

Original article

Comparative Study of Ambient Air Particles in Patients Hospitalized for Heart Failure and Acute Coronary Syndrome

Alberto Domínguez-Rodríguez,^{a,*} Javier Abreu-Afonso,^b Sergio Rodríguez,^c Rubén A. Juárez-Prera,^a Eduardo Arroyo-Ucar,^a Alejandro Jiménez-Sosa,^d Yenny González,^c Pedro Abreu-González,^e and Pablo Avanzas^f

^aServicio de Cardiología, Hospital Universitario de Canarias, La Laguna, Santa Cruz de Tenerife, Spain

^bDepartamento de Física Aplicada, Universidad de Valencia, Valencia, Spain

^cCentro de Investigación Atmosférica de Izaña (CIAI), AEMET-CSIC, Santa Cruz de Tenerife, Spain

^dUnidad de Investigación, Hospital Universitario de Canarias, La Laguna, Santa Cruz de Tenerife, Spain

^eDepartamento de Fisiología, Universidad de La Laguna, La Laguna, Santa Cruz de Tenerife, Spain

^fServicio de Cardiología, Hospital Universitario Central de Asturias, Oviedo, Asturias, Spain

Article history:

Received 30 November 2010

Accepted 26 December 2010

Available online 8 June 2011

Keywords:

Risk factors

Heart failure

Myocardial infarction

Unstable angina

Palabras clave:

Factores de riesgo

Insuficiencia cardíaca

Infarto de miocardio

Angina inestable

ABSTRACT

Introduction and objectives: Currently air pollution is considered as an emerging risk factor for cardiovascular disease. Our objective was to study the concentrations of particulate matter in ambient air and analyze their relationship with cardiovascular risk factors in patients admitted to a cardiology department of a tertiary hospital with the diagnosis of heart failure or acute coronary syndrome (ACS).

Methods: We analyzed 3950 consecutive patients admitted with the diagnosis of heart failure or ACS. We determined the average concentrations of different sizes of particulate matter (<10, <2.5, and <1 μm and ultrafine particles) from 1 day or up to 7 days prior to admission (1 to 7 days lag time).

Results: There were no statistically significant differences in mean concentrations of particulate matter <10, <2.5 and <1 μm in size in both populations. When comparing the concentrations of ultrafine particles of patients admitted due to heart failure and acute coronary syndrome, it was observed that the former had a tendency to have higher values (19 845.35±8 806.49 vs 16 854.97 ± 8005.54 cm⁻³, P <.001). The multivariate analysis showed that ultrafine particles are a risk factor for admission for heart failure, after controlling for other cardiovascular risk factors (odds ratio = 1.4; confidence interval 95%, from 1.15 to 1.66 P = .02).

Conclusions: In our study population, compared with patients with ACS, exposure to ultrafine particles is a precipitating factor for admission for heart failure.

© 2010 Sociedad Española de Cardiología. Published by Elsevier España, S.L. All rights reserved.

Estudio comparativo de las partículas en aire ambiente en pacientes ingresados por insuficiencia cardíaca y síndrome coronario agudo

RESUMEN

Introducción y objetivos: Actualmente se considera la contaminación atmosférica como un factor de riesgo emergente de enfermedades cardiovasculares. Nuestro objetivo fue comparar las concentraciones de partículas atmosféricas en aire ambiente y analizar su relación con los factores de riesgo cardiovascular en pacientes que ingresan en un servicio de cardiología de un hospital terciario con el diagnóstico de insuficiencia cardíaca y síndrome coronario agudo (SCA).

Métodos: Analizamos a un total de 3.950 pacientes ingresados de forma consecutiva con el diagnóstico de insuficiencia cardíaca y SCA. Se determinaron las concentraciones medias de material particulado con tamaño < 10, 2,5 y 1 μm y partículas ultrafinas, desde el día anterior hasta los 7 días previos al ingreso (1 a 7 días de retardo).

Resultados: No se observaron diferencias estadísticamente significativas en las concentraciones medias de material particulado con tamaño < 10, 2,5 y 1 μm en ambos grupos de población. Cuando se compararon las concentraciones de partículas ultrafinas de los pacientes ingresados por insuficiencia cardíaca y SCA, se observó que los primeros tenían tendencia a valores más altos (19.845,35 ± 8.806,49 frente a 16.854,97 ± 8.005,54/cm⁻³; p < 0,001). El análisis multivariable muestra que las partículas ultrafinas son un factor de riesgo para ingresar por insuficiencia cardíaca, tras controlar por los distintos factores de riesgo cardiovascular (odds ratio = 1,4; intervalo de confianza del 95%, 1,15-1,66; p = 0,02).

SEE RELATED ARTICLE:

DOI: 10.1016/j.rec.2011.05.006, Rev Esp Cardiol. 2011;64:642-5.

* Corresponding author: Servicio de Cardiología, Hospital Universitario de Canarias, Ofra s/n, La Cuesta, 38320 La Laguna, Tenerife, Spain.

E-mail address: adrvdg@hotmail.com (A. Domínguez-Rodríguez).

Conclusiones: En nuestra población de estudio, comparada con pacientes con SCA, la exposición a partículas ultrafinas constituye un factor precipitante del ingreso por insuficiencia cardiaca.

© 2010 Sociedad Española de Cardiología. Publicado por Elsevier España, S.L. Todos los derechos reservados.

Abbreviations

ACS: acute coronary syndrome
AMI: acute myocardial infarction
NSTEMI: non-ST-elevation myocardial infarction
PM: particulate matter
STEMI: ST-elevation myocardial infarction

INTRODUCTION

Cardiovascular diseases are the leading cause of death in Spain. Ischemic heart disease and heart failure are the main causes of cardiovascular deaths.^{1–3}

The main risk factors related to the development of cardiovascular diseases are tobacco smoking, diabetes mellitus, high blood pressure, and dyslipidemia.⁴ It is well-known that the risk of cardiovascular diseases multiplies if several of these factors are present. In Spain, 31% of individuals seen in primary health care have 2 risk factors and around 6% have 3.⁵ Atmospheric pollution and cardiovascular risk was recently presented as one of the key themes in the *XIV Simposio Internacional de Cardiopatía Isquémica* (14th International Meeting on Ischemic Heart Disease) organized in Girona, Spain, by the Department of Ischemic Heart Disease and Coronary Care Units of the *Sociedad Española de Cardiología* (Spanish Society of Cardiology) in April 2010. Atmospheric pollution was considered to be an emerging risk factor for ischemic heart disease.

The impact that atmospheric pollution has on health has been discussed since the middle of the 20th century. The large number of epidemiological and experimental studies shows that there has been a renewed interest in this subject. These have stated since 1990 that pollution levels that may be considered normal in developed countries are still a health risk.^{6,7} In the last few years, several multicenter studies have assessed the situation in different regions of the world, such as the APHEA study in Europe,^{8–10} the NMMAPS in the United States,¹¹ or national European projects such as *Air & Santé* in France¹² or MISA in Italy.¹³ The EMECAS (*Estudio Multicéntrico Español sobre la relación entre Contaminación Atmosférica y Salud*) project included 16 Spanish cities and analyzed the relationship between atmospheric pollution and health.^{14–16} These studies investigated the acute or short-term (on the same day or subsequent days) effects of an increase in pollution and concluded that for every daily 10 $\mu\text{g}/\text{m}^3$ increase in the concentration of suspended particles smaller than 10 μm (breathable), the number of people who die in the days immediately following increases by about 0.7%.⁶

The aim of this study was to test the concentrations of atmospheric particles in ambient air and to analyze their relationship with cardiovascular risk factors in patients admitted to a tertiary hospital's Department of Cardiology with a diagnosis of heart failure and acute coronary syndrome (ACS).

METHODS

Population

We analyzed 3950 patients admitted consecutively to our hospital from October 2006 to December 2009 with a diagnosis of heart failure and ACS. Only patients who complied with all the inclusion criteria and none of the exclusion criteria were considered for inclusion. The presence of viral or bacterial infection 15 days before admission was one of the exclusion criteria.

The inclusion criteria for patients with heart failure were: a) patients who survived admission to hospital for suspected heart failure and which was confirmed as the primary diagnosis on discharge, and b) who complied with the European Society of Cardiology's diagnostic regulations: symptoms compatible with heart failure according to the Framingham criteria and evidence of heart dysfunction by echocardiogram, isotopic ventriculography, or cardiac catheterization.¹⁷ The following were considered as criteria for exclusion: a) patient admitted to hospital for heart failure which was confirmed as the secondary diagnosis on discharge; b) heart failure secondary to serious heart valve diseases requiring surgery or secondary to chronic *pulmonary* heart disease; c) concomitant diseases with a survival prognosis of <12 months, and d) patients who died of heart failure in hospital.¹⁸

The inclusion criteria for patients with ACS^{19,20} were: patients who survived admission to hospital for suspected acute myocardial infarction (AMI) with ST-elevation (STEMI) and non-ST-elevation ACS, and non-ST-elevation AMI (NSTEMI) confirmed as the primary diagnosis on discharge. The following were considered as criteria for exclusion: a) patients admitted to hospital for ACS, confirmed as the secondary diagnosis at discharge; b) concomitant diseases with a survival prognosis of <12 months, and c) patients who died of ACS in hospital.²¹

STEMI was defined by the presence of compatible symptoms, persistent (>20 min) ST-segment elevation ≥ 1 mm in at least 2 contiguous leads or the presence of left bundle branch block presumed to be a new occurrence, and elevated cardiac troponin-I ≥ 0.5 ng/ml (cut-off point ≥ 0.5 ng/ml for the diagnosis of AMI; immunological reagents of the Orthoclinical Diagnostics Vitros 5100 system, United States). NSTEMI was defined by the presence of compatible symptoms, cardiac troponin-I ≥ 0.5 ng/ml and/or dynamic ST-segment changes (≥ 1 mm decrease in the ST-segment or non-persistent elevation in at least 2 contiguous leads). Unstable angina was defined by the presence of suggestive chest pain with or without re-polarization abnormalities in the baseline electrocardiogram. Serum levels of cardiac troponin-I had to be <0.5 ng/ml 24 h after the appearance of symptoms.

The study was approved by our hospital's clinical research ethics committee and all the patients signed an informed consent.

Baseline Variables on Admission

We studied age (years), sex, tobacco smoking (smokers and non-smokers), hypercholesterolemia (cut-off point, 250 mg/dl), hypercholesterolemia drug treatment, arterial hypertension (hypertensive patients, which included those taking hypertensive drugs, and non-hypertensive patients), hypertensive drug treatment,

diabetes mellitus, diabetes mellitus drug treatment, family history of ischemic heart disease; hemoglobin; creatinine and glycemia on admission to hospital, and presence of infections 15 days prior to admission.

Methodology for the Atmospheric Pollution Data

The atmospheric pollutants were measured in an urban background monitoring station. Concentrations of particulate matter (PM) smaller than 10, 2.5 and 1 μm (PM_{10} , $\text{PM}_{2.5}$ and PM_1 respectively) and ultrafine particles (diameter less than 0.1 μm) were measured using different techniques.²² The PM_{10} , $\text{PM}_{2.5}$ and PM_1 levels were monitored using two techniques: a) high-volume samplers (30m³/h; MCZTM) for filter-based and gravimetric analysis (European Directive 2008/50/EC) and b) GRIMMTM optical particle counter (model 1007). The number of particles per unit volume of air (cm⁻³) with a size greater than 2.5 nm was measured using an Ultrafine Condensation Particle Counter (UCPC, TSITM, model 3776, TSI Distributor, Shoreview, Minnesota, United States). This measurement was considered representative of the concentration of ultrafine particles, given that 80%-90% of the particles detected in urban air by the UCPC are smaller than 0.1 μm .²² In our study, all of the pollutants were expressed as the 24 h average concentrations from the previous day up to 7 days prior to admission.

The concentrations of gaseous pollutants were also measured using reference methods (Directive 2008/50/EC): a) sulphur dioxide (SO_2) was measured using ultraviolet (UV) fluorescence (ThermoTM, model 43C, Thermo Scientific Heraeus, Madrid, Spain); b) nitrogen oxides (NO_x), nitrogen dioxide (NO_2), and nitrogen monoxide were measured using chemiluminescence (ThermoTM, model 42C, Thermo Scientific Heraeus, Madrid, Spain); c) ozone (O_3) was measured using UV absorption (ThermoTM, Model 49C, Thermo Scientific Heraeus, Madrid, Spain); and d) carbon monoxide (CO) was measured using non-dispersive IR absorption (Thermo Environmental InstrumentsTM, model 48C, Thermo Fisher Scientific Inc, Madrid, Spain). The analyzers were calibrated every 3 months and they always had a high linearity ($r^2 \sim 0.99$).

Meteorological variables (temperature, relative humidity and wind speed) were measured using standard techniques. These variables were measured as the 24 h average measurements from the previous day up to 7 days prior to admission.

Statistical Analysis

A case-control study (case: patients with heart failure; control: patients with ACS) was performed to analyze exposure to average particle concentrations during the 7 days prior to admission. Continuous variables are presented as mean \pm standard deviation and the categorical variables are expressed as frequencies and percentages. The chi-square test and Fisher's exact test were used as applicable in order to compare the qualitative variables, and Student's t-test was used to compare the quantitative variables. A multivariate analysis was carried out using a binary logistic regression model to estimate the risk of admission for heart failure compared to admission for ACS according to exposure to ultrafine particles during the 7 days prior to admission. All of the variables with a value of $P < .05$ in the univariate analysis were included in the model. The results are presented with the odds ratio (OR) and the 95% confidence interval (CI). A value of $P < .05$ was considered to be significant in all cases. The statistical software package SPSS 17.0 (Chicago, Illinois, United States) for Windows was used for the statistical analysis.

RESULTS

Of the 3950 patients admitted to hospital, 721 met the criteria for exclusion, leaving 3229 patients in the study population. The characteristics of the population groups studied are shown in Table 1. Significant differences were seen between the population groups. Patients admitted for heart failure were older, and there were more women and diabetics in this group. Patients with ACS had a higher prevalence of family history of ischemic heart disease, arterial hypertension, dyslipidemia, and smoking. With regard to treatments prior to admission, there was a higher proportion of treatment for diabetes mellitus and diuretics in the group of patients admitted for heart failure. In contrast, patients admitted for ACS had a higher prevalence of treatments with statins and anti-hypertensive drugs, such as angiotensin-converting enzyme inhibitors and/or angiotensin II receptor antagonists. For the analytical parameters analyzed, higher levels of glycemia on admission were found in the patients admitted for heart failure.

No statistically significant differences were found in the meteorological variables between heart failure and ACS patients (Table 2). Likewise, no statistically significant differences in gaseous pollutants were found except that there were higher concentrations of NO_2 in heart failure patients. When exposure to concentrations of atmospheric particles in ambient air was compared between heart failure and ACS patients, the first group tended to have higher values of ultrafine particles (Table 2). The multivariate analysis showed that exposure to ultrafine particles was a risk factor for admission for heart failure compared to admission for ACS (OR = 1.4; 95% CI, 1.15-1.66; $P = .02$) after adjusting for age, sex, cardiovascular risk factors, and drug treatments (Table 3).

DISCUSSION

To our knowledge, this is the first study carried out in Spain which analyzes the relationship that exists between admission for heart failure and ACS and concentrations of particles in ambient air. A large consecutive cohort of subjects with heart failure and ACS was analyzed in this study and we concluded that heart failure patients had been more exposed to higher concentrations of ultrafine particles in ambient air.

Over the past 20 years, the results of many investigations have shown that atmospheric pollution continues to be an important health risk for the population.²³ Air pollutants are made up of a heterogeneous mixture of gases (for example: O_3 , CO, SO_2 and NO_x) and suspended particles. These suspended particles (also called aerosols or atmospheric PM) are made up of solid materials and/or liquids whose chemical composition is very diverse (generally a mixture of substances) and whose size varies from a couple of nanometers to tens of microns.²⁴

Atmospheric particles are usually classified according to their size into the following groups: a) thick particles (2.5-10 μm), mainly made up of minerals (for example, in dust from the ground re-suspended in the air), b) fine particles (<2.5 μm) made up of a complex mixture of different substances linked to emissions from combustion processes (sulphur, nitrate, organic matter, elemental carbon, and numerous metals such as Ni, Cd, As, Zn, Cu, etc.), and c) ultrafine particles (<0.1 μm), which are mainly made up of condensed hydrocarbons, elemental carbon and sulphur compounds (sulphate/sulphuric acid).²⁴ Recent studies have shown that motor vehicles are the main source of ultrafine particles in cities.²⁵ This is a very important finding, given that NO_2 and ultrafine particles are the only pollutants found in higher concentrations in the group of heart failure patients, and both of these pollutants are usually found in motor vehicle emissions.

Table 1
Clinical Characteristics of Both Groups

	Heart failure	Acute coronary syndrome	P
<i>Patients</i>	1090	2139	
<i>Age (years)</i>	65 ± 10	62 ± 11	<.001
<i>Sex (Male)</i>	731 (67.1)	1517 (70.9)	.02
<i>AHT</i>	545 (50)	1194 (55.8)	.002
<i>Dyslipidemia</i>	352 (32.3)	1113 (52)	<.001
<i>Smoker</i>	130 (11.9)	726 (33.9)	<.001
<i>Diabetes mellitus</i>	487 (44.7)	775 (36.2)	<.001
<i>Family history of IHD</i>	7 (0.6)	87 (4.1)	<.001
<i>Treatment prior to hospitalization</i>			
<i>Statins</i>	315 (28.8)	1050 (49.1)	<.001
<i>Antiaggregation agents</i>	117 (10.7)	255 (11.9)	.32
<i>ACE inhibitors/ARA-II</i>	300 (27.5)	715 (33.4)	<.001
<i>Diuretics</i>	253 (23.2)	410 (19.1)	.008
<i>Beta blockers</i>	155 (14.2)	283 (13.2)	.45
<i>Insulin/oral antidiabetic drugs</i>	487 (44.7)	775 (36.2)	<.001
<i>Hemoglobin* (g/dl)</i>	11.5 ± 2.3	11.38 ± 2.9	.23
<i>Creatinine* (mg/dl)</i>	1.03 ± 0.3	1.02 ± 0.28	.26
<i>Glycemia* (mg/dl)</i>	197 ± 45	141 ± 58	<.0001

ACE inhibitors, angiotensin-converting enzyme inhibitors; AHT, arterial hypertension; ARA-II, angiotensin II receptor antagonists; IHD, ischemic heart disease. Data are expressed as n (%) or mean ± standard deviation.

* Values on hospital admission.

It has been scientifically proven that fine and ultrafine particles reach the lung alveoli, get into the blood circulation and are deposited in the heart, increasing the risk of effects outside the lungs.²⁶ The concentration of PM in the air is associated with an immediate change in heart rate²⁷ and its variability,²⁸ even in healthy subjects. Similarly, several epidemiological studies have demonstrated that a moderate increase in atmospheric pollution puts subjects with chronic obstructive pulmonary disease^{24,29} as well as subjects with heart failure^{24,30} at a higher risk of death.

An Italian study carried out in Rome has recently demonstrated that fine and ultrafine particles in the air were associated with admission to the emergency department for heart failure.³¹ In this respect, we demonstrated in our study that heart failure cases were associated with ultrafine particles regardless of age, sex, cardiovascular risk factors, and drug treatments. Levels of PM is currently believed to be an emerging risk factor that may contribute to clinical risk in combination with cardiovascular risk factors such as arterial hypertension, hypercholesterolemia, tobacco smoking, diabetes and obesity.^{24,32}

Table 2
Data on Atmospheric Pollution in Ambient Air and Meteorological Variables Between the Previous Day and the 7 Days Prior to Admission for Both of the Study Groups. All of the Pollutants Are Expressed as the Average Concentration of the Pollutant

	Heart failure	Acute coronary syndrome	P
<i>Patients</i>	1090	2139	
<i>Meteorological variables</i>			
<i>Wind speed (m/s)</i>	2.54 (0.71)	2.55 (0.78)	.72
<i>Temperature (°C)</i>	21.08 (2.76)	21.04 (2.95)	.70
<i>Relative humidity (%)</i>	66.85 (9.75)	65.98 (15.07)	.08
<i>Gaseous pollutants</i>			
<i>CO (µg/m³)</i>	176.88 (30.45)	177.51 (31.19)	.67
<i>SO₂ (µg/m³)</i>	10.46 (8.23)	10.77 (9.10)	.47
<i>NO₂ (µg/m³)</i>	11.91 (8.90)	10.76 (8.34)	.01
<i>O₃ (µg/m³)</i>	54.64 (14.92)	54.18 (15.67)	.51
<i>Atmospheric particles</i>			
<i>PM-10 (µg/m³)</i>	25.93 (15.91)	27.26 (24.52)	.13
<i>PM-2.5 (µg/m³)</i>	15.65 (7.79)	16.12 (12.73)	.30
<i>PM-1 (µg/m³)</i>	9.593 (5.09)	9.598 (6.05)	.98
<i>UFP (cm⁻³)</i>	19 845.35 (8806.49)	16 854.97 (8005.54)	<.001

CO, carbon monoxide; NO₂, nitrogen dioxide; O₃, ozone; SO₂, sulphur dioxide.

PM, particulate material with an aerodynamic diameter; PM-10, PM < 10 µm; PM-2.5, PM < 2.5 µm; PM-1, < 1 µm; UFP, ultrafine particles (< 0.1 µm).

Table 3

Results of the Logistic Regression Analysis With Admission for Heart Failure or for Acute Coronary Syndrome (Reference Variable) Used as the Dependand Variable

	OR	95% CI	P
Average amount of ultrafine particles ($\times 10\ 000$)	1.40	1.15-1.66	.02
Age	1.02	1.00-1.046	.05
Sex	1.00	0.621-1.61	.99
Dyslipidemia	1.33	1.213-1.519	<.001
AHT	1.63	1.405-1.995	.04
Diabetes	2.40	1.523-3.812	<.001
Smoker	2.70	1.555-4.830	<.001
Glycemia	1.14	1.05-1.74	.03
Statins	1.18	1.07-1.65	.04
ACE inhibitors/ARA-II	1.24	0.98-1.67	.24
Diuretics	1.12	0.84-1.20	.56
Insulin/oral antidiabetic drugs	1.22	1.09-1.90	.01

ACE inhibitors, angiotensin-converting enzyme inhibitors; AHT, arterial hypertension; ARA-II, angiotensin II receptor antagonists; CI, confidence interval; OR, odds ratio.

It has been shown in human and animal experimental studies that ultrafine particles usually cause the most diseases.³² This is because they have more particles per μm^3 , as well as more organic carbon, which increases oxidative stress and cellular inflammation. As a result, greater amounts of pollutants can pass through the alveolar-capillary membrane and reach the blood, causing damage to coronary arteries and myocardium.³² In our study, we discovered that ultrafine particles may be a precipitating factor for admission for heart failure rather than the cause of this condition.

Limitations

We must point out some of the limitations of this study. We did not use time series analysis in our study to examine the short-term relationship between the variations in atmospheric pollution and heart problems. This was because daily variations in the pollutants during the 7 days prior to admission were small enough to allow us to exclude the time series analysis. It was widely discussed which model design should be used to analyze the relationship between atmospheric pollution and cardiovascular disease. However, the similar results found using different methodological techniques suggests that the associations found may be causal.²⁴

Another inherent problem for this type of study on the effects of atmospheric pollution is the errors made when measuring exposure. In our study, there were differences between what was measured in the sampling stations and the actual exposure of each member of the population (inter-individual variability).

Likewise, it was surprising to find that heart failure patients underused diuretics, angiotensin-converting enzyme inhibitors and/or angiotensin II receptor antagonists and beta blockers. Considering that most of these patients had acute decompensation of chronic heart failure, there may be various reasons why these treatments were rarely being taken: eg, the patient had stopped the treatment or, depending on the source of patient referral (cardiology department, internal medicine, or primary care consultation), might have been given unsuitable drug treatment for heart failure. It is well known that primary care physicians and other specialists provide patients with less suitable medication than cardiologists do.³³ These reasons were not used as baseline variables on admission to hospital. Nevertheless, the multivariate model found that exposure to ultrafine particles was a precipitating factor for heart failure admission after adjusting for drug treatments.

CONCLUSIONS

Exposure to ultrafine particles was a precipitating factor for heart failure admission in our study population, compared with ACS patients. Measures must be taken to reduce the concentrations of this pollutant.

FUNDING

Atmospheric pollutants were measured within the framework of 2 research projects: GRACCIE (CSD2007-00067, Spanish Ministry of Science and Technology) and EPAU (B026/2007/3-10.1, Spanish Ministry for the Environment).

CONFLICTS OF INTEREST

None declared.

REFERENCES

- Banegas JR, Villar F, Graciano A, Rodríguez-Artalejo F. Epidemiología de las enfermedades cardiovasculares en España. *Rev Esp Cardiol Supl.* 2006;6:G3–12.
- Marrugat J, Elosua R, Martí H. Epidemiología de la cardiopatía isquémica en España: estimación del número de casos y de las tendencias entre 1997 y 2005. *Rev Esp Cardiol.* 2002;55:337–46.
- Banegas JR, Rodríguez-Artalejo F, Guallar-Castillón P. Situación epidemiológica de la insuficiencia cardiaca en España. *Rev Esp Cardiol Supl.* 2006;6:C4–9.
- Bertomeu V, Castillo-Castillo J. Situación de la enfermedad cardiovascular en España. Del riesgo a la enfermedad. *Rev Esp Cardiol Supl.* 2008;8:E2–9.
- Baena JM, Del Val JL, Tomás J, Martínez JL, Martín R, González I, et al. Epidemiología de las enfermedades cardiovasculares y factores de riesgo en atención primaria. *Rev Esp Cardiol.* 2005;58:367–73.
- Sunyer J. Contaminación atmosférica y mortalidad. *Med Clin (Barc).* 2002; 119:453–4.
- Brunekreef B, Holgate ST. Air pollution and health. *Lancet.* 2002;360:1233–42.
- Katsouyanni K, Touloumi G, Spix C, Schwartz J, Balducci F, Medina S, et al. Short-term effects of ambient sulphur dioxide and particulate matter on mortality in 12 European cities: results from time series data from the APHEA project. *Air Pollution and Health: a European Approach.* *BMJ.* 1997;314:1658–63.
- Touloumi G, Katsouyanni K, Zmirou D, Schwartz J, Spix C, Ponce de León A, et al. Short-term effects of ambient oxidant exposure on mortality: a combined analysis within the APHEA project. *Air Pollution and Health: a European Approach.* *Am J Epidemiol.* 1997;146:177–85.
- Katsouyanni K, Touloumi G, Samoli E, Gryparis A, Le Tertre A, Monopoli Y, et al. Confounding and effect modification in the short-term effects of ambient particles on total mortality: results from 29 European cities within the APHEA2 project. *Epidemiology.* 2001;12:521–31.
- Samet JM, Zeger SL, Dominici F, Currier F, Coursac I, Dockery DW, et al. The National Morbidity, Mortality, and Air Pollution Study. Part II: Morbidity and mortality from air pollution in the United States. *Res Rep Health Eff Inst.* 2000;94:5–70.

12. Eilstein D, Declercq C, Prouvost H, Pascal L, Nunes C, Filleul L, et al. [The impact of air pollution on health. The "Programme de Surveillance Air et Santé 9 villes" (Air and Health surveillance program in 9 cities)]. *Presse Med.* 2004;33:1323-7.
13. Biggeri A, Bellini P, Terracini B. Meta-analysis of the Italian studies on short-term effects of air pollution—MISA 1996-2002. *Epidemiol Prev.* 2004;28(4-5 Suppl):4-100.
14. Grupo EMECAM. El proyecto EMECAM: Estudio multicéntrico español sobre la relación entre la contaminación atmosférica y la mortalidad. *Rev Esp Salud Pública.* 1999;73:165-75.
15. Ballester F, Iñiguez C, Sáez M, Pérez-Hoyos S, Daponte A, Ordóñez JM, et al.; Grupo EMECAM-EMECAS. Relación a corto plazo de la contaminación atmosférica y la mortalidad en 13 ciudades españolas. *Med Clin (Barc).* 2003;121:684-9.
16. Ballester F, Saez M, Daponte A, Ordóñez JM, Taracido M, Cambra K, et al.; EMECAS. El proyecto EMECAS: protocolo del estudio multicéntrico en España de los efectos a corto plazo de la contaminación atmosférica sobre la salud. *Rev Esp Salud Pública.* 2005;79:229-42.
17. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. *Eur Heart J.* 2001;22:1527-60.
18. Pope 3rd CA, Renlund DG, Kfoury AG, May HT, Horne BD. Relation of heart failure hospitalization to exposure to fine particulate air pollution. *Am J Cardiol.* 2008;102:1230-4.
19. Ardissino D, Boersma E, Budaj A, Fernández-Avilés F, Fox KA, Hasdai D, et al. Guía de práctica clínica para el diagnóstico y tratamiento del síndrome coronario agudo sin elevación del segmento ST. *Rev Esp Cardiol.* 2007;60:1070.e1-80.
20. Van de Werf F, Bax J, Betriu A, Lundqvist, Crea F, Falk V, et al. Guías de práctica clínica de la Sociedad Europea de Cardiología. Manejo del infarto agudo de miocardio en pacientes con elevación persistente del segmento ST. *Rev Esp Cardiol.* 2009;62:e1-47.
21. Rückel R, Greven S, Ljungman P, Aalto P, Antoniadis C, Bellander T, et al. Air pollution and inflammation (interleukin-6, C-reactive protein, fibrinogen) in myocardial infarction survivors. *Environ Health Perspect.* 2007;115:1072-80.
22. Querol X, Alastuey A, Rodríguez S, Viana MM, Artíñano B, Salvador P, et al. Levels of particulate matter in rural, urban and industrial sites in Spain. *Sci Total Environ.* 2004;334-335:359-76.
23. Sun Q, Hong X, Wold LE. Cardiovascular effects of ambient particulate air pollution exposure. *Circulation.* 2010;121:2755-65.
24. Brook RD, Rajagopalan S, Pope 3rd CA, Brook JR, Bhatnagar A, Diez-Roux AV, et al. Particulate matter air pollution and cardiovascular disease: an update to the scientific statement from the American Heart Association. *Circulation.* 2010;121:2331-78.
25. Rodríguez S, Van Dingenen R, Putaud JP, Dell'Acqua A, Pey J, Querol X, et al. A study on the relationship between mass concentrations, chemistry and number size distribution of urban fine aerosols in Milan, Barcelona and London. *Atmos Chem Phys.* 2007;7:2217-32.
26. Nemmar A, Hoet PH, Vanquickenborne B, Dinsdale D, Thomeer M, Hoylaerts MF, et al. Passage of inhaled particles into the blood circulation in humans. *Circulation.* 2002;105:411-4.
27. Magari SR, Hauser R, Schwartz J, Williams PL, Smith TJ, Christiani DC. Association of heart rate variability with occupational and environmental exposure to particulate air pollution. *Circulation.* 2001;104:986-91.
28. Gold DR, Litonjua A, Schwartz J, Lovett E, Larson A, Nearing B, et al. Ambient pollution and heart rate variability. *Circulation.* 2000;101:1267-73.
29. Sunyer J, Schwartz J, Tobias A, Macfarlane D, Garcia J, Antó JM. Patients with chronic obstructive pulmonary disease are at increased risk of death associated with urban particle air pollution: a case-crossover analysis. *Am J Epidemiol.* 2000;151:50-6.
30. Goldberg MS, Burnett RT, Bailar 3rd JC, Tamblyn R, Ernst P, Flegel K, et al. Identification of persons with cardiorespiratory conditions who are at risk of dying from the acute effects of ambient air particles. *Environ Health Perspect.* 2001;109 Suppl 4:487-94.
31. Belleudi V, Faustini A, Stafoggia M, Cattani G, Marconi A, Perucci CA, et al. Impact of fine and ultrafine particles on emergency hospital admissions for cardiac and respiratory diseases. *Epidemiology.* 2010;21:414-23.
32. Araujo JA, Nel AE. Particulate matter and atherosclerosis: role of particle size, composition and oxidative stress. *Part Fibre Toxicol.* 2009;6:24.
33. González-Juanatey JR, Alegría Ezquerro E, Bertoméu Martínez V, Conthe Gutiérrez P, De Santiago Nocito A, Zsolt Fradera I. Insuficiencia cardíaca en consultas ambulatorias: comorbilidades y actuaciones diagnóstico-terapéuticas por diferentes especialistas. Estudio EPISERVE. *Rev Esp Cardiol.* 2008;61:611-9.