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Variability of nutrients intake, lipid profile and cardiovascular mortality among geographical areas in Spain: The DRECE study

Agustín Gómez de la Cámara,[1,2] Eva de Andrés Esteban,[1,2] Gerard Urrútia Cuchí,[2,3] Enrique Calderón Sandubete,[2,4] Miguel Ángel Rubio Herrera,[5] Miguel Menéndez Orenga,[1] David Lora Pablos[1,2]

[1]Instituto de Investigación Hospital 12 de Octubre, Madrid; [2]CIBER Epidemiología y Salud Pública, Madrid; [3]Hospital Santa Creu i Sant Pau, Barcelona; [4]Hospital Virgen del Rocio, Sevilla; [5]Servicio de Endocrinología y Nutrición, Hospital Clínico Universitario de San Carlos, Madrid, Spain

Abstract

It has often been suggested that cardiovascular mortality and their geographical heterogeneity are associated with nutrients intake patterns and also lipid profile. The large Spanish study *Dieta y Riesgo de Enfermedades Cardiovasculares en España* (DRECE) investigated this theory from 1991 to 2010. Out of the 4,783 Spanish individuals making up the DRECE cohort, 220 subjects (148 men and 72 women) died (4.62%) during the course of the study. The mean age of patients who died from cardiovascular causes (32 in all) was 61.08 years 95% CI (57.47-64.69) and 70.91% of them were males. The consumption of nutrients and the lipid profile by geographical area, studied by geospatial models, showed that the east and southern area of the country had the highest fat intake coupled to a high rate of unhealthy lipid profile. It was concluded that the spatial geographical analysis showed a relationship between high fat intake, unhealthy lipid profile and cardiovascular mortality in the different geographical areas, with a high variability within the country.

Correspondence: Agustín Gómez de la Cámara, Instituto de Investigación Hospital 12 de Octubre, CAA 6ª planta Bloque D, Avda. de Córdoba s/n, 28041 Madrid, Spain.
Tel: +34917792837.
E-mail: acamara@h12o.es

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Introduction

Cardiovascular disease (CVD) is still a major public health problem and the leading cause of death in most of the developed countries (Kattainen, 2006). Previous studies ask for whether differences in the distribution of CVD risk factors between regions could explain geographical differences in the incidence and cardiovascular mortality. The IBERICA study (Moreno, 2001) demonstrates that there is a north-south increasing gradient in the incidence of, and mortality from, ischemic heart disease, and the ERICE study (Gabriel *et al*., 2008) shows that the distribution of cardiovascular risk factors is heterogeneous in Spain. Paradoxically, the geographic areas with a higher prevalence of CVD risk are mainly located in eastern and southern Spain, including the Mediterranean seaside, *i.e.* Levante, Andalusia and Extremadura (Gabriel *et al*., 2008). The variability between different geographical areas is known to be marked with a relevant high prevalence ratio for various risks, among them for hypercholesterolemia, diabetes, obesity, smoking and hypertension (Gabriel *et al*., 2008; Grau *et al*., 2011). Epidemiological studies indicate that the quality of diet, together with lifestyle factors, has considerable influence on mortality (Kaluza *et al*., 2009). Subsequent studies of diet and cardiovascular heart disease (CHD), have since evaluated the effects of numerous dietary nutrients and dietary patterns on CHD risk (Mente *et al*., 2009). The Seven Countries European Study (Yarnell and Evans, 2000) investigated the distribution of CVD mortality in Europe and found this diagnosis three times higher in some places than in others. This particular study dealt with the interaction of classic CVD risk factors with the dietary habits as well as with their combined effects on the occurrence of CVD, including mortality. The authors essentially point out the role of cholesterol in CVD and note the positive (healthy) influence of the Mediterranean diet with respect to serum cholesterol. More recently, prospective cohort studies and randomised controlled trials (RCTs) have examined these associations in large populations with long follow-up periods (Mente *et al*., 2009) and again emphasised the harmful effect of high concentrations of saturated fats in the diet. In fact, CVD prevention and treatment now focus on dietary recommendations to reduce the intake of saturated fat, primarily as a means of lowering cholesterol concentrations of the low-density lipoprotein (LDL) type (Siri-Trino *et al*., 2009). High-density lipoprotein (HDL) cholesterol (HDL-C) is inversely associated with CVD (Parish *et al*., 2012), while elevated LDL cholesterol (LDL-C) serum concentration is believed to strongly affect the CVD risk (Panagiotakos *et al*., 2004). It has later been shown that the inverse relationship between HDL-C levels and inflammatory markers illustrates the emerging role of HDL-C as an anti-inflammatory agent in reducing cardiovascular risk (Chrissohoou *et al*., 2007). It is known that diet modifies the lipid profile, but there are also data suggesting that the composition (quality fat diet) may be more important than the amount of fat *per se*, which has an important effect on CVD mortality (Chahoud *et al*., 2004). The Mediterranean diet has long been reported to protect against the occurrence of several different negative health outcomes (Trichopoulou *et al*., 2003; Knoops *et al*., 2004; Serra-Majem *et al*., 2004; Trichopoulou *et al*., 2005; Haveman-Nies *et al*., 2006) and conformity with the Mediterranean dietary pattern is associated with a reduction in mortality (Mitrou *et al*., 2007) and prevention of developing CVD (Trichopoulou *et al*., 2003). It has been observed that a 2-point adherence increase on a Mediterranean Diet Scale (Sofi *et al*., 2010) is associated with a significant reduction in overall mortality with a relative risk (RR) = 0.92 (95% CI: 0.90, 0.94) and CVD incidence or mortality (RR = 0.90; 95% CI: 0.87, 0.93). The effect on the lipid profile by to the Mediterranean diet has been evaluated in RCTs as well as non-randomised clinical trials, prospective cohort studies and a cross-sectional study. These studies demonstrate a decrease in total cholesterol (Ambring *et al*., 2004; Estruch *et al*., 2006), in LDL-C (Ambring *et al*., 2004; Vincent-Baudry *et al*., 2005) and in triglyceride levels (Ambring *et al*., 2004; Vincent-Baudry *et al*., 2005; Estruch *et al*., 2006), as well as an increase in HDL-C levels (Estruch *et al*., 2006). Socio-economic differences in the intake of fat have consistently been reported in Europe, *e.g.*, a positive relationship between socio-economic status and healthier behaviour, including dietary habits, has been found (De Irala-Estevez *et al*., 2000). Indeed, people with a higher socio-economic status are more likely to have a higher consumption of fresh fruits and vegetables and a lower intake of fat compared with those with lower levels of income and/or education (Lopez-Azpiazu *et al*., 2003).

In Europe, major differences in geographic regions regarding CVD-related mortality have been observed with high mortality in eastern and northeastern countries and a lower CVD mortality in southern countries (Muller-Nordhorn *et al*., 2008; Deckert *et al*., 2010; Scarborough *et al*., 2011). This has been attributed to several cultural and behavioural differences between the populations, including diet composition (Da Silva *et al*., 2009). People in Spain are very aware of the Mediterranean diet and its health benefits. However, dietary patterns differ according to geographical area, mainly due to climatic, cultural or traditional factors. The differences in nutrient intake observed seem to be related to cardiovascular events and, therefore, also to CVD-related mortality. The aim of this study was to describe the expected relationship between the rates of CVD mortality, lipid profile and nutrient intake. We used geospatial models because they allow description and analysis of a variety of spatial patterns, mostly in cases characterised by low rates of CVD-related mortality.

Materials and Methods

Study design and sample size

This was an observational and descriptive study of an historical cohort, *i.e*. the large Spanish CVD study *Dieta y Riesgo de Enfermedades Cardiovasculares en España (DRECE)* composed of a representative sample of the Spanish general population, for which selection and sampling have been previously described (Ballesteros-Pomar *et al*., 2000). The DRECE cohort comprised 4,783 subjects, who were followed from 1991 to 2010. At the start of the study, the cohort age range was from 5 to 60 years. All subjects comprising the DRECE cohort underwent medical examination including laboratory tests as well as a personal interview and responded to a nutritional and physical activity questionnaire. Until now, five cross-sectional studies have been done along with the ascertainment of vital status and cause of death follow-up on the entire cohort. Vital statistics and causes of mortality are provided annually by the Spanish National Institute of Statistics.

Variables and measures

Four data groups were gathered.

First, anthropometric and demographic data, such as age, gender, height, weight.

Second, baseline clinical and epidemiological data, such as basic physical examination (including blood pressure and heart rate) and lipid profile (including total cholesterol, total triglycerides, HDL-C and LDL-C).

Third, baseline nutritional data, for which a dietary habits survey was conducted through the application of a questionnaire on the frequency of consumption of food (CFCA) developed and validated for the adult Spanish population (Martin-Moreno *et al*., 1993). Fourth, mortality data for all causes based death certificates provided by the National Institute of Statistics (INE) in Spain.

Statistics

The obtained information was entered into a computerised support by standardised procedures with regular quality controls. Statistical treatment of data started with a descriptive analysis. Quantitative variables were summarised by mean and standard deviation (SD). Lipid profile comparison between individuals who died due to CVD was carried out by the Mann-Whitney test (Hart, 2001). In addition, descriptive analysis was stratified by geographical area, and comparisons were made by the Kruskal-Wallis test (Kruskal and Wallis, 1953).

Bayesian geospatial model

With regard to geographical analysis, in the area of statistical modelling of spatial data, the use of hierarchical spatial models in a Bayesian framework has become widespread since the 1990's, mainly in cases of outcomes with low incidence rates, as in our case. For that reason, we used an extension of the hierarchical Bayesian model proposed by Richardson *et al*. (2006). First, we considered the following approach:

$$O_{1i} \sim Poisson(m_{1i});\ RR_{1i} = \frac{m_{1i}}{e_{1i}} \qquad O_{2i} \sim Poisson(m_{2i});\ RR_{2i} = \frac{m_{2i}}{e_{2i}}$$

$$\log(m_{1i}) = \log(e_{1i}) + \alpha_1 + \mu_{1i} \qquad \log(m_{2i}) = \log(e_{2i}) + \alpha_2 + \mu_{2i}$$

where O_{1i}, O_{2i} with i=1,…,n are the observed number of CV deaths and the lipid profile or diet intake, respectively, and e_{1i}, e_{2i} with i=1,…,n the expected number of cases for both. The α values here are the specific factors and the space structure was introduced in the log scale by the joint structure of μ_{1i} and μ_{2i}. In this particular case we have:

$$\begin{pmatrix}\mu_{1i}\\ \mu_{2i}\end{pmatrix} \sim MVN\left(\begin{pmatrix}\eta_{1i}\\ \eta_{2i}\end{pmatrix}, \Sigma^{-1}\right)$$

The CVD mortality rate and each of diet intake or lipid profile in this model were divided into three spatial components, the first of which common for both and the others specific to each of them (the latter shown in the Results section).

$$\eta_{1i} = \lambda_i \delta + \phi_{1i}; \qquad RR_{\phi 1} = \exp(\mu_{1i} - \eta_{1i})$$
$$\eta_{2i} = \frac{\lambda_i}{\delta} + \beta_i + \phi_{2i}; \quad RR_{\phi 2} = \exp(\mu_{2i} - \eta_{2i})$$

where λ_i represents the shared spatial pattern and β_i the differential spatial pattern between the CVD mortality rate and lipid profile/diet intake. Inference was made by using Markov Chain Monte Carlo (MCMC) simulations that provide an estimate of the posterior distributes of the model parameters. The choice of prior distribution for the model was the following:

$$\alpha_1, \alpha_2 \propto 1$$
$$\lambda \sim \text{CARNormal}(\mathbf{W}, \tau_\lambda)\ \beta \sim \text{CARNormal}(\mathbf{W}, \tau_\beta) \qquad \tau\text{'s} \sim \text{Gamma}(0.5, 0.0005)$$
$$\log(\delta) \sim N(0, 0.2)$$
$$\begin{pmatrix}\phi_{1i}\\ \phi_{2i}\end{pmatrix} \sim MVN\left(\begin{pmatrix}0\\ 0\end{pmatrix}, \Sigma^{-1}\right) \qquad \Sigma^{-1} \sim Wishart\left(\begin{pmatrix}0.01 & 0\\ 0 & 0.01\end{pmatrix}, 2\right)$$

The statistical analyses were conducted using STATA 9.1/SE (Stata Corp, College Station, TX, USA), R, v. 4.1 (R Core Team, 2013) and Winbugs, v. 1.4 (The BUGS Project, 2007).

Results

Out of the 4,786 Spanish individuals making up the DRECE cohort, 220 subjects (148 men and 72 women) died (4.62%) during the course of the study. Thirty-two of these deaths were CVD-related. The mean age of people who died from cardiovascular causes was 61.08 years 95% CI (57.47-64.69) and 70.91% of them were males. Amongst males, the mean age was 58.58 years 95% CI (54.11-63.05) and amongst the females 66.54 years 95% CI (60.90-72.18).

Analysing lipid profile in both groups (Figure 1), we observed that total cholesterol as well as LDL-C and triglycerides were associated with CVD mortality with the highest levels in the group of people who died. On the other hand, there was an inverse relationship with HDL-C with lower concentrations in the mortality group compared with the survival group, *i.e.* 50.35 mg/dL *versus* 55.12 mg/dL (P=0.049).

Table 1 shows the nutrients consumption and the lipid profile by geographical area. The central and southern areas of the country stand out as having the worse lipid profiles and a high rate of fat intake. The spatial geographical analysis showed the relationship with CVD mortality in the different areas. Figure 2 shows a fat intake distribution very similar to that of the mortality rate and, similarly, in Figure 3, we see the least acceptable lipid profile in those areas together with the highest CVD-related mortality rate. However, we found a high variability within the country with respect to mortality and the nutritional food intake and lipid profile rates of regions. Large discrepancies are still observed among the different regions or areas in the macro-nutrients intake (Serra-Majem *et al*., 1993; Varela-Moreiras *et al*., 2013). With respect to differences between geographic areas by the total energy intake,

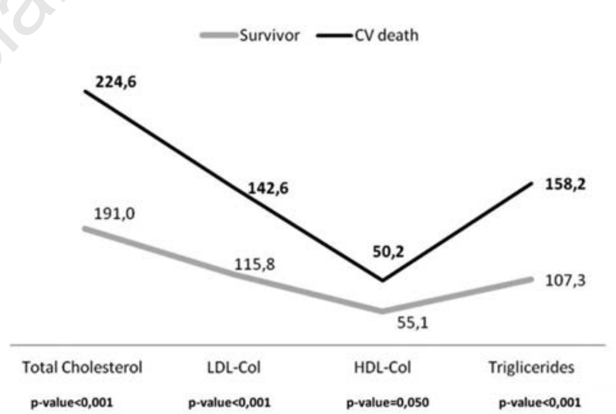

Figure 1. Lipid profile by cardiovascular mortality.

Table 1. Diet intake and lipid profile characteristics by region.

	Geographical areas								P
	North-West	North	North-East	West	Centre-South	East	South	Canary islands	
BMI	24.54 (4.80)	23.54 (4.49)	24.47 (4.67)	23.67 (4.49)	24.09 (5.09)	24.18 (4.75)	24.81 (5.68)	24.28 (5.52)	0.002
Carbohydrates	288.33 (102.58)	282.08 (90.58)	322.83 (101.42)	333.06 (108.76)	300.56 (98.60)	285.91 (115.44)	269.06 (104.42)	310.43 (102.74)	<0.001
Proteins	112.34 (3.22)	107.41 (27.54)	120.27 (35.31)	119.01 (30.09)	118.39 (31.80)	117.57 (40.21)	110.98 (39.89)	111.88 (33.56)	<0.001
Fats	107.37 (40.68)	110.56 (40.32)	120.52 (45.26)	110.06 (38.43)	117.72 (43.53)	127.36 (52.91)	125.50 (49.04)	127.80 (51.15)	<0.001
Kilocalories	2702 (801.41)	2660.72 (731.33)	2893.98 (830.54)	2946.14 (829.34)	2864 (801.73)	2742 (981.34)	2621.29 (912.18)	2882.06 (846.43)	<0.001
Total cholesterol	189.27 (42.44)	192.41 (43.42)	190.98 (45.90)	187.28 (43.19)	187.88 (40.97)	197 (45.93)	196.26 (43.24)	194.48 (46.80)	<0.001
HDL cholesterol	56.73 (13.91)	56.18 (13.809	53.60 (13.98)	57.49 (14.09)	55.89 (13.40)	54113 (13.26)	54.03 (13.64)	51.69 (12.89)	<0.001
LDL cholesterol	113.17 (36.69)	116.88 (38.27)	117.86 (39.41)	110.79 (38.33)	112.94 (36.08)	120.88 (39.53)	120.22 (37.01)	118.68 (36.56)	<0.001
Triglycerides	105.32 (70.41)	100.21 (60.65)	102.63 (80.43)	104.98 (112.16)	103.78 (106.38)	118.99 (90.35)	112.47 (83.36)	119.98 (76.55)	<0.001

BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

we noted that there was a percentage difference between geographic areas from 9.4% in total energy intake. The average caloric intake had a range of 2,660 kcal/day in the North to 2,946 kcal/day in the West. The caloric intake in these parts of the country was mainly in the form of carbohydrates, while in the Canaries, there was a higher fat intake. The percentage difference between geographic areas in fat intake was 15%, in carbohydrate intake 19% and in protein intake 10.8%. The areas with the highest fat intake were in the South, in the East and in the Canaries, while there was less consumption in the western and northern regions of the country. A clear gradient between regions in Spain with regard to intake of proteins or carbohydrates seems to have become established resulting in a north-south and east-west gradient with respect to fat intake.

As shown on Figures 2 and 3, there is a gradient of CVD-related mortality in the direction northwest to southeast. The geographical distribution of the cardiovascular mortality showed an aggregation in the South (11 deaths) and in the East (7 deaths) as well as in the south-eastern region (4 deaths) of the country, near areas with a history of adherence to healthy diet habits were observed. On the other hand, the regions with greater adherence to a recommended healthy diet had lower mortality in the northern and western parts of Spain. Adherence to nutritional recommendations related mainly to the western area (Castilla-León), which is characterised by a high intake of carbohydrates and proteins with comparatively little fat, and also by a relatively low mortality. Meanwhile, areas in the South and East (Andalusia, Extremadura, Murcia and Levante) showed the opposite situation, *i.e.* a higher mortality and a dietary pattern with high consumption of fats low in carbohydrates and proteins. We found the variables related to a low mortality to be i) a less aged population (OR 0.93, 95% CI 0.89-0.99); ii) a contextual dietary pattern marked by high contents of fish (OR 2.13, 95% CI 1.38-3.28) and wine consumption (OR 1.50, 95% CI 1.08-2.07); and iii) a low prevalence of obesity (OR 0.47, 95% CI 0.22-1.01). No significant associations were found with frequencies of arterial hypertension, hypercholesterolemia or smoking and socioeconomic factors.

Discussion

The identification of dietary patterns is of considerable interest in the study of the relationship between diet and chronic diseases and their possible association with mortality (Gonzalez *et al*., 2002). The impact of diet, diet patterns, macro-nutrient intake on CVD-related mortality in Spain has been demonstrated. There is a clear pattern characterised by low-fat intake with a high caloric intake of carbohydrates and proteins in the West and Northwest of Spain. Another dietary pattern, where energy intake is mainly due to fat intake, low intake of proteins and carbohydrates occurs in the southern and western regions, while the Canaries has a significant intake of both fats and carbohydrates together with a low level of proteins. The geographical pattern of cardiovascular mortality obviously correlates with the consumption of fats as the geographical areas that have higher consumption of this nutrient are associated with increased mortality. The excess mortality in the southern and eastern Spanish regions is thus attributed to, or at least associated with, high fat intake, while no pattern appears to be associated with the intake of proteins or carbohydrates. In addition, regions with high levels of LDL-C and low HDL-C (which can be called a negative lipid profile) correspond to the areas with the highest mortality rates. The gradient of CVD-related mortality from northwest to southeast is similar to the risk described between the European countries (Trichopoulou *et al*., 2002). The northern and western regions there are not only characterised by a lower CVD-related mortality, but also a healthier diet as previously noted by Kaluza *et al*. (2009).

One study identifying Spanish towns with very low ischemic heart disease mortality, describing their health care and social characteristics, was based on a small-area spatial analysis of mortality, with the study units being Spain's 8,073 towns as in 1991 and 2000 (Medrano *et al*., 2012). This study identified 32 towns, situated in lightly populated provinces spread across the northern half of Spain, in which ischemic heart disease mortality was half the national rate and four times lower than the rate in the European Union. Similar results were observed through our work, identify-

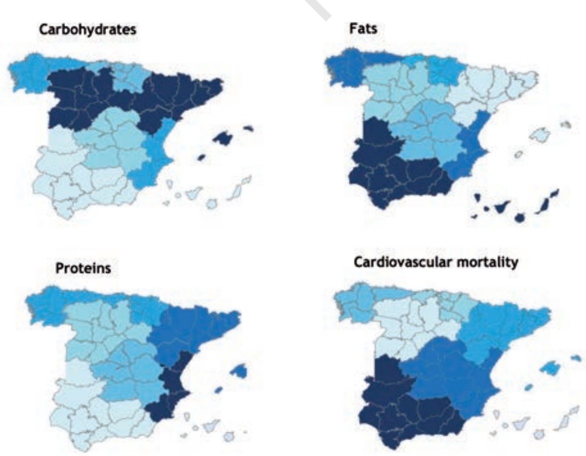

Figure 2. Variation of macronutrient intake in Spanish geographical areas.

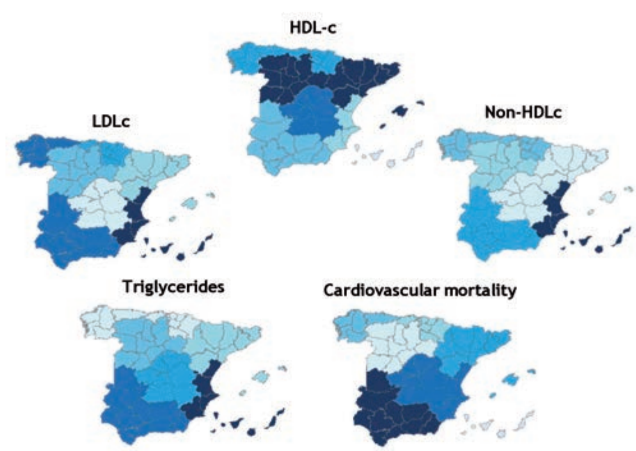

Figure 3. Variation of lipid profile in Spanish geographical areas.

ing the same geographical areas associated with lower cardiovascular mortality, although analysed from another perspective and with the application of another methodology to assess the effect of diet on cardiovascular mortality. Geographical areas with higher mortality are located on the Mediterranean coast, which at first might seem surprising as they are supposed to be more deeply linked with the culture and traditions of greater adherence to the recommended quality diet. However, this may be changing as studies examining adherence to the Mediterranean diet in the Spanish adult population and its evolution over time describe a modification of nutritional habits (Bach-Faig *et al*., 2011; León-Muñoz *et al.*, 2012). Indeed, the ENRICA (Rodríguez-Artalejo *et al.*, 2011) study described the diet in Spain as being rich in proteins and total fat (mostly unsaturated fat) and somewhat low in carbohydrates found a low accordance between the diet of the Spanish population and the Mediterranean diet (46%) with the goal set in MEDAS>7 (León-Muñoz *et al*., 2012), which confirms that Spaniards are drifting away from the Mediterranean diet to progressively adopt a less healthy diet. In another study, the progressive replacement of carbohydrates by proteins and fats is clearly described ending with the conclusion that *Food consumption patterns in Spain and energy and nutrient intakes have changed markedly in the last 40 years, differing at present from the traditional and healthy Mediterranean diet* (Varela-Moreiras *et al*., 2010). Indeed, these change are not only observed in Spain, but also in the rest of the world: throughout the last four decades the Mediterranean countries have moved away from the Mediterranean dietary pattern at the order of 42.5%. Within the Mediterranean area, the European countries are primarily responsible for this loss of adherence with changes in cultural, social and political factors likely to have had a heavy influence on changes in food habits. On the other hand, many countries in northern Europe and some other countries around the world are adopting the Mediterranean-like dietary pattern (Da Silva *et al*., 2009).

Income and economic environment assume a crucial role in the context of dietary pattern changes (De Irala-Estevez *et al*., 2000; Vareiro *et al*., 2009). Factors such as cultural differences, personal taste and traditions, education, geographic location, access to technology as well as health and health attitudes influence food preferences and food availability (Trichopoulou *et al*., 2002). The fact that the availability of several Mediterranean dietary components, such as fruits, vegetables and olive oil, has increased (or been maintained) could have led to a greater adherence to the Mediterranean dietary pattern. Contrary, however, the availability of the non-Mediterranean foods have increased to a much greater extent compared to Mediterranean foods (Da Silva *et al*., 2009). In our study, the lipid profiles differences between regions and the geographical distribution of macronutrients intake, mainly fats, were associated with cardiovascular mortality rates but did not fully explain the regional variation of these rates because they are not explained by the type of fat consumed. In areas or regions with high fat intake, this may be at the expense of mainly saturated fat as it is correlated with increased cardiovascular mortality and a less acceptable lipid profile (Cabrera *et al*., 2012; Hooper *et al*., 2012).

In a study, based on the identification of regions with lower mortality, socioeconomic factors showed no effect or association with mortality (Trichopoulou *et al*., 2002). However, the educational and cultural level factors were analysed in the EPIC study (Gonzalez *et al*., 2002); no significant differences were observed in adherence to this pattern in relation to educational level and social class. The Mediterranean dietary pattern appears to be evenly distributed between socioeconomic and demographic groups (Gonzalez *et al*., 2002). No significant differences were observed in the adhesion score in relation to educational level, some differences are instead related to the social class of origin (Gonzalez *et al*., 2002). This, though not necessarily representing the respondent's social class, expresses a past period (childhood and youth), which have a primary role in the acquisition of food habits of the adult. It has been demonstrated that if low saturated fat dietary counselling starts in infancy, it has a significant favourable effect on dietary saturated fat intake and on serum lipid values through childhood and adolescence extending to early adulthood (Maruthur *et al*., 2009; Siri-Trino *et al*., 2010; Niinikoski *et al*., 2012). Nutrition policy actions to tackle dietary *westernisation* and preserve the healthy dietary pattern are required to be designed and adapted to different populations groups to improve the situation (Da Silva *et al*., 2009; Hooper *et al*., 2012). Awareness campaigns to encourage a healthy diet have proven to be an effective strategy, and can be maintained over time (Wister *et al*., 2007). This can be achieved by using the media, as in the MOLI-SANI project (Bonnacio *et al*., 2012), a population-based cohort study to investigate the association between mass media information, dietary habits and CVD risk factors in 1,132 Italian adults. Exposure to mass media information is significantly associated with greater adherence to both a Mediterranean diet and a Mediterranean-eating pattern (Bonnacio *et al*., 2012). With regard to the extrapolation of our results to the general population, it should be noted that they are based on a representative sample of the Spanish population with a high level of participation from all social levels and geographic areas. Although we did not analyse the effect of socioeconomic status or education, we suggest that the recommended food accessibility is not dependent on cost and that the nutritional pattern acquired by the population does not differ due to these causes. Furthermore, when assessing food consumption, a potential bias must be taken into account, *i.e.* the potential recall bias introduced by respondents in reporting their diets connected with a tendency to overestimate food consumption accepted as healthy and underestimate the least healthy food.

Conclusions

Areas with increased cardiovascular mortality are located in the Spanish South and East, while lower mortality was predominantly found in the North and Northwest of the country with established risk strata coinciding with the level of fat intake. The observed north-south gradient of low to high cardiovascular mortality associated with dietary patterns considered as healthy confirms the role of inadequate fat intake and its contribution to CVD-related mortality. According to the distribution of macronutrients, two diet-related CVD mortality risk strata can be distinguished. In the Northwest and Southeast specific intervention strategies aimed at modifying nutritional/dietary habits to strengthen, improve and restore recommended nutritional habits, should be implemented.

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