistema de salud universal y gratuito basado en un modelo de atención primaria puede ser eficaz en la reducción de las desigualdades en la salud.

Abbreviations

CVD: cardiovascular disease
SES: socioeconomic status

INTRODUCTION

Cardiovascular diseases (CVD) continue to be the leading cause of death and disability worldwide, representing 30% of all deaths.[1] The impact of the main risk factors (smoking, hypertension, dyslipidemia, and diabetes mellitus [DM]) on this public health issue is well known. It has been estimated that 972 million people suffer from hypertension[2] and 366 million from DM.[3] The World Health Organization estimates that dyslipidemia is associated with more than half of all cases of ischemic heart disease and more than 4 million deaths per year.[4] It is well known that the elderly population has a higher incidence of CVD and a worse prognosis.[5] The population aged 65 and older in the United States has more than doubled, from 35 million in 2000 to 71 million in 2030, while the worldwide population aged 65 and older is projected to increase from 420 million to 973 million during 2000-2030.[6] Although researchers are increasingly interested in the study of multimorbidity and related determinants in this age group, this population is usually underrepresented in clinical trials.[7,8] Socioeconomic or demographic factors are among the many factors that have been associated with unequal access to health care services, which can produce inequalities in the diagnosis, treatment, and management of CVD risk factors.[9,10] Low socioeconomic status (SES) is directly related to a higher risk of CVD.[11,12] In a previous study carried out in patients with established coronary heart disease, we found no inequalities in cardiovascular prevention related to SES in Spain's health care system, which provides free, universal coverage.[13] The present study aimed to assess the relationship between SES and health inequalities for CVD prevention treatment in patients at high cardiovascular risk who have not yet developed CVD, within the context of a universal, free health care system.

METHODS

Study Design

We conducted a cross-sectional study using baseline data from the PREDIMED study, a trial aimed at assessing the effects of the traditional Mediterranean diet on the primary prevention of CVD. Details of the protocol have been described elsewhere[14] and are available online.[15] Briefly, the PREDIMED study involved long-term follow-up of 7447 participants (55-80 years of age) at high cardiovascular risk, but with no CVD at enrollment. Participants were included during 2003 to 2009, and follow-up ended in December 2010. All patients were assigned to one of 3 diets: traditional Mediterranean diet supplemented with extra-virgin olive oil, traditional Mediterranean diet supplemented with mixed nuts, or a low-fat diet (used as control group receiving advice to reduce dietary fat). Primary endpoints were myocardial infarction and stroke; secondary endpoints were death from any cause, heart failure, DM, major cancers, dementia, or other neurodegenerative disorders. The main inclusion criteria were age (women 60-80 years old and men 55-80 years old) with either type-2 DM or 3 or more cardiovascular risk factors: smoking, hypertension, elevated low-density lipoprotein cholesterol levels, low high-density lipoprotein cholesterol levels, overweight or obesity, or a family history of premature CVD. A total of 8713 participants were assessed for eligibility, of which 973 (11.1%) declined to participate and 293 (3.3%) were excluded for not meeting inclusion criteria.

PREDIMED participants were selected from the clinical records of primary care centers; eligible subjects were contacted by a health professional and invited to participate.

Researchers explained the study aims and interventions to potential participants. Signed informed consent was obtained. Participants were randomized to one of the 3 diet groups by a computer-generated random number sequence. At baseline, all participants underwent a medical examination; general practitioners were not informed of participants' group assignment. Variables were collected from medical records, clinical evaluation, and face-to-face interviews. Validated questionnaires were administered in order to obtain data on nutritional habits[16,17] and physical exercise.[18] Samples for laboratory tests were obtained. Information regarding pharmacological treatment was obtained by interview and confirmed by consulting electronic medical records. The study protocol was approved by the institutional review board of *Hospital Clínic* (Barcelona, Spain).The trial is registered.[19]

The present study is a cross-sectional analysis of baseline data from all 7447 PREDIMED study participants. Medical diagnostic criteria for hypertension, DM, and dyslipidemia were applied to identify participants according to these risk factors.

Outcomes Measured

Socioeconomic Status

We considered educational attainment as a socioeconomic indicator because it remains unchanged throughout life, and directly or indirectly affects an individual's adoption of health behaviors and their outcomes.[20] Educational level was grouped into three categories: high level (university education); middle level (secondary education, up to 16–18 years); and low level (no education or only primary school).

Treatment Assessment

We evaluated receipt of the treatment indicated according to the risk factor(s) present (hypertension, DM, dyslipidemia), defined as follows:

- Participants with hypertension: prescribed at least one antihypertensive drug, including angiotensin-converting-enzyme inhibitors, diuretics, calcium channel blockers, angiotensin receptor blockers, beta-blockers, alpha-blockers, or other(s).
- Participants with diabetes: prescribed insulin or/and oral hypoglycemic drugs.
- Participants with dyslipidemia: prescribed statins and/or fibrates.

Table 1
Characteristics of Study Participants (N=7447) According to Educational Attainment

Participant characteristics	High level[a]	Middle level[b]	Low level[c]	*P*-value	*P*-trend
Patients	534	1121	5657		
Age, years[d]	64,4±6,3	64,7±6,1	67,6±6,0	.001	–
Sex, women	168 (31.5)	451 (40.2)	3584 (63.4)	.001	.001
Body weight					
Normal (BMI=25)	61 (11.4)	99 (8.8)	390 (6.9)	.001	.001
Overweight (BMI 25-30)	280 (52.4)	571 (50.9)	2466 (43.6)	–	–
Obese (BMI>30)	193 (36.1)	451 (40.2)	2801 (49.5)	–	–
Lifestyle					
Smoking[e]	162 (30.3)	272 (24.3)	800 (14,1)	.001	.001
Low adherence to Mediterranean diet[f]	223 (41.8)	496 (44.2)	2657 (47.0)	.026	.007
Sedentary behavior[g]	144 (27.0)	391 (35.0)	2109 (37.5)	.001	.001
High alcohol intake[h]	43 (8.1)	84 (7.5)	273 (4.9)	.001	.001
Cardiovascular risk factors[i]					
Hypertension	435 (81.5)	924 (82.4)	4682 (82.8)	.737	.453
Diabetes	218 (40.8)	501 (44.7)	2834 (50.1)	.001	.001
Dyslipidemia	397 (74.3)	800 (71.4)	4088 (72.3)	.448	.605
Number of cardiovascular risk factors[i]					
One	105 (19.7)	233 (20.9)	955 (16.9)		
Two	336 (63.2)	651 (58.4)	3394 (60.2)	.001	.001
Three	91 (17.1)	230 (20.6)	1287 (22.8)	–	–

BMI, body mass index
Unless otherwise indicated, data are expressed as no. (%)
[a] High level: university studies.
[b] Middle level: secondary studies up to 16–18 years.
[c] Low level: Up to primary studies.
[d] Mean ± standard deviation. *P*-value: analysis of variance F-test.
[e] Smoking: current smoker or former smoker less than 1 year.
[f] Pattern of adherence to Mediterranean diet, less than 9 points (median) on a scale (0-14).
[g] Physical activity in leisure time<1000 kcal/week.
[h] Alcohol consumption more than 280 g/week in men and 170 g/week in women.
[i] Presence of hypertension, and/or diabetes and/or dyslipidemia.

- Participants with several cardiovascular risk factors: prescribed pharmacological treatment corresponding to the cardiovascular risk factors presented.

Other Variables

Age, sex, smoking habits, body mass index, adherence to the Mediterranean diet pattern, physical activity, and alcohol intake.

Statistical Analysis

Descriptive analysis of categorical variables was expressed as percentages and of quantitative variables as mean (standard deviation). Bivariate analyses included chi square tests for categorical variables and analysis of variance F-test for continuous variables. The crude and adjusted association between the outcomes (treatment received for DM, hypertension, and dyslipidemia) and educational level were performed using logistic regression. Multivariate analysis of treatment received in relation to educational level was performed by "ENTER method" adjusting for variables with a clinical and epidemiological relationship to receiving treatment in primary cardiovascular prevention and/or to educational level: sex, age, body weight, smoking, physical activity, alcohol intake, hypertension, DM, and dyslipidemia. Due to a lower educational level among women participants compared to men, we evaluated the interaction of educational level and sex related to the treatment received. All statistical tests had an alpha level<0.05 and a 95% confidence interval (95%CI). The Hosmer-Lemeshow test was used to assess the goodness of fit for multivariate models. The Statistical Package for the Social Sciences (SPSS) 17.0 software was used for all analyses.

RESULTS

A total of 7447 patients were included. Mean age was 67.0 (6.2) and 57.5% of the participants were women. Only 7.2% of the participants had attained a university education. At baseline, 81.2% (N=6041) of participants had hypertension; 47.7% (N=3553) DM, and 71.0% (N=5285) dyslipidemia.

Table 2
Pharmacological Treatment Received for Cardiovascular Risk Factors According to Educational Attainment

	High level[a] (N=534)	Middle level[b] (N=1121)	Low level[c] (N=5657)	*P*-value	*P*-trend
Participants with hypertension (N=6041)	435 (100)	924 (100)	4682 (100)	—	—
Treated[d]	355 (81.6)	720 (77.9)	3851 (82.3)	.008	.066
Number of drugs prescribed[e]					
None	80 (18.4)	204 (22.1)	831 (17.7)	.025	.303
One	229 (52.7)	466 (50.4)	2.458 (52.5)	—	—
Two	95 (21.8)	190 (20.6)	1116 (23.8)	—	—
Three or more	31 (7.1)	64 (6.9)	277 (5.9)	—	—
Participants with diabetes (N=3553)	218 (100)	501 (100)	2834 (100)		
Treated[f]	149 (68.3)	324 (64.7)	1889 (66.7)	.572	.954
Number of drugs prescribed[g]					
None	69 (31.7)	177 (35.3)	945 (33.3)	.731	.671
One	140 (64.2)	302 (60.3)	1742 (61.5)	—	—
Two	9 (4.1)	22 (4.4)	147 (5.2)	—	—
Participants with dyslipidemia (N=5285)	397 (100)	800 (100)	4088 (100)		
Treated[h]	224 (56.4)	455 (56.9)	2453 (60.0)	.126	.052
Number of drugs prescribed[i]					
None	173 (43.6)	345 (43.1)	1635 (40.0)	.231	.107
One	214 (53.9)	441 (55.1)	2380 (58.2)	—	—
Two	10 (2.5)	14 (1.8)	73 (1.8)	—	—
Number of cardiovascular risk factors[j]					
One (N=1293)	105 (100)	233 (100)	955 (100)		
Treated	77 (73.3)	161 (69.1)	659 (69.0)	.656	.457
Two (N=4381)	336 (100)	651 (100)	3394 (100)		
Treated	155 (46.1)	307 (47.2)	1704 (50.2)	.163	.063
Three (N=1608)	91 (100)	230 (100)	1287 (100)		
Treated	44 (48.4)	97 (42.2)	579 (45.0)	.570	.962

[a] High level: university studies.
[b] Middle level: secondary studies up to 16-18 years.
[c] Low level: up to primary studies.
[d] Prescribed at least one of following antihypertensive drugs: angiotensin-converting-enzyme inhibitors, diuretics, calcium channel blockers, angiotensin receptor blockers, beta blockers, alpha blockers, or other antihypertensive drugs.
[e] Number of antihypertensive drugs prescribed: none, angiotensin-converting-enzyme inhibitors, diuretics, calcium channel blockers, angiotensin receptor blockers, beta blockers, alpha blockers, or other antihypertensive drugs.
[f] Prescribed at least one of the following drugs: insulin and oral hypoglycemic drugs.
[g] Number of antidiabetic drugs prescribed(none, insulin or/and oral hypoglycemic).
[h] Prescribed at least one the following drugs: Statins and fibrates.
[i] Number of lipid-lowering drugs (Statins and/or fibrates) prescribed.
[j] Presence of hypertension and/or diabetes and/or dyslipidemia.

Among participants with hypertension, 81.4% (n=4922) received antihypertensive drugs; 66.5% of diabetic patients (n=2362) were prescribed insulin or oral antidiabetic agents, and 59.3% of patients with dyslipidemia (n=3132) received lipid-lowering therapy.

Participants in the lower educational level group were more frequently women, older, obese, less physically active, and had a lower adherence to the Mediterranean diet. Participants with a higher educational level were more often smokers and consumed more alcohol. Both the prevalence of DM and the proportion having 3 cardiovascular risk factors were higher in the lower educational level group (Table 1).

Participants with hypertension, DM, and a low educational level had more probability of receiving antihypertensive and lipid-lowering therapy. Participants with a low educational level and at least 2 cardiovascular risk factors were more likely to be treated (*P*=.063). In participants with dyslipidemia and in those with either 1 or 3cardiovascular risk factors, we observed no relationship between receiving treatment and educational level (Table 2).

Multivariate analysis did not show any relationship between treatment received and educational level (Table 3). Only participants with a middle educational level were less likely to be treated for hypertension (*P*=.049).

When the analysis was stratified by sex (Table 4), we observed that men with the lowest educational level had a 35% lower probability of receiving treatment for their hypertension than did participants at the highest level (odds ratio [OR]=0.65 [95%CI, 0.46-0.92]).No socioeconomic differences were observed for the other cardiovascular risk factors (DM, dyslipidemia) studied.

Figure presents the adjusted OR (95%CI) for receiving treatment for each of the cardiovascular risks factors. Table 5 shows the probability of receiving treatment depending on number of cardiovascular risk factors.

DISCUSSION

Our study found no overall differences related to SES in the pharmacological treatment prescribed for primary cardiovascular

Table 3
Odds Ratio of Receiving Treatment for Cardiovascular Risk Factors According to Educational Attainment

	High level (N=534)	Middle level (N=1121)	Low level (N=5657)
Participants with hypertension			
Unadjusted OR (95%CI)	1.00 (ref.)	0.79 (0.59-1.06)	1.04 (0.81-1.34)
P-value		.111	.746
aOR (95%CI)[a]	1.00 (ref.)	0.75 (0.56-1.00)	0.85 (0.65-1.10)
P-value		.049	.222
Participants with diabetes			
Unadjusted OR (95%CI)	1.00 (ref.)	0.87 (0.62-1.23)	0.93 (0.69-1.26)
P-value		.434	.651
aOR (95%CI)[b]	1.00 (ref.)	0.86 (0.61-1.22)	0.90 (0.67-1.22)
P-value		.404	.515
Participants with dyslipidaemia			
Unadjusted OR (95%CI)	1.00 (ref.)	0.94 (0.76-1.16)	1.04 (0.87-1.24)
P-value		.570	.684
aOR (95%CI)[c]	1.00 (ref.)	0.93 (0.75-1.15)	0.99 (0.82-1.19)
P-value		.499	.875
Number of cardiovascular risk factors			
One	1.00 (ref.)		
Unadjusted OR (95%CI)	1.00 (ref.)	0.82 (0.49-1.38)	0.80 (0.51-1.26)
P-value		.463	.339
aOR (95%CI)[d]	1.00 (ref.)	0.79 (0.47-1.33)	0.70 (0.44-1.12)
P-value		.368	.138
Two			
Unadjusted OR (95%CI)	1.00 (ref.)	1.05 (0.08-1.36)	1.18 (0.94-1.48)
P-value		.731	.151
aOR (95%CI)[d]	1.00 (ref.)	1.02 (0.78-1.33)	1.07 (0.84-1.35)
P-value		.888	.645
Three			
Unadjusted OR (95%CI)	1.00 (ref.)	0.77 (0.47-1.25)	0.85 (0.56-1.31)
P-value		.291	.471
aOR (95%CI)[d]	1.00 (ref.)	0.77 (0.47-1.26)	0.80 (0.52-1.24)
P-value		.296	.311

95%CI, 95% confidence interval; aOR, adjusted odds ratio; OR, odds ratio; ref., reference.
[a] Adjusted by sex, age, body weight, smoking, adherence to the Mediterranean diet, physical activity, alcohol intake, diabetes, and dyslipidemia.
[b] Adjusted by sex, age, body weight, smoking, adherence to the Mediterranean diet, physical activity, alcohol intake, hypertension and dyslipidemia.
[c] Adjusted by sex, age, body weight, smoking, adherence to the Mediterranean diet, physical activity, alcohol intake, hypertension and diabetes.
[d] Adjusted by sex, age, body weight, smoking, adherence to the Mediterranean diet, physical activity, alcohol intake.

Table 4
Odds Ratio of Receiving Treatment for Cardiovascular Risk Factors According to Educational Level, Stratified by Sex

	Women			Men		
	High level	Middle level	Low level	High level	Middle level	Low level
Patients, No.	168	451	3584	366	670	2073
Participants with hypertension						
aOR (95%CI)[a]	1.00 (ref.)	0.95 (0.60-1.50)	1.31 (0.87-1.98)	1.00 (ref.)	0.69 (0.47-1.01)	0.65 (0.46-0.92)
P-value		.820	.194		.059	.014
Participants with diabetes						
aOR (95%CI)[b]	1.00 (ref.)	1.23 (0.64-2.38)	1.35 (0.75-2.42)	1.00 (ref.)	0.76 (0.51-1.14)	0.76 (0.53-1.09)
P-value		.540	.316		.182	.141
Participants with dyslipidemia						
aOR (95%CI)[c]	1.00 (ref.)	0.97 (0.68-1.39)	1.11 (0.81-1.52)	1.00 (ref.)	0.93 (0.72-1.21)	0.94 (0.74-1.18)
P-value		.883	.525		.603	.578
Number of cardiovascular risk factors	1.00 (ref.)					
One						
aOR (95%CI)[d]	1.00 (ref.)	1.27 (0.52-3.11)	1.35 (0.62-2.93)	1.00 (ref.)	0.68 (0.36-1.29)	0.63 (0.36-1.12)
P-value		.597	.445		.237	.118
Two						
aOR (95%CI)[d]	1.00 (ref.)	0.95 (0.61-1.48)	1.10 (0.75-1.63)	1.00 (ref.)	1.11 (0.79-1.55)	1.06 (0.79-1.42)
P-value		.828	.630		.550	.720
Three						
aOR (95%CI)[d]	1.00 (ref.)	1.81 (0.71-4.62)	2.00 (0.85-4.72)	1.00 (ref.)	0.56 (0.31-1.03)	0.57 (0.33-0.96)
P-value		.217	.112		.060	.036

95%CI, 95% confidence interval; aOR, adjusted odds ratio; ref., reference.
[a] Adjusted by age, body weight, smoking, adherence to the Mediterranean diet, physical activity, alcohol intake, diabetes, and dyslipidemia.
[b] Adjusted by age, body weight, smoking, adherence to the Mediterranean diet, physical activity, alcohol intake, hypertension, and dyslipidemia.
[c] Adjusted by age body weight, smoking, adherence to the Mediterranean diet, physical activity, alcohol intake, hypertension, and diabetes.
[d] Adjusted by age body weight, smoking, adherence to the Mediterranean diet, physical activity, and alcohol intake.

prevention in an elderly population with high cardiovascular risk. Educational level was selected as an indicator of SES because it remains unchanged throughout life, influencing the adoption of lifestyles and the related health outcomes.[20] The greater proportion of women and of older participants with the lowest educational levels may be due to the particular historical situation of Spain. University access was limited until the last third of the 20th century, especially for women.[21] Higher tobacco and alcohol consumption observed at the upper educational levels in our sample is consistent with other studies in Spain, and is likely due to historical cultural patterns in this age group; these patterns are changing in younger populations.[22] The lower physical activity, less healthy dietary patterns, higher prevalence of DM and obesity, and larger number of cardiovascular risk factors observed in participants with lower educational levels also agrees with previous studies from Spain and other countries.[23–26]

Only a few studies have analyzed inequalities in preventive cardiovascular treatment depending on SES. with controversial results that vary depending on the country and population studied.[27,28] Results of the present study concur with our previous analysis of a general population aged 34 to 75 years, in which we did not observe differences related to SES in preventive treatment for CVD.[29] Reasons for such homogeneity could be that patients with CVD are more highly monitored or, as has been shown in other studies,[30] that men with lower SES received less treatment for their hypertension because they use primary care services less often than women.

Although the health of a population is not only determined by use of health services, the type of coverage may contribute to SES-related health inequalities in CVD prevention (eg, access to medical services at different levels).[9,10,31] Health care systems based on strong primary care models could be more effective in reducing inequalities for socioeconomically disadvantaged people because resources are better distributed according to population needs.[32] The day-to-day tasks of primary care include the provision of specific care for patients with chronic diseases through the implementation of systematic preventive programs. In the Spanish health care system, patients can visit their general practitioner as often as needed, and during the study period most retired people did not pay for their prescriptions (a "copayment" was implemented in July 2012). We did not find inequalities in preventive treatment based on SES in the elderly population studied, probably due to the higher utilization of primary care services by the population with lower educational levels, as reported by other studies.[33,34]

Strengths and Limitations

The design of our study does not allow causal inferences. However, its cross-sectional approach permits the assessment of whether prescription differences exist in a population at high CVD, within the frame of a universal health care model.

One strength of our study is the large sample size used and the careful conduct of all measurements using standardized protocols. A potential limitation could be the possibility that some participants used private health care services and therefore were not fully evaluated by their assigned general practitioner. However, this possibility is slight because most of the included population had a low SES. Eligible participants who declined to participate may have had a different distribution of educational level; however, while this may affect the distribution of

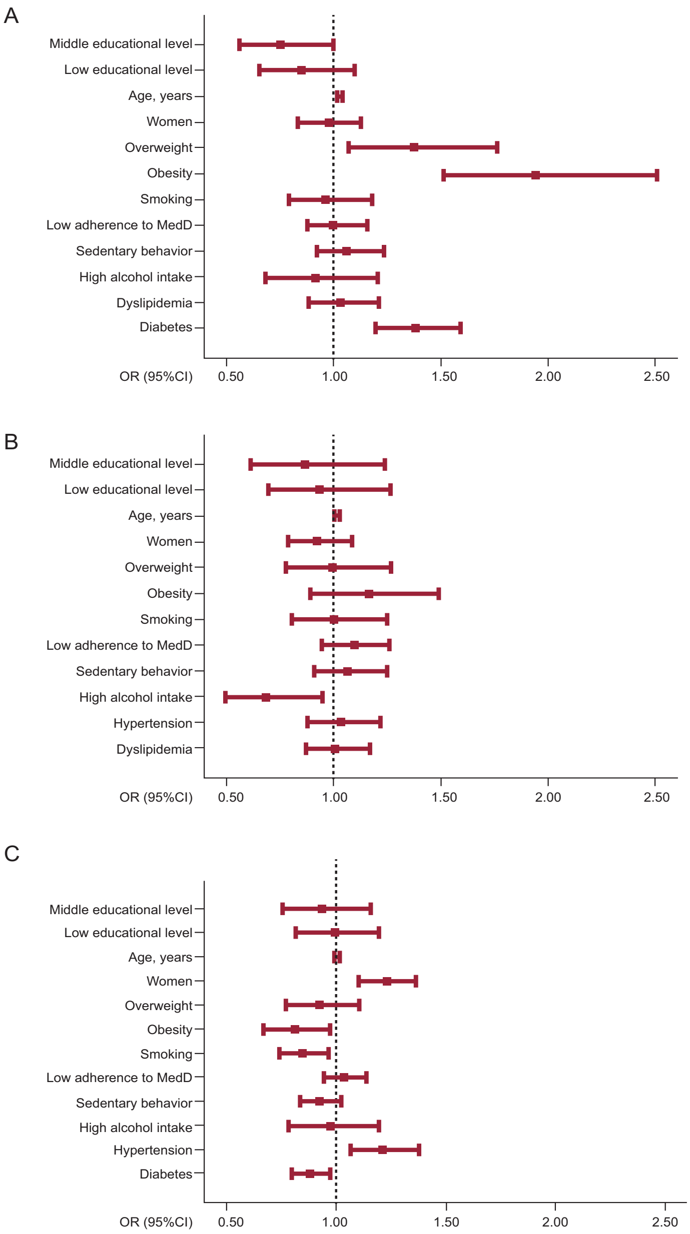


Figure. Adjusted odds ratios for all participant characteristics of receiving treatment, for each cardiovascular risk factor. A: hypertension. B: diabetes. C: dyslipidemia. Squares represent odds ratios of receiving pharmacological treatment. Horizontal lines indicate 95% confidence intervals. Vertical lines signify odds ratio=1. The following were the reference categories for the variables tested in different models: educational attainment, high level; sex, men; body weight, normal weight. Reference categories for lifestyle were non-smoking, high adherence to Mediterranean diet, physically active, and low alcohol intake, and for cardiovascular risk: no hypertension, no diabetes, and no dyslipidemia. 95%CI, 95% confidence interval; MedD, Mediterranean diet; OR, odds ratio.

participants according to educational level it should not affect the comparison between groups. On the other hand, it is important to highlight that socioeconomic conditions in Spain have changed significantly in recent years. We do not consider this factor to have influenced the measure of SES used in our study because educational level is one of the more stable social determinants during adulthood. Changes in prescription "copayment" policies have occurred in Spain because of the financial crisis, but these

Table 5
Adjusted Odds Ratio for All Participant Characteristics of Receiving Treatment, by Number of Cardiovascular Risk Factors

	Number of cardiovascular risk factors,[a] OR (95%CI)		
	One (N=105)	Two (N=233)	Three (N=955)
Educational attainment			
High level	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Middle level	0.79 (0.47-1.33)	1.02 (0.78-1.33)	0.77 (0.47-1.26)
Low level	0.70 (0.44-1.12)	1.07 (0.84-1.35)	0.80 (0.52-1.24)
Age, years	1.04 (1.02-1.06)[b]	1.02 (1.01-1.03)[b]	1.01 (0.99-1.02)
Men	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Women	0.83 (0.63-1.09)	0.94 (0.82-1.07)	1.14 (0.91-1.43)
Body weight			
Normal (BMI<25)	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Overweight (BMI 25-30)	1.13 (0.70-1.83)	0.95 (0.75-1.21)	1.06 (0.72-1.54)
Obese (BMI>30)	1.57 (0.96-2.55)	1.10 (0.87-1.40)	1.09 (0.75-1.58)
Lifestyles			
Nonsmoking	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Smoking	1.09 (0.82-1.45)	0.94 (0.78-1.12)	0.88 (0.63-1.21)
High adherence to Mediterranean diet	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Low adherence to Mediterranean diet	0.93 (0.73-1.19)	1.06 (0.94-1.19)	1.16 (0.95-1.42)
Physically active	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
Sedentary behavior	1.23 (0.94-1.61)	0.98 (0.87-1.12)	0.77 (0.62-0.95)[b]
Low alcohol intake	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
High alcohol intake	0.68 (0.44-1.07)	0.93 (0.71-1.21)	0.93 (0.56-1.55)

95%CI, 95% confidence interval; BMI, body mass index; OR: odds ratio; ref., reference.
Received corresponding pharmacological treatment considering their cardiovascular risks factors presented. Multivariate analysis including all variables into the entry mode for each number of cardiovascular risk factor presented.
[a] Presence of hypertension, and/or diabetes or/and dyslipidemia.
[b] *P*-value Wald Test <.05.

were implemented after the study had concluded. Finally, the results of our study can only be extrapolated to the elderly population at high cardiovascular risk.

CONCLUSIONS

Our study did not find that socioeconomic differences affected the treatment received for primary cardiovascular prevention in elderly patients in the context of a universal health care system based on a primary care model.

ACKNOWLEDGMENTS

We thank Stephanie Lonsdale for editing the paper in English.

FUNDING

This project has been funded by the Spanish Ministry of Health *(Instituto de Salud Carlos III, Fondo de Investigaciones Sanitarias)* projects PI051839, PI070240, PI070954, G03/140, RD06/0045 FEDER *(Fondo Europeo de Desarrollo Regional)* and CIBERobn (an initiative of *Instituto de Salud Carlos III*, Spain), and by the *Patrimonio Comunal Olivarero*, California Walnut Commission, *Borges, La Morella Nuts*, and *Hojiblanca*, which donated virgin olive oil and mixed nuts. *Agencia Canaria de Investigación, Innovación y Sociedad de la Información-EU FEDER* (PI 2007/050). None of these companies played or will play any role in the design, collection, analysis, or interpretation of the data or in the decision to submit manuscripts for publication.

CONFLICTS OF INTEREST

Dr. Estruch reports receiving lecture fees from FIVIN *(Fundación para la Investigación del Vino y Nutrición)* and serving on its scientific advisory board; receiving research grants from the *Fundación Cerveza y Salud* and serving on its scientific advisory board; and receiving lecturer fees from Sanofi-Aventis Laboratories. Dr. Salas-Salvadó reports receiving research funding from the International Nut and Dried Fruit Council, serving on its scientific advisory board, and receiving consultancy fees from Danone. Dr. Serra-Majem reports serving on the scientific advisory board of *Fundación Dieta Mediterránea* and *Fundación Cerveza y Salud.* No other co-authors have reported any potential conflict of interest relevant to this article.

REFERENCES

1. Mendis S, Puska P, Norrving B, editors. Global Atlas on cardiovascular disease prevention and control.. Geneva: World Health Organization; 2011.
2. International Society of Hypertension. Background information on high blood pressure (hypertension) [internet] [accessed 2012 Jun 20]. Available at: http://www.ish-world.com/default.aspx?BackgroundInformation
3. Unwin N, Whiting D, Guariguata L, Ghyoot G, Gan D, editors. IDF Diabetes Atlas. 5th ed. Brussels: International Diabetes Federation; 2012 [internet] [accessed 2012 Jul 3]. Available at: http://www.idf.org/diabetesatlas
4. Quantifying selected major risks to health. In: The World Health Report 2002—Reducing risks, promoting healthy life. Geneva: World Health Organization; 2002. p. 47-97.

5. Albert X, Sala J, Masiá R, Marrugat M; investigadores del REGICOR. Incidencia y pronóstico del infarto agudo del miocardio después de los 75 años en un registro poblacional. Rev Esp Cardiol. 1996;49 Suppl 3:84.
6. Centers for Disease Control and Prevention (CDC). Trends in aging-United States and worldwide. MMWR Morb Mortal Wkly Rep. 2003;52:101–6.
7. Le Reste JY, Nabbe P, Manceau B, Lygidakis C, Doerr C, Lingner H, et al. The European General Practice Research Network presents a comprehensive definition of multimorbidity in family medicine and long term care, following a systematic review of relevant literature. J Am Med Dir Assoc. 2013;14: 319–25.
8. Jackson CF, Wenger NK. Enfermedad cardiovascular en el anciano. Rev Esp Cardiol. 2011;64:697–712.
9. Starfield B, Gérvas J, Mangin D. Clinical care and health disparities. Annu Rev Public Health. 2012;33:89–106.
10. Andrulis DP. Access to care is the centerpiece in the elimination of socioeconomic disparities in health. Ann Intern Med. 1998;129:412–6.
11. González-Zobl G, Grau M, Muñoz MA, Martí R, Sanz H, Sala J, et al. Posición socioeconómica e infarto agudo de miocardio. Estudio caso-control de base poblacional. Rev Esp Cardiol. 2010;63:1045–53.
12. Stringhini S, Berkman L, Dugravot A, Ferrie JE, Marmot M, Kivimaki M, et al. Socioeconomic status, structural and functional measures of social support, and mortality: The British Whitehall II Cohort Study, 1985-2009. Am J Epidemiol. 2012;175:1275–83.
13. Munoz MA, Rohlfs I, Masuet S, Rebato C, Cabañero M, Marrugat J, et al. Analysis of inequalities in secondary prevention of coronary heart disease in a universal coverage health care system. Eur J Public Health. 2006;16:361–7.
14. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med. 2013;368:1279–90.
15. PREDIMED Study Group. Main Protocol [internet]. PREDIMED Study. [accessed 2012 June 4] Available at: www.predimed.org.
16. De la Fuente-Arrillaga C, Vázquez Z, Bes-Rastrollo M, Sampson L, Martinez-González MA. Reproducibility of a Food Frequency Questionnaire (FFQ) validated in Spain. Public Health Nutr. 2009;13:1364–72.
17. Martínez-González MA, Fernández-Jarne E, Serrano Martínez M, Wright M, Gomez-Gracia E. Development of a short dietary intake questionnaire for the quantitative estimation of adherence to a cardioprotective Mediterranean diet. Eur J ClinNutr. 2004;58:1550–2.
18. Elosua R, Marrugat J, Molina L, Pons S, Pujol E. Validation of the Minnesota Leisure Time Physical Activity Questionnaire in Spanish men. The MARATHOM Investigators Am J Epidemiol. 1994;139:1197–209.
19. Current Controlled Trials. Effects of Mediterranean diet on the primary prevention of cardiovascular disease (PREDIMED study). International Standard Randomised Controlled Trial Number Register: ISRCTN35739639 [accessed 2012 June 4]. Available at: http://www.controlled-trials.com/ISRCTN35739639.
20. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G. Indicators of socioeconomic position (part 1). J Epidemiol Community Health. 2006;60:7–12.
21. Muñoz-Repiso Izaguirre M, Muñoz-Victoria F, Baquero-Santander B, Buckhard Martínez E, Calzón-Álvarez J, García del Ordi B, et al. Informe: Las desigualdades en la educación en España. Madrid: Centro de Publicaciones del Ministerio de Educación y Ciencia (CIDE); 1992: p. 14–66.
22. Artazcoz L, Moya C, Vanaclocha H, Pont P. La salud de las personas adultas. Gac Sanit. 2004;18 Supl 1:56–68.
23. Redondo A, Subirana I, Ramos R, Solanas P, Sala J, Masiá R, et al. Tendencias en la práctica de actividad física en el tiempo libre en el periodo 1995-2005 en Girona. Rev Esp Cardiol. 2011;64:997–1004.
24. Mullie P, Clarys P, Hulens M, Vansant G. Dietary patterns and socioeconomic position. Eur J Clin Nutr. 2010;64:231–8.
25. Agardh E, Allebeck P, Hallqvist J, Moradi T, Sidorchuk A. Type 2 diabetes incidence and socio-economic position: a systematic review and meta-analysis. Int J Epidemiol. 2011;40:804–18.
26. Hoeymans N, Smit HA, Verkleij H, Kromhout D. Cardiovascular risk factors in relation to educational level in 36 000 men and women in The Netherlands. Eur Heart J. 1996;17:518–25.
27. Manderbacka K, Keskimäki I, Reunanen A, Klaukka T. Equity in the use of antithrombotic drugs, beta-blockers and statins among Finnish coronary patients. Int J Equity Health. 2008;7:16.
28. Reid FD, Cook DG, Whincup PH. Use of statins in the secondary prevention of coronary heart disease: is treatment equitable? Heart. 2002;88:15–9.
29. Redondo A, Benach J, Subirana I, Martinez JM, Muñoz MA, Masiá R, et al. Trends in the prevalence, awareness, treatment, and control of cardiovascular risk factors across educational level in the 1995-2005 period. Ann Epidemiol. 2011;21:555–63.
30. Savageu JA, McLoughlin M, Ursan A, Bai Y, Collins M, Cashman SB. Characteristics of frequent attenders at a community health center. J Am Board Fam Med. 2006;19:265–75.
31. Lalonde M. A new perspective on the health of Canadians—a working document. Otawa: Ministery of Supplay and Services of Canada; 1974.
32. Starfield B. Atención primaria, una creciente e importante colaboradora en la eficacia. La equidad y la eficiencia de los servicios de salud. Informe SESPAS 2012. Gac Sanit. 2012;Supl 26:20–6.
33. Crespo-Cebada E, Urbanos-Garrido RM. Equity and equality in the use of GP services for elderly people: the Spanish case. Health Policy. 2012;104:193–9.
34. Regidor E, Martínez D, Astasio P, Ortega P, Calle ME, Domínguez V. Asociación de los ingresos económicos con la utilización y la accesibilidad de los servicios sanitarios en España al inicio del siglo XXI. Gac Sanit. 2006;20:352–9.

Chapter 8:

Article 2: "Blood pressure values and depression in hypertensive individuals at high cardiovascular risk"

Mejia-Lancheros C, et al. Blood pressure values and depression in hypertensive individuals at high cardiovascular risk.
BMC Cardiovasc Disord. 2014, 14:109
doi: 10.1186/1471-2261-14-109.

Mejia-Lancheros et al. BMC Cardiovascular Disorders 2014, 14:109
http://www.biomedcentral.com/1471-2261/14/109

BMC Cardiovascular Disorders

RESEARCH ARTICLE Open Access

Blood pressure values and depression in hypertensive individuals at high cardiovascular risk

Cilia Mejia-Lancheros[1], Ramón Estruch[2,3,4], Miguel Angel Martínez-González[3,5], Jordi Salas-Salvadó[2,3,6], Dolores Corella[2,3,7], Enrique Gómez-Gracia[3,8], Miquel Fiol[2,9], José Manuel Santos[2,10], Montse Fitó[2,11], Fernando Arós[3,12], Lluis Serra-Majem[3,13], Xavier Pintó[3,14], Josep Basora[2,3,15], José Vicente Sorlí[2,3,7,16], Miguel-Angel Muñoz[1,17*] and for the PREDIMED Study Investigators

Abstract

Background: Hypertension and depression are both important risk factors for cardiovascular diseases. Nevertheless, the association of blood pressure on and depression has not been completely established. This study aims to analyze whether depression may influence the control of blood pressure in hypertensive individuals at high cardiovascular risk.

Methods: Cross-sectional study, embedded within the PREDIMED clinical trial, of 5954 hypertensive patients with high cardiovascular risk factor profiles. The relationship between blood pressure control and depression was analyzed. A multivariate analysis (logistic and log-linear regression), adjusting for potential confounders (socio-demographic factors, body mass index, lifestyle, diabetes, dyslipidemia, and antihypertensive treatment), was performed.

Results: Depressive patients, with and without antidepressant treatment, had better blood pressure control (OR: 1.28, CI 95%: 1.06-1.55, and OR: 1.30, CI 95%: 1.03-1.65, respectively) than non-depressive ones. Regarding blood pressure levels, systolic blood pressure values (mmHg) were found to be lower in both treated and untreated depressive patients (Log coefficient Beta: −1.59, 95% CI: −0.50 to −2.69 and Log coefficient Beta: −3.49, 95% CI: −2.10 to −4.87, respectively).

Conclusions: Among hypertensive patients at high cardiovascular risk, the control of blood pressure was better in those diagnosed with depression.

Trial registration: Unique identifier: ISRCTN35739639.

Keywords: Hypertension, Depression, Blood pressure

Background

High blood pressure is a key risk factor for cardiovascular disease (CVD) incidence [1-3]. Its prevalence is globally estimated to be around 40%, and it accounted for approximately 7.5 million deaths in 2008 [1]. The latest health statistics from the United States of America have reported a hypertension prevalence of 33% among adults, and within this population only 53% reached target levels recommended by guidelines [4]. In addition to the classical risk factors, in the last decade the impact of psychosocial determinants, such as educational level and depression, has received increasing attention [5-7]. The prevalence of depression has risen dramatically in recent years; in fact, the World Health Organization (2012) reported more than 350 million people suffering from this condition worldwide [8]. Depression has been found to coexist with CVD and its associated risk factors such as hypertension, diabetes, overweight, and unhealthy life styles (smoking and harmful alcohol consumption) [7,9,10]. Evidence supporting the relationship between depression and blood pressure (BP) is however, complex and remains controversial [11-13]. In addition, evidence addressing the relationship between depression and hypertension control in hypertensive populations with

* Correspondence: mamunoz.bcn.ics@gencat.cat
[1]Department of Paediatrics, Obstetrics, Gynaecology and Preventive Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain
[17]Catalan Institute of Health, Institut d'Investigació en Atenció Primària Jordi Gol, Sardenya 375,Entlo, 08025 Barcelona, Spain
Full list of author information is available at the end of the article

respect to the control of hypertension are scarce. The optimal control of BP is an essential key to reduce the risk level of cardiovascular diseases [3]. Since depression is an additional cardiovascular risk factor as some antidepressant medication may modify BP levels. The present study was, therefore, aimed at determining the association of depression and BP control in elderly hypertensive people at high cardiovascular risk.

Methods

Study design and participants

Cross-sectional study using baseline data of hypertensive participants at high cardiovascular risk from the PREDIMED Study (Prevention with the Mediterranean diet). All details of the PREDIMED study including enrollment, design, population, methods, and main results have been described elsewhere [14,15]. For the present work, all the hypertensive individuals (N = 5954) from the 7447 PREDIMED study participants were included. They fulfilled at least 1 of the 2 following criteria: 1) men (55–80 years old) and women (60–80 years old) with either type-2 diabetes or 2) three or more CVD risk factors (current smoking, dyslipidemia, body mass index (BMI) > =25 kg/m2, or family history of premature cardiovascular diseases). Exclusion criteria included previous history of CVD or other diseases such as food allergies, alcoholism, infection or acute inflammation, physical or mental disability, and those individuals taking part in any other clinical trial. Participants' data were collected from medical records, clinical evaluation, and face to face interviews. Validated questionnaires were administered in order to obtain data on nutritional and physical activity habits [16-18]. Blood samples for laboratory tests were also obtained. Details on collection and measurements have been published elsewhere [13,14].

Ethical considerations

All participants signed an informed consent. The project was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The PREDIMED study was approved by the Institutional Review Board of Hospital Clinic (Barcelona, Spain), and registered in the Current Controlled Trials (number: ISRCTN3573963, http://www.controlled-trials.com/ISRCTN35739639).

End points

Control of blood pressure

BP was considered well-controlled when systolic and diastolic blood pressure values (SBP, DBP) were below 140 mmHg and 90 mmHg, respectively, according to the recommendations of the European guidelines on cardiovascular disease prevention in clinical practice [18]. Both SBP and DBP were calculated based on the average of 4 measurements (two in the right arm and two in the left), taken in the primary care centers by well-trained primary care nurses. BP measures were assessed after a suitable resting period (more than 5 minutes) in a sitting position to avoid variability in the values due to patient movement/displacement. For the measurement of BP, a validated semiautomatic sphygmomanometer (Omron HEM-705CP) with an appropriately sized cuff for the arm of each participant was used. The determinations were performed at two minute intervals. The mean of the second and third measurement was recorded. When a difference > 5 mm Hg between the two determinations more than 5 mm Hg was detected the whole process was repeated.

Main independent variable

Depression

Diagnosis of depression was established at the visit of inclusion in the study, by face to face interview, and the information was further confirmed in the clinical records. Participants were asked if some doctor had previously diagnosed them from depression. In Spain, the diagnosis of depression is carried out both by psychiatrists and family doctors. Usually, diagnostic is made following the American Psychological Association clinical criteria (DSM-IV) and those of the International Classification of Diseases (ICD) related to Mental and Behavioral Disorders or other mental health scales, included in the standardized health guidelines from the Spanish Ministry of Health. Antidepressant treatment was registered according to the patients' self-reported information and consulting at the clinical records. In addition, participants were also asked whether they had taken any antidepressants in the previous month. They were finally classified as: *no diagnosis of depression* (no previous diagnosis of depression and not taking antidepressants), *untreated depression* (diagnosis of depression and not taking any antidepressants), and *treated depression* (diagnosis of depression and taking at least one of the following: selective serotonin reuptake inhibitors, non-selective monoamine reuptake inhibitors, monoamine oxidase A inhibitors, antidepressants in combination with psycholeptics, and other antidepressant agents). Participants were also asked about the time that had elapsed from since their first diagnosis of depression which was categorized as: ≤ 5 years, 6–10 years, and ≥ 11 years.

Co-variables

The following co-variables were taken into consideration: age, sex, anxiolytic or sedative treatment, comorbidity (diabetes and dyslipidemia), and antihypertensive treatment (angiotensin-converting-enzyme inhibitor (ACE inhibitors), diuretics, calcium channel blockers, angiotensin II receptor antagonists, β-blockers, α-blockers, or other antihypertensive drugs).

Potential confounding variables

Educational attainment, BMI, smoking habits, adherence to the Mediterranean diet pattern, physical activity, and alcohol intake were included in the analysis as they can be correlated with both depression and BP control.

Statistical analysis

The descriptive analysis of categorical variables was expressed as percentages and quantitative variables by mean and standard deviation (SD). Bivariate analyses included chi square tests and ANOVA F-test. A multivariate logistic model was fitted to evaluate the association and estimate Odds Ratio (OR) between depression level and length, and good BP control of blood pressure. To confirm the association observed between well-controlled BP and depression, continuous variables were adjusted by log-linear regression for potential confounders (age, sex, educational attainment, anxyolitic or sedative treatment, BMI, lifestyle, hypertension co-morbidity, and antihypertensive treatment). Those statistically significant at bivariate analysis, or which could have any clinical relationship with the final end-points, were included in the multivariate

Table 1 Main characteristics of study population by depression and depression length

	Depression levels				Time with depression diagnostic			
	No depression	Untreated depression	Treated depression[a]		≤ 5 years	6-10 years	≥ 11 years	
	(N = 5027)	(N = 569)	(N = 358)		(N = 268)	(N = 159)	(N = 500)	
Characteristics of participants	**%**	**%**	**%**	**P-value**	**%**	**%**	**P-value**	**P-value**
Age (years)[†]	67.3 (6.2)	66.9(6.0)	66.8(5.7)	0.137	66.4(6.0)	66.7(6.1)	67.1(5.8)	0.290
Sex (Women)	56.0	79.8	84.6	0.001	82.5	78.0	82.4	0.881
Educational attainment								
High level	7.6	4.9	6.4	0.003	7.1	7.5	4.0	0.280
Middle level	15.9	13.7	11.7		11.6	12.6	13.8	
Low level	76.6	81.4	81.8		81.3	79.9	82.2	
Antidepressant treatment[a]	—	—	—	—	45.9	37.7	35.0	0.004
Antianxiety or sedative treatment[b]	14.8	37.8	61.5)	0.001	45.5	48.4	47.2	0.700
Body Mass Index(Kg/m^2)[†]	30.1(3.8)	30.8(4.2)	30.5(3.6)	0.001	30.5(4.0)	30.8(3.8)	30.8(4.0)	0.521
Life styles								
Smoking[c]	38.3	24.6	23.5	0.001	22.8	24.5	24.8	0.543
Low adherence to the MeDiet pattern[d]	45.8	48.0	50.8	0.042	47.4	45.3	51.2	0.256
Sedentary[e]	35.0	44.6	50.0	0.001	47.8	45.3	46.6	0.800
High alcohol intake pattern[f]	21.7	16.2	10.3	0.001	14.6	15.1	13.2	0.567
Hypertension comorbidity								
Diabetes[g]	43.5	41.7	36.3	0.009	42.2	44.7	36.6	0.094
Dyslipidaemia[h]	73.7	76.4	83.2	0.001	81.0	73.6	79.8	0.894
Blood pressure								
Optimal control of blood pressure[i]	26.5	33.9	36.3	0.001	31.3	41.5	34.6	0.520
Systolic blood pressure(mmHg)[†]	151.1(19.0)	147.8(18.9)	150.4(18.9)	0.001	146.1(17.0)	145.8(18.7)	146.7(18.9)	0.832
Diastolic blood pressure(mmHg)[†]	83.7(10.2)	83.1(10.0)	82.6(9.4)	0.052	83.7(9.6)	83.3(10.4)	82.3(9.6)	0.143
Antihypertensive treatment[j]	80.6	85.8	87.2	0.001	85.5	85.5	86.8	0.680

[a]Taking at least one of the following drugs: Selective serotonin reuptake inhibitors, non-selective monoamine reuptake inhibitors, Monoamine oxidase A inhibitors, antidepressants in combination with psycholeptics, others antidepressant agents.
[b]Taking at least one of the following drugs: benzodiazepine derivatives, azaspirodecanedione derivatives, GABA (gamma-aminobutyric acid) analogues, natural antianxiety agents, ethanolamine derivatives, other anxiolytics, hypnotics and sedatives agents.
[c]Current smoker.
[d]Adherence to Mediterranean diet pattern < 9 points (median) on a scale of 0–14.
[e]Physical activity in leisure time < 1000 kcal/week in last year.
[f]Alcohol consumption more than 20gr. daily in men and 10 gr. daily in women.
[g]Diagnosis of diabetes.
[h]Diagnosis of dyslipidaemia.
[i]Systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg.
[j]Taking at least one of the following antihypertensive drugs: angiotensin-converting-enzyme inhibitor (ACE inhibitors), diuretics, calcium channel blockers, angiotensin II receptor antagonists, Beta-blockers, α-blockers, or other antihypertensive drugs.
[†]Mean - Standard Deviation, p - value: ANOVA F test.

Mejia-Lancheros *et al. BMC Cardiovascular Disorders* 2014, **14**:109
http://www.biomedcentral.com/1471-2261/14/109

models. An alpha level <0.05 and a confidence interval (CI) of 95% were employed for all statistical analyses. The goodness-of-fit logistic models were performed using Hosmer and Lemeshow test, and for linear model residual validation the Kolmogorov test was used.

Results

Mean age of the participants was 67.2 years (SD 6.2), 60.5% were women, and 15.6% had depression. Amongst this group 71% had had depression diagnosed more than six years ago.

Bivariate analysis

Characteristics of participants according to depression

Depressive participants were more commonly women, had low educational level, presented more obesity, and were sedentary and dyslipidemic. In contrast, members of this group were less frequently smokers and alcohol drinkers. With respect to BP, depressive participants had lower SBP and DBP values (Table 1). Participants with treated depression had a higher percentage of BP control, and a greater probability of receiving antihypertensive treatment. The percentage of patients receiving antidepressants was higher in those diagnosed more recently (less than 5 years).

Control of blood pressure

After adjusting for the main co-variables (age, sex, anti-anxiety or sedative treatment, diabetes, dyslipidemia and anti-hypertensive treatment) and potential confounding factors (educational levels, BMI, smoking, diet pattern, and physical activity) depressive participants, with or without antidepressants, more frequently presented well-controlled BP than non-depressive ones (OR: 1.28, CI95%: 1.06-1.55 and OR: 1.30, CI95%: 1.03-1.65, respectively). Participants whose depression had been previously diagnosed between six and ten years had better BP control than the more recently diagnosed ones (OR: 1.62, CI95%: 1.07-2.45) (Figure 1). When considering BP as a continuous variable, only SBP figures were significantly lower in depressive patients, whilst DBP ones were unaffected (Table 2). Women, younger participants, and lower BMI were found to be related to better SBP and DBP levels.

Discussion

In the present study we found that depressive, hypertensive participants at high cardiovascular risk had better BP values.

Although depression is considered an independent risk factor for hypertension incidence, and a number of authors have found it related to higher BP levels [19-21], its role in the control of BP values remains unclear [22]. Limited data have reported that hypertensive patients taking antidepressants have lower blood pressure levels [23]. One possible explanation for the effect of antidepressants on lowering blood pressure could be a reduction in vagal activity, decreased heart rate variability and baroreflex sensitivity [24], and neuro-endocrine pathways [25-29]. Our results concur with other studies performed in general populations [12,13,24,30]. Research analyzing a

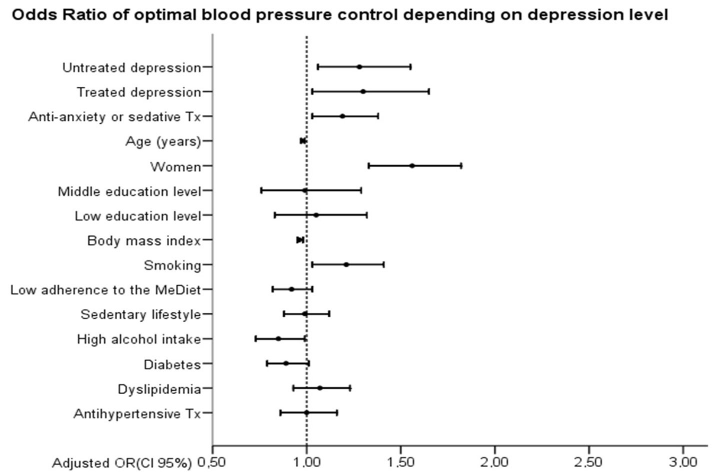


Figure 1 Odds Ratios of optimal blood pressure control according to depression level. Circles represent Odds Ratios, Horizontal lines indicate 95% confidence intervals and vertical line references OR = 1. Tx indicates treatment and MeDiet indicates the Mediterranean Diet. No depression is the reference category for the response variable.

Table 2 Log-linear model coefficients of systolic and diastolic blood pressure according to depression level and adjusted co-variables

	Natural logarithm of systolic blood pressure (mmHg)[†]				Natural logarithm of diastolic blood pressure (mmHg)[‡]			
	Coefficients[§]	Lower CI 95%[§]	Upper CI 95%[§]	P-value	Coefficients[§]	Lower CI 95%[§]	Upper CI 95%[§]	P-value
Depression level								
No Depression	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Untreated depression[a]	−1.59	−2.69	−0.50	0.004	−0.59	−1.64	0.462	0.272
Treated depression[b]	−3.49	−4.87	−2.10	0.001	−0.85	−2.18	0.49	0.213
Anti-Anxiety or sedative treatment[c]	−0.82	−1.66	0.02	0.056	−0.18	−0.99	0.62	0.657
Age (years)	0.25	0.20	0.31	0.001	−0.37	−0.42	0-.32	0.001
Sex (Women)	−2.60	−3.46	−1.75	0.001	−2.62	−3.44	−1.79	0.001
Educational attainment								
High level	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Middle level	0.96	−0.45	2.37	0.183	1.09	−0.27	2.44	0.117
Low level	0.13	−1.12	1.38	0.841	−0.42	−1.62	0.78	0.491
Body Mass Index(Kg/m^2)	0.24	0.16	0.33	0.001	0.42	0.34	0.50	0.001
Smoking[d]	−0.80	−1.65	0.05	0.064	−0.76	−1.57	0.05	0.067
Low adherence to the MeDiet pattern[e]	0.11	−0.56	0.78	0.746	−0.01	−0.65	0.64	0.989
Sedentary[f]	0.17	−0.46	0.80	0.600	−0.07	−0.68	0.54	0.816
High alcohol intake[g]	0.64	−0.17	1.45	0.122	0.72	−0.06	1.50	0.069
Diabetes[h]	1.28	0.62	1.94	0.001	−1.94	−2.57	−1.30	0.001
Dyslipidemia[i]	−0.34	−0.34	0.41	0.370	−0.60	−1.31	0.12	0.104
Antihypertensive treatment[j]	0.55	−0.26	1.37	0.182	0.46	−0.32	1.24	0.252

[a]Diagnosis of depression and not taking any antidepressant drugs.
[b]Diagnosis of depression and taking at least one of the following drugs: Selective serotonin reuptake inhibitors, non-selective monoamine reuptake inhibitors, Monoamine oxidase A inhibitors, antidepressants in combination with psycholeptics, others antidepressant agents.
[c]Taking at least one of the following drugs: benzodiazepine derivatives, azaspirodecanedione derivatives, GABA (gamma-aminobutyric acid) analogues, natural antianxiety agents, ethanolamine derivatives, other anxiolytics, hypnotics and sedatives agents.
[d]Current smoker.
[e]Adherence to Mediterranean diet pattern < 9 points (median) on a scale of 0–14.
[f]Physical activity in leisure time < 1000 kcal/week in last year.
[g]Alcohol consumption more than 20gr. daily in men and 10 gr. daily in women.
[h]Diagnosis of diabetes.
[i]Diagnosis of dyslipidaemia.
[j]Taking at least one of the following antihypertensive drugs: angiotensin-converting-enzyme inhibitor (ACE inhibitors), diuretics, calcium channel blockers, angiotensin II receptor antagonists, Beta-blockers, α-blockers, or other antihypertensive drugs.
[†]Kolmogorov-Smirnov Test (p value): 0.271.
[‡]Kolmogorov-Smirnov Test (p value): 0.56.
[§]Coefficients values multiplied by 100.

group of people with hypertension who were taking antihypertensive drugs has also shown that individuals with episodes, or symptoms of depression, tended to have lower SBP and DBP [31]. It is not clear whether depression is the cause or the consequence of differences in the control of BP values [32,33]. Confounders related to both hypertension and depression, such as physical activity, low-fat diet, non-smoking, and alcohol intake, were included in our analysis [34]. Some antidepressant, anti-anxiety, and antipsychotic agents, either alone or in combination with cardiovascular therapies including antihypertensive drugs, have been reported to induce a drop in BP [35-37]. Our participants diagnosed with depression, and those taking antidepressant treatments, received more antihypertensive drugs. Nevertheless, the association observed between depression and better blood pressure values persisted after adjusting for this variable in the multivariate analysis, which indicates that this association may be independent, as has been shown in previous studies [24,33].

It could be hypothesized, moreover, that the frequent use of health services by depressive patients could contribute to an accurate follow-up and good control of their hypertension. The Spanish Health System guarantees a free and universal access to primary healthcare services. In addition, family doctors have access to well-established chronic care protocols, which ensure the better control and follow-up of patients with co-morbidity (hypertension and depression).

Implication of our results

Our findings indicate the relevance of performing a holistic approach to the co-morbidity when tackling the care of chronic patients attended in primary care. Preventions among family physicians toward the use of antidepressants in hypertensive patients with depression should be addressed individually since many studies have shown an improvement in BP control.

Study limitations and strengths

The cross-sectional design of our study does not allow causal inferences to be drawn. Future observational research studies are needed to establish the role of psychosocial factors in the good control of cardiovascular risk factors and the prognosis of cardiovascular diseases, especially in hypertensive individuals or those at high cardiovascular risk.

For reasons of statistical power the different antidepressants were grouped together. It is possible that a larger sample could establish variations according to the antidepressant analyzed. The time elapsed from the first diagnosis of depression could not be used as a proxy for the current prevalence of depression as the only way to establish the current state of the disease is through the prescription of antidepressants, and no specific tests were conducted in the participants. We had information about the family history of cardiovascular diseases history but none concerning about family history of depression and hypertension.

Conclusion

Among hypertensive patients at high cardiovascular risk, blood pressure was better controlled in those diagnosed with depression.

Abbreviations

CVD: Cardiovascular diseases; BP: Blood pressure; BMI: Body mass index; SBP: Diastolic blood pressure; DBP: Diastolic blood pressure; SD: Standard deviation; OR: Odds ratio; CI: Confidence interval.

Competing interests

Dr. Estruch reports serving on the board of and receiving lecture fees from the Research Foundation on Wine and Nutrition (FIVIN), serving on the boards of the Beer and Health Foundation and the European Foundation for Alcohol Research (ERAB), receiving lecture fees from Cerveceros de España and Sanofi-Aventis, and receiving grant support through his institution from Novartis. Dr.Salas-Salvadó reports serving on the board of and receiving grant support through his institution from the International Nut and Dried Fruit Council, receiving consulting fees from Danone, and receiving grant support through his institution from Eroski and Nestlé. Dr. Arós reports receiving payment for the development of educational presentations from Menarini and AstraZeneca. Dr. Serra-Majem reports serving on the boards of the Mediterranean Diet Foundation and the Beer and Health Foundation. Dr. Pintó reports serving on the board of and receiving grant support through his institution from the Residual Risk Reduction Initiative (R3i) Foundation, serving on the board of Omegafort, serving on the board of and receiving payment for the development of educational presentations, as well as grant support through his institution, from Ferrer, receiving consulting fees from Abbott Laboratories, receiving lecture fees, as well as grant support through his institution, from Merck and Roche receiving lecture fees from Danone and Esteve, receiving payment for the development of educational presentations from Menarini, and receiving grant support through his institution from Sanof i-Aventis, Kowa, Unilever, Boehringer Ingelheim, and Karo Bio. No other potential conflict of interest relevant to this article was reported.

Authors' contributions

CM-L and MAM. conceived and designed the study. They also analyzed and interpreted the study data, and wrote the first draft of the manuscript. RE, MAM-G., JS.-S, DC, EG-G, M.F, JL, M.Fitó, FA, LS.-M, XP., JB, JVS, assisted in the acquisition of data and provided valuable, intellectual contributions to the manuscript draft. All authors have approval the final version submitted for publication.

Authors' information

This work has been carried out within the framework of the Predimed Study, one of the largest clinical trials ever performed to date regarding the association of a Mediterranean Intervention on cardiovascular morbi-mortality. The network consisted of more than seventeen different multidisciplinary research groups including experts on nutrition and internal medicine, cardiologists, and family physicians.
The main outcomes of the study were published last year [14].

Funding

This study was supported by the official funding agency for biomedical research of the Spanish government, Instituto de Salud Carlos III (ISCIII), through grants provided to research networks specifically developed for the trial (RTIC G03/140, RTIC RD 06/0045) and through Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y Nutrición [CIBERobn]), and by grants from Centro Nacional de Investigaciones Cardiovasculares (CNIC 06/2007), Fondo de Investigación Sanitaria–Fondo Europeo de Desarrollo Regional (PI04-2239, PI 05/2584, CP06/00100, PI07/0240, PI07/1138, PI07/0954, PI 07/0473, PI10/01407, PI10/02658, PI11/01647, and P11/02505), Ministerio de Ciencia e Innovación (AGL-200913906-C02 and AGL2010-22319-C03), Fundación Mapfre 2010, Consejería de Salud de la Junta de Andalucía (PI0105/2007), Public Health Division of the Department of Health of the Autonomous Government of Catalonia, Generalitat Valenciana (ACOMP06109, GVACOMP2010-181, GVACOMP2011-151, CS2010AP-111,CS2011-AP-042), and Regional Government of Navarra (P27/2011). None of the institutions described above have influenced the design, collection, analysis, and interpretation of data; the writing of the manuscript; and the decision to submit the manuscript for publication.

Author details

[1]Department of Paediatrics, Obstetrics, Gynaecology and Preventive Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain. [2]Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y Nutrición (CIBERobn), Instituto de Salud Carlos III, Madrid, Spain. [3]The PREDIMED Study (Prevención con Dieta Mediterránea) Network (RD 06/0045), Instituto de Salud Carlos III, Madrid, Spain. [4]The Department of Internal Medicine of Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi I Sunyer, University of Barcelona, Barcelona, Spain. [5]Preventive Medicine and Public Health, University of Navarra, Pamplona, Spain. [6]Human Nutrition Department, Hospital Universitari Sant Joan, Institut d'Investigació Sanitaria Pere Virgili, Universitat Rovira i Virgili, Reus, Spain. [7]The Department of Preventive Medicine, University of Valencia, Valencia, Spain. [8]The Department of Preventive Medicine, University of Malaga, Malaga, Spain. [9]Institute of Health Sciences (IUNICS), University of Balearic Islands, and Hospital Son Espases, Palma de Mallorca, Spain. [10]The Department of Family Medicine, Primary Care Division of Seville, San Pablo Health Center, Seville, Spain. [11]Cardiovascular Risk and Nutrition Research Group of Institut Mar d'Investigacions Mèdiques (IMIM)–Research Institute Hospital del Mar,

Barcelona, Spain. [12]The Department of Cardiology, University Hospital of Alava, Vitoria, Spain. [13]The Department of Clinical Sciences, University of Las Palmas de Gran Canaria, Las Palmas, Spain. [14]Lipids and Vascular Risk Unit, Internal Medicine, Hospital Universitario de Bellvitge, Hospitalet de Llobregat, Barcelona, Spain. [15]Primary Care Division, Catalan Institute of Health, Institut d'Investigació en Atenció Primària Jordi Gol, Tarragona-Reus, Spain. [16]Primary Care Division, Valencia Institute of Health, Valencia, Spain. [17]Catalan Institute of Health, Institut d'Investigació en Atenció Primària Jordi Gol, Sardenya 375, Entlo, 08025 Barcelona, Spain.

Received: 9 April 2014 Accepted: 20 August 2014
Published: 26 August 2014

References

1. Global Health Observatory (GHO), World Health Organization: **Raised blood pressure: Situation and trends.** [http://www.who.int/gho/ncd/risk_factors/blood_pressure_prevalence_text/en/]
2. Institute for Health Metrics and Evaluation: **The Global Burden of Disease: Generating Evidence, Guiding Policy.** Seattle: WA, IHM; 2013.
3. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren WM, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvänne M, Scholte Op Reimer WJ, Vrints C, Wood D, Zamorano JL, Zannad F, Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice; European Association for Cardiovascular Prevention and Rehabilitation: **European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts).** *Eur Heart J* 2012, **33:**1635–1701.
4. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, Bravata DM, Dai S, Ford ES, Fox CS, Franco S, Fullerton HJ, Gillespie C, Hailpern SM, Heit JA, Howard VJ, Huffman MD, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Magid D, Marcus GM, Marelli A, Matchar DB, McGuire DK, Mohler ER, Moy CS, Mussolino ME, *et al*: **Heart disease and stroke statistics-2013 update: a report from the American Heart Association.** *Circulation* 2013, **127:**e6–e245.
5. Hemingway H, Marmot M: **Evidence based cardiology: psychosocial factors in the aetiology and prognosis of coronary heart disease. Systematic review of prospective cohort studies.** *BMJ* 1999, **318:**1460–1467.
6. Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L: **The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology.** *J Am Coll Cardiol* 2005, **45:**637–651.
7. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L, INTERHEART Study Investigators: **Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case–control study.** *Lancet* 2004, **364:**937–952.
8. World Health Organization: **Depression.** *Fact sheet N 369*. [http://www.who.int/mediacentre/factsheets/fs369/en/]
9. Rutledge T, Hogan BE: **A quantitative review of prospective evidence linking psychological factors with hypertension development.** *Psychosom Med* 2002, **64:**758–766.
10. Elderon L, Whooley MA: **Depression and cardiovascular disease.** *Prog Cardiovasc Dis* 2013, **55:**511–523.
11. Scalco AZ, Scalco MZ, Azul JB, Lotufo NF: **Hypertension and depression.** *Clinics (Sao Paulo)* 2005, **60:**241–250.
12. Delaney JA, Oddson BE, Kramer H, Shea S, Psaty BM, McClelland RL: **Baseline depressive symptoms are not associated with clinically important levels of incident hypertension during two years of follow-up: the multi-ethnic study of atherosclerosis.** *Hypertension* 2010, **55:**408–414.
13. Licht CM, de Geus EJ, Seldenrijk A, van Hout HP, Zitman FG, van Dyck R, Penninx BW: **Depression is associated with decreased blood pressure, but antidepressant use increases the risk for hypertension.** *Hypertension* 2009, **53:**631–638.
14. Martínez-González MÁ, Corella D, Salas-Salvadó J, Ros E, Covas MI, Fiol M, Wärnberg J, Arós F, Ruíz-Gutiérrez V, Lamuela-Raventós RM, Lapetra J, Muñoz MÁ, Martínez JA, Sáez G, Serra-Majem L, Pintó X, Mitjavila MT, Tur JA, Portillo MP, Estruch R, PREDIMED Study Investigators: **Cohort profile: design and methods of the PREDIMED study.** *Int J Epidemiol* 2012, **41:**377–385.
15. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí JV, Martínez JA, Martínez-González MA, PREDIMED Study Investigators: **Primary prevention of cardiovascular disease with a Mediterranean diet.** *N Engl J Med* 2013, **368:**1279–1290.
16. Martinez-Gonzalez MA, Fernandez-Jarne E, Serrano-Martinez M, Wright M, Gomez-Gracia E: **Development of a short dietary intake questionnaire for the quantitative estimation of adherence to a cardioprotective Mediterranean diet.** *Eur J Clin Nutr* 2004, **58:**1550–1552.
17. Elosua R, Marrugat J, Molina L, Pons S, Pujol E: **Validation of the Minnesota Leisure Time Physical Activity Questionnaire in Spanish men. The MARATHOM Investigators.** *Am J Epidemiol* 1994, **139:**1197–1209.
18. Elosua R, Garcia M, Aguilar A, Molina L, Covas MI, Marrugat J: **Validation of the Minnesota Leisure Time Physical Activity Questionnaire In Spanish Women. Investigators of the MARATDON Group.** *Med Sci Sports Exerc* 2000, **32:**1431–1437.
19. Shinagawa M, Otsuka K, Murakami S, Kubo Y, Cornelissen G, Matsubayashi K, Yano S, Mitsutake G, Yasaka K, Halberg F: **Seven-day (24-h) ambulatory blood pressure monitoring, self-reported depression and quality of life scores.** *Blood Press Monit* 2002, **7:**69–76.
20. Nabi H, Chastang JF, Lefèvre T, Dugravot A, Melchior M, Marmot MG, Shipley MJ, Kivimäki M, Singh-Manoux A: **Trajectories of depressive episodes and hypertension over 24 years: the Whitehall II prospective cohort study.** *Hypertension* 2011, **57:**710–716.
21. Kabir AA, Whelton PK, Khan MM, Gustat J, Chen W: **Association of symptoms of depression and obesity with hypertension: the Bogalusa Heart Study.** *Am J Hypertens* 2006, **19:**639–645.
22. Meng L, Chen D, Yang Y, Zheng Y, Hui R: **Depression increases the risk of hypertension incidence: a meta-analysis of prospective cohort studies.** *J Hypertens* 2012, **30:**842–851.
23. Dawood T, Lambert EA, Barton DA, Laude D, Elghozi JL, Esler MD, Haikerwal D, Kaye DM, Hotchkin EJ, Lambert GW: **Specific serotonin reuptake inhibition in major depressive disorder adversely affects novel markers of cardiac risk.** *Hypertens Res* 2007, **30:**285–293.
24. Kim BS, Bae JN, Cho MJ: **Depressive symptoms in elderly adults with hypotension: different associations with positive and negative affect.** *J Affect Disord* 2010, **127:**359–364.
25. Joynt KE, Whellan DJ, O'Connor CM: **Depression and cardiovascular disease: mechanisms of interaction.** *Biol Psychiatry* 2003, **54:**248–261.
26. Huffman JC, Celano CM, Beach SR, Motiwala SR, Januzzi JL: **Depression and cardiac disease: epidemiology, mechanisms, and diagnosis.** *Cardiovasc Psychiatry Neurol* 2013, **2013:**695925.
27. Pozuelo L, Tesar G, Zhang J, Penn M, Franco K, Jiang W: **Depression and heart disease: what do we know, and where are we headed?** *Cleve Clin J Med* 2009, **76:**59–70.
28. Grippo AJ, Johnson AK: **Stress, depression and cardiovascular dysregulation: a review of neurobiological mechanisms and the integration of research from preclinical disease models.** *Stress* 2009, **12:**1–21.
29. Perlmuter LC, Sarda G, Casavant V, O'Hara K, Hindes M, Knott PT, Mosnaim AD: **A review of orthostatic blood pressure regulation and its association with mood and cognition.** *Clin Auton Res* 2012, **22:**99.
30. Hildrum B, Ulla R, Holmen J: **Anxiety and depression lower blood pressure: 22-year follow–up of the population based HUNT study. Norway.** *BMC Public Health* 2011, **11:**601.
31. Lenoir H, Lacombe JM, Dufouil C, Ducimetière P, Hanon O, Ritchie K, Dartigues JF, Alpérovitch A, Tzourio C: **Relationship between blood pressure and depression in the elderly. The Three-City Study.** *J Hypertens* 2008, **26:**1765–1772.
32. Stroup-Benham CA, Markides KS, Black SA, Goodwin JS: **Relationship between low blood pressure and depressive symptomatology in older people.** *J Am Geriatr Soc* 2000, **48:**250–255.
33. Barrett-Connor E, Palinkas LA: **Low blood pressure and depression in older men: a population based study.** *BMJ* 1994, **308:**446–449.
34. Dickey RA, Janick JJ: **Lifestyle modifications in the prevention and treatment of hypertension.** *Endocr Pract* 2001, **7:**392–399.

35. Januzzi JL Jr, Stern TA, Pasternak RC, DeSanctis RW: **The influence of anxiety and depression on outcomes of patients with coronary artery disease.** *Arch Intern Med* 2000, **160:**1913–1921.
36. Hill KD, Wee R: **Psychotropic drug-induced falls in older people: a review of interventions aimed at reducing the problem.** *Drugs Aging* 2012, **29:**15–30.
37. Tyberghein M, Philips JC, Krzesinski JM, Scheen AJ: **Orthostatic hypotension: definition, symptoms, assessment and pathophysiology.** *Rev Med Liege* 2013, **68:**65–73.

doi:10.1186/1471-2261-14-109
Cite this article as: Mejia-Lancheros *et al.*: **Blood pressure values and depression in hypertensive individuals at high cardiovascular risk.** *BMC Cardiovascular Disorders* 2014 **14**:109.

Chapter 9:

Article 3: "Impact of psychosocial factors on cardiovascular morbimortality: A prospective cohort study."

Mejia-Lancheros C, et al. Impact of psychosocial factors on cardiovascular morbimortality: A prospective cohort study.
BMC Cardiovasc Disord 2014, 14:135
doi: 10.1186/1471-2261-14-135

Mejía-Lancheros *et al. BMC Cardiovascular Disorders* 2014, **14**:135
http://www.biomedcentral.com/1471-2261/14/135

BMC Cardiovascular Disorders

RESEARCH ARTICLE Open Access

Impact of psychosocial factors on cardiovascular morbimortality: a prospective cohort study

Cília Mejía-Lancheros[1], Ramón Estruch[2,3,4], Miguel-Angel Martínez-González[3,5], Jordi Salas-Salvadó[2,3,6], Olga Castañer[2,7], Dolores Corella[2,3,8], Fernando Arós[3,9], Enrique Gómez-Gracia[3,10], Miquel Fiol[2,11], José Lapetra[2,12], Lluís Serra-Majem[3,13], Xavier Pintó[3,14], Emilio Ros[2,15], Javier Díez-Espino[16], Josep Basora[2,3,17], José-V Sorlí[2,3,8,18], Rosa-Maria Lamuela-Raventos[2,3,19], Valentina Ruiz-Gutiérrez[2,3,20], and Miguel-Ángel Muñoz[1,21,22*] on behalf of the PREDIMED Study Investigators

Abstract

Background: Whilst it is well known that psychosocial determinants may contribute to cardiovascular diseases (CVD), data from specific groups are scarce. The present study aims to determine the contribution of psychosocial determinants in increasing the risk of cardiovascular events (myocardial infarction and stroke), and death from CVD, in a high risk adult population.

Methods: Longitudinal prospective study of 7263 patients (57.5% women), mean age 67.0 (SD 6.2) free from CVD but at high risk, with a median follow-up of 4.8 years (from October 2003 to December 2010). The Hazard Ratios (HRs) of cardiovascular events (myocardial infarction, stroke, and death from cardiovascular causes) related to educational attainment, diagnosed depression (based on medical records), and low social support (number of people living in the household) were estimated by multivariate Cox regression models.

Results: Stroke incidence was associated with low educational level in the whole population (HR: 1.83, 95% CI: 1.09–3.09), and especially in men (HR: 2.11, 95% CI 1.09–4.06). Myocardial infarction and CVD mortality were not associated with any of the psychosocial factors considered.

Conclusion: Adults with low educational level had a higher risk of stroke. Depression and low social support were not associated with CVD incidence.

Trial registration: Clinical trial registration information unique identifier: ISRCTN35739639.

Keywords: Stroke, Acute myocardial infarction, Cardiovascular death, Educational level, Socioeconomic position, Depression, Social support, Health inequalities

Background

Cardiovascular disease (CVD) remains the leading cause of mortality worldwide, and in most developed countries is the major origin of disability among elderly people. In 2008, heart attacks and strokes were responsible for 7.3 and 6.2 million deaths, respectively [1]. Its incidence has been strongly related with classic risk factors (hypertension, dyslipidemia, and type 2 diabetes), and poor lifestyles (smoking, physical inactivity, and unhealthy diet) [2,3]. In recent decades, inadequate psychosocial and living conditions have also been found to be linked to CVD [4,5]. Individual conditions such as low socioeconomic status, weak social support, depression, and residing in disadvantaged neighborhoods may contribute to socioeconomic inequalities in cardiovascular health [4-9]. Their roles, however, are not yet entirely clear [8,9] and, in some contexts, not taken into consideration. In Spain, where socioeconomic health disparity is not as pronounced as in some other European countries [10], and CVD incidence is one of the lowest in the world [1,11,12], there are few studies which have evaluated the effect of psycho-social factors [13].

* Correspondence: mamunoz.bcn.ics@gencat.cat
[1]Department of Paediatrics, Obstetrics, Gynaecology and Preventive Medicine, Universitat Autònoma de Barcelona, Bellaterra, Spain
[21]Institut Català de la Salut, Barcelona, Spain
Full list of author information is available at the end of the article

Study aims

The present study aimed at determining whether adverse psychosocial conditions such as lower educational level, depression, and weak social support contribute to increasing the risk of cardiovascular events (myocardial infarction and stroke) and death from CVD in an adult population at high cardiovascular risk.

Methods

Study design and population

This is a longitudinal, prospective study embedded within the PREDIMED Study (Prevention with Mediterranean diet) carried out from October 2003 to December 2010, in Spain. Details of PREDIMED study enrollment, design, population, methods, and main results have been described elsewhere [14]. For the purpose of this article, we analyzed 7263 participants (women and men) aged 55–80 years old, at high cardiovascular risk, but free from cardiovascular disease at baseline (97.5% of PREDIMED participants), with complete, available data concerning psychosocial risk factors.

Inclusion criteria

participants had to have at least one of the following two conditions: a) Medical diagnosis of type 2 diabetes or receiving insulin or oral hypoglycemic drugs; or having fasting glucose >126 mg/dl or presented casual glucose >200 mg/dl with polyuria, polydipsia, or unexplained weight loss; or glucose > 200 mg/dl in two measurements after an oral glucose tolerance test. b) At least three of the following risk factors: smoking (>1 cig/day during the last month); hypertension (systolic blood pressure > =140 mm Hg or diastolic blood pressure > =90 mmHg or under antihypertensive medication); elevated low-density lipoprotein cholesterol levels (> = 160 mg/dl); low high-density lipoprotein cholesterol levels (<= 40 mg/dl); overweight (body mass index > = 25 kg/m^2); or a family history of premature coronary heart disease (CHD) (definite myocardial infarction or sudden death before 55 years in father or male 1st-degree relative, or before 65 years in mother or female 1st-degree relative). If the HDL-cholesterol level was > =60 mg/dL, one risk factor was subtracted.

Exclusion criteria

Participants with any of the following were excluded: documented history of previous cardiovascular disease or severe medical conditions (digestive disease with fat intolerance, advanced malignancy, major neurological, psychiatric or endocrine disease); immunodeficiency; illegal drug use; problematic alcohol intake (chronic alcoholism or total daily alcohol intake >80 g/d); body mass index > 40 kg/m^2; difficulties or major inconvenience to change dietary habits; impossibility of following a Mediterranean-type diet or understanding the recommendations of the protocol; and lack of autonomy.

Data were collected from medical records, clinical evaluations, and face to face interviews. Validated questionnaires were administered in order to obtain information on nutritional habits [15,16]. Blood samples for laboratory tests were gathered. All participants gave written informed consent. The study was approved by the Institutional Review Board of Hospital Clinic (Barcelona, Spain), and registered in the Current Controlled Trials (number: ISRCTN35739639, http://www.controlled-trials.com/ISRCTN35739639).

Study variables

Psychosocial conditions

Educational level: Educational level was used as a proxy of socioeconomic position (SP) since it is considered a strong determinant of social status that may condition employment and income opportunities [17]. For the purpose of the study, educational attainment in the bivariate analysis was classified into three groups: high education (secondary or university studies), primary education (completed primary school), and less than primary education. In the multivariate analysis, educational level was divided into two groups: high education (secondary or university studies) and low education (up to primary school).

Social support: Social support in the household was considered to be low when participants were living alone. Living alone has been reported as a valid proxy to evaluate social support, and has been found to be an independent social risk factor for adverse cardiovascular event outcome [18].

Depression: Information regarding history of diagnosis of depression was self-reported by participants during a face to face interview at the inclusion visit and further confirmed in clinical records. In Spain, the diagnosis of depression is carried out by both psychiatrists and GPs following the American Psychological Association clinical criteria (DSM-IV) or other mental health scales (e.g. the Beck Depression Inventory).

Other co-variables: socio-demographic variables: Age (years) and gender. Smoking status: Never smoked, former smoker, and current smoker. Alcohol intake: High alcohol consumption (Alcohol consumption more than 20 gr. daily in men and 10 gr. daily in women). Body mass index (BMI): Expressed as weight in kilograms divided by height in meters squared (Kg/m^2). Cardiovascular risk factors: Hypertension (Medical diagnosis of hypertension or receiving at least one of the following antihypertensive drugs: angiotensin-converting-enzyme inhibitor (ACE inhibitors), diuretics, calcium channel blockers, angiotensin II receptor antagonists, ß-blockers, α-blockers, or other antihypertensive drugs); Diabetes (medical diagnosis of Type 2 diabetes or receiving insulin and/or oral hypoglycemic drugs); Dyslipidemia (medical diagnosis of dyslipidemia or receiving lipid lowering therapy); Family history of premature coronary heart disease (CHD). Mediterranean dietary intervention: (i) Low fat Mediterranean diet (control diet): dietary recommendation which highlighted the consumption of lean meats, low-fat dairy products, cereals, potatoes, pasta, rice, fruit and vegetables. The use of olive oil for cooking and dressing and consumption of nuts, fatty meats, sausages, and fatty fish were discouraged. (ii) Mediterranean diet enriched with extra-virgin olive oil (EVOO): positive dietary recommendation about the Mediterranean diet pattern emphasizing the abundant use of olive oil for cooking and dressing dishes. One liter per week of EVOO was supplied to the participants in this group. (iii) Mediterranean diet enriched with mixed nuts: positive dietary recommendation about the Mediterranean diet pattern with the addition of nuts. Participants received 30 g of mixed nuts per day (15 g of walnuts, 7.5 g of almonds and 7.5 g hazelnuts).

The PREDIMED study dietitians supervised the dietary intervention. Further details about PREDIMED study dietary intervention has been previously published [14].

End points

Composite primary cardiovascular event

The primary end point was a composite variable made up of the first occurrence of cardiovascular death, or myocardial infarction, or stroke (combining ischemic and hemorrhagic). Diagnostic criteria are available in a supplementary appendix of a previously published article [14].

The three cardiovascular events were also considered separately in the analysis in order to individually ascertain the impact of psychosocial factors.

Cardiovascular events were reviewed and confirmed by an Adjudication Committee of the PREDIMED Study consisting of a team of cardiologists, endocrinologists, neurologists, and ophthalmologists. Members of the committee were blinded to the intervention and dietary habits of the participants; for an event to be accepted a consensus was required. Events that had occurred between October 1st, 2003 and December 1st, 2010 were analyzed. Transient Ischemic Attack was not considered as a stroke. All end points were ascertained by regular contacts with participants and/or families, annual revisions of medical records, data from GPs, and consultation of the National Death Index (Spain).

Statistical analyses

Bivariate analysis was performed using chi-square test for analyzing differences among proportions, and t-student or one-way ANOVA for differences among means. Crude Rate/1000 person-year (95% confidence interval: CI) of cardiovascular events was calculated. Crude and adjusted Hazard ratios (HR) with 95% CI were performed by Cox regression models for the analysis of time-dependent cardiovascular events in relation to psychosocial factors. Multivariate Cox models were adjusted for age, gender, smoking, alcohol consumption, BMI hypertension, type 2 diabetes, dyslipidemia, family history of premature CVD at baseline, and the randomized arm of the Mediterranean dietary intervention during the trial. To assess whether cardiovascular events could be predicted by unfavorable psychosocial factors related to gender, all multivariate adjusted analysis were stratified by sex. The proportional HR assumption from the multivariate Cox models was validated with time-varying tests (Schoenfeld residuals approach) [19]. The global test p-values were ≥ 0.05.

Participants were considered censored when no event was registered during the study or data had been lost during follow-up. Censoring was assumed to be independent of the main study variables and non-informative. The resulting bias was, however, minimized by our close participant follow-up.

On the other hand our study was right censoring because some events had not occurred when the study ended.

Individuals lacking information concerning their psychosocial risk factors were not included. As this represented an insubstantial percentage (2.5%), their exclusion was not expected to greatly affect the internal and external validity of the observed results.

Results

Main baseline characteristics of study participants

The mean age of participants was 67.0 years (SD 6.2), and 57.5% were women. Regarding psychosocial factors, 74.8% of the participants had only attained primary education and 2.5% had less than primary school, 18.0% had a previous diagnostic of depression, and 10.0% weak social support (living alone in the household). With respect to cardiovascular risk factors, 14.0% (n = 1020) of the participants were currently smokers, 91.1% (n = 6620) had hypertension, 72.1% (n = 5238) diabetes, 77.8% (n = 5648) dyslipidemia, and 22.2% (n = 1615) reported family history of coronary heart disease.

Characteristics of the population regarding psychosocial factors

Participants with primary and less than primary education were more frequently older, women, and overweight. They had low social support and a higher percentage of type 2 diabetes and depression. In contrast, they consumed less alcohol and were less frequently smokers. Participants with weak social support were more commonly older, women, with dyslipidemia, depression and low education, but they were less frequently smokers. Depression was associated with women, overweight, dyslipidemia, family history of coronary heart disease, weak social support, and a low educational level, however, they consumed less alcohol and tobacco (Table 1).

Mejía-Lancheros *et al. BMC Cardiovascular Disorders* 2014, **14**:135
http://www.biomedcentral.com/1471-2261/14/135

Table 1 Characteristics of participants according to psychosocial factors at baseline

	Education level				Social support in the household			Diagnosis of depression		
	High education* (N = 1646)	Primary education (N = 5433)	Less than primary education (N = 184)		Live with other (N = 6535)	Live alone (N = 728)		None (N = 5954)	Yes (N = 1309)	
	(%)	(%)	(%)	p-value	(%)	(%)	p-value	(%)	(%)	p-value
Age (mean; SD†)	64.6 (6.2)	67.7 (6.1)	69.4 (5.0)	<0.001	66.6 (6.1)	70.1 (6.2)	<0.001	67.0 (6.3)	66.8 (6.0)	0.217
Sex (Women)	37.4	62.6	89.7	<0.001	54.8	82.1	<0.001	52.7	79.8	0.001
Type of Mediterranean diet										
Low fat diet	29.0	34.0	26.1	0.453	32.4	34.9	0.130	32.2	34.4	0.096
With extra-Virgin Olive oil	33.8	34.2	42.4		34.7	31.0		34.2	35.1	
With mixed nuts	37.2	31.8	31.0		32.9	34.1		33.6	30.6	
High alcohol consumption‡	30.0	18.8	8.2	<0.001	21.5	17.1	0.007	22.5	14.6	<0.001
Smoking status										
Never smoked	41.4	66.5	84.8	<0.001	59.9	73.9	<0.001	58.4	74.5	<0.001
Former smoker	36.9	21.5	9.2		25.5	17.0		27.1	13.5	
Current-smoker	21.7	12.0	6.8		14.6	9.1		14.5	12.0	
Body-mass index (Kg/m²)	29.3 (3.7)	30.1 (3.8)	30.7 (4.1)	<0.001	30.0 (3.8)	30.0 (4.2)	0.743	29.9 (3.8)	30.5 (4.0)	<0.001
Cardiovascular risk factors§										
Hypertension	90.5	91.2	94.6	0.159	91.0	92.6	0.151	91.1	91.4	0.756
Type 2 diabetes	67.7	73.2	81.0	<0.001	72.1	72.1	0.998	72.1	72.3	0.840
Dyslipidemia	77.5	77.8	79.9	0.764	77.4	81.2	0.019	77.2	80.5	0.008
Family history of premature CHD¶	23.7	21.9	20.1	0.231	22.4	21.0	0.404	21.6	25.1	0.007
Living alone	8.3	10.5	12.5	0.022	——	——————	—————	9.0	14.7	<0.001
Diagnostic of depression	15.2	18.6	27.7	<0.001	17.1	26.5	<0.001	—————	————	——
Educational level										
High education*	—	———	——		23.1	18.8	0.022	23.4	19.1	<0.001
Primary education	—	———	——		74.4	78.0		74.3	77.0	
Less than primary education	—	———	——		2.5	3.2		2.2	3.9	

*High education means university studies or secondary school.
†Standard deviation.
‡Alcohol consumption presented 68 missing values in its denominator. Standard deviation.
§Hypertension (Medical diagnosis of hypertension or taking antihypertensive treatment), Type 2 diabetes (Medical diagnosis of diabetes or taking antidiabetic treatment) and Dyslipidemia (Medical diagnosis of dyslipidemia or taking lowering-lipid therapy).
¶CHD denotes coronary heart disease.

The median participant follow-up was 4.8 years (interquartile range 2.8 to 5.8). In our sample 280 CVD events occurred. Participants with a high educational level had 56 events (7.9 per 1000 person-year) versus 224 (9.2 per 1000 person-year) in those with a low educational one. Participants with higher social support had 257 CVD events (9.1 per 1000 person-year) versus 23 (7.5 per 1000 person-year) in those living alone. A total of 248 (9.6 per 1000 person-year) CVD events occurred in people without depression versus 32 (5.7 per

Mejía-Lancheros et al. BMC Cardiovascular Disorders 2014, 14:135
http://www.biomedcentral.com/1471-2261/14/135

Table 2 Incidence and adjusted hazard ratios for cardiovascular events according to psychosocial factors

	Educational level*		Social support in the household		Diagnosis of depression	
	High education (N = 1646)	Low education (N = 5617)	Live with other (N = 6535)	Live alone (N = 728)	No (N = 5954)	Yes (N = 1309)
Person-year of follow-up	7069,0	24280,89	28287,36	3062,56	25751,12	5598,79
Composite primary cardiovascular event						
Number of events	56	224	257	23	248	32
Crude Rate/1000 person-year (95% CI)	7.9 (5.8–10.0)	9.2 (8.0–10.4)	9.1 (8.0–10.2)	7.5 (4.4–10.6)	9.6 (8.4–10.8)	5.7 (3.7–7.7)
Adjusted Hazard Ratio (95% CI)†‡	1.00 (ref)	1.16 (0.85–1.57)	1.00 (ref)	0.85 (0.54–1.32)	1.00 (ref)	0.76 (0.52–1.11)
p-value		0.351		0.458		0.155
Myocardial Infarction						
Number of events	24	79	95	8	90	13
Crude Rate/1000 person-year (95% CI)	3.4 (2.0–4.8)	3.3 (2.5–4.0)	3.4 (2.7–4.0)	2.6 (0.8–4.4)	3.5 (2.8–4.2)	2.3 (1.1–3.6)
Adjusted Hazard Ratio (95% CI)†‡	1.00 (ref)	1.10 (0.69–1.78)	1.00 (ref)	1.01 (0.48–2.12)	1.00 (ref)	0.89 (0.49–1.62)
p-value		0.686		0.980		0.699
Stroke						
Number of events	17	119	127	9	121	15
Crude Rate/1000 person-year (95% CI)	2.4 (1.3–3.5)	4.9 (4.0–5.8)	4.5 (3.7–5.3)	2.9 (1.0–4.9)	4.7 (3.9–5.5)	2.7 (1.3–4.0)
Adjusted Hazard Ratio (95% CI)†‡	1.00 (ref)	1.83 (1.09–3.09)	1.00 (ref)	0.56 (0.28–1.12)	1.00 (ref)	0.66 (0.38–1.15)
p-value		0.023		0.102		0.145
Cardiovascular Death						
Number of events	25	58	73	10	73	10
Crude Rate/1000 person-year (95% CI)	3.5 (2.2–4.9)	2.4 (1.8–3.0)	2.6 (2.0–3.2)	3.3 (1.2–5.3)	2.8 (2.2–3.5)	1.8 (0.7–2.9)
Adjusted Hazard Ratio (95% CI)†‡	1.00 (ref)	0.63 (0.38–1.03)	1.00 (ref)	1.21 (0.60–2.46)	1.00 (ref)	0.93 (0.47–1.84)
p-value		0.064		0.598		0.832

*High education means university studies or secondary school; Low education: up to primary studies.
†Multivariable models were adjusted by: age, gender, smoking, alcohol consumption, body-mass index, hypertension, type 2 diabetes, dyslipidemia and family history of premature coronary heart disease, and type Mediterranean diet intervention.
‡Test of proportional-hazard assumption (p-value based on the scaled Schoenfeld residuals): Composite primary cardiovascular event model (specific p-value for Educational level: 0.529, Social support: 0.765 and Depression: 0.877); Myocardial infarction model (0.611, 0.717 and 0.914); Stroke model (p-values = 0.204, 0.598 and 0.411); Cardiovascular death model (p-values = 0.810, 0.831 and 0.129).

1000 person-year) in those with depression (Table 2). Low educational level was associated with an increased risk of stroke (adjusted Hazard Ratio (HR): 1.83, 95% CI: 1.09–3.09) (Table 2, Figure 1). The risk of stroke was higher in men (Adjusted HR: 2.11, 95% CI: 1.09–4.06) than in women (adjusted HR: 1.46, 95% CI: 0.62–3.43) (Table 3).

A Mediterranean diet with EVOO or nuts showed a protective combined cardiovascular effect. Current and former smokers had a higher risk of suffering cardiovascular events. Hypertensive individuals tended to have a greater risk of experiencing a cardiovascular event. Diabetics presented more risk of stroke (statistical significance at the limit point: p-value: 0.052). No higher risk for participants with dyslipidemia and family history of premature CHD was found (Table 4).

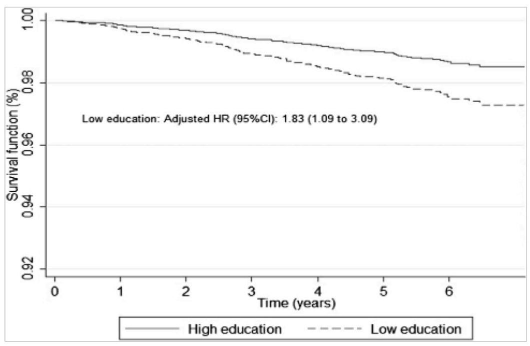


Figure 1 Survival function of stroke adjusted according education level based on Cox proportional hazard model. The Cox model was adjusted by Sex, age, smoking, alcohol consumption, body mass index, hypertension, type 2 diabetes, dyslipidemia, family history of premature cardiovascular disease, and type of Mediterranean diet intervention. High education means university education or secondary school, and low education denotes primary education.

Discussion

In our study it was observed that an adult population at high cardiovascular risk, with low education level, had an increased risk of stroke.

Mejía-Lancheros et al. BMC Cardiovascular Disorders 2014, 14:135
http://www.biomedcentral.com/1471-2261/14/135

Table 3 Adjusted hazard ratios for cardiovascular events according to psychosocial factors stratified by gender

	Composite primary cardiovascular event		Myocardial infarction		Stroke		Cardiovascular death	
	Adjusted HR (95% CI)†‡	p-value	Adjusted HR (95% CI)†‡	p-value	Adjusted HR (95% CI)†‡	p-value	Adjusted HR (95% CI)†‡	p-value
Men								
Educational level*								
High education	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Low education	1.25 (0.87–1.80)	0.223	1.34 (0.76–2.35)	0.308	2.11 (1.09–4.06)	0.026	0.65 (0.36–1.16)	0.148
Social support in the household								
Live with others	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Live alone	0.74 (0.30–1.61)	0.512	0.74 (0.18–3.05)	0.682	0.33 (0.46–2.39)	0.272	1.53 (0.47–4.98)	0.477
Diagnosis of Depression								
No	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Yes	0.76 (0.40–1.46)	0.414	0.50 (0.16–1.60)	0.241	0.56 (0.17–1.79)	0.327	1.42 (0.56–3.62)	0.460
Women								
Educational level*								
High education	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Low education	0.97 (0.56–1.70)	0.922	0.63 (0.27–1.50)	0.295	1.46 (0.62–3.43)	0.383	0.56 (0.22–1.39)	0.211
Social support in the household								
Live with others	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Live alone	0.81 (0.48–1.37)	0.437	1.12 (0.45–2.79)	0.810	0.54 (0.25–1.16)	0.114	1.04 (0.43–2.54)	0.926
Diagnosis of Depression								
No	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Yes	0.76 (0.48–1.22)	0.256	1.19 (0.57–2.48)	0.650	0.71 (0.38–1.33)	0.281	0.71 (0.27–1.88)	0.495

*High education means university studies or secondary school; Low education: up to primary studies.
†Multivariable models were adjusted by: age, smoking, alcohol consumption, body-mass index, hypertension, type 2 diabetes, dyslipidemia and family history of premature coronary heart disease, and type Mediterranean diet intervention.
‡Global test of proportional-hazard assumption (p-value based on the scaled Schoenfeld residuals) men: Composite primary cardiovascular event model (0.172); Myocardial infarction model (0.723); Stroke model (0.260); Cardiovascular death model (0.369); women: Global test of proportional-hazard assumption (p-value based on the scaled Schoenfeld residuals) women: Composite primary cardiovascular event model (0.553); Myocardial infarction model (0.320); Stroke model (0.870); Cardiovascular death model (0.458).

Educational level was employed as a measure to evaluate socioeconomic position (SP) because it tends to remain stable throughout life. It is strongly related to the possibility of greater social and material opportunities by influencing future employment and income, and the adoption of healthy lifestyles [17]. As a proxy of SP, educational level has been widely used in a number of cardiovascular research studies [8,20,21].

Although, in general, Spain has one of the lowest incidences of cardiovascular diseases, our results linking socioeconomic level and stroke concur with findings from other studies performed in Anglo-Saxon and Scandinavian countries [21-23].

Classic stroke risk factors and harmful lifestyles are likely to be more prevalent among socioeconomically deprived groups [6,22]. In some studies, the socioeconomic gradient observed in the relationship between SP and stroke was partially mediated by traditional risk and psychological factors [24,25]. In our population, however, the association between stroke and educational level was independent of the cardiovascular risk factor profile and unhealthy lifestyle, as has previously been observed [26].

CVD mortality is decling in Spain yet we observed a high prevalence of poor management of traditional risk factors, and a low rate of proper treatment for the population at risk. Findings that are in agreement with studies carried out on the population attended by the Health System in Catalunya, a region in Spain [27,28].

Strong primary healthcare models play a key role in reducing socioeconomic health inequalities [29]. The Spanish system, for instance is both free and universal with GPs acting as gatekeepers to specialist care. Yet we are of the opinion that, in contrast to other countries where health expenditure has been found to be inversely associated with stroke incidence [30,31], inequality regarding accessibility to health services had a negligible effect on CVD incidence in our population. Indeed, in a previous study we found no differences in the preventive treatment received according to educational level which could justify social inequalities in the incidence of CVD [32].

Table 4 Adjusted hazard ratios for cardiovascular outcomes within all covariables include in the final multivariable models

	Composite primary cardiovascular event		Myocardial infarction		Stroke		Cardiovascular death	
	HR (95% CI)†‡	p-value	HR (95% CI)†‡	p-value	HR (95% CI)†‡	p-value	HR (95% CI)†‡	p-value
Age (years)	1.08 (1.06–1.10)	<0.001	1.04 (1.00–1.07)	0.034	1.09 (1.05–1.12)	<0.001	1.15 (1.11–1.19)	<0.001
Type of Mediterranean diet								
With extra-Virgin Olive oil	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
With mixed nuts	0.97 (0.74–1.35)	0.984	0.98 (0.60–1.60)	0.938	0.76 (0.49–1.22)	0.277	1.37 (0.80–2.34)	0.255
Low fat diet	1.42 (1.07–1.88)	0.014	1.35 (0.84–2.15)	0.205	1.44 (0.98–2.12)	0.062	1.38 (0.80–2.38)	0.242
High alcohol consumption	0.85 (0.63–1.15)	0.292	0.59 (0.35–1.00)	0.052	1.17 (0.77–1.77)	0.472	0.98 (0.58–1.66)	0.949
Smoking status								
Never smoked	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Former smoker	1.45 (1–04–2.03)	0.031	1.47 (0.84–2.56)	0.176	1.14 (0.69–1.86)	0.615	2.27 (1.22- 4.24)	0.010
Current-smoker	1.94 (1–33–2.84)	0.001	2.18 (1.20–3.97)	0.011	1.46 (0.82–2.58)	0.197	2.51 (1.20–5.22)	0.014
Body-mass index (Kg/m^2)	1.01 (0.97–1.04)	0.661	1.01 (0.96–1.07)	0.697	1.00 (0.95–1.04)	0.875	1.03 (0.96–1.09)	0.421
Hypertension	1.79 (1.06–3.02)	0.030	1.53 (0.70–3.32)	0.284	2.19 (0.96–4.99)	0.063	2.22 (0.69–7.08)	0.179
Type 2 diabetes	1.30 (0.98–1.74)	0.071	1.23 (0.78–1.96)	0.374	1.53 (1.00–2.35)	0.052	1.21 (0.71–2.05)	0.477
Dyslipidaemia	0.91 (0.70–1.18)	0.468	0.82 (0.54–1.26)	0.376	0.94 (0.64–1.38)	0.762	0.89 (0.55–1.44)	0.630
Family history of premature CHD§	1.24 (0.92–1.68)	0.155	1.56 (0.98–2.48)	0.060	1.25 (0.82–1.91)	0.304	0.70 (0.34–1.40)	0.313

†All Hazard Ratios are adjusted by sex and psychosocial factors (educational level, depression and social support in the household).
‡Global test of proportional-hazard assumption (p-value based on the scaled Schoenfeld residuals): Composite primary cardiovascular event model (0.471); Myocardial infarction model (0.758); Stroke model (0.303); Cardiovascular death model (0.107).
§CHD denotes coronary heart disease.

The fact that the other psychosocial factors considered, such as depression and low social support, were not found to be related to CVD remains to be elucidated. Through the understanding of social disparities in stroke it would be possible to more effectively address social and clinical actions for cardiovascular prevention in the most disadvantaged social groups.

The Spanish population tends to use the health system quite often, as a result, the probability of being treated for comorbid conditions such as depression is high and the effect of this condition on stroke incidence could be reduced by proper treatment. The number of people living alone among our participants was low. It is possible that a longer follow-up or a larger sample might demonstrate some relationship between living alone and CVD incidence. It should also be taken into account that in the Mediterranean countries, families still play an important role in the care of elderly people; therefore, the effect of living alone could be lower than in other countries.

Strengths and limitations

Unfortunately, no other socioeconomic indicators were available to carry out a sensitivity analysis. Educational level has, however, been found to be a reliable indication of socioeconomic position [17]. With respect to evaluating the effect of social support on cardiovascular outcomes, we took into consideration the number of people living in the home as household size has proven to be a valid proxy [18]. We were, therefore, unable to assess this effect on institutionalized patients or those lacking autonomy. Moreover, since history of depression was self-reported it is possible that the real proportion of depressive patients was under-registered.

Although there are peculiarities in the pathogenesis of hemorrhagic and ischemic stroke, their prevention and management are quite similar, and previous studies have found a relationship between low SP, measured by a deprivation index, for both types. We could not differentiate between hemorrhagic and ischemic stroke because we only had aggregated data [33]. It could be useful in the future to carry out studies to demonstrate whether differences between ischemic and hemorrhagic stroke are due to socioeconomic status.

We are aware that, since several end points have been considered in the analysis and, multiple comparisons among different subgroups of participants may increase type I error. Nevertheless, since our study specifically tested the relationship between psychosocial determinants and cardiovascular events we did not carry out multiple analyses other than those needed to answer the main question.

Conclusions

In a population at high cardiovascular risk, the incidence of stroke was higher in those with lower educational level. History of depression and low social support were not associated with CVD incidence.

Abbreviations

CVD: Cardiovascular diseases; SD: Standard deviation; HR: Hazard ratios; CI: Confidence interval; SES: Socioeconomic status; GPs: General practitioners; BMI: Body mass index; CHD: Coronary heart disease; ACE: Angiotensin-converting-enzyme; EVOO: Extra-virgin olive oil.

Competing interests

Dr. Estruch reports as serving on the board of, and receiving lecture fees from, the Research Foundation on Wine and Nutrition (FIVIN); serving on the boards of the Beer and Health Foundation and the European Foundation for Alcohol Research (ERAB); receiving lecture fees from Cerveceros de España and Sanofi-Aventis; and receiving grant support through his institution from Novartis. Dr. Ros reports as serving on the board of, and receiving travel support, as well as grant support through his institution, from the California Walnut Commission; serving on the board of the Flora Foundation (Unilever); serving on the board of, and receiving lecture fees from, Roche; serving on the board of, and receiving grant support through his institution from, Amgen; receiving consulting fees from Damm and Abbott Laboratories; receiving consulting fees and lecture fees, as well as grant support through his institution, from Merck; receiving lecture fees from Danone, Pace, AstraZeneca, and Rottapharm; receiving lecture fees and payment for the development of educational presentations, as well as grant support through his institution, from Ferrer; receiving payment for the development of educational presentations from Recordati; and receiving grant support through his institution from Sanofi-Aventis, Takeda, Daiichi Sankyo, Nutrexpa, Feiraco, Unilever, and Karo Bio. Dr. Salas-Salvadó reports as serving on the board of, and receiving grant support through his institution, from the International Nut and Dried Fruit Council; reports as serving on the board of Institute Danone Spain; receiving consulting fees from Danone; and receiving grant support through his institution from Eroski and Nestlé. Dr. Arós reports receiving payment for the development of educational presentations from Menarini and AstraZeneca. Dr. Lamuela-Raventos reports as serving on the board of, and receiving lecture fees from, FIVIN; receiving lecture fees from Cerveceros de España; and receiving lecture fees and travel support from PepsiCo. Dr. Serra-Majem reports as serving on the boards of the Mediterranean Diet Foundation and the Beer and Health Foundation. Dr. Pintó reports as serving on the board of, and receiving grant support through his institution from the Residual Risk Reduction Initiative (R3i) Foundation; serving on the board of Omegafort; serving on the board of and receiving payment for the development of educational presentations, as well as grant support through his institution, from Ferrer; receiving consulting fees from Abbott Laboratories; receiving lecture fees, as well as grant support through his institution, from Merck and Roche receiving lecture fees from Danone and Esteve; receiving payment for the development of educational presentations from Menarini; and receiving grant support through his institution from Sanof i-Aventis, Kowa, Unilever, Boehringer Ingelheim, and Karo Bio. No other potential conflict of interest relevant to this article was reported.

Authors' contributions

CM-L and MAM conceived and designed the study. They also analyzed and interpreted the study data, and wrote the first draft of the manuscript. RE, MAM-G, JS-S, OC, DC, FA, EG-G, MF, JL, LS-M, XP, ER, JD-E, JB, JVS, RML-R,VR-G, assisted in the acquisition of data and provided valuable, intellectual contributions to the manuscript draft. All authors have approval the final version submitted for publication.

Acknowledgements

The authors acknowledge the contribution of Stephanie Lonsdale for the English review and edition.

Funding

Instituto de Salud Carlos III, and Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y Nutrición, and Centro Nacional de Investigaciones Cardiovasculares, Fondo de Investigación Sanitaria–Fondo Europeo de Desarrollo Regional, Ministerio de Ciencia e Innovación, Fundación Mapfre 2010, Consejería de Salud de la Junta de Andalucía, Public Health Division of the Department of Health of the Autonomous Government of Catalonia, Generalitat Valenciana, and the Regional Government of Navarra. None of the institutions described above have influenced the design, collection, analysis, and interpretation of data; the writing of the manuscript; and the decision to submit the manuscript for publication.

Author details

[1]Department of Paediatrics, Obstetrics, Gynaecology and Preventive Medicine, Universitat Autònoma de Barcelona, Bellaterra, Spain. [2]CIBER Fisiopatología de la Obesidad y Nutrición (CIBERobn), Instituto de Salud Carlos III, Madrid, Spain. [3]PREDIMED (Prevención con Dieta Mediterránea) Network (RD 06/0045), Instituto de Salud Carlos III, Madrid, Spain. [4]Department of Internal Medicine of Hospital Clinic, IDIBAPS, University of Barcelona, Barcelona, Spain. [5]Preventive Medicine and Public Health, University of Navarra, Pamplona, Spain. [6]Human Nutrition Department, Hospital Universitari Sant Joan, Institut d'Investigació Sanitaria Pere Virgili, Universitat Rovira i Virgili, Reus, Spain. [7]Cardiovascular Risk and Nutrition Research Group of Institute Hospital del Mar (IMIM), Barcelona, Spain. [8]Department of Preventive Medicine, University of Valencia, Valencia, Spain. [9]Department of Cardiology, University Hospital of Alava, Vitoria, Spain. [10]Department of Preventive Medicine, University of Malaga, Malaga, Spain. [11]Institute of Health Sciences (IUNICS), University of Balearic Islands, and Hospital Son Espases, Palma de Mallorca, Spain. [12]Department of Family Medicine, Primary Care Division of Seville, San Pablo Health Center, Seville, Spain. [13]Department of Clinical Sciences, University of Las Palmas de Gran Canaria, Las Palmas, Spain. [14]Lipids and Vascular Risk Unit, Internal Medicine, Hospital Universitario de Bellvitge, Hospitalet de Llobregat, Barcelona, Spain. [15]Lipid Clinic, Department of Endocrinology and Nutrition of Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi I Sunyer, University of Barcelona, Barcelona, Spain. [16]Centro de Salud de Tafalla, Servicio Navarro de Salud, University of Navarra, Pamplona, Spain. [17]Primary Care Division, Institut Català de la Salut, Institut d'Investigació en Atenció Primària IDIAP Jordi Gol, Tarragona-Reus, Spain. [18]Primary Care Division, Valencia Institute of Health, Valencia, Spain. [19]Department of Nutrition and Food Science, School of Pharmacy, Xarxa de Referència en Tecnologia dels Aliments, Instituto de Investigación en Nutrición y Seguridad Alimentaria, University of Barcelona, Barcelona, Spain. [20]Instituto de la Grasa, Consejo Superior de Investigaciones Científicas, Sevilla, Spain. [21]Institut Català de la Salut, Barcelona, Spain. [22]Institut d'Investigació en Atenció Primària IDIAP-Jordi Gol, Barcelona, Spain.

Received: 27 June 2014 Accepted: 22 September 2014
Published: 3 October 2014

References

1. World Health Organization: **Global Atlas on Cardiovascular Disease Prevention and Control.** [http://whqlibdoc.who.int/publications/2011/9789241564373_eng.pdf]
2. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB: **Prediction of coronary heart disease using risk factor categories.** *Circulation* 1998, **97:**1837–1847.
3. Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L, INTERHEART Study Investigators: **Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case–control study.** *Lancet* 2004, **364:**937–952.
4. Hemingway H, Marmot M: **Evidence based cardiology: psychosocial factors in the aetiology and prognosis of coronary heart disease. Systematic review of prospective cohort studies.** *BMJ* 1999, **318:**1460–1467.
5. Diez Roux AV: **Residential environments and cardiovascular risk.** *J Urban Health* 2003, **80:**569–589.
6. Kaplan GA, Keil JE: **Socioeconomic factors and cardiovascular disease: a review of the literature.** *Circulation* 1993, **88:**1973–1998.
7. Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L: **The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology.** *J Am Coll Cardiol* 2005, **45:**637–651.
8. Allen CL, Bayraktutan U: **Risk factors for ischaemic stroke.** *Int J Stroke* 2008, **3:**105–116.
9. Eller NH, Netterstrom B, Gyntelberg F, Kristensen TS, Nielsen F, Steptoe A, Theorell T: **Work-related psychosocial factors and the development of ischemic heart disease: a systematic review.** *Cardiol Rev* 2009, **17:**83–97.
10. Marmot M, Allen J, Bell R, Bloomer E, Goldblatt P, Consortium for the European Review of Social Determinants of Health and the Health Divide:

WHO European review of social determinants of health and the health divide. *Lancet* 2012, **380**:1011–1029.

11. Diaz-Guzman J, Egido JA, Gabriel-Sanchez R, Barbera-Comes G, Fuentes-Gimeno B, Fernandez-Perez C: **Stroke and transient ischemic attack incidence rate in Spain: the IBERICTUS study.** *Cerebrovasc Dis* 2012, **34**:272–281.
12. European Commission, Eurostat: **Diseases of the circulatory system.** In *Health statistics Atlas on mortality in the European Union, 2009 edition.* Luxembourg: Office for Official Publications of the European Communities; 2009:114–139.
13. Gonzalez-Zobl G, Grau M, Munoz MA, Martí R, Sanz H, Sala J, Masiá R, Rohlfs I, Ramos R, Marrugat J, Elosua R, Researchers of the REGICOR study: **Socioeconomic status and risk of acute myocardial infarction. Population-based case–control study.** *Rev Esp Cardiol* 2010, **63**:1045–1053.
14. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pintó X, Basora J, Muñoz MA, Sorlí JV, Martínez JA, Martínez-González MA, PREDIMED Study Investigators: **Primary prevention of cardiovascular disease with a Mediterranean diet.** *N Engl J Med* 2013, **368**:1279–1290.
15. Fuente-Arrillaga C, Ruiz ZV, Bes-Rastrollo M, Sampson L, Martinez-Gonzalez MA: **Reproducibility of an FFQ validated in Spain.** *Public Health Nutr* 2010, **13**:1364–1372.
16. Martinez-Gonzalez MA, Fernandez-Jarne E, Serrano-Martinez M, Wright M, Gomez-Gracia E: **Development of a short dietary intake questionnaire for the quantitative estimation of adherence to a cardioprotective Mediterranean diet.** *Eur J Clin Nutr* 2004, **58**:1550–1552.
17. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey SG: **Indicators of socioeconomic position (part 1).** *J Epidemiol Community Health* 2006, **60**:7–12.
18. Udell JA, Steg PG, Scirica BM, Smith SC, Ohman EM, Eagle KA, Goto S, Cho JI, Bhatt DL, for the Reduction of Atherothrombosis for Continued Health (REACH) Registry Investigators: **Living Alone and Cardiovascular Risk in Outpatients at Risk of or With Atherothrombosis.** *Arch Intern Med* 2012, **172**:1086–1095.
19. Grambsch PM, Therneau TM: **Proportional hazards tests and diagnostics based on weighted residuals.** *Biometrika* 1994, **81**:515–526.
20. Liu L, Xue F, Ma J, Ma M, Long Y, Newschaffer CJ: **Social position and chronic conditions across the life span and risk of stroke: a life course epidemiological analysis of 22,847 American adults in ages over 50.** *Int J Stroke* 2013, **8**(Suppl A100):50–55.
21. Addo J, Ayerbe L, Mohan KM, Crichton S, Sheldenkar A, Chen R, Wolfe CD, McKevitt C: **Socioeconomic status and stroke: an updated review.** *Stroke* 2012, **43**:1186–1191.
22. Grimaud O, Bejot Y, Heritage Z, Vallée J, Durier J, Cadot E, Giroud M, Chauvin P: **Incidence of stroke and socioeconomic neighborhood characteristics: an ecological analysis of Dijon stroke registry.** *Stroke* 2011, **42**:1201–1206.
23. Heeley EL, Wei JW, Carter K, Islam MS, Thrift AG, Hankey GJ, Cass A, Anderson CS: **Socioeconomic disparities in stroke rates and outcome: pooled analysis of stroke incidence studies in Australia and New Zealand.** *Med J Aust* 2011, **195**:10–14.
24. Avendano M, Kawachi I, Van LF, Boshuizen HC, Mackenbach JP, Van den Bos GA, Fay ME, Berkman LF: **Socioeconomic status and stroke incidence in the US elderly: the role of risk factors in the EPESE study.** *Stroke* 2006, **37**:1368–1373.
25. Kerr GD, Slavin H, Clark D, Coupar F, Langhorne P, Stott DJ: **Do vascular risk factors explain the association between socioeconomic status and stroke incidence: a meta-analysis.** *Cerebrovasc Dis* 2011, **31**:57–63.
26. Morris RW, Whincup PH, Emberson JR, Lampe FC, Walker M, Shaper AG: **North–south gradients in Britain for stroke and CHD: are they explained by the same factors?** *Stroke* 2003, **34**:2604–2609.
27. Catalán-Ramos A, Verdú JM, Grau M, Iglesias-Rodal M, Del Val García JL, Consola A, Comin E, GPC-ICS Group: **Population prevalence and control of cardiovascular risk factors: What electronic medical records tell us.** *Aten Primaria* 2014, **46**:15–24.
28. Baena-Díez JM, Félix FJ, Grau M, Cabrera de León A, Sanz H, Leal M, Elosua R, Rodríguez-Pérez M del C, Guembe MJ, Torán P, Vega-Alonso T, Ortiz H, Pérez-Castán JF, Frontera-Juan G, Lapetra J, Tormo MJ, Segura A, Fernández-Bergés D, Marrugat J: **Risk factor treatment and control in relation to coronary disease risk in the Spanish population of the DARIOS Study.** *Rev Esp Cardiol* 2011, **64**:766–773.
29. Starfield B: **Primary care: an increasingly important contributor to effectiveness, equity, and efficiency of health services. SESPAS report 2012.** *Gac Sanit* 2012, **26**(Suppl 1):20–26.
30. Kapral MK, Wang H, Mamdani M, Tu JV: **Effect of socioeconomic status on treatment and mortality after stroke.** *Stroke* 2002, **33**:268–273.
31. Thrift AG, Arabshahi S: **Is stroke incidence in low- to middle-income countries driven by economics?** *Int J Stroke* 2012, **7**:307–308.
32. Mejía-Lancheros C, Estruch R, Martínez-González MA, Salas-Salvadó J, Corella D, Gómez-Gracia E, Fiol M, Lapetra J, Covas MI, Arós F, Serra-Majem L, Pintó X, Basora J, Sorlí JV, Muñoz MA, PREDIMED Study Investigators: **Socioeconomic Status and Health Inequalities for Cardiovascular Prevention Among Elderly Spaniards.** *Rev Esp Cardiol* 2013, **66**:803–811.
33. Cesaroni G, Agabiti N, Forastiere F, Perucci CA: **Socioeconomic differences in stroke incidence and prognosis under a universal healthcare system.** *Stroke* 2009, **40**:2812–2819.

doi:10.1186/1471-2261-14-135
Cite this article as: Mejía-Lancheros *et al.*: **Impact of psychosocial factors on cardiovascular morbimortality: a prospective cohort study.** *BMC Cardiovascular Disorders* 2014 **14**:135.

Part IV: Discussion

Chapter 10:
Final discussion

10.1. Articles Discussion

The present thesis analyses the effect of psychological and socioeconomic factors (education (SEP), depression, social support) in three different aspects of cardiovascular risk: primary cardiovascular prevention treatment, degree of control blood pressure and major cardiovascular events in an adult population with high cardiovascular risk in Spain. The results and specific discussions have been presented separately in the three published articles included in the results section of the present thesis.

10.1.1. Relationship between the socioeconomic status of an elderly population at high cardiovascular risk and inequalities in receiving primary cardiovascular treatment, within the context of a universal health care system

In our study, the primary cardiovascular prevention treatment received for hypertension, diabetes and dyslipidaemia was not influenced by the participants' socioeconomic position. In addition, the presence of more than one risk factor was also evaluated (since cardiovascular risk factors try to cluster), showing either no socioeconomic differences among analysed groups. Finally, when differences in the treatment received depending on gender were assessed, men with low SEP were more likely to receive the antihypertensive treatment than those with higher SEP.

There are different indicators used as measures of SEP at an individual level such as education, income, occupation, among others (127). We chose education level as a good indicator of SEP because once the highest level is reached it remains stable throughout life, determining or facilitating better employment and income opportunities (127). Likewise, education can influence people's cognition, knowledge and skills that turn on the capability that people have to seek and use health care services, follow medical advice and adopt behavioural patterns (127).

Most of the studies have focused on addressing the socioeconomic inequalities in receiving secondary cardiovascular prevention rather than in primary cardiovascular prevention. Studies carried out in Scandinavian countries have shown that people at higher SEP had more possibilities of receiving diagnostic and invasive treatment (angiographies, revasculatation and thrombolysis) and prescribing pharmacological medication (antiplatelet agents, hypoglycaemic medication, β blockers and statin) after suffering a CHD event (228,229). Studies carried out in countries with similar Health Care Systems to that existing in Spain, have found that patients with the lowest SEP had less access to recovery health services such as physiotherapy and occupational therapy after experiencing a stroke (230), and to specialized medical invasive procedures (e.g. Angiography) after suffering IMA (231). In the Spanish context, a previous study that had addressed the socioeconomic inequalities in secondary cardiovascular prevention found no differences in the treatment prescribed (218).

Unobserved socioeconomic differences in primary preventive cardiovascular treatment in our study population might be due to the universal and free coverage and the existence of a good primary care model to which our participants had access anytime that they need regardless of their SEP (In Spain, until 2012, access to primary health care was universal and free). In fact, in the Spanish context, elderly people in a more disadvantaged socioeconomic condition had a tendency to use more primary health care services than those with better SEP (232). Despite health care systems are not themselves a direct determinant of a population's health, they can act as a critical facilitator or a barrier to access to medical care services as well as to general and specialized treatment, especially depending on the type of coverage set (payable, free or mix insurances)(113,233).

Health care systems with a strong primary care (PC) and universal insurance contribute to better health outcomes and to reduce socioeconomic disparities in health among population groups (113,234). Starfield B. et al (234), have suggested that PC benefits health level population and reduces health disparities through the following aspects: (1) acting as the first contact between a patient and health services, it helps not only in accessing basic medical care services but also those more specialised; (2) the high quality and holistic care provided by primary care physicians (GPs) especially for those more common health conditions (e.g. Chronic diseases); (3) providing extended preventive activities aiming to target many diseases rather than a specific one; (4) providing optimal management of illness states, preventing them from worsening; (5) approaching the patient as a person with all his/her contextual and medical factors associated rather than only focusing on his/her consulted disease; (6) reducing unnecessary and inappropriate use of specialised health care service (medical, diagnostic and therapeutic services), due to the fact that many diseases can be firstly treated in the PC setting in coordination with more specialised medical professionals and services.

The cross-sectional design of our study does not allow causal inferences to be set; however, our sample population represents the Spanish population with high cardiovascular risk but free of CVD well, allowing us to analyse the possible socioeconomic inequalities in receiving primary preventive treatment, under a universal and free coverage health system with a strong primary care model.

The low percentage of people having university education represents the socio-political history in Spain, where until around the seventies access to high education was limited, especially for women. Finally, our results should be generalized to people at high cardiovascular risk, more than to the general population.

10.1.2. Influence of depression on the control of blood pressure in hypertensive individuals at high cardiovascular risk

In our sample, we found that participants with depression had better control of their blood pressure. No disparities depending on SEP (education as indicator) were observed.

In relation to depression and incidence of hypertension, a recent meta-analysis based on prospective studies, found that people with depression have around a 42% risk of developing hypertension (235). However many of the studies included did not consider potential confounding factors such as unhealthy lifestyle (smoking, alcohol, physical activities) or concomitant mental disorders such as anxiety.

On the other hand, other studies have documented that hypertension could be a risk factor to developing depression) (236, 237). In spite of the evidence available, the role of depression on hypertension remains uncertain (161). The role of depression in the control of blood pressure values in hypertensive patients has been scarcely studied. Studies carried out in Scandinavian and European countries have revealed similar results to those found in ours (depressive participants tended to have better BP values) (238-240). Moreover, some studies have also documented a reverse association between low BP and high risk of depression in elderly people, where both low BP values at base line and consequently BP values decrease over the follow up, associated with high occurrence of depressive symptoms (241).

Possible explanations for the association between depression and low BP values may be related to changes in neuro-endocrine function regulation (low reactivity of the autonomic system and the catecholamines hormones activity) happening during the depressive states, or to the possible hemodynamic effect of some pharmacological treatment for mental disorders including depression and anxiety taken alone or in concomitance with cardiovascular medication (161). Behaviours such as smoking, physical activity, diet, alcohol can act as confounding factors between depression and good BP control because they can be associated with both depression and hypertension (242,243). However, in our analysis, we took into account this possibility by introducing them in the final adjusted models.

Other plausible explanation to our results could be that elderly with high cardiovascular risk are likely to be more followed-up and treated holistically by their GP especially in the context of a strong primary care model (234). In Spain, the PC team (GPS, nurse, social workers) comprehensively follows people with chronic comorbidity.

SEP have been found in other studies to be correlated with CVDs and associated with risk factors such as hypertension (135). Several disadvantaged socioeconomic aspects associated with household, childhood, race and ethnicity, health behaviours, awareness, accessibility to treatment, work environments and access and utilization of health care can be a way through which SEP may contribute to hypertension (244,245).

A plausible explanation for our findings might be the facilitator role of the universal and free health coverage to accessing health care services for all social groups, along with good PC services (234). A recent study analysed whether the availability of a universal health care (England) versus a non-universal health care insurance coverage (United States: US) might influence the presence of socioeconomic disparities in the optimal management of hypertension (244). It was found that people in the lowest SEP were more likely to have worse control of their BP in the US than in England (BP control goal: 60.9% for richer vs. 63.5% for poorer patients in England compared with 71.7% in rich vs. 55.2% for poorer in the US). This evidence supports that beyond the patient cardiovascular risk profile, race and SEP, the type of health care model and the insurance coverage may contribute to reduce or increase the socioeconomic differences in the management and optimal control of cardiovascular risk factors such as hypertension (234,245,246).

Due to the nature of the study design, we cannot establish the causal association between depression and lower blood pressure levels and/ or vice versa. However, our findings contribute to understanding the effect of depression on blood pressure once the hypertension condition has been well-established, and consider it in the daily medical practice, especially if we take into account that nowadays depression is a frequent and concomitant condition along with many chronic comorbidities (247,248).

Future observational studies with long-term follow up, in both hypertensive participants without depression (see if they develop depression/or depression symptoms) and in those with depression but without hypertension (see if they develop hypertension) may contribute to better understanding the bidirectional relationship between depression and the aetiology and management of hypertension.

10.1.3. Contribution of psychological and socioeconomic conditions in increasing the risk of cardiovascular events in a high cardiovascular risk adult population

In our population with high cardiovascular risk but free of CVDs at baseline, after a mean of 4.8 years of follow up, amongst the adverse psychological and socioeconomic factors (education (SEP), low social support in the household and depression) and cardiovascular outcomes considered (AMI, stroke, death from cardiovascular causes), only SEP negatively impacted their cardiovascular morbimortality risk. Participants with low SEP presented more risk of stroke than those with high SEP, being more remarkable in men, while depression and low social support show no contribution to any of the cardiovascular endpoints considered.

There are few studies addressing the influence of psychological and socioeconomic conditions at an individual level on the risk of suffering the major cardiovascular outcomes in the Spanish context (212,213,249). An inverse relationship between SEP and high rates of stroke mortality have been observed in residents of Madrid and Barcelona (212,214). A recent update review about SEP (with varying SEP measures including educational level) and stroke, based on studies performed in different socioeconomic, political and cultural settings (250), highlighted that the incidence of stroke, stroke related risk factors, and stroke mortality and disability rates are more frequent among socioeconomically disadvantaged groups than those with better SEP. Likewise, this review also evidenced that poor people groups were less likely to receive innovative and effective stroke medical/health interventions, which might explain the gap between the richer and poorer regarding stroke incidence.

In Spain, socioeconomic inequalities in receiving secondary cardiovascular treatment have not been observed (218). Furthermore, in our own study population as revealed in the results section, article 1(251) and in the discussion section paragraph 10.1.1 of the present thesis, no differences in receiving treatment for hypertension, dyslipidaemia and type 2 diabetes depending on SEP were found.

Our findings are in line with those evidenced in a meta-analysis performed by Kerr et al. (252). They showed that, although the high prevalence of classic cardiovascular risk factors among people with low SEP could explain in part the differences observed in the incidence of stroke among socioeconomic groups, they do not completely justify the observed association between low SEP and high risk of stroke. In our study, both classic cardiovascular risk factors (hypertension, dyslipidaemia, type 2 diabetes and family history of premature CHD) and unhealthy behaviours were taken into account in the adjusted analyses.

It might be possible that exposition of disadvantaged socioeconomic conditions during childhood and young adulthood can somehow explain the increased risk of stroke among our elderly participants with low SEP (253,254).

As other many chronic diseases, adverse cardiovascular outcomes seem to be a long-term consequence of many harmful factors throughout individual life. Early exposition to poorer socioeconomic circumstances and social patterning behaviours independently of or in synchrony with socioeconomic conditions during adulthood can contribute to increasing the risk of CVDs and mortality later in life (253). A systematic review performed by Galobardes et al, highlighted a particular strong influence of disfavoured socioeconomic childhood conditions on stroke (254). Unfortunately, we did not have available measures of SEP during the early ages of our participants' life to assess their contribution to the observed results. This would be an important point to take into consideration in future research focused on socioeconomic disparities in cardiovascular health carried out in a Spanish context.

On the other hand, the lack of influence of depression and low social support in any of the cardiovascular hard end-points studied, might be explained by the frequent, intensive and comprehensive medical monitoring that adults with high comorbidity and high cardiovascular risk receive in PC in Spain, regardless of their socioeconomic circumstances. In 2012, the Spanish government set new health reforms (treatment cost-sharing, limitation of universal health insurance coverage, and reductions in public expenditure) (255), however, our participants had free accessibility and free insurance coverage to health services during the study follow up (2003-2010).

Among our population, the percentage of people living alone was low (nearly 10%), which reflects the role of family and social networks around elders in the Spanish context. In terms of statistical power, it may also explain the lack of effect found in relation to the cardiovascular endpoint considered. In Mediterranean countries such as Spain, the family caregiving, help and high social contact exchange related to older people are still prevalent (256). Therefore, it is likely that living alone does not display well the functional or emotional support that people may have within and outside their household. In addition, unlike other studies (242,257), among our participants, those with depression and those with low social support were not smokers and alcoholic drinkers, which could reduce the impact of depression and social support on developing negative cardiovascular results.

Finally, in a recent review based on Hill's causality criteria, Meijer et al (258), suggested that depression rather than being a causal risk for CHD, could be a risk marker of the CHD and its course or progression. Our results might support in part this evidence, since our participants were free of cardiovascular disease at baseline.

Chapter 11:
Final Conclusions

11.1. Conclusions

1_. In our study, socioeconomic differences did not affect the treatment prescribed for primary cardiovascular prevention in elderly patients in Spain. Free, universal health care based on a primary care model can be effective in reducing health inequalities related to socioeconomic status.

2_. Among hypertensive patients with high cardiovascular risk, the control of blood pressure was better in those diagnosed with depression.

3_. Adults with low educational level had a higher risk of stroke. Depression and low social support were not associated with CVD incidence.

Chapter 12: Recommendations and future lines of research

12.1. Recommendations and future lines of research

1_. The economic crisis experienced in Spain in the last few years, has implied important changes in the public health policies such as the co-payment of some medical treatment, limiting the universal and free access and coverage to the health services, especially those relating to primary care. The impact of these reforms on the primary and secondary cardiovascular health prevention should be evaluated in future research studies.

2_. Considering that our study showed that hypertensive people with depression had their blood pressure better controlled than those without depression and no impact of depression on major primary cardiovascular outcomes was found, future prospective studies with longer-time follow up might contribute to evaluate better if the depression is more a marker of presence of cardiovascular diseases than a causal risk factor.

3_. Taking into account the socioeconomic and psychological circumstances of people such as socioeconomic position, depression and social support in the daily clinical practice guidelines alongside a systematic and comprehensive prevention, assessment, monitoring and treatment of the cardiovascular risk might contribute significantly to reduce the cardiovascular morbimortality burden.

4_. Assessing the multilevel effect of socioeconomic and psychological conditions on different aspects of the cardiovascular risk in the Spanish context, might contribute to better understanding the role of those circumstances on the “Spanish cardiovascular risk paradox”: low rates of cardiovascular morbidity and high prevalence of risk factors.

5_. To assess the effect of the socioeconomic circumstances over a lifetime can also contribute to explain better the high prevalence of classic cardiovascular risk factors in Spain and to adopt a proper medical approach in the prevention, assessment and treatment of cardiovascular diseases.

Appendices

Appendix A: Summary of the International Research Visit

Since February 1st 2014, the author of the present thesis is a visiting research student/fellow at the School of Social and Community Medicine, University of Bristol, United Kingdom.

Throughout this period, the candidate is collaborating with Dr Galobardes on projects related to the study of health inequalities. She has reviewed and evaluated the macroeconomic measures of socioeconomic development used in epidemiological and health-related research and is currently analysing the correlation of socioeconomic development with respiratory, cardiovascular and other health outcomes. It is anticipated that two publications in peer-review journals will arise from this work. This scientific paper(s) is not and will not be part of the main research of the present thesis.

References

References

1. Mendis S, Puska P, Norrving B, editors. Global Atlas on Cardiovascular Disease Prevention and Control.World Health Organization. Geneva; 2011.

2. Moran AE, Forouzanfar MH, Roth GA, Mensah GA, Ezzati M, Flaxman A, et al. The global burden of ischemic heart disease in 1990 and 2010: the Global Burden of Disease 2010 study. Circulation. 2014;129(14):1493-501.

3. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet. 2014;383(9913):245-54.

4. Moran AE, Forouzanfar MH, Roth GA, Mensah GA, Ezzati M, Murray CJ, et al. Temporal trends in ischemic heart disease mortality in 21 world regions, 1980 to 2010: the Global Burden of Disease 2010 study. Circulation. 2014;129(14):1483-92.

5. World Health Organization. Global status report on noncommunicable diseases 2010. World Health Organization. Geneva; 2010. ISBN 978 92 4 068645 8.

6. Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2197-223.

7. Medrano MJ, Boix R, Palmera A, Ramis R, Galan I, Lopez-Abente G. Towns with extremely low mortality due to ischemic heart disease in Spain. BMC Public Health. 2012;12:174.

8. Nichols M TN, Luengo-Fernandez R, Leal J, Gray A, Scarborough P, Rayner M. European Cardiovascular Disease Statistics 2012. European Heart Network, European Society of Cardiology. Brussels,Sophia Antipolis; 2012. Contract No.: ISBN 978-2-9537898-1-2.

9. Instituto Nacional de Estadística. Defunciones según la Causa de Muerte Año 2012.. INEbase, Instituto Nacional de Estadística. España;2014.

10. Cardiovascular disease [Internet]. Eciclopaedia Britannica. [cited 2014 Dic 18]. Available from: http://www.britannica.com/EBchecked/topic/720793/cardiovascular-disease#

11. Thomas M. The Role of medicine: dream, mirage or nemesis? 1 ed: Basil Blackwell, Oxford; 1976. 207 p.

12. Stampfer MJ, Ridker PM, Dzau VJ. Risk factor criteria. Circulation. 2004;109(25 Suppl 1):IV3-5.

13. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J, 3rd. Factors of risk in the development of coronary heart disease--six year follow-up experience. The Framingham Study. Ann Intern Med. 1961;55:33-50.

14. Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. BMJ. 1976;2(6051):1525-36.

15. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA. 1979;241(19):2035-8.

16. Fruchart JC, Nierman MC, Stroes ES, Kastelein JJ, Duriez P. New risk factors for atherosclerosis and patient risk assessment. Circulation. 2004;109(23 Suppl 1):III15-9.

17. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937-52.

18. Hemingway H, Marmot M. Evidence based cardiology: psychosocial factors in the aetiology and prognosis of coronary heart disease. Systematic review of prospective cohort studies. BMJ. 1999;318(7196):1460-7.

19. Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. J Am Coll Cardiol. 2005;45(5):637-51.

20. Maas AH, Appelman YE. Gender differences in coronary heart disease. Neth Heart J. 2010;18(12):598-603.

21. Roeters van Lennep JE, Westerveld HT, Erkelens DW, van der Wall EE. Risk factors for coronary heart disease: implications of gender. Cardiovasc Res. 2002;53(3):538-49.

22. Towfighi A, Zheng L, Ovbiagele B. Sex-specific trends in midlife coronary heart disease risk and prevalence. Arch Intern Med.2009;169(19):1762-6.

23. Vaidya D, Becker DM, Bittner V, Mathias RA, Ouyang P. Ageing, menopause, and ischaemic heart disease mortality in England, Wales, and the United States: modelling study of national mortality data. BMJ. 2011;343:d5170.

24. Jousilahti P, Vartiainen E, Tuomilehto J, Puska P. Sex, age, cardiovascular risk factors, and coronary heart disease: a prospective follow-up study of 14 786 middle-aged men and women in Finland. Circulation. 1999;99(9):1165-72.

25. Parikh NI. Sex differences in the risk of cardiovascular disease. BMJ. 2011;343:d5526.

26. Tan YY, Gast GC, van der Schouw YT. Gender differences in risk factors for coronary heart disease. Maturitas. 2010;65(2):149-60.

27. Lloyd-Jones DM, Nam BH, D'Agostino RB, Sr., Levy D, Murabito JM, Wang TJ, et al. Parental cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults: a prospective study of parents and offspring. JAMA. 2004;291(18):2204-11.

28. Murabito JM, Pencina MJ, Nam BH, D'Agostino RB, Sr., Wang TJ, Lloyd-Jones D, et al. Sibling cardiovascular disease as a risk factor for cardiovascular disease in middle-aged adults. JAMA. 2005;294(24):3117-23.

29. Nasir K, Budoff MJ, Wong ND, Scheuner M, Herrington D, Arnett DK, et al. Family history of premature coronary heart disease and coronary artery calcification: Multi-Ethnic Study of Atherosclerosis (MESA). Circulation. 2007;116(6):619-26.

30. Pandey AK, Blaha MJ, Sharma K, Rivera J, Budoff MJ, Blankstein R, et al. Family history of coronary heart disease and the incidence and progression of coronary artery calcification: Multi-Ethnic Study of Atherosclerosis (MESA). Atherosclerosis. 2014;232(2):369-76.

31. World Health Organization. Global health risks: Mortality and burden of disease attributable to selected major risks. Geneva; 2009. SBN 978 92 4 156387 1.

32. Braveman P, Gottlieb L. The social determinants of health: it's time to consider the causes of the causes. Public Health Rep. 2014;129 Suppl 2:19-31.

33. Lloyd-Sherlock P, Beard J, Minicuci N, Ebrahim S, Chatterji S. Hypertension among older adults in low- and middle-income countries: prevalence, awareness and control. Int J Epidemiol. 2014;43(1):116-28.

34. Catala-Lopez F, Sanfelix-Gimeno G, Garcia-Torres C, Ridao M, Peiro S. Control of arterial hypertension in Spain: a systematic review and meta-analysis of 76 epidemiological studies on 341 632 participants. J Hypertens. 2012;30(1):168-76.

35. Rapsomaniki E, Timmis A, George J, Pujades-Rodriguez M, Shah AD, Denaxas S, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1.25 million people. Lancet. 2014;383(9932):1899-911.

36. Antonakoudis G, Poulimenos L, Kifnidis K, Zouras C, Antonakoudis H. Blood pressure control and cardiovascular risk reduction. Hippokratia. 2007;11(3):114-9.

37. Leonor Guariguata TN, Jessica Beagley, Ute Linnenkamp, Olivier Jacqmain, editors. IDF Diabetes Atlas. 6 ed: International Diabetes Federation; 2013.

38. Soriguer F, Goday A, Bosch-Comas A, Bordiu E, Calle-Pascual A, Carmena R, et al. Prevalence of diabetes mellitus and impaired glucose regulation in Spain: the Di@bet.es Study. Diabetologia. 2012;55(1):88-93.

39. Grundy SM, Benjamin IJ, Burke GL, Chait A, Eckel RH, Howard BV, et al. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation. 1999;100(10):1134-46

40. Hatzitolios AI, Didangelos TP, Zantidis AT, Tziomalos K, Giannakoulas GA, Karamitsos DT. Diabetes mellitus and cerebrovascular disease: which are the actual data? Journal of diabetes and its complications. 2009;23(4):283-96.

41. Mannucci E, Dicembrini I, Lauria A, Pozzilli P. Is glucose control important for prevention of cardiovascular disease in diabetes?. Diabetes care. 2013;36 Suppl 2:S259-63.

42. Castelli WP. Lipids, risk factors and ischaemic heart disease. Atherosclerosis. 1996;124 Suppl:S1-9.

43. Farzadfar F, Finucane MM, Danaei G, Pelizzari PM, Cowan MJ, Paciorek CJ, et al. National, regional, and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country-years and 3.0 million participants. Lancet. 2011;377(9765):578-86.

44. Guallar-Castillon P, Gil-Montero M, Leon-Munoz LM, Graciani A, Bayan-Bravo A, Taboada JM, et al. Magnitude and management of hypercholesterolemia in the adult population of Spain, 2008-2010: The ENRICA Study. Rev Esp Cardiol (Engl Ed). 2012;65(6):551-8.

45. Austin MA, Hokanson JE, Edwards KL. Hypertriglyceridemia as a cardiovascular risk factor. Am J Cardiol. 1998;81(4A):7B-12B.

46. Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. Circulation. 2007;115(4):450-8.

47. Kannel WB, Vasan RS. Triglycerides as vascular risk factors: new epidemiologic insights. Curr Opin Cardiol. 2009;24(4):345-50.

48. Franceschini G. Epidemiologic evidence for high-density lipoprotein cholesterol as a risk factor for coronary artery disease. Am J Cardiol. 2001;88(12A):9N-13N.

49. Feig JE, Hewing B, Smith JD, Hazen SL, Fisher EA. High-density lipoprotein and atherosclerosis regression: evidence from preclinical and clinical studies. Circ Res. 2014;114(1):205-13.

50. Barter P. HDL-C: role as a risk modifier. Atheroscler Suppl. 2011;12(3):267-70.

51. Yamada Y, Matsuo H, Warita S, Watanabe S, Kato K, Oguri M, et al. Prediction of genetic risk for dyslipidemia. Genomics. 2007;90(5):551-8.

52. Musunuru K. Atherogenic dyslipidemia: cardiovascular risk and dietary intervention. Lipids. 2010;45(10):907-14.

53. Cai A, Li L, Zhang Y, Mo Y, Mai W, Zhou Y. Lipoprotein(a): a promising marker for residual cardiovascular risk assessment. Dis markers. 2013;35(5):551-9.

54. Mays EE. Cigarette smoking: its relationship to other diseases. J Natl Med Assoc. 1973;65(6):520-4.

55. Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and stroke. BMJ. 1989;298(6676):789-94.

56. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. Am J Cardiol. 2004;43(10):1731-7.

57. Bakhru A, Erlinger TP. Smoking cessation and cardiovascular disease risk factors: results from the Third National Health and Nutrition Examination Survey. PLoS Med. 2005;2(6):e160.

58. Critchley J, Capewell S. Smoking cessation for the secondary prevention of coronary heart disease. The Cochrane database of systematic reviews. 2004(1):CD003041.

59. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease: a systematic review. JAMA. 2003;290(1):86-97

60. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ. 2004;328(7455):1519.

61. World Health Organization. WHO report on the global tobacco epidemic, 2013: enforcing bans on tobacco advertising, promotion and sponsorship.World Health Organization. Geneva; 2013. ISBN 978 92 4 150587 1.

62. Sureda X, Martinez-Sanchez JM, Fu M, Perez-Ortuno R, Martinez C, Carabasa E, et al. Impact of the Spanish smoke-free legislation on adult, non-smoker exposure to secondhand smoke: cross-sectional surveys before (2004) and after (2012) legislation. PloS One. 2014;9(2):e89430.

63. Oliveros E, Somers VK, Sochor O, Goel K, Lopez-Jimenez F. The concept of normal weight obesity. Prog Cardiovasc Dis. 2014;56(4):426-33.

64. Swinburn BA, Sacks G, Hall KD, McPherson K, Finegood DT, Moodie ML, et al. The global obesity pandemic: shaped by global drivers and local environments. Lancet. 2011;378(9793):804-14.

65. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014.

66. Schuster DP. Obesity and the development of type 2 diabetes: the effects of fatty tissue inflammation. Diabetes Metab Syndr Obes. 2010;3:253-62.

67. Kaur J. A comprehensive review on metabolic syndrome. Cardiol Res Pract. 2014;2014:943162.

68. Berger NA. Obesity and cancer pathogenesis. Ann N Y Acad Sci. 2014;1311:57-76.

69. Bastien M, Poirier P, Lemieux I, Despres JP. Overview of epidemiology and contribution of obesity to cardiovascular disease. Prog Cardiovasc Dis. 2014;56(4):369-81.

70. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. Circulation. 1983;67(5):968-77.

71. Jahangir E, De Schutter A, Lavie CJ. The relationship between obesity and coronary artery disease. Transl Res. 2014;164(4):336-44.

72. De Schutter A, Lavie CJ, Milani RV. The impact of obesity on risk factors and prevalence and prognosis of coronary heart disease-the obesity paradox. Prog Cardiovasc Dis. 2014;56(4):401-8.

73. Jebb SA. Aetiology of obesity. Br Med Bull. 1997;53(2):264-85.

74. Urgently needed: a framework convention for obesity control. Lancet. 2011;378(9793):741.

75. Pampel FC, Krueger PM, Denney JT. Socioeconomic Disparities in Health Behaviors. Annual review of sociology. 2010;36:349-70.

76. Popkin BM. Global changes in diet and activity patterns as drivers of the nutrition transition. Nestle Nutrition workshop series Paediatric programme. 2009;63:1-10; discussion -4, 259-68.

77. Katzmarzyk PT, Mason C. The physical activity transition. J Phys Act Health. 2009;6(3):269-80.

78. Shetty P. Nutrition transition and its health outcomes. Indian J Pediatr. 2013;80 Suppl 1:S21-7.

79. Owen N, Sparling PB, Healy GN, Dunstan DW, Matthews CE. Sedentary behavior: emerging evidence for a new health risk. Mayo Clin Proc. 2010;85(12):1138-41.

80. Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2224-60.

81. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. Compr Physiol. 2012;2(2):1143-211.

82. Bhupathiraju SN, Tucker KL. Coronary heart disease prevention: nutrients, foods, and dietary patterns. Clinica chimica acta; international journal of clinical chemistry. 2011;412(17-18):1493-514.

83. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med. 2013;368(14):1279-90.

84. Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. BMJ. 2008;337:a1344.

85. Panagiotakos DB, Pitsavos C, Chrysohoou C, Skoumas I, Stefanadis C, Study A. Five-year incidence of cardiovascular disease and its predictors in Greece: the ATTICA study. Vasc Med. 2008;13(2):113-21.

86. Panagiotakos DB, Pitsavos C, Stefanadis C. Dietary patterns: a Mediterranean diet score and its relation to clinical and biological markers of cardiovascular disease risk. Nutr Metab Cardiovasc Dis: 2006;16(8):559-68.

87. Hu FB. Globalization of food patterns and cardiovascular disease risk. Circulation. 2008;118(19):1913-4.

88. Chiva-Blanch G, Arranz S, Lamuela-Raventos RM, Estruch R. Effects of wine, alcohol and polyphenols on cardiovascular disease risk factors: evidences from human studies. Alcohol Alcohol. 2013;48(3):270-7.

89. Ronksley PE, Brien SE, Turner BJ, Mukamal KJ, Ghali WA. Association of alcohol consumption with selected cardiovascular disease outcomes: a systematic review and meta-analysis. BMJ. 2011;342:d671.

90. Holmes MV, Dale CE, Zuccolo L, Silverwood RJ, Guo Y, Ye Z, et al. Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data. BMJ. 2014;349:g4164.

91. Lachenmeier DW, Przybylski MC, Rehm J. Comparative risk assessment of carcinogens in alcoholic beverages using the margin of exposure approach. Int J Cancer. 2012;131(6):E995-1003.

92. Fedirko V, Tramacere I, Bagnardi V, Rota M, Scotti L, Islami F, et al. Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. Ann Oncol. 2011;22(9):1958-72.

93. Govil SR, Weidner G, Merritt-Worden T, Ornish D. Socioeconomic status and improvements in lifestyle, coronary risk factors, and quality of life: the Multisite Cardiac Lifestyle Intervention Program. Am J Public Health. 2009;99(7):1263-70.

94. Barreto Pde S. Why are we failing to promote physical activity globally?. Bull World Health Organ. 2013;91(6): 390-390A.

95. Ciaccio M, Bellia C. Hyperhomocysteinemia and cardiovascular risk: effect of vitamin supplementation in risk reduction. Curr Clin Pharmacol. 2010;5(1):30-6.

96. Di Napoli M, Elkind MS, Godoy DA, Singh P, Papa F, Popa-Wagner A. Role of C-reactive protein in cerebrovascular disease: a critical review. Expert Rev Cardiovasc Ther. 2011;9(12):1565-84.

97. Casas JP, Shah T, Hingorani AD, Danesh J, Pepys MB. C-reactive protein and coronary heart disease: a critical review. J Intern Med. 2008;264(4):295-314.

98. Koenig W. High-sensitivity C-reactive protein and atherosclerotic disease: from improved risk prediction to risk-guided therapy. Int J Cardiol. 2013;168(6):5126-34.

99. Salazar J, Martinez MS, Chavez M, Toledo A, Anez R, Torres Y, et al. C-reactive protein: clinical and epidemiological perspectives. Cardiol Res Pract. 2014;2014:605810.

100. Ruberg FL, Loscalzo J. Prothrombotic determinants of coronary atherothrombosis. Vasc Med. 2002;7(4):289-99.

101. Marutsuka K, Hatakeyama K, Yamashita A, Asada Y. Role of thrombogenic factors in the development of atherosclerosis. J Atheroscler Thromb. 2005;12(1):1-8.

102. Kannel WB. Overview of hemostatic factors involved in atherosclerotic cardiovascular disease. Lipids. 2005;40(12):1215-20.

103. Vita JA, Loscalzo J. Shouldering the risk factor burden: infection, atherosclerosis, and the vascular endothelium. Circulation. 2002;106(2):164-6.

104. Smeeth L, Casas JP, Hingorani AD. The role of infection in cardiovascular disease: more support but many questions remain. Eur Heart J. 2007;28(10):1178-9.

105. Madjid M, Miller CC, Zarubaev VV, Marinich IG, Kiselev OI, Lobzin YV, et al. Influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed coronary heart disease death: results from 8 years of autopsies in 34,892 subjects. Eur Heart J. 2007;28(10):1205-10.

106. Warren-Gash C, Hayward AC, Hemingway H, Denaxas S, Thomas SL, Timmis AD, et al. Influenza infection and risk of acute myocardial infarction in England and Wales: a CALIBER self-controlled case series study. J Infect Dis. 2012;206(11):1652-9.

107. Udell JA, Zawi R, Bhatt DL, Keshtkar-Jahromi M, Gaughran F, Phrommintikul A, et al. Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis. JAMA. 2013;310(16):1711-20.

108. McKeown T. The Role of Medicine: Dream, Mirage, Or Nemesis? 1 ed: Blackwell; 1979. 207 p.

109. Colgrove J. The McKeown thesis: a historical controversy and its enduring influence. Am J Public Health. 2002;92(5):725-9.

110. Link BG, Phelan JC. McKeown and the idea that social conditions are fundamental causes of disease. Am J Public Health. 2002;92(5):730-2.

111. Marmot M. Social determinants of health inequalities. Lancet. 2005;365(9464):1099-104.

112. Wilkinson R, Marmot M, editors. Social Determinants of Health. The solid facts. World Health Organization. Denmark; 2003.

113. Commission on the Social Determinants of the Health. Closing the gap in a generation: health equity through action on the social determinants of health. World Health Organization. Geneva; 2008. ISBN 978 92 4 156370 3.

114. World Health Organization. Social determinants of health [Internet]. World Health Organization [cited 10/12/2014]. Available from: http://www.who.int/topics/social_determinants/en/.

115. Friel S, Marmot MG. Action on the social determinants of health and health inequities goes global. Annu Rev Public Health. 2011;32:225-36.

116. Mackenbach JP, Stirbu I, Roskam AJ, Schaap MM, Menvielle G, Leinsalu M, et al. Socioeconomic inequalities in health in 22 European countries. N Engl J Med. 2008;358(23):2468-81.

117. Sanchez-Santos MT, Mesa-Frias M, Choi M, Nuesch E, Asunsolo-Del Barco A, Amuzu A, et al. Area-level deprivation and overall and cause-specific mortality: 12 years' observation on British women and systematic review of prospective studies. PloS One. 2013;8(9):e72656.

118. Link BG, Phelan J. Social conditions as fundamental causes of disease. J Health Soc Behav. 1995;Spec No:80-94.

119. Phelan JC, Link BG, Tehranifar P. Social conditions as fundamental causes of health inequalities: theory, evidence, and policy implications. J Health Soc Behav 2010;51 Suppl:S28-40.

120. Solar O, Irwin A. A Conceptual Framework for Action on the Social Determinants of Health: Social Determinants of Health Discussion Paper 2 (Policy and Practice). Commission on the Social Determinants of the Health. World Health Organization. Geneva, 2010.

121. Magnus P, Beaglehole R. The real contribution of the major risk factors to the coronary epidemics: time to end the "only-50%" myth. Arch Intern Med. 2001;161(22):2657-60.

122. Skodova Z, Nagyova I, van Dijk JP, Sudzinova A, Vargova H, Studencan M, et al. Socioeconomic differences in psychosocial factors contributing to coronary heart disease: a review. J Clin Psychol Med Settings. 2008;15(3):204-13.

123. Diez Roux AV. Residential environments and cardiovascular risk. J Urban Health. 2003;80(4):569-89.

124. Sposato LA, Saposnik G. Gross domestic product and health expenditure associated with incidence, 30-day fatality, and age at stroke onset: a systematic review. Stroke. 2012;43(1):170-7.

125. Bartley M. Health Inequality: introduction to theories, concepts, methods: Cambridge, Polity Press; 2004. p. 22-34.

126. Barata RB, Ribeiro MCSdA, Silva ZPd, Antunes JLF. Classe social: conceitos e esquemas operacionais em pesquisa em saúde. Revista de Saúde Pública. 2013;47:647-55.

127. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G. Indicators of socioeconomic position (part 1). Journal of epidemiology and community health. 2006;60(1):7-12.

128. Kilander L, Berglund L, Boberg M, Vessby B, Lithell H. Education, lifestyle factors and mortality from cardiovascular disease and cancer. A 25-year follow-up of Swedish 50-year-old men. Int J Epidemiol. 2001;30(5):1119-26.

129. Mayer O, Jr., Simon J, Heidrich J, Cokkinos DV, De Bacquer D, Group EIS. Educational level and risk profile of cardiac patients in the EUROASPIRE II substudy. J Epidemiol Community Health. 2004;58(1):47-52.

130. Gupta R, Gupta VP, Ahluwalia NS. Educational status, coronary heart disease, and coronary risk factor prevalence in a rural population of India. BMJ. 1994;309(6965):1332-6.

131. Christensen S, Mogelvang R, Heitmann M, Prescott E. Level of education and risk of heart failure: a prospective cohort study with echocardiography evaluation. Eur Heart J. 2011;32(4):450-8.

132. Kuper H, Adami HO, Theorell T, Weiderpass E. The socioeconomic gradient in the incidence of stroke: a prospective study in middle-aged women in Sweden. Stroke. 2007;38(1):27-33.

133. Fletcher JM, Frisvold DE. Higher Education and Health Investments: Does More Schooling Affect Preventive Health Care Use?. J Hum Cap. 2009;3(2):144-76.

134. Chen AM, Yehle KS, Albert NM, Ferraro KF, Mason HL, Murawski MM, et al. Health Literacy Influences Heart Failure Knowledge Attainment but Not Self-Efficacy for Self-Care or Adherence to Self-Care over Time. Nurs Res Pract. 2013;2013:353290.

135. Kaplan GA, Keil JE. Socioeconomic factors and cardiovascular disease: a review of the literature. Circulation. 1993;88(4 Pt 1):1973-98.

136. Li C, Hedblad B, Rosvall M, Buchwald F, Khan FA, Engstrom G. Stroke incidence, recurrence, and case-fatality in relation to socioeconomic position: a population-based study of middle-aged Swedish men and women. Stroke. 2008;39(8):2191-6.

137. Johnson-Lawrence V, Kaplan G, Galea S. Socioeconomic mobility in adulthood and cardiovascular disease mortality. Ann Epidemiol. 2013;23(4):167-71.

138. Thomas AJ, Eberly LE, Davey Smith G, Neaton JD, Stamler J. Race/ethnicity, income, major risk factors, and cardiovascular disease mortality. Am J Public Health. 2005;95(8):1417-23.

139. Georgiades A, Janszky I, Blom M, Laszlo KD, Ahnve S. Financial strain predicts recurrent events among women with coronary artery disease. Int J Cardiol. 2009;135(2):175-83.

140. Kankeu HT, Saksena P, Xu K, Evans DB. The financial burden from non-communicable diseases in low- and middle-income countries: a literature review. Health Res Policy Syst. 2013;11:31.

141. Marmot MG, Rose G, Shipley M, Hamilton PJ. Employment grade and coronary heart disease in British civil servants. Journal of epidemiology and community health. 1978;32(4):244-9.

142. Park K, Hwang SY. 10-Year Risk for Cardiovascular Disease Among Male Workers in Small-Sized Industries. J Cardiovasc Nurs. 2014. doi: 10.1097/JCN.0000000000000146

143. Kivimaki M, Nyberg ST, Batty GD, Fransson EI, Heikkila K, Alfredsson L, et al. Job strain as a risk factor for coronary heart disease: a collaborative meta-analysis of individual participant data. Lancet. 2012;380(9852):1491-7.

144. Ferrie JE, Kivimaki M, Shipley MJ, Davey Smith G, Virtanen M. Job insecurity and incident coronary heart disease: the Whitehall II prospective cohort study. Atherosclerosis. 2013;227(1):178-81.

145. Cohen S, Wills TA. Stress, social support, and the buffering hypothesis. Psychol Bull. 1985;98(2):310-57.

146. Uchino BN. Social support and health: a review of physiological processes potentially underlying links to disease outcomes. J Behav Med. 2006;29(4):377-87.

147. Udell JA, Steg PG, Scirica BM, Smith SC, Jr., Ohman EM, Eagle KA, et al. Living alone and cardiovascular risk in outpatients at risk of or with atherothrombosis. Arch Intern Med. 2012;172(14):1086-95.

148. Schmaltz HN, Southern D, Ghali WA, Jelinski SE, Parsons GA, King KM, et al. Living alone, patient sex and mortality after acute myocardial infarction. J Gen Intern Med. 2007;22(5):572-8.

149. Kitamura T, Sakata Y, Nakatani D, Suna S, Usami M, Matsumoto S, et al. Living alone and risk of cardiovascular events following discharge after acute myocardial infarction in Japan. J Cardiol. 2013;62(4):257-62.

150. Quinones PA, Kirchberger I, Heier M, Kuch B, Trentinaglia I, Mielck A, et al. Marital status shows a strong protective effect on long-term mortality among first acute myocardial infarction-survivors with diagnosed hyperlipidemia--findings from the MONICA/KORA myocardial infarction registry. BMC Public Health. 2014;14:98.

151. Redondo-Sendino A, Guallar-Castillon P, Banegas JR, Rodriguez-Artalejo F. [Relationship between social network and hypertension in older people in Spain]. Rev Esp Cardiol. 2005;58(11):1294-301.

152. Hadi Khafaji HA, Al Habib K, Asaad N, Singh R, Hersi A, Al Falaeh H, et al. Marital status and outcome of patients presenting with acute coronary syndrome: an observational report. Clin Cardiol. 2012;35(12):741-8.

153. Lett HS, Blumenthal JA, Babyak MA, Strauman TJ, Robins C, Sherwood A. Social support and coronary heart disease: epidemiologic evidence and implications for treatment. Psychosom Med. 2005;67(6):869-78.

154. Cohen S, Herbert TB. Health psychology: psychological factors and physical disease from the perspective of human psychoneuroimmunology. Annu Rev Psychol. 1996;47:113-42.

155. Marmot M, Wilkinson RG. Psychosocial and material pathways in the relation between income and health: a response to Lynch et al. BMJ. 2001;322(7296):1233-6.

156. Macleod J, Davey Smith G. Psychosocial factors and public health: a suitable case for treatment?. J Epidemiol Community Health. 2003;57(8):565-70.

157. Martikainen P, Bartley M, Lahelma E. Psychosocial determinants of health in social epidemiology. Int J Epidemiol. 2002;31(6):1091-3.

158. Rugulies R. Depression as a predictor for coronary heart disease. a review and meta-analysis. Am J Prev Med. 2002;23(1):51-61.

159. Carney RM, Freedland KE. Depression in patients with coronary heart disease. Am J Med. 2008;121(11 Suppl 2):S20-7.

160. Barth J, Schumacher M, Herrmann-Lingen C. Depression as a risk factor for mortality in patients with coronary heart disease: a meta-analysis. Psychosom Med. 2004;66(6):802-13.

161. Scalco AZ, Scalco MZ, Azul JBS, Lotufo Neto F. Hypertension and depression. Clinics. 2005;60:241-50.

162. Lichtman JH, Bigger JT, Jr., Blumenthal JA, Frasure-Smith N, Kaufmann PG, Lesperance F, et al. AHA science advisory. Depression and coronary heart disease. Recommendations for screening, referral, and treatment. A science advisory from the American Heart Association Prevention Committee to the Council on Cardiovascular Nursing, Council on Clinical Cardiology, Council on Epidemiology and Prevention, and Interdisciplinary Council on Quality of Care Outcomes Research. Endorsed by the American Psychiatric Association. Prog Cardiovasc Nurs. 2009;24(1):19-26.

163. Roest AM, Martens EJ, de Jonge P, Denollet J. Anxiety and risk of incident coronary heart disease: a meta-analysis. J Am Coll Cardiol. 2010;56(1):38-46.

164. Player MS, Peterson LE. Anxiety disorders, hypertension, and cardiovascular risk: a review. Int J Psychiatry Med. 2011;41(4):365-77.

165. Janszky I, Ahnve S, Lundberg I, Hemmingsson T. Early-onset depression, anxiety, and risk of subsequent coronary heart disease: 37-year follow-up of 49,321 young Swedish men. J Am Coll Cardiol. 2010;56(1):31-7.

166. Bacon SL, Campbell TS, Arsenault A, Lavoie KL. The impact of mood and anxiety disorders on incident hypertension at one year. Int J Hypertens. 2014;2014:953094.

167. Suls J. Anger and the heart: perspectives on cardiac risk, mechanisms and interventions. Prog Cardiovasc Dis. 2013;55(6):538-47.

168. Chida Y, Steptoe A. The association of anger and hostility with future coronary heart disease: a meta-analytic review of prospective evidence. J Am Coll Cardiol. 2009;53(11):936-46.

169. Holt RI, Phillips DI, Jameson KA, Cooper C, Dennison EM, Peveler RC, et al. The relationship between depression, anxiety and cardiovascular disease: findings from the Hertfordshire Cohort Study. J Affect Disord. 2013;150(1):84-90.

170. Ohira T, Diez Roux AV, Polak JF, Homma S, Iso H, Wasserman BA. Associations of anger, anxiety, and depressive symptoms with carotid arterial wall thickness: the multi-ethnic study of atherosclerosis. Psychosom Med. 2012;74(5):517-25.

171. Stewart JC, Janicki DL, Muldoon MF, Sutton-Tyrrell K, Kamarck TW. Negative emotions and 3-year progression of subclinical atherosclerosis. Arch Gen Psychiatry. 2007;64(2):225-33.

172. Mwendwa DT, Ali MK, Sims RC, Cole AP, Lipscomb MW, Levy SA, et al. Dispositional depression and hostility are associated with inflammatory markers of cardiovascular disease in African Americans. Brain Behav Immun. 2013;28:72-82.

173. Steptoe A, Kivimaki M. Stress and cardiovascular disease: an update on current knowledge. Annu Rev Public Health. 2013;34:337-54.

174. Wei J, Rooks C, Ramadan R, Shah AJ, Bremner JD, Quyyumi AA, et al. Meta-analysis of mental stress-induced myocardial ischemia and subsequent cardiac events in patients with coronary artery disease. Am J Cardiol. 2014;114(2):187-92.

175. Dimsdale JE. Psychological stress and cardiovascular diseaseJ Am Coll Cardiol. 2008;51(13):1237-46.

176. Backe EM, Seidler A, Latza U, Rossnagel K, Schumann B. The role of psychosocial stress at work for the development of cardiovascular diseases: a systematic review. Int Arch Occup Environ Health. 2012;85(1):67-79.

177. Schwartz BG, French WJ, Mayeda GS, Burstein S, Economides C, Bhandari AK, et al. Emotional stressors trigger cardiovascular events. Int J Clin Pract. 2012;66(7):631-9.

178. Pickett KE, Pearl M. Multilevel analyses of neighbourhood socioeconomic context and health outcomes: a critical review. J Epidemiol Community Health. 2001;55(2):111-22.

179. Cubbin C, Sundquist K, Ahlen H, Johansson SE, Winkleby MA, Sundquist J. Neighborhood deprivation and cardiovascular disease risk factors: protective and harmful effects. Scand J Public Health. 2006;34(3):228-37.

180. Diez Roux AV, Merkin SS, Arnett D, Chambless L, Massing M, Nieto FJ, et al. Neighborhood of residence and incidence of coronary heart disease. N Engl J Med. 2001;345(2):99-106.

181. Pujades-Rodriguez M, Timmis A, Stogiannis D, Rapsomaniki E, Denaxas S, Shah A, et al. Socioeconomic deprivation and the incidence of 12 cardiovascular diseases in 1.9 million women and men: implications for risk prediction and prevention. PloS One. 2014;9(8):e104671.

182. Venkitachalam L, Wang K, Porath A, Corbalan R, Hirsch AT, Cohen DJ, et al. Global variation in the prevalence of elevated cholesterol in outpatients with established vascular disease or 3 cardiovascular risk factors according to national indices of economic development and health system performance. Circulation. 2012;125(15):1858-69.

183. Danaei G, Singh GM, Paciorek CJ, Lin JK, Cowan MJ, Finucane MM, et al. The global cardiovascular risk transition: associations of four metabolic risk factors with national income, urbanization, and Western diet in 1980 and 2008. Circulation. 2013;127(14):1493-502, 502e1-8.

184. Chaix B. Geographic life environments and coronary heart disease: a literature review, theoretical contributions, methodological updates, and a research agenda. Annu Rev Public Health. 2009;30:81-105.

185. Koren A, Steinberg DM, Drory Y, Gerber Y, Israel Study Group on First Acute Myocardial I. Socioeconomic environment and recurrent coronary events after initial myocardial infarction. Ann Epidemiol. 2012;22(8):541-6.

186. Allender S, Scarborough P, Keegan T, Rayner M. Relative deprivation between neighbouring wards is predictive of coronary heart disease mortality after adjustment for absolute deprivation of wards. J Epidemiol Community Health. 2012;66(9):803-8.

187. Augustin T, Glass TA, James BD, Schwartz BS. Neighborhood psychosocial hazards and cardiovascular disease: the Baltimore Memory Study. Am J Public Health. 2008;98(9):1664-70.

188. Woodward M, Brindle P, Tunstall-Pedoe H, estimation Sgor. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). Heart. 2007;93(2):172-6.

189. Pingali P. Westernization of Asian diets and the transformation of food systems: Implications for research and policy. Food Policy. 2007;32(3):281-98.

190. Egusa G, Watanabe H, Ohshita K, Fujikawa R, Yamane K, Okubo M, et al. Influence of the extent of westernization of lifestyle on the progression of preclinical atherosclerosis in Japanese subjects. J Atheroscler Thromb. 2002;9(6):299-304.

191. Yusuf S, Islam S, Chow CK, Rangarajan S, Dagenais G, Diaz R, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. Lancet. 2011;378(9798):1231-43.

192. Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):953-62.

193. Ornish D, Scherwitz LW, Billings JH, Brown SE, Gould KL, Merritt TA, et al. Intensive lifestyle changes for reversal of coronary heart disease. JAMA. 1998;280(23):2001-7.

194. Haskell WL, Alderman EL, Fair JM, Maron DJ, Mackey SF, Superko HR, et al. Effects of intensive multiple risk factor reduction on coronary atherosclerosis and clinical cardiac events in men and women with coronary artery disease. The Stanford Coronary Risk Intervention Project (SCRIP). Circulation. 1994;89(3):975-90.

195. Spring B, Moller AC, Colangelo LA, Siddique J, Roehrig M, Daviglus ML, et al. Healthy lifestyle change and subclinical atherosclerosis in young adults: Coronary Artery Risk Development in Young Adults (CARDIA) study. Circulation. 2014;130(1):10-7.

196. Daniels SR, Pratt CA, Hayman LL. Reduction of risk for cardiovascular disease in children and adolescents. Circulation. 2011;124(15):1673-86.

197. Franklin BA, Cushman M. Recent advances in preventive cardiology and lifestyle medicine: a themed series. Circulation. 2011;123(20):2274-83.

198. Weintraub WS, Daniels SR, Burke LE, Franklin BA, Goff DC, Jr., Hayman LL, et al. Value of primordial and primary prevention for cardiovascular disease: a policy statement from the American Heart Association. Circulation. 2011;124(8):967-90.

199. Fifth Joint Task Force of the European Society of C, European Association of E, European Association of Percutaneous Cardiovascular I, European Heart Rhythm A, Heart Failure A, European Association for Cardiovascular P, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur J Prev Cardiol. 2012;19(4):585-667.

200. Franco M, Bilal U, Guallar E, Sanz G, Gomez AF, Fuster V, et al. Systematic review of three decades of Spanish cardiovascular epidemiology: improving translation for a future of prevention. Eur J Prev Cardiol. 2013;20(4):565-76.

201. Cirera L, Tormo MJ, Chirlaque MD, Navarro C. Cardiovascular risk factors and educational attainment in Southern Spain: a study of a random sample of 3091 adults. Eur J Epidemiol. 1998;14(8):755-63.

202. Regidor E, Gutierrez-Fisac JL, Banegas JR, Dominguez V, Rodriguez-Artalejo F. Association of adult socioeconomic position with hypertension in older people. J Epidemiol Community Health. 2006;60(1):74-80.

203. Morales-Asencio JM, Mancera-Romero J, Bernal-Lopez R, Martos-Cerezuela I, Baca-Osorio AJ, Moyano-Paris MT, et al. Educational inequalities and cardiovascular risk factors. A cross-sectional population-based study in southern Spain. Public Health Nurs. 2013;30(3):202-12.

204. Regidor E, Gutierrez-Fisac JL, Banegas JR, Lopez-Garcia E, Rodriguez-Artalejo F. Obesity and socioeconomic position measured at three stages of the life course in the elderly. Eur J Clin Nutr. 2004;58(3):488-94.

205. Larranaga I, Arteagoitia JM, Rodriguez JL, Gonzalez F, Esnaola S, Pinies JA, et al. Socio-economic inequalities in the prevalence of Type 2 diabetes, cardiovascular risk factors and chronic diabetic complications in the Basque Country, Spain. Diabet Med. 2005;22(8):1047-53.

206. Redondo A, Benach J, Subirana I, Martinez JM, Munoz MA, Masia R, et al. Trends in the prevalence, awareness, treatment, and control of cardiovascular risk factors across educational level in the 1995-2005 period. Ann Epidemiol. 2011;21(8):555-63.

207. Espelt A, Kunst AE, Palencia L, Gnavi R, Borrell C. Twenty years of socio-economic inequalities in type 2 diabetes mellitus prevalence in Spain, 1987-2006. Eur J Public Health. 2012;22(6):765-71.

208. Basterra-Gortari FJ, Bes-Rastrollo M, Segui-Gomez M, Forga L, Martinez JA, Martinez-Gonzalez MA. [Trends in obesity, diabetes mellitus, hypertension and hypercholesterolemia in Spain (1997-2003)]. Med Clin (Barc). 2007;129(11):405-8.

209. Lopez Suarez A, Elvira Gonzalez J, Beltran Robles M, Alwakil M, Saucedo JM, Bascunana Quirell A, et al. [Prevalence of obesity, diabetes, hypertension, hypercholesterolemia and metabolic syndrome in over 50-year-olds in Sanlucar de Barrameda, Spain]. Rev Esp Cardiol. 2008;61(11):1150-8.

210. Schroder H, Rohlfs I, Schmelz EM, Marrugat J, investigators R. Relationship of socioeconomic status with cardiovascular risk factors and lifestyle in a Mediterranean population. Eur J Nutr. 2004;43(2):77-85.

211. Gonzalez-Zobl G, Grau M, Munoz MA, Marti R, Sanz H, Sala J, et al. Socioeconomic status and risk of acute myocardial infarction. Population-based case-control study. Rev Esp Cardiol. 2010;63(9):1045-53.

212. Avendano M, Kunst AE, Huisman M, van Lenthe F, Bopp M, Borrell C, et al. Educational level and stroke mortality: a comparison of 10 European populations during the 1990s. Stroke. 2004;35(2):432-7.

213. Avendano M, Kunst AE, Huisman M, Lenthe FV, Bopp M, Regidor E, et al. Socioeconomic status and ischaemic heart disease mortality in 10 western European populations during the 1990s. Heart. 2006;92(4):461-7.

214. Borrell C, Azlor E, Rodriguez-Sanz M, Puigpinos R, Cano-Serral G, Pasarin MI, et al. Trends in socioeconomic mortality inequalities in a southern European urban setting at the turn of the 21st century. J Epidemiol Community Health. 2008;62(3):258-66.

215. Dominguez-Berjon MF, Gandarillas A, Segura del Pozo J, Zorrilla B, Soto MJ, Lopez L, et al. Census tract socioeconomic and physical environment and cardiovascular mortality in the Region of Madrid (Spain). J Epidemiol Community Health. 2010;64(12):1086-93.

216. Machon M, Aldasoro E, Martinez-Camblor P, Calvo M, Basterretxea M, Audicana C, et al. Socioeconomic differences in incidence and relative survival after a first acute myocardial infarction in the Basque Country, Spain. Gac Sanit. 2012;26(1):16-23.

217. Medrano MJ, Alcalde-Cabero E, Ortiz C, Galan I. Effect of cardiovascular prevention strategies on incident coronary disease hospitalisation rates in Spain; an ecological time series analysis. BMJ Open. 2014;4(2):e004257.

218. Munoz MA, Rohlfs I, Masuet S, Rebato C, Cabanero M, Marrugat J, et al. Analysis of inequalities in secondary prevention of coronary heart disease in a universal coverage health care system. Eur J Public Health. 2006;16(4):361-7.

219. Barcelo MA, Saez M, de Tuero GC. Individual socioeconomic factors conditioning cardiovascular disease risk. Am J Hypertens. 2009;22(10):1085-95.

220. Martinez-Gonzalez MA, Corella D, Salas-Salvado J, Ros E, Covas MI, Fiol M, et al. Cohort profile: design and methods of the PREDIMED study. Int J Epidemiol. 2012;41(2):377-85.

221. PREDIMED Study Group. PREDIMED study questionnaires [Internet]. 221. PREDIMED Study. [cited 10/12/2014]. Available from: http://www.predimed.org/eng/Protocol/QUESTIONNAIRES/tabid/577/Default.aspx.

222. De la Fuente-Arrillaga C, Ruiz ZV, Bes-Rastrollo M, Sampson L, Martinez-Gonzalez MA. Reproducibility of an FFQ validated in Spain. Public Health Nutr. 2010;13(9):1364-72.

223. Fernandez-Ballart JD, Pinol JL, Zazpe I, Corella D, Carrasco P, Toledo E, et al. Relative validity of a semi-quantitative food-frequency questionnaire in an elderly Mediterranean population of Spain. Br J Nutr. 2010;103(12):1808-16.

224. Martinez-Gonzalez MA, Fernandez-Jarne E, Serrano-Martinez M, Wright M, Gomez-Gracia E. Development of a short dietary intake questionnaire for the quantitative estimation of adherence to a cardioprotective Mediterranean diet. Eur J Clin Nutr. 2004;58(11):1550-2.

225. Elosua R, Garcia M, Aguilar A, Molina L, Covas MI, Marrugat J. Validation of the Minnesota Leisure Time Physical Activity Questionnaire In Spanish Women. Investigators of the MARATDON Group. Med Sci Sports Exerc. 2000;32(8):1431-7.

226. Elosua R, Marrugat J, Molina L, Pons S, Pujol E. Validation of the Minnesota Leisure Time Physical Activity Questionnaire in Spanish men. The MARATHOM Investigators. Am J Epidemiol. 1994;139(12):1197-209.

227. Haskell WL, Lee IM, Pate RR, Powell KE, Blair SN, Franklin BA, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Circulation. 2007;116(9):1081-93.

228. Salomaa V, Miettinen H, Niemela M, Ketonen M, Mahonen M, Immonen-Raiha P, et al. Relation of socioeconomic position to the case fatality, prognosis and treatment of myocardial infarction events; the FINMONICA MI Register Study. J Epidemiol Community Health. 2001;55(7):475-82.

229. Manderbacka K, Keskimaki I, Reunanen A, Klaukka T. Equity in the use of antithrombotic drugs, beta-blockers and statins among Finnish coronary patients. Int J Equity Health. 2008;7:16.

230. Kapral MK, Wang H, Mamdani M, Tu JV. Effect of socioeconomic status on treatment and mortality after stroke. Stroke. 2002;33(1):268-73.

231. Alter DA, Naylor CD, Austin P, Tu JV. Effects of socioeconomic status on access to invasive cardiac procedures and on mortality after acute myocardial infarction. N Engl J Med. 1999;341(18):1359-67.

232. Crespo-Cebada E, Urbanos-Garrido RM. Equity and equality in the use of GP services for elderly people: the Spanish case. Health policy. 2012;104(2):193-9.

233. Andrulis DP. Access to care is the centerpiece in the elimination of socioeconomic disparities in health. Ann Intern Med. 1998;129(5):412-6.

234. Starfield B, Shi L, Macinko J. Contribution of primary care to health systems and health. Milbank Q. 2005;83(3):457-502.

235. Meng L, Chen D, Yang Y, Zheng Y, Hui R. Depression increases the risk of hypertension incidence: a meta-analysis of prospective cohort studies. J Hypertens. 2012;30(5):842-51.

236. Garcia-Fabela L, Melano-Carranza E, Aguilar-Navarro S, Garcia-Lara JM, Gutierrez-Robledo LM, Avila-Funes JA. Hypertension as a risk factor for developing depressive symptoms among community-dwelling elders. Rev Invest Clin. 2009;61(4):274-80.

237. Davidson K, Jonas BS, Dixon KE, Markovitz JH. Do depression symptoms predict early hypertension incidence in young adults in the CARDIA study? Coronary Artery Risk Development in Young Adults. Arch Intern Med. 2000;160(10):1495-500.

238. Licht CM, de Geus EJ, Seldenrijk A, van Hout HP, Zitman FG, van Dyck R, et al. Depression is associated with decreased blood pressure, but antidepressant use increases the risk for hypertension. Hypertension. 2009;53(4):631-8.

239. Hildrum B, Romild U, Holmen J. Anxiety and depression lowers blood pressure: 22-year follow-up of the population based HUNT study, Norway. BMC Public Health. 2011;11:601.

240. Lenoir H, Lacombe JM, Dufouil C, Ducimetiere P, Hanon O, Ritchie K, et al. Relationship between blood pressure and depression in the elderly. The Three-City Study. J Hypertens. 2008;26(9):1765-72.

241. Paterniti S, Verdier-Taillefer MH, Geneste C, Bisserbe JC, Alperovitch A. Low blood pressure and risk of depression in the elderly. A prospective community-based study. Br J Psychiatry. 2000;176:464-7.

242. Bonnet F, Irving K, Terra JL, Nony P, Berthezene F, Moulin P. Anxiety and depression are associated with unhealthy lifestyle in patients at risk of cardiovascular disease. Atherosclerosis. 2005;178(2):339-44.

243. Beilin LJ. Lifestyle and hypertension--an overview. Clin Exp Hypertens. 1999;21(5-6):749-62.

244. Dalton AR, Vamos EP, Harris MJ, Netuveli G, Wachter RM, Majeed A, et al. Impact of universal health insurance coverage on hypertension management: a cross-national study in the United States and England. PloS One. 2014;9(1):e83705.

245. Grotto I, Huerta M, Sharabi Y. Hypertension and socioeconomic status. Curr Opin Cardiol. 2008;23(4):335-9.

246. Minor D, Wofford M, Wyatt SB. Does socioeconomic status affect blood pressure goal achievement?. Curr Hypertens Rep. 2008;10(5):390-7.

247. Wu Z, Schimmele CM, Chappell NL. Aging and late-life depression. J Aging Health. 2012;24(1):3-28.

248. Naylor C PM, McDaid D, Knapp M, Fossey M, Galea A. . Long-term conditions and mental health. The cost of co-morbidities. The King's Fund and Centre for Mental Health. London; 2012. ISBN 9781857176339.

249. Gonzalez MA, Rodriguez Artalejo F, Calero JR. Relationship between socioeconomic status and ischaemic heart disease in cohort and case-control studies: 1960-1993. Int J Epidemiol. 1998;27(3):350-8.

250. Addo J, Ayerbe L, Mohan KM, Crichton S, Sheldenkar A, Chen R, et al. Socioeconomic status and stroke: an updated review. Stroke. 2012;43(4):1186-91.

251. Mejia-Lancheros C, Estruch R, Martinez-Gonzalez MA, Salas-Salvado J, Corella D, Gomez-Gracia E, et al. Socioeconomic status and health inequalities for cardiovascular prevention among elderly Spaniards. Rev Esp Cardiol (Engl Ed). 2013;66(10):803-11.

252. Kerr GD, Slavin H, Clark D, Coupar F, Langhorne P, Stott DJ. Do vascular risk factors explain the association between socioeconomic status and stroke incidence: a meta-analysis. Cerebrovasc Dis. 2011;31(1):57-63.

253. Galobardes B, Davey Smith G, Jeffreys M, McCarron P. Childhood socioeconomic circumstances predict specific causes of death in adulthood: the Glasgow student cohort study. J Epidemiol Community Health. 2006;60(6):527-9.

254. Galobardes B, Smith GD, Lynch JW. Systematic review of the influence of childhood socioeconomic circumstances on risk for cardiovascular disease in adulthood. Ann Epidemiol. 2006;16(2):91-104.

255. Gallo P, Gene-Badia J. Cuts drive health system reforms in Spain. Health policy. 2013;113(1-2):1-7.

256. Litwin H. Social networks and well-being: a comparison of older people in Mediterranean and non-Mediterranean countries. The journals of gerontology Series B, J Gerontol B Psychol Sci Soc Sci. 2010;65(5):599-608.

257. Croezen S, Picavet HS, Haveman-Nies A, Verschuren WM, de Groot LC, van't Veer P. Do positive or negative experiences of social support relate to current and future health? Results from the Doetinchem Cohort Study. BMC Public Health. 2012;12:65.

258. Meijer A, Zuidersma M, de Jonge P. Depression as a non-causal variable risk marker in coronary heart disease. BMC Med. 2013;11:130.